HHS Public Access

Author manuscript

Vaccine. Author manuscript; available in PMC 2021 February 28.

Published in final edited form as:

Vaccine. 2020 February 28; 38(10): 2326–2332. doi:10.1016/j.vaccine.2020.01.059.

Trivalent inactivated influenza vaccine (IIV3) during pregnancy and six-month infant development

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Abstract

Objective: Despite recommendations by professional organizations that all pregnant women receive inactivated influenza vaccine, safety concerns remain a barrier. Our objective was to assess the effect of trivalent influenza vaccines (IIV3) during pregnancy on parent report 6-month infant development.

Methods: We conducted a multi-site prospective birth cohort study during the 2010–2011 influenza season and followed pregnant women and their newborns through 6 months of age. Information on IIV3 during pregnancy was ascertained from the EHR and self-report. The Ages and Stages Questionnaire-3(ASQ-3) was completed by the mother to assess 6-month infant

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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Potential conflict of interest: The authors have no conflicts of interest relevant to this article to disclose.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

neurodevelopment in five domains (communication, gross motor, fine motor, problem-solving, and personal adaptive skills). Scores for each domain above the cut-off point indicating typical development were categorized as “on schedule” while scores in the zones indicating the need for either monitoring or further assessment were categorized as “not on schedule”. Multivariable logistic regression was conducted.

Results: Of the 1225 infant-mother pairs, 65% received IIV3 during pregnancy. In bivariate analysis, infants of women who received IIV3 during pregnancy were moderately-less likely to need monitoring or further assessment in the personal social domain compared with infants of unvaccinated women (10.0% vs. 14.1%, p=0.033; crude OR (cOR): 0.68(95%CI:0.48,0.97)). However, after controlling for potential confounders, the findings were no longer statistically significant (aOR:0.72,95%CI: 0.49,1.06,p=0.46). No significant unadjusted or adjusted associations emerged in any other ASQ-3 domain.

Conclusion: There was no significant association between IIV3 exposure during pregnancy and 6-month infant development. Studies of IIV3 during pregnancy to assess longer-term developmental outcomes are indicated.

Keywords

trivalent inactivated influenza vaccine (IIV3); pregnancy; infant development; Ages and Stages (ASQ)

INTRODUCTION

Influenza infection during pregnancy is related to an increased risk of severe maternal complications and adverse pregnancy outcomes including stillbirth and preterm delivery[1]. The Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP), the American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Pediatrics (AAP) recommend that all pregnant women receive an inactivated influenza vaccine regardless of the trimester of pregnancy, to protect themselves and their babies from complications of influenza infection[2,3].

An increasing body of epidemiological evidence on maternal and pregnancy outcomes suggests that influenza vaccination during pregnancy is safe[4,5] and efficacious in reducing influenza infections in pregnant women and their infants [6]. However, despite its demonstrated efficacy, concerns over safety for the fetus remain a barrier to influenza vaccination among pregnant women[7]. Research on influenza vaccination during pregnancy and child developmental outcomes is lacking. This is the first epidemiologic study to examine whether receipt of trivalent inactivated influenza vaccine (IIV3) during pregnancy impacts 6-month infant development.

METHODS

Study Design

The Pregnancy and Influenza Project (PIP) was a multi-site, prospective cohort study of pregnant women who were members of Kaiser Permanente Northern California (KPNC) and

Northwest (KPNW; Oregon and southwest Washington) during the 2010–2011 influenza season. Women and their newborns were followed until 6 months post-delivery. Details of the study have been described previously[10]. Potential participants were pregnant women identified through Kaiser Permanente's electronic health records (EHR) and were contacted for recruitment between December 2010 and May 2011. Women were contacted by telephone, screened for eligibility and administered the baseline enrollment interview by computer assisted telephone interview (CATI) after providing informed consent. Women were then asked to contact the study staff weekly via a web-based site or an interactive voice response system (IVR) to inform the study of any acute respiratory illness (ARI) symptoms from the time of enrollment through one month post-delivery. Information on ARI was ascertained through EHR data and self-report. Influenza infection was confirmed through reverse transcription polymerase chain reaction (RT-PCR) for participants who had ARI that included fever and cough within eight days of illness onset and consented to nasopharyngeal swab collection. At the 6-month post-delivery follow-up, women completed the Ages and Stages Questionnaire-3 (ASQ-3)[11] for their infant. Study staff scored the ASQ-3 and were blinded to the mother's vaccination status. The Institutional Review Boards at both Kaiser Permanente sites and Abt Associates which managed the contract for the CDC approved this study.

Exposure

Trivalent inactivated influenza vaccine (IIV3) vaccination status between the date of the last menstrual period (LMP) and the delivery date was ascertained from the EHR and from self-report (for vaccinations administered outside of KP). Trimester of vaccination was calculated by the following: 1st trimester, less than or equal to 91 days of gestation; 2nd trimester, greater than 91 days of gestation and less than or equal to 182; 3rd trimester greater than or equal to 183 days of gestation through delivery. A list of vaccine components in the study year (2010 – 2011) are included in Appendix A.

Outcome

Mothers completed the ASQ-3[11] as part of the 6-month post-delivery follow-up. The ASQ-3 is validated[12] and widely used in the US. It has been identified by the American Academy of Pediatrics[13] as a high-quality tool for use in clinical practice to screen for developmental delays in children between the ages of 1–66 months[11]. The ASQ-3 screens for delays in infant and child development in five domains: communication, gross motor, fine motor, problem-solving, and personal adaptive skills. Scores for each of the five domains were calculated based on the ASQ-3 scoring guide[14]. Scores for each domain above the cut-off point indicating typical development were categorized as "on schedule" while scores in the zones indicating the need for monitoring or the need for further assessment were categorized as "not on schedule". To age adjust for prematurity the number of weeks premature was subtracted from the infant's age[14], per the ASQ-3 scoring instructions. Infants with a completed ASQ-3 between 5 and 6 months of age and premature infants with a completed ASQ-3 between 5 and 6 months age adjusted were included in the analysis.

Covariates

Information on maternal demographic and behavioral characteristics, and medical conditions identified in the literature as related to either influenza vaccination during pregnancy or infant development were ascertained from the EHR and maternal interviews. These variables include maternal race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian, and Other/Unknown), age (<30, 30–34, 35+ years), education (high school or less, some college/college graduate, Master's degree or higher), prenatal vitamin use (yes/no), alcohol use during pregnancy (yes/no), smoking during pregnancy (yes/no), parity (0, 1+), and month of conception during typical wintertime flu season (November-March) or not during flu season (April – October). Influenza vaccination status in the year prior to pregnancy was also ascertained from the EHR.

A three-category variable was created to classify women as having ARI symptoms and positive influenza testing, ARI symptoms and negative or no influenza testing, and no ARI symptoms and no influenza testing. High risk medical conditions associated with an increased risk of influenza complications (e.g. cancer, diabetes, neurological disorders as well as lung, heart, immune system, and kidney disease) were defined by ICD-9 codes in the year prior to conception. Additional covariates examined included study site (KPNC, KPNW), infant sex and the infant age (or adjusted age for premature infants) in the month the ASQ-3 was completed (i.e. 5 or 6 months)[14].

Data Analysis

Chi-square tests were conducted to test differences between categorical variables. Multivariable logistic regression was conducted to assess the relationship between IIV3 vaccination during pregnancy and infant development for each of the five ASQ-3 domains while adjusting for potential confounders. It was decided a priori to include six variables in all models: study site and month of conception along with influenza vaccination receipt in the year prior to pregnancy, influenza/ ARI status during pregnancy, high risk medical conditions, and infant age when the ASQ-3 was completed (i.e. 5 or 6 months). Infant age when ASQ-3 was completed was included given the significant relationship with infant development. Month of conception was included given the significant relationship with IIV3 vaccination during pregnancy (e.g., women would not receive an IIV3 vaccination in non-influenza season months). IIV3 in the year prior to pregnancy is an important proxy for health seeking behavior. Women vaccinated in the year prior to pregnancy may be more likely to seek healthcare and be more aware of their child's development, which may influence the way the ASQ-3 was completed. The presence of ARI symptoms was also included as influenza infection induces an inflammatory response[15–17] which has been shown to induce abnormal brain structure and behavior in the offspring in animal models[18–20]. Further, high cytokine levels during pregnancy, as released through an inflammatory response, have resulted in neurodevelopmental abnormalities of the offspring[21,22]. Additionally, high risk medical conditions may exacerbate the immune response to influenza and thus, may adversely impact infant development. Additional covariates that were significantly associated ($p<0.05$) with both IIV3 vaccination and a given ASQ-3 domain in bivariate analysis were included in the respective model as potential confounders.

Sensitivity analyses were conducted restricting the sample to infants born at term or after (37 weeks or greater) to address potential confounding by preterm birth. A second sensitivity analysis was conducted to assess IIV3 status in relation to the outcome of *normal development* versus *delayed development* after adjusting for *a priori* confounders. Infants were categorized as *normal development* if they scored "on schedule" in all five ASQ-3 domains and *delayed development* if they scored "needs further assessment" in any of the five ASQ-3 domains. Infants whose scores across the five ASQ-3 domains did not match one of these outcomes were excluded from this sensitivity analysis.

RESULTS

The current analysis includes 1225 mother-infant pairs and excludes 391 (24%) of the 1616 women originally recruited into the PIP study. The reasons for exclusion (see Supplemental Table 1) were: missing vaccination status (n=16), multigestation pregnancy (n=38), lost to follow-up at 6-months of age (n=171), or the infant was not in the correct age range (5–6 months) when the ASQ-3 was completed (n= 166). Women excluded from the current analysis were similar to women included in the current analysis with regard to IIV3 vaccination status during pregnancy. While women of Other/Unknown race (45%) were less likely to be included in the current analysis compared to Non-Hispanic Whites (83%), Non-Hispanic Blacks (71%), Hispanics (75%) and Asians (77%; $p<0.001$), there were no other significant differences between women included in the current analysis and those who were not with regards to influenza or other ARI during pregnancy, high risk for influenza complications, or maternal age or education.

A majority of the women received IIV3 during pregnancy (n=799, 65%) (Table 1). Of these women, 40% received the IIV3 during the first trimester, 44% in the second trimester, and 16% in the third trimester. Overall, Non-Hispanic Blacks were less likely to receive IIV3 during pregnancy compared to women of all other races and ethnicities (Table 1). Additionally, women <30 years of age (compared to 30–34 or 35+) and women with a high school degree or less (compared to some college- college graduate or Master's degree or higher) were less likely to receive IIV3 during pregnancy. Participants from KPNW were less likely to receive IIV3 during pregnancy compared to participants from KPNC and women who conceived between November and March were also less likely to receive IIV3 during pregnancy compared to women who conceived between April and October. Women vaccinated in the year prior to pregnancy were more likely to receive IIV3 during pregnancy compared to women who were not vaccinated in the year prior to pregnancy. Finally, women who had confirmed influenza during pregnancy were less likely to receive IIV3 during pregnancy compared to women who did not have confirmed influenza during pregnancy.

In bivariate analysis, infants of women who received IIV3 during pregnancy were less likely to need monitoring or further assessment in the personal social domain compared with infants of unvaccinated women (10.0% vs. 14.1%, p=0.033; crude OR (cOR): 0.68 (95% CI: 0.48, 0.97)) (Table 2). However, after controlling for potential confounders, the findings were no longer statistically significant (aOR: 0.72, 95%CI: 0.49, 1.06). No significant bivariate associations emerged in any of the other four ASQ-3 domains: communication (cOR: 0.90, 95%CI: 0.56–1.44), gross motor (cOR: 0.89, 95% CI: 0.61–1.28), fine motor

(cOR: 1.14, 95%CI: 0.74, 1.75) and problem solving (cOR: 0.86, 95%CI: 0.54–1.38) (Table 2). These non-significant findings persisted after adjusting for potential confounders (Table 2). Similar findings emerged in our sensitivity analysis restricting the sample to infants born full term (Supplemental Table 2). In the second sensitivity analysis, a similar pattern was found such that there was no significant association between IIV3 status and any delayed development across the ASQ-3 domains after adjusting for potential confounders (aOR: 0.82, 95%CI: 0.50, 1.33). There were no significant associations by trimester of IIV3 exposure (Supplemental Table 3).

DISCUSSION

We did not observe an effect on 6-month infant development, as screened for using the ASQ-3, associated with IIV3 exposure during pregnancy after adjusting for potential confounders. The only other study on influenza vaccination during pregnancy and development of the offspring did not find an association with autism spectrum disorders[23]. Thus, our study adds to the nascent epidemiologic research on the longer-term impact of influenza vaccination during pregnancy on child development.

A significant body of research has demonstrated that pregnant women and young infants are at increased risk for complications from influenza. Influenza infections during pregnancy have been associated with adverse outcomes of the mother and offspring including preterm delivery, pneumonia, hospitalization for respiratory illness, sepsis, schizophrenia in the adult offspring and even death[24]. Further, animal models have documented an association between maternal influenza infection during pregnancy and behavioral and brain abnormalities of the offspring[19,25–27]. Thus, control of influenza infections for these vulnerable populations is an important public health concern. Influenza vaccination is the most effective way for controlling and protecting against infection. Influenza vaccination during pregnancy has consistently been found to be safe with regards to maternal, fetal and neonatal outcomes. Previous research, including from the PIP cohort[28], has found no association between influenza vaccination during pregnancy and maternal outcomes such as gestational diabetes, gestational hypertension, or chorioamnionitis[28,29]. A majority of the studies focusing on the association of influenza vaccination during pregnancy and fetal and neonatal outcomes such as spontaneous abortion and major structural defects similarly have not found an association[29–32]. Additionally, a few studies suggest a reduction in the risk of preterm birth and a small-for-gestational-age (SGA) or low birthweight infant[4,5] with a randomized control trial demonstrating a higher mean birth weight and smaller proportion of infants with SGA in mothers randomized to receive the influenza vaccination[33]. Further, studies have demonstrated the efficacy of the influenza vaccination in reducing severe influenza infections in pregnant women and their newborns[6]. However, despite the extensive amount of research suggesting influenza vaccination during pregnancy is safe with regards to maternal, fetal and neonatal outcomes, little research has been conducted assessing the longer-term outcomes of the offspring.

Research suggests that the relationship between maternal infection during pregnancy and brain abnormalities found in animal models may be mediated by immune activation and the subsequent increased cytokine levels[18,20]. Studies in humans have documented a

relationship between elevated levels of cytokines and developmental delay[21,34]. Although vaccination induces an inflammatory response during pregnancy, it is a transient increase in the levels of pro-inflammatory cytokines[35], lower in magnitude and shorter in duration than a viral infection[35]. Recent findings from animal models suggest that inactivated influenza vaccination during pregnancy improves cognitive function in the offspring, has a positive effect on postnatal neurogenesis including proliferation and neuronal differentiation, blocks viral-induced cognitive impairment of the offspring[8] and improves autism-related social interaction behaviors in mice[9]. These findings suggest inactivated influenza vaccination during pregnancy may induce a protective immune response in the development of the offspring. Although the direction of the relationship between IIV3 during pregnancy and infant development that emerged in our study is in line with the two recent animal models[8,9], our study did not find a significant association.

Limitations and Strengths

The ASQ-3 is not a diagnostic instrument, however it has been validated[12], is widely used in the US, and identified by the American Academy of Pediatrics[13] as a high-quality screener for developmental delays with high sensitivity (82%) and specificity (78%)[36]. Further, given the small number of infants with scores indicating the need for further assessment we combined infants with scores indicating the need for further assessment and need for monitoring into a single category which was defined as not on schedule. As a screening tool these categories are different and, for example, some children in the needs monitoring category at one point may later be on schedule. While approximately a quarter of infants of the women recruited into the original study were excluded from the current analysis, there were no differences in receipt of IIV3 between women included in the current analysis and those who were not included. Thus, the exclusion of those mother-infant pairs in our analysis is unlikely to have biased our results. Women recruited into the PIP study who were excluded from our analytic sample were more likely to be of Other/Unknown race than women in the study sample in large part because they were missing race/ethnicity data from the baseline survey. However, we do not believe this would bias our study findings. There is a possibility that our sample size was not large enough to detect a statistically significant association. Nevertheless, the direction of the observed relationship suggested more favorable infant developmental outcomes for women who received IIV3, which is opposite to the concern about the potential adverse effects of vaccination. Future studies with larger sample sizes are warranted. The influenza vaccine, which is safe and immunogenic for pregnant women[37] stimulates a cell-mediated immune response (with cytokine production) in addition to a neutralizing antibody response.[38] The immunogenicity of the influenza vaccine is influenced more by host characteristics such as baseline antibody titer and antibody landscape than the vaccine strain.[39] The FDA requires that all vaccine strains meet minimum standards for antibody response. Thus, it is reasonable to conclude that our findings are generalizable to seasonal IIV3 use in other flu seasons.

Our study has several strengths. First, it is among the limited epidemiological studies that have assessed longer-term outcomes in the offspring. Second, our prospective study design and enrollment of women during pregnancy decreased the possibility of recall bias. Additionally, our ascertainment of IIV3 exposure during pregnancy from a combination of

EHR and self-report allowed us to identify vaccines received outside of the Kaiser Permanente healthcare system. Finally, the study included a diverse sample of pregnant women from two large geographic areas.

CONCLUSIONS

Our findings further inform the evidence on the use of IIV3 during pregnancy. We found no association between IIV3 exposure during pregnancy and infant development at 6-months. Replication of these findings and longer-term follow-up of development are indicated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We would like to thank Linda Nkemere for her contributions with formatting and preparing the manuscript.

Financial disclosure: Dr. Naleway reports funding from GlaxoSmithKline at the time this study was conducted and currently receives funding from Pfizer. The remaining authors have no relevant disclosures to report.

Funding: This study was funded by the Centers for Disease Control and Prevention (CDC; Contract 200-2010-F-33132 to Abt Associates Inc). Investigators from the CDC were involved in the study design, interpretation of the analysis and made significant contributions to various drafts of the manuscript. The CDC provided approval for submission of this manuscript for publication. Participation on this study by Lyndsay A. Avalos was funded by National Institutes of Mental Health (K01MH103444).

Financial disclosures have been noted above. 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, Abt Associates Inc, Kaiser Permanente Center for Health Research, or Kaiser Permanente Northern California Division of Research.

References

1. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol. 2012;207(3 Suppl):S3–8. [PubMed: 22920056]
2. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices-United States, 2018–19 Influenza Season. MMWR Recomm Rep. 2018;67(3):1–20.
3. Diseases COI. Recommendations for Prevention and Control of Influenza in Children, 2017 – 2018. Pediatrics. 2017;140(4).
4. Omer SB, Goodman D, Steinhoff MC, et al. Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study. PLoS Med. 2011;8(5):e1000441. [PubMed: 21655318]
5. Richards JL, Hansen C, Bredfeldt C, 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 birth. Clin Infect Dis. 2013;56(9):1216–1222. [PubMed: 23378281]
6. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med. 2008;359(15):1555–1564. [PubMed: 18799552]
7. 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. 2013;17(1):156–164. [PubMed: 22367067]

8. Xia Y, Qi F, Zou J, Yang J, Yao Z. Influenza vaccination during early pregnancy contributes to neurogenesis and behavioral function in offspring. Brain Behav Immun. 2014;42:212–221. [PubMed: 25014010]
9. Wu Y, Qi F, Song D, et al. Prenatal influenza vaccination rescues impairments of social behavior and lamination in a mouse model of autism. J Neuroinflammation. 2018;15(1):228. [PubMed: 30103815]
10. Thompson M, Williams J, Naleway A, et al. The Pregnancy and Influenza Project: design of an observational case-cohort study to evaluate influenza burden and vaccine effectiveness among pregnant women and their infants. American journal of obstetrics and gynecology. 2011;204(6 Suppl 1):S69–76. [PubMed: 21411050]
11. Squires JDB Ages & Stages Questionnaires®, Third Edition (ASQ- 3™). A parent-completed child-monitoring system. Baltimore: Paul H Brooks Publishing Co.; 2009.
12. Gollenberg AL, Lynch CD, Jackson LW, McGuinness BM, Msall ME. Concurrent validity of the parent-completed Ages and Stages Questionnaires, 2nd Ed. with the Bayley Scales of Infant Development II in a low-risk sample. Child Care Health Dev. 2010;36(4):485–490. [PubMed: 20030657]
13. Developmental surveillance and screening of infants and young children. Pediatrics. 2001;108(1):192–196. [PubMed: 11433077]
14. Squires J, Twombly E, Bricker D, Potter L. Ages & Stages Questionnaires, Third Edition. ASQ-3 User's Guide. Baltimore: Paul H. Brooks Publishing Co.; 2009.
15. Hsiao EY, McBride SW, Chow J, Mazmanian SK, Patterson PH. Modeling an autism risk factor in mice leads to permanent immune dysregulation. Proc Natl Acad Sci U S A. 2012;109(31):12776–12781. [PubMed: 22802640]
16. Malkova NV, Yu CZ, Hsiao EY, Moore MJ, Patterson PH. Maternal immune activation yields offspring displaying mouse versions of the three core symptoms of autism. Brain Behav Immun. 2012;26(4):607–616. [PubMed: 22310922]
17. Patterson PH. Maternal infection and immune involvement in autism. Trends Mol Med. 2011;17(7):389–394. [PubMed: 21482187]
18. Bauman MD, Iosif AM, Smith SE, Bregere C, Amaral DG, Patterson PH. Activation of the maternal immune system during pregnancy alters behavioral development of rhesus monkey offspring. Biol Psychiatry. 2014;75(4):332–341. [PubMed: 24011823]
19. Short SJ, Lubach GR, Karasin AI, et al. Maternal influenza infection during pregnancy impacts postnatal brain development in the rhesus monkey. Biol Psychiatry. 2010;67(10):965–973. [PubMed: 20079486]
20. Smith SE, Li J, Garbett K, Mirnics K, Patterson PH. Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci. 2007;27(40):10695–10702. [PubMed: 17913903]
21. Goines PE, Croen LA, Braunschweig D, et al. Increased midgestational IFN-gamma, IL-4 and IL-5 in women bearing a child with autism: A case-control study. Mol Autism. 2011;2:13. [PubMed: 21810230]
22. Jones KL, Croen LA, Yoshida CK, et al. Autism with intellectual disability is associated with increased levels of maternal cytokines and chemokines during gestation. Mol Psychiatry. 2017;22(2):273–279. [PubMed: 27217154]
23. Zerbo O, Klein NP, Croen LA. Influenza Vaccination in the First Trimester of Pregnancy and Risk of Autism Spectrum Disorder-Reply. JAMA Pediatr. 2017;171(6):601–602.
24. Schanzer DL, Langley JM, Tam TW. Influenza-attributed hospitalization rates among pregnant women in Canada 1994–2000. J Obstet Gynaecol Can. 2007;29(8):622–629. [PubMed: 17714614]
25. Nawa H, Takei N. Recent progress in animal modeling of immune inflammatory processes in schizophrenia: implication of specific cytokines. Neurosci Res. 2006;56(1):2–13. [PubMed: 16837094]
26. Fatemi SH, Sidwell R, Akhter P, et al. Human influenza viral infection in utero increases nNOS expression in hippocampi of neonatal mice. Synapse. 1998;29(1):84–88. [PubMed: 9552178]
27. Fatemi SH, Emamian ES, Kist D, et al. Defective corticogenesis and reduction in Reelin immunoreactivity in cortex and hippocampus of prenatally infected neonatal mice. Mol Psychiatry. 1999;4(2):145–154. [PubMed: 10208446]

28. Naleway AL, Irving SA, Henninger ML, et al. Safety of influenza vaccination during pregnancy: a review of subsequent maternal obstetric events and findings from two recent cohort studies. Vaccine. 2014;32(26):3122–3127. [PubMed: 24742490]
29. Kallen B, Olausson PO. Vaccination against H1N1 influenza with Pandemrix((R)) during pregnancy and delivery outcome: a Swedish register study. Bjog. 2012;119(13):1583–1590. [PubMed: 22901103]
30. Chambers CD, Johnson D, Xu R, et al. Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants. Vaccine. 2013;31(44):5026–5032. [PubMed: 24016809]
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(12):e51734. [PubMed: 23341865]
32. Haberg SE, Trogstad L, Gunnes N, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. N Engl J Med. 2013;368(4):333–340. [PubMed: 23323868]
33. Steinhoff MC, Omer SB, Roy E, et al. Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. CMAJ. 2012;184(6):645–653. [PubMed: 22353593]
34. Bodnar TS, Raineki C, Wertelecki W, et al. Altered maternal immune networks are associated with adverse child neurodevelopment: Impact of alcohol consumption during pregnancy. Brain Behav Immun. 2018.
35. Christian LM, Porter K, Karlsson E, Schultz-Cherry S, Iams JD. Serum proinflammatory cytokine responses to influenza virus vaccine among women during pregnancy versus non-pregnancy. Am J Reprod Immunol. 2013;70(1):45–53. [PubMed: 23551710]
36. Limbos MM, Joyce DP. Comparison of the ASQ and PEDS in screening for developmental delay in children presenting for primary care. J Dev Behav Pediatr. 2011;32(7):499–511. [PubMed: 21760526]
37. Munoz FM, Jackson LA, Swamy GK, et al. Safety and immunogenicity of seasonal trivalent inactivated influenza vaccines in pregnant women. Vaccine. 2018;36(52):8054–8061. [PubMed: 30416018]
38. He XS, Holmes TH, Zhang C, et al. Cellular immune responses in children and adults receiving inactivated or live attenuated influenza vaccines. J Virol. 2006;80(23):11756–11766. [PubMed: 16971435]
39. He XS, Holmes TH, Sasaki S, et al. Baseline levels of influenza-specific CD4 memory T-cells affect T-cell responses to influenza vaccines. PLoS One. 2008;3(7):e2574. [PubMed: 18596908]

Table 1.

Characteristics of the Cohort by IIV Status during Pregnancy

	Total N	Vaccinated n=799 n (row %)	Not Vaccinated n=426 n (row %)	p-value
Demographic Characteristics				
Maternal Race/Ethnicity				
Non-Hispanic White	769	504 (65.5%)	265 (34.5%)	<0.01
Non-Hispanic Black	40	17 (42.5%)	23 (57.5%)	
Hispanic	151	94 (62.3%)	57 (37.8%)	
Asian	165	120 (72.7%)	45 (27.3%)	
Mixed/Other/Unknown	100	64 (64.0%)	36 (36.0%)	
Maternal Age (years)				
<30	418	249 (59.6%)	169 (40.4%)	<0.01
30–34	498	349 (70.1%)	149 (29.9%)	
35+	309	201 (65.1%)	108 (35.0%)	
Maternal Education				
High school or less	109	65 (59.6%)	44 (40.4%)	0.02
Some college - college graduate	647	404 (62.4%)	243 (37.6%)	
Master’s degree or higher	432	302 (69.9%)	130 (30.1%)	
Parity				
0	598	402 (67.2%)	196 (32.8%)	0.13
1+	598	377 (63.0%)	221 (37.0%)	
Behavioral Characteristics during Pregnancy				
Smoking Status				
Yes	63	39 (61.9%)	24 (38.1%)	0.59
No	1134	740 (65.3%)	394 (34.7%)	
Alcohol Use				
Yes	365	240 (65.8%)	125 (34.3%)	0.75
No	827	536 (64.8%)	291 (35.2%)	
Prenatal/Multivitamin Use				
Yes	1131	742 (65.6%)	389 (34.4%)	0.17
No	63	36 (57.1%)	27 (42.9%)	
Infant Characteristics				
Preterm Birth (birth < 37 weeks)				
Yes	39	25 (64.1%)	14 (35.9%)	0.87
No	1183	773 (65.3%)	410 (34.7%)	
Sex of Child				
Female	615	399 (64.9%)	216 (35.1%)	0.74
Male	608	400 (65.8%)	208 (34.2%)	
Other Characteristics				

	Total N	Vaccinated n=799 n (row %)	Not Vaccinated n=426 n (row %)	p-value
Month of Conception				
November-March	254	94 (37.0%)	160 (63.0%)	<0.01
April-October	971	705 (72.6%)	266 (27.4%)	
Vaccination in the Year Prior to Pregnancy				
Yes	413	295 (71.4%)	118 (28.6%)	<0.01
No	812	504 (62.1%)	308 (37.9%)	
Infant age (months) at ASQ-3				
5	225	145 (64.4%)	80 (35.6%)	0.79
6	1000	654 (65.4%)	346 (34.6%)	
High risk medical conditions				
Yes	260	170 (65.4%)	90 (34.6%)	0.95
No	965	629 (65.2%)	336 (34.8%)	
Influenza or ARI symptoms during pregnancy				
Influenza-positive/ARI symptoms	42	18 (42.9%)	24 (57.1%)	<0.01
Influenza negative or not tested/ARI symptoms	406	278 (68.5%)	128 (31.5%)	
Not tested/no ARI symptoms	777	503 (64.7%)	274 (35.3%)	
Site				
KPNW	552	325 (58.9%)	227 (41.1%)	<0.01
KPNC	673	474 (70.4%)	199 (29.6%)	

Abbreviations: IIV3, trivalent inactivated influenza vaccination, ASQ-3, Ages and Stages Questionnaire Third Edition; ARI, Acute Respiratory Illness; KPNW, Kaiser Permanente North West; KPNC, Kaiser Permanente Northern California

Table 2.

Crude (cOR) and Adjusted Odds Ratios (aOR) for the Relationship between IIV3 Vaccination during Pregnancy and 6-month Infant Development for the Five ASQ-3 Domains

ASQ-3 Screening Domain	Not On Schedule[a] n (%)	cOR	95% CI	aOR[b]	95% CI	p-value
Communication[c]						
Vaccinated during pregnancy (n=799)	51 (6.4%)	0.90	0.56–1.44	0.95	0.57–1.57	0.69
Not vaccinated during pregnancy (n=426)	30 (7.0%)	Ref		Ref		
Total (n=1225)[d]	81 (6.6%)	NA		NA		
Gross Motor[c]						
Vaccinated during pregnancy (n=799)	86 (10.8%)	0.89	0.61–1.28	0.92	0.62–1.37	0.69
Not vaccinated during pregnancy (n=426)	51 (12.0%)	Ref		Ref		
Total (n=1225)[d]	137 (11.1%)	NA		NA		
Fine Motor[c]						
Vaccinated during pregnancy (n=789)	70 (8.9%)	1.14	0.74–1.75	1.01	0.64–1.61	0.95
Not vaccinated during pregnancy (n=418)	33 (7.9%)	Ref		Ref		
Total (n=1207)[d,e]	103 (8.5%)	NA		NA		
Problem Solving[c,f]						
Vaccinated during pregnancy (n=798)	49 (6.1%)	0.86	0.54–1.38	0.82	0.49–1.37	0.46
Not vaccinated during pregnancy (n=426)	30 (7.0%)	Ref		Ref		
Total (n=1224)[d]	79 (6.5%)	NA		NA		
Personal Social[c,g]						
Vaccinated during pregnancy (n=799)	80 (10.0%) *	0.68	0.48–0.97	0.72	0.49–1.06	0.09
Not vaccinated during pregnancy (n=426)	60 (14.1%)	Ref		Ref		
Total (n=1225)[d,e]	140 (11.4%)	NA		NA		

[a]Not on schedule is defined as ASQ-3 scores in the respective domain indicating the need for monitoring or the need for further assessment.

[b] All ORs adjusted for study site, infant age (month) when ASQ-3 was completed, month of conception (Apr-Oct vs. Nov-Mar), trivalent inactivated vaccination (IIV3) in the year prior to pregnancy, high risk medical conditions, and influenza/acute respiratory illness (ARI) status during pregnancy.

[c] There were no significant associations in the reported adjusted models between ARI symptoms/influenza and development for any of the five ASQ-3 domains: (communication: ARI symptoms/influenza positive and ARI/influenza negative compared to no ARI or influenza [aOR: 1.09, 95% CI: 0.32, 3.37, aOR: 0.87, 95% CI: 0.522, 1.46, respectively], gross motor: ARI symptoms/influenza positive and ARI/influenza negative compared to no ARI or influenza [aOR: 0.89, 95% CI: 0.31, 2.59, aOR: 0.98, 95% CI: 0.66, 1.47, respectively], fine motor: ARI symptoms/influenza positive and ARI/influenza negative compared to no ARI or influenza [aOR: 0.78, 95% CI: 0.23, 2.65, aOR: 0.95, 95%CI: 0.61, 1.49], problem solving: ARI/influenza negative compared to no ARI or influenza [aOR:1.03, 95% CI: 0.62, 1.71], personal social: ARI symptoms/influenza positive and ARI/influenza negative compared to no ARI or influenza [aOR: 0.917, 95% CI: 0.31, 2.692, aOR:1.02, 95% CI: 0.69, 1.51, respectively]. No infants of a mother with ARI/influenza positive scored in the “not on schedule” range in the problem solving domain, thus an aOR could not be calculated.

[d] A small percentage of infants scored in the *needs further assessment* category across the five ASQ-3 domains: (communication: monitor 6%, needs further assessment <1%; gross motor: monitor 9%, needs further assessment 2%; fine motor: monitor 6%, needs further assessment 2%; problem solving: monitor 5%, needs further assessment 1%; personal social: monitor 8%, needs further assessment 3%). The percentages may not add to the reported percentage of infants categorized as not on schedule due to rounding.

[e] Scores for the Fine Motor and Problem Solving Domains could not calculated for 18 infants and 1 infant, respectively due to missing responses resulting in a sample size of 1207 for the Fine Motor Domain and 1224 for the Problem Solving Domain.

[f] Problem Solving domain is additionally adjusted for maternal race/ethnicity.

[g] The Personal Social domain is additionally adjusted for maternal age.

[*] $p<0.05$

Abbreviations: IIV3, trivalent inactivated influenza vaccination, ASQ-3, Ages and Stages Questionnaire Third Edition; ARI, Acute Respiratory Illness