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# A follow-up comparative safety analysis of pandemic H1N1 vaccination during pregnancy and risk of infant birth defects among U.S. military mothers

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ABSTRACT

*Objective:* To update a previous assessment of birth defects among infants born to active duty U.S. military mothers who received the 2009–2010 pandemic H1N1 vaccine, in comparison to the 2008–2009 seasonal influenza vaccine, during pregnancy. Here, we updated the previous comparative analyses with a more refined definition for birth defects using an additional year of follow-up data from both inpatient and outpatient medical encounters.

*Methods:* The study population included 15,510 live born infants born to active duty mothers vaccinated during pregnancy with either the 2009–2010 pandemic H1N1 vaccine (n = 9033) or the 2008–2009 seasonal influenza vaccine (n = 6477). Birth defect cases were defined as those infants who received a birth defect diagnosis on one inpatient record or two outpatient records on different days within the first year of life. Multivariable logistic regression models were conducted to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between birth defects and maternal vaccination during pregnancy with pandemic H1N1 vaccine versus seasonal influenza vaccine.

*Results:* Infants born to mothers vaccinated during pregnancy with the pandemic H1N1 vaccine, versus the seasonal influenza vaccine, were not at increased odds of birth defects in univariable (OR: 1.13, 95% CI: 0.95–1.34) or multivariable (OR: 1.14, 95% CI: 0.96–1.35) models. Findings were not significant when further limited to first trimester exposure. Multivariable models were adjusted for infant sex and plurality; maternal age, race/ethnicity, marital status, service branch, military rank, and occupation; timing of vaccination; and receipt of vaccination(s) not routinely recommended during pregnancy.

*Conclusion:* Comparable to our previous analyses assessing birth defects diagnosed at birth, no significant association was found between the pandemic H1N1 vaccination during pregnancy and birth defects, versus the seasonal influenza vaccine. These findings are reassuring and provide additional support for H1N1-containing seasonal influenza vaccination during pregnancy.



## 1. Introduction

The 2009 pandemic influenza H1N1 virus prompted an important and timely global public health response [1]. Within months of pandemic declaration, a novel H1N1 vaccine was available for use. During this time, the Advisory Committee on Immunization Practices considered pregnant women a prioritized target population for receipt of vaccination because of a higher risk of morbidity and mortality [2]. The urgency in response was not limited to the need for developing an effective H1N1 vaccine; the rapid assessment of vaccine safety was also an important aspect.

Previously, as part of the effort to promptly assess the safety of this novel vaccine, we examined adverse maternal and infant outcomes among active duty U.S. military mothers who were vaccinated during pregnancy with the pandemic H1N1 vaccine, during the 2009–2010 influenza season, compared with those vaccinated with the seasonal influenza vaccine, during the prior 2008–2009

*Abbreviations:* CI, confidence interval; LMP, last menstrual period; OR, odds ratio; Registry, Department of Defense Birth and Infant Health Registry.

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influenza season [3]. Results from this study found no associations between pandemic H1N1 vaccination during pregnancy and adverse outcomes when compared with seasonal influenza vaccination during pregnancy; specifically, there was no significant association with birth defects (odds ratio [OR]: 1.08, 95% confidence interval [CI]: 0.87–1.35). In order to conduct this assessment as close to real-time as possible, birth defects were limited to those diagnosed at birth on inpatient medical records.

Here, we conducted a follow-up analysis to further validate these past findings with an updated definition of birth defects, including diagnoses from both inpatient and outpatient medical records with extended follow-up through the first year of life, as some may not be identified until later in infancy.

## 2. Materials and methods

### 2.1. Study population

This retrospective cohort study population was derived from the previously identified live births (n = 16,194) among active duty military mothers vaccinated during pregnancy with the seasonal influenza vaccine, from October 1, 2008 to June 30, 2009, or the pandemic H1N1 vaccine, from October 1, 2009 to June 30, 2010. The population is further described in Conlin et al. [3]. Among these infants, 15,510 (95.8%) were identified in the Department of Defense Birth and Infant Health Registry (Registry) with up to 1 year of follow-up and comprised the analytic population of this study [4]. Briefly, the Registry, established in 1998, is an ongoing population-based surveillance effort that identifies pregnancies and adverse birth outcomes among Department of Defense beneficiaries through inpatient and outpatient health care encounters at military and civilian facilities captured in the Military Health System Data Repository, which houses medical encounter and administrative claims data.

Same-sex multiple births (eg, twins) are excluded from the Registry due to difficulty in distinguishing early neonatal care medical records. Estimated gestational age (EGA) was derived from International Classification of Diseases, 9th Revision, Clinical Modification codes, and date of last menstrual period (LMP) was calculated by subtracting the EGA from delivery date. Maternal demographic, military personnel, and immunization data were obtained from the Defense Manpower Data Center. This research was conducted in compliance with all applicable federal regulations governing the protection of human subjects in research. Institutional review board approval was obtained from Naval Health Research Center (protocol NHRC.2010.015) and informed consent was waived in accordance with criteria set forth by 32 CFR § 219.116(d).

### 2.2. Pandemic H1N1 and seasonal influenza vaccination during pregnancy

Maternal vaccination exposure during pregnancy was defined as receipt of the vaccine of interest on or after LMP up until the date of delivery. The exposed group included infants born to mothers who received the 2009–2010 pandemic H1N1 vaccine (strain A/California/7/2009 [H1N1]) during pregnancy. Vaccination was identified by use of the vaccine administered code set 125–128 provided in the immunization data (further defined in Supplementary Table 1). The comparison group included infants born to mothers who received the trivalent 2008–2009 seasonal influenza vaccine (A/Brisbane/59/2007 [H1N1]-like virus, A/Brisbane/10/2007 [H3N2]-like virus, and B/Florida/4/2006-like virus) during pregnancy, which was identified by the following vaccine administered codes: 015, 016, 088, 111, 123, 135, 140, and 141 (further defined in Supplementary Table 1).

### 2.3. Birth defects

Birth defects were identified using International Classification of Diseases, 9th Revision, Clinical Modification codes (740.xx–758.xx), according to criteria established by the National Birth Defects Prevention Network [5]. Birth defect cases were defined as those infants who received a birth defect diagnosis on one inpatient record or two outpatient records on different days within the first year of life. This method is implemented by many studies using electronic medical data sources [6,7], to reduce the capture of false positive cases, as was done here. As recommended in the Metropolitan Atlanta Congenital Defects Program guidelines, atrial septal defect and patent ductus arteriosus diagnoses in preterm infants were excluded from the birth defect definition [8].

### 2.4. Covariates

Additional maternal covariates included in the models were maternal age at delivery (<35 or ≥35 years of age), race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, or other/unknown), marital status (married or not married), military service branch (Army, Air Force, Navy or Coast Guard, or Marine Corps), rank (enlisted or officer), and occupation (health care, combat, or other/unknown). Infant covariates of interest included sex (female or male) and plurality (singleton or multiple). Receipt of any vaccine not routinely recommended during pregnancy (date of LMP up until the date of delivery) was also adjusted for and included: nasal mist formulations of both the pandemic H1N1 and seasonal influenza vaccines, and vaccines against measles, mumps, and rubella virus; tuberculosis; varicella virus; vaccinia (smallpox); poliovirus; rabies; yellow fever; meningococcal ACYW; human papillomavirus; zoster; and adenovirus (further defined in Supplementary Table 1).

### 2.5. Statistical analysis

Descriptive statistics for selected maternal and infant characteristics by vaccine exposure during pregnancy (2009–2010 pandemic H1N1 vs. 2008–2009 seasonal influenza) were calculated. Covariates included in adjusted models were selected a priori based on past literature, as was done in the previous analysis [3], in addition to the dichotomous variable receipt of vaccinations not recommended during pregnancy (yes or no). Univariable and multivariable logistic regression models were conducted to calculate the ORs and 95% CIs for the association between maternal vaccination during pregnancy with the pandemic H1N1 vaccine and the odds of diagnosis of infant birth defects, versus maternal vaccination during pregnancy with the 2008–2009 seasonal influenza vaccine. Additionally, infants of mothers who received the pandemic H1N1 vaccine during pregnancy were stratified by whether or not they also received a 2009–2010 seasonal influenza vaccination during pregnancy. They were then compared with infants of mothers who received the 2008–2009 seasonal influenza vaccination during pregnancy (referent) to further assess the odds of a birth defect diagnosis. No covariates were found to be collinear in final models (variance inflation factor <4.0). Model fit was assessed using the Hosmer and Lemeshow goodness-of-fit test ($P > 0.05$). All analyses were repeated in a subset limited to mothers vaccinated in the first trimester of pregnancy with the 2009–2010 pandemic H1N1 vaccine vs. the 2008–2009 seasonal influenza vaccine. Sensitivity analyses using generalized estimating equation models adjusting for repeated measures were conducted to account for plurality. All data management and statistical analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC).

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