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# Effects of prior influenza virus vaccination on maternal antibody responses: Implications for achieving protection in the newborns

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ABSTRACT

*Background:* In the US, influenza vaccination is recommended annually to everyone ≥6 months. Prior receipt of influenza vaccine can dampen antibody responses to subsequent vaccination. This may have implications for pregnant women and their newborns, groups at high risk for complications from influenza infection.

*Objective:* This study examined effects of prior vaccination on maternal and cord blood antibody levels in a cohort of pregnant women in the US.

*Study design:* Influenza antibody titers were measured in 141 pregnant women via the hemagglutination inhibition (HAI) assay prior to receipt of quadrivalent influenza vaccine, 30 days post-vaccination, and at delivery (maternal and cord blood). Logistic regression analyses adjusting for age, BMI, parity, gestational age at vaccination, and year of vaccination compared HAI titers, seroprotection, and seroconversion in women with versus without vaccination in the prior year.

*Results:* Compared to those without vaccination in the previous year (n = 50), women with prior vaccination (n = 91) exhibited higher baseline antibody titers and/or seroprotection rates against all four strains after controlling for covariates. Prior vaccination also predicted lower antibody responses and seroconversion rates at one month post-vaccination. However, at delivery, there were no significant differences in antibody titers or seroprotection rates in women or newborns, and no meaningful differences in the efficiency of antibody transfer, as indicated by the ratio of cord blood to maternal antibody titers at the time of delivery.

*Conclusion:* In this cohort of pregnant women, receipt of influenza vaccine the previous year predicted higher baseline antibody titers and decreased antibody responses at one month post-vaccination against all influenza strains. However, prior maternal vaccination did not significantly affect either maternal antibody levels at delivery or antibody levels transferred to the neonate. This study is registered with the NIH as a clinical trial (NCT02148874).



## 1. Introduction

Seasonal influenza virus vaccination is recommended by the Centers for Disease Control (CDC) and the American Congress of Obstetricians and Gynecologists (ACOG) to all women without contraindications who are pregnant or will be pregnant during influenza season [1,2]. This recommendation reflects recognition that pregnant women are at high risk for complications, hospitalization, and death due to influenza infection [3–7]. It is now established that influenza immunization during pregnancy reduces risk of influenza infection in pregnant women [8,9]. Studies show no adverse effects of vaccination in relation to outcomes including, but not limited to, risk of preterm labor, C-section, or fetal malformation [10–13].

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Via transplacental antibody transfer, maternal vaccination also confers protection against influenza virus to the neonate [8,9,14–20]. Infants from 0–6 months have among the highest rates of influenza-associated complications with >1000 hospitalizations per 100,000 infants in the US [21]. Influenza vaccine is not approved for infants <6 months. Thus, maternal vaccination in pregnancy is the only currently recommended effective strategy for protecting infants younger than 6 months. Prospective studies of laboratory-confirmed influenza show that maternal vaccination can reduce risk of influenza infection in infants by up to 63% and reduce influenza severity in infected infants [8,9,14–20].

Of clinical relevance, prior receipt of influenza vaccine can lower antibody responses to subsequent vaccination. In a study of 796 children and adolescents (6–17 years), receipt of seasonal trivalent inactivated influenza vaccine in the prior year predicted lower antibody responses against A/H1N1 and A/H3N2 strains [22]. Data from animal and human studies suggest that these blunting effects of prior vaccination are linked with higher basal antibody titers among previously vaccinated individuals, which may interfere with B-cell signaling [23,24]. However, lower antibody responses among those with prior vaccination have also been observed among those who did not exhibit elevated baseline titers [25,26].

Given the consistently observed effects of prior vaccination on subsequent antibody responses, concern has been raised that annual vaccination may interfere with development of protective immunity in the context of a lethal pandemic subtype [27]. In relation to this concern, a study of 150 pregnant women who received monovalent 2009 influenza A (H1N1) vaccine during the flu pandemic found that those who had already received trivalent seasonal vaccine in the same year exhibited less robust antibody responses to the monovalent H1N1 vaccine [28]. However, overall, data on effects of prior vaccination on maternal antibody responses are limited. Moreover, data on how prior maternal vaccination may affect antibody levels in the neonate is unknown.

Addressing gaps in the literature, the current study examined effects of prior vaccine receipt on antibody responses to seasonal influenza vaccine in a cohort of pregnant women in the US. This study included 141 women who were assessed prior to and following receipt of seasonal influenza vaccine during the 2013–2014 and 2014–2015 influenza seasons. We examined potential differences in maternal antibody status at baseline (i.e., prior to vaccination), antibody responses at ~30 days post-vaccination, antibody maintenance to the time of delivery, and cord blood antibody levels, as a function of maternal vaccination in the previous year.

## 2. Materials and methods

### 2.1. Study design

Pregnant women were recruited largely from faculty, staff, and students at the Ohio State University (OSU) and OSU Wexner Medical Center (OSUWMC) based on voluntary response to advertisements placed in online campus newsletters (n = 73, 51.8% of the final analytic sample). Women were also recruited from the OSUWMC Prenatal Clinic and surrounding community of Columbus, Ohio. All participants in the study were informed that they could discontinue participation at any time with no penalty and no change in their future relationship with The Ohio State University. Data collection occurred from October 2013 to September 2015, vaccinations occurred between late August and late April each vaccination year. Participants received an influenza vaccine at the first study visit, and provided blood samples at all three study visits (baseline, ~30 days post-vaccination, and delivery). Cord blood was also collected at delivery. This study is registered with the NIH as a clinical trial (NCT02148874).

### 2.2. Participants

Exclusion criteria included, chronic conditions (e.g., cancer, systemic lupus erythematosus) with implications for immune function. To ensure adequate time for follow-up assessment prior to delivery, women were excluded if they were beyond 30 weeks completed gestation; women were eligible to enroll at any other stage of gestation. Women were excluded if they reported weight and measured height consistent with a pre-pregnancy body mass index (BMI) > 50, or did not intend to deliver at OSUWMC. Women reporting acute illness, such as cold- or influenza-like symptoms, or antibiotic use within ten days of a study visit were rescheduled. The current analyses focused on the effects of prior receipt of influenza vaccination per self-report. A total of 145 women were recruited. Four women were excluded from analyses because they were uncertain about influenza vaccination status in the prior year, resulting in an analytic sample of 141. Cord blood samples were unavailable from 25 participants in this analytic sample. Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorizations were obtained from all participants and each received modest compensation. The study was approved by the OSU Biomedical Institutional Review Board.

### 2.3. Demographics

Age, race/ethnicity, marital status, education level, annual household income, employment status, and number of prior births (parity) were collected by self-report. Pre-pregnancy body mass index (BMI; $kg/m^2$) was calculated using self-reported pre-pregnancy weight and measured height at the first visit.

### 2.4. Influenza virus vaccine

Women received the 2013–2014 or 2014–2015 seasonal influenza vaccination, depending on the year recruited. Strains present in the seasonal influenza vaccine during the two study years, and one year preceding are presented in Table 1. Quadrivalent inactivated influenza vaccine (IIV4) which includes an A/H1N1, A/H3N2, and two B strains was introduced during the 2013–2014 season. The first 15 women vaccinated in this study year received

**Table 1**
Influenza virus vaccine strains by year.

| Influenza season | | |
|---|---|---|
| 2012–2013 | 2013–2014 | 2014–2015 |
| A/California/7/2009 (H1N1)-like virus | A/California/7/2009 (H1N1)-like virus | A/California/7/2009 (H1N1)-like virus |
| A/Victoria/361/2011 (H3N2)-like virus | A/Victoria/361/2011 (H3N2)-like virus | A/Texas/50/2012 (H3N2)-like virus |
| B/Wisconsin/1/2010-like virus | B/Massachusetts/2/2012-like virus | B/Massachusetts/2/2012-like virus |
| N/A | B/Brisbane/60/2008-like virus | B/Brisbane/60/2008-like virus |

Women were vaccinated during the 2013–2014 and 2014–2015 flu seasons. The first 15 women vaccinated received trivalent vaccine which did not include B/Brisbane. Information on the 2012–2013 vaccine is provided for comparison to strains present in the subsequent year.

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