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# Tetanus, diphtheria, and acellular pertussis vaccination during pregnancy and reduced risk of infant acute respiratory infections

Zeina G. Khodr *, Anna T. Bukowinski, Gia R. Gumbs, Ava Marie S. Conlin

*The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF), 6720A Rockledge Drive, Suite 100, Bethesda, MD 20817, United States*

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ABSTRACT

*Background:* To protect infants from pertussis infection, the Advisory Committee on Immunization Practices (ACIP) recommends women receive the tetanus toxoid, reduced diphtheria toxoid, acellular pertussis (Tdap) vaccine between 27 and 36 weeks of pregnancy. Here, we assessed the association between timing of maternal Tdap vaccination during pregnancy and acute respiratory infection (ARI) in infants <2 months of age.

*Methods:* This retrospective cohort study included 99,434 infants born to active duty military women in the Department of Defense Birth and Infant Health Registry from 2006 through 2013. Multivariable log-binomial regression was used to calculate relative risks (RRs) and 95% confidence intervals (CIs) for the association between maternal Tdap vaccination during pregnancy and infant ARI at <2 months of age.

*Results:* Infants of mothers who received Tdap vaccination during pregnancy vs those who did not were 9% less likely to be diagnosed with an ARI at <2 months of age (RR, 0.91; 95% CI, 0.84–0.99), and the risk was 17% lower if vaccination was received between 27 and 36 weeks of pregnancy (RR, 0.83; 95% CI, 0.74–0.93). Similar results were observed when comparing mothers who received Tdap vaccination prior to pregnancy in addition to Tdap vaccination between 27 and 36 weeks of pregnancy versus mothers who only received vaccination prior to pregnancy (RR, 0.85; 95% CI, 0.74–0.98).

*Conclusions:* Maternal Tdap vaccination between 27 and 36 weeks of pregnancy was consistently protective against infant ARI in the first 2 months of life vs no vaccination during pregnancy, regardless of Tdap vaccination prior to pregnancy. Our findings strongly support current ACIP guidelines recommending Tdap vaccination in late pregnancy for every pregnancy.



## 1. Introduction

Pertussis, or whooping cough, is a respiratory infection that has a secondary attack rate of up to 80% among unvaccinated household contacts of infected individuals [1]. Although childhood vaccination series against pertussis (diphtheria toxoid, tetanus toxoid, and acellular pertussis [DTaP]) exist, they are not routinely initiated until 2 months of age, per guidelines, leaving the newborn population unprotected. Not only are incidence rates of pertussis infection highest among infants, but higher risks for complications, hospitalization, and mortality in this population are of concern [2]. Starting in 2012, the Advisory Committee on Immunization Practices (ACIP) recommended women receive the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination between 27–36 weeks of pregnancy for every pregnancy, regardless of whether they were vaccinated before becoming pregnant [3,4], to provide transplacental passive immunity to the infant. Studies have found that passive protection for the infant can last through the early weeks of life when maternal vaccination is timed appropriately [5–11].

We conducted a retrospective analysis to assess the effectiveness of current ACIP guidelines for Tdap vaccination during pregnancy, with respect to protecting newborn infants from pertussis

*Abbreviations:* ACIP, Advisory Committee on Immunization Practices; ARI, acute respiratory infection; CAIR, California Immunization Registry; CI, confidence interval; CVX, vaccine administered code; DMDC, The Defense Manpower Data Center; DoD, Department of Defense; DTaP, diphtheria toxoid, tetanus toxoid, and acellular pertussis; EGA, estimated gestational age; FHA, filamentous hemagglutinin; GEE, generalized estimating equation; *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification*; LMP, last menstrual period; LOWESS, locally weighted scatterplot smoothing; OR, odds ratio; Registry, Department of Defense Birth and Infant Health Registry; PT, pertussis toxin; RR, relative risk; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; VE, vaccine effectiveness.

* Corresponding author at: Epidemiologist, Naval Health Research Center, 140 Sylvester Road, San Diego, CA 92106, United States.
*E-mail address:* zeina.g.khodr.ctr@mail.mil (Z.G. Khodr).

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and other acute respiratory infections (ARIs). By taking into consideration all ARIs, we can account for potentially misdiagnosed and uncaptured pertussis cases [12]. We used administrative medical data for military families available in the Department of Defense (DoD) Birth and Infant Health Registry (Registry) [13], a unique resource with linked maternal and infant data. Military personnel have complete immunization documentation and high rates of vaccination compliance [14], since they are required to be up-to-date on routine vaccinations. Therefore, active duty military mothers provide an ideal study population for assessing repeat Tdap vaccination. We hypothesized that infants of mothers vaccinated with the Tdap vaccine between 27 and 36 weeks of pregnancy have a reduced risk of being diagnosed with pertussis and ARIs in the first 2 months of life.

## 2. Methods

### 2.1. Study population

The Registry was established in 1998 and is an ongoing, population-based surveillance effort that identifies pregnancies and adverse birth and pregnancy outcomes among DoD beneficiaries [13]. Briefly, the Registry uses electronic administrative medical data available in the Military Health System Data Repository, and personnel and demographic data from the Defense Manpower Data Center (DMDC). *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnostic codes are collected for infants through the first year of life. Same-sex multiple gestations (eg, twins) are excluded from the Registry due to difficulty in distinguishing between their neonatal medical records. Estimated gestational age (EGA) is derived from *ICD-9-CM* codes, and last menstrual period (LMP) is calculated by subtracting EGA from delivery date. The present study focused on infants of active duty mothers, since full immunization records are captured throughout active duty service and maintained by the DMDC. The study population was further limited to records with LMP and delivery dates between January 01, 2006, and December 31, 2013, because the Tdap vaccine was not licensed until the spring of 2005 [2]. Of the 845,354 infants captured in the Registry during this time period, 101,789 were born to active duty mothers (Fig. 1). For the following analysis, the study population was limited to singleton births (n = 1391 infants were excluded). This study was approved by the institutional review board at the Naval Health Research Center, and informed consent was waived in accordance with 32 CFR § 219.116(d).

### 2.2. Maternal Tdap vaccination during pregnancy

Tdap vaccination during pregnancy was the exposure of interest; it was defined as the receipt of Tdap vaccine between LMP and delivery date, and identified in immunization data by the vaccine administered code (CVX) 115. Mothers who received more than 1 Tdap vaccination during pregnancy (n = 108) or received other vaccines against pertussis during pregnancy (n = 57, Supplementary Table 1) were excluded from analyses (Fig. 1). Additionally, 799 infants who received DTaP vaccination at <2 months of age were also excluded from analyses.

### 2.3. Infant acute respiratory infections

Cases were defined as infants diagnosed with pertussis, other ARIs, and symptoms associated with ARI in the first 2 months of life based on *ICD-9-CM* codes reported as clinical diagnoses at inpatient and outpatient encounters (Supplementary Table 1). Inpatient encounters included, but were not limited to, hospitals and skilled nursing facilities, and outpatient encounters included, but were not limited to, doctor's offices, emergency rooms, and urgent care centers. Clinical diagnosis of pertussis has a low sensitivity (30.2%) and high specificity (96.3%); therefore, we assessed infant ARIs to capture possible cases [12]. Infant ARI in the first 2 months of life was dichotomized in analyses as any diagnoses versus none.

### 2.4. Covariates

Additional maternal covariates included in models, as reported from DMDC demographic data, were maternal age at delivery (<35 or ≥35 years of age), race/ethnicity (white, black, Hispanic, or other/unknown), marital status (married or not married), military service branch (Army, Navy, Air Force, or Marine Corps), rank (enlisted or officer), and occupation (health care, combat, or other/unknown). Infant covariates included year of delivery, month of delivery (to account for influenza season), sex, diagnosis of major birth defects (yes or no), low birth weight (defined as <2500 g, yes or no), and preterm birth (defined as <37 weeks' EGA, yes or no). Maternal influenza vaccination during pregnancy was considered a potential confounder since the outcome of interest was diagnosis of any ARI in the first 2 months of life, and mothers who received Tdap vaccination during pregnancy were more likely to receive a seasonal influenza vaccine (Supplementary Table 1) [15]. The receipt of any vaccination(s) not routinely recommended during pregnancy was also adjusted for as a dichotomous variable (yes or no) and acts as a proxy for lack of pregnancy recognition (Supplementary Table 1) [16].

### 2.5. Statistical analyses

Frequencies and percentages were used to describe selected maternal and infant characteristics in the study population. Log-binomial models were used to calculate relative risks (RRs) and 95% confidence intervals (CIs) for associations between maternal Tdap vaccination during pregnancy and infant ARI in the first 2 months of life [17,18]. Exposure to Tdap vaccination during pregnancy was assessed dichotomously (yes vs no) and in conjunction with influenza vaccination during pregnancy (none, only influenza, only Tdap, and both influenza and Tdap). Further analyses assessed timing of Tdap vaccination, categorized by time of vaccination after LMP (0–13, 14–26, 27–36, and >36 weeks of pregnancy) and time of vaccination before delivery date (≥26, 25–13, 12–5, and 4–0 weeks before delivery). No receipt of Tdap vaccination during pregnancy was the referent group for all models. To reduce potential heterogeneity in exposure assessment, the referent population was stratified into 3 groups: mothers with no record of Tdap vaccination, pre-pregnancy Tdap vaccination, or post-pregnancy Tdap vaccination (i.e., during the 2 months following delivery). Covariates that were significantly associated with the exposure and outcome of interest in univariable models were included in multivariable models.

To better assess the need for repeat vaccination during each pregnancy (per ACIP guidelines), analyses were repeated in a subset of mothers who had received at least 1 Tdap vaccination pre-pregnancy. These mothers were categorized by whether they received an additional Tdap vaccination, stratified by timing of vaccination in relation to pregnancy, or only received Tdap vaccination pre-pregnancy. Analyses were also conducted in a subset of infants who were full-term (≥37 weeks of pregnancy) and not diagnosed with any birth defects. This subset was further reduced to infants born at 40 weeks' EGA with mothers who received influenza vaccination during pregnancy. Locally weighted scatterplot smoothing (LOWESS) regression was conducted to plot rates of infant ARI as a function of timing of Tdap vaccination during pregnancy for this subset [19]. Lastly, generalized estimating equation (GEE) models

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