Receipt of the tetanus, diphtheria, and acellular pertussis vaccine during pregnancy and risk for maternal acute respiratory infection within 6 months postpartum

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EXECUTIVE SUMMARY

Since October 2012, the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine has been recommended for administration during every pregnancy, with optimal timing between 27 and 36 weeks' gestation. This approach increases transplacental immunity and protects infants from pertussis infection before they begin the vaccination series against the disease. However, few studies have assessed whether pregnancy Tdap vaccine exposure affects maternal pertussis antibody levels or postpartum risk for pertussis infection. In this records-based analysis of pregnant active duty U.S. military women, Department of Defense Birth and Infant Health Research program data were leveraged to determine whether exposure to the Tdap vaccine during pregnancy influenced maternal risk for acute respiratory infection (ARI) within 6 months postpartum; ARI was used as a proxy for pertussis infection because clinical diagnosis of pertussis is rare. Overall, we identified 99,884 pregnancies that resulted in a singleton live birth; 13,573 (13.6%) pregnancies were exposed to the Tdap vaccine. Maternal ARI within 6 months postpartum was identified among 18.2% and 20.7% of exposed and unexposed women, respectively (adjusted risk ratio = 0.90, 95% confidence interval = 0.87–0.93). Associations were generally similar across exposure definitions (i.e., timing of exposure during pregnancy and before delivery) and subgroup analyses that considered other maternal vaccination characteristics (i.e., pre-pregnancy Tdap vaccine exposure, Tdap vaccine exposure within 6 months postpartum, and influenza vaccine exposure during pregnancy or within 6 months postpartum). Although we found that Tdap vaccine exposure during pregnancy was associated with a small, reduced risk for maternal ARI within 6 months postpartum, our results must be interpreted with caution because the Tdap vaccine does not confer immunity against all ARIs. Future epidemiologic studies on this topic would benefit from clinical laboratory data for determining pertussis diagnoses.

Introduction

Pertussis can cause severe morbidity and mortality in infants,[1] but the vaccination series against the disease is not routinely initiated until 2 months of age. To protect infants from pertussis infection, the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine is recommended for administration during every pregnancy, with optimal timing between 27 and 36 weeks' gestation.[2] This approach increases transplacental immunity and effectively reduces infant risk for pertussis infection[3–5]; however, few studies have assessed whether Tdap vaccination during pregnancy influences maternal pertussis antibody levels or risk for postpartum pertussis infection. One randomized clinical trial of 48 pregnant woman showed that Tdap vaccination during pregnancy induced a high maternal response to pertussis-specific antibodies through 2 months postpartum.[5] However, an observational study of 50 pregnant women found that pertussis-specific antibodies decreased among Tdap-immunized women 9–15 months after delivery, though their antibody levels were still higher than those of women who did not receive the Tdap vaccine during pregnancy.[6] More research is needed to determine how pregnancy Tdap vaccine exposure influences pertussis-specific antibody levels during the postpartum period, and whether any changes affect maternal risk for postpartum pertussis infection.

In this large, observational cohort study of pregnant active duty U.S. military women, we sought to determine whether exposure to the Tdap vaccine during pregnancy influenced maternal risk for acute respiratory infection (ARI) diagnosis within 6 months postpartum. Because clinical diagnosis of pertussis is rare and has a low sensitivity and high specificity,[7] maternal ARI diagnosis was used as a proxy.

Methods

This study utilized data from the Department of Defense (DoD) Birth and Infant Health Research (BIHR) program, which includes pregnancies and live births among DoD beneficiaries. Detailed methods for developing BIHR populations have been previously described.[8] Briefly, BIHR program data consist of electronic administrative medical data from the Military Health System Data Repository, and personnel and demographic data from the Defense Manpower Data Center (DMDC). Encounters are coded with Current Procedural Terminology codes and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic and procedure codes, which are used to define pregnancy episodes and outcomes of interest. Estimated gestational age (EGA) is derived from ICD-9-CM codes; estimated date of last menstrual period (LMP) is calculated by subtracting EGA from delivery date.

The study population consisted of active duty U.S. military women with singleton live births from January 1, 2007, through December 31, 2014. Women were excluded if they received more than one Tdap vaccine during pregnancy, if they received other pertussis vaccines during pregnancy, if they were not on active duty status through 6 months postpartum, or if they had no medical encounter records in the 6 months postpartum.

The main exposure of interest was receipt of Tdap vaccine during pregnancy, identified by the vaccine administered (CVX) code 115 from DMDC vaccination data. A secondary exposure of interest, receipt of influenza vaccine during pregnancy, was identified from the same data source

using CVX codes 015, 016, 088, 111, 125, 126, 127, 128, 141, 144, 149, 150, 151, 153, 155, and 158. Exposure to the Tdap vaccine was assessed dichotomously (yes or no) and by timing of receipt after estimated date of LMP (0–13, 14–26, 27–36, >36 weeks after) and before delivery (0–4, 5–12, 13–25, ≥26 weeks prior). Receipt of Tdap and/or influenza vaccine(s) during pregnancy was also assessed (none, Tdap only, influenza only, both Tdap and influenza).

Following previous methodology,[9] the outcome of interest was maternal ARI within 6 months postpartum (yes or no), which served as a proxy for pertussis infection. ARI cases were identified from ICD-9-CM codes on inpatient and outpatient encounters, as described in detail elsewhere.[9] Pertussis cases were identified using ICD-9-CM code 033.X, but there were too few (n=5) to analyze.

Frequencies and percentages were used to describe maternal demographic and vaccination characteristics. Multivariable log-binomial regression models were used to estimate risk ratios (RRs) and 95% confidence intervals (CIs) for associations between Tdap vaccine exposure during pregnancy and maternal ARI events within 6 months postpartum. All models were adjusted for the following maternal characteristics: age (years) at delivery (18–19, 20–24, 25–29, 30–34, 35+), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other/unknown), military rank (enlisted or officer), military service branch (Army, Navy, Air Force, Marine Corps, Coast Guard), and season of LMP for the index pregnancy (winter, spring, summer, fall). If not included in the exposure definition, receipt of influenza vaccine during pregnancy (yes or no) was also adjusted for in multivariable models.

Adjusted subgroup analyses were conducted to assess whether the association between maternal Tdap exposure during pregnancy and ARI was subject to effect measure modification by certain vaccination characteristics: pre-pregnancy Tdap vaccine exposure (none, <1 year, 1 to <3 years, 3–5 years, >5 years prior), Tdap vaccine exposure within 6 months postpartum (yes or no), and influenza vaccine exposure during pregnancy (yes or no) or within 6 months postpartum (yes or no). Pre-pregnancy influenza vaccine exposure was also considered in subgroup analyses, but ultimately not assessed due to the vaccine's waning effectiveness in this population after 180 days.[10] For analyses that considered postpartum Tdap or influenza vaccine exposure, women who received these vaccines after their ARI diagnosis, or within 14 days prior to their ARI diagnosis, were considered unexposed.

Sensitivity analyses employing generalized estimating equation (GEE) models were also conducted in order to account for repeated measures (i.e., multiple infants born to the same woman over the study period).

All statistical analyses were performed using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC).

Results

After exclusions, the analytic study population consisted of 82,041 active duty military women with 99,884 pregnancies resulting in a singleton live birth; overall, 13,573 pregnancies were exposed to the Tdap vaccine and 86,311 were unexposed.

Tdap vaccination in pregnancy was more common among married women (76.9% vs. 73.5%), women serving in the Navy (31.3% vs. 24.9%), and officers (18.6% vs. 13.7%) (Table 1). Exposed women were more likely to have received a pre-pregnancy Tdap vaccine (76.4% vs. 50.5%), less likely to have received a Tdap vaccine within 6 months postpartum (1.7% vs. 8.3%), and less likely to have received an influenza vaccine during pregnancy (42.6% vs. 53.8%) or within 6 months postpartum (30.9% vs. 39.0%). For pregnancies that began in 2013–2014 (i.e., after the current Tdap recommendations were implemented in October 2012), receipt of influenza vaccine in pregnancy was more common among women who also received Tdap vaccine in pregnancy (43.2% vs. 35.7%; data not shown).

There were 5 maternal pertussis cases within 6 months postpartum; none were exposed to the Tdap vaccine in pregnancy (data not shown). Maternal ARI within 6 months postpartum was identified among 18.2% and 20.7% of exposed and unexposed women, respectively (adjusted RR [aRR] = 0.90, 95% CI = 0.87–0.93) (Table 2). All estimates were similar when considering timing of Tdap vaccine exposure during pregnancy, but observed associations were most precise when exposure occurred 27–36 or >36 weeks EGA (aRR = 0.90, 95% CI = 0.87–0.95 and aRR = 0.86, 95% CI = 0.78–0.94, respectively). Similarly, estimates were of comparable magnitude when considering timing of exposure before delivery. Considering Tdap and/or influenza vaccine exposure during pregnancy, women exposed to both vaccines demonstrated the strongest reduced risk for ARI within 6 months postpartum compared with women who received neither vaccine (aRR = 0.88, 95% CI = 0.83–0.93). Women who only received the influenza vaccine had an ARI risk comparable to that of women who received neither vaccine (aRR = 0.98, 95% CI = 0.96–1.01).

In subgroup analyses that considered maternal vaccination characteristics, reduced risks for ARI within 6 months postpartum were observed among women with no prior Tdap vaccine exposure (aRR = 0.89, 95% CI = 0.82–0.96), women who received a Tdap vaccine <1 year prior to the index pregnancy (aRR = 0.84, 95% CI = 0.76–0.93), and women who did not receive a Tdap vaccine within 6 months postpartum (aRR = 0.87, 95% CI = 0.85–0.91) (Table 3). Conversely, ARI risks were increased among women who received a Tdap vaccine within 6 months postpartum (aRR = 1.17, 95% CI = 0.88–1.56), though the measure was imprecise. ARI risks were decreased and similar among women who did and did not receive an influenza vaccine during pregnancy or within 6 months postpartum.

GEE models accounting for repeated measures did not significantly change results (not shown).

Discussion

Overall, we found that exposure to the Tdap vaccine during pregnancy was associated with a small, reduced risk for maternal ARI within 6 months postpartum in this large, records-based cohort study of active duty U.S. military women. Associations were generally comparable across exposure definitions (i.e., timing of exposure during pregnancy and before delivery) and subgroup analyses that considered other maternal vaccination characteristics. However, our findings must be interpreted with caution because the Tdap vaccine does not confer immunity against all ARIs. The associations we observed are likely confounded by indication, i.e., women

who comply with pregnancy vaccine recommendations have a reduced risk for ARI within 6 months postpartum because they are more likely to be healthier and/or participate in other healthy behaviors compared with women who do not comply with pregnancy vaccine recommendations. This notion is supported by studies of factors related to influenza vaccine uptake during pregnancy among civilian women which found that healthy behaviors like vitamin use and not smoking during pregnancy were predictive of vaccine receipt.[11,12] To our knowledge, no studies have assessed factors related to vaccine uptake during pregnancy among active duty military women.

This study was strengthened by the use of large and complete administrative databases to determine maternal demographic and vaccination characteristics, including timing of Tdap vaccine receipt during pregnancy and history of other vaccines received while in military service. We were limited by the lack of reliable clinical laboratory data on pertussis diagnoses in women, and thus had to rely on the nonspecific proxy of any ARI diagnosis derived from ICD codes in medical claims data.

Additional clinical studies are needed to determine how pregnancy Tdap vaccine receipt influences pertussis-specific antibody levels among exposed women in the postpartum period. One such study is currently under way at the Naval Health Research Center as a Defense Health Agency Immunization Healthcare Division-funded collaborative effort with the Armed Forces Health Surveillance Branch. Still, more epidemiologic studies are needed to assess postpartum and long-term risk for maternal pertussis infection following Tdap vaccine exposure in pregnancy, particularly if exposure is found to be associated with decreasing concentrations of pertussis-specific antibodies over time. Future epidemiologic studies would benefit from clinical laboratory data for determining pertussis diagnoses.

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Table 1. Study population characteristics, stratified by pregnancy Tdap vaccine exposure status, active duty military women, DoD Birth and Infant Health Research program data, 2007–2014.[a]

	Pregnancy Tdap vaccine exposure			
	Yes		No	
Maternal characteristics	n	(%)	n	(%)
Total	13,573		86,311	
Age at delivery (years)				
18–19	182	(1.3)	2,294	(2.7)
20–24	4,572	(33.6)	36,053	(41.7)
25–29	4,558	(33.6)	26,682	(30.9)
30–34	2,932	(21.6)	14,560	(16.9)
≥35	1,329	(9.8)	6,722	(7.8)
Race/ethnicity				
Non-Hispanic White	6,330	(46.6)	41,387	(48.0)
Non-Hispanic Black	3,248	(23.9)	22,744	(26.4)
Hispanic	2,005	(14.8)	12,047	(14.0)
Other/unknown	1,990	(14.7)	10,133	(11.7)
Marital status				
Not married	3,142	(23.1)	22,884	(26.5)
Married	10,431	(76.9)	63,427	(73.5)
Service branch				
Army	4,420	(32.6)	30,063	(34.8)
Navy	4,245	(31.3)	21,448	(24.9)
Air Force	3,593	(26.5)	25,421	(29.5)
Marine Corps	1,136	(8.4)	7,177	(8.3)
Coast Guard	179	(1.3)	2,202	(2.6)
Rank				
Enlisted	11,050	(81.4)	74,461	(86.3)
Officer	2,523	(18.6)	11,850	(13.7)
Pre-pregnancy Tdap vaccine exposure				
None	3,201	(23.6)	42,710	(49.5)
<1 year prior	2,004	(14.7)	13,527	(15.7)
1 to <3 years prior	4,679	(34.5)	21,179	(24.5)
3–5 years prior	2,448	(18.0)	7,217	(8.4)
>5 years prior	1,241	(9.1)	1,678	(1.9)
Tdap vaccine exposure within 6 months postpartum				
No	13,336	(98.3)	79,157	(91.7)
Yes	237	(1.7)	7,154	(8.3)
Influenza vaccine exposure during pregnancy				
No	7,788	(57.4)	39,858	(46.2)
Yes	5,785	(42.6)	46,453	(53.8)
Influenza vaccine exposure within 6 months postpartum				
No	9,377	(69.1)	52,665	(61.0)
Yes	4,196	(30.9)	33,646	(39.0)

Abbreviations: DoD, Department of Defense; Tdap, tetanus, diphtheria, and acellular pertussis.
[a]Maternal characteristics and counts are presented for each pregnancy episode.

Table 2. Associations between Tdap vaccine exposure during pregnancy, including timing of vaccine exposure and record of influenza vaccine exposure during pregnancy, and maternal ARI within 6 months postpartum, active duty military women, DoD Birth and Infant Health Research program data, 2007–2014.

		ARI cases		RR (95% Cl)	
Maternal exposure characteristics	Total N	n	(%)	Unadjusted	Adjusted[a]
Tdap vaccine exposure during pregnancy					
No	86,311	17,857	(20.7)	1.00 (Referent)	1.00 (Referent)
Yes	13,573	2,472	(18.2)	0.88 (0.85–0.91)	0.90 (0.87–0.93)
Timing of Tdap vaccine exposure during pregnancy					
No vaccine exposure	86,311	17,857	(20.7)	1.00 (Referent)	1.00 (Referent)
0–13 weeks EGA	915	171	(18.7)	0.90 (0.79–1.03)	0.92 (0.80–1.05)
14–26 weeks EGA	784	141	(18.0)	0.87 (0.75–1.01)	0.90 (0.78–1.05)
27–36 weeks EGA	9,789	1,794	(18.3)	0.89 (0.85–0.93)	0.90 (0.87–0.95)
>36 weeks EGA	2,085	366	(17.6)	0.85 (0.77–0.93)	0.86 (0.78–0.94)
Timing of Tdap vaccine exposure before delivery					
No vaccine exposure	86,311	17,857	(20.7)	1.00 (Referent)	1.00 (Referent)
0–4 weeks before delivery	3,368	614	(18.2)	0.88 (0.82–0.95)	0.90 (0.84–0.97)
5–12 weeks before delivery	8,228	1,488	(18.1)	0.87 (0.83–0.92)	0.89 (0.85–0.94)
13–25 weeks before delivery	1,065	197	(18.5)	0.89 (0.79–1.01)	0.91 (0.81–1.04)
≥26 weeks before delivery	912	173	(19.0)	0.92 (0.80–1.05)	0.93 (0.82–1.07)
Tdap and influenza vaccine exposure during pregnancy					
Neither vaccine	39,858	8,542	(21.4)	1.00 (Referent)	1.00 (Referent)
Tdap vaccine only	7,788	1,476	(19.0)	0.88 (0.84–0.93)	0.90 (0.86–0.94)
Influenza vaccine only	46,453	9,315	(20.1)	0.94 (0.91–0.96)	0.98 (0.96–1.01)
Both Tdap and influenza vaccines	5,785	996	(17.2)	0.80 (0.76–0.85)	0.88 (0.83–0.93)

Abbreviations: ARI, acute respiratory infection; CI, confidence interval; DoD, Department of Defense; EGA, estimated gestational age; RR, risk ratio; Tdap, tetanus, diphtheria, and acellular pertussis.

[a]Multivariable models adjusted for maternal age at delivery, race/ethnicity, military rank, service branch, influenza vaccination during pregnancy (if not included in exposure definition), and season of last menstrual period for the index pregnancy.

Table 3. Associations between Tdap vaccine exposure during pregnancy and maternal ARI within 6 months postpartum, stratified by other maternal vaccine exposure characteristics, active duty military women, DoD Birth and Infant Health Research program data, 2007–2014.

	Pregnancy Tdap vaccine exposure				
	Yes		No		
	ARI cases		ARI cases		
Maternal exposure characteristics	n	(%)	n	(%)	RR (95% CI)[a]
Pre-pregnancy Tdap vaccine exposure					
None	572	(17.9)	8,882	(20.8)	0.89 (0.82–0.96)
<1 year prior	365	(18.2)	2,961	(21.9)	0.84 (0.76–0.93)
1 to <3 years prior	877	(18.7)	4,336	(20.5)	0.94 (0.88–1.00)
3–5 years prior	445	(18.2)	1,367	(18.9)	0.98 (0.89–1.08)
>5 years prior	213	(17.2)	311	(18.5)	0.97 (0.83–1.14)
Tdap vaccine exposure within 6 months postpartum					
No	2,432	(18.2)	16,897	(21.2)	0.87 (0.84–0.91)
Yes	40	(17.3)	960	(14.6)	1.17 (0.88–1.56)
Influenza vaccine exposure during pregnancy					
No	1,476	(19.0)	8,542	(21.4)	0.90 (0.85–0.94)
Yes	996	(17.2)	9,315	(20.1)	0.90 (0.84–0.95)
Influenza vaccine exposure within 6 months postpartum					
No	2,030	(21.7)	13,629	(25.9)	0.84 (0.81–0.88)
Yes	442	(10.5)	4,228	(12.6)	0.86 (0.78–0.94)

Abbreviations: ARI, acute respiratory infection; CI, confidence interval; DoD, Department of Defense; RR, risk ratio; Tdap, tetanus, diphtheria, and acellular pertussis.

[a]Multivariable models adjusted for maternal age at delivery, race/ethnicity, military rank, service branch, influenza vaccination during pregnancy (if not included in exposure definition), and season of last menstrual period for the index pregnancy.

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14. ABSTRACT

Since October 2012, the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine has been recommended for administration during every pregnancy, with optimal timing between 27 and 36 weeks' gestation. This approach increases transplacental immunity and protects infants from pertussis infection before they begin the vaccination series against the disease. However, few studies have assessed whether pregnancy Tdap vaccine exposure affects maternal pertussis antibody levels or postpartum risk for pertussis infection. In this records-based analysis of pregnant active duty U.S. military women, Department of Defense Birth and Infant Health Research program data were leveraged to determine whether exposure to the Tdap vaccine during pregnancy influenced maternal risk for acute respiratory infection (ARI) within 6 months postpartum; ARI was used as a proxy for pertussis infection because clinical diagnosis of pertussis is rare. Overall, we identified 99,884 pregnancies that resulted in a singleton live birth; 13,573 (13.6%) pregnancies were exposed to the Tdap vaccine. Maternal ARI within 6 months postpartum was identified among 18.2% and 20.7% of exposed and unexposed women, respectively (adjusted risk ratio = 0.90, 95% confidence interval = 0.87–0.93). Associations were generally similar across exposure definitions (i.e., timing of exposure during pregnancy and before delivery) and subgroup analyses that considered other maternal vaccination characteristics (i.e., pre-pregnancy Tdap vaccine exposure, Tdap vaccine exposure within 6 months postpartum, and influenza vaccine exposure during pregnancy or within 6 months postpartum). Although we found that Tdap vaccine exposure during pregnancy was associated with a small reduced risk for maternal ARI within 6 months postpartum, our results must be interpreted with caution because the Tdap vaccine does not confer immunity against all ARIs. Future epidemiologic studies on this topic would benefit from clinical laboratory data for determining pertussis diagnoses.

15. SUBJECT TERMS

tetanus, diphtheria, and acellular pertussis (Tdap) vaccine, Pertussis, pregnancy, active duty military women, Department of Defense (DoD) Birth and Infant Health Research (BIHR) program, acute respiratory infection (ARI)

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