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RESEARCH ARTICLE

Effectiveness of Prenatal Tetanus, Diphtheria, Acellular Pertussis Vaccination in the Prevention of Infant Pertussis in the U.S.

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Introduction: It is recommended that all pregnant women in the U.S. receive tetanus, diphtheria, acellular pertussis (Tdap) immunization to prevent infant pertussis. This study's objective was to examine the clinical effectiveness of prenatal Tdap, and whether effectiveness varies by gestational age at immunization.

Methods: A nationwide cohort study of pregnant women with deliveries in 2010–2014 and their infants was performed. Commercial insurance claims data were analyzed in 2016–2017 to identify Tdap receipt by the pregnant women, and hospitalizations and outpatient visits for pertussis in their infants until the infants reached 18 months of age. Pertussis occurrence was compared between infants of mothers who received prenatal Tdap (overall and stratified by gestational age at administration) and infants of unvaccinated mothers.

Results: There were 675,167 mother–infant pairs in the cohort. Among infants whose mothers received prenatal Tdap, the rate of pertussis was 43% lower (hazard ratio=0.57, 95% CI=0.35, 0.92) than infants whose mothers did not receive prenatal or postpartum Tdap; this reduction was consistent across pertussis definitions (hazard ratio for inpatient-only pertussis=0.32, 95% CI=0.11, 0.91). Pertussis rates were also lower for infants whose mothers received Tdap during the third trimester. Infants whose mothers received Tdap at <27 weeks of gestation did not experience reductions in pertussis rates (hazard ratio for pertussis=1.10, 95% CI=0.54, 2.25).

Conclusions: Infants of mothers who received prenatal Tdap experienced half the rate of pertussis as compared with infants of unimmunized mothers. These results do not provide evidence to support changing the currently recommended timing of Tdap administration in pregnancy.

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INTRODUCTION

Pertussis, or respiratory infection caused by *Bordetella pertussis*, has been rising in incidence in the U.S. since 2000.[1] In 2015, there were 20,762 pertussis cases reported to the National Notifiable Diseases Surveillance System, with an annual incidence rate of 99/100,000 in infants under age 6 months.[1] Disease in infants is more likely to be severe and result in hospitalization,[2,3] apnea, and pneumonia.[4,5] Most concerning, infants accounted for between 50% and 92% of all pertussis-related deaths.[1]

To reduce the burden of pertussis in children, the Centers for Disease Control and Prevention (CDC)

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recommends that all infants receive the primary series of diphtheria, tetanus, acellular pertussis (DTaP) at ages 2, 4, and 6 months, with booster doses at ages 15–18 months and 4–6 years. However, maximal protection is typically not attained until after the third dose of the vaccine at age 6 months,[6,7] leaving young infants at higher risk of pertussis. Additional CDC recommendations have been made in recent years, including the provision of a booster dose of tetanus, diphtheria, acellular pertussis (Tdap) to adolescents and Tdap immunization of close adult and adolescent contacts of infants.[8,9] These strategies have had limited success in decreasing rates of infant pertussis. Therefore, in 2011, the CDC recommended that pregnant women who previously had not received Tdap receive a one-time Tdap booster in pregnancy to provide passive immunity to their infants through transplacental antibody transfer.[9] New immunogenicity data following the recommendation showed that anti-pertussis antibodies are short-lived and mothers immunized before the current pregnancy or in early pregnancy may have insufficient pertussis-specific antibodies to protect their infants against infection.[10] Subsequently, the CDC recommended the provision of Tdap in each pregnancy, with the optimal timing of administration at 27–36 weeks of gestation.[11]

The optimal timing of Tdap immunization during pregnancy is currently under dispute. It is unclear if Tdap immunization in the second trimester of pregnancy could result in increased protection as compared with the third trimester, the currently recommended optimal timing.[12,13] The CDC recommendations for Tdap during pregnancy and its optimal timing were primarily informed by immunologic studies; limited clinical efficacy data exist on the best timing of Tdap administration during pregnancy. Another important concern is whether passively acquired maternal antibodies may blunt the infant's active immune response to the primary series of DTaP, potentially leaving infants at higher risk for pertussis once passively acquired antibodies wane over time. This concern is based on immunologic studies showing that infants whose mothers received Tdap during pregnancy or whose mothers had high titers of anti-pertussis antibodies had weaker antibody responses to pertussis antigens following the primary DTaP series.[14,15] The clinical significance of these immunologic findings is not known.

The goal of this study is to determine the clinical effectiveness of prenatal Tdap in the prevention of infant pertussis, and to understand if effectiveness varies by gestational age at Tdap administration. Further, the study examines rates of pertussis after the age of 6 months (the recommended age at primary DTaP series completion), to determine whether the immunologic finding of blunting by maternal antibodies has clinical relevance. If findings show that Tdap in pregnancy is highly effective at preventing infant pertussis, this may improve acceptability and uptake of the vaccine in pregnant women.

METHODS

Data Sample

An observational cohort of pregnant women and their infants (defined here as age ≤18 months) delivered between June 2010 and December 2014 was constructed using the Truven Health Analytics MarketScan® Commercial Claims and Encounters Databases (copyright© 2016 Truven Health Analytics Inc., all rights reserved), which contains insurance enrollment and billing data for commercially insured employees, spouses, and dependents from ≅100 large employers around the U.S.[16] These databases include billed, adjudicated, and paid insurance claims for inpatient and outpatient health facility visits, procedures, and their associated diagnosis codes; outpatient claims for medications filled by pharmacies; and claims for performing laboratory tests, but they do not include linkage back to the medical record to access the results of laboratory tests. Mothers with delivery claims (ICD-9-CM codes V27.0–V27.6) were linked within family enrollment groupings to newborns covered on the same insurance plan with birth codes (ICD-9-CM codes V30–V37) occurring within 30 days of the mother's delivery codes (to allow variation in the beginning of infant enrollment). Infants covered under insurance plans different from the mothers' would be unable to match. Enrollment was restricted to the first delivery per woman occurring between June 2010 and December 2014, and to those with singleton deliveries occurring >26 weeks of gestational age. Time periods prior to the recommendation were included to provide a better comparison group of unvaccinated women to avoid solely comparing recommendation-compliant women with noncompliant women after the recommendations were given, which could potentially introduce confounding by access or attitudes to health care. Methods used for estimating gestational age at delivery and vaccination have been described previously.[17] In brief, the hierarchical algorithm estimated gestational age based on diagnosis and procedure codes assigned to the mother and infant related to pre-maturity, post-maturity, and gestational length. Continuous insurance enrollment was required for mothers from estimated pregnancy onset to 7 days post-delivery to fully characterize maternal characteristics and vaccination status, and for infants until 7 days post-delivery. Infants were followed until censoring at the first occurrence of either the end of follow-up (6 months or 18 months, depending on the analysis) or the end of the study period (December 31, 2014), or disenrollment in the insurance claims database. Clinical and demographic characteristics were collected using diagnosis, procedure, and medication claims and enrollment information. Potential confounding variables, including demographic and clinical characteristics, were identified from the mothers during pregnancy and delivery, and from the infants at delivery and during the first 7 days, prior to the beginning of follow-up.

Measures

Maternal Tdap immunization was identified through procedure codes (Current Procedural Terminology code 90715, ICD-9-CM 99.37, 99.39) from estimated pregnancy onset until 7 days post-delivery, with the administration timing categorized as prenatal (from pregnancy onset to 2 weeks prior to delivery—also stratified