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Potential impact of parental Tdap immunization on infant pertussis hospitalizations

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ABSTRACT

We estimated the potential impact of parental Tdap immunization before delivery, at delivery and at the 2-week newborn visit on U.S. infant pertussis hospitalizations. We used published data for pertussis hospitalization rates among U.S. infants aged 0–4 months, the Tdap vaccine efficacy in adults, and the proportion of infants with pertussis <6 months of age in which either parent was the source (16–40% from mothers and 16–20% from fathers). Immunizing parents before pregnancy or ≥2 weeks prior to delivery should reduce pertussis hospitalizations among infants 0–4 months by 2694–9314 if both parents are vaccinated, and by 1347–6909 if only mothers are vaccinated. Greater reductions in pertussis hospitalizations would be achieved if parents are immunized ≥2 weeks prior to delivery than after delivery or the 2-week newborn visit. Although immunizing parents prior to pregnancy or delivery is best, immunizing parents in the postpartum period should provide protection to that newborn and to infants of subsequent pregnancies.

1. Introduction

Despite the tremendous success of immunization programs, pertussis remains a poorly controlled, vaccine preventable disease. The incidence of infant pertussis hospitalizations and deaths has increased since the 1980s, suggesting increases in disease rates rather than increases in disease reporting [1–4]. Reducing pertussis disease rates among children, adolescents and adults is an important public health goal given the severity of this disease among infants too young to be fully immunized.

An important approach to preventing pertussis hospitalizations is to immunize persons most likely to transmit pertussis to young, vulnerable infants, the age group with the highest rate of pertussis hospitalizations [5]. Transmission from family members is common, and mothers are the most commonly identified source of infant infection [6–8]. A "cocoon" approach to infant pertussis prevention, in which close contacts of infants are immunized against pertussis, is an attractive way to interrupt transmission. Several approaches to effectively implement pertussis cocooning have been studied [9–12].

There has been recent, heightened awareness of the burden of pertussis disease in adolescents and adults. In 2006 the U.S. Advisory Committee on Immunization Practices (ACIP) recommended that a single dose booster of combined tetanus, reduced-dose diphtheria, and acellular pertussis vaccine (Tdap) be given to adolescents and adults <65 years of age [13,14]. Further, the ACIP has recommended that Tdap vaccine be administered to women before pregnancy, in the third trimester or after week 20 of the second trimester of pregnancy, or in the immediate postpartum period, and to household and caregiver contacts of young infants [14,15]. Tdap is highly effective in preventing pertussis in adolescents and adults. In 2010, 11% of U.S. adults with infant contact had received Tdap [16].

Infant pertussis disease is potentially life-threatening, variable in clinical its manifestation, difficult to diagnose, and a significant threat to health worldwide. Enhanced Tdap coverage of parents of young infants will reduce infant pertussis hospitalization rates. Three approaches have been studied to enhance parental Tdap coverage – during pregnancy, during birth hospitalization, and at the 2-week newborn visit [9,12,17–19]. We sought to estimate the potential impact of parental Tdap vaccination for each of these three approaches on rates of pertussis hospitalizations among U.S. infants, using published data on infection source, hospitalization rates, and Tdap vaccine efficacy.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; Tdap, tetanus reduced-dose diphtheria, and acellular pertussis vaccine; U.S., United States; VE, vaccine effectiveness.

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Table 1
Assumptions from published data.

Published data	Low estimate	High estimate
Rates of pertussis hospitalization		
0 to <1 months	80/100,000	97/100,000
1 to <3 months	102/100,000	244/100,000
3 to <5 months	30/100,000	94/100,000
Baseline pertussis hospitalizations		
0 to <1 months	3453	4187
1 to <3 months	4403	10,534
3 to <5 months	1295	4058
0 to <5 months	9151	18,779
Source of pertussis		
Mother	16%	40%
Father	16%	20%
Either parent[a]	32%	55%
Tdap vaccine effectiveness	70%	92%
Single estimate		
United States Births in 2007		4,317,119 live births per year

[a] The sum of each parent as the source of pertussis may be less than that reported for either parent if both parents were determined to have pertussis.

2. Methods

The assumptions used in this analysis are summarized in Table 1, and include estimated rates of U.S. infant pertussis hospitalizations for 0 to <1 months, 1 to <3 months, and 3 to <5 months of life from 1980 to 1999 and from 1993 to 2004 [1,2]. These rates are comparable to other U.S. estimates and are lower than the rates reported from Australia, Canada, France, New Zealand and Spain [3,20–25].

Infant pertussis hospitalization rates after the 2006 ACIP recommendations for expanded Tdap use in adolescents and adults have not yet been published. Thus, we used pertussis hospitalization rates prior to 2006 and assumed no parental Tdap vaccinations for our calculations.

Estimates of the frequency that hospitalized infants acquired pertussis from their mother or father ("parent source %") were derived from the literature. Bisgard et al. demonstrated that mothers were more frequently identified as the source of pertussis for infants 0 to <4months than for those 4 to <12 months [6]. To estimate the frequency that mothers or fathers were the source of infant pertussis, we used data from studies evaluating household contacts of infants <6 months of age with pertussis [6,26–28]. Mothers were identified as the source of pertussis for 16–40% of infants <6 months of age [6,26–28], and fathers were the source for 16–20% of young infants [26–28]. Other family members and household contacts can be the source of pertussis for infants but were not included the model because limited specific data about the frequency in which other household contacts were the source was available for infants <6 months of age.

Estimate of vaccine effectiveness (VE) in preventing pertussis disease in vaccinated parents was derived from the literature. The Tdap trial among adolescents and adults demonstrated a vaccine efficacy of 92% (95% CI 32–99%) against laboratory-confirmed pertussis infection [29]. Similarly, both 95% confidence intervals for Tdap vaccine effectiveness against laboratory-confirmed disease in Australia encompassed 92%; Tdap vaccine effectiveness was 89% (95% CI 83–93%) against pertussis diagnosed by IgA serology and 84% (95% CI 56–94%) against pertussis diagnosed by polymerase chain reaction [30]. Based on this data, we assumed Tdap vaccine effectiveness among parents was 92%. Because case definitions and observer bias could lead to an overestimation of vaccine efficacy or effectiveness [29–31], we also assumed a lower Tdap vaccine effectiveness of 70%.

The annual number of U.S. infant pertussis hospitalizations for each age range was calculated by multiplying the rate of hospitalizations by the 4,317,119 U.S. births in 2007 [32]. The number of U.S. infant pertussis hospitalizations that could be prevented each year by parental vaccination was calculated by multiplying the number of pertussis hospitalizations by the parent source percentage by the vaccine effectiveness percentage: [hospitalizations prevented] = [pertussis hospitalizations] × [parent source %] × [VE%]. This equation assumed that parents are fully immunized, or had received Tdap at least ½ month earlier.

We made the following assumptions about parental immunizations. For the prenatal, immediate postpartum and newborn periods, we assumed that parents were immunized at least 2 weeks prior to delivery, on the day of birth, or at the 2-week newborn visit, respectively. We also assumed a half-month delay in the development of a full protective response after Tdap immunization. For parents immunized in the immediate postpartum period or when the newborn was 2 weeks of age, the full benefit would be reached when the infants were 0.5 months and 1 month of age, respectively. To calculate the potential direct effect on pertussis hospitalization rates among infants in the 1st month of life when parents are immunized in the immediate postpartum period, we used the formula [hospitalizations prevented] = [pertussis hospitalizations] × [parent source %] × [VE%] × [0.5].

The number of parents needed to be immunized to prevent one U.S. infant pertussis hospitalization ("number needed to be immunized") was calculated by dividing the number of hospitalizations prevented into the U.S. birth cohort.

Seropositivity to pertussis antigens after Tdap administration to adolescents and adults has been shown to persist with declining titers for up to 10 years [33]. Thus, we also computed the number of parents needed to be immunized to prevent one U.S. infant pertussis hospitalization assuming that they were immunized before or shortly after the birth of one infant and then had 1 or 2 subsequent children. For this computation, we used the estimated number of pertussis cases prevented based on the timing of the Tdap immunization for the first newborn and then added the number of cases prevented for 1 or 2 subsequent children assuming full benefit for all subsequent children. The number needed to be immunized assuming 1 or 2 subsequent children was calculated by summing the estimated number of pertussis hospitalizations prevented among a total of 2 or 3 infants divided into the U.S. birth cohort.

These calculations estimate the potential reduction in infant pertussis hospitalizations that would result from parental Tdap immunization based on known variation of rates and other assumptions that have statistical uncertainty. Our calculations were performed using both "low estimates" and "high estimates" of pertussis hospitalization rates and proportion for parental source of infant pertussis cases. Consequently, our results are expressed as a range that shows this underlying statistical uncertainty.

3. Results

The projected number of U.S. pertussis hospitalizations in 0 to <5 month old infants is 9151–18,779 (see Table 1 for interval breakdown). The estimated number of pertussis hospitalizations prevented among infants in the 1st month of life varied dramatically for each scenario (Table 2). For parents immunized ≥2 weeks prior to delivery, during the birth hospitalization, and at the 2-week newborn visits, respectively, infants in the 1st month of life were fully protected, protected for later half of the month, and had no protection.

Immunizing mothers with Tdap ≥2 weeks prior to delivery is expected to prevent 1347–6909 hospitalizations annually among

Table 2
Estimated number of pertussis hospitalizations prevented and number needed to be immunized to prevent one infant pertussis hospitalization among infants 0 to <5 of months of life by immunizing either parent or both with Tdap >2 weeks prior to delivery, during birth hospitalization or when infant is 2 weeks old assuming Tdap vaccine effectiveness of 92%.

	Estimated pertussis hospitalizations prevented				Number needed to be immunized to prevent 1 infant pertussis hospitalization
	0 to <1 mo	1 to <3 mos	3 to <5 mos	0 to <5 mos	
Parental immunization ≥2 weeks prior to delivery					
Mother vaccinated					
Low estimate[a]	508	648	191	1347	3204
High estimate[b]	1541	3876	1493	6909	625
Father vaccinated					
Low estimate[a]	508	648	191	1347	3204
High estimate[b]	770	1938	747	3455	1249
Both parents vaccinated					
Low estimate[a]	1017	1296	381	2694	1602
High estimate[b]	2118	5329	1866	9314	463
Parental immunization during the birth hospitalization					
Mother vaccinated					
Low estimate[a]	254	648	191	1093	3950
High estimate[b]	770	3876	1493	6139	703
Father vaccinated					
Low estimate[a]	254	648	191	1093	3950
High estimate[b]	385	1938	747	3070	1406
Both parents vaccinated					
Low estimate[a]	508	1296	381	2186	1975
High estimate[b]	1059	5329	1866	8255	523
Parental immunization when the infant is 2 weeks old					
Mother vaccinated					
Low estimate[a]	0	648	191	839	5147
High estimate[b]	0	3876	1493	5369	804
Father vaccinated					
Low estimate[a]	0	648	191	839	5147
High estimate[b]	0	1938	747	2684	1608
Both parents vaccinated					
Low estimate[a]	0	1296	381	1677	2573
High estimate[b]	0	5329	1866	7195	600

[a] Low estimate incorporates the low estimated rate of pertussis hospitalizations and low estimate of the proportion for that parent that are the source of pertussis exposure for infants.
[b] High estimate incorporates the high estimated rate of pertussis hospitalizations and high estimate of the proportion for that are the source of pertussis exposure for infants.

infants 0 to <5 months of age, assuming a vaccine effectiveness of 92%. The number of pertussis hospitalizations prevented would vary based on the prevalence of pertussis and the frequency that the mother is the identified source for cases of pertussis among young infants. Immunizing fathers with Tdap prior to delivery is expected to prevent 1347–3455 pertussis hospitalizations, which range from a similar estimate to half the estimate for immunizing mothers. The benefit would be greatest by immunizing both mothers and fathers with Tdap ≥2 weeks prior to delivery with the expected prevention of 2694–9314 hospitalizations annually among infants 0 to <5 months of age, assuming a vaccine effectiveness of 92%.

The number of mothers that need to be immunized with Tdap ≥2 weeks prior to delivery to prevent one pertussis hospitalization among infants 0 to <5 months of age ranged from 625 to 3204; this estimate varied based on the rate of pertussis hospitalizations and frequency that mothers are the source of pertussis. If both parents are immunized prior to delivery, the number of parents that need to be immunized to prevent one pertussis hospitalization is 463–1602.

Immunizing either or both parents at the birth hospitalization should reduce infant pertussis hospitalizations, though 11–19% less than immunizing parents ≥2 weeks prior to delivery. This translates into 13% and 23% more parents needing to be immunized to prevent one infant pertussis hospitalization in the immediate postpartum period than if immunized ≥2 weeks prior to delivery.

Immunizing either or both parents at the 2-week newborn visit should reduce infant pertussis hospitalizations, though 23% to 38% less than immunizing parents ≥2 weeks prior to delivery. This translates into 29% and 61% more parents needing to be immunized to prevent one infant pertussis hospitalization at the 2-week newborn visit than in the ≥2 weeks prior to delivery.

The largest change in the number of parents needed to be immunized to prevent one infant pertussis hospitalization occurred when 1 or 2 subsequent children are born while the parents have persistent immunity from a Tdap dose given before or shortly after the birth of a previous child (Table 3). For parents who are immunized ≥2 weeks prior to delivery of one infant, the number needed to be immunized is decreased by 50% and 67% for the second and third children born when the parent has persistent Tdap immunity. Using higher estimates of pertussis hospitalizations for infants and parents as the source of pertussis, the number of parents needed to be immunized prior to delivery to prevent one infant hospitalization decreases from 463 for one child to 154 for three children born when that parent has persistent Tdap immunity from one booster dose. Immunizing parents at birth or at the 2-week newborn visit provided less protection than ≥2 weeks prior to delivery for that child but the subsequent children should have full protection provided that they are born when the parents have persistent Tdap immunity. For this reason, the number of parents needed to be immunized is slightly lower for parental Tdap administration immediately or 2 weeks after birth when one computes the potential benefit for the birth of subsequent children.

A decrease in Tdap vaccine effectiveness from 92% to 70% would result in a 31–32% higher estimated number of parents needed to be immunized to prevent one infant pertussis hospitalization (Table 4).

Table 3
Number of parents needed to be immunized to prevent one infant from being hospitalized with pertussis if this child is the only one to benefit from this vaccination or if these parents have 1 or 2 subsequent children in the timeframe of persistent adult immunity from one dose of Tdap assuming a vaccine effectiveness of 92%.

Tdap vaccination for	Number needed to be immunized to prevent 1 infant pertussis hospitalization		
	This newborn	This newborn + 1 subsequent child	This newborn + 2 subsequent children
Parent immunized ≥2 weeks prior to delivery of this newborn			
Mother vaccinated			
Low estimate[a]	3204	1602	1068
High estimate[b]	625	312	208
Father vaccinated			
Low estimate[a]	3204	1602	1068
High estimate[b]	1249	625	416
Both parents vaccinated			
Low estimate[a]	1602	801	534
High estimate[b]	463	232	154
Parent immunized during birth hospitalization of this newborn			
Mother vaccinated			
Low estimate[a]	3950	1140	841
High estimate[b]	703	216	161
Father vaccinated			
Low estimate[a]	3950	1140	841
High estimate[b]	1406	433	321
Both parents vaccinated			
Low estimate[a]	1975	570	420
High estimate[b]	523	161	119
Parent immunized when this newborn is 2 weeks old			
Mother vaccinated			
Low estimate[a]	5147	1975	1222
High estimate[b]	804	352	225
Father vaccinated			
Low estimate[a]	5147	1975	1222
High estimate[b]	1608	703	450
Both parents vaccinated			
Low estimate[a]	2573	987	611
High estimate[b]	600	261	167

[a] Low estimate incorporates the low estimated rate of pertussis hospitalizations and low estimate of the proportion for that parent that are the source of pertussis exposure for infants.
[b] High estimate incorporates the high estimated rate of pertussis hospitalizations and high estimate of the proportion for that are the source of pertussis exposure for infants.

4. Discussion

Immunizing adults with Tdap represents a significant opportunity to reduce the incidence of severe infant pertussis disease. The determination to reduce pertussis disease overall and severe infant pertussis has driven recent ACIP recommendations for broadened Tdap immunization of adolescents and adults and includes pregnant women after week 20 of the second trimester of pregnancy and postpartum women [13–15]. Programs that specifically target parents for Tdap vaccination have been proposed and studied [9,12,17,19,26]. This analysis demonstrates the potential benefit of Tdap immunization of either or both parents on the prevention of infant hospitalization with pertussis if the Tdap vaccine was administered ≥2 weeks prior to delivery, in the immediate postpartum period, or at the 2-week newborn check.

Administering Tdap vaccine to approximately 460 parents (230 mothers and 230 fathers) prior to pregnancy or ≥2 weeks prior to delivery would prevent one pertussis hospitalization among infants 0 to <5 months of age. This finding assumes a Tdap vaccine effectiveness of 92%, a higher rate of pertussis disease in infants, and higher frequency of either parent being identified as the source. To prevent one pertussis hospitalization among infants 0 to <5 months of age assuming lower rates of infant pertussis hospitalizations and lower frequency of either parent being identified as the source, approximately 1600 parents (800 mothers and 800 fathers) would need to receive Tdap vaccine ≥2 weeks prior to delivery. This estimate is conservative because parental immunization would be expected to prevent pertussis disease in older infants as well.

Although the benefit of parental Tdap immunization should be greatest when administered ≥2 weeks prior to delivery, immunizing parents in the immediate postpartum and at the 2-week newborn visit remain important opportunities to protect vulnerable infants. Maternal Tdap immunization in the immediate postpartum period is attractive given the practicality of providing immunizations to hospitalized mothers, some of whom did not seek prenatal care [9,12]. Pediatricians can improve Tdap coverage among parents by immunizing parents at the 2-week newborn visit [9,19]. This discrepancy in benefits between parental immunization before delivery and parental immunization after delivery or at the 2-week visit would be partially offset over time, as successful programs would lead to higher rates of parental immunity for subsequent pregnancies.

This study has important limitations. Estimates of disease reductions due to immunization depend on disease rates, with projections of greater benefit when disease rates are high. Our calculations are based on rates of infant pertussis hospitalizations from 2004, before ACIP recommended adolescent and adult Tdap vaccination in 2006. Rates of Tdap coverage in adolescents have clearly increased since that time [34], and we hope that this will reduce rates of infant pertussis. Nonetheless, Tdap coverage among adults with infant contact was just 11% in 2010 [16,35]. Pertussis can be a difficult diagnosis in infants and actual rates of infant pertussis hospitalization may be higher than those published, in which case this study would underestimate benefits of parental immunization. Also, there are many challenges in fully immunizing all parents and household contacts of newborns. Although the estimated number of infant hospitalizations prevented assumes that all parents are immunized, the estimated number of parents needed to be immunized to prevent one hospitalization does not.

Table 4
Number of parents needed to be immunized to prevent one infant from being hospitalized with pertussis if this child is the only one to benefit from this vaccination or if these parents have 1 or 2 subsequent children in the timeframe of persistent adult immunity from one dose of Tdap assuming a vaccine effectiveness of 70%.

Tdap vaccination for	Number needed to be immunized to prevent 1 infant pertussis hospitalization		
	This newborn	This newborn + 1 subsequent child	This newborn + 2 subsequent children
Parent immunized ≥2 weeks prior to delivery of this newborn			
Mother vaccinated			
Low estimate[a]	4212	2106	1404
High estimate[b]	821	411	275
Father vaccinated			
Low estimate[a]	4212	2106	1404
High estimate[b]	1642	821	547
Both parents vaccinated			
Low estimate[a]	2106	1053	702
High estimate[b]	609	305	203
Parent immunized during birth hospitalization of this newborn			
Mother vaccinated			
Low estimate[a]	5191	1498	1105
High estimate[b]	924	284	211
Father vaccinated			
Low estimate[a]	5191	1498	1105
High estimate[b]	1848	568	422
Both parents vaccinated			
Low estimate[a]	2596	749	553
High estimate[b]	687	211	157
Parent immunized when this newborn is 2 weeks old			
Mother vaccinated			
Low estimate[a]	6764	2596	1606
High estimate[b]	1057	462	296
Father vaccinated			
Low estimate[a]	6764	2596	1606
High estimate[b]	2113	924	591
Both parents vaccinated			
Low estimate[a]	3382	1298	803
High estimate[b]	788	344	220

[a] Low estimate incorporates the low estimated rate of pertussis hospitalizations and low estimate of the proportion for that parent that are the source of pertussis exposure for infants.
[b] High estimate incorporates the high estimated rate of pertussis hospitalizations and high estimate of the proportion for that are the source of pertussis exposure for infants.

We did not include relative measures of disease severity in young infants nor did we include the benefit of Tdap immunization to the parents themselves or to infants ≥5 months of age and older children; therefore these estimates are conservative and likely underestimate the total expected benefit. The composition of households of young infants varies greatly but should be accounted for in the estimated frequency of the identified source of infant pertussis. Also, we have not estimated the benefits of immunizing non-parental infant contacts that are potential sources of infection. Immunizing all persons who have contact with infants should provide additional protection and further decrease infant pertussis hospitalizations [36]. As of 2012, the ACIP recommended that all adolescents and adults, including those ≥65 years of age, who have contact with infants should receive one dose of Tdap.

Another limitation of this study is the assumption that Tdap vaccine effectiveness is 92%. This estimate has wide confidence intervals and is based on an assessment of a single vaccine product over 2.5 years [29]. Further, this analysis assumes that pertussis vaccine effectiveness persists and is based on the fact that most adults after Tdap immunization have detectable antibodies with declining titers for up to 10 years [33]. However, if pertussis vaccine effectiveness is lower or protection against disease wanes faster than 10 years, this analysis would overestimate the potential benefit of parental immunization on infant disease. To address these uncertainties, we also computed the benefit assuming a vaccine effectiveness of 70%. Decreasing the vaccine effectiveness from 92% to 70% led to an estimated 31–32% more parents needed to be immunized to prevent one hospitalization.

In conclusion, we estimate that significant reductions in infant pertussis hospitalizations will occur in communities that increase parental Tdap immunizations. Our conclusions are consistent with a cost-effectiveness analysis [10], but contrast with another study that used different assumptions and a lower rate of pertussis hospitalizations than is reported in the U.S. [25]. Our estimates are conservative and demonstrate the wide range of anticipated results depending on the prevalence of pertussis in infants, the proportion of infant cases from either parent, and the timing of the immunization (prior to delivery, in the immediate postpartum period, or at the 2-week newborn visit). Parental pertussis cocooning may be a particularly effective answer to the challenge of severe pertussis disease in early infancy.

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