

Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis

Roger Baxter, MD,[†] Joan Bartlett, MPH, MPP, Bruce Fireman, MA, Edwin Lewis, MPH, Nicola P. Klein, MD, PhD

abstract

BACKGROUND: Vaccination against pertussis during pregnancy is recommended to protect newborns, yet there is limited information about the effectiveness of maternal tetanus toxoid, reduced diphtheria toxoid, acellular pertussis (Tdap) vaccine before the first infant dose of diphtheria, tetanus and acellular pertussis (DTaP) vaccine and during the first year of life in infants who have received DTaP.

METHODS: In a retrospective cohort study of infants born at Kaiser Permanente Northern California from 2010 to 2015, we estimated the effectiveness of maternal pertussis vaccination for protecting newborns against pertussis in the first 2 months of life and in the first year of life accounting for each infant DTaP dose.

RESULTS: Among 148 981 newborns, the vaccine effectiveness of maternal Tdap was 91.4% (95% confidence interval [CI], 19.5 to 99.1) during the first 2 months of life and 69.0% (95% CI, 43.6 to 82.9) during the entire first year of life. The vaccine effectiveness was 87.9% (95% CI, 41.4 to 97.5) before infants had any DTaP vaccine doses, 81.4% (95% CI, 42.5 to 94.0) between doses 1 and 2, 6.4% (95% CI, -165.1 to 66.9) between doses 2 and 3, and 65.9% (95% CI, 4.5 to 87.8) after infants had 3 DTaP doses.

CONCLUSIONS: Maternal Tdap vaccination was highly protective against infant pertussis, especially in the first 2 months of life. Even after infant DTaP dosing, there was evidence of additional protection from maternal Tdap vaccination for the first year of life. This study strongly supports the United States' current recommendation to administer Tdap during each pregnancy.

FREE

Kaiser Permanente Vaccine Study Center, Oakland, California

Dr Baxter contributed to study design and interpretation of results and drafted the initial manuscript; he died before the final manuscript was revised and submitted; Dr Klein, Mr Fireman, and Mr Lewis contributed to study design and interpretation of results, critically reviewed the manuscript, and approved the final manuscript; and Ms Bartlett contributed to study design, interpretation of results, extracted and analyzed the data, critically reviewed the manuscript, and approved the final manuscript.

[†]Deceased.

DOI: 10.1542/peds.2016-4091

Accepted for publication Feb 22, 2017

Address correspondence to Nicola P. Klein, MD, PhD, Kaiser Permanente Vaccine Study Center, 1 Kaiser Plaza, 16th Floor, Oakland, CA 94611. E-mail: nicola.klein@kp.org

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2017 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: Dr Klein reports research support from GlaxoSmithKline for a separate pertussis vaccine effectiveness study. Drs Baxter and Klein have received research grants from GlaxoSmithKline, Sanofi Pasteur, Merck, Pfizer, Protein Science, and MedImmune; the other authors have indicated they have no financial relationships relevant to this article to disclose.

WHAT'S KNOWN ON THIS SUBJECT: Tetanus toxoid, reduced diphtheria toxoid, acellular pertussis (Tdap) vaccination during pregnancy is recommended to protect newborns against pertussis, yet there is limited evidence about its effectiveness before and after infants are immunized with diphtheria, tetanus and acellular pertussis (DTaP) vaccine.

WHAT THIS STUDY ADDS: Maternal Tdap vaccination during pregnancy is highly effective during the first 2 months of life. There was no evidence of interference between maternal Tdap and infant DTaP vaccines; instead, maternal Tdap vaccination adds to the protection infants receive from DTaP.

To cite: Baxter R, Bartlett J, Fireman B, et al. Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis. *Pediatrics*. 2017;139(5):e20164091

Pertussis, or whooping cough, a respiratory infection caused by the bacteria *Bordetella pertussis*, can affect persons of any age, but it is particularly virulent and life-threatening in infants. Rates of pertussis infection have been increasing in recent years, in part due to rapidly waning immunity of diphtheria, tetanus and acellular pertussis (DTaP) vaccines and their diminished effectiveness in comparison with older whole-cell pertussis vaccines.¹⁻³

In the United States, primary immunization of infants with DTaP vaccines is recommended at 2, 4, and 6 months of age. In the early months of life before newborns can benefit from the DTaP vaccine, they receive some protection against pertussis from maternal antibodies transferred during pregnancy. Without pertussis vaccination during pregnancy, maternal pertussis antibodies in the infant decline substantially by 6 weeks of age and become undetectable by about 4 months of age.⁴ Infants born to women vaccinated with tetanus toxoid, reduced diphtheria toxoid, acellular pertussis (Tdap) during pregnancy have been found to have high levels of pertussis antibodies before receiving their first DTaP vaccine dose.⁵

The strategy of immunizing pregnant women to boost maternal antibody transfer appears to be more effective for protecting young infants against pertussis than are attempts at “cocooning,” in which mothers and other persons in close contact with newborns are vaccinated.⁶⁻⁹ To enhance protection in vulnerable infants too young to be vaccinated themselves, several countries now recommend routinely immunizing pregnant women with Tdap to increase the transfer of pertussis antibodies from mothers to infants.^{5,10,11} With this in mind, in October 2011, the Centers for Disease Control and Prevention’s Advisory Committee

on Immunization Practices (ACIP) recommended Tdap vaccination in pregnant women who had not previously received the Tdap vaccine.¹² In February 2013, the ACIP extended this recommendation to administer the Tdap vaccine during every pregnancy, regardless of previous Tdap vaccination, at any time during pregnancy, but preferably between 27 and 36 weeks’ gestation to maximize antibody transfer.^{13,14} These ACIP recommendations largely supplanted an earlier one, in place since 2006, to administer the Tdap vaccine to mothers in the immediate postpartum period.

There have been concerns that maternal Tdap vaccination during pregnancy may hinder the infant immune response to the 3-dose primary DTaP series. Blunting of the response to pertussis vaccines in infants after maternal Tdap immunization has been observed,^{5,15} but interference with infant pertussis protection may be less of a problem for acellular vaccines than for earlier whole-cell vaccines.¹⁶

Substantial evidence supports the safety of Tdap vaccination in pregnancy.¹⁷⁻²⁰ However, there is limited evidence on its effectiveness,^{21,22} and only 1 study has estimated Tdap vaccine effectiveness (VE) in infants who have also received the DTaP vaccine.²³ In this study, we assessed the effectiveness of maternal Tdap vaccination for preventing pertussis in infants during the first 2 months of life and during the first year of life. We also analyzed the effectiveness of maternal Tdap vaccination during pregnancy after each of the first 3 infant doses of DTaP to address concerns about interference.

Our analyses focused on the VE of administering Tdap during pregnancy, as currently recommended, using data from the 2010 and 2014 California epidemics. In 2010, California experienced its

highest incidence of pertussis in over 50 years, followed by an even larger outbreak in 2014.²⁴ In addition, we examined the VE of Tdap given to mothers postpartum, the cocooning strategy previously recommended.

METHODS

Setting

Kaiser Permanente of Northern California (KPNC) is a large integrated medical care organization that provides comprehensive medical services to ~3.7 million members. Members receive almost all medical care at KPNC-owned facilities, including clinics, hospitals, pharmacies, and laboratories. Databases capture detailed information on all medical services, including deliveries, vaccinations, laboratory tests, and on enrollment and demographics. Delivery records include medical record numbers for both babies and their mothers, so we can link their information. Since 2006, all pertussis testing has been conducted in a centralized laboratory using real-time polymerase chain reaction (PCR) on nasopharyngeal swabs.¹

Study Population

This study followed infants born in KPNC hospitals from 2010 to 2015 starting from the day of birth. Eligibility criteria required that infants were born full term (≥ 37 weeks’ gestation) and were enrolled in Kaiser health plan by age 4 months. We additionally restricted the study population to infants whose mothers were continuously enrolled in Kaiser during pregnancy to ensure correct classification of Tdap status. We also required that mothers be born before 1996 so that all the mothers had received whole-cell rather than acellular pertussis vaccines for their primary series. We identified pertussis cases among eligible infants during follow-up. We

defined cases as testing PCR positive for pertussis.

This study had 2 overlapping follow-up periods: birth to 2 months of age and birth to 1 year of age. We started infant follow-up on the day of birth and continued until the newborn tested positive for pertussis, reached 2 or 12 months of age (depending on the analysis), or the end of the study period (March 31, 2016). For the 1-year follow-up period, we also stopped following infants who disenrolled from Kaiser before their first birthday.

Statistical Methods

The analyses estimated the effectiveness of Tdap vaccination during pregnancy in protecting newborns against pertussis in 2 follow-up periods: the first 2 months of life and the first year of life. For each follow-up period, we modeled the risk of pertussis in the infant in relation to whether the mother received Tdap during pregnancy. We used stratified Cox regression to estimate the pertussis hazard ratio (HR) in infants of women vaccinated with Tdap versus women who were unvaccinated during pregnancy. We calculated VE as $1 - \text{HR}$.

Cox models were specified with a calendar time line and were stratified by the year and month of birth of the infant. We included covariates to adjust for sex, race, delivery hospital, and maternal Tdap vaccination before and after pregnancy. "Tdap before pregnancy" indicated the presence or absence of maternal Tdap vaccination during the 2 years before the start of pregnancy. "Tdap after pregnancy" was a time-varying covariate that indicated maternal Tdap vaccination from the day of birth onwards. The 3 main indicator variables of maternal Tdap vaccination status in the analyses (before pregnancy, during pregnancy at least 8 days before birth, and after pregnancy) are not exclusive; it was possible to receive Tdap

during >1 of these periods. For the 1-year follow-up period, we censored infants if their mother disenrolled from Kaiser to accurately ascertain maternal Tdap vaccination status after childbirth.

In the analyses that followed infants through the first year of life, we also included covariates to account for infant DTaP doses. We specified DTaP vaccination status as a set of time-varying variables that indicated the number of doses received (0, 1, 2, or 3).

All maternal Tdap and infant DTaP vaccine doses were counted beginning 8 days after receipt to allow time for the immune response.

We identified 3 groups of infants based on the Tdap vaccination status during pregnancy of their birth mother: (1) vaccinated (Tdap vaccination during pregnancy at least 8 days before birth); or (2) vaccinated too close to birth to boost maternal antibody transfer (Tdap vaccination 1–7 days before birth); or (3) unvaccinated (no Tdap vaccination during pregnancy). Our VE estimate was based on the pertussis HR for infants in group 1 versus group 3.

We ran separate Cox models to estimate the VE of maternal Tdap during pregnancy in preventing infant pertussis during 2 follow-up periods: (1) model for the first 2 months of life (as described above) and (2) models for the first 12 months of life. The first 12-month model estimated VE on average across the entire first year of life with adjustment for the number of infant DTaP vaccine doses. This model included both sets of pertussis vaccination variables (infant DTaP vaccine doses, maternal Tdap vaccination status during pregnancy) as separate covariates. The second 12-month model examined VE at each DTaP vaccine dose. The second model yielded 4 separate VE estimates for infants while they had

received 0, 1, 2, and 3 DTaP doses, respectively. An 8-level variable was created (ie, infants with 0 DTaP vaccine doses born to unvaccinated mothers; infants with 0 DTaP vaccine doses born to vaccinated mothers, infants with 1 DTaP vaccine dose born to unvaccinated mothers; infants with 1 DTaP vaccine dose born to vaccinated mothers, etc). We performed a sensitivity analysis of the second 12-month model that censored infants if they became 3 months late for a DTaP vaccine dose to restrict the analysis to infants who were following the recommended DTaP schedule.

This study was reviewed and approved by the KPNC Institutional Review Board.

RESULTS

Among all infants born in a KPNC hospital from 2006 to 2015, the percentage whose mothers received the Tdap vaccine during pregnancy increased from <1% in 2006 to 2008 to 11.9% in 2010 and to 87.4% by 2015, after the ACIP recommendations and reminders in the electronic medical record (Fig 1). The majority of pregnant women vaccinated in KPNC from 2010 to 2015 received the Tdap vaccine at ≥ 20 weeks' gestation (75.1% for infants born between 2010 and 2012 and 98.4% for infants born between 2013 and 2015); by 2013, most pregnant women were vaccinated between 27 and 36 weeks' gestation (44.8% for infants born between 2010 and 2012 and 91.7% for infants born between 2013 and 2015). The percentage of mothers who received the Tdap vaccine during postpartum days 0 to 14 peaked at 31.7% for infants born in 2010 and declined thereafter to 1.8% for infants born in 2015.

The study population consisted of 148 981 infants born from 2010, when KPNC began recommending Tdap vaccination in pregnancy,

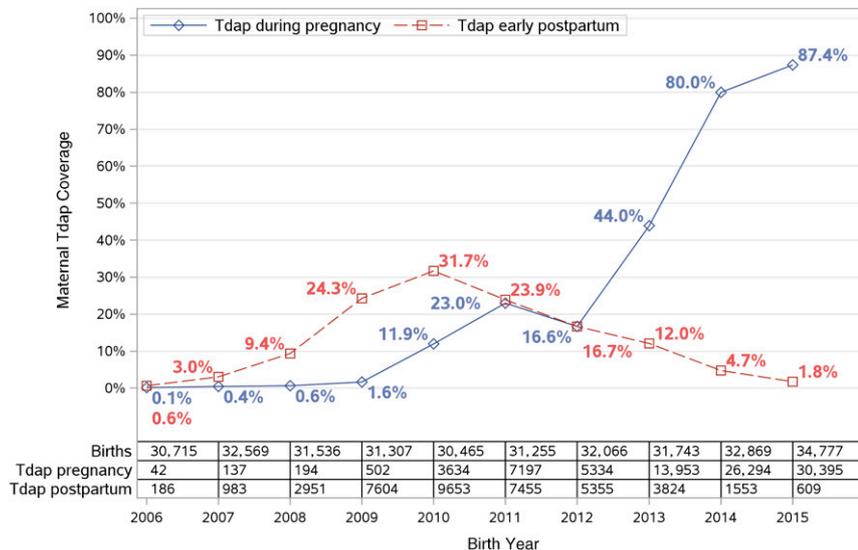


FIGURE 1 Percentage of infants born in KPNC hospitals whose mother received the Tdap vaccine during pregnancy (at least 8 days before birth) or early postpartum (from the day of birth to 14 days after birth), 2006 to 2015. We include infants whose mothers were continuously enrolled during pregnancy through 14 days postpartum. We exclude the <1% of infants missing data on gestational weeks.

TABLE 1 Characteristics of Newborns in the Study Population

Newborn Characteristic	N	%
Year of birth		
2010	24 363	16.4
2011	24 530	16.5
2012	24 775	16.6
2013	23 931	16.1
2014	25 184	16.9
2015	26 198	17.6
Sex		
Girl	73 406	49.3
Boy	75 575	50.7
Race or ethnic group		
American Indian or Alaskan native	539	0.4
Asian or Pacific Islander	38 596	25.9
Black or African American	8296	5.6
Hispanic (regardless of race)	31 378	21.1
White	58 714	39.4
Missing or other	11 458	7.7
Maternal Tdap vaccination during the 2 y before pregnancy		
No	112 385	75.4
Yes	36 596	24.6
Maternal Tdap vaccination during pregnancy		
No	79 292	53.2
1–7 d before birth	1521	1.0
8+ days before birth	68 168	45.8
Maternal Tdap vaccination during the 1 y after birth ^a		
No	122 962	82.5
0–14 d on or after birth	21 268	14.3
15 d to 1 y after birth	4751	3.2

^a Maternal Tdap vaccination after pregnancy is analyzed as a time-varying covariate.

through 2015. Table 1 shows the characteristics of newborns in the study. The mothers of 68 168 infants, 45.8% of the study population,

received the Tdap vaccine during pregnancy at least 8 days before birth. Seventeen infants (11.4 per 100 000 infants) in the study

population tested positive for pertussis by 2 months of age, and 110 (73.8 per 100 000 infants) tested positive by 1 year of age. Of the 110 pertussis cases in the first year of life, 103 were included in the analyses after censoring criteria for disenrollment were applied.

The unadjusted pertussis incidence was lower in infants whose mothers were vaccinated versus infants whose mothers were not vaccinated during pregnancy. Of the 17 cases in the first 2 months of life, only 1 was a “breakthrough” case where the mother was vaccinated in pregnancy >7 days prior to birth. The unadjusted incidence rate ratio was 0.08 (95% confidence interval [CI], 0.00 to 0.43) for the first 2 months of life and 0.35 (95% CI, 0.21 to 0.55) for the entire first year of life.

Maternal Tdap vaccination during pregnancy reduced pertussis risk by an estimated 91.4% during the first 2 months of life (Table 2). During the entire first year of life, maternal Tdap vaccination during pregnancy reduced pertussis risk by an estimated 69.0%, after adjustment for the effects of DTaP vaccination.

Tdap VE for infants who had 0 DTaP doses (from birth through 7 days after the first dose) was estimated at 87.9%; Tdap VE for infants who had protection from 1 DTaP dose (ie, from day 8 after dose 1 through day 7 of dose 2) was an estimated 81.4%; Tdap VE for infants who had protection from 2 DTaP doses, but not yet 3 doses, was an estimated 6.4%; and Tdap VE for infants who had 3 DTaP doses was an estimated 65.9% (Table 3). The VE at each DTaP dose was similar in the sensitivity analysis that censored infants who received DTaP at ages older than recommended (results not shown).

Maternal Tdap after pregnancy did not significantly reduce pertussis risk. Pertussis severity in the 17 cases in infants <2 months of age

TABLE 2 VE of Maternal Tdap and Infant DTaP Vaccination in Preventing Pertussis in 148 981 Newborns in the Study Population Followed From Birth Until 2 and 12 Months of Age

	2-mo Follow-up (Total Pertussis Cases = 17)				12-mo Follow-up (Total Pertussis Cases = 103)			
	No. of Pertussis Cases (Rate per 100 000 Person-Years)		VE, % (95% CI)	P	No. of Pertussis Cases (Rate per 100 000 Person-Years)		VE, % (95% CI)	P
Timing of maternal Tdap vaccination	No maternal Tdap	Maternal Tdap			No maternal Tdap	Maternal Tdap		
During pregnancy (8+ days before birth) ^a	15 (112.7)	1 (8.7)	91.4 (19.5 to 99.1)	.032	80 (109.1)	22 (38.0)	69.0 (43.6 to 82.9)	<.001
Before pregnancy	15 (79.4)	2 (32.5)	68.6 (−44.9 to 93.2)	.138	89 (89.4)	14 (42.4)	55.9 (20.7 to 75.5)	.006
After pregnancy	13 (59.3)	4 (129.4)	45.7 (−88.2 to 84.3)	.336	80 (72.1)	23 (106.2)	24.4 (−27.8 to 55.3)	.296
Infant DTaP vaccination								
First dose	—	—	—	—	—	—	48.2 (−6.4 to 74.8)	.073
Second dose	—	—	—	—	—	—	64.2 (17.9 to 84.4)	.015
Third dose	—	—	—	—	—	—	86.8 (69.2 to 94.4)	<.001

—, not applicable to these analyses.

^a VE of maternal Tdap vaccination during pregnancy was estimated from a Cox regression model, stratified on the year and month of birth of the infant and including covariates to adjust for sex, race, delivery hospital, maternal Tdap vaccination before and after pregnancy, and, for the 12-mo follow-up period, number of infant DTaP doses. Case counts do not include 1 infant, where maternal Tdap vaccination occurred 1 to 7 days before birth, because the VE estimate is based on comparing infants whose mothers received the Tdap vaccine during pregnancy at least 8 days before birth versus infants whose mothers had no Tdap vaccination during pregnancy. The VE estimate does not include infants whose mothers were vaccinated 1 to 7 days before birth as either vaccinated or unvaccinated during pregnancy; there were too few infants in this group to give a meaningful result, so the 1 case where this occurred is not included.

TABLE 3 Protection Against Pertussis From Maternal Tdap Vaccination During Pregnancy Before and After Infant DTaP Vaccination in 148 981 Newborns Followed From Birth Until 12 Months of Age

	12-mo Follow-up (Total Pertussis Cases = 103)		
	No. of Pertussis Cases (Rate per 100 000 Person-Years)		P
	No Maternal Tdap	Maternal Tdap	
Maternal Tdap during pregnancy (8+ days before birth) ^a			
0 DTaP doses (birth until day 7 after the first DTaP dose)	31 (177.2)	2 (14.8)	87.9 (41.4 to 97.5)
Protected by 1 DTaP dose ^b	23 (170.3)	5 (43.2)	81.4 (42.5 to 94.0)
Protected by 2 DTaP doses ^b	12 (88.5)	8 (72.8)	6.4 (−165.1 to 66.9)
Protected by 3 DTaP doses ^b	14 (48.7)	7 (32.1)	65.9 (4.5 to 87.8)
Maternal Tdap before pregnancy	89 (89.4)	14 (42.4)	55.6 (20.1 to 75.4)
Maternal Tdap after pregnancy	80 (72.1)	23 (106.2)	24.1 (−28.5 to 55.1)

^a We calculated the VE of maternal Tdap vaccination during pregnancy after each infant DTaP vaccine dose based on a Cox regression model that included an 8-level variable created by interacting a 2-level Tdap variable (0 = unvaccinated during pregnancy, 1 = vaccinated during pregnancy 8+ days before birth) and a 4-level DTaP variable (0, 1, 2, or 3 doses). The model was stratified on the year and month of birth of the infant and included covariates to adjust for sex, race, delivery hospital, and maternal Tdap before and after pregnancy. We used contrast statements to estimate the VE of maternal Tdap vaccination during pregnancy after each infant DTaP dose. Case counts do not include 1 infant whose mother received the Tdap vaccine 1 to 7 days before birth because the VE estimates do not include infants whose mothers were vaccinated 1 to 7 days before birth as either vaccinated or unvaccinated during pregnancy; there were too few infants in this group to give a meaningful result, so the 1 case where this occurred is not included.

^b Protected by DTaP dose: from day 8 after the DTaP dose until day 7 after the next dose.

ranged from mild to requiring hospitalization. Within 5 days before or after the PCR test, all infants received a diagnosis of cough or pertussis and/or had pertussis symptoms (eg, cough, apnea) and all received a prescription for azithromycin or erythromycin. Within 30 days before or after the PCR test, 10 of the 17 infants were hospitalized for pertussis, and an additional 3 had emergency

department visits related or possibly related to pertussis. The 1 case born to a mother vaccinated during pregnancy had a mild illness and was treated as an outpatient. All infants recovered without sequelae, and no death occurred.

DISCUSSION

We demonstrated a high level of effectiveness of 88% for maternal

Tdap vaccination during pregnancy in preventing pertussis in infants before their first dose of DTaP. This result is consistent with 2 earlier studies in the United Kingdom. Both studies examined maternal Tdap VE in preventing pertussis in infants <3 months of age, before any DTaP vaccination. The first, using a screening method, estimated VE at 90% (95% CI, 82 to 95).²⁵ The second, a case-control study, found

VE to be 93% (95% CI, 81 to 97).²¹ In addition, a recent US study compared Tdap vaccination during pregnancy with Tdap vaccination after pregnancy and estimated that Tdap vaccination during 27 to 36 weeks' gestation was 85% more effective than postpartum Tdap vaccination in preventing pertussis in infants up to 8 weeks of age.²⁶

In addition to finding a high VE in the first 2 months of life (91%), our study also demonstrated that maternal Tdap vaccination confers a significant amount of protection against pertussis over the entire first year of life (69%), even after infants are immunized with DTaP.

Most previous studies evaluated maternal Tdap VE in infants before DTaP vaccination. We evaluated the effectiveness of Tdap during pregnancy in relation to the first 3 doses of the DTaP vaccine. This is important because of concerns that maternal Tdap vaccination and infant DTaP vaccination may interfere with each other, potentially leading to decreased protection for the infant.²⁷ Evidence of such interference would be a negative VE estimate for maternal Tdap vaccination after infant DTaP vaccination, or lower-than-expected VE estimates for infant DTaP vaccination. We found neither type of evidence for interference. Protection from pertussis after maternal Tdap vaccination was high (>80%) both before and after the first infant dose of DTaP. After the second dose of DTaP and before the third dose, the point estimate of VE fell to 6.4%, with a wide CI, due to few pertussis cases and the modest difference in incidence rates during the brief follow-up time between doses 2 and 3. The Tdap VE estimate increased to 65.9%, and the CIs narrowed again after the third dose. We should be cautious about the interpretation of how much additional protection infants

are provided by maternal Tdap vaccination in addition to DTaP vaccination between the second and third doses, because the CI is wide. However, it is reassuring that at every level of DTaP vaccine exposure, children whose mothers received the Tdap vaccine are better protected. These results are broadly consistent with those from a recent study in the United Kingdom that also found that infants whose mothers received the Tdap vaccine were more protected at each of the first 3 doses of the DTaP vaccine. Using a screening method,²⁸ this study found a similarly high Tdap VE after the first DTaP vaccine dose (82%; 95% CI, 65 to 91), but a higher VE after the second dose (69%; 95% CI, 8 to 90) and a lower VE after the third dose (29%; 95% CI, -112 to 76), with a small number of cases and imprecise estimates after the second and, especially, the third dose.²³

Overall, the results in this study demonstrate that maternal Tdap vaccination during pregnancy is highly effective in preventing pertussis in infants. The protection afforded by Tdap vaccine administration during pregnancy was higher than that by Tdap vaccine administration after pregnancy (the cocooning strategy). Notably, we did not find evidence that postpartum Tdap administration to mothers was significantly protective during either the first 2 months or the first year of life. Our results demonstrate the substantial benefit of vaccinating during pregnancy rather than waiting until after birth and provide strong support for the current US recommendation to mothers and their medical providers to vaccinate with Tdap during pregnancy.

Receipt of the Tdap vaccine in the 2 years before the current pregnancy also appeared to provide some protection from pertussis.

However, the results of this study demonstrate that maternal Tdap vaccination during pregnancy provided the best protection against pertussis.

This study used data from a large integrated medical system in California over a time period encompassing 2 pertussis epidemics, which allowed us to accrue enough pertussis cases to assess VE before and after each of the 3 infant pertussis doses. We stratified the analyses by year and month of birth so that infants with pertussis were only compared with other infants of nearly the same age. The time-varying covariates (postpartum maternal Tdap vaccination and infant DTaP vaccine dose) were measured each day that a pertussis case occurred, and the exposure status for the case was compared with the exposure status on the same day for all other infants still being followed. Because we used calendar time as the time scale in the Cox regression model, cases were only compared with other infants at risk on the same day. Careful adjustment for calendar time is important because pertussis risk varies markedly as outbreaks come and go and because the rates of Tdap immunization of pregnant women rose substantially over the study period.

In some analyses, the number of pertussis cases was low, so CIs were wide, as was the case after the second dose of the DTaP vaccine. Because a large majority of mothers were vaccinated between 27 and 36 weeks' gestation, we did not have power to assess the optimal timing of Tdap vaccination during pregnancy. We restricted our study to mothers who had received whole-cell pertussis vaccines in infancy, so our results may not be generalizable to the coming generation of mothers vaccinated entirely with DTaP in childhood.

Finally, the decision of whether to test an infant was clinical, and we may not have had complete case ascertainment if physicians did not test for pertussis or parents did not seek care.

CONCLUSIONS

Maternal Tdap vaccination during pregnancy was highly effective at protecting infants against pertussis before their first dose of the DTaP vaccine, and protection continued after the first DTaP dose

through the first year of life. We did not find evidence supporting the effectiveness of maternal postpartum cocooning with the Tdap vaccine. Our study validates the current US recommendation to vaccinate with Tdap during pregnancy, and suggests that widespread use of Tdap vaccination in pregnancy can result in significant decreases in pertussis, particularly in young infants before their first DTaP vaccine dose or who are protected by only 1 dose of DTaP.

ABBREVIATIONS

ACIP: Advisory Committee on Immunization Practices
CI: confidence interval
DTaP: diphtheria, tetanus and acellular pertussis
HR: hazard ratio
KPNC: Kaiser Permanente Northern California
PCR: polymerase chain reaction
Tdap: tetanus toxoid, reduced diphtheria toxoid, acellular pertussis
VE: vaccine effectiveness

FUNDING: This work was supported by Kaiser Permanente.

POTENTIAL CONFLICT OF INTEREST: Drs Baxter and Klein report potential conflicts of interest relevant to this article: the pertussis vaccines purchased by Kaiser Permanente Northern California, which are the focus of this study, were manufactured by GlaxoSmithKline and Sanofi Pasteur; the other authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. *N Engl J Med*. 2012;367(11):1012–1019
2. Klein NP, Bartlett J, Fireman B, Rowhani-Rahbar A, Baxter R. Comparative effectiveness of acellular versus whole-cell pertussis vaccines in teenagers. *Pediatrics*. 2013;131(6). Available at: www.pediatrics.org/cgi/content/full/131/6/e1716
3. Gambhir M, Clark TA, Cauchemez S, Tartof SY, Swerdlow DL, Ferguson NM. A change in vaccine efficacy and duration of protection explains recent rises in pertussis incidence in the United States. *PLoS Comput Biol*. 2015;11(4):e1004138
4. Van Savage J, Decker MD, Edwards KM, Sell SH, Karzon DT. Natural history of pertussis antibody in the infant and effect on vaccine response. *J Infect Dis*. 1990;161(3):487–492
5. Ladhani SN, Andrews NJ, Southern J, et al. Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: single arm observational study with a historical comparator. *Clin Infect Dis*. 2015;61(11):1637–1644
6. Quinn HE, Snelling TL, Habig A, Chiu C, Spokes PJ, McIntyre PB. Parental Tdap boosters and infant pertussis: a case-control study. *Pediatrics*. 2014;134(4):713–720
7. Swamy GK, Wheeler SM. Neonatal pertussis, cocooning and maternal immunization. *Expert Rev Vaccines*. 2014;13(9):1107–1114
8. Carcione D, Regan AK, Tracey L, et al. The impact of parental postpartum pertussis vaccination on infection in infants: a population-based study of cocooning in Western Australia. *Vaccine*. 2015;33(42):5654–5661
9. Forsyth K, Plotkin S, Tan T, Wirsing von König CH. Strategies to decrease pertussis transmission to infants. *Pediatrics*. 2015;135(6). Available at: www.pediatrics.org/cgi/content/full/135/6/e1475
10. Siegrist CA. Mechanisms by which maternal antibodies influence infant vaccine responses: review of hypotheses and definition of main determinants. *Vaccine*. 2003;21(24):3406–3412
11. Niewiesk S. Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. *Front Immunol*. 2014;5:446
12. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months — Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60(41):1424–1426
13. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR Morb Mortal Wkly Rep*. 2013;62(7):131–135
14. Healy CM, Rench MA, Baker CJ. Importance of timing of maternal combined tetanus, diphtheria, and acellular pertussis (Tdap) immunization and protection of young infants. *Clin Infect Dis*. 2013;56(4):539–544
15. Maertens K, Caboré RN, Huygen K, et al. Pertussis vaccination during pregnancy in Belgium: follow-up of infants until 1 month after the fourth infant pertussis vaccination

- at 15 months of age. *Vaccine*. 2016;34(31):3613–3619
16. Englund JA, Anderson EL, Reed GF, et al. The effect of maternal antibody on the serologic response and the incidence of adverse reactions after primary immunization with acellular and whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids. *Pediatrics*. 1995;96(3 pt 2):580–584
 17. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. *JAMA*. 2014;312(18):1897–1904
 18. Sukumaran L, McCarthy NL, Kharbanda EO, et al. Association of Tdap vaccination with acute events and adverse birth outcomes among pregnant women with prior tetanus-containing immunizations. *JAMA*. 2015;314(15):1581–1587
 19. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, et al. Maternal Tdap vaccination: coverage and acute safety outcomes in the vaccine safety datalink, 2007-2013. *Vaccine*. 2016;34(7):968–973
 20. Berenson AB, Hirth JM, Rahman M, Laz TH, Rupp RE, Sarpong KO. Maternal and infant outcomes among women vaccinated against pertussis during pregnancy. *Hum Vaccin Immunother*. 2016;12(8):1965–1971
 21. Dabrera G, Amirthalingam G, Andrews N, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. *Clin Infect Dis*. 2015;60(3):333–337
 22. Winter K, Cherry JD, Harriman K. Effectiveness of prenatal tetanus, diphtheria, and acellular pertussis vaccination on pertussis severity in infants. *Clin Infect Dis*. 2017;64(1):9–14
 23. Amirthalingam G, Campbell H, Ribeiro S, et al. Sustained effectiveness of the maternal pertussis immunization program in England 3 years following introduction. *Clin Infect Dis*. 2016;63(suppl 4):S236–S243
 24. California Department of Public Health. Pertussis summary reports. Available at: www.cdph.ca.gov/programs/immunize/pages/pertussissummaryreports.aspx. Accessed February 6, 2017
 25. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet*. 2014;384(9953):1521–1528
 26. Winter K, Nickell S, Powell M, Harriman K. Effectiveness of prenatal versus postpartum tetanus, diphtheria, and acellular pertussis vaccination in preventing infant pertussis. *Clin Infect Dis*. 2017;64(1):3–8
 27. Maertens K, Caboré RN, Huygen K, Hens N, Van Damme P, Leuridan E. Pertussis vaccination during pregnancy in Belgium: results of a prospective controlled cohort study. *Vaccine*. 2016;34(1):142–150
 28. Farrington CP. Estimation of vaccine effectiveness using the screening method. *Int J Epidemiol*. 1993;22(4):742–746

Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis

Roger Baxter, Joan Bartlett, Bruce Fireman, Edwin Lewis and Nicola P. Klein

Pediatrics; originally published online April 3, 2017;

DOI: 10.1542/peds.2016-4091

Updated Information & Services	including high resolution figures, can be found at: /content/early/2017/03/30/peds.2016-4091.full.html
References	This article cites 27 articles, 12 of which can be accessed free at: /content/early/2017/03/30/peds.2016-4091.full.html#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Infectious Disease /cgi/collection/infectious_diseases_sub Vaccine/Immunization /cgi/collection/vaccine:immunization_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: /site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: /site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2017 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis

Roger Baxter, Joan Bartlett, Bruce Fireman, Edwin Lewis and Nicola P. Klein

Pediatrics; originally published online April 3, 2017;

DOI: 10.1542/peds.2016-4091

The online version of this article, along with updated information and services, is located on the World Wide Web at:

[/content/early/2017/03/30/peds.2016-4091.full.html](http://content.early/2017/03/30/peds.2016-4091.full.html)

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2017 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

