First Pertussis Vaccine Dose and Prevention of Infant Mortality

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abstract

BACKGROUND: American infants are at highest risk of severe pertussis and death. We investigated the role of ≥1 pertussis vaccinations in preventing pertussis-related deaths and risk markers for death among infants aged <42 days.

METHODS: We analyzed characteristics of fatal and nonfatal infant pertussis cases reported nationally during 1991–2008. Infants were categorized into 2 age groups on the basis of eligibility to receive a first pertussis vaccine dose at age 6 weeks; dose 1 was considered valid if given ≥14 days before illness onset. Multivariable logistic regression was used to estimate the effect of ≥1 pertussis vaccine doses on outcome and risk markers.

RESULTS: Pertussis-related deaths occurred among 258 of 45 404 cases. Fatal and nonfatal cases were confirmed by culture (54% vs 49%) and polymerase chain reaction (31% vs 27%). All deaths occurred before age 34 weeks at illness onset; 64% occurred before age 6 weeks. Among infants aged ≥42 days, receiving ≥1 doses of vaccine protected against death (adjusted odds ratio [aOR]: 0.28; 95% confidence interval [CI]: 0.11–0.74), hospitalization (aOR: 0.69; 95% CI: 0.63–0.77), and pneumonia (aOR: 0.80; 95% CI: 0.68–0.95). Risk was elevated for Hispanic ethnicity (aOR: 2.28; 95% CI: 1.36–3.83) and American Indian/Alaska Native race (aOR: 5.15; 95% CI: 2.37–11.2) and lower for recommended antibiotic treatment (aOR: 0.28; 95% CI: 0.16–0.47). Among infants aged <42 days, risk was elevated for Hispanic ethnicity and lower with recommended antibiotic use.

CONCLUSIONS: The first pertussis vaccine dose and antibiotic treatment protect against death, hospitalization, and pneumonia.

WHAT'S KNOWN ON THIS SUBJECT: Few studies have established the protective efficacy of 1 to 3 primary doses of diphtheria-tetanus-whole-cell pertussis (DTwP)/diphtheria-tetanus-acellular pertussis (DTaP) vaccines against pertussis, hospitalization, or pertussis complications in infants. However, vaccine effectiveness against infant pertussis death has not been previously reported.

WHAT THIS STUDY ADDS: This is the first study to report the protective role of ≥1 DTwP/DTaP doses among vaccine-eligible infants aged ≥6 weeks against death, hospitalization, and complications from pertussis. It describes risk markers for death among vaccine-ineligible infants aged <6 weeks.

ARTICLE

Pertussis causes significant morbidity and deaths, particularly among unvaccinated infants.[1–5] The trend in pertussis infant morbidity has increased steadily since 1977,[6–8] and the fatality rate increased at an average 9% annually during the 1990s, with Hispanics being overrepresented compared with the general population.[2] Most deaths occurred in infants who were either age-ineligible to commence the routine childhood immunization series at 2 months of age with combined diphtheria and tetanus toxoids and either whole-cell pertussis (wP) or acellular pertussis (aP) vaccines (diphtheria-tetanus-whole-cell pertussis [DTwP]/diphtheria-tetanus-acellular pertussis [DTaP]) or had received <3 DTwP/DTaP doses by age 6 months.[2]

Before 1997, wP vaccines were used exclusively for the primary childhood series but are now unavailable in the United States. In 1997, the Advisory Committee on Immunization Practices (ACIP) recommended that aP vaccines be used in the primary childhood series,[9] and aP vaccines have now completely replaced wP vaccines. Licensed aP vaccines may contain 2 to 5 pertussis antigens.[9,10] A licensed monovalent DTaP product was used from 1998 to 2000. Acellular vaccines with ≥3 antigenic components showed higher efficacy than 1- or 2-component vaccines and matched the protection afforded by wP vaccines.[11]

The ACIP recommends that children receive 5 doses of DTaP vaccine at ages 2, 4, 6, 15 to 18 months and at 4 to 6 years of age.[12] National coverage rates with 3 doses of DTwP/DTaP vaccines by 6 months of age were sustained at >90% over the past 2 decades.[13] In many countries, DTwP/DTaP vaccination routinely starts at 6 weeks of age. Studies have established the protective efficacy of DTwP/DTaP vaccines against pertussis,[14,15] hospitalization,[1,16] or pertussis complications in infants[15]

when 1 to 3 doses are administered by 6 months of age.[14–17] However, the protective role of each vaccine dose against death has not been reported. We evaluated the role of ≥1 DTwP/DTaP vaccinations in preventing deaths, hospitalizations, and complications from pertussis among infants aged ≥6 weeks and describe risk markers for fatal pertussis among infants aged <6 weeks who were age-ineligible for vaccination.

METHODS

An infant was defined as a child aged <365 days. We reviewed all confirmed or probable cases of nonfatal and fatal infant pertussis with disease onset from 1991 through 2008 reported to the National Notifiable Diseases Surveillance System (NNDSS) and the Centers for Disease Control and Prevention. The NNDSS is a passive reporting surveillance system that is dependent on electronically reported cases from all states every week[18]. Since 1990, the Council for State and Territorial Epidemiologists defined a clinically compatible case as an illness with cough lasting for ≥2 weeks plus 1 classic pertussis symptom (ie, paroxysms, whoop, or posttussive vomiting) and without any other cause. Clinically compatible cases were reported as probable cases. A clinically compatible case was classified as confirmed if *Bordetella pertussis* was isolated by culture from a nasopharyngeal swab or if epidemiologically linked to a culture-confirmed case. In 1995, the case definition for a confirmed case was expanded to include cases with acute cough of any duration from which *B pertussis* was isolated. In 1997, the polymerase chain reaction (PCR) test was also accepted as laboratory diagnostic test for confirmation in a clinically compatible case. However, a cough illness of <2 weeks' duration and with a positive PCR test was classified as a probable case.[19] For this study,

all probable and confirmed fatal and nonfatal infant pertussis cases were included as reported. We did not ascertain case definitions by confirming minimum duration of cough or presence of a pertussis symptom. Fatal cases were verified with state and local health departments by using pertussis case and death investigation worksheets, death certificates, available hospital medical records.

Statistical Analysis

Characteristics of fatal cases were compared with those of nonfatal cases by using bivariate analysis. Characteristics included year of disease onset, date of birth, age, gender, race, ethnicity (reportable from 1995), state of residence, vaccination history (pertussis vaccine doses received), vaccine type (wP or aP), symptoms and signs (paroxysmal cough, whoop, posttussive vomiting, and apnea), complications (hospitalizations, pneumonia, encephalopathy, and seizures), antibiotic treatment (a macrolide or co-trimoxozole), and method of laboratory confirmation (eg, culture or PCR). States of residence were grouped into regions (South, West, Northeast, and Midwest) as defined in the US census.[20] A case was considered as treated with a recommended antibiotic if a macrolide (erythromycin, clarithromycin, or azithromycin) or co-trimoxozole was given during the course of illness.[21] We evaluated the association between each characteristic and fatal pertussis by Pearson's χ^2 test and also estimated odds ratios (ORs) and 95% confidence intervals (CIs). The case fatality rate (CFR) was calculated as follows: (number of infant pertussis deaths/total number of infant pertussis cases) × 100.

The first pertussis vaccine dose is routinely administered from 56 days (8 weeks) of age.[12] However, the current ACIP recommendation allows for the first dose to be administered

as early as 6 weeks of age, particularly during outbreaks.[12,22] The timing of the first dose was considered to be valid if it was received ≥42 days after birth. The timing of the second and third pertussis vaccine doses were considered valid if they met the minimum age criteria for administering each respective dose (10 weeks for dose 2, 14 weeks for dose 3) and a minimum interval of 4 weeks between the 3 doses.[22] Because protection due to vaccination is unlikely to start from the day of vaccination, for our primary analysis we considered a dose as being effective if it was administered ≥14 days before the illness-onset date.[14]

The data were analyzed separately for infants aged <42 days who were ineligible to receive any dose of vaccine and for infants aged ≥42 days who were eligible to receive at least 1 dose of vaccine before the date of onset of disease. In addition, data were separately analyzed for infants who were between 56 and 90 days of age and eligible to routinely receive their first dose of vaccine under the routine childhood immunization schedule. We also investigated the effect of vaccine type (wP or aP) on fatal outcome.

We performed multivariable analysis to select independent variables for inclusion in a logistic regression model using a backward-elimination procedure. Candidate independent variables included age at onset of illness, gender, race, ethnicity, region of residence, recommended antibiotics during course of illness, and number of valid doses of pertussis vaccinations before illness onset. Age at onset (days) was treated as a continuous variable for model parsimony and was included with ethnicity in every model irrespective of its statistical significance. Separate analyses were performed for vaccine-ineligible infants aged <42 days, vaccine-eligible infants aged ≥42 days, and infants aged 56 to 90 days.

Last, we estimated the burden of fatal pertussis cases that could potentially be averted by timely vaccination with the first dose administered routinely at 56 to 90 days, and as early as 42 days of age.

Because not all reported cases were laboratory-confirmed and may have included false-positive reports, we refit multivariable models for cases that were laboratory-confirmed either by culture or PCR. Last, we performed multivariable analysis using 4 pertussis complications (hospitalization, pneumonia, encephalopathy, and seizures) as independent outcomes in a similar manner as for fatal outcome. All analyses were performed by using SAS software, version 9.3.23 (SAS Institute, Cary, NC).

RESULTS

From 1991 through 2008, pertussis-related deaths had occurred in 258 (0.57%) of 45 404 reported infant cases. In the bivariate analysis, an increased odds of a fatal outcome was shown in cases with Hispanic ethnicity, American Indian/Alaska Native race, southern region of residence, apnea, and pertussis-associated complications; a lower odds of fatal outcome was associated with cases with paroxysmal cough, whoop, or treatment with a recommended antibiotic (Table 1). The CFR among Hispanic infants was significantly higher than in non-Hispanic infants (1.26% vs 0.75%) (Table 1), even after the analysis was restricted to the period 1995–2008 when race/ethnicity was reportable. All fatal cases and 90% of nonfatal cases occurred among infants before age 34 weeks at illness onset (Fig 1). The CFR declined with increasing age, from 2.36% at age 1 week to 0.28% at age 12 weeks (Fig 1B), and was similar among boys and girls (0.53% vs 0.62%; P = .21).

Among infants aged <42 days of age (Table 2), the odds of a fatal outcome decreased with increasing weeks of

age (P < .01) and was higher for infants with Hispanic than for those with non-Hispanic ethnicity (OR: 1.46; 95% CI: 1.07–2.01; P = .02) and higher among cases from the South (OR: 2.31; 95% CI: 1.31–4.07) and West (OR: 1.78: 95% CI: 1.01–3.15) regions compared with those from the Northeast (referent). Among infants aged ≥42 days (Table 2), the odds of a fatal outcome decreased with each increasing week of age (P < .01) and was higher for infants with Hispanic compared with those with non-Hispanic ethnicity (OR: 1.64; 95% CI: 1.07–2.50) and for American Indian/Alaska Native race (OR: 3.7; 95% CI: 1.77–7.75); however, geographic region of residence was not associated with fatal pertussis.

Among infants aged ≥42 days, vaccination data were known for 91 (99%) cases and 15 291 (45%) of nonfatal cases; vaccination status was unknown for 1 fatal case and 18 807 nonfatal cases. When compared with no vaccine dose, the receipt of ≥1 pertussis vaccine doses was strongly protective against fatal pertussis (OR: 0.17; 95% CI: 0.08–0.36) (Table 2). The protective effect persisted in our sensitivity analyses, which assumed that all cases with unknown vaccination status were either vaccinated (OR: 0.04; 95% CI: 0.02–0.09) or unvaccinated (OR: 0.50; 95% CI: 0.24–1.03) (P = .06) (Table 2).

Multivariable Analysis

Among age-eligible infants (age ≥42 days), the receipt of ≥1 pertussis vaccine doses was associated with a 72% decrease in the estimated relative risk of fatal pertussis (adjusted OR [aOR]: 0.28; 95% CI: 0.11–0.74) after adjusting for age at onset, Hispanic ethnicity, race, and treatment with a recommended antibiotic (Table 3). The association strengthened (aOR: 0.20; 95% CI: 0.06–0.68) when only culture- or PCR-confirmed cases were included in the model. No fatal case but 2638 nonfatal cases had unknown

TABLE 1 Characteristics of All Fatal and Nonfatal Pertussis Cases in Infants: United States, 1991–2008

Characteristic	Fatal Cases, n (%)	Nonfatal Cases, n (%)	CFR[a]	P[b]	OR (95% CI)
Total	258 (100)	45 146 (100)	0.57		
Gender					
Male	121 (46.9)	22 780 (50.8)	0.53	.21	1.00 (Referent)
Female	137 (53.1)	22 039 (49.2)	0.62	—	1.17 (0.92–1.50)
Unknown, n, % missing	0, 0	327, 0.7	—	—	—
Race					
White	195 (82.3)	20 707 (78.2)	0.93	<.01	1.00 (Referent)
Black	25 (10.5)	4344 (16.4)	0.57	—	0.61 (0.40–0.93)
American Indian/Alaska Native	13 (5.5)	689 (2.6)	1.85	—	2.00 (1.14–3.53)
Asian/Pacific Islander	4 (1.7)	738 (2.8)	0.54	—	0.58 (0.21–1.55)
Other or unknown, n, % missing	21, 8.1	18 668, 41.4	—	—	—
Ethnicity					
Hispanic	111 (45.1)	8701 (32.8)	1.26	<.01	1.69 (1.31–2.17)
Non-Hispanic	135 (54.9)	17 860 (67.2)	0.75	—	1.00 (Referent)
Unknown, n, % missing	12, 4.7	18 585, 41.2	—	—	—
Region					
Northeast	25 (9.7)	7083 (15.7)	0.35	<.01	1.00 (Referent)
Midwest	52 (20.2)	11 599 (25.7)	0.45	—	1.27 (0.79–2.05)
South	92 (35.7)	12 154 (26.9)	0.75	—	2.14 (1.38–3.34)
West	89 (34.5)	14 310 (31.7)	0.62	—	1.76 (1.13–2.75)
Diagnosis					
Culture	136 (53.8)	14 403 (49.2)	0.94	.03	1.00 (Referent)
PCR	79 (31.2)	8017 (27.4)	0.98	—	1.04 (0.79–1.38)
Epidemiologic link	9 (3.6)	1229 (4.2)	0.73	—	0.78 (0.39–1.53)
DFA	28 (11.1)	5507 (18.8)	0.51	—	0.54 (0.36–0.81)
Serology	1 (0.4)	114 (0.4)	0.87	—	0.93 (0.13–6.70)
Unknown, n, % missing	5, 1.9	15 876, 35.2	—	—	—
Symptoms					
Any cough					
Yes	255 (99.6)	35 936 (99.8)	0.70	.64	0.64 (0.09–4.60)
No	1 (0.4)	90 (0.2)	1.10	—	1.00 (Referent)
Unknown, n, % missing	2, 0.1	9120, 20.2	—	—	—
Cough duration,[c] n, median (IQR), d	77, 14 (10– 23)	21 190, 24 (17–34)	—	—	—
Paroxysmal cough					
Yes	182 (82)	31 469 (90.9)	0.58	<.01	0.46 (0.32–0.64)
No	40 (18)	3155 (9.1)	1.25	—	1.00 (Referent)
Unknown, n, % missing	36, 14.0	10 522, 23.3	—	—	—
Apnea					
Yes	176 (76.2)	18 739 (55.6)	0.93	<.01	2.55 (1.88–3.46)
No	55 (23.8)	14 944 (44.4)	0.37	—	1.00 (Referent)
Unknown, n, % missing	27, 10.5	11 463, 25.4	—	—	—
Whoop					
Yes	82 (41.2)	18 578 (56.1)	0.44	<.01	0.55 (0.41–0.73)
No	117 (58.8)	14 546 (43.9)	0.80	—	1.00 (Referent)
Unknown, n, % missing	59, 22.9	12 022, 26.6	—	—	—
Posttussive vomiting					
Yes	133 (61.3)	22 893 (66.7)	0.58	.09	0.79 (0.60–1.04)
No	84 (38.7)	11 431 (33.3)	0.73	—	1.00 (Referent)
Unknown, n, % missing	41, 15.9	10 822, 24.0	—	—	—
Complications					
Hospitalized					
Yes	249 (98.4)	21 820 (63.4)	1.13	<.01	36.0 (13.4–96.6)
No	4 (1.6)	12 604 (36.6)	0.03	—	1.00 (Referent)
Unknown, n, % missing	5, 1.9	10 722, 23.7	—	—	—
Pneumonia					
Positive	201 (90.5)	4008 (19.6)	4.78	<.01	39.3 (25.0–61.6)
Negative	21 (9.5)	16 442 (80.4)	0.13	—	1.00 (Referent)
Unknown, n, % missing	36, 14.0	24 696, 54.7	—	—	—
Encephalopathy					
Yes	20 (9.9)	82 (0.2)	19.61	<.01	45.5 (27.3–75.7)
No	182 (90.1)	33 925 (99.8)	0.53	—	1.00 (Referent)
Unknown, n, % missing	56, 21.7%	11 139, 24.7	—	—	—

TABLE 1 Continued

Characteristic	Fatal Cases, n (%)	Nonfatal Cases, n (%)	CFR[a]	P[b]	OR (95% CI)
Seizures					
Yes	33 (16.0)	491 (1.5)	6.30	<.01	12.8 (8.7–18.7)
No	173 (84.0)	32 899 (98.5)	0.52	—	1.00 (Referent)
Unknown, n, % missing	52, 20.2	11 756, 26.0	—	—	—
Recommended antibiotics during course of illness					
Yes	156 (73.2)	28 941 (85.9)	0.54	<.01	0. 45 (0.33–0.61)
No or none	57 (27.8)	4734 (14.1)	1.19	—	1.00 (Referent)
Unknown, n, % missing	45, 17.4	11 471, 25.4			
Gestational age[d]		Not collected			
<32 weeks	20 (10.3)				
32–35 weeks	40 (20.5)				
≥36 weeks	135 (69.2)				
Unknown, n, % missing	63, 24.4				
Maternal age[d]		Not collected			
<20 years	48 (28.7)				
20–24 years	51 (30.5)				
≥25 years	68 (40.7)				
Unknown, n, % missing	91, 35.3				
Age at disease onset,[d] n, median (IQR), wk	258, 4 (2–7)	45 146, 10 (6–19)			
Age at death,[d] n, median (IQR), d	258, 51 (31–75)	—			

IQR, interquartile range; —, not applicable.

[a] (Number of deaths/number of cases) × 100.

[b] Pearson's χ^2 test.

[c] Of those coughing at final interview.

[d] Of those with available information.

vaccination status but had known values for the other variables included in the final model; in a sensitivity analysis and assuming that all of these cases with unknown vaccination had received 1 previous pertussis vaccination, the aOR was 0.10 (95% CI: 0.04–0.26), and assuming that all of these cases with unknown vaccination were unvaccinated, the aOR was 0.47 (95% CI: 0.18–1.23).

In a multivariable analysis that included only infants aged 56 to 90 days (the age when the first dose of pertussis vaccine is usually administered during the 2-month pediatric visit), data on 28 fatal cases and 2901 nonfatal cases were included in a model that adjusted for age at onset, Hispanic ethnicity, race, receipt of a recommended antibiotic, and pertussis vaccination (≥1 vs 0 doses). In this analysis, we found a similar effect of vaccination (aOR: 0.28; 95% CI: 0.03–2.24) as that for all infants ≥42 days of age (Table 3). Among infants aged 56 to 90 days with pertussis confirmed by culture-

or PCR (24 fatal cases and 2006 nonfatal cases), and including the same covariates, the effect of a single dose of vaccine was similar (aOR: 0.34; 95% CI: 0.04–2.81).

The protective effect of ≥1 doses of pertussis vaccine among all infants ≥42 days of age was clearly shown against hospitalization (aOR: 0.69; 95% CI: 0.63–0.77) and pneumonia (aOR: 0.80; 95% CI: 0.68–0.95) (Table 4) but not against seizures and encephalopathy.

Information on vaccine type (wP or aP) or brand was poorly reported, and we were unable to directly compare any effect of receiving wP versus aP vaccines during the study period. We used 2 time periods (1991–1996 and 1997–2008) as surrogates for vaccine type. Before 1997, wP vaccines were used exclusively. The ACIP recommended the aP vaccine for use in the primary series among infants in the United States in late 1996. Most infants born after 2000 likely received the DTaP vaccine as the first 3 doses of the series. The protective effect of

a pertussis vaccine dose was greater (Table 3) among cases reported during the DTaP period (1997–2008; aOR: 0.17; 95% CI: 0.04–0.73) compared with the DTwP period (1991–1996; aOR: 0.67; 95% CI: 0.11–2.82).

Preventing Pertussis Deaths by On-Time DTwP/DTaP Vaccination

In the analysis that included only infants eligible for their first dose (aged 56–90 days) and assuming that the first dose provided 72% protection (aOR: 0.28, above) and all infants received their first dose of pertussis vaccine at exactly age 8 weeks, then 41 (72%) of the 57 deaths that occurred after age 8 weeks could have been averted for an overall reduction of 16% (41 of 258) of all infant pertussis deaths.

We also fit the final multivariable model for infants aged ≥42 days where the number of doses of pertussis vaccinations was 0, 1, or ≥2 doses and found protective effects for the first dose (aOR: 0.27; 95% CI: 0.10–0.76) and for ≥2 doses (aOR:

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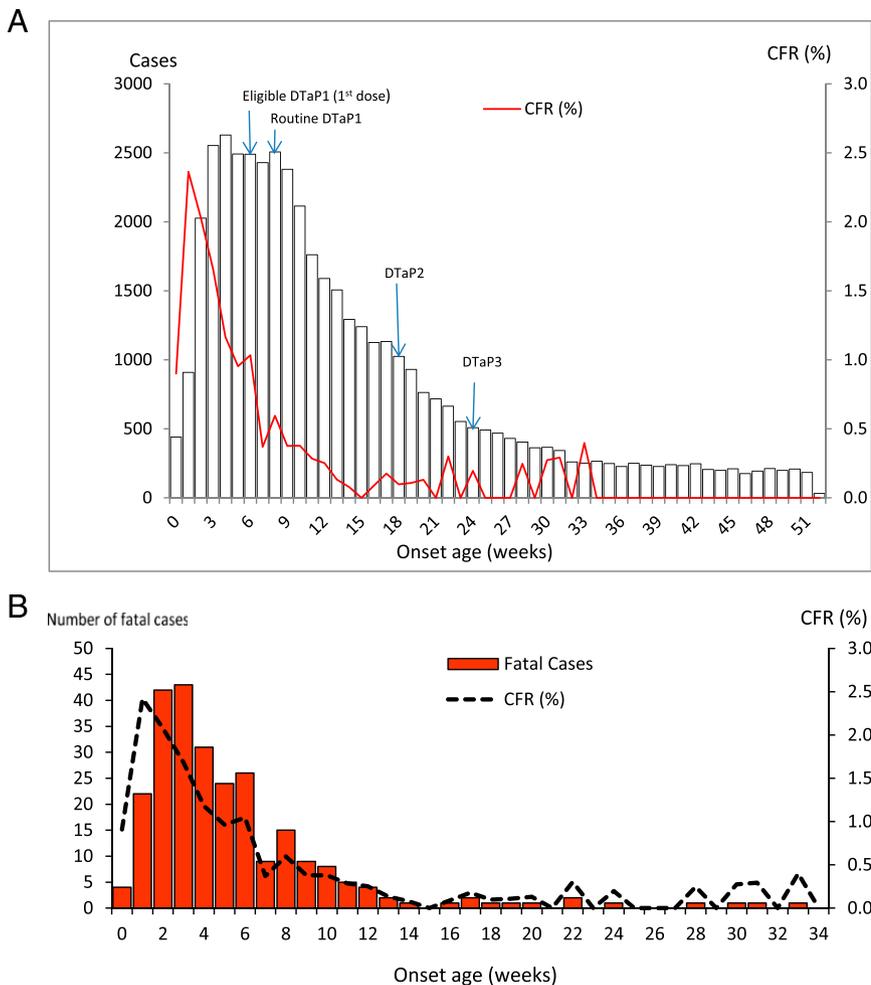
FIGURE 1

A, Distribution of pertussis cases by age at disease onset and CFR: United States, 1991–2008. B, Distribution of fatal cases and CFR by age at disease onset in infants: United States, 1991–2008.

0.38; 95% CI: 0.04–3.33) when compared with no dose. On the basis of these results, assuming that the first dose provided 73% protection against death and if all infants received their first dose of pertussis vaccine at exactly age 6 weeks (42 days), then 68 (74%) of the 92 deaths that occurred after age 42 days would have been averted for an overall reduction of 26% (68 of 258) of all infant pertussis deaths.

DISCUSSION

Among vaccine-eligible infants, our study shows a protective effect of ≥1 doses of pertussis vaccine in preventing pertussis-associated deaths, hospitalizations, and pneumonia. The protective effect persisted even after controlling for other potential risk markers, age at illness onset, Hispanic ethnicity, race, and use of a recommended antibiotic. Because only 2 fatal cases received ≥2 doses, we were unable to explore a vaccine dose-response. Although the protective effect of 1 dose of vaccine was also separately shown during the period when DTaP vaccines were exclusively administered, this effect was not statistically significant during the "DTP period." In outbreak situations, clinicians may attempt to commence vaccination at 6 weeks rather than at the 2-month well-child office visit when the vaccine is routinely given. Other routinely recommended vaccines at 2 months can also be given at this visit.

Although *B pertussis* possesses a range of antigenic factors, there is no established serologic correlate of protection with a quantifiable protective antibody response against any antigen. Because the first vaccine dose does not result in measurable antipertussis antibody levels, other mechanisms may be operative. The biological plausibility of 1 dose to evoke a cellular immune response was shown in murine[24–26] and nonhuman primate[27–29] studies. A T helper (Th) 1/Th17 cellular immune response and elimination of *B pertussis* organisms follows natural infection or vaccination with wP vaccines in murine[24–26] and baboon[28] models. However, a Th2/Th1, although predominantly Th2-mediated, humoral response is promoted by aP vaccination even though other cell-mediated cytokine pathways may also exist.[30–32] Additional studies are required to elucidate the mechanism of vaccine-induced cellular immune response to 1 pertussis vaccine dose because this pathway is not fully understood.

Vaccine-ineligible infants (aged <42 days) can develop severe disease and fatal complications. In this study, 24% of nonfatal infant cases and 64% of infant deaths occurred among infants aged <42 days. Because our findings suggest infant vaccination could potentially avert 16% to 26% of all infant deaths, additional strategies are required to enhance immunity in newborns or to reduce exposure to *B pertussis* among vaccine-ineligible infants. In 2012, the ACIP recommended the use of a dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap) during each pregnancy to provide passive transplacental maternal antibodies and to likely protect the newborn(s) during the period before the first DTaP dose.[33] The role of maternal immunization in preventing infant pertussis was shown in baboons.[34] The safety and effectiveness of maternal immunization when the

TABLE 2 Selected Characteristics of Fatal and Nonfatal Pertussis in Infants, by Age at Onset of Pertussis: United States, 1991–2008

Characteristic	<42 Days Old					≥42 Days Old				
	Fatal Cases, n (%)	Nonfatal Cases, n (%)	CFR	P^a	OR (95% CI)	Fatal Cases, n (%)	Nonfatal Cases, n (%)	CFR	P^a	OR (95% CI)
Total	166 (100)	11 048 (100)	1.48			92 (100)	34 098 (100)	0.27		
Age at onset of illness										
0–6 days	4 (2.4)	440 (4.0)	0.90	<.01	1.00 (Referent)	NA	NA	NA		NA
7–13 days	22 (13.2)	909 (8.2)	2.36		2.66 (0.91–7.77)	NA	NA	NA		NA
14–20 days	42 (25.3)	2026 (18.3)	2.03		2.28 (0.81–6.39)	NA	NA	NA		NA
21–27 days	43 (25.9)	2553 (23.1)	1.66		1.85 (0.66–5.19)	NA	NA	NA		NA
28–34 days	31 (18.7)	2629 (23.8)	1.17		1.30 (0.46–3.69)	NA	NA	NA		NA
35–41 days	24 (14.5)	2491 (22.6)	0.95		1.06 (0.37–3.07)	NA	NA	NA		NA
42–48 days	NA	NA	NA		NA	26 (28.3)	2490 (7.3)	1.03	<.01	1.00 (Referent)
49–55 days	NA	NA	NA		NA	9 (9.8)	2428 (7.1)	0.37		0.36 (0.17–0.76)
56–62 days	NA	NA	NA		NA	15 (16.3)	2506 (7.4)	0.60		0.57 (0.30–1.08)
63–69 days	NA	NA	NA		NA	9 (9.8)	2381 (7.0)	0.38		0.36 (0.17–0.77)
70–76 days	NA	NA	NA		NA	8 (8.7)	2115 (6.2)	0.38		0.36 (0.16–0.80)
77–83 days	NA	NA	NA		NA	5 (5.4)	1761 (5.2)	0.28		0.27 (0.10–0.71)
84–364 days	NA	NA	NA		NA	20 (21.7)	20 417 (59.9)	0.10		0.09 (0.05–0.17)
Gender										
Male	73 (44.0)	5450 (49.7)	1.32	.14	1.00 (Referent)	48 (52.2)	17 330 (51.2)	0.28	.85	1.00 (Referent)
Female	93 (56.0)	5517 (50.3)	1.66		1.26 (0.92–1.71)	44 (47.8)	16 522 (48.8)	0.27		0.96 (0.64–1.45)
Unknown, n, % missing	0, 0	81, 0.7				0, 0	246, 0.7			
Race										
White	129 (86.0)	5171 (79.2)	2.43	.12	1.00 (Referent)	66 (75.9)	15 536 (77.9)	0.42	<.01	1.00 (Referent)
Black	14 (9.3)	966 (14.8)	1.43		0.58 (0.33–1.01)	11 (12.6)	3378 (16.9)	0.32		0.77 (0.40–1.45)
AI/AN	5 (3.3)	180 (2.8)	2.70		1.11 (0.45–2.75)	8 (9.2)	509 (2.6)	1.55		3.70 (1.77–7.75)
A/PI	2 (1.3)	215 (3.3)	0.92		0.37 (0.09–1.52)	2 (2.3)	523 (2.6)	0.38		0.90 (0.22–3.68)
Other/unknown, n, % missing	16, 9.6	4516, 40.9				5, 5.4	14 152, 41.5			
Ethnicity										
Hispanic	74 (46.5)	2582 (37.3)	2.79	.02	1.46 (1.07–2.01)	37 (42.5)	6119 (31.2)	0.60	.02	1.64 (1.07–2.50)
Non-Hispanic	85 (53.5)	4341 (62.7)	1.92		1.00 (Referent)	50 (57.5)	13 519 (68.8)	0.37		1.00 (Referent)
Unknown, n, % missing	7, 4.2	4125, 37.3				5, 5.4	14 460, 42.4			
Region										
Northeast	15 (9.0)	1687 (15.3)	0.88	<.01	1.00 (Referent)	10 (10.9)	5396 (15.8)	0.18	.53	1.00 (Referent)
Midwest	29 (17.5)	2580 (23.4)	1.11		1.26 (0.68–2.36)	23 (25.0)	9019 (26.4)	0.25		1.38 (0.65–2.89)
South	64 (38.6)	3115 (28.2)	2.01		2.31 (1.31–4.07)	28 (30.4)	9039 (26.5)	0.31		1.67 (0.81–3.44)
West	58 (34.9)	3666 (33.2)	1.56		1.78 (1.01–3.15)	31 (33.7)	10 644 (31.2)	0.29		1.57 (0.77–3.21)
Recommended antibiotics during course of illness										
Yes	104 (74.8)	7517 (88.3)	1.36	<.01	0.39 (0.27–0.58)	52 (70.3)	21 424 (85.2)	0.24	<.01	0.41 (0.25–0.68)
No or none	35 (25.2)	997 (11.7)	3.39		1.00 (Referent)	22 (29.7)	3737 (14.8)	0.59		1.00 (Referent)
Unknown, n, % missing	27, 16.3	2534, 22.9				18, 19.6	8937, 26.2			
Number of valid doses of pertussis vaccinations before illness onset[b]										
0	NA	NA	NA		NA	83 (91.2)	9838 (64.3)	0.84	<.01	1.00 (Referent)
≥1	NA	NA	NA		NA	8 (8.8)[c]	5453 (35.7)[d]	0.15		0.17 (0.08–0.36)[e]
Unknown, n, % missing	NA	NA	NA		NA	1, 1.1	18 807, 55.2			

AI/AN, American Indian/Alaska Native; A/PI, Asian/Pacific Islander; NA, not applicable.

[a] Pearson's χ^2 test.

[b] Doses of pertussis vaccine were counted as valid if they were administered ≥14 days before illness onset.

[c] Seven fatal cases reported 1 dose, 0 fatal cases reported 2 doses, and 1 fatal case reported 3 doses.

[d] A total of 3674 nonfatal cases reported 1 dose, 917 nonfatal cases reported 2 doses, and 862 nonfatal cases reported 3 doses.

[e] One fatal case and 18 807 nonfatal cases had unknown vaccination status; assuming that all of these cases were truly vaccinated, the OR (95% CI) was 0.04 (0.02–0.09), and assuming that all of these cases were truly not vaccinated, the OR (95% CI) was 0.50 (0.24–1.03) (P = .06).

vaccine is administered at least 1 week before delivery in preventing disease and deaths in infants <3 months of age have been reported in England.[35,36] In addition to reducing exposure among newborns to sick household members, the ACIP recommends a strategy of "cocooning,"[37] which requires that persons who are likely to be in contact with the newborn be up-to-date with vaccination with an age-appropriate pertussis vaccine (DTaP, Tdap). A recent study in Tdap-vaccinated baboons challenged with B pertussis exposure showed protection from disease but not colonization,[38] and these animals transmitted

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TABLE 3 Multivariable Analysis of Factors Associated With Fatal Pertussis in All Infants and in Culture- or PCR-Positive infants, by Age at Onset of Pertussis: United States, 1991–2008

Characteristic	OR (95% CI) for All Infants		OR (95% CI) for Culture- or PCR-Positive Infants	
	<42 Days Old (n = 133 f, 5360 nf)[a]	≥42 Days Old (n = 66 f, 9001 nf)[b]	<42 Days Old (n = 110 f, 3593 nf)[a]	≥42 Days Old (n = 53 f, 5950 nf)[b]
Age at onset of illness (days)	0.976 (0.960–0.992)	0.990 (0.984–0.997)	0.973 (0.955–0.991)	0.991 (0.984–0.999)
Ethnicity				
Hispanic	1.49 (1.06–2.11)	2.28 (1.36–3.83)	1.45 (0.99–2.13)	2.16 (1.20–3.91)
Non-Hispanic	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Race	Not included		Not included	
White		1.00 (Referent)		1.00 (Referent)
Black		0.92 (0.40–2.09)		0.96 (0.39–2.37)
AI/AN		5.15 (2.37–11.2)		6.67 (2.84–15.6)
A/PI		1.39 (0.33–5.90)		1.82 (0.42–7.84)
Recommended antibiotics during course of illness				
Yes	0.43 (0.29–0.64)	0.28 (0.16–0.47)	0.42 (0.27–0.65)	0.27 (0.15–0.49)
No or none	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Number of valid doses of pertussis vaccinations before illness onset[c]				
0	NA	1.00 (Referent)	NA	1.00 (Referent)
≥1	NA	0.28 (0.11–0.74)[d]	NA	0.20 (0.06–0.68)

AI/AN, Native American/Alaska Native; A/PI, Asian/Pacific Islander; f, fatal cases; NA, not applicable; nf, nonfatal cases.

[a] The model included age at onset of illness, ethnicity, and recommended antibiotics during course of illness.

[b] The model included age at onset of illness, race, ethnicity, recommended antibiotics during course of illness, and number of valid doses of pertussis vaccinations before illness onset.

[c] Doses of pertussis vaccine were counted as valid if they were administered ≥14 days before illness onset.

[d] The aOR (95% CI) of applying this model to all infants aged 56 to 90 days, where the race categories AI/AN and A/PI were pooled to avoid model-fitting problems due to small numbers of fatal cases (28 fatal cases, 2901 nonfatal cases), was 0.28 (0.03–2.24) and for culture- or PCR-confirmed cases (24 fatal and 2006 nonfatal cases) was 0.34 (0.04–2.81). The aOR (95% CI) of applying this model to the wP vaccine era (1991–1996), where age was categorized into 2 groups on the basis of median age (<99 days, ≥99 days) to avoid model-fitting problems due to a small number of fatal cases (15 fatal cases, 835 nonfatal cases), was 0.67 (0.11–2.82); and the aOR (95% CI) of applying the original model with age as a continuous variable to the DTaP vaccine era (1997–2008; 51 fatal cases, 8166 nonfatal cases) was 0.17 (0.04–0.73).

infection to naive contacts. However, although aP-vaccinated persons may be colonized, transmission usually occurs from symptomatic persons. The "cocooning" strategy is also programmatically challenging to implement[39] and requires further evaluation. Last, a potential strategy to actively enhance immunity in newborns is to introduce a dose of DTaP,[40] an aP vaccine,[41,42] or another novel vaccine[43,44] at or shortly after birth. However, a stand-alone aP vaccine is not commercially available and few immunogenicity studies have been conducted to evaluate the protective effect of a birth dose of DTaP or aP vaccines[40–42] or the potential interference of the birth dose on antibody response to subsequent vaccine doses in the primary series.

NNDSS data may not have uniformly captured all fatal[2] or nonfatal cases due to underreporting. Our results are unlikely to have been biased, because it is unlikely that there was preferential underreporting of vaccinated cases compared with unvaccinated cases. It is also unlikely that incompletely vaccinated cases were less likely to be tested, diagnosed, and reported because providers are aware that 3 doses are needed for protection. Incomplete vaccine-related data prevented an evaluation of different aP (2–5 antigens) or wP vaccine types. Gestational age was not a data element in the NNDSS and prevented evaluation of prematurity risk.[45–48]

TABLE 4 Multivariable Analysis of Effect of ≥1 Pertussis Vaccine Doses on Death and Complications Among infants ≥42 Days Old: United States, 1991–2008

Outcome[a]	Number With Outcome in the Model		Effect of Pertussis Vaccine Doses (≥1 vs 0), OR (95% CI)
	Yes	No	
Death[b]	66	9001	0.28 (0.11–0.74)
Hospitalization[c]	4748	3999	0.69 (0.63–0.77)
Pneumonia[d]	947	4069	0.80 (0.68–0.95)
Encephalopathy[e]	27	8599	1.40 (0.56–3.46)
Seizures[e]	107	8524	0.82 (0.52–1.29)

[a] Each outcome was modeled separately and did not include any other outcome as an independent variable.

[b] The model included age at onset of illness, race, ethnicity, recommended antibiotics during course of illness, and number of valid doses of pertussis vaccinations before illness onset.

[c] The model included age at onset of illness, race, ethnicity, recommended antibiotics during course of illness, gender, region, and number of valid doses of pertussis vaccinations before illness onset.

[d] The model included age at onset of illness, race, ethnicity, recommended antibiotics during course of illness, region, and number of valid doses of pertussis vaccinations before illness onset.

[e] The model included age at onset of illness, race, ethnicity, and number of valid doses of pertussis vaccinations before illness onset.

CONCLUSIONS

Health professionals should ensure on-time first-dose pertussis

vaccination as early as 6 weeks of age during pertussis outbreaks and provide early recommended antibiotic treatment. The recommendations apply globally and particularly in countries where DTP/DTaP vaccinations routinely begin at 6 weeks of age. Infants who are age-ineligible for vaccination will benefit from strengthening strategies that provide immunity to newborns and prevent exposure to *B pertussis*.

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First Pertussis Vaccine Dose and Prevention of Infant Mortality

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