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Reduced Severity of Pertussis in Persons with Age-Appropriate Pertussis Vaccination — United States, 2010–2012

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Abstract

Background—In 2012, over 48,000 pertussis cases were reported in the United States. Many cases occurred in vaccinated persons, showing that pertussis vaccination does not prevent all pertussis cases. However, pertussis vaccination may have an impact on disease severity.

Methods—We analyzed data on probable and confirmed pertussis cases reported through Enhanced Pertussis Surveillance (Emerging Infections Program Network) between 2010 and 2012. Surveillance data were collected through physician and patient interview and vaccine registries. We assessed whether having received an age-appropriate number of pertussis vaccines (AAV) (for persons aged ≥3 months) was associated with reduced odds of post-tussive vomiting, a marker of more clinically significant illness, or of severe pertussis (seizure, encephalopathy, pneumonia, and/or hospitalization). Adjusted odds ratios (aOR) were calculated using multivariable logistic regression.

Results—Among 9,801 pertussis patients aged ≥3 months, 77.6% were AAV. AAV status was associated with a 60% reduction in odds of severe disease in children 7 months–6 years old in multivariable logistic regression and a 30% reduction in odds of post-tussive vomiting in persons aged 19 months–64 years.

Conclusions—Serious pertussis symptoms and complications are less common among AAV pertussis patients, demonstrating that the positive impact of pertussis vaccination extends beyond decreasing risk of disease.

Keywords

Pertussis; vaccination; DTaP; Tdap; severity

Background

Pertussis, or whooping cough, is a highly contagious respiratory illness caused by the bacterium *Bordetella pertussis*. Symptoms include paroxysmal cough, post-tussive vomiting, apnea, and the characteristic “whoop”, especially in children [1]. The illness has a broad clinical spectrum, ranging from a mild cough to a severe illness with complications that can include cracked ribs, pneumonia, or, especially in infants, death [2].

Whole-cell pertussis vaccines were introduced in the United States in the 1940s; they were replaced by acellular vaccines during the 1990s due to concerns about adverse reactions [3,4]. The current Advisory Committee on Immunization Practices (ACIP) pertussis vaccine recommendations include a 5-dose primary series with DTaP (diphtheria toxoid-, tetanus

toxoid-, and acellular pertussis-containing) vaccine for children 2 months through 6 years of age [5] and an adolescent booster dose of Tdap (tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis) vaccine at 11 or 12 years of age [6]. Older adolescents and adults who have not previously received Tdap are also recommended to receive a single dose of Tdap [6]. In October 2012, ACIP recommended that women receive a dose of Tdap during each pregnancy to protect infants through maternal antibody transfer [7]. US DTaP coverage is high: between 2008 and 2012, 83–85% of children aged 19–35 months had received ≥4 doses of DTaP [8]. Meanwhile, Tdap coverage among adolescents has increased steadily since its licensure in 2005, and in 2012, 85% of adolescents aged 13–17 years had received Tdap [9]. Although Tdap coverage has also increased among adults ≥19 years of age, only 14% of adults had received one Tdap dose in 2012 [10].

Despite high vaccination coverage in children and adolescents, the incidence of pertussis in the United States has been increasing since the late 1980s, with large outbreaks of disease in 2004–2005, 2010, and 2012. In 2012, 48,277 pertussis cases were reported in the United States, the largest number since 1955 [11]. Numerous studies have documented waning immunity following acellular pertussis vaccination [12–14, reviewed in 15]. This waning immunity is likely a major contributor to the resurgence in disease [16] and explains the large proportion of US pertussis cases occurring among fully vaccinated individuals [17].

An important question is whether pertussis vaccination protects against severe disease. Previous analyses have suggested that pertussis infection is less severe in immunized children [18–26]; however, most of these studies were conducted in primarily whole-cell primed populations and many had sample sizes too small to fully assess confounding variables such as age, which is highly associated with both vaccination status and severity of pertussis illness. An exception is a recent analysis by Barlow et al. which found that vaccinated children and adolescents in the Portland, Oregon metropolitan area, who had received primarily acellular vaccine, had decreased severity and duration of illness compared to unvaccinated peers [18]. However, it was not clear whether these findings could be extended to a broader population. In addition, there are few data on pertussis severity among Tdap-vaccinated adults.

Here we describe the impact of pertussis immunization on disease severity in a population that includes children and adolescents vaccinated primarily with acellular pertussis vaccines as well as adults eligible to receive Tdap. We use data collected through the multistate Emerging Infections Program Network's Enhanced Pertussis Surveillance (EPS) system to assess whether pertussis patients with age-appropriate vaccination were less likely to report serious pertussis symptoms or complications compared with unvaccinated or undervaccinated cases.

Methods

The analysis included pertussis cases in persons aged ≥3 months reported through EPS with cough onset between January 1, 2010 and December 31, 2012 [27]. Cases were reported statewide from Connecticut, Minnesota, and New Mexico, and from selected counties in Colorado (five Denver counties), New York (15 Rochester and Albany counties), and

Oregon (three Portland counties). Cases were included if they met the Council of State and Territorial Epidemiologists' 2010–2013 probable or confirmed case definitions [28]:

- Probable case: Cough illness lasting ≥2 weeks and at least one of the following symptoms: paroxysms, inspiratory whoop, or post-tussive vomiting
- Confirmed case: Probable case with positive PCR or epidemiologic link to a laboratory-confirmed case; *OR* cough of any duration with isolation of *B. pertussis*.[1]

Information on pertussis-containing vaccines that patients received was collected routinely by EPS surveillance staff. After report of a case, surveillance staff collected vaccination history using medical records, state immunization registries, patient shot cards, school vaccine records, or patient self-report if other sources were not available. Information on pertussis vaccines received ≥2 weeks prior to cough onset was used to classify pertussis patients as having received an age-appropriate number of pertussis vaccinations (AAV) or not (nAAV), consistent with ACIP guidelines (Table 1). For persons aged ≥7 years not previously vaccinated for pertussis, a single dose of Tdap is recommended [29–30]. Because of this recommendation and the high frequency of missing data on childhood vaccinations in older age groups, adolescents and adults aged ≥13 were considered AAV if they had received a single dose of Tdap, regardless of other vaccination history. Vaccinations received after cough onset or less than 2 weeks prior to cough onset were not counted for determination of AAV status, and patients were considered unvaccinated if they had only received pertussis vaccinations within 2 weeks prior to cough onset or after cough onset.

Post-tussive vomiting was used as a marker of more clinically significant pertussis illness. We defined "severe disease" as one or more of the following: hospitalization, seizure, encephalopathy, positive x-ray for pneumonia, or death. Patients were classified as having received antibiotic treatment if they received an antibiotic recommended for the treatment of pertussis during the course of their infection [31].

Data were analyzed in SAS 9.3 (Cary, NC). To assess effect modification and confounding by age, cases aged ≤19 years were stratified by patient age groups corresponding to the number of doses needed to be classified as AAV[2]. Adults were classified into two age groups: 20–64 years and ≥65 years. Odds ratios (OR) were calculated using bivariate logistic regression to compare clinical characteristics of patients who were AAV vs. nAAV for pertussis vaccination (ages ≥3 months). Association of vaccination status with other patient characteristics, including patient state of residence, sex, race, ethnicity, and timing of antibiotic treatment, was assessed to identify potential confounders.

For multivariable logistic regression, we created two models: one using AAV status to predict post-tussive vomiting and a second using AAV status to predict severe disease. In each model, we included all age groups with similar, statistically significant ($p<0.05$)

[1]In outbreak settings, outbreak-associated cases with cough illness lasting at least 2 weeks could also be reported as confirmed cases

[2]Age groups: 3–4 months (1 dose required to be AAV); 5–6 months (2 doses); 7–18 months (3 doses); 19 months–6 years (4 doses); 7–12 years (5 doses, or 4 with 4th dose received after the 4th birthday); and 13–19 years (6 doses, or 5 with 4th dose received after the 4th birthday; or Tdap received).

unadjusted ORs for the relationship between the relevant vaccination and clinical variables in the bivariate analysis. The models included all variables that were significant ($p<0.05$) in bivariate analysis as well as a continuous age variable.

For patients 3 months to 19 years of age, we also classified patients as having ever or never received a pertussis vaccination and repeated the bivariate and multivariate analyses using this variable instead of AAV status. We considered patients to have ever received a pertussis containing vaccine if they had documentation or self-report of pertussis vaccine receipt ≥2 weeks prior to cough onset; or if they had received ≥3 diphtheria-, tetanus-, or pertussis-containing vaccines of unknown type (i.e. not known whether the vaccines contained tetanus and/or diphtheria antigens only or also contained pertussis). Logistic regression was used to assess time since Tdap vaccination (in years) as a predictor of post-tussive vomiting or severe disease among adolescents and adults.

Results

A total of 9,801 cases in patients aged ≥3 months were included in the analysis; 7,733 (78.9%) were under 20 years of age and 55.8% were aged 7–19 years (Table 2). Overall 44.9% of patients reported post-tussive vomiting (Table 3). One or more of the complications classified as severe disease were identified in 3.2% of cases; the most common complications were positive x-ray for pneumonia (N=170, 1.8%) and hospitalization (N=156, 1.6%). No deaths were reported. Both post-tussive vomiting and severe disease were significantly more common among laboratory confirmed cases compared with non-laboratory confirmed cases (post-tussive vomiting: OR 1.15, 95% CI 1.05–1.26, p = 0.0019; severe disease: OR 1.61, 95% CI 1.20–2.15, p = 0.0014). Of patients aged ≥3 months, 77.6% were AAV for pertussis vaccination. Over 99% of patients with known antibiotic treatment status received an antibiotic for pertussis but the timing of antibiotic treatment varied from <7 days to ≥21 days after cough onset.

In bivariate logistic regression including patients from all age groups, we found that AAV status was protective against both post-tussive vomiting and severe disease (Table 4). Odds of post-tussive vomiting were highest among patients 3 months to 6 years of age and tended to decrease with increasing age (Table 4). Odds of post-tussive vomiting were also higher among patients with longer delays between cough onset and treatment initiation. Post-tussive vomiting was also associated with state of residence, race, and ethnicity, with increased odds of post-tussive vomiting among American Indian/Alaskan Native, African American, and Other race individuals and among Hispanic individuals compared with white and Non-Hispanic persons, respectively. Odds of severe disease were highest among those aged 3–6 months and decreased with age before increasing again in persons aged ≥20 years and reaching a second peak in those aged ≥65 years. Odds of severe disease were also associated with state of residence.

After stratifying by age, we found that being AAV for pertussis vaccination was protective against post-tussive vomiting only in the 19 month–6 year, 7–12 year, 13–19 year, and 20–64 year age groups and was protective against severe disease in the 7–18 month and 19 month–6 year age groups (Table 5). We also assessed the number of pertussis-containing

vaccines received and found reduced odds of post-tussive vomiting in individuals who received 5 doses (19 month–6 year and 7–12 year age groups) or 6 doses (13–19 year age group) compared to those who received just one fewer dose (Supplementary Table 1). A similar analysis could not be conducted for severe disease due to the small number of cases with severe disease. In addition to assessing AAV status in 13–19 year olds, a sub-analysis was performed including only individuals aged 16–19 years, who would have been expected to receive at least one dose of whole-cell pertussis vaccine if vaccinated according to ACIP guidelines. Findings in this age group were similar to those in the full 13–19 year old age category: AAV status was associated with reduced odds of post-tussive vomiting (OR 0.68, 95% CI 0.47–0.97, p=0.04) but not with severe disease (OR 1.76, 95% CI 0.48–6.37, p=0.39).

Multivariable models were constructed using all variables that were significant in the bivariate analysis, including age, state, race, ethnicity, AAV status, and timing of antibiotic treatment. The magnitude of association between vaccination status and clinical outcomes were similar across age groups in which a significant association between vaccination status and clinical outcome was detected in the bivariate analysis. Therefore, for the multivariable model for post-tussive vomiting, we combined all age groups that were significant in the bivariate analysis (19 months–64 years of age) and used a continuous variable for age. AAV status was associated with an approximately 30% reduction in odds of post-tussive vomiting after adjustment for confounders (Table 6). A multivariable model was also constructed to predict severe disease in persons 7 months–6 years of age; in this model, AAV status remained associated with an approximately 60% decrease in odds of severe disease (Table 6).

For patients aged 3 months to 19 years, we repeated the analyses after re-classifying patients as having ever or never received a pertussis vaccination. Overall, 91.9% of patients in this age group had received at least one pertussis-containing vaccine. Results were similar to the results for AAV status in both bivariate and multivariable analysis, with the exception that having ever been vaccinated for pertussis was not protective against post-tussive vomiting among persons aged 13–19 years (data not shown). A similar analysis was not attempted for older patients due to the high frequency of missing vaccination data for individuals aged ≥20 years.

Finally, we assessed whether the odds of post-tussive vomiting or severe disease increased with time since last pertussis vaccination. Due to the strong association between the outcomes of interest and age in younger age groups and the high collinearity of age and time since vaccination, we restricted this analysis to time since Tdap vaccination among adolescents and adults aged ≥13 years. We found a marginally significant association with each additional year since Tdap vaccination associated with a 1.33-fold increased odds of severe disease (95% CI 1.00–1.76, p = 0.049) among adolescents aged 13–19 years; no association between time since Tdap receipt and post-tussive vomiting or severe disease was observed for any other age group (data not shown).

Discussion

Although waning immunity from acellular pertussis vaccines has contributed to a resurgence of pertussis cases in fully-vaccinated individuals [12–15], our analysis provides reassurance that pertussis is less severe in fully vaccinated individuals compared to individuals who are not up-to-date for pertussis vaccines. Findings from our study are consistent with an analysis by Barlow et al., which demonstrated that pertussis patients aged 6 weeks to 18 years who had ever received pertussis vaccination were less likely to be hospitalized or to develop severe illness [18]. Importantly, and in contrast to prior studies that focused exclusively on children age 18 and under [18–26], our analysis also included adults. We found that the protective effect of pertussis vaccination against more serious disease extends to adults, demonstrating that, although acellular pertussis vaccines have a diminished duration of protection from infection compared with whole-cell vaccines, both the childhood and adult ACIP pertussis vaccine recommendations lead to a reduction in the clinical severity of pertussis across all age groups.

In our analysis, the majority of adults and adolescents aged ≥16 would likely have received one or more doses of whole-cell pertussis vaccine as children based on their age and the date of introduction of acellular vaccines [2,3]. There is substantial evidence showing that individuals who have received at least one whole-cell pertussis vaccine have slower waning of immunity than individuals who have received only acellular pertussis vaccines [15]. It will therefore be important to continue monitoring the impact of adult pertussis vaccination as individuals who have received exclusively acellular pertussis vaccines reach adulthood.

Pertussis illness is most serious in young infants, and the primary goal of the US pertussis vaccination program is to prevent serious illness and deaths in this vulnerable age group. Although our analysis did not show a protective effect of vaccination against severe disease in children under 7 months of age, our data included relatively few cases in this age group – especially among those not fully vaccinated – and therefore had limited power to detect such an effect. A previous analysis of pertussis severity in infants demonstrated that receipt of even one pertussis vaccine dose is protective against severe disease and death in infants [32], highlighting the importance of receiving DTaP promptly at 2 months of age according to ACIP guidelines [5]. CDC further recommends that all pregnant women receive Tdap during every pregnancy to prevent serious illness and death among infants too young to receive vaccines [7]. Because the recommendation for Tdap receipt during pregnancy was not implemented until 2013 [7], we could not assess the impact of Tdap vaccination during pregnancy in our analysis.

Although our findings suggest that pertussis vaccination is protective against severe pertussis illness, one alternate explanation for this finding is that people who have received pertussis vaccines may have different healthcare-seeking behaviors or different access to care than people who do not receive vaccines. An association between vaccination and care-seeking behavior has previously been described for several other vaccines [33–35]; meanwhile, reduced access to care has previously been reported to disproportionately affect African American, Hispanic, and American Indian/Alaskan Native populations in the United States [36,37]. For either or both of these reasons, vaccinated individuals may be more likely to

receive care rapidly upon becoming ill, thus receiving antibiotic treatment earlier and reducing illness severity. However, although vaccinated individuals in our analysis were more likely to have received antibiotic treatment earlier in the course of their illness (data not shown), vaccination, antibiotic treatment timing, race, and ethnicity all remained significant in multivariable analysis of factors associated with post-tussive vomiting. These findings affirm the importance of both vaccination and early antibiotic treatment in mitigating pertussis severity. The impact of access to care on pertussis vaccination and treatment remains an important area for further study.

The availability of EPS surveillance data was critical for this analysis, as EPS features improved data completeness and enhanced verification of vaccination status compared to pertussis data collected through the US National Notifiable Diseases Surveillance System [27]. Nevertheless, the use of surveillance data in this analysis presented several challenges. Surveillance data include only pertussis cases that meet the clinical case definition, and so mild pertussis cases that do not meet this definition could not be included in our analysis. Furthermore, as most sites did not capture data on the full duration of cough due to resource limitations, we were not able to assess whether pertussis vaccination might be associated with a shorter duration of cough in pertussis cases as was recently shown by Barlow et al. [18]. In addition, although EPS sites make extensive efforts to confirm patient vaccination status, some persons with incomplete vaccination histories may still have been misclassified as unvaccinated or having not received an age-appropriate number of vaccinations. It is also possible that some unvaccinated or under-vaccinated persons may have been misclassified as having received age-appropriate vaccination based on erroneous self-report. Non-systematic misclassification of vaccination status would most likely bias our estimates towards the null, resulting in an underestimate of the true impact of pertussis vaccination on serious pertussis symptoms and complications.

By demonstrating that vaccinated children and adults are more likely to have less severe pertussis disease, our analysis highlights a benefit of the US pertussis vaccination program that extends beyond decreasing risk of disease. The impact of pertussis vaccination on lessening disease severity is particularly important given the resurgence of pertussis that is being observed among vaccinated persons in the United States. Although currently available pertussis vaccines cannot prevent all cases of pertussis illness, adherence to ACIP pertussis vaccine recommendations for infants, children, and adults remain critical to reduce pertussis-associated morbidity and mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary

Analysis of US surveillance data demonstrates that both severe and clinically-significant pertussis illness are less common among patients who have received age-appropriate vaccination for pertussis, demonstrating that the positive impact of pertussis vaccination extends beyond decreasing risk of disease.

Table 1

Age-Appropriate Vaccination (AAV) Definitions

Category	Yes	No	Unknown
Age 3 months–12 years	• Patient received recommended number of pertussis vaccinations for age	• Patient reported not receiving any pertussis vaccinations and no documentation of vaccination was found • Patient received at least one pertussis vaccine, but not the full number recommended for age	• Not known whether patient had ever received a pertussis-containing vaccine • Patient received at least one pertussis vaccine, but number of pertussis vaccines received could not be verified (and more than one is recommended based on age)
Age ≥13 years	• Patient received recommended number of pertussis vaccinations for age • Patient received 1 or more doses of Tdap, regardless of other vaccination history	• Patient reported not receiving any pertussis vaccinations and no documentation of vaccination was found • Patient received at least one pertussis vaccine, but not the full number recommended for age AND had not received Tdap	• Not known whether patient had ever received a pertussis-containing vaccine • Patient received at least one pertussis vaccine, but neither Tdap receipt nor number of pertussis vaccines received could be verified

Table 2

Demographic characteristics of pertussis case in patients aged 3 months and older (N = 9,801)

Characteristic	N	%
State of residence		
Colorado	1208	12.3
Connecticut	224	2.3
Minnesota	5773	58.9
New Mexico	1097	11.2
New York	637	6.5
Oregon	862	8.8
Sex		
Male	4448	45.4
Female	5323	54.3
Unknown	30	0.3
Pregnancy at cough onset (females aged 15–44)		
Non-pregnant	1119	80.7
Pregnant	41	3.0
Unknown	227	16.4
Race		
White	8006	81.7
American Indian and Alaskan Natives	113	1.2
Asian/Pacific Islander	190	1.9
African American	389	4.0
Other	195	2.0
Unknown	908	9.3
Ethnicity		
Non-Hispanic	7578	77.3
Hispanic	1467	15.0
Unknown	756	7.7
Age		
3–4 months	194	2.0
5–6 months	115	1.2
7–18 months	366	3.7
19 months – 6 years	1596	16.3
7–12 years	3378	34.5
13–19 years	2084	21.3
20–64 years	1902	19.4
65+ years	166	1.7

Table 3

Clinical characteristics and vaccination status of pertussis cases in patients aged 3 months and older (N = 9,801).

Characteristic	N with non-missing information	% with characteristic
Laboratory confirmation		
Culture or PCR positive for *B. pertussis*	9801	72.6
Cardinal pertussis symptoms		
Paroxysmal cough	9764	96.4
Whoop	9529	28.7
Apnea	9563	24.8
Post-tussive vomiting	9662	44.9
Seizure	9665	0.2
Encephalopathy	9635	0.1
Positive x-ray for pneumonia	9535	1.8
Hospitalization	9690	1.6
Death	9792	0
Severe disease[1]	9362	3.2
Vaccination status		
Age-appropriate vaccination	8170	77.6
Timing of antibiotic treatment after cough onset		
< 7 days		20.2
7–13 days		32.2
14–20 days	9222	23.2
21+ days		23.8
Never		0.7

[1] Severe disease defined as having one or more of: seizure, encephalopathy, positive x-ray for pneumonia, hospitalization, or death

Table 4

Bivariate associations of case characteristics with post-tussive vomiting and severe disease. OR and p-values from logistic regression.

		Post-tussive vomiting				Severe disease				
Characteristic	**Total**	**N (%)**	**OR**	**95% CI**	**p-value**	**Total**	**N (%)**	**OR**	**95% CI**	**p-value**
Age										
3–4 months	187	115 (61.5)	**2.15**	**1.59–2.91**		180	34 (18.9)	**16.50**	**10.26–26.54**	
5–6 months	114	62 (54.4)	**1.61**	**1.10–2.34**		105	14 (13.3)	**10.90**	**5.78–20.57**	
7–18 months	360	238 (66.1)	**2.63**	**2.09–3.30**		352	25 (7.1)	**5.42**	**3.28–8.95**	
19 months – 6 years	1581	912 (57.7)	**1.84**	**1.63–2.07**	**<0.0001**	1524	43 (2.8)	**2.06**	**1.35–3.14**	**<0.0001**
7–12 years	3338	1422 (42.6)		Ref		3234	45 (1.4)		Ref	
13–19 years	2054	803 (39.1)	**0.87**	**0.77–0.97**		1999	34 (1.7)	1.23	0.78–1.92	
20–64 years	1866	744 (39.9)	0.89	0.80–1.0		1812	77 (4.2)	**3.15**	**2.17–4.56**	
65+ years	162	47 (29.0)	**0.55**	**0.39–0.78**		156	24 (15.4)	**12.89**	**7.62–21.78**	
State of residence										
Colorado	1199	674 (56.2)	**1.96**	**1.73–2.22**		1186	53 (4.5)	**1.79**	**1.30–2.47**	
Connecticut	224	104 (46.4)	**1.32**	**1.01–1.73**		220	11 (5.0)	**2.01**	**1.07–3.78**	
Minnesota	5692	2254 (39.6)		Ref	**<0.0001**	5533	141 (2.5)		Ref	**0.0016**
New Mexico	1075	567 (52.7)	1.70	1.49–1.94		1055	44 (4.2)	**1.66**	**1.18–2.35**	
New York	618	280 (45.3)	**1.26**	**1.07–1.49**		570	18 (3.2)	1.25	0.76–2.05	
Oregon	854	464 (54.3)	**1.82**	**1.57–2.10**		798	29 (3.6)	1.44	0.96–2.17	
Sex										
Male	4383	1934 (44.1)		Ref	0.15	4246	145 (3.4)		Ref	0.20
Female	5250	2394 (45.6)	1.06	0.98–1.15		5088	150 (2.9)	0.86	0.68–1.08	
Race										
White	7933	3445 (43.4)		Ref		7694	228 (3.0)		Ref	
American Indian and Alaskan Native	109	71 (65.1)	**2.43**	**1.64–3.62**		104	5 (4.8)	1.65	0.67–4.10	
Asian/Pacific Islander	188	92 (48.9)	1.25	0.94–1.67	**<0.0001**	186	6 (3.2)	1.09	0.48–2.49	0.24
African American	371	221 (59.6)	**1.92**	**1.55–2.37**		369	18 (4.9)	1.68	1.03–2.75	
Other	192	115 (59.9)	**1.95**	**1.45–2.61**		192	7 (3.6)	1.24	0.58–2.67	
Ethnicity										

		Post-tussive vomiting					Severe disease			
Characteristic	**Total**	**N (%)**	**OR**	**95% CI**	**p-value**	**Total**	**N (%)**	**OR**	**95% CI**	**p-value**
Non-Hispanic	7495	3221 (43.0)		Ref	**<0.0001**	7305	219 (3.0)		Ref	0.25
Hispanic	1449	815 (56.3)	**1.71**	**1.52–1.91**		1398	50 (3.6)	1.20	0.88–1.64	
Age-appropriate vaccination										
No	1804	941 (52.2)		Ref	**<0.0001**	1728	71 (4.1)		Ref	**0.0002**
Yes	6265	2762 (44.1)	**0.73**	**0.65–0.81**		6091	146 (2.4)	**0.58**	**0.43–0.78**	
Antibiotic treatment (days after cough onset)										
<7	1841	671 (36.5)		Ref		1797	53 (3.0)		Ref	
7–13	2935	1280 (43.6)	**1.35**	**1.20–1.52**		2850	86 (3.0)	1.02	0.72–1.45	
14–20	2108	1022 (48.5)	**1.64**	**1.44–1.86**	**<0.0001**	2053	63 (3.1)	1.04	0.72–1.51	0.63
21+	2157	1083 (50.2)	**1.76**	**1.55–2.00**		2080	66 (3.2)	1.08	0.75–1.56	
Never	57	31 (54.4)	**2.08**	**1.22–3.53**		61	4 (6.7)	2.31	0.81–6.60	

Note: significant associations are in bold.

Table 5

Bivariate associations of vaccination status with post-tussive vomiting and severe disease, stratified by age group

	Post-tussive vomiting					Severe disease				
Age-appropriate vaccination[1]	**Total**	**N (%)**	**OR**	**95% CI**	**p-value**	**Total**	**N (%)**	**OR**	**95% CI**	**p-value**
3–4 months										
Yes	144	88 (61.1)	1.02	0.44–2.33	0.97	140	24 (17.1)	1.59	0.44–5.71	0.48
No	28	17 (60.7)		Ref		26	3 (11.5)		Ref	
5–6 months										
Yes	72	39 (54.2)	0.79	0.35–1.79	0.57	68	10 (14.7)	1.12	0.32–3.91	0.86
No	35	21 (60.0)		Ref		30	4 (13.3)		Ref	
7–18 months										
Yes	233	151 (64.8)	0.80	0.50–1.30	0.34	230	11 (4.8)	**0.36**	**0.16–0.84**	**0.0179**
No	112	78 (69.6)		Ref		107	13 (12.2)		Ref	
19 months – 6 years										
Yes	1128	627 (55.6)	**0.71**	**0.56–0.90**	**0.0042**	1096	22 (2.0)	**0.40**	**0.21–0.74**	**0.0038**
No	411	262 (63.8)		Ref		388	19 (4.9)		Ref	
7–12 years										
Yes	2727	1139 (41.8)	**0.75**	**0.61–0.91**	**0.0038**	2651	37 (1.4)	0.85	0.37–1.91	0.69
No	445	218 (49.0)		Ref		425	7 (1.6)		Ref	
13–19 years										
Yes	1610	596 (37.0)	**0.66**	**0.52–0.84**	**0.005**	1567	26 (1.7)	0.92	0.38–2.25	0.85
No	342	161 (47.1)		Ref		333	6 (1.8)		Ref	
20–64 years										
Yes	335	120 (35.8)	**0.74**	**0.55–0.99**	**0.0442**	323	15 (4.6)	1.39	0.65–2.97	0.39
No	394	170 (43.2)		Ref		384	13 (3.4)		Ref	
65+ years										
Yes	16	2 (12.5)	0.29	0.055–1.49	0.14	16	1 (6.3)	0.35	0.037–3.25	0.35
No	33	11 (33.3)		Ref		31	5 (16.1)		Ref	

[1]Doses required for AAV: 1 dose for ages 3–4 months; 2 doses for ages 5–6 months; 3 doses for ages 7–18 months; 4 doses for ages 19 months–6 years; for ages 7–12 years, 5 doses, or 4 with 4th dose received after the 4th birthday; for ages 13–19 years, 6 doses, or 5 with 4th dose received after the 4th birthday; or Tdap received; and for ages ≥20 years, Tdap received regardless of other vaccination history.

Table 6

Multivariable logistic regression analysis using vaccination status and case characteristics to predict post-tussive vomiting and severe disease. **Model 1** uses age-appropriate vaccination status and other variables listed to predict post-tussive vomiting and includes persons aged 19 months–12 years and **model 2** uses age-appropriate vaccination status and other variables listed to predict severe disease and includes persons aged 7 months–6 years.

	Model 1: Post-tussive vomiting, ages 19 months–64 years, N=6262			**Model 2: Severe disease, ages 7 months–6 years, N=1570**		
	aOR	**95% CI**	**p-value (type 3)**	**aOR**	**95% CI**	**p-value (type 3)**
Age-appropriate vaccination						
No		Ref	**<0.0001**		Ref	**0.0017**
Yes	**0.71**	**0.62–0.80**		**0.41**	**0.23–0.71**	
Age (years)	**0.98**	**0.97–0.98**	**<0.0001**	**0.74**	**0.64–0.87**	**0.0002**
State of residence						
Colorado	**1.97**	**1.67–2.33**		1.20	0.56–2.56	
Connecticut	1.33	0.90–1.96		1.05	0.13–8.42	
Minnesota		Ref	**<0.0001**		Ref	0.91
New Mexico	1.54	1.24–1.93		0.75	0.21–2.73	
New York	1.16	0.93–1.44		0.53	0.12–2.30	
Oregon	1.69	1.42–2.01		1.14	0.55–2.35	
Race						
White		Ref			Ref	
American Indian and Alaskan Native	**2.26**	**1.30–3.92**		<0.001	<0.001 – >999	
Asian/Pacific Islander	1.11	0.77–1.58	**<0.0001**	1.16	0.27–5.09	0.75
African American	**2.14**	**1.63–2.81**		0.40	0.09–1.70	
Other	1.07	0.72–1.59		0.54	0.07–4.53	
Ethnicity						
Non-Hispanic		Ref	**0.0002**		Ref	0.44
Hispanic	**1.40**	**1.17–1.67**		0.71	0.31–1.67	
Antibiotic treatment (days after cough onset)						
<7		Ref			Ref	
7–13	**1.37**	**1.18–1.58**	**<0.0001**	1.26	0.57–2.81	0.73
14–20	**1.64**	**1.40–1.92**		1.08	0.46–2.55	
21+	**1.97**	**1.68–2.31**		1.68	0.75–3.77	

	Model 1: Post-tussive vomiting, ages 19 months–64 years, N=6262			Model 2: Severe disease, ages 7 months–6 years, N=1570		
	aOR	**95% CI**	**p-value (type 3)**	**aOR**	**95% CI**	**p-value (type 3)**
Never	**2.71**	**1.26–5.85**		<0.001	<0.001 – >999	