

Severe Pertussis Infections in the United States, 2011–2015

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Background. The incidence of pertussis in the United States has increased in recent years. While characteristics of severe pertussis infection have been described in infants, fewer data are available in older children and adults. In this analysis, we characterize pertussis infections in hospitalized patients of all ages.

Methods. Cases of pertussis with cough onset from 1 January 2011 through 31 December 2015 from 7 US Emerging Infections Program Network states were reviewed. Additional information on hospitalized patients was obtained through abstraction of the inpatient medical record. Descriptive and multivariable analyses were conducted to characterize severe pertussis infection and identify potential risk factors.

Results. Among 15942 cases of pertussis reported, 515 (3.2%) were hospitalized. Three hospitalized patients died. Infants aged <2 months accounted for 1.6% of all pertussis cases but 29.3% of hospitalizations. Infants aged 2–11 months and adults aged ≥65 years also had high rates of hospitalization. Infants aged <2 months whose mothers received acellular pertussis during the third trimester and children aged 2 months to 11 years who were up to date on pertussis-containing vaccines had a 43%–66% reduced risk of hospitalization. Among adolescents aged 12–20 years, 43.5% had a history of asthma, and among adults aged ≥65 years, 26.8% had a history of chronic obstructive pulmonary disease.

Conclusions. Individuals at the extreme ends of life may be the most vulnerable to severe pertussis infections, though hospitalization was reported across all age groups. Continued monitoring of severe pertussis infections will be important to help guide prevention, control, and treatment options.

Keywords. pertussis; hospitalization.

Infection due to *Bordetella pertussis* affects persons of all ages, with a clinical presentation ranging from a relatively mild-cough illness to a severe illness with pneumonia, seizures, encephalopathy, respiratory failure, and/or death [1]. Despite high coverage with pertussis-containing vaccines among children and adolescents, the incidence of pertussis has increased in the United States since the late 1980s [2–4]. More recently, older children and adolescents have accounted for an increasing proportion of infections, at least in part due to waning immunity following vaccination with acellular pertussis vaccines, which replaced whole-cell vaccines in the United States in the late 1990s [5].

While the risk for severe illness and death is greatest among infants, serious manifestations of pertussis infection are also reported in older children and adults [6]. However, characteristics of severe pertussis infections in these groups remain poorly

described. An improved understanding of severe pertussis infections across the life span will help guide prevention, control, and treatment options for those at risk for complications and death from pertussis. In this analysis, we characterize severe pertussis cases, defined as those that require hospitalization, and compare hospitalized and nonhospitalized pertussis patients, identify risk factors for hospitalization, and describe the clinical course and underlying health conditions of hospitalized pertussis patients.

METHODS

Cases of pertussis with cough onset from 1 January 2011 through 31 December 2015 were identified through Enhanced Pertussis Surveillance (EPS) as part of the Emerging Infections Program Network in 7 US states [7]. Cases were reported statewide from Connecticut, Minnesota, and New Mexico and from metropolitan areas in Colorado (5 Denver counties), Georgia (8 Atlanta counties), New York (15 counties in Rochester and Albany), and Oregon (3 Portland counties). Pertussis cases were classified according to the Council of State and Territorial Epidemiologists case definition [8].

Using information obtained from the patient's diagnosing healthcare provider and through patient interview, public health

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surveillance personnel completed a standardized case report form that included epidemiologic information, demographics, clinical presentation, and vaccination history on all pertussis cases. Vaccination status for pertussis-containing vaccines was determined by surveillance staff using medical records, state immunization registries, patient vaccination cards, school vaccine records, or, if other sources were unavailable, patient self-report. Starting in 2013, information on the receipt of maternal tetanus, diphtheria, and acellular pertussis (Tdap; tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine) vaccination during pregnancy was collected for infant cases aged <1 year. Patients aged 2 months through 11 years were considered up to date on pertussis-containing vaccines if they received all vaccines recommended for age by the Advisory Committee on Immunization Practices (ACIP). Patients aged ≥12 years were considered up to date if they had received Tdap. For this analysis, only documented vaccine doses administered at least 14 days prior to cough onset and, in the case of maternal Tdap, 14 days prior to infant birth were considered valid.

For hospitalized pertussis patients, defined as those admitted to an inpatient care facility, observation unit, or emergency department for ≥24 hours as a result of pertussis infection, additional information on the patient's clinical course, treatment, outcomes, and underlying medical conditions was abstracted from the inpatient medical record. For symptoms (eg, cyanosis, apnea) or complications (eg, pneumonia, new-onset seizures), information was collated from the provider or patient interview or documentation in any part of the medical record (eg, admission/discharge diagnoses, progress notes).

State and county-level population denominators by age group (<2 months, 2–11 months, 1–11 years, 12–20 years, 21–64 years, and ≥65 years) were obtained from the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics, and incidence was calculated as the number of confirmed or probable pertussis cases per 100 000 population. Significant differences ($P < .05$) between hospitalized and non-hospitalized pertussis patients were assessed using Pearson χ^2 or Fisher exact test statistics. Age-stratified estimates of relative risk for hospitalization and intensive care unit (ICU) admission were calculated by dividing the rate of hospitalization and ICU admission in the age group of interest by that in all other pertussis patients outside the age group.

To assess risk factors for hospitalization among pertussis patients by age group, bivariate log-linear regression with Poisson distribution and robust standard errors for the parameter estimates were used to calculate the relative risk (RR) and 95% confidence intervals (CIs) [9]. Variables associated with hospitalization at the $P \leq .10$ level in the bivariate models were retained for inclusion in multivariable models; birth weight of <2500 g was also included in the final model for infants aged <1 year due to the strong a priori suspicion of association with severe pertussis

infection. A P value of <.05 was used to determine statistical significance. All analyses were conducted using SAS 9.3.

This evaluation was determined to be public health practice and designated as nonresearch by the CDC Human Research Protection Office and therefore did not require full review by the CDC Institutional Review Board.

RESULTS

Pertussis Epidemiology and Risk of Hospitalization

From 1 January 2011 through 31 December 2015, 15 942 cases of pertussis were reported in the surveillance area, with an average annual incidence of 20.3 cases per 100 000 population. Pertussis incidence was relatively stable during 2011 and 2013–2015, ranging from 8.5 to 14.8 cases per 100 000, and peaked in 2012 with an incidence of 42.0 cases per 100 000 population. The average annual incidence by state ranged from 3.5 to 33.0 cases per 100 000 population, with a peak in incidence during 2012 reported in all sites. The proportion of pertussis patients who were hospitalized was lowest in 2012 at 2.3% and was relatively stable during 2011 and 2013–2015, ranging from 3.3% to 4.6%.

Among these cases, 15 427 (96.8%) occurred in patients treated as an outpatient and 515 (3.2%) occurred in patients who were hospitalized; 107 (21.0%) hospitalized patients required admission to the ICU. Although infants aged <2 months accounted for only 1.6% of all pertussis cases, they accounted for 29.3% of all hospitalized cases (Figure 1). Overall, compared to nonhospitalized patients, a significantly higher proportion of hospitalized patients were of a non-white race, of Hispanic ethnicity, received a macrolide antibiotic within 14 days of symptom onset, and had an infection that was laboratory confirmed by culture or polymerase chain reaction (PCR). Fewer hospitalized patients were up to date on pertussis-containing vaccines compared to nonhospitalized patients (Table 1). Three pertussis-related deaths were reported, all in hospitalized patients.

Infant patients aged <2 months had 26.2 times the risk of hospitalization (95% CI, 22.7–30.3) and 72 times the risk of ICU admission (95% CI, 50.3–103.0) compared to all other age groups combined. The RR of hospitalization and ICU admission was likewise higher among infants aged 2–11 months (RR, 7.7; 95% CI, 6.5–9.2 and RR, 6.3; 95% CI, 4.2–9.6, respectively) and adult patients aged ≥65 years (RR, 4; 95% CI, 3–5.4 and RR, 1.8; 95% CI, 0.67–4.9, respectively). The RR of hospitalization and ICU admission was low among patients in the 3 age groups between 1 and 64 years, ranging from 0.11 (95% CI, 0.07–0.17) and 0.05 (95% CI, 0.01–0.18), respectively, in 12- to 20-year-olds to 1.2 (95% CI, 0.9–1.7) and 0.8 (95% CI, 0.3–18), respectively, in 45- to 64-year-olds.

Results of the bivariate analyses are shown in Supplementary Tables 1–5. In multivariable analysis, factors associated with hospitalization differed by age group. Of note, infants aged <2 months were less likely to be hospitalized if their mother received a dose of Tdap during the third trimester of pregnancy;

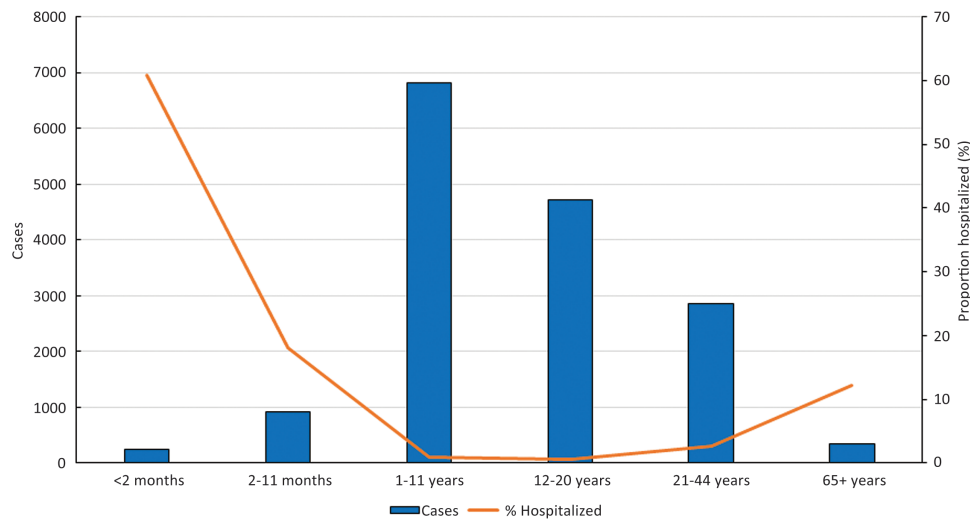


Figure 1. Number of pertussis cases and the proportion hospitalized by age group at Enhanced Pertussis Surveillance sites, United States, 2011–2015.

similarly, children aged 2 months to 11 years were less likely to be hospitalized if they were up to date with pertussis vaccines. Patients aged 2 months to 20 years of Hispanic ethnicity had an increased risk of hospitalization. Additionally, patients aged ≥ 2 months with more than 1 physician visit prior to diagnosis were more likely to be hospitalized (Table 2).

Clinical Characteristics of Hospitalized Patients

Overall, the most common hospital admission diagnoses included cough (39.2%), “pertussis” (33.2%), respiratory distress and/or failure (16.1%), bronchiolitis or bronchitis (10.3%), and pneumonia (7.7%), though differences in admission diagnosis were noted by age group (Table 3). Among all hospitalized patients ($n = 515$), the median length of time from onset to hospitalization was 11 days, ranging from 7 days in infants aged <2 months to 17 days in persons aged ≥ 65 years. The median length of hospital stay was 3 days, ranging from 1.8 days in children aged 1 to 11 years to 5.9 days among infants aged <2 months. Traditional pertussis clinical symptoms were more commonly reported in hospitalized patients compared to nonhospitalized patients; symptoms included paroxysmal cough (98.1% vs 95.9%, $P = .01$), post-tussive vomiting (61.2% vs 46.6%, $P < .01$), whoop (48.4% vs 28.9%, $P < .01$), cyanosis (44.1% vs 1.7%, $P < .01$), and apnea (35.7% vs 23.4%, $P < .01$).

Among patients who were tested during their hospitalization, 31 of 350 (8.9%) had a maximum white blood cell (WBC) count that surpassed $30 \times 10^9/L$ (previously associated with an increased risk of pertussis-related infant deaths [10]), and 54 of 271 (19.9%) had a viral codetection (diagnosed through PCR, direct fluorescent antibody testing, culture, or rapid antigen tests). Overall, 127 (24.7%) of hospitalized pertussis patients developed pneumonia, 3.1% developed new-onset seizures, and 1.4% developed encephalopathy (Table 4). In contrast, 254 (1.7%) of all nonhospitalized patients were reported to have

pneumonia, with none reporting new-onset seizures and 17 (0.1%) reporting encephalopathy.

At least 1 underlying medical condition was reported in 168 (32.6%) hospitalized patients; this was most commonly observed among adults aged ≥ 21 years (102/117, 87.2%). Asthma was frequently reported as an underlying condition among patients aged ≥ 1 year. Among adolescents aged 12 to 20 years, a relatively high proportion had an underlying immune, neurologic, and/or genetic disorder compared to other age groups. A high proportion of adults aged ≥ 21 years ($n = 117$) were obese (47.9%), current/former smoker (31.6%), had asthma (26.5%), had diabetes (23.9%), had a potentially immunocompromising condition (19.7%), or had chronic obstructive pulmonary disease (COPD; 18.8%) (Table 4).

Three hospitalized pertussis patients died from their infection: an infant aged 42 days and 2 adults aged 48 years and 76 years. All 3 developed respiratory failure that required mechanical ventilation. The infant was born full term with low birth weight and had a history of neonatal abstinence syndrome and prior history of cardiac arrest. This infant had rhinovirus codetection, a maximum WBC count of $48.5 \times 10^9/L$, and required extracorporeal membrane oxygenation (ECMO) for 20 days before death. The patient aged 48 years had a history of human immunodeficiency virus infection and developed pneumonia, sepsis (not further described), and encephalopathy. This patient had a normal WBC of $8.71 \times 10^9/L$. The patient aged 76 years had a previous history of asthma and COPD, was reported to have influenza A (though test results not reported through chart review), a maximum WBC count of $19.5 \times 10^9/L$, and developed pneumonia (not further described).

DISCUSSION

The reported incidence of pertussis has been increasing in the United States despite high coverage with pertussis-containing

Table 1. Characteristics of Pertussis Patients by Hospitalization Status at Enhanced Pertussis Surveillance Sites, United States, 2011–2015

Characteristic	Hospitalization Status			P Value
	All Cases (N = 15942)	Not Hospitalized (N = 15427)	Hospitalized (N = 515)	
	[Total Known (%) N (%)]	[Total Known (%) N (%)]	[Total Known (%) N (%)]	
State of residence	[15942 (100.0)]	[15427 (100.0)]	[515 (100.0)]	<.01
Colorado	3179 (19.9)	3055 (19.8)	124 (24.1)	...
Connecticut	492 (3.1)	439 (2.3)	53 (10.3)	...
Georgia	278 (1.7)	246 (1.6)	32 (6.2)	...
Minnesota	7173 (45.0)	7047 (45.7)	126 (24.5)	...
New Mexico	2410 (15.1)	2306 (15.0)	104 (20.2)	...
New York	1040 (6.5)	1010 (6.7)	30 (5.8)	...
Oregon	1370 (8.6)	1324 (8.7)	46 (8.9)	...
Age	[15905 (99.8)]	[15390 (99.8)]	[515 (100.0)]	...
<2 months	248 (1.6)	97 (0.6)	151 (29.3)	<.01
2–11 months	924 (5.8)	758 (4.9)	166 (31.9)	...
1–11 years	6808 (42.8)	6750 (43.8)	58 (11.4)	...
12–20 years	4725 (29.6)	4702 (30.6)	23 (4.5)	...
21–64 years	2864 (18.0)	2788 (18.1)	76 (14.8)	...
≥65 years	336 (2.1)	295 (1.9)	41 (8.3)	...
Sex	[15902 (99.7)]	[15389 (99.8)]	[513 (99.8)]	...
Male	7312 (46.0)	7070 (46.0)	242 (47.2)	.58
Female	8590 (54.0)	8319 (54.0)	271 (52.8)	...
Race	[14794 (92.8)]	[14325 (92.9)]	[469 (91.1)]	...
White	13056 (88.3)	12695 (88.6)	361 (77.0)	<.01
Black	654 (4.4)	604 (4.2)	50 (10.7)	...
Other ^a	1084 (7.3)	1026 (7.2)	58 (12.4)	...
Ethnicity	[15026 (94.3)]	[14530 (94.2)]	[496 (96.3)]	...
Hispanic	3108 (20.7)	2927 (20.1)	181 (36.5)	<.01
Not Hispanic	11918 (79.3)	11603 (79.9)	315 (63.5)	...
Birth weight (age <1 year) ^a	[944 (78.1)]	[668 (74.9)]	[276 (87.1)]	...
<2500 g	88 (9.3)	60 (9.0)	28 (10.1)	.58
≥2500 g	856 (90.7)	608 (91.0)	243 (89.9)	...
Maternal age <20 years (age <1 year) ^b	[1011 (83.60)]	[722 (80.9)]	[289 (91.2)]	...
Yes	114 (11.3)	73 (10.1)	41 (14.2)	.06
No	897 (88.7)	649 (89.9)	248 (85.8)	...
Maternal tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine during pregnancy (age <2 months) ^c	[103 (92.8)]	[38 (95.0)]	[65 (91.5)]	...
Third trimester	17 (16.5)	11 (29.0)	6 (9.2)	.03
First or second trimester	6 (5.8)	2 (5.2)	4 (6.2)	...
No documented pregnancy doses	80 (77.7)	25 (65.8)	55 (84.6)	...
Pertussis vaccines up-to-date (age ≥2 months) ^d	[13202 (84.1)]	[12935 (84.4)]	[267 (73.4)]	...
Yes	9836 (74.5)	9692 (74.9)	144 (53.9)	<.01
No	3366 (25.5)	3243 (25.1)	123 (46.1)	...
Macrolide antibiotics within 14 days of onset	[15837 (99.4)]	[15327 (99.4)]	[510 (99.0)]	...
Yes	7594 (48.0)	7284 (47.5)	310 (60.8)	<.01
No	8243 (52.0)	8043 (52.5)	200 (39.2)	...
>1 Physician visit prior to pertussis diagnosis	[14739 (92.5)]	[14224 (92.2)]	[515 (100.0)]	...
Yes	1860 (12.6)	1670 (11.7)	190 (36.9)	<.01
No	12879 (87.4)	12554 (88.3)	325 (63.1)	...
Laboratory confirmed (culture and/or polymerase chain reaction)	[15942 (100.0)]	[15427 (100.0)]	[515 (100.0)]	...
Yes	11538 (72.4)	11084 (71.9)	454 (88.2)	<.01
No	4404 (27.6)	4343 (27.2)	61 (11.8)	...
Outcome	[15940 (99.9)]	[15425 (99.9)]	[515 (100.0)]	...
Survived	15937 (99.98)	15425 (100.0)	512 (99.4)	<.01
Died	3 (0.02)	0 (0.0)	3 (0.6)	...

^aIncludes Native Americans, Asian/Pacific Islanders, multiple races, and other race (not specified).

^bDenominators: all (N = 1209), not hospitalized (N = 892), hospitalized (N = 317).

^cDenominators (includes 2013–2015): all (N = 111), not hospitalized (N = 40), hospitalized (n = 71).

^dDenominators: all (N = 15694), not hospitalized (N = 15330), hospitalized (N = 364).

Table 2. Multivariable Analysis of Risk Factors for Hospitalization Among Pertussis Patients by Age Group at Enhanced Pertussis Surveillance Sites, United States, 2011–2015

Characteristic	Age													
	<2 Months		2–11 Months		1–11 Years		12–20 Years		≥21 Years					
	aRR	95% CI	PValue	aRR	95% CI	PValue	aRR	95% CI	PValue	aRR	95% CI	PValue		
Residence in state with high pertussis incidence ^{a,b}	0.83	0.62–1.09	.18	0.71	0.36–1.37	.30	0.79	0.34–1.85	.59	0.29	0.11–0.73	<.01	—	—
Male sex ^c	—	—	—	—	—	—	—	—	—	—	—	—	1.50	1.05–2.14
Black race ^d	—	—	—	—	—	—	—	—	—	6.13	1.91–19.67	<.01	1.90	0.95–3.82
Hispanic ethnicity ^e	—	—	—	1.94	1.11–3.38	.02	1.88	1.03–3.42	.04	3.42	1.37–8.55	<.01	—	—
Birth weight <2500 g ^f	1.92	1.23–2.98	<.01	1.98	1.01–3.86	.046	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Maternal age <20 years ^g	—	—	—	1.20	0.54–2.70	.66	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Maternal Tdap receipt ^h
First or second trimester	0.99	0.58–1.68	.97
Third trimester	0.51	0.28–0.93	.03	—	—	—	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pertussis vaccination up-to-date ⁱ	N/A	N/A	N/A	0.57	0.33–0.99	.046	0.34	0.20–0.60	<.01	—	—	—	—	—
>1 Physician visit prior to pertussis diagnosis ^j	1.08	0.79–1.47	.65	2.09	1.08–4.03	.03	2.05	1.16–3.61	.01	3.94	1.57–9.91	<.01	3.52	2.38–5.21
Macrolide antibiotics within 14 days of onset ^k	1.64	1.09–2.45	.02	1.30	0.72–2.36	.38	—	—	—	—	—	—	—	—

Numbers, proportions, and result bivariate analysis of the relative risk of hospitalization shown in [Supplementary Tables 1–5](#). “—” signifies that the P value on bivariate analysis was ≥.10 and therefore not included in the multivariate analysis. “N/A” signifies that this variable was purposely excluded from the model (ie, maternal Tdap was only assessed for infants aged <2 months, up-to-date status only assessed for persons aged ≥2 months, low birth weight assessed only for infants aged <1 year). Bold indicates that values are significant at P < .05.

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; Tdap, tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine.

^aResidence in a state with pertussis incidence above the overall 2011–2015 incidence of 20.3 cases per 100 000 population.

^bReference level:

^cResidence in state with high pertussis incidence.

^dFemale sex.

^eNon-black race.

^fNon-Hispanic ethnicity.

^gBirth weight ≥2500 g.

^hMaternal age ≥20 years.

ⁱNo maternal Tdap receipt.

^jPertussis vaccination status not up-to-date.

^kOne physician visit.

^lNo receipt of a macrolide antibiotic within 21 days of symptom onset.

Table 3. Most Common Admission Diagnoses of Hospitalized Pertussis Patients at Enhanced Pertussis Surveillance Sites, United States, 2011–2015

Admission Diagnosis	By Age Group						
	All Ages (n = 515)	<2 Months (n = 151)	2–11 Months (n = 166)	1–11 Years (n = 58)	12–20 Years (n = 23)	21–64 Years (n = 76)	≥65 Years (n = 41)
Cough	202 (39.2)	56 (37.1)	68 (41.0)	21 (36.2)	9 (39.1)	33 (43.4)	15 (36.6)
Pertussis or whooping cough	171 (33.2)	63 (41.7)	76 (45.8)	18 (31.0)	2 (8.7)	6 (7.9)	6 (14.6)
Respiratory distress and/or failure	83 (16.1)	28 (18.5)	17 (10.2)	9 (15.5)	3 (13.0)	18 (23.7)	8 (19.5)
Bronchiolitis or bronchitis	53 (10.3)	18 (11.9)	15 (9.0)	5 (8.6)	0 (0.0)	9 (11.8)	6 (14.6)
Pneumonia	40 (7.7)	6 (4.0)	7 (4.2)	5 (8.6)	4 (17.4)	12 (15.8)	6 (14.6)
Hypoxia	39 (7.6)	17 (11.3)	8 (4.8)	7 (12.1)	2 (8.7)	4 (5.3)	1 (2.4)
Asthma and/or chronic obstructive pulmonary disease exacerbation ^a	33 (6.4)	0 (0.0)	4 (2.4)	7 (12.1)	2 (8.7)	10 (13.2)	10 (24.4)
Cyanosis	31 (6.0)	9 (6.0)	19 (11.5)	1 (1.7)	1 (4.4)	1 (1.3)	0 (0.0)
Underlying medical conditions	30 (5.8)	3 (2.0)	5 (3.0)	2 (3.5)	2 (8.7)	11 (14.5)	7 (17.1)
Apnea	29 (5.6)	18 (11.9)	9 (5.4)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory infection	20 (3.9)	4 (2.7)	8 (4.8)	4 (6.9)	1 (4.4)	1 (1.3)	2 (4.9)
Brief resolved unexplained event	17 (3.3)	4 (2.7)	13 (7.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever	14 (2.7)	4 (2.7)	4 (2.4)	2 (3.5)	1 (4.4)	2 (2.6)	1 (2.4)
Dehydration	12 (2.3)	2 (1.3)	3 (1.8)	4 (6.9)	2 (8.7)	0 (0.0)	1 (2.4)
Syncope	10 (1.9)	0 (0.0)	1 (0.6)	0 (0.0)	1 (4.5)	7 (9.2)	1 (2.4)

Numbers do not add up to 100% as multiple admission diagnoses per patient are possible.

^aChronic obstructive pulmonary disease is an admission diagnosis only in persons aged ≥21 years.

vaccines [2–4]. While the changing epidemiology of pertussis and several factors that contribute to the US resurgence have been described, fewer data exist on the current burden and characteristics of severe disease, especially in age groups outside of infancy. Our comprehensive analysis of 5 years of EPS data suggests that individuals at the extreme ends of life may be the most vulnerable to severe pertussis infections; 27% of pertussis patients aged <1 year and 12% of patients aged ≥65 years in our analysis were hospitalized for their pertussis infection. Understanding the spectrum of severe illness across all age groups is necessary for identifying additional populations at increased risk that could benefit from targeted vaccination or post-exposure prophylaxis.

Consistent with previous evaluations, we found that the highest risk of hospitalization and ICU admission occurs in infants aged <2 months, with low birth weight identified as a risk factor for hospitalization [10–14]. Although infants aged <2 months account for less than 2% of all pertussis cases in our analysis overall, they account for approximately 30% of pertussis-related hospitalizations. Among those who are hospitalized, they represent more than 50% of ICU admissions and have the highest rates of advanced medical interventions such as mechanical ventilation, ECMO, or exchange transfusion. Interestingly, we found that infants aged <2 months who had received a macrolide antibiotic within 14 days of symptom onset had an increased risk of hospitalization. While we had hypothesized that delayed initiation of antibiotic treatment may increase the risk of severe disease, this finding, along with the relatively short delay between symptom onset and hospitalization relative to older age groups, may be an indicator of severe

symptoms upon presentation at a healthcare facility or a more rapid progression to severe illness in this age group.

While severe pertussis-related morbidity and mortality have been well documented in young infants, pertussis hospitalizations in older children, adolescents, and adults—age groups in which severe pertussis is often not considered—are less well characterized. The association of hospitalization and multiple physician visits prior to a diagnosis of pertussis, along with the increasing delay from symptom onset to hospitalization with age, further suggest missed opportunities for diagnosis and treatment in these age groups, which may have contributed to illness severity. Potentially serious respiratory complications were reported among hospitalized patients across these older age groups, including admission diagnoses that reflected the need for a higher level of care (eg, respiratory distress or failure, hypoxia, apnea), high rates of pneumonia, and viral codetections (eg, respiratory syncytial virus, influenza), that could potentially exacerbate a pertussis infection. However, in some hospitalized patients, the severity of illness was not as clearly perceived from the data abstracted from the chart review. In addition, several of the states with the highest incidence had the lowest hospitalization rates, and vice versa. This suggests that other factors, such as differences in hospitalization practices, thresholds for admission, burden of disease, and differences in surveillance systems' detection of less severe cases, may all contribute and that use of hospitalization as a proxy for severe illness may overestimate the burden of severe cases across age groups.

Although the role of underlying medical conditions in the development of severe pertussis infections is not well understood,

Table 4. Clinical Characteristics and Underlying Conditions in Hospitalized Pertussis Patients by Age Group at Enhanced Pertussis Surveillance Sites, United States, 2011–2015

Characteristic	By Age Group						
	All Ages (n = 515)	<2 Months (n = 151)	2–11 Months (n = 166)	1–11 Years (n = 58)	12–20 Years (n = 23)	21–64 Years (n = 76)	≥65 Years (n = 41)
Median delay from onset to hospitalization (days) ^a	11 (6–17)	7 (4–13)	11 (7–16)	12 (6–21)	12 (9–14)	13 (7–23)	17 (10–30)
Median delay from onset to macrolide antibiotic administration (days) ^a	13 (7–21)	10 (6–16)	12 (17–19)	13 (7–20)	13 (7–20)	14 (7–22)	15 (8–26)
ICU admission	107 (21.0)	57 (38.0)	30 (18.3)	5 (8.6)	2 (8.7)	9 (12.0)	4 (10.0)
Median length of stay (days) ^a							
Hospitalization	3 (1.7–6.9)	5.9 (2.4–10.9)	2.6 (1.1–5.4)	1.8 (1–3.9)	2 (1–3.9)	3.5 (1.9–6.5)	3.1 (2–5.9)
ICU	4 (2–9)	5 (3–11)	3 (2–7)	3 (1–3)	1 (1–1)	2 (1–3)	3 (1–13)
Symptoms							
Paroxysmal cough	505 (98.1)	149 (98.7)	165 (99.4)	55 (94.8)	21 (91.3)	76 (100.0)	39 (95.1)
Whoop	249 (48.4)	76 (50.3)	39 (56.0)	31 (53.5)	7 (30.4)	27 (35.5)	15 (36.6)
Post-tussive emesis	315 (61.2)	97 (64.2)	109 (65.7)	45 (77.6)	18 (78.3)	33 (43.4)	13 (31.7)
Apnea	184 (35.7)	93 (61.6)	65 (39.2)	11 (19.0)	1 (4.4)	9 (11.4)	5 (12.2)
Cyanosis	227 (44.1)	102 (67.6)	101 (60.8)	16 (27.6)	5 (21.7)	3 (4.0)	0 (0.0)
Laboratory findings ^b							
Maximum white blood cell >30 × 10 ⁹ /L	31/351 (8.9)	15/100 (15.0)	7/86 (8.1)	5/33 (15.6)	2/18 (11.1)	2/74 (2.7)	0/40 (0.0)
Viral codetection	54/271 (19.9)	19/92 (20.7)	21/91 (23.1)	6/21 (28.6)	3/14 (21.4)	3/34 (8.8)	2/19 (10.5)
Respiratory syncytial virus	22 (8.1)	11 (12.0)	10 (11.0)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinovirus/enterovirus	14 (5.2)	5 (5.4)	4 (4.4)	2 (9.5)	2 (14.3)	1 (2.9)	0 (0.0)
Adenovirus	9 (3.3)	1 (1.1)	4 (4.4)	2 (9.5)	2 (14.3)	0 (0.0)	0 (0.0)
Human metapneumovirus	8 (3.0)	3 (3.3)	3 (3.3)	1 (4.8)	0 (0.0)	0 (0.0)	1 (5.3)
Other ^c	11 (4.1)	4 (4.3)	2 (2.2)	2 (9.5)	0 (0.0)	2 (5.9)	1 (5.3)
Complications							
Pneumonia	127 (24.7)	34 (22.5)	28 (16.9)	13 (22.4)	8 (34.8)	29 (38.2)	15 (36.6)
New-onset seizures	16 (3.1)	3 (2.0)	1 (0.6)	3 (5.2)	4 (17.4)	4 (5.3)	1 (2.4)
Encephalopathy	7 (1.4)	1 (0.7)	0 (0.0)	0 (0.0)	2 (8.7)	3 (4.0)	1 (2.4)
Pulmonary hypertension ^d	4 (0.8)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)
Underlying medical conditions							
At least 1 condition ^f	168 (32.6)	9 (6.0)	20 (12.1)	19 (32.8)	18 (78.3)	65 (85.5)	37 (90.2)
Asthma or reactive airway disease	58 (11.3)	0 (0.0)	4 (2.4)	13 (22.4)	10 (43.5)	20 (26.3)	11 (26.8)
Obesity	58 (11.3)	0 (0.0)	0 (0.0)	1 (1.7)	1 (4.4)	40 (52.6)	16 (39.0)
Smoking (current or past)	37 (7.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	26 (34.2)	11 (26.8)
Immunocompromising condition/medication use ^e	35 (6.8)	0 (0.0)	2 (1.2)	2 (3.5)	8 (34.8)	19 (25.0)	4 (9.8)
Cardiac condition	31 (6.0)	4 (2.7)	6 (3.6)	1 (1.7)	1 (4.4)	7 (9.2)	12 (29.3)
Diabetes	28 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (19.7)	13 (31.7)
Other respiratory tract/pulmonary condition	27 (5.2)	1 (0.7)	6 (3.6)	5 (8.6)	1 (4.4)	6 (7.9)	8 (19.5)
Chronic obstructive pulmonary disease	22 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (14.5)	11 (26.8)
Neurologic disorder	18 (3.5)	1 (0.7)	2 (1.2)	2 (3.5)	5 (21.7)	4 (5.3)	4 (9.8)
Renal disease	15 (2.9)	0 (0.0)	1 (0.6)	1 (1.7)	1 (4.4)	8 (10.5)	4 (9.8)
Genetic disorder	10 (1.9)	1 (0.7)	1 (0.6)	4 (6.9)	3 (13.0)	1 (1.3)	0 (0.0)
Illicit drug use or perinatal drug exposure	9 (1.8)	3 (2.0)	4 (2.4)	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)
Clinical interventions							
Mechanical ventilation	26 (5.1)	20 (13.3)	1 (0.6)	0 (0.0)	0 (0.0)	3 (4.0)	2 (4.9)
Extracorporeal membrane oxygenation	1 (0.2)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Exchange transfusion	1 (0.2)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Inhaled nitric oxide	5 (1.0)	2 (1.3)	1 (0.6)	1 (1.7)	0 (0.0)	0 (0.0)	1 (2.4)
Inotropic or vasopressor support	6 (1.2)	4 (2.7)	1 (0.6)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Outcome							
Died	3 (0.6)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	1 (2.4)
Discharged with supplemental oxygen	37 (7.3)	9 (6.0)	9 (5.5)	3 (5.4)	1 (4.4)	8 (10.7)	7 (18.9)

Abbreviations: ICU, intensive care unit.

^aExpressed as median (interquartile range).

Denominators:

^bOnly among case-patients in whom testing was performed (N = 350 for white blood cell and N = 271 for viral testing).

^cIncludes influenza A and B, coronavirus, parainfluenza, and human herpes virus 6.

^dTwenty-seven case-patients underwent echocardiogram or cardiac catheterization.

^eNot possible to determine based on chart review whether the case-patient was currently immunosuppressed.

^fIncludes other conditions not listed.

the high proportion of hospitalized adolescent and adult cases with underlying conditions suggests that they may be a contributing factor. Consistent with previous evaluations that have suggested asthma as a risk factor for pertussis [15, 16], we found high rates of asthma in hospitalized patients in our evaluation. Forty-four percent of hospitalized adolescents aged 12 to 20 years and approximately 26% of hospitalized adults aged ≥ 21 years had a history of asthma compared to approximately 10% of US adolescents and 8% of adults [17]. We also found higher than average rates of COPD, with 19% of hospitalized pertussis patients aged ≥ 21 years compared to 6.4% among US adults with a history of COPD [18]. Although 1 study demonstrated higher serum levels of anti-*B. pertussis* immunoglobulin G in persons with COPD [19], the risk of pertussis, including severe pertussis, in persons with COPD is unknown. Not only did a high proportion of patients report a history of asthma or COPD, these conditions appear to have played a role in their clinical severity, as asthma and/or COPD exacerbation were listed as a leading reason for hospital admission in adolescents and adults. In addition, high proportions of hospitalized adolescents aged 12 to 20 years in our evaluation had underlying neurologic, genetic, or potentially immunocompromising conditions, suggesting that of the few adolescents who are hospitalized for their pertussis infection, many have complex medical histories. This high rate of neurologic and genetic underlying conditions may help provide context for the higher rates of certain pertussis-related complications, such as new-onset seizures and encephalopathy, observed in adolescents compared to other age groups. As we did not have a comparison group, we are unable to determine whether certain underlying conditions are risk factors for severe pertussis or, rather, whether persons with these conditions are hospitalized at greater rates due to a perception of increased risk for severe disease.

Pertussis vaccination according to ACIP recommendations is not only effective at preventing disease but has also been shown to reduce the clinical severity of pertussis illness. Consistent with findings from a previous US study [20], our results demonstrate that infants aged < 2 months with pertussis infection whose mothers received Tdap during the third trimester of pregnancy had a 49% reduced risk of hospitalization compared to infant pertussis cases with unvaccinated mothers. In addition, a case-control study among pertussis patients age < 2 months with matched healthy controls demonstrated that maternal Tdap receipt during the third trimester was 90.5% effective against hospitalization with pertussis [21]. Among older infants and children, the risk of hospitalization in our analysis was reduced by 43% in 2- to 11-month-olds, and 66% in 1- to 10-year-olds who were up to date on pertussis vaccination. Although high amounts of missing vaccination information in adolescents and adults precluded our ability to fully assess this association in older age groups, a recent publication suggested that adolescents and adults vaccinated with Tdap have reduced incidence

of post-tussive vomiting, a marker of more clinically significant illness [22]. Thus, although vaccinated persons may still remain at risk for pertussis infection, these data highlight the role that pertussis vaccination plays in the prevention of severe and potentially life-threatening infections, suggesting an added benefit of vaccination that goes beyond disease prevention.

In the setting of a pertussis resurgence in the United States and other high-income countries worldwide, emphasis has been placed on the protection of young infants who are at highest risk of severe pertussis-related morbidity and mortality. While new strategies such as maternal immunization offer promise for the prevention of disease and death in the first months of life, our analysis shows that severe pertussis infections that require hospitalization are not limited to infants; certain risk factors, such as key underlying medical conditions, may predispose an individual to more severe infections. Continued monitoring of pertussis hospitalizations through enhanced surveillance systems such as EPS will help better define populations at increased risk of severe disease in order to appropriately target and prioritize current and future pertussis prevention and control strategies.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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