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Bordetella Pertussis is an Uncommon Pathogen in Children Hospitalized with Bronchiolitis During the Winter Season

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Abstract

Background—In the United States (U.S.), *Bordetella pertussis* incidence has increased. Cough and apnea are common findings in pertussis and also in bronchiolitis, the most common cause of hospitalization in U.S. infants. The objective was to determine the prevalence of *B. pertussis* infection in children hospitalized with bronchiolitis and to describe its clinical course.

Methods—Children hospitalized with bronchiolitis and age <2 years were eligible for a prospective, multicenter cohort study during three consecutive winter seasons (November to March) from 2007 to 2010. 16 sites in 12 states participated using a standardized enrollment protocol. Families were asked the 2010 Centers for Disease Control and Prevention (CDC) pertussis classification questions. Nasopharyngeal aspirates were obtained and tested by real time polymerase chain reaction for 16 viruses, *Mycoplama pneumoniae* and *B. pertussis*.

Results—2068 (94%) of 2,207 children had one or more respiratory pathogens. *B. pertussis* was identified in 4 children (0.2%; 95% CI, 0.1–0.5%) with 3 having a viral co-infection. All 4 were younger than four months; 2 met the CDC definition of probable pertussis, and 3 had received at least one dose of an acellular pertussis vaccine. During the hospitalization, 2 had paroxysmal cough, 1 required ICU care, and the median length of stay was 13 days.

Conclusion—Our data support that *B. pertussis* is an uncommon pathogen in U.S. children hospitalized with bronchiolitis in the winter. Making a diagnosis of pertussis can be challenging because the disease can be atypical, and may not meet the CDC definition of probable infection.

Keywords

infant; bronchiolitis; prospective multicenter cohort study; Bordetella pertussis; pertussis; paroxysmal cough; wheeze

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Clinical Trial Registration: not applicable

Introduction

There are conflicting data on the prevalence of *B. pertussis* in infants presenting with bronchiolitis ranging from that of an uncommon pathogen (< 1%) to that of a common pathogen (8 to 16%) (1–8). The typical presentation of pertussis is quite distinct from that of bronchiolitis (9–15). However, for both pertussis and bronchiolitis most of the severe illness occurs in young infants, both can present as apnea, and pertussis can manifest atypically in partially or fully vaccinated children. Also, the epidemiology of pertussis and bronchiolitis is distinct with pertussis causing cyclical epidemics every 2 to 5 years with increasing incidence in recent years and bronchiolitis epidemics occur annually during the fall and winter months. Complicating these distinctions is viral co-infection with RSV or other respiratory viruses frequently detected in infants with *B. pertussis* infection (2–7). We recently conducted a prospective, multicenter study of 2207 children hospitalized for bronchiolitis during three consecutive winter seasons (2007 to 2010) in the United States (US)(14). An objective of the study was to identify the putative respiratory pathogens in children hospitalized with bronchiolitis. In this report we describe the prevalence of *B. pertussis* infection in children hospitalized with bronchiolitis from November through March and describe their clinical presentation and hospital course.

Materials and Methods

Study Design

A prospective, multicenter cohort study was conducted for 3 consecutive years during the 2007 to 2010 winter seasons, as part of the Multicenter Airway Research Collaboration (MARC), a program of the Emergency Medicine Network (EMNet) (www.emnet-usa.org) (14, 15). The number of participating sites varied over the 3 years: 13 sites in year 1; 16 sites in year 2; and 14 sites in year 3. Each month from November 1 until March 31, site investigators across 12 U.S. states used a standardized protocol to enroll a target number of consecutive patients per month from the inpatient wards and the intensive care unit (ICU) with an aim to enroll 20% of the cohort from intensive care units (ICU).

All patients were treated at the discretion of the treating physician. Inclusion criteria were an attending physician's diagnosis of bronchiolitis, age <2 years, and the ability of the parent/guardian to give informed consent. Patients were enrolled within 18 hours of admission. The exclusion criteria were previous enrollment or transfer to a participating hospital >48 hours after the original admission time. The institutional review board at all participating hospitals approved the study.

Data Collection

A structured interview was conducted with the children's caretakers to assess patients' demographic characteristics, medical and environmental history, duration of symptoms, and details of the acute illness. In addition, caretakers were asked the Centers for Disease Control and Prevention (CDC) pertussis classification questions to identify a clinical case of probable pertussis (16, 17). Medical records were reviewed to obtain clinical data from the pre-admission evaluation (clinic or emergency department) and the child's inpatient course

and disposition. Information on immunization was based on parental history and was not confirmed by medical record or immunization registry. The adult acellular pertussis vaccine (Tdap) immunization status was not collected on the parents or legal guardians.

Nasopharyngeal aspirate collection and virology testing

Nasopharyngeal aspirates (NPAs) were performed and processed using a standardized protocol. All of the sites collected 98% of the samples within 24 hours of a child's hospital admission. After collection, the NPA samples were stored locally at −80°C and subsequently batch shipped on dry ice to the central laboratory at Baylor College of Medicine, where they were stored at −80°C for later testing.

Polymerase Chain Reaction (PCR) assay

All PCR assays were conducted as singleplex or duplex two-step real time PCR (rtPCR). Details of the primers and probes for the detection of the common respiratory viruses (RSV A and B, rhinovirus, influenza A and B, parainfluenza virus types 1, 2 and 3, enterovirus, human metapneumovirus A and B, coronavirus -OC43, -229E, -NL63 and -HKU1, and adenoviruses) and *Mycoplasma pneumoniae* have been described elsewhere (18–20). For *B. pertussis* the insertion sequence IS481 was targeted. IS481 sequence is unique to *B. pertussis* and *B. holmesii* (19). The genome of *B. pertussis* contains 80 to 100 copies of IS481 while the genome of *B. holmesii* contains 8 to 10 copies. The rtPCR for *B. pertussis* was shown to be specific for *B. pertussis* and did not identify *B. bronchiseptica* (ATCC # 4671™, ATCC Manassas, Virginia) or *B. parapertussis* (ATCC # 15311™) which can cause a pertussis like syndrome. All rtPCR assays were tested in duplicate and samples with incongruent values (one well positive) were retested. To reduce carryover contamination, sample preparation, RNA/DNA extraction, cDNA and amplification were performed in separate areas. All PCR runs had extraction and reagent positive and negative controls.

Statistical Analyses

All analyses were performed using Stata 11.2 (Stata Corp, College Station, TX). Data are presented as proportions with 95% confidence intervals (95%CIs) and medians with interquartile ranges (IQR). Unadjusted analyses were performed using chi-square or Fisher's exact test, as appropriate. All *P*-values were two-tailed, with $P<0.05$ considered statistically significant.

Results

One or more respiratory pathogens were identified in 2068 (94%) of 2207 enrolled children admitted for bronchiolitis. Demographic characteristics, ICU disposition and major respiratory pathogens by age groups are presented in Table 1. Overall, the median age was 4 months (IQR, 2–9 months); 59% were male; 61% were white; and 18% required ICU care. One or more respiratory pathogen was detected in 93.7% of cases. The two most common pathogens detected were respiratory syncytial virus (RSV) and rhinovirus (RV) which were found in 72% and 26% of all children, respectively. Co-infections with one or more respiratory pathogens occurred in 30% of children. *B. pertussis* was identified in only four cases (0.2%; 95% CI, 0.1–0.5%).

The four children infected with *B. pertussis* were all less than 6 months of age. Therefore, the subsequent analysis is restricted to the 1,405 (64%) infants less than 6 months of age. Of those age <6 months, the median age was 2 months (IQR, 1–4 months). The other demographic characteristics were similar to the overall cohort: 58% male; 63% white; 19% requiring ICU care, 78% with RSV, 23% with RV and 26% with co-infection. Applying the CDC clinical case definition for probable pertussis, 52 (3.7%) children were classified as having "probable" pertussis of which 2 were confirmed to have *B. pertussis* by rtPCR. Two other infants with laboratory confirmed *B. pertussis* did not meet the CDC clinical case definition for probable pertussis (Table 2). These 4 infants are grouped together in Table 2 as "*B. pertussis* confirmed". A second respiratory pathogen was identified in three of the infants with *B. pertussis*; two had a RV co-infection and 1 child had coronavirus HKU1.

The clinical characteristics of the 4 infants with *B. pertussis* confirmed by PCR were compared to the 50 infants less than 6 months who met the CDC clinical case definition of probable pertussis but were PCR-negative for *B. pertussis* and to the 1351 infants less than 6 months who did not meet the CDC clinical case definition of probable pertussis and were negative for *B. pertussis* (Table 3). A history of cough greater than 2 weeks was obtained in 52 (3.9%) of the 1351 infants who did not have probable or confirmed pertussis. These 52 infants did not meet the CDC clinical case definition of probable pertussis because they did not have a history of paroxysms of coughing, inspiratory whoop or post-tussive emesis. By clinical history, infants with confirmed *B. pertussis* had similar characteristics to the infants who met the CDC clinical case definition of probable pertussis. Most of the infants from both of these groups had 3 or more days of difficulty breathing at the time of hospitalization. The clinical findings on admission were similar between the three groups. However, infants with *B. pertussis* had median white blood cell (WBC) count that was twice as high and their median duration of hospitalization was longer than infants in the other two groups.

Discussion

In recent years there has been an increasing incidence of reported pertussis, with the highest incidence in infants (16, 21, 22). Bronchiolitis is the most common cause of hospitalization in infants and is generally attributed to common respiratory viruses (23–27). There is a strong interest in defining the role of *B. pertussis* in children with bronchiolitis in the current era because in both diseases the incidence is highest in infants, they cause life-threatening illness, symptoms can be atypical in young infants and have overlapping features in older infants, there are conflicting data on the prevalence of *B. pertussis* in bronchiolitis, and molecular diagnostics have improved the detection of *B. pertussis*. In the current study, we used modern molecular diagnostic methods to demonstrate that *B. pertussis* is an uncommon pathogen in bronchiolitis. The study population consisted of 2207 U.S. children hospitalized with bronchiolitis during three sequential respiratory seasons from 2007/2008 to 2009/2010. In each of the study years, there were 13 to 16 sites from 12 states participating from across the U.S. *B. pertussis* was identified in only four children (0.2%; 95% CI, 0.1–0.5%) and all occurred in infants less than 6 months of age. In three of the infants with *B. pertussis*, a viral co-pathogen was also detected.

The low prevalence of *B. pertussis* detected in our study is consistent with data reported in recent years (1–3). Siberry and colleagues identified 1case (0.6%) among 166 children less than 6 years of age hospitalized with respiratory symptoms during the 2000–01 RSV season in Baltimore (1). Similarly Walsh et al. detected three cases (0.6%) in 488 samples collected primarily from infants evaluated in the emergency department during the 2005–06 RSV season in Los Angeles (2). Dual infection with RSV was identified in 2 of the 3 children with pertussis. In a study conducted in Switzerland from November 2008 through October 2009, Heininger and Burckhardt identified 21 (1.9%) cases of pertussis from 1059 nasopharyngeal samples collected from children age 0 to 17 years evaluated for a coughing illness (3). Other investigators have identified *B. pertussis* as a common pathogen in children with bronchiolitis or RSV (4–7). Two studies conducted in Finland in infants less than 6 months of age hospitalized for a respiratory tract infection in 2005–06 (4) or bronchiolitis in 2001–02 (5) identified *B. pertussis* in 9 (10%) of 88 and 12 (8.5%) of 142 infants, respectively. Co-infection with RSV occurred in 15 of these 21 infants with pertussis. Miron and colleagues reported on the etiology of bronchiolitis in 490 hospitalized children less than 2 years of age during the 2005–06 winter in northern Israel (6). *B. pertussis* was detected in 29 (6.2%) hospitalized children with 3 of the pertussis cases as the sole pathogen. Cosse-Lambe and colleagues reported *B. pertussis* in 19 (16%) of 120 infants less than 4 months of age hospitalized for bronchiolitis during the 2005–06 winter in Paris (7).The variation in prevalence of *B. pertussis* in children presenting with bronchiolitis among the cited studies might be a reflection of the country's incidence of pertussis and the vaccination rate against pertussis.

Another possibility for our finding is that during the study years (2007–08, 2008–09 and 2009–10), two major pertussis epidemics bracketed but did not encompass our study (28). In 2004 and 2005 there were over 25,000 cases of pertussis reported each year. The number of pertussis cases dropped in the subsequent 4 years to 15,631 in 2006, 10,454 in 2007, 13,278 in 2008 and 16,858 in 2009. It jumped in 2010 to 27,550 cases and remained elevated in 2011 at 18,719. In 2006, ACIP recommended routine use of Tdap among adolescents 11 to 18 years of age. At least 34 states reported increased pertussis activity in 2010 despite the increase in pertussis vaccine coverage among adolescences from approximately 10% to 68% during the study period while pertussis vaccine coverage in children 19 to 35 months remained steady at 84% increasing to 95% in 2010. Thus our study suggests that during the interepidemic periods, pertussis appears to be an uncommon pathogen in severe bronchiolitis, however during pertussis epidemics our finding might not apply.

In 2012, approximately 4500 cases of *B. pertussis* were reported in infants less than 1 year old in the United States with an incidence of 1.13 cases per 1000 children (22). Bronchiolitis, however, is a common clinical entity in children less than 12 months of age and a common cause of hospitalization. Approximately 80% of bronchiolitis-associated hospitalization occurs in children less than 12 months with an annual hospitalization rate in 2009 of approximately 25 per 1000 person year or an average of 105,000 hospitalizations (27). In 2002 there was an estimated 149,000 bronchiolitis-associated hospitalizations in children less than 2 years in the United States (29). In more recent years there has been a trend for decrease in bronchiolitis hospitalization but with an increase in children with co-

morbid medical conditions (27). Children younger than 6 months are particularly vulnerable to severe bronchiolitis, with approximately 57% of all bronchiolitis-associated hospitalization occurring in this group or an annual average of 84,900 hospitalizations. Extrapolating from our study of 4 cases of *B. pertussis* in 1405 bronchiolitis-associated hospitalization among infants less than 6 months, we would predict approximately 240 cases of *B. pertussis* occur each respiratory season among U.S. infants less than 6 months who are hospitalized for bronchiolitis. This population is vulnerable to the most severe consequences of pertussis including apnea, pneumonia, encephalopathy and death (12, 22).

In children, *B. pertussis* is classically characterized by prolonged cough with a history of paroxysms of coughing, inspiratory whoop or post-tussive emesis. The CDC developed a clinical case definition to increase the likelihood of detecting pertussis, in particular, in situations when testing is not performed or laboratory tests are negative (16, 17). In endemic or sporadic cases, like those observed in our study, the clinical case definition of pertussis is met when a child has a history of a coughing illness at least 2 weeks in duration with paroxysms of coughing, inspiratory whoop or post-tussive emesis without other apparent cause. In our study, 52 children met the CDC clinical case definition of pertussis but only two had laboratory confirmation. Two other children in our study who did not meet the CDC clinical case definition of pertussis had laboratory confirmation. This is consistent with the observation that young infants with *B. pertussis* can present with atypical symptoms including apnea, cyanosis and wheezing (9, 12, 16). Of note, three of the 4 children with laboratory confirmed pertussis had a viral co-infection. The viral infection can be considered to constitute an apparent cause other than pertussis in infants who meet the clinical case definition of pertussis and thus has the potential to deter further diagnostic evaluation.

Laboratory confirmation of pertussis can be difficult depending on when persons are tested in the course of their disease and the type of laboratory method used. Leukocytosis early in the illness is characteristic of pertussis but occurs in the minority and is not specific for pertussis (9, 11, 30). The four infants with pertussis in our study presented with leukocytosis, with the WBC in all four being greater than 19,000 per microliter. PCR is considered the preferred test for confirmation of pertussis because of its increased sensitivity compared with other tests (11, 16). Not all PCR tests are created equally and some assays can give false positive results because of the region the primers target. For this study we used real time PCR with primers that target the insertion sequence IS481. *B. pertussis* and *B. holmesii* are the main species that contain IS481 with nearly 10 times as many copies found in the genome of *B. pertussis* compared with *B. holmesii* (19). A low percentage of *B. bronchiseptica* strains are also known to contain the IS481 gene. *B. holmesii* has been recovered in children with pertussis like syndrome (31). A large cohort study in Europe was conducted to determine if *B. holmesii* confounds PCR assays that target IS481 and IS1001 (32). Among 11,319 persons with pertussis like syndrome who were evaluated, 1581 (14%) persons were confirmed to have pertussis based on positive PCR tests. None of these persons were positive for *B. holmesii* using a species-specific real time PCR test that was based on the recA gene. All together the data suggest that *B. holmesii* is infrequently detected in persons confirmed to have pertussis based on PCR test that targets IS481.

Our study has some potential limitations. The sites involved are representative of academic hospitals and not community hospitals, and we oversampled for children admitted to the intensive care unit. Both of these factors might affect the prevalence of *B. pertussis* in children with bronchiolitis-associated hospitalization. Another possible limitation is that *B. pertussis* was confirmed with a single real time PCR test. A second PCR test is often used to exclude other Bordetella species. It is possible that one or more of these cases might have been due to *B. holmesii*. Lastly our study was restricted to the months of November through March of each study year. Although most cases of bronchiolitis occur from November through March, the prevalence of pertussis was not determined in those cases that occurred outside the study period.

In summary, *B. pertussis* is an uncommon pathogen in children hospitalized with bronchiolitis during the winter season and during interepidemic periods of pertussis. The clinical findings of pertussis in partially vaccinated infants can be atypical, may not meet the CDC definition of probable infection, and co-infection with a respiratory virus can add an additional challenge in making a diagnosis of pertussis. In children hospitalized with bronchiolitis, *B. pertussis* should be considered in young infants who are slow to improve with conservative management and have an elevated WBC. Making an accurate diagnosis in young infants is important because they are vulnerable to the most severe consequences of pertussis and account for the majority of pertussis deaths.

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Table 1

Demographic characteristics, disposition and presence of respiratory pathogens in children hospitalized for bronchiolitis by age group.

		Stratified by age groups		
Characteristics	**All (n = 2207)**	**12–<24 months (n=311)**	**6–<12 months (n=491)**	**<6 months (n=1405)**
Age in months, median (IQR)	4 (2–9)	16 (14–18)	8 (7–10)	2 (1–4)
Gender				
Male	59%	62%	61%	58%
Female	41%	38%	39%	42%
Race & ethnicity				
White	61%	58%	58%	63%
Black	24%	24%	31%	22%
Other or missing	14%	18%	11%	14%
Hispanic	36%	43%	35%	35%
Disposition				
ICU admission	18%	16%	14%	19%
Presence of one or more respiratory pathogens	93.7%	92.6%	94.1%	93.8%
B. pertussis	0.2%	0%	0%	0.3%

Abbreviations: IQR - interquartile range; ICU - intensive care unit; –

Nasopharyngeal aspirates were tested by polymerase chain reaction assays for RSV A and B, rhinovirus, influenza A and B, parainfluenza virus types 1, 2 and 3, enterovirus, human metapneumovirus A and B, coronavirus -OC43, -229E, -NL63 and -HKU1, adenoviruses, Mycoplasma pneumoniae and Bordetella pertussis.

Table 2

Demographic characteristics in infants less than 6 months old hospitalized with bronchiolitis by Centers for Disease Control and Prevention (CDC) clinical case definition for probable pertussis

Characteristics	*B. pertussis* negative (n=1351)	*B. pertussis* probable, but not confirmed (n=50)	*B. pertussis* confirmed (n=4)
Age in months, median (IQR)	2 (1–4)	4 (2–5)	4 (2–3)
<2	618 (46%)	8 (16%)	2 (50%)
2–3.9	452 (33%)	15 (30%)	2 (50%)
4–5.9	281 (21%)	27 (54%)	0 (0%)
Sex			
Male	783 (58%)	33 (66%)	3 (75%)
Female	568 (42%)	17 (34%)	1 (25%)
Race & ethnicity			
White	868 (64%)	21 (42%)	3 (75%)
Black	297 (22%)	16 (32%)	0 (0%)
Other or missing	186 (14%)	13 (26%)	1 (25%)
Hispanic	470 (35%)	22 (44%)	2 (50%)

Abbreviations: IQR - interquartile range

Table 3

History, clinical and laboratory presentation and hospital course of infants less than 6 months old hospitalized with bronchiolitis by Centers for Disease Control and Prevention (CDC) clinical case definition for probable pertussis

Characteristics	B. *pertussis* negative (n=1351)	B. *pertussis* probable, but not confirmed (n=50)	B. *pertussis* confirmed (n=4)
History			
Immunization up to date by history	1155 (86%)	39 (80%)	3 (75%)
Term at birth (≥37 wks)	1049 (78%)	32 (64%)	3 (75%)
Major co-morbid condition	184 (14%)	10 (20%)	1 (25%)
Exposure to person with ≥2 weeks of cough	310 (23%)	17 (34%)	2 (50%)
Subject with cough for at least 2 weeks	52 (4%)	50 (100%)	2 (50%)
Difficulty breathing for < 3 days	953 (70.5%)	16 (32%)	1 (25%)
Clinical			
Temperature ≥100.4 F	285 (22%)	13 (26%)	0 (0%)
RR per minute, median (IQR)	48 (40–60)	48 (40–60)	43 (34–53)
RR ≥70 per minute	139 (10%)	3 (6%)	0 (0%)
Presence of apnea	120 (9%)	5 (10%)	0 (0%)
Moderate or severe chest wall retraction	376 (28%)	11 (22%)	1 (25%)
Oxygen saturation, median (IQR)	96 (94–99)	96 (95–98)	100 (98–100)
Oxygen saturation <90%	128 (10%)	5 (10%)	0 (0%)
Inadequate oral intake	572 (42%)	25 (50%)	3 (75%)
ICU admission	258 (20%)	6 (13%)	1 (25%)
CPAP or intubation	127 (10%)	1 (2%)	1 (25%)
Laboratory			
Positive for one or more respiratory pathogens	93.7%	94%	75%
WBC, median (IQR)*	11,400 (9,000–14,700)	10,800 (7,600–13,400)	22,450 (19,900–29,700)
Duration of hospitalization			
LOS (days), median (IQR)	2 (1–4)	3 (2–4)	13 (6–20)
≥3 days LOS	645 (48%)	28 (56%)	3 (75%)

Abbreviations: F - Fahrenheit; IQR - interquartile range; RR - respiratory rate; ICU - intensive care unit; CPAP - continuous positive airway pressure; WBC, white blood cell count; LOS, length-of-stay.

Nasopharyngeal aspirates were tested by polymerase chain reaction assays for RSV A and B, rhinovirus, influenza A and B, parainfluenza virus types 1, 2 and 3, enterovirus, human metapneumovirus A and B, coronavirus -OC43, -229E, -NL63 and -HKU1, adenoviruses, Mycoplasma pneumoniae and Bordetella pertussis.