

Widespread *Bordetella parapertussis* Infections—Wisconsin, 2011–2012: Clinical and Epidemiologic Features and Antibiotic Use for Treatment and Prevention

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Background. During October 2011–December 2012, concurrent with a statewide pertussis outbreak, 443 *Bordetella parapertussis* infections were reported among Wisconsin residents. We examined clinical features of patients with parapertussis and the effect of antibiotic use for treatment and prevention.

Methods. Patients with polymerase chain reaction results positive for *B. parapertussis* reported during October 2011–May 2012 were interviewed regarding presence and durations of pertussis-like symptoms and receipt of azithromycin treatment. Data regarding acute cough illnesses and receipt of azithromycin prophylaxis among parapertussis patient household members (HHMs) were also collected. Using multivariate repeated measures log-binomial regression analysis, we examined associations of treatment receipt by the HHM with the earliest illness onset and prophylaxis receipt among other HHMs with the presence of any secondary cough illnesses in the household.

Results. Among 218 patients with parapertussis, pertussis-like symptoms were frequently reported. Illness durations were significantly shorter among patients with treatment initiated 0–6 days after cough onset, compared with nonrecipients (median durations: 10 vs 19 days, $P = .002$). Among 361 HHMs from 120 households, compared with nonrecipients, prompt prophylaxis of HHMs was associated with no secondary cough illnesses (relative risk: 0.16; 95% confidence interval, .04–.69).

Conclusions. *Bordetella parapertussis* infection causes pertussis-like illness that might be misclassified as pertussis if *B. parapertussis* testing is not performed. Prompt treatment might shorten illness duration, and prompt HHM prophylaxis might prevent secondary illnesses. Further study is needed to evaluate antibiotic effectiveness for preventing parapertussis and to determine risks and benefits of antibiotic use.

Keywords. *Bordetella parapertussis*; *Bordetella pertussis*; epidemiology.

Pertussis (whooping cough) is a highly contagious vaccine-preventable illness caused by infection with *Bordetella pertussis*. Symptoms include paroxysmal cough,

posttussive vomiting, and apnea, and can persist for weeks. Infants too young for vaccination are at greatest risk for pertussis and associated severe disease and complications, including hospitalization and death [1]. In the United States, reported cases of pertussis have increased since the 1990s [2], likely because of multiple factors, including the introduction of polymerase chain reaction (PCR) testing for *B. pertussis* and waning protection from available pertussis vaccines [3]. Azithromycin or other macrolide antibiotic treatment eliminates *B. pertussis* from an infected person and might reduce illness duration if received early

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during illness [4–6]. Because of incomplete protection from pertussis vaccination, antibiotic treatment of persons suspected of having pertussis and antibiotic prophylaxis of household members (HHMs) are recommended to prevent *B. pertussis* transmission [6, 7].

Infection with other *Bordetella* species (*Bordetella parapertussis*, rarely *Bordetella holmesii* or *Bordetella bronchiseptica*) can also cause pertussis-like illness [1, 8–15], and in the absence of laboratory confirmation might contribute to the number of reported or perceived pertussis cases [15–17]. *Bordetella parapertussis* infection is increasingly recognized in the United States because of PCR testing but likely remains underrecognized because PCR insertion sequence targets for *B. parapertussis* (IS1001) and *B. pertussis* (IS481) are different [18], and many laboratories do not test for IS1001 [19]. No national guidelines exist for antibiotic treatment of patients with parapertussis or prophylaxis of HHMs, but antibiotic susceptibility testing indicates that antibiotics recommended for pertussis might be useful for treating and preventing parapertussis [20, 21]. Because persons with pertussis-like illness are often treated and HHMs receive prophylaxis before PCR results are available and because some states (including Wisconsin) have guidelines for antibiotic management of parapertussis [22, 23], some patients with parapertussis and their HHMs might receive antibiotic treatment and prophylaxis. The effectiveness of these interventions has not been evaluated.

During October 2011–December 2012, concurrent with a statewide outbreak of pertussis, the Wisconsin Division of Public Health (WDPH) received numerous reports from laboratories of *B. parapertussis* infection. We examined clinical and epidemiologic features of reported parapertussis statewide. In Wood County, where simultaneous outbreaks of parapertussis and pertussis occurred, we compared clinical and epidemiologic features of parapertussis and pertussis cases. Additionally, statewide, we examined the effect of antibiotic treatment on duration of parapertussis illness and the effect of antibiotic treatment and prophylaxis on prevention of cough illnesses among parapertussis patient HHMs.

METHODS

Case Reporting and Definitions

In Wisconsin, *B. parapertussis* infection is not officially reportable. Among 11 laboratories that report *Bordetella* results to WDPH, 6 simultaneously test specimens for *B. pertussis* and *B. parapertussis* and 3 test for *B. parapertussis* when requested. In response to increased reporting of *B. parapertussis* infections since October, on 6 December 2011, WDPH requested all laboratories to report *B. parapertussis*-positive results.

A clinical case was defined as an acute cough illness in a Wisconsin resident reported as a suspected case of pertussis

to WDPH through the Wisconsin Electronic Disease Surveillance System during 1 October 2011–31 December 2012 (parapertussis outbreak period). A case of parapertussis was defined as a clinical case with a specimen positive for only *B. parapertussis* using PCR (IS1001) or culture. A case of pertussis was defined as a clinical case with a specimen positive for only *B. pertussis* using PCR (IS481) or culture. A case of parapertussis-pertussis coinfection was defined as a clinical case with PCR or culture results positive for both species.

Data Collection

Attempts were made to interview all patients with positive test results for *B. parapertussis* or *B. parapertussis*-*B. pertussis* coinfection reported during 1 October 2011–31 May 2012 (study interval). Patients, or their parents, were interviewed by local health department or WDPH staff using the parapertussis case report form (CRF). Additionally, in Wood County during the study interval, all patients with *B. pertussis*-positive test results were administered the parapertussis CRF.

The parapertussis CRF collected patient demographic data, antibiotic treatment history, and presence and durations of symptoms characteristic of pertussis and parapertussis including cough, paroxysmal cough, posttussive vomiting, whoop, apnea, fever, weight loss, cyanosis, sleep disturbance, and sleep disturbance among family members. The CRF also collected data regarding parapertussis patients' HHMs, including age, onset of acute cough illness, and antibiotic receipt. Vaccination histories were obtained from the Wisconsin Immunization Registry.

Data Analysis

Data were analyzed using SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina). Statewide, clinical characteristics of patients with parapertussis were summarized and stratified by age. Among Wood County patients, characteristics of parapertussis patients and pertussis patients were compared. Comparisons of clinical characteristics between groups on a categorical and continuous scale were conducted using chi-square tests (or Fisher exact tests) and nonparametric Mann–Whitney *U* tests, respectively.

Because 98% of treatments and 100% of prophylaxes were with azithromycin, we limited our evaluation of antibiotics for parapertussis treatment and prevention to recipients of azithromycin treatment or azithromycin prophylaxis of any duration, compared with nonrecipients who received no antibiotics or received antibiotics not recommended for pertussis.

To investigate the effect of treatment on parapertussis illness duration, we compared characteristics of parapertussis patients by whether and when treatment was initiated.

Among parapertussis patient households, receipt of prophylaxis by a HHM was defined as having received azithromycin

before any cough illness onset. In each household, the person with the earliest cough illness onset was considered the primary patient. Using the incubation period of pertussis (7–10 days; range: 4–21 days) [24], we compared attack rates (ARs) of coprimary and secondary cough illness (onsets 0–6 and 7–16 days after primary patient cough onset, respectively) among prophylaxis recipients with ARs among nonrecipients. Secondary cough illness was defined as onset 7–16 (rather than 7–28) days after primary patient cough onset because 81% of households were followed for ≥ 16 days, and only 57% were followed for ≥ 28 days.

To investigate effects of treatment and prophylaxis on prevention of secondary cough illnesses among paraptussis patient HHMs, we compared characteristics of households with and without secondary cough illnesses. To examine associations of treatment receipt by the household primary patient and prophylaxis receipt by HHMs with the presence of any secondary cough illnesses, we used multivariate log-binomial regression analysis accounting for repeated measurements (multiple HHMs) within the household on the basis of the generalized estimating equation approach. Potential confounders (HHM age and number of children aged <10 years in the household) were entered into the model individually, but were not included because they did not change associations by $\geq 10\%$. The final model included receipt of treatment by the household primary patient (no receipt, initiation <1 week or ≥ 1 week after cough onset) and receipt of prophylaxis by each HHM (no receipt, initiation <2 weeks or ≥ 2 weeks after cough onset in the household primary patient). Households with coprimary patients, unknown

dates of cough onset, or unknown HHM antibiotic histories were excluded. Sensitivity analyses, adjusting for household follow-up time, produced similar results (data not displayed). Results were summarized as relative risks (RRs) with corresponding 95% confidence intervals (CIs). All P -values were 2-sided; $P < .05$ was used to define statistical significance. This project was reviewed by the Centers for Disease Control and Prevention and determined to be nonresearch because it was applied public health evaluation and control.

RESULTS

Case Reporting and Inclusion

During the 15-month paraptussis outbreak period, 7022 *Bordetella* infections were reported to WDPH; 6579 (93.7%) were positive for *B. pertussis* only; 417 (5.9%) were positive for *B. paraptussis* only; and 26 (0.4%) were *B. paraptussis*-*B. pertussis* coinfections (Figure 1). Fifty-two of Wisconsin's 72 counties reported *B. paraptussis* infections among residents.

Figure 2 depicts inclusion of study subjects. During the study interval, WDPH received 3371 reports of patients with positive *Bordetella* PCR results; 218 illnesses met the paraptussis case definition, including 28 Wood County residents. Thirteen illnesses statewide met the coinfection case definition. Additionally, 103 illnesses among Wood County residents met the pertussis case definition.

During the study interval, 55% (144/261) of *B. paraptussis*-positive specimens from 261 patients were tested by 2 laboratories that simultaneously test all specimens for *B. pertussis* and

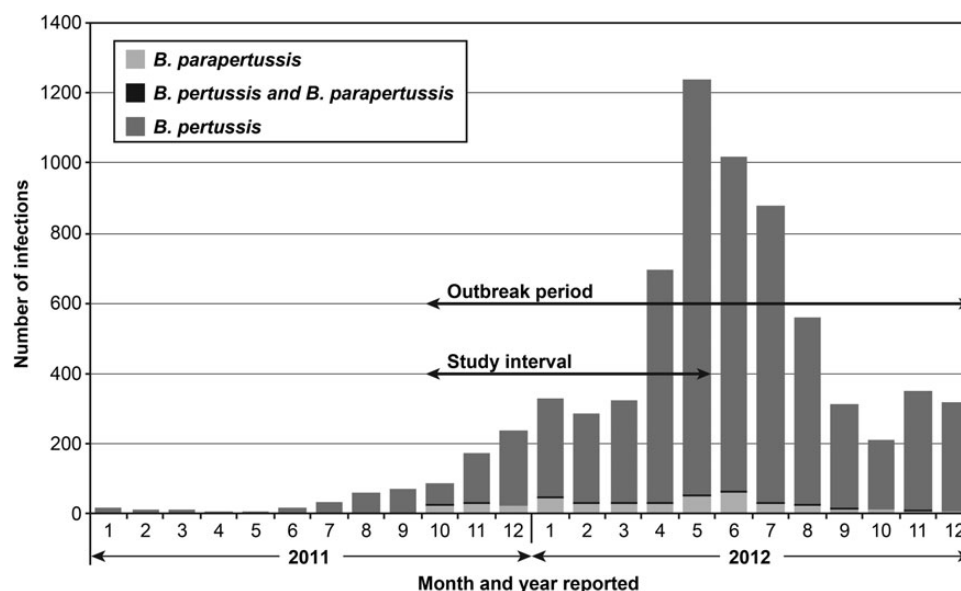


Figure 1. Number of reported cases of *Bordetella pertussis* and *B. paraptussis* infections and *B. paraptussis*-*B. pertussis* coinfections by month and year of report, Wisconsin. The outbreak period was 1 October 2011–31 December 2012. The study interval was 1 October 2011–31 May 2012.

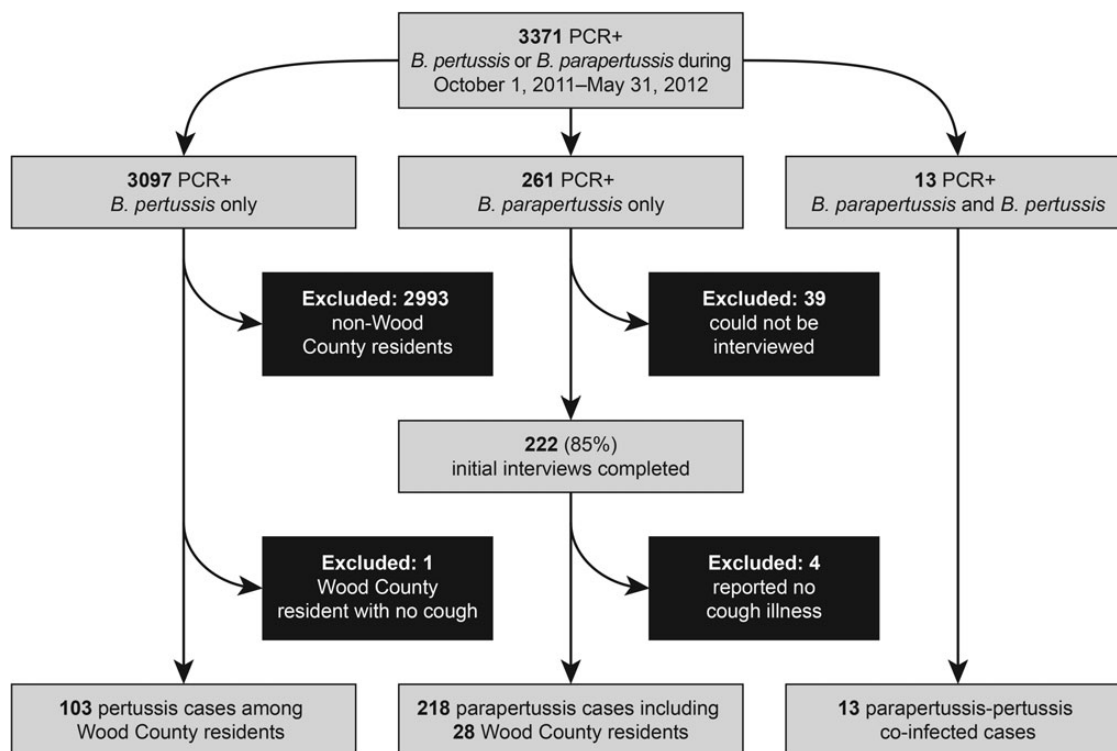


Figure 2. Inclusion of study subjects. During the 8-month study interval, the Wisconsin Division of Public Health received reports of 3371 patients residing in Wisconsin with positive *Bordetella* polymerase chain reaction (PCR) results. Among these patients, 261 had specimens positive for *Bordetella parapertussis* only, and 222 (85%) had initial interviews completed. Among the latter, 4 (2%) reported never having a cough and were excluded. In total, 218 illnesses met the parapertussis case definition, including 28 that occurred among Wood County, Wisconsin, residents. Thirteen persons had positive PCR results for both *Bordetella pertussis* and *B. parapertussis*; all had initial interviews completed and had illnesses that met the case definition of parapertussis-pertussis coinfection. Additionally, 103 Wood County residents had PCR results positive for *B. pertussis* with cough onsets during the study interval and were interviewed. A limited number of specimens were confirmed by culture during the study interval. Among 218 patients with parapertussis, 15 had specimens tested by using culture; of these, 5 had culture-results positive for *B. parapertussis* (2 were Wood County residents). Only 1 of 13 patients with coinfection had a specimen tested by using culture; neither species was isolated. Among 103 Wood County patients with pertussis, 19 had specimens tested by using culture; all results were negative.

B. parapertussis and consistently report all results. Among *Bordetella*-positive specimens tested at these 2 laboratories during the study interval, 1,133 (88.2%) were positive for *B. pertussis* only; 144 (11.2%) were positive for *B. parapertussis* only; and 8 (0.6%) were positive for both species.

Parapertussis, Statewide

Among 218 patients with parapertussis, median age was 5.6 years (range: 1 month–39 years); 11% were aged <1 year; and 86% were aged <10 years (Table 1). Frequently reported pertussis-like signs and symptoms included paroxysmal cough (60%), posttussive vomiting (31%), whoop (15%), and apnea (9%) (Table 2). Sleep disturbance was reported among 71% of patients and in ≥ 1 HHM among 55% of households. No seizures or encephalopathies were reported. Two patients (both aged <3 months) were each hospitalized for 3 days. Among 180 (83%) patients followed until all symptoms resolved, the median durations of cough and paroxysmal cough were 15 and 7 days,

respectively. Forty-seven percent of patients had illnesses meeting the pertussis clinical case definition. The majority of patients ($n = 194$; 89%) received an antibiotic recommended for treating pertussis (azithromycin [$n = 190$, 98%], trimethoprim/sulfamethoxazole [$n = 3$], and erythromycin [$n = 1$]); 8 (4%) received an unknown antibiotic; and 16 (7%) were classified as nonrecipients (no antibiotic treatment [$n = 13$] or amoxicillin [$n = 3$]).

Presence of paroxysmal cough, whoop and duration of cough were similar across all age groups (Table 2). Reports of posttussive vomiting and apnea decreased with increasing patient age.

Coinfection, Statewide

Coinfected patients ($n = 13$) were older (median age: 10.7 years; range: 7 months–55 years) than parapertussis patients (Table 1). Clinical features among coinfecting patients are presented in Supplementary Table 1. Frequencies of reported pertussis-like symptoms were similar among coinfecting patients and

Table 1. Demographic Characteristics of Study Patients, by Type of *Bordetella* Infection—Wisconsin, 1 October 2011–31 May 2012

Characteristic	Wisconsin ^a		Wood County ^b	
	Parapertussis No. (%) (n = 218)	Coinfection No. (%) (n = 13)	Parapertussis No. (%) (n = 28)	Pertussis No. (%) (n = 103)
Age (yrs)				
<1	25 (11)	1 (8)	2 (7)	3 (3)
1–4	69 (32)	2 (15)	11 (39)	7 (7)
5–9	93 (43)	3 (23)	11 (39)	20 (19)
10–14	22 (10)	4 (31)	3 (11)	49 (48)
15–20	6 (3)	2 (15)	0 (0)	17 (16)
≥21	3 (1)	1 (8)	1 (4)	7 (7)
Median (IQR) ^c	5.6 (3.4–7.7)	10.7 (5.5–14.5)	5.3 (3.5–7.9)	11.9 (9.2–14.6)
Sex				
Male	121 (56)	7 (54)	14 (50)	48 (47)
Female	97 (44)	6 (46)	14 (50)	55 (53)
Race ^d				
White	156 (94)	11 (92)	13 (87)	40 (95)
Black	4 (2)	0 (0)	0 (0)	0 (0)
Other	6 (4)	1 (8)	2 (13)	2 (5)
Ethnicity ^d				
Hispanic	12 (8)	0 (0)	2 (14)	0 (0)
Non-Hispanic	146 (92)	12 (100)	12 (86)	42 (100)

Coinfection: Test results positive for both *Bordetella parapertussis* and *Bordetella pertussis*.

Abbreviation: IQR, interquartile range.

^a 2010 US Census Bureau report for Wisconsin population of approximately 5.68 million persons.

^b 2010 U.S. Census Bureau reports for Wood County, Wisconsin, population of approximately 74 000 persons.

^c Statewide, parapertussis patients were significantly younger than patients with coinfection (Mann–Whitney *U* test, *P* = .010). Among Wood County patients, parapertussis patients were significantly younger than pertussis patients (Mann–Whitney *U* test, *P* < .001).

^d Percentages exclude patients with missing information.

parapertussis patients, but durations of cough and paroxysmal cough were longer among coinfecting patients.

Parapertussis and Pertussis, Wood County

Among Wood County patients, parapertussis patients were younger than pertussis patients (median age: 5.3 vs 11.9 years; *P* < .001) (Table 1). Pertussis-like symptoms were reported frequently among parapertussis and pertussis patients, including paroxysmal cough (75% and 76%), posttussive vomiting (29% and 35%), whoop (29% and 15%), and sleep disturbance (78% and 77%), respectively (Table 3). Among the 82% of parapertussis and 98% of pertussis patients followed until all symptoms resolved, median cough duration was longer among pertussis patients than parapertussis patients (28 vs 14 days; *P* = .004) (Table 3). Similarly, duration of paroxysmal cough was longer among pertussis patients. However, percentages of patients with illnesses meeting the pertussis clinical case definition did not differ significantly between parapertussis and pertussis patients (61% vs 74%; *P* = .177).

When stratified by age group, similar trends were observed; frequencies of pertussis-like symptoms were not significantly

different among patients with parapertussis and pertussis, and durations of cough and paroxysmal cough tended to be longer among pertussis patients (Table 3).

Antibiotics for Treatment, Statewide

Among parapertussis patients, 81% (154/190) of azithromycin treatment recipients and 88% (14/16) of nonrecipients were followed until coughing resolved. Among 150 (97%) treatment recipients with known initiation dates, 74 (49%), 42 (28%), and 34 (23%) received antibiotics 0–6, 7–13, and ≥14 days after cough onset, respectively. Patient ages were similar among treatment recipients and nonrecipients (Table 4). Cough illnesses were shorter among patients treated 0–6 days after cough onset, compared with nonrecipients (*P* = .002) and patients treated 7–13 and ≥14 days after cough onset (Table 4). Neither of the hospitalized patients received antibiotics 0–6 days after cough onset.

Antibiotics for Prevention, Statewide

The 218 parapertussis patients resided among 210 households; interviews were conducted with persons from 156 (74%) households, and 478 nonindex patient HHMs were identified.

Table 2. Clinical Features of Patients With Parapertussis, by Age—Wisconsin, 1 October 2011–31 May 2012

Clinical Feature	All Ages No. (%) ^a (n = 218)	Aged <1 y No. (%) ^a (n = 25)	Aged 1–4 y No. (%) ^a (n = 69)	Aged 5–9 y No. (%) ^a (n = 93)	Aged ≥10 y No. (%) ^a (n = 31)	P Value ^b
Cough	218 (100)	25 (100)	69 (100)	93 (100)	31 (100)	. . .
Cough duration (days), median (IQR)	15 (10–26)	15 (10–27)	16 (9–28)	15 (10–26)	15 (10–24)	.527
Paroxysmal cough	131 (60)	14 (56)	47 (68)	53 (57)	17 (55)	.931
Paroxysmal cough duration (days), median (IQR)	7 (4–11)	5 (3–8)	7 (5–9)	7 (3–12)	8 (6–12)	.074
Posttussive vomiting	67 (31)	11 (44)	23 (33)	28 (30)	5 (16)	.035 ^c
Whoop	33 (15)	5 (20)	11 (16)	11 (12)	6 (19)	1.000
Apnea	19 (9)	4 (16)	9 (13)	4 (4)	2 (6)	.047 ^c
Sleep disturbance in patient	154 (71)	19 (76)	52 (75)	65 (70)	18 (58)	.208
Sleep disturbance in any household member ^d	106 (55)	13 (57)	39 (64)	39 (48)	15 (54)	.833
Cyanosis ^d	2 (1)	1 (4)	1 (2)	0 (0)	0 (0)	.462
Fever ^d	51 (25)	10 (43)	16 (24)	19 (22)	6 (20)	.079
Weight loss ^d	15 (8)	1 (4)	5 (9)	7 (9)	2 (7)	1.000
Hospitalized	2 (1)	2 (8)	0 (0)	0 (0)	0 (0)	.184
Met pertussis clinical case definition ^e	103 (47)	9 (36)	36 (52)	46 (49)	12 (39)	.835
Received recommended antibiotic ^f	194 (89)	22 (88)	61 (88)	82 (88)	29 (94)	.579
Days from cough onset to antibiotic receipt, median (IQR)	7 (4–13)	7 (4–15)	7 (4–11)	6 (3–12)	7 (3–14)	.677

Abbreviation: IQR, interquartile range.

^a All data are presented as number and percentage except for the cough and paroxysmal cough durations, which are presented as median and IQR.

^b Difference among patients aged <1 year and patients aged ≥10 years were calculated using χ^2 or Fisher exact test for differences in categorical variables or Mann–Whitney *U* test for differences in continuous variables.

^c *P*-value of Cochran–Armitage test for trend with age.

^d Percentages exclude patients with missing information.

^e Illnesses were classified by whether they met the Council of State and Territorial Epidemiologists clinical case definition of pertussis (cough illness ≥14 days with ≥1 of the following: whoop, paroxysms, or posttussive vomiting) used during 2011–2012 [25].

^f Recommended antibiotic treatment includes azithromycin, erythromycin, clarithromycin, or trimethoprim-sulfamethoxazole.

Antibiotic prophylaxis was received by 27% (131/478) of HHMs; all prophylaxes were with azithromycin. Among HHMs aged 1–10 years, ARs of coprimary and secondary cough illnesses were significantly lower among prophylaxis recipients, compared with nonrecipients (Table 5). Among HHMs aged >10 years, ARs of secondary cough illness were significantly lower among prophylaxis recipients. Additionally, among 12 HHMs aged <1 year, ARs were lower among prophylaxis recipients.

Households with and without secondary illnesses were similar regarding the number of HHMs aged <10 years, duration of follow-up, and treatment receipt by the household primary patient (Table 6). Prophylaxis receipt by HHMs was more frequent among households with no secondary cough illnesses (*P* = .086). Treatment (*P* = .046) and prophylaxis (*P* < .001) occurred significantly earlier during the primary patients' cough illnesses among households without secondary illnesses.

In multivariate analysis, compared with no prophylaxis, prophylaxis receipt by HHMs <2 weeks after primary patient cough

onset was significantly associated with no secondary cough illnesses among HHMs (RR: 0.16; 95% CI, .04–.69) (Table 6). Treatment receipt by the primary patient <1 week after cough onset was also associated with having no secondary cough illnesses among HHMs, but the association was not statistically significant (RR: 0.60; 95% CI, .14–2.46).

DISCUSSION

The number of *B. parapertussis* infections observed in Wisconsin during October 2011–December 2012 (*n* = 443) is the largest reported in the United States. Observations of *B. parapertussis* infections [1, 16, 27–29], including a mixed outbreak of *B. pertussis*, *B. parapertussis*, and *B. holmseii* infections in Ohio during 2010–2011 [28], have been reported recently in the United States, likely because of increased use of PCR testing to detect *B. parapertussis*. Despite increased testing, the burden of *B. parapertussis* infection in the United States is challenging to measure because testing that differentiates *Bordetella* species

Table 3. Clinical Features of Patients With Parapertussis and Patients With Pertussis, by Age—Wood County, Wisconsin, 1 October 2011–31 May 2012

Clinical Feature	All Ages			Aged <5 y			Aged 5–10 y		
	Parapertussis No. (%) ^a (n = 28)	Pertussis No. (%) ^a (n = 103)	P Value ^b	Parapertussis No. (%) ^a (n = 13)	Pertussis No. (%) ^a (n = 10)	P Value ^b	Parapertussis No. (%) ^a (n = 13)	Pertussis No. (%) ^a (n = 32)	P Value ^b
Cough duration (days), median (IQR)	14 (11–28)	28 (17–40)	.004	14 (7–25)	31 (20–41)	.045	14 (12–37)	30 (17–35)	.265
Paroxysmal cough	21 (75)	78 (76)	.937	10 (77)	8 (80)	1.000	10 (77)	21 (66)	.724
Paroxysmal cough duration (days), median (IQR)	6 (4–7)	16 (8–30)	<.001	7 (5–7)	12 (7–18)	.254	5 (3–7)	14 (8–18)	.022
Posttussive vomiting	8 (29)	36 (35)	.603	5 (38)	7 (70)	.231	3 (23)	9 (28)	1.000
Whoop	8 (29)	15 (15)	.078	3 (23)	2 (20)	1.000	4 (31)	3 (9)	.075
Apnea	2 (7)	12 (12)	.512	2 (15)	5 (50)	.074	0 (0)	1 (3)	1.000
Sleep disturbance in patient ^c	21 (78)	78 (77)	.952	9 (75)	8 (80)	1.000	11 (85)	25 (78)	1.000
Sleep disturbance in any household member ^c	14 (54)	22 (56)	.839	5 (45)	2 (100)	.462	8 (62)	9 (69)	1.000
Hospitalized	0 (0)	2 (2)	1.000	0 (0)	2 (20)	.178	0 (0)	0 (0)	...
Met pertussis clinical case definition ^d	17 (61)	76 (74)	.177	8 (62)	8 (80)	.405	8 (62)	23 (72)	.502
Up-to-date for age with pertussis vaccinations, patients aged 3 mo–10 y ^{c,e}	24 (96)	34 (89)	.640	11 (92)	4 (67)	.245	13 (100)	30 (94)	1.000

Abbreviation: IQR, interquartile range.

^a All data are presented as number and percentage except for the cough and paroxysmal cough durations which are presented as median and IQR.^b P-value of χ^2 or Fisher exact test for difference in presence of symptoms by type of infection or Mann–Whitney U test for difference in symptom duration by type of infection.^c Percentages exclude patients with missing information.^d Illnesses were classified by whether they met the Council of State and Territorial Epidemiologists clinical case definition of pertussis (cough illness ≥ 14 days with ≥ 1 of the following: whoop, paroxysms, or posttussive vomiting) used during 2011–2012 [25].^e Patients aged 3 months–10 years were categorized as up-to-date for age with pertussis vaccinations on the basis of the Advisory Committee on Immunization Practices recommended vaccination schedule [26].**Table 4. Duration of Cough Illness Among Patients With Parapertussis, by Timing of the Initiation of Azithromycin Treatment—Wisconsin, 1 October 2011–31 May 2012**

Feature	Initiation of Azithromycin Treatment				P Value ^a
	Nonrecipients (n = 14)	0–6 d After Cough Onset (n = 74)	7–13 d After Cough Onset (n = 42)	≥ 14 d After Cough Onset (n = 34)	
Age (yrs), median (IQR)	5 (4–6)	5 (3–8)	5 (3–7)	5 (3–7)	.996
Duration of cough illness (days), median (IQR)	19 (14–29)	10 (8–15)	16 (14–25)	26 (24–38)	.002 ^b
Hospitalized, n (%)	0 (0)	0 (0)	2 (5)	0 (0)	...

Abbreviation: IQR, interquartile range.

^a P-value of Mann–Whitney U test for the difference between initiation of azithromycin treatment 0–6 days after cough onset vs nonrecipients.^b P-value of Mann–Whitney U test for differences in duration of cough illness by timing of initiation of azithromycin treatment: 0–6 days vs 7–13 days ($P < .001$); 0–6 days vs ≥ 14 days ($P < .001$); 7–13 days vs ≥ 14 days ($P = .001$).

Table 5. Attack Rates of Coprimary and Secondary Cough Illnesses Among Household Members of Patients With Parapertussis, by Receipt of Azithromycin Prophylaxis and Age of Household Members—Wisconsin, 1 October 2011–31 May 2012

Household Member Age Category	Household Members No.	Cough Illness Type Occurring Among Household Members	Azithromycin Prophylaxis Received				P Value ^a
			Yes		No		
			No.	Attack Rate (%)	No.	Attack Rate (%)	
All ages	478		131		347		
		Coprimary ^b		1/131 (1)		39/347 (11)	<.001
		Secondary ^c		0/130 (0)		36/308 (12)	<.001
Aged >10 y	317		90		227		
		Coprimary ^b		1/90 (1)		8/227 (4)	.45
		Secondary ^c		0/89 (0)		14/219 (6)	.013
Aged 1–10 y	149		36		113		
		Coprimary ^b		0/36 (0)		29/113 (26)	<.001
		Secondary ^c		0/36 (0)		20/84 (24)	<.001
Aged <1 y	12		5		7		
		Coprimary ^b		0/5 (0)		2/7 (29)	.470
		Secondary ^c		0/5 (0)		2/5 (40)	.444

The primary patient in each household was excluded from these analyses.

^a P-value of Fisher exact test for difference in attack rate by receipt of azithromycin prophylaxis.

^b Coprimary illness is defined as cough onset 0–6 days after cough onset in the household primary patient.

^c Secondary illness is defined as cough onset 7–16 days after cough onset in the household primary patient. Attack rate calculations exclude from the denominator all persons with coprimary illnesses because persons with coprimary illnesses were not at risk for having a secondary illness.

is not universal [18, 19]. Among specimens tested simultaneously for *B. pertussis* and *B. parapertussis*, we observed 11.2% of specimens positive for *Bordetella* were positive for *B. parapertussis* only, and an additional 0.6% were positive for *B. parapertussis* and *B. pertussis*. This percentage of *Bordetella* specimens positive for *B. parapertussis* is similar to previous observations in Wisconsin (culture: 11.9%; PCR: 14.3% [Supplementary Table 2]) and in other states (range: 10%–14.9%) [16, 27, 28], which indicates that infection with *B. parapertussis* is endemic in the United States and will be identified when testing for *B. parapertussis* is routinely conducted.

Our results provide additional evidence that *B. parapertussis* infection can cause pertussis-like illness [8–13]. Our results also demonstrate the duration of parapertussis illness and the presence of paroxysmal cough were generally similar among all age groups. Other pertussis-like signs and symptoms and hospitalization were most common among infants. Considering occurrences of *B. parapertussis* bacteremia among 2 children with underlying medical conditions [30], these findings underscore the importance of treating and preventing *B. parapertussis* infections, especially among infants and other populations at increased risk for severe disease.

Results of antibiotic susceptibility studies indicate the same antibiotics recommended for treating and preventing pertussis might be useful for treating and preventing parapertussis [20, 21]. Our results indicate that azithromycin treatment early

during parapertussis illness might reduce the duration of illness. Furthermore, our results indicate that prompt prophylaxis of HHMs and prompt treatment of parapertussis patients might prevent secondary cough illnesses among parapertussis patients' HHMs. Wisconsin is among a limited number of states [22] with guidelines for managing persons with *B. parapertussis* infection and recommends antibiotic treatment of infected persons and prophylaxis of contacts aged <6 months and all HHMs if an infant aged <6 months is in the household [23]. Although our results provide support for the effectiveness of these interventions, controlled studies are needed to evaluate the effectiveness of these interventions and determine risks for antibiotic use vs benefits of preventing illness among infants.

Although shorter in duration, parapertussis illnesses were similar to illnesses caused by *B. pertussis* and *B. parapertussis*-*B. pertussis* coinfection. The similarity in clinical presentation of these infections is important for the perception and measurement of pertussis vaccine effectiveness because available pertussis vaccines provide little or no protection from illnesses caused by *B. parapertussis* [31, 32] or *B. holmesii* [15]. Consequently, parapertussis cases misclassified as pertussis might be perceived as vaccine failures [17].

The younger age among parapertussis patients, compared with pertussis patients, has been observed previously [16, 27–29] and might be a result of selection bias because older persons with a mild illness might not seek care or testing. Others have suggested

Table 6. Univariate and Multivariate Analyses of Household and Household Member Characteristics Associated With Secondary Cough Illnesses in the Household — Wisconsin, 1 October 2011–31 May 2012

Characteristic	Univariate Analysis		
	Household Member had a Secondary ^a Cough Illness		P Value ^b
	No 101 Households With 300 Nonprimary Patient Household Members	Yes 19 Households With 61 Nonprimary Patient Household Members	
Number of members in household aged <10 y, median (IQR)	2 (1–2)	2 (2–2)	.156
Days household was followed, median (IQR)	29 (18–46)	32 (20–62)	.424
Azithromycin treatment received by household primary patient, No.(%)	84 (83)	15 (79)	.742
Days from cough onset to initiation of azithromycin treatment by household primary patient, median (IQR)	7 (4–12)	14 (8–15)	.046
Azithromycin prophylaxis received by household members, No. (%)	93 (31)	12 (20)	.086
Days from cough onset in household primary patient to initiation of azithromycin prophylaxis by household member, median (IQR)	8 (6–13)	15 (15–17)	<.001
	Multivariate Analysis		
	n (%)	n (%)	Adjusted ^c RR (95% CI)
Azithromycin treatment of household primary patient			
None	17 (17)	4 (21)	Reference
Initiated <1 wk after cough onset	39 (39)	3 (16)	0.60 (.14–2.46)
Initiated ≥1 wk after cough onset	45 (45)	12 (63)	1.31 (.46–3.70)
Azithromycin prophylaxis of individual household member			
None	211 (70)	49 (80)	Reference
Initiated <2 wks after cough onset in household primary patient	70 (23)	2 (3)	0.16 (.04–.69)
Initiated ≥2 wk after cough onset in household primary patient	19 (6)	10 (16)	1.40 (.66–2.99)

Abbreviations: CI, confidence interval; IQR, interquartile range; RR, relative risk.

^a Secondary cough illness is defined as cough onset in a household member 7–16 days after cough onset in the household primary patient.

^b P-value of χ^2 test or Fisher exact test for categorical variables and Mann–Whitney *U* test for continuous variables.

^c Adjusted relative risk of secondary cough illness in the household, adjusted for azithromycin prophylaxis of household members, azithromycin treatment of household primary patients, and for repeated measurements within each household.

the age difference might be because acellular pertussis vaccination of young children provides protection from *B. pertussis*, but might increase their susceptibility to *B. paraptussis* [27, 33].

Our study has several limitations. Because culture is now rarely used, few infections were culture confirmed, and studies to characterize strains were not conducted. Regarding *Bordetella* differentiation, only 1 Wisconsin laboratory (Wisconsin State Laboratory of Hygiene [WSLH]) uses a PCR that differentiates between *B. pertussis*, *B. paraptussis*, and *B. holmesii*. However, of 8505 specimens tested by WSLH during 2012–2013, none was positive for *B. holmesii*. Our estimate of the relative occurrence of *B. paraptussis* and *B. pertussis* infections was based

on patients with positive PCR results and thus may not reflect the true relative occurrence of paraptussis compared with pertussis. Because our study was observational, it is possible factors associated with antibiotic receipt and development of cough illness might confound our results. For example, households accepting antibiotics might have been more likely to use other preventive measures that were not measured. Additionally, because PCR testing among symptomatic HHMs was uncommon, the proportion of HHMs with secondary cough illness caused by *B. paraptussis* is unknown. Controlled studies are needed to evaluate azithromycin effectiveness to treat and prevent paraptussis.

The Ohio [15, 28] and Wisconsin outbreaks demonstrate the potential for cocirculation of *Bordetella* species and the importance of testing patients with pertussis-like illness using tests that differentiate *B. pertussis*, *B. parapertussis*, and *B. holmesii*. A PCR test that differentiates between these species has been developed and is used by many public health laboratories [18, 34] and can be used by any laboratory testing for *Bordetella*. Although empiric management of patients presenting with pertussis-like illness might be effective, when a patient infected with *B. parapertussis* is tested for *B. pertussis* only, the negative result might lead to unnecessary testing for non-*Bordetella* etiologies or ineffective treatments. Differentiation of *Bordetella* species can confirm diagnoses, permit assessment of treatments, and facilitate species-specific studies of disease burden and more accurate determination of pertussis vaccine effectiveness.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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