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Risk Factors Associated With *Bordetella pertussis* Among Infants ≤4 Months of Age in the Pre-Tdap Era:

United States, 2002–2005

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Abstract

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Background: In the United States, infants have the highest reported pertussis incidence and death rates. Improved understanding of infant risk factors is needed to optimize prevention strategies.

Methods: We prospectively enrolled infants ≤4 months of age with incident-confirmed pertussis from 4 sites during 2002–2005 (preceding pertussis antigen-containing vaccination recommendations for adolescents/adults); each case-patient was age and site matched with 2 control subjects. Caregivers completed structured interviews. Infants and their contacts ≥11 years of age were offered serologic testing for IgG; being seropositive was defined as ≥94 antipertussis toxin IgG enzyme-linked immunosorbent assay units per milliliter.

Results: Enrolled subjects (115 case-patients; 230 control subjects) had 4396 contacts during incubation periods; 83 (72%) case-patients had ≥1 contact with prolonged (≥5 days) new cough in primary or secondary households. In multivariable analysis, the odds for pertussis were higher for infants with primary/secondary household contacts who had a prolonged new cough, compared with infants who did not. These contacts included mother [adjusted matched odds ratio (aMOR), 43.8; 95% confidence interval (CI), 6.45–298.0] and ≥1 nonmother contact (aMOR, 20.1; 95% CI, 6.48–62.7). Infants receiving breast milk with 0–1 formula feedings daily had decreased pertussis odds (aMOR, 0.27; 95% CI, 0.08–0.89), compared with those receiving more formula. Of 41 tested case-patients, 37 (90%) were seropositive.

Conclusions: Pertussis in infants was associated with prolonged new cough (≥5 days) in infants' household contacts. Findings suggest that breastfeeding protects against pertussis and warrants recommendation with pertussis prevention strategies, which currently include pertussis vaccination of pregnant mothers and infants' close contacts.

Keywords

Bordetella pertussis ; whooping cough; infants; risk factors; breastfeeding; serology

Recent epidemic peaks demonstrate pertussis' persistent endemicity in the United States[1–3] despite childhood vaccine availability since the 1940s,[2] high ensuing coverage[4] and vaccine recommendations since 2006 for adolescents and adults.[5,6] Among infants ≤4 months of age, pertussis-related deaths tripled, from 49 during 1980–1989 to 152 during 2000–2009.[7–9] During the 2014 California epidemic, pertussis incidence was significantly higher among Hispanic infants; of 347 hospitalized patients, 214 (62%) were <4 months of age.[3] Because infants have highest reported pertussis incidence and death rates,[10] protecting young infants at greatest risk remains a priority.[11]

Bordetella pertussis is a highly infectious pathogen transmissible by respiratory droplet.[5,6] Identifying infants' transmission sources has challenged investigators. Frequently cited source studies were not designed to assess hypotheses including possible transmission by community contacts or persons with atypical symptoms and could not identify pertussis sources for ~40%–50% of infants.[12–15] In a 2006–2013 pertussis surveillance case series of infants younger than 1 year, source(s) were not identified for 737 (56%) of 1306 cases.[16] Previous publications describe possible factors for further study, including exposures among >1 household,[17] younger mothers,[17–19] mothers with ≥7 days' cough duration[17] or Hispanic ethnicity.[7,8,12,17,19] Investigation of these hypotheses and characterization of other potential

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factors remain needed for developing and promoting effective pertussis prevention strategies among infants of 4 months of age or younger.

MATERIALS AND METHODS

Study Participants

Participants included (1) incident-confirmed pertussis cases reported during 2002–2005 among infants of 4 months of age or younger in 4 health department jurisdictions (Arizona; Minnesota; Philadelphia, Pennsylvania; and Seattle, Washington); (2) 2 control subjects (controls) matched to each case-patient by age (0–7 days after case-patient's birthdate) and either birth institution (2 jurisdictions) or residential location (2 jurisdictions); (3) infants' contacts ≥11 years of age who submitted blood samples and (4) infants' caregivers (ie, the person who fed, changed and bathed the infant ≥50% of time on average, during the 4-week reference month before the matched case-patient's symptom onset). Pertussis symptom onsets were defined as caregiver-reported dates when case-patients were first noted to have cough or apnea (if not recalled, pertussis case report forms' cough onset or diagnosis dates were used).

Infants were excluded if caregivers spoke neither English nor Spanish or if residing outside jurisdiction. Controls' exclusion criteria included previous pertussis diagnosis, new cough lasting ≥5 days during the reference month, interviewer-observed pertussis symptoms, nontraumatic death or death before matched case-patient pertussis onset.

Institutional Review Boards at the Centers for Disease Control and Prevention (CDC), health departments and participating hospitals approved this study. We completed enrollment before 2006 publications of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine recommendations.[5,6]

Case Definitions, Laboratory Data and Analysis

Clinical case definition and confirmation were consistent with CDC and Council of State and Territorial Epidemiologists guidelines.[20,21] Noncoughing case-patients with apnea were eligible if diagnosis was culture-confirmed. Culture and polymerase chain reaction[20,22–24] were performed locally; CDC completed pulsed-field gel electrophoresis (PFGE)[25] on *B. pertussis* isolates and compared findings with >4000 US isolates collected during 1935–2009.[25,26] Caregivers consented (for themselves or their children) to blood collections and identified consenting contacts ≥11 years of age. CDC assayed blinded serum samples for IgG antipertussis toxin by using an enzyme-linked immunosorbent assay.[27] We analyzed samples obtained ≤182 days after illness onsets (n = 181) to control for waning antibody levels, vaccination status and potential interim pertussis exposures. Concentrations outside the standard curve [<15 enzyme-linked immunosorbent assay units/milliliter (EU/mL) or >480 EU/mL) were set as 15 or 480 EU/mL, respectively. Seropositivity was defined as ≥94 EU/mL antipertussis toxin IgG.[27]

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Questionnaire Data and Analysis

Investigators interviewed caregivers using a 92-item questionnaire during September 2002 to June 2005. Information collected included infants' exposures during the 4 weeks before symptom onset (pertussis incubation period[28,29]). Caregivers identified contacts residing in households where infants spent ≥8 hours/week or ≥1 night during reference months. Primary households (PHH) were where infant and caregiver resided; others were secondary households (SHH). Caregivers identified persons who visited when infants were present; general contacts were any other persons having infant contact. Caregivers identified persons having "face-to-face" contact (≥5 minutes at ≤3 feet proximity[30]) with infants.

Because adults might hypothetically have atypical pertussis symptoms,[6] questions regarding their illnesses were not restricted to clinical case definition.[20,21] For general contacts, caregivers indicated whether runny nose or congestion (respiratory symptoms) or new cough was present. For household and visitor contacts, caregivers also identified persons with new cough lasting ≥5 days (prolonged new cough).

Survey questions addressed birth history, health status, health care usage, insurance status, vaccination history, nutrition, smoking exposure, nonhousehold exposures, infant race/ethnicity, parental ages and birth countries, maternal education, maternal peripartum symptoms and caregivers' hypothetical vaccine acceptance for themselves. PHH variables included persons/room and total persons. We defined breastfed as breast milk receipt with 0–1 supplemental formula feedings daily before symptom onset and "other" as infants' receiving ≥2 formula feedings daily.

We reviewed caregiver-reported infant diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccination dates for consistency with recommendations (eg, infants of 42 days of age or older were eligible for first DTaP dose);[31] if inconsistent or missing, we abstracted immunization information systems or medical records data. Doses administered ≥14 days before symptom onsets were valid.[32]

By using conditional logistic regression (SAS version 9.2, SAS Institute, Incorporated, Cary, NC), we calculated matched odds ratios (MORs) and 2-sided 95% confidence intervals (CIs). We employed the Kaplan–Meier method to estimate case-patients' cough durations and the Wilcoxon rank-sum test to evaluate contact number distribution differences. To identify ≥1 symptomatic contact for each symptom for each infant, a symptom was treated as missing if ≥1 contact was missing data, and all other contacts were asymptomatic. Statistical significance was assessed at the 0.05 level.

By considering published literature,[1,3,7,8,12,13,17,19] statistically significant univariate associations, collinearity, data completeness, the number of candidate variables and sample size, we identified 13 factors for multivariable analysis [ie, maternal age, infant ethnicity (Hispanic vs. non-Hispanic), persons/room, insurance status, housing type, number of households, breastfeeding, 3 age-based (ie, 8–10, 11–18 and 19–29 years) PHH variables regardless of symptoms, number of persons (including infants) in PHH and 2 variables for PHH and SHH contacts with prolonged new cough]. By using the backward elimination procedure with a $P = 0.10$ significance level, the initial model was reduced to 5 factors. In

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the final model, to characterize disease associations with exposure to mother and household nonmother contacts with prolonged new cough, we combined nonmother PHH and SHH contacts and considered mothers as a separate variable. We assessed effect modification between each variable pair.

RESULTS

Of 129 eligible case-patients and 371 eligible controls with contact information, 115 (89%) case-patients and 230 (62%) controls were enrolled. Of 3 infants who died from pertussis, 2 were enrolled. At onsets, case-patients' ages were 6–122 (median, 50) days. During pertussis illnesses, most case-patients required ≥1 hospitalization; almost half were apneic (Table 1). Of 113 (98%) case-patients assessed, 16 were still coughing at caregiver interview. Approximately 25% of case-patients were still coughing at 114 days after onsets (median, 71 days' cough; 95% CI, 59–79 days).

Seventy-seven (67%) cases were culture-confirmed (Table 1). Compared with stored US isolates, 48 (96%) of 50 study isolates tested had commonly observed PFGE profiles; 28 (56%) had the profile identified most frequently during the study period (2000–2005) and beyond (2006–2009).[25,26]

Of 41 tested case-patients, 37 (90%) were seropositive (Table 2), including 24 (59%) confirmed by culture and 10 (24%) who received ≥2 DTaP vaccinations after illness and before sera collection. Among 32 controls, 5 (16%) infants who had each received ≥2 DTaP vaccinations precollection were seropositive. Among 63 case-patient contacts tested, 20 (45%) of 44 case-patient mothers and 8 (42%) of 19 nonmother contacts were seropositive. Of 45 control contacts, 1 (2%) was seropositive (Table 2).

Univariate Analysis

The majority of caregivers were mothers; all mothers and most fathers resided in PHHs (Table 3). Characteristics associated with pertussis included lacking insurance or having nonprivate coverage, being Hispanic or belonging to non-Hispanic racial minorities, having 2 foreign-born parents or having mothers lacking postsecondary education. Case-patient mothers' median age was lower (27 years; range, 16–42 years) than control mothers' median age (30 years; range, 14–43 years; $P = 0.01$). Infants receiving breast milk with 0–1 daily supplemental formula feedings were less likely to have pertussis than those with ≥2 daily formula feedings (MOR, 0.26; 95% CI, 0.15–0.46; Table 3).

Having ≥1 PHH, SHH or visitor contacts with prolonged new cough was associated with disease (Table 4). Compared with 19 (9%) controls, 83 (76%) case-patients had ≥1 PHH or SHH contacts with prolonged new cough [MOR, 19.7; 95% CI, 9.07–42.8 (Table 4)]. Having ≥1 contact with any new cough was significantly associated with pertussis only among case-patients with symptomatic PHH contacts (MOR, 2.38; 95% CI, 1.23–4.61). Having ≥1 contact with respiratory symptoms alone (without cough) was not associated with pertussis.

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Compared with controls, case-patients <42 days of age at illness onsets whose mothers experienced peripartum new cough illness had a 7.40-fold increased pertussis odds (Table 4).

Household factors significantly associated with pertussis included exposures in ≥3 households, apartments as PHHs, ≥7 persons per PHH, increasing ratios of persons per PHH room and ≥1 PHH contacts in specific age groups (Table 4).

Overall, 83 (76%) of 109 case-patients with complete contacts' symptom data had ≥1 PHH or SHH contact with prolonged new cough; the most frequent relationship types were sibling (34%), mother (28%) and father (12%; Table 5). Among these 83 case-patients, 24 (29%) had both coughing mothers and coughing nonmother contacts, 17 (20%) had only coughing mothers and 42 (51%) had only coughing nonmother contacts. Of 66 case-patients with coughing nonmother contacts, 33 (50%) case-patients had contacts ≤10 years of age, 21 (32%) had contacts 11–19 years of age, 10 (15%) had contacts 0–29 years of age and 25 (38%) had contacts ≥30 years of age. Of 32 case-patients without household contacts with prolonged new cough, 10 (31%) had ≥1 visitor contacts with prolonged new cough.

Case-patients and controls had 1475 and 2921 total contacts, respectively. Case-patients had higher mean numbers of household contacts both overall and by symptom (Table 6). Eighty-five (74%) case-patients and 196 (85%) controls had visitors; although controls had a higher overall mean ($P = 0.01$), case-patients had a 10-fold higher mean ($P < 0.01$) of visitors with prolonged new cough. Only 16 (13.9%) cases and 30 (13.0%) controls had general contacts; infants' exposures to general contacts with respiratory symptoms or new cough were not associated with pertussis.

Multivariable Analysis

Our final model included maternal age, breastfeeding, household type and prolonged new cough among nonmothers (residing in PHH or SHH) or mothers (Table 7); no significant effect modification was observed. For maternal age, the adjusted matched odds ratio (aMOR) was 0.92 (95% CI, 0.85–0.99), indicating an 8% decrease in odds for pertussis for each 1-year maternal age increase. Infants receiving breast milk with 0–1 formula feedings daily up to symptom onsets had significantly decreased odds for pertussis (aMOR, 0.27; 95% CI, 0.08–0.89). Compared with single-family housing, apartment-type housing was associated with pertussis (aMOR, 9.56; 95% CI 2.68–34.1). Compared with infants without exposure, infants with a mother with prolonged new cough had 43.8-fold (95% CI, 6.45–298.0) greater odds for pertussis; exposure to ≤1 PHH or SHH nonmother with prolonged new cough had 20.1-fold (95% CI, 6.48–62.7) greater odds for pertussis.

Sensitivity Analyses

We conducted multiple sensitivity analyses since a differential exposure variable misclassification might have introduced a bias.[33] Regarding interval between case symptom onset and interview, controls' longer intervals resulted from difficulties in identifying and contacting eligible controls; case-patients' intervals ranged from 19 to 330 (median, 75) days, compared with 22–592 (median, 160) days for controls. When restricted to 64 case-patients and 43 controls enrolled <90 days after illness onsets, the final model

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confirmed pertussis association with having a mother with prolonged new cough (exact conditional analysis aMOR, 11.8; 95% CI, 1.73–∞). When limited to case-patients with culture-confirmed illness and matched controls, results were similar to those for all cases (Table 7).

DISCUSSION

In our study preceding national Tdap recommendations, US infants ≤4 months of age during 2002–2005 whose mother had prolonged new cough (≥5 days) had 43.8-fold greater odds for pertussis; infants exposed to ≥1 nonmother contact with prolonged new cough in PHH or SHH had 20.1-fold greater odds for pertussis. In contrast with studies that failed to identify sources for ~40%–56% of infant cases,[12–16] our data indicate that 72% of case-patients had identifiable possible pertussis transmission sources with ≥1 PHH or SHH contact having a prolonged (≥5 days) new cough.

With ongoing changes in pertussis epidemiology related to waning immunity, aging of primary DTaP series recipients into later childhood and adolescence and questions concerning if recent Tdap vaccination will prevent pertussis or transmission,[34] speculation regarding transmission and infection sources will likely continue. However, we found no evidence to support hypotheses regarding transmission by persons with atypical symptoms, asymptomatic transmission or transmission by general contacts. This study also advances understanding of other hypothesized transmission factors; for example, exposures in ≥1 household were noted in a previous study,[17] were similarly significant in our univariate analyses, but were removed in this study's multivariable modeling.

Higher maternal age appears protective against pertussis infant mortality[19] and disease. Reasons might include differences in maternal vaccination or disease histories. Older mothers might have been more likely to have received whole-cell pertussis vaccines[1] during childhood or, given older age and longer lifetime exposure potential, boosted immunity after prior pertussis infections. Younger mothers have less lifetime pertussis exposure and might have received DTaP as booster doses (age <7 years) and had waning pertussis immunity. Future studies could validate infants' and mothers' vaccination histories and document maternal lifetime pertussis-like illness history or confirmed pertussis diagnoses.

In our study, receipt of a valid DTaP vaccination by infants at 42 days of age or older did not protect against pertussis. Analyses among fatal and nonfatal US infant pertussis cases reported during 1991–2008 demonstrated receipt of ≥1 pertussis vaccination among infants ≥42 days of age was protective against death, hospitalization and pneumonia. Appropriate antibiotic recommendation during pertussis illness was protective against death among infants regardless of age.[35]

Our study's findings support preventing transmission to infants by improving adherence to pertussis vaccination recommendations. The Advisory Committee on Immunization Practices (ACIP) recommends that females receive Tdap vaccination during every pregnancy.[11] Tdap immunization of pregnant mothers can provide transplacental pertussis antibodies to fetuses and likely confer protection to infants until age-appropriate DTaP

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vaccination can occur.[11] ACIP recommends Tdap vaccination for adults and adolescents without history of Tdap receipt if close contact with an infant younger than 12 months is ongoing or anticipated.[11] However, in 2014, despite ACIP recommendations,[6,11] Tdap coverage among adults who lived with an infant younger than 1 year of age was only 32%.[36]

We found breast milk receipt was protective against pertussis. If maternal pertussis antibodies have been boosted by Tdap vaccination,[37] previous pertussis, or have not waned, antibodies can be transferred to infants through breast milk.[38] Breastfeeding protects against respiratory infections;[39,40] since secondary bacterial pneumonia and concomitant respiratory infections can complicate pertussis,[41] breastfeeding's protection could help decrease morbidity and mortality from these infections.

In the multivariable model, household type, perhaps a surrogate for socioeconomic status or infrastructure (eg, shared ventilations), was associated with pertussis. However, Hispanic ethnicity was not associated. Future studies with greater statistical power might better assess any associations between these factors and infants' pertussis risks.

Rapid pertussis diagnosis is needed for optimal treatment.[20,22–27] We found that serologic testing (IgG antipertussis levels ≥94 EU/mL) might complement pertussis diagnostics among unvaccinated infants. Interpreting serologic results among infants whose mothers received Tdap during pregnancy will require additional efforts.

We determined that 96% of tested isolates had PFGE profiles commonly observed during 2000–2009.[25,26] Although PFGE profiles do not correlate with pathogenicity, other methods characterizing circulating *B. pertussis* strains indicate that strains are evolving.[42,43] This evolution's clinical implications, if any, remain unclear.[44,45]

Despite our study's strengths, including its prospective, matched case–control design, certain limitations evolved. The unexpectedly large number of statistically significant univariate associations and limited number of matched sets for multivariable modeling resulted in some wide CIs. Also, caregivers' responses were subject to recall bias, but maternal recall of breastfeeding initiation and duration has been demonstrated as valid and reliable, especially when duration is recalled within 3 years.[46] In addition, study questions' focus on early infancy likely enhanced recall; sensitivity analyses limited to <90 days from illness onset to caregiver interview were reassuring. Caregivers reported infants' known exposures, but some exposures (eg, those occurring in newborn nurseries away from families) might have been unknown. Serologic and confirmatory findings might be biased if eligible contacts did not participate due to nonrandom factors. Although polymerase chain reaction can yield false-positive results,[5] our model restricted to culture-confirmed cases demonstrated similar associations. The majority of enrolled case-patients had culture confirmation and were similar in severity (eg, proportion hospitalized) to those reported nationally.[3,47] In addition, case-patients included 2 of 3 identified infants who died from pertussis and, consistent with recently revised pertussis case definitions,[48] we enrolled case-patients with apnea, although we required culture confirmation.

Reducing pertussis-associated morbidity and mortality among young infants remains dependent on adherence to national vaccination recommendations and timely diagnosis

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and treatment of both infants and contacts; although this study occurred before national recommendations for Tdap vaccination of adolescents, adults and pregnant women,[5,6,10,11] its data can facilitate timely pertussis diagnosis and has implications underscoring the importance of vaccinating infants' contacts. When assessing infants with cough or apnea, clinicians should evaluate for pertussis and also ask about household contacts' cough histories. Infants' household contacts with new coughs, especially if lasting ≥5 days, should also be evaluated for pertussis. Coughing contacts' histories of receipt of acellular pertussis vaccines should not diminish clinical suspicion. Our data indicate that breastfeeding can help protect against pertussis, strengthening evidence that breastfeeding warrants strong support. Adherence to national breastfeeding recommendations, increased awareness among parents and clinicians regarding pertussis symptoms (leading to timely diagnosis and treatment), prompt pertussis vaccination of age-eligible infants and greater adherence to Tdap vaccine recommendations are needed to help reduce pertussis morbidity and mortality among young infants.

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TABLE 1.

Selected Clinical Characteristics of Pertussis Case-Patients (n = 115)

Characteristic	Cases, n (%)*
Diagnostic test	
Isolation of *Bordetella pertussis*	70 (60.9)
Isolation of *B. pertussis* and PCR positive	7 (6.1)
PCR positive alone	38 (33.0)
PCR by number of targets†	
3 target	17 (14.8)
2 target	14 (12.2)
1 target	14 (12.2)
Infant age at pertussis onset (days)‡	
≤28	24 (20.9)
29–41	23 (20.0)
42–124	68 (59.1)
Apnea§	
Yes¶	52 (45.6)
No	62 (54.4)
Unknown/missing	1
Number of doctor's office or clinic visits	
0	15 (13.3)
1	24 (21.2)
2	28 (24.8)
≥3	46 (40.7)
Unknown/missing	2
Number of emergency department visits	
0	25 (21.9)
1	54 (47.4)
2	21 (18.4)
≥3	14 (12.3)
Unknown/missing	1
Number of hospital admissions //	
0	25 (22.1)
1	77 (68.1)
≥2	11 (9.7)
Unknown/missing	2

*Percentages might not sum to 100 because of rounding.

†PCR targets included insertion sequence (IS) *481* for 1– 2- and 3-target PCR assays; IS *1001* for the 2-target PCR; pertussis toxin promoter region (ptxA), and the *Bordetella recA* gene for the 3-target PCR.[22–24]

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[‡]Pertussis onsets were defined as caregiver-reported dates when case-patients were first noted to cough or have apnea (if not recalled, as pertussis case report form-documented cough onset or diagnosis dates). Incident-confirmed pertussis cases prospectively reported among infants ≤4 months of age (≤124 d) were eligible for enrollment. Of enrolled control subjects, 222 (96.5%) were born within 7 d after their matched case-patients, 4 were born >7 d after (range, 9–33 d) and 4 were born before their matched cases (range, 2–19 d).

[§]Caregivers responded to the question, "During his or her illness, but not during a coughing spell, did your baby stop breathing for so long that his or her tongue or his or her whole face turned blue? Doctors and nurses may call this 'apnea.'"

[¶]Of 45 case-patients with apnea and cough onset dates, 41 (91%) had apnea onset after cough onset (median, 8 d; range, 1–30 d), 2 (4%) had same-day onsets, and 2 (4%) case-patients had apnea onset first.

[//]Required at least an overnight hospital stay and a move to a room that was not in an emergency department.

IS indicates insertion sequence; PCR, polymerase chain reaction.

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TABLE 2.

Serology Results for Subjects[*] (n = 181), With Interval From Matched Case-Patients' Pertussis Onsets[†] to Specimen Collection ≤182 Days

Subject Type	No. of Specimens	Seropositive (≥94 EU), n (%)	EU, Median (Range)
Case-patient	41	37[‡] (90.2)	480 (141–480)[§]
Mother	44	20 (45.5)	169 (96–480)[§]
Other	19	8 (42.1)	218 (108–480)[§]
Control subject	32	5[¶] (15.6)	120 (95–317)
Mother	38	1 (2.6)	178 (NA)
Other	7	0 (0)	NA

[*]All subjects in "mother" or "other" categories who submitted serology samples were family members of case-patients or control subjects.

[†]Pertussis onsets were defined as caregiver-reported dates when case-patients were first noted to cough or have apnea (if not recalled, as pertussis case report form-documented cough onset or diagnosis dates).

[‡]Of 4 (9.8%) cases with seronegative results, 3 were confirmed by 1-target PCR, with 2 having concomitant diagnoses (*Chlamydia* species and respiratory syncytial virus, respectively), and 1 case was identified by 3-target PCR and had testing confirming parainfluenza virus infection. Mothers of the 3 case-patients with concomitant diagnoses had seronegative results. The mother of the fourth seronegative case-patient did not submit a sample for serologic testing.

[§]ELISA concentrations outside the standard curve were set as 15 EU/mL (for values <15 EU/mL) and 480 EU/mL (for results >480 EU/mL).

[¶]Among 32 controls, 5 (15.6%) infants who had each received ≥2 DTaP vaccinations precollection were seropositive.

ELISA indicates enzyme-linked immunosorbent assay; EU, ELISA units; NA, not applicable; PCR, polymerase chain reaction.

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TABLE 3.

Univariate Analysis of Parental and Infant Characteristics

Characteristic	Case-Patients (n = 115), n (%)*	Control Subjects (n = 230), n (%)*	MOR (95% CI)	P†
Caregiver's relationship to infant‡				
Mother	108 (93.9)	223 (97.0)	1.00 (Referent)	0.18
Other	7 (6.1)	7 (3.0)	2.13 (0.71–6.43)	
Father listed as primary household contact				
Yes	89 (77.4)	194 (84.4)	1.00 (Referent)	0.08
No	26 (22.6)	36 (15.6)	1.75 (0.93–3.29)	
Infant sex				
Male	61 (53.0)	129 (56.1)	1.00 (Referent)	0.6
Female	54 (47.0)	101 (43.9)	1.13 (0.72–1.75)	
Infant birth weight				
<5.5 lbs	7 (6.1)	17 (7.4)	1.00 (Referent)	0.55
5.5–9 lbs	100 (87.0)	190 (82.6)	1.32 (0.50–3.50)	
>9 lbs	8 (7.0)	23 (10.0)	0.89 (0.26–3.00)	
Estimated gestational age§				
Born at <37 wk	10 (8.7)	28 (12.2)	0.65 (0.29–1.47)	0.29
Born at ≥37 wk	105 (91.3)	202 (87.8)	1.00 (Referent)	
Delivery type				
Vaginal	81 (70.4)	164 (71.3)	1.00 (Referent)	0.87
Cesarean	34 (29.6)	66 (28.7)	1.04 (0.64–1.69)	
Age at birth hospitalization discharge				
>48 h old	65 (57.0)	121 (52.8)	1.21 (0.76–1.92)	0.43
≤48 h old	49 (43.0)	108 (47.2)	1.00 (Referent)	
Missing	1	1		
Hospitalizations since birth (excluding pertussis-related events)				
Yes	8 (7.0)	13 (5.8)	1.26 (0.5–3.19)	0.63
No	106 (93.0)	211 (94.2)	1.00 (Referent)	
Missing	1	6		

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Characteristic	Case-Patients (n = 115), n (%)*	Control Subjects (n = 230), n (%)*	MOR (95% CI)	P †
Second-hand smoking exposure ¶				
Yes	8 (7.0)	15 (6.61)	1.08 (0.42–2.79)	0.87
No	106 (93.0)	212 (93.4)	1.00 (Referent)	
Missing	1	3		
Numbers of siblings				
0	37 (32.5)	93 (40.4)	1.00 (Referent)	0.2
1	37 (32.5)	77 (33.5)	1.22 (0.71–2.12)	
≥2	40 (35.1)	60 (26.1)	1.64 (0.95–2.83)	
Missing	1	0		
Number of outings ‖				
None	4 (3.6)	14 (6.1)	1.00 (Referent)	0.71
1–8	59 (52.7)	109 (47.6)	1.82 (0.5–6.01)	
9–16	25 (22.3)	53 (23.1)	1.64 (0.47–5.7)	
≥17 or more	24 (21.4)	53 (23.1)	1.46 (0.4–5.3)	
Missing	3	1		
Has infant ever been fed breast milk?				
Yes	83 (72.2)	193 (84.3)	0.45 (0.25–0.81)	0.01
No	32 (27.8)	36 (15.7)	1.00 (Referent)	
Missing	0	1		
Breastfeeding **				
Breastfed	30 (26.3)	124 (54.2)	0.26 (0.15–0.46)	<0.01
Other	84 (73.7)	105 (45.8)	1.00 (Referent)	
Unknown	1	1		
Infant's health insurance coverage during reference month				
Private	51 (45.1)	156 (68.7)	1.00 (Referent)	<0.01
Nonprivate/none ††	62 (54.9)	71 (31.3)	3.60 (2.06–6.32)	
Unknown	2	3		
Caregivers' reports of having ever been told infant has an underlying or ongoing illness				
Yes	2 (1.8)	15 (6.7)	0.24 (0.05–1.07)	0.08
No	109 (98.2)	209 (93.3)	1.00 (Referent)	

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Characteristic	Case-Patients (n = 115), n (%)*	Control Subjects (n = 230), n (%)*	MOR (95% CI)	P †
Missing	4	6		
Infants ≥42 days of age at matched case-patient's pertussis onsets‡‡ who received a valid DTaP dose ≥14 d before onset date				
Valid dose received	21 (30.9)	45 (34.9)	0.80 (0.32–2.01)	0.64
Invalid or no dose received	47 (69.1)	84 (65.1)	1.00 (Referent)	
Caregiver's vaccine acceptance§§				
Yes	110 (95.6)	194 (84.3)	NA	<0.01¶¶
No	2 (1.7)	25 (10.9)		
Unsure	3 (2.61)	11 (4.8)		
Infant race/ethnicity				
Non-Hispanic white	49 (43.0)	139 (60.7)	1.00 (Referent)	0.01
Non-Hispanic black	15 (13.2)	19 (8.3)	3.40 (1.27–9.05)	
Non-Hispanic other	18 (15.8)	26 (11.4)	2.15 (1.05–4.37)	
Hispanic, any race	32 (28.1)	45 (19.6)	2.45 (1.27–4.73)	
Unknown	1	1		
Parents' birth countries				
Both US born	81 (72.3)	188 (83.6)	1.00 (Referent)	0.03
One foreign born	11 (9.8)	12 (5.3)	1.96 (0.86–4.50)	
Both foreign born	20 (17.9)	25 (11.1)	2.28 (1.09–4.78)	
Unknown	3	5		
Mother's age (yr)				
≤19	13 (11.3)	12 (5.2)	2.90 (1.22–6.88)	0.01
20–24	33 (28.7)	46 (20.0)	1.91 (1.09–3.33)	
≥25	69 (60.0)	172 (74.8)	1.00 (Referent)	
Mother's education				
Less than high school	34 (29.8)	13 (5.7)	13.3 (5.69–31.1)	<0.01
High school//// completed	44 (38.6)	63 (27.5)	3.82 (2.06–7.08)	
At least some college***	36 (31.6)	153 (66.8)	1.00 (Referent)	
Unknown	1	1		

*Percentages might not total 100 because of rounding.

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[†] Likelihood ratio test for the null hypothesis of no association between the characteristic and case–control status.

[‡] During September 2002 to June 2005, caregivers participated in telephone or face-to-face interviews with investigators using a standardized 92-item questionnaire. Of the 14 nonmother caregivers interviewed, 12 were fathers and 2 were grandmothers.

[§] Ninety-six (83.5%) case-patients' caregivers and 198 (86.1%) control subjects' caregivers provided EGAs in weeks. Each group's median was 39 weeks (case-patients' range, 31–42 weeks; control subjects' range, 25.5–43 weeks). When analyzed on the basis of EGAs alone or with caregivers' responses to serial questions related to due dates that were used to categorize preterm (≤37.0 wk) vs. term (≥37.1 wk) deliveries for caregivers who could not state EGAs in weeks, gestational age was not associated with pertussis.

[¶] Inside any household during the 4-wk reference month before the matched case-patient's pertussis symptom onset.

[//] Number of visits to a place outside of home during the 4-week reference month before the matched case-patient's pertussis symptom onset; 4 case-patients and 3 control subjects attended child care.

[**] Because exclusive breast milk receipt is sometimes infeasible, the breastfed category includes infants receiving breast milk with 0–1 supplemental formula feedings daily up to the matched case-patient's pertussis symptom onset date; the "other" category includes infants receiving ≥2 formula feedings daily up to the matched case-patient's pertussis symptom onset date.

[††] Caregivers reported lack of insurance during reference months for 3 case-patients and 3 control subjects.

[‡‡] Pertussis symptom onsets were defined as caregiver-reported dates when case-patients were first noted to cough or have apnea (if not recalled, as pertussis case report form-documented cough onset or diagnosis dates). Sixty-eight (59%) case-patients and 129 (56%) control subjects were ≥42 days of age at illness onset and eligible for DTaP vaccination.[31]

[§§] Caregivers were asked to report acceptability of their receipt of a theoretical pertussis vaccine with the question, "If it were possible for you to take a safe vaccine, or 'shot,' that would protect you against whooping cough and therefore help keep the baby from getting sick with whooping cough, do you think that you would take it?"

[¶¶] Fisher's exact test.

[////] High school or equivalent qualifying testing completed.

[***] Or technical school.

CI indicates confidence interval; DTaP, diphtheria and tetanus toxoids and acellular pertussis (vaccine); EGA, estimated gestational age; NA, not applicable; MOR, matched odds ratio.

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TABLE 4.

Univariate Analysis of Transmission Sources and Household Factors

Characteristic	Case-Patients (n = 115), n (%)	Control Subjects (n = 230), n (%)*	MOR (95% CI)	*P* †
Primary household contacts with prolonged new cough‡				
0	35 (31.5)	202 (92.2)	1.00 (Referent)	<0.01
≥1	76 (68.5)	17 (7.8)	18.9 (8.71–41.2)	
Unknown	4	11		
Secondary household contacts with prolonged new cough‡				
0	101 (90.2)	222 (99.1)	1.00 (Referent)	<0.01
≥1	11 (9.8)	2 (0.9)	11.0 (2.44–49.6)	
Unknown	3	6		
Primary or secondary household contacts with prolonged new cough‡				
0	26 (23.8)	195 (91.1)	1.00 (Referent)	<0.01
≥1	83 (76.2)	19 (8.9)	19.7 (9.07–42.8)	
Unknown	6	16		
Visitors to any household with prolonged new cough‡				
0	83 (77.6)	202 (97.6)	1.00 (Referent)	<0.01
≥1	24 (22.4)	5 (2.4)	19.4 (4.54–82.7)	
Unknown	8	23		
New peripartum§ cough (among mothers of infants <42 days of age at matched case-patient's pertussis onset date)				
Yes	22 (46.8)	10 (10.7)	7.40 (2.77–19.75)	<0.01
No	25 (53.2)	83 (89.2)	1.00 (Referent)	
Missing	1	0		
Primary household type				
Single-family home	67 (58.8)	172 (75.4)	1.00 (Referent)	<0.01
Apartment	44 (38.6)	49 (21.5)	3.25 (1.74–6.09)	
Other	3 (2.6)	7 (3.1)	2.29 (0.47–11.2)	
Unknown	1	2		
Number of persons, including infant, in primary household				

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Characteristic	Case-Patients (n = 115), n (%)	Control Subjects (n = 230), n (%)*	MOR (95% CI)	P†
2–4	48 (41.7)	129 (56.1)	1.00 (Referent)	<0.01
5–6	29 (25.2)	74 (32.2)	1.10 (0.64–1.88)	
7–8	22 (19.1)	20 (8.7)	3.50 (1.61–7.57)	
≥9	16 (13.9)	7 (3.0)	6.66 (2.45–18.1)	
Persons/room in primary household¶				
≤0.49	7 (6.4)	38 (16.8)	1.00 (Referent)	<0.01
0.50–0.74	24 (21.8)	73 (32.3)	1.57 (0.62–4.00)	
0.75–0.99	24 (21.8)	44 (19.5)	2.96 (1.14–7.66)	
1.00–1.24	22 (20.0)	40 (17.7)	2.77 (1.05–7.31)	
≥1.25	33 (30.0)	31 (13.7)	6.35 (2.33–17.3)	
Unknown	5	4		
Primary household contacts 8–10 years of age				
0	83 (74.8)	197 (86.4)	1.00 (Referent)	0.01
≥1	28 (25.2)	31 (13.6)	2.20 (1.21–4.02)	
Unknown	4	2		
Primary household contacts 11–18 years of age				
0	66 (59.5)	191 (83.8)	1.00 (Referent)	<0.01
≥1	45 (40.5)	37 (16.2)	3.50 (2.06–5.94)	
Unknown	4	2		
Primary household contacts 19–29 years of age				
0	44 (38.3)	115 (50.2)	1.00 (Referent)	0.02
≥1	71 (61.7)	114 (49.8)	1.77 (1.08–2.90)	
Unknown	0	1		
Number of households //				
1	76 (66.1)	175 (76.1)	1.00 (Referent)	0.01
2	19 (16.5)	34 (14.8)	1.43 (0.74–2.77)	
≥3	20 (17.4)	21 (9.1)	3.71 (1.47–9.35)	

*Percentages might not total 100 because of rounding.

†Likelihood ratio test for the null hypothesis of no association between the characteristic and case–control status.

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[‡]Prolonged new cough was defined as a new cough that lasted ≥5 d.

[§]The maternal peripartum period was defined as 4 wk before and after infant's birthdate.

[¶]Including the infant case-patient or control subject, this is the ratio of the number of persons per room in the primary household. For example, a primary household with 3 persons living in 3 rooms including a bedroom, kitchen and den would have a ratio of 1. Four persons living in the same rooms would result in a ratio of 1.33. Four persons living in a primary household including a kitchen, a den, a dining room and 3 bedrooms would result in a ratio of 0.67.

[//]Total number of households, including the primary caregiver's, in which the case-patient or control subject spent ≥8 h/wk or ≥1 night/wk during the 4-wk reference month before the matched case-patient's pertussis symptom onset. Thirty-nine (33.9%) of case-patients' and 55 (23.9%) of control subjects' primary caregivers identified secondary households. The total number of households where infants resided was a mean of 1 household for each group; ranges of household numbers were similar (case-patients, 1–6; control subjects, 1–7).

CI indicates confidence interval; MOR, matched odds ratio.

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TABLE 5.

Possible Sources in Primary or Secondary Households (≥1 Contact with a Reported New Cough Lasting ≥5 Days)[*,†] for Pertussis Case-Patients, by Source's Age and Relationship to the Case-Patient

Source Characteristic	N (%)[†]	95% CI[‡]
Relationship to case-patient		
Mother	41 (27.9)	20.6–35.1
Father	17 (11.6)	6.4–16.7
Sibling	50 (34.0)	26.4–41.7
Grandmother	10 (6.8)	2.7–10.9
Grandfather	5 (3.4)	0.5–6.3
Aunt	5 (3.4)	0.5–6.3
Uncle	6 (4.1)	0.9–7.3
Cousin	8 (5.4)	1.8–9.1
Other[§]	5 (3.4)	0.5–6.3
Source's age (yr)		
≤7	36 (24.8)	17.8–31.9
8–10	6 (4.1)	0.9–7.3
11–19	27 (18.6)	12.3–25.0
20–29	32 (22.1)	15.3–28.8
30–39	26 (17.9)	11.7–24.2
40–64	17 (11.7)	6.5–17.0
≥65	1 (0.7)	0.0–2.0

[*]Overall, among primary and secondary household contacts in these households, 83 (76%) of 109 cases with complete contacts' symptom data had ≥1 contact with prolonged new cough. Fourteen (12%) case-patients' caregivers and 1 (0.4%) of 228 control subjects' caregivers indicated that ≥1 PHH contacts had had pertussis diagnoses. Case-patient contacts with diagnosed pertussis included 5 (36%) mothers, 5 (36%) siblings and 4 (29%) nonfirst-degree relatives.

[†]The total number (n = 147) of possible pertussis sources is greater than the number of total enrolled cases (n = 115) because multiple potential sources were reported by primary caregivers as having exposed infants before case-patients' pertussis symptom onset dates. Two (1.4%) of the 147 possible pertussis sources were missing age information.

[‡]Wald CIs.

[§]Other includes 2 adult family friends, 1 child family friend and 2 other relatives.

CI indicates confidence interval.

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TABLE 6.

Reported Symptoms[*] of Case-Patients' (n = 115) and Control Subjects' (n = 230) Contacts during the 4-Week Reference Month, by Contact Category

Contact Category and Symptoms[*†]	Case-Patient Contacts				Control Subject Contacts				Wilcoxon Rank Sum Test[¶] P Value
	Total	N (%) in Contact Category With Complete Reported Symptom Information[‡]	Mean	Median (IQR)[§]	Total	N (%) in Contact Category With Complete Reported Symptom Information[‡]	Mean	Median (IQR)[§]	
Primary household	531	NA	4.6	4 (3–6)	845	NA	3.7	3 (2–5)	<0.01
Prolonged new cough	128	513 (96.6)	1.1	1(0–2)	34	817 (96.7)	0.1	0	<0.01
New cough	157	514 (96.8)	1.4	1(0–2)	72	819 (96.9)	0.3	0	<0.01
Respiratory	151	522 (98.3)	1.3	1(0–2)	111	796 (94.2)	0.5	0 (0–1)	<0.01
Secondary household[//]	249	NA	2.2	0(0–3)	242	NA	1.1	0	0.02
Prolonged new cough	19	235 (94.4)	0.2	0	2	233 (96.3)	0.01	0	<0.01
New cough	24	235 (94.4)	0.2	0	5	232 (95.9)	0.02	0	<0.01
Respiratory	20	234 (94.0)	0.2	0	10	230 (95.0)	0.04	0	0.02
General	96	NA	0.8	0	296[†**]	NA	1.3[**]	0[**]	0.85
New cough	5	84 (87.5)	0.04	0	4	254 (84.4)	0.02	0	0.31
Respiratory	2	85 (88.5)	0.02	0	8	283 (94.0)	0.03	0	0.37
Visitor	599	NA	5.2	3 (0–7)	1538	NA	6.7	5 (2–10)	0.01
Prolonged new cough	37[††]	564 (94.2)	0.3	0	7	1386 (90.4)	0.03	0	<0.01
New cough	49	565 (94.3)	0.4	0 (0–1)	21	1392 (90.8)	0.1	0	<0.01
Respiratory	46	567 (94.7)	0.4	0	58	1400 (91.3)	0.3	0	0.06

[*]For every household or visitor contact, primary caregivers indicated if, during the 4-wk reference month before the matched case-patient's pertussis symptom onset, the following symptoms were present: runny nose and/or congestion (respiratory symptoms), new cough, new cough that lasted ≥5 d (prolonged new cough). Because general contacts were less likely than household contacts or visitors to be well known to primary caregivers, caregivers were asked only to recall general contacts' respiratory symptoms and cough.

[†]For all infants, >94% of primary and secondary household contacts were face to face. Of 599 case-patients' visitors, 478 (79.8%) were face to face and, of 1,538 control subjects' visitors, 1299 (84.5%) were face to face. Of case-patients' 96 general contacts, 74 (77.1%) were face to face; of control subjects' 296 general contacts, 166 (56.1%) were face to face.

[‡]To identify the total number of symptomatic contacts for each infant by each symptom, a symptom was classified as missing if ≥1 contact was missing symptom data and all other contacts with complete symptom data were asymptomatic.

[§]Cells reflect a 0 when median and ranges were 0 (0–0).

[¶]Differences in the distribution of numbers of contacts.

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[//]Thirty-nine (33.9%) of case-patients' and 55 (23.9%) of control subjects' primary caregivers identified secondary households. The total number of households where infants resided was a mean of 1 household for each group; ranges of household numbers were similar [case-patients (1–6); control subjects (1–7)].

[**]One control subject had 110 general contacts when that infant was passed from person to person during a church service.

[††]Of these 37 visitors with ≥5 d new cough, 27 (73.0%) were relatives of the case-patients.

IQR indicates interquartile range; NA, not applicable.

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TABLE 7.

Final Multivariable Model for All* Pertussis Case-Patients and Culture-Positive Case-Patients

Characteristic	aMOR (95% CI)	
	All* Case-Patients (Case-Patients = 107; Control Subjects = 211)	Culture-Positive Case-Patients (Case-Patients = 70; Control Subjects = 139)
Mother's age (yr; continuous variable)	0.92 (0.85–0.99)	0.93 (0.84–1.03)
Breastfeeding†		
Breastfed	0.27 (0.08–0.89)	0.34 (0.08–1.45)
Other	1.00 (Referent)	1.00 (Referent)
Type of household		
Single family	1.00 (Referent)	1.00 (Referent)
Apartment/other	9.56 (2.68–34.1)	11.9 (2.68–52.4)
Mothers with prolonged new cough‡		
0	1.00 (Referent)	1.00 (Referent)
≥1	43.8 (6.45–298.0)	29.0 (3.61–233.6)
Others (nonmothers) with prolonged new cough residing in primary or secondary households!		
0	1.00 (Referent)	1.00 (Referent)
≥1	20.1 (6.48–62.7)	26.4 (6.02–116.1)

*Eight (7.0%) case-patients and 19 (8.3%) control subjects were excluded from the final model because of missing values for ≥1 of the 5 final model independent variables.

†The breastfed category includes infants receiving breast milk with 0–1 supplemental formula feedings daily up to the matched case-patient's pertussis symptom onset; the "other" category includes infants receiving ≥2 formula feedings daily up to the matched case-patient's pertussis symptom onset.

‡Prolonged new cough was defined as a new cough that lasted ≥5 d. All mothers lived in primary households.

aMOR indicates adjusted matched odds ratio; CI, confidence interval.