

Sources of Infant Pertussis Infection in the United States

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abstract

BACKGROUND: Pertussis is poorly controlled, with the highest rates of morbidity and mortality among infants. Although the source of infant pertussis is often unknown, when identified, mothers have historically been the most common reservoir of transmission. Despite high vaccination coverage, disease incidence has been increasing. We examined whether infant source of infection (SOI) has changed in the United States in light of the changing epidemiology.

METHODS: Cases <1 year old were identified at Enhanced Pertussis Surveillance sites between January 1, 2006 to December 31, 2013. SOI was collected during patient interview and was defined as a suspected pertussis case in contact with the infant case 7 to 20 days before infant cough onset.

RESULTS: A total of 1306 infant cases were identified; 24.2% were <2 months old. An SOI was identified for 569 cases. Infants 0 to 1 months old were more likely to have an SOI identified than 2- to 11-month-olds (54.1% vs 40.2%, respectively; $P < .0001$). More than 66% of SOIs were immediate family members, most commonly siblings (35.5%), mothers (20.6%), and fathers (10.0%); mothers predominated until the transition to siblings beginning in 2008. Overall, the SOI median age was 14 years (range: 0–74 years); median age for sibling SOIs was 8 years.

CONCLUSIONS: In contrast to previous studies, our data suggest that the most common source of transmission to infants is now siblings. While continued monitoring of SOIs will optimize pertussis prevention strategies, recommendations for vaccination during pregnancy should directly increase protection of infants, regardless of SOI.

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Ms Skoff conceptualized and designed the analysis, supervised data collection at participating sites, carried out the initial and subsequent analyses, and drafted the initial manuscript; Ms Kenyon, Liko, and Kudish and Drs Cocoros, Miller, Baumbach, and Zansky contributed to the design of the analysis, supervised and participated in data collection at participating sites, contributed to interpretation of data, and provided critical review of the manuscript for important intellectual content; Ms Faulkner contributed to the design of the analysis; supervised data collection at the participating sites; contributed to the analysis, cleaning, and interpretation of data; and provided critical review of the manuscript for important intellectual content; Ms Martin contributed to the design of the analysis, provided supervision in the analysis and interpretation of data, and provided critical review of the manuscript for important intellectual content; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: The source of infant pertussis infection is typically identified ~50% of the time. Historically, mothers have been identified as the most common source of pertussis transmission to infants.

WHAT THIS STUDY ADDS: This analysis of 8 years of enhanced pertussis surveillance data has uncovered a shift in the most common source of infant pertussis infection in the United States from mothers to siblings.

Pertussis is a highly contagious, vaccine-preventable disease with secondary attack rates reaching as high as 80% in susceptible individuals.¹ Pertussis vaccines are included as part of routine childhood immunizations in the United States and are currently recommended as a 5-dose series for infants and young children.² Because these vaccines do not confer lifelong immunity, reduced-dose acellular pertussis vaccines combined with tetanus and diphtheria toxoids (Tdap) were introduced in the United States in 2005 for routine use as a single booster dose among adolescents and adults.^{3,4} Despite high or increasing coverage with pertussis vaccines, the incidence of disease has been slowly increasing in a number of countries with notable epidemic peaks in recent years. The epidemiology of pertussis has also evolved, with a growing burden of disease among recently vaccinated children and adolescents.⁵ This trend is particularly evident in countries that have replaced whole-cell vaccine formulations with acellular pertussis vaccines (aP); the transition from whole-cell vaccine to aP vaccines in the United States occurred during the 1990s. Waning immunity in cohorts that received aP vaccines for their childhood series has been well-documented in recent studies.^{6–12}

Infants are at greatest risk for disease and death from pertussis, especially during the first 2 months of life before pertussis immunizations begin. Numerous studies have evaluated the source of pertussis transmission to infants and typically report an unknown source of infection for $\geq 50\%$ of infant cases.^{13–15} When a source is identified, mothers have been the most commonly cited source of infection in the United States (32%–37%).^{13,15} However, recently published data from Australia and the Netherlands suggest that siblings are playing an increasingly important role in the transmission of pertussis to young infants in these countries.^{16–18}

The objective of this evaluation was to use Enhanced Pertussis Surveillance (EPS) data collected between 2006 and 2013 to identify the most common sources of infant pertussis infections in the United States and identify any changes in transmission of disease to infants in light of the shifting epidemiology.

METHODS

Surveillance

Cases of pertussis were identified through Enhanced Pertussis Surveillance in 7 states between January 1, 2006, and December 31, 2013. The surveillance area and dates of participation varied by state and included Colorado (5-county Denver metropolitan area; January 1, 2011–December 31, 2013), Connecticut (statewide; January 1, 2011–December 31, 2013), Massachusetts (statewide; January 1, 2006–December 31, 2010), Minnesota (statewide; January 1, 2006–December 31, 2013), New Mexico (statewide; January 1, 2011–December 31, 2013), New York (15-county Rochester and Albany areas; January 1, 2011–December 31, 2013), and Oregon (3-county Portland metropolitan area; January 1, 2010–December 31, 2013). EPS became part of the Emerging Infections Program Network in 2011 and is characterized by improved completeness and quality of pertussis surveillance data and augmented data collection that surpasses what is currently reported through the National Notifiable Diseases Surveillance System (NNDSS). As part of EPS, pertussis cases are reported to local or state health departments by clinical or reference laboratories after a positive laboratory result. Using information obtained from the case's diagnosing health care provider and through case-patient interview, public health surveillance personnel complete a standardized case report form that includes information on demographics, clinical presentation,

vaccination history, and epidemiologic information, including source of infant infection (SOI).

Definitions

Cases were defined as those < 1 year of age on date of cough onset and were classified according to the Council of State and Territorial Epidemiologists case definition for pertussis that was in place during the study period. The clinical case definition used for this analysis required cough of ≥ 2 weeks' duration with at least 1 clinical symptom (paroxysms, inspiratory whoop, or posttussive vomiting). Probable cases were defined as those persons meeting the clinical case definition. Confirmed cases were persons who had isolation of *Bordetella pertussis* from culture and a cough illness of any duration. Cases were also classified as confirmed if they met the clinical case definition and were either positive by polymerase chain reaction or had contact with a laboratory-confirmed case of pertussis; cases in persons ≥ 11 years of age from Massachusetts with a single acute serum immunoglobulin G antipertussis toxin antibody level of $\geq 20 \mu\text{g/mL}$ were also classified as confirmed.¹⁹ Confirmed and probable cases were included in our analysis for all states except Massachusetts, where only confirmed cases were reported.

The SOI was collected at time of interview of the case-patient's parent or guardian and was defined as a person with cough illness consistent with pertussis who had contact with the infant case-patient in the 7- to 20-day period before the date of infant cough onset. Infant parents/guardians were asked whether another person with cough illness was known (source), the relationship of that source to the case infant, and the source's age. When > 1 source was identified, information was recorded for the source with the earliest cough onset date to identify the first known exposure to pertussis.

Immediate family members were defined as mothers, fathers, and siblings and extended family members included grandparents, aunts/uncles, and cousins. An SOI identified as a day-care contact could represent another child attendee of the day care or an adult caregiver.

Analytic Methods

Disease incidence was calculated using observed case counts as numerators and surveillance population estimates from bridged-race, postcensal population estimates from the National Center for Health Statistics as denominators. The racial and ethnic distributions of cases, as well as the proportion of cases hospitalized, or who died during their pertussis illness, were calculated from those with a known response; race (black, white, and other race) and ethnicity (Hispanic and non-Hispanic) were analyzed separately. Pearson's χ^2 or Fischer's exact tests were used for the comparison of proportions; trends over time were assessed using the χ^2 linearity test and test for trend. Trends in annual median age over time were assessed using the Jonckheere-Terpstra test. Additionally, to further understand changes in the age of identified SOIs over time, we compared SOI age distributions between 2006 and 2009 and 2010 and 2013. This breakpoint was used to mirror the changing epidemiology of pertussis in the United States and the increasing burden of disease among older children and adolescents beginning in 2010; medians were compared using the Wilcoxon Mann-Whitney test. *P* values of $<.05$ were considered statistically significant for all tests.

RESULTS

Between 2006 and 2013, a total of 1306 cases were identified in infants <1 year of age; $\sim 24.2\%$ were <2 months of age, and 50.5% were male. Case infants were predominantly white (852/1149 [74.2%]) with

known race), and 28.9% were of Hispanic ethnicity (344/1191 with known ethnicity); Hispanic ethnicity was overrepresented among cases when compared with the infant population in the participating surveillance areas during the study period (18%). Among our study population, 34.0% (440/1294) of the case infants were hospitalized, 15.4% (86/559) had pneumonia, and $<1\%$ (2/1274) died during their pertussis illness. The average overall incidence of pertussis among infants <1 year of age was 94.9 of 100 000 population, ranging from a high of 227.4 per 100 000 population in 2012 to a low of 58.0 per 100 000 in 2006 (Fig 1). Overall, an SOI was identified for 569 (43.6%) of the infant cases; 44.1% of the parents interviewed were unable to identify an SOI for their infants, and the remaining 12.3% did not provide a response. Of the infants with a known SOI, the most commonly identified sources were siblings (35.5%), mothers (20.6%), fathers (10.0%), grandparents (7.6%), aunts/uncles (6.5%), and other source, not specified (6.3%); day-care contacts, cousins, friends, babysitters, nieces/nephews, and unknown source accounted for $<5\%$ each of identified sources. Altogether, immediate family members were identified as the source of pertussis transmission for 66.1% of infant cases; immediate plus extended family members were identified as

the source for 85.2% of infant cases. Overall, the most common sources identified were similar by race and ethnicity, with siblings (32.7%–36.2%) accounting for the greatest proportion of identified SOIs across all racial and ethnic groups, followed by mothers (17.2%–21.7%). The only significant differences identified was the proportion of SOIs identified as friends (non-Hispanic case infants were significantly more likely than Hispanic case infants to have a friend identified as an SOI; 4.8% vs 0% , $P = .004$) and those identified as other source, not specified (black case infants were significantly more likely than white case infants to have the source of infection identified as other source; 11.8% vs 4.3% , $P = .004$).

During the first 2 years of the study period (2006–2007), mothers were identified most frequently as the source of pertussis transmission to infants. However, a shift to siblings occurred in 2008, and with the exception of 2009, this predominance continued through 2013 (Fig 2). The proportion of mothers identified as the SOI declined significantly during the study period ($P = .0014$), whereas the proportion of sibling SOIs increased ($P = .0333$); no other significant trends were observed among the other identified SOIs (Fig 2).

Overall, the median age of the identified SOIs was 14 years (480 of

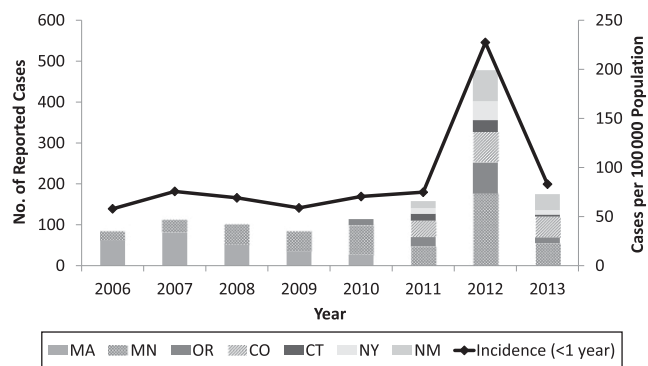


FIGURE 1

Annual pertussis incidence among infants <1 year of age and number of reported infant cases by EPS site and year, 2006–2013.

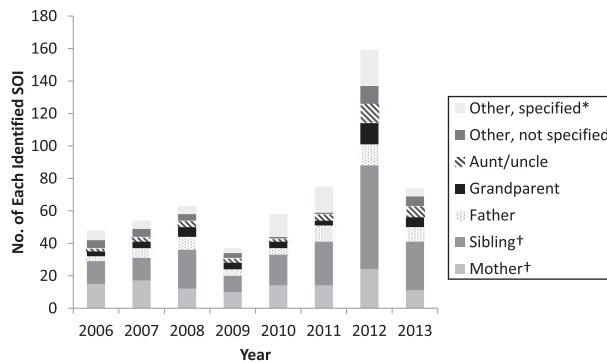


FIGURE 2

Relationship of identified sources of infection, by year, 2006–2013. * Includes day-care contacts, cousins, friends, babysitters, and nieces/nephews, unknown source ($n = 1$). † $P < .05$.

TABLE 1 Age Distribution of Identified SOIs, 2006–2013

Source of Infection	N	% With Known Age	Median Age (y)	Range (y)
Sibling	202	96	8	1–19
Mother	117	85	28	1–43
Father	57	72	28	20–51
Grandparent	43	67	57	37–74
Aunt/uncle	37	76	23.5	5–74
Other, not specified	36	86	12	0–52
Day care	26	62	5.5	1–44
Cousin	26	88	8.5	0–30
Friend	17	65	13	1–37
Babysitter	4	100	17	10–19
Niece/nephew	3	66.7	11.5	6–17
Unknown	1	100	3	—
Overall	569	84.4	14	0–74

569 with known age; range: 0–74 years; Table 1). Although not steadily decreasing, there was a borderline significant trend in the annual median age of SOIs over time ($P = .0537$). When the years were grouped according to the changing epidemiology of pertussis in the United States, a significant decrease in median age was observed when we compared 2006–2009 (18 years of age) to 2010–2013 (12 years of age; $P = .0160$). Among sibling sources, the overall median age during the study period was 8 years of age, and fluctuated between a high of 9 years of age in 2008, to a low of 4.5 years of age in both 2009 and 2013; no significant trend in sibling age was observed over time ($P = .2202$) or when comparing the 2 time periods (8 years in 2006–2009 and 7 years in 2010–2013, $P = .9855$).

Younger infant age was significantly associated with the identification of

a source of infection; 54.1% of infants 0 to 1 month of age had a source identified compared with 40.2% of infants 2 to 11 months of age ($P < .001$). Additionally, hospitalized infant cases were more likely to have a source of infection identified than those not hospitalized for their pertussis infection (51.6% vs 39.8%, respectively, $P < .001$); however, when stratified by infant age group, hospitalization was only significantly associated with the identification of an SOI for infants 2 to 11 months of age. The proportion of white cases that had an SOI identified was similar to cases classified as other race (46.0% and 41.8%, respectively; $P = .34$). However, a significantly higher proportion of sources were identified among white cases when compared with black cases (35.4%, $P = .02$). Council of State and Territorial Epidemiologists–confirmed cases

were also more likely than cases classified as probable to have a source of infection identified (44.2% of confirmed cases vs 31.3% of probable cases, $P = .04$). No significant difference was observed for ethnicity (45.7% of Hispanic cases had an SOI identified vs 42.3% of non-Hispanic cases; $P = .31$).

Because younger infant age was a predictor of whether a source of infection was identified, we explored differences in the relationship of the sources identified between the 2 infant age groups (Fig 3). Across all SOIs, significant differences between the 2 infant age groups were found for mother and day-care contact only. Infants 0 to 1 month of age were significantly more likely to acquire pertussis infection from their mothers ($P = .002$), whereas infants 2 to 11 months of age were more likely to have day-care contact identified as their source of infection ($P = .003$).

DISCUSSION

Consistent with previous studies, our analysis of 8 years of enhanced surveillance data identified an SOI for less than half of reported infant pertussis cases, with a similar proportion of sources identified as family members. However, contrary to the published US data, our study revealed the emergence of siblings as the major reservoir of infection and represents an important shift in the dynamics of pertussis transmission to young infants in the United States. Children 7 to 10 years of age began to emerge as a high-incidence age group for pertussis in the United States in 2008 and continue to experience elevated rates of disease, along with adolescents, as aP-vaccinated cohorts age.²⁰ As our data suggest, mothers and fathers still play an important role in transmitting disease to unprotected infants, but the transition to siblings and other school-age children as the main source of infection is not unexpected in this era of waning aP immunity and

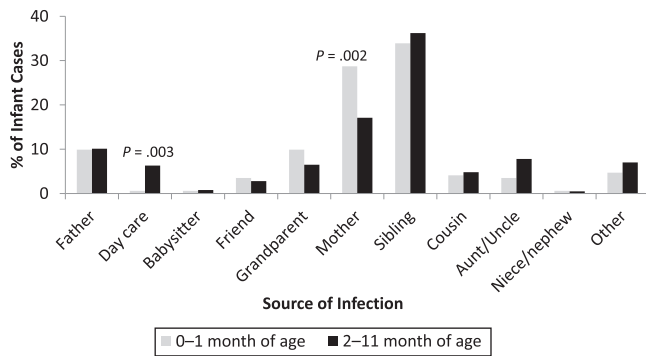


FIGURE 3 Differences in relationship of identified SOIs, by case infant age, 2006–2013.

an increasing burden of pertussis in these age groups. Changes in the median age of the SOIs identified in our analysis mirror the changing epidemiology observed in the United States.

The Advisory Committee on Immunization Practices (ACIP) has recommended 2 strategies to protect young infants from pertussis: the “cocooning” strategy, which involves vaccination of adolescent and adult close contacts of an infant with a single dose of Tdap, and Tdap vaccination during every pregnancy.^{4,21} We observed the beginning of the shift from mothers to siblings in 2008, 3 years after the introduction of Tdap in the United States for routine use among adolescents and adults. Before the current recommendation for Tdap vaccination during every pregnancy, a postpartum dose of Tdap among new mothers and other infant contacts was the preferred strategy for preventing infant pertussis. Despite slightly higher Tdap coverage in 2012 among women 18 to 49 years of age compared with male adults of the same age (18.8% vs 14.7%, $P \leq .0001$), Tdap uptake still remains low among women of childbearing age [CDC’s National Health Interview Survey (NHIS), unpublished data]. Increasing Tdap coverage among new mothers may be conferring some indirect protection to young infants; however, given the low coverage, the impact is likely minimal and not

a major contributor to the shift in identified sources of infection.

Another factor that may be associated with the transition away from mothers as the most common SOI is the age distribution of infant cases. In our study, the proportion of infant cases <2 months of age decreased from 36.9% in 2006 to 23.4% in 2013 (data not shown). We found a significant association between younger infant age and mothers as the source of infection; however, infants <2 months of age and infants 2 to 11 months of age had the same proportion of sibling SOIs identified (Fig 3). Although changes in infant age distribution may be contributing to the transition away from mothers, it does not explain the observed shift to siblings as the major source of infant infection.

In the current setting of waning vaccine-induced immunity after both the childhood pertussis series and the Tdap booster vaccine among aP-vaccinated cohorts, additional doses of Tdap are unlikely to reduce the overall burden of pertussis and are therefore not likely to be routinely recommended for the general population.^{10–12} Although there is much debate around the benefits of Tdap revaccination for subsets of the population, such as infant close contacts, adult uptake of a single dose remains poor (<15% of adults in 2012), and coverage would presumably be lower for subsequent doses.²² Regardless, as our data

suggest, revaccination of adult cocoon members is unlikely to halt transmission of disease to infants if siblings are the predominant reservoirs of infection. Additionally, recent studies suggest that aP-vaccinated baboons can be colonized with *B pertussis* and successfully transmit the organism to cohoused animals.²³ Therefore, even in settings where all household contacts are up-to-date with pertussis vaccinations, asymptomatic transmission of pertussis may occur, further impeding the success of the cocooning strategy.^{23,24} For the cocooning strategy to be successful, there is also the assumption that infants are infected by close contacts. However, as our analysis and other studies have shown, a source of infection is identified less than half the time, suggesting either infection by someone outside the household or asymptomatic transmission of disease. For these reasons, the cocooning strategy is less than ideal, and strong support of vaccination during pregnancy is needed to maximize the protection of infants in the first critical months of life.

In contrast to previously published US studies on the infant source of infection, our analysis of Enhanced Pertussis Surveillance data allowed us to monitor the source of infant infection in a large sample size over multiple years. Despite notable strengths of our study, there were some challenges to identifying the source of infant pertussis in our analysis of surveillance data. Although >1 person with cough illness may have had contact with an infant case, we only captured information on the potential source with the earliest cough onset and were unable to quantify the level of contact with the case. Potential sources who were asymptomatic or had mild illness without cough may have also been missed in our study as we relied solely on parent report without laboratory testing of household members or other infant

contacts; additionally, without laboratory confirmation, we were unable to determine if *B pertussis* was the actual cause of cough illness in the identified SOIs. It is also important to note that although we did have a large sample size, there were changes in participating sites over time, potentially making data from the earlier years less generalizable.

CONCLUSIONS

Our analysis of US Enhanced Pertussis Surveillance data revealed a shift in the source of infant pertussis infection from mothers to siblings, mirroring the shifting epidemiology of pertussis in the United States. Continued monitoring of the source of infant infection through surveillance is important, especially as the epidemiology of pertussis changes. In this era of

resurgent pertussis and widespread transmission, the primary focus of prevention and control strategies is to protect those at highest risk for severe disease, with emphasis on young infants in the first few months of life before immunizations begin. With evidence of waning immunity and possible transmission of pertussis through subclinical infections, the current cocooning strategy is unlikely to offer sufficient protection of vulnerable infants. Prevention efforts should therefore focus on increasing Tdap coverage during pregnancy because this is currently our best strategy for providing direct protection to the infant, regardless of the changing source of infant infection.

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ABBREVIATIONS

aP: acellular pertussis vaccine
EPS: Enhanced Pertussis Surveillance
SOI: source of infection
Tdap: reduced-dose acellular pertussis vaccine combined with tetanus and diphtheria toxoids

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Sources of Infant Pertussis Infection in the United States

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