

Transmission of *Bordetella pertussis* to Young Infants

Aaron M. Wendelboe, PhD,* Elisabeth Njamkepo, PhD,† Antoine Bourillon, MD,‡ D. Daniel Floret, MD,§ Joel Gaudelus, MD,|| Michael Gerber, MD,¶ Emmanuel Grimprel, MD, PhD,# David Greenberg, MD,** Scott Halperin, MD,†† Johannes Liese, MD, MSc,‡‡ Flor Muñoz-Rivas, MD,§§ Remy Teyssou, MD,|||| Nicole Guiso, PhD,† and Annelies Van Rie, MD, PhD,* for the Infant Pertussis Study Group

Background: Pertussis vaccination has reduced the number of notified cases in industrialized countries from peak years by more than 95%. The effect of recently recommended adult and adolescent vaccination strategies on infant pertussis depends, in part, on the proportion of infants infected by adults and adolescents. This proportion, however, remains unclear, because studies have not been able to determine the source case for 47%–60% of infant cases.

Methods: A prospective international multicenter study was conducted of laboratory confirmed infant pertussis cases (aged ≤6 months) and their household and nonhousehold contacts. Comprehensive diagnostic evaluation (including PCR and serology) was performed on all participants independent of symptoms. Source cases were identified and described by relationship to the infant, age and household status.

Results: The study population comprised 95 index cases and 404 contacts. The source of pertussis was identified for 48% of infants in the primary analysis and up to 78% in sensitivity analyses. In the primary analysis, parents accounted for 55% of source cases, followed by siblings (16%), aunts/uncles (10%), friends/cousins (10%), grandparents (6%) and part-time caretakers (2%). The distribution of source cases was robust to sensitivity analyses.

Conclusions: This study provides solid evidence that among infants for whom a source case was identified, household members were responsible for 76%–83% of transmission of *Bordetella pertussis* to this high-risk group. Vaccination of adolescents and adults in close contact with young infants may thus eliminate a substantial proportion of infant pertussis if high coverage rates can be achieved.

Key Words: transmission, source case, sensitivity analysis, diagnosis, asymptomatic
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B*ordetella pertussis* continues to circulate and cause disease even in populations with high vaccination coverage of infants and children. Waning of vaccine-induced immunity^{1–4} is cited as an important factor contributing to this persistent problem.^{5–8} Despite widespread vaccination coverage (ie, 95% for the primary series^{9,10}), the reported incidence of infant pertussis in the United States tripled in the past 2 decades from 34.2 cases/100,000 in the 1980s to 103.5 cases/100,000 infant population in 2003.^{11,12} Infants too young to have completed their primary vaccine series account for the majority of pertussis related complications, hospitalizations and deaths.^{12,13}

One strategy for protecting infants is to increase herd immunity by vaccinating close contacts. France was the first country to introduce a booster dose for adolescents in 1998,¹⁴ followed by Germany, other European countries, Canada, Australia and Japan.¹⁵ France and Germany have also recommended a booster for parents and health care workers in contact with young children.^{14,16} The United States Advisory Committee on Immunization Practices (ACIP) recently recommended that all adolescents and adults receive a single booster dose of Tdap (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine) in place of Td (tetanus and diphtheria toxoids vaccine).^{17,18} Modeling has shown that the effect on infant pertussis of routinely vaccinating all adolescents and adults critically depends on the proportion of infants infected by family members.¹⁹

Several studies have investigated the transmission of pertussis within households using a variety of study designs: case control studies in outbreak settings,^{20–22} investigations using general and hospital-based surveillance data,^{5,23–25} and secondary analyses using vaccine efficacy trial data.²⁶ These studies reported that parents (20%–48%)^{5,23–25,27} and siblings (19%–53%)^{5,23–25} were common sources of infection for infants for whom a source was identified. However, interpretation of these findings is subject to important limitations. In these studies, the primary source of infection could not be identified in 47%–60% of infant index cases. Further, except in one small study,²⁷ the diagnosis of the index case was not always laboratory confirmed, and identification of source cases relied predominantly on a clinical diagnosis of

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From the *Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; †Centre National de Référence de la Coqueluche et autres Bordetelloses, Unité de Prévention et Thérapie Moléculaires des Maladies Humaines, FRE CNRS 2849, Institut Pasteur, Paris, France; ‡Hôpital Robert Debré, Paris, France; §Université Claude Bernard Lyon, Cedex, France; ||Hôpital Jean Verdier, Bondy, France; ¶Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; #Hôpital Armand Trousseau, Paris, France; **Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; ††Dalhousie University and the IWK Health Centre, Halifax, Canada; ‡‡Ludwig-Maximilians-Universität, Munich, Germany; §§Baylor College of Medicine and Texas Children's Hospital, Houston, Texas; and ||||Sanofi Pasteur, Lyon, France.

Address for correspondence: Annelies Van Rie, MD, PhD, Department of Epidemiology, School of Public Health, The University of North Carolina at Chapel Hill, 2104F Mc Gavran Greenberg Hall, Chapel Hill, NC 27599-7435. E-mail: vanrie@email.unc.edu.

Dr. Greenberg is a current employee of sanofi Pasteur, Swiftwater, PA.

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pertussis. It remains therefore unclear who transmits pertussis to young infants.

This study was designed to determine more precisely who transmits *B. pertussis* to young infants. We collected comprehensive clinical and biologic diagnostic data on close contacts to infant cases with laboratory confirmed pertussis.

METHODS

Study Setting and Population. A hospital based prospective study was conducted in France (4 hospitals), Germany (4 hospitals), the United States (3 hospitals) and Canada (1 hospital) from February 2003 to October 2004 (see list of participating hospitals of the Infant Pertussis Study Group). Data were analyzed at the University of North Carolina at Chapel Hill. Institutional Review Boards at each hospital and UNC approved the study.

Three categories of participants were included in the study: infant index cases, household contacts and close non-household contacts. Index cases were eligible if the infants were aged ≤ 6 months, unvaccinated or partially vaccinated (< 3 doses) and diagnosed with laboratory confirmed pertussis (confirmed by culture or polymerase chain reaction [PCR]). Household contacts of the index cases were defined as persons living in the same residence as the infant index case during the month preceding pertussis diagnosis in the infant. Nonhousehold contacts were eligible if, during the month before symptom onset in the index case, they were either a full-time caretaker (> 30 hours/week), or a person with an acute cough illness lasting ≥ 7 days and had at least 10 hours of contact per week. Potential participants were excluded if their residence was too distant for the family to attend for evaluation.

Upon enrollment of the infant index case, data on age, gender, pertussis vaccination status, type and duration of pertussis symptoms, laboratory test results, family composition, and type of child care were collected. Enrollment of the index case and contacts was required to occur within one week after the diagnosis of pertussis.

All household members of the index case were recruited upon informed consent and interviewed face-to-face using a standard questionnaire to obtain demographic and clinical data to identify potential nonhousehold sources of pertussis. A respiratory sample (nasopharyngeal aspirate or swab) for culture and PCR detection of *B. pertussis* and a blood sample for IgG antipertussis toxin (anti-PT) antibody detection were collected. One month later, follow-up data on symptoms and a convalescent blood sample were collected. Potential nonhousehold sources of infection were contacted by telephone, recruited, and followed the same study protocol as household contacts.

Diagnostic Laboratory Procedures and Quality Control. PCR and serum samples were sent frozen to the Reference Laboratory for Whooping Cough and other Bordetellosis, Institut Pasteur in Paris. PCR samples were analyzed by real-time PCR using the IS481 target according to recommendations of the PCR pertussis consensus group.²⁸ Serum samples were analyzed using a standardized enzyme-linked immunosorbent assay (ELISA) to quantify IgG anti-PT, as

previously described,²⁹ and using purified PT from sanofi pasteur. Assay cut-off was set at ≥ 20 EL U/mL.

Case Definitions. Contacts were classified into one of 4 pertussis outcome categories: (1) laboratory confirmed symptomatic case, (2) epidemiologically linked symptomatic case, (3) laboratory confirmed asymptomatic infection, and (4) not infected. Outcomes were assigned using a case definition algorithm (Fig. 1 available online only). Laboratory confirmed symptomatic cases reported symptoms of rhinorrhea or cough and met at least one of the following criteria: positive culture, positive PCR,²⁸ a ≥ 4 -fold change³⁰ in anti-PT IgG levels in paired serum samples, or a single anti-PT IgG antibody titer ≥ 125 EU/mL.^{31–33} For immunized children aged 3 months through 2 years, or 4 years through 7 years, single anti-PT titer results were not used for laboratory confirmation because recent vaccination may have influenced the IgG titers.⁸

Epidemiologically linked cases were persons in contact with the index case in the month preceding symptom onset in the index case and who had an acute cough illness lasting ≥ 2 weeks, and had no laboratory confirmed pertussis.³⁴

Laboratory confirmed asymptomatic cases met the same criteria as laboratory confirmed cases, but did not report any cough or cold symptoms at either visit. Those classified as uninfected failed to meet any of the above criteria.

A primary case was defined as a laboratory confirmed or epidemiologically-linked case with symptom onset between 7 and 30 days before symptom onset in the index case.^{25,35–39}

Primary Analysis. The primary analysis consisted of a *complete case analysis* in which only contacts with complete critical diagnostic information (ie, PCR and serology) were included. Multiple source cases were allowed for an index case when more than one laboratory confirmed index case reported symptom onset on the same day.

Sensitivity Analyses Investigating the Effect of Missing Data. To determine the impact of missing data on the study results 2 sensitivity analyses were conducted. In a highly conservative analysis, the *strict complete enrollment analysis*, the entire family was included only if every household member was enrolled and critical diagnostic results were available for every contact. In a less restrictive analysis, the *all participant analysis*, data on all participants were analyzed. When PCR and/or serology results were missing, pertussis outcome was assigned using the case definition algorithm (Fig. 1, available online only).

Sensitivity Analyses Investigating Infants for Whom a Primary Case was not Identified. Additional sensitivity analyses investigated why the primary analysis failed to identify a source case for some infants despite complete enrollment and diagnostic investigation. In the *expanded primary case definition analysis*, the timing of symptom onset to meet the primary case definition was expanded to 2–48 days before symptom onset in the index case based on evidence from early transmission studies of pertussis.^{40,41} In the *asymptomatic case analysis*, contacts with asymptomatic laboratory confirmed infection were included as potential source cases⁴² in families

where no symptomatic primary case (using the expanded primary case definition) was identified.

Data management and statistical analyses using Mantel-Haenzel χ^2 tests were conducted in SAS 9.1.3 (Cary, NC). Ninety-five percent confidence intervals were calculated using Stata 8 (College Station, TX).

RESULTS

Participants. Ninety-five infant index cases (France = 15, Germany = 16, United States = 62, Canada = 2) and 404 contacts (France = 60, Germany = 67, United States = 269, Canada = 8,) were enrolled. Of the eligible index cases and household contacts, 84.1% and 86.0%, respectively, participated. A mean of 4.2 (range = 1–13) contacts were enrolled per index case, and 29 (30.5%) of the index cases had at least one nonhousehold contact enrolled. There were 206 adult household members (aged ≥ 18 years, except in the case of emancipated minors), 127 child household members (aged < 18 years) and 71 nonhousehold contacts enrolled.

The mean age of the infant index cases was 2.9 months (range = 0.53–6.9 months); 70.5% were vaccinated at the appropriate age (ie, had received the correct dose no later than 30 days past the country specific scheduled date). Thirty-four (35.8%) infants had received one dose of pertussis vaccine and 8 (8.4%) had received 2 doses. Associations between age and number of received vaccine doses with being hospitalized are presented in Table 1.

The distributions of collected diagnostic specimens for PCR and serology among close contacts to the infant index cases, contact level with the index case, and vaccination history stratified by type of contact are presented in Table 2. **Primary Analysis.** Among the 95 families enrolled, 3 had no contacts for whom complete data were available; one family had twin infant index cases with identical contact patterns and was analyzed as a single case. Of the remaining 91 (96.8%) unique families, 91 index cases and 347 (85.9%) contacts had complete data. The prevalence of pertussis was 65.1% among all close contacts included in this analysis. The distribution of case-type is shown in Table 2. A source of infection was identified for 44 (48.4%) index cases. The majority (79.5%) of primary cases were laboratory confirmed. For 4 index cases, multiple primary cases were assigned as more than one

laboratory confirmed primary case reported symptom onset on the same day.

Among the 44 infants for whom a primary case was identified, household members were more often identified as primary cases than nonhousehold contacts (75.5% versus 24.5%). Parents accounted for 55.1% of the primary cases identified (18 mothers and 9 fathers), followed by siblings (16.3%), aunts/uncles (10.2%), friends/cousins (10.2%), grandparents (6.1%) and part-time caretakers (2.0%) (Table 3a). Among the 8 siblings identified as primary cases, 4 (two 3 year olds, a 9-year-old and an 11-year-old) had a documented history of age appropriate pertussis immunization, one 15-year-old reported no previous vaccination and 3 siblings (aged 4 years, 17 years and 23 years) reported unknown vaccination status. Five of these cases were from the United States, 2 from Germany and one from France.

When calculating the proportion of source cases among all index cases, parents were identified as the source case for 30% of infants, siblings 9%, aunts/uncles 5%, friends/cousins 5%, grandparents 3% and part-time caretakers 1%.

Among the 47 (51.6%) index cases for whom no source case could be identified, complete enrollment and complete laboratory diagnostic tests for all household and eligible nonhousehold contacts were available for 21 (44.7%), indicating potential transmission from a casual contact. For the remaining 26 families, there was at least one identifiable close contact who did not participate in the study, limiting our ability to draw conclusions regarding the source of infection for the infant.

Sensitivity Analyses Investigating the Effect of Missing Data. In the conservative *strict complete enrollment analysis* 49 (52.1%) families were excluded due to missing data for one or more contacts. Among the 45 infants and 193 contacts included in the analysis, a source case was identified for 62.2% of index cases. In the *all participant analysis*, all data for the 94 index cases and 404 contacts were included and a source case was identified for 53.2% of index cases. The differences in the distribution of relationships of the source cases in these sensitivity analyses and the primary analysis were small (0.2%–5.1%), with overlapping 95% confidence intervals. [Table 3b, available online only.]

Sensitivity Analyses Investigating Infants for Whom a Primary Case was not Identified. In the *expanded primary case definition analysis*, a primary case was identified for an additional 12 (13.2%) index cases. Seven primary cases had symptoms 31–48 days before onset in the index case, and 5 primary cases had symptoms 2–6 days before onset in the index case. A primary case was thus identified for 61.5% of all infants, when compared with 48.4% in the primary analysis. The distribution of the relationships of the primary case to the index case remained similar. [Table 3b, available online only.]

When transmission from asymptotically infected close contacts was assumed possible, a source case was identified for an additional 15 (16.5%) index cases beyond those identified when using the expanded case definition, 6 of which were confirmed by serology only, 5 by PCR only, and 4 by both PCR and serology. In this sensitivity analysis, a

TABLE 1. Associations of Age and Number of Received Vaccine Doses With Being Hospitalized Among Infant Index Cases

Characteristic	Hospitalized		Not Hospitalized		P
	n	%	n	%	
Index cases	75	100.0	20	100.0	
Age (mo)					0.015
<2	32	42.7	3	15.0	
2–3	30	40.0	8	40.0	
4–6	13	17.3	9	45.0	
Number of vaccine doses					<0.001
0	46	61.3	7	35.0	
1	27	36.0	7	35.0	
2	2	2.7	6	30.0	

TABLE 2. Distribution of Diagnostic Specimens Collected, Amount of Contact With the Index Case, Vaccination History, and Pertussis Outcome Status Stratified by Household Category

Characteristic	Adult Household (≥18 yr)		Child Household (<18 yr*)		Nonhousehold	
	n	%	n	%	n	%
Lab specimen collection						
PCR	200	97.1	110	86.6	60	84.5
Acute serology	201	97.6	93	73.2	60	84.5
Convalescent serology	168	81.6	73	57.5	46	64.8
Close contact with index case (hr/d)						
≥5	183	88.8	105	82.7	26	36.6
1–5	19	9.2	15	11.8	25	35.2
<1	3	1.5	5	3.9	19	26.8
No close contact	1	0.5	2	1.6	1	1.4
Timing of vaccination†						
Infant (2–18 mo)	127	61.7	113	90.4	47	66.2
Child (4–6 yr)	89	43.2	58	100.0	27	42.9
Unknown‡	45	21.8	3	2.4	14	19.7
Pertussis case classification§						
Lab confirmed symptomatic	73	37.2	40	42.6	23	40.4
Epidemiologic-linked	14	7.1	23	24.5	5	8.8
Lab confirmed asymptomatic	31	15.8	8	8.5	5	8.8
No infection (no case)	78	39.8	23	24.5	24	42.1

*Child household members are less than 18 yr of age except when teenage mothers (n = 1, age = 16) qualifies as an emancipated minor and thus categorized as adult.

†Number and percent of persons vaccinated during infancy (2–18 mo) and childhood (4–6 yr). Proportions were calculated among those old enough to be administered the specified dose.

‡Persons reporting unknown vaccination for both doses were treated as not vaccinated.

§Data from primary complete case analysis. Distributions from sensitivity analyses were similar (data not shown).

TABLE 3a. Proportion of Infants for Whom a Primary Case was Identified and the Distribution of Primary Cases According to Relationship to the Index Case, Age Group, and Household Status for the Primary Complete Case Analysis

	Primary Complete Case Analysis		
	N	%	95% CI
Index case			
Included in analysis	91	100.0	—‡
For whom a primary case identified	44	48.4	(37.7–59.1)
Primary case			
Relationship*			
Parent	27†	55.1	(40.2–69.3)
Sibling	8	16.3	(7.3–29.7)
Aunt/uncle	5	10.2	(3.4–22.2)
Friend/cousin	5	10.2	(3.4–22.2)
Grandparent	3	6.1	(1.3–16.9)
Part-time caretaker	1	2.0	(0.5–10.9)
Age group*			
Child <13	7	14.3	(5.9–27.2)
Adolescent 13–18	8	16.3	(7.3–29.7)
Adult 19–39	30	61.2	(46.2–74.8)
Adult 40–64	4	8.2	(2.3–19.6)
Adult 65+	0	0.0	—‡
Household type*			
Adult household	29	59.2	(44.2–73.0)
Child household	8	16.3	(7.3–29.7)
Adult nonhousehold	7	14.3	(5.9–27.2)
Child nonhousehold	5	10.2	(3.4–22.2)

*The number of source cases is greater than the number of infants for whom a source case was identified because multiple source cases were allowed for infants whose source cases reported symptom onset on the same day.

†Mothers accounted for 18 and fathers accounted for 9 of these parents.

‡Unable to calculate confidence intervals for proportions containing 0% and 100%.

primary case was identified for 71 (78.0%) index cases. Again, the distribution of relationships to the infant index cases remained similar to that in the primary analysis. [Table 3b, available online only.]

Stratified Analysis by Continent. Data from the European sites were compared with the North American sites. No differences were observed in the demographic characteristics at $\alpha = 0.05$. The mean age of European parents was 32.6 years and the mean age of North American parents was 30.0 years ($P = 0.07$). The distributions of primary cases by relationship to the infant and by age were not statistically significantly different between the 2 continents (data not shown).

COMMENT

This study shows that parents (48%–55%), siblings (16%–21%) and nonhousehold close contacts (18%–29%) are important sources of pertussis transmission to young infants. Although these findings corroborate those from prior studies^{5,23–25,27} (Table 4), they were robust to sensitivity analyses as evidenced by the relatively small range (<8%) in point estimates among each stratum of source cases. Additionally it had fewer limitations than previous studies. The prospective study design limited recall error in reporting the timing of symptom onset in contacts. The collection of biologic specimens (PCR and serology) on all household members, irrespective of symptoms, allowed laboratory confirmation of symptomatic cases and identification of asymptomatic infection. Inclusion of close nonhousehold contacts allowed inves-

TABLE 4. Comparison of Studies Estimating the Source of Infection to Young Children

	Renacoq 2005 ²⁴	Bisgard et al 2004 ⁵	Crowcroft et al 2003 ²⁷	Halperin et al 1999 ²³	Present Study
No. of index cases	1519	616	33	1082	94
Age range	<6 mo	<1 yr	<5 mo	<1 yr	≤6 mo
Index cases with identified source (%)	53	43	42	40	48–78
Source of pertussis					
Parent (%)	56	47	42	20	48–55
Sibling (%)	23	20	NA	53	16–21
Nonhousehold* (%)	19	26	NA	20	18–27
Laboratory confirmation [†] in index case (%)	84	Some [‡]	100	Some [‡]	100
Diagnostic method in contacts					
Symptoms	Yes	Yes	Yes	Yes	Yes
Culture	No	No	Yes	Some [§]	Yes
PCR	No	No	Yes	No	Yes
Serology	No	No	Some	No	Yes
Design type	Prospective surveillance	Retrospective surveillance	Prospective case enrollment	Retrospective surveillance	Prospective case enrollment

NA, Not available.

*Identifiable contacts among nonhousehold members.

[†]Laboratory confirmation included culture, polymerase chain reaction (PCR), and/or serology.

[‡]Data not available, but assumed that some proportion of diagnoses in index cases of pertussis were laboratory confirmed.

[§]7.5% of contacts were verified by culture.

^{||}Single serology taken for adult contacts only, stored serum samples used for mothers where available.

tigation of their role in pertussis transmission to young infants. Analysis of PCR and anti-PT ELISA at a reference laboratory avoided misclassification because of potential interlaboratory variation in test performance. Further, the relatively large sample size allowed us to draw robust conclusions about who transmitted infection to young infants.

Finally, in contrast to prior studies, we explored alternative hypotheses for index cases for whom no source could be identified. We evaluated the effect of missing data resulting from nonparticipation by household members, potential transmission from casual contact in the community, the effect of increasing the sensitivity of the definition for primary cases, and the potential role of individuals with asymptomatic laboratory confirmed infection in the transmission of pertussis to infants. We also expanded the period of infectiousness and reduced the incubation period based on data from Stocks,⁴⁰ who used cough plates to determine the start and end of the infectious period among sequential cases within a household. In our study, we identified a substantial number of source cases with symptom onset 2–6 days and 31–48 days before onset in the index case. The finding that individuals with asymptomatic laboratory confirmed infection were the only pertussis cases among close contacts for 16.5% of index cases raises questions about the dogma that asymptomatic “carriers” do not transmit pertussis.^{43,44}

These results are important for evaluating the impact of current vaccination strategies and predicting the effect of new vaccination strategies on infant pertussis. The study corroborates the findings from Olin et al⁴⁵ that infant vaccination protects against hospitalization. Although it is vital to maintain high coverage rates and timely vaccination of infants and children against pertussis, we did not find that nonvaccination of siblings was a driving force for infant pertussis in this population. Although adolescents (aged 13–18) accounted for

16%–21% of the primary cases identified (10% were non-household contacts and 6% were siblings in the primary analysis), their relative role in transmission may be greater, because 66% of the infants did not have an adolescent contact in this study. However, the results of this study suggest that vaccination of parents, especially mothers, is of primary importance for the control of infant pertussis. The effectiveness of vaccinating adolescents will depend on the proportion of families in which adolescents are in close contact with infants, and the vaccine coverage achieved.

In this population of young children, the role of non-household caretakers as sources of pertussis was small as only one (2.0%) part-time caretaker and no full-time caretakers were identified as a source case. It is possible that individuals who served a role as informal caretakers identified themselves as relatives (aunts, grandparents). In addition, because only 8 (8.5%) infants enrolled had a caretaker, the relative role of caretakers as a source of pertussis for infants who do have a caretaker other than their parents may be greater than the absolute 2% identified in the study.

The generalization of these findings to other settings may be limited as the socioeconomic characteristics, epidemiologic patterns of pertussis, social contact patterns and immunization strategies may differ between countries. However, the finding that the results were not significantly different between the North American and European continents likely indicates the external validity of the study. Another limitation is the inability to determine the temporality of infection between the index case and those asymptotically infected. It is also possible some asymptotically infected individuals failed to recall and report mild symptoms.

We could not identify a source case in 22.0%–51.6% of infants. While this may be due to missing data and/or variability of residual immunity among contacts, it may also

suggest that transmission from casual contact may be an important source of transmission and warrants further investigation. If casual contacts play an important role, it is likely that optimal prevention of pertussis among young infants will not be achieved until universal vaccination of adolescents and adults is highly successful.

In conclusion, this study provides robust evidence that household members are responsible for 73%–82% of *B. pertussis* transmission to infants for whom a source case could be identified, and for 39% of transmission to all infants with pertussis in this study. Parents accounted for half of all *B. pertussis* transmissions to infants. It is therefore likely that the implementation of the recent ACIP recommendation for adult and adolescent vaccination could substantially reduce the burden of infant pertussis, if high coverage rates among those in contact with young infants can be achieved.

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Infant Pertussis Study Group: Isabelle Poilane, MD (Hôpital Jean Verdier, Bondy, France), C. Berchiche, MD (Hôpital Edouard Herriot, Lyon, France), Albert Faye, MD, PhD, E. Bingen, PhD, and S. Bonacorsi, MD, PhD (Hôpital Robert Debré, Paris, France), Dominique Moissenet, MD (Hôpital Armand Trousseau, Paris, France), Bernard Belohradsky, MD and Michaela Hamm, MD, (von Haunersches Kinderspital, Ludwig-Maximilians-Universität, Munich, Germany), A. Hofmiller, MD (Kinderklinik der Technischen Universität, Munich, Germany), A. Koelzer (Kinderkrankenhaus 3. Orden, Munich, Germany), B. Kreuz, MD (Kinderklinik Harlaching, Munich, Germany), Klara Posfay-Barbe, MD and Marian G. Michaels, MD, MPH (Children's Hospital of Pittsburgh, Pittsburgh, PA).

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