A Ten-Year Case-Control Study of Passive Smoke Exposure as a Risk Factor for Pertussis in Children

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ABSTRACT

Context: Passive exposure to cigarette smoke in the household as a risk factor for pertussis disease has not been well characterized.

Objective: To determine whether pertussis was associated with household secondhand smoke in children.

Methods: We conducted a matched case-control study of laboratory-confirmed pertussis cases occurring from January 1, 1996, through December 31, 2005, in children up to 12 years of age who were members of a large managed care organization. Controls were matched one-to-one on age group and type of Health Plan account. Passive cigarette smoking was determined through a retrospective review of the medical records of cases, controls, and their respective household members.

Main Outcome Measures: Cases of pertussis infection were identified from a microbiology laboratory database and through diagnostic codes from the International Classification of Diseases, Ninth Revision, with the diagnosis confirmed by culture or polymerase chain reaction.

Results: Sixty-five laboratory-confirmed cases of pertussis were identified. Cases and controls were similar in sex (p = 0.73), race (p = 0.57), and receipt of pertussis antigen-containing vaccine (p = 0.24). Using multivariable conditional logistic regression analysis, we did not detect a statistically significant association between pertussis and household passive exposure to cigarette smoking (adjusted odds ratio = 1.2; 95% confidence interval = 0.5-2.9).

Conclusion: Although we did not detect an association in this analysis, the possible relationship between passive exposure to smoking and childhood pertussis remains an important research question and should be a priority for future studies.

INTRODUCTION

Pertussis, or whooping cough, is a respiratory tract infection and a major public health burden because of its high infectivity and severe manifestations among infants. Pertussis is caused by the bacterial species, *Bordetella pertussis*, which is transmitted from person to person via aerosolized droplets. Rates of childhood immunization against pertussis in the US are high, with more than 83% of children younger than age 3 years having received 4 doses of pertussis antigen-containing vaccine.[1] However, children too young to be fully immunized, older underimmunized children, and immunized teenagers and adults with waned immunity are at risk of pertussis infection acquired from symptomatically infected individuals. Whereas adolescents and adults may have a relatively mild illness, pertussis in infants is particularly severe. According to the Centers for Disease Control and Prevention in 2011, infants younger than age 2 months who were too young to be immunized accounted for 57% of all infant hospitalizations and 85% of all infant deaths due to pertussis in the US.[2]

Passive cigarette smoke exposure (PSE) in the household as a possible risk factor for pertussis infection among children has not been well characterized in the literature. Our prior work investigating the impact of PSE on pneumococcal infection[3] prompted us to conduct a case-control study within the population of a large managed care organization to compare household smoking exposure histories recorded in the electronic medical record (EMR) of pediatric pertussis cases with those of matched controls.

METHODS

We conducted our study among the member population of the Kaiser Permanente Northwest (KPNW) Health Plan, using a similar protocol and the same control group described for our investigation of PSE as a risk factor for invasive pneumococcal disease.[3] We selected pertussis cases occurring from January 1, 1996, through December 31, 2005, among KPNW members from birth through age 12 years. Potential cases were identified from either of the following: 1) a microbiology laboratory database as having pertussis confirmed by culture, direct fluorescent-antibody testing, or polymerase chain reaction or 2) the EMR as having a pertussis-related code from the International Classification of Diseases, Ninth Revision (ICD-9; 033, 033.0, 033.8, 033.9, and 484.3). When ICD-9 codes were used for case identification, we manually reviewed the EMR to exclude those without documented laboratory confirmation of pertussis infection.

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Where possible, we used our control population from the study of invasive pneumococcal disease. Among this group, we determined which potential controls were closest in age to our cases on their "reference date," defined as the collection date of the pertussis-positive specimen from the case, and matched 1 control to each pertussis case, by age group (0-2, 3-5, and 6-12 years) and type of Health Plan account. We matched controls and cases on the basis of the reference date to avoid confounding the relationship between smoking exposure and pertussis occurrence by secular changes in pertussis incidence and capture of smoking history within the EMR. Because the study design involved collecting PSE information from the EMR of family members if available to us, we matched group members based on Health Plan account (child plus family members or child alone) to equalize our access to the family member's EMR between cases and their matched controls. For 11 pertussis cases without a suitable control from this control population, we randomly selected 1 control for each case from the KPNW member population, using the same criteria.

We reviewed the health records of all cases and new controls, plus the records of their family members where available, to collect PSE history, using standardized data collection instruments. We categorized each case and control as definitely exposed, probably exposed, probably not exposed, definitely not exposed, or unknown (Table 1). For all cases and controls, we collected information about receipt of pertussis antigen-containing vaccines before the collection date of the pertussis-positive specimen (cases) or equivalent reference date (controls) through electronic abstraction of the Vaccine Safety Datalink vaccine dataset.[4,5] We defined vaccine exposure as "vaccinated" if the subject had received at least one pertussis antigen-containing vaccine before the reference date or "unvaccinated" if they had not. We determined whether cases and controls were up to date with the receipt of pertussis antigen-containing vaccines, as appropriate for age, using Advisory Committee on Immunization Practices recommendations.[6]

We constructed conditional logistic regression models to investigate the relationship between PSE and pertussis. Our main model included only the matched case-control pairs for whom PSE history was categorized for both members of the pair. Because of the small number of study participants, we considered participants to be "exposed" if they were categorized as "definitely exposed" or "probably exposed." We considered participants to be "unexposed" if they were categorized as "definitely not exposed" or "probably not exposed." Variables evaluated for confounding in multivariable models included sex, race, history of being breastfed, daycare attendance, and receipt of pertussis antigen-containing vaccine before the reference date. The latter was retained in the final multivariable model.

To account for any possible selection bias related to the exclusion of case-control pairs in which at least one of the members had an unknown PSE history, we conducted a sensitivity analysis, including all case-control pairs in two separate models. For Model 1, we compared the combination of unexposed and unknown pairs with exposed pairs; for Model 2, we compared the combination of unexposed pairs with exposed and unknown pairs. We included vaccine history in both models to adjust for potential confounding.

This protocol was reviewed and approved by the KPNW institutional review board.

RESULTS

We identified 65 laboratory-confirmed pertussis cases meeting our criteria, 33 of which occurred in infants younger than 1 year of age. Positive test results for pertussis included 53 cases confirmed by culture, 5 by direct fluorescent-antibody testing, 4 by

Table 1. Categorization of passive household smoking exposure for pertussis cases and matched controls	
Category of exposure	**Definition**
Definitely exposed	One or more persons in the household (including babysitter) smokes, recorded within two years of the reference date (RD). No conflicting information from family members' charts. No mention in the child's record that adults smoke outside.
Probably exposed	Conflicting information on smoking in the household, but at least one record that someone in the household smokes, *or*
	Meets criteria for "definitely exposed" but the child's record mentions that adults smoke outside. Evidence must show that all adults in the household smoke outside for the child to be classified as "probably exposed" rather than "definitely exposed," *or*
	Meets criteria for "definitely exposed" except that the only available information is recorded more than two years before RD.
Probably not exposed	One parent is a nonsmoker. No information on smoking status of the other parent, *or*
	One or more adults quit smoking but either quit within the last five years or quit at some unknown date, *and* the child's record says household is nonsmoking, *or*
	Any notation in any family member's record that no one in the household smokes, *or*
	Both parents are documented nonsmokers or former smokers but information on at least one parent is more than two years old.
Definitely not exposed	Unequivocal information from a child's record within two years of RD that no one in the household smokes, *or*
	Information present within two years before RD that both parents are nonsmokers. Former smoker parents quit more than five years before RD.
Unknown	No smoking-related information found in any family member's medical record.

culture and direct fluorescent-antibody testing, and 3 by polymerase chain reaction. Table 2 describes demographic and exposure information of pertussis cases and matched controls. Cases and controls were similar with respect to sex (p = 0.73) and white vs nonwhite race (p = 0.57). A similar proportion of cases (68%; n = 44) and controls (78%; n = 51) had received a pertussis antigen-containing vaccine (p = 0.24). Among those vaccinated, a similar proportion of cases (77%; n = 34) and controls (40; 78%) were up to date with pertussis vaccination for their age (p = 0.89). Because cases and controls were similar by up-to-date vaccination status and because our small sample size would potentially limit our ability to consider additional variables in our main model, we decided to consider only whether our subjects were vaccinated or unvaccinated for the remainder of the analysis. A higher proportion of cases than controls was categorized as exposed to PSE (37% vs 27%), but the control group had a higher proportion of subjects with missing data on PSE (18% in controls vs 8% in cases).

For 15 (23%) of the case-control pairs, 1 or both members had unknown PSE, and these pairs were excluded from our main-effects analysis. Among the remaining 50 case-control pairs, 28 (56%) had concordant case-control exposure histories (7 in which both members were exposed and 21 in which both members were unexposed). In our conditional logistic regression model, which calculated the odds ratio (OR) using data from the 22 discordant pairs, we found no statistically significant relationship between pertussis and PSE in the household (OR = 1.2; 95% confidence interval [CI] = 0.5-2.8; Table 3). Our results remained similar after adjusting for receipt of pertussis antigen-containing vaccine (adjusted OR = 1.2; 95% CI = 0.5-2.9). We included the 15 case-control pairs with at least 1 member with unknown PSE in our sensitivity analyses. In Model 1, we placed those with missing PSE data in the unexposed category; in Model 2, we placed them in the exposed category. Thus, the range of ORs that could have resulted from this study if there had been no missing data was 1.1 to 1.7.

DISCUSSION

We did not detect an association between laboratory-confirmed pertussis and PSE in the household in this analysis; however, this remains an important

Table 2. Demographic and exposure characterization of 65 pertussis cases and matched controls

	Cases, no. (%)[a]	Controls, no. (%)[a]	Chi squared p value
Demographic			
Sex (male)	33 (51)	36 (56)	0.73
Race (white)	18/20 (90)	25/26 (96)	0.57
Age			
< 1 year[b]	33 (51)	23 (35)	
1-2 years[b]	7 (11)	17 (26)	
3-5 years	7 (11)	7 (11)	
6-12 years	18 (28)	18 (28)	
Exposure			
Vaccinated against pertussis	44 (68)	51 (78)	0.24
Up-to-date vaccination for age	34/44 (77)	40/51 (78)	0.89
< 1 year	19/21 (90)	11/12 (92)	
1-2 years	2/3 (67)	2/3 (67)	
3-5 years	1/3 (33)	11/12 (92)	
6-12 years	12/17 (71)	16/24 (67)	
Passive smoke[c]			
Exposed	24 (37)	18 (27)	0.69
Unexposed	36 (55)	35 (54)	
Unknown	5 (8)	12 (18)	

[a] N = 65 unless otherwise noted (eg, 18/20, in which case n = 20).
[b] Cases were matched to controls in the 0- to 2-year age group; this group had a total of 40 cases and 40 controls.
[c] "Exposed" includes participants categorized as "definitely exposed" or "probably exposed." "Unexposed" includes participants categorized as "definitely not exposed" or "probably not exposed."

Table 3. Adjusted odds ratios of conditional logistic models assessing the relationship between passive smoke exposure and pertussis, adjusting for receipt of pertussis vaccine

Variable[a]	Odds ratio (95% CI)[b]	p value
Main analysis		
Unexposed	Reference	Reference
Exposed	1.2 (0.5-2.9)	0.67
Vaccinated	0.9 (0.5-2.3)	0.75
Sensitivity analysis, Model 1		
Unexposed + unknown	Reference	Reference
Exposed	1.7 (0.8-3.8)	0.19
Vaccinated	0.5 (0.2-1.2)	0.11
Sensitivity analysis, Model 2		
Unexposed	Reference	Reference
Exposed + unknown	1.1 (0.5-2.3)	0.87
Vaccinated	0.5 (0.2-1.3)	0.15

[a] "Exposed" includes participants categorized as "definitely exposed" or "probably exposed." "Unexposed" includes participants categorized as "definitely not exposed" or "probably not exposed."
[b] Conditional adjusted odds ratio for main model included 50 pairs with known passive smoke exposure, 22 of which were discordant. Conditional adjusted odds ratio for sensitivity analysis models included 65 pairs, 35 of which were discordant.
CI = confidence interval.

research question to study. In an in vitro model, cigarette smoke exposure was associated with an increased number of *B pertussis* organisms binding to buccal epithelial cells from nonsmokers compared with unexposed cells.[7] Among cigarette smokers, studies have described decreased mucociliary clearance,[8] decreased levels of circulating immunoglobulins, decreased natural killer cell activity, depressed neutrophil chemotaxis and phagocytic activity, and decreased release of pro-inflammatory cytokines.[9] Cigarette smoking also is associated with increased permeability of the respiratory epithelium.[10] Further research is needed to investigate whether similar immune alterations occur in children exposed to cigarette smoke.

Among children, PSE has been associated with an increased risk of invasive bacterial infections from *Streptococcus pneumoniae*,[11,12] *Neisseria meningitidis*,[13-18] *Haemophilus influenzae type b*,[18,19] pulmonary *Mycobacterium tuberculosis* infection,[20] and viral infections, including respiratory syncytial virus.[21] In addition, smokers with pertussis infection are more infectious than nonsmokers because of greater severity and duration of cough.[22] This is especially important, as household members are the estimated source for 60% to 83% of infant cases of pertussis, and adults have been responsible for introducing pertussis into the household in 26% of household outbreaks and for 42% of all household secondary cases.[23-26]

Our main study strengths were the use of information from EMR and laboratory records, reducing exposure misclassification and outcome misclassification, and a study period that extended over 10 years. Our main limitation was the small sample size of the study population because of a low incidence of pertussis during the study period.[27] Our sample size was further restricted by incomplete household PSE history for some study participants, although

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we accounted for this through our sensitivity analysis and this limitation did not alter our findings.

CONCLUSION

Pertussis is now considered a resurgent disease; its incidence has increased overall during the past 3 decades, with more notable increases and multiple outbreaks since the mid- to late 2000s.[28] In 2012, Oregon had an outbreak of pertussis and recorded more than 900 cases (23.3 cases per 100,000)—its highest occurrence since 1953.[29] The incidence rate was highest among infants (253/100,000 persons), followed by children aged 10 to 14 years (104/100,000), aged 1 to 4 years (81/100,000), and aged 5 to 9 years (67/100,000). Twenty-six infants had severe disease requiring hospitalization. If PSE is linked to increased risk or severity of pertussis in childhood, this would allow targeted education for parents about eliminating household PSE and would assist clinicians in assessing the child's risk for pertussis infection. Improved documentation of PSE in the EMR would assist future studies of the relationship between PSE and pertussis risk in children. ❖

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Pertussis

Fevers attacked boys of four months, of ten months and a little older, countless numbers of whom died. Principally that common cough, which is usually called *Quinta or Quintana* … . Serious are the symptoms of this … . For they are without this troublesome coughing for … four or five hours … then this paroxysm of coughing returns, now so severe that blood is expelled with force through the nose and through the mouth.

— Guillaume de Baillou (Ballonius), 1538-1616, French physician and considered founder of modern epidemiology