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ARTICLE

Parental Refusal of Pertussis Vaccination Is Associated With an Increased Risk of Pertussis Infection in Children

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What's Known on This Subject

Ecological studies have shown that exemptions to school immunization requirements are associated with an increased incidence of pertussis. However, these studies did not examine this relationship using individual-level data in a well-defined study population of children.

What This Study Adds

We examined the relationship between parental vaccine refusal and the risk of pertussis infection in children by using medical chart–verified data on vaccination and disease status.

ABSTRACT

OBJECTIVE. The objective of this study was to determine if children who contracted pertussis infection were more likely to have parents who refused pertussis vaccinations than a similar group of children who did not develop pertussis infection.

METHODS. We conducted a case-control study of children enrolled in the Kaiser Permanente of Colorado health plan between 1996 and 2007. Each pertussis case was matched to 4 randomly selected controls. Pertussis case status and vaccination status were ascertained by medical chart review.

RESULTS. We identified 156 laboratory-confirmed pertussis cases and 595 matched controls. There were 18 (12%) pertussis vaccine refusers among the cases and 3 (0.5%) pertussis vaccine refusers among the controls. Children of parents who refused pertussis immunizations were at an increased risk for pertussis compared with children of parents who accepted vaccinations. In a secondary case-control analysis of children continuously enrolled in Kaiser Permanente of Colorado from 2 to 20 months of age, vaccine refusal was associated with a similarly increased risk of pertussis. In the entire Kaiser Permanente of Colorado pediatric population, 11% of all pertussis cases were attributed to parental vaccine refusal.

CONCLUSIONS. Children of parents who refuse pertussis immunizations are at high risk for pertussis infection relative to vaccinated children. Herd immunity does not seem to completely protect unvaccinated children from pertussis. These findings stress the need to further understand why parents refuse immunizations and to develop strategies for conveying the risks and benefits of immunizations to parents more effectively. *Pediatrics* 2009;123:1446–1451

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Key Words
immunizations, pertussis, vaccinations, vaccine refusal, epidemiology

Abbreviations
KPCO—Kaiser Permanente Colorado
PCR—polymerase chain reaction
OR—odds ratio
CI—confidence interval
URI—upper respiratory infection

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OVER THE LAST 4 decades, routine childhood immunization in the United States has led to the eradication or control of several vaccine-preventable diseases, including smallpox, polio, diphtheria, *Haemophilus influenzae* type b, measles, mumps, and rubella.[1–3] Now that these illnesses have become rare, however, parental concern seems to have shifted from preventing disease transmission to vaccine safety. Some parents believe vaccines "overload" the immune system and cause chronic illnesses.[4,5] Other parents express concerns that their children are at low risk for infection and that many vaccine-preventable diseases are not serious.[6,7] A proportion of these concerned parents refuse some or all recommended immunizations for their children. Although this vaccine-refusing population represents a small percentage of the overall population, there is evidence to suggest that the number of parents who refuse immunizations has steadily increased over the last decade.[8–12]

Currently, all states permit a medical exemption to vaccination for children entering school; 48 states also allow a religious exemption, and 21 allow a personal belief exemption.[13] Previous studies have demonstrated that states with high nonmedical exemption rates have an increased incidence of pertussis among children ages 3 to 18 years.[8,11] These studies, however, were not able to assess which specific immunizations were refused among all children with vaccine exemptions, and they did not follow children forward in time to ascertain the incidence of pertussis. To our knowledge, no study has used medical chart–verified, individual-level data on both vaccination and disease status to determine if children of parents who refuse vaccinations are at increased risk for pertussis infection.

To better establish the relationship between vaccine refusal and the risk of pertussis infection, we examined detailed, individual-level clinical data in a population of children enrolled in a managed care health plan over a 12-year period. We hypothesized that children of parents who refuse pertussis vaccination would be at greater risk for pertussis infection than children of parents who accepted vaccinations.

METHODS

Setting and Study Population

The setting was Kaiser Permanente Colorado (KPCO), a Denver-based health plan with more than 430 000 current members. KPCO members receive full coverage of all pediatric vaccines as recommended by the Advisory Committee on Immunization Practices.[14] We conducted a case-control study among children ages 2 months to 18 years, who were members of the health plan between 1996 and 2007. The study was designed to determine if children who contracted pertussis infection were more likely to have parents who refused pertussis vaccinations than a similar group of children who did not develop pertussis infection. The study was reviewed and approved by the KPCO institutional review board.

Definition and Selection of Cases

All potential pediatric cases of pertussis in children were identified by using KPCO medical databases. Potential cases were selected if they had 1 or more of the following: a positive polymerase chain reaction (PCR) laboratory test for *Bordetella pertussis*, a positive pertussis culture result, or an *International Classification of Diseases, Ninth Revision, Clinical Modification* code for *B pertussis* (033.0, 033.1, 033.8, or 033.9). These diagnosis codes and laboratory tests represented medical encounters in the outpatient, emergency department, and inpatient settings. All potential cases were identified without knowledge of vaccination status.

The medical charts of potential cases were then reviewed by a trained abstractor, who was blinded to vaccination status. Details from the pertinent medical encounter and all records up to 14 days after this encounter were abstracted. The abstractor recorded pertussis PCR and culture results, clinical diagnoses of pertussis, duration of cough, presenting symptoms (paroxysms, posttussive emesis, whoop), sequelae of pertussis (apnea, pneumonia, seizures, encephalopathy), and previous exposures to close contacts infected with pertussis. A close contact was defined as someone at day care, school, or home with known pertussis. Additional variables included birth date, gender, home address, ethnicity, age, and medical setting of the qualifying encounter. Patients were classified as confirmed cases if they had a medical chart–verified positive PCR test or a positive culture for *B pertussis*.[15] Confirmed cases between 2 months and 18 years of age were eligible for the final analyses, because infants are not immunized before 2 months of age.

Selection of Controls

For each case, the date of pertussis diagnosis represented the index date. Each case was matched to 4 randomly selected controls by gender, length of KPCO enrollment, and age at the index date (within 7 days). The controls were selected from a pool of pediatric members enrolled in the KPCO health plan between 1996 and 2007. Eligible controls did not have a record of pertussis infection before the index date. Vaccination status was ascertained retrospectively from the index date (see below). This matching scheme helped to simultaneously control for age and season.

Ascertainment of Vaccination Status

The medical charts of the cases and controls were reviewed by a trained medical charts abstractor to determine each child's vaccination status. Diphtheria, tetanus, and acellular pertussis vaccination is recommended at ages 2, 4, 6, 12 to 18, and 48 to 59 months.[14] Before 1996, the diphtheria, tetanus, and whole-cellular pertussis vaccine was recommended on a similar schedule.[16] The medical abstractor, who was blinded to pertussis case status, documented the types and dates of vaccinations received, and whether immunizations were refused by parents for personal, nonmedical reasons. Children were classified as "vaccine refusers" if it was explicitly documented in the medical chart that their parents had refused 1 or more pertussis immunizations for nonmedical reasons. Children were classified as "vaccine acceptors" if they were age-appropriately vaccinated against pertussis at the index date. Children were also classified as vaccine acceptors if they were partially vaccinated against pertussis at the index date and the reason for lack of vaccination was not vaccine refusal. In many instances, a child was partially vaccinated (or not up-to-date) because the physician delayed immunizations due to an acute illness or the parent scheduled his or her child's immunizations after the recommended ages. Cases and controls were excluded if they had a documented medical contraindication to vaccination or if the reason for lack of vaccination was not explicitly documented in the medical charts.

Statistical Analysis

The final case-control population was analyzed with conditional logistic regression to estimate matched odds ratios (ORs) and 95% confidence intervals (CIs). In the regression model, the dependent variable was pertussis case status and the independent variable was vaccine refuser status; each case and control was either a vaccine refuser or vaccine acceptor. The matched ORs from the conditional logistic regression models were then used to calculate the percentage attributable risk in the vaccine refusers and the attributable risk in the total population.[17,18]

Secondary Analyses

Some of the children in our primary case-control analysis were not KPCO members during their first 20 months of life. These children were not continuously enrolled during the period in which they would have received the primary 4-dose series of pertussis vaccination in KPCO clinics. As a result, the immunization records for some of these children may have been incomplete. To address the potential for misclassification of vaccination status in our primary analysis, we conducted an additional analysis using a cohort of children who were continuously enrolled in the health plan from 2 to 20 months of age. Within this cohort, we conducted a case-control study of continuously enrolled children using the same methods as the primary case-control study. For this analysis, however, we matched 10 randomly selected controls for each case, because the cohort entry criteria limited the number of available cases and vaccine refusers for analysis.

We also explored 2 potential sources of bias in our study. First, parents who refuse or accept vaccinations may exhibit different health care–seeking behavior when their children are acutely ill. For example, when compared with vaccine-accepting parents, parents who refuse vaccinations may be less likely to bring their children to medical attention for acute illnesses.[11] This would decrease the likelihood of detecting pertussis among vaccine refusers, thereby underestimating the association between vaccine refusal and pertussis infection. Second, a child's vaccination status may influence a physician's decision to test for pertussis. For instance, a physician may be more likely to test unvaccinated than vaccinated children when they present with acute illnesses. An increase in testing of unvaccinated children would lead to an overestimate of the association between vaccine refusal and pertussis infection.

To examine these potential sources of bias, we conducted separate analyses using the cohort of children followed continuously from 2 to 20 months of age. We excluded laboratory-confirmed cases and patients with strong clinical suspicion for pertussis (cough at the date of the ordered laboratory test and 1 or more of the following: paroxysms, posttussive emesis, and a close contact with known pertussis), because these children should be tested for pertussis regardless of vaccination status. Among vaccine refusers and vaccine acceptors, the analyses compared the odds of visiting the clinic for an upper respiratory infection (URI) and the odds of receiving a pertussis laboratory test at a URI-related clinic visit. URIs were identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* codes (460.xx, 464.xx, and 465.xx) in the automated databases.

RESULTS

Cases of Pertussis

We identified 439 patients with a diagnosis of pertussis in the automated databases. Of these, 178 (41%) had a medical chart–verified positive PCR or positive culture for pertussis, and 165 were between 2 months and 18 years of age. We excluded 9 (5%) patients who were either unvaccinated or partially vaccinated, because the reason for lack of vaccination was not documented in the medical charts. This resulted in a final study population of 156 laboratory-confirmed cases. The annual incidence rate of confirmed pertussis cases increased over time, with 78% of the cases occurring after year 2001. There was, however, no evidence of clustering of cases in a specific time period or geographic location.

TABLE 1 Demographic Characteristics of the Study Population

	Cases (*N* = 156)	Controls (*N* = 595)
Gender, *n* (%)		
Female	73 (47)	274 (46)
Male	83 (53)	321 (54)
Vaccine refusers, *n* (%)	18 (12)	3 (.5)
Age, mean ± SD, y	9.4 ± 5.9	9.3 ± 5.9
Age groups, *n* (%)		
≤3 y	35 (22)	137 (23)
4–6 y	19 (12)	74 (12)
7–9 y	14 (9)	56 (10)
10–12 y	17 (11)	66 (11)
13–15 y	40 (26)	147 (25)
≥16 y	31 (20)	115 (19)

In the final case population, 17 (11%) patients had parents who refused all pertussis immunizations and 1 (0.6%) had parents who refused 4 of the 5 recommended doses. Of these 18 refuser cases, 14 had parents who refused all routine immunizations. The parents of the remaining 4 cases refused some but not all of the following vaccinations: polio, *H influenzae* type b, hepatitis B, varicella, and measles-mumps-rubella. A majority of the parents were white, >30 years of age, and of higher socioeconomic status (based on median income for census tract of home address).

The mean age of the cases was 9 years, and 47% were female (Table 1). A majority of the cases presented in the clinic or emergency department; 6% were hospitalized. The mean reported duration of cough at time of diagnosis was 11.7 days, and 30% of the cases had clinical symptoms of pertussis other than cough documented in the medical charts (Table 2). There were no significant differences in the reported duration of cough, symp-

TABLE 2 Clinical Characteristics Documented in the Medical Charts of 156 Pertussis Cases

Hospitalizations, *n* (%)	9 (6)
Reported duration of cough at diagnosis, mean ± SD, d	11.7 ± 7.3
Symptoms, *n* (%)	
Paroxysms	46 (29)
Posttussive emesis	48 (31)
Sequelae, *n* (%)	
Pneumonia	4 (3)
Apnea	2 (1)
Hypoxia	2 (1)
Seizure	0 (0)
Encephalopathy	0 (0)
Death	0 (0)

TABLE 3 **ORs and Percent Attributable Risks for Risk of Pertussis in Primary and Secondary Case-Control Analyses**

	OR (95% CI)	% AR Refusers (95% CI)	% AR Population (95% CI)
Case-control study			
Refused vaccination (all ages)	22.8 (6.7–77.5)[a]	99.5 (98.1–99.9)	11.0 (5.9–16.0)
Secondary case-control study[b]			
Refused vaccination (2–20 mo)	19.3 (3.5–104.5)[a]	99.3 (95.4–99.9)	12.2 (0.0–23.4)

The reference group for all ORs is children who received the full schedule of pertussis vaccinations. AR indicates attributable risk.

[a] $P < .001$.

[b] Secondary analysis with subjects who were continuously enrolled in the health plan between 2 and 20 months of age.

toms, or sequelae between the vaccine refusers and vaccine acceptors who contracted pertussis (data not shown).

Controls

Of the 624 controls, we excluded 29 (5%) children who were either unvaccinated or partially vaccinated, because the reason for lack of vaccination was not documented in the medical charts. This resulted in a final study population of 595 controls. The controls had similar gender and age distributions as the cases. In the final control population, 3 (0.5%) children had parents who refused 1 or more pertussis immunizations.

Secondary Analysis

In the secondary case-control analysis of continuously enrolled children, we identified a cohort of 27 748 children who were continuously enrolled in KPCO from 2 to 20 months of age. In this cohort, we identified 31 laboratory-confirmed pertussis cases and 308 matched controls. The proportion of cases and controls with parents who refused all pertussis immunizations was 13.0% ($n = 4$) and 0.7% ($n = 2$), respectively.

Risk of Pertussis in Vaccine Refusers

In the primary case-control analysis, vaccine refusal was strongly associated with laboratory-confirmed pertussis (OR: 22.8 [95% CI: 6.7–77.5]) (Table 3). In the secondary case-control analysis of continuously enrolled children, vaccine refusal was also strongly associated with pertussis infection (OR: 19.3 [95% CI: 3.5–104.5]). The percentage attributable risk in the vaccine refuser population was 99.5% (95% CI: 98.1%–99.9%), and the total population attributable risk was 11.0% (95% CI: 5.8%–16.0%). These estimates suggest that all 18 of the unvaccinated pertussis cases were attributed to vaccine refusal, and 11% of the pertussis cases in the total population were associated with vaccine refusal.

Potential Diagnostic Bias

To evaluate the potential for a diagnostic bias, we compared the odds of receiving a laboratory test for pertussis between the vaccine refusers and vaccine acceptor study groups. Of the 27 748 cohort members with continuous follow-up from 2 to 20 months of age, there were 161 (0.6%) medical chart–verified vaccine refusers. In total, 33 PCR- or culture-confirmed pertussis cases and 53 patients with strong clinical suspicion for pertussis testing were excluded from the cohort. In the remaining vaccine refuser and vaccine acceptor study groups, 73 (48%) and 17 785 (65%) of the children had at least 1 URI visit during the follow-up period, respectively. Vaccine acceptors were twice as likely to visit the clinic for an URI than children of parents who refused pertussis vaccines (OR: 2.0 [95% CI: 1.5–2.8]). Conversely, among children who presented to the clinic with URI symptoms, vaccine refusers were >3 times as likely to be tested for pertussis than vaccine acceptors (OR: 3.2 [95% CI: 1.0–10.1]).

DISCUSSION

Our study found a strong association between parental vaccine refusal and the risk of pertussis infection in children. Vaccine refusers had a 23-fold increased risk for pertussis when compared with vaccine acceptors, and 11% of pertussis cases in the entire study population were attributed to vaccine refusal. This study is the first to examine this relationship in a well-defined cohort with verified individual-level data on vaccination and disease status. Access to individual patients' medical charts and laboratory results allowed us to identify and validate cases of pertussis. We were also able to validate which vaccinations were administered, when they were administered, and whether an immunization was refused. These precise measurements helped to minimize potential biases because of misclassification of exposure (pertussis vaccine refusal status) and outcome (pertussis disease).

Our results are consistent with 3 previous studies that showed an association between school vaccination exemptions and an increased incidence of vaccine-preventable diseases.[8,11,19] These studies found increased risks of both pertussis and measles among vaccine-exempt, school-aged children 3 to 18 years of age. However, these studies relied on measles and pertussis cases reported to state health departments and on public school records and census data to estimate the populations at risk. These studies, therefore, did not calculate risks on the basis of individual-level data on children followed forward in time. Other recent investigations have linked individual-level vaccine refusal and disease data, but these were conducted in outbreak settings and did not reflect the risk in the general pediatric population over time.[20,21]

One previous study found a sixfold increased risk of pertussis among vaccine-exempt children compared with nonexempt children in Colorado.[11] Our larger estimate of the association between parental vaccine refusal and the risk of pertussis infection (OR: 22.8) is likely a result of our more precise methods of determining vaccination status. Previous work has shown that a significant proportion of children classified as vaccine exempt according to school records may have actually been immunized.[4] School records, moreover, do not typically specify which immunizations were refused when a parent claims a personal exemption. A majority of parents choose to forego some but not all recommended immunizations.[6] Therefore, using school vaccination records likely results in an underestimate of the risk associated with vaccine refusal, because a proportion of children classified as vaccine exempt may have been immunized against pertussis. Having access to each child's medical charts allowed us to reduce misclassification of exposure and outcome.

Despite high pertussis immunization rates in Colorado, herd immunity did not prevent a high relative-risk for pertussis in vaccine refusers.[22] This is likely because of a combination of waning immunity to pertussis in adolescents and adults, ongoing endemic circulation, the highly contagious nature of the bacterium, and frequent asymptomatic infections.[23–26] Of note, herd immunity to pertussis may increase over time because of the impact of the newly recommended adolescent and adult pertussis booster vaccines.

This study has several potential limitations. First, our population was drawn from a single health plan in Colorado. Although this may limit the generalizability of our findings, the health plan is a large integrated health care delivery system, with broad representation of the state's population, and the rate of pertussis vaccine refusal in our study population was similar to previous estimates of vaccine refusal in states that offer personal belief exemptions.[4,8] Moreover, the demographic characteristics of parental vaccine refusers in our study were similar to what has been published previously.[9]

Second, we found that physicians were more than 3 times as likely to obtain pertussis laboratory tests on unvaccinated children than vaccinated children presenting with URI symptoms but without classic pertussis symptoms. This type of diagnostic bias could artificially elevate the relative-risk estimates. However, we also found that fully immunized children were twice as likely to visit the clinic for an URI than children of parents who refuse immunizations. These results suggest that, although more cases of pertussis may have been identified from the clinic visits in the vaccine-refusing group, cases may have also been missed, because the vaccine refusers used the medical system less frequently. Such biases would distort the relative-risk estimates in opposite directions. The magnitudes of these associations, however, were relatively modest when compared with our overall estimate (OR: 22.8), suggesting that the impact of the net bias was small.

CONCLUSIONS

These results have important implications for families and the physicians who care for them. We found that children of parents who refuse pertussis vaccination are at a greatly increased risk for pertussis infection. This result dispels 1 of the commonly held beliefs among vaccine-refusing parents that their children are not at risk for vaccine-preventable diseases. Future research should focus on the community impact of vaccine refusal and the risks to other vulnerable populations, including children who are too young to be fully immunized and older adults with waning immunity. Furthermore, our study highlights the need for effective risk communication between parents and physicians about vaccines and the diseases they prevent.

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STUDY OF GENES AND DISEASES AT AN IMPASSE

"The era of personal genomic medicine may have to wait. The genetic analysis of common disease is turning out to be a lot more complex than expected. Since the human genome was decoded in 2003, researchers have been developing a powerful method for comparing the genomes of patients and healthy people, with the hope of pinpointing the DNA changes responsible for common diseases. This method, called a genome-wide association study, has proved technically successful despite many skeptics' initial doubts. But it has been disappointing in that the kind of genetic variation it detects has turned out to explain surprisingly little of the genetic links to most diseases. A set of commentaries in this week's issue of *The New England Journal of Medicine* appears to be the first public attempt by scientists to make sense of this puzzling result. One issue of debate among researchers is whether, despite the prospect of diminishing returns, to continue with the genome-wide studies, which cost many millions of dollars apiece, or switch to a new approach like decoding the entire genomes of individual patients. The unexpected impasse also affects companies that offer personal genomic information and had assumed they could inform customers of their genetic risk for common diseases, based on researchers' discoveries. These companies are probably not performing any useful service at present, said David B. Goldstein, a Duke University geneticist who wrote one of the commentaries appearing in the journal."

Wade N. *New York Times*. April 16, 2009

Noted by JFL, MD