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Parental Decline of Pneumococcal Vaccination and Risk of Pneumococcal Related Disease in Children

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Abstract

Background—An increasing number of parents are choosing to decline immunizations for their children. This study examined the association between the parental decision to decline pneumococcal conjugate (PCV7) vaccinations and the risk of hospitalization due to pneumococcal disease or lobar pneumonia in children.

Methods—We conducted a case-control study nested within a cohort of children enrolled in the Kaiser Permanente Colorado (KPCO) health plan between 2004 and 2009. Each child hospitalized with pneumococcal disease or lobar pneumonia (n=106) was matched to 4 randomly selected controls (n=401). Cases were matched to controls by age, sex, high-risk status, calendar time, and length of enrollment in KPCO. Disease status and parental vaccination decisions were validated with medical record review. Cases and controls were classified as vaccine decliners or vaccine acceptors.

Results—Among 106 cases, there were 6 (6%) PCV7 vaccine decliners; among 401 controls, there were 4 (1%) vaccine decliners. Children of parents who declined PCV7 immunization were 6.5 times (OR=6.5; 95% CI=1.7, 24.5) more likely to be hospitalized for invasive pneumococcal disease or lobar pneumonia than vaccinated children.

Conclusions—Parental decline of pneumococcal vaccination apparently increases the risk for hospitalization due to pneumococcal disease or lobar pneumonia in children. Providers can use this information when helping parents weigh the benefits and risks of immunizing their children.

Keywords

case control study; pneumococcal vaccine; vaccine decliner; lobar pneumonia; invasive pneumococcal disease

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INTRODUCTION

Immunization is one of the most significant public health achievements of the 20th century[1]. Widespread immunization in the United States has reduced the incidence of polio, smallpox, *Haemophilus influenzae* type b and measles by greater than 98%[2]. Recent trends, however, suggest that public trust in the national immunization program is eroding[3-5]. As incidence rates of vaccine-preventable diseases continue to decline, the perceived seriousness of those diseases tends to decrease, and parents are less likely to believe their children are at risk for infection[6-8]. Public concern, as a consequence, has shifted from disease transmission to vaccine safety, and an increasing number of parents are choosing to either decline or delay immunizations for their children[9;10].

Deciding not to vaccinate has a negative impact on the health of children and their surrounding communities. Population-based studies have demonstrated that the local risk of vaccine-preventable diseases increases in communities with high rates of children with nonmedical exemptions to school immunization requirements[11;12]. Studies using individual-level data have shown that children of parents who declined immunizations were approximately 23- times more likely to acquire pertussis and 9-times more likely to contract varicella than vaccinated children[13;14].

Pneumococcal disease is a serious vaccine-preventable disease that is still endemic in the United States. Before the introduction of the seven-valent pneumococcal conjugate vaccine (PCV7) in 2000, an estimated 17,000 cases of invasive pneumococcal disease occurred annually among children younger than 5 years[15]. Since routine use of PCV7, rates of invasive pneumococcal disease and pneumonia hospitalizations in children have decreased by 17 to 77%[16-19]. The disease risks associated with the parental choice to decline PCV7 vaccination are currently not known. We examined the association between the parental decision to decline PCV7 vaccinations and the risk of hospitalization due to invasive pneumococcal disease or lobar pneumonia in children.

METHODS

Setting and study cohort

We conducted a case-control study nested within a cohort of children enrolled in the Kaiser Permanente Colorado (KPCO) health plan, a Denver-based plan with more than 430,000 members. KPCO provides its members with full coverage for all pediatric vaccines as recommended by the Advisory Committee on Immunization Practices[20]. Immunization records are captured in the KPCO electronic medical record, which also includes data from the KPCO immunization registry and Colorado state immunization registry. The study cohort included children ages 2 months to 5 years, who were health plan members between October 2004 and September 2009. During the study period, PCV7 was routinely administered to children at ages 2, 4, 6, and 12-15 months. Early in the cohort, however, many children did not receive all 4 doses due to a national shortage. Across the study period, approximately 90% of children received ≥ 3 doses of PCV7 by age 24 months. To be eligible for the cohort, children had to be born after December 31, 1999, and continuously enrolled in KPCO for at least 6 months. The study was approved by the KPCO Institutional Review Board.

Case definition

Potential cases of children hospitalized with pneumococcal disease or lobar pneumonia were identified in the study cohort using KPCO databases. Children between ages 2 months and 5 years were selected if they had an ICD-9 code for one of the following conditions during an inpatient stay: pneumococcal pneumonia (ICD-9 code: 481), bacterial pneumonia

unspecified (482.9), bronchopneumonia (485), pneumonia organism unspecified (486), influenza with pneumonia (487), empyema (510.9), pneumococcal meningitis (320.1), meningitis due to unspecified bacterium (320.9), bacteremia (790.7), pneumococcal septicemia (038.2), septicemia unspecified (038.9), pneumococcal peritonitis (567.1), mastoiditis (383), and hemolytic-uremic syndrome (283.11).

The medical records of potential cases were then reviewed by a trained abstractor. The abstractor recorded detailed information on hospital discharge diagnoses, symptoms, underlying medical conditions (e.g., asthma diagnoses), laboratory results, chest radiograph results, hospital discharge notes, CT scan results, treatment with antibiotics, and length of hospital stay. The abstractor was blinded to vaccination status.

The detailed case information was then reviewed by a pediatric infectious disease specialist, who adjudicated the final case status. The adjudicator, also blinded to vaccination status, used a clinical definition to identify hospitalizations due to pneumococcal-related disease[21-23]. Four separate conditions were defined: lobar pneumonia (for which *Streptococcus pneumoniae* is the primary cause)[24], pneumococcal meningitis, pneumococcal sepsis, and pneumococcal bacteremia.

Cases of lobar pneumonia were confirmed if a radiologist read the radiograph as lobar infiltrate, lobar consolidation, lobar pneumonia, or consolidative infiltrate. Patients were excluded if the radiograph was read as possible infiltrate, early infiltrate, perihilar infiltrate, or infiltrate versus atelectasis.

Pneumococcal meningitis was defined as any patient with clinical meningitis and a CSF culture positive for *Streptococcus pneumoniae*. Patients were excluded if they had any of the following conditions that predisposed them to pneumococcal meningitis in the medical record: central nervous system shunt, cochlear implants, prior skull fracture, or cranial anatomic abnormality. Cases of pneumococcal sepsis and bacteremia were defined as having a positive blood culture for *Streptococcus pneumoniae*.

Control definition

For cases, the date of hospitalization for pneumococcal disease or lobar pneumonia represented the *index date*. Each case was matched to 4 randomly selected, non-diseased controls by gender, length of enrollment in KPCO (months), high-risk status, calendar time, and age at index date (± 7 days). High-risk status was defined as having a medical condition that increases the risk for pneumococcal infection. These conditions included sickle cell disease, HIV infection, chronic cardiac disease, chronic pulmonary disease, diabetes mellitus, renal failure, congenital immunodeficiencies, and diseases associated with immunosuppressive or radiation therapy[25]. High-risk status was determined with medical record review for both cases and controls.

Controls were selected from the pool of non-diseased children enrolled in the study cohort. Each 1:4 case-to-control match represented a unique stratum. The date of hospitalization for pneumococcal disease or lobar pneumonia in the cases represented the index date in the controls. In each stratum, matched controls had to be enrolled in KPCO at the index date. Vaccination status was assessed retrospectively from the index date.

Vaccination status

A trained medical records abstractor – different from the case abstractor and clinical adjudicator – reviewed the medical records of cases and controls to ascertain PCV7 vaccination status. Blinded to case status, the medical abstractor documented the dates of PCV7 vaccinations received, and whether parents had either declined doses of PCV7 for

personal, non-medical reasons. Children were classified as *vaccine decliners* if it was explicitly documented in the medical records that the parent had declined more than one PCV7 vaccination for personal, non-medical reasons. Children were classified as *vaccine acceptors* if they were age-appropriately vaccinated by the index date. Receiving 3 of the 4 recommended doses of PCV7 vaccine defined up-to-date status, since the national shortage of PCV7 vaccine in the first part of the decade affected a large number of children in the early years of the cohort. For example, a case or control matched at age 15 months with ≥ 3 PCV7 immunizations would be classified as a potential vaccine acceptor. Conversely, a child with ≤ 2 immunizations at this age would be classified as a potential vaccine decliner. Cases and controls were excluded if they had a medical contraindication to vaccination, or if the reason for lack of vaccination was not documented in the medical records.

Analysis

Conditional logistic regression was used to estimate the association between declining PCV7 vaccination and the risk of hospitalization due to invasive pneumococcal disease or lobar pneumonia. Matched odds ratios (ORs) and 95% confidence intervals were calculated. In the primary regression model, case status was the dependent variable; independent variables were vaccination status (vaccine decliner vs. vaccine acceptor) and asthma diagnosis (yes / no). Asthma diagnoses were ascertained with medical records review. The matching variables – gender, age, high-risk status, calendar time, and length of enrollment – defined the strata in the conditional logistic analysis. Matching on age and calendar time helped to control for secular trends in disease incidence across the study period.

Asthma was analyzed as an independent variable, rather than a matching variable, for the following reasons: the 2000 CDC recommendations for PCV7 vaccination did not include asthma as a high-risk condition[25], asthma is a known risk factor for invasive pneumococcal disease[26], and an asthma diagnosis may be associated with vaccination status[27]. We therefore evaluated asthma both as a risk factor for hospitalization and as a confounding variable in the regression model.

We conducted a sub-analysis excluding children with asthma. Including the diagnosis of asthma as a dichotomous variable may not control for confounding because asthma has a broad range of clinical presentation. Therefore, restricting the analysis to children without an asthma diagnosis helped to control for residual confounding.

Sensitivity Analyses

A proportion of the cases of pneumococcal disease and lobar pneumonia may have been misclassified as disease that could have been prevented by PCV7 vaccination. To illustrate, *S. pneumoniae* is the primary cause of lobar pneumonia in 40-80% of cases[24;28], and PCV7 vaccination prevents up to 63% of lobar pneumonia in children younger than age 5 years[21;22;29;30]. This implies that up to 60% of the cases may have been caused by pathogens other than *S. pneumoniae* or by non-PCV7 serotypes. Since PCV7 is 97% efficacious against PCV7 serotypes[31], it is also reasonable to assume that a larger proportion of misclassified cases occurred among the vaccinated cases. In other words, the risk of infection from PCV7 serotypes would be lower in the vaccinated than unvaccinated cases. To explore the potential impact of this differential misclassification, we conducted a series of sensitivity analyses. We held the level of misclassification constant in the vaccinated cases at 60%, reflecting the proportion of cases that may have been caused by organisms other than *S. pneumoniae* or by non-PCV7 serotypes. In the unvaccinated cases, we varied the level of misclassification from 0% to 50% by increments of 10%. For each of the 6 sensitivity analyses, we performed 100 simulations in which strata of matched cases

and controls were randomly selected. For each set of 100 simulations, the mean and 95% confidence interval of the estimated odds ratios were calculated.

RESULTS

Study cohort and cases

We assembled a cohort of 50,857 children ages 2 months to 5 years, who were born after 1999, and continuously enrolled in KPCO for a minimum of 6 months between October 2004 and September 2009. In this cohort, we identified 803 patients hospitalized with an ICD-9 diagnostic code for a potential pneumococcal-related illness in the clinical databases. We excluded 690 children (86%) for conditions other than lobar pneumonia, pneumococcal meningitis, pneumococcal sepsis, and pneumococcal bacteremia. The most common reasons for exclusion were inconclusive chest x-ray findings, lack of x-ray result, and alternative microbiologic diagnoses, such as staphylococcal, Group A streptococcal, or meningococcal disease.

The remaining 113 (14%) patients were confirmed cases. To ensure accurate classification of parental vaccination decisions, we excluded 7 (6%) patients for whom the reason for lack of vaccination was not documented in the medical records. All of these children had few or no medical visits, and therefore appeared to be receiving their care outside of KPCO. This resulted in a final study population of 106 cases (Figure 1). The demographic characteristics of cases are shown in Table 1. Of the confirmed cases, a majority were classified as lobar pneumonia (90%), followed by pneumococcal meningitis (5%), sepsis and bacteremia (6%). The 11 cases of pneumococcal meningitis, sepsis and bacteremia had positive CSF or blood cultures for *S. pneumoniae*; pneumococcal serotype data was not available for these cases. Approximately 38% of cases had an asthma diagnosis and 37% had a high risk condition. The median length of hospital stay was 2 days (range 1 to 31 days), and there were no deaths. Five (5%) cases were intubated and 5 (5%) cases required chest tube insertion and drainage.

In the final case population of 106 cases, 4 (4%) had parents who declined all doses of PCV7 vaccination, 1 (1%) had parents who declined 3 doses, and 1 (1%) had parents who declined 2 doses.

Controls

A total of 424 controls were matched to 106 cases. Twenty-three (5%) controls were excluded because they had incomplete immunization records and the reason for lack of vaccination was not documented in the medical records. These excluded children appeared to be receiving their medical care outside of KPCO. In the final population of 401 controls, 2 (0.5%) children had parents who declined all doses of PCV7 vaccination, 1 (0.3%) had parents who declined 3 doses, and 1 (0.5%) had parents who declined 2 doses.

Risk of hospitalization due to invasive pneumococcal disease or lobar pneumonia in vaccine decliners

The overall incidence rate of invasive pneumococcal disease and lobar pneumonia in children ages 2 months to 5 years was 45 cases/100,000 person-years. Children of parents who declined PCV7 were at increased risk for hospitalization due to invasive pneumococcal disease or lobar pneumonia (OR=6.5; 95% CI=1.7, 24.5) compared to children of parents who accepted PCV7 vaccination. Children with asthma, independent of vaccination status, were 4 times (OR=4.4; 95% CI=2.6, 7.4) more likely to be hospitalized with pneumococcal disease or lobar pneumonia than children without an asthma diagnosis.

In the sub-analysis of children without an asthma diagnosis, vaccine decliners were 10 times more likely (OR=10.0; 95% CI=2.3, 43.0) to be hospitalized than vaccine acceptors. In the sensitivity analysis with 0 to 50% misclassification in the unvaccinated cases, mean ORs ranged from 15.4 (95% CI=2.5, 94.8) to 6.7 (95% CI=0.9, 49.4). The mean ORs were statistically significant in 5 of the 6 sensitivity analyses.

DISCUSSION

We report an apparent association between the parental decision to decline pneumococcal immunization and the risk of hospitalization due to invasive pneumococcal disease or lobar pneumonia in children. Children of parents who declined pneumococcal vaccination were 6.5 times more likely to be hospitalized for clinically-defined pneumococcal disease than vaccinated children; the association was 10-fold in children without asthma.

PCV7 vaccination of young children is highly efficacious against invasive pneumococcal disease[31], and moderately efficacious against radiograph-confirmed pneumonia and otitis media[21;32]. PCV7 also decreases nasopharyngeal colonization of vaccine serotype pneumococci in both adults and unvaccinated children living with vaccinated household members[33;34]. Routine PCV7 vaccination of infants in the US, as a consequence, has had a direct benefit for immunized children and indirect effect on reducing the overall incidence of pneumococcal-related disease in the general population[17-19;23;35]. It is therefore likely that parents who decline PCV7 vaccination not only place their children at increased risk for pneumococcal disease, but may also increase the risk to the community.

Many parents report concerns about vaccine safety and some choose not to vaccinate their children[7;36-39]. When compared to parents who accept vaccinations, parents who decline immunizations are more likely to believe their children are not at risk for vaccine-preventable diseases and that vaccine-preventable diseases are not dangerous[8;37]. Results of this case-control study demonstrate that choosing to decline PCV7 immunization apparently places children at an increased risk for serious illness requiring hospitalization. We believe providers can use this information to help parents weigh the benefits and risks of immunizing their children.

Children diagnosed with asthma were 4 times more likely to be hospitalized for pneumococcal disease or lobar pneumonia than children without an asthma diagnosis. This finding is consistent with a study that showed a greater than 2-fold risk for invasive pneumococcal disease among persons ages 2 to 49 years with asthma[26]. Although our study was not designed to examine the association between asthma and pneumococcal disease, this ancillary result further stresses the importance of maintaining high immunization rates to protect populations susceptible to severe illness.

This study has several limitations. It was conducted in a single managed health care plan in Colorado. While this may limit the generalizability of the findings, KPCO is an integrated health delivery system that represents the larger Colorado population. Colorado is an appropriate setting to study vaccine hesitancy because it is one of 21 states that allow personal belief exemptions to school immunization requirements, and has among the most lenient policies for obtaining personal exemptions[9].

PCV7 serotypes have become increasingly rare over time, and a majority of invasive pneumococcal disease is now caused by non-PCV7 serotypes[15;40-44]. This suggests that there may be alternative explanations for the high rate of probable pneumococcal disease in the cases whose parents declined vaccination. If the cases came from isolated communities, they would not benefit from the indirect effects of vaccination. However, all of these cases were KPCO members from across the greater Denver area. If the parents objected to

traditional medicines, they may have delayed care until the illness became more serious. All of the cases, however, received regular outpatient care while enrolled at KPCO. In addition to these explanations, it is important to note that PCV7 serotypes are still present in the environment[34;45-47], and most cases of lobar pneumonia are not confirmed microbiologically.

We used methods similar to other studies of pneumococcal morbidity and mortality to ascertain probable and proven cases of pneumococcal disease[21-23]. In our study, 90% of the cases were identified as radiologically-confirmed lobar pneumonia. It is therefore likely that a proportion of these cases were caused by pathogens other than *S. pneumoniae* or by non-PCV7 serotypes[21;24]. Such misclassification of disease status likely occurred at a greater rate in the vaccinated case population for the following reasons: non-*S. pneumoniae*-associated pneumonia would not be preventable by PCV7 vaccination, and rates of non-PCV7 serotype carriage are greater in vaccinated than unvaccinated populations[34;48]. As shown in our sensitivity analyses, this differential misclassification of disease status would have biased the results to the null hypothesis. Despite this potential for negative bias, we found a statistically significant association between declining PCV7 vaccinations and the risk of hospitalization in children.

The decision to immunize can be difficult for some parents. It is important for physicians to clearly convey the benefits and risks of vaccination to help parents make informed decisions about protecting their children from infection. Physicians should also inform parents of the consequences associated with choosing not to vaccinate. As vaccine hesitancy continues to grow, future research should focus on developing effective risk communication messages that resonate with parents. Maintaining public trust in the US national immunization program is essential to the health of children and the community.

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Abbreviations

ICD-9	International Classification of Diseases, Ninth Revision
KPCO	Kaiser Permanente Colorado
PCV7	Seven-valent Pneumococcal Conjugate Vaccine

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Figure 1.
Case Ascertainment

Table 1

Demographic Characteristics of the Study Population

		Cases (n=106)	Controls (n=401)
Sex	no. (%)		
Female		46 (43.4)	171 (42.6)
Male		60 (56.6)	230 (57.4)
Vaccine Decliners	no. (%)	6 (5.6)	4 (1.0)
Age (years)	mean $\pm$ sd	2.3 $\pm$ 1.3	2.3 $\pm$ 1.3
Age Groups	no. (%)		
2 - < 12 mo		16 (15.1)	62 (15.5)
1 - < 2 y		32 (30.2)	118 (29.4)
2 - < 3 y		24 (22.6)	94 (23.4)
3 - < 4 y		17 (16.0)	63 (15.7)
4 - < 5 y		17 (16.0)	64 (16.0)
Asthma Diagnosis	no. (%)	41 (38.7)	50 (12.5)
High Risk Status ^a	no. (%)	39 (36.8)	138 (34.4)
Well child visits per child per year	mean $\pm$ sd	1.71 $\pm$ 0.97	1.98 $\pm$ 0.98

^aHigh-risk conditions included sickle cell disease, HIV infection, chronic cardiac disease, chronic pulmonary disease, diabetes mellitus, renal failure, congenital immunodeficiencies, and diseases associated with immunosuppressive or radiation therapy.