CASE-CONTROL STUDY TEMPLATE

Title of the study: Pertussis vaccination and the risk of respiratory syncytial virus associated hospitalization

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Abstract:

Respiratory syncytial virus (RSV) is the most common cause of severe respiratory infections in infants and young children, accounting for as many as 125,000 U.S. hospitalizations each year.[1, 2] RSV infection can have particularly dire consequences for infants with congenital heart disease (CHD), bronchopulmonary dysplasia (BPD), or a history of premature birth.[3] However, these risk factors fail to explain the variable severity of RSV infection in otherwise healthy children, who account for the majority of RSV hospitalizations.[4]

Recent animal data suggest that receipt of pertussis toxin could increase the severity of RSV infection.[5] This hypothesis has not been tested in humans. **We hypothesize that children who have recently received a pertussis vaccination are at an increased risk of RSV-associated hospitalization.**

To test this hypothesis, we will complete the following specific aims:

Specific Aims

Specific Aim 1. To determine whether recent vaccination with a pertussis-containing vaccine is associated with RSV hospitalization.

Specific Aim 2. To determine whether, among children hospitalized with RSV infection, recent vaccination with a pertussis-containing vaccine is associated with greater severity of illness.

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BACKGROUND AND SIGNIFICANCE

It is estimated that RSV is responsible for 75,000 to 125,000 hospitalizations each year in the United States.[1, 2] Despite its importance, no licensed vaccine is available, and pharmacologic prevention is limited to the administration of RSV antibodies to certain groups of children at high risk for hospitalization.[11] However, more than half of all RSV hospitalizations occur in previously healthy full-term children, and approximately 85% of all RSV hospitalizations occur in children for whom RSV antibodies are not recommended.[4] Furthermore, factors known to predispose children to severe RSV disease, such as chronic cardiopulmonary conditions, fail to explain the variable disease severity in otherwise healthy children. Determining modifiable risk factors for severe RSV infection is critical to decreasing the burden of respiratory illness among children in their first year of life.

While nearly three-fourths of all children in the first year of life become infected with RSV, only about 30% of infected children experience lower respiratory tract involvement, manifested by bronchiolitis or pneumonia.[1] Several observations support the role of the host immune response as a determinant of RSV severity. Infants immunized with an experimental formalin-inactivated RSV vaccine developed more severe disease following exposure to wild-type virus than did an unvaccinated cohort.[12-14] Murine models suggest that enhanced illness was the result of selective activation of type 2 CD4+ lymphocytes, leading to altered cytokine and immunoglobulin production.[15] For many pathogens, a type 1 immune response (leading to IgG2a production) correlates with disease resolution, whereas a type 2 response (with predominance of IgG1, IgA, and IgE) correlates with enhanced pathology.[16] Among infants with RSV infection, those manifesting bronchiolitis have significantly higher titers of RSV-specific IgE in nasopharyngeal secretions than those without bronchiolitis.[17] What determines whether the immune response to RSV infection is directed to a predominantly type 1 or type 2 response remains unknown.

One potential modulator of the immune response in infancy is vaccination with pertussis toxin (PT). All whole-cell and acellular pertussis vaccines incorporate an inactivated form of PT.[18] PT, like other bacterial toxins, enhances the magnitude of the antibody response to simultaneously delivered antigens.[19] Recently, Fischer et al have demonstrated that administration of PT intramuscularly before and at the time of RSV challenge in mice is associated with a predominant type 2 immune response to RSV.[20] In a subsequent study, the same authors demonstrated that mice primed with PT or diphtheria, tetanus, and acellular pertussis vaccine (DTaP) experienced more severe RSV disease than unvaccinated or diphtheria-tetanus (DT)-primed controls.[5] This raises the concern that our current vaccination schedule could be causing harm in certain situations. Determining whether this is true or not is the primary goal of this proposal.

The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention currently recommends that children receive a primary series with DTaP vaccine at 2, 4, and 6 months of age, with a booster dose between ages 15 and 18 months.[21] The peak age for acquisition of, and hospitalization for, RSV infection is 2-3 months, which corresponds to the timing of first exposure to DTP.[4, 7, 22] In addition, rates

of recognized bronchiolitis hospitalizations among U.S. children increased from 12.9 per 1000 in 1980 to 31.2 per 1000 in 1996,[2] concurrent with increasing vaccine coverage rates.[23] However, no epidemiologic data currently exist demonstrating either an association or lack of association between pertussis immunization and severity of RSV infection in humans. Should such an association exist, it could have a profound impact on immunization policy as well as implications for development of RSV vaccines. Regarding immunization policy, a strong association between pertussis vaccine and RSV hospitalization might lead to a recommendation to avoid DTaP vaccination during the peak RSV season, unless there was a known pertussis outbreak occurring simultaneously. Concerted effort would need to be made to ensure that overall DTaP vaccination rates did not decline. Regarding future RSV vaccine candidates, stringent criteria for their safety in the context of DTaP vaccination would need to be demonstrated to ensure that enhanced illness did not occur upon subsequent exposure to wild-type RSV.

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PRELIMINARY STUDIES

Our previous work on the epidemiology of RSV has provided a strong foundation for the proposed project. Utilizing the Tennessee Medicaid database, we determined rates of RSV-associated hospitalization among healthy children and those with underlying medical conditions.[4] Prior to our study, population-based data on age-specific rates of hospitalization in the subgroups of children at high risk had not been published. Knowledge of such rates is important in determining which children should receive costly immunoglobulin prophylaxis, in estimating the potential benefits of an effective vaccine, and in formulating the economic rationale for vaccine development.
In our study, a retrospective cohort of all children <3 years old enrolled at birth in Tennessee Medicaid from July 1989 through June 1993 was analyzed. RSV season was defined as occurring from November through April. Children were put into 4 mutually exclusive high-risk categories with the following priority: bronchopulmonary dysplasia (BPD), congenital heart disease (CHD), prematurity (≤28 weeks, 29 to <33 weeks, and 33 to <36 weeks), and all other medical conditions combined. All other children were considered low risk and served as the reference group. Demographic factors analyzed included race, sex, maternal age, education, and smoking status, number of siblings, residence (urban, suburban, or rural), and age at time of hospitalization (0 to <6 months, 6 to <12 months, 12 to <24 months, and 24 to <36 months). The primary study outcome was hospitalization caused by RSV infection or bronchiolitis. For each high-risk group, incidence rate ratios were calculated by dividing the rate of RSV-associated hospitalization among children in that risk group by the corresponding rate among children at low risk. Adjusted incidence rate ratios were calculated with Poisson regression models.

For each age group, children with BPD had the highest rates, with more than 500 hospitalizations per 1000 children with BPD in the first 6 months of life. Children with CHD or prematurity had rates that were lower than rates among children with BPD but still two- to fourfold higher than children at low risk.

By age 6 to <12 months, children with CHD or prematurity had rates of hospitalization that were only slightly higher (range, 34-64 per 1000) than those of low-risk children in the first 6 months of life (44 per 1000). In addition, by 12 to <24 months of age, rates in children with CHD or prematurity were lower (range, 8-30 per 1000) than those of low-risk children in the first 6 months of life. Accordingly, we determined that RSV immunoglobulin prophylaxis is unlikely to be cost-effective in children with CHD or prematurity after the first 6 to 12 months of life. In contrast, children with BPD have high rates of RSV hospitalization through the first 24 months of life (73 per 1000), justifying the use of RSV prophylaxis in this population until their second birthday.

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RESEARCH DESIGN AND METHODS

Overview

The proposed study will utilize the Rochester Epidemiology Project (REP) resources. All children <2 years old who were residents of Olmsted County, MN from January 1, 1987 through December 31, 1999 will be eligible for inclusion in the study. A case-control study will be performed to determine risk factors for RSV hospitalization. Cases will consist of children hospitalized during the study period with a discharge or primary diagnosis of RSV infection or bronchiolitis, and controls will be nonhospitalized children frequency matched by sex and age. The primary exposure variable will be receipt of a pertussis-containing vaccine in the 10 days prior to the case's date of hospitalization. Secondary cutoffs for receipt of pertussis-containing vaccine within 5, 20, and 30 days will also be studied. Odds ratios will be calculated using logistic regression.

Data Resource

Epidemiologic research in Olmsted County is possible because the county is relatively isolated from other urban centers and nearly all medical care is delivered to patients in the population by a limited number of local health care providers. The primary providers of health care to the community (the Mayo Clinic, Olmsted Medical Center, the Rochester Family Medicine Clinic, and their affiliated hospitals) have agreed to share their medical records for research (with appropriate patient permissions) under the auspices of the Rochester Epidemiology Project (REP; AG034676).

The medical records of the health care institutions participating in the REP contain details of every inpatient hospitalization, every outpatient visit to the offices, clinics, or emergency departments, as well as laboratory results and correspondence concerning each patient. The medical records are easily retrievable because the Mayo Clinic has maintained, since the early 1900s, extensive indices based on clinical and histologic diagnoses and surgical procedures. The REP has developed a similar index for the records of most of the other providers of medical care to Olmsted County residents. The result is the linkage of medical records from the vast majority of medical care available to and utilized by the Olmsted County population.

Identification of Cases and Controls

Using the REP electronic indices, we will identify all children <2 years old hospitalized (not including birth hospitalization) from January 1, 1987 to December 31, 1999 with a discharge, primary, or secondary diagnosis of RSV infection or bronchiolitis (ICD-9-CM codes 079.6, 480.1 and 466.1, excluding 466.19). Only community-acquired cases will be included. Community-acquired cases will be defined as those with at least one of the following terms documented within 3 days before or within 3 days after the date of hospitalization: RSV test sent, bronchiolitis, wheezing, apnea, pneumonia, pneumonitis, respiratory distress (difficulty, failure), bronchospasm, oxygen requirement, hypoxia, tachypnea, retractions, oxygen desaturation, chest x-ray obtained, or albuterol use. For children with more than one RSV- or bronchiolitis-associated hospitalization, only the initial hospitalization will be considered. Two controls per case will be randomly selected from the Olmsted County population using

all registrants in the Rochester Epidemiology Project database. Controls will be frequency matched to cases by sex and date of birth.

Baseline Measurements

Once potential cases and controls are identified, abstractors will review the complete inpatient and outpatient medical records of each subject to confirm the diagnosis of RSV infection or bronchiolitis. The diagnosis of RSV infection will be established by a positive culture or rapid test for RSV obtained during the hospitalization or within 3 days before hospitalization. The diagnosis of bronchiolitis will be verified by the presence of wheezing on physical examination during the hospitalization or within 3 days before hospitalization.

The date of all previous immunizations with a pertussis-containing vaccine will be determined from all available medical records. In addition, the site of vaccination (physician's office, county health department, hospital, or other site) will be recorded. Variables known to influence the risk of RSV hospitalization will also be recorded, including congenital heart disease (CHD), bronchopulmonary dysplasia (BPD), gestational age, birthweight, sex, race/ethnicity, daycare attendance, number of siblings, and exposure to environmental tobacco smoke in the home. The following underlying medical conditions will also be recorded: asthma, cystic fibrosis, cancer, human immunodeficiency virus infection, and seizure disorder. Because the number of children with coexisting medical conditions is expected to be small, a combined category that includes children with any of these medical conditions will also be included in the analysis.

All exposure variables will be considered only if present prior to or including the index date. In addition, an exposure variable will be considered to be present if noted at any time prior to the index date. This is because variables such as daycare attendance and exposure to environmental tobacco smoke may not be recorded at the time of hospitalization but may be recorded during an earlier visit. Because we are only studying children <2 years old, number of siblings is primarily a measurement of number of older siblings. Although an attempt will be made to ascertain this information in close proximity to the index date, the only restriction is that it be recorded prior to or on the index date.

For cases, the following information will be recorded: the site of hospitalization, results of any RSV testing (during or within 3 days before hospitalization), presence of wheezing (during or within 3 days before hospitalization), whether the patient required oxygen (during or within 3 days before hospitalization), whether the patient was admitted to the intensive care unit, whether the patient required mechanical ventilation, and the date of hospital discharge (to calculate length of stay).

Statistical Analysis

Variables that are known to influence the risk of RSV hospitalization (see Baseline measurement section) will be descriptively summarized among the cases and the

controls. The primary exposure variable for all subjects will be defined as the receipt of a pertussis-containing vaccine in the 10 days prior to the case's date of hospitalization; secondary variables of interest will be defined for 5, 20 and 30 days. In addition, we will define an exposure variable as the number of days between the case's date of hospitalization and the receipt of a pertussis-containing vaccine prior to that date and analyze this variable on the subset of subjects that have received a vaccination. Among cases only, we will determine if receipt of recent pertussis immunization is a predictor of severity. The association between pertussis-containing vaccination and RSV-associated hospitalization will be summarized based on calculating an odds ratio (the odds of RSV-associated hospitalization among subjects with a recent pertussis-containing vaccination relative to the odds among subjects without a recent pertussis-containing vaccination).

RSV/bronchiolitis hospitalizations will be stratified by season (November through April and May through October) as bronchiolitis hospitalizations occurring in the winter are most likely to be due to RSV infection. Logistic regression models will be fit to calculate the odds ratios and the corresponding 95% CIs, with and without adjusting for potential confounding factors. All calculated p-values will be two-sided, and p-values less than 0.05 will be considered statistically significant.

Power

Approximately 1,700 children are born in Olmsted County each year. The incidence of RSV-associated hospitalization among children <12 months old ranges from 1% to 4%, depending on the population studied and the year of the study.[2,4,6,7] Urban populations[7] and populations with a higher proportion of children with underlying medical conditions[4] have higher rates of RSV-associated hospitalizations. In addition, rates in the 1990s are higher than those seen in the 1980s.[2] Given that Olmsted County is a relatively healthy, non-urban population, RSV-associated hospitalization rates are likely to be closer to 1-2%. This would translate to approximately 17-34 hospitalizations among children <12 months old each year or 221 to 442 hospitalizations over the 13-year study period. After the first year of life, rates of RSV hospitalization decrease substantially.[2,4] Thus, children between 12 and 24 months old are not expected to provide many additional cases. Given that approximately 5% of RSV-associated hospitalizations are rehospitalizations,[4] we would expect 210 to 420 cases available for the case-control study. The table shows the power to detect a significant difference in exposure to pertussis vaccination within the 10 days prior to the case's hospitalization among children in the first year of life.

Power calculations assume 2 controls per case and $\alpha=0.05$ using a two-sided test and were performed using public domain software.[27]

Table. Power calculations for children in the first year of life.

No. of cases	P_0 *	OR**	Correlation***	Power
210	0.1	2	0.4	0.58
420	0.1	2	0.4	0.87
210	0.2	2	0.4	0.81

420	0.2	2	0.4	0.98
210	0.1	2	0.7	0.31
420	0.1	2	0.7	0.56
210	0.2	2	0.7	0.50
420	0.2	2	0.7	0.81

* P_0 refers to the probability of exposure (i.e., pertussis immunization within 10 days of matched case's hospitalization date) among the controls.
** OR refers to the expected odds ratio or odds ratio worth detecting.
*** Correlation refers to the correlation coefficient for exposure between cases and controls.

As can be seen from the table, the power of the study depends on several factors, including the number of cases detected, how common recent pertussis vaccination is in the general population, and the extent to which recent pertussis immunization is correlated among cases and controls. Given that cases and controls will be similar in age and that pertussis immunization is typically given close to the 2, 4, and 6 month birthday of the child, a relatively high degree of correlation among exposure is expected between cases and controls.

Time Lines

Based on the estimated sample size, data collection and entry should be completed within 6 months of approval. Data editing should be completed in the following 2 months and analyses by 10 months following award. A draft manuscript will be delivered within 12 months following award.

Strengths and Limitations

There are several limitations to the proposed study. First, a discharge diagnosis of bronchiolitis may be used as a surrogate for RSV infection. This is necessary because the majority of RSV infections, even among hospitalized children, are not specifically recorded as being due to RSV infection.[4] However, the majority of bronchiolitis hospitalizations are due to RSV infection, particularly during the winter months, when RSV circulates widely and is responsible for approximately 80% of bronchiolitis.[28] In addition, the effect of this ascertainment bias would be to decrease the strength of association between pertussis immunization and RSV-associated hospitalization.

Second, a physician visit itself may be a risk factor for acquiring a respiratory infection such as RSV, irrespective of whether the child receives an immunization. Because most children in Olmsted County receive their immunizations in a physician's office, the effect of this potential confounding, which would tend to increase the strength of association between pertussis immunization and RSV hospitalization, will be difficult to control for. However, we will obtain information on the site of immunization and attempt to control for this in the analysis. A prospective study done during the winter of 1983-1984 in

Boston showed no increased risk of respiratory or gastrointestinal illness within 7 days of visiting a pediatric office.[29]

Third, children who receive vaccines may be in better general health than those in whom vaccination is deferred. This “healthy vaccinee” effect may be the explanation for the apparent protective effect of DTP vaccination on the risk of sudden infant death syndrome.[30,31] Should our results show that DTP vaccination is protective against subsequent RSV hospitalization, this will be the likely explanation, as there is no biologically plausible reason for a protective effect. We will be able to quantify this effect by comparing the ages at vaccination among cases and controls.

Finally, because the residents of Olmsted County are predominantly white and middle class, generalizing the results to persons of other races or settings may not be appropriate. Thus, as with any study, results will need to be corroborated by studies in other settings before policy changes are considered.

HUMAN SUBJECTS

We will abstract pertinent information from the charts of children resident in Rochester, MN between 1987 and 1999, but do not plan to directly contact any of the children in the study. This project does not involve experimentation on human subjects and is limited only to a retrospective review of medical records. The usual policies and safeguards enforced by the Mayo Clinic, Department of Health Sciences Research (as described below) will be used to protect the confidentiality of the patient record.

Patient Consent

This study is minimal risk and consists only of a retrospective review of patient medical records. However, since January 1, 1997, Minnesota State law requires a general authorization to review medical records for research from each patient who attended a health care facility after this date. All health care providers who participate in the REP have implemented systems to track and document patient research authorizations to comply with this law. No records will be reviewed from patients who have not provided this authorization.

Confidentiality

Privacy of patient medical information will be maintained as follows. Information will be abstracted from medical records and collected and stored electronically. Standard procedures are in place to insure appropriate handling and review of medical records and only persons with appropriate authorization will have access to the study computer files. All staff at Mayo Clinic are trained about the importance of confidentiality and procedures by which this must be maintained. All data will be managed and analyzed anonymously, and all reports will be of a summary nature and no individual will be identified. Additionally, no comparisons of any kind will be made between health care institutions.

Benefits

While we do not expect this research to directly benefit the children participating in this study, we do expect this study to generate information that may eventually lead to interventions that will decrease the incidence of RSV-associated hospitalization.

GENDER/MINORITY MIX

All children <2 years old who were residents of Olmsted County from 1987 to 1999 will be considered for this study. No person will be excluded because of race, ethnicity, or gender. Given the demographic characteristics of the population of Olmsted County, we anticipate that approximately 50% of the children in the study will be girls, and that approximately 10% of the children will belong to racial or ethnic minority groups.

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