Severe Pneumococcal Pneumonia in Previously Healthy Children: The Role of Preceding Influenza Infection

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An outbreak of severe pneumococcal pneumonia among children occurred in Iowa from November 1995 through January 1996. An associated outbreak of influenza disease was predominantly caused by influenza A (H1N1) for the first time since 1989. We conducted a case-control study to determine whether preceding influenza infection was directly associated with pneumococcal illness. We identified 13 children with severe pneumococcal pneumonia. Patients were more likely than control subjects to report experiencing an influenza-like illness in the 7–28 days preceding admission (matched odds ratio [OR], 12.4; 95% confidence interval [CI], 1.7–306). Likewise, family members of patients were more likely than those of control subjects to report experiencing an influenza-like illness in the 28 days preceding their admission date (OR, 2.6; 95% CI, 1.0–6.3). Patients were more likely than control subjects to have a positive influenza A (H1N1) convalescent serology (matched OR, 3.7; 95% CI, 1.0–18.1). This study provides direct and indirect evidence that influenza infection led to severe pneumococcal pneumonia among these children. Prevention of pneumococcal disease should be included among the potential benefits of influenza vaccination.

Influenza infection is a commonly cited risk factor for secondary bacterial pneumonia among adults and children. Pneumonia caused by Staphylococcus aureus is especially associated with preceding influenza infection [1]. Pneumonia caused by Streptococcus pneumoniae has also been associated with preceding influenza infection among adults, but not among children [2–4]. This association is based on observations of simultaneous epidemics of influenza and pneumonia and on serologic evidence of previous influenza infection among patients with bacterial pneumonia. We are not aware of any studies that firmly support the direct association between influenza infection and pneumococcal pneumonia. Moreover, very few data demonstrate even indirect seasonal or individual associations between pneumococcal disease and influenza among children, for whom controversy surrounds the benefit of routine annual influenza vaccination [5].

From December 1995 to January 1996, 7 previously healthy children with severe pneumonia were admitted to a hospital in Des Moines, Iowa. By comparison, only 4 children had been admitted with a similar diagnosis in the preceding 24 months. S. pneumoniae was isolated from blood or pleural fluid of 5 of these 7 children. Immediately preceding this cluster of severe pneumonia there had been a community-wide epidemic of influenza A (H1N1), which had not circulated widely in this state or in other states since the 1988–1989 season, when it accounted for 49% of influenza illness [6].

We initiated an investigation to determine the extent of the outbreak of severe pneumococcal pneumonia and to identify whether preceding influenza infection was directly associated with this illness.

Patients and Methods

Case definitions. We defined a case of severe pneumonia as clinical pneumonia that included empyema or lung abscess that required surgery and that occurred in a previously healthy child (aged <18 years), who was a resident of Iowa and was discharged from the hospital between 1 November 1995 and 20 February 1996.

We classified these cases as definite pneumococcal pneumonia if the pneumococci were isolated from blood or pleural fluid; probable pneumococcal pneumonia if gram staining of the pleural fluid or sputum was consistent with pneumococcus but the cultures were negative; and possible pneumococcal pneumonia if the gram stains and cultures were negative and no other pathogen was identified.

In the case-control study, we defined influenza-like illness as a respiratory illness consisting of fever and cough, coryza, or pharyngitis.

Data collection. To determine the extent of the outbreak, we used several strategies. We searched ICD-9 discharge code databases at 6 hospitals in Iowa for cases of pneumococcal disease, empyema, lung abscess, lobectomy, lung decortication, and other...
associated procedures or diagnoses. We reviewed microbiology laboratory records to identify patients with pneumococci isolated from a normally sterile site. We contacted infection control practitioners at 11 other hospitals throughout the state to determine whether children with severe pneumonia had been admitted.

To categorize and describe the case patients, we reviewed the patients’ medical records from the hospitals where they had received inpatient care. To identify preceding influenza-like illness among the patients and their household members, we conducted detailed telephone interviews with the parents of each patient after obtaining verbal informed consent.

Two ongoing state surveillance systems were used to determine the extent and type of influenza illness circulating in the community. First, weekly telephone notification of student absences due to influenza-like illness is made to the Iowa Health Department by 17 sentinel schools throughout the state. Second, strains of influenza-like illness is made to the Iowa Health Department by 17 sentinel physicians throughout the state from patients sent to schools throughout the state. Second, strains of influenza-like illness are characterized by the US World Health Organization Collaborating Laboratories in the region.

**Case-control study.** To determine whether preceding influenza infection was a risk factor for severe pneumococcal pneumonia, we conducted a case-control study. We aimed to identify 3 control subjects per case patient. The control subjects we selected were friends of patients or from the same primary care practice as the patient and were age matched within 1 year of the patient. The parents of patients suggested names of children who were not household members but who lived in the same or neighboring county. After obtaining verbal consent, telephone interviews were conducted with patients and with eligible control subjects who had not had pneumonia since November 1995. We asked if household members had shown symptoms of respiratory illness between 1 November 1995 and the date of the interview. We also asked about potential confounders, including medical history, household size, and demographic information. Interviews with patients and control subjects were conducted in the same 2-week period. Patients were interviewed between 6 and 18 weeks after admission (mean, 9.1 weeks).

**Laboratory testing.** Pneumococcal isolates were tested for penicillin susceptibility, by using oxacillin disc diffusion, at the hospital where they had been isolated. The serotype of pneumococcal isolates was determined by using the quellung reaction, by the Streptococcus Reference Laboratory at the Centers for Disease Control and Prevention (CDC) in Atlanta.

A venous serum specimen for influenza-strain-specific convalescent serology was collected from patients and control subjects between 6 and 18 weeks after the patient’s admission. The serum was tested at CDC by hemagglutination inhibition assay for influenza A (H1N1) antibodies. On the basis of studies of influenza vaccine among children, a titer >1: 40 was considered positive [7, 8].

**Statistical methods.** Epi-Info version 6.0 (CDC, Atlanta, GA) was used for entering data and analyzing results. Maximum likelihood estimates (MLEs) of ORs were used to analyze matched case patients and control subjects, and the $\chi^2$ test was used to compare proportions of unmatched case patients and control subjects. SUDAAN (Release 7.5, Research Triangle Institute, Research Triangle Park, NC) was used to fit a logistic regression model of the influenza-like illness rates among family members of patients and control subjects, adjusting the calculation of variance for clustering of disease within households.

**Results**

**Severe cases of pneumococcal infection.** We identified 13 children from 7 counties in Iowa who had infections that met our case definition for severe pneumonia (table 1). Seven of the children (54%) were girls. All children were previously healthy, and none had ever received influenza vaccine or pneumococcal
A pneumococcal etiology was considered definite in 7 cases, probable in 4 cases, and possible in 2 cases. Three (50%) of 6 children with negative cultures had received antibiotics before specimens were obtained for cultures. No serologic tests were conducted to determine whether these subjects had a group A streptococcal infection. All 7 pneumococcal isolates were susceptible to penicillin. Of the 4 isolates available for serotype determination, 2 were serotype 1, 1 was serotype 3, and 1 was serotype 5. Although none of the children died, all 13 required prolonged hospital stays (range, 9–44 days; mean, 18 days); 12 children required chest tube placement, 10 required decortication of lung tissue, and 2 required pulmonary lobectomies. The patients ranged in age from 3 to 16 years (mean, 7 years).

**Case occurrence and community influenza activity.** Figure 1 shows the number of patients admitted to the hospital each week and the percentage of students absent from sentinel schools for influenza-like illness each week. The cases occurred between mid-October and mid-January; however, 11 of the 13 cases occurred in a 23-day period between 13 December and 5 January. The peak of the influenza epidemic among school-aged children occurred during the week of 13 December, when >20% of the students were absent from school.

**Influenza strains.** The relative proportion of various influenza strains circulating in the Iowa region is shown in figure 2. During the time of the pneumococcal epidemic and the high rates of school absences, the predominant strain circulating was influenza A (H1N1).

**Influenza-like illness among patients, household members, and control subjects.** Six (46%) of the 13 patients reported experiencing an influenza-like illness in the 7–28 days preceding admission of the patient to the hospital, but only 5 (12%) of 41 control subjects (matched OR, 12.4; 95% CI, 1.7–306). The 7 days before admission were excluded from the analysis to ensure that symptoms possibly caused by the pneumococcal disease were not misclassified as attributable to a preceding influenza infection and included in the analysis of influenza-like illness. In the 28 days preceding the admission of the patient, 12 (23%) of 52 household members of case patients reported experiencing an influenza-like illness, compared with only 14 (10%) of 135 household members of control subjects (OR, 2.6; 95% CI, 1.1–6.3).

**Influenza A (H1N1) titers among case patients and control subjects.** Serum from all 13 patients and 36 control subjects was tested for influenza A (H1N1) antibodies. Table 2 shows the proportion of patients and control subjects with a positive H1N1 antibody titer, stratified by age. Overall, 10 patients (77%) and 16 control subjects (44%) had positive H1N1 serologic results (matched OR, 3.7; p = 0.05; 95% CI, 1.0–18.1). Among those aged ≤10 years, 7 (88%) of 8 patients and 9 (39%) of 23 control subjects had positive H1N1 serologic test results (matched OR, 9.4; 95% CI, 1.3–227.8). Positive H1N1 serologic evidence was associated with influenza-like illness among both case patients and control subjects, although the association did not reach statistical significance (RR, 2.4; 95% CI, 0.7–7.9).

**Discussion**

Infection due to influenza is commonly considered vulnerable to complication by secondary bacterial pulmonary infections, notably by *S. aureus* and *S. pneumoniae*. Epidemiologic evidence of this association rests either on ecologic studies that demonstrate a temporal association between outbreaks or peaks of both influenza disease and bacterial pneumonia among adults, or isolation of pneumococcus from sputum or blood cultures of patients hospitalized with pneumonia during influenza outbreaks [1–5, 9–13]. Some of these studies interpreted a single high influenza-antibody titer among individuals with bacterial pneumonia as conclusive evidence that influenza had contributed to the development of the bacterial pneumonia. However, among adults, influenza-antibody titers from single (rather than paired) serum samples are extremely difficult to interpret because infections with cross-reacting strains of influenza from previous infections can result in high titers. In addition, few of these studies evaluated a control population; therefore, it is not possible to conclude that the individuals with bacterial pneumonia were any more likely than those without pneumonia to have had influenza. These studies, although suggestive, do not provide direct evidence of an increased risk of pneumococcal respiratory illness following influenza infection. Moreover, only 1 of these studies involved children [5], for whom significant controversy surrounds the usefulness of routine annual influenza vaccination.

The theoretical bases for susceptibility to bacterial pneumonia following influenza infection are plentiful and include decreases in the function of polymorphonuclear leukocytes, macrophages, lymphocytes, and monocytes; increases in the adherence of bacteria to the respiratory epithelium; and decreased mucociliary clearance [14–19]. In studies of pneumococcal pneumonia in mice and squirrel monkeys, greater severity of disease and mortality resulted from infections due to pneumococcus and influenza virus together than from infections of either organism alone [20–21]. These animal studies support the hypothesis that influenza truly increases susceptibility to bacterial pneumonia, rather than the hypothesis that simultaneous epidemics have occurred by chance alone.

Our study provides direct and indirect evidence that preceding infection with influenza A (H1N1) was a risk factor for severe pneumococcal pneumonia among previously healthy school children in Iowa. First, the patients were significantly older than the typical ages of children who get invasive pneumococcal disease. Most children with invasive pneumococcal disease are younger than 2 years and have bacteremia; young children are susceptible to invasive pneumococci because they lack a mature and effective immune response to this encap-
sulated organism. The observation that this outbreak of pneumococcal pneumonia occurred among older children, who are usually not susceptible to invasive pneumococci highlights the probability that they experienced a new exposure, making them susceptible to a pneumococcal infection. There was no evidence for an increase in pneumococcal pneumonia among adults at this time.

Second, we identified coincident outbreaks of severe pneumococcal disease and influenza-like illness in the community. We also determined that influenza A (H1N1) was the predominant strain circulating at that time and that this strain had been absent since the 1988-1989 season. This unique and fortuitous situation allowed us to use single convalescent-phase serum samples to determine whether children had been infected with this strain of influenza during the current influenza season.

Third, the case-control study revealed significant differences between the proportion of patients and their household members and of control subjects and their household members who had influenza-like illness before the admission of the patient. These differences were more pronounced when older children (who may have been exposed to influenza H1N1 in 1988–1989 or before) were excluded from the analysis. Finally, because the definition of influenza-like illness is not agent-specific, we analyzed results of influenza-strain-specific convalescent-phase serologic testing from case patients and control subjects and found that patients were more likely than control subjects to have had a preceding infection with influenza A (H1N1).

This study has several limitations. Patients and their household members may be more likely than control subjects and their household members to recall details of illness. Therefore,
analysis of reported illness supports but does not alone implicate influenza infection in the development of bacterial respiratory complications. We selected control subjects from among the patients’ friends, rather than at random from their neighborhoods or school districts. It is possible that our control subjects were over-matched to the case patients, and might have had similar respiratory viral infections. However, over-matching would have only biased the study toward the null hypothesis; that is, that there is no association between preceding influenza infection and pneumococcal pneumonia. Finally, pneumococcal pneumonia was confirmed in only 7 of the 13 children. The bacterial etiology of pneumonia in children is typically difficult to determine [22]. Two children we chose to include in the study had negative gram stains and negative cultures of blood and pleural fluid. The cause of their severe pneumonia remains unknown but could have been from pneumococcus, other bacteria such as S. aureus or Haemophilus influenzae, or even influenza. Because both of these children had empyema requiring lung decortication, a bacterial superinfection is most likely. We believed they had pneumococcal disease, since none of the children with severe pneumonia had a pathogen other than pneumococcus isolated from their body fluids. Therefore, we chose to include these 2 patients in the analysis. Furthermore, when these 2 children and their matched control subjects were excluded from the analysis, the ORs and conclusions were not substantially changed.

This study provides additional support for the hypothesis that influenza infection among children can result directly in serious complications. Other studies have documented high rates of hospitalization among children with influenza, both for primary respiratory involvement and for complications such as reactive airway disease, encephalopathy, febrile convulsions, pericarditis, or involvement of other major organs [23–28]. Studies have also shown that influenza vaccine can reduce the incidence of acute otitis media among children in day care [29, 30]. Opportunities to prevent bacterial pneumonia in children rest predominantly on the development of bacterial vaccines that are immunogenic and efficacious in young children. Until recently, no pneumococcal vaccine was sufficiently immunogenic in young children to warrant its use. With the advent of soon-to-be-licensed pneumococcal-protein-conjugate vaccines, routine pediatric vaccination against pneumococcus may decrease pneumonia cases. However, only 7 serotypes are contained in the pneumococcal-conjugate vaccine, and in this series of cases, of those for which a serotype was identified, none were contained in the vaccine. Given the broad range of bacterial antigens for which vaccines would be needed, another approach to prevention of bacterial pneumonia would be the use of effective viral respiratory vaccines. The findings from this study not only demonstrate the direct association between influenza infection and pneumococcal infection among children but also suggest that prevention of severe pneumococcal pneumonia is a potential benefit of influenza vaccination.

Acknowledgments

We gratefully acknowledge the participation of the patients, control subjects, families, primary care practitioners, and public health nurses throughout Iowa, without whom the study would not have been possible. We are indebted to the medical care providers who cared for the patients and identified the outbreak and to Judy Goddard of the Iowa Department of Public Health who coordinated many of the investigation activities. We also gratefully acknowledge Nancy Arden and Nancy Cox of the Influenza Branch, Centers for Disease Control and Prevention (CDC), for advice and guidance, and Richard Facklam of the Streptococcus Reference Laboratory of the Respiratory Diseases Branch, CDC, for pneumococcal serotyping.

Table 2. Number and proportion of patients and control subjects with positive influenza A (H1N1) titer (≥1:40).

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<th>Age, y</th>
<th>Case patients</th>
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<td>n</td>
<td>No. (%) positive</td>
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<td>Total</td>
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References

11. Kim PE, Musher DM, Glezen WP, Rodriguez-Barrada MC, Nahm WK, Wright CE. Association of invasive pneumococcal disease with season,