Association of Invasive Pneumococcal Disease with Season, Atmospheric Conditions, Air Pollution, and the Isolation of Respiratory Viruses

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We examined the relation of invasive pneumococcal disease to season, atmospheric conditions, and the rate of respiratory virus isolation in a community-wide surveillance program in Houston. Among adults, the number of cases of pneumococcal bacteremia peaked in midwinter and declined strikingly in midsummer, indicating a high degree of inverse correlation with the ambient temperature. We detected significant correlations between the occurrence of pneumococcal disease and the isolation of respiratory syncytial virus ($P < .001$), influenza virus ($P < .001$), and all viruses except influenza virus ($P < .001$), as well as with air pollution, as measured by SO$_2$ levels ($P < .001$). In contrast, the rate of invasive pneumococcal disease among infants and children was relatively more sustained from October through May, with a notable decrease in summer months; the incidence of pneumococcal disease was therefore less strongly correlated with cold weather and less closely associated with the isolation of respiratory syncytial virus or influenza virus. However, pneumococcal disease among infants and children was associated with isolation of these viruses after a 4-week lag period as well as with isolation of adenovirus and ragweed pollen counts. The finding, with regard to children, that correlations tended to be stronger for events that occurred 1 month previously than for those that occurred contemporaneously is consistent with the concept that viral or allergic events predispose to otitis media with effusion, which becomes suppurative and leads to pneumococcal bacteremia or meningitis. For adults, a more immediate predisposition to pneumococcal pneumonia and bacteremia because of viral infection or air pollution was suggested.

Methods

Isolation of S. pneumoniae. We tabulated data on invasive pneumococcal disease by recording all blood and CSF isolates

Prior infection by respiratory viruses and exposure to cold weather have long been regarded as factors that predispose to pneumococcal pneumonia [1, 2]. Air pollution is believed to play a role in the development of symptomatic influenza-like illness [3] and in exacerbations of chronic pulmonary disease [4, 5], but, to our knowledge, a specific association with pneumococcal infection has not been reported. The existence of surveillance programs that monitor viral activity and air pollutants in and around Houston provided a unique opportunity to examine the extent to which cold weather, viral infection, and/or air pollution precede and, therefore, potentially predispose to infection with *Streptococcus pneumoniae*.

Isolation of viruses. During 31 of the 36 months under study, the Acute Viral Respiratory Diseases Unit (AVRDU) of the Baylor College of Medicine (Houston) monitored respiratory virus activity via a community surveillance system that encompasses Houston and surrounding Harris County. Beginning in November 1990, a network of participating primary care clinics, family physicians, and pediatricians provided throat swab specimens and nasal washing specimens from patients who presented with febrile illnesses accompanied by
upper respiratory symptoms. Since participating physicians obtained a specimen only when a patient was evaluated for a symptomatic respiratory illness, the frequency with which specimens were obtained is regarded as a reflection of trends in the incidence of viral illness in the community [6, 7]. About two-thirds of the culture specimens were obtained from children ≤15 years of age, and the majority of these were obtained from children ≤5 years of age. Adenoviruses were identified on the basis of the common antigen and were not further differentiated. Influenza, parainfluenza, and respiratory syncytial viruses were typed by conventional techniques. Picornaviruses were not further differentiated. The total number of specimens collected and the number that were positive for each virus were recorded according to the day the specimen was obtained from the patient. Data were tabulated biweekly.

Meteorologic data. Meteorologic data for Houston were obtained from the National Weather Service and the National Climatic Data Center of the U.S. Department of Commerce National Oceanic and Atmospheric Administration. Daily average temperatures were recorded. The average temperature was calculated by determining the mean of the daily averages for each of the 2-week periods.

The Bureau of Air Quality Control of the City of Houston Department of Health and Human Services records hourly average concentrations of SO₂ and ozone in ambient air at several locations as well as daily counts of ragweed, grass, and tree pollens trapped on a silicone-adhesive coated rod at a single location in Harris County. For the purposes of this study, biweekly averages were determined in order to parallel the results obtained for other variables.

Statistical analysis. The numbers of pneumococcal and viral isolates were tabulated for 2-week periods in order to construct graphs and perform statistical analyses. SigmaPlot (Jandel Scientific, Corte Medera, CA) was used to generate figures. The Mantel-Haenszel test was used to estimate the OR for the stratified data; 95% CI estimates were calculated with use of the test-based method. WinSTAR (Anderson-Bell, Arvada, CO) was used to generate Pearson correlation coefficients (r) for the association between pneumococcal disease and other variables studied. Correlations were examined by comparing variables, as determined on the day the pneumococcal culture was reported as positive (time 0), as well as after periods of 2, 4, 8, or 12 weeks preceding or following the positive culture result. With this approach, the correlations were cumulative. Thus, an association observed at time 0 is reflected, albeit to a lesser extent, at a lag time of 4 weeks and to a substantially lesser extent at a lag time of 8 weeks. Multivariate analysis was performed with use of forward, stepwise multiple regression. A P value of ≤ .05 indicated statistical significance.

Results

Isolation of S. pneumoniae. During the 36-month period, there were 238 cases of invasive pneumococcal infections in adults and 242 cases in infants and children. In each of the 3 years of the study, the numbers of isolates were similar (i.e., 161, 149, and 170, respectively). The four hospitals surveyed accounted for 21.4% of the yearly hospital admissions in Greater Houston between 1990 and 1993. The average total number of cases per year (n = 160) was divided by 0.214, yielding an estimate of 748 patients hospitalized for invasive pneumococcal disease in Harris County each year. This number was divided by the population of the Houston Metropolitan Statistical Area (3,301,937 persons, as determined by the U.S. Bureau of Census in 1990), yielding 22.6 cases of invasive pneumococcal disease per 100,000 population; this incidence was similar to that reported elsewhere in the United States [8–10]. A potential source of imprecision in this calculation of incidence is our inability to stratify data on isolation of pneumococci and hospital admissions by age.

Relation of pneumococcal disease to season and ambient temperature. A seasonal incidence of invasive pneumococcal disease was observed (figure 1, table 1), with 67% of pneumococci isolated during the 6-month period October through March (OR, 2.06; 95% CI, 1.58–2.66) and 36% isolated during the 3-month period November through January (OR, 1.69; 95% CI, 1.27–2.23; P < .05). More striking, however, was the decrease in pneumococcal disease in the summer months. For all 3 years of the study, only 52 cases occurred in the 3-month period June through August (OR, 0.36; 95% CI, 0.26–0.52) and only seven cases occurred in August (OR, 0.16; 95% CI, 0.07–0.36; P < .01).

A clear midwinter peak could be observed for adults (figure 1). This peak was especially apparent on analysis of cumulative results reported by month for 5 years at the VAMC, which provides care for a population that consists largely of middle-aged and older men (figure 2). The inverse correlation between infection and ambient temperature (i.e., the presence of cold weather) for adults was high (r = 0.71 [P < .0001] at lag time 0, and r = 0.57 [P < .0001] at lag time 4 weeks; table 2). It
is of interest that in the case of infants and children, a midwinter peak was not readily discernible (figure 1); the clearest seasonal variation resulted from the striking decrease in the number of cases that occurred during July and August. The inverse correlation between temperature and infection was also less apparent for children than for adults and was greater, with a lag time of 1 month \((r = 0.27 [P = .015] \text{ and } 0.34 [P = .002], \text{ respectively})\). On the basis of multivariate analysis, the association with cold weather was also found to be significant for both groups \((P < .0001 \text{ [adults]} \text{ and } P < .05 \text{ [children]})\).

**Viral respiratory illness.** The AVRDU received 6,907 specimens for viral culture during the 31 months of study (November 1990 through May 1993). A strong correlation was observed between submission of specimens for viral cultures and the rate of isolation of respiratory viruses \((r = 0.96)\), suggesting that the clinical suspicion of a viral respiratory illness was highly associated with the actual finding of a positive viral culture. The rate of specimen acquisition reflected a seasonal incidence of infection, with a distinct increase in the fall, a decline each spring, and a nadir in the summer (figure 3).

Of the 6,907 respiratory specimens submitted for viral culture, 2,066 (29.9%) yielded a respiratory virus. Influenza viruses A and B accounted for the majority of positive cultures (1,388 isolates [67.2%]). Other isolates included 240 picornaviruses (11.6%), 198 adenoviruses (9.6%), 125 respiratory syncytial viruses (6.1%), and 115 parainfluenza viruses (5.6%).
cornaviruses were associated with the most indolent isolation pattern, with peaks of isolation in October and November during 2 years of the study (figure 4). Respiratory syncytial viruses were isolated primarily in the winter months, increasing in activity just prior to or around the same time as outbreaks of influenza. As a group, parainfluenza viruses had a biphasic pattern of activity, with peaks in the fall and spring; this pattern was more apparent for serotypes 1 and 3 than for serotype 2. In each year of the study, isolation of adenoviruses increased in the 8–10 weeks before influenza outbreaks. Peaks in isolation of influenza viruses were distinctive, as expected.

As shown in table 2, a clear temporal association between invasive pneumococcal infection and the isolation of influenza virus \((r = 0.46)\), respiratory syncytial virus \((r = 0.56)\), all respiratory viruses \((r = 0.48)\), and all respiratory viruses except influenza virus \((r = 0.36; \ P < .001\) for all comparisons) was observed for adults. A significant (but generally lesser degree of) association was observed after a 4-week time lag. A weaker correlation was also seen with isolation of adenoviruses; no correlation was detected for the other viruses studied. The association between virus isolation and pneumococcal disease was not as strong for children as for adults. Each association with an individual virus was stronger after a 4-week lag, at which time a significant association was observed for adenovirus \((r = 0.55, \ P < .001)\) respiratory syncytial virus \((r = 0.26, \ P = .014)\), influenza virus \((r = 0.22, \ P = .004)\), and all viral isolates except influenza virus \((r = 0.43, \ P < .001)\). There was no association between pneumococcal infection and isolation of parainfluenza virus or picornavirus.

**Other environmental factors.** As shown in table 2, a significant association between pneumococcal infection and levels of \(SO_2\) (a marker for air pollution that is itself an irritating substance [11]) was observed for adults \((r = 0.50, \ P < .001)\). The inverse association with ozone levels \((r = -0.42)\) is probably best explained by the fact that ozone is released as a result of the direct effect of the sun’s rays on the atmosphere, yielding peak ozone levels at the height of summer. An association between \(SO_2\) levels and pneumococcal disease was much weaker for children and was observed only after a lag time of 4 weeks. In contrast, higher ragweed pollen counts were associated with pneumococcal infection in children, as was

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**Table 2.** Association between invasive pneumococcal disease in adults and children and ambient temperature, virus isolation, and atmospheric factors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time lag (w)</td>
<td>Time lag (w)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Ambient temperature*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.71&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.57&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Virus isolated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza virus</td>
<td>0.46&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.35&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>0.56&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.54&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>0.25&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.29&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>All viruses</td>
<td>0.48&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.37&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>All viruses except influenza</td>
<td>0.38&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.35&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Atmospheric factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SO_2) level</td>
<td>0.50&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.29&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ozone level</td>
<td>-0.42&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-0.24&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Measurable precipitation</td>
<td>0.20</td>
<td>0.36&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ragweed pollen count</td>
<td>-0.11</td>
<td>-0.22</td>
</tr>
<tr>
<td>Tree pollen count</td>
<td>0.17</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**NOTE.** Numbers are correlation \((r)\) values for the indicated association.

* Reported as inverse correlation with ambient temperature.

<sup>1</sup> \(P < .001\).

<sup>2</sup> \(P < .05\).
also detected by multivariate analysis \((P < .005)\); this association was not found for adults. There was no association between tree pollen or mold spore counts and pneumococcal infection. A significant negative association with grass pollens was observed, consistent with the flourishing of grasses during summer months. Finally, although data on humidity were not available, rainfall was associated with pneumococcal disease in adults but not in children.

Discussion

We believe that our study is the first that attempts to correlate documented invasive pneumococcal disease with season, atmospheric conditions, and isolation of respiratory viruses in the community. Our results show clearly that the frequency of pneumococcal disease in adults correlates inversely with the ambient temperature; distinct midwinter peaks and midsummer nadirs were detectable. This kind of pattern has been well documented in earlier studies of lobar pneumonia [1]. Exposure to cold has long been thought to increase the likelihood of lower respiratory disease—specifically pneumococcal disease—in humans [12] or experimental animals [13], albeit by mechanisms that have not been fully defined. Socioeconomic factors that might lead to exposure to cold weather among subgroups of susceptible individuals, such as alcoholics, may contribute to the seasonal variation. Recent reports from Israel [14], Alaska [15], and Winnipeg, Canada (Y. Mirzanejad, unpublished data) have documented the decline of pneumococcal infection in summer but have failed to demonstrate a midwinter peak, the pattern that we observed for infants and children. The failure of these studies to show a clear increase in pneumococcal infection in winter may have resulted from the lack of distinction between pediatric and adult infections. Why there is no distinct wintertime increase in invasive pneumococcal disease in children is unclear. In societies where such studies are done, children may be better protected against adverse environmental conditions than are adults. Furthermore, cold weather may not predispose to otitis media (the cause of most
invasive pneumococcal disease in young children [16]) in the way that it predisposes to lower respiratory disease in adults.

Many studies [1, 17-21] have shown the rate of nasopharyngeal colonization by S. pneumoniae to be greatest in fall, winter, and early spring among families, adults in a closed environment (such as military recruits), and in the population at large. A distinct midwinter peak has not been detected, although, in most instances, a distinct decrease in isolation of pneumococci during the summer has also been noted. The observed association between season and pneumococcal carriage or pneumococcal infection may be mediated through the seasonal incidence of viral illness. In our community surveillance, the numbers of samples submitted for viral culture and the numbers of viruses isolated were much higher in the fall, winter, and spring than in the summer, and the increase preceded that of invasive pneumococcal disease. The cause for this phenomenon is uncertain, although the typical school cycle, which brings children together from September through May or June, with a traditional summertime vacation, may contribute to the rate of isolation of both viruses and pneumococci.

Extensive, older literature [1, 19] shows an association between a presumed viral respiratory illness and nasopharyngeal carriage of pneumococci, and observations in vitro suggest that pneumococci adhere more readily to virus-infected cells than to uninfected cells [22, 23]. In the past, strong associations have been demonstrated between pneumococcal infection and the prior occurrence of a viral-type respiratory infection [1, 24], influenza-like respiratory illness [15], or influenza [18, 25]. Viral infections predispose to pulmonary infection by causing bronchoconstriction, increased mucus production [26, 27], decreased ciliary action [28], and damage to mucosal cells and dysfunction of leukocytes [26]. Older studies showed that a carefully obtained medical history suggested the prior occurrence of a viral-type respiratory illness in 50%-80% of cases of pneumococcal pneumonia [1]. Using the novel approach of a community-based viral surveillance system, we found a distinct temporal association between invasive pneumococcal disease in adults and viral-type respiratory illnesses of all kinds; we also found that pneumococcal disease was associated with isolation of adenoviruses, respiratory syncytial viruses, and influenza viruses.

For infants and children, the association with viral infections was less apparent, and certainly less immediate, than it was for adults; to the extent that such an association was observed, it was stronger with a 4-week lag period. Although a direct temporal association between viral respiratory illness and pneumococcal infection in infants and young children has been found in some studies [20, 21, 29], an extremely careful, journal-based study [30] failed to confirm such a finding. Henderson et al. [31] monitored viral respiratory isolates from children in a day care center and observed that, with a 2-week lag time, a temporal association could be detected between viral infection and the development of otitis media with effusion. Our results are consistent with the concepts that (1) otitis media is a more common source of invasive pneumococcal disease in early years than is pneumonia and (2) a variety of viral infections or other nonspecific factors contribute to otitis, which may then progress to suppurrative infection and bacteremia. Glezen [32] found data supporting these concepts when he demonstrated a two to threefold increase in hospitalizations of adults with acute respiratory disease during most influenza outbreaks, while the increase was no more than 50% and was often negligible in the case of children. The positive association between invasive pneumococcal infection and ragweed pollen counts for children, but not for adults, provides further support for this explanation.

Our study is the first to document an association between a recognized air pollutant and invasive pneumococcal disease. Several investigations have correlated air pollution with acute or chronic pulmonary disease [4, 5] or influenza [3], but the association with pneumonia has received little attention; in addition, there has been no reported attempt to find a relation with disease caused by a specific bacterial pathogen. The temporal association between elevated SO2 levels [11, 33] and invasive pneumococcal disease in adults was highly significant, and that found for children was significant (albeit less so, and only with a 4-week lag). The inverse correlation between ozone levels and pneumococcal disease is best explained by the fact that ozone results from the effects of solar rays on the atmosphere; solar rays are strongest in summer, which is when, for reasons that remain unclear, the rate of pneumococcal disease is at its nadir.

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References


