The Association of Respiratory Viruses, Temperature, and Other Climatic Parameters with the Incidence of Invasive Pneumococcal Disease in Sydney, Australia

M. Watson,1 R. Gilmour,2 R. Menzies,3 M. Ferson,4 and P. McIntyre,2 for the New South Wales Pneumococcal Network

1The New South Wales Pneumococcal Reference Laboratory, Children’s Hospital at Westmead Department of Microbiology, 2National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, The Children’s Hospital at Westmead and University of Sydney, New South Wales, 3Communicable Disease Surveillance and Control Unit, New South Wales Department of Health, and 4South Eastern Sydney Public Health Unit, Sydney, Australia

Background. Increases in incidence of invasive pneumococcal disease (IPD) during the colder months of the year in temperate regions are well recognized, but few detailed studies of possible interactions are available. We examined the relationship between virus activity, climatic parameters, and IPD during a winter in which there were separate peak incidences of influenza and respiratory syncytial virus (RSV) infection.

Methods. We performed an ecological study that correlated population-based data on IPD and respiratory virus activity in the year 2000 in metropolitan New South Wales, Australia, with climatic parameters, including weekly mean maximum and minimum temperature, relative humidity, rainfall, and wind speed.

Results. In children, RSV activity was significantly positively correlated with IPD activity ($r = 0.578; P < 0.002$) but not with influenza virus activity. There was a weak inverse relationship between parainfluenza virus activity and IPD activity ($r = -0.401; P = 0.043$) and a stronger inverse relationship between weekly mean maximum temperature ($r = -0.458; P = 0.001$), weekly mean minimum temperature ($r = -0.437; P = 0.001$), and IPD activity. In adults, there was no significant correlation between RSV or influenza virus activity alone and IPD, but the combination of RSV and influenza was significantly correlated with IPD ($r = 0.481; P = 0.013$).

Conclusions. This study suggests that RSV infection and influenza contribute to IPD incidence peaks differently for children than for adults. Data from other geographic areas and more rigorous study designs are required to confirm these findings.

Streptococcus pneumoniae is a major cause of morbidity and mortality among children and adults in Australia and worldwide [1–6]. The seasonal nature of invasive pneumococcal disease (IPD) has been well recognized, and with the exception of IPD in Alaskan natives [7], disease activity peaks in the colder winter months [6, 8–10]. It has generally been assumed that the increase in IPD seen in winter relates to increased activity of respiratory viruses, especially influenza virus [11, 12].

Only one study has attempted to examine the relationship between climatic conditions, respiratory viral infections, and IPD, but the study was unable to separately consider influenza and respiratory syncytial virus (RSV) infection, because their times of peak activity coincided [8]. Our large population-based study was able to examine the relationship between climatic conditions and influenza virus and RSV activity in a year when distinct peaks in the incidences of infection with these 2 viruses were evident.

METHODS

Study Population and Data Collection

IPD surveillance. The New South Wales Pneumococcal Network comprises all public and private microbiology laboratories in metropolitan New South Wales, Australia, that process all clinical microbiology specimens for the greater Sydney region. Patients were
eligible for the study if their postal code of residence was within this region. Greater Sydney has a population of ~5 million people. The pneumococcal surveillance system consists of active laboratory surveillance with regular audits to confirm compliance.

**Respiratory virus infection surveillance.** Surveillance of respiratory virus infections was conducted by a collaboration of 7 major teaching hospital virology laboratories coordinated by the Communicable Disease Surveillance and Control Unit of the New South Wales Department of Health. These virology laboratories serve the same geographic area as the New South Wales Pneumococcal Network. Respiratory viruses were detected by means of direct immunofluorescence (or other antigen-detection methods) and tissue culture of samples obtained from children and adults with clinical viral illnesses who presented to these hospitals. The indications for testing were determined on clinical grounds by clinicians at these hospitals. The virological methods used were not rigorously standardized between laboratories, but the methods for each laboratory did not change during the study period. PCR for detection of respiratory viruses was not used during the study period. Respiratory virus surveillance is conducted from autumn (when the first respiratory virus activity is seen) until a sustained decrease in respiratory viral activity occurs in late spring. In the year 2000, active surveillance was conducted from the week ending 5 May 2000 until 27 October 2000. The year 2000 was chosen for data analysis because there was clear separation of the peaks of activity of RSV and influenza virus in that year.

A sentinel general practice clinical surveillance system for influenza activity was also active during the surveillance period [13]. Results of this community-based clinical surveillance system were used to independently confirm that the timing of influenza activity in the community mirrored the hospital-based laboratory viral surveillance used in our study.

**Meteorological data.** Meteorological data were obtained from the New South Wales Bureau of Meteorology’s Climate and Consultancy Section for 10 weather stations corresponding to the area under study. Weekly mean values were calculated for maximum temperature, minimum temperature, rainfall, relative humidity, and wind speed from the daily results, and the data from the 10 weather stations were then combined into a weekly mean for the region as a whole. The Sydney metropolitan area has a temperate climate, with the colder months occurring during the middle of the year. Minimum temperatures rarely (if ever) fall below the freezing point, but there is marked seasonal variation in temperatures.

**Case definition of IPD.** IPD was defined as isolation of *S. pneumoniae* from a normally sterile body site. We did not include patients with suspected pneumococcal infection or those with only a positive pneumococcal antigen test result. IPD activity was defined as the number of cases of IPD detected within a 1-week period.

**Case definition of respiratory viral infection.** A case was defined as a positive result of an antigen detection test (usually direct immunofluorescence) or tissue culture positive for a respiratory virus in either an adult or a child. The date recorded was the date of collection of the specimen. The definition did not include serologically confirmed cases of viral disease. Respiratory virus activity was defined as the total number of cases of a respiratory virus isolated by the surveillance system per week. Influenza activity was defined as the number of cases per week of influenza A or B virus. RSV isolates were not subtyped. Surveillance for parainfluenza viruses 1–3, adenovirus, and rhinoviruses was also conducted.

**Statistical Methods**

Statistical analysis was performed using the 2-tailed Pearson correlation coefficient in SPSS software, version 10 for Windows (SPSS). The correlation between weekly respiratory virus case numbers and weekly numbers of IPD episodes was examined over a 26-week period. The continuous variables of mean temperature (in degrees Centigrade), rainfall (in millimeters), relative humidity (as a percentage), and wind speed data (in kilometers per hour) were correlated with the weekly numbers of IPD over 52 weeks of the year 2000.

**RESULTS**

**Number of episodes.** During the 52-week study period, the New South Wales pneumococcal network detected 454 episodes of IPD in adults and 227 episodes in children. During the 26-week period in which respiratory virus activity and IPD activity were compared, there were 310 episodes of IPD in adults and 146 episodes in children. During this same 26-week period, there were 10,045 virological specimens submitted for antigen detection and/or culture to the 7 participating laboratories. Respiratory viruses were detected in 2586 respiratory specimens by either method. These included 676 influenza virus isolates, 1519 RSV isolates, 164 parainfluenza virus isolates, 116 adenovirus isolates, and 111 rhinovirus isolates. The circulating influenza viruses during the study period included A/H3N2/Sydney and A/H1N1/New Caledonia and influenza B virus. Although these were evenly distributed throughout the viral season, A/H3N2/Sydney was the predominant strain.

**IPD in children.** There was a significant positive correlation between RSV and IPD activity (*r* = 0.578; *P* = .002) but no significant correlation between influenza virus activity and IPD activity in children (figure 1). A borderline significant relationship existed between parainfluenza virus activity and IPD in children (*r* = -0.401; *P* = .043) during the 26-week period examined. No significant correlation was demonstrated...
with adenovirus or rhinovirus activity, but this was limited by the small numbers of viruses identified. A strong inverse relationship was found between the weekly mean maximum temperature ($r = -0.458; P = .001$) and weekly mean minimum temperature ($r = -0.437; P = .001$) and IPD activity. No correlation was found between mean weekly relative humidity, wind speed, or rainfall and IPD activity in children.

**IPD in adults.** An apparent chronological association between RSV or influenza virus and peaks of IPD activity was evident on inspection (figure 2), but there was no statistically significant correlation for either virus alone during the study period. When the correlation between the combined RSV and influenza virus activity and IPD was examined, a significant positive correlation was found ($r = 0.481; P = .013$). No significant correlation was found between IPD activity in adults and parainfluenza virus, adenovirus, or rhinovirus activity during the 26-study period, but analysis was limited by the small number of isolates.

As in children, there was a strong inverse relationship between weekly mean maximum temperature ($r = -0.586; P < .001$) and weekly mean minimum temperature ($r = -0.739; P < .001$) and IPD activity in adults. There was no relationship found between IPD activity in adults and the weekly mean relative humidity, wind speed, or rainfall during the 52-week study period.

**DISCUSSION**

It is recognized that the incidence of IPD in both adults and children increases in winter; however, possible underlying causes have not been carefully studied. Laboratory studies provide...
biologically plausible reasons why influenza virus may be important in the pathogenesis of IPD [14–17], but the epidemiological features of influenza virus in relation to winter epidemics of pneumococcal disease have not been well studied. The year 2000 was chosen for our study because, in this year, there were clearly separated peaks of RSV and influenza virus activity. This allowed us to examine the individual associations between influenza virus and RSV activity and IPD. In other years, there was often considerable overlap of activity of the 2 viruses. In the only previously published study [8] of this kind, the peaks of RSV and influenza virus activity occurred virtually simultaneously, making the current study unique in its ability to examine the separate effects of these 2 viruses in a large population-based study. However, there were limitations in the study design, which included the limited number of cases of IPD, which precluded subset analysis by age. In addition, detailed clinical data were not available that would allow different syndromes, such as pneumococcal pneumonia, to be separately correlated with viral activity. The small number of cases of IPD would also have limited our ability to examine this important question.

Although anecdotal reports have associated IPD and influenza [12], the only previous epidemiological study [8] did not find any direct association between RSV or influenza virus activity and IPD activity in children, except when a 4-week lag period was examined. In our study, which was conducted in a year with good separation of RSV and influenza virus activity, no significant correlation between influenza virus activity and IPD in children was found, but there was a significant correlation with RSV activity and IPD activity in children. The previous epidemiological study required 3 years of data to achieve sufficient power for statistical analysis; this was not necessary in our study because of the large study population included. When our data were examined, no lag was found in the activity of respiratory viruses and IPD. Other data also support a role for RSV in increasing IPD activity in children. Retrospective studies demonstrated that pneumococcal bacteremia complicated 3 of 108 episodes of RSV infection in one study [18] and 4 of 189 episodes in another [19]. The rate of concomitant pneumococcal infection was even higher in another study from Pakistan [20]. Furthermore, it has been well documented that RSV infection has been strongly associated with acute otitis media [21] and that pneumococcus is one of the most common bacterial pathogens associated with otitis media. Although it is inappropriate to imply causality in ecological studies of this type, it is possible to say that influenza virus played little apparent role in the winter increase in IPD activity seen among children in metropolitan New South Wales in the year 2000. Although it would be desirable to confirm these findings in another location or in subsequent years, it is rare to find separate peaks of RSV and influenza virus activity.

In adults, the epidemic curves of RSV and influenza virus activity correspond with peaks of IPD, but it was only possible to demonstrate a statistically significant correlation when the activity of both viruses was combined. A possible confounding factor was the change in mean ambient minimum and maximum temperatures during the same time period. It is worthy of note, however, that the majority of IPD cases in the region during the winter of 2000 did not occur during the period of greatest influenza activity, as determined by either hospital virology laboratory surveillance or general practice Sentinel Influenza Surveillance [13]. This suggests that other factors, such as RSV activity and changes in weekly mean ambient temperature, may also be important in predisposing to IPD. A case-control study comparing the isolation of respiratory viruses in patients with IPD with age-, sex-, location-, and time-matched control subjects without IPD would be required to specifically examine the role that respiratory viruses play in predisposing to IPD. The association of both adult and pediatric IPD and RSV disease is an important issue for determining the future role of new RSV vaccines that are currently under development [22, 23].

Of the climatic parameters, only weekly mean minimum and maximum temperatures were correlated with IPD activity in adults and children. There was a clear inverse relationship between these variables and IPD activity. The relationship was more closely associated with weekly mean minimum temperature than with weekly maximum temperature in adults and seemed to have a stronger association in adults than in children. This is consistent with the findings of a previous study [8]. The climate in New South Wales is temperate, with mean minimum and maximum temperatures that decrease to a nadir in mid-winter. The lowest weekly mean maximum temperature in the year 2000 was 15°C, and the lowest weekly mean minimum temperature was 4°C. The lowest temperatures occurred in the month of June. The monthly rainfall is said to occur uniformly throughout the year, allowing separation of the effect of rainfall from temperature. The close association of temperature and IPD activity is interesting. Although most studies have demonstrated increased activity of IPD during the colder winter months [6, 8–10], when mean ambient temperatures decrease, the opposite was found in Alaskan natives [7]. A possible explanation for this is that Alaskan native people may be more likely to be exposed to the cold air of the arctic summer when the climate was more compatible with outside activities. Interestingly, in that study, no correlation could be found between influenza activity and IPD activity. It is possible that this may be the result of a failure to take into account the added role of RSV. The effect of falling temperatures on the pathogenicity of pneumococci has not been extensively studied and warrants further investigation.

Possible interactions between influenza vaccine and pneu-
mococcal conjugate vaccine are complex, particularly if effects differ between children and adults. The findings of this study require confirmation in other temperate geographic locations and data obtained after the introduction of vaccines. The introduction of universal conjugate pneumococcal vaccine for children <2 years of age in Australia and of influenza vaccine for children aged 6–24 months in the United States may provide important opportunities to further understand these complex relationships.

**THE NEW SOUTH WALES PNEUMOCOCCAL NETWORK**

**Microbiology departments.** Central Coast Pathology, Concord Hospital, Davies Campbell & De Lambert Pathology, Douglass Hanley Moir Pathology, Hunter Area Pathology Service, Centre for Infectious Diseases and Microbiology–Institute Clinical Pathology and Medical Research, Latyney Pathology, THE Pathology, Nepean Hospital, Pacific Area Laboratory Medical Services, Royal Prince Alfred Hospital, South East Area Laboratory Services, St George Hospital, St Vincents Hospital, South West Area Pathology Services, Sydney Adventist Hospital, and Illawarra Area Health Services Pathology.

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**References**