Influenza Circulation and the Burden of Invasive Pneumococcal Pneumonia during a Non-pandemic Period in the United States

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Background. Animal models and data from influenza pandemics suggest that influenza infection predisposes individuals to pneumococcal pneumonia. Influenza may contribute to high winter rates of pneumococcal pneumonia during non-pandemic periods, but the magnitude of this effect is unknown. With use of United States surveillance data during 1995–2006, we estimated the association between influenza circulation and invasive pneumococcal pneumonia rates.

Methods. Weekly invasive pneumococcal pneumonia incidence, defined by isolation of pneumococci from normally sterile sites in persons with clinical or radiographic pneumonia, was estimated from active population-based surveillance in 3 regions of the United States. We used influenza virus data collected by World Health Organization collaborating laboratories in the same 3 regions in seasonally adjusted negative binomial regression models to estimate the influenza-associated fraction of pneumococcal pneumonia.

Results. During ∼185 million person-years of surveillance, we observed 21,239 episodes of invasive pneumococcal pneumonia; 485,691 specimens were tested for influenza. Influenza circulation was associated with 11%–14% of pneumococcal pneumonia during periods of influenza circulation and 5%–6% overall. In 2 of 3 regions, the association was strongest when influenza circulation data were lagged by 1 week.

Conclusions. During recent seasonal influenza epidemics in the United States, a modest but potentially preventable fraction of invasive pneumococcal pneumonia was associated with influenza circulation.

Influenza and Streptococcus pneumoniae (pneumococcus) are leading infectious causes of death in the United States [1, 2]. Both pathogens have strong seasonal patterns, with illness rates peaking in winter. Animal models and in vitro studies indicate that influenza infection predisposes to pneumococcal pneumonia [3–11], with greatest host susceptibility approximately 1 week after infection with influenza [6, 10]. Data from influenza pandemics indicate that a substantial proportion of influenza-related deaths were attributable to secondary bacterial infection [3, 4, 9, 12]. On the basis of these observations, influenza is considered to be an important factor in high winter rates of pneumococcal pneumonia during non-pandemic periods. However, the magnitude of influenza’s effect on pneumococcal pneumonia incidence has not been established.

The correlation between influenza circulation and all invasive pneumococcal disease in published studies varies from nil to modest [13–18]. However, the interpretation of these data is difficult, because these studies did not distinguish pneumococcal pneumonia from other forms of invasive disease, including bacteremia without pneumonia. Influenza’s effect on pneumonia may differ from its effect on non-pneumonia syndromes, such as bacteremia and meningitis, because mechanisms of increased host susceptibility occur at
the level of respiratory epithelium [4, 7, 8, 10, 11]. In addition, most of these studies did not control for the underlying seasonality of either pathogen. Rates of serious disease due to influenza and *S. pneumoniae* peak each winter, but similar winter seasonality is also observed in a wide variety of infectious, environmental, and social phenomena [1, 14, 17]. Unadjusted analyses of seasonally correlated phenomena may overestimate temporal associations [19].

We estimated the influenza-associated burden of pneumococcal pneumonia by analyzing the association between the weekly incidence of invasive pneumococcal pneumonia and isolation of influenza viruses in two separate United States (US) surveillance systems during 1995–2006. We hypothesized that if influenza circulation is a major driver of invasive pneumococcal pneumonia, then elevations in influenza circulation should consistently be followed by higher-than-seasonally expected rates of pneumococcal pneumonia. In secondary analyses, we tested this hypothesis in different age groups and for non-pneumonia invasive pneumococcal disease.

**METHODS**

**Study design and data sources.** We conducted an ecological analysis with use of surveillance data for influenza and invasive pneumococcal pneumonia in the United States. Data on weekly numbers of respiratory specimens tested and numbers of influenza-positive results aggregated into the 4 US census regions (Northeast, Midwest, South, and West) were obtained from US World Health Organization collaborating laboratories for 11 seasons from 1995 through 2006. A season was defined as 1 July through 30 June of the following year. Weeks were defined as beginning on Sunday and were numbered sequentially (1–52 or 53), with the first week of the year having ≥4 days in that calendar year [20, 21]. Laboratories reported influenza during weeks 40–20 in 1995–2002 and year-round thereafter. The number of laboratories increased from 50 to 75 during the study period.

Data on laboratory-confirmed invasive pneumococcal pneumonia were obtained from the Active Bacterial Core surveillance (ABCs) Emerging Infections Program Network from 1 July 1995 through 30 June 2006 [22]. The number of participating sites increased from 6 in 1995 (Connecticut and parts of California, Georgia, Maryland, Oregon, and Tennessee) to 9 in 2006 (addition of New Mexico and parts of Colorado and New York), and the surveillance population increased from 11.3 to 22.5 million persons. State-based surveillance officers contacted all clinical microbiology laboratories in the surveillance area at least once every 6 months to perform audits, ascertain cases, and record clinical data pertaining to each case [22].

We defined invasive pneumococcal pneumonia as isolation of *S. pneumoniae* from normally sterile body sites with a recorded diagnosis of pneumonia or isolation of *S. pneumoniae* from pleural fluid. Cases were grouped by week according to the date the specimen was collected, and weekly rates per 10 million persons were calculated using linear interpolation between annual census population estimates. Because influenza circulation and pneumococcal pneumonia rates vary geographically, we grouped ABCs sites by US census region for comparison with influenza circulation (Northeast: New York, Connecticut; South: Georgia, Maryland, Tennessee; West: California, Colorado, New Mexico, Oregon). Because a fourth census region (Midwest) contained a single surveillance site (Minnesota) with insufficient numbers of pneumococcal cases for analysis, we did not analyze data from this region. To account for the substantial changes in pneumococcal pneumonia with introduction of pediatric pneumococcal conjugate vaccine, pneumococcal conjugate vaccine periods were defined as prevaccine (1995–2000 seasons), transitional (2000–2001 season), and postvaccine (2001–2006 seasons).

**Statistical analysis.** Influenza-associated excess outcomes are typically estimated by comparing observed rates with a seasonal baseline representing outcome rates expected in the absence of influenza circulation [2, 13, 21, 23–26]. We applied this established concept to estimate the number of pneumococcal pneumonia cases in each region that were influenza-associated during weeks 40–20 from 1995 through 2006.

First, to define the timing of influenza, we used standard methods to classify each week as an influenza or non-influenza week [23]. For each region, we identified the first and last week in which the percentage of specimens submitted that tested positive for influenza was ≥10% for 2 consecutive weeks. Weeks within this period were considered to be influenza weeks; all others were considered to be non-influenza weeks.

Second, to establish a region-specific seasonal pneumococcal baseline expected in the absence of influenza, we fitted models to the pneumococcal data during non-influenza weeks by least-squares regression with a 52-week harmonic curve, an indicator for the pneumococcal conjugate vaccine period, and a linear term for secular trend. This model fitted to non-influenza periods was used to interpolate the pneumococcal seasonal baseline for influenza weeks. The residuals of this model (observed minus baseline rates) represented variation in pneumococcal syndromes not explained by the seasonal model. Third, we fitted log-linked negative binomial regression models to pneumococcal data in each region. Models included coefficients for the region-specific seasonal harmonic baseline curves described above, linear time trends, and a continuous term representing the weekly percentage of specimens that tested positive for influenza. The negative binomial distribution was specified to account for over-dispersion in pneumococcal incidence. We examined the association between influenza circulation and pneumococcal pneumonia by evaluating models with 0- to 4-week lags between influenza circulation and the
outcome; a 1-week lag was considered to be the most biologically plausible, on the basis of available animal and pandemic data [4, 6, 10, 11].

Finally, we estimated the number of influenza-associated pneumococcal pneumonia cases by evaluating the negative binomial regression model under 2 conditions. First, we simulated a winter without influenza by setting the weekly percentage of specimens that tested positive for influenza to zero. We then repeated the analysis, setting the influenza term to the weekly percentage of positive specimens actually observed in surveillance. Comparing pneumococcal cases predicted under these scenarios is analogous to comparing observed cases with cases expected in the absence of influenza. The difference between weekly rates of pneumococcal pneumonia predicted under these 2 model scenarios was considered to be the influenza-associated excess rate. This rate was applied to the weekly surveillance population denominators to estimate influenza-associated cases. We calculated the mean number of influenza-associated cases per week during influenza weeks and used the standard error of the mean to establish 95% confidence intervals (CIs).

We estimated the influenza-associated excess rate by age group (<5, 5–64, and >64 years). We repeated the analysis with the alternative outcome of non-pneumonia invasive pneumococcal disease (isolation of *S. pneumoniae* from non-pleural normally sterile body sites in persons without a pneumonia diagnosis) to see if the association between influenza circulation and invasive pneumococcal disease differed by syndrome. Strata with a mean of <5 pneumococcal cases per week over the study period were considered to be insufficiently granular and were not modeled.

Analysis was conducted in SAS, version 9.1 (SAS Institute), with use of PROC NLIN for least squares regression and PROC GENMOD for negative binomial regression. Because these data were collected as part of routine surveillance activities, no personal identifying data were used, and no linkage to personal identifiers were available; this analysis was considered to be exempt from human subjects review.

RESULTS

From 1 July 1995 through 30 June 2006, 21,239 episodes of invasive pneumococcal pneumonia and 13,035 episodes of non-pneumococcal invasive pneumococcal disease were reported from 9 ABCs sites in 3 US regions. World Heath Organization collaborating laboratories tested 485,691 specimens for influenza during the study period in these regions, and 80,961 (17%) had positive results for influenza.

The seasonal baseline curves fit pneumococcal pneumonia closely during non-influenza weeks throughout the study period, suggesting that our model approximated the seasonal behavior of pneumococcal pneumonia (Figure 1). In the southern, northeastern, and western regions, $R^2$ values demonstrated that the seasonal baseline explained 89%, 75%, and 74%, respectively, of variation in invasive pneumococcal pneumonia during non-influenza weeks. Seasonality was similar in the pre-and postvaccine periods.

In contrast to the consistent and predictable seasonal cycles of pneumococcal pneumonia, the timing and duration of influenza circulation varied among seasons and regions (Figure 1). During 1995–2006, influenza periods began between week 42 and week 4 and ended between week 52 and week 23. The mean duration of influenza periods was 14 weeks, with an interquartile range of 5 weeks.

Figure 2 illustrates influenza circulation and residual variation in invasive pneumococcal pneumonia (the weekly discrepancy between expected seasonal baseline rates and rates actually observed). After accounting for the seasonal pattern in pneumococcal pneumonia, residual variation did not appear to be strongly associated with the weekly percentage of specimens with positive test results for influenza. Therefore, we attempted to quantify any weaker associations between pneumococcal pneumonia and influenza circulation through regression analysis.

In our negative binomial regression models, the influenza parameter is the output that quantifies the strength of association between influenza and pneumococcal time series, with a more positive parameter indicating a stronger association. In southern and western regions, the association most significant when pneumococcal data were lagged by 1 week (Table 1). In the northeastern region, the association was significant with no lag and with a 1-week lag. Because a 1-week lag was significant in all 3 regions, we used a 1-week lag in our final model. We estimated that during influenza periods, 13.5% (95% CI, 12.3%–14.7%), 11.4% (95% CI, 10.7%–12.7%), and 11.9% (95% CI, 11.1%–13.6%) of pneumococcal pneumonia cases were influenza-associated in the northeastern, southern, and western regions, respectively (Table 1). Influenza-associated pneumococcal pneumonia cases represented 4.5%–6.0% of total annual cases of pneumococcal pneumonia.

Among persons aged 5–64 years, we estimated that 16.7% (95% CI, 15.3%–18.2%) and 15.4% (95% CI, 14.5%–17.2%) of pneumococcal pneumonia cases occurring during influenza weeks in the northeastern and southern regions, respectively, were associated with influenza. These cases represent 6.2% (95% CI, 5.7%–6.7%) and 7.1% (95% CI, 6.7%–7.9%) of the total annual burden of invasive pneumococcal pneumonia in this age group in the northeastern and southern regions, respectively. Influenza circulation was not significantly associated with pneumococcal pneumonia with use of any lag time examined among persons aged 5–64 years in the western region or among persons aged >64 years in any of the 3 regions. Insufficient data were available to model pneumococcal pneumonia among children aged <5 years.

Two regions, the Northeast and the South, had sufficient
data available to repeat this analysis with non-pneumonia invasive pneumococcal disease incidence as the outcome. Strong winter seasonality was evident (Figure 3). In negative binomial regression models, there was no statistically significant association between influenza circulation and non-pneumonia invasive pneumococcal disease when tested with 0–4 week lags.

DISCUSSION

We found that annual increases in rates of invasive pneumococcal pneumonia during the winter were modestly associated with influenza circulation during a non-pandemic period in the United States. Rates of invasive pneumococcal pneumonia followed a highly consistent seasonal pattern in the 3 US regions examined, despite substantial variation in the timing and duration of influenza circulation. We estimated that 11%–14% of invasive pneumococcal pneumonia occurring during weeks with elevated influenza activity and 5%–6% of invasive pneumococcal pneumonia on an annual basis may have been associated with influenza circulation.

The fraction of pneumococcal pneumonia that may have been associated with preceding influenza infection during pandemic periods cannot be quantified, because population-based data comparable to ours were not collected. However, contemporaneous observational reports during several influenza pandemics in the United States suggest that influenza was a powerful driver of secondary pneumococcal pneumonia [12, 27]. Thus, our findings suggest that the influence of influenza circulation on the epidemiology of invasive pneumococcal pneumonia differs during pandemic and non-pandemic periods. It appears that data from animal experiments and case series reported during influenza pandemics cannot be generalized to estimate population-level effects of influenza circulation on pneumococcal pneumonia during non-pandemic periods.

Given the enormous global burden of pneumococcal disease [28], even a modest association between the incidence of invasive pneumococcal pneumonia and influenza is an important finding, because some fraction of pneumococcal disease might be preventable through influenza vaccination. Our data collected over many non-pandemic seasons from a population of 11–22 million US residents actively followed for the occurrence of invasive pneumococcal pneumonia represent a first effort in understanding the effects of influenza circulation on pneumococcal pneumonia in temperate regions. We believe that these results need to be replicated, in both temperate and in non-temperate countries, where the seasonality of influenza and pneumococcal disease may differ substantially [29]. Our find-

Findings suggest other important determinants of the seasonality of invasive pneumococcal pneumonia remain unidentified. Although a number of hypotheses have been advanced, including roles for other respiratory viruses and atmospheric conditions, few have substantial supporting evidence [1, 14, 15, 17, 30, 31]. Several strategies prevent pneumococcal disease among adults. In the United States, universal infant vaccination with 7-valent pneumococcal conjugate vaccine has reduced rates of invasive pneumococcal disease among adults through indirect or “herd effects” [32]. The primary direct method of prevention among adults remains pneumococcal polysaccharide vaccine, which in the United States is recommended for all persons aged ≥65 years and for persons aged 2–64 years with chronic conditions. Provider recognition of the strikingly predictable rise in pneu-

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<th>Surveillance region and lag, weeks</th>
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**NOTE.** CI, confidence interval.

- a Number of weeks in region during 1995–2006 study period classified as influenza weeks (beginning with the first week and ending with the last week in each season in which influenza percentage positive was ≥10% for 2 consecutive weeks).
- b Model estimate of mean weekly number of influenza-associated cases of invasive pneumococcal pneumonia during influenza weeks.
- c Model estimate of total number of influenza-associated cases of invasive pneumococcal pneumonia during 1995–2006 (mean weekly cases × number of influenza weeks).
- d Estimated fraction of invasive pneumococcal pneumonia during influenza weeks that is influenza associated (influenza-associated cases/total cases during influenza weeks × 100).
- e Estimated fraction of invasive pneumococcal pneumonia during entire year that is influenza associated (influenza-associated cases/total cases in year × 100).
mucococcal disease each winter may provide an opportunity to communicate the importance of administering pneumococcal polysaccharide vaccine to those for whom it is recommended [33, 34].

Our estimates of the annual proportions of pneumococcal pneumonia that are associated with influenza circulation are slightly lower than those of a Swedish study that estimated that 6%–10% of the annual burden of all invasive pneumococcal disease (including meningitis, bacteremia, and other non-pneumonia syndromes) was influenza-associated [13]. We believe our estimates may be more robust and precise for 4 reasons. First, through active, population-based surveillance, we identified a sufficient number of cases to analyze invasive pneumococcal pneumonia independently of non-pneumonia invasive pneumococcal disease. The finding that influenza circulation was associated only with invasive pneumococcal pneumonia and not other forms of invasive disease is consistent with the hypothesized mechanisms through which influenza predisposes individuals to pneumococcal pneumonia at the level of the respiratory epithelium [4, 6–8, 10]. Second, use of influenza surveillance data based on the testing of >485,000 specimens over an 11-year period provided a relatively precise measure of the timing of influenza

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**Figure 3.** A. Weekly rates per 10 million residents of non-pneumonia invasive pneumococcal disease in southern surveillance sites during 1995–2006. B. Weekly rates per 10 million residents of non-pneumonia invasive pneumococcal disease in northeastern surveillance sites during 1995–2006.
circulation. These data enabled us to model influenza as a continuous variable rather than as a present/absent event [13]. Third, our findings were consistent with data from animal experiments and observational data from influenza pandemics [4, 6, 10], which suggest that host susceptibility is greatest 1 week after infection with influenza. In our analyses, associations were strongest with a 1-week lag in 2 of the 3 regions and no lag in a third region. Finally, our findings were replicated in analyses conducted separately in 3 US regions.

Our study has several limitations. First, it is ecologic in design, using data from 2 independent and unlinked surveillance systems. An optimal design would follow a cohort prospectively and monitor each individual for infection with influenza or S. pneumoniae. However, the relative rarity of invasive pneumococcal disease means that such a study is likely not feasible in the United States, given the present system of monitoring invasive bacterial infection. Furthermore, because even mild influenza infection might predispose individuals to pneumococcal infection, participants would have to be monitored closely and tested frequently for influenza infection. Retrospective cohort or case-control studies would also be difficult to design, because at the time secondary pneumococcal pneumonia is likely to occur (about 1 week following influenza infection), the sensitivity of currently commercially available clinical tests for influenza are low in children and adults [35, 36]. Second, because evidence supporting causal effects is limited [1, 15, 17, 30], our models did not explicitly incorporate other potential factors, such as cold temperatures or respiratory syncytial virus circulation that have been postulated to affect pneumococcal pneumonia incidence. Instead, we represented pneumococcal seasonality with a constant harmonic baseline, which should account for the consistent seasonal patterns of respiratory syncytial virus circulation and temperature in each US region studied. Third, we compared invasive pneumococcal pneumonia rates from 8 ABCs sites with influenza circulation data from all states within these US Census regions. Differences in timing or intensity of influenza circulation between ABCs sites and surrounding regions could bias our estimates toward the null. To evaluate this possibility, we compared influenza data between states within each census region. State-level data were less robust with greater week-to-week variation, but no systematic or pervasive differences between states were noted. Fourth, population-based data on the incidence of influenza infections were not available for use during most of the respiratory seasons included in this study. Currently, the only data on annual rates of influenza incidence available come from the placebo arms of vaccine clinical trials. As a surrogate, we used the weekly percentage of respiratory specimens obtained during laboratory surveillance that had positive test results for influenza. The temporal patterns of viral surveillance data and clinical influenza cases correspond closely. Finally, for some subanalyses, our study had limited power.

In summary, we found that influenza circulation was modestly associated with annual winter increases in rates of invasive pneumococcal pneumonia during a non-pandemic period in the United States. Influenza circulation was associated with 11%–14% of cases of invasive pneumococcal pneumonia during periods with elevated influenza circulation and 5%–6% of cases annually. In temperate climates, influenza likely plays a modest but possibly preventable role in susceptibility to subsequent invasive pneumococcal pneumonia. Adoption of vaccine programs for these pathogens in such areas might be most effective if they are implemented in a coordinated manner.

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