Detection of Excess Influenza Severity: Associating Respiratory Hospitalization and Mortality Data With Reports of Influenza-Like Illness by Primary Care Physicians

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Objectives. We explored whether excesses in influenza severity can be detected by combining respiratory syndromic hospital and mortality data with data on influenza-like illness (ILI) cases obtained from general practitioners.

Methods. To identify excesses in the severity of influenza infections in the population of the Netherlands between 1999 and 2005, we looked for increases in influenza-associated hospitalizations and mortality that were disproportionate to the number of ILI cases reported by general practitioners. We used generalized estimating equation regression models to associate syndromic hospital and mortality data with ILI surveillance data obtained from general practitioners. Virus isolation and antigenic characterization data were used to interpret the results.

Results. Disproportionate increases in hospitalizations and mortality (relative to ILI cases reported by general practitioners) were identified in 2003/04 during the A/Fujian/411/02 (H3N2) drift variant epidemic.

Conclusions. Combined surveillance of respiratory hospitalizations and mortality and ILI data obtained from general practitioners can capture increases in severe influenza-associated illness that are disproportionate to influenza incidence rates. Therefore, this novel approach should complement traditional seasonal and pandemic influenza surveillance in efforts to detect increases in influenza case fatality rates and percentages of patients hospitalized.

Syndromic surveillance is increasingly used to monitor symptoms or clinical diagnoses such as shortness of breath or pneumonia as indicators of infectious disease. The primary objective of many syndromic

surveillance systems is the detection of unexpected disease increases such as those that occur as a result of bioterrorism attacks or outbreaks of emerging diseases such as severe acute respiratory syndrome (SARS). However, the signals generated by such syndromic surveillance also reflect influenza activity.1–4 Worldwide, influenza continues to result in serious morbidity and mortality.5,6 The recurrence of influenza epidemics is predominantly caused by both the antigenic drift of influenza viruses and changes in the dominant virus types or subtypes. Antigenic drift occurs during the replication process of influenza viruses when mutations in surface proteins lead to declines in the level of immunity acquired through natural infection or vaccination.7 In addition, the annual variations in dominant virus types or subtypes, such as A(H1), A(H3), and B, can lead to differences in influenza-related morbidity and mortality. For example, in recent decades levels of morbidity and mortality seem to have been lower in the influenza A(H1) and B epidemic seasons than in the A(H3) seasons.8,9 In the Netherlands, as in many countries, surveillance of influenza is conducted by a network of sentinel general practitioners. Influenzalike illness (ILI) consultations are reported weekly, and antigenic properties of isolated viruses are analyzed to determine their effects on annual ILI fluctuations.10,11 Such sentinel surveillance is considered adequate for monitoring the onset and magnitude of annual influenza epidemics. However, it is not sufficient for monitoring the incidence of severe influenza infections leading to hospitalization or death. Although the relationship between the virulence and transmission capacity of influenza viruses is still incompletely understood,7 variations in virulence may result in disproportionate increases in severe illness relative to increases in the number of patients with ILI consulting their general practitioners. Such increases might be captured by monitoring temporal changes in the association of ILI data obtained from general practitioners (hereafter GP–ILI data) with hospitalization and mortality surveillance data. Such monitoring is not a part of current global influenza monitoring activities, although in some countries ILI data in addition to hospitalization and mortality data are included in influenza surveillance.12,13 We explored the potential of this monitoring strategy to detect excesses in influenza infection severity by investigating shifts in the annual association of respiratory hospitalizations and mortality with GP–ILI incidence data in the Netherlands between 1999 and 2005. In addition, we evaluated whether such shifts were associated with reported circulation of influenza virus drift variants, mismatches with vaccine strains, or changes in dominant circulating virus types or subtypes.

METHODS

We obtained hospital and mortality data from the Dutch national medical register (99% coverage of discharge and secondary diagnoses by date of hospitalization) and the Dutch causes of death registry (100% coverage of primary causes of death, as well as complicating causes and other additional causes of death, by date of death). We formulated respiratory hospitalization and mortality syndrome definitions guided by the syndrome definitions of the Centers for Disease Control and Prevention, as coded in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM; see Appendix A, available as an online supplement to this article at http:// www.ajph.org).14 It has been demonstrated that these respiratory hospitalization and mortality syndrome data reflect respiratory pathogen activity as measured via laboratory counts.4 We collected ILI data from a sentinel network of general practitioners.10 Data on influenza viruses detected in the Netherlands between 1999 and 2005 were derived from the Dutch influenza surveillance consortium (comprising the National Influenza Centre and the Netherlands Institute for Health Services Research). 11,15 We used weekly counts of various respiratory pathogens to adjust for the effects on respiratory hospitalizations and mortality of pathogen activity other than influenza. We collected data on respiratory syncytial virus (RSV), rhinovirus, Mycoplasma pneumoniae, parainfluenza virus, enterovirus, and adenovirus pathogen counts from a routine laboratory surveillance system (the Weekly Sentinel Surveillance System of the Dutch Working Group on Clinical Virology, which covers 38%–73% of the population of the Netherlands).16 We also used national mandatory notifications to obtain weekly pertussis counts.

DATA ANALYSIS

With the exception of laboratory pathogen counts (for which data on age were not available), we aggregated data by week and age category (0–4 years, 5–19 years, 20–64 years, 65 years or older). In our analyses, we excluded respiratory mortality among those in the 0- to 4-year and 5- to 19-year age groups because of the sporadic counts in these groups. SAS version 9.1 (SAS Institute Inc, Cary, NC) was used in conducting the analyses. For the general practitioner, hospital, and mortality data, we calculated incidence rates instead of counts to quantify risk differences between age categories and to correct for changes in the age distribution of the population and (for the general practitioner sentinel data) changing registry coverage over time. After plotting time series of GP–ILI, respiratory hospitalization, and mortality incidence data, we looked for increases in hospitalizations and mortality that seemed disproportionate to increases in ILI cases as a measure of severity of illness. We also examined time series of respiratory pathogens other than influenza to assess whether elevations in respiratory hospitalizations or mortality might be associated with other pathogen activity (measured via routine laboratory surveillance). We used additive generalized estimating equation (GEE)17 models with a Poisson error distribution to detect elevations in respiratory hospitalizations and mortality that were disproportionate to seasonal rises in ILI incidence in the general practitioner sentinel data. We estimated hospitalization and mortality time series, stratified by age, according to lagged ILI incidence. We then used the 95% upper limits of the models (details on the model variables are provided in Appendix B, available as an online supplement to this article at http://www.ajph.org) to determine distinct episodes in time in which hospitalizations and mortality increases were disproportionate to average modeled associations with ILI incidence rates. To adjust for the activity of respiratory pathogens other than influenza, we considered RSV, rhinovirus, parainfluenza virus, M pneumoniae, adenovirus enterovirus, and pertussis counts for inclusion in the models as well. We also assumed a constant basic syndrome level attributable to factors other than respiratory pathogen activity. In the summer months, however, as the basic syndrome level appeared to be lower with respect to hospitalizations (possibly as a result of fewer planned hospitalizations during that period), we used a lower basic syndrome level (by including a dummy variable for ‘‘summer’’). The regression model coefficients for each of the lagged pathogens and for the GP–ILI incidence data were assumed to be constant in time. We initially built a generalized linear model with a Poisson error distribution and an identity link. To do so we used a forward stepwise regression approach, selecting the lagged ILI incidence and lagged pathogen counts that contributed most to the model fit (5-week lags were used; e.g., in step 1, ILI was included with a 1-week lag if that exhibited a better model fit than all other pathogen–lag combinations, assessed with Akaike’s information criterion18). We included lagged GP–ILI incidence and the counts for each pathogen in the model only once and only if results were significant at the $P \leq .05$ level. We analyzed age-stratified hospitalization, mortality, and GP–ILI incidence data in the regression models. Age stratification was not possible for pathogen counts. We excluded negative associations for pathogen counts to avoid spurious model fits due to biologically implausible associations (e.g., negative associations between enterovirus, which peaks in summer, and respiratory syndromes, which peak in winter). Also, we added seasonal variables (sine and cosine terms)—guided by periodograms of the model residuals, which reflect the importance of specific cyclical periods (e.g., 26 weeks, 52 weeks) in explaining the variance in the residuals—to correct for seasonal variation and used GEEs to correct the model outcomes for autocorrelation between observations. To quantify temporal heterogeneity in associations of GP–ILI data with data on hospitalizations and mortality respiratory syndromes, we modified the models by using time-dependent (by epidemic year, defined as July 1 through June 30) ILI regression coefficients (instead of a single regression coefficient for all years). These annual ILI regression coefficients can be seen as scaling factors for the number of hospitalizations or deaths associated with a one-case increase in ILI incidence per 10000 population. We plotted estimates for these coefficients on a bar chart. The years with the highest estimated ILI regression coefficients were considered as those associated with the most severe illness per ILI case. We conducted F tests (with a null hypothesis of no differences in associations over the study period) to determine whether the coefficients differed across the years of the study (Appendix B, available as an online supplement to this article at http:// www.ajph.org).

Influenza Virus Isolation and Antigenic Characterization

To assess whether disproportionate levels of respiratory hospitalizations and mortality (relative to GP–ILI incidence rates) might be related to the circulation of specific influenza virus variants or subtypes, we

explored weekly reports of influenza virus subtypes A(H1), A(H3), and B and assessed, on the basis of antigenic characterization, which influenza virus drift strains were present in the Netherlands during 1999–2005.

[FIGURE 1]

We also evaluated to what extent these drift strains were reported to match or not match the vaccine strains for those years. Individuals at increased risk for complications of influenza (elderly people and those with specific comorbid conditions) are offered annual influenza vaccination19 (during the study period, vaccine coverage levels in the Netherlands were above 65% for individuals aged 65 years or older and approximately 80%for those aged older than 75 years). Data on antigenic characteristics and the match between vaccines and circulating viruses were derived from annual influenza surveillance reports.11 To assess other possible explanations for disproportionate levels of respiratory hospitalizations and mortality relative to GP–ILI incidence rates, we also compared the analysis results against plotted time series of specific morbidity patterns associated with respiratory hospitalizations, as measured via ICD-9-coded hospital diagnosis incidence rates.

RESULTS

Plots of GP–ILI time series and respiratory hospitalization and mortality time series showed approximately concurrent peaks in all winter seasons. The highest peaks were observed in 1999/00 and 2004/05 (data not shown). The influenza epidemics in 2000/01, 2001/02, and 2002/03 were relatively mild. When data on respiratory pathogen counts (other than influenza) were plotted (data not shown), RSV showed the clearest winter peaks, concurrent with elevations in respiratory hospitalizations and mortality. Therefore, we plotted respiratory hospitalizations and mortality against GP–ILI incidence rates and laboratory RSV counts stratified by age (Figure 1). Elevations in respiratory hospitalizations were highest in the youngest and oldest age groups (0–4 years and 65 years or above), and elevations in respiratory mortality were highest in the oldest age group. Hospitalizations in the 0–4-year age group corresponded more with the RSV time series than with the ILI time series (Figure 1). During the 2003/04 winter season, steep peaks in respiratory hospitalizations were observed among those aged 5 to 19 years and those 65 years or older, and (although RSV counts peaked at the same time) these peaks seemed disproportionately high relative to the ILI time series during that season (Figure 1). This trend was also observed for mortality among individuals 65 years or older (Figure 1, indicated by ellipse).

Regression Analysis

In the models with constant ILI regression coefficients over the entire study period, variations in respiratory hospitalizations and mortality among individuals 65 years or older and variations in hospitalizations among those aged 0 to 4 years were explained quite well by variations in ILI incidence and respiratory pathogen counts. The explained variance was lower for the other age groups. Periodograms of the model residuals showed sharp peaks at 1 year along with smaller harmonics for shorter periods. We therefore added sine and cosine terms to the models to adjust for seasonal trends, and we used GEEs to correct for autocorrelation in the residuals. These model refinements led to only minimal changes in the ILI regression coefficients and the explained variance of the models; percentages of explained variance for hospitalizations were 95% among those aged 0 to 4 years, 47% among those aged 5 to 19 years, 68% among those aged 20 to 64 years, and 78% among those 65 years or older. Percentages of explained variance for mortality were 37% among those aged 20 to 64 years and 76% among those 65 years or older. With respect to periods of peak influenza activity (as measured by peaks in GP–ILI incidence concurrent with peaks in the counts of influenza isolates), the time series of actual hospitalizations among both those aged 0 to 4 years (data not shown) and those 65 years or older (Figure 2) most clearly exceeded the 95% upper limit of the models during winter 2003/04. A subsequent (Ftest) analysis of the model in which yearspecific ILI regression coefficients were used showed significant annual heterogeneity in these coefficients for all age categories ($P \leq .001$). Figure 3a shows the annual GP–ILI regression coefficients for respiratory hospitalizations. For example, the regression coefficient value of 3.94 for hospitalizations in the 0- to 4-year age group in 2003/04 indicates that, for a hypothetical ILI incidence of 100 per 10000 population, the estimated respiratory hospitalization incidence for that age group is 3.94 (per 10000

population). The annual GP–ILI regression coefficients for respiratory hospitalizations were highest among those 65 years or older and those aged 0 to 4 years. In addition, the regression coefficients for these age groups were significantly higher in 2003/04 than in any other study year (P ≤.001). Figure 3 (panel b) shows that, as expected, the mortality regression coefficient was much higher for those 65 years or older than for those aged 20 to 64 years. Similar to the data for hospitalizations, the ILI regression coefficient for those 65 years or older was clearly higher in 2003/04 than in any other study year (P ≤.03). In 2000/01, some of the estimated ILI regression coefficients were below zero, reflecting the mild influenza impact in that season.

Influenza Virus Isolation and Antigenic Characterization

Figure 2 presents data on influenza virus subtypes and reported introductions of drift variants.11,20–22 All reported influenza drift strains mismatched to some extent with the vaccine strains observed over the study period with the exception of the Caledonia/20/99 (H1N1) strain in 2000/01.

Specific Hospital Diagnoses

In visually exploring respiratory hospitalization discharges and diagnoses (data not shown), we focused on elevations in time that may have been related to the excess number of respiratory hospitalizations observed in 2003/04. The elevations in hospitalizations involving a diagnosis of pneumococcal pneumonia (ICD-9 code 481) or pneumonia due to streptococcus (ICD-9 code 4823) during peak winter influenza activity in 2003/04 and, to a lesser extent, 2002/03 were among the highest observed in the study period (in 2002/03, as a percentage of respiratory hospitalizations overall, pneumococcal pneumonia showed the highest elevation over the study period). The second highest elevation in hospitalizations involving an influenza diagnosis (ICD-9 codes 4870 and 4871) was observed in 2003/04 (the highest elevation was in 1999/00; no significant elevations were observed in 2002/03).

[FIGURE 2]

[FIGURE 3]

Regression Analysis

In the models with constant ILI regression coefficients over the entire study period, variations in respiratory hospitalizations and mortality among individuals 65 years or older and variations in hospitalizations among those aged 0 to 4 years were explained quite well by variations in ILI incidence and respiratory pathogen counts. The explained variance was lower for the other age groups. Periodograms of the model residuals showed sharp peaks at 1 year along with smaller harmonics for shorter periods. We therefore added sine and cosine terms to the models to adjust for seasonal trends, and we used GEEs to correct for autocorrelation in the residuals. These model refinements led to only minimal changes in the ILI regression coefficients and the explained variance of the models; percentages of explained variance for hospitalizations were 95% among those aged 0 to 4 years, 47% among those aged 5 to 19 years, 68% among those aged 20 to 64 years, and 78% among those 65 years or older. Percentages of explained variance for mortality were 37% among those aged 20 to 64 years and 76% among those 65 years or older. With respect to periods of peak influenza activity (as measured by peaks in GP–ILI incidence concurrent with peaks in the counts of influenza isolates), the time series of actual hospitalizations among both those aged 0 to 4 years (data not shown) and those 65 years or older (Figure 2) most clearly exceeded the 95% upper limit of the models during winter 2003/04. A subsequent (Ftest) analysis of the model in which year specific ILI regression coefficients were used showed significant annual heterogeneity in these coefficients for all age categories (P ≤.001). Figure 3a shows the annual GP–ILI regression coefficients for respiratory hospitalizations. For example, the regression coefficient value of 3.94 for hospitalizations in the 0- to 4-year age group in 2003/04 indicates that, for a hypothetical ILI incidence of 100 per 10000 population, the estimated respiratory hospitalization incidence for that age group is 3.94 (per 10000 population). The annual GP–ILI regression coefficients for respiratory hospitalizations were highest among those 65 years or older and those aged 0 to 4 years. In addition, the regression coefficients for these age groups were significantly higher in 2003/04 than in any other study year (P ≤.001). Figure 3 (panel b) shows that, as expected, the mortality regression coefficient was much higher for those 65 years or older than for those

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DISCUSSION

We observed increases in severe illness due to influenza in the Netherlands between 1999 and 2005 that were disproportionate to ILI incidence rates. Our observations reveal the existence of temporal heterogeneities in the severity of influenza infections, possibly stemming from variations in the virulence of circulating influenza viruses. Several studies have shown that syndromic data on general respiratory symptoms and clinical diagnoses can be useful in influenza surveillance.2,3,23–25 We combined respiratory syndrome data on hospitalizations and mortality with traditional ILI surveillance data obtained from general practitioners to determine year-to-year differences in the number of respiratory hospitalizations and deaths in proportion to the number of ILI cases. We linked our observations to virological changes by visually exploring time series of influenza subtype counts and reported antigenic information about influenza virus strains. Five drift variants were reported in the period under study—2 A(H3) variants, 1 A(H1) variant, and 2 B variants (Figure 2)—but only in 2003/04, in the case of A/Fujian/411/ 02(H3N2),20 did this reporting of a drift variant concur with disproportionate levels of hospitalizations and mortality. Although at first glance these results seem to suggest that it is difficult to predict clinical effects from virological data, a more thorough look at our virological findings explains the absence of excess effects in years other than 2003/04. The relatively low hospitalization and mortality levels in comparison with ILI incidence rates in 2000/01 and 2001/02 can be explained by the relative lack of fitness of the A/New Caledonia/20/99(H1N1) and B/ Victoria/2/87 variants (respectively), as morbidity and mortality levels tend to be lower in seasons with predominantly A(H1)21 or B22 strains than in A(H3) seasons.8,9 In addition, the A/New Caledonia/20/ 99(H1N1) drift variant reported during 2000/ 01 had emerged in 1999/00, and the vaccine for the 2000/01 season contained this strain and probably provided optimal protection against this drift variant, thereby reducing severe illness in elderly people who had been vaccinated.21 In 2004/05, influenza A(H3) and influenza B drift strains were reported,11but their impact was only moderate. During this season, the antigenic distance of the dominant A/California/ 7/04-like(H3N2) drift variant virus toward the influenza A(H3N2) virus in 2003/04 (A/Fujian/411/02-like) was relatively small.11 This was not the case for A/Fujian/411/02- like(H3N2) viruses in 2003/04, which were quite distinct from preceding A(H3N2) viruses, 11 thereby representing a likely explanation for the observed excess hospitalizations and mortality in that flu season. The high influenza impact among young children and the elderly, relative to the limited size of the 2003/04 epidemic measured according to GP-ILI data, seems to be consistent with the high hospitalization rates during the 2003 influenza season in New Zealand in combination with the limited size of the epidemic also according to GP-ILI data.26 There A/Fujian/411/02(H3N2) was the dominant subtype as well. Some other European countries reported dominant activity or more severe outbreaks of A/Fujian/411/02(H3N2) in 2002/03, but there was great variation across Europe in circulating strains during that winter.27,28 In the Netherlands,

A/Fujian/411/02(H3N2) strains were also circulating in that period, but they were isolated only sporadically; 5 isolates were observed, accounting for 4% of A(H3N2) isolates overall.29 The introduction of new influenza drift variants and shifts in influenza subtypes are not the only possible explanations for the observed differences in influenza impact. Other viral factors (e.g., viral replication capacity, virulence, viral transmissibility) and climatic factors (e.g., temperature and relative humidity) may likewise influence the impact of seasonal influenza on morbidity and mortality. For instance, studies have suggested that the antigenic drift of the A(H3N2) viruses reported in 2003/04 resulted in declines in the level of population immunity (leading to A/Fujian/411/02 in 2002) but that this drift variant became widespread only after gaining a higher viral replication capacity through additional reassortment-related changes in internal genes.30–32

Limitations

A limitation of this study is that it was based on associating time series of hospitalizations and mortality with ILI data, and such associations could be confounded by seasonally circulating pathogens other than influenza. To minimize this possibility, we adjusted for the possible impact of RSV and other respiratory pathogens by including them in our regression models. We also included seasonal terms to correct for possible confounding by other seasonally varying factors. Our use of autocorrelation in our models corrected for other, possibly transient causes of hospitalization and mortality. Another observation lent additional support for the association of influenza with excess elevations. That is, in 2003/04, concurrent with a moderately high ILI peak, hospitalizations involving an influenza diagnosis exhibited the second highest elevation over the study, and hospital diagnoses of pneumococcal pneumonia showed a high elevation as well (which seems to be in line with observations that influenza infections may predispose patients for S pneumoniae infections33–35). Also, to enhance prospective surveillance, there is a need to further evaluate how increases in hospitalizations and mortality that are disproportionate to ILI incidence rates can be detected on a timely basis within a particular influenza season. Quality control chart approaches36,37 might be developed for the timely detection of such temporal changes that require the attention of health authorities.

Conclusions

Our results show that increases in severe influenza-associated illness that are disproportionate to the incidence of influenza in the community can be detected through combined analyses of GP–ILI data and data on respiratory hospitalizations and mortality. This novel approach should be implemented in global influenza surveillance programs to provide better estimates of increases in severe morbidity and mortality due to influenza infections. Our data also show that there is a possible relationship between influenza impact and specific influenza strains. Further research is needed to better understand the causes of such relationships. It seems worthwhile to develop prospective respiratory syndromic surveillance of hospitalizations and mortality complementing traditional seasonal and pandemic influenza surveillance to allow detection of increases in influenza case fatality rates and percentages of patients hospitalized. During ongoing (pandemic) influenza epidemics, such surveillance

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Contributors

C. C. van den Wijngaard contributed to the study design, analyzed the data, and wrote the article. L. van Asten contributed to the study design, data analysis, and drafting of the article. A. Meijer interpreted the virological data and helped draft the article. W. van Pelt and M. P. G. Koopmans contributed to the study design and the interpretation of data and reviewed drafts of the article. N. J.D. Nagelkerke contributed to

the statistical design and the interpretation of data and reviewed drafts of the article. G. Donker collected surveillance data and reviewed drafts of the article. M.A. B. van der Sande helped interpret the results and reviewed drafts of the article.

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Human Participant Protection

Because the data examined in this study were obtained from surveillance or medical research registries, no protocol approval was needed.

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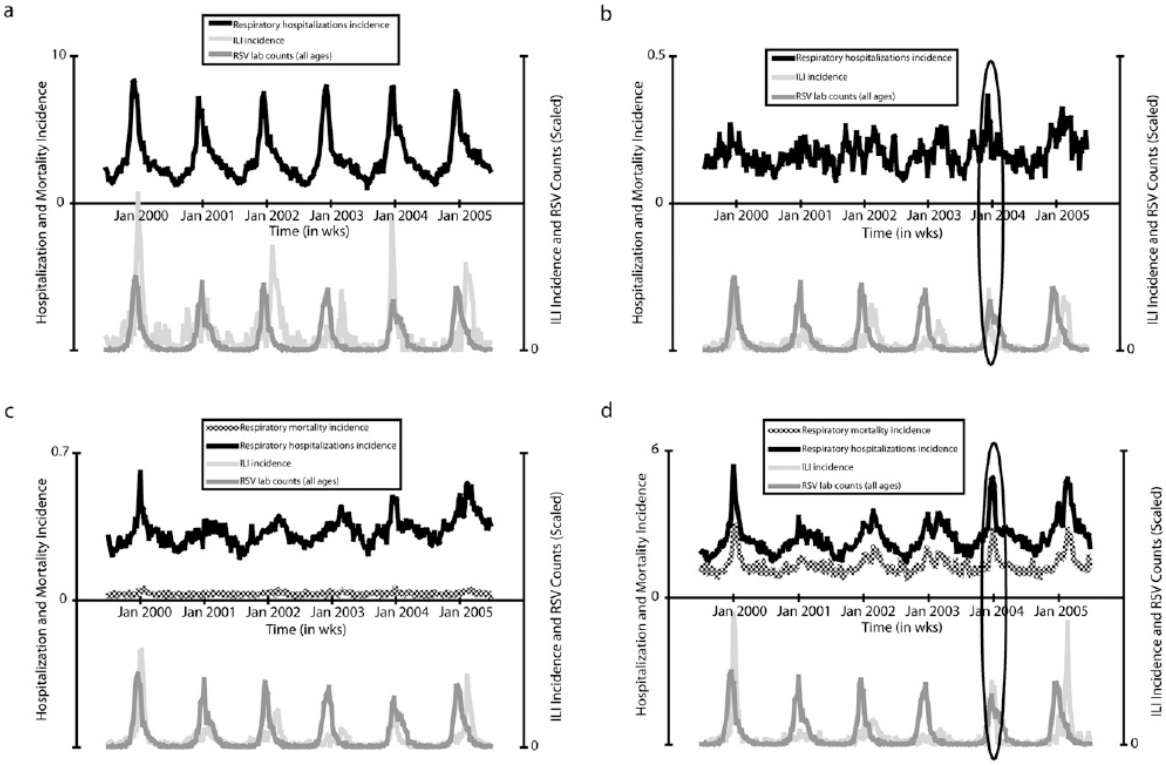
FIGURES

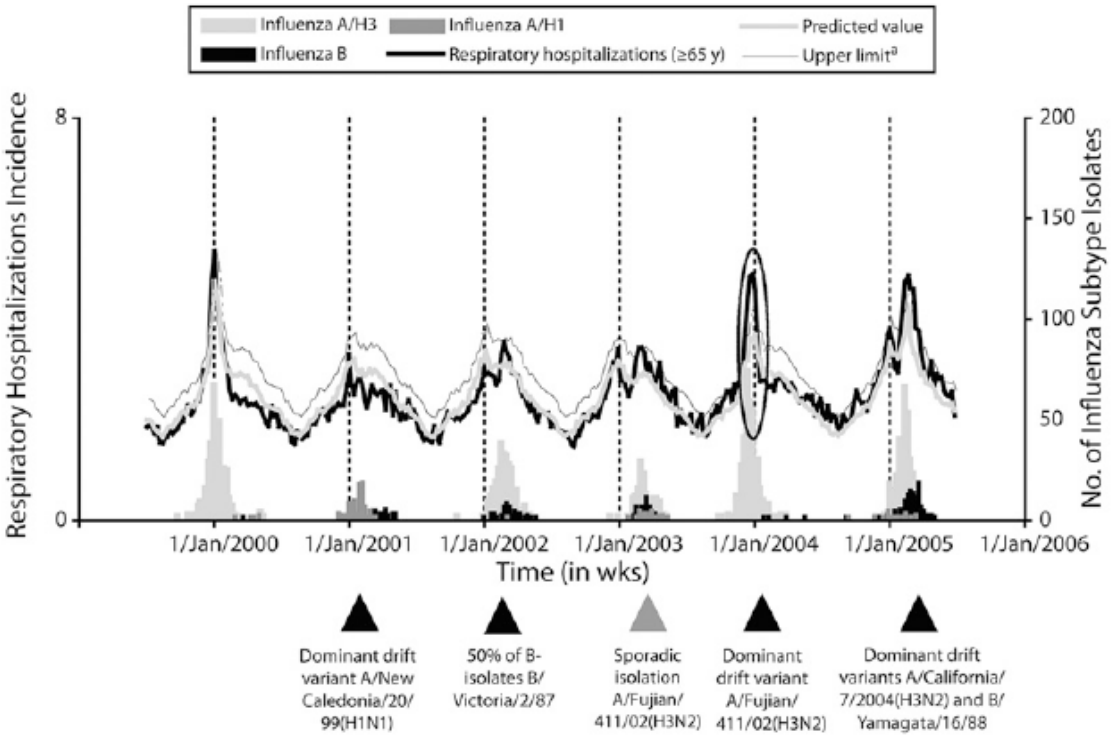
[FIGURE 1]



Note. RSV = respiratory syncytial virus; ILI = influenza-like illness. No mortality time series were plotted for the 0–4-year and 5–19-year age groups because of their low numbers. RSV counts were plotted for all age groups (because no age data were available), and the counts were scaled to fit the graph.

FIGURE 1—Respiratory hospitalizations and mortality incidences versus ILI incidence rates and RSV laboratory counts, by age group (a) 0–4 years, (b) 5–19 years, (c) 20–64 years, and (d) 65 years or older: the Netherlands, 1999–2005.

[FIGURE 2]

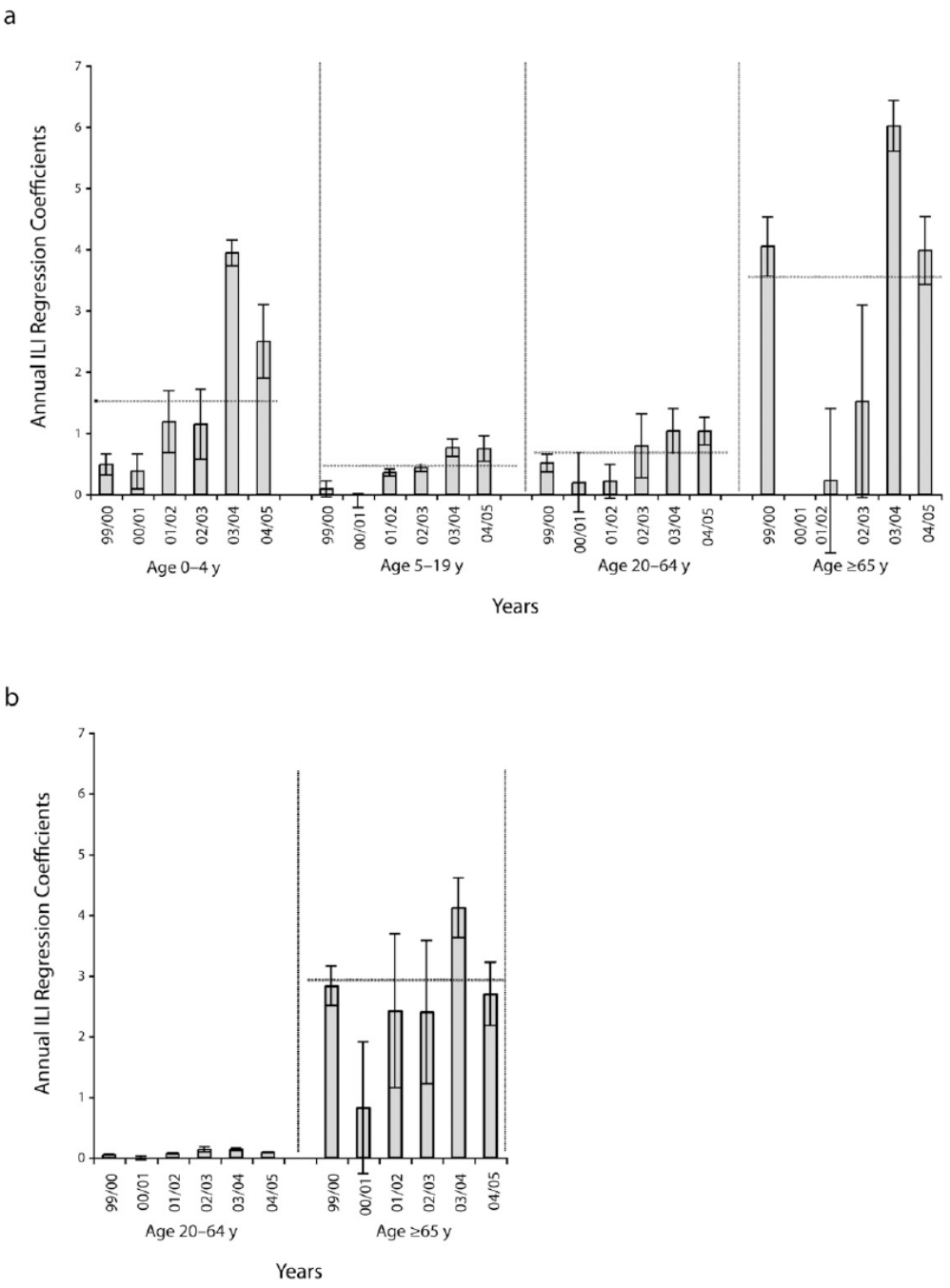


Note. The hospitalization incidence for individuals aged 65 years or older is plotted in a line graph with the predicted value and the 95% upper limit (Appendix B, available as an online supplement at http://www.ajph.org). Values exceeding the model's upper limit are indicated by the ellipse. Below the line graphs, the counts of influenza isolates by subtype—A(H3), A(H1), and B—are presented as bars on the x-axis, and reports of drift variants are indicated.

[a]Because we used generalized estimating equation models, confidence intervals for prediction were not available.

FIGURE 2—Respiratory hospitalization incidence explained by influenza-like illness incidence versus influenza virus subtype counts and reports of drift variants: the Netherlands, 1999–2005.

[FIGURE 3]



Note. The horizontal line in each chart gives the value of an ILI regression coefficient that is constant in time, as an indication of the average value of the ILI regression coefficients over the study period. The 95% confidence intervals for the regression coefficients are presented in the figure as well.

FIGURE 3—Annual (July 1–June 30) estimates of the association of influenza-like illness (ILI) incidence with (a) respiratory hospitalization incidence in all age groups and (b) respiratory mortality incidence for individuals aged 20–64 years and individuals 65 years or older: the Netherlands, 1999–2005.