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Association of Hospitalizations for Asthma with Seasonal and Pandemic Influenza

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Abstract

Background and objective—Although influenza has been associated with asthma exacerbations, it is not clear the extent to which this association affects healthcare use in the United States (U.S.). The first goal of this project was to determine whether, and to what extent, the incidence of asthma hospitalizations is associated with seasonal variation in influenza. Second, we used influenza trends (2000-2008) to help predict asthma admissions during the 2009 H1N1 influenza pandemic.

Methods—We identified all hospitalizations between 1998 and 2008 in the Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project during which a primary diagnosis of asthma was recorded. Separately, we identified all hospitalizations during which a diagnosis of influenza was recorded. We performed time series regression analyses to investigate the association of monthly asthma admissions with influenza incidence. Finally, we applied these time series regression models using 1998-2008 data, to forecast monthly asthma admissions during the 2009 influenza pandemic.

Results—Based on time series regression models, a strong, significant association exists between concurrent influenza activity and incidence of asthma hospitalizations (p -value<0.0001). Use of influenza data to predict asthma admissions during the 2009 H1N1 pandemic improved the mean squared prediction error by 60.2%.

Conclusions—Influenza activity in the population is significantly associated with asthma hospitalizations in the U.S., and this association can be exploited to more accurately forecast asthma admissions. Our results suggest that improvements in influenza surveillance, prevention, and treatment may decrease hospitalizations of asthma patients.

Keywords

Asthma; Forecasting; Health Care Utilization; Influenza; Resource Allocation

INTRODUCTION

Asthma is a major cause of morbidity and mortality in the United States.^{1,2} As of 2010, an estimated 25.7 million people were affected.³ Asthma is also a major driver of healthcare costs.⁴ Asthma exacerbations requiring inpatient hospitalizations result in a substantial

proportion of these costs, with approximately 250,000 people being hospitalized each year for a primary diagnosis of asthma.⁵

Asthma exacerbations are thought to be caused by acute inflammatory episodes triggered by environmental factors. A number of different viral pathogens have been identified as potentially causing asthma exacerbations.^{6,7} For example, the association between influenza and development of asthma exacerbations is mediated via airway injury caused by the virus.⁸ The epithelial damage caused by the influenza virus can increase airway hyperactivity by direct activation of smooth muscle cells and can also enhance allergen-specific asthma responses.^{9,10} Epidemiologic studies have also linked influenza virus to asthma exacerbations.^{11,12} In children, influenza-attributable hospitalization rates are higher for patients with asthma than those without.¹³

Despite associations between influenza and asthma exacerbations, it is not clear how clinically significant these associations are at a population level. Prior studies have been, for the most part, limited to single center studies over short periods of time, and focused on pediatric patients. Thus, the purpose of this study is to use time series modeling to determine whether, and to what extent, the incidence of asthma hospitalizations is associated with the seasonal variation in the incidence of influenza in adults over an eleven year period in the United States. Furthermore, we estimate the burden of asthma hospitalizations attributable to influenza. Finally, to further test the association between influenza and asthma hospitalizations, we determined if we could accurately predict asthma admissions with concurrent influenza admissions during the 2009 H1N1 pandemic, which peaked during non-winter months.

METHODS

All data were extracted from the Nationwide Inpatient Sample, the largest all-payer database of national discharges in the United States. The database is maintained as part of the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality (AHRQ), and contains data from a 20% stratified sample of nonfederal acute care hospitals.⁵ To adjust for yearly changes in the sampling design, we applied weights provided by AHRQ.¹⁴ Our institutional review board determined that this project was non-human subjects research, as all data are de-identified.

We first identified all hospitalizations during the period from January 1998 to June 2010 during which a primary diagnosis of asthma was received. For case ascertainment, we used the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 493.0 – 493.9. We then aggregated all hospitalizations by month to produce a national time series of asthma exacerbations over time. Hospitalizations were assigned to a calendar month on the basis of the date the patient was admitted to the hospital. In a similar fashion, we identified all hospitalizations during the same time period in which a primary or secondary diagnosis of influenza was recorded. For case ascertainment, we used ICD-9-CM codes 487.0 (influenza with pneumonia), 487.1 (influenza with other respiratory manifestations), and 487.8 (influenza with other manifestations).

To investigate the association between asthma and influenza, we computed a cross-correlation function between the two series. A cross-correlation function indicates the temporal correlations between two time series: specifically, a series at time t and another series at time $t+m$, where m is referred to as the lag. Because cross-correlations between time series can be spurious due to effects of common temporal patterns, we employed a prewhitening process before computing the cross-correlation function.¹⁵ The prewhitening process involves the filtering of the two time series as a means of removing common

temporal patterns. By removing common temporal patterns we are then able to detect correlations based on prominent local peaks or troughs in two time series that are temporally aligned, as opposed to coincidental correlations based on shared seasonal patterns. The former are representative of a legitimate association, whereas the latter are merely due to common cyclic behavior. In our application, common yearly cycles are present in the asthma series as well as the influenza series, because both are elevated during the winter months.

Using the prewhitened cross-correlation function, as well as clinical judgment, to determine the leading/lagging associations between the series, we formulated time series regression models with autocorrelated errors. Because only monthly data was available, we considered that any temporal association between the asthma series and the influenza series would be instantaneous (i.e. occurring during the same month). In these models, asthma incidence served as the response series and influenza incidence served as the explanatory series. The errors in the models were described using seasonal autoregressive integrated moving-average (ARIMA) processes. The orders in the seasonal ARIMA processes were identified by inspecting the autocorrelation function and the partial autocorrelation function for the residuals from an ordinary linear regression model fit to the asthma and influenza series.

To further confirm the association between asthma and influenza, we used the novel H1N1 pandemic as a natural experiment. Specifically, we applied the fitted time series models based on the 1998-2008 data to predict monthly asthma admissions during the 2009 pandemic and the trend following this outbreak. We made predictions of asthma from the models with and without influenza. Mean squared prediction errors were employed to compare the forecasting performances of different time series models. In particular, we investigated whether inclusion of the external influenza information would help predict the asthma admissions in October 2009, when there was an early influenza outbreak, and the subsequent trend at the beginning of 2010.

A measure akin to an attributable risk was then calculated to assess the burden of influenza activity on asthma incidence. To compute the attributable risk measure for a specific year, we first found the peak influenza month during a 12 month period extending from July to June of the following year. We then calculated the ratio of (1) the average asthma incidence for the year, less the incidence during the peak influenza month, over (2) the average asthma incidence for the year. This attributable risk measure reflects the proportion of the overall incidence of asthma hospitalizations that could be potentially eliminated if influenza activity during the peak month could be reduced to the baseline level corresponding to the average over the eleven non-peak months.

Finally, to investigate whether the association between asthma and influenza is affected by age, we performed similar analyses for five different age groups (18-30, 30-45, 45-60, 60-75, 75+). The model structure based on the national series was applied to all the age-specific asthma series. All statistical analyses were performed using R, version 2.14.1 (The R Foundation for Statistical Computing).

RESULTS

Time series plots of asthma and influenza incidences from January 1998 to December 2008, along with the predictions for the 2009 H1N1 pandemic and the first half of 2010, are displayed in Figure 1. During the study period, strong seasonal patterns (peaking during the winter months) were observed for both the asthma and influenza series. The prewhitened cross-correlation function suggested a concurrent association between asthma and influenza admissions (results not shown). Table 1 summarizes the time series regression model fit to the seasonally differenced asthma series from January 1998 to December 2008. In addition

to influenza incidence, the final model also features an autoregressive component of order 1 (AR1), a seasonal moving-average component of order 1 (SMA1), and an additive outlier adjustment for January 2000. The influenza effect is highly statistically significant in the final model (p -value < 0.0001), indicating that the incidence of asthma hospitalization is positively associated with the incidence of influenza. We observed a large increase in the Akaike information criterion (AIC) after the influenza series was removed from the seasonal ARIMA model. The AIC for the model with the influenza series is 2074.93; the AIC for the model without the series is 2227.81. (A difference of two is viewed as meaningful.) Therefore, inclusion of the influenza information significantly improved the model fit to the asthma series. Figure 2 illustrates detailed monthly predictions of asthma in the 2009 influenza pandemic and the subsequent trend based on the seasonal ARIMA models with and without influenza as an explanatory series. Including the influenza series in the model substantially improved the forecasting, especially in October 2009 when there was an early influenza outbreak due to H1N1. A 60.2% reduction in mean squared prediction error was observed when the external influenza information was used in the forecasting.

In age-specific seasonal ARIMA models, the effect of influenza on asthma increases with age, as indicated by the z -values in Table 2. The magnitude of the z -value, reflecting the size of the standardized effect, tends to grow larger as the age category advances. This dose-response relationship was further confirmed by age-specific attributable risk measures in Figure 3. Thus, the risk of an asthma attack during an influenza outbreak increases with age in adults.

DISCUSSION

Our time series analysis clearly shows that the national incidence of hospitalizations for asthma is significantly associated with influenza activity. Our models also show that knowledge of concurrent influenza activity in the population can be used to substantially improve our ability to predict admissions due to asthma. Thus, improvements in influenza surveillance, prevention, and treatment could provide significant opportunities to anticipate, and perhaps, decrease the burden of hospitalizations caused by asthma.

Prior studies have shown increased healthcare utilization in young asthmatic children due to influenza-related illness, but these results have not been consistent in older age groups or over consecutive years.¹³ Prospective observational studies have not been able to show that influenza is a sole contributor to exacerbation requiring hospitalization, although studies in asthmatics in outpatient and emergency departments indicate that influenza may play a causal role in less severe exacerbations.^{16,17} However, the timing and severity of influenza seasons vary; thus, the results of a particular study may depend on when the study was performed. Although we cannot establish direct causality between the two diseases using our ecological analysis, our modeling framework exploits the fact that hospitalizations for influenza vary in timing, and indeed, we show in our forecasting models that asthma hospitalizations vary in a similar pattern. Furthermore, the “natural experiment” of the influenza pandemic strengthens the argument in favor of a causal relationship, especially given the biological plausibility of such an association.^{8,18}

Our results indicate the importance of influenza surveillance in prediction of resource utilization among patients with asthma. Our time series models show that by using concurrent influenza activity, we dramatically improve our ability to predict hospitalizations for asthma. We were able to markedly improve prediction of asthma hospitalizations during the large second peak of the 2009 H1N1 pandemic hospitalizations by including influenza data in the models. At this time in the U.S., the most widely available surveillance data is at the state level, which can often be 1-2 weeks old when it becomes available. However, novel

surveillance methods using Internet search queries or other forms of social media (i.e., Twitter) can also provide timely estimates, and perhaps, even forecasts of influenza activity.¹⁹⁻²² Thus, with more timely influenza activity reports, physicians can better target early interventions. For example, patients with asthma exacerbations could potentially benefit from early antiviral, mucolytic, or anti-inflammatory treatment strategies.²³⁻²⁸

Seasonal influenza vaccination is also effective in preventing influenza and may decrease the frequency of asthma hospitalizations. Our results indicate that there is still a significant burden of asthma hospitalizations related to influenza. Based on our attributable risk measure, we estimate that if influenza activity in the peak month of the year alone could be decreased to the baseline level that occurs during the rest of the year, then approximately 3.84% of asthma hospitalizations per year could potentially be avoided. Thus, our results clearly demonstrate the importance of vaccinating patients with asthma against influenza. We realize that influenza vaccination may not be as effective in people who need it most^{29,30}, and that effectiveness of the vaccine may vary from year to year³¹.

Our study has several limitations. First, we use administrative data rather than clinical or microbiologic data for case ascertainment. ICD-9-CM codes have reasonable sensitivity, specificity, and positive predictive value for detecting influenza.^{32,33} In addition, it is possible that awareness of influenza changed during the study period changing the sensitivity and specificity of influenza codes. Thus, we re-ran our analysis using an expanded set of ICD-9 codes that are correlated with influenza as a sensitivity analysis.³³ However, using this set of expanded codes actually improves the reduction in the mean squared prediction error from 60.2% to 83.9%. Second, other respiratory viral pathogens that we did not analyze may co-circulate during winter months, possibly contributing to asthma incidence. However, our findings during the pandemic make this less likely. Third, our study is ecological. We used the aggregate incidence for each disease and did not study associations at the individual level; instead, we focused on influenza as an “environmental” risk factor. Fourth, we do not use temperature or humidity data. However, we re-did our analysis by partitioning the asthma and influenza series for the four different US census regions (Northeast, Midwest, South and West) and fitting time series regression models for each of these regions. Our results were consistent across the regions (data not shown). Fifth, we do not have a measure of influenza vaccination. Although, we would expect that increased levels of vaccination coverage would diminish the association between the two diseases. Last, because we do not know the percentage of patients with asthma and influenza who did not get hospitalized, we cannot calculate a traditional measure of attributable risk. However, we did calculate a modified risk measure of asthma hospitalizations for the peak month of influenza each year as compared to the risk during non-peak months, as an indicator of excess asthma morbidity (hospitalizations) due to influenza activity in the peak month each year. This is a conservative estimate, as it does not take into account the potential for decreasing influenza outside the peak month. Future work should be focused on building confidence intervals for our modified attributable risk measures. Also, this same analytical framework could be used to study other diseases that might be associated with influenza (e.g. bacterial pneumonia). Despite these limitations, we are able to explore the impact of influenza on asthma hospitalizations across a large geographic area.

In conclusion, we found a strong association between hospitalization for asthma and influenza activity. Our results show that, despite guidelines for routine vaccination in patients with asthma, influenza continues to have a significant influence on patient outcomes, hospital resource utilization, and health care costs. Understanding this association could lead to more focused and cost-effective efforts to prevent hospitalizations by encouraging vaccination efforts and developing novel clinical and public health interventions for patients with asthma during the influenza season.

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Abbreviations List

AHRQ	Agency for Healthcare Research and Quality
AIC	Akaike information criterion
AR1	Autoregressive Component of Order 1
ARIMA	Autoregressive Integrated Moving-Average
HCUP	Healthcare Cost and Utilization Project
ICD-9-CM	International Classification of Diseases, 9 th Revision, Clinical Modification
SMA1	Seasonal Moving-average Component of Order 1 with a Periodicity of 12
U.S.	United States

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Summary at a Glance

On a population basis, influenza activity is associated with asthma hospitalizations in the United States, and this association can be exploited to more accurately forecast asthma admissions. Our results suggest that improvements in influenza surveillance, prevention, and treatment may help predict and decrease hospitalizations of asthma patients.

Figure 1.

Asthma admissions (upper panel) and influenza admissions (lower panel) by month. In the upper panel, prior to 2009, the solid red series represents the fitted values based on the time series model with concurrent influenza activity as an explanatory variable. After 2009, the dotted red series represents forecasts of asthma admissions with influenza; the dotted blue series represents forecasts of asthma admissions without influenza.

Figure 2.

Time series forecasting for asthma admissions during the 2009 influenza pandemic and the first half of 2010. In the upper panel, the black series represents the actual asthma series; the dotted red series represents forecasts of asthma admissions with influenza; the dotted blue series represents forecasts of asthma admissions without influenza. The corresponding influenza series is shown in the lower panel.

Figure 3.

Attributable risk measures for influenza activity on asthma hospitalization incidence by age. The risk of an asthma hospitalization during an influenza season increases with age. Note: To calculate an attributable risk, we first found the peak influenza month during each 12 month period from July of one year to June of the following year. We then calculated the excess risk of asthma admissions related to influenza in the peak influenza month of each year by computing the difference between the average rate of admissions for asthma during all twelve months, representing the overall risk, and the average rate of admissions for asthma during the eleven non-peak months. The attributable risk for the year was then defined as a ratio of the excess risk to the overall risk. The final attributable risk measure was based on the average of the yearly ratios.

Table 1

Summary of the final time series regression model for national asthma incidence of hospitalizations.

-	Coef.	S.E.	Z-value	P-value
AR1	0.6488	0.0782	8.2967	<0.0001
SMA1	-0.6991	0.1008	-6.9355	<0.0001
Influenza	0.4382	0.0237	18.4895	<0.0001
Outlier Adjustment	-4681.078	1069.901	-4.3752	<0.0001

AR1: Autoregressive component of order 1

SMA1: Seasonal moving average component of order 1

Note: The autoregressive and moving average components are included in the models to account for autocorrelation in the residuals. The influenza coefficients represent the instantaneous associations between the influenza series and the asthma series. The instantaneous associations were confirmed through the cross-correlation functions.

Table 2

Effects of influenza on admissions for asthma in the age-specific time series regression mode s.

Age	Influenza Coef.	S.E.	Z-value	P-value
18 – 30	0.0268	0.0032	8.3750	<0.0001
30 – 45	0.0495	0.0050	9.9000	<0.0001
45 – 60	0.0732	0.0050	14.6400	<0.0001
60 – 75	0.0656	0.0028	23.4286	<0.0001
75 +	0.0577	0.0030	19.2333	<0.0001