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Pneumonia in US hospitalized patients with influenza-like illness: BioSense, 2007–2010

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SUMMARY

We used data from BioSense, a national electronic surveillance system, to describe pneumonia in hospitalized patients with influenza-like illness (ILI). Ninety-five hospitals from 20 states reported ICD-9-CM-coded inpatient final diagnosis data during the study period of September 2007 to February 2010. We compared the characteristics of persons with and without pneumonia among those with ILI-related hospitalizations. BioSense captured 26 987 ILI-related inpatient hospitalizations; 8979 (33%) had a diagnosis of pneumonia. Analysis of trends showed highest counts of pneumonia during the 2007–2008 season and the second 2009 pandemic wave. Pneumonia was more common with increasing age. Microbiology and pharmacy data were available for a subset of patients; 107 (5%) with pneumonia had a bloodstream infection and 17% of patients were prescribed antiviral treatment. Our findings demonstrate the potential utility of electronic healthcare data to track trends in ILI and pneumonia, identify risk factors for disease, identify bacteraemia in patients with pneumonia, and monitor antiviral use.

Key words: Epidemiology, influenza, pneumonia, public health, surveillance system.

INTRODUCTION

Every year in the USA, infection with influenza viruses results in an estimated 86 000–544 000 hospitalizations [1] and 3349–48 614 deaths [2]. Persons with underlying medical conditions are at high risk for influenza-associated severe outcomes such as hospitalization and death [3]. Pneumonia is a one of the most common complications of influenza [4, 5]. The characteristics of hospitalized patients with seasonal and pandemic influenza have been described using clinical data obtained through manual medical chart abstraction [6–9]. However, to our knowledge, this is the first study to focus on factors associated with pneumonia in hospitalized patients with influenza-like illness (ILI) over multiple influenza seasons using national electronic data.

BioSense is a US national automated surveillance system operated by the Centers for Disease Control and Prevention (CDC) that receives, analyses, and visualizes electronic patient-level healthcare data for public health use [10–12]. Data types include chief

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Fig. 1 [*colour online*]. Map showing the location of the 95 BioSense study facilities.

complaints and final diagnoses from outpatient, emergency department (ED), and inpatient clinical settings; a subset of hospitals send detailed clinical data including microbiology, pharmacy, and radiology information. We used administrative and clinical data from BioSense to (1) track secular trends in ILI and pneumonia, (2) identify risk factors for pneumonia in patients hospitalized with ILI, (3) identify bloodstream infections in patients with ILI and pneumonia, and (4) study the use of influenza antiviral medications in hospitalized ILI patients with and without pneumonia.

METHODS

Study design and case definitions

As of March 2011, over 650 non-federal facilities contributed healthcare data to BioSense. For the purposes of this study, we included only facilities that sent inpatient final diagnosis data consistently over the entire study period (1 September 2007 to 10 February 2010), which reduced the sample size to 95 non-federal facilities in 20 states (Fig. 1).

This study includes only patients with ILI admitted to the inpatient setting. Chief complaints and diagnosis codes are categorized and assigned to specific sub-syndrome concepts. A hospitalization was classified as ILI-related if its electronic records included a chief complaint and/or final diagnosis of influenza or a combination of BioSense sub-syndromes including fever plus cough or fever plus upper respiratory infection (URI) [13]. We selected this ILI definition because it is used by the majority of US state and local health departments and was adopted by the US Influenza-like Illness Surveillance Network (ILINet) [14, 15]. Furthermore, the positive predictive value of symptoms approximating these criteria has been reported at 79–87% in studies during the influenza season [16, 17]. The definition was validated using BioSense and ILINet data from 2005 to 2008 and produced time-series graphs agreeing in global and local trend behaviour, characterized by mean and median differences below 0·5% [13]. Of patients hospitalized with ILI, we compared those with pneumonia to those without pneumonia, defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) final diagnosis codes of 480.x to 486.x and 487·0 which include viral, pneumococcal, other bacterial, and unspecified pneumonia as well as bronchopneumonia and influenza with pneumonia.

Other variables used in the analysis included age group, underlying conditions, and influenza epidemic period. We categorized age as 0–4, 5–17, 18–24, 25–49, 50–64, and $\geqslant$65 years groups which are similar to the age groups used in ILINet [14]. We analysed whether certain underlying conditions considered

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high risk by the Advisory Committee on Immunization Practices (ACIP) for severe influenza outcomes (asthma, chronic obstructive pulmonary disease (COPD), chronic cardiac disease, diabetes, haemoglobinopathies, immunosuppressive disorders, malignancy, neuromuscular disorders, chronic renal disease, pregnancy, and obesity [3]) were associated with a pneumonia diagnosis in hospitalized ILI patients. The ACIP high-risk underlying conditions were defined based on final diagnosis using ICD-9-CM codes classified by the Agency for Healthcare Research and Quality (AHRQ) Clinical Classification System (CCS) or as described by Mullooly and colleagues [18, 19]. The CCS categories were used to supplement definitions where more specificity was needed (e.g. asthma instead of chronic pulmonary conditions). Each condition was a separate dichotomous variable.

Influenza epidemic periods were defined as contiguous weeks when $\geqslant 10\%$ of weekly respiratory samples submitted for influenza testing to the national World Health Organization/National Respiratory and Enteric Virus Surveillance System Laboratory Surveillance Network were positive [14]. The 2007–2008 influenza season was from 30 December 2007 to 13 April 2008; the 2008–2009 season from 11 January 2009 to 5 April 2009; the 2009 pandemic H1N1 spring wave from 15 April 2009 to 24 July 2009; and the 2009 pandemic H1N1 autumn wave was from 1 September 2009 to 31 December 2009. The influenza epidemic period was a categorical variable with five levels; 'no influenza epidemic' was the reference.

Clinical data

A subset of BioSense facilities sends electronic clinical data (e.g. microbiology, pharmacy). In BioSense, patients are given a unique longitudinal identifier. We used this identifier to link administrative and clinical data associated with a particular hospitalization. For patients with an ICD-9-CM pneumonia diagnosis, we searched the microbiology data for blood culture results by identifying tests with a Logical Observation Identifiers Names and Codes (LOINC) code of 600–7. Most BioSense laboratory data are not Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT)-coded, so we used text-parsing methods utilizing Perl regular expressions to identify positive test results [20]. To avoid identifying contaminant pathogens, we defined a bloodstream infection as a positive blood culture result with one of the following pathogens: *Staphylococcus aureus*, *Steptococcus pneumoniae*, beta-haemolytic streptococci, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Bacteroides* spp., and *Candida* spp. [21].

After identifying pneumonia patients with bloodstream infections, we stratified by influenza epidemic period and characterized the patients based on pathogen, age group, underlying conditions, and disposition. A patient was considered to have a hospital-onset bloodstream infection if the specimen yielding the positive result was collected on or after the fourth day of hospitalization (where the date of hospitalization was day 1) [22]. An infection was defined as community-onset, hospital associated if a positive specimen was collected before the fourth day of hospitalization and the patient had been hospitalized overnight at least once in the same healthcare system $\leqslant 30$ days before the date of specimen collection [20]. Otherwise, the patient was considered to have a community-onset infection which included patients whose infection onset was in the community and who had either no hospitalizations in the previous 30 days or who had a hospitalization in a healthcare system not captured by the BioSense system.

Inpatient pharmacy data were used to assess the proportion of patients receiving an influenza antiviral medication (oseltamivir or zanamivir) during their hospitalization, stratifying by influenza epidemic period and pneumonia diagnosis. We used text parsing methods and searched for brand names in addition to the generic-named oseltamivir and zanamivir. Only patients with at least one medication on record were included in the analysis.

Data analysis

We describe the population of hospitalized ILI patients by pneumonia status stratified by age group, underlying disease, and influenza epidemic period. Differences between those with and without pneumonia were assessed using the χ^2 test. ILI, ILI + pneumonia, and pneumonia (no ILI) visit counts were displayed with a time-series plot. Logistic regression was used to investigate the association of a pneumonia diagnosis with underlying conditions while controlling for influenza epidemic periods. A preliminary model showed significant interaction terms between age groups and some underlying

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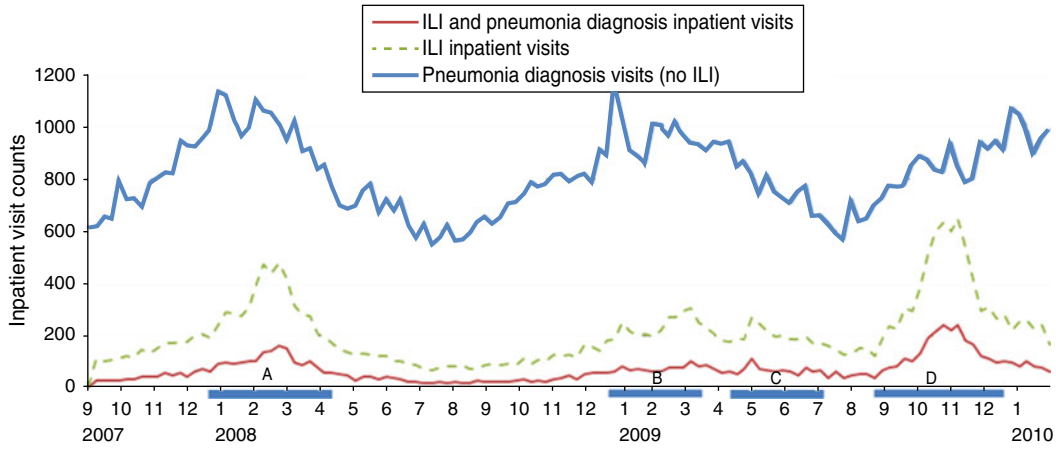

Fig. 2 [*colour online*]. Hospitalized patients with influenza-like illness (ILI) and ILI + pneumonia, BioSense (1 September 2007 to 10 February 2010). (*a*) 2007–2008 seasonal H3N2 period (30 December 2007 to 13 April 2008); (*b*) 2008–2009 seasonal H1N1 (11 January 2009 to 5 April 2009); (*c*) 2009 pandemic H1N1 spring wave (15 April 2009 to 24 July 2009); (*d*) 2009 pandemic H1N1 autumn wave (1 September 2009 to 31 December 2009).

medical conditions. Therefore, separate multivariable models were created for four age groups; i.e. 0–4 and 5–17 years age groups as well as the 18–24 and 25–49 years age groups were combined so that the sample sizes within each category were adequate for analysis. All applicable underlying conditions were included in the models because many patients had multiple conditions. A separate model was run to test the association of pregnancy and pneumonia in females in the 18–49 years age group while controlling for underlying conditions and influenza epidemic periods. Goodness of fit of each model was assessed with the Hosmer–Lemeshow test. Statistical analyses were conducted using SAS 9.2 (SAS Institute Inc., USA).

RESULTS

Characteristics of study patients

From 1 September 2007 to 10 February 2010, BioSense captured 26 987 inpatient hospitalizations with ILI from 26 000 unique patients; 8979 (33%) hospitalizations (8794 unique patients) had an ICD-9-CM diagnosis of pneumonia. Figure 2 displays weekly counts of ILI, ILI + pneumonia, and pneumonia (no ILI) hospitalizations; in general, the two ILI curves trend together. The pneumonia-only curve shows more gradual rises during the winter months. The 2009 rise in the ILI and ILI + pneumonia curves occur early relative to the usual influenza season and out of proportion to the usual number of visits. While ILI and ILI + pneumonia visits start to fall in December of 2009, the pneumonia-only visits continue to rise. The four influenza epidemic periods totalled 58 weeks compared to 71 non-epidemic weeks, yet 65% of the pneumonia-with-ILI diagnoses occurred during the influenza epidemic periods (Tables 1 and 2). The number of pneumonia admissions per week peaked during the 2009 pandemic H1N1 autumn season (147 per week compared to 44 per week during non-epidemic periods, relative risk 3·4) and was highest in the 25–49 years age group (41 compared to nine per week) (Table 1).

The age distribution of hospitalizations with ILI and pneumonia was different than those with ILI alone ($P < 0{\cdot}001$, Table 2). A greater proportion of hospitalizations with ILI and pneumonia occurred among those aged $\geqslant 65$ years. The relative risk of pneumonia increased from 1·0 in the 0–4 years age group to 1·8 in the $\geqslant 65$ years age group (Table 1). Additionally, the proportion of ILI hospitalizations that occurred during the 2009 pandemic H1N1 autumn wave was higher for those with pneumonia (28%) than the corresponding proportion without pneumonia (24%). With the exception of haemoglobinopathies and pregnancy, the prevalence of underlying conditions was significantly higher in hospitalized ILI patients with *vs*. those without pneumonia ($P < 0{\cdot}001$) (Table 2).

Logistic regression models were constructed separately for each of four age groups, including indicator variables for underlying conditions while controlling for influenza epidemic period. The Hosmer–Lemeshow goodness-of-fit test for similarity of

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Table 1. *Pneumonia diagnosis per week and pneumonia diagnosis counts stratified by age group and influenza epidemic period for hospitalized patients with influenza-like illness, BioSense, 1 September 2007 to 10 February 2010*

No. of weeks	Influenza epidemic period*	0–4 yr (diagnoses per week)‡	5–17 yr (diagnoses per week)	18–24 yr (diagnoses per week)	25–49 yr (diagnoses per week)	50–64 yr (diagnoses per week)	⩾65 yr (diagnoses per week)	All ages (diagnoses per week)	All ages, relative risk
71	No influenza epidemic	8·5	3·2	1·7	9·1	8·9	12·2	43·7	1·0
15	2007–2008 seasonal influenza	17·1	5·2	2·6	22·3	18·2	38·7	104·2	2·4
12	2008–2009 seasonal influenza	15·7	5·8	2·5	17·4	12·5	20·8	74·8	1·7
14	2009 pandemic H1N1 spring wave	9·6	6·8	2·7	15·4	12·1	18·4	65·3	1·5
17	2009 pandemic H1N1 autumn wave	18·8	17·6	8·1	41·4	33·2	28·0	147·1	3·4
	Pneumonia diagnosis counts	1503	772	365	2112	1789	2431	8 972	
	Total admissions	6538	2557	1424	6011	4625	5804	26 959	
	Pneumonia proportion	0·23	0·30	0·26	0·35	0·39	0·42	0·33	
	Relative risk†	1	1·3	1·1	1·5	1·7	1·8	n.a.	

n.a., Not applicable.

* Influenza seasons: 2007–2008 influenza season (from 30 December 2007 to 13 April 2008); 2008–2009 season (from 11 January 2009 to 5 April 2009); 2009 pandemic H1N1 spring wave (from 15 April 2009 to 24 July 2009); and the 2009 pandemic H1N1 autumn wave (from 1 September 2009 to 31 December 2009).

† 0–4 years is the reference.

‡ The number of pneumonia diagnoses for the corresponding influenza epidemic period and age group divided by the number of weeks for that epidemic period.

predicted/observed values by decile gave P values from 0·6 to 0·9 except for the 50–64 years age group where the P value was still acceptable at 0·09. In the 0–17 years age group, neuromuscular disease [odds ratio (OR) 1·9] and asthma (OR 1·7) were associated with pneumonia after controlling for influenza epidemic period and all other underlying conditions (Table 3). In the older age groups, COPD (OR 1·2–2·1) and immunosuppressive disorder (OR 1·4–1·5) were consistently associated with pneumonia. In the 18–49 years age group, the odds of pneumonia was 1·3 times higher in obese patients, and pregnancy (OR 0·4) was protective for pneumonia.

Clinical data

Blood culture data were available for 2212 (25%) hospitalizations with a pneumonia diagnosis, and of those, 107 (5%) patients had a bloodstream infection (110 pathogens), including 2% of children aged <18 years and 5% of adults aged ⩾18 years. The most commonly identified pathogen was *S. pneumoniae* (37%) followed by *S. aureus* (22%). Of the 107 patients with bloodstream infection, the median age was 52 years [interquartile range (IQR) 35–61 years]. Eighty-eight (82%) of the patients had at least one ACIP high-risk underlying condition with the most common being cardiac disease (49%). Forty (37%) of the 107 patients were hospitalized during the 2009 pandemic H1N1 autumn epidemic period, equating to 2·4 hospitalizations with bloodstream infections per week compared to 0·5 per week during non-influenza epidemic periods. The majority (63%) of bloodstream infections was community-onset; 26% were hospital-onset and 11% were community-onset, hospital associated. Of the hospital-onset infections, the most commonly identified pathogens were *Candida* spp. ($n=8$), *S. aureus* ($n=6$), *K. pneumoniae* ($n=5$), and *E. coli* ($n=5$). Seventeen (16%) of the 107 patients with a bloodstream infection died; of those, 10 (59%) infections were hospital-onset, the median age of patients was 55 years (IQR 47–66 years), and the most commonly identified pathogen was *Candida* spp. ($n=5$).

Pharmacy data were available for about 48% of the study hospitalizations ($n=11\,947$). Overall, 17% of study patients received influenza antiviral treatment, including 10% of children aged <18 years and 19% of adults aged ⩾18 years. Except for the 2008–2009 seasonal influenza period, use of influenza antiviral treatment was higher during influenza epidemic periods

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Table 2. *Characteristics of hospitalized patients with influenza-like illness stratified by pneumonia diagnosis, BioSense, 1 September 2007 to 10 February 2010*

	With pneumonia diagnosis, count (%) ($N=8979$)	Without pneumonia diagnosis, count (%) ($N=18008$)	χ^2 statistic P value
Age group (years)			<0·0001
0–4	1503 (16·7)	5035 (28·0)	
5–17	772 (8·6)	1785 (9·9)	
18–24	365 (4·1)	1059 (5·9)	
25–49	2112 (23·5)	3899 (21·7)	
50–64	1789 (19·9)	2836 (15·7)	
⩾65	2431 (27·1)	3373 (18·7)	
Missing age	7 (0·1)	21 (0·1)	
Influenza epidemic period*			<0·0001
No influenza epidemic	3104 (34·6)	6702 (37·2)	
2007–2008 seasonal influenza	1563 (17·4)	3245 (18·0)	
2008–2009 seasonal influenza	898 (10·0)	1960 (10·9)	
2009 pandemic H1N1 spring wave	914 (10·2)	1824 (10·1)	
2009 pandemic H1N1 autumn wave	2500 (27·8)	4277 (23·8)	
Underlying conditions			
Asthma	1698 (18·9)	2928 (16·3)	<0·0001
Malignancy	655 (7·3)	1113 (6·2)	0·00049
Cardiac disease	2929 (32·6)	4363 (24·2)	<0·0001
COPD	901 (10·0)	1011 (5·6)	<0·0001
Diabetes	1656 (18·4)	2823 (15·7)	<0·0001
Haemoglobinopathies	435 (4·8)	1001 (5·6)	0·0138
Immunosuppressive disorder	743 (8·3)	1207 (6·7)	<0·0001
Neuromuscular disease	488 (5·4)	713 (4·0)	<0·0001
Obesity	797 (8·9)	1271 (7·1)	<0·0001
Pregnancy†	100 (7·7)	598 (20·2)	<0·0001
Renal disease	1115 (12·4)	1758 (9·8)	<0·0001
Any condition above	6300 (70·2)	10990 (61·0)	<0·0001

COPD, Chronic obstructive pulmonary disease.

* Influenza seasons: 2007–2008 (from 30 December 2007 to 13 April 2008); 2008–2009 (from 11 January 2009 to 5 April 2009); 2009 pandemic H1N1 spring wave (from 15 April 2009 to 24 July 2009); and 2009 pandemic H1N1 autumn wave (from 1 September 2009 to 31 December 2009).

† Sample is restricted to females aged 18–49 years, denominator for those with pneumonia and no pneumonia was 1296 and 2957, respectively.

than during non-epidemic periods, regardless of pneumonia status (Table 4). This epidemic-associated influenza antiviral use increase was especially true during the 2009 pandemic H1N1 autumn period when 55% of those with pneumonia were treated with an antiviral *vs.* 9% during non-epidemic periods (37% *vs.* 3% for those without pneumonia). Overall, antiviral treatment was more common in those with pneumonia (23%) than those without pneumonia (14%) (χ^2, $P<0·0001$). These proportions were higher when limiting the ILI hospitalizations to just those with an influenza ICD-9-CM diagnosis code; 44% with pneumonia *vs.* 28% without pneumonia received an influenza antiviral (not shown in Table 4, $P<0·0001$).

DISCUSSION

We analysed administrative and clinical data from 26000 hospitalized patients with ILI reported to BioSense from 1 September 2007 to 10 February 2010 to evaluate characteristics associated with a pneumonia diagnosis. Hospitalized patients with ILI and ILI + pneumonia followed a similar pattern with the 2007–2008 influenza season and 2009 pandemic H1N1 autumn wave being more severe than the 2008–2009 season. Overall, hospitalized patients with ILI and a pneumonia diagnosis compared to those without pneumonia were older and had a higher proportion of underlying conditions. Almost 5% of pneumonia patients had a bloodstream infection and

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Table 3. *Underlying conditions associated with a pneumonia diagnosis stratified by age group and controlling for influenza epidemic period* in hospitalized patients with influenza-like illness, BioSense, 1 September 2007 to 10 February 2010*

Underlying condition	0–17 years ($N=9095$) OR† (95% CI)	18–49 years ($N=7435$) OR† (95% CI)	50–64 years ($N=4625$) OR† (95% CI)	⩾65 years ($N=5804$) OR† (95% CI)
Asthma	**1·7 (1·5–1·9)**	**1·1 (1·0–1·3)**	1·1 (0·9–1·3)	1·0 (0·9–1·2)
Malignancy	0·4 (0·2–0·8)	0·9 (0·7–1·2)	0·8 (0·7–1·0)	1·0 (0·9–1·1)
Cardiac disease	**1·2 (1·0–1·5)**	**1·4 (1·2–1·5)**	**1·1 (1·0–1·3)**	**1·1 (1·0–1·2)**
COPD	n.a.	**2·1 (1·6–2·7)**	**1·2 (1·1–1·5)**	**1·4 (1·2–1·6)**
Diabetes	0·9 (0·5–1·7)	1·0 (0·8–1·1)	0·9 (0·8–1·0)	0·8 (0·7–0·9)
Haemoglobinopathies	0·8 (0·6–1·0)	0·8 (0·7–1·0)	1·0 (0·7–1·3)	1·0 (0·8–1·3)
Immunosuppressive disorder	1·0 (0·8–1·3)	**1·4 (1·2–1·6)**	**1·5 (1·2–1·9)**	**1·4 (1·0–1·9)**
Neuromuscular disease	**1·9 (1·5–2·3)**	**1·4 (1·1–1·9)**	1·0 (0·7–1·3)	1·1 (0·9–1·4)
Obesity	1·5 (0·9–2·4)	**1·3 (1·1–1·5)**	1·0 (0·8–1·2)	0·9 (0·7–1·1)
Renal disease	1·1 (0·7–1·7)	0·9 (0·7–1·1)	1·0 (0·8–1·2)	1·0 (0·9–1·2)
Any condition above‡	**1·5 (1·3–1·6)**	1·0 (0·9–1·1)	**1·2 (1·0–1·4)**	1·0 (0·9–1·2)

OR, Odds ratio; CI, confidence interval; COPD, Chronic obstructive pulmonary disease; n.a., not applicable.
* Influenza seasons: 2007–2008 influenza season (from 30 December 2007 to 13 April 2008); 2008–2009 (from 11 January 2009 to 5 April 2009); 2009 pandemic H1N1 spring wave (from 15 April 2009 to 24 July 2009); and 2009 pandemic H1N1 autumn wave (from 1 September 2009 to 31 December 2009).
† Multivariable odds ratio.
‡ This variable was not included in the multivariable model; a separate model was run with this variable only plus influenza epidemic period.
Bold values are statistically significant at an alpha level of 0·05.

Table 4. *Antiviral treatment* for hospitalized patients with influenza-like illness stratified by influenza epidemic period† and pneumonia status, BioSense, 1 September 2007 to 10 February 2010*

	No influenza epidemic (71 weeks) Count (%)	2007–2008 seasonal influenza (15 weeks) Count (%)	2008–2009 seasonal influenza (12 weeks) Count (%)	2009 pandemic H1N1 spring wave (14 weeks) Count (%)	2009 pandemic H1N1 autumn wave (17 weeks) Count (%)	All Count (%)
Admissions with pneumonia diagnosis	$n=1515$	$n=743$	$n=384$	$n=359$	$n=1182$	$N=4183$
Antiviral treatment	128 (8·5)	127 (17·1)	10 (2·6)	65 (18·1)	650 (55·0)	980 (23·4)
Admissions without pneumonia diagnosis	$n=3053$	$n=1408$	$n=747$	$n=753$	$n=1803$	$N=7764$
Antiviral treatment	105 (3·4)	175 (12·4)	24 (3·2)	90 (12·0)	659 (36·6)	1053 (13·6)

* Oseltamivir or zanamivir.
† Influenza seasons: 2007–2008 influenza season (from 30 December 2007 to 13 April 2008); 2008–2009 season (from 11 January 2009 to 5 April 2009); 2009 pandemic H1N1 spring wave (from 15 April 2009 to 24 July 2009); and 2009 pandemic H1N1 autumn wave (from 1 September 2009 to 31 December 2009).

patients with pneumonia were more likely to be treated with influenza antiviral agents, especially during influenza epidemic periods. These data correlate well with published studies using primary data collection of seasonal [4, 5] and pandemic [6, 7] influenza hospitalizations, including influenza-associated pneumonia [5]. To our knowledge, this is the first study in the USA to use strictly electronic healthcare data to describe ILI and pneumonia over multiple influenza seasons including the pandemic influenza season of 2009–2010.

Administrative healthcare data such as final diagnosis codes are a low cost, readily available means of obtaining a broad picture of clinical events and trends

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Table 5. *Pneumonia, bloodstream infection, and antiviral data from BioSense compared to other studies*

	BioSense (2007–2010)	Dawood *et al*. [5] (2003–2008)	Dao *et al*. [4] (2005–2008)	Jain *et al*. [6] (2009)	Skarbinski *et al*. [7] (2009)
Pneumonia in hospitalized patients with influenza					
<18 years	25%	36%	—	42%	48%
⩾18 years	38%	—	34%	39%	44%
Bloodstream infection in hospitalized patients with influenza and pneumonia					—
<18 years	2·4%	2·0%*	—	—	
Antiviral treatment in hospitalized patients with influenza					
<18 years	22%†, 53%‡	20%	—	69%	77%
⩾18 years	58%§, 75%‡	—	54%§	79%	84%
All ages					
2009 pandemic H1N1 spring wave	14%, 49%¶	—	—	75%	—
2009 pandemic H1N1 autumn wave	44%, 74%¶	—	—	—	82%

* Includes all sterile sites (blood, cerebrospinal fluid, pleural fluid, and tissue specimen).
† Includes only 2007–2008 data and patients with a final diagnosis code of influenza to attempt to match time period and methods of Dawood *et al*. [5].
‡ Includes only 2009 pandemic H1N1 spring and autumn waves and patients with a final diagnosis code of influenza to attempt to match time period and methods of Jain *et al*. [6] and Skarbinski *et al*. [7]
§ Includes only 2007–2008 data and patients with a final diagnosis code of influenza to attempt to match time period and methods of Dao *et al*. [4].
¶ Includes only patients with a final diagnosis code of influenza.

without the challenges of primary data collection. The magnitude and volume of these data potentially outweigh their imperfections. Furthermore, these data allow a quantitative grasp of the burden of disease that can be compared across years and cannot be achieved with small, time-limited and expensive clinical studies. For example, the number of hospitalizations with ILI and a pneumonia diagnosis per week was higher during the 2007–2008 seasonal epidemic than during non-influenza epidemic periods by an overall factor of 2·4 (104·2 *vs*. 43·7) (Table 1, Fig. 2). However, that factor varied by age group and was 3·2 for the ⩾65 year age group, 2·0 for patients aged <5 years, and 1·6 for other patients aged <25 years. By contrast, the 2009 pandemic H1N1 autumn wave saw an overall pneumonia increase factor of 3·4, clearly a greater burden overall, with more than fourfold increases for age groups from 5–44 years and with the largest factor increase of 5·4 in the 5–17 years group. The morbidity seen in the younger age groups during the 2009 pandemic H1N1 autumn wave was in contrast to previous trends. From 1979 to 2001, Thompson *et al*. [1] demonstrated increasing pneumonia and influenza hospitalization rates in older age groups using representative discharge diagnosis data. BioSense data, available in near real-time, can identify changes in these patterns of disease.

The US healthcare sector is now focused on the 'meaningful use' of electronic health records (EHR), a Department of Health and Human Services legislation incentivizing healthcare providers and institutions to adopt EHR. Given the movement towards EHR implementation, it is reassuring that our study correlated well with current surveillance data and published literature on influenza and pneumonia. We found the trend in pneumonia among hospitalized ILI patients increased by age group; a finding consistent with national hospital discharge data [23]. During influenza epidemic periods, the proportion of pneumonia in hospitalized adults (⩾18 years) and children (<18 years) with ILI in BioSense was 38% and 25%, respectively. Our results are similar to findings from a large multi-site influenza hospitalizations surveillance system in which among patients hospitalized with laboratory-confirmed influenza over multiple non-pandemic influenza seasons, 34% of adults and 36% of children had evidence of pneumonia [4, 5] (Table 5).

The majority of patients hospitalized with ILI and pneumonia had underlying medical conditions.

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Although there are no comparable data sources that evaluate the prevalence of underlying conditions in hospitalized patients with ILI, our findings are consistent with published studies of laboratory-confirmed influenza hospitalizations which also report that a large proportion of both children [5] and adults [4] hospitalized with influenza have underlying medical conditions. In children, similar to our study, underlying conditions of asthma and neuromuscular disease have been significantly associated with influenza-related pneumonia while haemoglobinopathies were protective [5]. Dawood *et al*. [5] gave the explanation that the protective effect of haemoglobinopathy relative to pneumonia may result from a lower threshold for hospitalization due to this chronic condition in children [5]. We also found a protective effect of pregnancy with pneumonia. The same explanation may apply to this association.

Overall, we found that almost 5% of the ILI-hospitalized patients with pneumonia also had a bloodstream infection; the event rate for bloodstream infections was 2·5-fold higher during influenza epidemic periods than non-epidemic periods. In children, this proportion was lower (2·4%), similar to the result of Dawood *et al*. (2·0%) [5] (Table 5). In contrast to other studies [4, 5] where *S. aureus* was the predominant pathogen in invasive infections, we found *S. pneumoniae* most commonly identified. The relationship between influenza, with and without pneumonia, and bacterial co-infections has been well described [24]. Possible mechanisms for influenza and bacterial co-infection include the destruction of the epithelial cell layer of the tracheobronchial tree by the influenza virus [25, 26] and influenza virus-induced immunosuppression [26–28], both of which would allow for vulnerability to acquire a bacterial infection. The strong association between ILI and pneumonia during influenza epidemic periods in our study supports the described biological mechanisms but we can not infer causation using our data.

This is the first study to correlate clinical information about ILI and pneumonia to the receipt of antiviral agents for the treatment of influenza. Of 9035 ILI hospitalizations with pharmacy data for adults and 2912 for children, 19% and 10%, respectively, were treated with oseltamivir or zanamivir. These proportions were higher in adults (25%) and children (16%) when restricting the sample to those with ILI and pneumonia. Compared to previous seasons, there was a marked increase in influenza antiviral use from 3% to 14% during the 2007–2009 season to 36% during the 2009 pandemic H1N1 season which is in accordance with CDC guidelines and findings from other observational studies [7, 8, 29, 30]. During the 2003–2008 influenza seasons, Dawood *et al*. found that 20% of children hospitalized with laboratory-confirmed influenza who had pneumonia were treated with antivirals [5]. For BioSense hospitalizations restricted to the 2007–2008 season and including only those with a final diagnosis of influenza in order to attempt to best match time period and diagnostic precision of the Dawood *et al*. [5] study, 22% of children received antivirals (Table 5). The antiviral treatment proportions in our study (14% in the 2009 pandemic H1N1 spring and 44% in the autumn wave) were lower compared to $\geqslant$75% in Jain *et al*. [6] and Skarbinski *et al*. [7], perhaps because BioSense receives only inpatient pharmacy data and some patients may have received treatment prior to hospitalization. Further, our data are based on ILI rather than laboratory-confirmed influenza. When restricting the sample to patients with a final diagnosis of influenza, the proportions receiving influenza antiviral treatment rose (Table 5). Finally, the completeness of BioSense pharmacy data is also unknown. However, it is plausible that patients in our study, especially those without laboratory-confirmed influenza, may not have received influenza antivirals, suggesting the underutilization of influenza antivirals. CDC and ACIP guidelines state the importance of early and aggressive antiviral treatment in all hospitalized patients when influenza is suspected, even if testing is not done [31].

This study was subject to several limitations. First, our ILI definition may have caused under-ascertainment of influenza in the elderly who are less likely to mount a fever. However, even if fever was not present, elderly patients would be captured with an ICD-9-CM code for influenza or a chief complaint of ILI or influenza. BioSense facilities are not representative of all U.S. hospitals; they are a convenience sample of facilities that are able and willing to send electronic healthcare data. Additionally, only a subset of the facilities sent microbiology and pharmacy data so we were unable to link these clinical data types for all hospitalizations. ICD-9-CM codes are not confirmatory for underlying conditions or pneumonia and we did not validate these diagnoses with hospital chart abstraction. Similarly, completeness or accuracy of electronic healthcare data was not verified by chart

abstraction. Pneumonia can be attributed to multiple factors which were not accounted for in this study. Pneumococcal vaccination, for example, was not available in BioSense data and whether the magnitude or direction of the multivariable model findings would change with the inclusion of other factors is unknown. Finally, our study was based on a syndromic ILI definition using either patient chief complaint or ICD-9-CM final diagnosis codes. However, depending on the codes used, the correlation between laboratory-based and syndromic influenza detection is as high as 0·86 ($P<0·0001$), suggesting syndromic-based detection may be a useful approach [32].

Our study also has several strengths. As pointed out above, some of our findings are markedly consistent with data from laboratory-confirmed influenza hospitalizations surveillance and these data add insights into epidemic trends. Overall, the volume of BioSense's electronic data may facilitate study of selected issues which are less affected by its limitations. Our study of 26 000 unique ILI patients from 95 facilities in 20 states would not have been feasible with medical chart abstraction. Electronic systems require start-up costs, but, once established, provide timely data without burdening healthcare personnel with manual data abstraction.

This study is the first to explore ILI-related pneumonia in hospitalized patients using exclusively electronic administrative and clinical data. The clinical data, although only available for a subset of the hospitalizations, supplement the diagnosis codes with a richer characterization of the disease and treatment course without any additional burden on data collection. Although these data are not derived from an EHR, these are the types of data that will become available as 'meaningful use' compliant EHRs become more widely available. This study provides an example of how electronic data can be used to track ILI and pneumonia disease trends, explore risk factors for disease, identify bloodstream infections using microbiology data, and study influenza antiviral prescribing patterns.

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DECLARATION OF INTEREST

None.

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