Pneumonia among adults hospitalized with laboratory-confirmed seasonal influenza virus infection—United States, 2005–2008

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Abstract

Background: Influenza and pneumonia combined are the leading causes of death due to infectious diseases in the United States. We describe factors associated with pneumonia among adults hospitalized with influenza.

Methods: Through the Emerging Infections Program, we identified adults ≥18 years, who were hospitalized with laboratory-confirmed influenza during October 2005 through April 2008, and had a chest radiograph (CXR) performed. Pneumonia was defined as the presence of a CXR infiltrate and either an ICD-9-CM code or discharge summary diagnosis of pneumonia.

Results: Among 4,765 adults hospitalized with influenza, 1392 (29 %) had pneumonia. In multivariable analysis, factors associated with pneumonia included: age ≥75 years, adjusted odds ratio (AOR) 1.27 (95 % confidence interval 1.10–1.46), white race AOR 1.24 (1.03–1.49), nursing home residence AOR 1.37 (1.14–1.66), chronic lung disease AOR 1.37 (1.18–1.59), immunosuppression AOR 1.45 (1.19–1.78), and asthma AOR 0.76 (0.62–0.92). Patients with pneumonia were significantly more likely to require intensive care unit (ICU) admission (27 % vs. 10 %), mechanical ventilation (18 % vs. 5 %), and to die (9 % vs. 2 %).

Conclusions: Pneumonia was present in nearly one-third of adults hospitalized with influenza and was associated with ICU admission and death. Among patients hospitalized with influenza, older patients and those with certain underlying conditions are more likely to have pneumonia. Pneumonia is common among adults hospitalized with influenza and should be evaluated and treated promptly.

Keywords: Influenza, Pneumonia, Hospitalizations

Background

Influenza illness is generally characterized by acute onset of fever, myalgias, and respiratory symptoms, and while disease usually resolves without complications in healthy individuals, influenza is associated with an annual increase in hospital admissions for pulmonary, cardiovascular and neuromuscular complications [1–3]. The etiology of influenza-associated pneumonia may include primary influenza pneumonia, secondary bacterial pneumonia, or concomitant viral and bacterial pneumonia [1, 4, 5]. Pulmonary complications of influenza, including pneumonia and exacerbations of chronic pulmonary disease, are common and result in significant morbidity and mortality. Oliveira and colleagues found that among all patients admitted to a large metropolitan hospital with influenza during the 1999–2000 season, 49 % had pneumonia [6]. Further, in a study conducted over 4 influenza seasons (1999–2003), Murata and colleagues found that among 193 patients hospitalized with influenza A, 52 % had some type of acute findings on
chest radiograph and 17% had definitive pneumonia infil-
trates [7]. Although there is evidence that adult patients
with underlying cardiac or pulmonary disease are more
likely to develop influenza-associated pneumonia than
those without underlying medical conditions [6, 7], much
of the data describing factors associated with influenza-
associated pneumonia among adults comes from case
series conducted at single sites and during a limited num-
ber of seasons. Using data from a large multi-center, geo-
graphically diverse, population-based surveillance system,
we describe factors associated with pneumonia among
adults hospitalized with influenza over three consecutive
years in which seasonal influenza viruses circulated.

Methods
The Emerging Infections Program (EIP) network conducts
active population-based surveillance for laboratory-confirmed
influenza-associated hospitalizations. The network began
adult surveillance in 2005 and covers over 80 counties in
10 states (California, Colorado, Connecticut, Georgia,
Maryland, Minnesota, New Mexico, New York, Oregon,
and Tennessee), representing approximately 7% of the
adult U.S. population [8]. Patients were included in EIP in-
fluenza surveillance if they resided and were hospitalized
in an EIP catchment area and were hospitalized within
14 days of a positive influenza diagnostic test result.
Patients were excluded if the first positive influenza speci-
men was obtained >3 days after hospital admission be-
cause these patients might have had healthcare-associated
influenza infection. Influenza testing was performed at the
discretion of health care providers. Medical charts of hos-
pitalized patients with laboratory-confirmed influenza were retrospectively reviewed [8, 9].

The study period comprised 3 influenza seasons, 2005–
2006 to 2007–2008. Patients were included in this analysis
if they were ≥18 years of age, were hospitalized with
laboratory-confirmed influenza during the 2005–2006
through 2007–2008 influenza seasons, and had a chest
radiograph (CXR) performed during hospitalization. The
following data were collected on patients: demographics,
results of laboratory tests for influenza, influenza vaccin-
ation status for the current season, underlying medical
conditions, bacterial coinfections, CXR data, antiviral
treatment, clinical outcomes, and discharge diagnoses. La-
boratory confirmation of influenza was based on viral cul-
ture, direct or indirect immunofluorescence antibody
staining, reverse-transcription polymerase chain reaction,
or a rapid antigen test. Surveillance staff completed med-
ical record abstractions using check boxes to indicate
whether or not a new infiltrate or consolidation was re-
corded on the official CXR transcript. Discharge diagnoses
were captured in two ways: 1) the first nine international
classification of diseases (ICD-9-CM) codes for each case
were abstracted from the medical record; 2) check boxes
were marked for certain diagnoses, including pneumonia,
if they were recorded by clinicians on the discharge sum-
mary. Pneumonia was defined as the presence of a new in-
filtrate on CXR and either an ICD-9-CM discharge
diagnosis code for pneumonia (480–487.0) or a diagnosis
of pneumonia recorded on discharge summary.

Information on the presence of selected bacterial in-
fec tions was available only for patients who had a posi-
tive culture. A bacterial infection was recorded if
bacteria other than those that are commonly considered
to be contaminants grew from a sterile body site or a
non-sterile respiratory site culture obtained within 3 cal-
endar days of hospital admission. Sterile body sites for
bacterial infections included blood, pleural fluid, cere-
bospinal fluid, bronchoalveolar lavage fluid, and deep
tissue biopsy. Non-sterile respiratory sites included sput-
um and endotracheal aspirates.

Use of influenza antiviral therapy was examined for all
individuals. Among those who were treated with anti-
viral agents, timing of treatment was assessed in relation
to hospitalization date. Early antiviral treatment was de-
efined as initiation of antiviral treatment within 2 days of
hospital admission.

We used bivariate analysis to compare adults hospital-
ized with influenza with and without pneumonia. We
used χ² and Fisher exact tests for categorical variables
and t-tests and Wilcoxon-rank sum tests for continuous
and ordinal variables. All variables significant in bivariate
analysis, as well as biologically plausible variables, and
potential confounders were included in a multivariable
logistic regression model to identify factors independ-
ently associated with influenza-associated pneumonia.
We used the Breslow-Day test for homogeneity to assess
effect modification of select variables. All tests were
two-tailed and a p-value of 0.05 was considered signifi-
cant. Analyses were conducted using SAS Version 9.2
(SAS Institute Inc., Cary, NC).

Ethics statement EIP adult influenza hospitalization
surveillance activities during the 2005–2007 influenza
seasons were determined by the Centers for Disease
Control and Prevention (CDC) Institutional Review
Board (IRB) not to involve research in accordance with
the federal regulations for the protection of human sub-
jects in research. Starting with the 2007-2008 season,
research questions were added to evaluate factors associ-
ated with severe outcomes during hospitalizations, and
IRB review was conducted at all surveillance sites and
the CDC. The protocol was approved by the CDC IRB
and was either approved or received exempt status by all
surveillance site IRBs. Because all surveillance data was
analyzed anonymously, neither verbal nor written in-
formed consent was obtained from participants.
Results

Patient characteristics

During the study period, of 5055 adults hospitalized with laboratory-confirmed influenza, 4765 (94.3%) had an available CXR report and discharge diagnosis information and were therefore included in our study. Of the 4765 adults, 1392 (29%) had pneumonia. The prevalence of pneumonia did not vary significantly over the 3 influenza seasons included in the analysis. Adults ≥75 years of age represented the age group with the highest proportion of patients hospitalized with and without influenza-associated pneumonia (Fig. 1). The median age of patients with pneumonia compared with patients without pneumonia was 74 years versus 69 years (p < 0.01) (Table 1). The majority of patients hospitalized with and without influenza-associated pneumonia were white. White patients were older (median age 74 years) than black patients (53 years), Hispanic patients (56 years), and patients of other races including Asian, Pacific Islander, American Indian, Alaskan Native, and multi-race (69 years) (p < 0.01). Patients aged 65 years and above had a higher proportion of underlying conditions (90%) compared to patients aged < 65 years (79%) (p < 0.01). Influenza was diagnosed by rapid test only in 1048/1390 (75%) patients with pneumonia and in 2396/3368 (71%) patients without pneumonia (p < 0.01).

The median number of days from symptom onset to hospital admission was 2 days for patients with and without pneumonia (Table 1). Patients with pneumonia were significantly more likely than patients without pneumonia to reside in a nursing home prior to hospital admission, to have received influenza vaccine, and to have the following underlying medical conditions: chronic lung disease, cardiovascular disease, and immunosuppression. Patients with pneumonia were significantly less likely than patients without pneumonia to have asthma (Table 1). A description of the most frequent discharge diagnoses (based on first listed ICD-9 diagnosis code) among patients with and without pneumonia can be found in Additional file 1: Table S1.

Except for influenza vaccination and cardiovascular disease, all factors included in a multivariable model remained independently associated with pneumonia including age ≥75 years [adjusted odds ration (AOR) 1.27], white race (AOR 1.24), nursing home residence (AOR 1.37) chronic lung disease (AOR 1.37), immunosuppression (AOR 1.45) and asthma (AOR 0.76) (Table 1).

Outcomes

Sixty-one patients with pneumonia and 68 patients without pneumonia had sterile site bacterial infections, 90% of which were cultured from the blood (Table 2). The most common pathogens cultured from sterile sites in patients with pneumonia were *Staphylococcus aureus* (*S. aureus*) and *Streptococcus pneumonia* (*S. pneumoniae*).

Patients with pneumonia had a longer median length of hospital stay than patients without pneumonia (5 days versus 3 days; p < 0.01). Patients with pneumonia were also significantly more likely to have a hospital length of stay greater than one week (AOR 2.99), require intensive care unit (ICU) admission (AOR 3.62), require mechanical ventilation (AOR 4.79), and die (AOR 6.06) (Table 3). Among patients with pneumonia, factors independently associated with a poor outcome, defined as ICU admission, need for mechanical ventilation or death, included nursing home residence (AOR 1.6), chronic lung disease (AOR 1.6), cardiovascular disease (AOR 1.4),...
renal disease (AOR 1.5) and immunosuppression (AOR 1.5) (Table 4). Of note, older age was inversely associated with a poor outcome (AOR 0.7) among patients hospitalized with pneumonia (Table 4).

**Treatment**

Patients with pneumonia [823/1392 (59 %)] were significantly more likely to receive influenza antiviral therapy than patients without pneumonia [1815/3373 (54 %);  𝑃 < 0.01].

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**Table 1** Comparison of characteristics of adults hospitalized with laboratory-confirmed influenza with and without pneumonia, Emerging Infections Program, 2005–2008 (𝑛 = 4765)

| Characteristic                  | Patients with pneumonia;  𝑛 = 1392 no. (%) | Patients without pneumonia;  𝑛 = 3373 no. (%) | Unadjusted odds ratio (95 % CI) | Adjusted odds ratio (95 % CI) |
|---------------------------------|-------------------------------------------|----------------------------------------------|--------------------------------|-----------------------------|
| Age in years, median (range)    | 74 (18–101)                               | 69 (18–102)                                  | ---                           | ---                         |
| Age ≥75 years                   | 663 (48)                                  | 1333 (40)                                    | 1.39 (1.23–1.58)              | 1.27 (1.10–1.46)            |
| Male Sex                        | 660 (47)                                  | 1430 (42)                                    | ---                           | ---                         |
| Race/Ethnicity                  |                                           |                                              |                               |                             |
| White, non-Hispanic             | 900 (65)                                  | 2016 (60)                                    | 1.41 (1.18–1.69)              | 1.24 (1.03–1.49)            |
| Black, non-Hispanic             | 204 (15)                                  | 642 (19)                                     | ref                           | ref                         |
| Hispanic                        | 67 (5)                                    | 180 (5)                                      | 1.18 (0.85–1.63)              | 1.13 (0.80–1.58)            |
| Othera                          | 48 (3)                                    | 115 (4)                                      | 1.32 (0.91–1.92)              | 1.26 (0.86–1.85)            |
| Unknown                         | 173 (12)                                  | 420 (12)                                     | ---                           | ---                         |
| Virus Type                      |                                           |                                              |                               |                             |
| Influenza A                     | 1037 (74)                                 | 2484 (74)                                    | 1.10 (0.95–1.28)              | ---                         |
| Influenza B                     | 298 (21)                                  | 787 (23)                                     | ref                           | ---                         |
| Unknown                         | 57 (4)                                    | 98 (3)                                       | ---                           | ---                         |
| Influenza Vaccineb              |                                           |                                              |                               |                             |
| Yes                             | 677 (49)                                  | 1586 (47)                                    | 1.20 (1.04–1.38)              | 1.00 (0.86–1.17)            |
| No                              | 438 (31)                                  | 1228 (36)                                    | ref                           | ---                         |
| Unknown                         | 265 (19)                                  | 536 (16)                                     | 1.39 (1.16–1.67)              | ---                         |
| Nursing Home Residentc          | 228 (16)                                  | 382 (11)                                     | 1.53 (1.28–1.83)              | 1.37 (1.14–1.66)            |
| Underlying Conditionsd          | 1179 (85)                                 | 2855 (85)                                    | 1.01 (0.85–1.19)              | ---                         |
| Asthma                          | 174 (13)                                  | 599 (18)                                     | 0.66 (0.55–0.76)              | 0.76 (0.62–0.92)            |
| Chronic Lung Disease            | 417 (30)                                  | 787 (23)                                     | 1.40 (1.22–1.62)              | 1.37 (1.18–1.59)            |
| Cardiovascular Disease          | 652 (47)                                  | 1462 (43)                                    | 1.15 (1.02–1.31)              | 0.99 (0.86–1.13)            |
| Chronic Metabolic Disease       | 481 (35)                                  | 1161 (34)                                    | 1.01 (0.88–1.15)              | ---                         |
| Renal Disease                   | 216 (15)                                  | 499 (15)                                     | 1.05 (0.88–1.25)              | ---                         |
| Immunosuppression               | 186 (13)                                  | 348 (10)                                     | 1.33 (1.09–1.61)              | 1.45 (1.19–1.78)            |
| Cognitive Dysfunction           | 136 (10)                                  | 276 (8)                                      | 1.22 (0.98–1.51)              | ---                         |
| Neuromuscular Disease           | 79 (6)                                    | 168 (5)                                      | 1.15 (0.87–1.51)              | ---                         |
| Seizure Disorder                | 51 (4)                                    | 127 (4)                                      | 0.97 (0.69–1.36)              | ---                         |
| Cancer                          | 52 (4)                                    | 118 (4)                                      | 1.07 (0.77–1.49)              | ---                         |
| Other Condition                 | 67 (5)                                    | 165 (5)                                      | 0.98 (0.73–1.32)              | ---                         |
| Symptom onset to admission, median days (range)e | 2 (0–63) | 2 (0–83) | --- | --- |

aOther Races include Asian, Pacific Islander, American Indian, Alaskan Indian, and multi-race
bIncludes 4730 cases with non-missing data
cIncludes 4713 cases with non-missing data
dChronic lung disease: all diseases other than asthma, reactive airways disease and cystic fibrosis; Cardiovascular disease: structural cardiac defects, arrhythmias, current ischemic heart disease, and congestive heart failure or other functional impairment; Chronic metabolic disease: diabetes, thyroid disorders, adrenal insufficiency and pituitary abnormalities; Renal disease: chronic renal failure, nephrotic syndrome, renal tubular acidosis, glomerulonephritis, medullary cystic disease, and polycystic kidney disease; Immunosuppression: HIV/AIDS, immunoglobulin deficiency, and immunosuppressive therapy; Cognitive dysfunction: conditions where handling of respiratory secretions is impaired; Neuromuscular disease: muscular dystrophy, cerebral palsy, quadriplegia, spinal cord injury, and spinal abnormalities, and stroke; Cancers: diagnosed within the past 12 months and exclude non-melanoma skin cancers, lymphoma, and leukemia; Other conditions include pregnancy, hemoglobinopathy, lymphoma, leukemia, cystic fibrosis, Guillain Barré Syndrome
*Includes 4404 cases with non-missing data
Overall, among 2,638 patients who received influenza antiviral therapy, 98% received oseltamivir. When limiting our analysis to 2,386 patients who presented to the hospital within 2 days of symptom onset, 456/687 (66%) patients with pneumonia and 1,118/1,697 (66%) patients without pneumonia received antiviral treatment (p = 0.82). Among 1,574 people who presented to the hospital within 2 days of symptom onset and who received antiviral treatment, data was available on length of time from admission to start of antiviral treatment for 1,534 people. The majority, 1469/1534 (96%) received early antiviral treatment; 871 (57%) on the day of admission, 470 (31%) within one day of admission, and 128 (8%) within two days of admission. Among 445 people with pneumonia, 418 (94%) received early antiviral treatment and among 1,089 people without pneumonia 1,051 (96%) received early antiviral treatment (p = 0.02).

### Table 2: Sterile site bacterial coinfections among adults hospitalized with laboratory-confirmed influenza with and without pneumonia, Emerging Infections Program, 2005–2008 (n = 129)

| Pathogen                  | Patients with pneumonia n = 61; no. (%) | Patients without pneumonia n = 68; no. (%) |
|---------------------------|-----------------------------------------|-------------------------------------------|
| Streptococcus pneumoniae | 17 (28)                                 | 6 (9)                                     |
| Group A streptococcus    | 4 (7)                                   | 3 (4)                                     |
| Haemophilus influenzae    | 1 (2)                                   | 0                                         |
| Neisseria meningitidis    | 1 (2)                                   | 0                                         |
| Staphylococcus aureus     | 28 (46)                                 | 30 (44)                                   |
| MRSA                      | 15                                      | 14                                        |
| MSSA                      | 10                                      | 16                                        |
| Unknown                   | 3 (5)                                   | 0                                         |
| Gram negative rodsb       | 3 (5)                                   | 10 (15)                                   |
| Other streptococci        | 4 (7)                                   | 8 (12)                                    |
| Other pathogensd          | 2 (3)                                   | 5 (7)                                     |
| Unknown pathogens         | 1 (2)                                   | 6 (9)                                     |

Information on the presence of select bacterial infections was available only for patients who had a positive culture. 
aSterile site infections included the following: 118 (91%) obtained from blood; 3 (2%) obtained from CSF; 4 (3%) obtained from pleural fluid; 4 (3%) obtained from biopsy tissue.
bGram negative rods include: Escherichia coli, Acinetobacter baumannii, Enterobacter cloacae, Klebsiella pneumoniae, Proteus mirabilis and Pseudomonas aeruginosa.
cOther streptococcus species include: agalactiae, group G streptococcus, oralis, mitis, parasanguinis, salivarus, viridians group streptococci.
dOther pathogens include: Aerococcus viridans, Enterococcus faecium, Propionibacterium acnes, Clostridium perfringens, Corynebacterium striatum, Staphylococcus hominis.

### Table 3: Clinical course and outcomes among adults hospitalized with laboratory-confirmed influenza with and without pneumonia, Emerging Infections Program, 2005–2008 (n = 4765)

| Outcome             | Patients with pneumonia n = 1392; no. (%) | Patients without pneumonia n = 3373; no. (%) | Unadjusted odds ratio (95 % CI) | Adjusted odds ratioa (95 % CI) |
|---------------------|-------------------------------------------|---------------------------------------------|--------------------------------|--------------------------------|
| Length of stay >7 days | 414 (30)                                | 408 (12)                                   | 3.06 (2.62–3.57)              | 2.99 (2.54–3.53)              |
| Intensive Care Unit | 370 (27)                                 | 329 (10)                                   | 3.34 (2.83–3.94)              | 3.62 (3.04–4.32)              |
| Mechanical ventilation | 254 (18)                               | 162 (5)                                    | 4.38 (3.56–5.39)              | 4.79 (3.82–6.01)              |
| Death               | 120 (9)                                  | 55 (2)                                     | 5.69 (4.11–7.88)              | 6.06 (4.21–8.71)              |

aEach outcome is adjusted for age, nursing home residence, the presence of underlying medical conditions, and days from symptom onset to hospital admission.
when influenza viruses are circulating [2] and should be diagnosed and treated promptly. Influenza vaccination is the most effective method to prevent influenza and its complications, and older adults, residents of nursing homes and other long-term-care facilities, and adults with underlying medical conditions should be considered high priority groups for receipt of annual influenza vaccination [15].

Similar to earlier studies conducted during periods of seasonal influenza virus circulation, patients with pneumonia in this study were more likely to have underlying medical conditions including chronic lung disease and heart disease [6, 7]. An unexpected finding was that patients with asthma in our analysis were less likely to have a diagnosis of pneumonia than patients without pneumonia. Our study results contrast with EIP surveillance data in hospitalized children <18 years of age which has shown that children with influenza-associated pneumonia were more likely to have asthma than those without pneumonia [16]. Studies of the association between asthma and seasonal influenza-associated pneumonia among adults are lacking. A possible explanation for our finding is that respiratory distress caused by influenza-associated asthma exacerbation provided an alternate reason for hospitalization in adult patients in the absence of pneumonia. Biases in hospital admission practices based on the presence of underlying conditions may have also contributed to admission of asthmatic patients with a less severe respiratory presentation compared to patients without underlying medical conditions.

Invasive bacterial infections, especially due to S. aureus and S. pneumoniae, were observed among patients with influenza-associated pneumonia in this study as well as other studies conducted during inter-pandemic [7] and pandemic periods [17]. Among patients with pneumonia, S. aureus was the most common organism cultured from specimens collected from sterile sites. Influenza virus and S. aureus co-infections are increasing [18–20] and have been associated with particularly severe cases of community-acquired pneumonia during periods of seasonal influenza virus circulation [21]. In patients hospitalized with influenza, sterile site cultures should be collected as early as possible for detection of bacterial infections.

### Table 4
Factors associated with poor outcomes among adults hospitalized with laboratory-confirmed influenza and pneumonia, Emerging Infections Program, 2005–2008 (n = 1392)

| Characteristic | Patients without poor outcomes a | Patients with poor outcomes a | Unadjusted odds ratio (95% CI) | Adjusted odds ratio b (95% CI) |
|---------------|---------------------------------|------------------------------|-----------------------------|-------------------------------|
| Age*          |                                 |                              |                             |                               |
| ≥75 years     | 472 (50)                        | 191 (43)                     | 0.8 (0.6–0.9)               | 0.7 (0.5–0.8)                |
| <75 years     | 478 (50)                        | 251 (57)                     | Ref                         |                               |
| Sex           |                                 |                              |                             |                               |
| Male          | 452 (48)                        | 208 (47)                     | 1.0 (0.8–1.2)               |                               |
| Female        | 498 (52)                        | 234 (53)                     | Ref                         |                               |
| Race/Ethnicity|                                 |                              |                             |                               |
| White, Non-Hispanic | 603 (64)                  | 297 (67)                     | 1.1 (0.8–1.4)               |                               |
| Other c       | 219 (23)                        | 100 (23)                     | Ref                         |                               |
| Unknown       | 128 (13)                        | 46 (10)                      | 0.8 (0.5–1.2)               |                               |
| Virus Type    |                                 |                              |                             |                               |
| Influenza A   | 700 (74)                        | 237 (76)                     | 1.3 (1.0–1.7)               |                               |
| Influenza B   | 216 (23)                        | 82 (19)                      | Ref                         |                               |
| Unknown       | 34 (4)                          | 23 (5)                       | 1.8 (1.0–3.2)               |                               |
| Nursing Home Resident* | 139 (15)                  | 89 (20)                      | 1.5 (1.1–2.0)               | 1.6 (1.2–2.2)                |
| Underlying Conditions* | 784 (83)                   | 395 (90)                     | 1.8 (1.3–2.6)               |                               |
| Chronic Lung Disease* | 250 (26)                  | 167 (38)                     | 1.7 (1.3–2.2)               | 1.6 (1.2–2.0)                |
| Cardiovascular Disease* | 413 (44)                 | 239 (54)                     | 1.5 (1.2–1.9)               | 1.4 (1.1–1.8)                |
| Chronic Metabolic Disease* | 298 (31)                | 183 (41)                     | 1.5 (1.2–1.9)               | 1.3 (1.0–1.7)                |
| Renal Disease* | 123 (13)                        | 93 (21)                      | 1.8 (1.3–2.4)               | 1.5 (1.1–2.0)                |
| Immunosuppression* | 109 (11)                       | 77 (17)                      | 1.6 (1.2–2.2)               | 1.5 (1.1–2.1)                |

*aP-value for bivariate association < 0.05

*bPoor outcome defined as ICU admission, need for mechanical ventilation or death

*cVariables included in adjusted model included age, nursing home residence, chronic lung disease, cardiovascular disease, chronic metabolic disease, renal disease and immunosuppression

\*Other Race/Ethnicities include Black, Hispanic, Asian, Pacific Islander, American Indian, Alaskan Indian, and multi-race
infection and empiric antimicrobial coverage of the most likely bacterial organisms should be considered [22, 23]. In our study, S. pneumoniae was the only organism to be cultured from a sterile site more frequently in patients with pneumonia that in patients without pneumonia. In addition to annual influenza vaccination, pneumococcal vaccine should be administered to adults aged 18–64 years with certain health conditions and to all persons aged ≥65 years [24].

Patients with influenza-associated pneumonia had a significantly increased risk of ICU admission, respiratory failure requiring mechanical ventilation, and death compared with patients without pneumonia. While case series conducted during the 2009 H1N1 pandemic demonstrated elevated frequencies of ICU admission (36–58 %) [25, 26], respiratory failure (10–67 %) [25, 27] and death (7–39 %) [25–28] among patients hospitalized with pandemic H1N1 influenza-associated pneumonia, limited data is available on the association between seasonal influenza-associated pneumonia and severe outcomes. In a small case series of patients hospitalized with influenza during the 1999–2000 season, 10 (58 %) of 17 patients with pneumonia were admitted to the ICU and 5 (29 %) patients died [7]. In another observational study of patients hospitalized with influenza during 1999–2003, 16 (16 %) of 101 patients with acute pulmonary disease were admitted to the ICU, 10 (10 %) required mechanical ventilation, and 6 (6 %) died [6]. While pneumonia and acute respiratory distress syndrome (ARDS) have been shown to account for a majority of deaths associated with influenza virus infection during pandemics [28], data is limited on the association between seasonal influenza virus infection and death from pneumonia or ARDS.

In our analysis, only 55 % of patients hospitalized with laboratory-confirmed influenza received influenza antiviral treatment. When limiting the analysis to patients who presented to the hospital within 2 days of symptom onset, only 66 % of all patients received antiviral treatment; the majority received antiviral treatment within 1 day of hospital admission. Multiple studies have found early antiviral treatment to be associated with a reduction in serious influenza-associated outcomes including the development of lower respiratory tract infections [29–31]. The Advisory Committee on Immunization Practices recommends empiric influenza antiviral treatment for all adults with suspected or confirmed influenza who are hospitalized, have severe, complicated, or progressive illness, or are at high risk for influenza-associated complications [32].

Several limitations to this study should be noted. Influenza diagnostic testing was performed at the discretion of treating clinicians at the various EIP hospital sites. While all hospitalized patients who tested positive for influenza were included in surveillance, data is unavailable for hospitalized patients who tested negative for influenza or who were not tested. Thus, these data may not be representative of all individuals hospitalized with influenza who may not have been tested or have laboratory confirmation of influenza virus infection. It is possible that patients included in surveillance were more likely to be tested for influenza because they were more severely ill; thus a higher proportion of patients exhibiting pneumonia-like symptoms may have been tested for influenza than patients presenting with other symptoms. Furthermore, in our analysis, patients with pneumonia were compared to patients without pneumonia but with a wide array of other diagnoses. Clinical influenza testing practices based on patient diagnoses at presentation may have biased our findings. In one study conducted in an emergency department in Australia, patients presenting with fever and respiratory diagnoses were more likely to be tested for influenza than patients presenting with cardiac or other diagnoses [33]. This study assessed pneumonia specifically among adults hospitalized with laboratory-confirmed influenza, including those whose influenza virus infection preceded hospitalization by more than a few days, and findings are not generalizable to all hospitalized individuals with pneumonia of other etiologies or to non-hospitalized individuals.

Several of the findings in this study may have been biased by hospital admission practices. For example, the finding of an inverse association between asthma and pneumonia may have been due to more aggressive admission of asthmatic patients presenting with respiratory distress despite the absence of pneumonia, compared with patients without asthma. Biases related to hospital admission practices were likely reduced by including patients from multiple hospital sites in geographically diverse settings. For certain underlying conditions such as chronic lung disease and cardiovascular disease, disease type and severity were not captured by the case report form. Availability of detailed data on type and severity of underlying conditions may have helped to better identify factors more strongly associated with development of influenza-associated pneumonia.

Radiographic data were based on review of CXR reports by surveillance officers and not by actual review of radiographs by a designated study radiologist. As a result, some individuals may have been misclassified as having pneumonia based upon a report of infiltrates or opacities, when in fact they had a more chronic pulmonary condition or a transient episode of pulmonary edema or effusion. There was no requirement regarding timing of identification of radiologic abnormalities during the hospitalization, and the timing of chest radiographs during the hospitalization was not collected as part of EIP surveillance; thus, some misclassification of community-acquired pneumonia versus nosocomial pneumonia may have occurred. Using ICD-9-CM code data may also
have led to misclassification if a diagnosis code was listed incorrectly or not listed at all. A joint case definition for pneumonia which used both radiographic data and discharge diagnosis data from ICD-9-CM codes or discharge summaries was utilized to minimize some of these biases. Bacterial culture data was only available for patients with a positive culture result rather than for all specimens spent, thus limiting the interpretation of the culture data.

Conclusions
Pneumonia is common among adults hospitalized with seasonal influenza virus infection. Among patients hospitalized with influenza, older adults and those with underlying medical conditions may be more likely to have pneumonia. Further studies are needed to explore the association between influenza-associated pneumonia and asthma in adults. Influenza-associated pneumonia can lead to severe outcomes including ICU admission and death. Adults hospitalized with suspected or confirmed influenza should receive early antiviral therapy, prompt evaluation for pneumonia, and appropriate management upon diagnosis of pneumonia.

Additional file

Additional file 1: Table S1. The 10 most frequent ICD-9 diagnosis categories based on first ICD-9 code listed among adults hospitalized with laboratory-confirmed influenza with and without pneumonia (n=4117).

Abbreviations
CXR: Chest radiograph; AOR: Adjusted odds ratio; EIP: Emerging infections program; ICD-9-CM: International classification of diseases; CDC: Centers for Disease Control and Prevention; IRB: Institutional Review Board; ICU: Intensive care unit; S. aureus: Staphylococcus aureus; S. pneumoniae: Streptococcus pneumoniae.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
SG: contributed to conception and design of study, analysis of data and interpretation of results, and drafting of the manuscript; SJ: contributed to conception and design of study, interpretation of data, and critical review of the manuscript; FD: contributed to conception and design of study, analysis of data, and critical review of the manuscript; MJ: contributed to conception and design of study, interpretation of data, and critical review of the manuscript; AP: contributed to analysis and cleaning of data, interpretation of results, and critical review of the manuscript; AR: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; TK: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; KG: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; MZ: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; NG: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; LS: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; AT: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; GH: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; SM: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; WS: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; KS: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; RW: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; MJ: contributed to conception and design of study, interpretation of data, and critical review of the manuscript; RP: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; PM: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; LF: contributed to conception and design of study, acquisition of data, interpretation of results, and critical review of the manuscript; DJ: contributed to conception and design of study, interpretation of data, and critical review and revision of manuscript; All authors read and approved the final manuscript.

Acknowledgements
We wish to thank the following individuals for their help with surveillance efforts: Deborah Aragon at the Colorado Department of Public Health and Environment, Denver, Colorado; Darcy Fazio at the Connecticut Emerging Infections Program, Yale University, New Haven, CT; Kyle Openo; Suzanne Seger, Olivia Almendares, Norisse Tellman, Megan Pearson, Wendy Baughman, Jaimie Cope, and Ariana Reeves at the Georgia Emerging Infections Program—a collaboration between Georgia Division of Public Health, Emory University and the Atlanta Veterans Administration Medical Center, Atlanta, GA; Maya Monroe at the Maryland Department of Health and Mental Hygiene, Baltimore, MD; Elisabeth Vaeth, Johns Hopkins School of Public Health, Baltimore, MD; Brenda Jewell, Lori Triden, and Team Influenza at the Minnesota Department of Health, St. Paul, MN; Kathy Angeles, MPH, Lisa Butler, MPH, Sarah Khanlian, MPH, and Robert Mannmannat, MPH at the New Mexico Emerging Infections Program, a collaboration between the New Mexico Department of Health, Santa Fe, NM and the University of New Mexico, Albuquerque; NK; Kevin Malloy, and Nancy Spina, MPH at the New York State Health Department, Albany, NY; Ruth Bellow RN, MPH at the Center for Community Health and Dentistry, Rochester, NY; Meredith Vandermeer, MPH at the Oregon Public Health Division, Portland, OR; Brenda G. Barnes, RN, Terri L. McMillin, Lynne Fenner, RN, Karen A. Leib, RN, David Kirschke, MD at Vanderbilt University School of Medicine, Nashville, TN.

Disclaimer
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Received: 21 January 2015 Accepted: 29 June 2015
Published online: 26 August 2015

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