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How deadly is seasonal influenza-associated pneumonia? The German Competence Network for Community-Acquired Pneumonia

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ABSTRACT: The emergence of new influenza virus subtypes has rekindled the interest in the clinical course and outcome of patients with influenza-associated pneumonia.

Based on prospective data from 5,032 patients with community-acquired pneumonia (CAP) included in the German Competence Network for Community-Acquired Pneumonia (CAPNETZ), we studied the incidence, clinical characteristics and outcome of patients with influenza-associated CAP and compared these findings with patients without influenza. Diagnosis relied on a positive PCR for influenza in throat washings.

160 patients with influenza-associated CAP were identified (3.2% of total population, 12% of those with defined aetiology). 34 (21%) patients with seasonal influenza had a concomitant pathogen (mostly *Streptococcus pneumoniae*). Patients with influenza-associated CAP were significantly older, had been vaccinated less often and had preceding antibacterial treatment less often. 30-day mortality was low (4.4%) and not different to that of patients with pneumonia caused by bacterial (6.2%) or viral (other than influenza) pathogens (4%). Patients with influenza plus a bacterial pathogen (mixed influenza-associated pneumonia) had a higher mortality than those with pure influenza-associated pneumonia (9% *versus* 3.2%).

Mortality was higher in patients with mixed compared with pure influenza-associated pneumonia. However, we could not observe any excess mortality in patients with influenza-associated pneumonia.

KEYWORDS: Community-acquired pneumonia, seasonal influenza

Influenza infection is generally assumed to be responsible for a considerable excess mortality, particularly in elderly and comorbid patients, at least in seasons with high influenza activity [1]. Most recently, from 1976–1977 through to 2002–2003 seasons, an annual average of >25,000 influenza-associated respiratory and circulatory deaths (9.9 deaths per 100,000) have been calculated in the USA [2]. Similarly, average influenza-associated excess mortality in Germany is estimated to be around 16 per 100,000 inhabitants [3]. Corresponding vaccination policies are based on this perception, and in fact, several studies have shown considerable decreases in influenza mortality in vaccinated subjects [1], particularly in high-risk patients [4]. Moreover, the Infectious Disease Society of America/American Thoracic Society guidelines recommend specific anti-viral treatment in patients with evidence for influenza aetiology in community-acquired pneumonia (CAP) [5]. Together with allusions to the Spanish flu disaster, influenza might be considered as a major killer in respiratory tract infections.

In sharp contrast to this, there are only very few reports addressing influenza in CAP and reported mortality rates do not seem to support excess mortality in the presence of influenza-associated pneumonia [6–8]. It has to be realised that the notion of influenza causing excess mortality is based on surveillance data and statistical models to estimate the burden of disease [9]. However, these data only show associations and not causal relations of excess mortality. In fact, excess mortality might be caused by reasons other than respiratory diseases.

Therefore, we studied the incidence, initial severity, clinical presentation and outcomes of

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patients with influenza-associated pneumonia within the large German Competence Network for Community-Acquired Pneumonia (CAPNETZ) cohort in order to assess the contribution of influenza-associated pneumonia to pneumonia mortality. We compared this data with the general population without influenza-associated pneumonia. We also investigated the bearing of secondary bacterial infection.

MATERIALS AND METHODS

Patient population

A detailed description of the CAPNETZ methodology is given elsewhere [10]. The study was approved by the ethical review board and all patients included gave informed consent.

Data collection

In this prospective study, all demographic, clinical and diagnostic data of the patients were recorded using standardised web-based data sheets created by 2mt® (Ulm, Germany). The study period comprised 58 months starting on June 1, 2002 and ending April 30, 2007, thus including five autumn–winter seasons.

Microbiological and virological processing and examination

Methods applied were as described previously [10, 11]. In short, sputum and/or other respiratory secretions were immediately processed in the participating local microbiological laboratories according to the German Quality Standards in Clinical Microbiology and Infectious Diseases (MIQ).

All respiratory specimens and blood cultures if available were immediately processed in the local microbiology laboratories of the participating clinical centres. Gram-staining and culture were performed for all respiratory samples. Validated sputum, blood culture samples, pleural fluid and undiluted and serially diluted tracheobronchial aspirates, PBS and bronchoalveolar lavage fluid (BALF) samples were plated on blood-sheep agar, CDC agar and chocolate agar. Undiluted PBS and BALF samples were also cultured on charcoal–yeast extract agar if *Legionella* spp. was suspected. Urine was tested for the presence of *Streptococcus pneumoniae* and *Legionella* spp. antigen. Standardised throat washings of all patients using sterile 0.9% NaCl were sent immediately to the German reference centre for influenza (Berlin, Germany). PCR for influenza A and B was performed in the throat washings of all 5,032 patients.

RNA extraction and cDNA synthesis

Viral RNA was extracted using a commercial kit (QIAamp Viral RNA Kit; Qiagen, Hilden, Germany). Briefly, 150 μL of clinical specimen (throat swab, nasal swab or gargle) were mixed with an equal volume of lysis buffer AL, heated for 15 min at 70°C and applied to a spin column. Unbound material was removed by several washing steps and the RNA eluted using 50 μL of RNAse-free water. The complementary DNA (cDNA) synthesis was carried out at 37°C for 1 h using 10 μL of RNA, 100 U of murine leukaemia virus reverse transcriptase (Gibco BRL, Life Technologies GmbH, Karlsruhe, Germany), 10 mM dithiothreitol, 150 μM (each) dATP, dCTP, dGTP and dTTP (20 U RNAsin (Promega, Mannheim, Germany)) and 0.25 μM random hexamer primers.

PCR and sequence analysis

The TaqMan-PCR was carried out in a 96-well flat-bottomed microtitre plate format (PerkinElmer, Rodgau, Germany). The PCR mix was made up to a volume of 25 μL, containing 5 μL of cDNA, 50 mM Tris-hydrochloride, pH 9, 50 mM KCl, 4 mM $MgCl_2$, 0.2 mM (each) dATP, dCTP, dGTP dUTP, 0.5 units uracil-*N*-glycosylase (Gibco BRL, Life Technologies), 1.25 units Taq DNA polymerase (InViTek, Berlin, Germany), 0.25 μM each of the forward and reverse primer, 0.2 μM of a fluorescence-labelled probe and 1 μM ROX as passive reference. Virus identification and further subtyping was carried out as described previously [11] with some modifications (primer and probe sequences available on request). The cDNA was amplified by 45 two-step cycles (1 min 92°C and 1 min 60°C). The amplification in the TaqMan-PCR was followed on the ABI Prism™ 7700 Sequence Detector (Applied Biosystems, Foster City, CA, USA). The plate was scanned at 518 nm (carboxyfluorescein) and 582 nm (carboxytetramethylrhodamine). Data acquisition analysis was handled by using the Fluorescence Data Manager (Perkin Elmer) and Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheets. ROX was used as a passive reference to which the reporter dye signal was normalised (R_n) during data analysis.

Definitions

We defined patients with PCR-positive influenza respiratory samples as ''influenza-associated pneumonia'' as we ignore the exact contribution of influenza virus infection as an aetiological pathogen in CAP. In particular, we cannot exclude the presence of bacterial co-pathogens that we might have missed.

Comparisons

We compared clinical characteristics, severity at admission and outcomes of: 1) patients with influenza-associated pneumonia and those without; and 2) pure influenza-associated pneumonia and influenza pneumonia with bacterial co-infection (mixed influenza-associated pneumonia).

Statistical analysis

Comparisons between groups were performed by means of the Chi-squared test for categorical variables or Fisher's exact test in the case of small expected frequencies and ANOVA for continuous variables including multiple comparisons. All analyses were performed with SPSS software (SPSS 10.0; SPSS, Inc., Chicago, IL, USA). All tests of significance were two-tailed and α was set at 0.05.

RESULTS

General characteristics of study population

Overall, 5,032 patients with CAP from 12 clinical centres throughout Germany were included in our analysis from 2002 to 2007. The 2,781 male and 2,251 female patients had a mean age of 60 ± 18 yrs. 65% (n=3,274) of the patients were hospitalised when first contacted for participation in CAPNETZ. 307 (6%) patients were nursing home residents. 31% of the patients were smokers. Severity scores as assessed using the confusion, respiratory frequency and blood pressure in those aged $\geqslant$65 yrs (CRB-65) index were available for 90% of the patients and distributed as follows: CRB-65 0 (37%), 1 (38%), 2 (13%), 3 (3%) and 4 (0.3%), respectively. CRB-65 status was not available for 8.7% of the patients. 134 (3%) patients required

mechanical ventilation. 238 (4.7%) patients died within 30 days after diagnosis and 180-day mortality in all patients was 8.8% (445 patients).

General microbial patterns

In 1,337 (27%) patients a definite pathogen causing CAP could be identified. 124 (2.5%) patients carried more than one pathogen.

S. pneumoniae was identified as the predominant respiratory pathogen in the study population, followed by *Mycoplasma pneumoniae*. In <5% of the patients *Legionella* spp., *Haemophilus influenzae* and *Staphylococcus aureus* were identified. Even less frequent were *Moraxella catarrhalis* and *Chlamydophila pneumoniae*.

Overall, 160 patients (3.2% of total population, 12% of those with defined aetiology) had CAP associated with seasonal influenza A (134 patients) and B (26 patients), respectively. Incidence was higher in autumn–winter seasons (4.7% and 16.2%, respectively).

124 of these patients were classified as pure influenza-associated CAP, 34 (21%) patients had influenza and a concomitant pathogen (mixed influenza-associated pneumonia), predominantly S. *pneumoniae* (n=17) (table 1).

In an additional 73 patients, respiratory syncytial virus (RSV) (29 patients), enterovirus (28 patients) and adenovirus (16 patients) were detected.

Ambulatory and hospitalised patients

3,274 patients were hospitalised; 102 (3%) of these had influenza-associated pneumonia. 78 (62%) of the patients with pure influenza-associated pneumonia and 24 (71%) of the patients with mixed influenza-associated pneumonia had been admitted to a hospital. Data concerning intensive care unit (ICU) admission of the patients were scarce and thus not included in the analysis.

Seasonal variability of seasonal influenza

Seasonal variability is reflected in figure 1. As expected, there were seasonal peaks of incidence during January and March each year, with considerable variations in numbers within years. In accordance with national surveillance data, 2003, 2005 and 2007 were years with high influenza activity, whereas 2004 and 2006 were relatively modest [12].

TABLE 1 Concomitant pathogens of influenza-associated pneumonia

Bacterial pathogen	Patients n
Streptococcus pneumoniae	17#
Haemophilus influenzae	7
Mycoplasma pneumoniae	5
Staphylococcus aureus	2
Legionella spp.	2
Klebsiella oxytoca	1
Serratia marcescens	1

#: one patient had two co-pathogens.

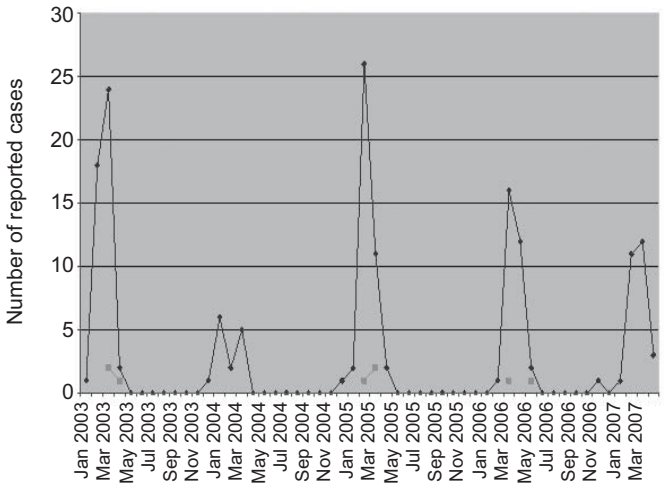

FIGURE 1. Seasonal distribution of influenza-associated pneumonia throughout five autumn–winter seasons. ◆: number of cases; ■: number of deaths.

Vaccination status

26% of patients with influenza-associated pneumonia had received seasonal influenza vaccination and 9% pneumococcal vaccination. These rates were not significantly different from the comparator groups.

Clinical characteristics of influenza-associated CAP

Patients with pure influenza-associated pneumonia were significantly older, had received significantly less preceding antibiotic therapies and had significantly lower leukocyte counts. They had been less frequently vaccinated (26% *versus* 33%) (table 2).

Patients with mixed viral pneumonia had no distinguishing features when compared with the study population without influenza. If comparing patients with pure influenza-associated pneumonia to patients with bacterial co-pathogens, patients with bacterial co-pathogens were significantly younger and had significantly higher inflammatory markers (table 2).

Outcome of influenza-associated CAP

Anti-viral therapy was not a specific query on the data sheet but could be documented voluntarily. Thus, no data regarding anti-viral treatment were analysed.

Nine patients had a high CRB-65 score of 3 (seven patients) or 4 (two patients) when admitted and four patients received mechanical ventilation.

Seven patients with influenza-associated pneumonia died (4.2% of patients with influenza). Of these, three had a concomitant pathogen, including *S. pneumoniae* (n=2) and *H. influenzae* (n=1). Mortality was three out of 34 (9%) if a co-pathogen was present, as compared to four out of 126 (3.2%) in the case of influenza being the only pathogen (p=0.166). The clinical characteristics of these patients are listed in table 3. Lethal outcome was associated with pneumonia severity at admission (CRB-65 p< 0.0001), smoking habits (p=0.02) and older age (p=0.068).

TABLE 2 Clinical characteristics of patients with no influenza and influenza-associated pneumonia

Variable	No influenza	p-values[#]	Pure influenza-associated pneumonia	p-values[¶]	Mixed influenza-associated pneumonia	Influenza-associated pneumonia (all)
Patients n	4872		126		34	160
Males %	55	NS	52	NS	53	53
Median age yrs %	62.5	0.023	68	0.052	58	66.5
>65 yrs	46		58		44	55
>85 yrs	7		9		6	8
CRB-65 score %						
0/1	74		78		77	82
2	13		10		15	11
3	3		4		6	4
4	0.3		2		0	1.3
Hospitalised %	65	NS	62	NS	71	64
Nursing home resident %	6	NS	6	NS	3	5
PEG %	2	NS	2	NS	3	1
Diabetes %	16	NS	20	NS	6	19
Congestive heart failure %	18	NS	21	NS	12	19
Other chronic cardiac condition %	27	NS	29	NS	21	28
Cerebrovascular disease %	10	NS	12	NS	9	11
Other chronic neurological disorder %	6	NS	6	NS	3	5
COPD %	35	NS	33	NS	41	34
Malignancy %	9	NS	6	NS	6	6
Smoker %	31	NS	27	NS	29	28
Preceding antibiotic therapy %	26	0.008	17	NS	27	19
Vaccinated influenza %	33[+]	0.067	26[§]	NS	24[ƒ]	26
Vaccinated pneumococci %	11[##]	NS	10[¶¶]	NS	6[++]	9
CRP median	81	NS	55	0.001	135	67
Leukocytes median	11.3	0.000	8.6	0.001	11.2	9 100
Mechanical ventilation %	3	NS	3	NS	0	2.5
30-day mortality n (%)	231 (4.7)	NS	4 (3.2)	NS	3 (8.8)	7 (4.4)

Influenza-associated pneumonia consists of pure influenza-associated pneumonia and influenza-associated pneumonia plus bacterial co-pathogen (mixed influenza-associated pneumonia (MV)). CRB-65: confusion, respiratory frequency and blood pressure in those aged ⩾65 yrs; PEG: percutaneous endoscopic gastrostomy; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; NS: nonsignificant. [#]: no influenza *versus* pure influenza-associated pneumonia; [¶]: pure influenza-associated pneumonia *versus* MV; [+]: information concerning influenza vaccination available in 4,567 (94%) patients; [§]: information concerning influenza vaccination available in 122 (97%) patients; [ƒ]: information concerning influenza vaccination available in 32 (94%) patients; [##]: information concerning pneumococcal vaccination available in 4,532 (93%) patients; [¶¶]: information concerning pneumococcal vaccination available in 121 (96%) patients; [++]: information concerning pneumococcal vaccination available in 31 (91%) patients.

DISCUSSION

The main findings of this study are the following: 1) influenza was an important pathogen associated with CAP in our population, with an incidence of 160 cases (3.2% of the total population; 12% of patients with defined aetiology); 2) related to autumn–winter seasons, the incidence was even higher (4.7% of the total population and 16.2% of patients with defined aetiology); 3) influenza-associated pneumonia was usually mild, only few patients required ventilatory support, 30-day mortality was low (4.2%) and not different to that of patients with pneumonia caused by bacterial (6.2%) or viral pathogens other than influenza (4%), respectively; and 4) concomitant bacterial pneumonia was observed in 21% of patients with influenza and there was a trend for higher mortality in patients with co-infection.

The true incidence and mortality of seasonal influenza-associated CAP is difficult to assess since there is a year-to-year variability in activity of influenza and many previous studies relied on serology with its inherent severe selection bias (only patients with paired serology are detected). Accordingly, aetiological studies in general populations have reported varying incidences ranging from around 6% to 19% depending on the study duration and the methodology used [13–15]. Only very few data are available for severe CAP requiring ICU admission. In 16 studies, viral CAP was reported

TABLE 3 Individual records of patients who died with influenza-associated pneumonia

Patient	Sex	Age yrs	BMI	CRB-65	Hospitalised	Concomitant diseases	Smoker	Pack-yrs	Concomitant pathogen	Influenza vaccination	Antibiotic treatment	CRP mg·L^{-1}	Leukocytes µL	Time of death day	Cause of death
1	F	66	21	2	Yes	None	Yes	42	*S. pneumoniae*	No	Ceph III + macrolide	226	6.3	6	Pneumonia
2	M	89	20	3	Yes	CHF COPD	Yes	70	No respiratory material available	Yes	Ceph II + macrolide	259	12.8	4	Pneumonia
3	F	74	15	2	Yes	CHF COPD	Yes	50	*H. influenzae*	No	Ceph II	324	20.3	30	Other
4	M	86	NA	4	Yes	CHF	NA	NA	None	NA	Macrolide	36	8.9	25	Other
5	M	84	25	1	Yes	COPD	Yes	NA	*S. pneumoniae*	No	Ceph II	231	14.6	9	Pneumonia
6	M	60	28	1	No	None	No	80	None	No	FQ	320		2	Unknown
7	M	67	23	3	Yes	COPD neurological disease	NA	NA	No respiratory material available	NA	FQ	28	1.6	23	Pneumonia

None of the patients had received antibiotic treatment before study participation. BMI: body mass index; CRB-65: confusion, respiratory frequency and blood pressure in those aged ⩾65 yrs; CRP: C-reactive protein; F: female; M: male; ceph III: 3rd generation cephalosporin; *S. pneumoniae*: *Streptococcus pneumoniae*; *H. influenzae*: *Haemophilus influenzae*; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; NA: information not avalaible; FQ: fluoroquinolone.

in 1–5%, with influenza being the most common, but it is impossible to retrieve valid data of mortality from these reports [16]. In a study addressing elderly patients with severe CAP, the incidence of influenza was found to be trivial, however, the bias of serology-based detection has to be taken into account [17]. As far as reported, mortality was always very low.

In a recent study primarily focused on comparing RSV infections with influenza infections, healthy elderly patients (aged ⩾65 yrs), high-risk adults (those with chronic heart and lung disease) and hospitalised patients with acute cardiopulmonary illnesses were included using cultures and PCR of nasopharyngeal swabs as well as serology during four consecutive winters. Influenza was found in 5.1%, 5.9% and 12.2%. None of the 44 healthy and high-risk adults with influenza died, as compared with 10 out of 144 (7%) of the hospitalised group with influenza [18]. Bacterial infection was indentified in 10% of hospitalised patients with influenza [19].

To our knowledge, only three recent studies have exclusively addressed viral CAP. Based on paired serology, DE ROUX *et al.* [6] found influenza in 11.5% of patients with CAP in a 5-yr monocentric study. Due to the methodology applied, mortality could not be assessed. JOHNSTONE *et al.* [7] investigated viral CAP during a 3-yr period in five hospitals. Influenza diagnosis was based on nucleic acid amplification tests and direct fluorescent antigen assay testing of nasopharyngeal swabs. 19% had viral aetiology, including 4% with a mixed aetiology. Influenza was found in 3.6% of cases. Mortality rate of viral CAP was low (3%). Finally, JENNINGS *et al.* [8] investigated viral CAP in a 1-yr monocentric study based on the detection of respiratory viruses in nasopharyngeal swabs by immunofluorescence, culture and PCR. They found influenza in 9.5% of cases, with a mortality of 7%.

Since the classical descriptions of influenza pneumonia from the 1957 and 1968 epidemics [20–22], we are aware only of one single study assessing specifically seasonal influenza pneumonia [23]. In this study comprising 35 patients who tested positive for influenza by direct enzyme immunoassay during a 5-yr period, 17 patients had pneumonia. Of these, 10 (58.8%) had to be admitted at the ICU and mortality was high (n=5, 29%), despite anti-viral treatment in 15 out of 17 patients. Bacterial co-infection was identified in five patients and *S. aureus* was present in all of them [23]. However, the very low number of cases per year makes selection bias quite probable.

A recent review stated that fatal cases of influenza-associated viral pneumonia considered to be primary continue to be identified, but that their incidence appears to be low even in pandemic peaks [24]. In line with this notion, we found an incidence of 3.2% and 12% related to patients with a defined aetiology. Of note, the rates varied significantly from year-to-year and had a high seasonal variability. Mortality was 5%, similar to that of two most recent reports [7, 8] and not significantly different from that of the general population of CAP and patients with bacterial CAP.

It has been argued that the majority of influenza deaths are related to secondary bacterial pneumonia [24]. It is quite difficult to assess the true incidence of dual bacterial and influenza aetiology in patients with CAP, since both are missed by current investigational methodology in a considerable

amount of cases. In our series, such dual aetiology was present in 21% of influenza cases, and this may be an underestimate. As a matter of fact, we found only a nonsignificant slightly higher mortality rate of patients with bacterial co-pathogens.

In our study, *S. pneumoniae* and not *S. aureus* was found to be the most frequent bacterial co-pathogen, followed by *H. influenzae*. This is in accordance with a recent study specifically addressing mixed aetiologies in patients with CAP [25]. Variations in primarily involved bacterial pathogens according to antigenic subtypes may be explained by differences in pathogenicity factors [26, 27]. In any case, initial empirical antimicrobial treatment has to be administered to all patients with influenza-associated CAP, regardless of concurrent or subsequent detection of bacterial pathogens. An initial antimicrobial treatment covering primarily *S. pneumoniae* as well as *H. influenzae* and *S. aureus* is mandatory. An adequate bacterial coverage seems more important than anti-viral treatment with neuraminidase inhibitors. In fact, there is currently no evidence to recommend anti-viral treatment other than theoretical inference derived from studies of patients with lower respiratory tract infections [28].

Taken together, seasonal influenza-associated pneumonia does not seem to be a particularly deadly condition. Much of the observed excess mortality might be associated with influenza-associated cardiovascular deaths, a notion supported by a reduction in cardiovascular mortality in vaccinated patients [29, 30].

We are not aware of another aetiological study of CAP including such a high number of patients where influenza was systematically investigated using PCR. PCR is more sensitive than virus culture or detection of influenza viruses by immunofluorescence or ELISA. The sensitivity of the PCR assays applied in this study is about 0.1 50% tissue culture infection dose corresponding to 10 genome copies per assay [11]. Validation of the assays did not indicate any problems concerning analytical sensitivity, cross-reactivity or detection capability. Therefore, this study represents a new reference for the estimate of the incidence and mortality of seasonal influenza-associated CAP. However, there are several limitations of our study. As in all studies dealing with the aetiology of CAP the availability of respiratory samples is a problem. If only considering patients with a respiratory sample in addition to the throat washings, 2,076 patients (43% of the study population) would have been included in our analysis. We found that excluding these patients made no significant difference for the individual statements, but might weaken the generalisation and conclusiveness of the study and thus included all patients for whom a PCR for influenza had been performed. Another problem is the low number of patients studied with severe CAP requiring ICU admission. However, available series studying patients with severe CAP requiring ICU admission do not suggest influenza to be an aetiology causing excess mortality [16]. Another limitation is that we have no data on anti-viral treatment of this population; however, since the German guidelines for management of adult CAP do not recommend such treatment, and since the results of viral investigations were not available during the treatment period, it is highly probable that none of the patients received it.

In conclusion, our data do not support excess mortality in influenza-associated pneumonia or in cases of secondary bacterial infection. Mortality of influenza-associated pneumonia may be limited to the excess incidence of influenza-associated pneumonia cases and deaths during autumn–winter seasons. Bacterial co-pathogens that should always be covered primarily include *S. pneumoniae, S. aureus* and *H. influenzae*. Further studies should assess the role of influenza, particularly in patients with severe CAP.

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STATEMENT OF INTEREST

None declared.

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REFERENCES

1 Fiore AE, Shay DK, Broder K, *et al.* Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. www.cdc.gov/mmwr/preview/mmwrhtml/rr58e0724a1.htm Date last accessed: February 17, 2011. Date last updated: July 24, 2009.

2 Thompson WW, Weintraub E, Dhankhar P, *et al.* Estimates of US influenza-associated deaths made using four different methods. *Influenza Other Respi Viruses* 2009; 3: 37–49.

3 Zucs P, Buchholz U, Haas W, *et al.* Influenza associated excess mortality in Germany, 1985-2001. *Emerg Themes Epidemiol* 2005; 2: 6.

4 Hak E, Nordin J, Wei F, *et al.* Influence of high-risk medical conditions on the effectiveness of influenza vaccination among elderly members of 3 large managed-care organizations. *Clin Infect Dis* 2002; 35: 370–377.
5 Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44: Suppl. 2, S27–S72.
6 De Roux A, Marcos MA, Garcia E, *et al.* Viral community-acquired pneumonia in nonimmunocompromised adults. *Chest* 2004; 125: 1343–1351.
7 Johnstone J, Majumdar SR, Fox JD, *et al.* Viral infection in adults hospitalised with community-acquired pneumonia: prevalence, pathogens, and presentation. *Chest* 2008; 134: 1141–1148.
8 Jennings LC, Anderson TP, Beynon KA, *et al.* Incidence and characteristics of viral community-acquired pneumonia in adults. *Thorax* 2008; 63: 42–48.
9 Thompson WW, Comanor L, Shay DK. Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. *J Infect Dis* 2006; 194: Suppl. 2, S82–S91.
10 Welte T, Suttorp N, Marre R. CAPNETZ-community-acquired pneumonia competence network. *Infection* 2004; 32: 234–238.
11 Schweiger B, Zadow I, Heckler R, *et al.* Application of a fluorogenic PCR assay for typing and subtyping of influenza viruses in respiratory samples. *J Clin Microbiol 2000; 38*, 4: 1552–1558.
12 Robert Koch Institute. Association of influenza. www.influenza.rki.de/ Date last accessed: February 17, 2011. Date last updated: February 15, 2011.
13 Ruiz M, Ewig S, Marcos MA, *et al.* Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. *Am J Respir Crit Care Med* 1999; 160: 397–405.
14 Díaz A, Barria P, Niederman M, *et al.* Etiology of community-acquired pneumonia in hospitalized patients in Chile: the increasing prevalence of respiratory viruses among classic pathogens. *Chest* 2007; 131: 779–787.
15 Lim WS, Macfarlane JT, Boswell TC, *et al.* Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. *Thorax* 2001; 56: 296–301.
16 Ewig S, Torres A. Severe community-acquired pneumonia. *Clin Chest Med* 1999; 20: 575–587.
17 El-Solh AA, Sikka P, Ramadan F, *et al.* Etiology of severe pneumonia in the very elderly. *Am J Respir Crit Care Med* 2001; 163: 645–651.
18 Falsey AR, Hennessey PA, Formica MA, *et al.* Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med* 2005; 352: 1749–1759.
19 Falsey AR, Walsh EE. Viral pneumonia in older adults. *Clin Infect Dis* 2006; 42: 518–524.
20 Louria DB, Blumenefeld HL, Ellis JT, *et al.* Studies on influenza in the pandemic of 1957–1958. II. Pulmonary complications of influenza. *J Clin Invest* 1959; 38: 213–265.
21 Lindsay MI Jr, Herrmann EC Jr, Morrow GW Jr, *et al.* Hong Kong influenza: clinical, microbiologic, and pathologic features in 127 cases. *JAMA* 1970; 214: 1825–1832.
22 Martin CM, Kunin CM, Gottlieb LS, *et al.* Asian influenza A in Boston, 1957–1958. II. Severe staphylococcal pneumonia complicating influenza. *Arch Intern Med* 1959; 103: 532–542.
23 Oliveira EC, Marik PE, Colice G. Influenza pneumonia: a descriptive study. *Chest* 2001; 119: 1717–1723.
24 Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *J Infect Dis* 2008; 198: 962–970.
25 de Roux A, Ewig S, García E, *et al.* Mixed community-acquired pneumonia in hospitalised patients. *Eur Respir J* 2006; 27: 795–800.
26 Peltola VT, Murti KG, McCullers JA. Influenza virus neuraminidase contributes to secondary bacterial pneumonia. *J Infect Dis* 2005; 192: 249–257.
27 McAuley JL, Hornung F, Boyd KL, *et al.* Expression of the 1918 influenza A virus PB1-F2 enhances the pathogenesis of viral and secondary bacterial pneumonia. *Cell Host Microbe* 2007; 2: 240–249.
28 Jefferson T, Jones M, Doshi P, *et al.* Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ* 2009; 339: b5106.
29 Nichol KL, Nordin J, Mullooly J, *et al.* Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Engl J Med* 2003; 348: 1322–1332.
30 Gurfinkel EP, Leon de la Fuente R, Mendiz O, *et al.* Flu vaccination in acute coronary syndromes and planned percutaneous coronary interventions (FLUVACS) Study. *Eur Heart J* 2004; 25: 25–31.