How Deadly is Seasonal Influenza Associated Pneumonia?

The German Competence Network for Community-acquired pneumonia (CAPNETZ)

Heike von Baum¹, Brunhilde Schweiger², Tobias Welte³, Reinhard Marre⁴, Norbert Suttorp⁵, Mathias W. R. Pletz³, Santiago Ewig⁶ and the THE CAPNETZ STUDY GROUP

¹ Institute for Medical Microbiology and Hygiene, Ulm University Hospital, Germany
² Nat. Reference Laboratory for Influenza, Robert-Koch-Institut, Berlin, Germany
³ Dept. of Pneumology, Hannover University Hospital, Germany
⁴ Ulm University Hospital, Germany
⁵ Dept. of Infectious Diseases and Pulmonary Medicine, Charité Berlin, Germany
⁶ Dept. of Respiratory and Infectious Diseases, Thoraxzentrum Ruhrgebiet, Herne and Bochum, Germany

Keywords: CAP, Seasonal Influenza

*Corresponding author:

Heike von Baum, MD
Institute for Medical Microbiology and Hygiene
University Hospital of Ulm
Steinhövel Str. 8
D-89075 Ulm, Germany
Phone: +49-731-500 65350
Fax: +49-731-500 65349
email: heike.von-baum@uniklinik-ulm.de
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 5032 patients with CAP included in the German CAP-Competence Network (CAPNETZ), we studied the incidence, clinical characteristics, and outcome of patients with influenza-associated CAP and compared these to 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 etiology). 34 patients (21%) with seasonal influenza had a concomitant pathogen (mostly *S. pneumoniae*). Patients with influenza associated CAP were significantly older, had been less often vaccinated, and had less often preceding antibacterial treatment. Thirty-day mortality was low (4.4%), not different to that of patients with pneumonia caused by bacterial (6.2%) or viral other than influenza pathogen (4%). Patients with influenza plus a bacterial pathogen (mixed influenza-associated pneumonia) had a higher mortality than those with pure influenza associated pneumonia (9% vs 3.2%).

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

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 the 1976/1977 through the 2002/2003 seasons an annual average of more than 25,000 influenza-associated respiratory and circulatory deaths (9.9 deaths per 100,000) have been calculated in the United States (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, IDSA/ATS guidelines recommend specific antiviral treatment in patients with evidence for influenza etiology in 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 realized 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 casual relations of excess mortality. In fact, excess mortality might be caused by other than respiratory diseases.

Therefore, we studied the incidence, initial severity, clinical presentation, and outcomes of patients with influenza associated pneumonia within the large CAPNETZ cohort in order to assess the contribution of influenza associated pneumonia to pneumonia mortality. We compared it to 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 standardized web-based data sheets created by 2mt® Ulm, Germany. The study period comprised 58 months starting on 1st June 2002 and ending 30th April 2007, thus including five autumn-winter seasons.

Microbiological and virological processing and examination

Methods applied were described previously. 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 centers. 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 BAL fluid samples were plated on blood-sheep agar, CDC agar and chocolate agar. Undiluted PSB and BAL fluid 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. Standardized throat washings of all patients using sterile 0.9 % NaCL were sent immediately to the German reference center for influenza in Berlin. PCR for influenza A and B was performed in the throat washings of all 5032 patients.
RNA extraction and complementary DNA (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 cDNA synthesis was carried out at 37°C for 1 hour using 10 µl of RNA, 100 U of murine leukemia 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, Germany) and 0.25 µM random hexamer primers.

PCR and sequence analysis

The TaqMan-PCR was carried out in a 96-well flat-bottomed microtiter plate format (Perkin Elmer). 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 MgCl₂, 0.2 mM (each) dATP, dCTP, dGTP dUTP, 0.5 units uracil-N-glycosylase (UNG) (Gibco BRL, Life Technologies, Germany), 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-labeled probe and 1µM ROX as passive reference. Virus identification and further subtyping was carried out as described previously (11) with some modifications (primer and probe sequences on request). The cDNA was amplified by 45 two-step cycles (1 min 92°C, 1 min 60°C). The amplification in the TaqMan-PCR was followed on the ABI Prism™ 7700 Sequence Detector (Applied Biosystems, Foster City, Calif. USA). The plate was scanned at 518 nm (FAM) and 582 nm (TAMRA). Data acquisition analysis was handled by using the Fluorescence Data Manager (Perkin Elmer) and
Excel (Microsoft Corporation, Redmond, Wash.) spreadsheets. ROX was used as a passive reference to which the reporter dye signal was normalized ($R_o$) during data analysis.

**Definitions.**

We defined patients with PCR - positive influenza respiratory samples as “influenza associated pneumonia” since we ignore the exact contribution of influenza virus infection as etiological pathogen in CAP. In particular, we cannot exclude the presence of a bacterial co-pathogen which 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) of 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 square test for categorical variables or Fisher’s exact test in case of small expected frequencies and analysis of variances (ANOVA) for continuous variables including multiple comparisons. All analyses were performed with SPSS software (SPSS 10.0, Chicago, IL). All tests of significance were 2-tailed, and alpha was set at 0.05.
Results

General characteristics of study population

Overall, 5032 patients with CAP from twelve clinical centers throughout Germany were included in our analysis from 2002 to 2007. The 2781 male and 2251 female patients had a mean age of 60 ± 18 years. Sixty-five percent (n = 3274) of the patients were hospitalized when first contacted for participation in CAPNETZ. 307 patients (6 %) were nursing home residents. Thirty-one percent of the patients were smokers. Severity scores as assessed by CRB-65 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 patients (3%) required mechanical ventilation. 238 patients (4.7%) died within 30 days after diagnosis, and 180-day mortality in all patients was 8.8% (445 patients).

General microbial patterns

In 1337 patients (27 %) a definite pathogen causing CAP could be identified. 124 patients (2.5%) carried more than one pathogen. 

*Streptococcus pneumoniae* was identified as the predominant respiratory pathogen in the study population, followed by *Mycoplasma pneumoniae*. In less than 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 etiology) 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 patients (21%) had influenza and a concomitant pathogen, predominantly *Streptococcus pneumoniae* (n=17) (mixed influenza-associated pneumonia) (Table 1).

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

**Ambulatory and hospitalized patients**

3274 patients were hospitalized, 102 of these (3 %) 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. of the patients.

Data concerning 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).

**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 leucocyte counts. They had been less frequently vaccinated (26% vs. 33%) (table 1).

Patients with mixed viral pneumonia had no distinguishing features when compared to 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 1).

**Outcome of influenza associated CAP**

Antiviral therapy was no specific query in the data sheet, but could be documented voluntarily. Thus no data as regards antiviral treatment were analyzed.

Nine patients had a high CRB-65 score of 3 (7 patients) or 4 (2 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 3/34 (9%) if a copathogen was present as compared to 4/126 (3.2%) in 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 < .000), smoking habits (p = 0.02) and older age (p = 0.068).
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 etiology); 2) related to autumn-winter seasons, the incidence was even higher (4.7% of the total population and 16.2% of patients with defined etiology); 3) influenza associated pneumonia was usually mild, only few patients required ventilatory support, and 30 day-mortality was low (4.2%), not different to that of patients with pneumonia caused by bacterial (6.2%) or viral other than influenza pathogens (4%), respectively; 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, etiological 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 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 RS viral infections and comparing these with influenza infections, healthy elderly patients (aged ≥ 65 years), high risk adults (those with chronic heart and lung disease), and hospitalized patients with acute cardio-pulmonary 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 to 10/144 (7%) of the hospitalized group with influenza (18). Bacterial infection was indentified in 10% of hospitalized patients with influenza (19).

To our knowledge, only three recent studies have exclusively addressed viral CAP. Based on paired serology, de Roux et al. found influenza in 11.5% of patients with CAP in a five year monocentric study. Due to the methodology applied, mortality could not be assessed (6). Johnstone et al. investigated viral CAP during a three year period in five hospitals. Influenza diagnosis was based on NAT and DFA testing of nasopharyngeal swabs. 19% had viral etiology, including 4% with a mixed etiology. Influenza was found in 3.6% of cases. Mortality rate of viral CAP was low (3%) (7). Finally, Jennings et al. investigated viral CAP in a one year 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% (8).

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 tested positive by direct enzyme immunoassay during a five year 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 antiviral treatment in 15/17 patients. Bacterial co-infection was identified in 5 patients, and Staphylococcus 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 etiology. 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 etiology in patients with CAP since both are missed by current investigational methodology in a considerable amount of cases. In our series, such dual etiology was present in 21% of influenza cases, and this may be an underestimate. As a matter of fact, we found only a non-significant slightly higher mortality rate of patients with bacterial co-pathogens.

In our study, *Streptococcus pneumoniae* and not *Staphylococcus aureus* was found to be the most frequent bacterial co-pathogen, followed by *Haemophilus influenzae*. This is in accordance with a recent study specifically addressing mixed etiologies 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 empiric 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 *Streptococcus pneumoniae* as well as *Haemophilus influenzae* and *Staphylococcus aureus* is mandatory. An adequate bacterial coverage seems more important than antiviral treatment with neuraminidase inhibitors. In
fact, there is currently no evidence to recommend antiviral 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 etiological study of CAP including such a high number of patients where influenza was systematically investigated relying on PCR technique. 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 TCID50 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. On the other hand, there are several limitations of our study. As in all studies dealing with the etiology of CAP the availability of respiratory samples is a problem. If only considering patients with a respiratory sample in addition to the throat washings 2076 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 generalization 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 etiology causing excess mortality (16). Another limitation is that we have no data on antiviral 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 of influenza associated pneumonia, neither as such nor in case of secondary bacterial infection. Mortality of influenza associated pneumonia may be limited to the excess incidence of influenza associated pneumonia cases and its deaths during autumn/winter seasons. Bacterial co-pathogens which should always be covered primarily include *Streptococcus pneumoniae, Staphylococcus aureus* and *Haemophilus influenzae*. Further studies should assess the role of influenza particularly in patients with severe CAP.
Acknowledgements

CAPNETZ is a multidisciplinary approach to better understand and treat patients with community-acquired pneumonia. The network has only been made possible by the contribution of many investigators. We are especially indebted to the work of the investigators in the local clinical centres (LCC) who established and kept contact to all practitioners, physicians, and respiratory specialists cooperating within the network.

In addition, we would like to acknowledge the work of the central computing unit and the central service unit with Anna Sawazki providing excellent technical support.

It is also our responsibility and pleasure to express our appreciation to all clinical physicians and physicians in private practice who saw and identified patients with community acquired pneumonia for their work dedicated to CAPNETZ.

Members of the CAPNETZ study group except the authors: G. Rohde, B. Hauptmeier (University Hospital Bergmannsheil, Dept. of Pneumology, Allergology and Sleep Medicine, Bochum), T. Schaberg, I. Hering (Dept. of Pneumology, Diakoniekrankenhaus Rotenburg), K. Dalhoff, P. Heyer (Department of Internal Medicine III, Pulmology, University Hospital Schleswig-Holstein, Lübeck), C. Schumann (Department of Internal Medicine II, University Hospital Ulm), T. Bauer, F. Kunitz (HELIOS Klinikum Emil von Behring, Berlin), H. Schütte, A. Tessmer (Department of Infectious Disease and Respiratory Medicine, Charité-University Medicine, Berlin), J. Rademacher (Department of Respiratory Medicine, Hannover Medical School, Hannover), A. Gillissen (Robert-Koch-Klinik, Thoraxzentrum des Klinikums St. Georg, Leipzig), B. Drewelow, J. Majcher-Peszynska (Center of Pharmacology and Toxicology, Institute of Clinical Pharmacology, University of Rostock), S. Krüger (Medical Clinic I, University Hospital RWTH Aachen), R. Bals (University Hospital Marburg), P. Martus (Institute for Biostatistics and Clinical Epidemiology, Charité University Medicine Berlin), T. Illmann, M. Wallner (2mt Software GmbH, Ulm), G. Barten, L. Gosman (Main Office, Hannover) and all study nurses.

Potential conflicts of interests

All authors have declared no conflict of interests.

The network is supported by

German Ministry of Education and Research (Bundesministerium für Bildung und Forschung) Berlin, Germany.
References

(1) http://www.cdc.gov/mmwr/preview/mmwrhtml/rr58e0724a1.htm


(12) http://www.influenza.rki.de/


Table 1.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>No influenza N= 4872</th>
<th>p-values</th>
<th>Pure Influenza-associated pneumonia N = 126</th>
<th>p-values</th>
<th>Mixed Influenza-associated Pneumonia N = 34</th>
<th>Influenza-associated pneumonia (all) n = 160</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No influenza Vs Pure Influenza-associated pneumonia</td>
<td>Pure Influenza-associated pneumonia Vs MV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>55 %</td>
<td>ns</td>
<td>52 %</td>
<td>ns</td>
<td>53 %</td>
<td>53 %</td>
</tr>
<tr>
<td>Age (median)</td>
<td>62.5</td>
<td>.023</td>
<td>68</td>
<td>.052</td>
<td>58</td>
<td>66.5</td>
</tr>
<tr>
<td>older than 65 y</td>
<td>46%</td>
<td>7 %</td>
<td>58 %</td>
<td>9 %</td>
<td>44 %</td>
<td>6 %</td>
</tr>
<tr>
<td>older than 85 y</td>
<td>7 %</td>
<td></td>
<td></td>
<td></td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>CRB 0/1-2-3-4 (%)</td>
<td>74-13-3-0.3</td>
<td>ns</td>
<td>78-10-4-2</td>
<td>ns</td>
<td>77-15-6-0</td>
<td>82-11-4-1.3</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>65 %</td>
<td>ns</td>
<td>62 %</td>
<td>ns</td>
<td>71 %</td>
<td>64 %</td>
</tr>
<tr>
<td>Nursing Home</td>
<td>6 %</td>
<td>ns</td>
<td>6 %</td>
<td>ns</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>PEG</td>
<td>2 %</td>
<td>ns</td>
<td>2 %</td>
<td>ns</td>
<td>3 %</td>
<td>1%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 %</td>
<td>ns</td>
<td>20 %</td>
<td>ns</td>
<td>6 %</td>
<td>19%</td>
</tr>
<tr>
<td>Cong heart failure</td>
<td>18 %</td>
<td>ns</td>
<td>21 %</td>
<td>ns</td>
<td>12%</td>
<td>19%</td>
</tr>
<tr>
<td>Other chronic card. condition</td>
<td>27 %</td>
<td>ns</td>
<td>29%</td>
<td>ns</td>
<td>21%</td>
<td>28%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>10 %</td>
<td>ns</td>
<td>12 %</td>
<td>ns</td>
<td>9 %</td>
<td>11%</td>
</tr>
<tr>
<td>Other chon. neuro. disorder</td>
<td>6 %</td>
<td>ns</td>
<td>6 %</td>
<td>ns</td>
<td>3 %</td>
<td>5%</td>
</tr>
<tr>
<td>COPD</td>
<td>35 %</td>
<td>ns</td>
<td>33 %</td>
<td>ns</td>
<td>41%</td>
<td>34%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>9 %</td>
<td>ns</td>
<td>6 %</td>
<td>ns</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Smoker</td>
<td>31 %</td>
<td>ns</td>
<td>27 %</td>
<td>ns</td>
<td>29%</td>
<td>28%</td>
</tr>
<tr>
<td>Preceding antibiotic therapy</td>
<td>26 %</td>
<td>.008</td>
<td>17%</td>
<td>ns</td>
<td>27%</td>
<td>19%</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>33% #</td>
<td>.067</td>
<td>26 % *</td>
<td>ns</td>
<td>24 % §</td>
<td>26%</td>
</tr>
<tr>
<td>Influenza Vaccinated Pneumococci</td>
<td>11 % #²</td>
<td>ns</td>
<td>10 % *²</td>
<td>ns</td>
<td>6 % §²</td>
<td>9 %</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---------</td>
<td>----</td>
<td>---------</td>
<td>----</td>
<td>--------</td>
<td>----</td>
</tr>
<tr>
<td>CRP median</td>
<td>81</td>
<td>ns</td>
<td>55</td>
<td>.001</td>
<td>135</td>
<td>67</td>
</tr>
<tr>
<td>Leucocytes med</td>
<td>11.3</td>
<td>.000</td>
<td>8.6</td>
<td>.001</td>
<td>11.2</td>
<td>9.100</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>3 %</td>
<td>ns</td>
<td>3 %</td>
<td>ns</td>
<td>0 %</td>
<td>2.5 %</td>
</tr>
<tr>
<td>Died (30 dys)</td>
<td>231 (4.7%)</td>
<td>ns</td>
<td>4 (3.2 %)</td>
<td>ns</td>
<td>3 (8.8 %)</td>
<td>7 (4.4 %)</td>
</tr>
</tbody>
</table>

# Information concerning influenza vaccination available in 4567 (94%) patients; #² Information concerning pneumococcal vaccination available in 4532 (93%) patients; * Information concerning influenza vaccination available in 122 (97%) patients; *² Information concerning pneumococcal vaccination available in 121 (96%) patients; § Information concerning influenza vaccination available in 32 (94%) patients; §² Information concerning pneumococcal vaccination available in 31 (91%) patients.
Table 2.

Concomitant pathogens of influenza-associated pneumonia (n = 34)

* One patient had two co-pathogens

<table>
<thead>
<tr>
<th>Bacterial pathogen</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>17 *</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>7</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>5</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>2</td>
</tr>
<tr>
<td><em>Legionella spp.</em></td>
<td>2</td>
</tr>
<tr>
<td><em>Klebsiella oxytoca</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>1</td>
</tr>
</tbody>
</table>
### Table 3.

Individual records of patients who died with influenza-associated pneumonia

<table>
<thead>
<tr>
<th>Pat ID</th>
<th>Sex</th>
<th>Age</th>
<th>BMI</th>
<th>CRB -65</th>
<th>Hospitalized</th>
<th>Concomitant Diseases</th>
<th>Smoker</th>
<th>Pack years</th>
<th>Concomitant Pathogen</th>
<th>Influenza vaccination</th>
<th>Antibiotic treatment</th>
<th>CRP (mg/L)</th>
<th>Leuocytes (µL)</th>
<th>Time of death (day)</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>f</td>
<td>66</td>
<td>21</td>
<td>2</td>
<td>yes</td>
<td>none</td>
<td>yes</td>
<td>42</td>
<td>S. pneumoniae</td>
<td>no</td>
<td>ceph III + macrolide</td>
<td>226</td>
<td>6.3</td>
<td>6</td>
<td>pneumonia</td>
</tr>
<tr>
<td>2</td>
<td>m</td>
<td>89</td>
<td>20</td>
<td>3</td>
<td>yes</td>
<td>CHF, COPD</td>
<td>yes</td>
<td>70</td>
<td>no resp. material available</td>
<td>yes</td>
<td>ceph II + macrolide</td>
<td>259</td>
<td>12.8</td>
<td>4</td>
<td>pneumonia</td>
</tr>
<tr>
<td>3</td>
<td>f</td>
<td>74</td>
<td>15</td>
<td>2</td>
<td>yes</td>
<td>CHF, COPD</td>
<td>yes</td>
<td>50</td>
<td>H. influenzae</td>
<td>no</td>
<td>ceph II</td>
<td>324</td>
<td>20.3</td>
<td>30</td>
<td>other</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>86</td>
<td>na</td>
<td>4</td>
<td>yes</td>
<td>CHF</td>
<td>na</td>
<td>na</td>
<td>none</td>
<td>na</td>
<td>makrolide</td>
<td>36</td>
<td>8.9</td>
<td>25</td>
<td>other</td>
</tr>
<tr>
<td>5</td>
<td>m</td>
<td>84</td>
<td>25</td>
<td>1</td>
<td>yes</td>
<td>COPD</td>
<td>yes</td>
<td>na</td>
<td>S. pneumoniae</td>
<td>no</td>
<td>ceph II</td>
<td>231</td>
<td>14.6</td>
<td>9</td>
<td>pneumonia</td>
</tr>
<tr>
<td>6</td>
<td>m</td>
<td>60</td>
<td>28</td>
<td>1</td>
<td>no</td>
<td>none</td>
<td>no</td>
<td>80</td>
<td>none</td>
<td>no</td>
<td>FQ</td>
<td>320</td>
<td>1.6</td>
<td>2</td>
<td>unknown</td>
</tr>
<tr>
<td>7</td>
<td>m</td>
<td>67</td>
<td>23</td>
<td>3</td>
<td>yes</td>
<td>COPD, neurological disease</td>
<td>na</td>
<td>na</td>
<td>no resp. material available</td>
<td>na</td>
<td>FQ</td>
<td>28</td>
<td>1.6</td>
<td>23</td>
<td>pneumonia</td>
</tr>
</tbody>
</table>

None of the patients had received antibiotic treatment before study participation

na = information not available; CHF = congestive heart failure
Figure 1.

Seasonal distribution of influenza-associated pneumonia throughout five autumn-winter seasons.

Influenza

Cases
Died