Influenza vaccination is associated with reduced severity of community acquired pneumonia

Antje Tessmer *, Tobias Welte #, Ruprecht Schmidt-Ott ¶, Sonja Eberle ¶,
Grit Barten †, Norbert Suttorp * and Tom Schaberg § for the CAPNETZ study group

* Dept. of Infectious Disease and Respiratory Medicine, Charité-University Medicine, Berlin, Germany
# Dept. of Pulmonary Medicine, Medical University Hannover, Hannover, Germany
¶ Medical Department GlaxoSmithKline, Munich, Germany
† CAPNETZ Office, Medical University Hannover, Hannover, Germany
§ Dept. of Pulmonary Medicine, Diakonie Hospital Rotenburg (Wümme), Rotenburg, Germany

Corresponding author:

Antje Tessmer

Medical Department of Infectious Disease and Respiratory Medicine
Charité-University Medicine Berlin,
Campus Virchow Klinikum and Campus Mitte
Augustenburger Platz 1, 13353 Berlin, Germany
Tel: +49-30-450-653326, Fax: +49-30-450-565937
antje.tessmer@charite.de
ABSTRACT

Pneumonia is an important cause of influenza-associated morbidity and mortality. Influenza vaccination has been shown to reduce morbidity and mortality during influenza-seasons. Protection from severe pneumonia may contribute to the beneficial effect of influenza vaccination. Therefore we investigated the impact of prior influenza vaccination on disease severity and mortality in patients with CAP.

Analysis from an observational, multicenter cohort study initiated by the German competence network for community acquired pneumonia was performed. Patients were analysed separately as an influenza season and off-season cohort. Associations between vaccination status and outcome parameters were evaluated by multivariate analyses.

In the season cohort (2368 patients) CAP in vaccinated patients was significantly less severe according to most of analysed parameters (OR for CURB \[\geq 1\] 0.76 (95% CI: 0.60-0.98); for procalcitonin \[\geq 2.0 \text{ ng/ml}\] 0.53 (CI: 0.35-0.81), for procalcitonin \[\geq 0.5 \text{ ng/ml}\] 0.71 (CI: 0.51-0.99)) and these patients showed a significantly better overall survival within the 6-month follow-up period (HR 0.63, CI: 0.45-0.89). Within the off-season cohort (2632 patients) there was no significant influence of vaccination status on CAP severity or disease outcome.

In conclusion, prior influenza vaccination was associated with less severe clinical course and improved overall long-term survival in patients with CAP during influenza-seasons.

Key words: community acquired pneumonia, influenza, mortality, vaccination
INTRODUCTION

Yearly influenza epidemics are a major cause of seasonal morbidity and mortality worldwide. Influenza vaccination is therefore recommended for elderly people and those who are at highest risk from its complications, such as immunocompromised patients or individuals with underlying chronic comorbidities. A common and serious complication of influenza infection is community acquired pneumonia (CAP), which either results from direct viral infection of the lung parenchyma or from secondary bacterial infections (1;2). Ciliary dysfunction and airway obstruction by increased mucus secretion and oedema might contribute to subsequent bacterial colonisation. Damage to the epithelial cell barrier by viral infection, for instance by TNF-related apoptosis-inducing ligand expressing macrophage induced alveolar epithelial apoptosis (3), might enhance adhesion of bacteria to lung tissue. Recent findings suggest that influenza associated impaired recruitment of neutrophil granulocytes (4) and sustained functional impairment of alveolar macrophage (5;6) contribute to severe courses of secondary bacterial pneumonia.

Influenza is a vaccine preventable disease and efficacy of available annual vaccines in preventing influenza infection can be as high as 80 percent if the vaccine matches the circulating strain and circulation is high (7). Several studies have shown that vaccination also reduces the risk of CAP (8;9), risk of hospitalization for pneumonia (10;11), deaths from pneumonia (11) and all-cause mortality (9;10). In Patients with CAP, influenza vaccination is associated with a lower risk of treatment failure (12) and with improved survival in hospitalized patients (13). The hypothesis of the current study was that influenza can lead to severe pneumonia and that, in turn, influenza vaccination is associated with lower disease severity in patients with CAP. Therefore the objective of our study was to evaluate whether influenza-vaccination was
associated with less severe CAP during influenza-season. To estimate severity of
CAP and risk of mortality we used the prospectively validated CURB-score (14),
which has been included into current pneumonia treatment guidelines (15-18) and
recently gained a widespread application. In addition, the inflammatory biomarker
procalcitonin (PCT) has been shown to predict the severity of CAP (19-21) and was
also used in this study. Its serum level increases rapidly in bacterial infections but
remains low in viral diseases. The secondary aim was to estimate the benefit of
influenza-vaccination on pneumonia outcome variables such as mortality and health
economic parameters.
METHODS

Data collection and CAP diagnosis

Data are derived from a multicenter observational study initiated by the German competence network for community-acquired pneumonia (CAPNETZ; http://www.capnetz.de) which is funded by the German Ministry of Education and Research (BMBF). Details of this prospective observational study have been presented elsewhere (22). The study design was approved by the local Ethics Committee and all patients gave written informed consent and received a pseudonym from an independent third party to ensure data safety. Data collection was performed prospectively based on a standard protocol, starting in July 2002 and was censored for this analysis in December 2006. Data validity and consistency checks were performed by an independent party prior to data analysis.

CAP was diagnosed in patients aged ≥ 18 years who presented a new pulmonary infiltrate on chest x-ray, together with a history of fever and at least one symptom or sign of lower respiratory tract infection (cough, purulent sputum or focal auscultatory chest sign). Patients were excluded if they had been hospitalised during the previous 28 days or if they were chronically immunosuppressed (chemotherapy and/or neutropenia <1000/μl; therapy with prednisone ≥ 20mg or equivalent; HIV-infection, immunosuppressive therapy). All patients were assessed at the first presentation. Demographic parameters, vital signs, clinical symptoms, laboratory and radiological findings and therapy data were recorded.

Microbiological specimens were processed in the participating local laboratories and sent afterward to the CAPNETZ Central Study Unit (Ulm, Germany) with the exception of specimens for influenza testing, which were sent to the National
Reference Center for Influenza (Robert Koch Institute, Berlin, Germany). The following specimens were taken: 1.) if available, a sample of the lower respiratory tract for gram staining, culture and susceptibility testing, 2.) urine for pneumococcal and legionella antigen testing, 3.) serum for antibody testing and 4.) throat swab / wash for Influenza testing by real time PCR (RT-PCR). Investigations and pathogen definitions were applied according to German Quality Standards in Clinical Microbiology and Infectious Diseases (23). Serum PCT was determined by an immunofluorescent assay (B.R.A.H.M.S PCT sensitive Kryptor; B.R.A.H.M.S AG, Henningsdorf, Germany).

After 14 days (and facultative after 30 days) all patients or relatives were contacted either personally or per telephone for a structured interview on outcome parameters (e.g. lengths of hospitalisation, mortality). The last follow up was performed per telephone after 6 month.

**Study population**

The present analysis included all consecutive CAP-patients with documented influenza-vaccination status regarding that year’s inactivated trivalent vaccine before the CAP onset date. All patients were vaccinated during the autumn season of the same year the influenza season started. Patients were stratified according to their influenza-vaccination status in the influenza vaccinated (FluVac\(^+\)) and unvaccinated (FluVac\(^-\)) group, and were analysed separately as an influenza season (CAP diagnosis between 1\(^{st}\) December to 30\(^{th}\) April) and off-season (CAP diagnosis between 1\(^{st}\) May to 30\(^{th}\) November) cohort (see Figure 1). The off-season period represents the control time when a true benefit of influenza vaccine is biologically not plausible. The annual influenza activity was changing within the 4\(\frac{1}{2}\) seasons (24).
**Outcome measurement**

To estimate the benefit of influenza vaccination, we investigated risk of pneumonia outcome by multivariate analyses as severity of CAP, all-cause-mortality (on 14 and 30 days, 6 months) and health-economic parameters (duration of hospitalization, lengths of antimicrobial therapy and change of antimicrobial therapy). Severity of CAP on admission was assessed using the CURB-score (14). “CURB” is the acronym of four core severity criteria: Confusion, Blood-urea nitrogen (BUN >7mmol/L), Respiratory rate (≥ 30/min) and Blood Pressure (diastolic pressure ≤ 60 mmHg or systolic blood pressure <90mmHg). One point was given for each criterion present (range 0-4 points). In addition PCT was used as a biomarker to describe inflammatory disease activity due to pneumonia. The following different cutoff-values for PCT were used in analysis for sensitivity reasons: 0.228, 0.5 and 2.0 ng/ml (19;21).

**Statistical analysis**

All data were analysed descriptively. Continuous data were presented as means ± standard deviation (sd) and categorical data as counts and percentages. Two-sample t-test for means and chi-square and Fisher’s exact test, respectively, for proportions were used to compare baseline characteristics between FluVac+ and FluVac− patients. Adjusted influence of influenza-vaccination on parameters was analysed by multivariate logistic (odds ratio, OR), cox (hazard ratio, HR) and linear regression models (slope, SE), respectively. We adjusted for the following confounders: age, gender, pneumococcal vaccination status, body mass index, nursing home
residency, smoking behaviour, previous antibiotic therapy, long-term oxygen therapy
and presence of comorbidities. Statistical significance was set at a two-sided 5%
level. All analyses were performed using SAS 9.1® software (SAS Institute Inc., Cary,
NC, USA). Statistical analyses were performed in cooperation with GlaxoSmithKline.
RESULTS

Up to December 2006, 5677 consecutive patients with CAP were recruited in CAPNETZ and followed up. Of these patients, 5000 had a documented status of influenza vaccination with an actual seasonal influenza vaccine before the CAP onset date and were included into the analysis. In 2368 of these patients CAP occurred during influenza season (47.4%) whereas in 2632 patients CAP occurred off-season (52.6%). Figure 1 shows the flow of patients in this study. Approximately one-third (34.4%) of the patients were vaccinated against influenza (season-cohort: n=858, 36.2% vs off-season cohort: n=863, 32.8%). About 27.9% of the FluVac+ patients were additionally vaccinated against pneumococci (season-cohort: 28.7% vs off-season cohort: 27.2%). In contrast pneumococcal vaccination rate of the FluVac- patients was low (season-cohort: 2.7% vs off-season cohort: 2.4%).

General characteristics of the study population

Table 1 demonstrates the demographic and baseline characteristics of both cohorts (season and off-season). FluVac+ patients were significantly older than those who were not vaccinated within the season and off-season. Corresponding to the higher age and the existing recommendations for influenza vaccination, FluVac+ patients were more likely to have comorbid illnesses such as congestive heart disease, diabetes mellitus, chronic renal disease, neoplastic disease and COPD / asthma and were more frequently users of long-term oxygen therapy. These patients had a higher body-mass-index (BMI), were less likely to be smokers, and were more frequently vaccinated against pneumococci. No differences were found with respect to the occurrence of previous antibiotic treatment or nursing home residence status. About
63.3% of patients in the season-cohort and 65.1% in the off-season cohort were hospitalized for their CAP episode. The hospitalization rate of FluVac$^+$ patients was comparable to the unvaccinated patients (64.8 vs 62.5% and 67.1 vs 64.1%) for the season and off-season cohort, respectively. The remaining patients were treated on an outpatient basis by their physician.

A causative pathogen was found in 20.4% (n=1018) of patients. *Streptococcus pneumoniae* was the most frequent detected cause of CAP (8.7%; n=434) and more common during season (10.0 vs 7.2%, p=0.004). No other differences of bacterial pathogens were found between season and off-season. Furthermore no significant differences were seen after stratifying patients according to their vaccination status within season as well as off-season (data are not shown). In the season cohort, influenza A/B -virus detection rate was generally low and less frequent in the influenza-vaccinated group (3.9 vs 6.2%; p=0.017). Only few other viral pathogens were identified (respiratory syncytial virus (RSV), n=21; enterovirus, n=24). Detection of RSV occurred predominantly during season (in 19 of 21 cases) whereas enteroviruses were found in both seasons (season: n=13 vs off-season: n=11). No significant differences were identified between FluVac$^+$ and FluVac$^-$ patients. The antibiotic therapies, initiated by the attending physician, were classified by mono- and combination therapy. Both therapy-arms were well balanced between FluVac$^+$ and FluVac$^-$ patients as well as between the two study cohorts.
## Table 1 Demographics, clinical characteristics and therapy data

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Season cohort FluVac+ N =</th>
<th>FluVac- N =</th>
<th>p-value</th>
<th>Off-season cohort FluVac+ N =</th>
<th>FluVac- N =</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>858</td>
<td>1510</td>
<td></td>
<td>863</td>
<td>1769</td>
<td></td>
</tr>
<tr>
<td>Age, mean ± sd</td>
<td>67.6 ± 14.5</td>
<td>55.7 ± 19.0</td>
<td>&lt;0.001</td>
<td>66.7 ± 14.9</td>
<td>55.3 ± 18.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass Index, mean ± sd</td>
<td>26.1 ± 4.7</td>
<td>25.1 ± 5.0</td>
<td>&lt;0.001</td>
<td>26.0 ± 4.8</td>
<td>25.0 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>491 (57.2)</td>
<td>793 (52.5)</td>
<td>0.027</td>
<td>468 (54.2)</td>
<td>990 (44.0)</td>
<td>0.401</td>
</tr>
<tr>
<td>Nursing home residency, n (%)</td>
<td>51 (5.9)</td>
<td>98 (6.5)</td>
<td>0.596</td>
<td>54 (6.3)</td>
<td>107 (6.0)</td>
<td>0.837</td>
</tr>
<tr>
<td>Pneumococcal vaccination, n (%)</td>
<td>246 (28.7)</td>
<td>41 (2.7)</td>
<td>&lt;0.001</td>
<td>235 (27.2)</td>
<td>42 (2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous antibiotic therapy (4 weeks), n (%)</td>
<td>212 (24.7)</td>
<td>417 (27.6)</td>
<td>0.137</td>
<td>215 (24.9)</td>
<td>494 (27.9)</td>
<td>0.106</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>182 (21.2)</td>
<td>531 (35.2)</td>
<td>&lt;0.001</td>
<td>205 (23.8)</td>
<td>667 (37.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Long-term oxygen therapy, n (%)</td>
<td>55 (6.4)</td>
<td>51 (3.4)</td>
<td>&lt;0.001</td>
<td>59 (6.8)</td>
<td>47 (2.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient CAP, n (%)</td>
<td>556 (64.8)</td>
<td>943 (62.5)</td>
<td>0.320</td>
<td>579 (67.1)</td>
<td>1134 (64.1)</td>
<td>0.051</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>215 (25.1)</td>
<td>209 (13.8)</td>
<td>&lt;0.001</td>
<td>217 (25.1)</td>
<td>276 (15.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular disease, n (%)</td>
<td>75 (8.7)</td>
<td>123 (8.1)</td>
<td>0.639</td>
<td>109 (12.6)</td>
<td>145 (8.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>210 (24.5)</td>
<td>192 (12.7)</td>
<td>&lt;0.001</td>
<td>195 (22.6)</td>
<td>198 (11.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic renal disease, n (%)</td>
<td>94 (11.0)</td>
<td>95 (6.3)</td>
<td>&lt;0.001</td>
<td>101 (11.7)</td>
<td>103 (5.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic liver disease, n (%)</td>
<td>24 (2.8)</td>
<td>51 (3.4)</td>
<td>0.434</td>
<td>32 (3.7)</td>
<td>52 (2.9)</td>
<td>0.291</td>
</tr>
<tr>
<td>Neoplastic disease, n (%)</td>
<td>109 (12.7)</td>
<td>112 (7.4)</td>
<td>&lt;0.001</td>
<td>106 (12.3)</td>
<td>127 (7.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD / Asthma, n (%)</td>
<td>403 (47.0)</td>
<td>443 (29.3)</td>
<td>&lt;0.001</td>
<td>397 (46.0)</td>
<td>532 (30.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CURB-Index *</td>
<td>N=608</td>
<td>N=1070</td>
<td>N=663</td>
<td>N=1279</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, n (%)</td>
<td>304 (50.0)</td>
<td>600 (56.1)</td>
<td>0.005</td>
<td>326 (49.2)</td>
<td>708 (55.4)</td>
<td>0.020</td>
</tr>
<tr>
<td>1, n (%)</td>
<td>202 (33.2)</td>
<td>321 (30.0)</td>
<td>217 (32.7)</td>
<td>383 (30.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2, n (%)</td>
<td>68 (11.2)</td>
<td>123 (11.5)</td>
<td>88 (13.3)</td>
<td>155 (8.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3, n (%)</td>
<td>28 (4.6)</td>
<td>20 (1.9)</td>
<td>29 (4.4)</td>
<td>29 (2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4, n (%)</td>
<td>6 (1.0)</td>
<td>6 (0.6)</td>
<td>3 (0.5)</td>
<td>4 (0.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# CURB-Index: range 0-4 points. One point was given for each present criterion:
confusion, blood-urea nitrogen (BUN >7mmol/L), respiratory rate (≥ 30/min) and
blood Pressure (diastolic pressure ≤ 60 mmHg or systolic blood pressure < 90mmHg).

Outcome analyses

Severity of CAP was investigated using the patient’s CURB-score upon their
ingclusion in the study. Multivariate analyses were performed to adjust for differences
in the baseline characteristics (table 2). Investigation of all patients revealed that
influenza-vaccination was associated with a lower adjusted risk of severe pneumonia
defined by CURB-score ≥1 within the season (OR 0.76; CI 0.60-0.98). Out of season
this effect was not detectable. Influenza-vaccination was associated with a lower
adjusted risk for PCT values ≥ 0.5 (OR 0.71; CI 0.51-0.99) and ≥ 2 ng/ml (OR 0.53;
0.35-0.81) respectively. Again, these effects were not seen in the off-season cohort.

A total of 114 of 5,000 patients (2.3%) died within 14 days after study inclusion while
30-day mortality amounted to 163 patients (3.3%). Mortality increased with
augmenting CURB-risk factors. By univariate analyses the 14-day mortality of the overall season cohort was significantly higher compared to the overall off-season (2.7 vs 1.9%, p=0.037) but not on 30 days (3.9 vs 2.7%, p=0.172). No statistical differences were seen in mortality between FluVac\(^+\) and FluVac\(^-\) patients within season and off-season (see table 3). A similar result was found during late 6-month follow-up. However, general mortality was very low.

When mortality was investigated as an outcome parameter within the season by multivariate analyses (see table 2), influenza-vaccination revealed no decreased risks for mortality on day 14 as well as on day 30 after adjustment for potential confounders. However, with respect to the 6-month long-term follow up, influenza-vaccination was associated with lower mortality risk (HR 0.63; CI 0.45-0.89).

The analyses of health-economic parameters such as duration of antimicrobial therapy, necessity to change the initial antimicrobial regimen, or duration of hospitalization, revealed no statistically significant result according to the influenza-vaccination status in neither of both cohorts (see table 2).
Table 2 Influence of Influenza-vaccination on different outcome parameters by multivariate analyses for the Season and Off-Season Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Season cohort</th>
<th>Off-season cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR # / 95% CI</td>
<td>OR # / 95% CI</td>
</tr>
<tr>
<td>CURB $\geq 1$</td>
<td>0.763 (0.595-0.978)</td>
<td>0.830 (0.659-1.046)</td>
</tr>
<tr>
<td>PCT $\geq 0.228$ ng/ml</td>
<td>0.878 (0.652-1.183)</td>
<td>0.948 (0.723-1.244)</td>
</tr>
<tr>
<td>PCT $\geq 0.5$ ng/ml</td>
<td>0.709 (0.508-0.988)</td>
<td>0.940 (0.695-1.272)</td>
</tr>
<tr>
<td>PCT $\geq 2$ ng/ml</td>
<td>0.530 (0.348-0.808)</td>
<td>0.807 (0.541-1.203)</td>
</tr>
<tr>
<td>14-day mortality</td>
<td>0.660 (0.343-1.270)</td>
<td>0.760 (0.369-1.566)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>0.650 (0.379-1.113)</td>
<td>0.876 (0.487-1.577)</td>
</tr>
<tr>
<td>overall survival (during 6 month observational periods)</td>
<td>0.630 $\dagger$ (0.446-0.891)</td>
<td>0.809 $\ddagger$ (0.589-1.111)</td>
</tr>
<tr>
<td>Necessity to change the initial antimicrobial therapy</td>
<td>0.884 (0.704-1.110)</td>
<td>0.944 (0.762-1.169)</td>
</tr>
<tr>
<td>Duration of antimicrobial therapy (Slope ± SE) *</td>
<td>$0.074 \pm 0.236$ (p=0.754) $#$</td>
<td>$-0.135 \pm 0.236$ (p=0.569) $#$</td>
</tr>
<tr>
<td>Duration of hospitalization (Slope ± SE) *</td>
<td>$-0.705 \pm 0.469$ (p=0.133)</td>
<td>$-0.421 \pm 0.487$ (p=0.388) $#$</td>
</tr>
</tbody>
</table>

$\#$ Adjusted for age, gender, pneumococcal vaccination status, BMI, nursing home residency, smoking, previous antibiotic therapy, long-term oxygen therapy and number of comorbidities.
\* Adjusted Hazard Ratio.

\* Linear regression analysis

<table>
<thead>
<tr>
<th></th>
<th>Season cohort</th>
<th></th>
<th>Off-season cohort</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FluVac(^+) N</td>
<td>FluVac(^-) N</td>
<td>p-value</td>
<td>FluVac(^+) N</td>
</tr>
<tr>
<td>14-day mortality (%)</td>
<td>2.4</td>
<td>2.9</td>
<td>0.601</td>
<td>1.9</td>
</tr>
<tr>
<td>30-day mortality (%)</td>
<td>3.4</td>
<td>4.2</td>
<td>0.442</td>
<td>3.0</td>
</tr>
<tr>
<td>6-month mortality (%)</td>
<td>7.6</td>
<td>8.8</td>
<td>0.316</td>
<td>8.7</td>
</tr>
</tbody>
</table>

**Table 3** Vaccination status and mortality rates during Season and Off-season
DISCUSSION

To our knowledge this is the largest observational study of adult patients with CAP evaluating the impact of influenza-vaccination on CAP-severity worldwide. The results of this study suggest that during the influenza-season prior influenza vaccination reduces the risk of severe courses of pneumonia. Out of season, these effects were not found.

To provide more confidence, two different approaches for severity assessment were used in our study. Analysis was done using the in clinical practice widely used CURB score. Secondly, analyses were performed using the biomarker PCT, which also gained emerging significance in clinical routine and is readily measurable in serum, reflecting systemic inflammatory reactions due to bacterial activity.

Influenza has a prominent role in the development of secondary bacterial infections and various mechanisms by which influenza sensitizes patients to secondary bacterial infections have been described. These mechanisms include sustained impairment of macrophage and neutrophile responses (4-6;25), increased bacterial adherence to epithelia due to upregulation of plateled-activating factor receptor expression (26) and induction of inhibitory interleukin-10 (27). These factors might not only predispose for bacterial infection but also enhance the severity of resulting pneumonial disease. Thus, prevention or attenuation of the predisposing viral illness through vaccination should reduce the risk for more severe secondary pneumonia. Our results support this hypothesis.

In the northern hemisphere, influenza infection is a seasonal disease, occurring during the winter months. Consequently, influenza-virus triggered secondary CAP predominantly occurs during influenza season and any beneficial effect of influenza
vaccination on CAP should operate only during influenza season. The use of the off-season cohort as an additional control allowed us to validate the statistical approach to control for confounding. The number of CAP patients with RT-PCR confirmed influenza was low in our study. However, it is known that secondary bacterial infections often occur when the virus is no longer detectable (28). Thus, we assume that the real influenza-associated CAP cases in the season cohort are underestimated in our study. With respect to our study, the beneficial effect of prior influenza-vaccination on CAP severity during season is most likely based on influenza-virus triggered secondary pneumonia cases.

Most pneumonia-related deaths occur within 30 days after onset of disease. Therefore, we used short-term all-cause mortality as outcome parameters to narrow the question whether vaccination was associated with lower CAP mortality or not. In spite of the lower risk of severe pneumonia course, influenza vaccination showed no impact on adjusted short-time mortality at day 14 and day 30 in our study. However, the general mortality rate in our study population was very low. In addition, we didn’t observe a significant difference between overall season and off-season 30-day mortality (3.9 vs 2.7%). Excess mortality attributable to influenza has been 5% on average during flu seasons in the past several decades in large study cohorts (29). However, we lost 677 patients in our study (see figure 1) because of missing information about vaccination status. After including those patients into the analysis, overall season and off-season 30-day mortality increased up to 6.0 vs 4.5%. Possibly, our mortality analyses are impaired by the fact that a significant number of patients died and we were lacking vaccination history respectively.
In contrast, the results of our study revealed a significantly better overall survival of the FluVac$^+$ patients after 6 month. This long-term follow up represents all-cause mortality and cannot be attributed to CAP mortality. However, recent animal studies suggest sustained impairment of antibacterial defense after influenza infection, lasting for several months (5;6). This could possibly explain the long-term beneficial association observed with influenza vaccination. Confirmation of this would require further studies, investigating the long-term effect of influenza infection on the immune system.

In Germany and most other countries influenza vaccination is recommended for the frail and the elderly. This explains the higher age of the FluVac$^+$ patients in our study. Most of the evidence on short and long-term benefit of the influenza vaccines has been derived from observational data, which are at greater risk of bias through confounding. This might have lead to an over or under estimation of benefits of vaccination. A debate has arisen in the last years that previous observational studies have overestimated the mortality benefits of the influenza vaccination due to non-specific endpoints and confounding (29;30). Influenza vaccinated patients in our study were older, had more comorbidities and had been more vaccinated against pneumococci. All these variables have been taken into account in the multivariate analysis that resulted in the mentioned protective effects of the influenza vaccine.

We further investigated the impact of influenza vaccination in patients with CAP on health-economic parameters. By multivariate analyses our data revealed no influence on duration of antimicrobial therapy, the necessity to change the initial antimicrobial regimen or duration of hospitalization of inpatients. However, we think that these endpoints represent relatively “weak” outcome parameters which can be influenced by various factors. Current pneumonia treatment guidelines give fixed
recommendations for duration of antibiotic therapy. In addition duration of hospitalization can be influenced by subjective doctor’s specific considerations or by the patient’s comorbidities or social background.

The strengths of this study include its prospective nature and the thorough collection of data from a cohort of consecutive CAP patients with a clear defined CAP diagnosis and a high number of influenza vaccinated cases. Furthermore, our study was not restricted to hospitalized patients with pneumonia, about one third of patients were treated ambulatory.

Our study, however, has several limitations related to an observational study in which influenza-vaccination has not been selected by randomisation. Despite of multivariate analyses, residual confounding factors (unknown or not collected in database) cannot be excluded completely. However, the lack of significant differences between FluVac+ and FluVac− patients in the off-season cohort indicates that residual confounding is low.

To conclude: Based on severity of CAP, this study suggests that prior influenza vaccination is associated with less severe course of CAP during influenza season and improved long-term survival. Therefore, results of this study support the current recommendations for influenza vaccination.
**Acknowledgments**

CAPNETZ is a multidisciplinary approach to better understand and treat patients with CAP. The network has been made possible by the contributions of many investigators. We are especially indebted to the work of the CAPNETZ Study Group in the local clinical centers who established and kept contact with all practitioners, physicians and respiratory specialists cooperating within the network (Heike von Baum, Anna Sawazki, Gernot Rohde, Barbara Hauptmeier, Santiago Ewig, Iris Hering, Klaus Dalhoff, Petra Heyer, Christian Schumann, Torsten Bauer, Frank Kunitz, Jessica Rademacher, Reinhard Marre, Adrian Gillissen, Stefan Krüger, Mathias Pletz, Bernd Drewelow, Jolanta Majcher-Peczynska, Ludmilla Gosman, Hartwig Schütte, Robert Bals, Peter Martus, Torsten Illmann and Michael Wallner). In addition, we especially would like to acknowledge the work of Brunhilde Schweiger from the National Reference Center for Influenza (Robert Koch Institute, Berlin, Germany) and the central service unit.

**Funding**

CAPNETZ was funded by the German Ministry of Education and Research (BMBF). For this study CAPNETZ received funding from GlaxoSmithKline.


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Figure 1  Origin of the evaluated patient cohort from CAPNETZ

Patients with CAP
prospectively recruited
July 2002 - December 2006
N = 5677

Season-Cohort
(1st December – 30th April)
N = 2686

- Documented status for influenza- & pneumococcal vaccination
  N = 2368

- Influenza-vaccinated (FluVac⁺)
  N = 858

- Unvaccinated (FluVac⁻)
  N = 1510

Off-Season-Cohort
(1st May – 30th November)
N = 2991

- Documented status for influenza- & pneumococcal vaccination
  N = 2632

- Influenza-vaccinated (FluVac⁺)
  N = 863

- Unvaccinated (FluVac⁻)
  N = 1769