Influenza vaccination is associated with reduced severity of community-acquired pneumonia

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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 community-acquired pneumonia (CAP).

Analysis from an observational, multicentre cohort study initiated by the German competence network for CAP 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 (2,368 patients) CAP in vaccinated patients was significantly less severe according to most analysed parameters (CURB index ≥ 1 : OR 0.76, 95% CI 0.60–0.98; procalcitonin ≥ 2.0 ng·mL⁻¹: OR 0.53, 95% CI 0.35–0.81; procalcitonin ≥ 0.5 ng·mL⁻¹: OR 0.71, 95% CI 0.51–0.99) and these patients showed a significantly better overall survival within the 6-month follow-up period (HR 0.63, 95% CI 0.45–0.89). Within the off-season cohort (2,632 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.

KEYWORDS: Community-acquired pneumonia, influenza, mortality, vaccination

Annual influenza epidemics are a major cause of seasonal morbidity and mortality worldwide. Therefore, influenza vaccination is 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 TRAIL (tumour necrosis factor-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% 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 hospitalisation 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 improved survival in hospitalised 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

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we used the prospectively validated CURB (confusion, blood-urea nitrogen (>7 mmol·L⁻¹), respiratory rate (≥ 30 breaths·min⁻¹) and blood pressure (diastolic pressure ≤ 60 mmHg or systolic blood pressure <90 mmHg) score [14], which has been included in current pneumonia treatment guidelines [15–18] and recently gained widespread use. In addition, the inflammatory biomarker procalcitonin (PCT) has been shown to predict the severity of CAP [19–21] and was also used in our 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 were derived from a multicentre observational study initiated by the German competence network for CAP (CAPNETZ; www.capnetz.de), which is funded by the German Ministry of Education and Research (*Bundesministerium für Bildung und Forschung*). Details of this prospective observational study have been presented previously [22]. The study design was approved by the local Ethics Committees in Berlin, Bochum, Hanover, Cologne/Bonn, Leipzig, Lübeck, Lüdenscheld, Magdeburg, Rotenburg, Ulm and Würzburg (all Germany). 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 yrs who presented with a new pulmonary infiltrate on a chest radiograph, 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 $<1,000$ cells· μ L⁻¹; therapy with prednisone ≥ 20 mg or equivalent; HIV infection; or 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 then sent 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 RT-PCR. Investigations and pathogen definitions were applied according to German quality standards in clinical microbiology and infectious diseases [23, 24]. Serum PCT was determined by an immuno-fluorescent assay (PCT sensitive Kryptor; Brahms AG, Henningsdorf, Germany).

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

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: influenza vaccinated (FluVac⁺) and unvaccinated (FluVac⁻). The patients were analysed separately as an influenza season cohort (CAP diagnosis between December 1st to April 30th) and off-season cohort (CAP diagnosis between May 1st to November 30th) (fig. 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 four and half seasons [25].

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 days 14 and 30 and at 6 months) and health-economic parameters (duration of hospitalisation, lengths of antimicrobial therapy and change of antimicrobial therapy). Severity of CAP on admission was assessed using the CURB score [14], 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 cut-off values for PCT were used in analysis for sensitivity reasons: 0.228, 0.5 and 2.0 ng·mL⁻¹ [19, 21].

FIGURE 1. Origin of the evaluated patient cohort from CAPNETZ. CAP: community-acquired pneumonia.

Statistical analysis

All data were analysed descriptively. Continuous data are presented as mean $\pm$ SD and categorical data as n (%). A two-sample unpaired t-test for means and Chi-squared and Fisher's exact test 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 analysis (odds ratio), Cox regression analysis (hazard ratio) and linear regression models (slope $\pm$ SE). We adjusted for the following confounders: age, sex, pneumococcal vaccination status, body mass index (BMI), 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 (Munich, Germany).

RESULTS

Up to December 2006, 5,677 consecutive patients with CAP were recruited in CAPNETZ and followed up. Of these patients, 5,000 had a documented status of influenza vaccination with an actual seasonal influenza vaccine before the CAP onset date and were included in the analysis. In 2,368 of these patients CAP occurred during the influenza season (47.4%) whereas in 2,632 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%) *versus* off-season cohort n=863 (32.8%)). Approximately 27.9% of the FluVac⁺ patients were additionally vaccinated against pneumococci (season cohort 28.7% *versus* off-season cohort 27.2%). In contrast, the pneumococcal vaccination rate of the FluVac⁻ patients was low (season cohort 2.7% *versus* 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 chronic obstructive pulmonary disease/asthma, and were more frequently users of long-term oxygen therapy. These patients had a higher 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. Approximately 63.3% of patients in the season cohort and 65.1% in the off-season cohort were hospitalised for their CAP episode. The hospitalisation rate of FluVac⁺ patients was comparable to the unvaccinated patients for the season (64.8% *versus* 62.5%) and off-season cohort (67.1% *versus* 64.1%). The remaining patients were treated on an outpatient basis by their physician.

A causative pathogen was found in 1,018 (20.4%) patients. *Streptococcus pneumoniae* was the most frequently detected cause of CAP (n=434, 8.7%) and more common in the season

cohort (10.0% *versus* 7.2%, p=0.004). No other differences of bacterial pathogens were found between the season and off-season cohorts. Furthermore no significant differences were seen after stratifying patients according to their vaccination status in the season and off-season cohort (data are not shown). In the season cohort, influenza A/B virus detection rate was generally low and less frequent in the FluVac⁺ group (3.9% *versus* 6.2%, p=0.017). Only a few other viral pathogens were identified (respiratory syncytial virus (RSV) n=21 and enterovirus, n=24). Detection of RSV occurred predominantly in the season cohort (19 out of 21 cases), whereas enteroviruses was found in both cohorts (season n=13 *versus* 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 monotherapy and combination therapy. Both therapy arms were well balanced between FluVac⁺ and FluVac⁻ patients, as well as between the two study cohorts.

Outcome analyses

Severity of CAP was investigated using the patient's CURB score upon their inclusion 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 in the season cohort (OR 0.76, 95% CI 0.60–0.98). This effect was not detectable in the off-season cohort. Influenza vaccination was associated with a lower adjusted risk for PCT values ≥ 0.5 ng·mL⁻¹ (OR 0.71, 95% CI 0.51–0.99) and ≥ 2 ng·mL⁻¹ (OR 0.53, 95% CI 0.35–0.81) in the season cohort. Again, these effects were not seen in the off-season cohort.

114 (2.3%) out of 5,000 patients died within 14 days of study inclusion while 30-day mortality was 3.3% (n=163). Mortality increased with augmenting CURB risk factors. By univariate analyses, the 14-day mortality of the overall season cohort was significantly higher compared with the overall off-season cohort (2.7% *versus* 1.9%, p=0.037) but not after 30 days (3.9% *versus* 2.7%, p=0.172). No statistical differences were seen in mortality between FluVac⁺ and FluVac⁻ patients in the season and off-season cohorts (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 in the season cohort by multivariate analyses (table 2), influenza vaccination revealed no decreased risks for mortality on day 14 or 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, 95% 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 hospitalisation, revealed no statistically significant result according to the influenza vaccination status in both cohorts (table 2).

DISCUSSION

To our knowledge, this is the largest observational study of adult patients with CAP evaluating the impact of influenza

TABLE 1 Demographics, clinical characteristics and therapy data of both cohorts

Patient characteristics	Season cohort			Off-season cohort		
	FluVac ⁺	FluVac ⁻	p-value	FluVac ⁺	FluVac ⁻	p-value
Subjects n	858	1510		863	1769	
Age yrs	67.6 ± 14.5	55.7 ± 19.0	<0.001	66.7 ± 14.9	55.3 ± 18.9	<0.001
Body mass index	26.1 ± 4.7	25.1 ± 5.0	<0.001	26.0 ± 4.8	25.0 ± 5.1	<0.001
Males	491 (57.2)	793 (52.5)	0.027	468 (54.2)	990 (44.0)	0.401
Nursing home residency	51 (5.9)	98 (6.5)	0.596	54 (6.3)	107 (6.0)	0.837
Pneumococcal vaccination	246 (28.7)	41 (2.7)	<0.001	235 (27.2)	42 (2.4)	<0.001
Antibiotic therapy in the past 4 weeks	212 (24.7)	417 (27.6)	0.137	215 (24.9)	494 (27.9)	0.106
Smoker	182 (21.2)	531 (35.2)	<0.001	205 (23.8)	667 (37.7)	<0.001
Long-term oxygen therapy	55 (6.4)	51 (3.4)	<0.001	59 (6.8)	47 (2.7)	<0.001
In-patient CAP	556 (64.8)	943 (62.5)	0.320	579 (67.1)	1134 (64.1)	0.051
Congestive heart failure	215 (25.1)	209 (13.8)	<0.001	217 (25.1)	276 (15.6)	<0.001
Cerebrovascular disease	75 (8.7)	123 (8.1)	0.639	109 (12.6)	145 (8.2)	<0.001
Diabetes mellitus	210 (24.5)	192 (12.7)	<0.001	195 (22.6)	198 (11.2)	<0.001
Chronic renal disease	94 (11.0)	95 (6.3)	<0.001	101 (11.7)	103 (5.8)	<0.001
Chronic liver disease	24 (2.8)	51 (3.4)	0.434	32 (3.7)	52 (2.9)	0.291
Neoplastic disease	109 (12.7)	112 (7.4)	<0.001	106 (12.3)	127 (7.2)	<0.001
COPD/asthma	403 (47.0)	443 (29.3)	<0.001	397 (46.0)	532 (30.1)	<0.001
CURB index n[#]	608	1070		663	1279	
0	304 (50.0)	600 (56.1)	0.005	326 (49.2)	708 (55.4)	0.020
1	202 (33.2)	321 (30.0)		217 (32.7)	383 (30.0)	
2	68 (11.2)	123 (11.5)		88 (13.3)	155 (8.8)	
3	28 (4.6)	20 (1.9)		29 (4.4)	29 (2.3)	
4	6 (1.0)	6 (0.6)		3 (0.5)	4 (0.2)	
PCT value n	480	727		511	1023	
≥ 0.228 ng·mL ⁻¹	165 (34.4)	225 (31.0)	0.213	170 (33.3)	307 (30.0)	0.194
≥ 0.5 ng·mL ⁻¹	102 (21.3)	165 (22.7)	0.554	114 (22.3)	207 (20.2)	0.347
≥ 2.0 ng·mL ⁻¹	51 (10.6)	101 (13.9)	0.094	57 (11.2)	104 (10.2)	0.552
Antibiotic therapy <i>po/i.v.</i>						
Monotherapy	579 (67.5)	1028 (68.1)	0.640	577 (66.9)	1185 (67.0)	0.769
Combination therapy	263 (30.7)	447 (29.6)		269 (31.2)	538 (30.4)	

Data are presented as mean ± SD or n (%), unless otherwise stated. FluVac⁺: influenza vaccinated; FluVac⁻: unvaccinated; CAP: community-acquired pneumonia; COPD: chronic obstructive pulmonary disease; CURB: confusion, blood-urea nitrogen (>7 mmol·L⁻¹), respiratory rate (≥30 breaths·min⁻¹) and blood pressure (diastolic pressure ≤60 mmHg or systolic blood pressure <90 mmHg); PCT: procalcitonin; *po/i.v.*: per os/intravenous infusion. #: range 0–4 points, one point was given for each criterion.

vaccination on CAP severity worldwide. The results of this study suggest that during the influenza season prior influenza vaccination reduced 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 performed using the common clinical practice, the CURB score. Additionally, analyses were performed using the biomarker PCT, which also gained emerging significance in clinical practice 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 sensitises patients to secondary bacterial infections have been described. These mechanisms include sustained impairment of macrophage and neutrophil responses [4–6, 26], increased bacterial adherence to epithelia

due to upregulation of platelet-activating factor receptor expression [27] and induction of inhibitory interleukin-10 [28]. 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 the influenza season and any beneficial effect of influenza vaccination on CAP should operate only during the 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

TABLE 2 Influence of influenza vaccination on different outcome parameters by multivariate analyses for both cohorts

Variable	Season cohort	Off-season cohort
CURB index ≥ 1	0.763 (0.595–0.978)	0.830 (0.659–1.046)
PCT		
$\geq 0.228 \text{ ng}\cdot\text{mL}^{-1}$	0.878 (0.652–1.183)	0.948 (0.723–1.244)
$\geq 0.5 \text{ ng}\cdot\text{mL}^{-1}$	0.709 (0.508–0.988)	0.940 (0.695–1.272)
$\geq 2 \text{ ng}\cdot\text{mL}^{-1}$	0.530 (0.348–0.808)	0.807 (0.541–1.203)
14-day mortality	0.660 (0.343–1.270)	0.760 (0.369–1.566)
30-day mortality	0.650 (0.379–1.113)	0.876 (0.487–1.577)
Overall survival during 6-month observational periods	0.630 (0.446–0.891)	0.809 (0.589–1.111)
Necessity to change the initial antimicrobial therapy	0.884 (0.704–1.110)	0.944 (0.762–1.169)
Duration of antimicrobial therapy days	$0.074 \pm 0.236^{\#,\S}$	$-0.135 \pm 0.236^{\#,+}$
Duration of hospitalisation days	$-0.705 \pm 0.469^{\#,\S}$	$-0.421 \pm 0.487^{\#,\S}$

Data are presented as OR (95% CI) or linear regression analysis slope $\pm$ SE. Data for overall survival are presented as adjusted HR (95% CI). CURB: confusion, blood-urea nitrogen ($>7 \text{ mmol}\cdot\text{L}^{-1}$), respiratory rate ($\geq 30 \text{ breaths}\cdot\text{min}^{-1}$) and blood pressure (diastolic pressure $\leq 60 \text{ mmHg}$ or systolic blood pressure $<90 \text{ mmHg}$); PCT: procalcitonin. $\#$: adjusted for age, sex, pneumococcal vaccination status, body mass index, nursing home residency, smoking, previous antibiotic therapy, long-term oxygen therapy and number of comorbidities; $\S$: $p=0.754$; $+$: $p=0.569$; $\S$: $p=0.133$; f : $p=0.388$.

often occur when the virus is no longer detectable [29]. 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 the influenza season is most probably 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 of whether vaccination was associated with lower CAP mortality or not. Despite the lower risk of severe pneumonia, 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 did not observe a significant difference between overall 30-day mortality in the season and off-season cohorts (3.9% *versus* 2.7%). Excess mortality attributable to influenza has been 5% on average during influenza seasons in the past decades in large study cohorts [30]. However, we lost 677 patients in our study (fig. 1) because of missing information regarding vaccination status. After including those patients into the analysis, overall season and off season 30-day mortality increased to 6.0% *versus* 4.5%. Possibly, our mortality

analyses were impaired by the fact that a significant number of patients died and we were lacking vaccination history.

In contrast, the results of our study revealed a significantly better overall survival of the FluVac⁺ patients after 6 months. 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 defence 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 benefits of the influenza vaccine has been derived from observational data, which are at greater risk of bias through confounding. This might have led to an over- or underestimation of the benefits of vaccination. Debate has arisen in the last few years that previous observational studies have overestimated the mortality benefits of the influenza vaccination due to nonspecific end-points and confounding [30, 31]. Influenza-vaccinated patients in our

TABLE 3 Vaccination status and mortality rates during both cohorts

	Season cohort			Off-season cohort		
	FluVac ⁺	FluVac ⁻	p-value	FluVac ⁺	FluVac ⁻	p-value
Subjects n	858	1510		863	1769	
14-day mortality	2.4	2.9	0.601	1.9	1.9	0.974
30-day mortality	3.4	4.2	0.442	3.0	2.5	0.440
6-month mortality	7.6	8.8	0.316	8.7	7.7	0.320

Data are presented as %, unless otherwise stated. FluVac⁺: influenza vaccinated; FluVac⁻: unvaccinated.

study were older, had more comorbidities and had been more frequently vaccinated against pneumococci. All these variables have been taken into account in the multivariate analysis that resulted in the reported 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 hospitalisation of inpatients. However, we think that these end-points 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 hospitalisation 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 clearly defined CAP diagnosis and a high number of influenza vaccinated cases. Furthermore, our study was not restricted to hospitalised patients with pneumonia as approximately one-third of patients were treated ambulatory.

However, our study has several limitations related to an observational study in which influenza vaccination has not been selected by randomisation. Despite 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.

In conclusion, based on severity of CAP this study suggests that prior influenza vaccination is associated with a less severe course of CAP during the influenza season and improved long-term survival. Therefore, results of this study support the current recommendations for influenza vaccination.

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STATEMENT OF INTEREST

Statements of interest for T. Welte, R. Schmidt-Ott, S. Eberle and T. Schaberg can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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