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Preventive effects of influenza and pneumococcal vaccination in the elderly – results from a population-based retrospective cohort study

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ABSTRACT

Influenza and pneumococcal vaccinations are recommended in the elderly to reduce life-threatening complications like sepsis. Protection may be reduced with increasing age. We aimed to assess the effectiveness of both vaccines in the elderly by performing a retrospective cohort study of 138,877 individuals aged ≥60 y in Germany, who were insured in a large statutory health insurance (AOK PLUS). We used longitudinal claims data to classify individuals according to vaccination status 2008–2014, and assessed vaccine effectiveness (VE) in 2015 and 2016. Inverse probability weighting based on generalized propensity scores was used to adjust for systematic between-group differences. Influenza vaccination was associated with a reduction of hospital treatment in laboratory-confirmed influenza in 2015 (VE = 41.32 [95%CI 0.85, 65.26]), but had no significant impact on the overall influenza incidence. Complications of influenza (pneumonia and sepsis) were reduced in 2016. We found a rise in influenza-like illness and acute respiratory infections in both years and an increased 90-d mortality after hospital-treated pneumonia in vaccinees in 2015. Pneumococcal vaccination was effective in preventing hospital-treated pneumonia within the first and second year after vaccination (VE = 52.45 [13.31, 73.92] and 46.04 [5.46, 69.21], respectively), but had no impact on sepsis incidence or pneumonia mortality. Influenza and pneumococcal vaccination can prevent severe complications from influenza and hospital-treated pneumonia in the elderly, respectively. Vaccine effects differ between years and seasons and are partly difficult to interpret. Despite extensive efforts to adjust for between-group differences, residual bias cannot be ruled out, possibly explaining signals like increased ILI or pneumonia mortality.

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Vaccine effectiveness; influenza; pneumococci; pneumonia; sepsis

Introduction

Influenza and pneumococcal disease including pneumonia and invasive pneumococcal disease (IPD) are major contributors to morbidity and mortality in the elderly.[1] Individuals aged ≥60 y are at increased risk for severe complications such as sepsis, hospitalizations, and death from influenza and pneumonia. Vaccination against influenza and pneumococci is therefore recommended by WHO for the elderly, and is emphasized as a major strategy in the prevention of sepsis in a recent WHO resolution.[2]

Reliable estimates on their effectiveness are important for the conceptualization of evidence-informed vaccination policies and campaigns. Effectiveness of influenza vaccines against influenza varies by season and may be reduced in elderly, who were found to develop lower postvaccination antibody titers than younger controls.[3] A meta-analysis based on 64 studies concluded a vaccine effectiveness of 23% for the protection against influenza-like-illness (ILI) in nursing home residents, but non-significant vaccine effectiveness against influenza in both nursing home residents and community-dwelling elderly.[4] However, there is evidence for a decline in complications and related hospital admissions and death in vaccinated individuals in this age group.[4,5] Pneumococcal vaccinations were found to be effective against IPD in the elderly, but studies on vaccine effectiveness against non-bacteremic pneumonia and protection effects in patients with immunosuppression are contradictory – particularly for pneumococcal polysaccharide vaccines.[1,6] There may be additive vaccine effects by combining influenza and pneumococcal vaccination,[7] since pneumococcal infections are

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frequent in influenza patients[8] and were found to contribute in 1/4 of influenza deaths. Evidence on the prevention of sepsis by influenza and pneumococcal vaccination is limited to cases of culture-proven pneumococcal bacteremia,[6,9] which are known to occur in less than 50% of sepsis cases.[10]

The evaluation of vaccine effects in a population-based design is exacting and costly. Health claims data can offer vaccination and morbidity data for large populations and are increasingly used to evaluate vaccine effectiveness.[11,12] The objective of this study was to investigate influenza, pneumococcal, and combined vaccine effectiveness in preventing influenza (laboratory confirmed/ILI), IPD, pneumonia, and sepsis cases as well as hospital admissions and deaths from these causes in elderly individuals aged ≥60 y in 2015 and 2016 by using population-based health claims data. The study forms part of the vaccination60+ project that was designed to increase influenza and pneumococcal vaccination rates and knowledge about sepsis in individuals aged ≥60 y in Thuringia as a model region for Germany.

Material and methods

Data source and study population

Our analyses based on health insurance claims data from individuals ≥60 y living in Thuringia, who were insured with the German statutory health insurance AOK PLUS. The AOK PLUS is the largest provider of statutory health insurance in Central Germany and currently covers about 50% of its population. Enrollment in the AOK PLUS is unrestricted regarding age, health status, income, or employment. Data were derived from the billing data for inpatient and outpatient care. They include a unique patient identification number that allows for longitudinal analyses. Data provision was approved by the responsible authority in accordance with § 75 SGB X (SGB = social security statute book). In Germany, annual influenza vaccination (IV) is recommended for adults aged ≥60 y as well as for those with immunosuppression, chronic health impairments and close contacts of patients at risk including health care workers.[13] Pneumococcal vaccination (PV) is recommended for those aged ≥60 y with a 23-valent pneumococcal polysaccharide vaccine (PPV). For individuals with underlying chronical conditions associated with high risk of pneumococcal infection (e.g. immunosuppression, chronic renal failure, chronic liver insufficiency, or patients with cerebrospinal fluid fistula or cochlea implant) a sequential immunization with a 13-valent pneumococcal conjugate vaccine (PCV) and PPV is recommended.[13] Our study population included individuals aged ≥60 y who were continuously insured with AOK PLUS between 2008 and 2016 or until death in 2015 or 2016 (n = 209,703). We analyzed data between 2008 and 2016 and identified patients according to a predefined vaccination scheme which is depicted in Table 1. Vaccination effects were analyzed in 2015 and 2016. Data from 2008 to 2014 were used to identify risk factors and prior vaccination status. Based on vaccinations received in 2014–2016, we defined three treatment groups: Group IV comprised individuals vaccinated against influenza in quarter 3/4 of 2014–2016, and excluded patients vaccinated against pneumococci in 2014–2016. Group PV included individuals vaccinated incidentally against pneumococci in 2014, and excluded individuals vaccinated against influenza in 2014–2016. Group BOTH were individuals vaccinated against influenza in quarter 3/4 of 2014–2016 and incidentally vaccinated against pneumococci in 2014. Individuals vaccinated neither against pneumococci nor influenza in 2014–2016 comprised the control group (group NONE). To rule out biased estimation of vaccine effectiveness due to previous vaccinations, we also excluded individuals with pneumococcal vaccination between 2008 and 2013 in all groups and influenza vaccination in 2012 or 2013 in groups with comparisons to non-influenza-vaccinated individuals (PV, NONE groups). We also excluded individuals with repeated pneumococcal vaccination after 2 y to avoid biased estimates of long-term effects in this group.

Study design

We performed a retrospective cohort study with group-wise comparisons between unvaccinated and vaccinated individuals to assess (i) influenza vaccine effectiveness (IV vs. NONE group) and (ii) pneumococcal vaccine effectiveness (PV vs. NONE group) as well as (iii) the effectiveness of the combined vaccination (BOTH vs. NONE group). Additionally, the effect of the combined vaccination compared to single vaccination against influenza or pneumococci were considered (BOTH vs. PV group and BOTH vs. IV group). We denote these two effects as incremental vaccine effectiveness. In order to adjust for systematic differences between the groups, we used inverse probability weighting (IPW) based on generalized propensity scores[14] (GPSs). As pre-treatment covariates, we included individual risk factors such as comorbidities, need for long-term

Table 1. Inclusion criteria according to vaccination scheme in 2014–2016.

	year	2008	2009	2010	2011	2012				2013				2014				2015				2016			
Group	quarter					1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
IV	PV-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	IV+					+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+	+	+/-	+/-	+	+	+/-	+/-	+	+
PV	PV+	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+/-	+/-	+/-	+/-	-	-	-	-
	IV-					-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Both	PV+	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+/-	+/-	+/-	+/-	-	-	-	-
	IV+					+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+	+	+/-	+/-	+	+	+/-	+/-	+	+
None	PV-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	IV-					-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

IV, Influenza vaccinated group; PV, Pneumococcal Vaccination group.
+ = vaccination, - = no vaccination, +/- = vaccination or no vaccination.

care according to the three graded care levels in the German health care system which entitle for long-term care insurance benefits, prior health care utilization and prior influenza, pneumonia and sepsis occurrence. A detailed description and definition of all covariates can be found in Table S1 in the Supplement.

Outcome measures

We analyzed (i) influenza vaccine effectiveness as the incidence of overall laboratory confirmed influenza and the incidence of influenza-like illness (ILI) for two consecutive influenza vaccines and seasons as primary outcome. As the estimated duration of the influenza seasons was between calendar week 2–16 in 2015[15] and calendar week 2–15 in 2016[16] in Germany, we assessed the effectiveness of the 2014 influenza vaccine in calendar year 2015, and the effectiveness of the 2015 vaccine in calendar year 2016 as surrogates of the influenza seasons. Pneumococcal vaccine effectiveness (ii) was assessed after pneumococcal vaccination in 2014 in a follow-up time frame of 2 y (2015, 2016). Primary outcome was the overall incidence of all-cause pneumonia in 2015, 2016. We (iii) analyzed the effectiveness of combined influenza/pneumococcal vaccination compared to unvaccinated individuals as well as compared to individuals with only one vaccination (either influenza or pneumococcal vaccination) regarding the incidence of laboratory confirmed influenza, ILI, and all-cause pneumonia in 2015 or 2016 as primary outcome. Secondary outcomes comprised the incidence of all-cause pneumonia in (i), IPD in (ii–iii), acute respiratory infections (ARI), and sepsis in (i)–(iii), as well as 90-d mortality after ILI, all-cause pneumonia, IPD, and sepsis in (i)–(iii). Overall incidence of laboratory confirmed influenza/ILI, pneumonia, IPD, ARI, and sepsis was defined as at least one hospitalization or outpatient visit coded with the ICD-10-GM (German Modification) codes in Table S2 in the Supplement in 2015 or 2016. Both primary and secondary discharge diagnoses as well as outpatient diagnoses were included in the analysis. Ninety-day mortality was defined as death within 90 d after hospital discharge of a hospital-treated episode with the disease or in the three months after the quarter in which the disease was diagnosed.

Statistical analyses

Average vaccine effectiveness was estimated using IPW. Individual weights based on the GPS were estimated using a non-parametric tree-based generalized boosted regression model (GBRM), which allows for a large number of pre-treatment variables and accounts for possible higher-order interactions among covariates in predicting group membership.[17] Covariates used for propensity score estimation are given in Table S2. Pairwise absolute standardized mean differences (ASMD) in the covariates between the groups were used for assessing covariate balancing. ASMDs < 0.2 indicate good covariate balancing.[18] We utilized the implementation of the GBRM algorithm in the R package *twang*[19] for estimating GPS.

Vaccine effectiveness regarding incidences and mortalities was tested by means of design corrected Rao-Scott χ^2-Tests for complex data.[20,21] We estimated the vaccine effectiveness $VE = (1 - RR_{10}) \cdot 100$ and their 95%-confidence intervals (CI). RR_{10} denotes the relative risk of an adverse event in treatment group 1 compared to the reference group 0. We used the PROC SURVEYFREQ procedure implemented in SAS 9.4. Detailed information about the statistical analyses can be found in the Supplement.

Results

A total of 138,877/363,007 individuals met the inclusion criteria, of which 61,541 were vaccinated against influenza only (IV), 1,136 against pneumococci only (PV), 3,333 against pneumococci and influenza (BOTH), and 72,867 were neither vaccinated against pneumococci nor influenza (NONE) in the respective time frames (Figure 1). Table 2 shows the demographic characteristics of the included individuals. Individuals of the PV group were youngest, and had the lowest number of comorbidities and incident influenza, pneumonia, and sepsis cases in 2013 among all vaccination groups, whereas the IV group included the highest proportion of women and nursing home residents as well as they were most elderly and comorbid. After IPW, the pairwise ASMDs of the baseline characteristics and risk factors between all pairs of the four groups were below the critical value of 0.2, which indicates good covariate balance (Figure 2).

Effectiveness of the influenza vaccination (IV vs. NONE)

Table 3 displays influenza VE comparing individuals vaccinated against influenza with non-vaccinated individuals.

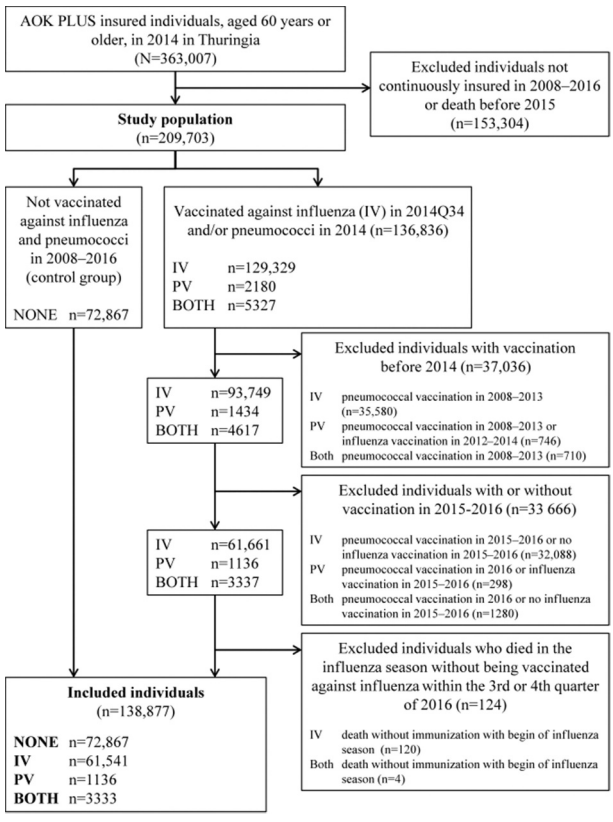

Figure 1. Flow of study inclusion.

Table 2. Baseline characteristics of study subjects according to vaccination status in the unmatched cohort.

	NONE	BOTH	PV	IV	Overall
Age, mean (SD)	72.38 (8.61)	72.87 (8.91)	69.62 (7.83)	76.94 (7.94)	74.39 (8.63)
Male sex, %	42.22	43.53	43.84	39.12	40.89
Charlson Comorbidity Index (CCI) in 2013, %					
CCI: 0	39.63	19.92	34.15	17.38	29.25
CCI: 1	22.91	23.43	25.35	22.54	22.78
CCI: 2–4	30.91	43.68	33.54	46.12	37.98
CCI: 4	6.55	12.96	6.95	13.96	9.99
Underlying chronic conditions and comorbidity in 2013, %					
Chronic immunosuppression	13.20	17.91	13.47	19.88	16.27
Heart disease	42.18	58.36	43.31	64.32	52.39
Lung disease	17.76	27.87	19.10	25.60	21.49
Renal disease	14.50	25.26	16.73	24.37	19.15
Metabolic disease	58.05	76.06	67.25	78.80	67.75
Neurological disorders	19,87	29,40	21,92	33,07	25,96
Health care use in 2013					
Nursing home residence, %	1.94	7.38	1.76	8.62	5.03
Number of hospitalizations, mean (SD)	0.41 (1.01)	0.57 (1.13)	0.41 (0.95)	0.57 (1.10)	0.48 (1.05)
Number of GP outpatient visits, mean (SD)	8.53 (6.94)	13.08 (7.52)	9.77 (7.05)	13.63 (7.36)	10.91 (7.57)
Number of specialist outpatient visits, mean (SD)	7.63 (11.86)	12.49 (16.98)	9.38 (11.68)	11.81 (14.79)	9.62 (13.54)
Incident diseases in 2013, %					
Influenza-like Illness	0.39	0.66	0.26	0.39	0.40
Pneumonia	1.93	4.29	2.46	3.29	2.59
Sepsis	1.16	1.86	1.23	1.80	1.46

GP, General Practitioner; IV, Influenza vaccinated group; PV, Pneumococcal vaccination group.

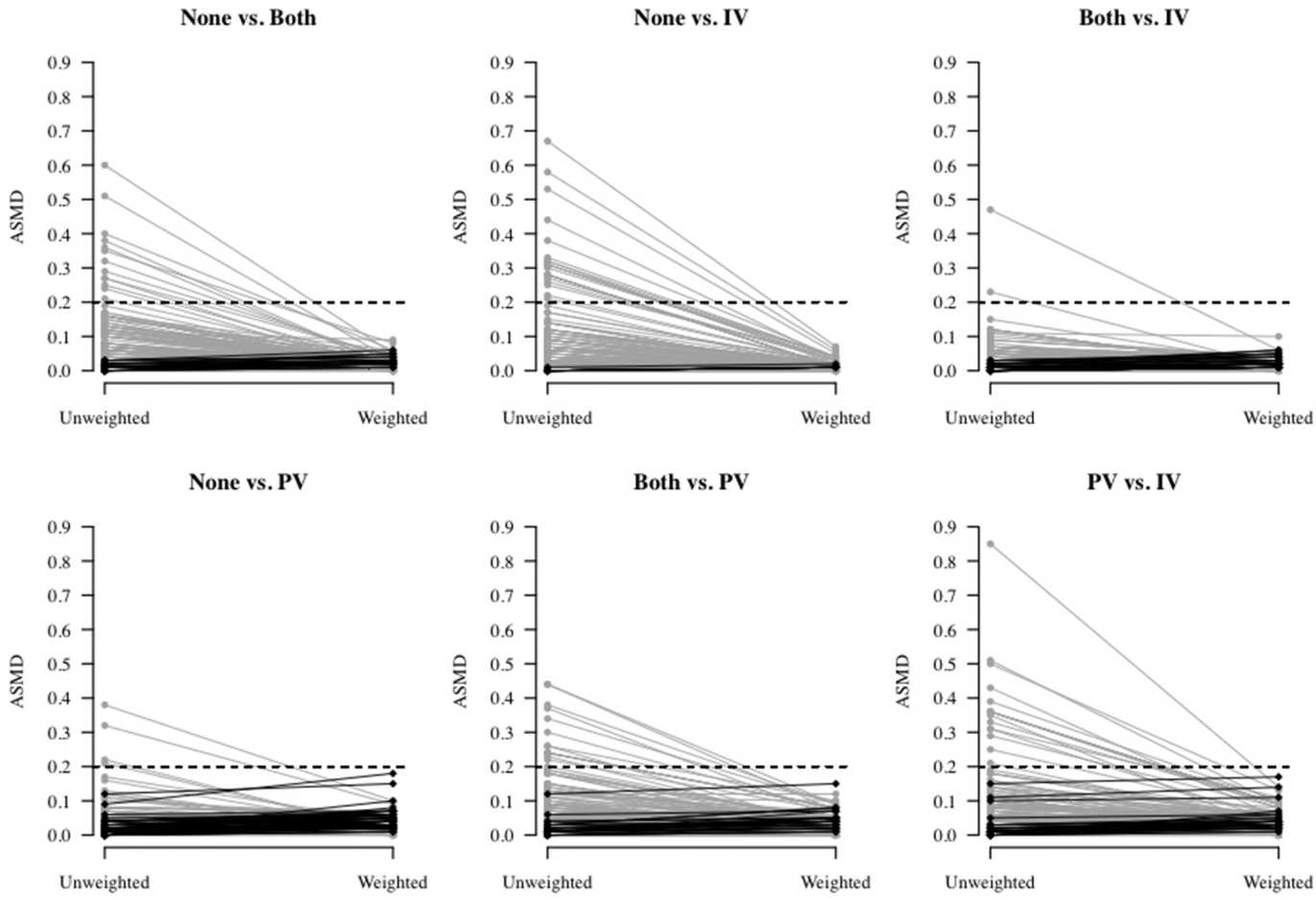

Figure 2. Pairwise absolute standardized mean differences in all covariates used for propensity score estimation before (unweighted) and after IPW (weighted).

Table 3. Influenza vaccine effectiveness comparing groups IV (n = 61,541) and NONE (n = 72,867).

	2015				2016			
	Risk in %		VE [95% CI]	p	Risk in %		VE [95% CI]	p
Outcome	IV	NONE			IV	NONE		
Overall incidence								
ARI	17.953	15.733	-14.107 [-17.475, -10.836]	0.000	15.412	13.880	-11.033 [-14.679, -7.503]	0.000
LC-Influenza	0.095	0.096	0.530 [-52.559, 35.145]	0.981	0.0217	0.0364	40.480 [-19.199, 70.279]	0.139
- ILI	0.649	0.532	-21.984 [-46.788, -1.372]	0.035	0.430	0.257	-67.510 [-108.072, -34.856]	0.000
- Pneumonia	4.831	4.917	1.754 [-4.082, 7.263]	0.548	3.946	4.465	11.624 [5.16, 17.647]	0.001
Incidence of outpatient-treated								
ARI	16.892	14.467	-16.76 [-20.368, -13.26]	0.000	14.476	12.764	-13.412 [-17.257, -9.692]	0.000
LC-Influenza	0.058	0.035	-67.409 [-225.524, 13.905]	0.125	0.012	0.019	37.374 [-63.876, 76.067]	0.336
ILI	0.609	0.472	-28.956 [-56.789, -6.064]	0.011	0.417	0.236	-76.764 [-121.088, -41.326]	0.000
Pneumonia	2.524	2.518	-0.252 [-8.542, 7.405]	0.951	2.196	2.208	0.52 [-10.619, 10.538]	0.923
Incidence of hospital-treated								
LC-Influenza	0.040	0.068	41.315 [0.853, 65.264]	0.044	0.013	0.021	39.587 [-54.741, 76.414]	0.289
ILI	0.056	0.073	24.055 [-20.078, 51.967]	0.238	0.020	0.022	23.13 [-77.43, 66.7]	0.537
Pneumonia	3.108	3.193	2.672 [-4.93, 9.723]	0.480	2.566	3.012	14.825 [6.491, 22.416]	0.001
Sepsis	1.602	1.651	2.954 [-9.113, 13.686]	0.616	1.339	1.745	23.273 [14.172, 31.409]	0.000
90-d mortality after								
ILI	0.075	0.043	-74.312 [-352.976, 32.922]	0.248	0.014	0.011	-31.34 [-238.22, 49]	0.571
Pneumonia	1.864	1.671	-11.52 [-22.507, -1.518]	0.023	1.374	1.543	10.973 [-1.012, 21.537]	0.071
Sepsis	0.816	0.761	-7.179 [-22.728, 6.4]	0.316	0.640	0.830	22.937 [9.48, 34.394]	0.002

ARI, Acute respiratory infection; LC-Influenza, Laboratory confirmed influenza; ILI, Influenza-like illness; IV, Influenza vaccinated group.

Table 4. Pneumococcal vaccine effectiveness comparing groups PV (n = 1,136) and NONE (n = 72,867).

	2015				2016			
	Risk in %		VE [95% CI]	p	Risk in %		VE [95% CI]	p
Outcome	PV	NONE			PV	NONE		
Overall incidence								
ARI	16.662	15.733	-5.900 [-23.571, 9.243]	0.469	14.347	13.880	-3.360 [-22.174, 12.556]	0.699
Pneumonia	3.139	4.917	36.156 [4.103, 57.496]	0.028	3.093	4.465	30.732 [-6.069, 54.765]	0.088
Incidence of outpatient-treated								
ARI	15.753	14.467	-8.888 [-27.652, 7.118]	0.297	13.131	12.764	-2.879 [-22.65, 13.705]	0.752
Pneumonia	2.207	2.518	12.354 [-43.304, 46.396]	0.598	2.108	2.208	4.502 [-65.098, 44.761]	0.869
Incidence of hospital-treated								
Pneumonia	1.518	3.193	52.449 [13.309, 73.918]	0.012	1.625	3.012	46.044 [5.462, 69.205]	0.028
Sepsis	1.009	1.651	38.906 [-20.186, 68.944]	0.148	1.656	1.745	5.085 [-59.989, 43.691]	0.845
90-d mortality after								
Pneumonia	0.779	1.671	53.409 [-6.83, 79.681]	0.064	1.086	1.543	29.619 [-60.856, 69.205]	0.402
Sepsis	0.415	0.761	45.438 [-56.51, 80.979]	0.252	0.459	0.830	44.637 [-47.909, 79.277]	0.231

ARI, Acute respiratory infection; PV, Pneumococcal Vaccination.

There was a significant difference in the incidence of laboratory confirmed, hospital-treated influenza between vaccinated and unvaccinated individuals in 2015 (0.040 vs. 0.068/100, VE 41.32% [95%CI 0.85, 65.26], for unweighted and weighted frequencies see Table S3, Supplement), but not in 2016. The positive effect was neither found for the outpatient-treated laboratory confirmed influenza nor the overall incidence of the laboratory confirmed influenza. We found a significant increase of overall ILI incidence in 2015 and 2016 in vaccinated compared to unvaccinated individuals (0.65 vs. 0.53/100, VE -21.98% [-46.79, -1.37] (2015), 0.43 vs. 0.26/100, VE -67.51% [-108.07, -34.86] (2016)) that was driven by the increase of ILI cases in the outpatient setting. The number of hospitalizations for ILI was similarly low in both groups. The overall and outpatient incidence of ARI in vaccinated was higher than in non-vaccinated individuals (17.95 vs. 15.73/100, VE -14.11% [-17.48, -10.84] (2015), 15.41 vs. 13.88/100, VE -11.03% [-14.68, -7.50] (2016)). After influenza vaccination in 2015, we found significantly lower risks for severe complications of influenza as expressed by a decline in overall and hospital incidence of pneumonia (3.95 vs. 4.47/100, VE 11.62% [5.16, 17.65] (overall), 2.57 vs. 3.01/100, VE 14.83% [6.49, 22.42] (hospital)), and hospital incidence (1.33 vs. 1.74/100, VE 23.27% [14.17, 31.41]) and 90-d mortality (0.64 vs. 0.84/100, VE 22.94% [9.48, 34.39]) of sepsis in 2016. None of these vaccine effects was found in 2015, but an elevated 90-d mortality after pneumonia in the group of influenza vaccinated individuals in 2015 (VE -11.52% [-22.51, -1.52]).

Effectiveness of the pneumococcal vaccination (PV vs. NONE)

Results of the analyses on pneumococcal vaccination effectiveness are shown in Table 4. In the first year after vaccination, overall pneumonia incidence was significantly reduced in the vaccination group (3.14 vs. 4.92/100, VE 36.16% [4.10, 57.50]), whereas in 2016, there was no significant difference between groups (Table 4). Outpatient pneumonia incidence was not significantly different between groups in both years, whereas incidence of hospital-treated pneumonia was approximately

Table 5. Effectiveness of combined influenza and pneumococcal vaccination comparing groups BOTH (n = 3,333) and NONE (n = 72,867).

	2015				2016			
	Risk in %		VE [95% CI]	p	Risk in %		VE [95% CI]	p
Outcome	BOTH	NONE			BOTH	NONE		
Overall incidence								
ARI	18.896	15.733	-20.1 [-30.37, -10.639]	0.000	16.277	13.880	-17.269 [-28.519, -7.005]	0.001
ILI	0.551	0.532	-3.697 [-63.475, 34.223]	0.876	0.247	0.257	3.678 [-98.525, 53.266]	0.919
LC-Influenza	0.121	0.096	-26.231 [-277.930, 57.838]	0.677	-	-	-	-
Pneumonia	4.983	4.917	-1.352 [-22.686, 16.272]	0.890	4.356	4.465	2.45 [-20.069, 20.745]	0.815
Incidence of outpatient-treated								
ARI	17.595	14.467	-21.622 [-32.404, -11.719]	0.000	15.425	12.764	-20,846 [-32.862, -9.917]	0.000
ILI	0.479	0.472	-1.382 [-62.175, 36.622]	0.954	0.247	0.236	-4,785 [-116.318, 49.242]	0.899
LC-Influenza	0.022	0.035	35.380 [-388.847, 91.458]	0.700	-	-	-	-
Pneumonia	2.773	2.518	-10.14 [-40.246, 13.504]	0.434	2.417	2.208	-9.462 [-46.841, 18.402]	0.547
Incidence of hospital-treated								
ILI	0.099	0.073	-34.388 [-374.402, 61.931]	0.645	-	-	-	-
LC-Influenza	0.099	0.068	-44.591 [-413.026, 59.249]	0.566	-	-	-	-
Pneumonia	2.920	3.193	8.554 [-18.608, 29.496]	0.500	2.514	3.012	16.556 [-11.075, 37.313]	0.213
Sepsis	1.301	1.651	21.176 [-15.573, 46.24]	0.221	1.275	1.745	26.934 [-9.54, 51.263]	0.127
90-d mortality after								
ILI	0.077	0.043	-78.29 [-721.513, 61.307]	0.452	0.022	0.010	-31.34 [-238.22, 49]	0.571
Pneumonia	1.642	1.671	1.717 [-38.621, 30.317]	0.921	1.585	1.543	-2.686 [-48.706, 29.093]	0.889
Sepsis	0.770	0.761	-1.147 [-53.348, 33.284]	0.957	0.441	0.830	46.841 [-10.8, 74.496]	0.086

ARI, Acute respiratory infection; LC-Influenza, Laboratory confirmed influenza; ILI, Influenza-like illness.

halved in vaccinated individuals in 2015 and 2016 (1.52 vs. 3.2/100, VE 52.45% [13.31, 73.92] (2015), 1.62 vs. 3.01/100, VE 46.04% [5.46, 69.21] (2016)). The number of IPD cases was too small to allow for comparisons between groups. There was no reduction of sepsis incidence in the vaccination group in both years after vaccination. Ninety-day mortality after pneumonia and sepsis did not differ significantly between groups.

Effectiveness of the combined vaccination (BOTH vs. NONE) and incremental vaccine effects (BOTH vs. IV, BOTH vs. PV)

Table 5 includes the results of the analyses on combined vaccine effectiveness comparing individuals that received influenza and pneumococcal vaccinations with unvaccinated individuals. We found no significant differences in the occurrence and 90-d mortality of pneumonia, influenza, and sepsis. Again, the incidence of overall and hospital-treated ARI was increased in vaccinated individuals compared to unvaccinated controls in 2015 and 2016 (overall ARI incidence: 18.9 vs. 15.73/100, VE -20.10 [-30.37, -10.64] (2015), 16.28 vs. 13.9/100, VE -17.27 [-28.52, -7.01] (2016)). Assessing incremental vaccine effectiveness, we found no significant effects that indicated a dominance of the combined vaccination over the respective single vaccinations (Tables S4 and S5, Supplement).

Discussion

We undertook a large retrospective cohort study on influenza and pneumococcal vaccine effectiveness in individuals aged ≥60 y in Germany. Using a population-based health claims database that includes integrated data on inpatient and outpatient care of 138,877 individuals, we were able to compare outcomes of vaccinated individuals with unvaccinated controls in a follow-up period of 24 months after index vaccination. This comprehensive database also allowed us to apply a rigorous adjustment for systematic differences regarding pre-vaccination comorbidities, dependence for chronic care and health care seeking behavior, that addressed major sources of confounding in observational cohort studies on vaccine effectiveness by healthy vaccinee or indication bias.[22,23]

We found that influenza vaccination of elderly persons was associated with an increase in ILI and unspecific ARI – mainly driven by an increase of outpatient diagnoses –, whereas the results on the incidence of laboratory confirmed influenza are inconsistent. Significant lower incidence rates in vaccinated individuals were only found with respect to hospital-treated influenza cases in 2015. Other vaccine effects varied between the two influenza seasons observed. After influenza vaccination in 2015, we found reductions in overall pneumonia, hospital-treated pneumonia and sepsis incidence, and sepsis mortality in 2016, whereas the mortality 90 d after hospital-treated pneumonia was elevated in 2015 in the vaccination group.

An increase of unspecific ARI and ILI after influenza vaccination was also observed in a Chinese RCT that compared ARI incidence after influenza or placebo vaccination in children and found a relative risk of confirmed non-influenza virus infections among influenza vaccinees of 4.40 [95% CI, 1.31–14.8].[24] In Taiwan, a similar increase in outpatient visits for influenza and pneumonia after influenza vaccination was observed in several influenza seasons (OR up to 1.09 [95% CI, 1.02–1.16] after propensity score matching) whereas hospitalizations for the respective diseases were reduced.[25] There are several possible explanations for this observation. The reduction of complications such as severe pneumonia and sepsis may indicate not a prevention but attenuation of disease reflected by a shift from hospitalization to outpatient treatment.[26] This notion supports the observation of the Taiwanese cohort study.[25] Second, regarding observational trials like ours, a bias by indication, i.e. that patients with higher risk due to comorbidities are more likely to get the vaccination, cannot be completely ruled out despite rigorous effort to adjust for the above-mentioned covariates. However, this possible bias should be minimized or eliminated in RCTs. In the Chinese

RCT[24] that have seen a similar effect, this phenomenon was interpreted as reduced immunity against nonspecific respiratory infection for the benefit of immunity against influenza or expression of a temporary nonspecific immunity after influenza virus infection by the authors.[24] Furthermore, we cannot rule out that the increase in outpatient consultations for ILI/ARI and 90-d mortality after pneumonia observed in 2015 is related to unmeasured confounders, such as differences in health care seeking behavior, frailty, or disease severity which may not be specifically captured by ICD-coding and medications.[27] Other than inpatient care utilization, the extent of outpatient care utilization is generally stronger affected by the intensity of health care seeking behavior of patients.

With the exception of a significant positive effect of the influenza vaccination on the hospital-treated influenza in 2015, we did not found a reduction of laboratory confirmed influenza. This is in line with different observational studies that delivered inconclusive results on influenza vaccine effectiveness in preventing (proven) influenza in particular in community dwelling elderly.[4] A recent Cochrane review concluded based on the evidence from eight RCTs, that compared to a placebo group, vaccinated elderly may have lower risk of influenza (RR = 0.42 [95% CI 0.27–0.66]) and ILI (RR = 0.59 [95% CI 0.47–0.73]), but underlined the low to moderate certainty evidence of results.[28] According to the review, a major benefit of the vaccination however is the reduction of severe manifestations and hospitalizations that was also provable in our study in 2016. In 2015, this effect was absent. The superior influenza VE in the Influenza season 2015/2016 compared to Influenza season 2014/2015 is in line with other vaccine effectiveness studies that found a poor performance of the 2014/2015 vaccine due to a mismatch with circulating A/H3N2 virus strains,[29] while the 2015/2016 vaccine was more effective.[30] When comparing and interpreting our 2015 and 2016 results, it must be taken into account that the 2016 sample in our study is a subsample without the individuals that died in 2015 (n = 10,044, 7.23%). As mortality depends on many individual characteristics (e.g., age, morbidity), the 2016 subsample is on average younger, less dependent on nursing care, and may therefore be more capable to build immunity after vaccination.

Our study demonstrated that pneumococcal vaccination is effective in reducing around 50% of hospital-treated pneumonia cases within the first and second year after PV. Similar results were observed in an RCT in Japanese nursing home residents[31] and a prospective cohort study in community-dwelling elderly in Spain,[32] which found a hazard ratio for pneumonia of 0.74 [95% CI, 0.59–0.92] in vaccinated individuals. IPD case numbers were too small to allow for statistical analyses in our study. We observed no significant effects on sepsis incidence or disease-specific 90-d mortality.

We were unable to confirm additive effects from combining influenza and pneumococcal vaccination in the elderly that was found in other observational studies regarding a reduction of hospitalizations for pneumonia and influenza.[7,12]

Sepsis incidence was only reduced after influenza vaccination in 2016. PV had no significant impact on the occurrence of sepsis. Given that coding of sepsis is known to be incomplete in hospital discharge data and miss 2/3 clinically diagnosed sepsis cases,[33] we hypothesize that the reduction of severe complications, hospitalizations and death we found after influenza and pneumococcal vaccination may be a surrogate for the decrease in sepsis as life-threatening complication and final common pathway of death in infectious diseases.[34]

Our analyses included a population-based unselected cohort, and the use of a health claims database made it possible to rely them on a complete record of inpatient and outpatient care covering a time frame of nine consecutive years, which is a major strength of our study. Our ICD-code identification criteria for influenza, ARI, ILI, and pneumonia were based on definitions used by the Robert Koch Institute for routine electronic influenza and pneumonia surveillance in Germany.[35] This ICD-based surveillance was evaluated as valid source for syndromic influenza surveillance compared to laboratory data in a previous study.[36] After comprehensive adjustment for confounders, we investigated a broad set of vaccine effects. Despite these strengths, our study has also several limitations, including the retrospective design and reliance on administrative data, which is generated for reimbursement, not for research purposes. We are unable to validate the quality of influenza and pneumonia diagnoses since results from microbiology or imaging are unavailable in health claims data and therefore cannot rule out under- and misdiagnoses, which may impact the estimation of vaccine effectiveness. The accuracy of comorbidity coding may also vary between diseases.[37] Although it was found that comorbidity codes have a good predictive value,[38] there seems to be an underreporting of comorbidities in health claims data.[37,39] Although we used a rigorous adjustment for between-group differences including 236 variables on demographic characteristics, comorbidities, and health seeking behavior, the methodological options to control for all dimensions of patient characteristics that affect the probability of vaccination such as individual health behavior functional impairment or sociodemographic characteristics (e.g. family status) are limited. In a case-control study comparing adjustment for functional impairments based on administrative diagnoses vs. diagnoses from manual patient chart review, Jackson and colleagues concluded that diagnosis code covariates did not fully avoid healthy vaccinee bias in the assessment of prevention of influenza deaths by vaccination.[40] We therefore included also the prescription of medication, the number of outpatient visits, the participation in Disease Management Programs (offered for patients with chronic diseases in Germany) and nursing care information to mirror functional status/activities of daily living in our adjustment (see Supplement). Furthermore, several outcomes such as hospitalizations due to influenza occurred rarely, increasing the uncertainty of estimations. Replication of analyses is therefore needed using larger databases or other study designs.

Conclusions

In conclusion, the interpretation of the result pattern of this study is challenging. Nevertheless, we found evidence for beneficial effects of influenza and pneumococcal vaccination in the elderly such as a considerable prevention in hospital-treated pneumonia or severe complications from influenza infection in

single seasons, likely depending on vaccine matching with circulating strains. The mechanisms behind the observed increase in unspecific ILI/ARI after vaccination are still unclear. This may indicate residual bias due to unknown covariates, which cannot be ruled out despite the large number of potential confounding variables addressed in our analyses.

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Author contribution

CFS, AF, JS, AM, and KR designed the study. CF, HCV, and MP participated in the planning of the study. JS and AF prepared approval of data provision. AM and JS prepared and managed data. NR and AF checked data plausibility. NR, TL, AM, AF, JS conceptualized, NR and TL performed the statistical analyses. CFS, NR, AF, JS, and KR interpreted the data. CFS, NR, AF, and JS drafted the manuscript. AF and KR applied for funding. All authors revised the manuscript for intellectual content.

Disclosure of potential conflicts of interest

The other authors declared no competing interest.

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