Effects of Influenza Vaccination in Patients with Interstitial Lung Diseases: An Epidemiological Claims Data Analysis

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Authors' contributions: All authors were involved in the conception of the study. Michael Kreuter and Larissa Schwarzkopf initiated the project. Pavo Marijic conducted the data preparation and analysis in close coordination with Michael Kreuter, Larissa Schwarzkopf, Lars Schwettmann, Werner Maier, and Franziska Trudzinski. Pavo Marijic wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Abstract

Rationale: Vaccination is the most effective protection against influenza. Patients with interstitial lung diseases (ILD) represent a high-risk group for influenza complications. Thus, yearly influenza vaccination is recommended, but evidence on its effects is sparse.

Objective: This study aimed to compare all-cause mortality and all-cause and respiratory-related hospitalization between vaccinated and unvaccinated patients with ILD.

Methods: Using data from the largest German statutory health insurance fund (about 27 million insurees in 2020), we analyzed four influenza seasons from 2014/15 to 2017/18 and compared vaccinated to unvaccinated ILD patients. Starting from September 1 of each year we matched vaccinated to unvaccinated patients in a 1:1 ratio using a rolling cohort design. Mortality and hospitalization were compared with Kaplan-Meier plots and effects were calculated during the influenza season (in-season) with risk ratios (RR).

Results: Both, the vaccinated and the unvaccinated cohort included 7,503 patients in 2014/15, 10,318 in 2015/16, 12,723 in 2016/17, and 13,927 in 2017/18. Vaccination rates were low with 43.2% in season 2014/15 and decreased over time to 39.9% in season 2017/18. The RR for all-cause mortality were 0.79 (95%CI: 0.65, 0.97; p = 0.02) in season 2014/15, 0.66 (95%CI: 0.54, 0.80; p < 0.001) in 2015/16, 0.89 (95%CI: 0.76, 1.04; p = 0.15) in 2016/17, and 0.95 (95%CI: 0.81, 1.12; p = 0.57) in 2017/18. The effects on all-cause hospitalization and respiratory-related hospitalization were similar in all seasons.

Conclusions: Although an unequivocally beneficial impact of influenza vaccination in patients with ILD could not be demonstrated, we observed promising results regarding avoidance of all-

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cause mortality in half of the seasons observed. Given the low vaccination rates, further efforts are necessary to improve rates in ILD patients.

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Interstitial lung diseases (ILD) comprise a diverse group of pulmonary diseases summarized on the basis of similar clinical, physiologic, or pathologic characteristics and characterized by a high mortality (1, 2).

Influenza has a high public health relevance and is associated with an increased risk of hospitalization and death, especially in high-risk groups based on their underlying health conditions (3-5). Information on influenza in patients with ILD is scarce. However, a seasonality in hospitalizations and mortality in ILD was reported, with peaks in the winter, which might be related to the influenza season (6, 7). The most effective protection is vaccination (8). According to the World Health Organization, all individuals with chronic pulmonary diseases should receive an influenza vaccination (8, 9). Therefore, yearly vaccination of patients with ILD is highly recommended. However, vaccination rates appear to be rather low among patients with ILD. For example, Mohr et al. (2020) reported vaccination rates below 30% in a single-center study in south east Germany for the 2016/17 to 2019/20 seasons (10).

As evidence on the impact of influenza vaccination on individuals with ILD is clearly lacking, we aimed to compare all-cause mortality as well as all-cause and respiratory-related hospitalization in influenza-vaccinated vs. unvaccinated ILD patients in Germany.

Methods

Data set and sample selection

We performed an epidemiological claims data analysis with completely anonymized statutory health insurance (SHI) data. According to national guidelines on secondary data analysis ethical

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approval and consent to participate is not required (11). In Germany, health insurance is mandatory with about 87% of the resident population being insured by statutory funds (12). Access to membership in the statutory health insurance is available to everyone, regardless of factors such as professional affiliation, income, age or comorbidities (12). SHI is financed via risk-independent, income-dependent contributions and offers free access to a wide range of services. Particularly for outpatient physician care no copayments are due, while for inhospital care a flatrate of €10/day is charged.(12). The present analyses refer to data from the largest German SHI fund (Allgemeine Ortskrankenkasse - AOK), which insures approximately one third of the German resident population (13), and were provided by the AOK Research Institute (WIdO).

The initial data set contained all insured adults with an ICD-10 diagnosis of ILD, including Idiopathic Interstitial Pneumonia [J84.1], other fibrosing ILD [J84.0, J84.8, J84.9, D48.1], sarcoidosis [D86.0-D86.9], drug-associated ILD [J70.2-J70.4], pneumoconiosis [J62.0-J62.8, J63.0-J63.8], radiation-associated pneumonitis [J70.1], eosinophilic pneumonia [J82], hypersensitivity pneumonitis [J67.9] and connective tissue-associated ILD (CTD) [J99.1], from January 1, 2013 to December 31, 2018.

To ensure best possible identification of true ILD patients and, therefore, to minimize the risk of false-positive classifications, we used a previously applied algorithm (14) (Figure 1). Accordingly, we excluded individuals without a confirmed outpatient diagnosis (outpatient ICD diagnoses in Germany have to be categorized as: ‘Z’ = condition after, ‘A’ = exclusion diagnosis, ‘V’ = suspected diagnosis, and ‘G’ = confirmed diagnosis) by a pulmonologist, an internal medicine specialist, or a rheumatologist (the latter for CTD only) or any inpatient diagnosis.

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Furthermore, we omitted individuals who did not have at least one relevant diagnostic procedure (bronchoscopy, computerized tomography of the lungs, pulmonary function testing, and assessment of antibodies). Individuals with implausible ILD diagnoses were also disregarded. First, this group contained patients who received an exclusion diagnosis of ILD after a confirmed ILD diagnosis. Second, it included patients either with radiation-associated pneumonitis, but without diagnosis of malignancy, or with CTD but without diagnosis of autoimmune disease. Finally, we left out patients assigned to different ILDs simultaneously as well as individuals without continuous enrollment with the AOK.

Influenza vaccination was identified via codes from the physician's fee scale (Einheitlicher Bewertungsmaßstab, EBM) in the outpatient setting, as influenza vaccination is only provided in outpatient care and not in hospitals (Table E1). The four influenza seasons investigated included the years 2014/15, 2015/16, 2016/17, and 2017/18.

Out of the identified ILD patients, we selected patients for each influenza season separately, as the seasons were analyzed independently. The German federal government agency for disease control and prevention (Robert Koch-Institute - RKI) suggests yearly vaccination in October or November, but provision is also feasible during an influenza wave (15). Against this background, for each season we set the period between September 1 and January 31 of the following year as vaccination season. Patients vaccinated outside this time frame were excluded. To be eligible for selection in a vaccination season, only patients who had received their ILD diagnosis before the beginning of the respective season were considered. Additionally, we excluded patients with palliative treatment, which was identified via outpatient and inpatient treatment and diagnosis (Table E1), during the three months before

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the matching date. Such patients are at high risk of experiencing adverse outcomes but receive vaccination only if their state of health allows it. Consequently, they would increase a healthy vaccinee bias (16). Finally, patients with missing data on matching variables were excluded.

Matching procedure and outcome variables

We performed a day-specific exact matching using a rolling cohort design (17). Starting from the beginning of each season on September 1, we matched patients receiving influenza vaccination to patients without vaccination in a 1:1 ratio. For each individual patient, follow-up ended in case of an event (hospitalization, death) or at the end of the influenza season. Furthermore, both patients of a matched pair were censored if the previously unvaccinated control received vaccination during the observation period. With vaccination, the previously unvaccinated control patients were included in the treatment group on the day of vaccination and thus eligible for matching. As influenza vaccination is only provided in the outpatient setting, hospitalized patients were not eligible for matching during the hospital stay. After discharge they were considered again for matching.

By using a rolling cohort study design, our methodological approach enabled us to partially overcome some weaknesses of previous vaccination studies. More specifically, due to the day-specific exact matching of patients in the treatment and control group, covariates were exactly balanced, which reduces biases such as confounding by indication and the healthy vaccinee bias (16). Furthermore, we were able to take a prospective view on the data, and thus to account for the timing of the vaccination (before/after an outcome) as well as the

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occurrence of the outcomes (within/outside the influenza season). Finally, our methodological approach has enabled us to visualize outcomes by Kaplan-Meier curves.

Based on pre-existing literature and clinical expertise, covariates included in the matching process considered categorized age in years (18-29, 30-39, 40-49, 50-59, 60-69, 70-79, >80), sex (male, female), German federal state, ILD diagnosis, and Elixhauser comorbidity score (18). The Elixhauser comorbidity index includes a set of 31 comorbidity categories, which were dummy coded. The index was implemented using the ICD-10 coding algorithm of Quan et al. (19). To avoid false-positive comorbidity diagnosis, at least two confirmed outpatient diagnosis in two separated quarters or one primary inpatient diagnosis in the year before matching were necessary. To avoid double-counting for the categories hypertension (complicated and uncomplicated), diabetes (complicated and uncomplicated), and cancer (solid tumor without metastasis and metastasis cancer), only the more severe category was counted. The Elixhauser score per person was built by summing up individual comorbidities. Furthermore, we coded a dummy for nursing home residency and the need for nursing care according to care levels, as these patients are considered a highly vulnerable population (20). Before 2017, need for nursing care was operationalized by three and thereafter by five care levels. The classification of care levels is based on the need for assistance with activities of daily living measured in terms of time, with higher levels indicating higher need for care (21). Additionally, we included information on receipt of in- or outpatient radiotherapy or chemotherapy in the three months before matching, as these variables indicate severe conditions and, therefore, are closely linked to short-term mortality.

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Standardized mean differences (SMD) were used to assess group balancing, with differences less than 0.1 indicating a good balance (22).

All-cause mortality and all-cause as well as respiratory-related hospitalization were defined as outcomes for each season. Respiratory-related hospitalizations included all hospital stays with a primary or secondary ICD-10 diagnosis of “acute upper respiratory infections” [J00-J06], “influenza and pneumonia” [J09-J18] or “other acute lower respiratory infections” [J20-J22], or a primary ILD-specific diagnosis.

Definition of influenza periods

For the analysis the observation period was divided into time intervals before (pre-season), during (in-season), and after (post-season) the influenza season. The periods varied for each season and were defined based on influenza surveillance data from the RKI (23). The pre-season started on the day of matching until the beginning of the influenza season. This beginning was set at the time when influenza viruses were described as being detected continuously. End of in-season coincided with the beginning of post-season and was set at calendar week 20 each year (15). Each post-season lasted until August 31 as September 1 marks the beginning of the vaccination period and, therewith, the start of the next pre-season. Exact dates for all seasons are reported in Table E2.

Statistical analysis

Each influenza season was analyzed separately to capture potential differences in the effects between the different seasons.

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We visualized the overall observation time for mortality and hospitalization from matching until August 31 of each season with Kaplan-Meier curves. The association between influenza vaccination and mortality as well as hospitalization was estimated during the influenza seasons (in-season period) by risk ratios (RR) with bootstrapped 95% confidence intervals (95% CI) with 1000 replications. As the effect of the vaccine is only gradually building, the first 14 days after matching were disregarded for the estimation.

Within a first sensitivity analysis, we analyzed effects of vaccination for pre-, in- and post-season to check our results for residual confounding (24). Here, vaccination should not have any effect in pre- and post-season. The impact of biases on the estimation of effects of influenza vaccination in observational studies has already been described before (16, 25, 26). The most important biases are the healthy vaccinee bias and confounding by indication. It is suspected that a small subset of frail and terminally ill patients induces the healthy vaccinee bias (16), which we tried to control for by excluding palliative patients. Furthermore, we considered important variables with high influence on the short-term mortality such as chemotherapy/radiotherapy, nursing home residency and the care level of the patients. With sensitivity analysis 1, however, we can check whether residual confounding nevertheless remains.

In a second sensitivity analysis, we re-defined the periods and set the beginning of in-season at the time, when 10% of the specimen where classified positive according to the RKI influenza surveillance data. The dates for all seasons are reported in Table E1.

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In addition to the main analysis, we performed subgroup analyses for patients with IIP and patients aged 60 years and older (data not shown). No noteworthy differences between the groups appeared compared to the main analyses.

All analyses were performed at a significance level of 5% using R-Software version 4.0.3.

Results

Population characteristics

Of the 450,076 patients in the initial data set, 87,477 individuals met the selection criteria and were identified as patients having an ILD (Figure 1). Vaccination coverage rate was 43.2% in season 2014/15, 41.2% in 2015/16, 41.2% in 2016/17, and 39.9% in 2017/18. The season-specific participant flow with detailed information on exclusion characteristics, eligibility, and matching is provided in the supplement (Figure E1-E4). Table 1 displays selected baseline characteristics of the matched population for each season. All other variables are presented in Table E3. Here, we also included all Elixhauser categories in dummy-coded format to check for group differences. Balance, indicated by SMDs < 0.1, was achieved for all variables in all seasons covered, including the Elixhauser categories that were not included in the matching procedure, suggesting similar comorbidity burden in vaccinated and unvaccinated patients.

Mortality

Kaplan-Meier curves for mortality from the day of matching until August 31 of the following year (Figure 2) were very similar in the immediate time after the matching and diverged later

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on at different time points per season. The mean follow-up time was 210 days in season 2014/15, 216 days in 2015/16, 213 days in 2016/17, and 218 days in 2017/18. The in-season RR estimates for the effects of vaccination were 0.79 (95%CI: 0.65, 0.97; p = 0.02) in season 2014/15, 0.66 (95%CI: 0.54, 0.80; p < 0.001) in 2015/16, 0.89 (95%CI: 0.76, 1.04; p = 0.15) in 2016/17, and 0.95 (95%CI: 0.81, 1.12; p = 0.57) in 2017/18. More specifically, in-season mortality rates per 100 person years were 6.0 (95%CI: 5.1; 7.0) for vaccinated and 7.5 (95%CI: 6.6; 8.7) for unvaccinated patients in season 2014/15, 4.8 (95%CI: 4.1; 5.6) and 7.3 (95%CI: 6.5; 8.3) in 2015/16, 6.4 (95%CI: 5.6; 7.1) and 7.2 (95%CI: 6.4; 8.0) in 2016/17, and 5.3 (95%CI: 4.7; 6.0) and 5.6 (95%CI: 5.0; 6.3) in 2017/18.

Hospitalization

The course of the Kaplan-Meier curves for all-cause (Figure E5) and respiratory-related hospitalizations (Figure E6) was similar for vaccinated and unvaccinated individuals. The corresponding in-season RR estimates for all-cause hospitalization were 0.99 (95%CI: 0.92, 1.08; p = 0.46) in season 2014/15, 1.00 (95%CI: 0.94, 1.06; p = 0.99) in 2015/16, 1.01 (95%CI: 0.96, 1.07; p = 0.61) in 2016/17, and 0.98 (95%CI: 0.93, 1.04; p = 0.34) in 2017/18. The RR estimates for respiratory-related hospitalization were 0.93 (95%CI: 0.82, 1.07; p = 0.31) in season 2014/15, 0.92 (95%CI: 0.82, 1.04; p = 0.18) in 2015/16, 0.99 (95%CI: 0.89, 1.11; p = 0.91) in 2016/17, and 0.99 (95%CI: 0.89, 1.09; p = 0.78) in 2017/18. The in-season hospitalization rates per 100 person years are included in Table E4.

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Sensitivity analyses

The results of the first sensitivity analysis, where the influenza seasons was divided into periods to check for residual confounding, are presented in Figure 3 and included the in-season estimates as comparison. An indication of bias only appeared in the post-season estimate of 2017/18 for respiratory-related hospitalization. However, especially in mortality analysis the estimates were below one for three of the four seasons, which might also indicate residual confounding.

The second sensitivity analysis, where we re-defined the periods, yielded similar results as the main analysis (See Table E6 and Figure E7). An indication for residual confounding appeared in the pre-season estimate for 2016/17 in the mortality analysis, for 2015/16 in the all-cause hospitalization analysis, and in the post-season estimate for respiratory-related hospitalization in 2017/18.

Discussion

In our study, we describe for the first time a comparison of patients with ILD receiving influenza vaccination vs. unvaccinated patients for four different influenza-seasons. We found a protective effect of influenza vaccination regarding mortality in seasons 2014/15 and 2015/16, which however was not significant within the other two seasons. In all seasons, all-cause and respiratory-related hospitalizations did not significantly differ between the vaccinated and the unvaccinated group.

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The vaccination coverage rate for ILD patients included was similar to claims data-based estimates of vaccination rates for patients with other severe chronic diseases, such as COPD, in Germany with about 40% (27). Also, the decline of the vaccination rate observed over time resembles the trends reported for other chronic diseases (27). However, considering the recommendation that all ILD patients should be vaccinated, the vaccination rates are very low. As of today, analyses investigating effects of influenza vaccination in ILD patients have not been published. Therefore, we compare our results with studies evaluating effectiveness of influenza vaccination in COPD patients. According to a Cochrane Review published in 2018 and including six RCT's (28), vaccinated COPD patients experience fewer exacerbations. However, no effect on mortality rates or hospitalizations was reported. Noteworthy, the most recent study included was published in 2004. A recent systematic review and meta-analysis evaluating effectiveness of influenza vaccination in COPD patients with severe airflow limitation demonstrated a significant reduction in exacerbations and a tendency towards fewer hospitalizations, but also found no differences regarding mortality (29). However, the included studies were evaluated to be of low or very low overall quality of evidence for the mortality analysis. Certainly, a direct comparison of our results to these studies is difficult as clinical characteristics differ between ILD and COPD patients. Nevertheless, viral infections might be associated with acute exacerbations in ILD patients, especially in IPF patients (30), and thus influenza should be prevented. An increased risk of death for patients with ILD was also recently reported for COVID-19 (31). In addition, ILD patients in our sample had on average four Elixhauser comorbidities, including particularly a high prevalence of cardiovascular diseases and

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diabetes, which themselves represent risk factors for hospitalization and death after influenza infection.

Mortality analysis unveiled that group differences do not appear immediately after vaccination. This is plausible, as immunity is gradually building within the first 14 days after vaccination. To check our results for residual confounding in a sensitivity analysis, we evaluated the effects of vaccination outside the influenza season, where no effect should be present (26). Although there were almost no significant effects in the pre- and post-seasons, the point estimates were below one for almost all seasons. Therefore, residual confounding might have remained. However, residual confounding appeared to be higher in those seasons where no significant effect of the vaccination could be detected. Even though some confounding might remain, we are convinced that the study design is well suited for the evaluation of the vaccination effectiveness, as it is possible to take a prospective view on the data, adjust appropriately for possible confounders, and check the results for residual confounding. Furthermore, we revealed differences between vaccination seasons, with significant in-season estimates for mortality in 2014/15 and 2015/16. Although not significant, the point estimates for respiratory-related hospitalizations were also lower in 2014/15 and 2015/16 compared to the other seasons, which also indicates differences for these seasons. The population investigated varies slightly between the seasons, as the selection criteria leads to an increasing number of patients over time.

Considering excess mortality, the season 2017/18 was reported to be the worst influenza season since the start of RKI surveillance in 2001. In 2017/18, the trivalent influenza vaccine did not contain the influenza B Yamagata lineage, which was the most prevalent in this

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season (32). The quadrivalent vaccine contained the Yamagata lineage. However, we are not able to identify in our data whether the patient received a trivalent or quadrivalent vaccine. The quadrivalent vaccine is recommended by the German Standing Committee on Vaccination (STIKO) since the 2018/19 season (33). Therefore, this might be a possible explanation for the missing effects of the vaccine in the season 2017/18. However, it does not explain the missing effects in the season 2016/17. Here the most prevalent type was influenza A (H3N2), which is included in the trivalent vaccine (32). The seasons 2014/15 and 2016/17 also marked seasons with a relatively high excess hospitalization and mortality, while the season 2015/16 was mild in comparison. The season 2015/16 was the season with the highest vaccination effects in our study. Nevertheless, with our study we are not able to conclude that this season was mild because of the high impact of the vaccine, as our analysis focuses only on ILD patients. In addition, influenza vaccination is usually seen as a public health intervention with beneficial effects rather at the population than at the individual level. Especially, low community prevalence of influenza and a high vaccination rate in the immediate vicinity of the included patients might result in a protective effect also for those without vaccination. This might lead to an underestimation of the positive external effects of influenza vaccination.

Our study has several limitations. First, although we used strict selection criteria for the inclusion of ILD patients, some misidentification cannot be ruled out. However, this uncertainty is present in both groups. Second, we used a 1:1 matching in a rolling cohort design to adjust for confounding. Nonetheless, residual confounding might remain, especially due to the healthy vaccinee bias as discussed above. In this context, clinical information, which could be used to further minimize the bias are missing in claims databases. Particularly the force vital capacity

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(FVC) or the diffusing capacity for carbon monoxide (DPCO) which are associated with mortality would have been important parameters to assess disease severity. Third, the definition of respiratory-related hospitalizations might overestimate the occurrence of influenza-caused infections. Infection-related hospitalization in ILD patients might often be coded as ILD-specific, not as influenza-specific. Fourth, in some German regions, there are selective contracts that result in different coding of influenza vaccination in the physician's fee scale (EBM). These specific codes could not be accounted for. However, considering the regional restriction and the vaccination coverage rate this impact should be very small. Fifth, due to the matching approach about 25% of the vaccinated patients could not be matched despite their eligibility, which reduces to some degree the transferability of our findings to populations with different characteristics.

Our study also has various strengths. It is the first study investigating the effects of influenza vaccination in ILD patients, which represent an extremely vulnerable group for which respiratory infections should be avoided. Due to the rarity of ILD diseases, our large data set covering a considerable part of the German population serves as an asset. With our study design we tried to alleviate important biases, which appear in vaccination studies and our approach might be promising for further studies.

Conclusion

The impact of influenza vaccination has varied across the four seasons investigated, with some years showing very promising results on all-cause mortality. Although not significant, risk of hospitalization was also lower in vaccinated patients for those seasons, which underlines the

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clinical relevance of vaccination. Although group differences appeared only after some time rather than immediately after the vaccination and the sensitivity analysis showed no significant off-season effects for most outcomes, our results should be interpreted with caution, as residual confounding may remain.

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Figure Legends:

Figure 1. Participant flow of the study population

Figure 2. Kaplan-Meier curves for mortality comparison with 95% confidence intervals. Curves depict the whole period from matching until end of follow-up (maximum August 31). Colored areas represent 95% confidence intervals

Figure 3. Sensitivity analyses for residual confounding by dividing the influenza season into periods of pre-, in- and post-season. Horizontal bars represent 95% confidence intervals. Pre-season: From September 1 until continuous detection of influenza viruses; In-season: From continuous detection of influenza viruses until calendar week 20 of the following year; Post-season: From calendar week 20 until August 31.

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Table 1. Patient characteristics in the matched population for each season

	Season 2014/15		Season 2015/16		Season 2016/17		Season 2017/18	
	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
Number of patients	7,503	7,503	10,318	10,318	12,723	12,723	13,927	13,927
Age (years), mean (SD)	68.9 (11.7)	69.0 (11.7)	69.4 (11.6)	69.5 (11.6)	69.8 (11.7)	69.9 (11.6)	69.8 (11.8)	70.0 (11.7)
Age groups (years), n (%)								
20-29	23 (0.3)	23 (0.3)	13 (0.1)	13 (0.1)	22 (0.2)	22 (0.2)	20 (0.1)	20 (0.1)
30-39	101 (1.3)	101 (1.3)	105 (1.0)	105 (1.0)	135 (1.1)	135 (1.1)	163 (1.2)	163 (1.2)
40-49	359 (4.8)	359 (4.8)	499 (4.8)	499 (4.8)	558 (4.4)	558 (4.4)	573 (4.1)	573 (4.1)
50-59	1,079 (14.4)	1,079 (14.4)	1,470 (14.2)	1,470 (14.2)	1,743 (13.7)	1,743 (13.7)	1,912 (13.7)	1,912 (13.7)
60-69	1,669 (22.2)	1,669 (22.2)	2,445 (23.7)	2,445 (23.7)	3,081 (24.2)	3,081 (24.2)	3,456 (24.8)	3,456 (24.8)
70-79	2,998 (40.0)	2,998 (40.0)	3,770 (36.5)	3,770 (36.5)	4,400 (34.6)	4,400 (34.6)	4,616 (33.1)	4,616 (33.1)
80-89	1,261 (16.8)	1,261 (16.8)	1,970 (19.1)	1,970 (19.1)	2,717 (21.4)	2,717 (21.4)	3,109 (22.3)	3,109 (22.3)
90 +	13 (0.2)	13 (0.2)	46 (0.4)	46 (0.4)	67 (0.5)	67 (0.5)	78 (0.6)	78 (0.6)
Sex (male), n (%)	3,613 (48.2)	3,613 (48.2)	4,909 (47.6)	4,909 (47.6)	6,090 (47.9)	6,090 (47.9)	6,632 (47.6)	6,632 (47.6)
ILD diagnosis [ICD-10], n (%)								
Idiopathic interstitial pneumonia	3,306 (44.1)	3,306 (44.1)	4,443 (43.1)	4,443 (43.1)	5,440 (42.8)	5,440 (42.8)	5,767 (41.4)	5,767 (41.4)
Other fibrosing ILDs	853 (11.4)	853 (11.4)	1,428 (13.8)	1,428 (13.8)	2,004 (15.8)	2,004 (15.8)	2,380 (17.1)	2,380 (17.1)
Sarcoidosis	2,866 (38.2)	2,866 (38.2)	3,678 (35.6)	3,678 (35.6)	4,284 (33.7)	4,284 (33.7)	4,631 (33.3)	4,631 (33.3)
Drug-associated ILDs	6 (0.1)	6 (0.1)	10 (0.1)	10 (0.1)	22 (0.2)	22 (0.2)	25 (0.2)	25 (0.2)
Pneumoconiosis	212 (2.8)	212 (2.8)	286 (2.8)	286 (2.8)	311 (2.4)	311 (2.4)	318 (2.3)	318 (2.3)
Radiation-associated pneumonitis	6 (0.1)	6 (0.1)	18 (0.2)	18 (0.2)	19 (0.1)	19 (0.1)	20 (0.1)	20 (0.1)
Eosinophilic pneumonia	24 (0.3)	24 (0.3)	71 (0.7)	71 (0.7)	115 (0.9)	115 (0.9)	155 (1.1)	155 (1.1)
Hypersensitivity pneumonitis	162 (2.2)	162 (2.2)	249 (2.4)	249 (2.4)	304 (2.4)	304 (2.4)	336 (2.4)	336 (2.4)
Connective tissue-associated ILD	68 (0.9)	68 (0.9)	135 (1.3)	135 (1.3)	224 (1.8)	224 (1.8)	295 (2.1)	295 (2.1)
Comorbidities Elixhauser score, mean (SD)	3.6 (2.0)	3.6 (2.0)	3.8 (2.1)	3.8 (2.1)	4.0 (2.1)	4.0 (2.1)	4.0 (2.2)	4.0 (2.2)
Care dependency[a], n (%)								
No care level	6,953 (92.7)	6953 (92.7)	9,408 (91.2)	9,408 (91.2)	11,342 (89.1)	11,342 (89.1)	12,150 (87.2)	12,150 (87.2)
Care level 1	463 (6.2)	463 (6.2)	736 (7.1)	736 (7.1)	1,088 (8.6)	1,088 (8.6)	86 (0.6)	86 (0.6)

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Care level 2	83 (1.1)	83 (1.1)	172 (1.7)	172 (1.7)	279 (2.2)	279 (2.2)	1,205 (8.7)	1,205 (8.7)
Care level 3	4 (0.1)	4 (0.1)	2 (0.0)	2 (0.0)	14 (0.1)	14 (0.1)	403 (2.9)	403 (2.9)
Care level 4	-	-	-	-	0 (0.0)	0 (0.0)	79 (0.6)	79 (0.6)
Care level 5	-	-	-	-	0 (0.0)	0 (0.0)	4 (0.0)	4 (0.0)
Nursing Home Residency, n (%)	15 (0.2)	15 (0.2)	47 (0.5)	47 (0.5)	77 (0.6)	77 (0.6)	80 (0.6)	80 (0.6)
Radiotherapy or chemotherapy in three month before matching, n (%)	10 (0.1)	10 (0.1)	39 (0.4)	39 (0.4)	80 (0.6)	80 (0.6)	106 (0.8)	106 (0.8)

SD: Standard deviation

a: Care dependency until 2017 in three levels, after 2017 in five levels

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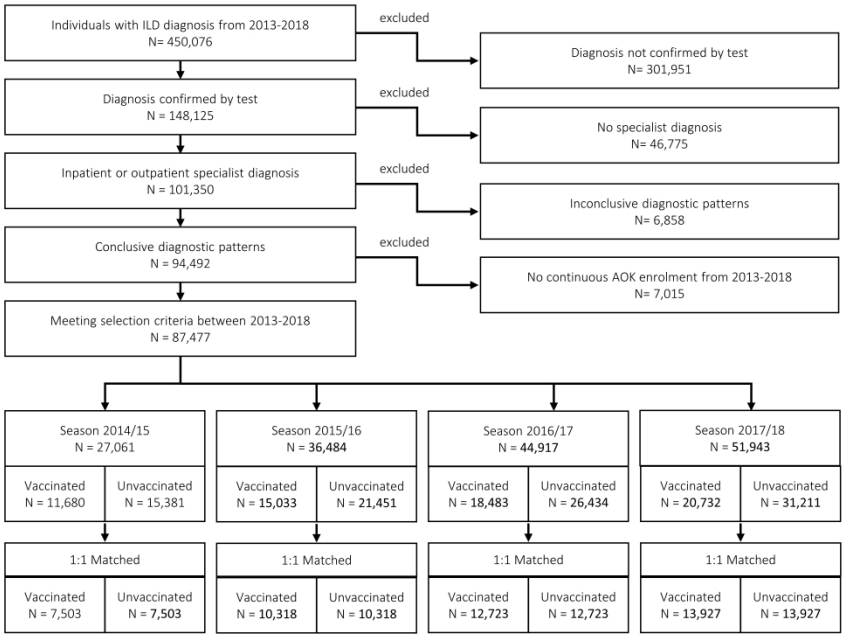

Figure 1 Participant flow of the study population

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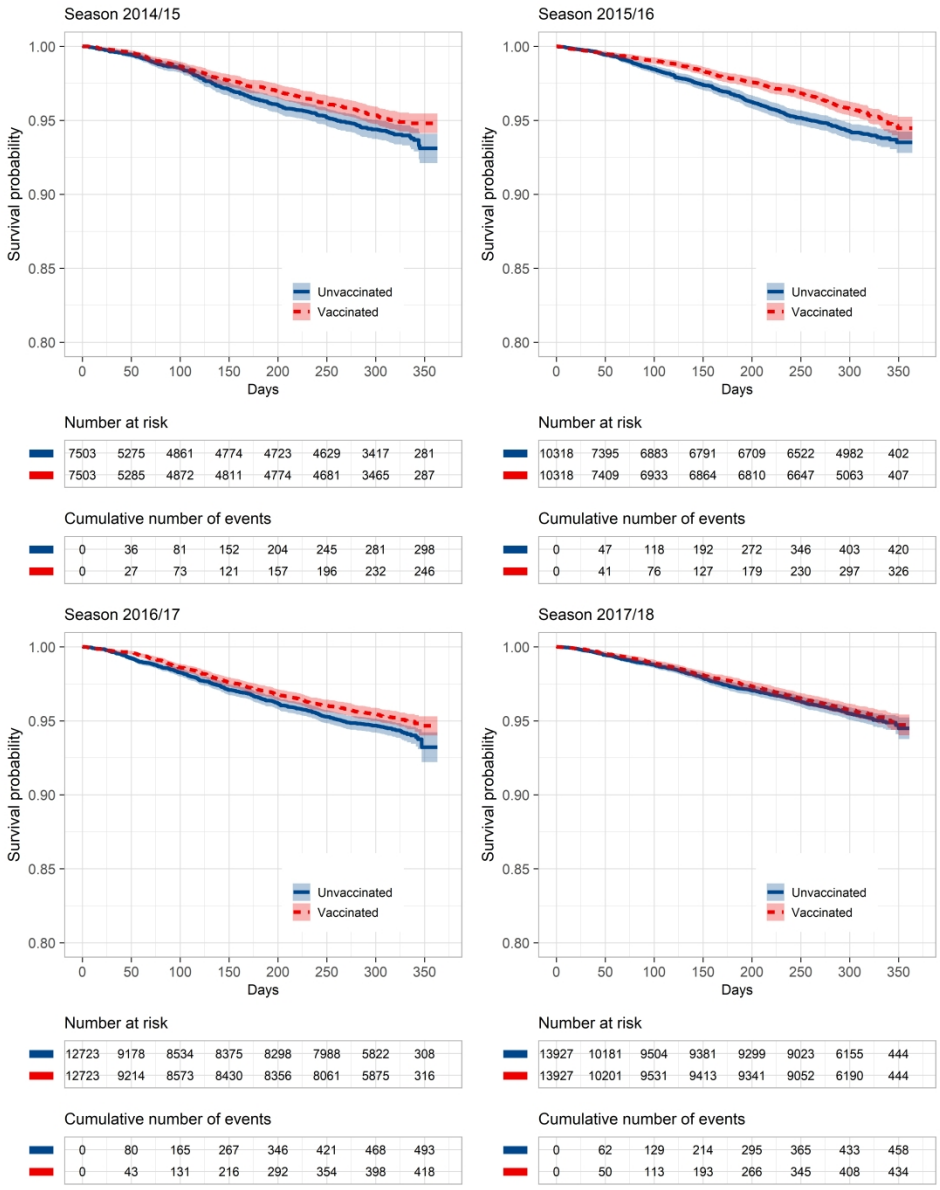

Figure 2 Kaplan-Meier curves for mortality comparison with 95% confidence intervals
Curves depict the whole period from matching until end of follow-up (maximum August 31). Colored areas represent 95% confidence intervals

481x608mm (276 x 276 DPI)

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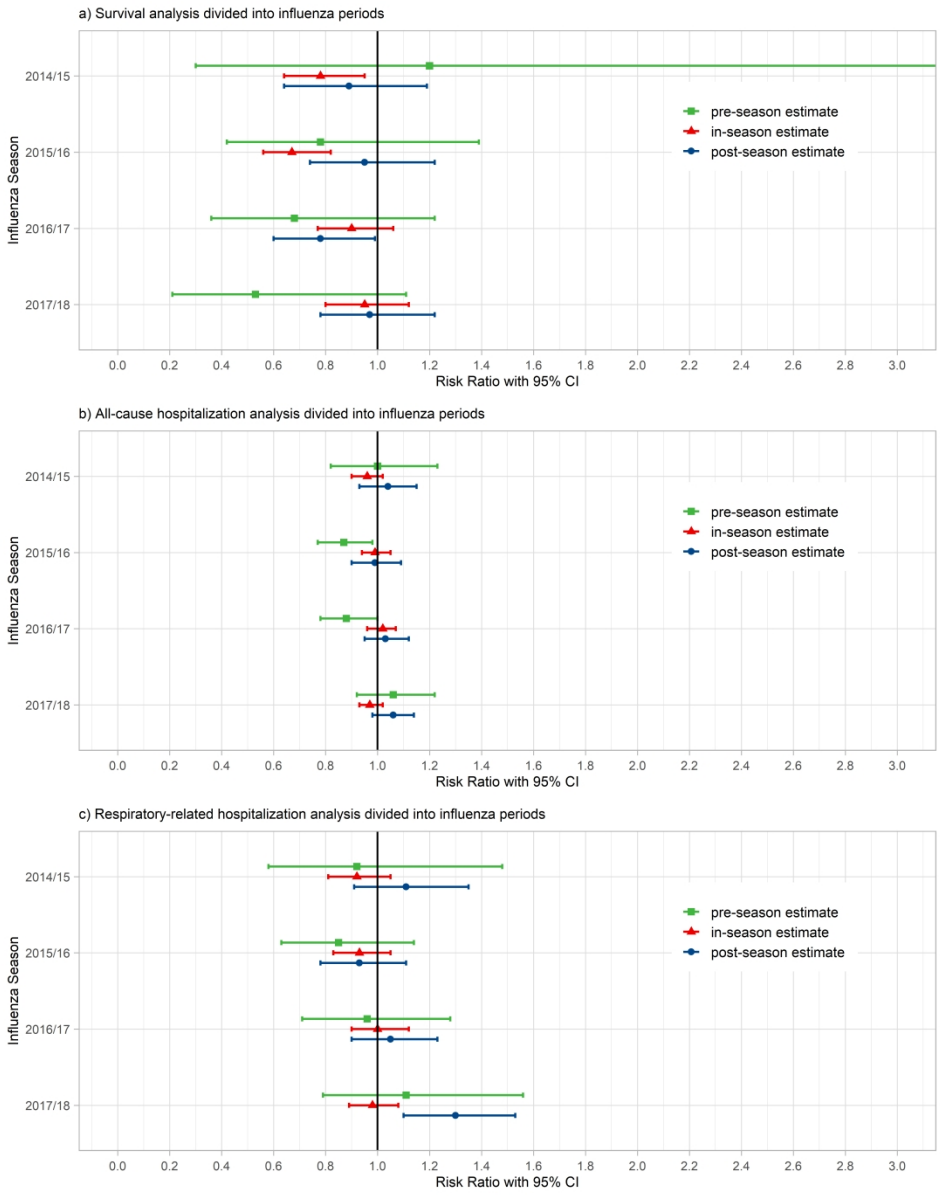

Figure 3 Sensitivity analyses for residual confounding by dividing the influenza season into periods of pre-, in- and post-season Horizontal bars represent 95% confidence intervals
Pre-season: From September 1 until continuous detection of influenza viruses
In-season: From continuous detection of influenza viruses until calendar week 20 of the following year
Post-season: From calendar week 20 until August 31

481x608mm (276 x 276 DPI)

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Online Supplement

Title:

Effects of influenza vaccination in patients with interstitial lung diseases: an epidemiological claims data analysis

Authors:

Pavo Marijic, Larissa Schwarzkopf, Werner Maier, Franziska Trudzinski, Lars Schwettmann, Michael Kreuter

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Figure E1 Detailed participant flow of the season 2014/15

Figure E2 Detailed participant flow of the season 2015/16

Figure E3 Detailed participant flow of the season 2016/17

Figure E4 Detailed participant flow of the season 2017/18

Figure E5 Cumulative incidence curves for all-cause hospitalization with 95% confidence intervals
Cumulative incidence curves (1 minus the Kaplan-Meier risk) depict the whole period from matching until end of follow-up (maximum June 30). Colored areas represent 95% confidence intervals

Figure E6 Cumulative incidence curves for respiratory-related hospitalization with 95% confidence intervals
Cumulative incidence curves (1 minus the Kaplan-Meier risk) depict the whole period from matching until end of follow-up (maximum June 30). Colored areas represent 95% confidence interval

Figure E7 Sensitivity analyses for residual confounding by dividing the influenza season into periods of pre-, in- and post-season
Horizontal bars represent 95% confidence intervals
Pre-season: From September 1 until 10% of specimen were positive for influenza viruses according to the RKI influenza surveillance data
In-season: From 10% positive specimens until calendar week 20 of the following year
Post-season: From calendar week 20 until August 31

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Table E1 Treatment-related codes of the physician's fee scale (EBM) and ICD-10 codes to identify treatments and procedures

Treatment	Codes
Palliative Care	EBM-codes: 01425, 01426, 03370 ,03371, 03372, 03373, 04370, 04372, 04371, 04373, 37300, 37305, 37306, 37318 ICD-codes: Z51.5
Influenza vaccine	EBM-codes: 89111, 89112

Table E2 Influenza season divided in pre-, in- and post-season periods identified by national surveillance data of the Robert-Koch-Institute for each season

Season	Pre-season	In-season	Post-season
Main analysis: influenza viruses continuously detected			
2014/15	Sep 1 - Oct 19, 2014	Oct 20, 2014 - May 17, 2015	May 18 - Aug 31, 2015
2015/16	Sep 1 - Nov 08, 2015	Nov 09, 2015 - May 22, 2016	May 23 - Aug 31, 2016
2016/17	Sep 1 - Nov 06, 2016	Nov 07, 2016 - May 21, 2017	May 22 - Aug 31, 2017
2017/18	Sep 1 - Oct 29, 2017	Oct 30, 2017 - May 20, 2018	May 21 - Aug 31, 2018
Sensitivity analysis: 10% of the specimen positive			
2014/15	Sep 1 - Dec 12, 2014	Dec 13, 2014 - May 17, 2015	May 18 - Aug 31, 2015
2015/16	Sep 1 - Dec 18, 2015	Dec 19, 2015 - May 22, 2016	May 23 - Aug 31, 2016
2016/17	Sep 1 - Dec 09, 2016	Dec 10, 2016 - May 21, 2017	May 22 - Aug 31, 2017
2017/18	Sep 1 - Dec 15, 2017	Dec 16, 2017 - May 20, 2018	May 21 - Aug 31, 2018

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Table E3 Patient characteristics in the matched population for each season

	Season 2014/15			Season 2015/16			Season 2016/17			Season 2017/18		
	Un-vaccinated	Vaccinated	SMD	Un-vaccinated	Vaccinated	SMD	Un-vaccinated	Vaccinated	SMD	Un-vaccinated	Vaccinated	SMD
Number of patients	7503	7503		10318	10318		12723	12723		13927	13927	
Age (years), mean (SD)	68.9 (11.7)	69.0 (11.7)	0.012	69.4 (11.6)	69.5 (11.6)	0.017	69.8 (11.7)	69.9 (11.6)	0.013	69.8 (11.8)	70.0 (11.7)	0.017
Age groups (years), n (%)			<0.001			<0.001			<0.001			<0.001
20-29	23 (0.3)	23 (0.3)		13 (0.1)	13 (0.1)		22 (0.2)	22 (0.2)		20 (0.1)	20 (0.1)	
30-39	101 (1.3)	101 (1.3)		105 (1.0)	105 (1.0)		135 (1.1)	135 (1.1)		163 (1.2)	163 (1.2)	
40-49	359 (4.8)	359 (4.8)		499 (4.8)	499 (4.8)		558 (4.4)	558 (4.4)		573 (4.1)	573 (4.1)	
50-59	1079 (14.4)	1079 (14.4)		1470 (14.2)	1470 (14.2)		1743 (13.7)	1743 (13.7)		1912 (13.7)	1912 (13.7)	
60-69	1669 (22.2)	1669 (22.2)		2445 (23.7)	2445 (23.7)		3081 (24.2)	3081 (24.2)		3456 (24.8)	3456 (24.8)	
70-79	2998 (40.0)	2998 (40.0)		3770 (36.5)	3770 (36.5)		4400 (34.6)	4400 (34.6)		4616 (33.1)	4616 (33.1)	
80-89	1261 (16.8)	1261 (16.8)		1970 (19.1)	1970 (19.1)		2717 (21.4)	2717 (21.4)		3109 (22.3)	3109 (22.3)	
90+	13 (0.2)	13 (0.2)		46 (0.4)	46 (0.4)		67 (0.5)	67 (0.5)		78 (0.6)	78 (0.6)	
Sex (male), n (%)	3613 (48.2)	3613 (48.2)	<0.001	4909 (47.6)	4909 (47.6)	<0.001	6090 (47.9)	6090 (47.9)	<0.001	6632 (47.6)	6632 (47.6)	<0.001
ILD diagnosis, n (%)			<0.001			<0.001			<0.001			<0.001
Idiopathic interstitial pneumonia	3306 (44.1)	3306 (44.1)		4443 (43.1)	4443 (43.1)		5440 (42.8)	5440 (42.8)		5767 (41.4)	5767 (41.4)	
Other fibrosing ILDs	853 (11.4)	853 (11.4)		1428 (13.8)	1428 (13.8)		2004 (15.8)	2004 (15.8)		2380 (17.1)	2380 (17.1)	
Sarcoidosis	2866 (38.2)	2866 (38.2)		3678 (35.6)	3678 (35.6)		4284 (33.7)	4284 (33.7)		4631 (33.3)	4631 (33.3)	
Drug-associated ILDs	6 (0.1)	6 (0.1)		10 (0.1)	10 (0.1)		22 (0.2)	22 (0.2)		25 (0.2)	25 (0.2)	
Pneumoconiosis	212 (2.8)	212 (2.8)		286 (2.8)	286 (2.8)		311 (2.4)	311 (2.4)		318 (2.3)	318 (2.3)	
Radiation-associated pneumonitis	6 (0.1)	6 (0.1)		18 (0.2)	18 (0.2)		19 (0.1)	19 (0.1)		20 (0.1)	20 (0.1)	
Eosinophilic pneumonia	24 (0.3)	24 (0.3)		71 (0.7)	71 (0.7)		115 (0.9)	115 (0.9)		155 (1.1)	155 (1.1)	
Hypersensitivity pneumonitis	162 (2.2)	162 (2.2)		249 (2.4)	249 (2.4)		304 (2.4)	304 (2.4)		336 (2.4)	336 (2.4)	
Connective tissue-associated ILD	68 (0.9)	68 (0.9)		135 (1.3)	135 (1.3)		224 (1.8)	224 (1.8)		295 (2.1)	295 (2.1)	
Care dependency, n (%)			<0.001			<0.001			<0.001			<0.001
No care level	6953 (92.7)	6953 (92.7)		9408 (91.2)	9408 (91.2)		11342 (89.1)	11342 (89.1)		12150 (87.2)	12150 (87.2)	
Care level 1	463 (6.2)	463 (6.2)		736 (7.1)	736 (7.1)		1088 (8.6)	1088 (8.6)		86 (0.6)	86 (0.6)	
Care level 2	83 (1.1)	83 (1.1)		172 (1.7)	172 (1.7)		279 (2.2)	279 (2.2)		1205 (8.7)	1205 (8.7)	
Care level 3	4 (0.1)	4 (0.1)		2 (0.0)	2 (0.0)		14 (0.1)	14 (0.1)		403 (2.9)	403 (2.9)	

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Care level 4	-	-		-	-		0 (0.0)	0 (0.0)		79 (0.6)	79 (0.6)	
Care level 5	-	-		-	-		0 (0.0)	0 (0.0)		4 (0.0)	4 (0.0)	
Nursing Home Residency, n (%)	15 (0.2)	15 (0.2)	<0.001	47 (0.5)	47 (0.5)	<0.001	77 (0.6)	77 (0.6)	<0.001	80 (0.6)	80 (0.6)	<0.001
Federal state, n (%)			<0.001			<0.001			<0.001			<0.001
Baden-Wuerttemberg	928 (12.4)	928 (12.4)		1303 (12.6)	1303 (12.6)		1644 (12.9)	1644 (12.9)		1860 (13.4)	1860 (13.4)	
Bavaria	835 (11.1)	835 (11.1)		1561 (15.1)	1561 (15.1)		1964 (15.4)	1964 (15.4)		2193 (15.7)	2193 (15.7)	
Berlin	189 (2.5)	189 (2.5)		230 (2.2)	230 (2.2)		290 (2.3)	290 (2.3)		301 (2.2)	301 (2.2)	
Brandenburg	262 (3.5)	262 (3.5)		356 (3.5)	356 (3.5)		453 (3.6)	453 (3.6)		475 (3.4)	475 (3.4)	
Bremen	38 (0.5)	38 (0.5)		47 (0.5)	47 (0.5)		64 (0.5)	64 (0.5)		65 (0.5)	65 (0.5)	
Hamburg	21 (0.3)	21 (0.3)		50 (0.5)	50 (0.5)		97 (0.8)	97 (0.8)		104 (0.7)	104 (0.7)	
Hesse	428 (5.7)	428 (5.7)		596 (5.8)	596 (5.8)		726 (5.7)	726 (5.7)		761 (5.5)	761 (5.5)	
Lower Saxony	946 (12.6)	946 (12.6)		1168 (11.3)	1168 (11.3)		1333 (10.5)	1333 (10.5)		1514 (10.9)	1514 (10.9)	
Mecklenburg-Vorpommern	213 (2.8)	213 (2.8)		276 (2.7)	276 (2.7)		344 (2.7)	344 (2.7)		365 (2.6)	365 (2.6)	
North Rhine-Westphalia	1294 (17.2)	1294 (17.2)		1791 (17.4)	1791 (17.4)		2231 (17.5)	2231 (17.5)		2423 (17.4)	2423 (17.4)	
Rhineland-Palatinate	145 (1.9)	145 (1.9)		218 (2.1)	218 (2.1)		295 (2.3)	295 (2.3)		317 (2.3)	317 (2.3)	
Saarland	30 (0.4)	30 (0.4)		43 (0.4)	43 (0.4)		56 (0.4)	56 (0.4)		47 (0.3)	47 (0.3)	
Saxony	1067 (14.2)	1067 (14.2)		1370 (13.3)	1370 (13.3)		1596 (12.5)	1596 (12.5)		1742 (12.5)	1742 (12.5)	
Saxony-Anhalt	480 (6.4)	480 (6.4)		534 (5.2)	534 (5.2)		654 (5.1)	654 (5.1)		703 (5.0)	703 (5.0)	
Schleswig-Holstein	148 (2.0)	148 (2.0)		192 (1.9)	192 (1.9)		254 (2.0)	254 (2.0)		319 (2.3)	319 (2.3)	
Thuringia	479 (6.4)	479 (6.4)		583 (5.7)	583 (5.7)		722 (5.7)	722 (5.7)		738 (5.3)	738 (5.3)	
Comorbidities Elixhauser score, mean (SD)	3.6 (2.0)	3.6 (2.0)	<0.001	3.8 (2.1)	3.8 (2.1)	<0.001	4.0 (2.1)	4.0 (2.1)	<0.001	4.0 (2.2)	4.0 (2.2)	<0.001
Comorbidities Elixhauser categories, n (%)												
Congestive heart failure	1459 (19.4)	1513 (20.2)	0.018	2228 (21.6)	2168 (21.0)	0.014	2786 (21.9)	2759 (21.7)	0.005	3096 (22.2)	3107 (22.3)	0.002
Cardiac arrhythmias	1601 (21.3)	1618 (21.6)	0.006	2367 (22.9)	2405 (23.3)	0.009	3096 (24.3)	3145 (24.7)	0.009	3450 (24.8)	3478 (25.0)	0.005
Valvular disease	895 (11.9)	918 (12.2)	0.009	1367 (13.2)	1359 (13.2)	0.002	1794 (14.1)	1757 (13.8)	0.008	2026 (14.5)	2015 (14.5)	0.002
Pulmonary circulation disorders	530 (7.1)	565 (7.5)	0.018	747 (7.2)	830 (8.0)	0.030	942 (7.4)	1055 (8.3)	0.033	1052 (7.6)	1141 (8.2)	0.024
Peripheral vascular disorders	1180 (15.7)	1127 (15.0)	0.020	1794 (17.4)	1779 (17.2)	0.004	2326 (18.3)	2370 (18.6)	0.009	2691 (19.3)	2618 (18.8)	0.013
Hypertension, uncomplicated	4540 (60.5)	4499 (60.0)	0.011	6225 (60.3)	6192 (60.0)	0.007	7708 (60.6)	7598 (59.7)	0.018	8406 (60.4)	8325 (59.8)	0.012
Hypertension, complicated	920 (12.3)	890 (11.9)	0.012	1360 (13.2)	1317 (12.8)	0.012	1704 (13.4)	1672 (13.1)	0.007	1890 (13.6)	1921 (13.8)	0.006
Paralysis	91 (1.2)	83 (1.1)	0.010	158 (1.5)	166 (1.6)	0.006	213 (1.7)	214 (1.7)	0.001	231 (1.7)	238 (1.7)	0.004
Other neurological disorders	269 (3.6)	269 (3.6)	<0.001	440 (4.3)	420 (4.1)	0.010	551 (4.3)	553 (4.3)	0.001	617 (4.4)	603 (4.3)	0.005
Chronic pulmonary disease	4084 (54.4)	4150 (55.3)	0.018	5537 (53.7)	5692 (55.2)	0.030	6851 (53.8)	7005 (55.1)	0.024	7285 (52.3)	7594 (54.5)	0.044
Diabetes, uncomplicated	1144 (15.2)	1164 (15.5)	0.007	1566 (15.2)	1564 (15.2)	0.001	1846 (14.5)	1824 (14.3)	0.005	1974 (14.2)	1830 (13.1)	0.030

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Diabetes, complicated	1269 (16.9)	1331 (17.7)	0.022	1961 (19.0)	2067 (20.0)	0.026	2593 (20.4)	2657 (20.9)	0.012	2806 (20.1)	2930 (21.0)	0.022
Hypothyroidism	876 (11.7)	827 (11.0)	0.021	1292 (12.5)	1222 (11.8)	0.021	1687 (13.3)	1672 (13.1)	0.003	1962 (14.1)	1956 (14.0)	0.001
Renal failure	957 (12.8)	1007 (13.4)	0.020	1548 (15.0)	1626 (15.8)	0.021	2247 (17.7)	2273 (17.9)	0.005	2642 (19.0)	2757 (19.8)	0.021
Liver disease	932 (12.4)	948 (12.6)	0.006	1446 (14.0)	1392 (13.5)	0.015	1821 (14.3)	1760 (13.8)	0.014	2075 (14.9)	1965 (14.1)	0.022
Peptic ulcer disease, excluding bleeding	106 (1.4)	111 (1.5)	0.006	144 (1.4)	149 (1.4)	0.004	175 (1.4)	184 (1.4)	0.006	179 (1.3)	195 (1.4)	0.010
AIDS	6 (0.1)	5 (0.1)	0.005	8 (0.1)	10 (0.1)	0.007	9 (0.1)	19 (0.1)	0.024	15 (0.1)	20 (0.1)	0.010
Lymphoma	125 (1.7)	123 (1.6)	0.002	168 (1.6)	160 (1.6)	0.006	216 (1.7)	224 (1.8)	0.005	253 (1.8)	250 (1.8)	0.002
Metastatic cancer	122 (1.6)	110 (1.5)	0.013	179 (1.7)	164 (1.6)	0.011	249 (2.0)	226 (1.8)	0.013	307 (2.2)	294 (2.1)	0.006
Solid tumour without metastasis	818 (10.9)	808 (10.8)	0.004	1242 (12.0)	1163 (11.3)	0.024	1540 (12.1)	1505 (11.8)	0.008	1771 (12.7)	1694 (12.2)	0.017
Rheumatoid arthritis/collagen vascular diseases	1060 (14.1)	1046 (13.9)	0.005	1489 (14.4)	1482 (14.4)	0.002	1878 (14.8)	1907 (15.0)	0.006	2149 (15.4)	2135 (15.3)	0.003
Coagulopathy	211 (2.8)	240 (3.2)	0.023	302 (2.9)	319 (3.1)	0.010	408 (3.2)	439 (3.5)	0.014	506 (3.6)	489 (3.5)	0.007
Obesity	1493 (19.9)	1486 (19.8)	0.002	2238 (21.7)	2163 (21.0)	0.018	2935 (23.1)	2900 (22.8)	0.007	3215 (23.1)	3242 (23.3)	0.005
Weight loss	83 (1.1)	87 (1.2)	0.005	121 (1.2)	153 (1.5)	0.027	161 (1.3)	167 (1.3)	0.004	234 (1.7)	203 (1.5)	0.018
Fluid and electrolyte disorder	126 (1.7)	120 (1.6)	0.006	218 (2.1)	201 (1.9)	0.012	313 (2.5)	304 (2.4)	0.005	330 (2.4)	341 (2.4)	0.005
Blood loss anemia	26 (0.3)	21 (0.3)	0.016	35 (0.3)	38 (0.4)	0.005	56 (0.4)	50 (0.4)	0.007	56 (0.4)	50 (0.4)	0.005
Deficiency anaemia	306 (4.1)	282 (3.8)	0.016	421 (4.1)	443 (4.3)	0.011	550 (4.3)	558 (4.4)	0.003	645 (4.6)	654 (4.7)	0.003
Alcohol abuse	162 (2.2)	156 (2.1)	0.006	271 (2.6)	255 (2.5)	0.010	372 (2.9)	331 (2.6)	0.020	462 (3.3)	366 (2.6)	0.041
Drug abuse	40 (0.5)	36 (0.5)	0.008	70 (0.7)	70 (0.7)	<0.001	123 (1.0)	109 (0.9)	0.012	143 (1.0)	120 (0.9)	0.017
Psychoses	62 (0.8)	65 (0.9)	0.004	110 (1.1)	111 (1.1)	0.001	142 (1.1)	157 (1.2)	0.011	142 (1.0)	129 (0.9)	0.010
Depression	1652 (22.0)	1540 (20.5)	0.036	2418 (23.4)	2390 (23.2)	0.006	3122 (24.5)	3020 (23.7)	0.019	3410 (24.5)	3358 (24.1)	0.009
Radiotherapy or chemotherapy in three month before matching, n (%)	10 (0.1)	10 (0.1)	<0.001	39 (0.4)	39 (0.4)	<0.001	80 (0.6)	80 (0.6)	<0.001	106 (0.8)	106 (0.8)	<0.001

SD: Standard deviation; SMD: Standardized mean difference

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Table E4 Hospitalization rates per 100 person-years for vaccinated and unvaccinated patients for all-cause and respiratory-related hospitalization

	Season 2014/15	Season 2015/16	Season 2016/17	Season 2017/18
All-cause hospitalization				
Vaccinated	53.4 (50.5; 56.5)	55.9 (53.3; 58.6)	56.8 (54.4; 59.3)	53.2 (51.1; 55.4)
Unvaccinated	55.4 (52.4; 58.6)	56.3 (53.4; 59.1)	56.8 (54.5; 59.3)	54.8 (52.7; 57.1)
Respiratory-related hospitalization				
Vaccinated	14.6 (13.2; 16.1)	14.2 (13.1; 15.5)	14.8 (13.7; 16.0)	14.0 (12.9; 15.0)
Unvaccinated	15.7 (14.2; 17.3)	15.2 (14.3; 16.9)	14.9 (13.8; 16.1)	14.2 (13.2; 15.3)

CI: confidence interval

Table E5 Sensitivity analysis of influenza in-season Risk Ratio estimates for influenza effectiveness

	Season 2014/15	Season 2015/16	Season 2016/17	Season 2017/18
	RR (95% CI)	*RR (95% CI)*	*RR (95% CI)*	*RR (95% CI)*
Mortality	**0.80 (0.64; 0.99), p = 0.04**	**0.67 (0.54; 0.81), p < 0.001**	0.95 (0.80; 1.12), p = 0.51	0.98 (0.82; 1.17), p = 0.79
All-cause hospitalization	0.99 (0.91; 1.08), p = 0.86	1.01 (0.94; 1.08), p = 0.80	1.00 (0.94; 1.06), p = 0.99	0.98 (0.93; 1.04), p = 0.55
Respiratory-related hospitalization	0.96 (0.82; 1.12), p = 0.60	0.92 (0.81; 1.05), p = 0.23	0.99 (0.88; 1.11), p = 0.81	1.00 (0.89; 1.12), p = 0.99

CI: confidence interval, RR: Risko Ratio

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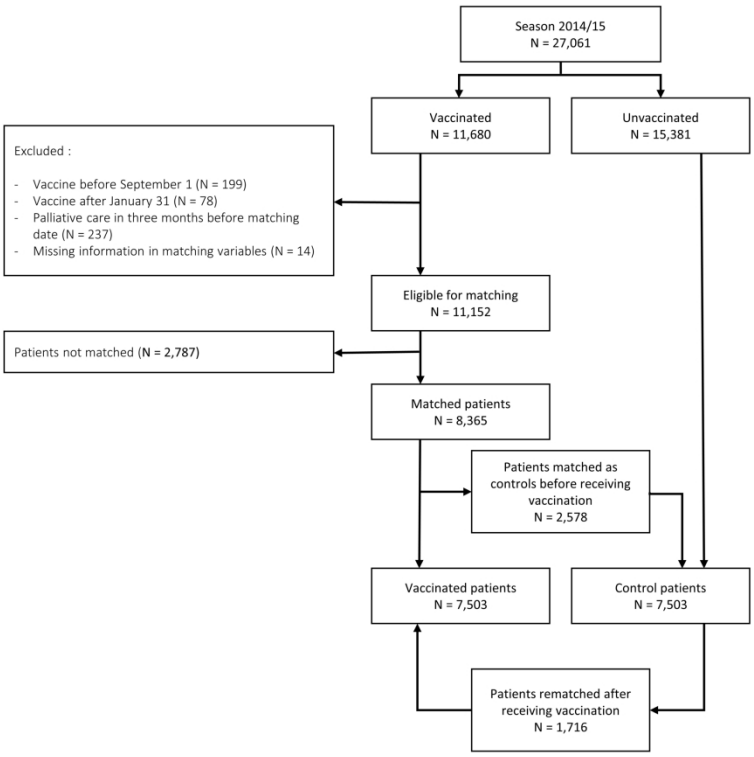

Figure E1 Detailed participant flow of the season 2014/15

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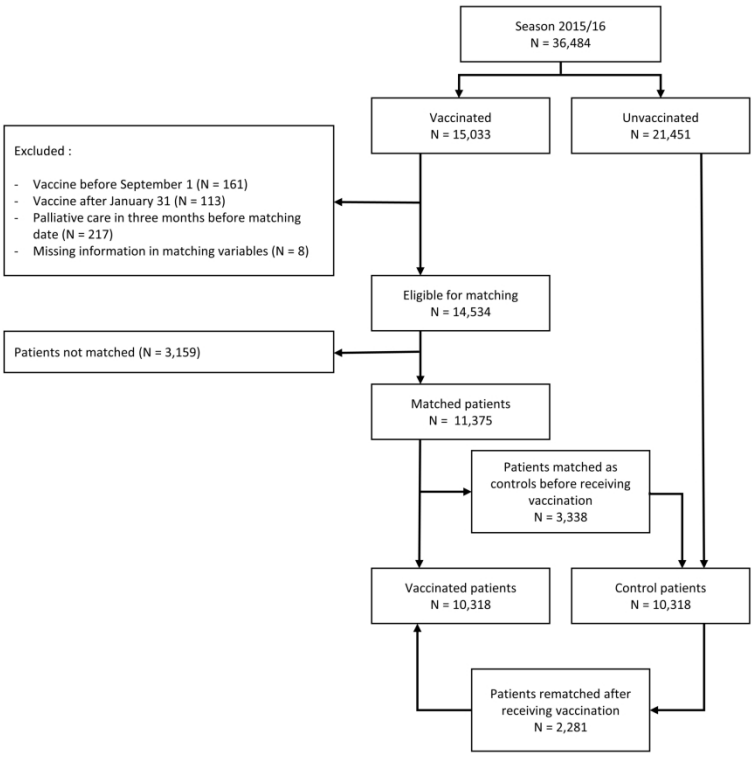

Figure E2 Detailed participant flow of the season 2015/16

254x190mm (300 x 300 DPI)

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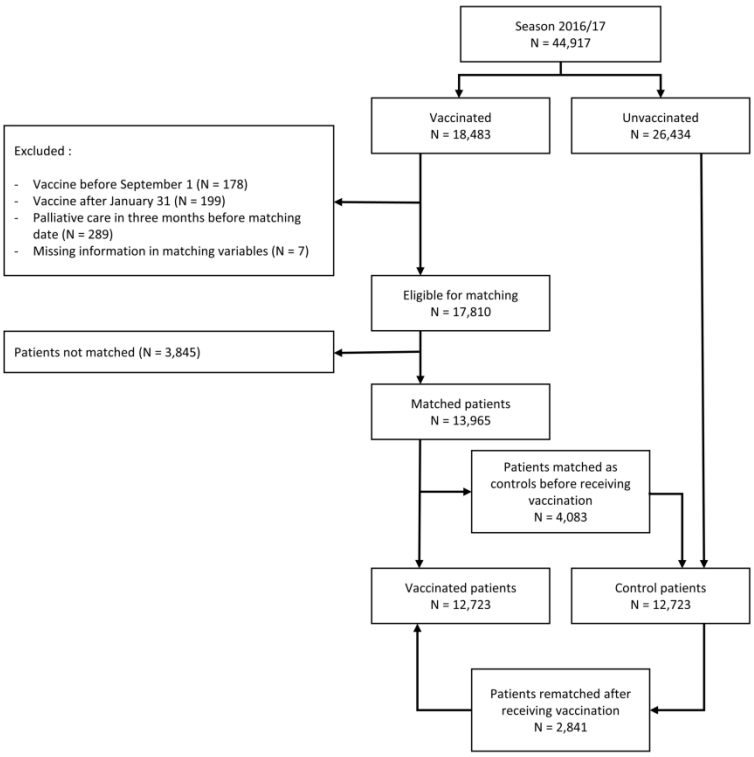

Figure E3 Detailed participant flow of the season 2016/17

254x190mm (300 x 300 DPI)

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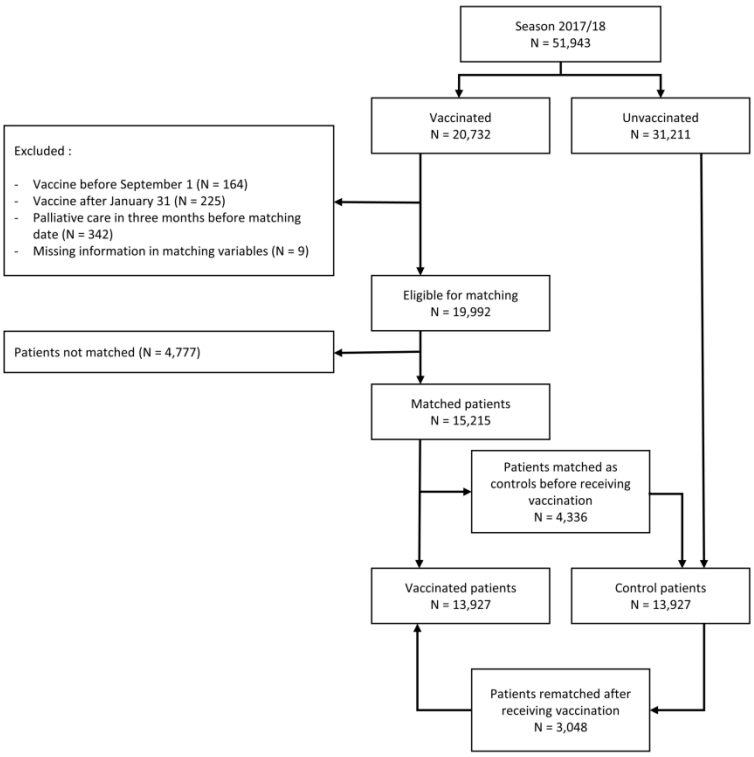

Figure E4 Detailed participant flow of the season 2017/18

254x190mm (300 x 300 DPI)

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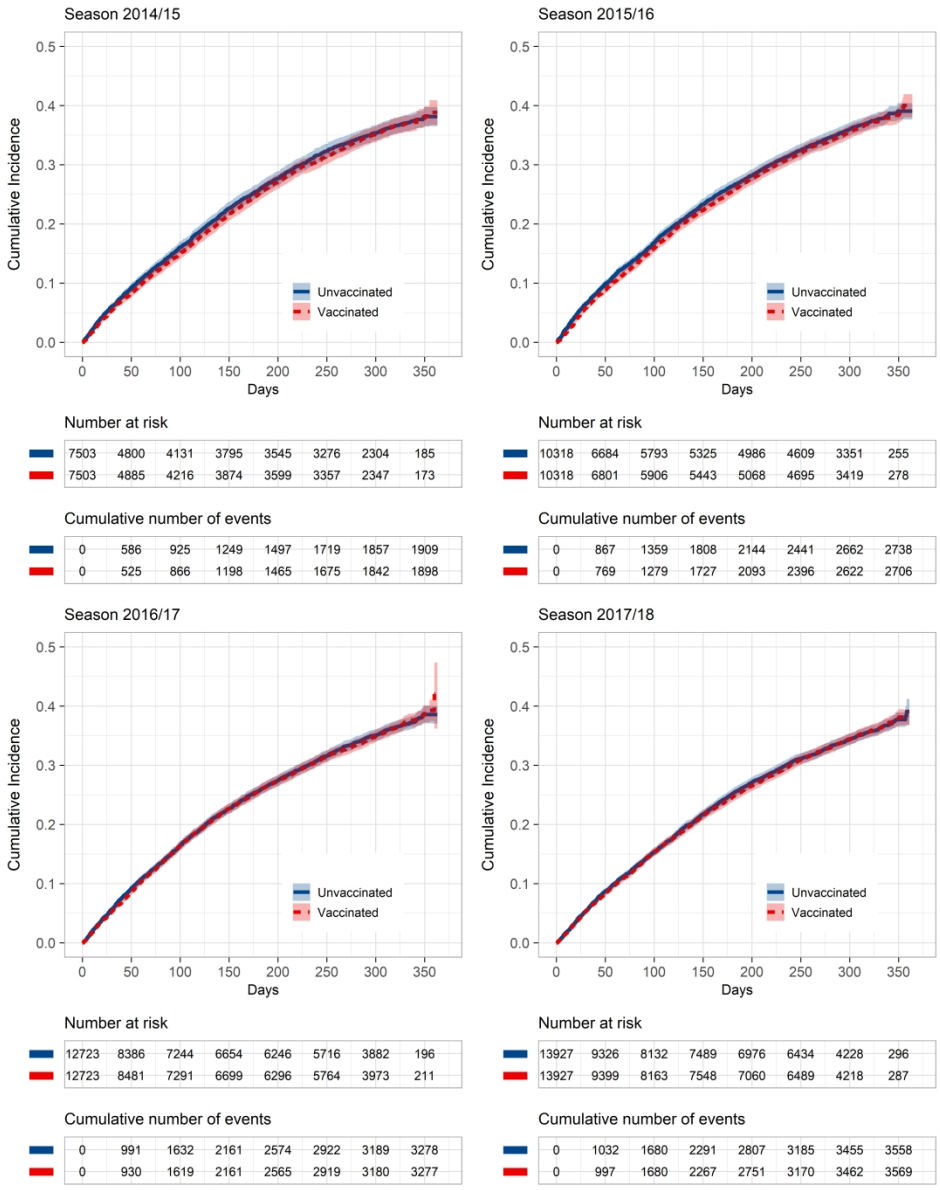

Figure E5 Cumulative incidence curves for all-cause hospitalization with 95% confidence intervals
Cumulative incidence curves (1 minus the Kaplan-Meier risk) depict the whole period from matching until end of follow-up (maximum June 30). Colored areas represent 95% confidence intervals

481x608mm (276 x 276 DPI)

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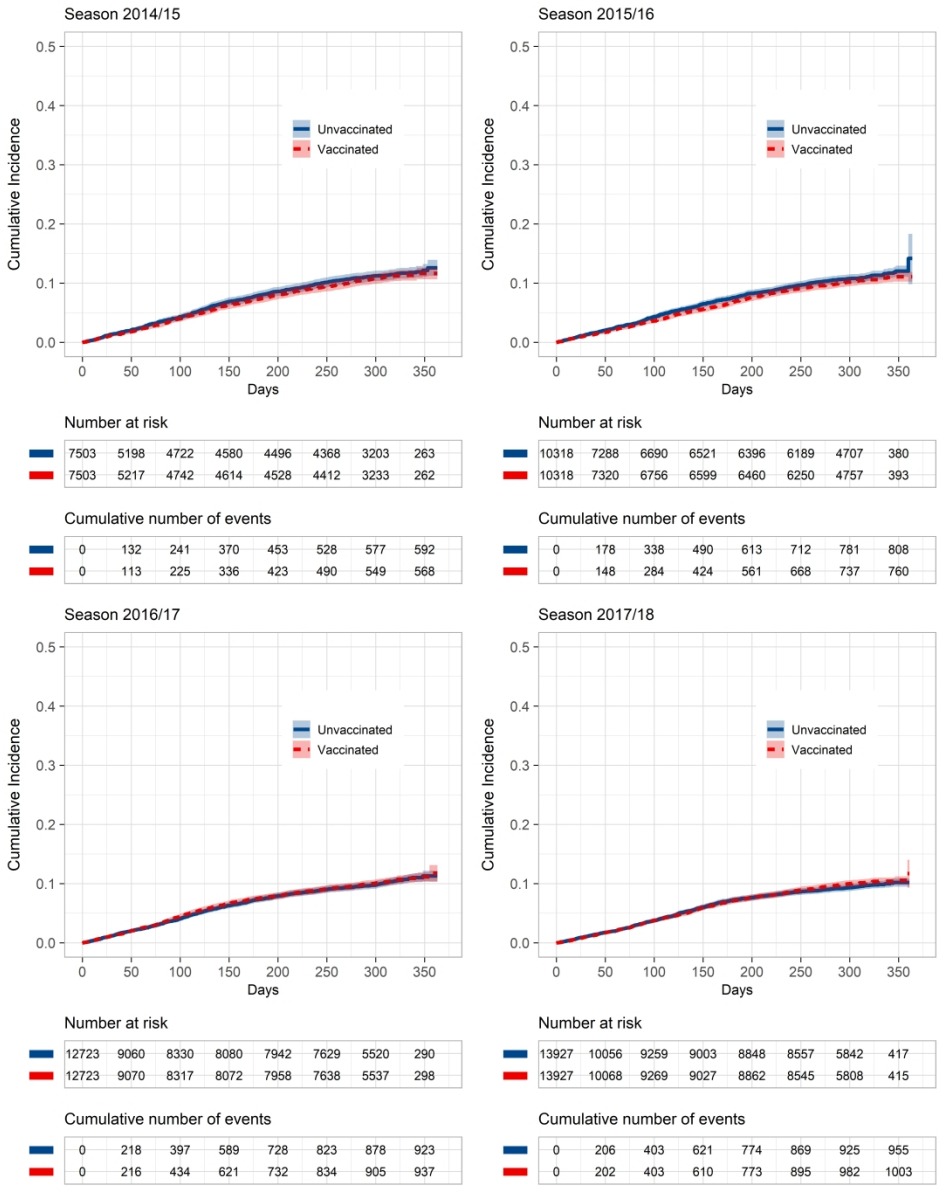

Figure E6 Cumulative incidence curves for respiratory-related hospitalization with 95% confidence intervalsCumulative incidence curves (1 minus the Kaplan-Meier risk) depict the whole period from matching until end of follow-up (maximum June 30). Colored areas represent 95% confidence interval

481x608mm (276 x 276 DPI)

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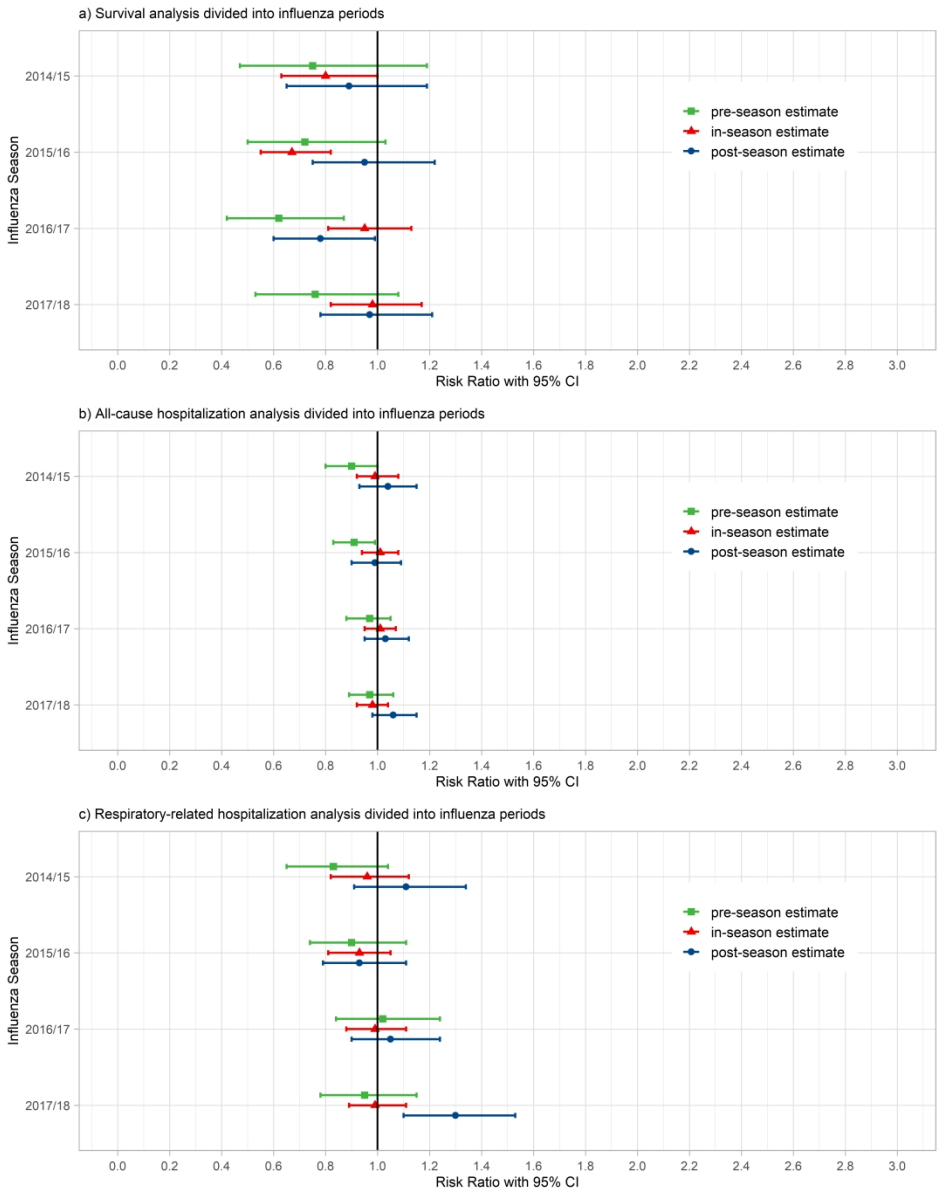

Figure E7 Sensitivity analyses for residual confounding by dividing the influenza season into periods of pre-, in- and post-season
Horizontal bars represent 95% confidence intervals
Pre-season: From September 1 until 10% of specimen were positive for influenza viruses according to the RKI influenza surveillance data
In-season: From 10% positive specimens until calendar week 20 of the following year
Post-season: From calendar week 20 until August 31

481x608mm (276 x 276 DPI)

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