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Influenza vaccination and 1-year risk of myocardial infarction, stroke, heart failure, pneumonia, and mortality among intensive care unit survivors aged 65 years or older: a nationwide population-based cohort study

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Abstract

Purpose: We examined whether influenza vaccination affects 1-year risk of myocardial infarction, stroke, heart failure, pneumonia, and death among intensive care unit (ICU) survivors aged ≥ 65 years.

Methods: Danish Intensive Care Database data on all elderly (≥ 65 years) patients hospitalized in Danish ICUs in the period 2005–2015, and subsequently discharged, were linked with data from other medical registries, including data on uptake of the seasonal influenza vaccine. We computed these patients' 1-year risk of hospitalization for myocardial infarction, stroke, heart failure, or pneumonia, and their 1-year risk of all-cause mortality. Hazard ratios (HRs) with 95% confidence intervals (CIs) were computed using Cox proportional hazards regression, with adjustment and propensity score matching applied to handle confounding.

Results: The study included 89,818 ICU survivors. The influenza vaccinated patients ($n = 34{,}871$, 39%) were older, had more chronic diseases, and used more prescription medications than the unvaccinated patients. Adjusted 1-year mortality was decreased among the vaccinated versus the unvaccinated patients (19.3% versus 18.8%; adjusted HR, 0.92; 95% CI 0.89–0.95). Influenza vaccination was also associated with a decreased risk of stroke (adjusted HR, 0.84; 95% CI 0.78–0.92), but only a small, non-significantly decreased risk of myocardial infarction (adjusted HR, 0.93; 95% CI 0.83–1.03). There was no association between vaccination and subsequent hospitalization for heart failure or pneumonia. Propensity score matched analyses confirmed these findings.

Conclusions: Compared with the unvaccinated ICU survivors, the influenza vaccinated ICU survivors had a lower 1-year risk of stroke and a lower 1-year risk of death, whereas no substantial association was observed for the risk of hospitalization for myocardial infarction, heart failure, or pneumonia. Our findings support influenza vaccination of individuals aged ≥ 65 years.

Keywords: Cardiovascular diseases, Cohort studies, Infection, Influenza vaccines, Intensive care, Mortality

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Introduction

Critical illness survivors are at increased risk of long-term morbidity and mortality [1–3]. One-year mortality after hospital discharge is 21–27% among intensive care unit (ICU) patients aged 65 years or older [4, 5], which is three- to fourfold higher than the mortality rate in the general population of the same age [4, 6, 7]. This difference is likely related both to underlying comorbidities and to complications of critical illness, including infections and cardiovascular morbidity [3, 4, 7]. Given the increasing number of critically ill elderly patients admitted to ICUs and surviving intensive care, long-term morbidity and mortality after the immediate critical illness are major concerns in this fragile population.

Influenza vaccination could reduce morbidity after intensive care, including bacterial infections and vascular events triggered by influenza [8–14], but less than 40% of Europeans aged 65 years or older receive the influenza vaccine [15]. No studies have addressed this topic in patients admitted to ICUs and evidence is limited in other critically ill patients. In two small meta-analyses of patients with coronary disease, the risks of composite cardiovascular endpoints and death were found to be reduced by more than 50% in influenza vaccinated versus unvaccinated patients [16, 17]. Similarly, a meta-analysis of observational studies in the general population found an almost 20% reduced risk of stroke in influenza vaccinated individuals compared with unvaccinated individuals [18]. Influenza vaccination may also reduce mortality following pneumonia, although this association remains controversial [19, 20].

Any beneficial effect of influenza vaccination among critical illness survivors would have a major clinical impact, especially as influenza vaccination is safe, inexpensive, and likely cost-effective [21, 22]. We examined the impact of influenza vaccination on the risk of hospitalization for myocardial infarction, stroke, heart failure, or pneumonia, and on mortality, among patients aged 65 years or older surviving an ICU admission.

Take-home message

Critical illness survivors are at increased risk of long-term morbidity and mortality and preventive interventions are needed. We found that influenza vaccination was associated with a 16% reduced 1-year risk of hospitalization for stroke and an 8% decreased risk of death among intensive care unit survivors aged 65 years or older.

Methods

Study design and setting

We conducted this population-based cohort study in Denmark among persons aged 65 years or older (1,051,129 persons in 2015). Denmark has a tax-supported healthcare system that guarantees all residents unfettered access to medical care. All 43 ICUs in Denmark are located in public hospitals [23]. The unique civil personal registration number assigned to all Danish residents at birth or upon immigration permits individual-level linkage of medical databases and complete follow-up of cases [24].

Study population

We included all patients aged ≥ 65 years who, between January 1st, 2005 and December 31st, 2015, had an inpatient hospitalization that included admission to an ICU in Denmark (the index hospitalization), and survived to hospital discharge. Patients were identified through the Danish Intensive Care Database (DID), a nationwide clinical quality database that covers virtually all patients admitted to ICUs in Denmark [23]. The main variables in the database are date and time of ICU admission, Simplified Acute Physiology Score (SAPS) II score, vital status, and receipt of mechanical ventilation, non-invasive ventilation, inotropes/vasopressors, or dialysis. Patients were considered admitted for surgical reasons if they had a surgical procedure on the day of or within seven days before ICU admission.

Influenza vaccination

We obtained information on preadmission influenza vaccination from the National Health Insurance Service Registry [25], which compiles data on health services provided by primary care physicians. General practitioners and other physicians providing influenza vaccinations must report them to this Registry to receive reimbursement. In Denmark, influenza vaccinations administered to residents with selected chronic diseases and to adults aged 65 years or older are fully reimbursed through the National Health Insurance program. We also obtained data from the Danish National Patient Registry (DNPR) on influenza vaccinations administered during hospitalizations [26]. The DNPR contains data on all non-psychiatric hospital admissions in Denmark since 1977 and on outpatient clinic and emergency room visits since 1995 [26]. The data recorded in the DNPR include dates of hospital admission and discharge, whether the admission was acute or elective, one primary diagnosis, and an optional number of secondary diagnoses, as well as treatments administered and procedures performed [26]. These diagnoses have been coded according to the International Classification of Diseases, Tenth Revision (ICD-10) since 1994. All diagnosis and procedure codes are provided in eAppendix 1. We defined patients as vaccinated against influenza if they received the vaccine between September 1st and August 31st for the current influenza season, either before or during the index

hospitalization with ICU admission. Other patients were considered unvaccinated. In addition, we obtained information on previous influenza vaccinations and post-discharge vaccinations received during the follow-up.

Outcomes: myocardial infarction, stroke, heart failure, pneumonia, and death

For each ICU survivor, we searched DNPR data on all hospital admissions in Denmark during the 1 year following the discharge from the index hospitalization, looking specifically for hospitalizations with a primary or secondary diagnosis of myocardial infarction, stroke (ischemic or hemorrhagic), heart failure, or pneumonia. The Danish Civil Registration System (CRS) [26] was consulted for data on deaths within 1 year of discharge. As a negative control outcome [27], we included hospitalization for injury, which has no expected association with influenza vaccination.

Potential confounders

The CRS contains daily updated data on all Danish residents, including vital status, marital status, country of birth (proxy for ethnicity), and place of residence [26]. In this study, to adjust for potential confounders, the CRS was used to obtain data on age, sex, marital status, country of birth, and urbanization of residence [24]. The DNPR was consulted for data on hospitalizations and outpatient specialist clinic visits for chronic diseases within the 10 years before the index hospitalization with ICU admission. Using DNPR data, we described the patients' comorbidity levels based on the prevalence and the sum of the scores for the 19 conditions included in the Charlson Comorbidity Index (CCI) [28, 29]. Patients who had received a prescription for respiratory drugs within the year before ICU discharge were considered to have chronic pulmonary disease. Similarly, patients with a prescription for antidiabetic drugs within the past year were considered to have diabetes. Data on prescription drugs were obtained from the Danish Health Service Prescription Database, which includes data on all prescriptions redeemed at Danish pharmacies since 2004 [30]. This database also provided data on prescriptions for low-dose aspirin, beta-blockers, statins, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-2-receptor inhibitors, diuretics, nitrates, vitamin K antagonists, immunosuppressants, and glucocorticoids that were redeemed within the 90 days before the index hospitalization.

The DNPR and the DID also furnished information on variables describing the index hospitalization with ICU admission. These included the primary diagnosis during hospitalization (see eAppendix 1 for codes), any diagnosis of influenza or pneumonia, ICU admission type (non-surgical, acute non-cardiac surgery, elective non-cardiac surgery, acute cardiac surgery, or elective cardiac surgery), intensive care treatments provided (mechanical ventilation, renal replacement therapy, infusion with inotropes/vasopressors), length of stay from ICU admission to hospital discharge, SAPS II score, number of days of hospitalization before ICU admission, and, to account for seasonality, month of discharge.

Statistical methods

Distributions of patient and admission characteristics were tabulated by influenza vaccination status at hospital discharge. Patients were followed up from discharge from their first hospitalization with ICU admission in the study period, until an outcome, death, emigration, or for up to 1 year.

We computed the 1-year risk of hospitalization for any diagnosis of myocardial infarction, stroke, heart failure, pneumonia, or injury using the cumulative incidence method, which accounts for the competing risk of death [31]. One-year mortality was computed as one minus the Kaplan-Meier survival estimate. Hazard ratios (HRs) were computed using Cox proportional hazards regression analysis, adjusted for the potential confounders listed in Tables 1 and 2. The proportional hazards assumption was checked graphically and found to be valid.

The analyses were further stratified by subgroups of ICU patients defined according to age, sex, comorbidity level, history of chronic pulmonary disease, history of heart failure, reason for ICU admission, and diagnostic group, to detect any differences in the heterogeneous ICU population. We also conducted the analyses after propensity score matching, which may be a more robust technique than traditional regression modelling when there are few outcomes per variable [32]. We computed the propensity score, which is the probability of having an influenza vaccination, for each study participant using a multivariate logistic regression model including all the variables listed in Tables 1 and 2. Each influenza vaccinated patient was matched with the unvaccinated patient having the closest propensity score, allowing a caliper width of 0.02 of the logit of the propensity score [33].

Additional analyses were performed to assess the robustness of our findings. First, to assess the impact of viral influenza risk on outcomes, we examined outcomes separately in patients discharged before (between September 1st and 30 days before the start of the annual influenza season), during (from 30 days before the start of the influenza season to the end of the season), and after (from the end of season to August 31st) each year's influenza season, focusing on 30-day post-discharge risks (since 1-year risks spanned both the influenza and

Table 1 Preadmission characteristics of all ICU patients and of the propensity score matched cohort, by vaccination status, Denmark, 2005–2015

	All ICU patients			Propensity score matched cohort		
	Unvaccinated	Vaccinated	Total	Unvaccinated	Vaccinated	Total
	No (%)	No (%)	No (%)	No (%)	No (%)	No (%)
Total	54,947 (100)	34,871 (100)	89,818 (100)	30,877 (100)	30,877 (100)	61,754 (100)
Age group						
65–70 years	17,648 (32.1)	7667 (22)	25,315 (28.2)	7516 (24.3)	7492 (24.3)	15,008 (24.3)
70–75 years	14,457 (26.3)	8863 (25.4)	23,320 (26)	8290 (26.8)	8122 (26.3)	16,412 (26.6)
75–80 years	11,259 (20.5)	8391 (24.1)	19,650 (21.9)	7176 (23.2)	7167 (23.2)	14,343 (23.2)
80+ years	11,583 (21.1)	9950 (28.5)	21,533 (24)	7895 (25.6)	8096 (26.2)	15,991 (25.9)
Sex						
Female	23,478 (42.7)	15,260 (43.8)	38,738 (43.1)	13,545 (43.9)	13,530 (43.8)	27,075 (43.8)
Male	31,469 (57.3)	19,611 (56.2)	51,080 (56.9)	17,332 (56.1)	17,347 (56.2)	34,679 (56.2)
Urban residence						
No (< = 25,000 inhabitants)	24,214 (44.1)	15,030 (43.1)	39,244 (43.7)	13,411 (43.4)	13,406 (43.4)	26,817 (43.4)
Yes (> 25,000 inhabitants)	26,755 (48.7)	16,878 (48.4)	43,633 (48.6)	15,096 (48.9)	15,045 (48.7)	30,141 (48.8)
Unknown	3978 (7.2)	2963 (8.5)	6941 (7.7)	2370 (7.7)	2426 (7.9)	4796 (7.8)
Marital status						
Married	29,291 (53.3)	19,588 (56.2)	48,879 (54.4)	16,799 (54.4)	17,065 (55.3)	33,864 (54.8)
Never married	3285 (6)	1632 (4.7)	4917 (5.5)	1574 (5.1)	1529 (5.0)	3103 (5.0)
Divorced	7857 (14.3)	3853 (11)	11,710 (13)	3725 (12.1)	3600 (11.7)	7325 (11.9)
Widowed	14,497 (26.4)	9792 (28.1)	24,289 (27)	8774 (28.4)	8677 (28.1)	17,451 (28.3)
Unknown	17 (0)	6 (0)	23 (0)	5 (0)	6 (0)	11 (0)
Ethnicity						
Born outside Denmark	2124 (3.9)	1103 (3.2)	3227 (3.6)	1073 (3.5)	1025 (3.3)	2098 (3.4)
Born in Denmark	52,823 (96.1)	33,768 (96.8)	86,591 (96.4)	29,804 (96.5)	29,852 (96.7)	59,656 (96.6)
Comorbidity						
Myocardial infarction	5895 (10.7)	4067 (11.7)	9962 (11.1)	3525 (11.4)	3512 (11.4)	7037 (11.4)
Stroke	8093 (14.7)	5080 (14.6)	13,173 (14.7)	4577 (14.8)	4458 (14.4)	9035 (14.6)
Congestive heart failure	5877 (10.7)	4847 (13.9)	10,724 (11.9)	3824 (12.4)	3882 (12.6)	7706 (12.5)
Kidney disease (moderate to severe)	2174 (4.0)	1735 (5.0)	3909 (4.4)	1383 (4.5)	1410 (4.6)	2793 (4.5)
Dementia	989 (1.8)	657 (1.9)	1646 (1.8)	580 (1.9)	594 (1.9)	1174 (1.9)
Chronic pulmonary disease	11,042 (20.1)	10,136 (29.1)	21,178 (23.6)	7564 (24.5)	7806 (25.3)	15,370 (24.9)
Connective tissue disease	2189 (4.0)	1760 (5.0)	3949 (4.4)	1392 (4.5)	1419 (4.6)	2811 (4.6)
Liver disease	920 (1.7)	521 (1.5)	1441 (1.6)	486 (1.6)	475 (1.5)	961 (1.6)
Cancer (solid tumor, leukemia, lymphoma)	10,655 (19.4)	6697 (19.2)	17,352 (19.3)	5911 (19.1)	5920 (19.2)	11,831 (19.2)
Metastatic cancer	1326 (2.4)	814 (2.3)	2140 (2.4)	732 (2.4)	724 (2.3)	1456 (2.4)
Hypertension	17,065 (31.1)	12,773 (36.6)	29,838 (33.2)	10,607 (34.4)	10,692 (34.6)	21,299 (34.5)
Obesity	2294 (4.2)	1734 (5.0)	4028 (4.5)	1436 (4.7)	1458 (4.7)	2894 (4.7)
Alcoholism	2399 (4.4)	1074 (3.1)	3473 (3.9)	1074 (3.5)	1034 (3.3)	2108 (3.4)
Diabetes	9084 (16.5)	7019 (20.1)	16,103 (17.9)	5720 (18.5)	5807 (18.8)	11,527 (18.7)
Atrial fibrillation/flutter	7455 (13.6)	6234 (17.9)	13,689 (15.2)	4838 (15.7)	4979 (16.1)	9817 (15.9)
Heart valve disease	6790 (12.4)	5123 (14.7)	11,913 (13.3)	4222 (13.7)	4251 (13.8)	8473 (13.7
Osteoporosis	3174 (5.8)	2713 (7.8)	5887 (6.6)	2065 (6.7)	2118 (6.9)	4183 (6.8)
Psychiatric disease	3455 (6.3)	2162 (6.2)	5617 (6.3)	1922 (6.2)	1893 (6.1)	3815 (6.2)
Rheumatoid arthritis or connective tissue disease	2165 (3.9)	1713 (4.9)	3878 (4.3)	1361 (4.4)	1384 (4.5)	2745 (4.4)
Peptic ulcer disease	3096 (5.6)	2161 (6.2)	5257 (5.9)	1856 (6.0)	1858 (6.0)	3714 (6.0)
Comorbidity burden						
Low	18,157 (33)	9393 (26.9)	27,550 (30.7)	9152 (29.6)	8869 (28.7)	18,021 (29.2)

Table 1 (continued)

	All ICU patients			Propensity score matched cohort		
	Unvaccinated	Vaccinated	Total	Unvaccinated	Vaccinated	Total
	No (%)	No (%)	No (%)	No (%)	No (%)	No (%)
Moderate	12,790 (23.3)	8450 (24.2)	21,240 (23.6)	7348 (23.8)	7545 (24.4)	14,893 (24.1)
Severe	11,288 (20.5)	7309 (21)	18,597 (20.7)	6503 (21.1)	6456 (20.9)	12,959 (21)
Very severe	12,712 (23.1)	9719 (27.9)	22,431 (25)	7874 (25.5)	8007 (25.9)	15,881 (25.7)
Co-medications						
Low-dose aspirin	15,834 (28.8)	12,010 (34.4)	27,844 (31)	10,157 (32.9)	10,138 (32.8)	20,295 (32.9)
Beta-blockers	14,845 (27.0)	10,802 (31)	25,647 (28.6)	9196 (29.8)	9142 (29.6)	18,338 (29.7)
Statins	16,526 (30.1)	12,611 (36.2)	29,137 (32.4)	10,464 (33.9)	10,484 (34)	20,948 (33.9)
Calcium channel blockers	10,728 (19.5)	8137 (23.3)	18,865 (21)	6766 (21.9)	6823 (22.1)	13,589 (22)
Angiotensin converting enzyme/angiotensin-2-receptor inhibitors	17,896 (32.6)	13,252 (38)	31,148 (34.7)	11,259 (36.5)	11,169 (36.2)	22,428 (36.3)
Diuretics	17,548 (31.9)	13,737 (39.4)	31,285 (34.8)	11,250 (36.4)	11,323 (36.7)	22,573 (36.6)
Nitrates	4797 (8.7)	3820 (11)	8617 (9.6)	3121 (10.1)	3149 (10.2)	6270 (10.2)
Vitamin K antagonists	4311 (7.8)	3954 (11.3)	8265 (9.2)	2889 (9.4)	3010 (9.7)	5899 (9.6)
Glucocorticoids	4660 (8.5)	4084 (11.7)	8744 (9.7)	3057 (9.9)	3204 (10.4)	6261 (10.1)
Immunosuppressants	450 (0.8)	387 (1.1)	837 (0.9)	290 (0.9)	307 (1.0)	597 (1.0)

non-influenza seasons). Annual influenza season dates are provided in eAppendix 2 [34]. Second, we restricted the analysis to patients with no previous diagnoses of the outcomes of interest within the 10 years before discharge, and no such diagnoses during the index hospitalization. Third, to address the potential impact of incident influenza vaccinations administered during follow-up, we repeated the analyses using influenza vaccination as a time-varying exposure.

All analyses were performed using the SAS 9.4 statistical software package. According to Danish law, ethical approval and informed consent were not required for this registry-based study. The study was approved by the Danish Data Protection Agency (record number 2015-57-0002, Aarhus University record number 2016-051-000001-432).

Results

Patient characteristics

This study included 89,818 ICU patients, after the exclusion of 36,239 (28.8%) patients who died before hospital discharge (30.0% of the total vaccinated and 27.9% of the total unvaccinated groups).

Of the 89,818 ICU patients comprising the study population, 34,871 (38.8%) had received the seasonal influenza vaccination. Among the 54,947 unvaccinated patients, 19,678 (35.8%) had received the vaccination in previous years, as had 29,891 (85.7%) of the vaccinated group. Compared with the unvaccinated patients, the vaccinated patients were older, and more frequently had a history of chronic pulmonary disease (29.1% vs. 20.1%), diabetes (20.1% vs. 16.5%), heart failure (13.9% vs. 10.7%), atrial fibrillation or flutter (17.9% vs. 13.6%), and hypertension (36.6% vs. 31.1%). There was virtually no difference in the prevalence of stroke (14.6% vs. 14.7%), cancer (19.2% vs. 19.4%) or ethnicity (96.8% vs. 96.1% born in Denmark) (Table 1). Preadmission use of cardiovascular drugs and glucocorticoids was more frequent among the influenza vaccinated patients. These characteristics were balanced between vaccinated and unvaccinated in the propensity score matched cohort (Table 1).

Characteristics of the index hospitalization with ICU admission

Compared with the unvaccinated patients, the influenza vaccinated patients were more frequently hospitalized with a primary diagnosis of respiratory disease (11.4% vs. 9.8%), but less frequently with a cancer diagnosis (11.8% vs. 13.8%). Only a few patients (0.1%) were admitted with a diagnosis of influenza. However, 10.4% of the influenza vaccinated patients received a diagnosis of pneumonia at their index admission, compared with 9.2% of the unvaccinated patients.

Non-surgical reasons for ICU admission were slightly more frequent in the patients with an influenza vaccination than in the unvaccinated patients (34.3% vs. 31.5%). The proportions receiving mechanical ventilation were very similar (44.8% vs. 46.6%). The median SAPS II score was 41 (IQR: 33–51) in patients with an influenza

Table 2 Index hospitalization characteristics of all ICU patients and of the propensity score matched cohort, by vaccination status

	All ICU patients			Propensity score matched cohort		
	Unvaccinated	Vaccinated	Total	Unvaccinated	Vaccinated	Total
	No (%)	No (%)	No (%)	No (%)	No (%)	No (%)
Total	54,947 (100)	34,871 (100)	89,818 (100)	30,877 (100)	30,877 (100)	61,754 (100)
Primary diagnosis during current hospitalization						
Pneumonia	1792 (3.3)	1421 (4.1)	3213 (3.6)	1157 (3.7)	1172 (3.8)	2329 (3.8)
Septicemia	1467 (2.7)	1003 (2.9)	2470 (2.8)	862 (2.8)	867 (2.8)	1729 (2.8)
Infectious diseases excluding pneumonia	2060 (3.7)	1381 (4.0)	3441 (3.8)	1199 (3.9)	1212 (3.9)	2411 (3.9)
Diabetes	288 (0.5)	163 (0.5)	451 (0.5)	165 (0.5)	144 (0.5)	309 (0.5)
Cardiovascular diseases	19,242 (35.0)	11,866 (34.0)	31,108 (34.6)	10,783 (34.9)	10,636 (34.4)	21,419 (34.7)
Respiratory diseases	5404 (9.8)	3984 (11.4)	9388 (10.5)	3316 (10.7)	3378 (10.9)	6694 (10.8)
Gastrointestinal and liver diseases	5035 (9.2)	3529 (10.1)	8564 (9.5)	3047 (9.9)	3027 (9.8)	6074 (9.8)
Cancer	7567 (13.8)	4122 (11.8)	11,689 (13)	3769 (12.2)	3801 (12.3)	7570 (12.3)
Injury or poisoning	5709 (10.4)	3520 (10.1)	9229 (10.3)	3121 (10.1)	3158 (10.2)	6279 (10.2)
Other	6383 (11.6)	3882 (11.1)	10,265 (11.4)	3458 (11.2)	3482 (11.3)	6940 (11.2)
Influenza (primary or secondary diagnosis)	43 (0.1)	40 (0.1)	83 (0.1)	31 (0.1)	31 (0.1)	62 (0.1)
Pneumonia (primary or secondary diagnosis)	5076 (9.2)	3641 (10.4)	8717 (9.7)	3114 (10.1)	3116 (10.1)	6230 (10.1)
Admission type						
Medical	17,305 (31.5)	11,953 (34.3)	29,258 (32.6)	10,176 (33)	10,288 (33.3)	20,464 (33.1)
Surgical, acute, non-cardiac	15,847 (28.8)	9884 (28.3)	25,731 (28.6)	8765 (28.4)	8805 (28.5)	17,570 (28.5)
Surgical, acute, cardiac	1815 (3.3)	992 (2.8)	2807 (3.1)	927 (3.0)	917 (3.0)	1844 (3.0)
Surgical, elective, non-cardiac	9989 (18.2)	5848 (16.8)	15,837 (17.6)	5327 (17.3)	5295 (17.1)	10,622 (17.2)
Surgical, elective, cardiac	9991 (18.2)	6194 (17.8)	16,185 (18)	5682 (18.4)	5572 (18)	11,254 (18.2)
Simplified Acute Physiology Score II (SAPS II) available[a]	7770 (14.1)	5348 (15.3)	13,118 (14.6)	4083 (13.2)	4633 (15.0)	8716 (14.1)
Median SAPS II (IQR)	42 (33–53)	41 (33–51)	42 (33–52)	42 (33–53)	41 (33–51)	42 (33–52)
Organ support treatment						
Mechanical ventilation	25,610 (46.6)	15,633 (44.8)	41,243 (45.9)	14,193 (46)	13,968 (45.2)	28,161 (46.6)
Renal replacement therapy	3702 (6.7)	2194 (6.3)	5896 (6.6)	2006 (6.5)	1973 (6.4)	3979 (6.4)
Treatment with inotropes/vasopressors	19,822 (36.1)	12,483 (35.8)	32,305 (36)	11,122 (36)	11,044 (35.8)	22,166 (35.9)
Length of stay (from ICU admission to hospital discharge)						
< 1 week	15,386 (28)	10,192 (29.2)	25,578 (28.5)	8944 (29.0)	8901 (28.8)	17,845 (28.9)
1–2 weeks	17,313 (31.5)	11,848 (34.0)	29,161 (32.5)	10,263 (33.2)	10,308 (33.4)	20,571 (33.3)
> 2–3 weeks	7901(14.4)	5227 (15.0)	13,128 (14.6)	4557 (14.8)	4584 (14.8)	9141 (14.8)
3 + weeks	14,347 (26.1)	7604 (21.8)	21,951 (24.4)	7113 (23.0)	7084 (22.9)	14,197 (23.0)
Number of days hospitalized before ICU admission						
0	15,598 (28.4)	10,194 (29.2)	25,792 (28.7)	8825 (28.6)	8914 (28.9)	17,739 (28.7)
1	17,156 (31.2)	11,302 (32.4)	28,458 (31.7)	9978 (32.3)	9919 (32.1)	19,897 (32.2)
2+	22,193 (40.4)	13,375 (38.4)	35,568 (39.6)	12,074 (39.1)	12,044 (39)	24,118 (39.1)
Discharge timing according to influenza season						
Before	13,968 (25.4)	1189 (3.4)	15,157 (16.9)	1231 (4.0)	1189 (3.9)	2420 (3.9)
During	20,487 (37.3)	14,558 (41.7)	35,045 (39)	13,657 (44.2)	13,463 (43.6)	27,120 (43.9)
After	20,492 (37.3)	19,124 (54.8)	39,616 (44.1)	15,989 (51.8)	16,225 (52.5)	32,214 (52.2)

[a] SAPS II scores were recorded since 2010 in patients with an ICU stay ≥ 24 h [23]

vaccination and 42 (IQR 33–53) in unvaccinated patients. The vaccinated patients were less likely to be hospitalized for more than three weeks (21.8% vs. 26.1%), but had a similar number of days in the hospital before ICU

admission. These characteristics were balanced between vaccinated and unvaccinated after propensity score matching (Table 2).

Outcomes

The 1-year risk of hospitalization for myocardial infarction was 1.9% in the vaccinated patients and 1.8% in the unvaccinated patients (Table 3), with a corresponding adjusted HR of 0.93 (95% CI 0.83–1.03). The risk of hospitalization for stroke was 2.9% in the vaccinated and 3.3% in the unvaccinated patients, with a corresponding adjusted HR of 0.84 (95% CI 0.78–0.92), whereas the risk of hospitalization for heart failure was 1.4% vs. 1.2% [adjusted HR = 0.98 (95% CI 0.86–1.12)].

The 1-year risk of hospitalization for pneumonia was not decreased in the patients who received an influenza vaccination compared with the unvaccinated patients [10.8% vs. 9.4%, adjusted HR = 1.02 (95% CI 0.98–1.07)].

One-year mortality was 19.3% in the vaccinated patients compared with 18.8% in the unvaccinated patients, with a corresponding adjusted HR of 0.92 (95% CI 0.89–0.95). The 1-year adjusted HR for hospitalization for injury was 0.96 (95% CI 0.90–1.03). The propensity score matched analysis yielded similar estimates (Table 3).

Outcomes in subgroups of ICU patients

The association between influenza vaccination and hospitalization for myocardial infarction, heart failure, stroke, or pneumonia, like the association between influenza vaccination and death, was robust across most subgroups of ICU patients (eTable 1–5). The association with hospitalization for stroke was similar in patients with a history of chronic pulmonary disease or heart failure (eTable 3), while the association with hospitalization for myocardial infarction was attenuated in these two groups (eTable 1). The strongest protective association between vaccination and 1-year mortality was observed in patients admitted to the ICU after acute or elective cardiac surgery (eTable 5).

Additional analyses

Among the patients who were unvaccinated at hospital discharge, 31.4% received a post-discharge vaccination. The estimates did not change after including post-discharge influenza vaccination as a time-varying exposure in the analysis (Table 3). Restriction of the analysis to first-time outcomes yielded similar estimates (eTable 6).

No clear relationship was found between timing of discharge in relation to the influenza season and 30-day outcomes, although the relationship in patients hospitalized for stroke was most pronounced in those admitted during and after than for patients admitted before the influenza season (Table 4).

Discussion

In this nationwide cohort study of almost 90,000 ICU survivors, influenza vaccinated patients showed decreased 1-year risks of hospitalization for stroke and death. Cardiac surgery patients were the subgroup that benefitted most. No association was found between vaccination and subsequent hospitalization for heart failure

Table 3 Risk and hazard ratios for hospital admission for each of the 1-year outcomes after discharge from the index hospitalization

	Seasonal influenza vaccination	No. of events	1-year risk (%)	Hazard ratio (95% CI)			
				Crude	Adjusted[a]	Adjusted with time-varying exposure[a]	Propensity- score matched cohort (*n* = 75,648)
Myocardial infarction	Unvaccinated	935	1.8 (1.7–1.9)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Vaccinated	649	1.9 (1.8–2.1)	1.09 (0.99-1.21)	0.93 (0.83-1.03)	0.93 (0.83–1.03)	0.93 (0.82–1.06)
Heart failure	Unvaccinated	620	1.2 (1.1–1.3)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Vaccinated	477	1.4 (1.3–1.5)	1.21 (1.08-1.37)	0.98 (0.86-1.12)	0.98 (0.86–1.12)	1.02 (0.87–1.19)
Stroke	Unvaccinated	1750	3.3 (3.2–3.5)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Vaccinated	968	2.9 (2.7–3.0)	0.87 (0.80-0.94)	0.84 (0.78-0.92)	0.84 (0.78–0.92)	0.81 (0.74–0.90)
Pneumonia	Unvaccinated	4987	9.4 (9.1–9.6)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Vaccinated	3676	10.8 (10.5–11.2)	1.17 (1.12-1.22)	1.02 (0.98-1.07)	1.02 (0.98–1.07)	1.04 (0.98–1.10)
Death	Unvaccinated	9963	18.8 (18.5–19.2)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Vaccinated	6518	19.3 (18.9–19.7)	1.03 (1.00-1.06)	0.92 (0.89-0.95)	0.92 (0.89–0.95)	0.92 (0.89–0.96)
Injury	Unvaccinated	2619	5.0 (4.8–5.1)	1 (ref.)	1 (ref.)		1 (ref.)
	Vaccinated	1631	4.8 (4.6–5.1)	0.98 (0.92 - 1.04)	0.96 (0.90 - 1.03)	0.96 (0.90–1.03)	0.97 (0.89–1.04)

[a] Adjusted for age group, sex, urbanization of residence, marital status, preadmission medication, each comorbid condition, admission diagnosis, discharge in relation to influenza season (before, during, or after), length of stay, and ICU treatments. (See Tables 1, 2)

Table 4 Risk and hazard ratios for outcomes within 30 days after discharge from the index hospitalization, stratified by timing of discharge in relation to the influenza season

Time of discharge	30-day risk (%)		Hazard ratio (95% CI)	
	Vaccinated	Unvaccinated	Crude	Adjusted[a]
Myocardial infarction				
Any time	0.5 (0.4–0.5)	0.4 (0.4–0.5)	1.09 (0.9–1.33)	0.99 (0.79–1.23)
Before influenza season	0.3 (0.1–0.8)	0.4 (0.3–0.5)	0.85 (0.31–2.35)	0.76 (0.25–2.31)
During influenza season	0.5 (0.4–0.7)	0.5 (0.4–0.6)	1.12 (0.83–1.50)	1.07 (0.78–1.47)
After influenza season	0.4 (0.3–0.5)	0.4 (0.3–0.5)	1.06 (0.78–1.44)	0.93 (0.68–1.28)
Heart failure				
Any time	0.3 (0.2–0.4)	0.3 (0.2–0.3)	1.05 (0.82–1.34)	0.91 (0.70–1.20)
Before influenza season	0.4 (0.2–0.9)	0.3 (0.2–0.4)	1.33 (0.53–3.36)	1.48 (0.52–4.24)
During influenza season	0.3 (0.2–0.4)	0.3 (0.2–0.4)	1.01 (0.67–1.51)	0.78 (0.51–1.19)
After influenza season	0.3 (0.2–0.4)	0.3 (0.2–0.4)	1.11 (0.77–1.59)	0.99 (0.68–1.45)
Stroke				
Any time	0.6 (0.5–0.7)	0.8 (0.7–0.8)	0.82 (0.70–0.97)	0.82 (0.68–0.98)
Before influenza season	0.8 (0.4–1.5)	0.8 (0.6–0.9)	1.11 (0.58–2.11)	1.09 (0.54–2.22)
During influenza season	0.6 (0.5–0.7)	0.7 (0.6–0.9)	0.79 (0.60–1.03)	0.80 (0.60–1.05)
After influenza season	0.6 (0.5–0.8)	0.8 (0.7–0.9)	0.83 (0.65–1.05)	0.81 (0.64–1.04)
Pneumonia				
Any time	3.0 (2.8–3.2)	2.5 (2.4–2.7)	1.18 (1.09–1.28)	1.03 (0.94–1.13)
Before influenza season	3.2 (2.3–4.3)	2.6 (2.3–2.8)	1.26 (0.90–1.76)	1.13 (0.78–1.65)
During influenza season	3.1 (2.8–3.4)	2.7 (2.5–2.9)	1.14 (1.01–1.30)	1.01 (0.88–1.15)
After influenza season	2.9 (2.7–3.2)	2.4 (2.2–2.6)	1.24 (1.10–1.40)	1.05 (0.92–1.19)
Death				
Any time	4.5 (4.3–4.8)	4.1 (4.0–4.3)	1.10 (1.03–1.18)	0.96 (0.90–1.03)
Before influenza season	3.5 (2.6–4.7)	4.0 (3.7–4.4)	0.88 (0.64–1.20)	0.84 (0.60–1.18)
During influenza season	4.6 (4.2–4.9)	4.3 (4.1–4.6)	1.06 (0.95–1.17)	0.94 (0.85–1.05)
After influenza season	4.6 (4.3–4.9)	4.0 (3.7–4.3)	1.15 (1.05–1.27)	0.98 (0.88–1.08)
Injury				
Any time	1.1 (0.9–1.2)	1.1 (1.0–1.2)	0.97 (0.85–1.10)	0.98 (0.85–1.13)
Before influenza season	1.6 (1.0–2.4)	1.2 (1.0–1.4)	1.37 (0.85–2.21)	1.21 (0.71–2.06)
During influenza season	1.0 (0.8–1.2)	1.0 (0.9–1.2)	0.96 (0.78–1.19)	1.01 (0.81–1.27)
After influenza season	1.1 (0.9–1.2)	1.1 (1.0–1.2)	0.97 (0.80–1.18)	0.92 (0.75–1.12)

[a] Adjusted for age group, sex, urbanization of residence, marital status, preadmission medication, each comorbid condition, admission diagnosis, discharge in relation to influenza season (before, during, or after), length of stay, and ICU treatments. (See Tables 1, 2)

or pneumonia. The lower risks of stroke and death may have been mediated through mechanisms other than influenza illness, as we found no clear relationship between the timing of discharge in relation to the influenza season and 30-day outcome risks.

When interpreting our findings, several strengths and weaknesses need to be considered. We identified patients from the Danish Intensive Care Database, which covers approximately 95% of ICU admissions in Denmark. This minimized referral bias [23]. The study relied on routine registration of influenza vaccinations, hospital diagnoses, and deaths. Data on influenza vaccination were recorded, likely with high validity, for the purpose of reimbursing physicians administering the vaccine [25]. We did not adjust for previous seasons' vaccinations because these were unlikely to influence the current season [35]. Pneumonia, myocardial infarction, and stroke are diagnosed and coded accurately in our registries [26, 36]. Any lack of specificity is likely unrelated to vaccination status and would bias the estimates towards the null. We were able to obtain virtually complete follow-up data with regard to hospitalizations and deaths [24]. Our results should, however, be interpreted cautiously because non-randomized studies are prone to confounding and, although we included a large number of potential confounders in the models, we cannot entirely rule out that unmeasured or residual confounding influenced our findings. While confounding linked to a healthy lifestyle may play a role

in studies of influenza vaccination [37], influenza vaccinated older persons in Denmark do not have a healthier lifestyle, higher socioeconomic status, or less frailty than their unvaccinated peers [38]. Any uncontrolled confounding may have led us to underestimate the effect of influenza vaccination. In addition, the null association with injury provides evidence countering a major healthy-user bias [39].

To our knowledge, no previous studies have examined the impact of influenza vaccination on long-term outcomes of patients requiring ICU admission. Our findings extend those relating to specific critical illnesses. A meta-analysis of three small randomized trials with a total of 789 patients with recent acute coronary syndrome found that influenza vaccination was associated with a reduced rate of a composite cardiovascular outcome (RR = 0.45; 95% CI 0.32–0.63) [16]. Similarly, a Cochrane review found reduced cardiovascular mortality (RR = 0.44; 95% CI 0.26–0.76) in a meta-analysis of four small secondary prevention trials [17]. In the same way, our finding of a decreased risk of stroke in influenza vaccinated older ICU patients extends the results of a meta-analysis of 11 studies on stroke risk in adults, which found that influenza vaccination was associated with reduced odds for stroke (OR = 0.82; 95% CI 0.75–0.91) [18]. A propensity score matched cohort study including 352 influenza vaccinated pneumonia patients and 352 unvaccinated pneumonia patients found a statistically non-significant reduction in in-hospital mortality with influenza vaccination (adjusted OR = 0.81; 95% CI 0.35–1.85) [19]. In a small cohort study of 466 pneumonia patients with self-reported vaccination, 30-day mortality after pneumonia was 9.6% in unvaccinated patients compared with 5.3% in patients reporting influenza vaccination, with or without pneumococcal vaccine [20].

We can only speculate about the potential mechanisms underlying these findings as complete data on the role of influenza infection is unavailable. Growing evidence links influenza infection and inflammation to cardiovascular events, as an inflammatory stimulus may lead to destabilization of vulnerable atherosclerotic plaque [10, 14]. Influenza vaccination could also have a biological effect through nonspecific immunomodulatory actions on the innate immune system [40]. This is consistent with a recent trial in 10,061 patients that found a decreased risk of recurrent cardiovascular events among patients treated with an anti-inflammatory drug targeting the innate immune system [41].

Our study focused on clinical outcomes among elderly intensive care survivors. We observed a slightly higher crude mortality during the index hospitalization with ICU admission in the vaccinated patients, which was unsurprising due to their higher age and comorbidity levels versus the unvaccinated patients. Further studies should address whether influenza vaccination decreases the risk of ICU admission or ICU mortality, a question that needs to be answered in order to fully understand the public health impact of influenza vaccination. However, our finding suggests a potential effect of influenza vaccination on the post-discharge prognosis of critical illness, and thereby supports the current recommendations to administer influenza vaccination to all persons aged 65 years or older.

In conclusion, the influenza vaccinated ICU patients in this study had lower adjusted relative risks of hospitalization for stroke and death within 1 year after hospital discharge compared with the unvaccinated ICU patients, while the association between vaccination and hospitalization for myocardial infarction was less clear. Our study supports current recommendations to provide an influenza vaccination to all adults aged 65 years or older.

Electronic supplementary material
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Author contributions
CFC, RWT, MS, and HTS conceived the study idea and designed the study. CFC and HTS obtained the funding. CFC and LP collected the data and carried out the analyses. CFC organized the writing and wrote the first draft. All authors participated in the discussion and interpretation of the results. All authors critically revised the manuscript for intellectual content and approved the final version before submission. CFC is the guarantor.

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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflicts of interest.

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