Received: 19 July 2021 | Revised: 29 March 2022 | Accepted: 29 March 2022

DOI: 10.1111/ajt.17055

ORIGINAL ARTICLE

Effect of influenza vaccination in solid organ transplant recipients: A nationwide population-based cohort study

Zitta Barrella Harboe[1,2,3] | Daniel Modin[4] | Finn Gustafsson[3,5] | Michael Perch[3,5] | Gunnar Gislason[3,4] | Søren Schwartz Sørensen[3,6] | Allan Rasmussen[7] | Tor Biering-Sørensen[4,8] | Susanne Dam Nielsen[1,3]

[1]Department of Infectious Diseases, Vaccination Clinic for Immunocompromised, University Hospital of Copenhagen, Copenhagen, Denmark

[2]Department of Pulmonary and Infectious Diseases, University Hospital of Copenhagen, Copenhagen, Denmark

[3]Department of Clinical Medicine, Faculty of Health and Medical Science, University of Copenhagen, Copenhagen, Denmark

[4]Department of Cardiology, University of Copenhagen, Herlev & Gentofte Hospital, Copenhagen, Denmark

[5]Department of Cardiology, Heart and Lung Transplant Unit, University Hospital of Copenhagen, Copenhagen, Denmark

[6]Department of Nephrology, Kidney Transplant Unit, University Hospital of Copenhagen, Copenhagen, Denmark

[7]Department of Surgical Gastroenterology, Liver Transplant Unit, University Hospital of Copenhagen, Copenhagen, Denmark

[8]Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Correspondence
Zitta Barrella Harboe,
Department of Infectious Diseases,
University Hospital of Copenhagen,
Rigshospitalet, and North Zealand,
Copenhagen, Denmark.
Email: zitta.barrella.harboe@regionh.dk

Funding information
Danish Independent Research Foundation,
Grant/Award Number: 0134-00257B

Vaccination can prevent influenza in solid organ transplant (SOT) recipients. Using a modified season-specific approach over nine consecutive influenza seasons, we investigated influenza vaccination coverage and effectiveness in a population-based nationwide cohort study that included all SOT recipients aged ≥18 years who were living in Denmark from December 1, 2007 to April 1, 2016. The primary outcome was the season-specific risk of all-cause pneumonia admission. Secondary outcomes were season-specific influenza-related admission, intensive care unit (ICU) admission, and all-cause mortality. Crude and adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models. In total, 11 381 person-years of follow-up data were collected from 5745 SOT recipients, 48% of whom were vaccinated. Influenza vaccination was associated with a reduced risk of all-cause pneumonia admission (aHR, 0.83; 95% CI, 0.69–0.99; $p = .035$) and all-cause mortality (aHR, 0.60; 95% CI, 0.47–0.76; $p = .001$), but not influenza-related admission (aHR, 0.75; 95% CI, 0.46–1.22; $p = .24$) or ICU admission (aHR, 0.84; 95% CI, 0.67–1.06; $p = .14$) during the same season. Despite these benefits, uptake of influenza vaccination among SOT recipients was low. Therefore, annual influenza vaccination needs to be prioritized.

KEYWORDS
Influenza, pneumonia, SOT, vaccination

Abbreviations: CI, confidence interval; HR, hazard ratio; ICD-10, tenth revision of the International Statistical Classification of Diseases and Related Health Problems; ICU, intensive care unit; IR, incidence rate; PYFU, person-years of follow-up; SD, standard deviation; SOT, solid organ transplant.

1 | INTRODUCTION

The influenza virus is a common cause of respiratory tract infections in both immunocompromised and immunocompetent populations.[1] Influenza is a potentially serious infection in solid organ transplant (SOT) recipients and may result in hospitalization, admission to an intensive care unit (ICU), or even death.[2,3] Annual seasonal influenza vaccination is widely recommended and considered the main strategy for preventing influenza and its complications in immunocompromised patients, including SOT candidates and recipients.[4-6]

The American Society of Transplantation recommends annual influenza vaccination for all SOT recipients.[4] Nevertheless, SOT recipients are reportedly under-immunized against influenza, and nearly half of SOT recipients were unvaccinated in both US and European settings.[7] Therefore, a substantial proportion of this high-risk group of patients is susceptible to influenza infection, despite the widespread availability of vaccines.[6]

Even though the influenza vaccine is the most extensively studied vaccine in transplant recipients,[8] its effectiveness remains controversial. Most studies indicate that antibody responses in SOT recipients are suboptimal after influenza vaccination and that these responses vary depending on the immunosuppressive drug regimen used, the time since transplantation, and the type of graft.[3,9] There have been few randomized clinical trials involving SOT recipients.[9,10] Data from multicenter observational studies on SOT recipients with laboratory-confirmed influenza infection indicated that vaccination during the same influenza season was associated with a decrease in disease severity, assessed as pneumonia occurrence and ICU admission.[2,3] Thus, recommendations for influenza vaccination in SOT recipients rely on immunogenicity data, observational studies, and efficacy results from non-immunocompromised populations.[4,9]

We investigated the effects of seasonal influenza vaccination. Our primary outcome was the incidence of all-cause pneumonia admission. Secondary outcomes were the incidences of influenza-related admission and ICU admission, as well as all-cause mortality in SOT recipients. We conducted a large, nationwide, population-based observational study using medical registers, and we linked information on vaccinations, hospital admissions, and deaths for all SOT recipients in Denmark to investigate these outcomes during nine consecutive influenza seasons.

Summary

Influenza vaccination is recommended for solid organ transplant (SOT) recipients. Seasonal influenza vaccination was associated with a reduced risk of hospitalization for all-cause pneumonia. However, in this nationwide cohort study, seasonal vaccination coverage was <50%. Therefore, annual influenza vaccination should be prioritized in SOT recipients.

2 | MATERIALS AND METHODS

2.1 | Study setting and data sources

This is a population-based nationwide cohort study including all kidney, heart and/or lung, and liver transplant recipients aged ≥18 years living in Denmark from December 1, 2007 to April 1, 2016. Nationwide administrative registers were used to collect information on comorbidities, medications other than immunosuppressants, household income, and educational level. Immunosuppressants are provided free of charge from hospital departments, and immunosuppression data are, therefore, not available from the Danish National Prescription Register.

All persons living in Denmark are assigned a unique 10-digit personal registration number which enables cross-referencing among Danish national registers, facilitating comprehensive population-based studies.[11] Nationwide registers that collect health and social data on all citizens have been described elsewhere.[12] We retrieved information from the following registers: (1) The Danish Civil Registration System,[13] which includes information on the date of birth, sex, vital status, date of death, emigration, and residential location; (2) The Danish National Patient Register, which includes dates of admission and hospital discharge, department of admission, and all primary and secondary discharge diagnoses and procedure codes from hospital contacts in accordance with the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)[14]; (3) The Danish National Population Register, which includes information on household income and educational level; (4) The Danish National Prescription Register,[15] including data on all prescription drugs sold in Danish community pharmacies to each individual; and (5) The National General Practitioners Reimbursement Register, including unique governmental reimbursement codes and from which we extracted data on influenza vaccine administration before each season. All residents in Denmark have access to free universal health care. The registers used in this study are listed in Supplementary Table S1.

2.2 | Study design

We used a modified cohort study design with a season-specific approach to assessing the association between influenza vaccination and outcomes, as previously described.[16] In brief, we assumed that influenza vaccination could improve outcomes either by reducing the likelihood of influenza infection or reducing the severity of infection. However, such effects are only relevant if influenza is actively circulating in the population. Therefore, we chose to restrict the analysis to the calendar period during which influenza is most active in Denmark (December, January, February, and March), based on previous epidemiological data[17] Nine influenza seasons between 2007 and 2016 were included, representing nine different observation periods. For each season, we identified all SOT recipients alive on December 1 and followed them until April 1, of the following year

by retrieving information from the National Patient Register (ICD-10 code DZ94). Patient characteristics were assessed at the beginning of each season (December 1). Thus, each patient could contribute to multiple observation periods or seasons.

2.3 | Exposure (influenza vaccination status)

In Denmark, seasonal influenza vaccination is offered to all SOT recipients free of charge. Vaccines administered by general practitioners are recorded in the General Practitioners Reimbursement Register, and we used these data to assess the exposure to influenza vaccination before the beginning of each season. A patient was considered vaccinated if they had received an influenza vaccine during the previous 4 months before the beginning of the corresponding influenza season. We chose this period because most influenza vaccines dispensed in Denmark are administered from September to November (14% were administered in September, 64% in October, and 17% in November). In addition to the main analysis and to evaluate whether more acutely ill patients would have been vaccinated during a hospitalization (and, therefore, categorized in the "non-vaccinated" group), we conducted a chart review of 100 randomly selected SOT recipients who had transplants between 2010 and 2019 in our center and verified their influenza vaccination status.

2.4 | Variables and outcomes

The following variables were included in the statistical analysis: sex, age, type of graft, time since transplantation, underlying medical conditions, prescribed medications, vaccination in the previous season, household income, and educational level. Relevant underlying medical conditions and prescribed medications are listed in Supplementary Tables S2 and S3. The time since transplantation was the time since the first transplant, regardless of re-transplantation. We reassessed and updated patient characteristics on the index date of each season (December 1) to take season-to-season changes into account. The primary outcome was hospitalization with all-cause pneumonia, including influenza admissions (ICD-10 codes DJ09–DJ18). Secondary outcomes were influenza-related hospital admission (ICD-10 codes DJ09–DJ11), all-cause ICU admission, and all-cause mortality during the corresponding influenza season. ICD-10 diagnoses of pneumonia were made by clinicians and based on clinical, microbiological, and radiological criteria, as previously described.[18,19] For all non-fatal outcomes, only the first event was analyzed. Influenza was diagnosed in SOT recipients in Denmark in accordance with national guidelines[20] and confirmed by a polymerase chain reaction test.

2.5 | Statistical analysis

Differences in baselines characteristics between groups were evaluated by the χ^2 test and Fisher's exact test, as appropriate. Differences were considered significant at $p < .05$. To assess the association between influenza vaccination and outcomes, we used multivariable Cox regression with multiple follow-up intervals per patient, and we adjusted the model for the following confounders: age, sex, type of transplant, time since transplant, comorbidities, household income, educational level, prescribed medications, and influenza vaccination status during the previous season. All prescribed medications and comorbidities listed in Supplementary Tables S2 and S3 were included in the adjusted models. Patients were followed from December 1 until the date they died or until April 1 of the following year, whichever came first, allowing a contribution of up to 120 days per patient per season. We stratified the models by season and used a clustered variance estimator considering observations from the same patient as clustered to account for multiple observation periods per patient, as previously described (https://www.stata.com/manuals/ststcox.pdf). We also assessed the association between mortality and vaccination in the "off-season" months (April 1 to December 1 the following year). For this analysis, we extended the follow-up from the 4-month "in-season" period to 1 year (December 1 to December 1 the following year). Estimates presented are pooled estimates for all influenza seasons.

2.6 | Sensitivity analysis

To assess whether influenza vaccination was associated with a healthier patient, we performed two different sensitivity analyses. First, we looked at the same outcomes during the non-influenza season period (June, July, and August). Second, we looked at whether there was an association between influenza vaccination and the incidence of any cancer diagnosis.

2.7 | Ethics

The authors had full access to raw, anonymized data stored by Statistics Denmark. According to Danish law, informed consent or approval by an ethics committee is not required for studies based solely on anonymized data from nationwide administrative registers.

3 | RESULTS

3.1 | Study subjects and baseline characteristics

A total of 5745 adult SOT recipients with a mean age of 50 years (standard deviation [SD], 14.4) were included. Among these, 62% ($n = 3553$) were male and 48% ($n = 2790$) were vaccinated against influenza before at least one of the nine influenza seasons included in the study period. Patients who were vaccinated before the beginning of at least one influenza season ($n = 2790$) were older (mean age, 53.6 [SD, 10.6] vs. 46.8 [SD, 14.5] years; $p < .001$). Vaccinated patients were also more likely to have underlying comorbidities than

non-vaccinated patients (Tables 1 and 2). Vaccinated patients had higher household incomes but similar educational levels (Table 3). In addition, among 326 influenza vaccinations provided to 100 SOT recipients during 2010–2019, only 16 vaccinations (0.05%) were given during a hospital contact.

3.2 | Follow-up and outcomes

During the nine influenza seasons, 5745 SOT recipients (≥18 years) provided 11 381 person-years of follow-up (PYFU) data. The mean number of influenza seasons per patient was 7 (interquartile range, 3–9 seasons). During the nine seasons, there were 948 all-cause pneumonia admissions, corresponding to an incidence rate (IR) of 83 per 1000 PYFU; 150 influenza-related admissions (IR, 13 per 1000 PYFU); and 532 ICU admissions (IR, 47 per 1000 PYFU).

Crude and adjusted (a) hazard ratios (HRs) for all patients are shown in Figure 1. Before adjustment, influenza vaccination was associated with an increased risk of all-cause pneumonia admission (HR, 1.18; 95% confidence interval [CI], 1.02–1.38; $p = .021$) and all-cause mortality (HR, 1.10; 95% CI, 0.91–1.33; $p = .033$), a non-significant increased risk of ICU admission (HR, 1.10; 95% CI, 0.92–1.32; $p = .30$), but a reduced risk of influenza-related hospital admission (HR, 0.65; 95% CI, 0.46–0.92; $p = .016$). After adjusting for confounders (age, sex, type of transplant, time since transplant, comorbidities, household income, educational level, prescribed medicines, and influenza vaccination status in the previous season), we found a statistically significant reduction in the risk of all-cause pneumonia admission (aHR, 0.83; 95% CI, 0.69–0.99; $p = .035$) and all-cause mortality during the influenza season (aHR, 0.60; 95% CI, 0.47–0.76; $p = .001$), but no statistically significant reduction in the risk of influenza-related hospital admission (aHR, 0.75; 95% CI, 0.46–1.22; $p = .24$) or ICU admission (aHR, 0.84; 95% CI, 0.67–1.06; $p = .14$).

As a sensitivity analysis, we investigated the association between seasonal influenza vaccination and cancer diagnoses in the same influenza season. We excluded patients with prevalent cancers ($n = 363$). Among the remaining patients ($n = 5382$), 330 cancer events were registered during the influenza season. In the unadjusted analysis, influenza vaccination was significantly associated with incident cancer (HR, 1.71; 95% CI, 1.38–2.14; $p < .001$). However, in the fully adjusted model, influenza vaccination was not significantly associated with incident cancer (aHR, 1.25; 95% CI, 0.91–1.71; $p = .16$). We also tested for the effect of influenza vaccination on the same outcomes during the non-influenza season months (June, July, and August). We found a non-significant increased risk of all-cause pneumonia admission ($n = 203$ events) in the fully adjusted model (aHR, 1.39; 95% CI, 0.96–2.02; $p = .078$). For the off-season mortality analysis ($n = 305$ events), we found that influenza vaccination was associated with a non-significant reduced risk of death in the fully adjusted model (aHR, 0.76; 95% CI, 0.55–1.06; $p = .103$).

TABLE 1 Demographic characteristics of solid organ transplant recipients according to influenza vaccination status

	All patients ($n = 5745$)	Non vaccine ($n = 2955$)	Vaccine ($n = 2790$)	
	No. (%)	No. (%)	No. (%)	*p*-value
Age in years, mean (SD)	50 (14.4)	46.8 (14.5)	53.6 (10.6)	<.001
Age group				
18–34	951 (16.5%)	654 (22.1%)	297 (25.6%)	<.001
35–49	1725 (30%)	1012 (34.2%)	713 (21.0%)	
50–64	2236 (39%)	1001 (33.9%)	1235 (44.3%)	
≥65	833 (14.5%)	288 (9.7%)	545 (19.5%)	
Male	3553 (62%)	1891 (64.0%)	1662 (59.6%)	.007
Solid organ transplant				
Kidney	3981 (69.3%)	2180 (73.8%)	1801 (64.6%)	<.001
Heart	582 (10.3%)	225 (7.6%)	357 (12.8%)	
Lung	499 (8.7%)	184 (6.2%)	315 (11.3%)	
Heart and lung	32 (0.5%)	16 (0.5%)	16 (0.6%)	
Liver	651 (11.3%)	350 (11.8%)	301 (10.8%)	
Days since transplant, median (interquartile range)		656 (182–3480)	794.5 (211–3460)	.15

Note: Patients in the non-vaccine group had never received an influenza vaccination, according to the registers. Patients in the vaccine group include patients who had received at least one influenza vaccination before any influenza season during the nine influenza seasons included in the study. Solid organ transplant recipients' characteristics are reported at the time of patients' first inclusion into the study. *p* values <.05 were considered significant.

Abbreviation: SD, standard deviation.

TABLE 2 Underlying comorbid conditions in solid organ transplant recipients according to influenza vaccination status

	All patients (n = 5745)	No vaccine (n = 2955)	Vaccine (n = 2790)	
	No. (%)	No. (%)	No. (%)	p-value
Hypertension	3342 (58.2%)	1629 (55.1%)	1713 (61.4%)	<.001
Acute myocardial infarction	237 (4.5%)	95 (3.8%)	142 (5.1%)	<.001
Ischemic heart disease	940 (16.3%)	393 (13.3%)	547 (19.6%)	<.001
Valvular disease	257 (4.5%)	125 (4.2%)	132 (5.5%)	.36
Cerebrovascular disease	329 (5.7%)	152 (5.1%)	177 (6.3%)	.05
History of cancer	543 (9.5%)	259 (8.8%)	284 (10.2%)	.067
Atrial fibrillation or flutter	479 (8.3%)	197 (6.7%)	282 (10.1%)	<.001
Chronic renal failure	3078 (53.6)	1648 (55.8%)	1430 (51.3%)	<.001
Anemia	387 (6.7%)	190 (14.2%)	197 (7.1%)	.34
Diabetes	901 (15.7%)	420 (14.2%)	481 (17.2%)	.002
COPD	356 (6.2%)	115 (3.9%)	241 (8.6%)	<.001
Liver disease	493 (8.6%)	264 (8.9%)	229 (8.2%)	.33

Note: Patients in the non-vaccine group had never received an influenza vaccination, according to the registers. Patients in the vaccine group include patients who had received at least one influenza vaccination before any influenza season during the nine influenza seasons included in the study. Solid organ transplant recipients' characteristics are reported at the time of patients' first inclusion into the study. p values <.05 were considered significant.

Abbreviation: COPD, chronic obstructive pulmonary disease.

TABLE 3 Socioeconomic and educational level of solid organ transplant recipients according to influenza vaccination status

	All patients (n = 5745)	No vaccine (n = 2955)	Vaccine (n = 2790)	
	No.	No. (%)	No. (%)	p-value
Household income quartile				
First quartile	1395	810 (27.4%)	585 (21.0%)	<.001
Second quartile	1394	674 (22.8%)	720 (25.8%)	
Third quartile	1395	633 (21.4%)	762 (27.3%)	
Fourth quartile	1394	689 (23.3%)	705 (25.3%)	
Missing	167	149 (5.0%)	18 (0.6%)	
	No. (%)	No. (%)	No. (%)	
Highest educational level				
Basic school, <10 years	1894 (32.9%)	977 (33.1%)	917 (32.9%)	
High school, +3 years	312 (5.4%)	183 (6.2%)	129 (4.6%)	<.001
Vocational education	2045 (35.6%)	973 (32.9%)	1072 (38.4%)	
Short/medium higher, +2–4 years	903 (15.7%)	435 (14.7%)	468 (16.8%)	
Long higher, +5 years or more	261 (4.5%)	131 (4.4%)	130 (4.7%)	
Unknown	330 (5.7%)	256 (8.7%)	74 (2.7%)	

Note: Patients in the non-vaccine group had never received an influenza vaccination, according to the registers. Patients in the vaccine group include patients who had received at least one influenza vaccination before any influenza season during the study period. Solid organ transplant recipients' characteristics are reported at the time of patients' first inclusion into the study. p values <.05 were considered significant.

4 | DISCUSSION

In this nationwide cohort study, we evaluated the effects of influenza vaccination in SOT recipients over many seasons and found that vaccination was associated with a reduction in admissions to hospital with all-cause pneumonia. Vaccinated SOT recipients also had a reduced risk of all-cause mortality. However, influenza vaccination coverage was low in this high-risk population during the nine influenza seasons included in the study.

More than 100 000 SOTs are performed annually worldwide.[21] SOT candidates and recipients are highly susceptible to influenza and have an increased risk of complications due to influenza.[3,4]

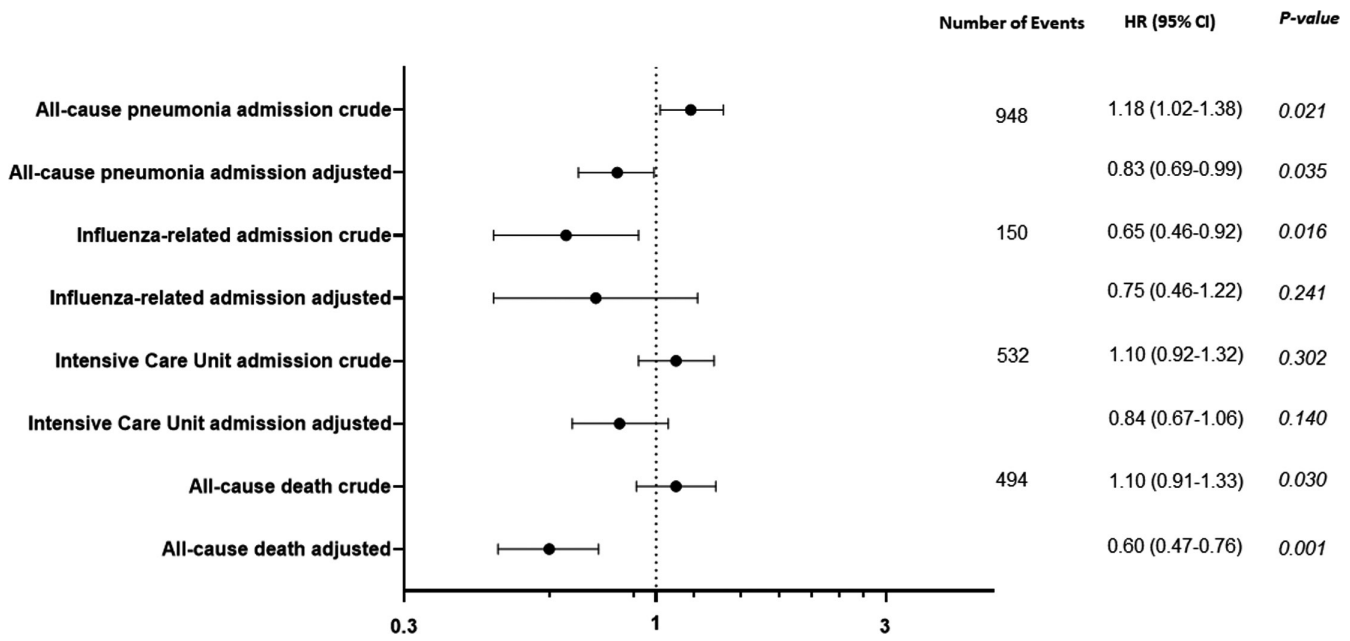

FIGURE 1 Association between influenza vaccination status and outcomes in solid organ transplant recipients stratified by age group. Crude and adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) are presented. Adjustment for age, time since transplant, transplant type, level of education, income, comorbidities, prescribed medicines, and vaccination status in the previous season was done

Despite current recommendations, influenza vaccination coverage among SOT recipients is reportedly low.[22,23] This may be due to vaccine hesitancy, concerns about vaccine effectiveness, adverse effects, and/or a lack of awareness regarding vaccine recommendations.[24] Initiatives to improve vaccination uptake in this vulnerable population are needed, ideally involving patient organizations, general practitioners, infectious disease clinicians, and transplant program specialists. Even though most seasonal influenza vaccinations in Denmark are administered by general practitioners, we cannot rule out the possibility that some vaccines may have been given in hospital settings or pharmacies, because we cannot access this information. This would partly explain the low estimate of vaccine coverage in our study population.

We found that influenza vaccination was associated with a 17% overall reduction in the incidence of all-cause pneumonia admissions during the same influenza season and that 16% of pneumonia hospitalizations were due to influenza. These results are consistent with findings reported in a large multicenter observational study that included 477 adult SOT recipients diagnosed with influenza,[2] in which investigators found a decrease in disease severity measured as admission for pneumonia or to an ICU. Such an effect could be related to a "healthy vaccinees" bias; however, we found that vaccinated SOT recipients were older, more likely to have comorbidities, and used more medications than unvaccinated SOT recipients. Thus, our findings suggest that influenza vaccination is associated with a significant reduction in all-cause pneumonia admission in this high-risk population, with a substantial proportion of these hospitalizations being attributable to influenza.

We found that influenza vaccination was associated with an overall reduction in mortality during the same season. A single-center retrospective study that included 187 pediatric kidney transplant recipients found that influenza vaccination was associated with a reduced risk of mortality during the first year after transplantation, but this finding was not reproduced over subsequent seasons,[25] whereas studies in adult SOT recipients produced inconsistent results.[23,26] To test for a healthy-vaccinee bias,[16] we compared the risk of hospitalization for vaccinated and unvaccinated SOT recipients during the non-influenza season months and evaluated the association between influenza vaccination and incident cancer during follow-up, because influenza vaccination should have no effect on the risk of cancer during influenza seasons. In the off-season adjusted analyses, influenza vaccination was not associated with altered rates of admission for pneumonia or altered mortality rates. Similarly, although influenza vaccination was associated with an increased risk of cancer, this finding was not significant in the adjusted analysis. Thus, even though we have attempted to control for confounders, there must be some residual confounding (e.g., smoking status or pneumococcal vaccine coverage).

Our study has strengths and limitations. Several sources of confounding may have affected our estimates. First, outcomes in any given influenza season will be determined by differences in the circulating viruses and differences in the antigenic match of vaccine products and their efficacy.[27] In particular, the 2014–2015 influenza vaccines were less effective against the influenza A/H3N2 virus, with an overall vaccine effectiveness of 19%.[28,29] Two randomized studies showed that high doses of non-adjuvant inactivated vaccines improved serological outcomes in SOT recipients compared to standard doses.[9,18] The current study did not allow us to control the dose or valency of the administered influenza vaccines. However, one strength of our analysis is that we obtained pooled estimates across

vaccine products and multiple influenza seasons, suggesting that influenza vaccines reduce the risk of adverse outcomes in SOT recipients, including pneumonia hospitalization, despite the considerable heterogeneity between seasons and administered vaccine doses.

Second, we used nonspecific outcomes to assess the potential effects of influenza vaccines, including all-cause pneumonia admission, influenza-related hospitalization, and all-cause mortality. These outcomes are widely used in observational studies to evaluate the effectiveness of influenza vaccination.[27] Due to the nature of the data used in this study, we were unable to track individual patients back to their medical files. Therefore, we cannot be certain that the patients who were admitted fulfilled clinical, diagnostic, and radiological criteria for pneumonia. Influenza vaccines are only effective against influenza virus. However, influenza infection can predispose individuals to secondary bacterial pneumonia and other adverse outcomes such as cardiovascular events.[16] In these cases, analyzing only one outcome (e.g., influenza-specific hospitalization or death) may underestimate the benefits of the vaccine. A study that analyzed laboratory-confirmed influenza data or radiologically confirmed pneumonia cases would have been able to assess the effects of vaccination with more precision, but these data were not available to us. Furthermore, information on the different types of immunosuppressive drugs and treatments used to counteract acute organ rejection was not available, and these factors may also affect vaccine effectiveness.

Furthermore, in the unadjusted analysis, vaccination was significantly associated with a reduced risk of influenza-related hospital admission. However, after full adjustment, this association was no longer significant, although the HRs for the unadjusted and adjusted estimates are similar (unadjusted HR, 0.65; 95% CI, 0.46–0.92; $p = .016$ vs. adjusted HR, 0.75; 95% CI, 0.46–1.22; $p = .24$). Because we recorded only 150 influenza-related hospital admissions, the statistical power for this analysis was low compared to our pneumonia admissions analysis, which included more than 900 outcome events. Hence, the influenza analysis may have been underpowered. After adjustment, the effect of influenza vaccination on mortality during the same season was very large. Vaccination did not have a statistically significant effect on all-cause mortality during the months outside the influenza season, and the large estimated effect suggests some residual confounding.

Finally, we attempted to adjust for measurable confounders using the available data. However, unmeasured confounders and residual bias will have affected our assessment of vaccine effectiveness on all-cause mortality. For example, we did not have data on treatment with oseltamivir, which may affect the severity of disease and increase the proportion of false-negative laboratory tests.[2,30] In addition, we did not have data on pneumococcal vaccinations, which might affect the risk of hospitalization due to pneumonia. The sensitivity analysis suggests that residual confounding, which is common in this type of study, has affected our assessments in both the influenza season and the non-influenza season.[26] After conducting a chart review, we found that less than 1% of influenza vaccinations provided to SOT recipients during our study period were given during a hospital contact. Thus, misclassification due to vaccination at hospitals is probably a minor confounder. A similar study from the Netherlands that investigated the effect of influenza vaccination on elderly patients also found a substantial reduction in the risk of mortality after adjustment for both measured and unmeasured confounders.[19] Factors such as functional health status and frailty, which are not available from medical registers, may also be important confounders.

Because Danish health care registers are independently compiled and comprehensive, the risks of selection bias and loss to follow-up were minimal.[30] Danish registers are of high quality, and they are used in many studies, including studies on SOT recipients and studies that evaluate the similar outcomes that we have used.[19,30-33] However, we cannot rule out the possibility of misclassification of both exposure and outcomes, although these differences would not be recorded systematically throughout the cohort. Differences in patients' approaches to seeking health care may also affect vaccine evaluation. However, this is probably a less important factor, because access to health care in Denmark is free and universal. Finally, the generalizability of our results to other settings may be limited due to differences in the organization and capacity of health care systems in different countries, particularly regarding the definition of ICU admission. Because we used anonymized register data for our analyses, individual chart reviews were not included in this study. These could have improved our assessments of vaccination coverage within the study population.

In conclusion, influenza vaccination of SOT recipients was associated with a reduced risk of hospitalization due to all-cause pneumonia and a reduced risk of all-cause mortality during the same influenza season. Vaccination coverage was low, indicating that efforts to increase vaccine coverage are needed and that there are major opportunities for improvements in preventing this disease.

ACKNOWLEDGMENTS

This study was investigator initiated. ZBH has received grants from the Danish Independent Research Foundation to investigate vaccine-preventable diseases and vaccination response in immunosuppressed patients, including organ transplant recipients. One travel grant was provided by Pfizer within the last 5 years. The funding body had no role in the study design, data collection, interpretation, analysis, decision to publish, or preparation of the manuscript.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

Data collected for this study, including individual participant data and a data dictionary defining each field in the set, can be made available to others in form of de-identified participant data. Informed consent forms will not be available according to Danish legislation. Such requests, including study protocol with clear hypotheses, should be

sent to the principal investigator, and will be further reviewed by the author group.

ORCID

Zitta Barrella Harboe https://orcid.org/0000-0001-5552-0095
Daniel Modin https://orcid.org/0000-0002-7566-0519
Finn Gustafsson https://orcid.org/0000-0003-2144-341X
Michael Perch https://orcid.org/0000-0001-9740-1246
Søren Schwartz Sørensen https://orcid.org/0000-0001-5898-8048
Tor Biering-Sørensen https://orcid.org/0000-0003-4209-2778
Susanne Dam Nielsen https://orcid.org/0000-0001-6391-7455

REFERENCES

1. Reckziegel M, Weber-Osel C, Egerer R, et al. Viruses and atypical bacteria in the respiratory tract of immunocompromised and immunocompetent patients with airway infection. *Eur J Clin Microbiol Infect Dis*. 2020;39(8):1581-1592. doi:10.1007/s10096-020-03878-9
2. Kumar D, Ferreira VH, Blumberg E, et al. A 5-year prospective multicenter evaluation of influenza infection in transplant recipients. *Clin Infect Dis*. 2018;67(9):1322-1329. doi:10.1093/cid/ciy294
3. Kumar D, Michaels MG, Morris MI, et al. Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. *Lancet Infect Dis*. 2010;10(8):521-526. doi:10.1016/s1473-3099(10)70133-x
4. Danziger-Isakov L, Kumar D. Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice. *Clin Transplant*. 2019;33(9):e13563. doi:10.1111/ctr.13563
5. Feldman AG, Beaty BL, Curtis D, Juarez-Colunga E, Kempe A. Incidence of hospitalization for vaccine-preventable infections in children following solid organ transplant and associated morbidity, mortality, and costs. *JAMA Pediatr*. 2019;173(3):260-268. doi:10.1001/jamapediatrics.2018.4954
6. Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. *Lancet Infect Dis*. 2009;9(8):493-504. doi:10.1016/S1473-3099(09)70175-6
7. Harris KaLynne, Baggs J, Davis RL, et al. Influenza vaccination coverage among adult solid organ transplant recipients at three health maintenance organizations, 1995–2005. *Vaccine*. 2009;27(17):2335-2341. doi:10.1016/j.vaccine.2009.02.026
8. Hirzel C, Kumar D. Influenza vaccine strategies for solid organ transplant recipients. *Curr Opin Infect Dis*. 2018;31(4):309-315. doi:10.1097/qco.0000000000000461
9. Cordero E, Roca-Oporto C, Bulnes-Ramos A, et al. Two doses of inactivated influenza vaccine improve immune response in solid organ transplant recipients: results of TRANSGRIPE 1–2, a randomized controlled clinical trial. *Clin Infect Dis*. 2017;64(7):829-838. doi:10.1093/cid/ciw855
10. Mombelli M, Rettby N, Perreau M, Pascual M, Pantaleo G, Manuel O. Immunogenicity and safety of double versus standard dose of the seasonal influenza vaccine in solid-organ transplant recipients: a randomized controlled trial. *Vaccine*. 2018;36(41):6163-6169. doi:10.1016/j.vaccine.2018.08.057
11. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish civil registration system. A cohort of eight million persons. *Dan Med Bull*. 2006;53(4):441-449.
12. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health*. 2011;39(7 Suppl):12-16. doi:10.1177/1403494811399956
13. Pedersen CB. The Danish civil registration system. *Scand J Public Health*. 2011;39(7 Suppl):22-25. doi:10.1177/1403494810387965
14. World Health Organization. International Classification of Diseases and Related Health Problems 10th Revision. Accessed May 1, 2022. https://icd.who.int/browse10/2010/en
15. Kildemoes HW, Sørensen HT, Hallas J. The Danish national prescription registry. *Scand J Public Health*. 2011;39(7 Suppl):38-41. doi:10.1177/1403494810394717
16. Modin D, Claggett B, Køber L, et al. Influenza vaccination is associated with reduced cardiovascular mortality in adults with diabetes: a nationwide cohort study. *Diabetes Care*. 2020;43(9):2226-2233. doi:10.2337/dc20-0229
17. Statens Serum Institut. Weekly Influenza Report. Accessed May 1, 2022. https://www.ssi.dk/sygdomme-beredskab-og-forskning/sygdomsovervaagning/i/influenza-ugens-opgoerelse
18. Kumar D, Chen M, Wong G, et al. A randomized, double-blind, placebo-controlled trial to evaluate the prime-boost strategy for pneumococcal vaccination in adult liver transplant recipients. *Clin Infect Dis*. 2008;47(7):885-892. doi:10.1086/591537
19. Hommel K, Rasmussen S, Madsen M, Kamper AL. The Danish Registry on regular dialysis and transplantation: completeness and validity of incident patient registration. *Nephrol Dial Transplant*. 2010;25(3):947-951. doi:10.1093/ndt/gfp571
20. Danish Infectious Disease Society. Guideline for the management of influenza. Accessed April 1, 2022. https://infmed.dk/site/tools/download.php?UID=97eb817cf47d1e20171d11bd9a13d030c311d852
21. World Health Organization. Global knowledge base on transplantation (GKT). Accessed April 1, 2022. https://www.who.int/transplantation/gkt/statistics/en/
22. Boey L, Bosmans E, Ferreira LB, et al. Vaccination coverage of recommended vaccines and determinants of vaccination in at-risk groups. *Hum Vaccin Immunother*. 2020;16(9):2136-2143. doi:10.1080/21645515.2020.1763739
23. Helanterä I, Janes R, Anttila VJ. Clinical efficacy of seasonal influenza vaccination: characteristics of two outbreaks of influenza A(H1N1) in immunocompromised patients. *J Hosp Infect*. 2018;99(2):169-174. doi:10.1016/j.jhin.2017.12.003
24. Restivo V, Vizzini G, Mularoni A, Di Benedetto C, Gioè SM, Vitale F. Determinants of influenza vaccination among solid organ transplant recipients attending Sicilian reference center. *Hum Vaccin Immunother*. 2017;13(2):346-350. doi:10.1080/21645515.2017.1264792
25. Camerino M, Jackson S, Chinnakotla S, Verghese P. Effects of the influenza vaccine on pediatric kidney transplant outcomes. *Pediatr Transplant*. 2019;23(2):e13354. doi:10.1111/petr.13354
26. Campitelli MA, Rosella LC, Stukel TA, Kwong JC. Influenza vaccination and all-cause mortality in community-dwelling elderly in Ontario, Canada, a cohort study. *Vaccine*. 2010;29(2):240-246. doi:10.1016/j.vaccine.2010.10.049
27. World Health Organization Evaluation of influenza vaccine effectiveness: a guide to the design and interpretation of observational studies. 2017. ISBN 978-92-4-151212-1. https://apps.who.int/iris/handle/10665/255203
28. Zimmerman RK, Nowalk MP, Chung J, et al. 2014–2015 influenza vaccine effectiveness in the United States by vaccine type. *Clin Infect Dis*. 2016;63(12):1564-1573. doi:10.1093/cid/ciw635
29. Centers for Disease Control and Prevention: Past Seasons Vaccine Effectiveness Estimates. Accessed February 4, 2022. https://www.cdc.gov/flu/vaccines-work/past-seasons-estimates.html
30. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563-591. doi:10.2147/clep.S179083

31. Søgaard M, Nielsen RB, Schønheyder HC, Nørgaard M, Thomsen RW. Nationwide trends in pneumonia hospitalization rates and mortality, Denmark 1997–2011. *Respir Med*. 2014;108(8):1214-1222. doi:10.1016/j.rmed.2014.05.004
32. Åberg F, Isoniemi H, Pukkala E, et al. Cancer after liver transplantation in children and young adults: a population-based study from 4 nordic countries. *Liver Transpl*. 2018;24(9):1252-1259. doi:10.1002/lt.25305
33. Jensen A, A. F. Simões E, Bohn Christiansen C, Graff Stensballe L. Respiratory syncytial virus and influenza hospitalizations in Danish children 2010–2016. *Vaccine*. 2021;39(30):4126-4134. doi:10.1016/j.vaccine.2021.05.097

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Harboe ZB, Modin D, Gustafsson F, et al. Effect of influenza vaccination in solid organ transplant recipients: A nationwide population-based cohort study. *Am J Transplant*. 2022;22:2409-2417. doi:10.1111/ajt.17055