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2021-05

Helantera , I , Gissler , M , Rimhanen-Finne , R , Ikonen , N , Kanerva , M , Lempinen , M & Finne , P 2021 , ' Epidemiology of laboratory-confirmed influenza among kidney transplant recipients compared to the general population-A nationwide cohort study ' , American Journal of Transplantation , vol. 21 , no. 5 , pp. 1848-1856 . https://doi.org/10.1111/ajt.16421

http://hdl.handle.net/10138/341363
https://doi.org/10.1111/ajt.16421

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Article type : O - Original Article

EPIDEMIOLOGY OF LABORATORY-CONFIRMED INFLUENZA AMONG KIDNEY TRANSPLANT RECIPIENTS COMPARED TO THE GENERAL POPULATION – A NATIONWIDE COHORT STUDY

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Abbreviations

SIR, standardized incidence ratio; ICU, intensive care unit

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/AJT.16421

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ABSTRACT

Seasonal influenza causes morbidity and mortality after organ transplantation. We quantified the detection of laboratory-confirmed influenza among kidney transplant recipients compared to the general population in a nationwide cohort.

All laboratory-confirmed cases of influenza and hospitalizations due to influenza among all kidney transplant recipients in our country between 1995 and 2017 were captured with database linkage from statutory national registries. Data from the general population of Finland, population 5.5 million, were used for comparisons. Annual incidences of influenza and hospitalizations due to influenza, and standardized incidence ratios (SIR) were calculated.

Altogether 3904 kidney transplant recipients with a total follow-up of 37175 patient-years were included. Incidence of laboratory-confirmed influenza was 9.0 per 1000 patient years in 2003-2019, and 18.0 per 1000 patient years during 2015-2019. The risk of laboratory-confirmed influenza was significantly higher among kidney transplant recipients compared to the general population (SIR 5.1, 95% CI 4.5-5.7). SIR for hospitalization due to influenza was 4.4 (95% CI 3.4-4.7). Mortality of the hospitalized patients was 9%, and 5% of the patients with laboratory-confirmed influenza. Detection of laboratory-confirmed influenza is increased five-fold and risk of hospitalization due to influenza more than four-fold among kidney transplant recipients compared to the general population.

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1. INTRODUCTION

Seasonal influenza is a significant cause of morbidity and mortality among recipients of solid-organ transplantation (1,2). During the 2009 influenza A(H1N1) pandemic, increased risk of severe disease, including intensive care unit (ICU) admission and mortality, was observed in organ transplant recipients (3). In addition to laboratory-confirmed influenza, a range of potentially serious respiratory tract infections causing influenza-like illness is estimated to cause excess mortality of >1000 deaths among patients with end-stage kidney disease in the US (4). Thus, increasing efforts have been focused on the optimal prevention and treatment of influenza also in transplant recipients, including increased coverage of seasonal influenza vaccination (5). Although the protective effect of vaccination may not be optimal in immunosuppressed patients (6-8), our study and others have shown good protective effect of vaccination also after organ transplantation (2,9). In addition, new strategies with high-dose vaccines may even further improve the efficacy of vaccination (10).

New diagnostic tests, such as multiplex PCR tests, for the diagnosis of respiratory tract viral infections have improved the diagnostics of community-acquired respiratory virus infections and influenza-like illness (5,11), and a microbiological diagnosis can be rapidly achieved in an increasing number of patients. The incidence of laboratory-confirmed cases of influenza has increased with better diagnostic tools in the last years. However, no studies have characterized the incidence of influenza infections among kidney transplant recipients on a population-level during recent years. In addition, no studies have compared the incidence of influenza infections among kidney transplant recipients with the incidence in the general population. Especially since the COVID-19 pandemic, the epidemiology of respiratory tract viruses has gained increasing importance, also among transplant recipients. Kidney transplant recipients represent the biggest population of solid-organ transplant patients within all age groups, and can serve as a model for chronic immunosuppression causing increased susceptibility for respiratory tract infections among patients who mostly are active within the society.

The aim of this study was to characterize the epidemiology of laboratory-confirmed influenza infections and hospitalizations due to influenza in a large nationwide cohort of kidney transplant recipients, and to compare the disease burden caused by influenza virus among kidney transplant recipients with the burden of the general population in Finland.

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2. METHODS

2.1 Patients

All kidney transplant recipients in Finland in 1995 to 2017 were included. Helsinki University Hospital is the only transplant center in Finland, and all transplantations were performed in our institution. Altogether 4101 kidney transplantations were performed to 3900 adult recipients in our institution between 1995 and 2017. Data about influenza findings were recorded in the Infectious Disease Register since 1995, but the first patient in our cohort was diagnosed with influenza in 2003. Therefore, follow-up was started in 2003, i.e. only patients who were alive with a functioning transplant at the beginning of 2003 or received a transplant between 2003 and 2017 were included, which resulted in a total number of 3904 transplantations analysed for this study. Follow-up was calculated as patient-years, separately for each calendar year, starting from the day of transplantation (or Jan 1st 2003 for patients transplanted before 2003) and continued until death, graft loss, moving abroad, or 31 December 2019. In case of retransplantation within the study time-period, all years spent with a functioning transplant were included in the follow-up. Patients and transplant-related data were identified from the Finnish Transplant Registry, which is a follow-up registry obliged by law. No patients were lost to follow-up. Baseline immunosuppression consisted mainly of cyclosporine or tacrolimus, mycophenolate or azathioprine, and steroids. Before the year 2000, azathioprine was used instead of mycophenolate. After 2001, cyclosporine was replaced by tacrolimus only in patients with higher immunological risk (retransplantation, poor HLA mismatch). During the 2000s, induction with basiliximab was similarly given to patients with higher immunological risk, and since 2014, antithymocyte globulin was given to patients with known or presumed donor-specific HLA antibodies at the time of transplantation. Steroids were usually withdrawn during the second post-transplant year. Complete baseline transplant data were available for all patients. Data about patient deaths (including cause of death evaluated by the treating clinician) and graft losses are continuously reported to the registry by the local nephrology centers and confirmed from other national registries. Missing causes of death were annually acquired from the official National Cause-of-Death Register at Statistics Finland.

2.2 Data linkage

Data from all kidney transplant recipients were linked with the registry database of the Finnish Institute for Health and Welfare (THL), using the personal identity code (PIC) as a key. All citizens and permanent residents in Finland have a unique PIC, which was introduced in 1964-1967. The PIC code is given already in the birth hospital, and it remains unchanged during an individual's life span. The PIC is used in all main registers in Finland and allows reliable deterministic record

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linkage. The statistical authorities replaced the PICs by a study code after the linkage. This study had the approval of the institutional review board of Helsinki University Hospital Abdominal Center (HUS/333/2019) and the Finnish Institute for Health and Welfare (THL/1877/5.05.00/2019).

2.3 Ascertainment of laboratory-confirmed influenza

Finnish Institute for Health and Welfare maintains a statutory Infectious Disease Register since 1995, and the registry information is used in the prevention and control of infectious diseases and research. All clinical microbiology laboratories (also private laboratories outside public healthcare) notify findings of approximately 70 specified microbes, such as influenza directly to the registry. Reporting is obliged by law. Diagnostic criteria for influenza notification include nucleic acid or antigen detection. These methods have become commonly available throughout the country during the 2000s, and increasingly after the 2009 pandemic. Data from the Infectious Disease Register were available until the end of 2019. No data about the possible antiviral treatment of influenza infections or about the vaccination status of the patients were available from the registries.

2.4 Ascertainment of hospitalizations due to influenza

The Finnish Care Register for Health Care is a national health care registry maintained by the Finnish Institute for Health and Welfare. It includes data on all inpatient care since 1967 and on outpatient care in public hospitals since 1998. The register collects information on hospitalizations (day of admission and discharge), outpatient visit (day of visit), diagnoses given during the inpatient care (ICD-10 codes since 1996) and surgical procedure codes (NOMESCO Classification of Surgical Procedures since 1997). About 1.7 million persons are reported to the registry annually, with >1.5 million periods of care and >6 million outpatient visits every year. Finland has a universal public health care system, and all transplant-related activities are done solely within public health care. Reporting to the registry is mandatory and obliged by law. Hospitalizations with the ICD-10 codes J09 (Influenza due to certain identified influenza virus), J10 (Influenza due to other identified influenza virus), or J011 (Influenza, virus not identified) as main or secondary diagnosis codes were included. Outpatient visits for specialized health care are also recorded in the registry, but as both transplant patients and general population frequently also visit primary health with influenza-like illnesses, we did not include outpatient encounters in our primary analyses. Data from the Finnish Care Register for Health Care were available until the end of 2018.

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2.5 Statistical analyses

Differences between two groups in continuous variables were compared with the Mann-Whitney U test and in categorical variables with the Fisher's exact test. Nonparametric statistics was chosen, as all distributions were not normal. The association between patient characteristics and detection of influenza was analyzed using multivariable Cox proportional hazards models, with first episode of laboratory-confirmed influenza, or hospitalization due to influenza as the event. Follow-up started at time of first kidney transplantation and patients were censored at time of death, start of dialysis, if moving abroad, or at end of follow-up on 31 December 2019. Variables that were significant risk factors in univariable analyses ($p<0.10$) were selected to the multivariable models. Cumulative incidence of first episode of laboratory-confirmed influenza was estimated using the Kaplan-Meier method. Incidence rate of laboratory-confirmed influenza infections and hospitalizations due to influenza was calculated per 1000 patient-years for each calendar year for kidney transplant recipients. Comparison with the general population in Finland was calculated as standardized incidence ratios (SIR). Due to small annual numbers of laboratory-confirmed influenza cases in age and sex groups of kidney transplantation patients, SIR was calculated using the indirect standardization method with the influenza rates in the general population within age (20-44, 45-64, 65-74, and ≥75 years) and sex categories as the reference ('expected' vs. 'observed') (12). The number of laboratory-confirmed influenza cases and hospitalizations due to influenza in the general population of Finland (approximately 5.5 million) was identified from the Infectious Disease Register and from The Finnish Care Register for Health Care, respectively, for each calendar year in different age and sex categories (age 20-44, 45-64, 65-74, and 75 or more). As the population of Finland has remained relatively stable during the last two decades, the number of persons alive at the start of each calendar year was used to estimate the number of person-years in the general population. Age distribution among the population of Finland was captured from Statistics Finland, from which official population figures are publicly available for each calendar year (13). Calculations were performed using IBM SPSS Statistics (version 22, IBM Corporation, Somers, NY).

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3. RESULTS

In total, 3904 kidney transplant recipients were included, and the total number of patient-years with a functioning transplant was 37175. Baseline characteristics of patients with or without laboratory-confirmed influenza are presented in table 1. No significant differences were seen in the baseline characteristics between patients with or without laboratory-confirmed influenza after transplantation, except in the frequency of mycophenolate use, which was higher among patients with laboratory-confirmed influenza, and in the era of transplantation.

3.1 Laboratory-confirmed influenza between 2003 and 2019

In total, 294 episodes of laboratory-confirmed influenza in 277 kidney transplant patients were documented to the Infectious Disease Register between 2003 and 2019. Annual number of laboratory-confirmed influenza- findings in kidney transplant recipients is presented in table 2, and annual incidence of influenza (per 1000 patient-years) in figure 1. Annual population of Finland is shown in supplemental table 1. Total incidence of laboratory-confirmed influenza among kidney transplant recipients was 9.0 per 1000 patient years in 2003-2019, and 18.0 per 1000 patient years during 2015-2019. As the number of laboratory-confirmed influenza cases was very low before 2009, annual standardized incidence ratio (SIR) and related confidence intervals were calculated only for the years between 2009 and 2019 (table 2, figure 2). The risk of laboratory-confirmed influenza was five-fold among kidney transplant recipients compared to the general population in 2009-2019 (SIR 5.1, 95% CI 4.5-5.7, P<0.001). When SIRs were analysed separately for different age groups (table 3), SIR for age groups between 20 and 74 years remained relatively stable (5.5-6.4), whereas the SIR for the highest age group of patients ≥75 years was only 1.7 (95% CI 1.1-2.7). Annual variation between Influenza A and B was similar among transplant recipients compared with the general population (supplemental figure 1). The time of year (month) of the seasonal influenza infection in kidney transplant recipients is presented in supplemental figure 2, and was very similar to that seen in the general population in seasonal influenza (data not shown). The timing of laboratory-confirmed influenza related to transplantation was analysed among patients transplanted 2003 or later. The occurrence of laboratory-confirmed influenza with regard to time since transplantation is shown in figure 3. Altogether 54 of the laboratory-confirmed influenza cases were detected during the first posttransplant year, with an incidence rate of 20.0 per 1000 patient years. The risk of detecting laboratory-confirmed influenza was significantly higher during the first posttransplant year compared to later years (incidence rate ratio 2.5, 95% CI 1.8-3.4, p<0.001).

3.2 Hospitalizations due to influenza between 2003 and 2018

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Altogether 166 episodes of hospital admission with the main or secondary diagnosis of influenza were recorded in 152 patients between 2003 and 2018. Annual numbers of hospitalizations due to influenza among kidney transplant recipients are reported in table 4, including also hospitalizations in the general population of Finland. Median duration of hospitalization in kidney transplant recipients was four days (interquartile range 2-7). Of these 152 patients, 13 (9%) died within three months of hospital admission. Influenza was recorded as a cause of death in 9/13, and baseline renal disease with probable contribution of influenza to the death mechanism in 4/13. Of the deaths, 6/13 were due to acute respiratory distress syndrome (ARDS)- type pulmonary reaction, while the exact mechanism of death was unknown in 7/13 patients. Median age of the deceased patients was 57 (range 49-85 years), and median time from transplantation 11 years (range 13 days to 20 years). In addition, eight more patients died within one year from influenza diagnosis to causes of death not related to influenza (cardiovascular causes, malignancies, complications of baseline disease). Eight patients lost their graft function within 90 days from the diagnosis of influenza, and additional two lost their grafts within one year from influenza diagnosis. The causes of graft loss are not recorded in the registries and remain unknown. SIR for hospitalization due to influenza was calculated for each calendar year between 2008 and 2018 (figure 4). During this period, SIR of hospitalization due to influenza was significantly increased, 4.4 (95% CI 3.4-4.7, $p<0.001$), and it varied over the years between 2.9 and 9.0 (significantly increased in all years except 2010 and 2011).

In addition to hospitalizations, altogether 88 visits to specialized care emergency room due to influenza were recorded in 73 patients between 2003 and 2018. As the annual numbers were small, and the threshold of visiting specialized care may not be comparable among the transplant recipients and general population (data about primary health care visits were not available in the registries), no SIRs were calculated for emergency room visits.

3.3 Risk factors for detection of laboratory-confirmed influenza

Risk factors for laboratory-confirmed influenza were analyzed with multivariable Cox regression (supplemental table 2). In the multivariable model, the only significant independent risk factor for laboratory-confirmed influenza was the era of transplantation (HR 2.89 for transplantation between 2003-2010, and HR 12.39 for transplantation between 2011-2017, compared to the reference 1995-2002). As the risk of laboratory-confirmed influenza could be calculated only starting from the year 2003 when the first case was confirmed, a sensitivity analysis was performed including only patients transplanted 2003 or later. In this model, increased donor age

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was the only significant independent risk factor for influenza (HR 1.02 per one year increase, 95% CI 1.01-1.03, P=0.009, other data not shown).

3.4 Risk factors for hospitalization due to influenza

Risk factors for hospitalization due to influenza were analyzed in similar multivariable models as for the detection of laboratory-confirmed influenza (supplemental table 3). In the multivariable model, dialysis duration (HR 1.11 per one year increase), recipient age (HR 1.02 per one year increase), and the era of transplantation (HR 3.01 for transplantation between 2003-2010, and HR 11.1 for transplantation between 2011-2017, compared to the reference 1995-2002) were independent risk factors for hospitalization due to influenza. In a sensitivity analysis among patients transplanted in 2003 or later, dialysis duration (HR 1.14 per one year increase, 95% CI 1.05-1.23, P=0.002) and recipient age (HR 1.02 per one year increase, 95% CI 1.01-1.04, P=0.01) remained independent risk factors for hospitalization due to influenza (other data not shown).

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4. DISCUSSION

Although it is well known that seasonal influenza can cause severe disease among recipients of solid-organ transplants, the increase in disease burden in the transplant population compared to the general population has not been characterized in detail. To the best of our knowledge, this study shows for the first time, that kidney transplant patients have a five-fold risk of detection of laboratory-confirmed seasonal influenza compared to the general population, and more than four-fold risk for hospitalization due to influenza. Seasonal occurrence of influenza, and variation between influenza A and B between different seasons were similar among transplant patients and the general population. The high relative risk of detection of laboratory-confirmed influenza among transplant patients was lower among the oldest patients of more than 75 years of age. The low number of transplant recipients more than 75 years of age might suggest that this is a highly selected population of healthier transplant recipients. On the other hand, elderly patients in the general population may be more immunocompromised due to age-related immune senescence, whereas elderly kidney transplant patients may have somewhat lower level of immunosuppression, suggesting that the difference between the general population and transplant recipients may be smaller among the elderly compared to younger individuals.

Previous studies have shown that influenza causes significant morbidity and mortality among solid-organ transplant recipients. Especially during the 2009 influenza A(H1N1) pandemic, several studies analyzed the outcome of solid-organ transplant recipients, and reported ICU admission in 14-23% and mortality in 4-9% of patients (3,14-16). The largest multicenter cohort of solid-organ transplant or hematopoietic stem cell transplant recipients with influenza reported to date was from five consecutive influenza seasons between 2010 and 2015 and included 616 patients with laboratory-confirmed influenza. In this cohort 67% of patients were hospitalized, 11% required intensive care, and 30-day all-cause mortality was 2.9% (2). Although our current study was limited by the lack of information about ICU admission or need of oxygenation or ventilation, mortality rate and hospitalization rate were comparable to those reported in previous studies.

One possible explanation to the higher incidence of laboratory-confirmed influenza might be different testing strategies among the transplant patients compared to the general population, as transplanted patients visit specialized health care more frequently and may contact health care more easily in case of upper respiratory symptoms, and the threshold of acquiring laboratory testing might be lower in transplanted patients. Data about testing frequencies among transplant patients or in the general population, or the sensitivity or specificity of all the different diagnostic

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tests used were unfortunately not available, limiting our possibilities to draw firm conclusions about the risk of influenza in kidney transplant recipients. During the current COVID-19 pandemic, this has been acknowledged as a weakness in the current reporting of statutory data, and efforts are ongoing to include data on testing frequency to the National Infectious Disease Registry. However, we had the possibility to examine hospitalizations due to influenza, and the risk of hospitalization due to influenza was more than four-fold among transplant recipients and mortality among hospitalized patients was 9%. In addition to hospitalization, emergency room visits were frequently recorded. The lower SIR for hospitalization among transplant recipients (SIR 4.4) compared to laboratory-confirmed influenza (SIR 5.1) supports the possibility that the frequency of testing among transplant patients may be higher compared to the general population. Although the threshold of hospital admission may be lower for transplant recipients with often multiple comorbidities and immunosuppression, the high mortality rate seen in our transplant cohort suggests that also the risk of severe influenza is significantly increased in immunosuppressed transplant recipients. We analyzed possible risk factors for laboratory-confirmed influenza among immunosuppressed transplant recipients, but in addition to the era of transplantation, no statistically significant risk factors for influenza were identified.

Several studies have shown that the efficacy of seasonal influenza vaccination is limited among immunosuppressed transplant recipients and patients with end-stage kidney disease, who often have impaired immune functions (6-8,17-19). Despite the lack of serological response to vaccination, vaccination may produce cellular immunity and provide clinically efficient protection (17,20), as described in an outbreak of influenza A(H1N1) in our kidney transplant ward in 2014, during which none of the vaccinated patients developed serious disease (9). Similar findings were later reported in our institution among patients receiving immunosuppressive chemotherapy for malignancies (21). Other larger studies have similarly shown that vaccination is associated with improved outcomes also in immunocompromised patients (2). One limitation in the current study is the lack of information about vaccination coverage in the transplanted cohort. In the general population in Finland, seasonal influenza vaccination is offered free of charge to all aged 6 months to 6 years, and 65 years or more. In addition, vaccination is offered free of charge to all people belonging to risk groups, such as dialysis and transplant patients, and all patients wait-listed for organ transplantation. The seasonal influenza vaccination coverage among age group 65 years or more in the general population of Finland has been ranging between 36 and 48 % in the recent years (22). Collection of individual-level data on seasonal influenza vaccination of the whole general population to the National Vaccination Registry was recently started, but since it does not yet include all health care contacts and the coverage is far from complete, the

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vaccination coverage of the whole general population is currently not known. Vaccination coverage of Finnish kidney transplant recipients has not been studied in detail, but in our earlier study the seasonal influenza vaccination coverage was 74 % among 23 kidney transplant recipients in 2014, and 40 % among 53 patients treated for malignancies on the oncology ward in 2016 (21). Studies from other populations also show that the vaccination coverage among immunocompromised patients is higher compared to the general population (1), suggesting that higher risk of influenza seen in transplant patients in the current study is probably not due to lower coverage of seasonal vaccination.

Our study has some limitations of note. Although the kidney transplant cohort in this study was relatively large, the annual number of influenza episodes remained fairly small, limiting the possibility to reliably quantify the risk of influenza especially during the earlier years of this study. No validation of the completeness of influenza-related data collection to the Infectious Disease Registry exists, which limits the validity of our conclusions, but as the reporting is automatic and statutory and derives directly from microbiological laboratories, the coverage is estimated being high. The most likely reason for the lack of positive influenza findings before 2003 relates to testing frequency and available methods, as before 2003, antigen or nucleic acid testing for influenza were not widely used in daily practice. The awareness and methodology for laboratory-confirmed influenza improved with the 2009 pandemic, explaining the increase in the number of cases seen after 2009. We do not know the proportion of healthcare associated influenza infections and whether transmission among the transplant patients might have explained some of the annual cases, except for the outbreak of influenza A(H1N1) on our kidney transplant ward in 2014, as described (9). In addition, the transplant patients were all from one country with relatively conservative immunosuppression and almost exclusively Caucasian patients, and the results may not be generalizable to other transplant populations. No data on possible treatment of influenza with antiviral medications were available for this study, and no data about the hospital days or ICU admission were available for the general population. Mortality due to influenza in the general population in Finland has ranged between 14 and 436 patients between 2003 and 2018, with some of the mortality variation being explained by differences in reporting practices, suggesting a case mortality between 1-3% (23). However, the data do not allow direct comparison of the mortality rates. In addition, the general population data includes patients with other solid-organ transplants than kidney, or patients who have received a kidney transplant in other countries. The number of these patients, however, can be identified from other registries and is very low, and comprises <0.01% of the population of Finland, being unlikely to significantly affect our findings. On the other hand, the strengths of our study include population-level data

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from statutory registries during a long time-period, which gives us unique possibilities to calculate standardized incidence-ratios for the risk of influenza infections and hospitalizations.

In conclusion, the likelihood of detecting laboratory-confirmed influenza and hospitalization due to influenza are highly increased in kidney transplant recipients compared to the general population, highlighting the importance of continuous efforts to prevent respiratory tract infections among transplant recipients.

Acknowledgments

This study was funded by Government funding for health research (VTR to I.H., TYH2019214). The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation.* IH reports receiving research grants form Finska Läkaresällskapet, and consultancy fees from Aplagon, Astellas, Hansa Biopharma, and Novartis not related to the submitted work. The other authors have no conflicts of interest.

Data Availability Statement

Restrictions issued by the statistical authorities in Finland apply to the availability of the data from transplant patients for sharing. Public data concerning the general population in Finland are available from the corresponding author upon reasonable request.

Author contributions

IH, RR-F, MK, MI, and PF designed the study; IH, MG, ML, and PF collected data;
IH, MG, RR-F, NI, MK, and PF analyzed and interpreted the data;
IH, MG, and PF drafted the paper; All authors participated in manuscript revision and approved the final version of the paper.

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Figure legends

Figure 1. Annual incidence of laboratory-confirmed influenza (per 1000 patient-years) among kidney transplant patients in Finland between 2003 and 2019

Figure 2. Standardized incidence ratio (SIR, solid line) and 95% confidence intervals (dashed lines) of laboratory-confirmed influenza between 2009 and 2019 among kidney transplant patients compared to the general population of Finland. Total SIR between 2009 and 2019 was 5.1 (95%CI 4.5-5.7)

Figure 3. Occurrence of first laboratory-confirmed influenza in relation to kidney transplantation, including patients transplanted in 2003 or later (N=2809 subjects).

Figure 4. Standardized incidence ratio (SIR, solid line) and 95% confidence intervals (dashed lines) of hospitalization due to influenza between 2009 and 2018 among kidney transplant patients compared to the general population of Finland. Total SIR between 2009 and 2018 was 4.4 (95% CI 3.4-4.7.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Table 1. Baseline characteristics of patients who received a kidney transplant in 1995 to 2017, and were alive with a functioning graft after 2003, with or without laboratory-confirmed influenza infection.

	Influenza (N=277)	**No influenza (N=3626)**
Mean age (years, 1 SD)	50 (13)	50 (13)
Male (%)	177 (64%)	2332 (64%)
1st transplant	250 (90%)	3208 (89%)
On tacrolimus (vs. cyclosporine)	74 (27%)	973 (27%)
On mycophenolate (vs. azathioprine) *	243 (88%)	2922 (81%)
Induction immunosuppression (other than iv steroids)	36 (13%)	430 (12%)
Baseline kidney disease:		
Glomerulonephritis	87 (31%)	998 (28%)
Diabetic nephropathy	78 (28%)	972 (27%)
Polycystic disease	43 (16%)	667 (18%)
Other	69 (25%)	989 (27%)
Deceased donor kidney (vs. living donor)	267 (96%)	3501 (97%)
Mean duration of pretransplant dialysis (years, 1 SD)	2.3 (1.9)	2.1 (1.8)
Era of transplantation *		
1995-2002	55 (20%)	1038 (29%)
2003-2010	95 (34%)	1241 (34%)
2011-2017	127 (46%)	1347 (37%)

* All differences are nonsignificant, except for use of mycophenolate (P=0.003), and era of transplantation (P=0.002).

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Table 2. Annual number of laboratory-confirmed influenza findings between 2003 and 2019 among kidney transplant recipients compared with the general population of Finland, including standardized incidence ratios (SIR) and 95% confidence intervals. The total population of Finland ranged between 5.2 in 2003 and 5.5 million in 2019.

year	Number of influenza episodes among transplant recipients	Number of follow-up years among transplant patients	Number of influenza episodes in general population	SIR	Lower 95% CI	Upper 95% CI
2003	3	1001	3156	10.0	2.5	27.2
2004	1	1272	195	53.3	2.7	262.6
2005	4	1386	1156	19.7	6.2	47.4
2006	2	1492	1183	11.8	2.0	38.9
2007	1	1595	1983	2.8	0.1	13.6
2008	3	1672	3714	4.0	1.01	10.8
2009	16	1759	13412	7.0	4.1	11.1
2010	1	1845	209	7.1	0.35	34.8
2011	4	1943	2542	3.1	0.99	7.5
2012	10	2033	2315	5.8	2.9	10.3
2013	12	2109	3215	4.8	2.6	8.1
2014	19	2199	3006	7.8	4.9	11.9
2015	20	2311	7157	3.9	2.5	6.0
2016	57	2425	10370	6.0	4.6	7.7
2017	36	2516	6505	5.9	4.2	8.1
2018	72	2497	21215	4.5	3.5	5.6
2019	33	2382	7592	4.2	2.9	5.8

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Table 3. Standardized incidence ratios (SIR) and 95% confidence intervals for laboratory-confirmed influenza among kidney transplant recipients between 2009 and 2019. in different age groups.

Age group	SIR	95% CI
20-44	6.0	4.5-7.8
45-64	5.5	4.6-6.5
65-74	6.4	5.1-7.9
≥75	1.7	1.1-2.7

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Table 4. Annual number of hospitalizations due to influenza between 2003 and 2018 among kidney transplant patients compared with the general population of Finland. including standardized incidence ratios (SIR) and 95% confidence intervals.

year	Number of hospitalizations among transplant recipients	Number of follow-up years among transplant patients	Number of hospitalizations in general population	SIR	Lower 95% CI	Upper 95% CI
2003	5	1001	1934	12.1	4.4	26.8
2004	2	1272	837	9.7	1.6	32.1
2005	1	1386	1073	3.3	0.17	16.4
2006	2	1492	615	10.0	1.7	33.2
2007	0	1595	602	N/A		
2008	2	1672	599	9.0	1.5	29.8
2009	14	1759	6308	5.4	3.1	8.8
2010	1	1845	629	3.5	0.17	17.5
2011	2	1943	1547	2.9	0.48	9.6
2012	5	2033	1693	6.7	2.4	14.8
2013	10	2109	2487	7.8	3.9	13.9
2014	6	2199	2923	3.8	1.5	7.8
2015	9	2311	5839	2.8	1.3	5.1
2016	36	2425	12267	4.9	3.5	6.7
2017	24	2516	10216	3.9	2.5	5.7
2018	47	2497	22694	3.3	2.5	4.4

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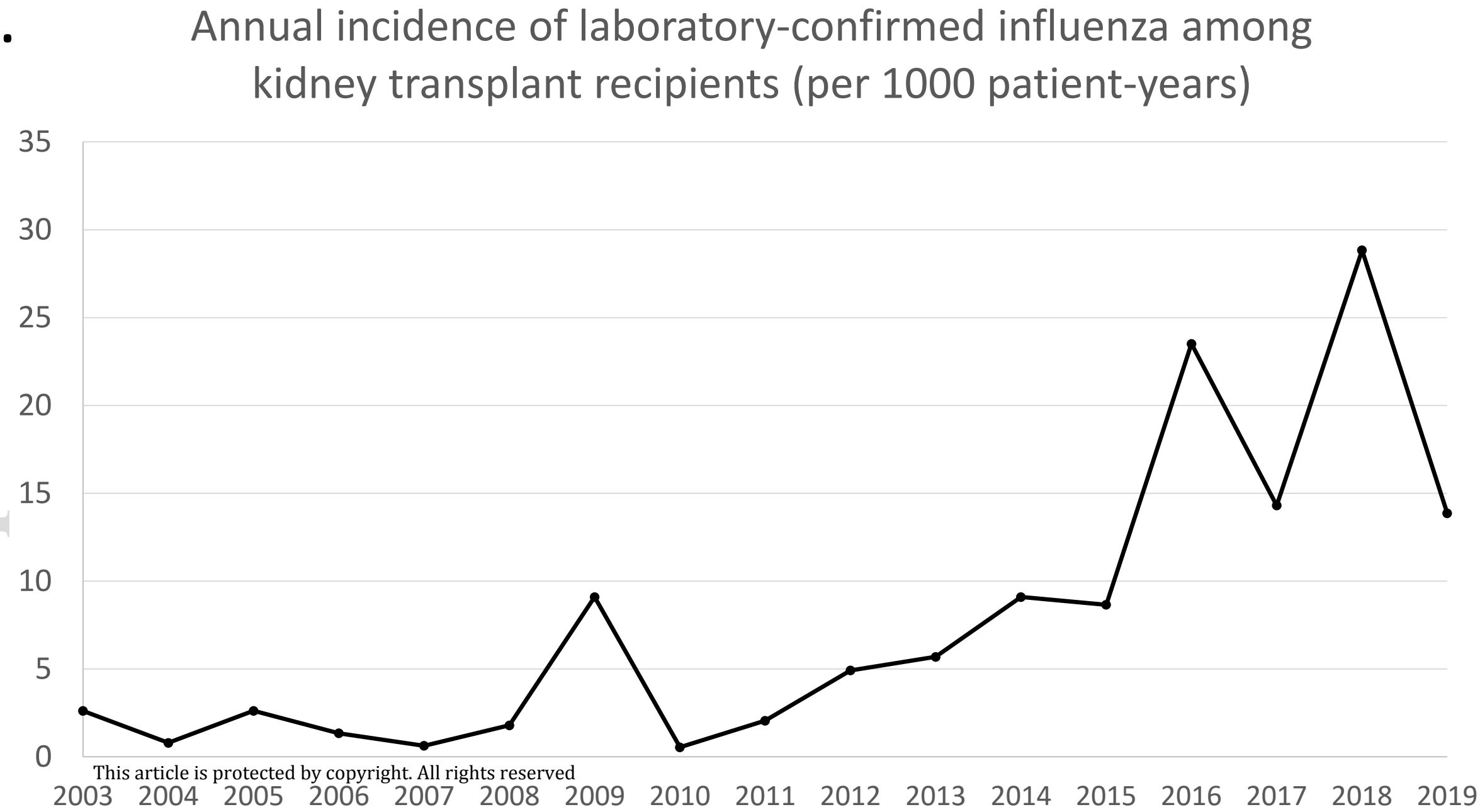
1.



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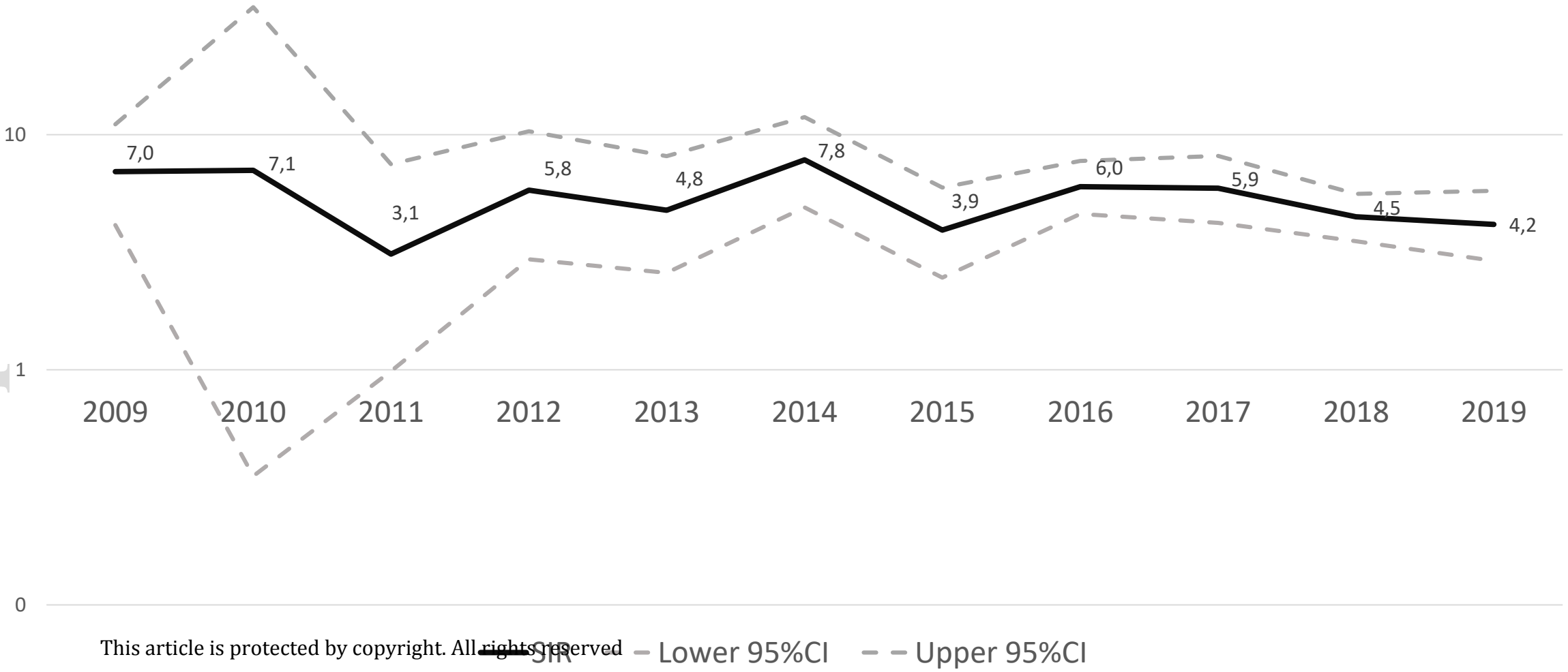
2.

Standardized incidence ratio (SIR) of laboratory-confirmed influenza between 2009 and 2019 in kidney transplant recipients compared to the whole population of Finland
Total SIR 5.1 (95%CI 4.5-5.7) 2009-2019



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3.

Number of subjects at risk	2809	2609	2525	2252	1954	1684	1453	1244	1051	881	729
Number of events	0	54	79	97	115	131	144	156	165	175	182

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4.

Standardized incidence ratio (SIR) of hospitalization due to influenza between 2009 and 2018 in kidney transplant recipients compared to the whole population of Finland
Total SIR 4.4 (95% CI 3.4-4.7) 2008-2018

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