Influenza vaccination and risk of hospitalization in patients with heart failure: a self-controlled case series study

Hamid Mohseni¹, Amit Kiran¹, Reza Khorshidi¹, and Kazem Rahimi^{1,2*}

¹The George Institute for Global Health, University of Oxford, Oxford Martin School, 34 Broad Street Oxford OX1 3BD, UK; and ²Oxford University Hospitals NHS Foundation Trust, Cardiology, Oxford, UK

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Aims

Evidence supporting yearly influenza vaccination in patients with chronic heart failure (HF) is limited, consequently leading to inconsistent guideline recommendations. We aimed to investigate the impact of influenza vaccination on the risk of hospitalization in HF patients.

Methods and results

We used linked primary and secondary health records in England between 1990 and 2013. Using a self-controlled case series design with conditional Poisson regression, we estimated the incidence rate ratio (IRR, 95% CI) of the number of hospitalizations in a year following vaccination with an adjacent vaccination-free year in the same individuals. We found the uptake of vaccination to be varied and generally low (49% in 2013). Among 59,202 HF patients, influenza vaccination was associated with a lower risk of hospitalization due to cardiovascular disease (0.73 [0.71, 0.76]), with more modest effects for hospitalization due to respiratory infections (0.83 [0.77, 0.90]), and all-cause hospitalizations (0.96 [0.95, 0.98]). The relative effects were somewhat greater in younger patients but with no material difference between men and women. In validation analyses, effects were not significant for consecutive years without vaccination (0.96 [0.92, 1.00]) or hospitalization due to cancer (1.02 [0.84, 1.22]).

Conclusion

In HF patients, influenza vaccination is associated with reduced risk of hospitalizations, especially for cardiovascular disease. Improved efforts for wider uptake of vaccination among HF patients are needed.

Keywords

Influenza vaccination • Heart failure • Hospitalization

Introduction

Heart failure (HF) patients are at increased risk of experiencing cardiovascular and respiratory related hospitalizations compared with the general public, and for those with influenza infection these risks are substantially elevated.^{1–4} However, whether such risks can be reduced with influenza vaccination is less certain.

In a meta-analysis of randomized trials in patients with coronary artery disease, influenza vaccination was shown to reduce the risk for major adverse cardiovascular events compared with no vaccination (risk ratio 0.64 [95% confidence interval (CI) 0.49, 0.84]).⁵ However, to our knowledge, no randomized trial has investigated the effect of influenza vaccination in patients with HF. Indeed, limited evidence

suggests that vaccination in HF patients could paradoxically trigger an infection or be less effective than in the general population because of their blunted immune response.⁶

In the absence of reliable evidence for the effectiveness of influenza vaccination in HF, clinical practice guidelines have not been making consistent recommendations. For instance, whilst the UK National Institute for Health and Care Excellence (NICE)⁷ and the American Heart Association (AHA)⁸ have called for annual influenza vaccination, the European Society of Cardiology Practice Guidelines make no such recommendations for HF patients.⁹

In this study, we aim to reliably investigate the impact of influenza vaccination on the risk of hospitalization for patients with HF, using a self-controlled case series design.

*Corresponding author. Tel: +44 (0)1865 607200, Fax: +44 (0)186 5607202, Email: kazem.rahimi@georgeinstitute.ox.ac.uk

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Methods

Database and data linkage

We used electronic health records from UK primary care (Clinical Practice Research Datalink database, or CPRD) linked to inpatient records in secondary care in England (Hospital Episode Statistics, or HES) between 1990 and 2013.

The CPRD is a primary care database containing anonymized patient data from 674 general practices in the UK.¹⁰ It includes approximately 6.9% of the UK population and is broadly representative of the population by age, sex, and ethnicity. The data set has been extensively validated and considered as the most comprehensive longitudinal primary care database¹¹ with several large-scale epidemiological reports.^{12–14} Similarly, HES contains patient level data of all inpatient as well as outpatient and accident and emergency admissions to National Health Service (NHS) hospitals in England.¹⁵

Approximately 75% of CPRD General Physician (GP) practices in England (58% of all UK CPRD GP practices) participate in patient level record linkage with HES, which is performed by the Health and Social Care Information Centre. In this study, we used data from GP practices that consented to record linkage with HES.

Participants

The study population comprised of all patients in the CPRD who were registered for at least 1 year in ‘up to standard practices’ and had linked records with HES. We included adults (age 18 years and over) who had a diagnosis of HF (for diagnostic codes see Supplementary Tables), and who had at least one record of an influenza vaccination in any subsequent year, with an adjacent vaccination-free year for comparison (before or after). Patients may have contributed more than one pair of years (vaccination year and adjacent vaccination-free year) to the study (see Supplementary material online, *Figure S1* for design overview). Patients with an inpatient record in HES for either years were included. We excluded patients who died within 12 months of their date of HF diagnosis, or died in the last year of study period.

Exposures and outcomes

The exposure variable was influenza vaccination and was identified using CPRD’s immunization database, which records the type and date of vaccination, and whether this was administered by the GP practice or other healthcare providers outside the practice. As influenza is seasonal, we considered vaccinations from 1 September to 31 December and defined a patient’s vaccination year as 12 months following their date of vaccination. Multiple vaccinations recorded on the same day were considered as single vaccination, and for patients with multiple vaccinations at different days (between September and December), we used the date of first vaccination. Following vaccination, we dismissed the 30-day post-vaccination period to minimize the risk of healthy user and related biases^{16,17} and to allow time for the intended health effects to occur.^{18,19} We then categorized risk periods into subsequent 30-day intervals (10 risk periods from 31 to 330 days post-vaccination). The start of the adjacent vaccination-free year was indexed with the date (day and month) of vaccination, giving the same risk periods by day and month.

We identified those who had a discharge diagnosis of cardiovascular disease (myocardial infarction, angina, HF, and stroke) or respiratory infections (COPD and pneumonia), as well as all-cause hospitalizations (for diagnostic codes see Supplementary material online, *Table S1*). For respiratory hospitalizations, we were mainly interested in a subset of events that are more likely to be related to the seasonal influenza. Therefore, conditions such as asthma, pleural disease, pulmonary embolism, or lung cancer hospitalizations, which are less likely to be caused by influenza infection, were excluded.

Statistical analysis

We employed self-controlled case series (SCCS) design with conditional Poisson regression to estimate incident rate ratio (IRR) with 95% CI, for hospitalizations due to cardiovascular disease, respiratory infections and all-causes (three separate analyses). The SCCS design uses within-person comparison (self-matched), thereby implicitly controlling for fixed within-person confounders during the period of the observation.²⁰ To control for seasonality and to minimize time-varying confounding, we restricted analyses to compare two consecutive years of observation, where vaccination during September to December was reported in either of the years, but not the other. We adjusted for the ordering of the year of vaccination by including a binary variable in the conditional Poisson regression model. We further adjusted for patients’ tendency for missing a vaccination in a certain year because of acute illness by including a binary variable for cause-specific admissions 30 days prior to the indexed date of vaccination. In secondary analyses, we stratified the regression model by age groups as at date of vaccination (<66, 66–75, 76–85, 85+), sex, prior history of ischaemic heart disease or myocardial infarction, year and month of vaccination and type of cardiovascular outcome, and tested for heterogeneity across the groups using the Q test (fixed-effect model, weighted using inverse-variance method).

We investigated the effect of possible residual selection bias with two validation analyses that estimated (i) the effects on cardiovascular hospitalizations from two consecutive years, where patients had no vaccination in either year, (ii) the effects on hospitalizations due to cancer (uncorrelated outcome). In both cases, we expected vaccination to be ineffective. Statistical analyses were performed using R 3.2.²¹

Results

Of 4.9 million patients in the database, 59 202 HF patients met the inclusion criteria (see Supplementary material online, *Figure S2*). Key patient features are presented in *Table 1*. The mean age at the time of diagnosis of HF was 74.7 years (SD ± 11.3) and half of all patients were male (50.1%). Vaccinations administered between September and December accounted for nearly all vaccinations (2% administered between January and August). In these four months, the peak months for vaccination were October and November (84% administered).

The uptake of vaccination each year varied, and ranged from 8% in 1990 to 49% in 2013, with a peak of 63% in 2006 (*Figure 1*).

Using conditional Poisson regression (IRR [95% CI]), patients in the vaccination year, compared with the adjacent vaccination-free year, were 27% less likely to have hospitalization due to cardiovascular disease (overall IRR for period of 31 to 330 days post-vaccination

Table 1 Patient characteristics

Characteristics	n (%)
Age at first influenza vaccination (years)	
<66	7778 (13.1%)
66–75	14 136 (23.9%)
76–85	22 591 (38.2%)
>85	14 697 (24.8%)
Sex	
Male	29 649 (50.1%)
Female	29 553 (49.9%)
Total number of vaccinations by month ^a	
September	30 471 (11.8%)
October	160 900 (62.1%)
November	56 760 (21.9%)
December	11 045 (4.3%)
Discharges from hospital ^b	
All-cause	132 878 (100%)
Of which any record of cardiovascular disease	6984 (5.3%)
Of which any record of respiratory infections	3889 (2.9%)
Comorbidities	
Hypertension	38 753 (46.0%)
Ischaemic heart disease/myocardial infarction	41 502 (49.2%)
Obesity	11 464 (13.6%)
Stroke	14 522 (17.2%)
Diabetes	16 236 (19.7%)
Peripheral arterial disease	9803 (11.6%)
Chronic kidney disease	14 992 (17.8%)

^aSome patients had more than one vaccination during the follow-up period; Vaccinations between January and August were not included in the analysis (5210 episodes (2.0%).

^bSome patients had more than one discharge from hospital.

0.73 [0.71, 0.76]). We observed modest protective effects on the number of hospitalizations due to respiratory infections (0.83 [0.77, 0.90]) and all-causes (0.96 [0.95, 0.98]). The effects varied across exposure periods, and were greatest during 31–120 days post-vaccination (Figure 2).

In subgroup analyses, the overall relative effects (31 to 330 days post-vaccination) were greatest among patients aged less than 66 years, although the test for heterogeneity was statistically only significant for hospitalizations due to all-causes (Figure 3). The effect estimates were similar between men and women, with the test for heterogeneity being non-significant for cardiovascular disease, respiratory infections, and weak heterogeneity for all-causes (Figure 3).

Whilst there was no evidence for a differential association by year of vaccination or prior history of ischaemic heart disease, we observed significant heterogeneity between components of the cardiovascular outcome and whether patients received their vaccination early or late in the year (Figure 4). In particular, vaccination early in the year was associated with a significantly stronger incidence rate ratio, likely because of longer vaccine-protected periods among patients with earlier vaccination.

It is expected that events occurring after the influenza season are not closely related to the influenza, and thus the influenza vaccine to

Figure 1 Vaccination uptake in heart failure patients in England between September and December, by year.

be effective before summer. We ran a sensitivity analysis to compare the results for events occurred before summer compared with those occurred after summer (Summer begins on 20 June). The results showed that vaccination was more effective before summer IRR 0.70, (0.66, 0.73) compared with after summer IRR 0.87 (0.70, 0.96).

In validation exercises, the effects on cardiovascular hospitalizations were non-significant for consecutive years without vaccination (0.96 [0.92, 1.00] $P=0.06$), and when pairs of years with and without vaccination were selected to investigate the effects on hospitalizations due to cancer (1.02 [0.84, 1.22], $P=0.87$).

Discussion

Using English primary care and secondary care databases, we observed HF patients who have an influenza vaccination in 1 year but no vaccination in the preceding or subsequent year to have lower risks of hospitalizations due to cardiovascular disease (27%), respiratory infections (17%), with minor impact on all-cause hospitalizations (4%). The effects were largest in the peak influenza season 31–120 days post-vaccination and in younger HF patient groups. The uptake of influenza vaccination in HF patients was generally low. Although the uptake increased in 2001, most likely due to the promotion of vaccination by the Vaccine Administration Taskforce,²² by 2013 only half of HF patients in that year had a record of influenza vaccination.

This study is one of the few studies to investigate the impact of influenza vaccination on hospitalization in patients with HF. Whilst previous studies have suggested a beneficial effect of the vaccination in acute HF patients,^{2,23} and that vaccination is most effective in younger patient groups^{24,25}, the results were from small studies, in which study designs were susceptible to unmeasured confounding and selection bias. To our knowledge, there have been no randomized trials on the effect of influenza vaccination in patients with HF. In the absence of reliable evidence, it is perhaps unsurprising that the call for annual influenza vaccination has not been consistent among health policy makers, with NICE⁷ and the AHA⁸ recommending annual influenza vaccination, and the European Society of

Figure 2 Effect of influenza vaccination on the risk of hospitalizations due to cardiovascular disease, respiratory infections and all-causes. Model adjusted for the order of the year of vaccination; estimated (non-pooled) overall effects derived for the period of 31–330 days post-vaccination. IRR denotes incident rate ratio.

Cardiology Practice Guidelines making no such recommendations for patients with HF.⁹

To fill the gap in evidence, we employed a self-controlled case series design which limits the risk of fixed between-individual confounding that non-randomized comparisons typically suffer from.^{20,26} We modified this further with use of multiple paired risk periods to eliminate differences in seasonal patterns of exposure which could lead to within-patients time-varying confounding. We applied this technique to a large sample of HF patients from a representative database. This provided sufficient power for assessment of effects overall and in important subgroups. The validation exercises together with indirect

comparison of our main result with findings from a meta-analysis of randomized trials in people with acute coronary syndrome, provided additional assurance to the credibility of our findings.

Influenza vaccination is a key measure for reducing the incidence of influenza infection and subsequent complications²⁷, reducing the rate of hospital admissions, and preventing influenza-related and cardiovascular related deaths.^{19,28} In our study, the strength of association for respiratory infections was weaker than that for cardiovascular admissions. Although this is consistent with evidence from meta-analyses of randomized trials showing a 35% lower risk of serious cardiovascular events⁵ but no statistically significant effect on risk

Figure 3 Effect of influenza vaccination on the risk of hospitalizations due to cardiovascular disease, respiratory infections and all-causes, by (A) age and (B) sex. Models adjusted for the order of the year of vaccination. Q test used to test for heterogeneity across the groups, and IRR denotes incident rate ratio.

Figure 4 Effect of influenza vaccination on the risk of hospitalizations due to cardiovascular disease, by type of cardiovascular hospitalization, presence or absence of ischaemic heart disease, and by year or month of vaccination.

of COPD exacerbation (Odds Ratio 0.89, 95% CI 0.49 to 1.62)²⁹, we are unable to reliably investigate the mechanisms behind such differential effects. One possible explanation is that the diagnostic codes for respiratory admissions are not specific to influenza infections and because many of the hospitalized cases of pneumonia and exacerbation of COPD are unrelated to influenza infection, effects on such outcomes are more modest. We aimed to investigate this by stratifying the outcomes further but there were too few explicit mentions of influenza infection and as record-linkage study we did not have information about serological effect of vaccination. However, observational studies that have measured the association between influenza infection and myocardial infarction have shown that recent influenza infection was about two times more likely in patients with myocardial infarction than those without³⁰ which may be due to influenza infection triggering the rupture of a vulnerable atherosclerotic plaque, or leading to myocarditis, fluid overload or dysrhythmia.^{3,18} Further studies could investigate the mechanisms for the heterogeneity of effect in more detail.

Our findings reinforce efforts for wider recommendation and implementation of annual influenza vaccination in patients with HF. The uptake of influenza vaccination in patients with HF, whilst higher compared with some countries, is variable and often low, which has

also been reported in other studies.^{2,4} This partly relates to lack of reliable evidence on its effectiveness among vulnerable HF patients. We believe that this study adds substantially to the evidence-base to increase vaccination rates globally.

As with any observational study, this study has its own limitations. We use routinely collected clinical data, which were not specifically designed for this study. Despite substantial reports on validity of diagnostic coding in CPRD^{31,32}, to our best of knowledge no previous study has reported the validity of the record of influenza vaccination in CPRD. However, in view of Public Health England's policy for mandatory recording of all influenza vaccinations in GP records, we expect the quality of coding in 'Up to Standard practices' to be high. Nevertheless, we cannot entirely rule out a certain degree of under or misreporting, which future validation studies could explore. CPRD does not capture information about the vaccine brand. Therefore, any differential effects by brand type could not be investigated. We evaluated vaccine effectiveness among patients who were physically and cognitively able to attend health centres (functional status^{32,33}) and who sought a consultation. We further excluded fatal outcomes because SCCS design is not suitable for analysis of effects on non-recurrent outcomes such as death. We are therefore unable to investigate any beneficial or harmful effects of vaccination on fatal

outcomes. These restrictions may also limit the generalizability of our findings to the very high-risk HF patient groups. In addition, they may introduce sampling (healthy-user) bias when the probability of receiving vaccination differs for the same individuals over time. To mitigate such effects, we restricted the time interval of our analysis to two consecutive years and excluded the first and last year of observation when patients may be less stable. In addition, we excluded pre-vaccination periods from our analyses, as previously performed in other studies,^{14,34} in an effort to adjust for patients' tendency for vaccination. However, even with these precautionary measures, we cannot entirely rule out residual confounding, which could at least explain a proportion of risk differences observed. Independent validation of the findings, ideally in large-scale randomized trials, would help to dispel any remaining uncertainties about the magnitude of effect.

Conclusion

The findings in this study provide insight on the magnitude of the transient relationship between influenza vaccination and hospitalizations, and offer strong support for annual vaccination for patients with HF to help alleviate the burden of influenza-related admissions.

Public health strategies, working closely with primary care, should be adopted in order to increase the uptake of influenza vaccination in patients with HF, especially among high-risk subgroups.

Authors' contributions

All authors conceived and designed the research. H.M., A.K. and K.R. acquired the data. H.M. performed statistical analysis. H.M. and A.K. drafted the manuscript. R.K. and K.R. made critical revision of the manuscript for key intellectual content. K.R. handled funding and supervision.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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