Influenza vaccination to improve outcomes for patients with acute heart failure (PANDA II): a multiregional, seasonal, hospital-based, cluster-randomised, controlled trial in China

Craig S Anderson, Chang Hua*, Zhiyan Wang*, Chi Wang*, Chao Jiang*, Rong Liu, Rong Han, Qiang Li, Sana Shan, Laurent Billot, C Raina Macintyre, Anushka Patel, Hongjia Zhang†, Changsheng Ma†, Jianzeng Dong†, Xin Du†*

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*Joint first authors

†Joint corresponding authors

The Institute of Science and Technology for Brain-inspired Intelligence, Fudan University, Shanghai, China (Prof C S Anderson MD PhD); **The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia** (Prof C S Anderson, Q Li MBiostat, S Shan MBiostat, Prof L Billot MRes, Prof A Patel MD PhD); **Neurology Department, Royal Prince Alfred Hospital, Sydney, NSW, Australia** (Prof C S Anderson); **Heart Health Research Center, Beijing, China** (Prof C S Anderson, R Han ME, Prof X Du MD PhD); **Beijing Anzhen Hospital, Capital Medical University, Beijing, China** (C Hua MD, Z Wang MD, C Jiang MD, Prof H Zhang MD, Prof C Ma MD, Prof J Dong MD, Prof X Du); **College of Public Health, University of Iowa, Iowa City, IA, USA** (C Wang MPH); **Centre for Infectious Diseases and Microbiology – Public Health, Westmead Hospital, Westmead, NSW, Australia** (R Liu PhD); **Sydney Infectious Disease Institute, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia** (R Liu); **The Kirby Institute, University of New South Wales, Sydney, NSW, Australia** (Prof C R Macintyre MD PhD); **Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China** (Prof J Dong)

Summary

Background Influenza vaccination is widely recommended to prevent death and serious illness in vulnerable people, including those with heart failure. However, the randomised evidence to support this practice is limited and few people are vaccinated in many parts of the world. We aimed to determine whether influenza vaccination can improve the outcome of patients after an episode of acute heart failure requiring admission to hospital in China.

Methods We undertook a pragmatic, multiregional, parallel-group, cluster (hospital)-randomised, controlled, superiority trial over three winter seasons in China. Participating hospitals were located in the counties of 12 provinces with the capability of establishing a point-of-care service to provide free influenza vaccination to a sufficient number of patients before their discharge, if allocated to the intervention group. No such service was used in hospitals allocated to usual care (control) but patients were informed of fee-for-service influenza vaccination being available at local community medical centres, as per usual standard of care. Hospitals were randomised (1:1) in each year, stratified by province and up to three times (ie, new randomisation for each season), to include eligible adult (aged ≥18 years) patients with moderate to severe heart failure (New York Heart Association class III or IV) and no contraindication to influenza vaccination. Patient enrolment was conducted over three consecutive winter seasons, from October in each year to March of the following year, between 2021 and 2024. All patients received usual standard of care and were followed up at 1, 3, 6, and 12 months after their hospital discharge by trained study personnel using a standardised protocol. The primary outcome was a composite of all-cause mortality or any hospital readmission over 12 months, excluding events that occurred within 30 days after hospital discharge at all sites and in the summer season only for sites in northern China. The effect of the intervention was assessed at an individual level in the modified intention-to-treat population (all randomly assigned patients with available information until the time of last follow-up, excluding censored events) with a two-level hierarchical logistic regression model that included study period (year) as a fixed effect, and hospital and hospital-period as random effects, with the censored events excluded. The trial is registered at the Chinese Clinical Trial Registry (ChiCTR2100053264).

Findings Of 252 hospitals assessed for eligibility, 196 hospitals agreed to join and were randomised in three batches at the beginning of each winter season from October, 2021, but 32 hospitals subsequently withdrew before any patients were included. Overall, 7771 participants were enrolled at 164 hospitals in each winter season between Dec 3, 2021, and Feb 14, 2024, with 3570 assigned to the influenza vaccination group and 4201 to the usual care (control) group. The primary outcome occurred in 1378 (41·2%) of 3342 patients in the vaccination group and in 1843 (47·0%) of 3919 patients in the usual care group (odds ratio 0·83 [95% CI 0·72–0·97]; p=0·019). The result was consistent in the sensitivity analysis. The number of participants with a serious adverse event was significantly lower in the vaccination group (1809 [52·5%] of 3444) than the usual care group (2426 [59·0%] of 4110; odds ratio 0·82 [0·70–0·96]; p=0·013).

Interpretation Influenza vaccination during a hospital admission in patients with acute heart failure can improve their survival and reduce likelihood of readmission to hospital over the subsequent 12 months. The integration of influenza vaccination into inpatient care could offer a widely applicable strategy for an underserved high-risk patient group, that is relevant to resource-limited and possibly resource-rich settings.

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Introduction

Patients with heart failure are particularly susceptible to infectious diseases, which can be a major cause of their clinical deterioration. In one large cohort study, the rate of pneumonia was three times higher in adults with heart failure compared with the general population, and it resulted in a four-fold increase in mortality.[1] Infections lead these patients to decompensate with recurrent

Research in context

Evidence before this study

We searched PubMed (from Jan 1, 1970, to May 1, 2025) and Embase (from Jan 1, 1947, to May 1, 2025) on May 10, 2025, with no language or data restrictions, for publications with relevant text words in the title or abstract or keywords that included: "influenza" AND "cardiac". Our search yielded seven randomised controlled trials, predominantly focused on patients with coronary artery disease. One trial of 2532 patients with recent myocardial infarction reported that the use of influenza vaccination early after the onset of myocardial infarction reduced the risk for a composite cardiovascular outcome compared with placebo. Similarly, a trial of 658 patients with stable coronary disease and another trial involving 439 patients with an acute coronary syndrome reported that influenza vaccination reduced a composite cardiovascular outcome compared with placebo and a non-vaccinated group, respectively. Only one previous randomised trial limited to patients with heart failure was found. It enrolled 5129 patients to show that influenza vaccination did not significantly reduce a composite cardiac outcome, but it was associated with reduced rates of all-cause hospitalisation and community-acquired pneumonia.

Added value of this study

To our knowledge, this study is the first randomised trial to systematically implement an in-hospital influenza vaccination programme for high-risk patients with advanced heart failure (New York Heart Association class III or IV). By training ward staff to administer the vaccine and through a temporary point of vaccination service, the intervention embedded influenza vaccination into routine care pathways. The intervention achieved a 94·4% vaccination rate compared with 0·5% in the usual care group, proving that hospital-based vaccination during an admission for acute heart failure is both feasible and transformative for coverage. Through the conduct across 164 county-level hospitals in China, this trial has shown that systematic in-hospital vaccination reduces the odds of the composite risk of all-cause mortality or rehospitalisation by 17% within 12 months. These findings extend previous evidence by focusing on a high-risk and understudied population to quantify the benefits of a potentially applicable treatment for low-resource settings and establish a scalable model to overcome systemic barriers to accessing vaccination.

Implications of all the available evidence

Our trial provides strong evidence to support in-hospital use of influenza vaccination for patients admitted with acute heart failure as a potentially transformative strategy to improve their outcome. By integrating vaccination into inpatient care, the strategy overcomes systemic barriers such as frailty, limited mobility, and provider hesitancy, with the ability to achieve near-universal coverage in a historically underserved high-risk patient group. The significant reduction in post-discharge adverse outcomes highlights the phase of hospitalisation for acute heart failure as a critical window for prevention, challenging the traditional separation of acute management and preventive care. As shown through the conduct of the trial across a diverse range of locations of hospitals in China, this approach can be adaptable to resource-limited settings.

Correspondence to:
Prof Hongjia Zhang, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China
zhanghongjia722@ccmu.edu.cn
or
Prof Changsheng Ma, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China
chshma@vip.sina.com
or
Prof Jianzeng Dong, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China
jzdong@ccmu.edu.cn
or
Prof Xin Du, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China
duxinheart@sina.com

presentations to hospital, deterioration in quality of life, and accelerated decline in cardiac function.

Influenza is the most prevalent infectious disease worldwide, representing a substantial global health burden causing 290 000 to 650 000 respiratory-related deaths each year.[2] Patients with heart failure are particularly vulnerable to influenza and its deleterious effects: in one study, a 5% absolute increase in influenza activity in the community was associated with a 24% increase in heart failure-related admissions to hospital in the same month.[3] Implementing strategies to prevent or mitigate the effects of influenza infection is critically important for patients with heart failure.

Observational studies indicate that influenza vaccination is associated with reduced mortality in patients with cardiovascular disease.[4–6] This finding has largely been confirmed in meta-analyses of randomised trials where influenza vaccination is associated with a significant reduction in serious cardiovascular events in patients with established ischaemic heart disease.[7,8] However, the evidence specifically in patients with heart failure is inconclusive. In the only randomised trial to investigate this topic, the international double blind, placebo controlled Influenza Vaccine to Prevent Adverse Vascular Events study involving 5129 participants recruited from outpatient clinics in whom 70% had New York Heart Association (NYHA) grade II severity of heart failure, an annual influenza vaccination did not significantly reduce the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or stroke, nor of a secondary broader outcome that included hospitalisation from heart failure. However, in a prespecified analysis restricted to events occurring during periods of peaks in circulating influenza, there was a significant reduction in the primary outcome in participants who were vaccinated.[9]

Although clinical guidelines from leading cardiovascular societies recommend annual influenza vaccination for adults with heart failure,[10–12] global vaccination rates for this patient group remain suboptimal, reaching levels of approximately 60% in western Europe and the USA, but fewer than 3% in many parts of Asia.[4] In China, the coverage of influenza vaccination in patients with heart failure is estimated to be less than 1%,[13] due to multiple barriers that include out-of-pocket costs for the patient, cultural perceptions,

poor public awareness, and concerns about vaccine safety.[14–16]

Following completion of an initial observational time-series study,[13] and then a pilot randomised feasibility study which showed good reach and fidelity of the planned intervention in 518 patients recruited at 11 hospitals in Henan Province, China, between December, 2020, and April, 2021,[14] we conducted the expanded phase of providing free influenza vaccination before hospital discharge compared with routine care in patients with heart failure in the main phase of the Population Assessment of Influenza and Disease Activity (PANDA II) study. The aim was to determine whether routine administration of a free influenza vaccine before a patient is discharged from hospital after an admission for acute heart failure would reduce all-cause mortality and readmissions to hospital over the subsequent 12 months. A cluster design was deemed to provide logistical efficiencies and be ethically justified, as an individual patient randomised design would be challenging to conduct when a guideline-recommended intervention was to be withheld from participants allocated to the usual care (control) group.

Methods

Study design

The PANDA II study was a multiregional, two-arm, parallel-group, open-label, multiple period, cluster randomised controlled trial, in which hospitals were the unit of randomisation. The full study protocol and statistical analysis plan have been published previously[17,18] and are available in the appendix (pp 88–212). The trial is reported in accordance with the CONSORT extension for cluster randomised trials (appendix pp 7–9).[19–21]

See Online for appendix

The type 1 hybrid discovery implementation design[22] allowed clusters of patients to be prospectively followed up to determine their outcome according to being allocated to a new model of care or not. The study was conducted over 4 years, with hospitals randomly assigned to the intervention group or control group in each of 3 respective years from 2021. Hospitals that agreed to participate in multiple years were re-randomised in each year. The study was approved by the ethics committees of Beijing Anzhen Hospital, which is affiliated with Capital Medical University (research ethics review approval number 18, 2021; initial approval date Sept 16, 2021, and final approval date for an updated protocol version 3.0 was May 30, 2024; appendix pp 10–11), and at all participating sites. The only changes to the protocol were the inclusion of sites in southern China and a decrease in sample size in relation to an increase in influenza activity in the final year of recruitment. Written informed consent was obtained from all participants for the collection of data during follow-up. An independent data and safety monitoring board reviewed progress, safety, and efficacy in the trial. The study is registered with the Chinese Clinical Trial Registry (registration identifier: ChiCTR2100053264).

Participating hospitals, each constituting a cluster, were recruited through professional networks of the researchers. Eligible sites were county-level hospitals capable of managing a high volume of patients with heart failure such that they could enrol approximately 50 patients in a winter season. To minimise the risk of contamination between the intervention and control groups, hospitals were selected from geographically dispersed regions that served relatively stable local populations, and they received quality control monitoring. Details of the hospitals are outlined in the appendix (pp 3–6, 15–23, and 81).

Hospitals were randomised in batches before each enrolment winter season. In the first and second years of the study, hospitals were purposively selected from nine northern provinces of China (Henan, Jilin, Hebei, Shanxi, Inner Mongolia, Liaoning, Heilongjiang, Shandong, and Shaanxi), where influenza activity is typically higher during the winter than in the spring and autumn months, and there is minimal influenza infection in the summer months (June 1 to Aug 31). In the third year, in response to an increase in influenza activity recorded in southern China during the previous winter season, hospitals from three southern provinces (Hunan, Anhui, and Guangxi) were also included (appendix pp 18–23). There is minimal seasonal variation in influenza infection in the southern region of China.

The study design and its implementation were informed by the feedback gained from the PANDA II pilot phase which incorporated a process evaluation involving interviews with 51 key informants (patients, health professionals, and policy makers) from nine of the 11 participating hospitals in 2021.[14] Of particular relevance was the need to educate all stakeholders at hospitals on the purpose of the trial, for patients to be informed about influenza vaccination upon admission, during the consent process, and at the time of discharge, and for the point-of-vaccination service to be tailored to local circumstances.

Participants

Patient enrolment was to be conducted between October in one year and March of the following year, over three influenza seasons beginning in 2021, 2022, and 2023. Eligible patients were adults aged 18 years or older who were hospitalised with a primary diagnosis of acute heart failure that was classified as moderate to severe (NYHA functional class III or IV). Key exclusion criteria included a contraindication to influenza vaccination, previous enrolment in the study during a previous influenza season, two or more admissions to hospital for acute heart failure within the preceding 2 months, and plans for discharge from hospital that involved a transfer to another medical facility for ongoing care. Checks were made to ensure that patients were not enrolled on multiple occasions (appendix p 12).

During each enrolment period, all consecutive eligible patients admitted to participating hospitals were

approached for inclusion. A patient screening log was maintained at each site to ensure the integrity of consecutive recruitment. Baseline data, including socio-demographic characteristics, including ethnicity according to the National ID registration card, anthropometric measures, medical history, medications, laboratory test results, and echocardiographic findings and management details were collected by trained research personnel according to a standardised protocol.

Randomisation and masking

At the start of each season, all hospitals were randomised in a 1:1 ratio to either the intervention or control group, according to stratification within each province to ensure balanced allocation. Randomisation schedules were generated using SAS software (version 9.4) by an independent statistician who was not involved in the implementation or data analysis.

Due to the cluster design and the nature of the intervention, both participants and site investigators were unmasked. However, site investigators remained masked to the generation of the randomisation sequence to prevent any anticipation of group allocation prior to disclosure. The assignment to intervention or control was communicated to site investigators only after randomisation was completed. Additionally, data assessors and statisticians at the central coordinating centre were masked to the group assignments throughout the analysis. The outcome assessors were also unmasked as they were required to ask participants about the receipt of influenza vaccination; however, they were not made aware of the purpose of the study.

Procedures

Hospitals in the intervention group established points of vaccination within wards to offer free influenza vaccination for patients with heart failure. As part of the intervention, health-care teams received training on the study protocol and procedures, and were educated on the method of vaccination, to enhance their willingness and capacity to vaccinate patients. Eligible patients in the intervention group received either a trivalent or quadrivalent influenza vaccine according to local availability. It was provided free of charge and administered within 24 h of a patient's planned discharge from hospital.

Hospitals in the control group continued with routine care, whereby patients were advised at the time of their discharge from hospital that they could receive influenza vaccination at a community health-care centre, but that this was an out-of-pocket expense. Guideline-directed medical therapy was maintained in both groups.

Centrally coordinated telephone follow-up was conducted at 1, 3, 6, and 12 months after discharge from hospital by trained study personnel using a standardised protocol. The follow-up staff were independent of the study team. Information on all deaths and rehospitalisations was systematically collected through interviews with participants (or an appropriate surrogate). Central review of the electronic medical records of participating hospitals was used to check the quality of baseline data and verify the completeness of ascertainment of outcome events in participants.

Outcomes

The primary outcome was a composite of all-cause mortality or any hospital readmission over 12 months. We excluded events that occurred within 30 days of hospital discharge because this is a particularly vulnerable period for patients with heart failure due to early worsening of cardiovascular haemodynamics that is unlikely to be responsive to influenza vaccination.[23,24] Moreover, it takes up to 14 days for an immune response to occur after influenza vaccination, and possibly longer in patients with heart failure, many of whom are elderly.[25] We also excluded events that occurred in the summer season between June 1 and Aug 31 only for sites located in northern China, as it was considered that these events are unlikely to be preventable by influenza vaccination when influenza rates are very low. Hospitalisation was defined as any admission to hospital or visit to an emergency department that lasted for 24 h or more. Only limited data on the cause of death or hospitalisation were collected because reliably establishing a diagnosis through interview is difficult in patients with advanced disease.

Secondary outcomes were, separately, all-cause mortality or any hospital readmission within 12 months; and the combination and individual components of all-cause mortality and any hospital readmission within 6 months. We also collected information on medication use, health-related quality of life on the EuroQoL EQ-5D-3L questionnaire, and patients experiencing any influenza-like symptoms during follow-up.

Any serious adverse events were recorded until the end of follow-up. They were classified according to standard definitions as: an adverse event that results in death; is life-threatening; requires or prolongs hospitalisation; causes persistent or significant disability or incapacity; results in congenital anomalies or birth defects; or is important in that it might jeopardise the patient or require intervention to prevent the occurrence of a serious outcome. Any unexpected clinical signs or symptoms occurring within 7 days post-vaccination were reported as an adverse event.

Statistical analysis

The required sample size was reduced during the course of the study as there was an increase in influenza activity noted after the COVID-19 pandemic, and according to the various assumptions. At the population level, the average influenza infection rate was estimated at 15%, with 80% of infected individuals experiencing a primary outcome, and six out of ten vaccinated people protected

from influenza in the community. Vaccination coverage was expected to be 90% and 10% in the intervention group and control group, respectively, the dropout was estimated at 10% over 12 months, and the intra-class correlation coefficient was 0·03 across participating hospitals in a season. Thus, enrolment of 50 patients from each of 122 hospitals (total 6100 participants) was estimated to provide 90% power to detect a reduction in the primary outcome from 50 per 100 person-years in the usual care group to 43·5 per 100 person-years in the vaccination group, at a two-sided significance level of p<0·05. A post-hoc analysis indicates that power was maintained in the study (appendix p 12).

Continuous variables were summarised as mean (SD) for normally distributed data, and median (IQR) for skewed distributions with normality assessed using the Shapiro–Wilk test. Discrete variables were summarised by frequencies and percentages.

The main analysis was conducted in the modified intention-to-treat population conducted at the individual level involving all patients with available information until the time of last follow-up, excluding censored events. A two-level hierarchical logistic regression model was used to assess the effect of the intervention on the composite outcome of all-cause mortality and rehospitalisation within 12 months, excluding those events that occurred within 30 days of hospital discharge or during the summer season only for northern hospitals. In the model, intervention allocation (influenza vaccine *vs* control) and study period (years 1, 2, and 3) were included as fixed effects. Although each hospital-year combination was treated as an independent cluster, we recognised that some hospitals participated in multiple influenza seasons. To account for potential correlation arising from repeated participation of the same hospital across years, we included two levels of random effects in the hierarchical logistic regression model: one for hospital and another for hospital-year, which means study period was nested within the hospital. This approach allowed us to adjust for both between-hospital variation and within-hospital temporal variation. A random intercept for hospital was specified to model clustering between individuals from the same hospital, and an additional random effect for hospital-period was included to model differential clustering for individuals from the same hospital but different period.

A further adjusted analysis was conducted using the same model as the primary analysis by adding the following baseline prognostic covariates: age, sex, severity (NYHA level), history of ischaemic heart disease (defined as any myocardial infarction, coronary stent insertion, coronary artery bypass surgery, or coronary artery disease), level of left ventricular ejection fraction (LVEF; <40% *vs* ≥40%), and renal function (estimated glomerular filtration fraction [eGFR] <30 mL/min per 1·73 m² *vs* ≥30 mL/min per 1·73 m²). Both the main and adjusted analysis results are reported as an odds ratio (OR) with 95% CIs. The primary result is also reported as an OR from the difference in rates between the intervention and control groups, with the associated 95% CIs estimated using the Wald method with logarithmic transformation, and as an incidence rate ratio expressed as the number of events over the duration of follow-up.

As a sensitivity analysis, a cluster level analysis was conducted using weighted mixed linear regression. The model was weighted proportionally to the inverse of the binomial variance,[21] with the intervention and period as fixed effects, and hospital as a random effect. Hospital was planned to be included as a fixed effect in the model. However, as this caused overparameterisation and inflated standard errors due to the large number of sites and limited data per site, a mixed-effects model was used whereby hospital was treated as a random effect, which allowed account of between-site variability and improved convergence and efficiency of the model. The result is reported as a mean difference with 95% CI. The Holm–Sidak correction was applied to control the family-wise error rate for all the secondary endpoints. Each ordered p value was compared with a sequential threshold in the formula $\alpha_i=1-(1-\alpha)^{1/(m-i+1)}$, where i is the rank of the p value (from smallest to largest), m is the total number of tests, and α is 0·05. Subgroup analyses were done by adding the subgroup variable and its interaction with the intervention as fixed effects to the main analysis model. Several post-hoc analyses were performed: using all randomly assigned patients except those who withdrew consent or were lost to follow-up; using a new composite endpoint of death, hospitalisation, or loss to follow-up; with adjustments for the baseline imbalance in the variables of medical insurance and N-terminal pro-B-type natriuretic peptide; and with adjustment using the alternative eGFR cut-point of less than 60 mL/min per 1·73 m² versus 60 mL/min per 1·73 m² or greater. We also conducted time to event analyses using both the log-rank test and Kaplan–Meier analysis. Analysis of the safety outcomes was conducted at the cluster and individual levels. All statistical analyses were done using SAS version 9.4, with a significance level set at 5%.

No formal interim analyses were planned or conducted during the trial. However, at the end of each enrolment season, interim safety reports were provided to the data and safety monitoring board.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 252 hospitals assessed for eligibility in 2021, 2022, and 2023, 196 hospitals agreed to join and were randomly assigned. 45, 72, and 79 hospitals were included in each year, respectively, but 32 subsequently withdrew before any patients were enrolled. Of the

remaining 164 hospitals, 43, 57, and 64 hospitals were randomised in each season, including 24 and 26 hospitals that participated in two and three seasons, respectively. Hospitals that participated on multiple occasions were treated as independent clusters in each year of participation. Overall, 20, 28, and 29 hospitals were assigned to the influenza vaccination intervention group in 2021, 2022, and 2023, respectively, and

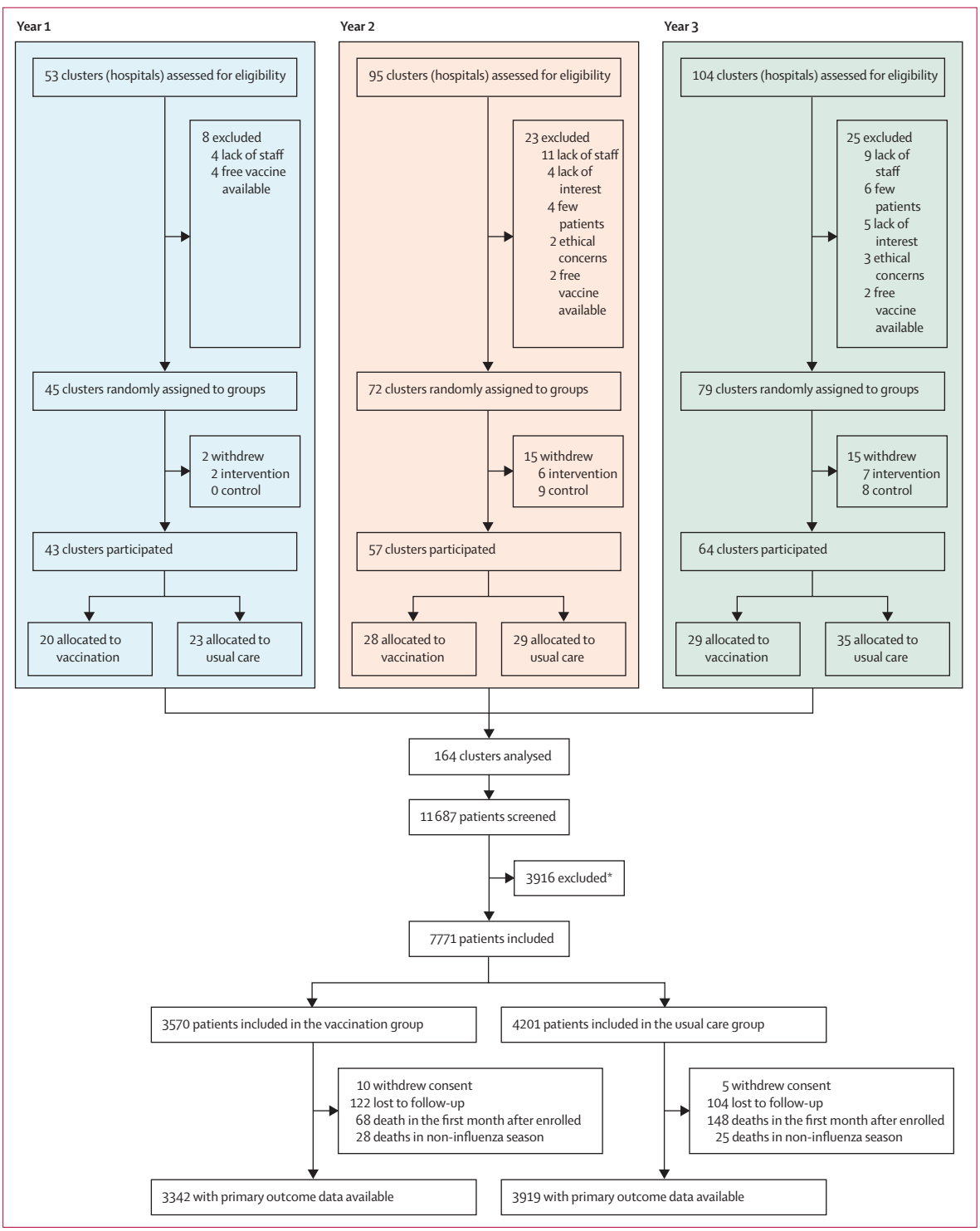

Figure 1: **Trial profile**
*The main reason for exclusion was refusal to participate in the study (n=3550), for the full list of reasons see appendix p 24.

23, 29, and 35 hospitals were assigned to the usual care control group in these corresponding years (figure 1).

Overall, 11 687 patients were screened for eligibility and 7771 (66·5%) patients were recruited in the trial, with 3570 assigned to the vaccination group and 4201 assigned to the usual care group between Dec 3, 2021, and Feb 11, 2022; Sept 9, 2022, and Jan 31, 2023; and Sept 5, 2023, and Feb 14, 2024. The number of patients recruited across seasons and reasons for excluding patients are outlined in the appendix (pp 18–24). However, ten patients in the vaccination group (including one patient with a non-fatal rehospitalisation within 30 days after hospital discharge) and five in the usual care group later withdrew their consent to participate.

	Influenza vaccination (n=3570)	Usual care (n=4201)
Age, years	71·7 (11·0)	72·0 (11·5)
Sex		
Female	1682/3570 (47·1%)	1983/4201 (47·2%)
Male	1888/3570 (52·9%)	2218/4201 (52·8%)
Ethnicity		
Han Chinese	3389/3570 (94·9%)	4150/4201 (98·8%)
Other	181/3570 (5·1%)	51/4201 (1·2%)
Level of education		
Primary school or below	2630/3568 (73·7%)	2975/4200 (70·8%)
Secondary school or above	938/3568 (26·3%)	1225/4200 (29·2%)
Type of medical insurance		
Urban employees or residents	1095/3570 (30·7%)	1957/4200 (46·6%)
Rural cooperative medical care	2313/3570 (64·8%)	2131/4200 (50·7%)
Other	162/3570 (4·5%)	112/4200 (2·7%)
Medical history		
Hypertension	2043/3566 (57·3%)	2330/4201 (55·5%)
Coronary artery disease	1252/3566 (35·1%)	1545/4201 (36·8%)
Diabetes	754/3566 (21·1%)	1007/4201 (24·0%)
Atrial fibrillation or atrial flutter	1006/3566 (28·2%)	1140/4201 (27·1%)
Cerebrovascular disease	680/3566 (19·1%)	867/4201 (20·6%)
Heavy drinking*	186/3566 (5·2%)	225/4201 (5·4%)
Current smoker†	397/3566 (11·1%)	449/4201 (10·7%)
Vital signs		
Systolic blood pressure, mm Hg	136·1 (24·7); n=3566	136·8 (25·4); n=4199
Diastolic blood pressure, mm Hg	82·0 (15·7); n=3566	82·5 (16·1); n=4199
Heart rate, bpm	87·2 (21·9); n=3566	89·1 (21·9); n=4199
NYHA class		
III	1923/3566 (53·9%)	2281/4201 (54·3%)
IV	1643/3566 (46·1%)	1920/4201 (45·7%)
BMI, kg/m²	23·9 (4·0); n=3055	24·0 (4·2); n=3426
Laboratory results		
Sodium, mmol/L	139·5 (4·4); n=3512	139·2 (4·5); n=4120
Potassium, mmol/L	4·2 (0·6); n=3515	4·2 (0·6); n=4123
eGFR, mL/min per 1·73 m²	71·2 (23·8); n=3493	69·3 (24·3); n=4077
Natriuretic peptide tests		
BNP, ng/L	1197 (481–2586); n=440	1002 (420–2207); n=495
NT-proBNP, ng/L	3176 (1183–7637); n=2783	3940 (1458–8657); n=3240

(Table 1 continued on next page)

The mean number of participants per hospital was 47 (SD 23; range 3–111). Over the 12-month follow-up period, 122 participants (3·4%) in the vaccination group (including five patients with a non-fatal rehospitalisation) and 104 participants (2·5%) in the usual care group (including 18 patients with a non-fatal rehospitalisation) were lost to follow-up before the 12-month assessment.

Baseline demographics, medical history, clinical characteristics, and the in-hospital management of patients were well balanced between the treatment groups overall and by age and sex (table 1, and appendix pp 25–34). The mean age was 71·9 years (SD 11·3), 3665 (47·2%) of 7771 patients were female, and 7539 (97·0%) were Han Chinese. 4204 (54·1%) patients were classified as NYHA class III and 3563 (45·9%) as class IV; 5395 (75·8%) of 7115 patients had an LVEF 40% or greater. The most common comorbid medical conditions were hypertension (n=4373; 56·3%), coronary artery disease (n=2797; 36·0%), diabetes (n=1761; 22·7%), atrial fibrillation or flutter (2146; 27·6%), and cerebrovascular disease (n=1547; 19·9%). The inter-class correlation coefficients across sites for the within and between periods were 0·023 and 0·041, respectively. Details of the medical management during the initial hospital admission and during follow-up are outlined in the appendix (pp 35–61). In the vaccination group, 3368 patients (94·4%) received the influenza vaccine, including 2968 (88·1%) who received quadrivalent forms and 400 (11·9%) who received trivalent forms (appendix p 62). In the usual care group, 21 patients (0·5%) received an influenza vaccine, with 12 receiving it before their admission to hospital, three during their admission, and six after their admission (table 1). The pattern of influenza activity in China during the study is outlined in the appendix (p 82).

For the primary analysis, 228 patients in the influenza vaccination group were excluded for the following reasons: eight patients died before hospital discharge, 60 patients died within 30 days after hospital discharge, 28 patients died during the non-influenza season at northern sites without a primary endpoint, 122 patients were lost to follow-up (including four patients with hospital readmissions within 30 days and one during the non-influenza season, all without a primary endpoint), and ten patients withdrew consent (including one with a hospital readmission within 30 days of initial hospital discharge). Similarly, 282 patients in the usual care group were excluded for the following reasons: 16 patients died before hospital discharge, 132 patients died within 30 days after hospital discharge, 25 patients died during the non-influenza season at northern sites without a primary endpoint, 104 patients were lost to follow-up (including seven patients with hospital readmissions within 30 days, and 11 patients in the non-influenza season but without a primary endpoint), and five patients withdrew their consent. In total, 102 (2·9%) of 3570 patients in the influenza vaccination group and

191 (4·5%) of 4201 patients in the usual care group died or had a hospital readmission within 30 days or during the summer months at northern sites, but without a primary endpoint during the influenza season. However, these patients were included in the reporting of serious adverse events (table 2). Full details of the deaths and hospital readmissions are outlined in the appendix (p 67), and the pattern of primary events over the 3 years is outlined in the appendix (pp 63–66).

In the primary analysis, 1378 (41·2%) of 3342 patients in the vaccination group and 1843 (47·0%) of 3919 patients in the usual care group experienced the composite endpoint of all-cause mortality or hospital readmission, which corresponded to an unadjusted OR of 0·83 (95% CI 0·72 to 0·97; p=0·019). After the inclusion of the baseline covariates of age, sex, NYHA class, history of ischaemic heart disease, LVEF, and renal function, the treatment effect remained significant in an adjusted model (adjusted OR 0·85 [95% CI 0·72 to 0·99]; p=0·042) and the group difference was –0·037 (–0·073 to –0·002; p=0·037) in a cluster level linear regression analysis (table 2). This translates to a number needed to vaccinate at the participating hospitals of 27 (95% CI 14–500) to prevent one death or hospital readmission. Additionally, there was a lower rate of the primary endpoint in the vaccination group, with a relative risk ratio of 0·90 (95% CI 0·86 to 0·94; p<0·0001; table 2) and a lower incidence of the primary endpoint per 100 person-years in the vaccination group compared with the usual care group (54·63 *vs* 65·72; appendix p 68). Post-hoc analysis of the intention-to-treat population that included all randomly assigned patients with events until the time of last follow-up showed an unadjusted OR of the primary composite outcome of 0·82 (95% CI 0·70 to 0·96; p=0·012; appendix p 69). Post-hoc analyses with additional covariates included in the model showed consistency in the point estimate but a loss of statistical significance with the reduction in sample size (appendix pp 70–71).

The secondary endpoint of all-cause mortality within 12 months, after excluding events that occurred within 30 days post-discharge or in the northern summer season, occurred in 335 patients (10·0%) in the vaccination group and 500 patients (12·8%) in the usual care group, which corresponded to an OR of 0·76 (95% CI 0·69 to 0·84; p<0·0001; table 2, appendix p 83). This difference remained statistically significant after adjustment for multiple comparisons using the Holm–Sidak method (p=0·0005). Any hospital readmission within 12 months occurred in 1182 patients (35·4%) in the vaccination group and 1587 patients (40·5%) in the usual care group (OR 0·83 [95% CI 0·70 to 0·99]; p=0·037 in unadjusted and p=0·060 in adjusted for multiple comparisons).

Consistent reductions were observed in the separate and combined secondary outcomes of all-cause mortality and any hospital readmission at 6 months. However, these differences only remained statistically significant for mortality after applying the Holm–Sidak correction for multiple testing. The profile of health-related quality of life in patients is outlined in the appendix (pp 72–77, 84–87). The rates of influenza-like symptoms reported by participants at each follow-up visit were low (appendix p 78). There was no significant heterogeneity in the treatment effect on the primary outcome across the subgroups (figure 2).

The number of patients with at least one serious adverse event was significantly lower in the vaccination group compared with the usual care group, both at the individual level (1809 [52·5%] of 3444 patients *vs* 2426 [59·0%] of 4110 patients; OR 0·82 [95% CI 0·70 to 0·96]; p=0·013) and cluster level (mean difference –0·042 [95% CI –0·079 to –0·004]; p=0·030; table 2). A full list of the serious adverse events by disease category is outlined in the appendix (p 79).

	Influenza vaccination (n=3570)	Usual care (n=4201)
(Continued from previous page)		
Echocardiographic parameters		
LVEF ≥40%	2467/3286 (75·1%)	2928/3829 (76·5%)
Moderate or severe mitral regurgitation	1021/3286 (31·1%)	1128/3829 (29·5%)
Interventions in the hospital		
Use of antibiotics	1369/3563 (38·4%)	1471/4179 (35·2%)
Use of intravenous inotropes	833/3563 (23·4%)	1070/4179 (25·6%)
Intravenous vasodilators	1628/3563 (45·7%)	1964/4179 (47·0%)
Percutaneous coronary revascularisation	154/3558 (4·3%)	158/4185 (3·8%)
Other cardiac procedure	77/3558 (2·2%)	48/4185 (1·1%)
Medications at hospital discharge		
Spironolactone	2631/3416 (77·0%)	299/3991 (7·5%)
ARB, ACEI, or ARNI	2147/3416 (62·9%)	2407/3991 (60·3%)
Beta blocker	2288/3416 (67·0%)	2415/3991 (60·5%)
SGLT2 inhibitor	902/3416 (26·4%)	955/3991 (23·9%)
Diuretic	2302/3416 (67·4%)	2757/3991 (69·1%)
Length of hospital stay, days	8·6 (4·2); n=3558	8·6 (4·0); n=4184
Influenza vaccination given	3368/3566 (94·4%)	21/4201 (0·5%)‡

Data are n, n (%), mean (SD), or median (IQR). ACEI=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor-neprilysin inhibitor. BNP=B-type natriuretic peptide. eGFR=estimated glomerular filtration rate. bpm=beats per minute. LVEF=left ventricular ejection fraction. NT-proBNP=N-terminal pro-B-type natriuretic peptide. NYHA=New York Heart Association classification system for heart failure. *Heavy drinking defined according to consumption for more than 5 days within 1 month: more than four shots of liquor or five cans of beer in men, and more than three shots of liquor or more than four cans of beer in women. †Smoking one cigarette or more per day in 1 month. ‡Includes 12, three, and six patients who had the vaccine before, during, and after admission to hospital, respectively.

Table 1: **Baseline characteristics and patient management**

Discussion

This study found that systematic in-hospital influenza vaccination before hospital discharge significantly reduced the risk of death or hospital readmission from 47·0% to 41·2% over 12 months in patients with acute heart failure of a moderate-to-severe degree. This translates to a number needed to vaccinate at the participating hospitals of 27 (95% CI 14–500) to prevent

	Influenza vaccination (n=3570)	Usual care (n=4201)	Effect size (95% CI)	p value	Adjusted p value*
Primary outcome					
All-cause mortality or hospital readmission at 12 months	1378/3342 (41·2%)	1843/3919 (47·0%)	OR 0·83 (0·72 to 0·97); RR 0·90 (0·86 to 0·94)	OR: 0·019; RR: <0·0001†	..
Adjusted mortality or hospital admission at 12 months‡	1243/3037 (40·9%)	1614/3487 (46·3%)	OR 0·85 (0·72 to 0·99)	0·042	..
Cluster level regression of primary outcome incidence§	0·40 (0·11); n=77	0·46 (0·14); n=87	–0·037 (–0·073 to –0·002)	0·037	..
Secondary outcomes					
All-cause mortality at 12 months	335/3342 (10·0%)	500/3919 (12·8%)	OR 0·76 (0·69 to 0·84)	<0·0001	0·0005
Hospital readmission at 12 months	1182/3342 (35·4%)	1587/3919 (40·5%)	OR 0·83 (0·70 to 0·99)	0·037	0·060
All-cause mortality or hospitalisation at 6 months	1018/3449 (29·5%)	1393/4010 (34·7%)	OR 0·84 (0·72 to 0·97)	0·018	0·053
All-cause mortality at 6 months	263/3449 (7·6%)	398/4010 (9·9%)	OR 0·74 (0·61 to 0·90)	0·0025	0·010
Hospital readmission at 6 months	882/3449 (25·6%)	1213/4010 (30·2%)	OR 0·83 (0·70 to 0·98)	0·030	0·060
Serious adverse events during follow-up					
Events reported	2863	4113	..	..	..
Patients with at least one event	1809/3444 (52·5%)	2426/4110 (59·0%)	OR 0·82 (0·70 to 0·96)	0·013	..
Sites with at least one event§	0·52 (0·14); n=77	0·58 (0·14); n=87	–0·042 (–0·079 to –0·004)	0·030	..

Data are n/N (%), median (IQR), and mean difference (95% CI). OR=odds ratio. RR=risk ratio. *Holm–Sidak correction applied to control the family-wise error rate. Each ordered p value was compared to a sequential threshold in the formula: $\alpha_i = 1-(1-\alpha)^{1/(m-i+1)}$. †p value was calculated using the Chi-square test. ‡Adjusted model included age, sex, New York Heart Association class, history of ischaemic heart disease (myocardial infarction, coronary stent insertion, coronary artery bypass surgery, or coronary artery disease), left ventricular ejection fraction (<40% *vs* ≥40%), renal function (estimated glomerular filtration rate <30 mL/min per 1·73 m² *vs* ≥30 mL/min per 1·73 m²). §Cluster level analysis conducted using weighted mixed linear regression. The model was weighted proportionally to the inverse of the binomial variance, with intervention and period as fixed effects, and hospital as a random effect.

Table 2: **Primary and secondary outcomes, and safety of influenza vaccination**

one death or hospital readmission. The benefits were consistently observed across the secondary outcomes and prespecified subgroups of patients. Importantly, the intervention did not increase the likelihood of a serious adverse event, further supporting the safety and feasibility of integrating influenza vaccination into routine inpatient care.

To our knowledge, this is the first study to demonstrate the effectiveness of influenza vaccination in patients hospitalised with acute heart failure. Although current international guidelines[10–12] are consistent in recommending an annual influenza vaccination in this patient group, coverage remains suboptimal and varies widely across countries. Even in high-income settings, the uptake is often limited to 50–60% of patients with heart failure, but is much lower in many Asian countries.[4] Therefore, our findings have important global implications in providing robust evidence that a pragmatic hospital-based vaccination strategy can reduce death and hospital readmissions in a high-risk population. Administering influenza vaccine before discharge ensures timely coverage and could address structural barriers that limit its uptake in outpatient settings. Given the favourable safety profile and substantial clinical benefit, implementation of in-hospital influenza vaccination should be considered a part of the standard of care for patients who are admitted to hospital for acute heart failure. Policy efforts aimed at improving influenza vaccine delivery in hospitals, particularly in low-uptake regions, could yield meaningful reductions in the global burden of heart failure.

The benefits of influenza vaccination were similarly shown in the influenza vaccination after myocardial infarction trial, where its administration to patients shortly after they had a myocardial infarction significantly reduced the composite outcome of all-cause death, myocardial infarction, or stent thrombosis at 12 months (hazard ratio 0·72 [95% CI 0·52–0·99]; p=0·040).[26] Whether the findings of our study can be generalised to an outpatient setting or other patient groups remains uncertain. Nevertheless, given the consistent benefits observed with influenza vaccination across high-risk cardiac conditions,[7] and the practicality of delivering vaccination during an admission to hospital, it is plausible that this strategy could be extended more broadly to people with established cardiovascular disease. However, further research is warranted to establish the effectiveness beyond patients with heart failure.

It has been postulated that patients with heart failure exhibit an impaired immune response and might only benefit from an influenza vaccination administered at a high dose.[27] Evidence from randomised trials suggests otherwise. For example, a study that compared the use of high-dose trivalent inactivated influenza vaccine with standard-dose quadrivalent inactivated vaccine found no significant difference in the odds of reduction in all-cause

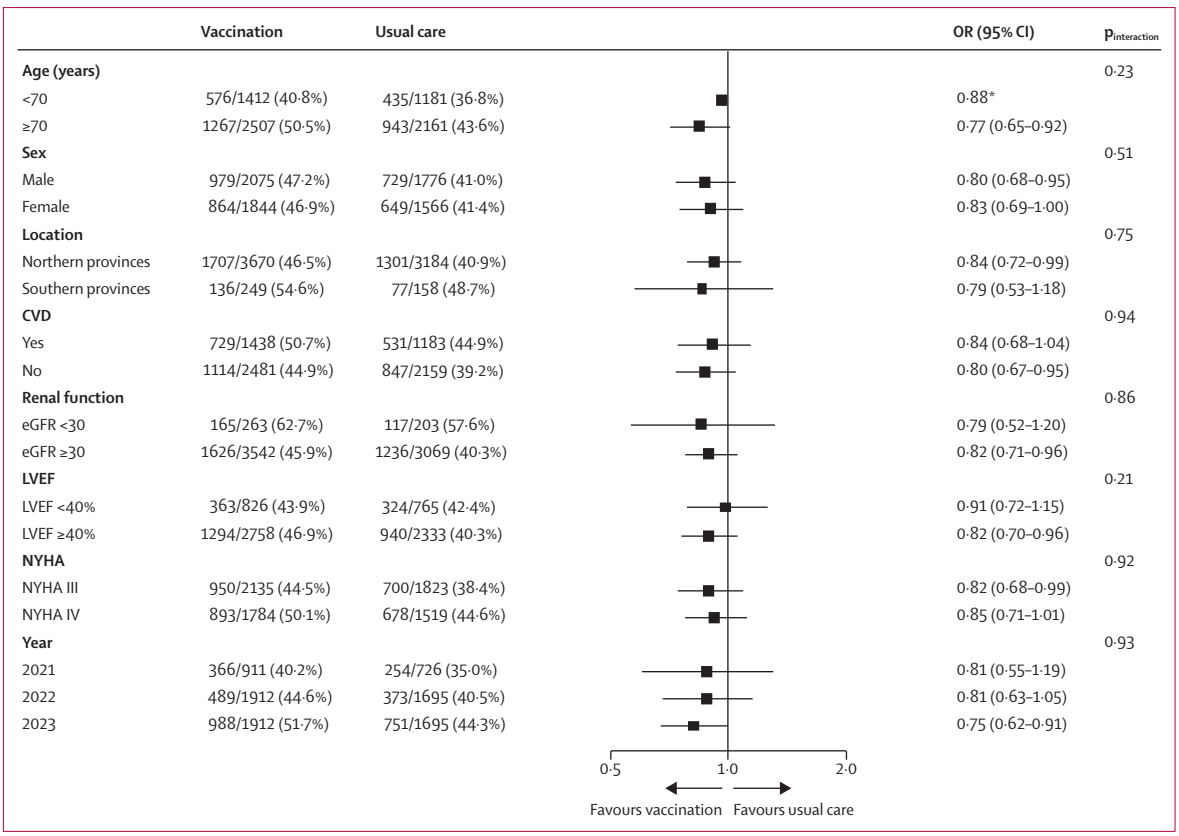

Figure 2: **Forest plot of the primary outcome according to subgroups**
CVD=cardiovascular disease. LVEF=left ventricular ejection fraction. eGFR=estimated glomerular filtration fraction. NYHA=New York Heart Association. OR=odds ratio. *95% CIs unable to be calculated due to convergence issues from small numbers in the model.

mortality or hospitalisation from a cardiopulmonary event in patients with high-risk cardiovascular disease.[28] In our study, standard doses of the quadrivalent and trivalent inactivated influenza vaccines were used in this clinically vulnerable and frail population. The low rate of influenza-like illness reported by participants during follow-up likely reflects low-grade influenza triggering a deterioration in cardiac function, leading to an admission to hospital for acute heart failure rather than pneumonia. This is supported by the high rate of use of antibiotics in participants by clinicians.

It should be noted that the effectiveness of influenza vaccine varies across seasons, being moderate during the study periods at 36% in 2021, 30% in 2022, and 42% in 2023. In much earlier seasons, such as 2010 and 2013, vaccine effectiveness reached as high as 60% and 52%, respectively.[29,30] It is possible that in years of higher vaccine–virus match, the clinical benefit of in-hospital influenza vaccination could be even more pronounced.

The COVID-19 pandemic significantly influenced the conduct of our study. In 2021, influenza activity was notably low in relation to strict isolation policies, and this led to a delay in the study being initiated until there was a clear increase in influenza activity in the community. The reduced influenza activity during this period might have attenuated the observed effect size of the intervention. In 2022, though, as isolation policies were relaxed, there was a substantial rise in COVID-19-related mortality, which in turn could have diluted the benefit of influenza vaccination. In the latter half of 2023 and continuing into 2024, influenza activity rebounded to pre-pandemic levels, with influenza virus positivity in patients presenting with influenza-like illness reaching approximately 50%.[31] These temporal fluctuations in influenza activity and COVID-19-related deaths not only highlight the challenges of assessing the true impact of influenza vaccination in this population, but also underscore the importance of sustained vaccination strategies, particularly as influenza activity fluctuates.

Several other limitations to our study are acknowledged. First, some hospitals that were initially randomised to the intervention group withdrew from the study before activation or patient recruitment. This might have introduced bias and contributed to the observed imbalance in participant numbers between groups. However, the robustness of our findings was supported by balance in the characteristics of patients between the two groups, as well as the consistent results in both intention-to-treat and cluster level analyses, all of which

demonstrated a significant reduction in adverse outcomes associated with influenza vaccination. Second, as the study was not blinded at the patient or care provider level, performance or detection bias might have been introduced. Although the objective nature of the primary outcome (mortality and hospital admission) helps mitigate concerns regarding subjective assessment, the lack of blinding remains an inherent limitation of the trial design. Nonetheless, the follow-up and data collection were centrally managed by staff independent of the study, which supports the validity of our findings. Finally, as the study was conducted primarily in semi-urban regions of China where the participants had relatively low socioeconomic status, there could be concerns over the generalisability of the findings.

In summary, our pragmatic, cluster-randomised, hybrid discovery implementation clinical trial has shown that the use of influenza vaccination before hospital discharge in patients who have recovered from an episode of acute heart failure can significantly reduce the risk of death or hospital readmission over the subsequent year. The benefits are consistent across patients with a broad range of demographic and clinical characteristics without any increase in serious adverse events. These results provide strong support for the safety, feasibility, and effectiveness of integrating influenza vaccination into the routine care of patients with acute heart failure across the world.

Contributors

CSA, CW, CJ, RL, and XD designed the study. CH, ZW, and RH provided quality control oversight. CW generated the randomisation schedule, SS and LB wrote the statistical analysis plan with input from CSA, CJ, and XD, and CW undertook the statistical analysis and reports. CRM, AP, QL, HZ, CM, and JD provided comments on the study design. CSA wrote the first draft of the manuscript. All authors commented on drafts of the manuscript. CSA, CW, RH, and XD verified all the raw study data, and all authors were permitted access to all the data if they wished. All authors accept responsibility for the decision to submit the paper for publication.

Declaration of interests

CSA has received grants from the National Health and Medical Research Council (NHMRC) and Medical Research Futures Fund of Australia, the Medical Research Foundation, and AstraZeneca; he is a consultant to Auzone BioTech, AstraZeneca; a Chair of the data and safety monitoring boards for several investigator-initiated trials for Huashan and Changhai hospitals, Shanghai, China, and Radboud University Medical Center, Nijmegen, Netherlands; is President-elect of the World Stroke Organisation; and the Editor-in-Chief of *Cerebrovascular Diseases*. AP is supported by an NHMRC investigator grant. CRM has received a research grant from Sanofi. XD has received a research grant from Sanofi. All other authors declare no competing interests.

Data sharing

Individual, de-identified participant data used in these analyses might be able to be shared on request from any qualified investigator following approval of a protocol and signed data access agreement via the first corresponding author, Xin Du.

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