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Effectiveness of high-dose versus standard-dose quadrivalent influenza vaccine against recurrent hospitalizations and mortality in relation to influenza circulation

A post-hoc analysis of the DANFLU-1 randomized clinical trial

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Original article

Effectiveness of high-dose versus standard-dose quadrivalent influenza vaccine against recurrent hospitalizations and mortality in relation to influenza circulation: A post-hoc analysis of the DANFLU-1 randomized clinical trial

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ABSTRACT

Objectives: To evaluate the relative effectiveness of high-dose quadrivalent influenza vaccine (QIV-HD) versus standard-dose quadrivalent influenza vaccine (QIV-SD) against recurrent hospitalizations and its potential variation in relation to influenza circulation.
Methods: We did a post-hoc analysis of a pragmatic, open-label, randomized trial of QIV-HD versus QIV-SD performed during the 2021–2022 influenza season among adults aged 65–79 years. Participants were enrolled in October 2021–November, 2021 and followed for outcomes from 14 days post-vaccination until 31 May, 2022. We investigated the following outcomes: Hospitalizations for pneumonia or influenza, respiratory hospitalizations, cardio-respiratory hospitalizations, cardiovascular hospitalizations, all-cause hospitalizations, and all-cause death. Outcomes were analysed as recurrent events. Cumulative numbers of events were assessed weekly. Cumulative relative effectiveness estimates were calculated and descriptively compared with influenza circulation. The trial is registered at Clinicaltrials.gov: NCT05048589.

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Registry
Vaccine

Results: Among 12,477 randomly assigned participants, receiving QIV-HD was associated with lower incidence rates of hospitalizations for pneumonia or influenza (10 vs. 33 events, incidence rate ratio [IRR] 0.30 [95% CI, 0.14–0.64]; p 0.002) and all-cause hospitalizations (647 vs. 742 events, IRR 0.87 [95% CI, 0.76–0.99]; p 0.032) compared with QIV-SD. Trends favouring QIV-HD were consistently observed over time including in the period before active influenza transmission; i.e. while the first week with a ≥10% influenza test positivity rate was calendar week 10, 2022, the first statistically significant reduction in hospitalizations for pneumonia or influenza was already observed by calendar week 3, 2022 (5 vs. 15 events, IRR 0.33 [95% CI, 0.11–0.94]; p 0.037).

Discussion: In a post-hoc analysis, QIV-HD was associated with lower incidence rates of hospitalizations for pneumonia or influenza and all-cause hospitalizations compared with QIV-SD, with trends evident independent of influenza circulation levels. Our exploratory results correspond to a number needed to treat of 65 (95% CI 35–840) persons vaccinated with QIV-HD compared with QIV-SD to prevent one additional all-cause hospitalization per season. Further research is needed to confirm these hypothesis-generating findings. **Niklas Dyrby Johansen, Clin Microbiol Infect 2024;30:1453**

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Introduction

High-dose (HD) influenza vaccine was developed to provide older adults with better protection against influenza and its complications than standard-dose (SD) influenza vaccines. In an individually randomized trial among adults aged 65 years and older, HD trivalent influenza vaccine (TIV-HD) demonstrated superior efficacy against laboratory-confirmed influenza infection and was associated with a lower incidence of serious pneumonia compared with SD trivalent influenza vaccine (TIV-SD) [1,2]. In cluster-randomized trials among nursing home residents, TIV-HD was more effective in reducing the incidence of hospitalization due to influenza-like illness or pneumonia and all-cause hospitalization compared with SD [3,4]. In the recent individually randomized DANFLU-1 trial of HD quadrivalent influenza vaccine (QIV-HD) versus SD quadrivalent influenza vaccine (QIV-SD), similar observations were made as the incidence of hospitalization for influenza or pneumonia and even all-cause mortality was lower in the QIV-HD group compared with the QIV-SD group in a traditional first-event analysis [5]. However, no previous analysis has assessed the relative effectiveness of QIV-HD versus QIV-SD on the total burden of clinical outcomes using a recurrent-events approach.

Traditionally, vaccines have been thought to only protect against specific infections and their directly related complications. However, recent observations challenge this assumption suggesting that influenza vaccination may have nonspecific effects independent of influenza activity and circulating strain [2,6–10]. These effects may reduce susceptibility to nonspecific events before, during, and after the influenza season, hypothesized to be driven by immunomodulatory changes [11–13]. For example, in the previously mentioned trial of TIV-HD versus TIV-SD, similar effectiveness against serious events was observed regardless of vaccine strain match or mismatch [2]. Whether these previous findings translate to the comparison of QIV-HD versus QIV-SD as compared with vaccination versus placebo or no vaccination remains unexplored. Interestingly, in the only individually randomized trial of HD versus SD specifically powered for clinical outcomes, no reduction in all-cause death or cardiopulmonary hospitalizations was found in patients with high-risk cardiovascular (CV) disease [14]. In this post-hoc analysis of the DANFLU-1 trial, which enrolled a general population sample aged 65–79 years, we aimed to investigate the temporal relative effectiveness (rVE) of QIV-HD compared with QIV-SD in relation to influenza circulation and against recurrent specific and nonspecific events.

Methods

Study design and participants

The design [15] and main findings [5] of the DANFLU-1 trial have been published previously. The full trial protocol was published with the main findings. In short, we conducted a pragmatic, registry-based, open-label, active-controlled, randomized trial of QIV-HD versus QIV-HD during the 2021–2022 northern hemisphere influenza season to assess the feasibility of conducting large-scale vaccine trials within the Danish health system with an assessment of rVE as an additional prespecified descriptive objective. The study was approved by the Regional Danish Committee on Biomedical Research Ethics (H-21035316) and the Danish Medicines Agency (EudraCT no. 2021-003170-31). The trial is registered at Clinicaltrials.gov: NCT05048589.

The only trial eligibility criteria were: (1) aged 65–79 years at enrolment, and (2) no allergies toward the study vaccines. Participants were recruited by a private vaccination provider responsible for organizing vaccination sessions under the Danish governmental vaccination programme. A central trial site oversaw the study and was responsible for subsequent registry-based data collection and safety monitoring. All participants provided written informed consent.

Randomization and blinding

Participants were randomly allocated in a 1:1 ratio to QIV-HD or QIV-SD using centralized blocked randomization. Neither participants, investigators, nor study personnel were masked to treatment assignment; however, all subsequent data was passively collected from nationwide registries of routinely obtained health data using prespecified definitions; hence, minimizing the risk of differential ascertainment bias.

Study treatment and procedures

For each influenza strain, QIV-HD (Fluzone High-Dose Quadrivalent)/Efluelda Sanofi) contained 60 mg of hemagglutinin antigen, whereas QIV-SD contained 15 mg. Both vaccine types contained the strains recommended by the World Health Organization for the 2021–2022 northern hemisphere influenza season. All QIV-SD administered in the study were Influvac Tetra (Viatris).

All trial data besides personal identifying information and information on randomization groups and the administered vaccine

were obtained from nationwide health registries by the central trial site. Registry data were linked at the individual level to each participant using a unique social security number. Data were accessed at a secure remote-access server administered by the Danish Health Data Authority. The Danish registries contain data on all contacts, procedures, and filled prescriptions in the Danish universal public health system [16,17].

Baseline conditions, medication use, and outcomes were evaluated using the International Classification of Disease, 10th Edition (ICD-10) and the anatomical therapeutic chemical classification codes. The prespecified definitions have previously been published [15]. We used a 10-year look-back period for baseline conditions. In an additional evaluation of randomization balance, we assessed the number of participants with outcome events during the previous influenza season defined as October 1, 2020, to May 31, 2021, using the same prespecified outcome definitions. Influenza circulation levels were obtained from the official Danish surveillance data [18]. The influenza season was defined as weeks with a ≥10% positivity rate in sentinel specimens. Peak influenza circulation was defined as the week with the highest positivity rate. The follow-up period for clinical outcomes was defined as from 14 days postvaccination until May 31, 2022.

Outcomes

For this post-hoc analysis, we evaluated the following prespecified outcomes in relation to influenza circulation levels: Hospitalizations for (1) pneumonia or influenza; (2) respiratory disease; (3) cardio-respiratory disease; (4) CV disease; (5) all causes; and (6) all-cause mortality. To capture the full burden of these outcomes in the trial population, all outcomes besides all-cause mortality were evaluated as recurrent events. This approach may be advantageous in single-administration vaccine trials because the entire intervention is administered at baseline eliminating the risk of treatment discontinuation after a first event [19].

Statistical analysis

All outcome analyses were intention-to-treat. The cumulative number of events accrued during the follow-up period was assessed on a weekly basis starting at calendar week 45, 2021, and ending at calendar week 21, 2022, enabling weekly cumulative assessment of rVE. For all-cause death, we calculated rVE as 1 minus the relative risk of the outcome with CI calculated using the Clopper-Pearson method [20]. For all other outcomes, which were assessed as recurrent-event outcomes, we calculated incidence rate ratios (IRR) using negative binomial regression models. We included interaction terms to test for effect modification across subgroups for the all-cause hospitalizations outcome. Numbers needed to treat were calculated as the inverse of the absolute difference between the per-season incidence rates in the QIV-HD versus QIV-SD group.

Because the trial was not specifically powered for this post-hoc analysis and no adjustment for multiplicity was applied, the findings should be considered hypothesis-generating. We used a two-sided statistical significance threshold of 0.05. Analyses were performed using SAS Software, version 9.4 (SAS Institute), Stata MP, version 17.0 (StataCorp), and R, version 4.2.2 (R Foundation for Statistical Computing).

Results

The trial included participants from October 1, 2021, to November 20, 2021, and the trial dataset was finalized on June 15, 2022. A total of 12,477 randomized participants were included in the final analysis set, 6245 randomized to QIV-HD and 6232 to QIV-SD. Full baseline characteristics of the trial population have previously been reported, both overall and stratified by randomized assignment [5]. Overall, the mean age was 71.7 years (SD 3.9), 5877 (47.1%) were women, 2540 (20.4%) had established CV disease, 417 (3.3%) had chronic obstructive pulmonary disease, 1363 (10.9%) cancer, 1162 (9.3%) diabetes, and 6469 (51.9%) hypertension (Table 1). A total of 21 (0.2%) participants had been hospitalized for pneumonia or influenza during the previous season, whereas 992 (8.0%) had been hospitalized for any cause. Baseline characteristics and previous event rates were balanced across randomized groups.

During the 2021 or 2022 influenza season in Denmark, test positivity rates increased sharply from week 6, 2022. The first week with a ≥10% positivity rate during the 2021/2022 Danish influenza season was week 10, 2022, with the influenza season lasting until week 15. The highest positivity rate (27%) was observed in week 12, 2022.

In the recurrent-events analysis, QIV-HD was associated with a lower incidence rate of hospitalizations for pneumonia or influenza (10 vs. 33 events, IRR 0.30 [95% CI, 0.14–0.64]; p = 0.002) and all-cause hospitalizations (647 vs. 742 events, IRR 0.87 [95% CI, 0.76–0.99]; p = 0.032) (Fig. 1) compared with QIV-SD. The remaining outcomes trended in favour of QIV-HD but did not reach nominal statistical significance. A lower incidence of all-cause death in the QIV-HD group has previously been reported [5].

Relative effectiveness point estimates against hospitalizations for pneumonia or influenza, all-cause hospitalizations, and all-cause death consistently favoured QIV-HD including in the period before the influenza season (Fig. 2). For example, although the first week with a ≥10% positivity rate was calendar week 10, 2022, the first statistically significant reduction in hospitalizations for pneumonia or influenza was already observed by calendar week 3, 2022 (5 vs. 15 events, IRR 0.33 [95% CI, 0.11–0.94]; p = 0.037). Initial trends favouring QIV-HD were observed for the remaining outcomes but attenuated during the follow-up period.

In our exploratory subgroup analysis for the all-cause hospitalizations outcome, increased relative effectiveness of QIV-HD versus QIV-SD was suggested among those without chronic CV disease compared with those with (no chronic CV disease: 427 vs. 531 events, IRR 0.79 [95% CI, 0.67–0.92]; chronic CV disease: 220 versus 211 events, IRR 1.11 [95% CI, 0.88–1.39]; $p_{interaction} = 0.026$) (Fig. 3). Relative effectiveness was consistent across all other examined subgroups.

Discussion

In this post-hoc analysis of a large-scale, pragmatic, randomized trial of almost 12,500 participants, besides being associated with a reduction in the incidence rate of hospitalizations for pneumonia or influenza, QIV-HD was also associated with reductions in the incidence rates of the nonspecific events of all-cause hospitalizations and, as previously reported [5], all-cause mortality compared with QIV-SD. Our exploratory findings correspond to numbers needed to treat with QIV-HD compared with QIV-SD of 65 (95% CI, 35–840) to prevent one additional all-cause hospitalization per season and 271 (95% CI, 220–525) to prevent one additional hospitalization for pneumonia or influenza. The observed trends were consistent throughout the follow-up period and were evident both before, during, and after the influenza season.

Compared with the trial's primary analysis [5], which used a traditional first-event approach, the present recurrent-events analysis yielded an additional nominally significant reduction in all-cause hospitalizations whereas the previously reported reduction in first hospitalization for pneumonia or influenza remained significant in this analysis. Effectiveness estimates for all significantly reduced outcomes (hospitalizations for pneumonia or influenza, all-cause hospitalizations, and all-cause death)

Table 1
Baseline characteristics

Characteristic	QIV-HD n = 6245	QIV-SD n = 6232
Demographics		
Age (y), mean ± SD	71.8 ± 3.9	71.7 ± 3.9
Female sex, n (%)	2956 (47.3)	2921 (46.9)
Comorbidity		
Diabetes, n (%)	574 (9.2)	588 (9.4)
Chronic lung disease, n (%)	435 (7.0)	415 (6.7)
Chronic obstructive pulmonary disease, n (%)	227 (3.6)	190 (3.0)
Cancer, n (%)	695 (11.1)	668 (10.7)
Chronic cardiovascular disease, n (%)	1227 (19.7)	1313 (21.1)
Hypertension, n (%)	3254 (52.1)	3215 (51.6)
Immunodeficiency, n (%)	244 (3.9)	239 (3.8)
Event in previous influenza season		
Hospitalization for pneumonia or influenza, n (%)	8 (0.1)	13 (0.2)
Respiratory hospitalization, n (%)	14 (0.2)	22 (0.4)
Cardio-respiratory hospitalization, n (%)	101 (1.6)	97 (1.6)
Cardiovascular hospitalization, n (%)	89 (1.4)	77 (1.2)
All-cause hospitalization, n (%)	508 (8.1)	484 (7.8)

We were unable to obtain registry data for two participants in each group; only age and sex were available for these. These participants are not counted towards the denominator for other baseline variables. The previous influenza season was defined as October 1, 2020, to May 31, 2021. QIV-HD, high-dose quadrivalent influenza vaccine; QIV-SD, standard-dose quadrivalent influenza vaccine; SD, standard deviation.

consistently favoured QIV-HD in our temporal analysis. The observed effectiveness even before active influenza transmission during the study season may point to beneficial immunomodulatory effects of vaccination independent of the prevention of overt influenza infection. Proposed cellular mechanisms behind nonspecific effects and in particular those involving atherosclerosis and plaque stability include decreasing plasma levels of interferon gamma, interleukin 2, and tumour necrosis factor-α and upregulation of interleukins 4 and 6 [11,12]; however, further research is required to explore the mechanisms underlying the full spectrum of potential nonspecific effects.

Although our results should surely be considered hypothesis-generating, the observed effectiveness against less specific outcomes with trends evident outside of influenza circulation support previous literature on nonspecific effects of influenza vaccination. Several previous reports have indicated effectiveness of influenza vaccination in seasons with substantial vaccine mismatch. Over two influenza seasons, DiazGranados et al. [2] found similar effectiveness estimates with HD compared with SD against serious events despite a mismatch during the second season. A systematic review and meta-analysis of 94,821 participants across 34 randomized controlled trials of influenza vaccination versus placebo additionally found evidence of cross-protection against nonmatching circulating influenza strains [21]. Indeed, the 2021–2022 Danish influenza season, during which DANFLU-1 was performed, was characterized by a mismatch against the circulating influenza A (H3N2) strain, which belonged mainly to clade 3C.2a1b.2a.2 [22]. Despite this, we still observed additional rVE of QIV-HD compared with QIV-SD against several clinical outcomes, supporting the cross-protection of QIV-HD against nonmatching circulating strains and the concept of nonspecific effects. In particular, we observed almost 100 fewer hospitalizations from any cause in the QIV-HD group compared with the QIV-SD group despite the fact that we only observed 23 fewer events for our most specific outcome of hospitalizations for pneumonia or influenza.

Recent randomized trials investigating the effects of influenza vaccination versus placebo on CV events have generated new evidence to improve the understanding of the relationship between vaccine effectiveness and influenza circulation levels. In the Influenza Vaccination After Myocardial Infarction (IAMI) trial performed over four influenza seasons, the investigators found an overall reduction in the primary composite endpoint of all-cause death, myocardial infarction, or stent thrombosis with influenza vaccine versus placebo in patients with recent myocardial infarction or other high-risk coronary disease; however, effectiveness did seem to attenuate during the two seasons with potential vaccine mismatch [8]. In addition, the Influenza Vaccine to Prevent Adverse Vascular Events (IVVE) trial randomized patients with heart failure to either influenza vaccine or placebo and found reductions in CV events only during periods of peak influenza circulation, but reductions in all-cause hospitalizations and pneumonia were consistent during the entire observation period [23]. Collectively, these findings match those in our study, where we also did not observe reductions in CV events during a season with vaccine mismatch but observed reductions in hospitalizations for pneumonia or influenza and all-cause hospitalizations; however, comparisons should be made cautiously because our trial compared two influenza vaccines and not vaccine versus placebo.

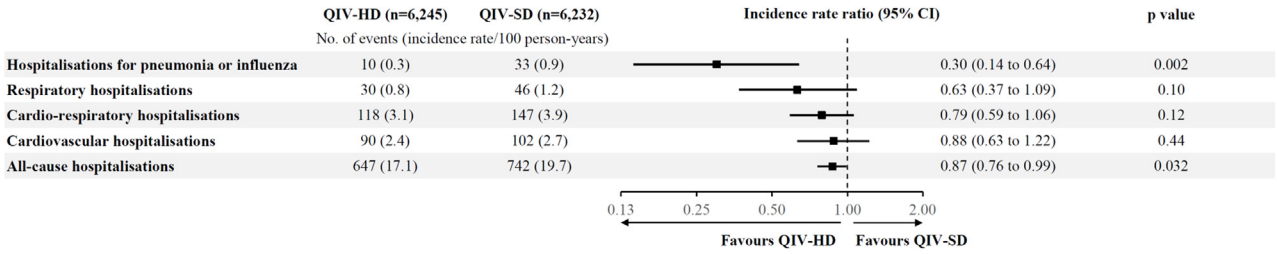

Fig. 1. Relative effectiveness of QIV-HD versus QIV-SD against recurrent outcomes. Incidence rate ratios and p values were derived from negative binomial regression models. QIV-HD, high-dose quadrivalent influenza vaccine. QIV-SD, standard-dose quadrivalent influenza vaccine.

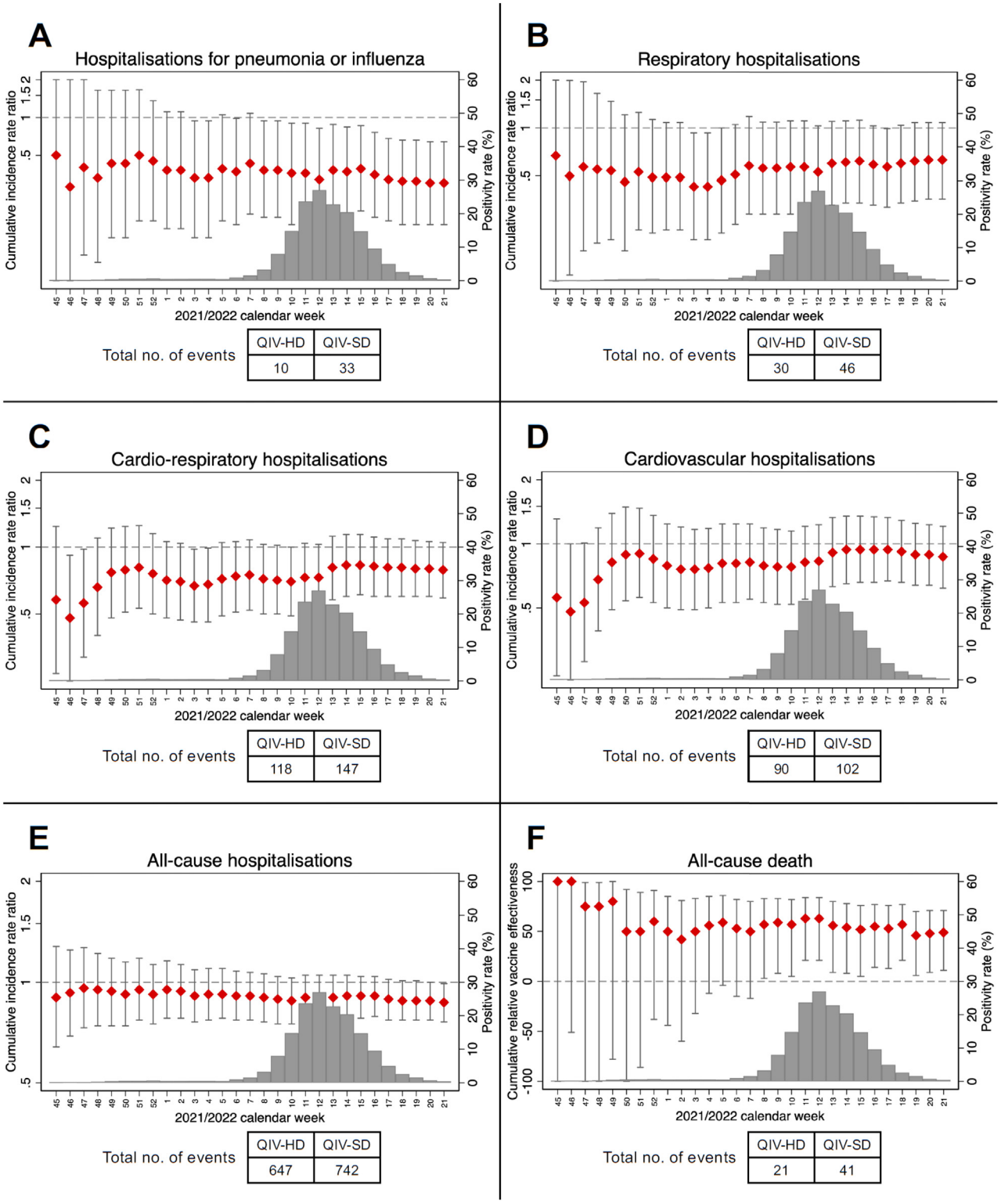

Fig. 2. Temporal cumulative relative effectiveness of QIV-HD versus QIV-SD against recurrent outcomes in relation to influenza circulation. Effectiveness estimates were calculated weekly from the total number of events accumulated up until the specified calendar week. Error bars represent 95% CIs. Incidence rate ratios and CIs were calculated using negative binomial regression models for the outcomes of hospitalizations for pneumonia or influenza (panel A), respiratory hospitalizations (panel B), cardio-respiratory hospitalizations (panel C), cardiovascular hospitalizations (panel D), and all-cause hospitalizations (panel E). Incidence rate ratios below 1 favour QIV-HD. The CIs for incidence rate ratios were constrained to [0.05–2.0] to improve readability of the figure. For all-cause death (panel F), relative vaccine effectiveness was calculated as 1 minus the relative risk with CIs calculated using the Clopper-Pearson method. Relative vaccine effectiveness estimates of above 0 against all-cause death favour QIV-HD. Relative vaccine effectiveness estimates and their CIs were constrained to [−100–100] to improve readability of the figure. No adjustment for multiplicity has been made for the CIs. The histogram shows weekly influenza test positivity rate in sentinel specimens. QIV-HD, high-dose quadrivalent influenza vaccine. QIV-SD, standard-dose quadrivalent influenza vaccine.

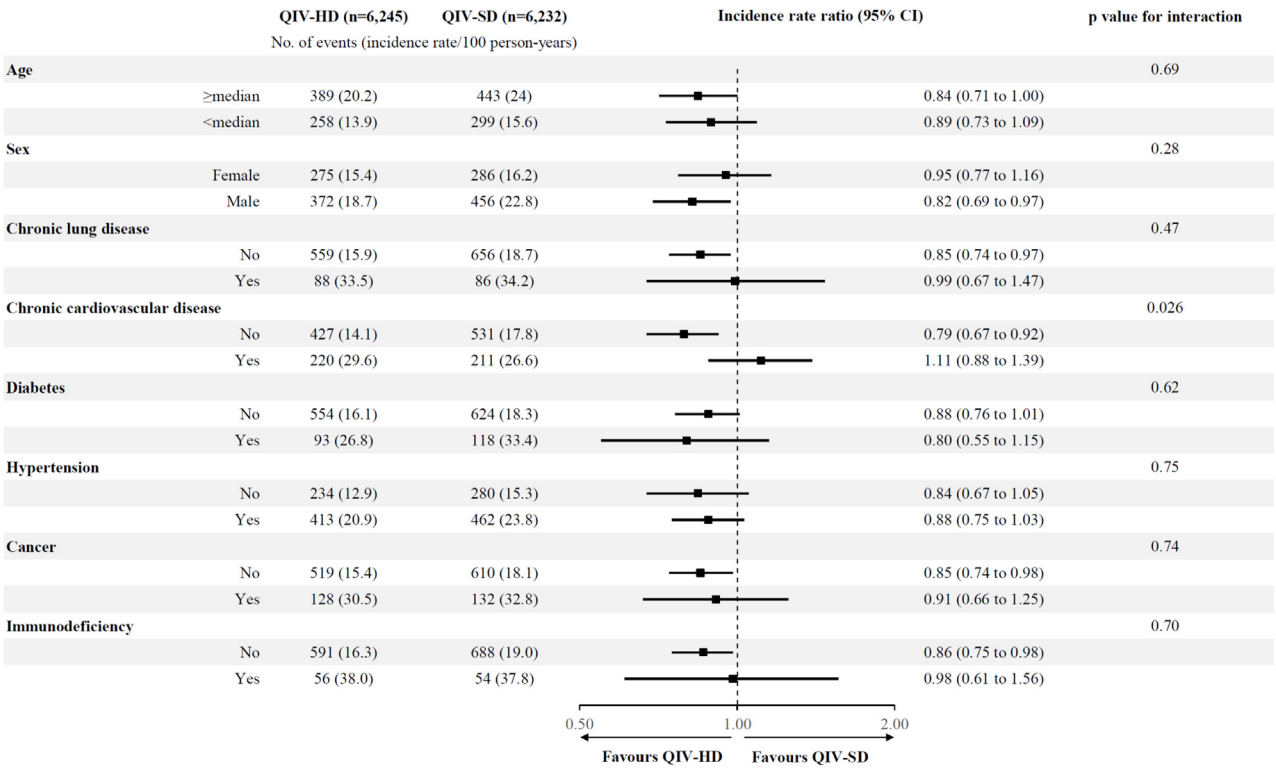

Fig. 3. Relative effectiveness of QIV-HD versus QIV-SD against all-cause hospitalizations across subgroups. Incidence rate ratios and p values for interaction were derived from negative binomial regression models. Median age was 71.5 years. QIV-HD, high-dose quadrivalent influenza vaccine. QIV-SD, standard-dose quadrivalent influenza vaccine.

The only individually randomized trial of HD vs. SD specifically powered for clinical outcomes was the INVESTED trial, which found no reduction in all-cause death or cardiopulmonary hospitalizations in patients with high-risk CV disease [14]. This finding is comparable with the effect modification observed in our exploratory subgroup analysis where attenuated effectiveness of QIV-HD compared with QIV-SD against all-cause hospitalizations was suggested in patients with established CV disease indicating that the additional effectiveness of HD compared with SD may not be sufficient to modify disease trajectories for patients with CV disease, whereas the opposite has been observed for vaccine versus placebo. However, we cannot exclude that our findings occurred because of play of chance.

Interesting methodological insights were obtained from this post-hoc analysis. Using a recurrent-events approach increasing the number of events analysed provided both a more complete assessment of disease burden and additional statistical power. First-event approaches have traditionally been used in vaccine trials; however, vaccine trials have several characteristics which favour the recurrent-events approach: the risk of treatment discontinuation after the first event is nonexistent by virtue of the nature of single shot vaccines, and high degrees of heterogeneity in patient-level risk are often present where outcome events are contributed by only a small number of participants [19]. The evaluation of previous event rates using the same prespecified registry-based definitions as for prospective outcome events during follow-up highlights the diverse advantages in using administrative registries as data sources in randomized trials and provides another method to assess randomization balance. Previous event rate adjustment is occasionally used to reduce confounding in observational analyses [24,25].

As with all post-hoc analyses of randomized trials, this study has limitations. The pretrial sample size calculation did not consider this analysis. No adjustments for multiplicity were applied and our results may indeed be chance findings. Using routinely collected registry data as data source for clinical outcomes may introduce imprecision but this would not be expected to differ across randomized groups. Based on the data available in the registries, we were unable to discern with certainty whether recurrent events were new, clinically separate events or whether they represented repeated events during a single disease process; however, it also seems relevant for an intervention to be able to lower the risk of repeated hospitalizations during the same disease process. In addition, due to the pragmatic nature of the trial, no systematic influenza testing was performed. The trial was performed during only one influenza season with substantial vaccine strain mismatch, and we were therefore unable to compare effectiveness estimates across seasons with different degrees of matching.

In conclusion, in this post-hoc analysis of a large-scale, pragmatic, randomized trial of QIV-HD versus QIV-SD, we found that QIV-HD was associated with reductions in the incidence rates of hospitalizations for pneumonia or influenza and all-cause hospitalizations with consistent trends observed both before, during, and after the influenza season. Further research is required to confirm these findings.

Author contributions

NDJ, DM, KGS, JN, SS, MD, MML, RCH, CSL, AMRJ, NEL, BLC, SDS, MJL, GHG, LK, JUSJ, PS, LSV, PV-B, TGK, and TB-S made substantial contributions to the conceptualisation and design of the study. TB-S obtained funding. NDJ, DM, CSL, and TB-S were responsible for data collection. NDJ, DM, and TB-S had unrestricted access to, verified, and analysed the raw data. NDJ, KGS, and TB-S wrote the first draft of this manuscript. All authors reviewed the manuscript draft and approved the final submitted manuscript. NDJ, DM, and TB-S are

guarantors of the study. The corresponding author (TB-S) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Transparency declaration

KGS has served on an advisory board for Sanofi. JN was previously employed by Sanofi and may own shares and/or stock options in the company. SS, MD, MML, and RCH are full-time employees of Sanofi and may own shares and/or stock options in the company. CSL is chief physician at Danske Lægers Vaccinations Service, part of European LifeCare Group, and has received speaker fees and served on advisory boards for GSK, MSD, Pfizer, Takeda, and Valneva. BLC has received consulting fees from Amgen, Cardurion, Corvia, Myokardia, and Novartis. SDS has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi, Theracos, US2.AI and consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Puretech Health. LK has received speaker fees from Novo Nordisk, Novartis, AstraZeneca, Boehringer Ingelheim, and Bayer. TB-S has served as steering committee member of the Amgen financed GALACTIC-HF trial, the Boehringer Ingelheim financed SHARP3 trial, and the Boston Scientific financed LUX-Dx TRENDS trial, served on advisory boards for Sanofi, GSK, and Amgen, received speaker honoraria from Bayer, GSK, Novartis, Novo Nordisk, and Sanofi, and received research grants from GE Healthcare, AstraZeneca, Novo Nordisk, and Sanofi. All other authors declare no competing interests. The study was funded by Sanofi, who provided QIV-HD and a financial contribution. The protocol was co-developed with the funder. The funder had no responsibilities during trial conduct or data collection and did not have access to raw data but was involved in the interpretation of the results and manuscript writing. The authors made the final decision to submit. The trial sponsor was Copenhagen University Hospital—Herlev and Gentofte.

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