Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines

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A B S T R A C T

Background: A recent study showed that a high-dose inactivated influenza vaccine (IIV-HD) was 24.2% more efficacious than a standard-dose inactivated influenza vaccine (IIV-SD) in preventing laboratory-confirmed symptomatic influenza in adults ≥65 years. Here we evaluate the effectiveness of IIV-HD compared to IIV-SD in preventing serious illnesses considered potential sequelae or complications of influenza infection.

Methods: The original study was a double-blind, randomized, active-controlled, multicenter trial. Participants were adults ≥65 years randomized to receive IIV-HD or IIV-SD, and followed for 6–8 months post-vaccination for the occurrence of influenza and serious adverse events (SAEs). SAEs were events: leading to death or hospitalization (or its prolongation); considered life-threatening or medically important; or resulting in disability. For the present analysis, reported SAEs were classified as possibly related to influenza by three blinded physicians and rates per 1000 participant-seasons were calculated. Relative vaccine effectiveness (rVE) was estimated as (1 – Rate Ratio) × 100.

Results: 31,989 participants were enrolled, with 15,991 and 15,998 randomized to receive IIV-HD and IIV-SD, respectively. IIV-HD was significantly more effective than IIV-SD in preventing SAEs possibly related to influenza overall (rVE, 17.7%; 95% confidence interval [CI], 6.6–27.4%) and serious pneumonia (rVE, 39.8%; 95% CI, 19.3–55.1%). Borderline significance was observed for the efficacy of IIV-HD relative to IIV-SD for the prevention of all-cause hospitalizations (rVE, 6.9%; 95% CI, 0.5–12.8%).

Conclusions: Compared to IIV-SD, IIV-HD reduced the risk of SAEs possibly related to influenza. The observed relative effectiveness against serious pneumonia is particularly noteworthy considering the burden of influenza and pneumonia in older adults.

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1. Introduction

Adults 65 years of age and older are particularly vulnerable to complications from influenza infection, accounting for most seasonal influenza-related hospitalizations and deaths [1,2]. The high burden of influenza in this population persists despite documented improvements in vaccination rates [3]. Accordingly, the availability of improved influenza vaccines for older adults had been considered an unmet medical need [4,5]. A recently completed double-blind, randomized, controlled trial (NCT01427309) demonstrated that a high-dose inactivated influenza vaccine (IIV-HD) was 24.2% (95% confidence interval [CI], 9.7%–36.5%) more efficacious than a standard-dose inactivated influenza vaccine (IIV-SD) in preventing laboratory-confirmed symptomatic influenza in adults 65 years of age and older [6].

In addition to the observed improvement in efficacy, 119 fewer study participants developed at least one serious adverse event (SAE) of any cause in the IIV-HD group compared to the IIV-SD group. The risk of developing at least one SAE during the study was
significantly lower among IIV-HD recipients than IIV-SD recipients (relative risk 0.92, 95% CI, 0.85–0.99), suggesting that IIV-HD may improve protection against the occurrence of influenza-related serious events [6].

According to results from the last National Hospital Discharge Survey conducted by the National Center for Health Statistics in the United States, the top leading causes of hospitalization in adults 65 years or older are heart disease (including ischemic heart disease and congestive heart failure), cerebrovascular disease, pneumonia, and malignant neoplasms [7]. Excluding malignancy, influenza may play an important role in the occurrence of these hospitalization-related events, either by triggering exacerbations of pre-existing conditions or by direct involvement of affected organs or tissues [8–13]. It is therefore of particular interest for individual and public health to evaluate the impact of influenza vaccines on the occurrence of serious cardio-respiratory events traditionally considered potential complications or sequelae of influenza. To this end, the present supplementary analysis of the original efficacy trial evaluated the effectiveness of IIV-HD compared to IIV-SD in preventing all-cause hospitalizations and serious cardio-respiratory events possibly related to influenza infection.

2. Methods

2.1. Overall study design

Details of the original study design are presented elsewhere [6]. Briefly, the study was a double-blind, randomized, active-controlled, multicenter clinical trial, conducted during the 2011–2012 (Year 1) and 2012–2013 (Year 2) influenza seasons in 126 research centers in the United States and Canada. Adults 65 years of age and older were randomly assigned in a 1:1 ratio to receive IIV-HD (Fluzone® High-Dose [SanofiPasteur, Swiftwater, PA, USA], containing 60 μg of hemagglutinin per vaccine strain) or IIV-SD (Fluzone [Sanofi Pasteur, Swiftwater, PA, USA], containing 15 μg of hemagglutinin per strain). Each season, participants were followed for 6–8 months post-vaccination for the occurrence of influenza and SAEs. SAEs were defined as events: leading to death or hospitalization (or its prolongation); considered as life-threatening or medically important; or resulting in disability [14]. Based on available medical information, study investigators reported the diagnoses associated with all SAEs.

2.2. Adjudication of SAEs as “serious events possibly related to influenza”

Two physicians blinded to treatment group independently reviewed all SAE diagnostic categories that were reported during the study; these diagnostic categories had been coded as “preferred terms” using the Medical Dictionary for Regulatory Activities [15] versions 14.0 (for Year 1) and 15.0 (for Year 2) before study unblinding. There were a total of 1347 SAE preferred terms reviewed. Cardio-respiratory SAE categories considered as possibly related to influenza infection were selected by each reviewer, based solely on the medical nature of the reported preferred term for the diagnosis (for example, SAEs with a diagnosis preferred term of “pneumonia” were selected as possibly related to influenza, whereas SAEs with a diagnosis preferred term of “hip fracture” were excluded). The physician-reviewers then compared their respective selections and exclusions to attempt consensus, which was attained for 1335 (99.1%) SAE preferred terms. The 12 remaining discrepant SAE preferred term categorizations were arbitrated by a third blinded physician-reviewer. Final adjudication of SAE categories as “possibly related to influenza” was done before study unblinding, and the selected categories were pre-specified in a supplementary analysis plan. Adjudication was done without regard to influenza confirmation in the study. Events were grouped in seven larger categories: pneumonia events, asthma/COPD (chronic obstructive pulmonary disease)/bronchial events, influenza events (serious laboratory-confirmed influenza diagnosed outside study procedures by a participant’s health-care provider), other respiratory events, coronary artery events, congestive heart failure events, and cerebrovascular events. The selected preferred terms and their classification are available in Supplementary appendix. All preferred terms for the SAEs reported in the study (selected and not selected) are publicly available at clinicaltrials.gov [16].

2.3. Statistical methods

Rates of all-cause hospitalizations and selected serious cardio-respiratory events were calculated for IIV-HD and IIV-SD groups as the number of hospitalizations or events per 1000 participants-seasons. Rate ratios (RRs) and corresponding 2-sided 95% CIs were estimated using the method given by Blackwelder [17]. Relative vaccine effectiveness (rVE) was calculated as (1 – RR) × 100.

Analyses were done in the Full Analysis Set (FAS) according to the vaccine assigned at randomization (intent-to-treat [ITT] analysis). The FAS comprised all participants who received study vaccine.

Estimates were obtained for each study season and for both seasons combined. Statistical significance was defined as a 2-sided 95% CI excluding the null value (1 for RR and 0 for rVE).

3. Results

A total of 31,989 participants were enrolled in the study, of whom 15,991 were randomized to IIV-HD (15,990 included in the ITT analysis) and 15,998 were randomized to IIV-SD (15,993 included in the ITT analysis). Only 24 participants did not receive the vaccine as randomized (0.08%). Enrollees included 14,500 participants in Year 1 and 17,489 in Year 2.

Baseline clinical and demographic characteristics were well balanced between groups [6]. In both groups, the mean age was 73.3 years, 56–57% of participants were female, approximately 67% had at least one high-risk pre-specified comorbid illness, and approximately 74% had received influenza vaccination the previous season. The frequency of historical pneumococcal vaccination prior to study start was essentially the same for IIV-HD (65.17%) and IIV-SD (64.81%) recipients. Pneumococcal vaccination during the study was rare, and of approximate equal frequency between groups (3.57% for IIV-HD, 3.53% for IIV-SD). Study mean participant follow-up time was 226 days for both groups.

There were a total of 3173 hospitalization events (all-cause), 1590 in Year 1 and 1583 in Year 2. The number and rate of occurrence of all SAEs reported in the study (selected and not selected for this supplementary analysis) by treatment group and study year are available at clinicaltrials.gov [16].

A total of 948 serious cardio-respiratory events adjudicated as possibly related to influenza were reported in the study, 440 in Year 1 and 508 in Year 2. The vast majority of these cardio-respiratory events resulted in hospitalization (94.8%) and a smaller proportion were fatal (6.9%).

Rates of all-cause hospitalizations and serious cardio-respiratory events possibly related to influenza (overall and by category) for IIV-HD and IIV-SD are presented in Table 1. Corresponding RRs and CIs are depicted graphically in Fig. 1.

Rates of all-cause hospitalization did not differ between groups in Year 1, whereas they were significantly lower for the IIV-HD group in Year 2; for both study years combined, the rate of all-cause hospitalization was 6.9% (95% CI, 0.5–12.8%) lower in the IIV-HD group.
Table 1
Rates of all-cause hospitalization and serious cardio-respiratory events possibly related to influenza (intent-to-treat analysis).

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IIV-HD</td>
<td>IIV-SD (N=7244),</td>
<td>IIV-HD</td>
</tr>
<tr>
<td></td>
<td>(N=7253), n (rate)</td>
<td>n (rate)</td>
<td>(N=8737), n (rate)</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>797 (109.89)</td>
<td>793 (109.47)</td>
<td>733 (83.90)</td>
</tr>
<tr>
<td>Serious cardio-respiratory events</td>
<td>204 (28.13)</td>
<td>236 (32.58)</td>
<td>224 (25.64)</td>
</tr>
<tr>
<td>Asthma/COPD/bronchial events</td>
<td>29 (4.00)</td>
<td>54 (7.45)</td>
<td>42 (4.81)</td>
</tr>
<tr>
<td>Influenza events*</td>
<td>40 (5.51)</td>
<td>21 (2.90)</td>
<td>34 (3.89)</td>
</tr>
<tr>
<td>Coronary artery events</td>
<td>55 (7.58)</td>
<td>70 (9.66)</td>
<td>66 (7.55)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>24 (3.31)</td>
<td>28 (3.87)</td>
<td>33 (3.78)</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>43 (5.93)</td>
<td>39 (5.38)</td>
<td>29 (3.32)</td>
</tr>
<tr>
<td>Other respiratory events</td>
<td>13 (1.79)</td>
<td>24 (3.31)</td>
<td>18 (2.06)</td>
</tr>
</tbody>
</table>

Abbreviations: IIV-HD, high-dose inactivated influenza vaccine; IIV-SD, standard-dose inactivated influenza vaccine; COPD, chronic obstructive pulmonary disease
* n = number of events; rate = events per 1000 participant-seasons.
* Corresponding to serious laboratory-confirmed influenza diagnosed outside study procedures by a participant’s health-care provider.

<table>
<thead>
<tr>
<th></th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>YEAR 1</strong></td>
<td></td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>1.00 (0.91; 1.10)</td>
</tr>
<tr>
<td>Serious cardio-respiratory events</td>
<td>0.86 (0.72; 1.04)</td>
</tr>
<tr>
<td>Pneumonia events</td>
<td>0.54 (0.34; 0.84)</td>
</tr>
<tr>
<td>Asthma/COPD/bronchial events</td>
<td>1.90 (1.12; 3.22)</td>
</tr>
<tr>
<td>Influenza events</td>
<td>NA</td>
</tr>
<tr>
<td>Coronary artery events</td>
<td>0.78 (0.55; 1.12)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.86 (0.50; 1.48)</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>1.10 (0.71; 1.70)</td>
</tr>
<tr>
<td>Other respiratory events</td>
<td>0.54 (0.28; 1.06)</td>
</tr>
<tr>
<td><strong>YEAR 2</strong></td>
<td></td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>0.86 (0.79; 0.95)</td>
</tr>
<tr>
<td>Serious cardio-respiratory events</td>
<td>0.79 (0.66; 0.94)</td>
</tr>
<tr>
<td>Pneumonia events</td>
<td>0.66 (0.45; 0.97)</td>
</tr>
<tr>
<td>Asthma/COPD/bronchial events</td>
<td>0.63 (0.41; 0.97)</td>
</tr>
<tr>
<td>Influenza events</td>
<td>0.50 (0.13; 2.00)</td>
</tr>
<tr>
<td>Coronary artery events</td>
<td>1.22 (0.86; 1.75)</td>
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<tr>
<td>Congestive heart failure</td>
<td>0.70 (0.45; 1.10)</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>0.76 (0.47; 1.24)</td>
</tr>
<tr>
<td>Other respiratory events</td>
<td>0.78 (0.42; 1.45)</td>
</tr>
<tr>
<td><strong>COMBINED (YEAR 1 AND YEAR 2)</strong></td>
<td></td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>0.93 (0.87; 1.00)</td>
</tr>
<tr>
<td>Serious cardio-respiratory events</td>
<td>0.82 (0.73; 0.93)</td>
</tr>
<tr>
<td>Pneumonia events</td>
<td>0.60 (0.45; 0.81)</td>
</tr>
<tr>
<td>Asthma/COPD/bronchial events</td>
<td>0.99 (0.72; 1.36)</td>
</tr>
<tr>
<td>Influenza events</td>
<td>0.67 (0.19; 2.36)</td>
</tr>
<tr>
<td>Coronary artery events</td>
<td>0.98 (0.76; 1.23)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.76 (0.54; 1.07)</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>0.94 (0.68; 1.29)</td>
</tr>
<tr>
<td>Other respiratory events</td>
<td>0.66 (0.42; 1.04)</td>
</tr>
</tbody>
</table>

Fig. 1. Rate ratios (IIV-HD/IIV-SD) for all-cause hospitalization and serious cardio-respiratory events possibly related to influenza (intent-to-treat analysis). Each horizontal line represents the 95% confidence interval of the rate ratio for each comparison, with the center being the corresponding point estimate. The vertical line represents the null value of 1. Horizontal lines that do not intersect with the vertical line are statistically significant. Point estimates to the left of vertical line favor IIV-HD, and those to the right favor IIV-SD. “Influenza Events” refer to serious laboratory-confirmed influenza diagnosed outside study procedures by a participant’s health-care provider. Abbreviations: IIV-HD, high-dose inactivated influenza vaccine; IIV-SD, standard-dose inactivated influenza vaccine; COPD: chronic obstructive pulmonary disease.
For the 2 study years combined, the aggregate rates of serious cardio-respiratory events possibly related to influenza were lower in the IIV-HD group for any event overall and for each of the seven pre-specified categories. For each of the 2 study years, consistently lower rates in the IIV-HD group were observed for any serious cardio-respiratory event possibly related to influenza overall, serious pneumonia, serious congestive heart failure, and other serious respiratory events (i.e., selected respiratory diagnoses other than pneumonia, asthma/COPD/bronchial events, or influenza; see Supplementary appendix for details).

Significantly lower rates in the IIV-HD group were observed for: any serious cardio-respiratory event possibly related to influenza overall in Year 2 and both years combined; serious pneumonia in each study year and the 2 years combined; and serious asthma/COPD/bronchial events in Year 2. A significantly lower rate for IIV-SD compared to IIV-HD was observed only for the occurrence of serious asthma/COPD/bronchial events in Year 1.

Point estimates and 95% CIs for the effectiveness of IIV-HD compared to IIV-SD for the prevention of all-cause hospitalization and serious cardio-respiratory events possibly related to influenza are presented in Table 2. The largest reduction in disease burden was observed for serious pneumonia, which was reported 39.8% less frequently among IIV-HD recipients than among IIV-SD recipients overall (both years combined; 46.4% in Year 1 and 34.3% in Year 2. All three measures of rate reduction for serious pneumonia were statistically significant (p values 0.001, 0.006, and 0.040 for both years combined, Year 1 and Year 2, respectively).

4. Discussion

Influenza is associated with high morbidity and mortality in older adults [4]. Although vaccination currently represents the most effective intervention in preventing influenza and its complications [2,18], antibody responses and protection elicited by standard-dose influenza vaccines are lower in persons ≥65 years of age and older compared to younger adults [19–21]. Strategies to improve immune responses to influenza vaccines in this population may have a favorable impact on morbidity and mortality [22]. Several approaches have been developed to improve immune responses to influenza in older adults, including the use of higher doses of antigen, adjuvants [23–26], and alternative delivery systems [27]. One of such approaches is IIV-HD, which contains four times the amount of hemagglutinin antigen per strain compared to standard-dose intramuscular influenza vaccines.

Because of the recognized association of influenza with serious illness in older adults, we explored the impact of IIV-HD beyond its demonstrated superior efficacy over IIV-SD in preventing laboratory-confirmed influenza illness, by evaluating IIV-HD effectiveness in preventing hospitalization and serious illness possibly related to influenza. To achieve this objective, we performed a supplementary analysis of data collected during the original large-scale efficacy study.

We observed that IIV-HD was significantly more effective than IIV-SD in preventing serious cardio-respiratory events possibly related to influenza, most of which corresponded to hospitalizations, with an overall relative vaccine effectiveness of 17.7%. Two recently published studies have evaluated the effect of IIV-HD compared to IIV-SD on similar outcomes: consistent with our findings, a large retrospective cohort study [28] reported an overall relative effectiveness estimate of 20.6% against influenza hospital admissions or emergency department visits, with similar estimates observed for individuals 65–74 years, 75–84 years, and ≥85 years; in contrast, another retrospective cohort study found evidence of improved effectiveness of IIV-HD against influenza and pneumonia hospitalizations only in individuals ≥85 years of age [29]. Compared to previous reports, our results have the major strength of resulting from a large double-blind, randomized, controlled trial, which minimizes the likelihood of bias, including the so-called healthy vaccinee bias [30,31]. Moreover, we observed a borderline significant overall effectiveness of IIV-HD relative to IIV-SD for the prevention of all-cause hospitalization.

As the original study was only powered to evaluate the primary endpoint of laboratory-confirmed influenza associated with a protocol-defined influenza-like illness, the present supplementary analysis cannot be expected to reveal all true effects with statistical significance. Therefore, an important aspect for the evaluation of a possible causal association between IIV-HD and prevention of serious cardio-respiratory events compared to IIV-SD is the reproducibility of the results under independent observations. The efficacy study was performed over 2 years characterized by distinct influenza seasons: the first had low influenza activity and was characterized by moderate to good match between the vaccine and circulating strains; the second had high influenza activity and was characterized by mismatch between the predominant circulating influenza virus strain and the vaccine strains. Because of the heterogeneity of the two influenza study seasons, the consistency of the association between IIV-HD and prevention of serious events could be evaluated based on these two independent sets of data. Rates of serious events were consistently lower for IIV-HD than for IIV-SD in both study years for three of the seven pre-selected serious cardio-respiratory event categories (pneumonia, other selected respiratory events, and heart failure) and for the aggregate occurrence of any serious event possibly related to influenza. Moreover, the various point estimates (Fig. 1) were nearly all arrayed in favor of IIV-HD, demonstrating an important consistency of results.

It is well-established that influenza can cause primary viral pneumonia and predispose infected individuals to secondary bacterial pneumonia [13,32]. Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality in older adults, with 915,900 episodes estimated to occur annually in the United States
in adults 65 years of age and older [33]. Pneumonia is the third leading cause of hospitalization and sixth leading cause of death in older adults [7,34]. Strategies to prevent CAP have targeted Streptococcus pneumoniae, which is the major bacterial pathogen associated with this illness. Two vaccines are currently licensed in the United States for the prevention of pneumococcal disease in older adults: 23-valent pneumococcal polysaccharide vaccine and 13-valent pneumococcal conjugate vaccine. Although the polysaccharide vaccine is considered efficacious in preventing invasive pneumococcal disease in older adults [35], its role in the prevention of non-bacteremic CAP has been a matter of debate [36]. The 13-valent pneumococcal conjugate vaccine recently demonstrated significant efficacy in the prevention of invasive pneumococcal disease and pneumococcal pneumonia due to included serotypes in a randomized placebo-controlled trial conducted in the Netherlands among approximately 85,000 adults aged ≥65 years [37]. The study showed 45.6% efficacy against vaccine-type pneumococcal pneumonia. In this context, the observed 39.8% overall effectiveness of IIV-HD compared to IV-SD against serious pneumonia of any etiology in our study is particularly noteworthy. Moreover, IIV-HD effectiveness against serious pneumonia was consistent and statistically significant in each of the two study years. Previous reports have also signaled a favorable impact of influenza vaccines on CAP [25,38].

A recent meta-analysis of randomized controlled trials reported that the use of influenza vaccines was associated with a lower risk of major adverse cardiovascular events (cardiovascular death or hospitalization associated with myocardial infarction, unstable angina, stroke, heart failure, or urgent coronary revascularization) [39]. We observed 24.0% overall effectiveness of IIV-HD over IV-SD against serious congestive heart failure. Of note, although not statistically significant, positive relative effectiveness point estimates (favoring IIV-HD) for preventing serious heart failure were consistently observed in both years of the study. This was not the case for serious coronary and cerebrovascular events, for which the relative effectiveness estimates were imprecise and variable across study years.

The interpretation of the results for serious asthma/COPD/bronchial events and all-cause hospitalization in our study is challenging: the rate of asthma/COPD/bronchial events for IIV-HD recipients was significantly higher than the rate for IV-SD recipients in Year 1 of the study, but significantly lower in Year 2; and the rate of all-cause hospitalization events for IIV-HD recipients was the same as the rate for IV-SD recipients in Year 1 of the study, significantly lower for the IIV-HD group in Year 2, and also lower for the IIV-HD group with borderline statistical significance for both years combined. The apparent disparate estimates from year to year for these outcomes may be explained by the large differences in the epidemiology of the two influenza seasons encompassing the study, the role that influenza may have played in triggering new onset or exacerbations of bronchial events and any hospitalization, and the fact that evaluated outcomes in this supplementary analysis did not require laboratory confirmation of influenza. Since the first year of the study coincided with very low influenza activity [40], and the second year of the study coincided with very high influenza activity [41], it is conceivable that the majority of bronchial events and hospitalizations in Year 1 of the study may have been unrelated to influenza and therefore unlikely to be affected by a more efficacious influenza vaccine. Given the higher level of influenza activity during the second year of the study, it is likely that the proportion of influenza-related bronchial events and hospitalizations increased meaningfully in Year 2, revealing a possible protective effect from IIV-HD over IV-SD. Therefore, while investigating influenza vaccine effects, the influenza specificity of the bronchial and all-cause hospitalization events might have been higher in the second year of the study than in the first year. It has been well established that the use of non-specific outcomes can affect efficacy/effectiveness estimates by biasing them towards the null [42]. While this can explain null estimates for hospitalization in Year 1, it may not completely explain the observed significantly higher rate of bronchial events in the IIV-HD arm in Year 1. In our view, the most likely explanation for this observation is random error in the context of multiple comparisons.

It is also interesting that while the analyses showed that IIV-HD was not effective in preventing serious bronchial events in Year 1, it showed strong effectiveness of the vaccine against serious pneumonia during the same period. This suggests that the observed serious pneumonia events may have been more likely to be associated with influenza than the observed serious bronchial events, making the pneumonia outcomes more specific than the bronchial outcomes and therefore less likely to be negatively biased. However, the fact that strong effectiveness against serious pneumonia was observed in the context of a weak influenza season in Year 1 of the study suggests that IIV-HD may have ancillary effects on the most common etiologies of serious pneumonia (beyond its prevention or modulation of influenza), mediated directly through a cross-pathogen immune response or indirectly through alterations of the nasopharyngeal microbiome. These interpretations remain speculative at this time and further research is required to test them as formal hypotheses.

This supplementary analysis of the original study has several limitations. As mentioned earlier, the original study was not powered to address the objectives of this analysis, and the outcomes evaluated here were not necessarily influenza-specific. These two factors likely affected both the magnitude and precision of the observed effects. In addition, the study compared IIV-HD with IV-SD, an active control that likely provided some protective effects against the evaluated outcomes. Accordingly, the supplementary analysis may underestimate the effect that IIV-HD may have on the prevention of serious cardio-respiratory events. Finally, this analysis evaluated multiple associations without correcting for multiplicity. Therefore, even statistically significant effects need to be interpreted with caution.

In conclusion, this supplementary analysis suggests that compared to IV-SD, IIV-HD may better prevent serious cardio-respiratory illnesses considered potential sequelae or complications of influenza infection. The observed effectiveness against serious pneumonia is particularly noteworthy considering the disproportionate burden of influenza and pneumonia in older adults.

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Conflict of interest statement: The study was sponsored by Sanofi Pasteur.


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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.07.006

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