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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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ABSTRACT

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.

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

Abbreviations: IIV-HD, high-dose inactivated influenza vaccine; CI, confidence interval; IIV-SD, standard-dose inactivated influenza vaccine; SAE, serious adverse event; COPD, chronic obstructive pulmonary disease; RR, rate ratios; rVE, relative vaccine effectiveness; FAS, Full Analysis Set; ITT, intent-to-treat; CAP, community-acquired pneumonia.

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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 [Sanofi Pasteur, 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 participant-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 $(1 - \mathrm{RR}) \times 100$.

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.