ORIGINAL ARTICLE

# Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults

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## ABSTRACT

### BACKGROUND

As compared with a standard-dose vaccine, a high-dose, trivalent, inactivated influenza vaccine (IIV3-HD) improves antibody responses to influenza among adults 65 years of age or older. This study evaluated whether IIV3-HD also improves protection against laboratory-confirmed influenza illness.

### METHODS

We conducted a phase IIIb–IV, multicenter, randomized, double-blind, active-controlled trial to compare IIV3-HD (60 μg of hemagglutinin per strain) with standard-dose trivalent, inactivated influenza vaccine (IIV3-SD [15 μg of hemagglutinin per strain]) in adults 65 years of age or older. Assessments of relative efficacy, effectiveness, safety (serious adverse events), and immunogenicity (hemagglutination-inhibition [HAI] titers) were performed during the 2011–2012 (year 1) and the 2012–2013 (year 2) northern-hemisphere influenza seasons.

### RESULTS

A total of 31,989 participants were enrolled from 126 research centers in the United States and Canada (15,991 were randomly assigned to receive IIV3-HD, and 15,998 to receive IIV3-SD). In the intention-to-treat analysis, 228 participants in the IIV3-HD group (1.4%) and 301 participants in the IIV3-SD group (1.9%) had laboratory-confirmed influenza caused by any viral type or subtype associated with a protocol-defined influenza-like illness (relative efficacy, 24.2%; 95% confidence interval [CI], 9.7 to 36.5). At least one serious adverse event during the safety surveillance period was reported by 1323 (8.3%) of the participants in the IIV3-HD group, as compared with 1442 (9.0%) of the participants in the IIV3-SD group (relative risk, 0.92; 95% CI, 0.85 to 0.99). After vaccination, HAI titers and seroprotection rates (the percentage of participants with HAI titers ≥1:40) were significantly higher in the IIV3-HD group.

### CONCLUSIONS

Among persons 65 years of age or older, IIV3-HD induced significantly higher antibody responses and provided better protection against laboratory-confirmed influenza illness than did IIV3-SD. (Funded by Sanofi Pasteur; ClinicalTrials.gov number, NCT01427309.)

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Between 1990 and 1999, seasonal influenza caused an average of 36,000 deaths and 226,000 hospitalizations per year in the United States.[1-3] Adults 65 years of age or older are particularly vulnerable to complications associated with influenza and account for most seasonal influenza–related hospitalizations and deaths.[2,3] Although vaccination currently represents the most effective intervention against influenza and associated complications,[3,4] antibody response and protection elicited by the vaccine are lower among persons 65 years of age or older than among younger adults.[5-7] Strategies to improve antibody responses to influenza vaccine in the older population, such as increasing the amount of antigen in the vaccine, may improve protection and have a favorable effect on morbidity and mortality.[8]

The high-dose, trivalent, inactivated influenza vaccine (IIV3-HD) contains four times as much hemagglutinin (HA) as is contained in standard-dose vaccines. On the basis of its safety profile and superior immunogenicity as compared with a standard-dose vaccine,[9] IIV3-HD was licensed for use in the United States in December 2009, with a requirement to show clinical benefit. The primary objective of this study was to show the efficacy of IIV3-HD as compared with a standard-dose vaccine for the prevention of laboratory-confirmed influenza illness in adults 65 years of age or older.

## Methods

### Study Design and Oversight

We conducted a phase IIIb–IV, multicenter, randomized, double-blind, active-controlled trial comparing IIV3-HD with a standard-dose vaccine (IIV3-SD) in persons 65 years of age or older at 126 centers in the United States and Canada from September 6, 2011, through May 31, 2013. The study was approved by three institutional review boards (Quorum Review IRB, Western Institutional Review Board, and Vanderbilt University Institutional Review Board) and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All participants gave written informed consent for study participation. There were two enrollment periods, from September 6 through October 9, 2011 (year 1), and from October 9 through October 21, 2012 (year 2). An independent data and safety monitoring committee assessed the study data.

The study was funded by Sanofi Pasteur. The sponsor had primary responsibility for study design, protocol development, study monitoring, data management, and statistical analyses. The investigators at the study centers had primary responsibility for critical protocol review, study procedures, and data collection. The coordinating investigator (the last author) had a primary role in reviewing and approving the protocol and the clinical study report. The manuscript was drafted by the corresponding author. All the authors critically reviewed, edited, and approved the manuscript and made the decision to submit it for publication. No persons other than the named authors played any role in writing the manuscript. All the authors assume responsibility for the accuracy and completeness of the data and for the fidelity of the study to the protocol, which is available with the full text of this article at NEJM.org.

### Participants and Group Allocation

The study included adults 65 years of age or older without moderate or severe acute illnesses. Details on exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org. Each study year, participants were randomly assigned in a 1:1 ratio to receive a single dose of IIV3-HD or IIV3-SD. Those who were participants in both years underwent rerandomization the second year. The study used concealed allocation through an interactive voice-response system that centrally assigned participants on the basis of computer-generated block randomization. Approximately one third of participants were selected randomly by the same system to be in the immunogenicity subset. Participants, investigators, and the sponsor's study staff remained unaware of the study assignments.

### Vaccines

Vaccines were formulated according to Food and Drug Administration (FDA) recommendations. The standard-dose vaccine (IIV3-SD; Fluzone, Sanofi Pasteur) contained 15 $\mu$g of HA per strain. IIV3-HD (Fluzone High-Dose, Sanofi Pasteur) contained 60 $\mu$g of HA per strain. Both vaccines were produced in embryonated chicken eggs, were inactivated with formaldehyde, were split with a

nonionic detergent, and contained A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 strains for the year 1 season and A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2), and B/Texas/6/2011 (B/Wisconsin/1/2010-like virus) strains for the year 2 season. The vaccines were provided in ready-to-use 0.5-ml syringes and administered intramuscularly, in the deltoid.

### SURVEILLANCE AND ASCERTAINMENT OF INFLUENZA

Participants were instructed to contact their study site if they had any respiratory symptoms. In addition, participants were contacted by a call center twice weekly (between the beginning of January and the end of February) or weekly until the end of illness surveillance (April 30 each year). Three definitions of clinical illness were evaluated in the study.

Respiratory illness was defined as the occurrence of one or more of the following: sneezing, nasal congestion or rhinorrhea, sore throat, cough, sputum production, wheezing, or difficulty breathing. This definition provided high sensitivity for the detection of cases of influenza and triggered key study procedures.

A protocol-defined influenza-like illness (the illness definition for the primary analysis) provided increased specificity and clinical relevance beyond the respiratory illness definition. It was defined as a respiratory illness with sore throat, cough, sputum production, wheezing, or difficulty breathing, concurrent with one or more of the following: temperature above 37.2°C, chills, tiredness, headaches, or myalgia.

A modified CDC-defined influenza-like illness was based on the Centers for Disease Control and Prevention (CDC) surveillance network definition of an influenza-like illness and was defined as a respiratory illness with cough or sore throat, concurrent with a temperature above 37.2°C. The modified CDC-defined influenza-like illness incorporated a lower threshold for the temperature criterion than did the original CDC definition (≥37.8°C) because of the documented low frequency of temperatures of 37.8°C or higher in older adults with confirmed influenza,[10,11] because specificity was being provided by laboratory confirmation in this clinical trial, and because of the precedent for a lower threshold in other influenza efficacy studies in similar populations.[12,13]

If a participant met the criteria for any respiratory illness, staff members at the study site were to collect a nasopharyngeal swab within 5 days after onset of the illness. Laboratory confirmation of influenza in nasopharyngeal swabs was accomplished by a positive result on culture, a polymerase-chain-reaction (PCR) assay, or both. A hemagglutination-inhibition (HAI) assay against a panel of standard ferret antiserum specimens was performed to determine whether a sample strain was antigenically similar to a vaccine strain.[14] Genetic sequencing further evaluated similarity to vaccine components. The ferret HAI assay was the primary method for classification of similarity to the vaccine, with genetic sequencing used only for laboratory-confirmed samples for which ferret HAI assay results were not available. Further details about the laboratory methods and similarity assessments are provided in the Supplementary Appendix.

Investigators at the study sites were instructed to make follow-up telephone calls to collect effectiveness information associated with events occurring within 30 days after the start of any respiratory illness. These events included pneumonia, cardiorespiratory conditions, health care visits (hospitalizations for any cause, visits to the emergency department, and nonroutine medical visits), and medication use (restricted to antipyretic agents, analgesic agents, nonsteroidal antiinflammatory drugs, antiviral agents, and antibiotics).

Safety surveillance extended from vaccination to approximately May 15 of the following year. Because the side-effect profile of IIV3-HD had been evaluated previously, in a large-scale pivotal study,[9] the safety data that were collected in this trial were limited to serious adverse events.

### IMMUNOGENICITY

Blood samples were collected from participants in the immunogenicity subset approximately 28 days after vaccination and were assayed for HAI titers[14] by Focus Diagnostics. HAI titers were summarized as geometric mean titers and seroprotection rates (i.e., the percentage of participants with an HAI titer ≥1:40).

### MEASURES OF EFFICACY

The primary end point of the study was the occurrence, at least 14 days after vaccination, of laboratory-confirmed influenza caused by any influenza viral types or subtypes, in association with

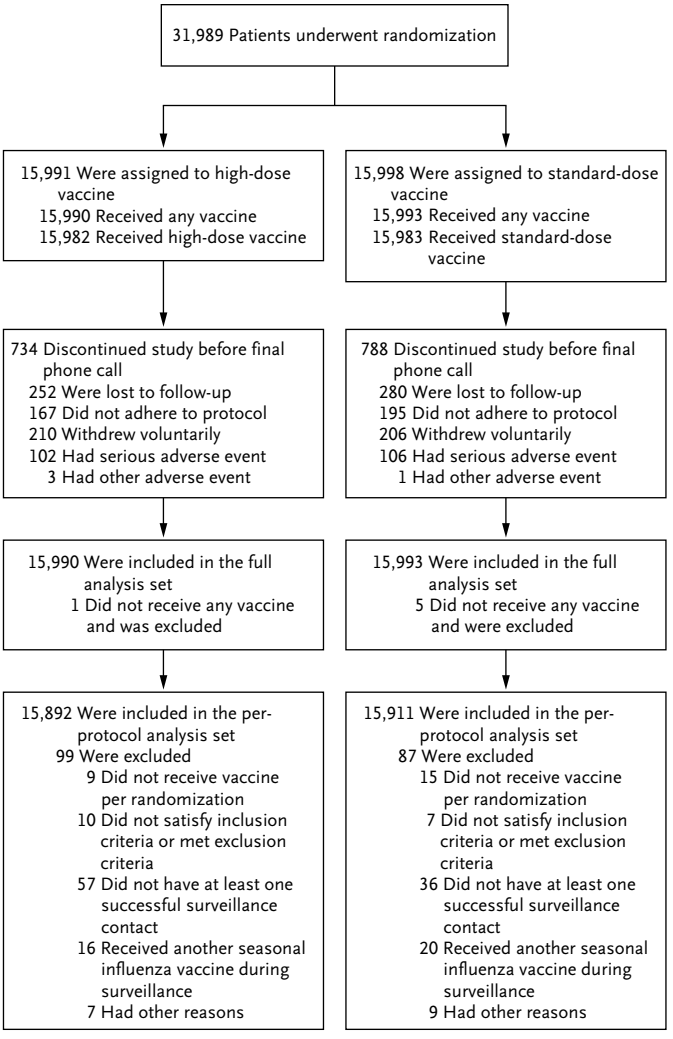


**Figure 1. Enrollment and Follow-up of Study Participants.**

Three participants in each group who had serious adverse events were institutionalized and unable to speak on the phone at the final call before study termination.

a protocol-defined influenza-like illness. Several secondary efficacy and observational effectiveness end points were also evaluated, according to various clinical illness definitions, methods of laboratory confirmation, and levels of similarity to the vaccine.

### STATISTICAL ANALYSIS

The total sample size required to provide 80% power to show the superior efficacy of IIV3-HD was 30,000 participants, assuming a relative vaccine efficacy of 30% and an influenza incidence of 2% for the IIV3-SD group; furthermore, IIV3-HD would be considered superior to IIV3-SD if the lower bound of the 95% confidence interval for relative vaccine efficacy exceeded 9.1% for the primary end point. By agreement with the FDA, a 9.1% margin for superior vaccine efficacy was used to provide confidence that the risk of the primary end point was at least 10% higher with the administration of IIV3-SD than with the administration of IIV3-HD.

The efficacy of IIV3-HD relative to IIV3-SD was estimated as 1 minus the relative risk. The confidence interval for efficacy estimates was calculated with the Clopper–Pearson exact method for binomial proportions.[15]

Statistical significance was defined by a 95% confidence interval excluding the null value (0 for relative vaccine efficacy and seroprotection rate differences, and 1 for relative risks and the geometric mean titer ratios [the ratio of the geometric mean titer for IIV3-HD to the geometric mean titer for IIV3-SD]).

Two analysis sets were used. The full analysis set comprised all participants who received study vaccine; participants were grouped according to their treatment assignment for efficacy and effectiveness analyses (intention-to-treat) and according to the vaccine actually received for safety analyses. Efficacy and effectiveness were also analyzed in the per-protocol analysis set; conditions under which participants were excluded from the per-protocol analysis set are shown in Figure 1. All statistical analyses were performed with SAS Enterprise Guide 5.1 (SAS Institute).

## RESULTS

### PARTICIPANTS

A total of 14,500 participants were enrolled in year 1, and 17,489 in year 2. Of year 1 participants, 7645 reenrolled in year 2. Of all 31,989 participant-seasons (termed "participants") enrolled, 15,991 were randomly assigned to IIV3-HD and 15,998 were randomly assigned to IIV3-SD (Fig. 1). Of the participants who underwent randomization, 31,983 (>99.9%) received study vaccine; all 31,983 were included in the full analysis set, and 31,803 (99.4%) were included in the per-protocol analysis set. Baseline characteristics of the recipients of IIV3-HD and the recipients of IIV3-SD were similar (Table 1).

**Table 1. Baseline Demographic and Clinical Characteristics of the High-Dose and Standard-Dose Vaccine Groups.***

| Characteristic | IIV3-HD (N=15,990) | IIV3-SD (N=15,993) |
|---|---|---|
| Female sex — no. (%) | 9,131 (57.1) | 8,963 (56.0) |
| Mean age — yr | 73.3±5.8 | 73.3±5.8 |
| Racial background — no. (%)† | | |
| White | 15,103 (94.4) | 15,167 (94.8) |
| Asian | 118 (0.7) | 105 (0.7) |
| Black | 670 (4.2) | 612 (3.8) |
| Other | 97 (0.6) | 106 (0.7) |
| Hispanic ethnic group — no. (%)† | 958 (6.0) | 982 (6.1) |
| At least one prespecified chronic coexisting condition — no. (%)‡ | 10,750 (67.2) | 10,752 (67.2) |
| At least two prespecified chronic coexisting conditions — no. (%) | 5,385 (33.7) | 5,403 (33.8) |
| Cardiac and respiratory disorders — no. (%) | | |
| Coronary artery disease | 2,735 (17.1) | 2,732 (17.1) |
| Atrial fibrillation | 1,103 (6.9) | 1,112 (7.0) |
| Valvular heart disease | 744 (4.6) | 741 (4.6) |
| Congestive heart failure | 451 (2.8) | 446 (2.8) |
| Chronic obstructive lung disease | 1,500 (9.4) | 1,495 (9.4) |
| Asthma | 1,415 (8.8) | 1,408 (8.8) |
| Received influenza vaccine the previous season — no. (%) | 11,758 (73.5) | 11,773 (73.6) |

* There were no significant differences between the treatment groups. IIV3-HD denotes high-dose, trivalent, inactivated influenza vaccine, and IIV3-SD standard-dose, trivalent, inactivated influenza vaccine. Plus–minus values are means ±SD.

† Racial background and ethnic group were self-reported. The category "Other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and mixed origin. Information on racial background was missing for two recipients of the high-dose vaccine and three recipients of the standard-dose vaccine. Percentages may not total 100.0% because of rounding.

‡ Prespecified chronic coexisting conditions include the listed cardiac and respiratory disorders, as well as sickle cell disease, diabetes mellitus, hypothyroidism, epilepsy, stroke, spinal cord injury, Parkinson's disease, chronic kidney disease, chronic hepatitis, cirrhosis, human immunodeficiency virus–acquired immunodeficiency syndrome, cancer, long-term systemic glucocorticoid therapy, and other potentially immunosuppressive therapies (per-group frequencies of these conditions are provided in the Supplementary Appendix).

### ILLNESS SURVEILLANCE AND COLLECTION OF NASOPHARYNGEAL SWABS

In the full analysis set (according to treatment assignment), 3745 participants in the IIV3-HD group (23.4%) had at least one protocol-defined influenza-like illness, 758 (4.7%) had at least one modified CDC-defined influenza-like illness, and 8168 (51.1%) had at least one respiratory illness. In the IIV3-SD group, 3827 participants (23.9%) had at least one protocol-defined influenza-like illness, 838 (5.2%) had at least one modified CDC-defined influenza-like illness, and 8270 (51.7%) had at least one respiratory illness. In the IIV3-HD group, nasopharyngeal swabs were collected within the protocol-specified time frame for 80.0% of protocol-defined influenza-like illnesses, 73.6% of modified CDC-defined influenza-like illnesses, and 67.2% of respiratory illnesses. In the IIV3-SD group, nasopharyngeal swabs were collected within the protocol-specified time frame for 79.3% of protocol-defined influenza-like illnesses, 73.7% of modified CDC-defined influenza-like illnesses, and 66.8% of respiratory illnesses.

### EFFICACY

In the full analysis set, 529 participants met the primary end point; 228 (1.4%) were in the IIV3-HD group, and 301 (1.9%) were in the IIV3-SD group. The efficacy of IIV3-HD relative to IIV3-SD for the primary end point was 24.2% in both

the full analysis set (Table 2) and the per-protocol analysis set. For both analyses, the lower bound of the 95% confidence interval for relative vaccine efficacy was 9.7%, satisfying the prespecified superiority criterion. In addition, the point estimate for relative vaccine efficacy was consistently positive across influenza types, clinical illness definitions, methods of laboratory confirmation (Table 2), and study years (see the Supplementary Appendix).

Overall, relative efficacy estimates were higher in analyses restricted to cases caused by vaccine-similar strains (Table 3): relative vaccine efficacy against laboratory-confirmed protocol-defined influenza-like illness caused by similar strains was 35.4% (95% confidence interval [CI], 12.5 to 52.5). Details on characterization and distribution of influenza isolates are available in the Supplementary Appendix.

### EFFECTIVENESS

Per-group rates and corresponding relative risks of events occurring within 30 days after a study illness are available in the Supplementary Appendix. Most rates for pneumonia, cardiorespiratory conditions, hospitalizations, nonroutine medical office visits, and medication use were lower for participants in the IIV3-HD group than for those in the IIV3-SD group, with 62 of 66 relative risks that could be evaluated having a point estimate below 1.

### SAFETY

During the safety surveillance period (approximately 6 to 8 months after vaccination), 1323 participants (8.3%) in the IIV3-HD group and 1442 participants (9.0%) in the IIV3-SD group had at least one serious adverse event. The relative risk for having at least one serious adverse event with IIV3-HD, as compared with IIV3-SD, was 0.92 (95% CI, 0.85 to 0.99).

During the surveillance period, 83 (0.5%) of the participants in the IIV3-HD group died, as did 84 (0.5%) of the participants in the IIV3-SD group. Six recipients of IIV3-HD died within 30 days after vaccination. Two deaths were deemed accidental (smoke inhalation and traumatic head injury) and the other four were caused by heart failure, cerebral bleeding, pneumonia, and myocardial infarction and occurred in participants who had established risk factors for those conditions. Site investigators classified these six events as unrelated to the study vaccine. No deaths occurred within 30 days after vaccination in the IIV3-SD group.

Three IIV3-HD recipients had serious adverse events categorized by their site investigators as related to vaccination: cranial-nerve VI palsy starting 1 day after vaccination; hypovolemic shock associated with diarrhea starting 1 day after vaccination; and acute disseminated encephalomyelitis starting 117 days after vaccination. All three events resolved before study completion; none resulted in discontinuation from the study. No serious adverse events occurring in IIV3-SD recipients were considered to be related to vaccination by the investigators.

A total of 99 participants (0.6%) in the IIV3-HD group and 103 participants (0.6%) in the IIV3-SD group discontinued the study owing to serious adverse events, none considered to be related to vaccination. Cardiac disorders and infections were the most frequent types of serious adverse events in both groups (see the Supplementary Appendix for serious adverse events according to organ systems).

### IMMUNOGENICITY

HAI antibody geometric mean titers and seroprotection rates 28 days after vaccination were significantly higher after vaccination with IIV3-HD than with IIV3-SD for all three vaccine strains (Table 4).

## DISCUSSION

A few randomized, controlled trials have shown moderate efficacy of influenza vaccines among older adults.[5,7,12] However, given the persistently high burden of influenza in this population despite increased vaccination rates,[17] improved vaccines are needed.[18,19] Some strategies to improve influenza vaccines for older adults involve higher doses of antigen or the use of adjuvants,[20-23] as well as alternative delivery systems.[24]

This randomized, double-blind, active-controlled efficacy trial showed that IIV3-HD provided improved protection against laboratory-confirmed influenza illness among adults 65 years of age or older. The overall efficacy of 24.2% against the primary end point indicates that about one quarter of all breakthrough influenza illnesses could be prevented if IIV3-HD were used instead of IIV3-SD. More than a third of break-

**Table 2. Efficacy of High-Dose Vaccine Relative to Standard-Dose Vaccine against Confirmed Influenza Caused by Any Viral Type or Subtype.***

| Variable | Laboratory-Confirmed Influenza† | | | Culture-Confirmed Influenza | | |
|---|---|---|---|---|---|---|
| | IIV3-HD (N=15,990) | IIV3-SD (N=15,993) | Relative Efficacy (95% CI) | IIV3-HD (N=15,990) | IIV3-SD (N=15,993) | Relative Efficacy (95% CI) |
| | *no. (%)* | | % | *no. (%)* | | % |
| Protocol-defined influenza-like illness | 228 (1.4) | 301 (1.9) | 24.2 (9.7 to 36.5)‡ | 206 (1.3) | 268 (1.7) | 23.1 (7.5 to 36.2) |
| Influenza A | 190 (1.2) | 250 (1.6) | 24.0 (7.8 to 37.4) | 170 (1.1) | 222 (1.4) | 23.4 (6.0 to 37.6) |
| A/H1N1 | 8 (<0.1) | 9 (0.1) | 11.1 (–159.6 to 70.2) | 7 (<0.1) | 9 (0.1) | 22.2 (–134.7 to 75.4) |
| A/H3N2 | 171 (1.1) | 223 (1.4) | 23.3 (6.0 to 37.5) | 156 (1.0) | 199 (1.2) | 21.6 (2.8 to 36.8) |
| Influenza B | 38 (0.2) | 51 (0.3) | 25.5 (–15.7 to 52.4) | 36 (0.2) | 46 (0.3) | 21.7 (–23.8 to 50.8) |
| Modified CDC-defined influenza-like illness | 96 (0.6) | 121 (0.8) | 20.6 (–4.6 to 39.9) | 84 (0.5) | 110 (0.7) | 23.6 (–2.4 to 43.2) |
| Influenza A | 86 (0.5) | 104 (0.7) | 17.3 (–11.1 to 38.6) | 75 (0.5) | 94 (0.6) | 20.2 (–9.3 to 41.9) |
| A/H1N1 | 3 (<0.1) | 2 (<0.1) | –50.0 (–1696.0 to 82.8) | 2 (<0.1) | 2 (<0.1) | 0.0 (–1280.0 to 92.8) |
| A/H3N2 | 77 (0.5) | 95 (0.6) | 18.9 (–10.7 to 40.8) | 69 (0.4) | 85 (0.5) | 18.8 (–12.9 to 41.8) |
| Influenza B | 10 (0.1) | 17 (0.1) | 41.2 (–36.0 to 75.9) | 9 (0.1) | 16 (0.1) | 43.7 (–35.2 to 78.1) |
| Respiratory illness | 316 (2.0) | 387 (2.4) | 18.3 (5.0 to 29.8) | 277 (1.7) | 339 (2.1) | 18.3 (3.9 to 30.5) |
| Influenza A | 262 (1.6) | 313 (2.0) | 16.3 (1.0 to 29.2) | 227 (1.4) | 272 (1.7) | 16.5 (0.1 to 30.3) |
| A/H1N1 | 14 (0.1) | 10 (0.1) | –40.0 (–252.4 to 42.2) | 13 (0.1) | 10 (0.1) | –30.0 (–231.3 to 47.33) |
| A/H3N2 | 231 (1.4) | 281 (1.8) | 17.8 (1.8 to 31.2) | 205 (1.3) | 246 (1.5) | 16.6 (–0.7 to 31.1) |
| Influenza B | 54 (0.3) | 74 (0.5) | 27.0 (–5.1 to 49.6) | 50 (0.3) | 67 (0.4) | 25.4 (–9.3 to 49.3) |

* CDC denotes Centers for Disease Control and Prevention.
† Laboratory confirmation of influenza was accomplished by a positive result on culture of a nasopharyngeal swab, a positive polymerase-chain-reaction assay, or both.
‡ The primary end point of the study was the occurrence, at least 14 days after vaccination, of laboratory-confirmed influenza caused by any influenza viral types or subtypes, in association with a protocol-defined influenza-like illness.

**Table 3. Efficacy of High-Dose Vaccine Relative to Standard-Dose Vaccine against Confirmed Influenza Caused by Strains Similar to the Vaccine Components.**

| Variable | Laboratory-Confirmed Influenza* | | | Culture-Confirmed Influenza† | | |
|---|---|---|---|---|---|---|
| | IIV3-HD (N=15,990) | IIV3-SD (N=15,993) | Relative Efficacy (95% CI) | IIV3-HD (N=15,990) | IIV3-SD (N=15,993) | Relative Efficacy (95% CI) |
| | *no. (%)* | | % | *no. (%)* | | % |
| Protocol-defined influenza-like illness | 73 (0.5) | 113 (0.7) | 35.4 (12.5 to 52.5) | 63 (0.4) | 92 (0.6) | 31.5 (4.6 to 51.1) |
| Influenza A | 56 (0.4) | 82 (0.5) | 31.7 (2.9 to 52.3) | 46 (0.3) | 63 (0.4) | 27.0 (–8.5 to 51.2) |
| A/H1N1 | 7 (<0.1) | 8 (0.1) | 12.5 (–176.2 to 73.0) | 3 (<0.1) | 3 (<0.1) | 0.0 (–646.8 to 86.6) |
| A/H3N2 | 49 (0.3) | 74 (0.5) | 33.8 (3.7 to 54.8) | 43 (0.3) | 60 (0.4) | 28.3 (–7.8 to 52.7) |
| Influenza B | 17 (0.1) | 31 (0.2) | 45.2 (–2.2 to 71.5) | 17 (0.1) | 29 (0.2) | 41.4 (–10.3 to 69.8) |
| Modified CDC-defined influenza-like illness | 26 (0.2) | 51 (0.3) | 49.0 (16.7 to 69.5) | 22 (0.1) | 45 (0.3) | 51.1 (16.8 to 72.0) |
| Influenza A | 21 (0.1) | 36 (0.2) | 41.7 (–2.7 to 67.6) | 17 (0.1) | 31 (0.2) | 45.2 (–2.2 to 71.5) |
| A/H1N1 | 2 (<0.1) | 2 (<0.1) | 0.0 (–1280.0 to 92.8) | 0 | 1 (<0.1) | 100.0 (–3801.0 to 100.0) |
| A/H3N2 | 19 (0.1) | 34 (0.2) | 44.1 (–0.8 to 69.9) | 17 (0.1) | 30 (0.2) | 43.3 (–6.1 to 70.7) |
| Influenza B | 5 (<0.1) | 15 (0.1) | 66.7 (3.5 to 90.5) | 5 (<0.1) | 14 (0.1) | 64.3 (–5.0 to 89.9) |
| Respiratory illness | 106 (0.7) | 146 (0.9) | 27.4 (6.1 to 44.0) | 85 (0.5) | 118 (0.7) | 28.0 (4.0 to 46.1) |
| Influenza A | 82 (0.5) | 101 (0.6) | 18.8 (–9.8 to 40.1) | 61 (0.4) | 75 (0.5) | 18.6 (–15.6 to 43.0) |
| A/H1N1 | 12 (0.1) | 9 (0.1) | –33.4 (–258.4 to 48.4) | 5 (<0.1) | 3 (<0.1) | –66.7 (–973.5 to 67.6) |
| A/H3N2 | 70 (0.4) | 92 (0.6) | 23.9 (–5.0 to 45.0) | 56 (0.4) | 72 (0.5) | 22.2 (–11.9 to 46.1) |
| Influenza B | 24 (0.2) | 45 (0.3) | 46.7 (10.6 to 68.9) | 24 (0.2) | 43 (0.3) | 44.2 (5.9 to 67.6) |

* Laboratory confirmation of influenza was determined by a positive result on culture of a nasopharyngeal swab, a positive polymerase-chain-reaction assay, or both. For laboratory-confirmed influenza assessments, similarity was determined by ferret antigenicity testing complemented by genetic sequencing.

† For culture-confirmed influenza assessments, similarity was determined solely by the ferret antigenicity testing method.

**Table 4. Hemagglutination Inhibition Immunogenicity of High-Dose Vaccine and Standard-Dose Vaccine against Influenza Viral Types and Subtypes Contained in the Vaccine.***

| Viral Type/ Subtype | Year 1 | | | Year 2 | | | Combined† | | |
|---|---|---|---|---|---|---|---|---|---|
| | IIV3-HD (N=2375) | IIV3-SD (N=2382) | IIV3-HD vs. IIV3-SD | IIV3-HD (N=2879) | IIV3-SD (N=2872) | IIV3-HD vs. IIV3-SD | IIV3-HD (N=5254) | IIV3-SD (N=5254) | IIV3-HD vs. IIV3-SD |
| | *geometric mean titer (95% CI‡)* | | *ratio of geometric mean titers (95% CI‡)* | *geometric mean titer (95% CI‡)* | | *ratio of geometric mean titers (95% CI‡)* | *geometric mean titer (95% CI‡)* | | *ratio of geometric mean titers (95% CI‡)* |
| A/H1N1 | 481.8 (457.7–507.1) | 271.8 (257.4–287.1) | 1.8 (1.6–1.9) | 407.0 (390.2–424.4) | 227.4 (216.8–238.5) | 1.8 (1.7–1.9) | 439.2 (425.1–453.8) | 246.6 (237.9–255.6) | 1.8 (1.7–1.9) |
| A/H3N2 | 685.5 (651.4–721.4) | 349.8 (332.1–368.6) | 2.0 (1.8–2.1) | 460.0 (440.8–480.0) | 252.8 (241.6–264.4) | 1.8 (1.7–1.9) | | | |
| B | 138.1 (132.2– 144.2) | 97.6 (93.3–102.0) | 1.4 (1.3–1.5) | 98.2 (94.5–102.0) | 61.8 (59.4–64.2) | 1.6 (1.5–1.7) | | | |
| | *% with seroprotection (95% CI§)* | | *percentage-point difference (95% CI¶)* | *% with seroprotection (95% CI§)* | | *percentage-point difference (95% CI¶)* | *% with seroprotection (95% CI§)* | | *percentage-point difference (95% CI¶)* |
| A/H1N1 | 98.1 (97.5–98.6) | 94.2 (93.2–95.1) | 3.9 (2.8–5.0) | 98.8 (98.3–99.2) | 93.3 (92.3–94.2) | 5.5 (4.5–6.5) | 98.5 (98.1–98.8) | 93.7 (93.0–94.3) | 4.8 (4.1–5.5) |
| A/H3N2 | 99.2 (98.7–99.5) | 96.5 (95.6–97.2) | 2.7 (1.9–3.5) | 98.6 (98.2–99.0) | 95.0 (94.2–95.8) | 3.6 (2.7–4.5) | | | |
| B | 91.6 (90.4–92.7) | 83.9 (82.3–85.3) | 7.7 (5.9–9.6) | 86.2 (84.9–87.4) | 72.8 (71.1–74.4) | 13.4 (11.4–15.5) | | | |

* The number of participants in the high-dose and standard-dose categories are those participants in the full analysis set and the immunogenicity subset who had at least one hemagglutination inhibition (HAI) assay result for the year. Seroprotection is defined as an HAI titer of at least 1:40.

† The type A (H1N1) virus used to make the 2012–2013 influenza vaccine was the same virus used to make the 2011–2012 vaccine, but the type A (H3N2) and type B viruses used to make the 2012–2013 influenza vaccine were different from those in the 2011–2012 influenza vaccine, so only the results from the type A (H1N1) strain can be combined.

‡ The geometric mean titer confidence intervals were calculated according to the t distribution and the assumption that log (HAI titer) follows a normal distribution.

§ The confidence intervals were calculated with the use of the Clopper–Pearson exact method.[15]

¶ The confidence intervals were calculated with the use of the Newcombe–Wilson score method.[16]







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through influenza illnesses caused by strains similar to the vaccine could be prevented.

This study provides an estimate of relative efficacy (i.e., the efficacy of IIV3-HD as compared with IIV3-SD). The absolute efficacy of IIV3-HD can only be inferred, on the basis of estimates external to the study of the absolute efficacy of standard-dose vaccines. Previous studies have suggested that inactivated vaccines similar to IIV3-SD provide approximately 50% protection against influenza in older adults.[5,7] Assuming 50% absolute efficacy for IIV3-SD in older adults, the absolute efficacy of IIV3-HD would be estimated at 62%, a level of protection similar to that seen with standard-dose vaccines in younger adults.[19,25] This estimate is consistent with an immunogenicity study that showed that immune responses induced by IIV3-HD in adults 65 years of age or older were similar to those observed with IIV3-SD in younger adults.[26]

This study included two heterogeneous influenza seasons. The first had low influenza activity and was characterized by a moderate-to-good match between the vaccine and circulating strains[27]; the second had high influenza activity[28,29] and was characterized by mismatch between predominant circulating strains and egg-propagated vaccines such as those tested in this study.[29,30] Despite the substantial differences in these two influenza seasons, IIV3-HD showed significant efficacy as compared with IIV3-SD against the primary end point in each season, a finding that provides reassurance that the benefit of IIV3-HD persists despite varying seasonal conditions.

The clinical benefit shown in this study may translate into public health benefits. The effectiveness analyses signaled a favorable effect of IIV3-HD on the prevention of hospitalization, pneumonia, cardiorespiratory events, medication use, and nonroutine medical visits. Since influenza infections with type A (H3N2) viruses are considered more burdensome than other viral types and subtypes in older adults,[1,2] it is expected that a benefit of IIV3-HD in this population will remain even in the context of quadrivalent standard-dose vaccines.

The safety data in this study are consistent with the data in previous studies of IIV3-HD.[9,26,31] Moreover, significantly fewer IIV3-HD recipients than IIV3-SD recipients reported serious adverse events, which suggests that IIV3-HD may protect against the occurrence of influenza-related serious events.

This study has several limitations. First, some of the efficacy estimates according to influenza type, definitions of secondary illness, and confirmation methods were based on a limited number of cases and may therefore lack sufficient precision. Second, only a minority of influenza viruses identified in the study were characterized as similar to the vaccine. Different results might be obtained in years when the relatedness of vaccine and circulating strains differed materially from that observed in the study seasons. Third, although the study allowed inclusion of persons with high-risk conditions, participants were excluded if they had moderate or severe acute illnesses or if they were deemed unable to comply with study procedures. Extrapolation of study results to such persons should be made with caution.

In conclusion, this study showed that IIV3-HD as compared with IIV3-SD significantly improved protection against laboratory-confirmed influenza illness. It also showed that IIV3-HD was associated with superior immune responses as compared with IIV3-SD.

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