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RESEARCH PAPER



Immunogenicity and safety of a quadrivalent high-dose inactivated influenza vaccine compared with a standard-dose quadrivalent influenza vaccine in healthy people aged 60 years or older: a randomized Phase III trial

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ABSTRACT

A quadrivalent high-dose inactivated influenza vaccine (IIV4-HD) is licensed for adults ≥ 65 y of age based on immunogenicity and efficacy studies. However, IIV4-HD has not been evaluated in adults aged 60–64 y. This study compared immunogenicity and safety of IIV4-HD with a standard-dose quadrivalent influenza vaccine (IIV4-SD) in adults aged ≥ 60 y. This Phase III, randomized, modified double-blind, active-controlled study enrolled 1,528 participants aged ≥ 60 y, randomized 1:1 to a single injection of IIV4-HD or IIV4-SD. Hemagglutination inhibition (HAI) geometric mean titers (GMTs) were measured at baseline and D 28 and seroconversion assessed. Safety was described for 180 d after vaccination. The primary immunogenicity objective was superiority of IIV4-HD versus IIV4-SD, for all four influenza strains 28 d post vaccination in participants aged 60–64 and ≥ 65 y. IIV4-HD induced a superior immune response versus IIV4-SD in terms of GMTs in participants aged 60–64 y and those aged ≥ 65 y for all four influenza strains. IIV4-HD induced higher GMTs in those aged 60–64 y than those aged ≥ 65 y. Seroconversion rates were higher for IIV4-HD versus IIV4-SD in each age-group for all influenza strains. Both vaccines were well tolerated in participants ≥ 60 y of age, with no safety concerns identified. More solicited reactions were reported with IIV4-HD than with IIV4-SD. IIV4-HD provided superior immunogenicity versus IIV4-SD and was well tolerated in adults aged ≥ 60 y. IIV4-HD is assumed to offer improved protection against influenza compared with IIV4-SD in adults aged ≥ 60 y, as was previously assessed for adults aged ≥ 65 y.

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Introduction

Influenza is a highly contagious acute respiratory disease caused by influenza type A (subtypes H1N1 and H3N2) and type B (lineages B/Yamagata and B/Victoria) viruses, which provoke seasonal epidemics.^{1,2} The burden of disease is high, with annual epidemics resulting in 3–5 million individuals worldwide developing severe illness.¹ Additionally, the impact of influenza extends beyond respiratory disease, and it is now widely acknowledged that it can exacerbate existing chronic conditions, increase susceptibility to secondary bacterial infections; trigger cardiac events, including acute myocardial infarction and heart failure; and lead to an irreversible decline in quality of life.^{3,4} Although influenza affects all generations, it is associated with greater morbidity and mortality in those over ≥ 65 y of age, with an increase in influenza-related pneumonia and influenza hospitalization in this age-group.^{1,5–7}

Vaccination remains the most effective public health intervention in reducing morbidity and mortality associated with seasonal influenza infection and associated complications.¹ However, those over 65 y of age have been found to have a sub-optimal immune response to standard-dose influenza vaccines

compared with healthy young adults.⁸ In order to ensure better protection in older adults, a trivalent high-dose influenza vaccine (IIV3-HD; Fluzone[®] high-dose, Sanofi Pasteur, available in the USA since 2009) and a subsequent quadrivalent high-dose influenza vaccine (IIV4-HD, licensed in the USA, Canada, and Australia as Fluzone[®] High-Dose Quadrivalent, in November 2019, June 2020, and July 2020, respectively, and in numerous European countries as Efluelda[®] in April 2020) were developed, which contain 60 μ g hemagglutinin (HA) of each of the virus strains contained in the vaccine instead of the standard dose of 15 μ g HA/strain.^{8–11} IIV4-HD contains an A/H1N1, an A/H3N2, and two B strains, one from each of the Victoria and Yamagata lineages.^{9,10}

IIV4-HD efficacy was demonstrated in a Phase III trial in adults ≥ 65 y of age, which found the addition of a second B strain in IIV4-HD resulted in superior immunogenicity against the additional B strain compared with IIV3-HD, while maintaining a similar safety profile to IIV3-HD and providing a non-inferior antibody response against the other three strains, compared with IIV3-HD.¹¹ A further Phase II descriptive safety and immunogenicity trial

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performed in people ≥ 65 y of age in Japan found IIV4-HD to be well tolerated and immunogenic in the study population.¹²

With IIV3-HD, the demonstrable higher immunogenicity versus standard-dose vaccine has been shown to translate into significantly higher protection against influenza in people ≥ 65 y of age, with a relative vaccine efficacy of 24.2%.¹³ This translates into a reduction in associated clinical complications, with influenza-like illness and hospital admissions in adults ≥ 65 y of age being reduced by 15.9% and 8.4%, respectively, as shown by a recent meta-analysis.¹⁴ From an economic standpoint, reductions in cardiovascular disease hospitalizations in recipients of IIV3-HD vaccine have been shown to result in net cost savings of US\$138 per recipient, compared with IIV3-SD, and US\$62 per participant for respiratory disease-related hospitalizations.⁴

The definition of older adults who are at increased risk of influenza and its complications and thus recommended to receive influenza vaccination differs between countries.¹⁵ In Europe, all the member states recommend seasonal influenza vaccination for older adults, but the starting age for vaccination ranges from 50 to 65 y of age.¹⁵ Although clinical data on IIV3-HD or IIV4-HD use in adults ≥ 65 y of age has been established, the immune response to IIV4-HD in adults 60–64 y of age has not previously been studied.⁹ To address the different definitions of age-groups and to complement previous work,¹⁶ we aimed to demonstrate that vaccination with IIV4-HD in people 60–64 and ≥ 65 y of age and older induced a superior immune response 28 d post vaccination for all four virus strains versus IIV4-SD, which is the standard of care in Europe for the four virus strains.

Materials and methods

Study design

This was a Phase III, randomized, modified double-blind, active-controlled study in adults 60 y of age and over conducted in 17 centers in six European Union (EU) countries: Belgium, France, Germany, Italy, Poland, and the Netherlands (ClinicalTrials.gov NCT04024228, EudraCT no. 2019–000655-14). Further details are listed in the supplementary material. The duration of the study was approximately 6 months, including the safety follow-up.

The conduct of the study was approved by the appropriate Independent Ethics Committee or Institutional Review Board for each study site and was consistent with the standards established by the Declaration of Helsinki and compliant with the International Council for Harmonization guidelines for Good Clinical Practice, as well as with all local and/or national regulations and directives.

Study population

The study enrolled adults over 60 y of age who had not been vaccinated against influenza in the previous 6 months preceding trial vaccination and who had not received any other vaccination in the 28 d preceding trial vaccination. Individuals were required to sign and date informed consent forms, attend all scheduled visits, comply with all trial

procedures, and, if applicable to the country, be covered by health insurance. The criteria for exclusion are listed in the supplementary material.

Vaccines

IIV4-HD (Fluzone® High-Dose Quadrivalent/Efluelda®, Sanofi Pasteur, Swiftwater, US) is a split-virion inactivated quadrivalent influenza vaccine containing 60 μ g HA for each of the four influenza strains included in the vaccine. IIV4-SD (Influvac™, Tetra, Mylan, Hatfield, UK) is a subunit quadrivalent influenza vaccine, containing 15 μ g HA per influenza strain. IIV4-HD and IIV4-SD both contained the World Health Organization and EU recommendations for the 2019–2020 Northern Hemisphere influenza season: A/Brisbane/02/2018 (H1N1) pdm09-like strain (A/Brisbane/02/2018, IVR-190), A/Kansas/14/2017 (H3N2)-like strain (A/Kansas/14/2017, NYMC X-327), B/Colorado/06/2017-like strain (B/Maryland/15/2016, NYMC BX-69A) (Victoria lineage), and B/Phuket/3073/2013-like strain (B/Phuket/3073/2013, wild type) (Yamagata lineage). The dose volume administered was 0.7 mL for IIV4-HD and 0.5 mL for IIV4-SD.

Randomization and blinding

Participants were randomized using interactive response technology by permuted block method in a 1:1 ratio, stratified by site and age-group (60–64 and ≥ 65 y), to receive a single intramuscular injection in the upper arm of either IIV4-HD or IIV4-SD at D 0. A subset of participants per treatment group was randomly selected by interactive response technology for measurement of anti-neuraminidase (NA) and seroneutralization (SN) antibodies (Ab).

The study was modified double-blind, such that administrators at each site administering the vaccines were unblinded but that investigators (or delegates) in charge of the safety assessment, the trial staff who collected the safety data, the laboratory personnel who analyzed the blood sample, and the participants did not know which product was administered. The vaccine administrator was independent of the immunogenicity and safety evaluations. Due to the different volumes of injection between the two vaccines, an unblinded administrator administered the vaccines at each site, and the syringes were masked to maintain blinding for participants and other members of the clinical site.

Objectives

The primary objective was to demonstrate the superior immunogenicity of IIV4-HD, relative to IIV4-SD, in all four influenza strains 28 d post vaccination in participants 60–64 and ≥ 65 y of age. Superior immunogenicity was defined through the comparison of hemagglutination inhibition (HAI) (Ab) titers obtained on D 28 between vaccination groups in each age-group. Secondary immunological and safety objectives are included in the supplementary material.

Assessment methods

Immunogenicity

Participants provided a baseline blood sample on D 0 and a sample at the end of the active phase of the trial on D28 for HAI testing. HAI Ab titers were detected as described previously.¹¹ The immune response after 28 d was also described as an observational endpoint using the virus SN method and NA immune response, both described previously.¹¹

Safety

Participants were observed for 30 min after vaccination for safety and any immediate adverse events (AE) were recorded in the case report book. Participants recorded information about solicited reactions from D 0 to 7, and unsolicited AEs, serious AEs (SAEs) and adverse events of special interest (AESIs) from D 0 to 28 in a diary card, which were reviewed by staff with the participants at Visit 2 (D 28). Participants continued to collect information on SAEs and AESI until D 180, and participants were asked to notify the site immediately in the event of SAEs and AESIs. AESIs included new-onset Guillain-Barré syndrome, encephalitis/myelitis (including transverse myelitis), Bells' palsy, optic neuritis, and brachial neuritis. Participants were contacted 180 d after vaccination to capture any follow-up safety data.

Erythema, swelling, induration, and bruising were designated Grade 1 for ≥ 25 –50 mm, Grade 2 for 51–100 mm, and Grade 3 for > 100 mm. Fever was designated Grade 1 for 38.0–38.4°C, Grade 2 for 38.5–38.9°C, and Grade 3 for ≥ 39.0 °C. All other reactions and AEs were designated Grade 1 for not generally interfering with usual activities of daily living, Grade 2 for some interference with usual activities of daily living, and Grade 3 for significant prevention of usual activities of daily living. Investigators assessed the causal relationship between each unsolicited systemic AE, SAE, and AESI and the product administered as either not related or related.

Statistical analysis

The full analysis set (FAS) ($N = 1,527$) was comprised of trial participants who received one dose of the study vaccine and provided a blood sample at the end of the active phase. At inclusion, participants were randomized into subsets for SN and neuraminidase NA. Further information about the additional analysis groups can be found in the supplementary material.

To demonstrate a superior IIV4-HD immune response, HAI antibody titers were obtained in duplicates on D 28 and compared between vaccination groups in each age-group. The geometric mean titers (GMT) between the two values were calculated at the time of statistical analysis.

The immunogenicity of IIV4-HD was compared with that of IIV4-SD using a superiority approach. Post-vaccination GMTs were compared between IIV4-HD and IIV4-SD groups for each strain and in each age-group using a one-sided test with type I error rate of 0.025 following the individual hypotheses H_0 s and H_1 s, where s represents the strain

$$H_0^s : \frac{GMT_{QIV-HD}^s}{GMT_{QIV-SD}^s} \leq 1 \Leftrightarrow \log_{10}(GMT_{QIV-HD}^s) - \log_{10}(GMT_{QIV-SD}^s) \leq 0$$

$$H_0^s : \frac{GMT_{QIV-HD}^s}{GMT_{QIV-SD}^s} > 1 \Leftrightarrow \log_{10}(GMT_{QIV-HD}^s) - \log_{10}(GMT_{QIV-SD}^s) > 0$$

The statistical methodology was based on the use of the lower bound of the two-sided 95% confidence intervals (CIs) of the ratio of post-vaccination GMTs between the IIV4-HD and IIV4-SD groups. The CIs were calculated by normal approximation of log₁₀ transformed titers for GMTs.

For each of the eight null hypotheses (for each age-group and each of the four strains), the null hypothesis was considered rejected if the lower bound of the CI of the ratio in GMTs between the IIV4-HD and IIV4-SD groups was above 1.

Superiority was demonstrated for a given age-group if the null hypothesis was rejected for the four strains in this age-group. The superiority objective was achieved if superiority was demonstrated for both age-groups.

This was performed using the FAS population and confirmed on the Per-Protocol Analysis Set (PPAS). Superiority was determined if the lower bound of the two-sided 95% CIs of the ratio of post-vaccination GMTs between the IIV4-HD and IIV4-SD groups was > 1 for each strain and in each age-group. The CIs were calculated by normal approximation of log-transformed titers for GMTs.

Immunogenicity and safety endpoints were summarized by age-group, in pooled age and vaccine groups with 95% CIs. CIs of geometric mean of titers and individual titer ratios were calculated assuming normal approximation of log-transformed values. CIs of proportions were calculated using the Clopper-Pearson method.¹⁷

Statistical analysis was performed using SAS version 9.4 or later (SAS Institute, Cary, NC, USA). Missing or incomplete data were not replaced except in cases below lower limit of quantitation or above upper limit of quantification, as described in the earlier sections.

Sample size estimation

Approximately 1,540 adults ≥ 60 y (770 in the 60–64 age-group, 770 in the ≥ 65 y age-group) were to be enrolled as determined by simulations based on an overall power of 90% for demonstrating the primary objective. The thresholds for superiority were defined as 1 for GMTs and no alpha adjustment was needed. Each test was performed at one-sided 0.025 level. Other assumptions were GMT ratio of 1.5 for all strains, standard deviations (SD) of log₁₀-transformed titers in IIV4-SD group of 0.6 for two strains and 0.5 for the other two strains, and an attrition rate of 5% in the FAS. Power per strain was 97.7% when SD was 0.6 and 99.7% when SD was 0.5.

Results

Patient demographics and baseline characteristics

A total of 1,539 participants were enrolled in the study between October 28 and November 15, 2019, at two centers in Belgium ($N = 212$), three in France ($N = 271$), five in Germany ($N = 327$),

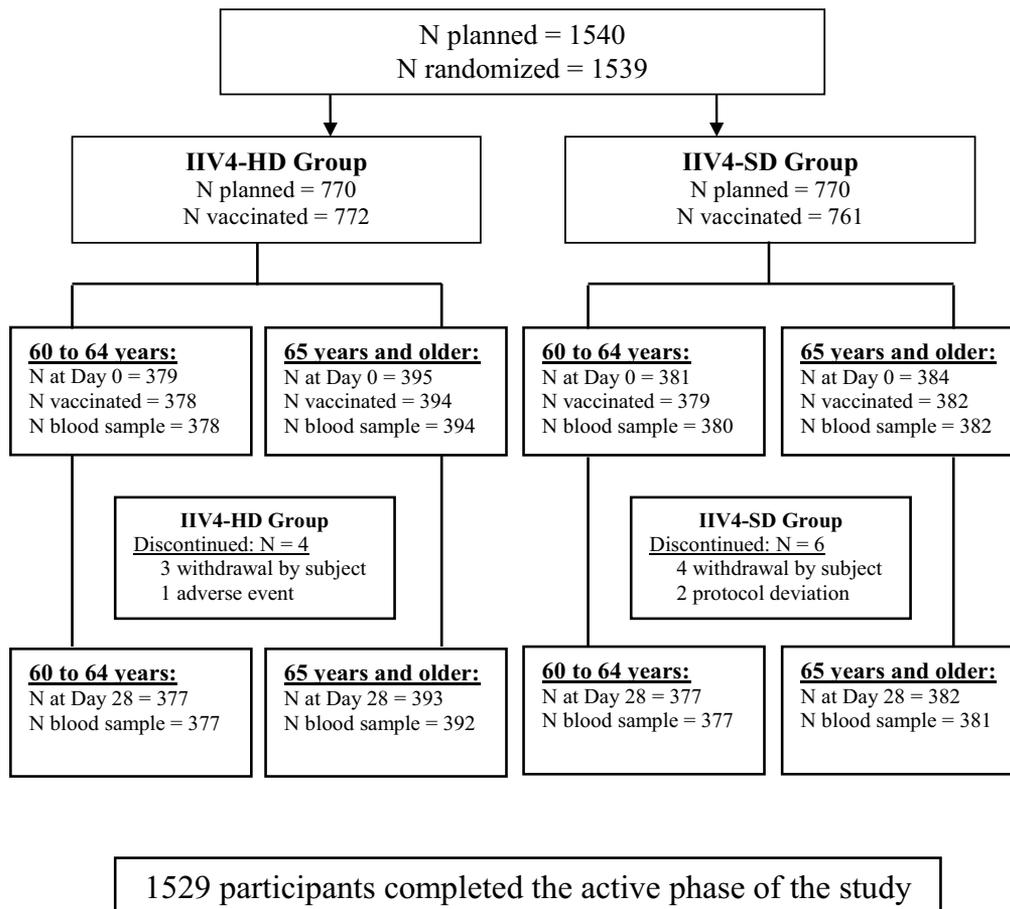


Figure 1. Participant disposition. IIV4-HD, quadrivalent high-dose inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent influenza vaccine; *n*, number of participants.

Table 1. Baseline demographics by randomized group – randomized patients.

	60–64 y			≥65 y			Overall		
	IIV4-HD (N = 379)	IIV4-SD (N = 381)	All (N = 760)	IIV4-HD (N = 395)	IIV4-SD (N = 384)	All (N = 779)	IIV4-HD (N = 774)	IIV4-SD (N = 765)	All (N = 1539)
Sex: <i>n</i> (%)									
Male	175 (46.2)	192 (50.4)	367 (48.3)	214 (54.2)	183 (47.7)	397 (51.0)	389 (50.3)	375 (49.0)	764 (49.6)
Female	204 (53.8)	189 (49.6)	393 (51.7)	181 (45.8)	201 (52.3)	382 (49.0)	385 (49.7)	390 (51.0)	775 (50.4)
Age (y)									
Mean (SD)	62.0 (1.31)	62.0 (1.37)	62.0 (1.34)	71.0 (4.93)	71.3 (5.40)	71.2 (5.17)	66.6 (5.82)	66.6 (6.11)	66.6 (5.97)
Min; Max	60.0; 64.0	60.0; 64.0	60.0; 64.0	65.0; 93.0	65.0; 88.0	65.0; 93.0	60.0; 93.0	60.0; 88.0	60.0; 93.0
Age subgroup: <i>n</i> (%)									
<65 y							379 (49.0)	381 (49.8)	760 (49.4)
≥65 y							395 (51.0)	384 (50.2)	779 (50.6)
65 to <75 y				302 (76.5)	278 (72.4)	580 (74.5)	302 (39.0)	278 (36.3)	580 (37.7)
≥75 y				93 (23.5)	106 (27.6)	199 (25.5)	93 (12.0)	106 (13.9)	199 (12.9)
≥75 to <85 y				90 (22.8)	99 (25.8)	189 (24.3)	90 (11.6)	99 (12.9)	189 (12.3)
≥85 y				3 (0.8)	7 (1.8)	10 (1.3)	3 (0.4)	7 (0.9)	10 (0.6)
Racial origin: <i>n</i> (%)									
Asian	2 (0.5)	2 (0.5)	4 (0.5)	2 (0.5)	1 (0.3)	3 (0.4)	4 (0.5)	3 (0.4)	7 (0.5)
Black or African American	1 (0.3)	0	1 (0.1)	1 (0.3)	2 (0.5)	3 (0.4)	2 (0.3)	2 (0.3)	4 (0.3)
Native Hawaiian or Other Pacific Islander	4 (1.1)	1 (0.3)	5 (0.7)	0	1 (0.3)	1 (0.1)	4 (0.5)	2 (0.3)	6 (0.4)
White	367 (96.8)	377 (99.0)	744 (97.9)	391 (99.0)	379 (98.7)	770 (98.8)	758 (97.9)	756 (98.8)	1514 (98.4)
Other	5 (1.3)	1 (0.3)	6 (0.8)	1 (0.3)	1 (0.3)	2 (0.3)	6 (0.8)	2 (0.3)	8 (0.5)
History of influenza vaccination, <i>n</i> (%)									
Between 01 September 2016 and 31 August 2017	130 (34.3)	143 (37.5)	273 (35.9)	229 (58.0)	232 (60.4)	461 (59.2)	359 (46.4)	375 (49.0)	734 (47.7)
Between 01 September 2017 and 31 August 2018	151 (39.8)	157 (41.2)	308 (40.5)	239 (60.5)	241 (62.8)	480 (61.6)	390 (50.4)	398 (52.0)	788 (51.2)
Since 01 September 2018	176 (46.4)	188 (49.3)	364 (47.9)	270 (68.4)	269 (70.1)	539 (69.2)	446 (57.6)	457 (59.7)	903 (58.7)

n: number of participants fulfilling the item listed.

The age of a participant in the study was the calendar age in y only.

IIV4-HD, quadrivalent high-dose inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent influenza vaccine; SD, standard deviation.

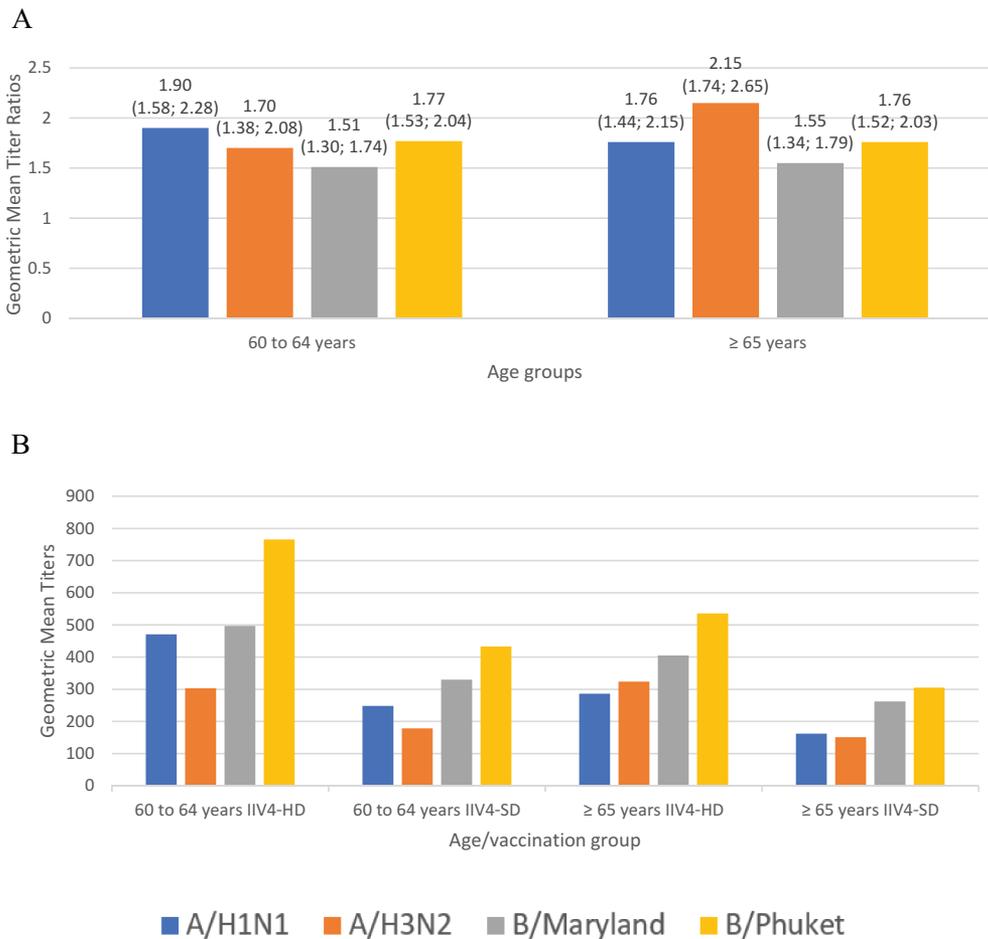


Figure 2. Immunogenicity primary objective: Superiority of IIV4-HD compared with IIV4-SD using GMTs at D 28 after vaccination – Full Analysis Set. (a) Geometric mean titer ratios for each strain in each analysis group. GMTRs calculated as geometric mean of individual ratios at D 28 and 0. Labels GMTR (95% CI). (b) GMTs for each strain in each analysis group. GMT, geometric mean titer; GMTR, geometric mean titer ratio; IIV4-HD, quadrivalent high-dose inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent influenza vaccine.

two in Italy ($N = 85$), four in Poland ($N = 300$), and one in the Netherlands ($N = 344$); 1,529 of these (IIV4-HD 770, IIV4-SD 759) completed the active phase period (Figure 1). A total of 1,528 participants completed the 6-month follow-up period. The duration of the 6-month follow-up was 194 d and the overall study duration 222 d. A total of 1,527 (99.2%) participants were included in the FAS, 920 (59.8%) in the FAS-SN, 308 (20.0%) in the FAS-NA, and 1,435 (92.9%) in the PPAS.

Demographic characteristics are shown for the overall study population and age subgroups in Table 1. Baseline characteristics, including medical history and previous influenza vaccination data, were similar between the vaccination groups in the overall population and each age-group. Characteristics were similar across all analysis groups. A total of 903 (58.7%) participants received influenza vaccination in the previous year (i.e., since September 01, 2018). There was no difference in the number of participants who had received previous vaccinations across the IIV4-HD and IIV4-SD groups.

Immunogenicity outcomes

Superiority of IIV4-HD compared with IIV4-SD was determined by HAI GMTs for the FAS and PPAS as the lower limit of the two-sided 95% CI was above 1 for the ratio of GMTs for

all influenza strains in each age-group (Figure 2(a)). A sensitivity analysis using GMTs at D 28 adjusted for the baseline showed similar results for the FAS and PPAS. In participants 60–64 y of age, ratios of GMTs between groups ranged from 1.51 (B/Maryland) to 1.90 (A/H1N1). In the ≥65 age-group, ratios of GMTs between groups ranged from 1.55 (B/Maryland) to 2.15 (A/H3N2).

At baseline, HAI GMTs were similar between vaccination groups for the four influenza strains; participants in the 60–64 age-group displayed lower GMT for B/Maryland than participants in the ≥65 age-group (Table 2). GMTs for the other three strains were similar between age-groups at baseline. At D 28, GMTs for the four influenza strains had increased compared with baseline and were higher in the IIV4-HD group than the IIV4-SD group (Table 2). GMTs in the IIV4-HD group were higher in the 60–64 age-group than the ≥65 age-group for the A/H1N1, B/Maryland, B/Phuket strains and were similar between age-groups for the A/H3N2 strain (Figure 2(b) and Table 2).

Geometric means of individual titer ratios at D 28 and 0 (GMTR) were higher in the IIV4-HD group compared with the IIV4-SD group in each age-group for all influenza strains (Table

Table 2. Summary of HAI antibody response for each antigen – Full Analysis Set

	≥ 65 years															
	60–64 years						≥ 65 years									
	IV4-HD			IV4-SD			IV4-HD			IV4-SD						
	A/H1N1 (N=377)	A/H3N2 (N=376)	B1 (N=377)	B2 (N=377)	A/H1N1 (N=377)	A/H3N2 (N=377)	B1 (N=377)	B2 (N=377)	A/H1N1 (N=392)	A/H3N2 (N=392)	B1 (N=392)	B2 (N=392)	A/H1N1 (N=381)	A/H3N2 (N=381)	B1 (N=381)	B2 (N=381)
Pre-dose (Day 1)	376	376	377	377	377	377	377	375	392	391	390	388	381	380	380	380
Geometric mean	50.2	11.5	54.7	80.4	50	12.5	68.7	93.2	47.1	15.2	74.2	99.7	42.8	13.5	80.7	100
(95% CI)	(42.7; 59.0)	(10.4; 12.8)	(47.4; 63.2)	(68.6; 94.3)	(42.6; 58.8)	(11.2; 14.0)	(59.4; 79.5)	(79.5; 109)	(40.1; 55.2)	(13.5; 17.1)	(64.3; 85.6)	(86.1; 115)	(36.6; 50.0)	(12.1; 15.0)	(70.1; 92.9)	(86.8; 115)
Participants with titers ≥ 1:10; n (%)	305 (81.1)	196 (52.1)	338 (89.7)	341 (90.5)	305 (80.9)	219 (58.1)	344 (91.2)	341 (90.9)	314 (80.1)	240 (61.4)	360 (92.3)	359 (92.5)	311 (81.6)	222 (58.4)	347 (91.3)	354 (93.2)
(95% CI)	(76.8; 84.9)	(46.9; 57.3)	(86.1; 92.5)	(87.0; 93.2)	(76.6; 84.7)	(52.9; 63.1)	(87.9; 93.9)	(87.6; 93.6)	(75.8; 83.9)	(56.4; 66.2)	(89.2; 94.8)	(89.4; 94.9)	(77.4; 85.4)	(53.3; 63.4)	(88.0; 93.9)	(90.1; 95.5)
Participants with titers ≥ 1:40; n (%)	229 (60.9)	59 (15.7)	234 (62.1)	260 (69.0)	234 (62.1)	66 (17.5)	264 (70.0)	272 (72.5)	228 (58.2)	100 (25.6)	272 (69.7)	300 (77.3)	216 (56.7)	78 (20.5)	291 (76.6)	293 (77.1)
(95% CI)	(55.8; 65.9)	(12.2; 19.8)	(57.0; 67.0)	(64.0; 73.6)	(57.0; 67.0)	(13.8; 21.7)	(65.1; 74.6)	(67.7; 77.0)	(53.1; 63.1)	(21.3; 30.2)	(64.9; 74.3)	(72.8; 81.4)	(51.6; 61.7)	(16.6; 24.9)	(72.0; 80.7)	(72.5; 81.2)
Post-dose (Day 28)	377	376	377	377	377	377	377	377	392	392	392	392	381	381	381	381
Geometric mean	471	303	497	766	248	178	330	433	286	324	405	536	162	151	262	305
(95% CI)	(416; 533)	(262; 350)	(450; 548)	(690; 849)	(217; 283)	(154; 206)	(297; 367)	(391; 480)	(250; 326)	(281; 374)	(366; 447)	(485; 592)	(139; 190)	(129; 176)	(236; 291)	(274; 340)
Participants with titers ≥ 1:10; n (%)	377 (100)	376 (100)	377 (100)	377 (100)	375 (99.5)	373 (98.9)	377 (100)	377 (100)	390 (99.5)	387 (98.7)	392 (100)	392 (100)	376 (98.7)	372 (97.6)	381 (100)	381 (100)
(95% CI)	(99.0; 100)	(99.0; 100)	(99.0; 100)	(99.0; 100)	(98.1; 99.9)	(97.3; 99.7)	(99.0; 100)	(99.0; 100)	(98.2; 99.9)	(97.0; 99.6)	(99.1; 100)	(99.1; 100)	(97.0; 99.6)	(95.6; 98.9)	(99.0; 100)	(99.0; 100)
Participants with titers ≥ 1:40; n (%)	370 (98.1)	357 (94.9)	377 (100)	376 (99.7)	348 (92.3)	336 (89.1)	375 (99.5)	375 (99.5)	373 (95.2)	363 (92.6)	388 (99.0)	389 (99.2)	322 (84.5)	319 (83.7)	377 (99.0)	370 (97.1)
(95% CI)	(96.2; 99.3)	(92.2; 96.9)	(99.0; 100)	(98.5; 100)	(89.1; 94.8)	(85.5; 92.1)	(98.1; 99.9)	(98.1; 99.9)	(92.5; 97.1)	(89.5; 95.0)	(97.4; 99.7)	(97.8; 99.8)	(80.5; 88.0)	(79.6; 87.3)	(97.3; 99.7)	(94.9; 98.6)
Post-dose response based on pre-dose (Day 28/Day 1)	9.36 (7.86; 11.1)	26.2 (22.8; 30.2)	9.07 (7.84; 10.5)	9.52 (8.19; 11.1)	4.96 (4.20; 5.85)	14.2 (12.2; 16.6)	4.8 (4.11; 5.60)	4.66 (4.03; 5.39)	6.07 (5.22; 7.05)	21.4 (18.6; 24.7)	5.48 (4.78; 6.28)	5.39 (4.72; 6.15)	3.8 (3.27; 4.41)	11.2 (9.66; 13.0)	3.25 (2.83; 3.73)	3.06 (2.70; 3.46)
Seroconversion rate: n (%)	250 (66.5)	336 (89.4)	257 (68.2)	266 (70.6)	156 (41.4)	289 (76.7)	180 (47.7)	182 (48.5)	227 (57.9)	340 (87.0)	222 (56.9)	214 (55.2)	141 (37.0)	273 (71.8)	132 (34.7)	132 (34.7)
(95% CI)	(61.5; 71.2)	(85.8; 92.3)	(63.2; 72.8)	(65.7; 75.1)	(36.4; 46.5)	(72.1; 80.8)	(42.6; 52.9)	(43.4; 53.7)	(52.8; 62.8)	(83.2; 90.1)	(51.8; 61.9)	(50.1; 60.2)	(32.1; 42.1)	(67.0; 76.3)	(30.0; 39.8)	(30.0; 39.8)

A/H1N1 = A/Brisbane/02/2018; A/H3N2 = A/Kansas/14/2017; B1 = B/Maryland/15/2016 BX-69A (B Victoria lineage); B2 = B/Phuket/3073/2013 (B Yamagata lineage)

N: number of participants with available data for the considered endpoint.

Seroconversion is defined as either a pre-vaccination HAI titer <1:10 and a post-vaccination titer ≥1:40 or a pre-vaccination titer ≥1:10 and a post-vaccination titer <1:10 and a ≥4-fold increase in post-vaccination titer.

The two-sided exact 95% CI for the single proportion is based on the Clopper–Pearson method. The two-sided 95% CI for the GM is based on the Student *t*-distribution.

CI, confidence interval; GM, geometric mean; GMTR, geometric means of individual titer ratios (post-dose over pre-dose); HAI, hemagglutination inhibition; IV4-HD, quadrivalent high-dose inactivated influenza vaccine; IV4-SD, standard-dose quadrivalent influenza vaccine.

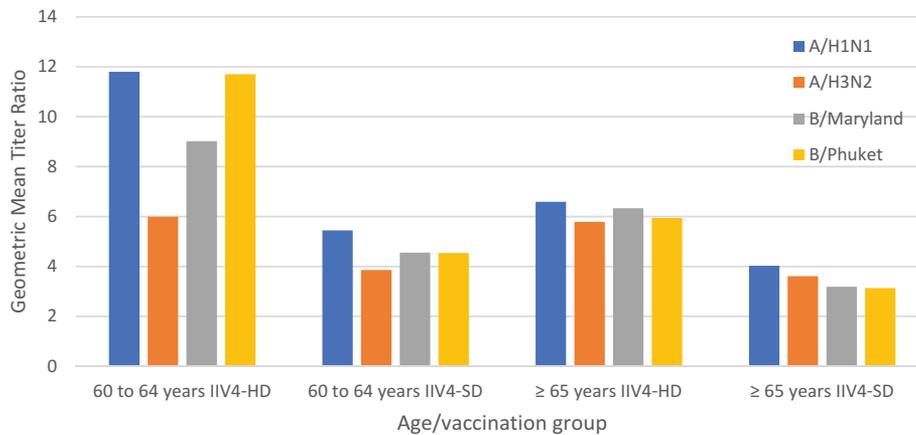


Figure 3. Summary of neutralizing Ab titers (SN assay) at baseline and at D 28 after vaccination – Full Analysis Set SN Subset. Ab, antibody; IIV4-HD, quadrivalent high-dose inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent influenza vaccine; SN, seroneutralization.

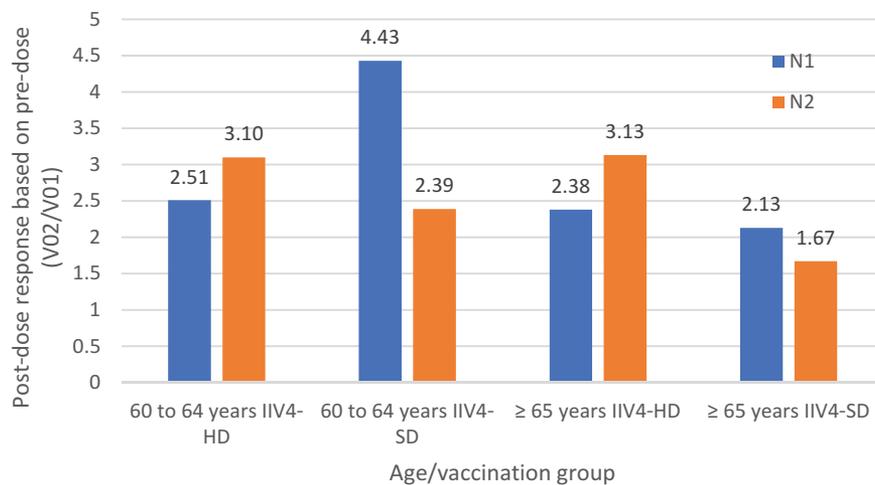


Figure 4. Summary of anti-NA antibody response (ELLA) at baseline and at D 28 after vaccination – Full Analysis Set-NA Subset. Geometric mean titer ratios calculated from GMT at D 28/GMT at D 0. IIV4-HD, quadrivalent high-dose inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent influenza vaccine; NA, neuraminidase.

2). GTMRs in the IIV4-HD group were also higher in the 60–64 age-group than in the ≥65 age-group for A/H1N1, B/Maryland, and B/Phuket strains, with similar GMTRs for the A/H3N2 strain between age-groups. Similar results were seen in the PPAS group.

At D 28, in each age-group, the seroconversion rates were higher for the IIV4-HD group compared with the IIV4-SD group for the four influenza strains, with similar results in the PPAS (Table 2). In the IIV4-HD group, the seroconversion rates for the 60–64 age-group were higher for the B/Maryland and B/Phuket strains than for the ≥65 age-group. Seroconversion rates for the A influenza strains were similar between age-groups.

The percentage of participants with titers ≥40 was higher at D 28 than at baseline for all strains in each age-group and was higher for the IIV4-HD group compared with the IIV4-SD group for the influenza A strains and similar for the influenza B strains. Similar results were found in the PPAS. Percentages of participants achieving titers ≥1:40 were slightly higher for the 60–64 age-group for influenza A strains and similar for influenza B strains versus the ≥65 age-group (Table 2).

For the neutralizing SN Ab method, GMTs were similar between vaccination groups at baseline. At D 28, GMTs for the four strains had increased in both vaccination groups, compared with baseline, and were higher for the IIV4-HD group than the IIV4-SD group (Figure 3). The percentages of participants with a two- and fourfold increase in SN antibody titers were higher for the IIV4-HD group, compared with IIV4-SD, for the four strains. The percentages of participants with titers ≥1:10 were similar between all vaccination and age-groups for the four strains, and percentages were between 99.2% and 100%.

At D 28, there was an increase for the N1 antigen in the A/H1N1 strain and the N2 antigen in the A/H3N2 strain in each age-group (Figure 4). GMTs, GMTRs, and fold rise (two- and fourfold) were similar overall in the IIV4-HD and IIV4-SD groups. The percentages of participants with titers ≥1:10 for the two influenza A strains ranged from 94.8% to 100% and 92.2% to 100% for the 60–64 and ≥65 age-groups, respectively.

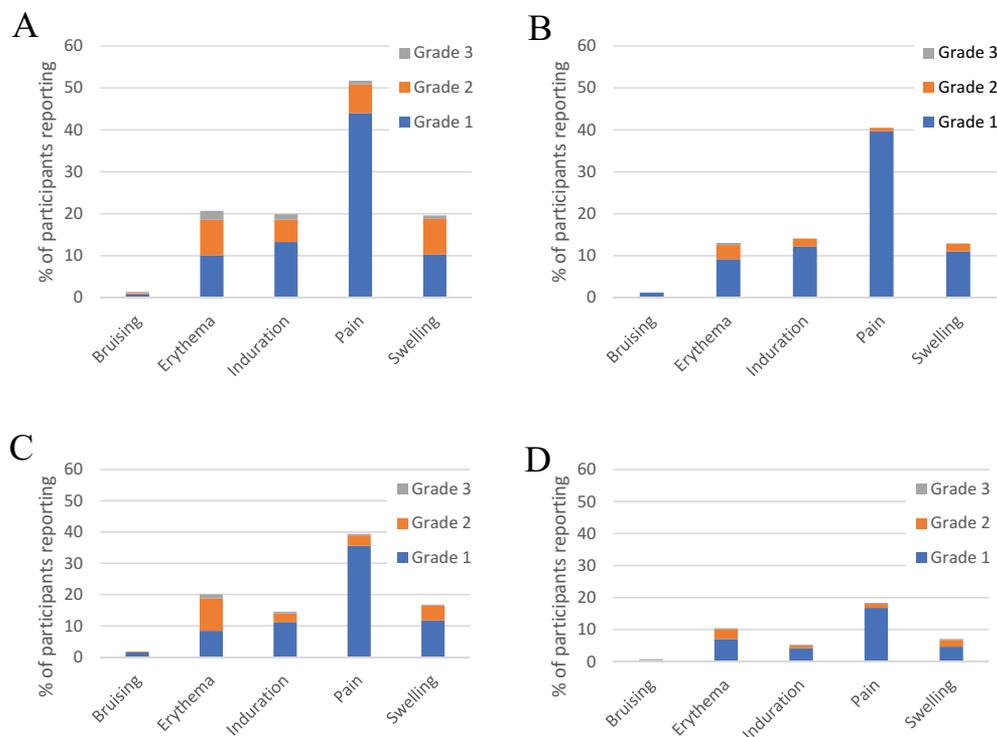


Figure 5. Solicited injection-site reactions after vaccine injection, by maximum intensity during the solicited period (7 d following vaccination) – Safety Analysis Set. (a) 60–64 y IIV4-HD. (b) 60–64 y IIV4-SD. (c) ≥ 65 y IIV4-HD. (d) ≥ 65 y IIV4-SD. IIV4-HD, quadrivalent high-dose inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent influenza vaccine.

Additional descriptive analysis was performed in participants with a condition putting them at risk of severe effects of influenza (i.e., participants with stable chronic illness which did not interfere with study conduct or completion) and participants without an at-risk condition. In general, for QIV-HD, the baseline and post-vaccination GMTs and seroconversion rates were similar in participants with and without an at-risk condition for the four influenza strains. Similar trends were observed for the QIV-SD groups and between both age-groups (60–64 y of age and ≥ 65 y of age); see the supplementary material.

Influence of previous season's influenza vaccine

GMTs at D 28 for individuals vaccinated in the previous year against four influenza strains were lower than those in individuals with no history of influenza vaccination. This was consistent across both vaccination and age-groups. Seroconversion rates at D 28 for individuals vaccinated in the previous year against four influenza strains were lower than those in individuals with no history of influenza vaccination. This was consistent across both vaccination and age-groups.

Safety outcomes

In the 7 da following vaccination, the most frequently reported solicited injection-site reaction was pain (Figure 5). In the 60–64 age-group, 51.7% and 23.6% of the participants in the IIV4-HD and IIV4-SD groups, respectively, reported injection-site pain; in the ≥ 65 age-group this was 39.4% and 18.3%, respectively. Erythema, induration, swelling, and bruising at the

injection site were recorded less frequently. In all groups, these reactions mostly started within 3 d of vaccination and resolved spontaneously within 3 d; most were of Grade 1 or 2 intensity.

A total of 12 participants 60–64 y of age reported at least one Grade 3 solicited injection-site reaction within 7 d of vaccination, 11 (2.9%) in the IIV4-HD group and one (0.3%) in the IIV4-SD group. The most common Grade 3 reaction was erythema, reported by eight (2.1%) participants in the IIV4-HD group and one (0.3%) participant in the IIV4-SD group. In the ≥ 65 age-group, nine participants reported a Grade 3 solicited injection-site reaction – seven (1.8%) in the IIV4-HD group and two (0.5%) in the IIV4-SD group. The most common Grade 3 injection-site reaction reported was erythema ($n = 5$, 1.3%) for the IIV4-HD group and bruising, erythema, induration, pain, and swelling ($n = 1$, 0.3% for each reaction) for the IIV4-SD group.

In the 60–64 age-group, the most common solicited systemic reactions within 7 d of vaccination were myalgia (31.0%) and headache (30.2%) in the IIV4-HD group and headache (19.9%) in the IIV4-SD group (Figure 6). Eighteen participants reported at least one Grade 3 solicited reaction within 7 d of vaccination – 14 in the IIV4-HD group and four in the IIV4-SD group. Myalgia was the most common reaction, reported in six participants in the IIV4-HD group and three in the IIV4-SD group. In the ≥ 65 age-group, the most common solicited systemic reactions within 7 d of vaccination were myalgia (21.6%) and headache (17.3%) in the IIV4-HD and IIV4-SD groups, respectively. Nine participants reported at least one Grade 3 solicited systemic reaction – seven in the IIV4-HD

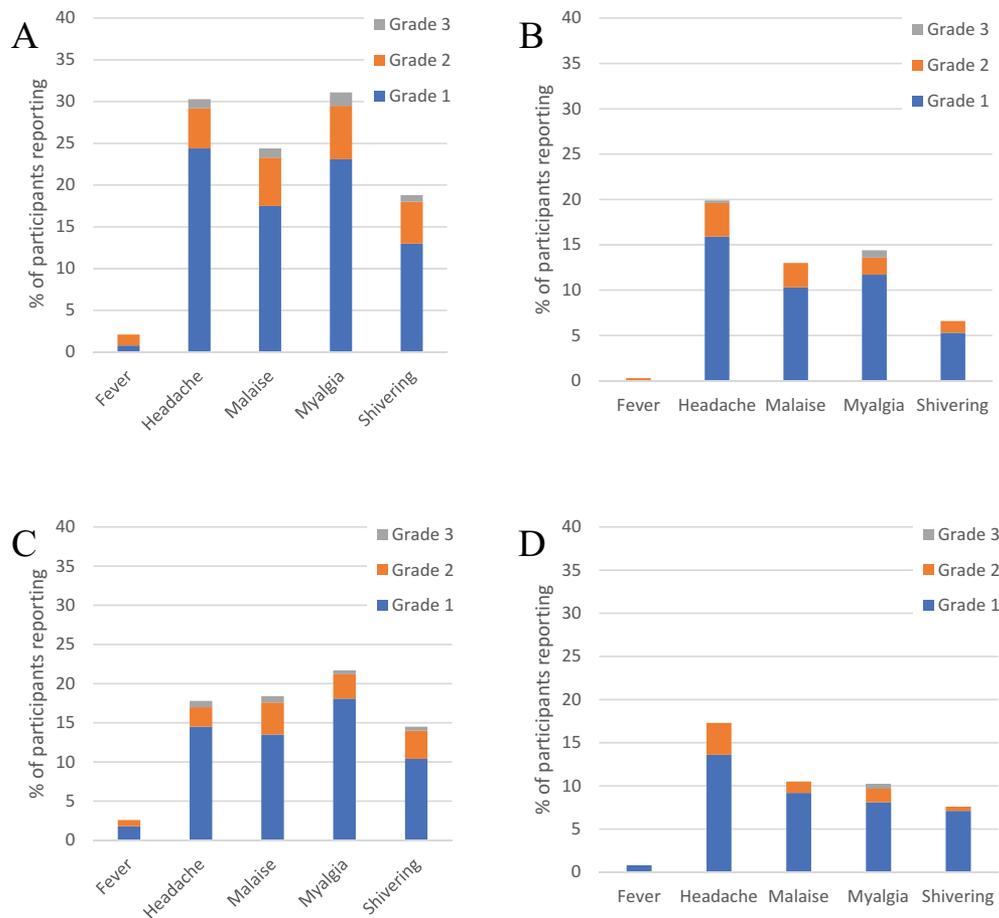


Figure 6. Solicited systemic reactions after vaccine injection, by maximum intensity during the solicited period (7 d after vaccination) – Safety Analysis Set. (a) 60–64 y IIV4-HD. (b) 60–64 y IIV4-SD. (c) ≥ 65 y IIV4-HD. (d) ≥ 65 y IIV4-SD. IIV4-HD, quadrivalent high-dose inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent influenza vaccine.

group and two in the IIV4-SD group. Headache and malaise were the most common reactions reported in the IIV4-HD group ($n = 3$, 0.8% for each reaction) and myalgia was the most common reaction reported in the IIV4-SD group ($n = 2$, 0.5%). In each age-group, most solicited systemic reactions began within 3 d of vaccination, resolved within 3 d, and were of Grade 1 or 2 intensity.

Two participants in the 60–64 age-group reported unsolicited AEs that occurred within 30 min of vaccination, one participant in the IIV4-HD group reporting dizziness and one participant in the IIV4-SD group reporting vessel puncture-site hematoma (Table 3). Neither AE was of Grade 3 intensity. Unsolicited AEs reported within 28 d of vaccination occurred in 25.1% (95/378) and 26.4% (100/379) of participants in the IIV4-HD and IIV4-SD groups, respectively. In all vaccination groups, most unsolicited AEs began within 3 d of vaccination, resolved within 3 d, and most were of Grade 1 or 2 intensity. Grade 3 unsolicited AEs were reported in 2.1% and 0.8% of the participants in the IIV4-HD and IIV4-SD groups, respectively. In the ≥ 65 age-group, within 30 min of vaccination, one participant in the IIV4-HD group reported an unsolicited AE (par-esthesia) which was not of Grade 3 intensity, with no AEs reported in the IIV4-SD group. Within 28 d of vaccination, 23.1% (91/394) and 17.8% (68/382) of the participants in the

IIV4-HD and IIV4-SD groups, respectively, had reported at least one unsolicited non-serious AE. In the IIV4-HD group, most unsolicited AEs began within 3 d of vaccination and were resolved within 3 d. In the IIV4-SD group, most unsolicited AEs started on or after D 15 and were resolved within 4–7 d. Grade 3 unsolicited AEs were reported in 1.3% and 1.6% of the participants in the IIV4-HD and IIV4-SD groups, respectively. Overall SAE rates were low in both vaccine groups and both age-groups but were higher in the ≥ 65 age-group than the 60–64 age-group. No SAEs occurred within 28 d of vaccination that were considered related to the study vaccine, but there were two SAEs during the 180 follow-up in two patients in the IIV4-SD group that were considered related to the vaccine by the investigator: rheumatoid arthritis and thyroid neoplasm. No AESIs were reported in either group. Two participants died (one car accident, one pneumococcal sepsis) but were not considered related to the study vaccine and trial procedures.

Discussion

We present here the first head-to-head study demonstrating that IIV4-HD induces a superior immune response 28 d post vaccination for all four virus strains compared with a IIV4-SD, which is the current standard of care in Europe.

Table 3. Summary of unsolicited AEs within 28 d after vaccine injection – Safety Analysis Set.

Participants experiencing at least one:	60–64 y							
	IIV4-HD				IIV4-SD			
	(N = 378)				(N = 379)			
	n	%	(95% CI)	No. of AEs	n	%	(95% CI)	No. of AEs
Immediate unsolicited AE	1	0.3	(0; 1.5)	1	1	0.3	(0; 1.5)	1
Immediate unsolicited AR	1	0.3	(0; 1.5)	1	0	0	(0; 1.0)	0
Unsolicited non-serious AE	95	25.1	(20.8; 29.8)	144	100	26.4	(22.0; 31.1)	147
Unsolicited non-serious AR	25	6.6	(4.3; 9.6)	47	23	6.1	(3.9; 9.0)	33
Unsolicited non-serious injection-site AR	9	2.4	(1.1; 4.5)	10	8	2.1	(0.9; 4.1)	11
Unsolicited non-serious systemic AE	90	23.8	(19.6; 28.4)	134	96	25.3	(21.0; 30.0)	136
Unsolicited non-serious systemic AR	18	4.8	(2.8; 7.4)	37	17	4.5	(2.6; 7.1)	22
SAE	1	0.3	(0; 1.5)	1	2	0.5	(0.1; 1.9)	2
AESI	0	0	(0; 1.0)	0	0	0	(0; 1.0)	0

Participants experiencing at least one:	≥65 y							
	IIV4-HD				IIV4-SD			
	(N = 394)				(N = 382)			
	n	%	(95% CI)	No. of AEs	n	%	(95% CI)	No. of AEs
Immediate unsolicited AE	1	0.3	(0; 1.4)	1	0	0	(0; 1.0)	0
Immediate unsolicited AR	1	0.3	(0; 1.4)	1	0	0	(0; 1.0)	0
Unsolicited non-serious AE	91	23.1	(19.0; 27.6)	135	68	17.8	(14.1; 22.0)	96
Unsolicited non-serious AR	26	6.6	(4.4; 9.5)	32	16	4.2	(2.4; 6.7)	19
Unsolicited non-serious injection-site AR	8	2	(0.9; 4.0)	8	2	0.5	(0.1; 1.9)	2
Unsolicited non-serious systemic AE	84	21.3	(17.4; 25.7)	127	66	17.3	(13.6; 21.4)	94
Unsolicited non-serious systemic AR	18	4.6	(2.7; 7.1)	24	14	3.7	(2.0; 6.1)	17
SAE	4	1	(0.3; 2.6)	4	5	1.3	(0.4; 3.0)	5
AESI	0	0	(0; 0.9)	0	0	0	(0; 1.0)	0

n: number of participants experiencing the endpoint listed in the first column.

N: number of participants with available data for the relevant endpoint.

"AE leading to study discontinuation" includes those participants meeting at least one of the two following criteria:

1. Termination form marked "not completed" due to "adverse event"

2. Any AE of at least Grade 1 within the time period (missing intensity is included) marked "caused study termination/discontinuation."

Unsolicited non-serious systemic AEs (including SAEs) within 30 min are considered immediate.

Missing relationship (for the definition of AR) was considered at the time of analysis as related to the vaccine.

AE, adverse event; AESI, adverse event of special interest; AR, adverse reaction; IIV4-HD, quadrivalent high-dose inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent influenza vaccine; SAE, serious adverse event.

Influenza is associated with considerable morbidity in the older adults (defined as ≥ 65 y of age), particularly those with underlying comorbidities, who have a high risk of serious outcomes or complications.^{1,5,6,18,19} Although influenza vaccination is recommended for older adults, the lower age definition for this population in national vaccine recommendation differs between countries, varying from as low as 50 y up to 65 y of age.¹⁵ High-dose vaccination has been shown to offer improved protection against influenza,¹³ reduce hospitalizations¹⁴ with a cost saving per recipient, relative to a standard-dose equivalent, in adults ≥ 65 y of age.⁴ IIV4-HD, which has been shown to be well tolerated and to have comparable reactogenicity to IIV3-HD in people ≥ 65 y of age,¹¹ was initially licensed for use in adults ≥ 65 y of age.²⁰ The main aim of the current study was to assess if vaccination with IIV4-HD in adults 60–64 y of age induces a superior immune response versus IIV4-SD and reduces the disease burden of influenza in these individuals.

Given the difference in appearance between IIV4-HD and IIV4-SD, it was not possible to blind the vaccine administrator. As a result, the study was conducted in an observer-blind manner, i.e., the person who administered the vaccine was different from the person assessing safety and collecting the

data to avoid bias in safety evaluation. Therefore, since the assessor was blinded, the unblinding of the administrator was unlikely to impact the findings.

Superiority of IIV4-HD to IIV4-SD, as assessed by HAI GMTs, was demonstrated for both the FAS and the PPAS for all influenza strains in both age-groups. Post-vaccination GMTs, as assessed by HAI and SN assay, increased for the four influenza strains in both age-groups and were higher in the IIV4-HD compared with the IIV4-SD group. In general, the GMTRs, HAI, seroconversion rates, and SN were higher in the IIV4-HD compared with the IIV4-SD group for both age-groups. In addition, the immune response for the IIV4-HD group, in terms of HAI GMTs, GMTRs, and seroconversion rates, was higher in those aged 60–64 y compared with those aged ≥ 65 y for the A/H1N1 and B/strains and was similar between both age-groups for the A/H3N2 strain. Vaccination with IIV4-HD elicited an increased GMT for the N1 and N2 antigens for both age-groups. Similar results were observed for the PPAS group. The reproducibility of the GMT results using two different methods of assessment is a strength of our study.

Overall, vaccination with IIV4-HD was found to be safe and well tolerated, with no major safety concerns. The safety outcomes of IIV4-HD and IIV4-SD were similar in both age-groups, except

in the number of solicited reactions reported which, as expected, were higher with IIV4-HD than IIV4-SD in those 60–64 y of age. The most frequently reported solicited injection-site reaction occurring within 7 d of vaccination was pain, and the more commonly reported systemic reactions were myalgia and headache. Most of the reported solicited reactions were Grade 1 or 2 in intensity and resolved quickly. The incidence of unsolicited AEs and SAEs within 28 d of vaccination was comparable between the IIV4-HD and IIV4-SD groups. None of the SAEs within 28 d or deaths were considered to be related to the vaccine, and there were no AEs of special interest. The occurrence of unsolicited AEs and SAEs was comparable among IIV4-HD and IIV4-SD groups and was found to be acceptable in both age-groups.

Our results in adults 60–64 y of age are in line with previous Phase III studies, which have shown that high-dose vaccine administration improves immunogenicity responses versus standard-dose vaccines in individuals ≥ 65 y of age.^{11,13,16,21} The efficacy of high-dose versus standard-dose vaccine has also been evaluated in a large Phase IIIb–IV, multicenter, randomized, double-blind trial, which showed that IIV3-HD induced significantly higher HAI responses compared with IIV3-SD, and this corresponded to improved protection with IIV3-HD compared with IIV3-SD against laboratory-confirmed influenza illness among adults ≥ 65 y of age.¹³ As the ratios of GMTs seen with IIV3-HD versus IIV3-SD were comparable to those in the present study with IIV4-HD versus IIV4-SD,¹³ there is an expectation that the relative vaccine efficacy between IIV4-HD and IIV4-SD in participants ≥ 60 y of age may be similar to that seen with IIV3-HD.

IIV4-HD has also been shown to be safe and immunogenic compared with IIV3-HD. A recent Phase III study, comparing IIV4-HD with IIV3-HD in individuals ≥ 65 y of age, showed that the IIV4-HD vaccine resulted in improved immunogenicity against the additional influenza strain without compromising the immunogenicity of the other strains or the vaccine's tolerability compared with IIV3-HD. Although IIV4-HD was associated with more injection-site and systemic adverse reactions than the IIV3-HD, $<1\%$ of reactions were reported as severe and most resolved within 3 d of onset.¹¹

The current study showed IIV4-HD should provide good protection against all four included strains of influenza, even in individuals with high-risk conditions for influenza-related complications and individuals vaccinated the previous year for seasonal influenza. A limitation of our study is that data were not collected or analyzed according to comorbidities. Consequently, these results may not be generalizable to frail, elderly populations. However, a subgroup analysis from a previous study stratified patients by age at enrollment (65–75 y and ≥ 75 y of age), presence or absence of high-risk comorbidities, and frailty, and IIV3-HD significantly improved HAI responses for all strains and in all subgroups, irrespective of baseline age, comorbidity, or frailty,¹⁶ suggesting that IIV4-HD may promote a similar response. Further investigation is warranted to assess if the results presented here are reproduced in elderly people with underlying comorbidities or frailty.

In conclusion, the results of our study demonstrate that IIV4-HD generated superior immunogenicity to a standard-dose vaccine and was well tolerated with no major safety concerns in adults ≥ 60 y of age. Furthermore, IIV4-HD induced a robust

immune response irrespective of prior influenza vaccination status or high-risk conditions for influenza-related complications. As improved immunogenicity with IIV3-HD has previously been shown to correlate with improved clinical efficacy relative to IIV3-SD, it is anticipated that IIV4-HD will offer similarly improved protection against influenza compared with IIV4-SD in people ≥ 60 y of age, as well as for adults ≥ 65 y of age.

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Disclosure statement

All authors acquired, analyzed, or interpreted data; drafted or critically revised the manuscript; approved the submitted version; and agreed to be accountable for its accuracy and integrity. In addition, SP and CT designed the study.

SP, AS, and CT are Sanofi Pasteur employees and may/may not hold stock/shares in the company.

MB reports fees paid to UMC Utrecht from Sanofi Pasteur, during the conduct of the study; fees paid to UMC Utrecht from Sanofi Pasteur, Janssen, and Pfizer, outside the submitted work. HS reports personal fees, nonfinancial support and other from Sanofi Pasteur during the conduct of the study; personal fees, nonfinancial support and other from Ablynx, GSK, Janssen, and Pfizer, outside the submitted work; also, personal fees and other from MSD and Seqirus, outside the submitted work.

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Data availability statement

Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data

sharing criteria, eligible studies, and process for requesting access can be found at: <https://www.clinicalstudydatarequest.com/>.

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