Safety of Adjuvanted versus High-Dose Inactivated Influenza Vaccines in Older Adults: Preliminary Safety Results

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Disclaimer

The findings and conclusions in this presentation are those of the presenter and do not necessarily represent the official position of the Centers for Disease Control and Prevention

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Study Background and Significance

- To prevent influenza in older persons, ACIP* recommends vaccination with any U.S.-licensed, age-appropriate influenza vaccine
- Trivalent high dose (HD-IIV3; Fluzone® High-Dose) and adjuvanted (aIIV3; FLUAD®) influenza vaccines are licensed for use only in persons aged 65 years and older in the U.S. and may have improved effectiveness compared to SD-IIV3**
- The safety of HD-IIV3 and aIIV3 has not been compared directly in the same clinical trial in the United States
- The relative impact of HD-IIV3 and aIIV3 reactions on health-related quality of life (HRQOL) has not been studied.

*ACIP: Advisory Committee on Immunization Practices
**SD-IIV3: Trivalent inactivated influenza vaccine, standard dose

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Study Objectives: Primary

1. To compare the proportions of moderate-severe injection-site pain after aIIV3 and HD-IIV3

Research hypothesis: the proportion of subjects who have moderate-severe injection-site pain within the first week post-vaccination will be noninferior (not higher) for aIIV3 (newer U.S. vaccine) compared to HD-IIV3

2. To compare serious adverse events (SAE) and adverse events of clinical interest (AECI) after aIIV3 and HD-IIV3 in the study population and by age-group (65-79 years and ≥80 years)

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Study Objectives: Secondary

1. To compare the proportions of local and systemic reactions (other than moderate-severe injection-site pain) after aIIV3 and HD-IIV3 in the full study population and by age group (65-79 years and ≥80 years).
2. To describe and compare change in health-related quality of life (HRQOL) after aIIV3 and HD-IIV3 in the full study population and by age group.

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Study Design and Participants

- Design
  - Randomized, blinded clinical trial of aIIV3 versus HD-IIV3 during the 2017-2018 and 2018-2019 influenza seasons
- Setting
  - Duke University (2017-2019), Boston University (2017-2019), Cincinnati Children's Hospital Medical Center (2018-2019)
- Participants
  - Community-dwelling volunteers aged ≥65 years
  - Not immunosuppressed, cognitively intact, no co-vaccination, no influenza vaccine contraindications
    - Goal to enroll ≥20% aged ≥80 years
- Intervention
  - Randomized 1:1 to 0.5 ml IM dose of aIIV3 or HD-IIV3
    - Stratified by age group (65-79) and (≥80) years

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Safety and Reactogenicity Assessment

- Participants monitored in clinic ≥15 minutes post-vaccination for adverse events, including syncope
- Solicited reactogenicity events and unsolicited adverse events assessed using standard symptom diary Day 1 (vaccination day) through Day 8
- SAEs during Day 1 through Day 43 post-vaccination
- Adverse events of clinical interest (AECI)
  - Syncope during clinic post-vaccination monitoring
  - Anaphylaxis in first 24 hours after vaccination
  - Guillain-Barré syndrome within 43 days post-vaccination
  - New onset immune-mediated conditions within 43 days post-vaccination

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Health-Related Quality of Life (HRQOL) Assessments

- EuroQOL-5 dimensions-5 levels: EQ-5D-5L*
  - Mobility, self-care, usual activities, pain/discomfort and anxiety/depression rated on 5 levels:
    - no problems, slight problems, moderate problems, severe problems, and extreme problems
  - Responses converted to a Utility Index summary measure
  - Ranges from -0.109 (worst health) to 1.000 (best health)
- EuroQol-Visual Analogue Scale: EQ-VAS
  - Self-rated health on 0 – 100 scale

*Herdman M, et al. Qual Life Res 2011;20:1727-36.

Analysis Plan – Safety Sample Size

- 668 participants (334 per group)
  - Assumes 5% of older adults have moderate-severe injection-site pain after aIIV3 or HD-IIV3 based on prelicensure studies*
  - Clinically meaningful noninferiority margin of 5%
  - alpha of 0.025 (one-sided)
  - At least 80% power to demonstrate proportion of moderate-severe pain noninferior after aIIV3 vs. HD-IIV3

*https://www.fda.gov/media/94583/download
*https://www.fda.gov/media/119870/download

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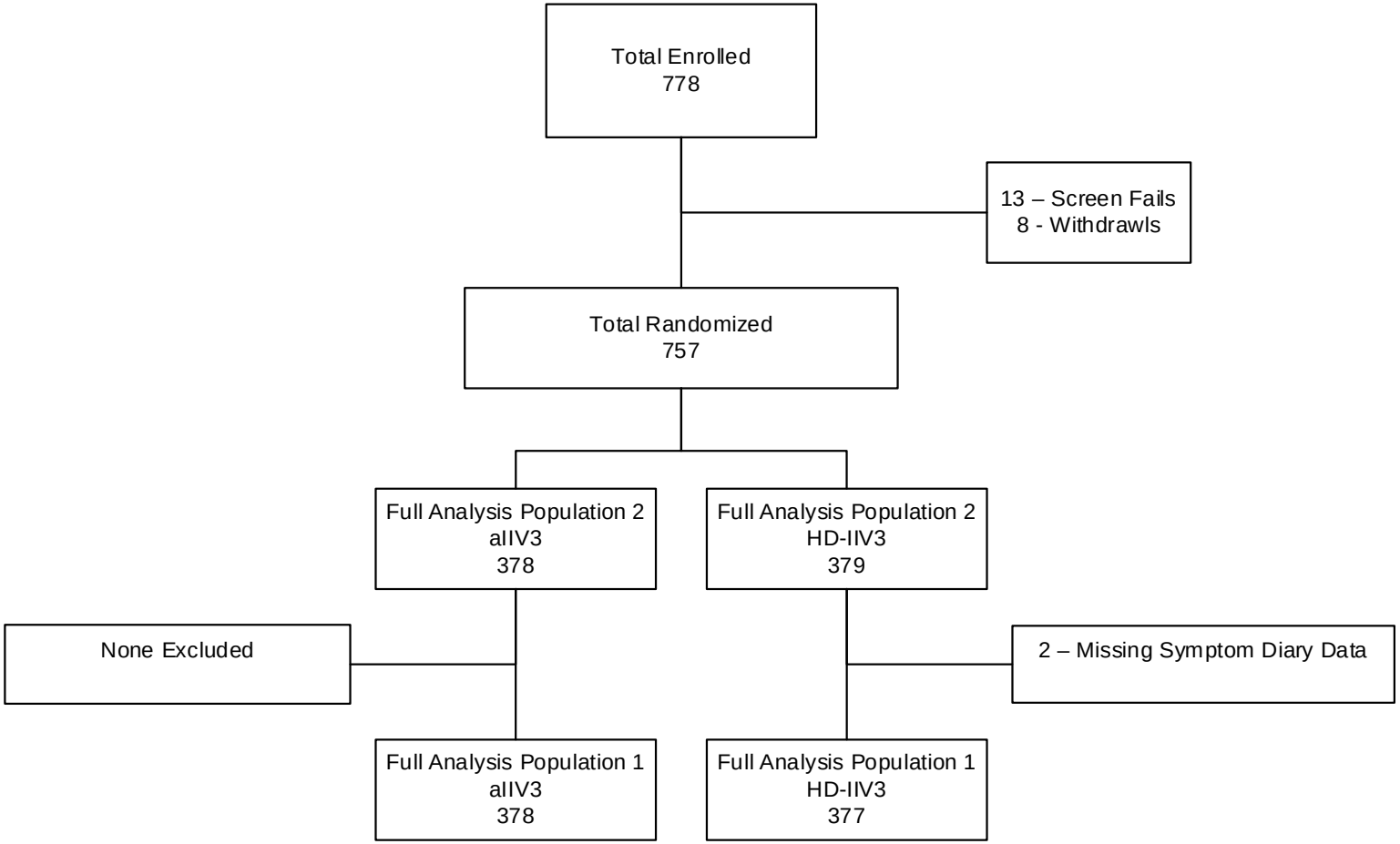
Analysis Plan
Statistical Tests

- Reactogenicity Outcomes
  - Moderate-severe injection-site pain (primary)
    - one-sided alpha 0.025 level
    - Upper bound of a stratified by site Newcombe binomial confidence interval
    - Noninferiority margin of 5%
  - Other moderate-severe reactions: one sided alpha 0.01 level to adjust for multiple comparisons, otherwise used same statistical tests as above
- SAEs and AECIs (primary): two-sided alpha 0.05 level, 95% exact binomial confidence interval
- Change in HRQOL day 1 to day 3 (secondary): two sided alpha 0.01 level to adjust for multiple comparisons, Mann-Whitney U tests

Results

Study Consort Diagram*



*Full Analysis Population 2: all subjects who were randomized and vaccinated
*Full Analysis Population 1: all subjects who were randomized, vaccinated, and provided at least one day of complete data on the symptom diary form.

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Summary of Participants Enrolled and Randomized By Site

Site	All Ages	65-79 Years	≥80 Years
Duke	428	349	79
Boston	243	215	28
Cincinnati	86	30	56
Total	757	594	163
Percentage	100%	78.5%	21.5%

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Demographic Characteristics

Characteristic	aIIV3 (N=378)	HD-IIV3 (N=379)
	Median (Range) or N (%)	Median (Range) or N (%)
Age in Years	72 (65 - 96)	72 (65 - 97)
65-79 years	298 (78.8)	296 (78.1)
≥80 years	80 (21.2)	83 (21.9)
Sex		
Female	213 (56.3)	207 (54.6)
Male	165 (43.7)	172 (45.4)
Race		
White Only	286 (75.7)	303 (79.9)
Black Only	70 (18.5)	59 (15.6)
Other*	22 (5.8)	17 (4.5)
Ethnicity: Hispanic or Latino	7 (1.9)	1 (0.3)

*American Indian/Alaskan Native, Asian, More Than One Race

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Primary Outcome (1) Results
Injection-Site Pain

Group	None	Mild	Moderate	Severe	**Mod-Severe**
aIIV3	297 (78.6%)	69 (18.3%)	10 (2.7%)	2 (0.5%)	**12 (3.2%)**
HD-IIV3	282 (74.8%)	73 (19.4%)	21 (5.6%)	1 (0.3%)	**22 (5.8%)**

Moderate-Severe Pain Difference for aIIV3 minus HD-IIV3 = -2.7%
95% Confidence Interval (-5.8% to 0.36%)

Upper limit of the 95% CI of the difference for aIIV3 minus HD-IIV3 was 0.36% and the noninferiority margin was 5%

The proportion of participants with moderate-severe injection-site pain after aIIV3 was noninferior (not higher) than the proportion after HD-IIV3

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Primary Outcome (2) Results Serious Adverse Events (SAEs) and Adverse Events of Clinical Interest (AECI)

- No SAE was determined to be related to vaccination
- No significant difference in proportion of SAEs between vaccine groups
  - 9 participants had ≥1 SAE after aIIV3 (2.4%; 95% CI:1.1, 4.5)
  - 3 participants had ≥1 SAE after HD-IIV3 (0.8%; 95% CI 0.2, 2.2).
- No AECI occurred

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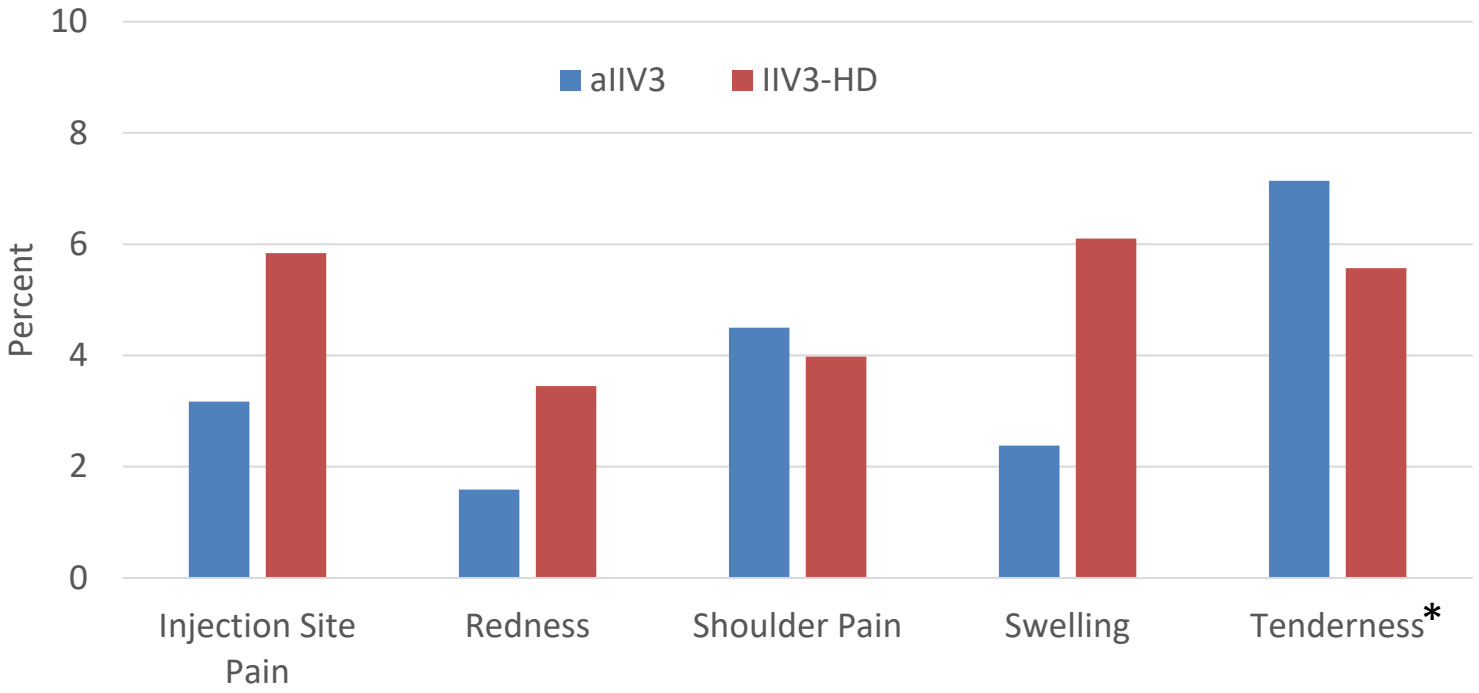
Primary and Secondary Outcome (1) Results Proportions of Moderate-Severe Local Reactions after aIIV3 and HD-IIV3[§]



[§]No local reactions led to a medical visit

*Noninferiority criteria were not met for aIIV3

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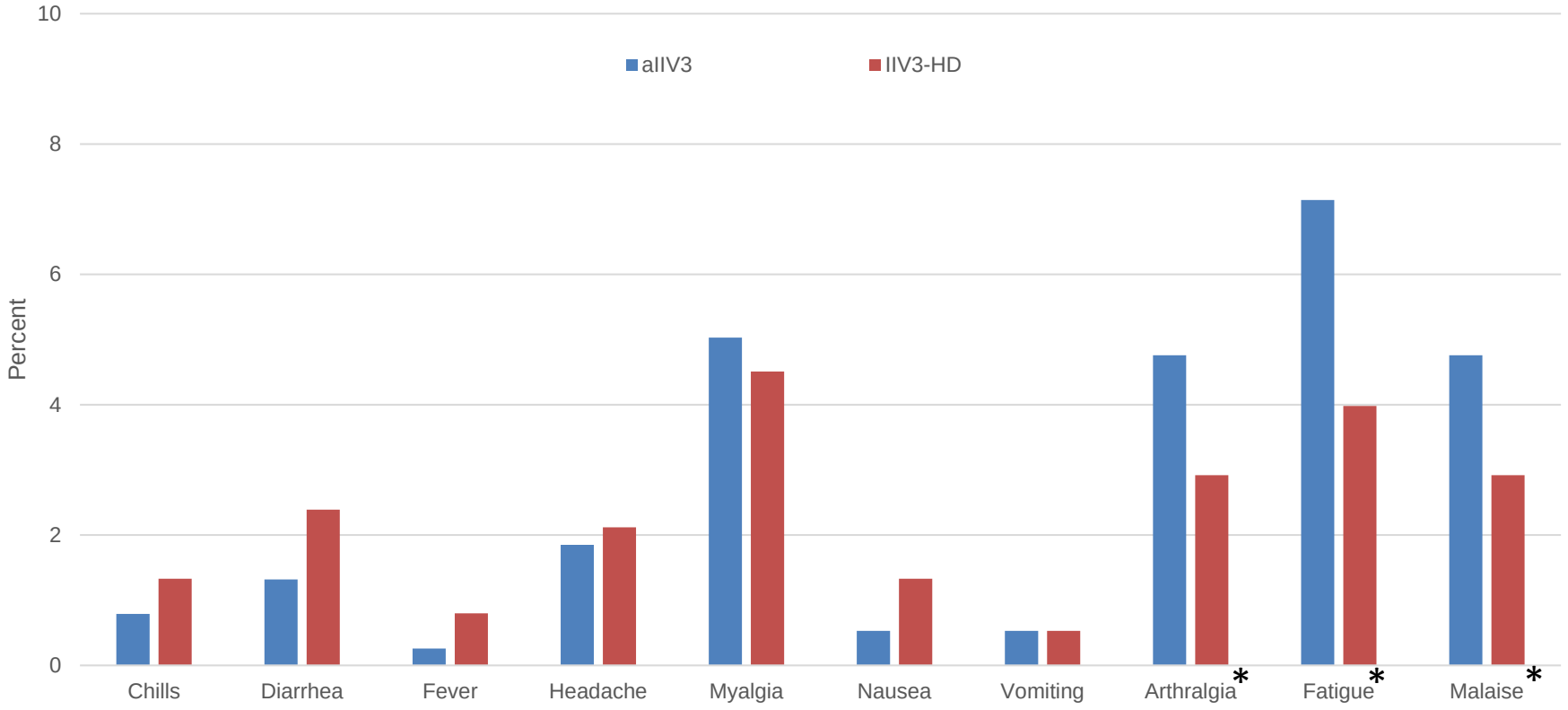
Secondary Outcome (1) Results
Proportions of Moderate-Severe Systemic Reactions after aIIV3 and HD-IIV3[§]



[§]No systemic reactions led to a medical visit

*Noninferiority criteria were not met for aIIV3

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EQ-5D-5L and EQ-VAS Between Group Analysis Change in Score From Day 1 Pre-vaccination to Day 3 Post-vaccination

EQ-5D-5L

Group	Mean Day 1	Mean Day 3	Difference (95% CI)
aIIV3	0.89	0.95	-0.05 (-0.06, -0.04)
HD-IIV3	0.90	0.95	-0.05 (-0.06, -0.04)

No Significant Between Group Difference:
aIIV3 -0.05 vs. HD-IIV3 -0.05, p = 0.74

EQ-VAS

Group	Mean Day 1	Mean Day 3	Difference (95% CI)
aIIV3	85.5	88.1	-2.22 (-3.38, -1.06)
HD-IIV3	85.8	88.3	-2.45 (-3.45, -1.54)

No Significant Between Group Difference:
aIIV3 -2.22 vs. HD-IIV3 -2.45, p = 0.79

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Summary

- The proportion of participants with moderate-severe injection-site pain was not higher after aIIV3 than HD-IIV3
- There were no vaccine-related SAE
- The short-term post-vaccination HRQOL was not affected by either vaccine.
- The safety findings in our study were consistent with prelicensure data for aIIV3 and HD-IIV3.
- From the standpoint of safety, either vaccine is an acceptable option for the prevention of influenza in older adults.

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