sanofi

High-Dose Influenza Vaccine

Summary of Clinical Evidence

in older adults

MAT-BE-2400361 – V1.0 April 2024

Content table

Flu can wreak havoc across major organ systems

An unpredictable virus, leading to severe complications impacting people's lives

8x increased risk of **stroke**[1]

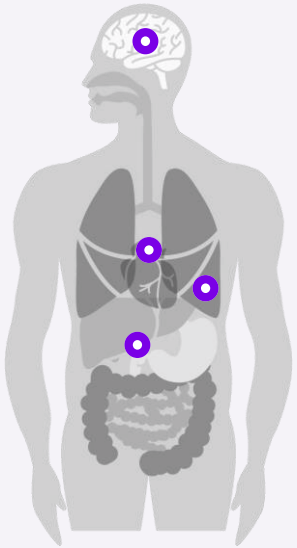
Neurological

23% experience **loss of independence**[2]

Loss of autonomy

74% increased abnormal **glycemic events**[3]

Diabetic complications



Cardiovascular

10x Increased risk of **heart attack**[1]

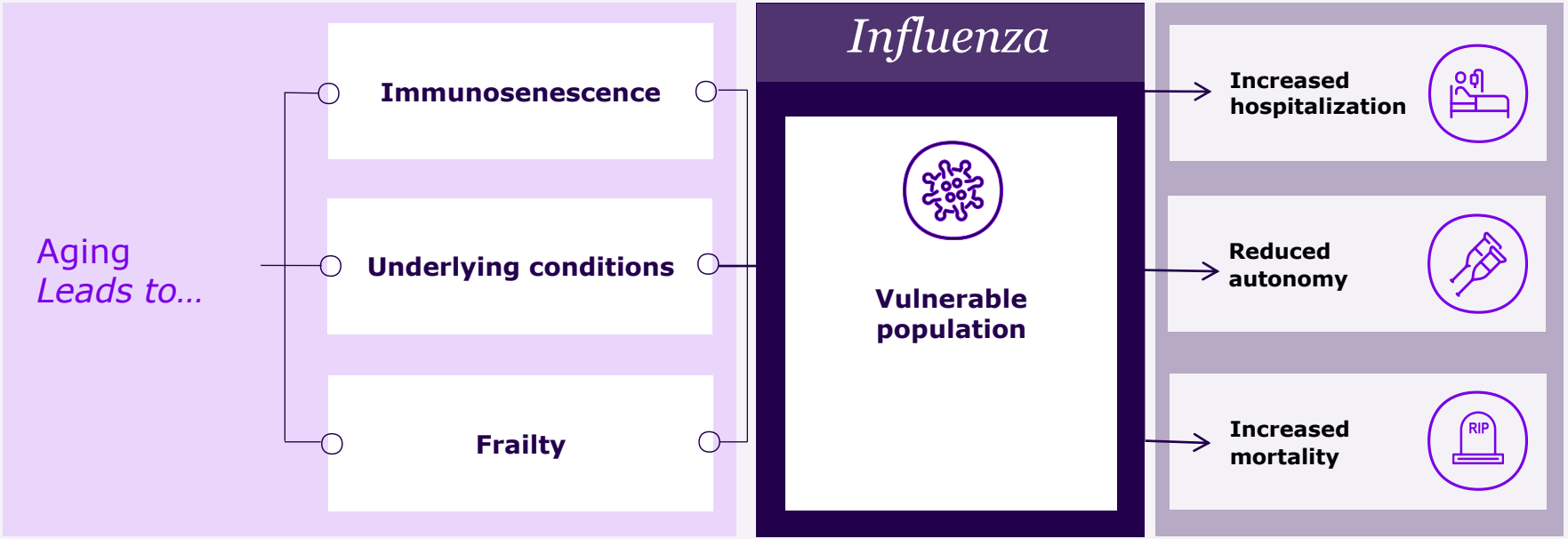
Lower respiratory

8x increased risk of **pneumonia**[4]

References: 1. Warren-Gash C, et al. *Eur respir J*. 2018;29;51:1701794. doi: 10.1183/13993003.01794-2017; 2. Andrew MK, et al. *J Am Geriatr Soc*. 2021; 69:696–703. doi: 10.1111/jgs.16950; 3. Samson SI, et al. *J Diabetes Sci Technol*. 2019; 15:44–52. doi: 10.1177/1932296819883340; 4. Kubale J, et al. *Clin Inf Dis*. 2021. doi: 10.1093/cid/ciaa1053.

Older adults are the most vulnerable to severe outcomes from influenza infection

The relationship between aging and influenza[1–5]



References: 1. CDC. MMWR. 1990;39(RR-7):1–15; 2. CDC. Flu & People 65 Years and Older. Available at: https://www.cdc.gov/flu/highrisk/65over.htm (Accessed 20 December 2022); 3. CDC. Study Shows Hospitalization Rates and Risk of Death from Seasonal Flu Increase with Age. Available at: https://www.cdc.gov/flu/spotlights/2018-2019/hopitalization-rates-older.html (Accessed 20 December 2022); 4. CDC. Key Facts About Influenza (Flu). Available at: https://www.cdc.gov/flu/about/keyfacts.htm (Accessed 13 December 2022); 5. Gavazzi G, et al. *Lancet Infect Dis* 2002;2(11):659–66. doi: 10.1016/s1473-3099(02)00437-1.

High-dose (HD) influenza vaccine has been developed to answer the medical and public health burden in older adults

HD vaccine is a split inactivated influenza vaccine containing 60 µg of hemagglutinin (HA) per strain[1,2]

- It contains 4× the amount of HA compared with standard-dose influenza vaccines
- It was first developed in a trivalent formulation (US license in 2009)
- It was then developed into a quadrivalent formulation (US license in 2019: Fluzone HD quadrivalent® and EU license in 2020: Efluelda®[3–5])

HD vaccine is indicated for the prevention of influenza in people 60[7] years of age and older

281 M doses of HD vaccine (including 142 M doses of QIV-HD) have been distributed, as of October 2023[6]

EU: European Union; HA: hemagglutinin; HD: high-dose; M: million; QIV-HD: high-dose quadrivalent influenza vaccine; TIV-HD: high-dose trivalent influenza vaccine; US: United States.
References in slide notes.

HD vaccine's data generation plan has been built to ensure HD vaccine demonstrates *Protection Beyond Flu*

Protection Beyond Flu

Our commitment to ensure people have access to influenza vaccines with proven better protection against flu infection and its severe complications

CLINICAL OUTCOMES

Infection data
on lab-confirmed flu cases

Hospitalization data
to show impact on severe complications

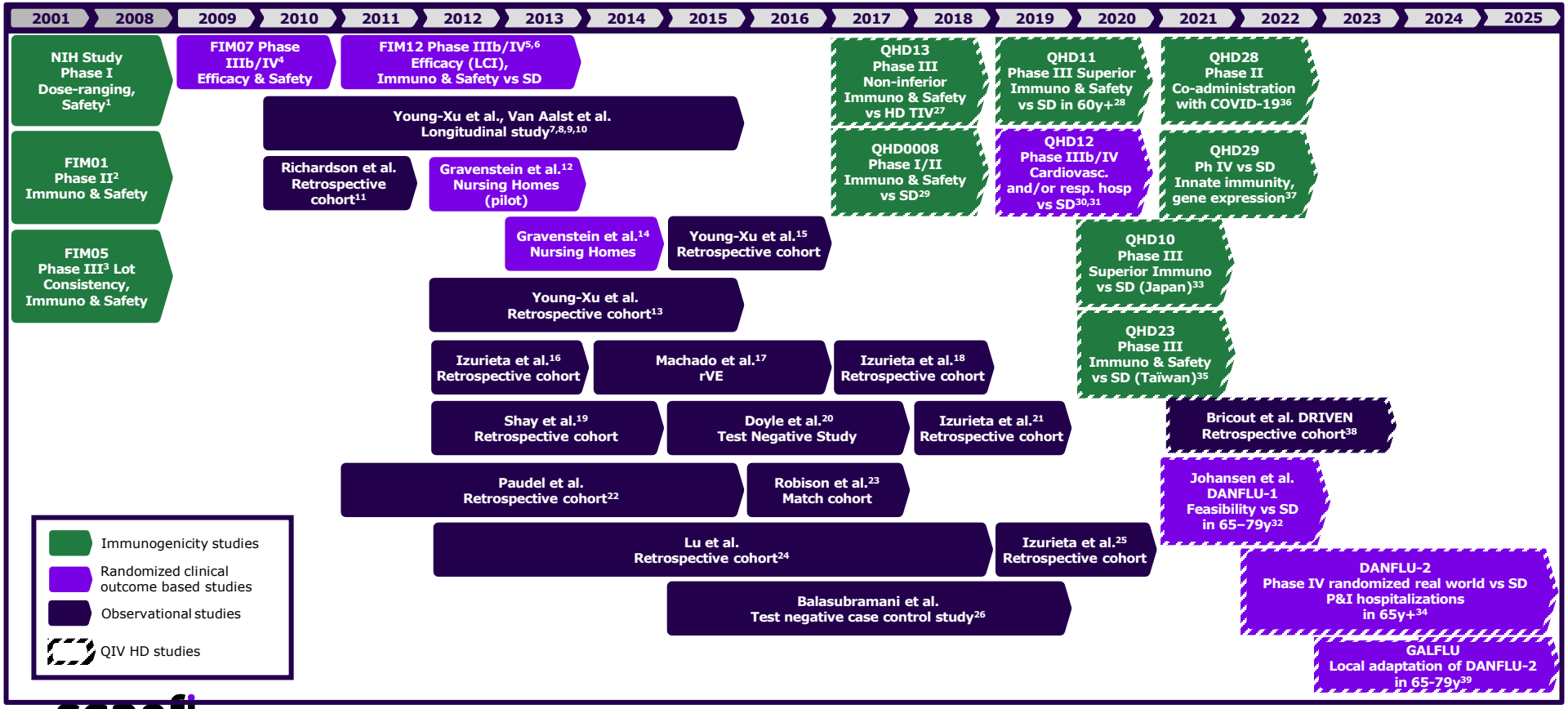
ROBUST METHODOLOGY

Randomized studies
in clinical and real-world settings

Standard dose
as minimum comparator

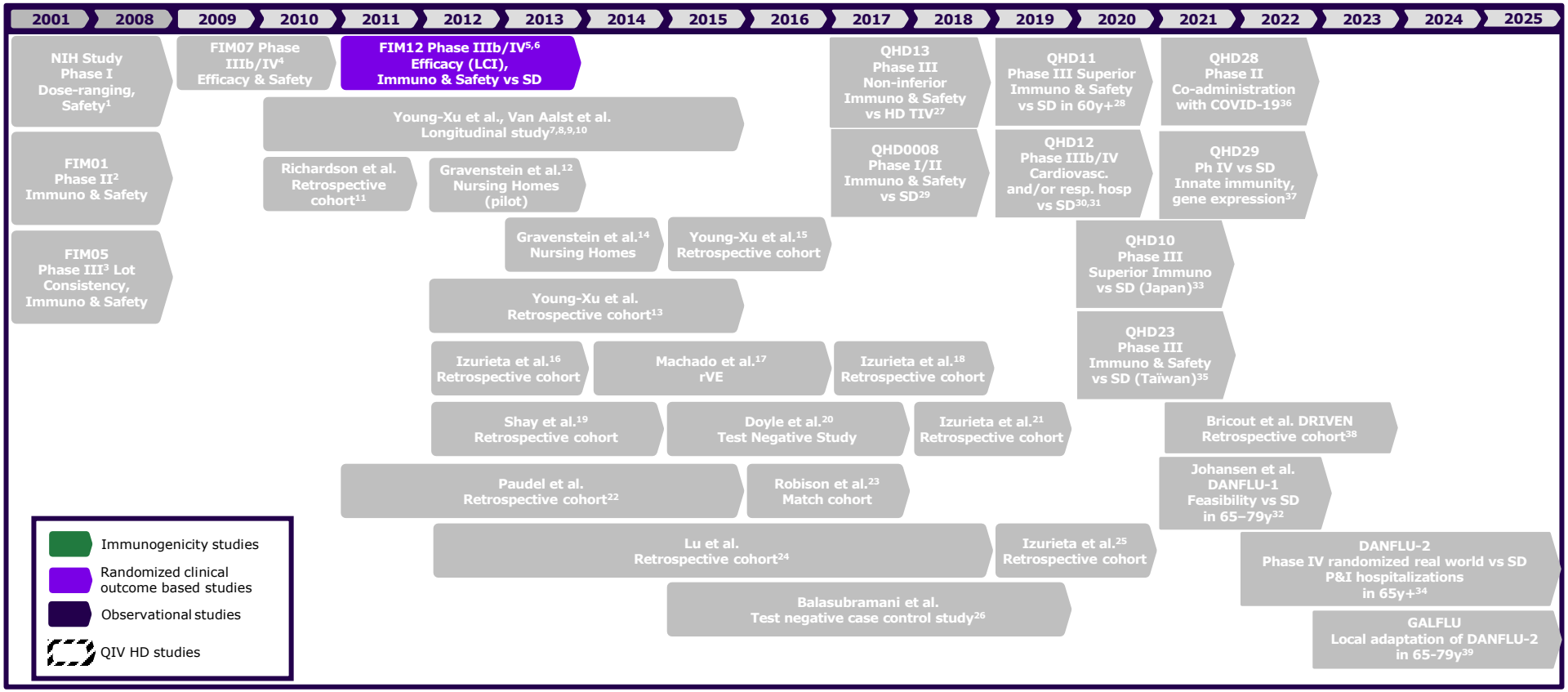
Consistent results
across multiple seasons and study designs

HD vaccine data generation plan*
Focus on immunogenicity/efficacy/effectiveness in older adults



*As of October 2023, completed/ongoing/previously planned studies.
References in slide notes. The duration of the studies corresponds to the influenza season in which the study was conducted. Observational studies are reported here only if published.
As per EMA requirements, Annual Enhanced Passive Safety Surveillance studies are conducted every NH flu season in Europe, starting from NH21/22 for QIV-HD

Focus on RCT of High-Dose vaccine Superiority vs. Standard-dose vaccine against laboratory-confirmed influenza



References in slide notes.

Trivalent HD vaccine is the only influenza vaccine with *a proven superior efficacy* versus standard dose influenza vaccine in a randomized clinical trial in adults aged 65 years and older

31,989
Adults ≥65 years old

Randomized 1:1

126
sites

2
Influenza seasons
2011–12
2012–13

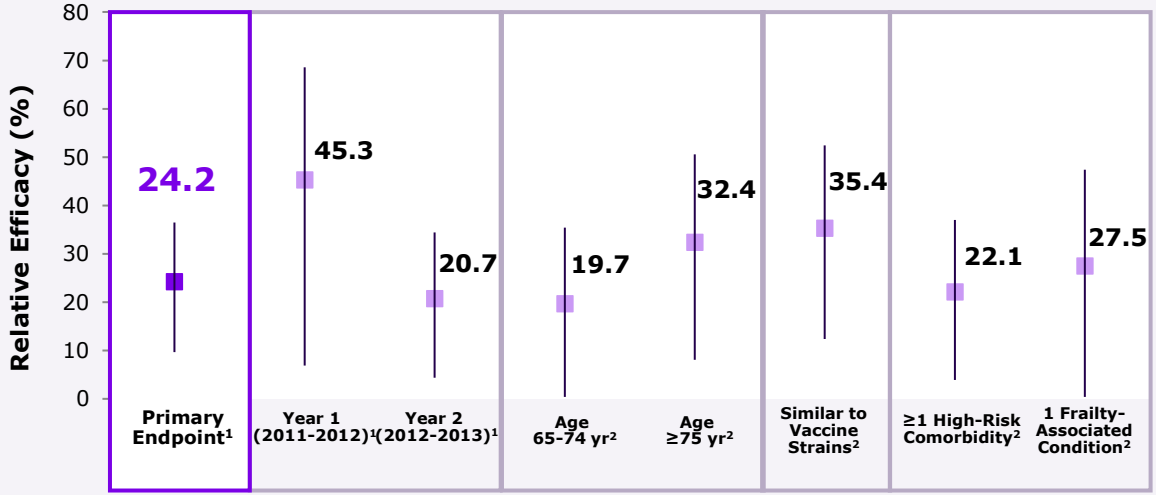
High-dose trivalent influenza vaccine (TIV-HD)

or

Standard-dose trivalent influenza vaccine (TIV-SD)

Primary endpoint

Laboratory-confirmed influenza associated with protocol defined influenza-like illness



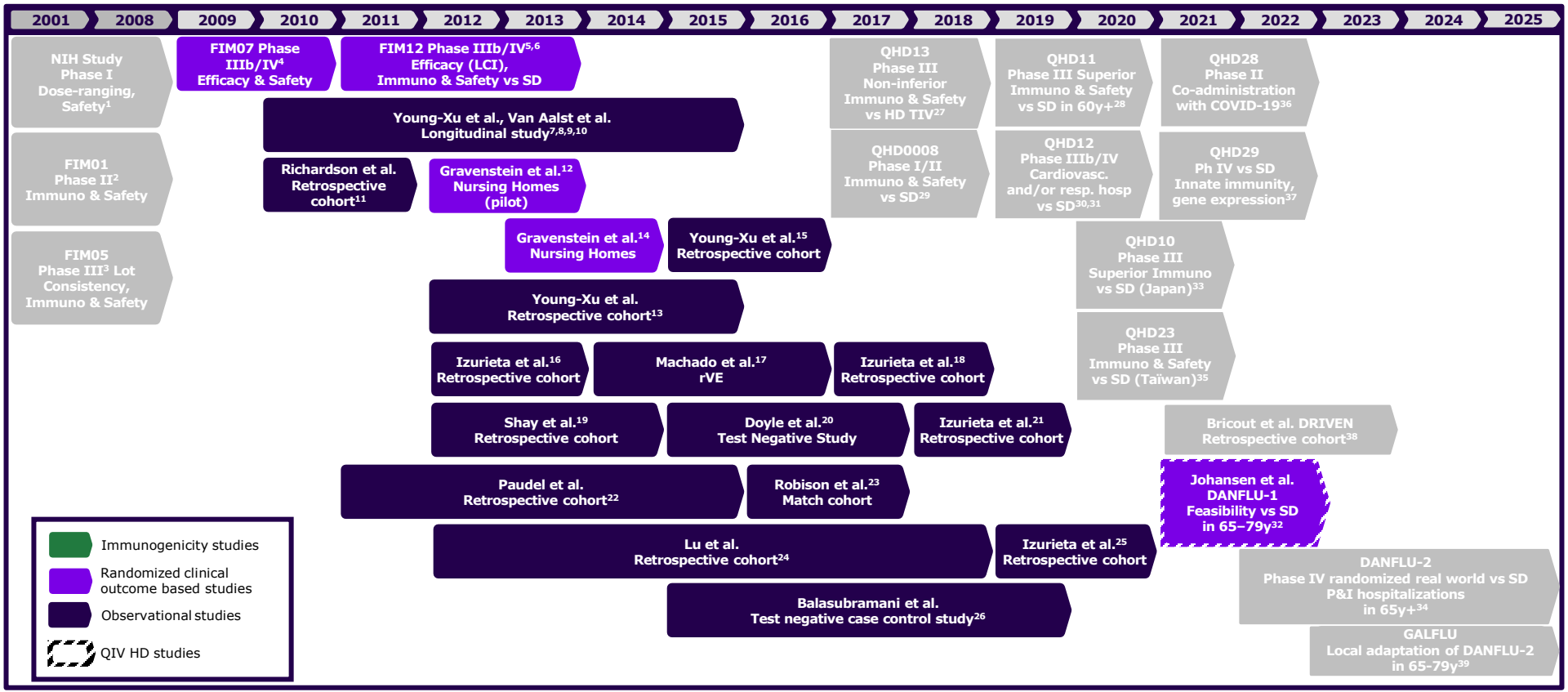
Compared with SD influenza vaccine, the benefit of HD vaccine was demonstrated across age groups, comorbidities/frailty conditions in community-dwelling seniors over 2 influenza seasons

HD: high-dose; SD: standard-dose; TIV-HD: high-dose trivalent influenza vaccine; TIV-SD: standard-dose trivalent influenza vaccine.

References: 1. DiazGranados CA et al. *N Engl J Med* 2014;371:635-45. doi: 10.1056/nejmoa1315727. 2. DiazGranados CA et al. 2015 *Vaccine*;33:4565-71. doi: 10.1016/j.vaccine.2015.07.003.

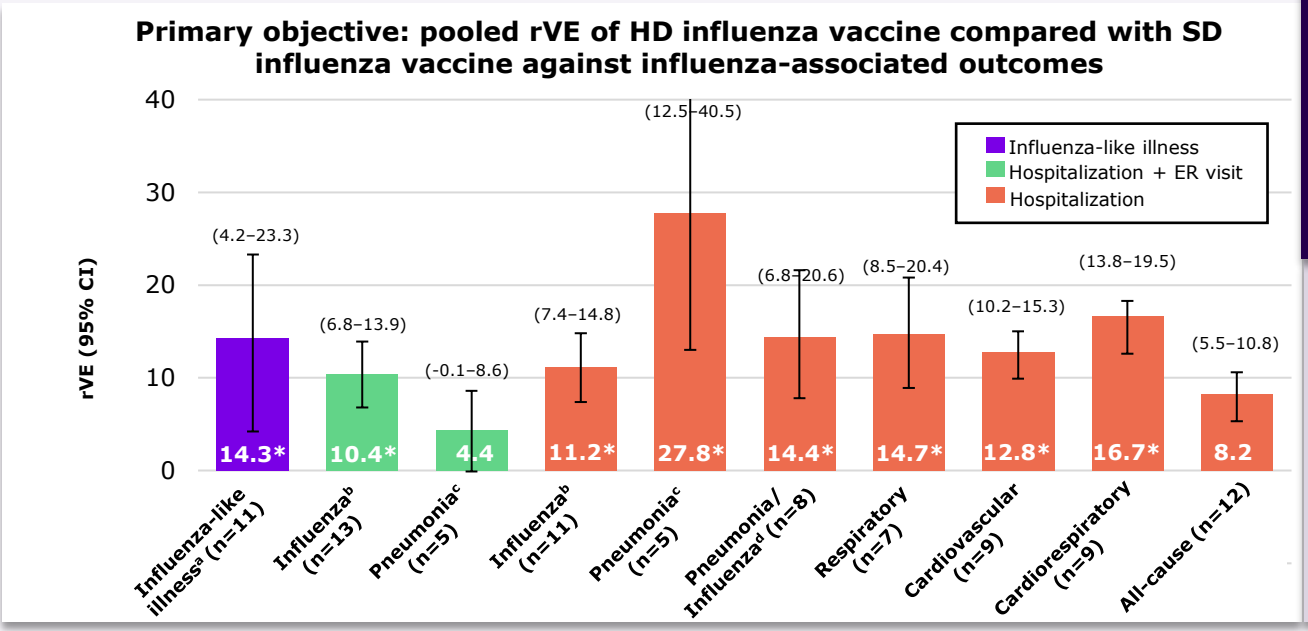
sanofi

Focus on 12-year HD efficacy/effectiveness meta-analysis[40]



References in slide notes.

HD vaccine is consistently *more effective than SD* influenza vaccines at reducing the *clinical outcomes associated with influenza* infection in older adults



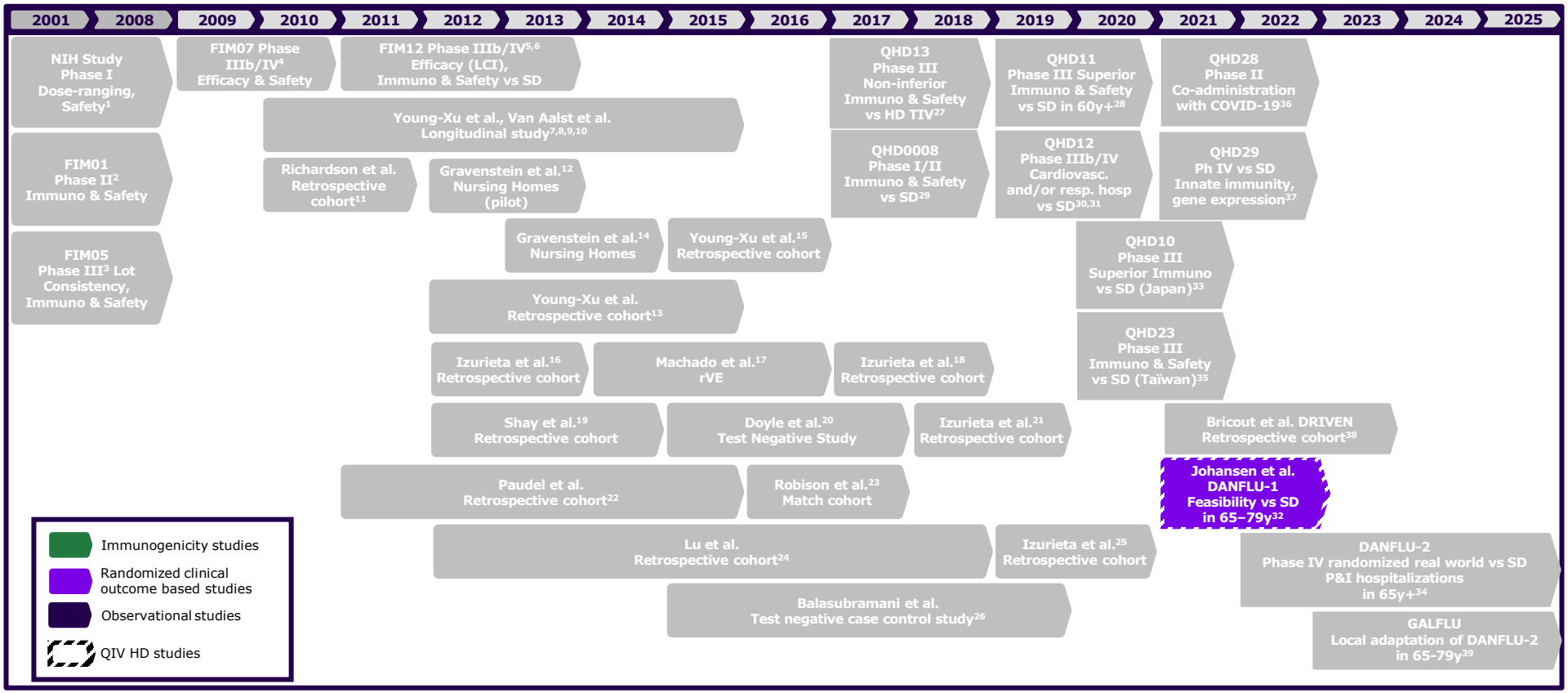
- **Literature search up to April 2023**
- **21 publications meta-analyzed**
  - 6 from randomized studies
  - 15 from observational studies
- **12 seasons, >45M people**

HD vaccine is **consistently** more effective than SD influenza vaccines at reducing the clinical outcomes associated with influenza infection in older adults **irrespective of outcome, season, circulating strain, antigenic match, study type, study setting and age subgroup.**

*p<0.05; [a]Probable/laboratory confirmed influenza like illness; [b]ICD-9-CM 487 coded hospitalizations; [c]ICD-9-CM 480–486 coded hospitalizations; [d]ICD-9-CM 480–488 coded hospitalizations.
CI: confidence interval; ER: emergency room; HD: high-dose; rVE: relative vaccine efficacy/effectiveness; RCT: randomized controlled trial; SD: standard-dose.
Reference: Lee J, et al. Vaccine: X. 2023 doi:10.1016/j.jvacx.2023.100327.

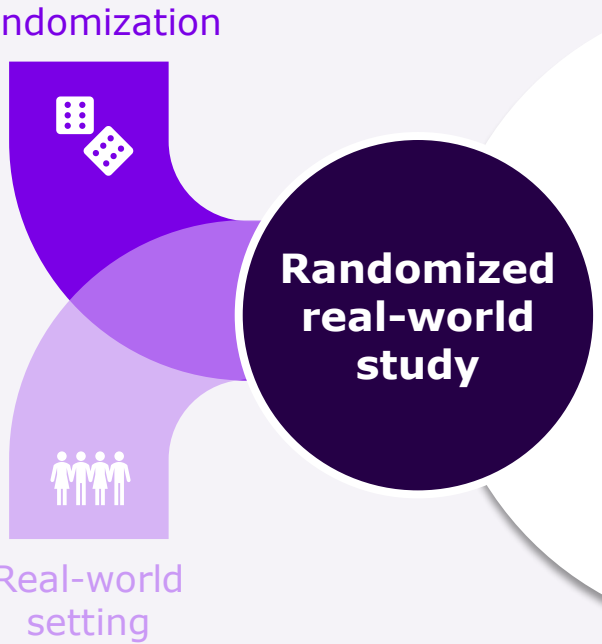
sanofi

Focus on Randomized Real-World study of HD-QIV vs. SD-QIV



References in slide notes.

DANFLU-1 study: innovating with randomized real-world evidence



- Randomized to demonstrate causal relationship
- Large populations to study many outcomes, across different seasons & settings

Impact on critical *public health endpoints*

NEJM Evidence

Published January 23, 2023
NEJM Evid 2023; 2 (2)
DOI: 10.1056/EVIDoa2200206

ORIGINAL ARTICLE

A Pragmatic Randomized Feasibility Trial of Influenza Vaccines

Niklas Dyrby Johansen, M.D.,[1,2] Daniel Modin, M.B.,[1,2] Joshua Nealon, Ph.D.,[3] Sandrine Samson, Ph.D.,[4] Camille Salamand, M.Sc.,[4] Matthew M. Loiacono, Ph.D.,[5] Carsten Schade Larsen, M.D., D.M.Sc.,[6] Anne Marie Reimer Jensen, M.D.,[1,2] Nino Emanuel Landler, M.D.,[1,2] Brian L. Claggett, Ph.D.,[7] Scott D. Solomon, M.D.,[7] Martin J. Landray, Ph.D.,[8,9] Gunnar H. Gislason, M.D., Ph.D.,[1,10,11,12] Lars Køber, M.D., D.M.Sc.,[10,13] Jens Ulrik Stæhr Jensen, M.D., Ph.D.,[14] Pradeesh Sivapalan, M.D., Ph.D.,[14] Lasse Skafte Vestergaard, M.D., Ph.D.,[15] Palle Valentiner-Branth, M.D., Ph.D.,[15] Tyra Grove Krause, M.D., Ph.D.,[15] and Tor Biering-Sørensen, M.D., Ph.D., M.P.H.[1,2]

Reference: Johansen ND, et al. *NEJM Evid* 2023;2. doi: 10.1056/EVIDoa2200206.

DANFLU-1 study overview

Description			Study characteristics
Study Population	**Age:**	65 to 79 years*	**NCT number**: NCT05048589 **EudraCT number**: 2021-003170-31 **Sponsor:** Copenhagen University Hospital-Herlev and Gentofte (Danmark) **Principal Investigator:** Dr. Tor Biering-Sorensen *Conducted collaboratively with Sanofi*
	Number of subjects:	12,477 randomly assigned participants	
Interventions	**Group 1**	Randomly assigned to quadrivalent high dose influenza vaccine (QIV-HD; Fluzone High-Dose); n = 6281	
	Group 2	Randomly assigned to quadrivalent standard dose influenza vaccine (QIV-SD; Influvac Tetra); n=6270	
Study Design	Phase II, pragmatic, open-label, active-controlled, individually-randomized feasibility trial in Denmark Randomly assigned 1:1		
Enrollment	Electronic invitation & consent (or consent at vaccination)		
Duration	2021/2022 flu season (start: October 1st 2021; follow-up period: 14 days after vaccination to May 31st 2022)		
Location	Denmark (>1,000 decentralized vaccination sites across the country)		
Objectives	1. Assess feasibility, reliability, and validity of the proposed pragmatic randomized study design 2. Demonstrate comparability of the QIV-HD vs QIV-SD cohorts to the overall Danish population 3. Assuming adequate influenza circulation**, validate the feasibility conditions above by describing event rates in the QIV-HD and QIV-SD participants and calculating rVE for respiratory endpoints • ICD-coded hospitalization for pneumonia/influenza, respiratory disease, and cardio-respiratory disease 4. Validate the feasibility conditions above by describing event rates in the QIV-HD and QIV-SD participants and calculating rVE for cardiovascular disease, all-cause hospitalization, all-cause mortality, and COVID-19		

*QIV-HD was preferentially recommended for those 80+ during the 2021/22 season; ** >4 weeks (consecutive or non-consecutive) of ≥10% influenza test positivity in national Danish surveillance data.
ICD: International Classification of Diseases; QIV-HD: high-dose quadrivalent influenza vaccine; QIV-SD: standard-dose quadrivalent influenza vaccine; rVE: relative vaccine effectiveness.
Reference: Johansen N, et al. *NEJM Evidence.* 2023;2(2); doi: 10.1056/EVIDoa2200206.

The first and only published data from a *randomized real-world study* comparing QIV-HD to QIV-SD in *2021–22 in Europe*

12,477 participants (mean age: 71.7 years; 5877 [47.1%] were women) with 99.9% complete follow-up data

Outcome	Events QIV-HD (n=6245) n, (%)	Events QIV-SD (n=6232) n, (%)	rVE (95% CI)
Hospitalization for influenza or pneumonia	**10 (0.2)**	**28 (0.4)**	**64.4 (24.4 to 84.6)**
Hospitalization for respiratory disease	24 (0.4)	40 (0.6)	40.1 (-1.8 to 65.5)
Hospitalization for cardiorespiratory disease	103 (1.6)	117 (1.9)	12.1 (-15.5 to 33.3)
Hospitalization for cardiovascular disease	82 (1.3)	81 (1.3)	-1.0 (-39.1 to 26.6)
Hospitalization for COVID-19	15 (0.2)	12 (0.2)	-24.7 (-191.9 to 45.5)
Hospitalization for any cause	513 (8.2)	550 (8.8)	6.9 (-5.2 to 17.6)
All-cause death	**21 (0.3)**	**41 (0.7)**	**48.9 (11.5 to 71.3)**

Conclusions

This study showed:

- A **pragmatic randomized trial** of QIV-HD vs QIV-SD using existing infrastructure and registry-based data was **feasible**
- **Lower incidence of hospitalization** for **influenza or pneumonia** and **all-cause mortality** in the QIV-HD group compared with the QIV-SD group
- Positive rVE trends provide new high-quality evidence for QIV-HD, however, findings require confirmation in an adequately powered trial to confirm exact magnitude of effect size → DANFLU-2

CI: confidence interval; QIV-HD: high-dose quadrivalent influenza vaccine; QIV-SD: standard-dose quadrivalent influenza vaccine; rVE: relative vaccine effectiveness.

Reference: Johansen ND, et al. *NEJM Evid* 2023;2. doi: 10.1056/EVIDoa2200206.

High-Dose flu vaccine sets the bar for Protection Beyond Flu

CLINICAL OUTCOMES

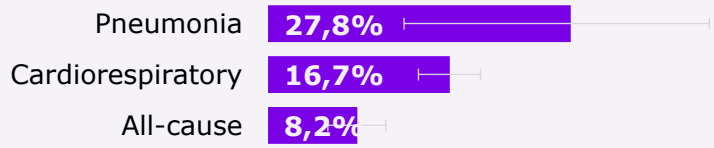
INFECTION DATA[1]

- Randomized clinical trial
- vs standard dose (SD)
- 32,000 subjects aged 65+ years across two seasons
- Lab-confirmed influenza

+24.2%
(95% CI: 9.7–36.5)
relative efficacy

HOSPITALIZATION DATA[2]

Reduction in hospitalizations vs SD



ROBUST METHODOLOGY

RANDOMIZED STUDIES

Clinical settings

Real-world settings

VS STANDARD DOSE

All results *over and above* standard dose

CONSISTENT RESULTS

12 seasons[2]

>45M older adults[2]

DANFLU-1 **Randomized real-world study** *Season 2021-22* QIV HD associated with *64.4%* (95% CI: 24.4–84.6) lower rates of flu and pneumonia hospitalizations vs QIV SD[3]

CI: confidence interval; M: million; QIV-HD: high-dose quadrivalent influenza vaccine; QIV-SD: standard-dose quadrivalent influenza vaccine; SD: standard-dose.

References: 1. DiazGranados CA, et al. *N Engl J Med*. 2014; 371:635-45. doi: 10.1056/nejmoa1315727; 2. Lee J, et al. Vaccine: X. 2023 doi:10.1016/j.jvacx.2023.100327. ; 3. Johansen ND, et al. *NEJM Evid* 2023;2. doi: 10.1056/EVIDoa2200206.

No safety concerns identified during clinical development nor post-marketing surveillance

Both the clinical trial and post-licensure data demonstrate that the safety profile of HD in adults 60 years of age and older is acceptable[1,2]

Independent ECDC and CDC assessments:

- HD vaccines are likely associated with a higher frequency of local and systemic reactions […] Notably these symptoms are typically reported as mild and transient in nature[5]
- Studies conducted using VAERS demonstrate no new or unexpected safety concerns among individuals aged≥65 years[3–5]

Enhanced Passive Safety Surveillance (EPSS) for 2021/22 and 2022/2023 in Germany[6,7]

- While used in routine as the preferred influenza vaccine for people 60+, HD showed a safety profile consistent with former clinical studies.

Solicited local reactions[1] n (%)	**TIV-HD (n=2572)**	**TIV-SD (n=1260)**
Pain	915 (**36%**)	306 (**24%**)
Erythema	384 (**15%**)	136 (**11%**)
Swelling	165 (**9%**)	45 (**6%**)

CDC: Centers for Disease Control and Prevention; ECDC: European Centre for Disease Prevention and Control; HD: high-dose; SD: standard dose; TIV: tetravalent influenza vaccine; VAERS: Vaccine Adverse Event Reporting System.

References: 1. Falsey A, et al. *J Infect Dis*. 2009 200:172-80. doi: 10.1086/599790.; 2. Kaka et al. *Open Forum Infect Dis*. 2017;4:ofx001. doi: 10.1093/ofid/ofx001.; 3. Moro PL et al. *Infect Dis*. 2012; 54:1608-14. doi: 10.1093/cid/cis256.; 4. Moro PL et al. *Vaccine.* 2020; 38:5923-26. doi: /10.1016/j.vaccine.2020.07.007.; 5. ECDC. Seasonal influenza vaccines systematic review. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/seasonal-influenza-vaccines-systematic-review-efficacy.pdf (Accessed April 2023); 6. Gandhi-Banga S, et al. *Influenza Other Respi Viruses*. 2023;17:e13071. doi: 10.1111/irv.13071. 7. Brysch P, et al. ESWI conference 2023 Poster 458.

All published "GRADE-like" analyses of benefit-risk of influenza vaccines in older adults acknowledge the highest level of evidence for HD

GRADE

ECDC 2020

"High-dose trivalent influenza vaccination was shown to have higher relative vaccine efficacy in preventing influenza compared with standard-dose trivalent influenza vaccines in older adults ≥ 65 yo (VE=24%, 95%CI 10 to 37, one RCT, moderate-certainty evidence)."

"HD may provide better protection against laboratory-confirmed influenza and proxy outcome measures"[2]

NACI 2018

For 65+: "There is good evidence that the Fluzone® HD vaccine provides superior protection (e.g., decrease in ILI, influenza-related death and all-cause hospitalization compared with SD-TIV in the elderly (Grade A Evidence)"[1]

RKI 2021

"For 60+: "Evidence of relative efficacy/effectiveness and safety is better for HD than for the three other enhanced vaccines"[3]

"HD shows small but significant superiority against lab-confirmed influenza and not lab-confirmed endpoints. For the other vaccines, this statement can not be made with such certainty currently"[3]

US CDC 2022

For 65+: "HD-IIV, RIV and aIIV have shown relative benefit compared with SD-IIVs certain studies, with the most evidence available for high dose vaccine"[5]

NCIRS 2022

"For HD-IIV vs SD-IIV in people aged 65+, the overall certainty of evidence in GRADE was rated as "moderate""

"For the MF59 vaccine vs the SD-IIV vaccine in people aged 65+, the overall certainty of evidence in GRADE was rated as "low""[4]

RECO

NACI

Recommendation season 2023–2024[6]

- "IV-HD should be used over IIV-SD, given the burden of influenza A(H3N2) disease and the good evidence of IIV3-HD providing better protection compared to IIV3-SD in adults 65 years of age and older" (Individual recommendation)
- Any available influenza vaccine (Public level)

STIKO

Recommendation season 2023–2024[7]

- Preferential recommendation for all persons ≥60 years of age with inactivated, high-dose quadrivalent influenza vaccine

ACIP

Recommendation season 2023–2024[9]

- "ACIP recommends that adults aged ≥65 years preferentially receive any one of the HD or adjuvanted influenza vaccines: HD-IIV4, RIV4, or aIIV4"
- ***"HD-IIV4 was associated with lower risk for diagnostic pneumonia and influenza hospitalizations (rVE 64.4; 95% CI = 24.4–84.6)"***

ATAGI

Recommendation season 2023[8]

- "For adults aged ≥65 years, both the adjuvanted (Fluad® Quad) and high dose influenza vaccine (Fluzone High Dose Quadrivalent) are preferentially recommended over standard influenza vaccine."

The evidence for HD in *older adults* demonstrates *Protection Beyond Flu*

- The ONLY RCT demonstrating superiority vs SD in those aged 65+ with LCI as a primary endpoint[1]
- Protection against influenza-associated hospitalizations[2, 3]
- Consistent efficacy/effectiveness data in 12 influenza seasons: meta-analyzed, >45 M subjects[2]
- The 1st and only published data from a randomized real-world study comparing QIV-HD to QIV-SD in 2021–22[4]
- No safety concerns[5], with more than 281M doses distributed as of October 2023*
- Concomitant administration with mRNA-COVID vaccine safe and immunogenic[6]

Quality of evidence acknowledged by the five independent critical appraisals publicly available (**GRADE-like analyses**)[7-10]

*Sanofi data on file; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; LCI: laboratory-confirmed influenza; M: million; QIV-HD: high-dose quadrivalent influenza vaccine; QIV-SD: standard-dose quadrivalent influenza vaccine; RCT: randomized controlled trial; SD: standard-dose.
References in slide notes.

What's next? Two randomized real-world studies are currently ongoing to further document the incremental clinical benefit of HD over SD beyond prevention of influenza infection

	Population	Intervention	Comparator	Outcomes

1. DANFLU-2 (Denmark)[1]	• Target 287k Danish citizens 65+ years over three seasons (2022-25)	High-Dose Quadrivalent Influenza Vaccine (**randomized 1:1**)	Standard-Dose Quadrivalent Influenza Vaccine (**randomized 1:1**)	• Primary: pneumonia and/or influenza hospitalization
				• Secondary:
				  • Cardio-respiratory hospitalization
				  • All-cause hospitalization
				  • All-cause mortality
				  • Hospitalization for influenza
				  • Hospitalization for pneumonia

2. GALFLU (Galicia, Spain)[2] (local adaptation of Danflu-2 study design)	• Target 114k adults aged 65 to 79 years over two seasons (2023-25)	High-Dose Quadrivalent Influenza Vaccine (**randomized 1:1**)	Standard-Dose Quadrivalent Influenza Vaccine (**randomized 1:1**)	

Abbreviations: QIV-HD: high-dose quadrivalent vaccine. References: 1. https://clinicaltrials.gov/study/NCT05517174 2. https://euclinicaltrials.eu/.