DANFLU-1

Feasibility of a pragmatic randomized trial to assess the relative effectiveness of high-dose vs. standard-dose quadrivalent influenza vaccine on severe cardio-respiratory outcomes in elderly adults

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ESC CONGRESS 2022
Barcelona & Online

Background

- Influenza infection is associated with an increased risk of subsequent cardiovascular (CV) events[1] – a risk that can be decreased by vaccination[2]

- Accumulating evidence has demonstrated additional protection against influenza infection and related complications with high-dose (HD) influenza vaccines compared with standard-dose (SD)[3-4]

- No individually randomized trial has previously assessed the relative vaccine effectiveness (rVE) of HD quadrivalent influenza vaccines (QIV-HD) compared with SD quadrivalent influenza vaccines (QIV-SD) against CV and respiratory hospitalizations and mortality in an older adult population

- Due to large sample size requirements (approx. 200,000 participants[5]), conducting such a trial would require a number of pragmatic features

[1]Chow EJ, et al. *Ann Intern Med* 2020;173:605-613.
[2]Behrouzi B, et al. *JAMA Netw Open* 2022;5:e228873.
[3]DiazGranados CA, et al. *N Engl J Med* 2014;371:635–645.
[4]Lee JKH, et al. *Vaccine* 2021;39:A24–A35.
[5]Nealon J, et al. *NPJ Vaccines* 2022;7:25.

Objectives

- To evaluate the feasibility of integrating an individually randomized trial into routine seasonal influenza vaccination practice and using administrative health registries for collection of both baseline, outcome, and safety data

- Secondarily, to descriptively assess the rVE of QIV-HD vs. QIV-SD against a range of severe clinical outcomes

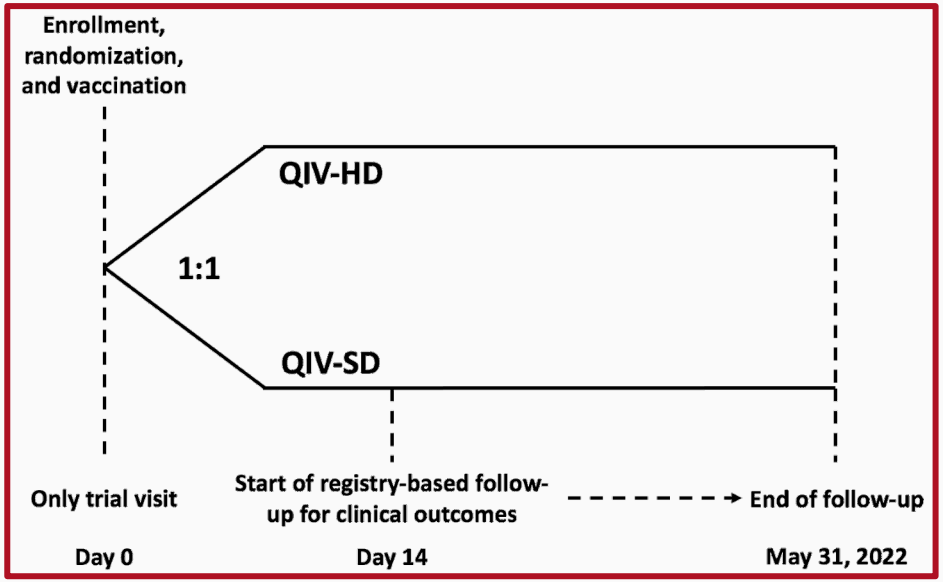
Methods

- The DANFLU-1 trial was a pragmatic, open-label, active-controlled, randomized feasibility trial conducted in Denmark during the 2021/2022 northern hemisphere influenza season

Planned sample size:
- 40,000 participants

Inclusion criteria:
- Age 65-79 years
- Signed informed consent

Exclusion criterion:
- Allergy/hypersensitivity towards the vaccines used in the study



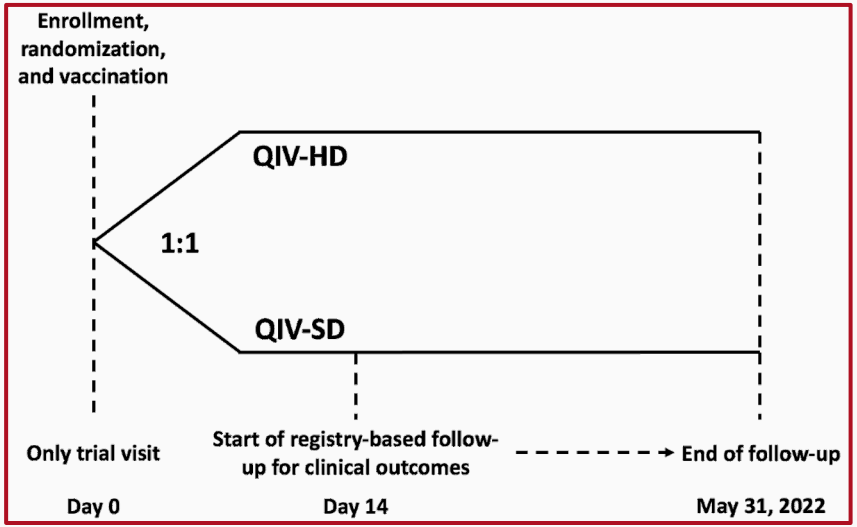
Johansen ND, Modin D, … , Biering-Sørensen T. *Pilot Feasibility Stud* 2022;8(1):87.

Methods

- Collection of baseline and outcome data including safety surveillance was performed using the Danish nationwide administrative health registries requiring cross-linkage of several registries

- Definitions of baseline conditions, medication use, and clinical outcomes were prespecified and based on ICD-10 and ATC classification codes

- Data were retrieved directly from registries without further validation or adjudication



Johansen ND, Modin D, … , Biering-Sørensen T. *Pilot Feasibility Stud* 2022;8(1):87.

Trial organization and data flow

Vaccination sessions

- >1,000 decentral vaccination sessions
- Organized by private vaccination provider
- Responsible for inclusion, randomization, and vaccination

Initial data

UNIVERSITY OF COPENHAGEN

REGION H Gentofte Hospital

Center for Pragmatic Randomized Trials

- Central trial site
- Study oversight and database management
- Nationwide access to all medical records and lab results

SSN

Data

Registry data

- Nationwide tax-funded public health system
- Nationwide administrative health registries can be crosslinked using social security numbers (SSN)
- Every hospital contact, death, redeemed prescription is captured in the registries
- Used for collection of both baseline, outcome, and safety data

Johansen ND, Modin D, … , Biering-Sørensen T. *Pilot Feasibility Stud* 2022;8(1):87.

Outcomes

- **Feasibility outcomes:**
- Participation and inclusion rate
- Agreement between randomization group and administered vaccine
- Balance in baseline characteristics between groups
- Comparison of baseline characteristics between the study population and the general Danish population aged 65-79 years

Johansen ND, Modin D, … , Biering-Sørensen T. *Pilot Feasibility Stud* 2022;8(1):87.

Outcomes

- Participants were followed for clinical outcomes from 14 days after vaccination (October-November 2021) until May 31, 2022

- **Prespecified clinical outcomes:**
- Hospitalization for pneumonia or influenza
- Hospitalization for respiratory disease
- Hospitalization for cardio-respiratory disease
- Hospitalization for cardiovascular disease
- Hospitalization for any cause
- All-cause death

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Outcomes

- **Additional cardiovascular outcomes:**
- Hospitalization for myocardial infarction
- Hospitalization for atrial fibrillation
- Hospitalization for stroke
- Hospitalization for heart failure
- Cardiovascular death

- The study was not powered for assessment of clinical outcomes

Johansen ND, Modin D, … , Biering-Sørensen T. *Pilot Feasibility Stud* 2022;8(1):87.

Statistical analysis

- rVE was calculated as 1 minus the relative risk of the specified outcome in the QIV-HD group vs. the QIV-SD group
- rVE = relative risk reduction

Johansen ND, Modin D, … , Biering-Sørensen T. *Pilot Feasibility Stud* 2022;8(1):87.

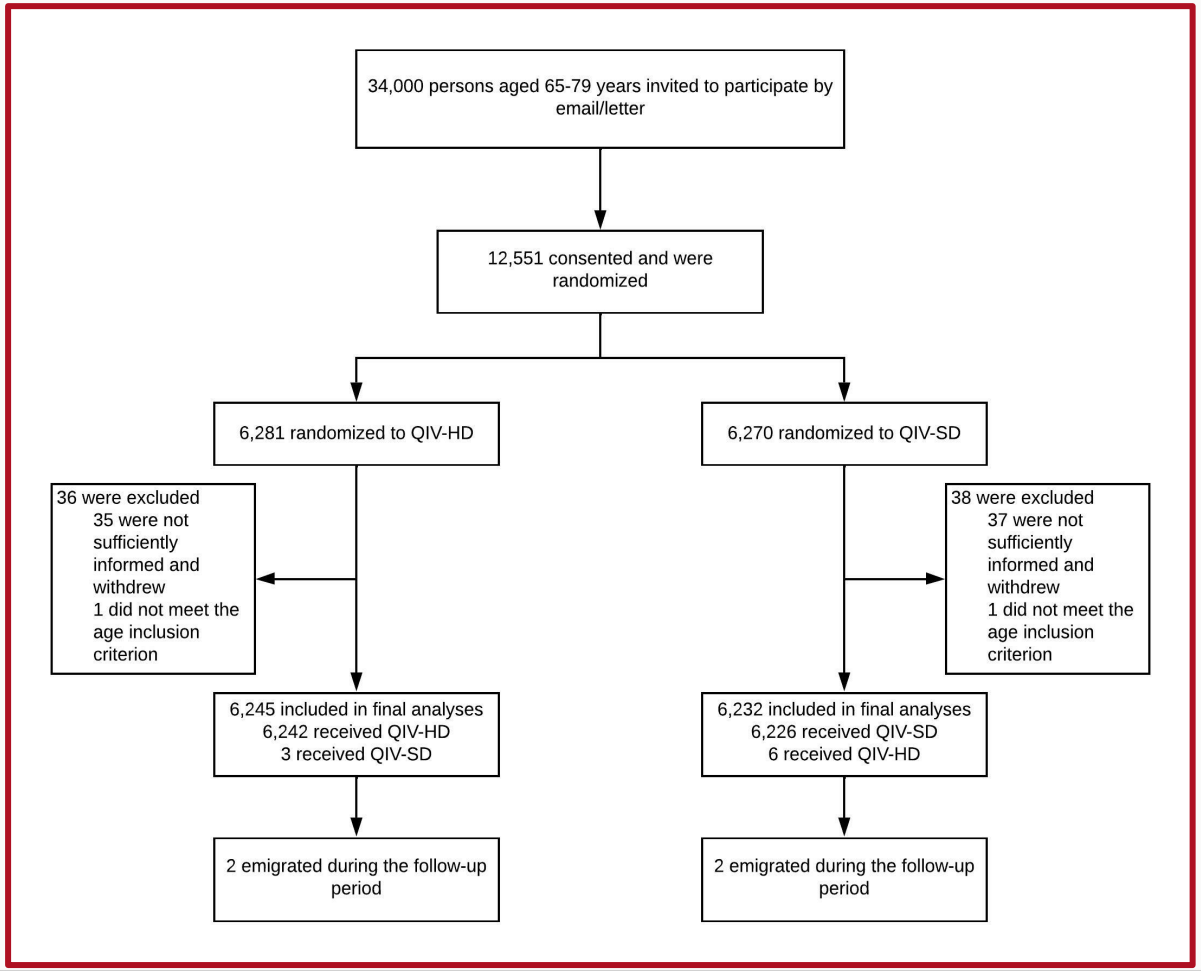
Methods - summary

- **The design of the DANFLU-1 trial aimed to:**
  - Integrate the conduct of a large-scale randomized trial into routine influenza vaccination practice
  - Minimize the burden on participants by requiring only 1 trial visit and no further contacts
  - Rely solely on cross-linked Danish administrative health registries for collection of both baseline, outcome, and safety data
  - Provide a first look at HD rVE against outcomes beyond influenza infection that are critical to public health
  - Raise the bar for quality of evidence in post-licensure vaccine studies

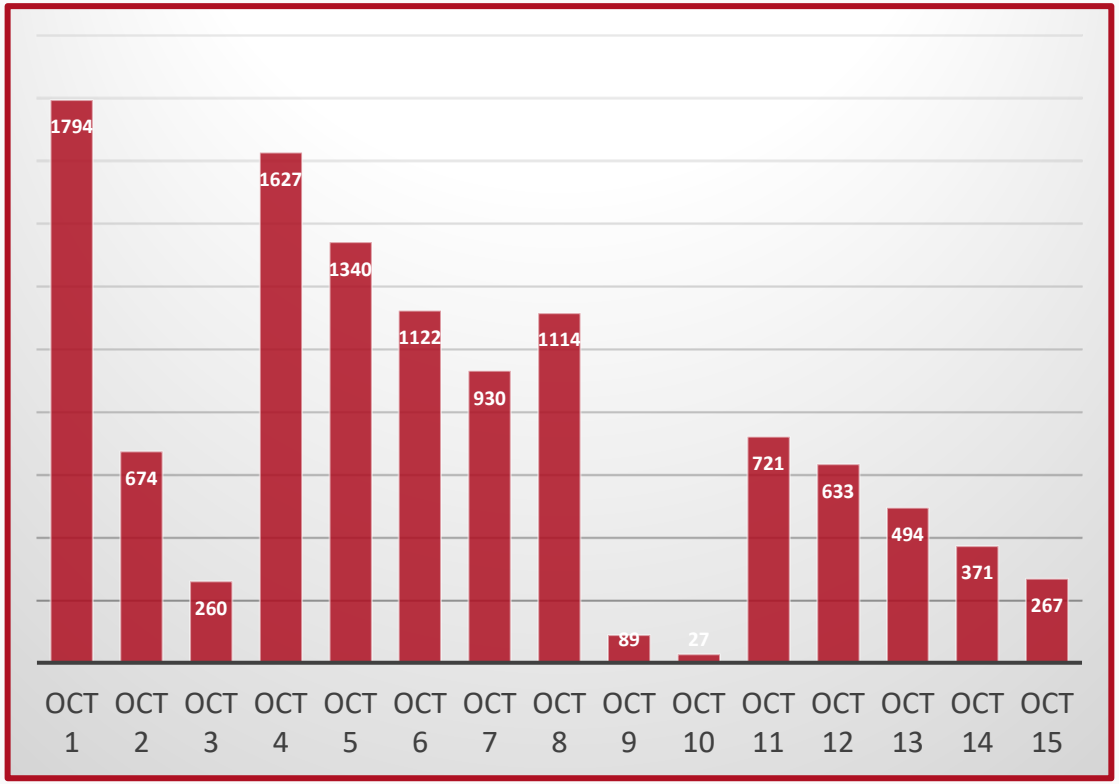
Study flow

99.93% received allocated study vaccine

Complete follow-up data available for 99.97% of participants



Recruitment rate



11,463 participants enrolled in first 15 days = median 674 per day!

Baseline characteristics

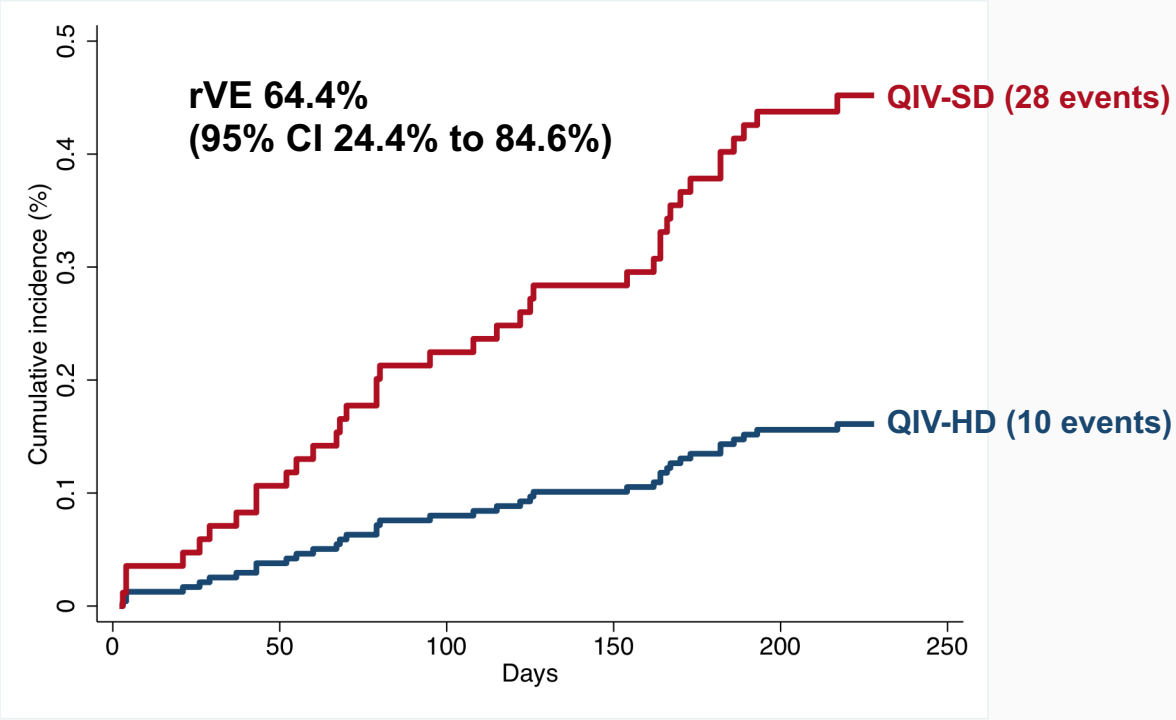
Characteristic	QIV-HD n = 6,245	QIV-SD n = 6,232
Age, mean (SD)	71.8 (3.9)	71.7 (3.9)
Female sex, n (%)	2,956 (47.3)	2,921 (46.9)
Chronic cardiovascular disease, n (%)	1,227 (19.6)	1,313 (21.1)
Ischemic heart disease, n (%)	450 (7.2)	512 (8.2)
Heart failure, n (%)	137 (2.2)	138 (2.2)
Atrial fibrillation, n (%)	458 (7.3)	420 (6.7)
Cerebrovascular disease, n (%)	219 (3.5)	237 (3.8)
Hypertension, n (%)	3,254 (52.1)	3,215 (51.6)
Diabetes, n (%)	574 (9.2)	588 (9.4)
Chronic lung disease, n (%)	435 (7.0)	415 (6.7)
Chronic obstructive pulmonary disease, n (%)	227 (3.6)	190 (3.0)
Cancer, n (%)	695 (11.1)	668 (10.7)
Immunodeficiency, n (%)	244 (3.9)	239 (3.8)

Comparison with Danish general population

Characteristic	DANFLU-1 population n = 12,477	Overall Danish population aged 65-79 years n = 889,689	Absolute difference (95% CI)
Demographics			
Female sex, n (%)	5,877 (47.1)	463,645 (52.1)	-5.0% (-5.9% to -4.1%)
Age, mean (SD)	71.7 (3.9)	72.2 (4.2)	-0.4 (-0.3 to -0.5)
Comorbidity			
Chronic cardiovascular disease, n (%)	2,540 (20.4)	203,488 (22.9)	-2.5% (-3.2% to -1.8%)
Ischemic heart disease, n (%)	962 (7.7)	75,251 (8.5)	-0.7% (-1.2% to -0.3%)
Myocardial infarction, n (%)	306 (2.5)	25,299 (2.8)	-0.4% (-0.7% to -0.1%)
Heart failure, n (%)	275 (2.2)	26,632 (3.0)	-0.8% (-1.0% to -0.5%)
Atrial fibrillation, n (%)	878 (7.0)	68,663 (7.7)	-0.7% (-1.1% to -0.2%)
Valvular disease, n (%)	358 (2.9)	29,276 (3.3)	-0.4% (-0.7% to -0.1%)
Cerebrovascular disease, n (%)	456 (3.7)	51,402 (5.8)	-2.1% (-2.5% to -1.8%)
Hypertension, n (%)	6,469 (51.8)	497,413 (55.9)	-4.1% (-4.9% to -3.2%)
Diabetes, n (%)	1,162 (9.3)	117,852 (13.2)	-3.9% (-4.4% to -3.4%)
Chronic lung disease, n (%)	850 (6.8)	64,158 (7.2)	-0.4% (-0.8% to 0.0%)
Chronic obstructive pulmonary disease, n (%)	417 (3.3)	41,301 (4.6)	-1.3% (-1.6% to -1.0%)
Asthma, n (%)	442 (3.5)	24,322 (2.7)	+0.8% (+0.5% to +1.1%)
Cancer, n (%)	1,363 (10.9)	96,498 (10.8)	+0.1% (-0.5% to +0.6%)
Chronic kidney disease, n (%)	275 (2.2)	24,315 (2.7)	-0.5% (-0.8% to -0.3%)
Liver disease, n (%)	140 (1.1)	13,185 (1.5)	-0.4% (-0.5% to -0.2%)
Immunodeficiency, n (%)	483 (3.9)	41,293 (4.6)	-0.8% (-1.1% to -0.4%)

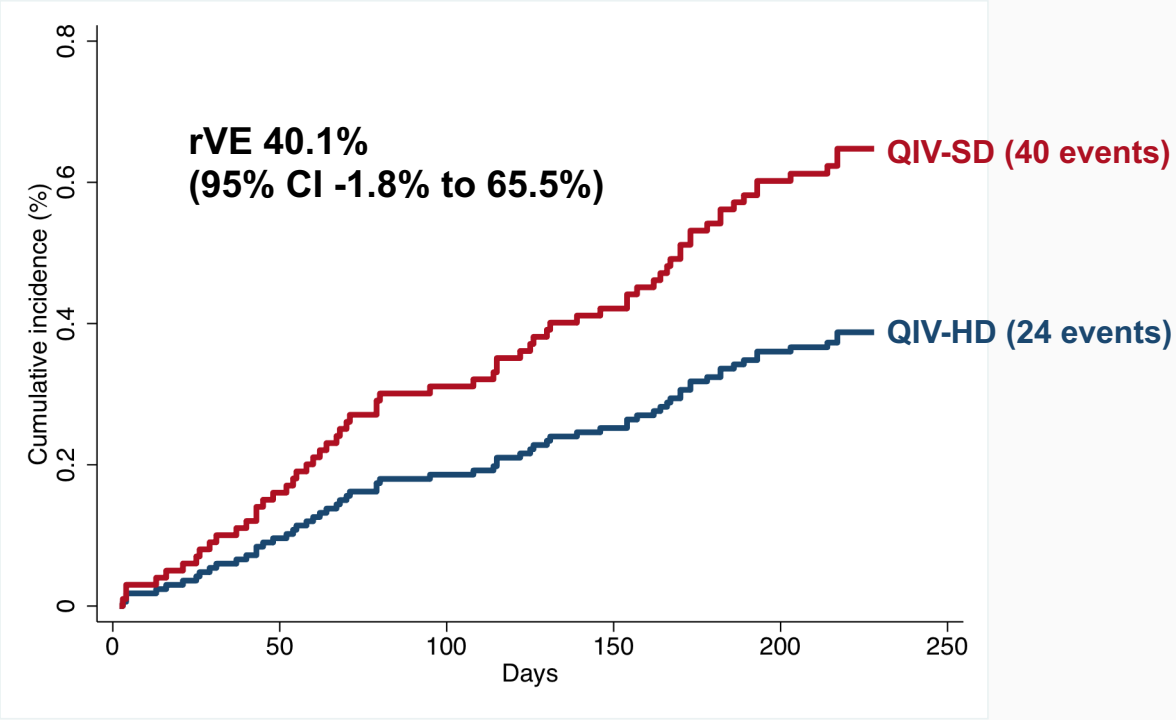
Clinical outcomes

- **Hospitalization for influenza or pneumonia:**



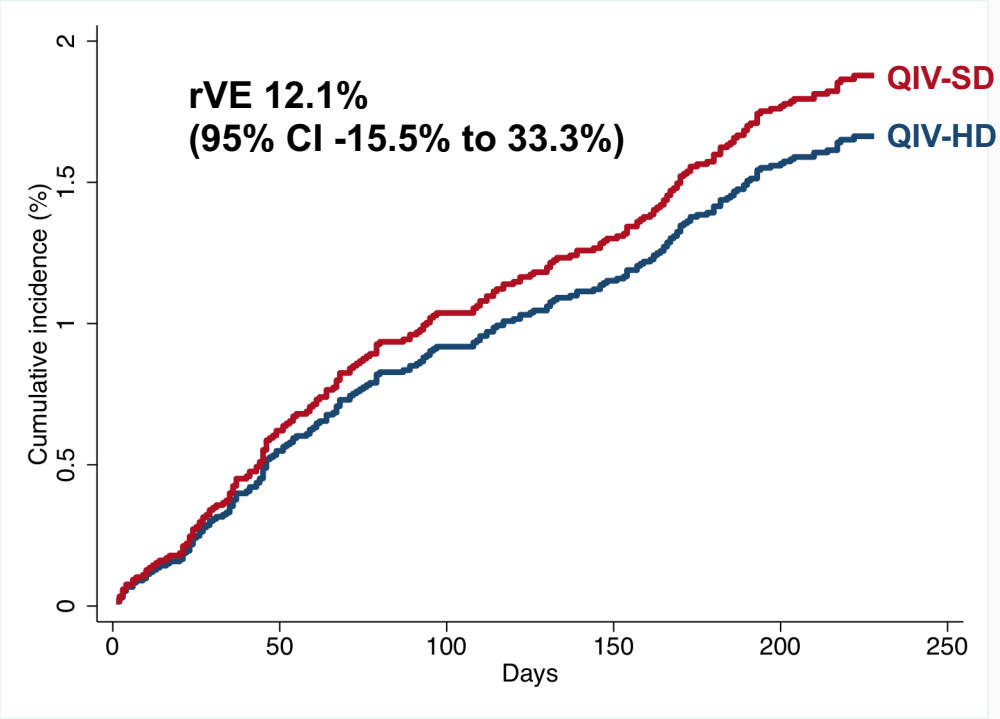
Clinical outcomes

- **Hospitalization for respiratory disease:**



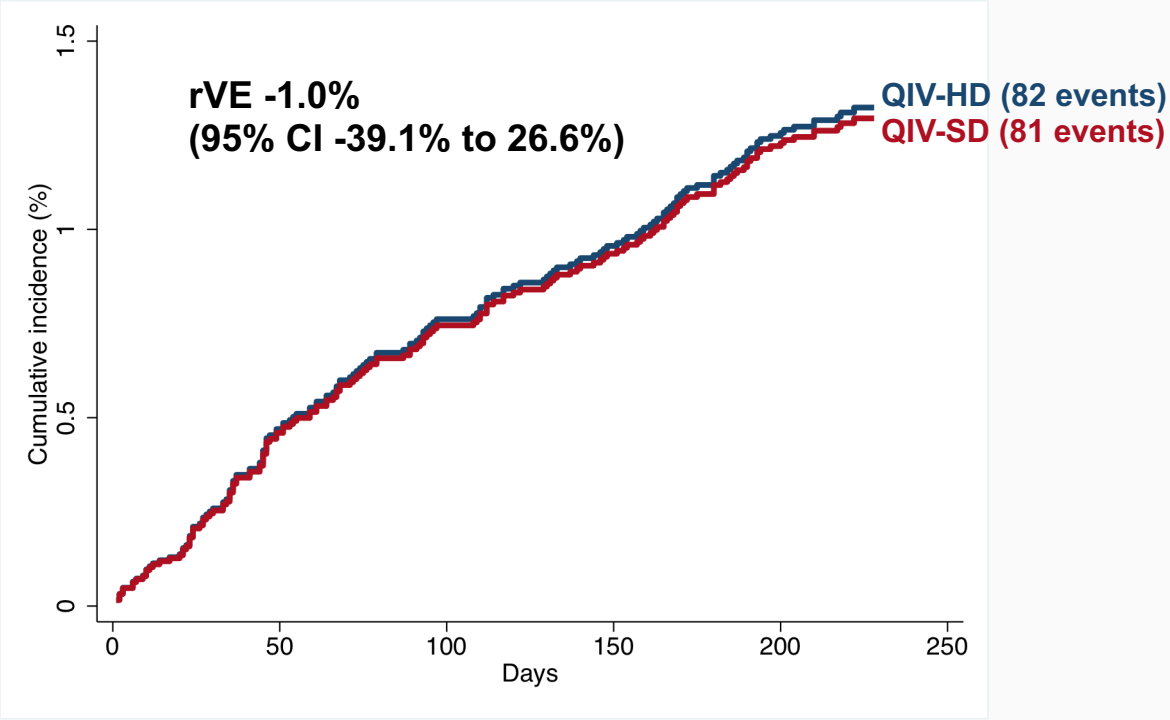
Clinical outcomes

- **Hospitalization for cardio-respiratory disease:**



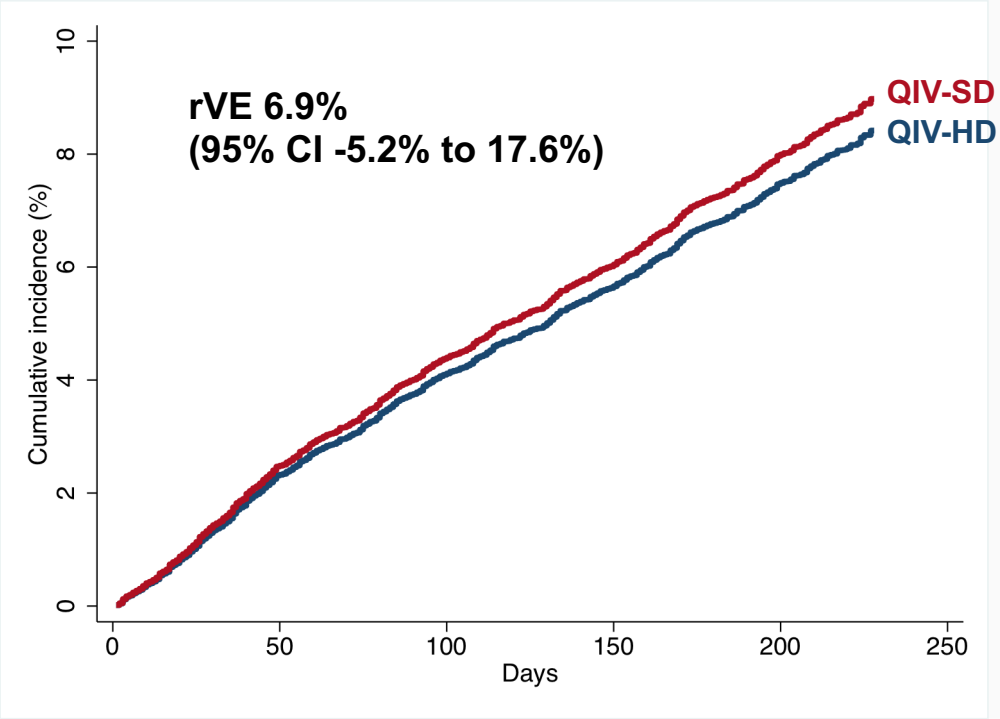
Clinical outcomes

- **Hospitalization for cardiovascular disease:**



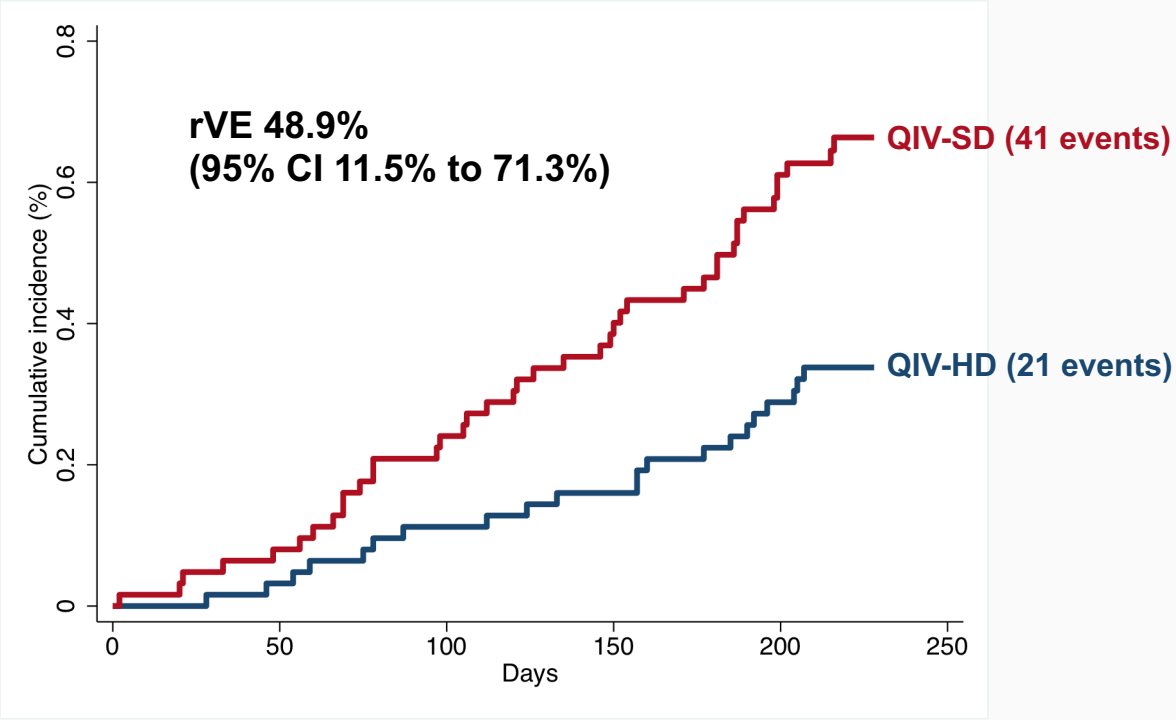
Clinical outcomes

- **Hospitalization for any cause:**



Clinical outcomes

- **All-cause death:**



Additional cardiovascular outcomes

Outcome	QIV-HD n = 6,245	QIV-SD n = 6,232	rVE (95% CI)
	No. of events		%
Hospitalization for myocardial infarction	11	10	-9.8 (-188.3 to 57.7)
Hospitalization for atrial fibrillation	31	44	29.7 (-13.9 to 57.1)
Hospitalization for stroke	19	10	-89.6 (-356.5 to 16.1)
Hospitalization for heart failure	8	11	27.4 (-98.1 to 74.7)
Cardiovascular death	4	11	63.7 (-22.5 to 91.6)

Safety/adverse events

Event	QIV-HD n = 6,248	QIV-SD n = 6,229	*p*-value
	No. of participants (%)		
Any serious adverse event (SAE)	373 (6.0)	405 (6.5)	0.22
Any cardiovascular SAE	63 (1.0)	87 (1.4)	0.047
Any respiratory SAE	24 (0.4)	26 (0.4)	0.77
Any gastro-intestinal SAE	23 (0.4)	24 (0.4)	0.88
Any infection-related SAE	22 (0.4)	19 (0.3)	0.65
Any injury-related SAE	94 (1.5)	98 (1.6)	0.75
Fatal SAE	8 (0.1)	13 (0.2)	0.27
Any serious adverse reaction	1 (0.0)	4 (0.1)	0.18

Limitations

- The study was not powered for clinical outcomes
- No adjustment for multiplicity was performed
  - The outcome findings should be considered hypothesis-generating only
- The trial was open-label
  - Not expected to affect hard clinical outcomes such as hospitalizations and deaths coded by physicians not involved in the trial and assessed using prespecified definitions
- Outcomes were retrieved directly from registries without adjudication
  - Several prior reports indicate that adjudication might not alter effect estimates in randomized trials[1-2]

[1]Pfeffer MA, et al. *Circulation* 2022;145:87-9.
[2]BNdounga Diakou LA, et al. *Cochrane Database Syst Rev* 2016;3:MR000043.

Conclusions

- Conducting a pragmatic randomized trial of QIV-HD vs. QIV-SD utilizing existing infrastructure for recruitment, inclusion, randomization, and vaccination and relying solely on registry-based data collection was established as feasible

- The design features can be applied to future fully powered vaccine trials as well as to trials investigating other interventions

- In prespecified analyses of rVE, the incidence of hospitalization for influenza or pneumonia and all-cause mortality was significantly lower in the QIV-HD group compared with QIV-SD
  - The findings require confirmation in a future fully powered trial

Acknowledgements

ALL STUDY PARTICIPANTS

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