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

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

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

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

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

- 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
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

Outcomes

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

• The study was not powered for assessment of clinical outcomes
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
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

ESC CONGRESS 2022
Barcelona & Online
Recruitment rate

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

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

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

• Hospitalization for influenza or pneumonia:

- QIV-SD (28 events): rVE 64.4% (95% CI 24.4% to 84.6%)
- QIV-HD (10 events)
Clinical outcomes

• Hospitalization for respiratory disease:

![Graph showing cumulative incidence over days for QIV-SD (40 events) and QIV-HD (24 events). The graph indicates a relative efficacy (rVE) of 40.1% with a 95% CI of -1.8% to 65.5%.)
Clinical outcomes

• Hospitalization for cardio-respiratory disease:

- QIV-SD (117 events)
  - rVE 12.1%
  - (95% CI -15.5% to 33.3%)

- QIV-HD (103 events)
Clinical outcomes

• Hospitalization for cardiovascular disease:

- QIV-SD (81 events)
- QIV-HD (82 events)

rVE -1.0%
(95% CI -39.1% to 26.6%)
Clinical outcomes

- Hospitalization for any cause:

  rVE 6.9%
  (95% CI -5.2% to 17.6%)
Clinical outcomes

- All-cause death:

  - QIV-SD (41 events): rVE 48.9% (95% CI 11.5% to 71.3%)
  - QIV-HD (21 events)
### Additional cardiovascular outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>QIV-HD n = 6,245</th>
<th>QIV-SD n = 6,232</th>
<th>rVE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization for myocardial infarction</td>
<td>11</td>
<td>10</td>
<td>-9.8 (-188.3 to 57.7)</td>
</tr>
<tr>
<td>Hospitalization for atrial fibrillation</td>
<td>31</td>
<td>44</td>
<td>29.7 (-13.9 to 57.1)</td>
</tr>
<tr>
<td>Hospitalization for stroke</td>
<td>19</td>
<td>10</td>
<td>-89.6 (-356.5 to 16.1)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>8</td>
<td>11</td>
<td>27.4 (-98.1 to 74.7)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>4</td>
<td>11</td>
<td>63.7 (-22.5 to 91.6)</td>
</tr>
</tbody>
</table>
## Safety/adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>QIV-HD n = 6,248</th>
<th>QIV-SD n = 6,229</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any serious adverse event (SAE)</strong></td>
<td>373 (6.0)</td>
<td>405 (6.5)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Any cardiovascular SAE</strong></td>
<td>63 (1.0)</td>
<td>87 (1.4)</td>
<td>0.047</td>
</tr>
<tr>
<td><strong>Any respiratory SAE</strong></td>
<td>24 (0.4)</td>
<td>26 (0.4)</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Any gastro-intestinal SAE</strong></td>
<td>23 (0.4)</td>
<td>24 (0.4)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Any infection-related SAE</strong></td>
<td>22 (0.4)</td>
<td>19 (0.3)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Any injury-related SAE</strong></td>
<td>94 (1.5)</td>
<td>98 (1.6)</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Fatal SAE</strong></td>
<td>8 (0.1)</td>
<td>13 (0.2)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Any serious adverse reaction</strong></td>
<td>1 (0.0)</td>
<td>4 (0.1)</td>
<td>0.18</td>
</tr>
</tbody>
</table>
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\textsuperscript{1-2}

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

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