How does frailty impact the efficacy, reactogenicity, immunogenicity and safety of the adjuvanted recombinant zoster vaccine?

A secondary analysis of the ZOE-50 and ZOE-70 studies

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Disclosures

- **Dr. Andrew** reports grants from the GSK group of companies (GSK) during the study, as well as grants from GSK, the Canadian Frailty Network, the Canadian Institutes of Health Research, the Foundation for Influenza Epidemiology, and grants and personal fees from Sanofi and Pfizer outside the submitted work.

- **Dr. Levin** reports grants and fees for Advisory Boards from GSK during the study and is serving as an Advisory Board member for GSK and Merck. **Mr. Matthews** is a freelance consultant for GSK. **Dr. Schmader** reports grants from GSK during the study. **Dr. McNeil** reports grants, personal fees and support for the conduct of clinical trials from GSK and Pfizer, personal fees and support for the conduct of clinical trials from Sanofi Pasteur, as well as personal fees from Merck outside the submitted work. **Dr. Kim, Mr. Dessart, Dr. Riley and Dr. Curran** are employees, and **Dr. Oostvogels** and **Dr. Schuind** former employees of GSK. **Dr. Kim, Dr. Oostvogels, Dr. Riley, Dr. Schuind and Dr. Curran** own GSK stock options or (restricted) shares. **Dr. Oostvogels** is an employee of CureVac AG and is inventor on a patent owned by GSK and relevant to RZV.

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Frail older adults are more vulnerable to herpes zoster’s negative impact on health and quality of life\(^1\)

ZOE-50 and ZOE-70 randomized controlled trials showed high efficacy of adjuvanted recombinant zoster vaccine (RZV) in older adults\(^2,3\)

Our aim: Retrospective evaluation of frailty in ZOE-50/70 participants based on collected health status data and patient reported outcomes

Some treatments and vaccines are less effective in frail older adults\(^4\)

**Aim:** Retrospective evaluation of frailty in ZOE-50/70 participants

1. **ZOE-50**
   - **(NCT01165177)**
   - ≥50 years

2. **ZOE-70**
   - **(NCT01165229)**
   - ≥70 years

1:1 randomized

- **RZV**
- **Placebo**

**ZOE-50 and ZOE-70 pooled TVC**

- **N=29,305**

**1° objective**
- Evaluate participants' baseline frailty status

**2° objectives**
- Efficacy against herpes zoster (HZ) by frailty
- Efficacy against HZ burden of illness by frailty
- Humoral and cell-mediated immunogenicity by frailty
- Reactogenicity and safety by frailty

**ZOE-frailty**

- **3**
- **(NCT03563183)**

**1° objective**

- Evaluate participants' baseline frailty status

**2° objectives**

- Efficacy against herpes zoster (HZ) by frailty
- Efficacy against HZ burden of illness by frailty
- Humoral and cell-mediated immunogenicity by frailty
- Reactogenicity and safety by frailty

Methods: Determination of frailty index and categories

Frailty index (FI)\(^1\)
\[
= \frac{\text{total deficits}}{41 - n \text{ missing QoL items}}
\]

Medical history
- 12 deficits
  - (e.g., cancer, diabetes, high blood pressure, heart attack, arthritis)

SF-36 QoL questionnaire
- 25 deficits
  - (related to general health, physical functioning, vitality, mental health)

EQ-5D QoL questionnaire
- 4 deficits
  - (mobility, self-care, anxiety, usual activities)

Non-frail: \(FI \leq 0.08\)
Pre-frail: \(0.08 < FI \leq 0.25\)
Frail: \(FI > 0.25\)

Methods: Measures

- **Vaccine efficacy:** VE = \( \frac{\text{herpes zoster incidence in RZV group}}{\text{herpes zoster incidence in placebo group}} \times 100 \)

- **Humoral immunogenicity:** anti-glycoprotein E (gE) ELISA

- **Cell-mediated immunogenicity:** flow cytometry → frequencies of CD4+ T cells expressing ≥2 activation markers (IFN-γ, IL-2, TNF-α, CD40 ligand) after ex vivo stimulation with gE

- **Reactogenicity:** solicited AEs in random subset (7 days after each dose)

- **Safety:** unsolicited AEs (30 days after each dose), unsolicited AEs with medically attended visit (8 months post-dose 1), SAEs (14 months post-dose 1), deaths and pIMDs (entire study)

IFN-γ, interferon-γ; IL-2, interleukin-2; TNF-α, tumor necrosis factor-α; (S)AE, (serious) adverse event; pIMD, potential immune-mediated disease.
Results: Demographics and frailty were balanced between RZV and placebo groups and frailty increased with age.
Results: Vaccine efficacy against herpes zoster was >90% across frailty categories

Vaccine efficacy, % (95% CI)

- Non-frail: 95.8
- Pre-frail: 90.4
- Frail: 90.2

First or only episode of herpes zoster during entire study period, modified total vaccinated cohort. CI, confidence interval.
Results: Vaccine efficacy against zoster burden of illness decreased with frailty, but absolute reduction in burden of illness was largest in frail participants.

Vaccine efficacy, % (95% CI)

<table>
<thead>
<tr>
<th>Status</th>
<th>RZV Efficacy</th>
<th>Placebo Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-frail</td>
<td>98.6</td>
<td>92.6</td>
</tr>
<tr>
<td>Pre-frail</td>
<td>92.6</td>
<td></td>
</tr>
<tr>
<td>Frail</td>
<td>85.2</td>
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</table>

ZBPI burden of illness score

<table>
<thead>
<tr>
<th>Status</th>
<th>RZV Score</th>
<th>Placebo Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-frail</td>
<td>2.5</td>
<td>1.17</td>
</tr>
<tr>
<td>Pre-frail</td>
<td>1.48</td>
<td>0.35</td>
</tr>
<tr>
<td>Frail</td>
<td>2.33</td>
<td>0.02</td>
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</tbody>
</table>

ZBPI, Zoster Brief Pain Inventory; score based on “worst pain”, modified total vaccinated cohort. CI, confidence interval.
Results: RZV induced robust, persistent anti-gE antibody responses across frailty categories.

### Anti-gE antibody GMC, mIU/mL (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Non-frail</th>
<th>Pre-frail</th>
<th>Frail</th>
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<tbody>
<tr>
<td>Pre-vaccination</td>
<td></td>
<td></td>
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<tr>
<td>1 M post-dose</td>
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<tr>
<td>12 M post-dose</td>
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<tr>
<td>24 M post-dose</td>
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<tr>
<td>36 M post-dose</td>
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</table>

Adapted according-to-protocol cohort for immunogenicity – humoral. **GMC**, geometric mean concentration; **CI**, confidence interval; **M**, months.
**Results:** RZV induced robust, persistent gE-specific CD4$^{2+}$ responses across frailty categories.

Frequency of CD4$^{2+}$ cells/10$^6$ CD4 T cells

Adapted according-to-protocol cohort for immunogenicity – cell-mediated immunity. M, months; Q1–Q3, interquartile range.

N non-frail = 60–76
N pre-frail = 36–50
N frail = 9–13
Results: Reactogenicity decreased with increasing frailty in RZV recipients

Any solicited AE, 7 days after each dose
% of participants

Most common local solicited AE: pain

Most common general solicited AE: fatigue

Total vaccinated cohort, diary card subset. AE, adverse event.
Results: Unsolicited medically attended visits and serious adverse events increased with frailty and were balanced between placebo and RZV groups.

Unsolicited AEs, 30 days after each dose

- Non-frail: RZV 51.6 ± 3.4, Placebo 29.6 ± 1.5
- Pre-frail: RZV 49.7 ± 2.7, Placebo 32.7 ± 2.4
- Frail: RZV 47.9 ± 3.5, Placebo 35.5 ± 3.5

Medically attended visits, 8 months post-dose-1

- Non-frail: RZV 32.4 ± 1.3, Placebo 34.1 ± 1.3
- Pre-frail: RZV 42.7 ± 1.4, Placebo 43.1 ± 1.4
- Frail: RZV 51.9 ± 1.8, Placebo 53.4 ± 1.8

SAEs, 14 months post-dose 1

- Non-frail: RZV 6.2 ± 1.3, Placebo 5.7 ± 1.2
- Pre-frail: RZV 11.5 ± 2.1, Placebo 12.1 ± 2.1
- Frail: RZV 18.6 ± 2.7

Deaths, entire study

- Non-frail: RZV 2.1 ± 0.5, Placebo 1.9 ± 0.5
- Pre-frail: RZV 4.9 ± 1.4, Placebo 5.5 ± 1.4
- Frail: RZV 11.1 ± 2.4, Placebo 12.4 ± 2.4

pIMDs, entire study

- Non-frail: RZV 1.3 ± 0.4, Placebo 1.2 ± 0.4
- Pre-frail: RZV 1.3 ± 0.4, Placebo 1.4 ± 0.4
- Frail: RZV 1.0 ± 0.4, Placebo 1.8 ± 0.4

Total vaccinated cohort. (S)AE, (serious) adverse event; pIMD, potential immune-mediated disease.
Conclusions

- RZV significantly reduces the risk of herpes zoster and is safe to use across the spectrum of frailty.
- A frailty index was readily calculated based on data sometimes collected in randomized trials for vaccines and other interventions. Frailty could thus be considered retrospectively in other studies even where a frailty measure was not included up front.
- The relatively nonrestrictive in/exclusion criteria in the parent ZOE studies resulted in a range of participants that included frail and pre-frail older adults.
- Vaccine efficacy was high (>90%) across frailty subgroups. Immunogenicity was robust and there was no safety signal in relation to frailty.
Thank you!