Statistical Analysis

- Analyses were performed on symptomatic participants only
- Analysis of variance (ANOVA) was used to test the ability of FLU-PRO severity scores to differentiate two or more clinical groups on Day 3 by
  - Viral shedding status (shedding or no shedding)
  - Baseline HAI (high vs. low titer)
  - Baseline NAI (high vs. low titer)
  - Combination of baseline HAI/NAI titers

RESULTS (CONTINUED)

Figure 5. Mean (SE) FLU-PRO domain and total scores on Day 3 by Baseline HAI status

- Mean scores were significantly different (p<0.05) among all three subgroups for the FLU-PRO total score and the Flu, Body/Systemic, Chest, Eyes and Eyes/Respiratory domains
- Mean scores were significantly different (p<0.05) between the low HAI/low NAI and low HAI/low NAI groups, except the Gastrointestinal domain
- Scores were also significantly different (p<0.05) between the low HAI-high NAI and low HAI/low NAI groups for the total and all domain scores except the Chest/Respiratory and Gastrointestinal domains

REFERENCES


Figure 6. Mean (SE) FLU-PRO domain and total scores on Day 3 by Baseline Joint HAI/NAI status

- Mean scores were significantly different (p<0.05) among all three subgroups for the FLU-PRO total score and the Flu, Body/Systemic, Nose, Throat, Eyes, Eyes/Respiratory, and Chest/Respiratory domains
- Mean scores were significantly different (p<0.05) between the low HAI-high NAI and low HAI-low NAI groups, except in the Chest/Respiratory domain
- Scores were also significantly different (p<0.05) between the low HAI-high NAI and low HAI/low NAI groups for the total and all domain scores except the Gastrointestinal and Gastrointestinal domains

Contributors:


Figure 3. Mean (SE) FLU-PRO domain and total scores on Day 3 by Viral shedding status

- Participants were blinded to viral shedding and antibody titers results.
- Participants completed the FLU-PRO questionnaire Day -1 PM, Day 0 AM (pre-inoculation), Day 0 PM post-inoculation, and twice daily thereafter to Day 14 post-inoculation and then once more on Day 28.
- Paired tests showed no significant domain or total score differences between the two pre-inoculation administrations (Day -1 PM) and Day 0 AM or the AM and PM of Days 5-14 post inoculation.
- All subsequent analyses used mean daily scores with no additional discrimination with twice daily administration (data not shown).

RESULTS (CONTINUED)

Table 1. Demographic and clinical characteristics

| Race, n (%) | Male, n (%) | Age at enrollment, Mean (SD) [Median, Min-Max] | Number of days with shedding, Mean (SD) [Median, Min-Max] | Total Score | PRO domain and total scores
<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>33 (54.1%)</td>
<td>24 (39.3%)</td>
<td>28.7 (6.5) [27.0, 18.0]</td>
<td>73.8%</td>
<td>Flu (0.08-0.25)</td>
</tr>
<tr>
<td>African American</td>
<td>10 (16.4%)</td>
<td>7 (11.5%)</td>
<td>5.0 (6.8) [5.0, 0.0]</td>
<td>39.3%</td>
<td>Eyes (0.04-0.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 (11.5%)</td>
<td>3 (5.0%)</td>
<td>0.0 (0.0) [0.0, 0.0]</td>
<td>50.8%</td>
<td>Throat (0.02-0.13)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (5.0%)</td>
<td>0 (0.0%)</td>
<td>0.0 (0.0) [0.0, 0.0]</td>
<td>1.6%</td>
<td>Eyes/Respiratory (0.01-0.07)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.6%)</td>
<td>0 (0.0%)</td>
<td>0.0 (0.0) [0.0, 0.0]</td>
<td>0.4%</td>
<td>Gastrointestinal (0.00-0.04)</td>
</tr>
</tbody>
</table>

Figure 2. FLU-PRO scores (Day -1 to Day 10)

- Inoculation day and day 0 AM post challenge study investigating the role of hemagglutination inhibition (HAI) and neutralization inhibition (NAI) titers
- PRO scoring method to assess influenza symptom severity
- Evaluate the early stages of vaccine or therapeutic development
- Study the pathogenesis and immune response after influenza infection
- PRO has been tested as a once daily measure of influenza symptoms
- PRO is a 32-item measure of influenza symptoms
- Items in each domain are averaged to obtain a domain score and all items are averaged to obtain a total FLU-PRO score
- The FLU-PRO has been tested as a once-daily measure and its psychometric properties and scoring method are established and validated.

BACKGROUND

- Seasonal influenza is a global public health problem
- Healthy volunteer human challenge studies (HCS) are used to:
  - Study the pathogenesis and immune response after influenza infection
  - Evaluate the early stages of vaccine or therapeutic development
- Memoli et al. (2016) applied the FLU-PRO to a HCS study

METHODS

Study Design

- Peak-flow, secondary analyses of data from healthy volunteers enrolled in an influenza challenge study investigating the role of hemagglutination inhibition (HAI) and neutralization inhibition (NAI) in conferring protection against influenza A virus
- Participants were blinded to viral shedding
- Participants completed the FLU-PRO questionnaire Day -1 PM, Day 0 AM (pre-inoculation), Day 0 PM post-inoculation, and twice daily thereafter to Day 14 post-inoculation and then once more on Day 28.
- Paired tests showed no significant domain or total score differences between the two pre-inoculation administrations (Day -1 PM) and Day 0 AM or the AM and PM of Days 5-14 post inoculation.
- All subsequent analyses used mean daily scores with no additional discrimination with twice daily administration (data not shown)

RESULTS

Figure 1. Symptom prevalence by FLU-PRO scores

- Participants with low NAI titers (<1:40) had significantly higher mean FLU-PRO scores on Day 3 by Baseline HAI status
- Scores were also significantly different (p<0.05) between the low HAI-high NAI and low HAI/low NAI groups for the total and all domain scores except the Chest/Respiratory and Gastrointestinal domains

Table 2. Flu, Body/Systemic, Nose, Throat, Eyes, Eyes/Respiratory, and Chest/Respiratory domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Mean (SD) [Median, Min-Max]</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu</td>
<td>2.0 (2.4) [1.0, 0.0]</td>
<td>73.8%</td>
</tr>
<tr>
<td>Eyes</td>
<td>0.0 (0.0) [0.0, 0.0]</td>
<td>39.3%</td>
</tr>
<tr>
<td>Throat</td>
<td>0.0 (0.0) [0.0, 0.0]</td>
<td>50.8%</td>
</tr>
<tr>
<td>Eyes/Respiratory</td>
<td>0.0 (0.0) [0.0, 0.0]</td>
<td>1.6%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0.0 (0.0) [0.0, 0.0]</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Figure 4. Mean (SE) FLU-PRO domain and total scores on Day 3 by Baseline NAI status

- Mean scores were significantly different (p<0.05) among all three subgroups for the FLU-PRO total score and the Flu, Body/Systemic, Nose, and Throat domains
- Mean scores were significantly different (p<0.05) between the high HAI-high NAI and high HAI/low NAI groups, except in the Gastrointestinal domain
- Scores were also significantly different (p<0.05) between the low HAI-high NAI and low HAI/low NAI groups for the total and all domain scores except the Chest/Respiratory and Gastrointestinal domains

Figure 6. Mean (SE) FLU-PRO domain and total scores on Day 3 by Baseline Joint HAI/NAI status

- Mean scores were significantly different (p<0.05) among all three subgroups for the FLU-PRO total score and the Flu, Body/Systemic, Nose, Throat, Eyes, Eyes/Respiratory, and Chest/Respiratory domains
- Mean scores were significantly different (p<0.05) between the high HAI-high NAI and low HAI/low NAI groups, except in the Chest/Respiratory domain
- Scores were also significantly different (p<0.05) between the low HAI-high NAI and low HAI/low NAI groups for the total and all domain scores except the Gastrointestinal and Gastrointestinal domains

CONCLUSIONS

- This study demonstrated the ability of the FLU-PRO to quantify the severity and intensity of influenza in an HCS model
- Using FLU-PRO in an HCS model, we were able to monitor the evolution of symptoms from baseline/pre-challenge through symptom development and resolution
- Using the FLU-PRO as a standardized measure of influenza symptoms in HCS may facilitate our understanding of the symptomatic evolution of influenza and the effects of new vaccines and drugs to prevent and treat influenza infection

Contributors:

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WHAT IS FLU-PRO?

- The InFLUenza Patient-Reported Outcome (FLU-PRO) measure was developed to evaluate the severity and duration of influenza symptoms
- The FLU-PRO is a 32-item daily diary assessing influenza signs and symptoms across 6 body systems: Nose (4), Throat (3), Eyes (3), Chest/Respiratory (7), Gastrointestinal (4), and Body/Systemic (11)
- All items are rated on a five-point (0-4) ordinal severity scale
- Items in each domain are averaged to obtain a domain score and all items are averaged to obtain a total FLU-PRO score
- The FLU-PRO has been tested as a once-daily measure and its psychometric properties and scoring method are established and validated.