Novavax NanoFlu vaccine induced improved immune responses against homologous and drifted A(H3N2) viruses in older adults compared to egg-based, high-dose, influenza vaccine

World Vaccine Congress
April 4, 2018
Two critical problems undermine seasonal influenza VE:

1) **Classical antigenic drift** (long-standing):
   - Exemplified by poor VE during 2014-15 US flu season (emergence of A/Switzerland H3N2)

2) **Egg-adaptive antigenic changes** (recently recognized):
   - Exemplified by poor A(H3N2) VE during 2017-18 US flu season in spite of an apparent “match”
   - Existence of well-characterized egg-adaptive mutations in HA antigenic epitopes (T160K)
   - Problematic given that 87% of flu vaccines deployed in the US are produced in eggs

Compounding effect of both problems likely contributed to recent poor A(H3N2) VE noted during the 2017 influenza season in Australia

- A level of drift likely present with the emergence of A/Singapore-NFIMH (H3N2)-like viruses, though not rising to the strict definition of “drift” by WHO
- A significant concomitant impact of egg-adaptive antigenic changes was observed

**CAN WE DO BETTER?**

Broader protection? Eliminate egg-adaptive changes?
Playing catch-up and does “one strain fit all”? Rapid evolution and diversity of A(H3N2) viruses

Most common in Australia summer ‘17

Most common in U.S. 17/18 season

Playing catch-up and does “one strain fit all”? Rapid evolution and diversity of A(H3N2) viruses

Epitope Changes

1
15
Number of significant changes to important regions of the hemagglutinin gene
=X= Vaccine Viruses

Most common in Australia summer ‘17

Most common in U.S. 17/18 season

Circulating H3N2 viruses present in 2017-18 Season

The nanoparticle influenza vaccine and Matrix-M adjuvant

- **Recombinant hemagglutinin (HA) nanoparticle vaccine**
  - Baculovirus/Sf9 insect cell system
  - Express recombinant, full-length, wild-type HA that assembles into HA homotrimers
  - Purified HA homotrimers form higher order nanoparticle structures of 20-40 nm
  - 2 to 9 HA homotrimers per nanoparticle held together by hydrophobic interactions
  - Rapid, high-yield, high purity, production process

- **Potent saponin-based Matrix-M adjuvant**
  - Extracted from bark of *Quillaja saponaria* Molina
  - Enhancement of activated T cell, B cell, and APC populations
  - Induction of functional, and broadly cross-reactive antibodies
  - Induction of polyfunctional T cells, both CD4+ and CD8+
  - Antigen sparing in the context of pandemic influenza
In ferrets, tNIV induced broadly cross-neutralizing immune responses to drifted A(H3N2) viruses.

Novel hemagglutinin nanoparticle influenza vaccine with Matrix-M™ adjuvant induces hemagglutination inhibition, neutralizing, and protective responses in ferrets against homologous and drifted A (H3N2) subtypes.

G Smith, Y Liu, et al.
Vaccine 35 (2017) 5366-5372
• Conducted in U.S.¹ across 3 sites in North Carolina
• 330 clinically-stable adults ages ≥60 years
• Randomized 1:1:1, stratified by age (60-74, and 75+)
• Single IM dose on day 0 of:
  • tNIV: 15µg each HA (45µg total) + 50µg Matrix-M, or
  • tNIV: 60µg each HA (180µg total) + 50µg Matrix-M, or
  • Licensed egg-based high-dose (180µg total), trivalent, inactivated influenza vaccine (IIV3-HD)(Fluzone-HD)
• Day 21 rescue dose of IIV3-HD or placebo
• All 3 vaccines included 2017-18 WHO recommended NH strains:
  • A/Michigan (H1N1); A/Hong Kong (H3N2); B/Brisbane
• Objectives
  • Safety: assessed through Day 21
  • Immunogenicity: HAI and MN against vaccine-homologous and drifted H3N2 strains through Day 21

1. Clinicaltrials.gov NCT#03293498
### Demographic data

<table>
<thead>
<tr>
<th>Variable</th>
<th>45µg tNIV HA + MxM</th>
<th>180µg tNIV HA + MxM</th>
<th>IIV3-HD (Fluzone HD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>109</td>
<td>111</td>
<td>110</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>69 (6.3)</td>
<td>68 (6.2)</td>
<td>69 (6.1)</td>
</tr>
<tr>
<td>Median age</td>
<td>68</td>
<td>67</td>
<td>69</td>
</tr>
<tr>
<td>Count (%) ≥65 y.o.</td>
<td>73 (66.9)</td>
<td>76 (68.4)</td>
<td>79 (71.8)</td>
</tr>
<tr>
<td>Count (%) ≥75 y.o.</td>
<td>19 (17.4)</td>
<td>20 (18.0)</td>
<td>20 (18.2)</td>
</tr>
<tr>
<td>%M / % F</td>
<td>46.8/53.2</td>
<td>45.9/54.1</td>
<td>48.2/51.8</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (%)</td>
<td>83.5</td>
<td>88.3</td>
<td>90.0</td>
</tr>
<tr>
<td>Black/African American (%)</td>
<td>15.6</td>
<td>11.7</td>
<td>8.2</td>
</tr>
<tr>
<td>All other (%)</td>
<td>0.9</td>
<td>0</td>
<td>0.9</td>
</tr>
<tr>
<td>Self-identified as Hispanic (%)</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Flu vaccine in 2016-17 (%)</td>
<td>95 (87.2)</td>
<td>94 (84.7)</td>
<td>93 (84.5)</td>
</tr>
<tr>
<td>Any flu vaccine w/i 3 yrs (%)</td>
<td>102 (93.6)</td>
<td>101 (91.0)</td>
<td>102 (92.7)</td>
</tr>
</tbody>
</table>
## Top-line safety data

<table>
<thead>
<tr>
<th>Safety events (thru 21 days)</th>
<th>45µg tNIV HA + MxM</th>
<th>180µg tNIV HA + MxM</th>
<th>IIV3-HD (Fluzone HD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>109</td>
<td>111</td>
<td>110</td>
</tr>
<tr>
<td>Any treatment emergent adverse event (TEAE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 (37%)</td>
<td>52 (47%)</td>
<td>51 (46%)</td>
<td></td>
</tr>
<tr>
<td>Any Solicited TEAE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 (28%)</td>
<td>37 (33%)</td>
<td>38 (35%)</td>
<td></td>
</tr>
<tr>
<td>Local solicited</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 (14%)</td>
<td>26 (23%)</td>
<td>30 (27%)</td>
<td></td>
</tr>
<tr>
<td>Severe local solicited</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Systemic Solicited</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23 (21%)</td>
<td>24 (22%)</td>
<td>20 (18%)</td>
<td></td>
</tr>
<tr>
<td>Severe systemic solicited</td>
<td>2 (2%)</td>
<td>4 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Unsolicited TEAE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 (20%)</td>
<td>24 (22%)</td>
<td>20 (18%)</td>
<td></td>
</tr>
<tr>
<td>Severe unsolicited</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Severe &amp; related unsolicited</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Medically-attended unsolicited</td>
<td>9 (8%)</td>
<td>6 (5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Serious adverse events (SAEs)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
HAI antibody responses (GMTs) against wild-type vaccine-homologous strains (2017-18)
HAI antibody response (GMFRs) against wild-type vaccine-homologous strains (2017-18)

Ratio of Day 21 GMTs
47% ↑ p=0.0056

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>A/HongKong H3N2</th>
<th>A/Michigan H1N1</th>
<th>B/Brisbane</th>
</tr>
</thead>
<tbody>
<tr>
<td>45µg NanoFlu</td>
<td>2.1</td>
<td>2.1</td>
<td>1.5</td>
</tr>
<tr>
<td>180µg NanoFlu</td>
<td>2.7</td>
<td>3.2</td>
<td>1.9</td>
</tr>
<tr>
<td>IIV3-HD</td>
<td>1.9</td>
<td>2.6</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Geometric Mean Fold Titer Rise (95% CI)
HAI antibody responses (GMFRs) against 5 generations of drifted wild-type A(H3N2) strains

Geometric Mean Fold Titer Rise (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>45µg NanoFlu</th>
<th>180µg NanoFlu</th>
<th>IIV3-HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Victoria H3N2</td>
<td>2.3</td>
<td>3.4</td>
<td>2.3</td>
</tr>
<tr>
<td>A/Texas H3N2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>A/Switzerland H3N2</td>
<td>2.5</td>
<td>3.9</td>
<td>2.5</td>
</tr>
<tr>
<td>A/Hong Kong H3N2</td>
<td>2.5</td>
<td>2.7</td>
<td>2.1</td>
</tr>
<tr>
<td>A/Singapore H3N2</td>
<td>1.9</td>
<td>1.9</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Ratio of Day 21 GMTs
- 38% ↑ p=0.0058
- 28% ↑ p=0.036
- 54% ↑ p=0.0065
- 47% ↑ p=0.0056
- 64% ↑ p=0.0009
HAI antibody responses (GMFRs) against 5 generations of drifted wild-type A(H3N2) strains

Geometric Mean Fold Titer Rise (95% CI)

- **A/Victoria H3N2**
  - 45µg NanoFlu: 2.3
  - 180µg NanoFlu: 2.2
  - IIV3-HD: 3.4
- **A/Texas H3N2**
  - 45µg NanoFlu: 2.3
  - 180µg NanoFlu: 2.2
  - IIV3-HD: 3.0
- **A/Switzerland H3N2**
  - 45µg NanoFlu: 2.2
  - 180µg NanoFlu: 2.1
  - IIV3-HD: 2.5
- **A/Hong Kong H3N2**
  - 45µg NanoFlu: 1.9
  - 180µg NanoFlu: 1.9
  - IIV3-HD: 2.7
- **A/Singapore H3N2**
  - 45µg NanoFlu: 1.9
  - 180µg NanoFlu: 1.9
  - IIV3-HD: 2.2

**A(H3N2) viruses currently circulating in North America**

Ratio of Day 21 GMTs

- 38% ↑ p=0.0058
- 28% ↑ p=0.036
- 54% ↑ p=0.0065
- 47% ↑ p=0.0056
- 64% ↑ p=0.0009
Neutralization antibody responses (GMTs) against wild-type vaccine-homologous strains (2017-18)
Neutralization antibody responses (GMFRs) against wild-type vaccine-homologous strains (2017-18)
Neutralization antibody responses (GMFRs) against circulating *wild-type* H3N2 strains

<table>
<thead>
<tr>
<th>Vaccine Strain 2015-16 Historic Drift</th>
<th>Vaccine Strain 2016-17 and 17-18</th>
<th>Vaccine Strain 2018-19 Forward Drift</th>
</tr>
</thead>
<tbody>
<tr>
<td>45µg NanoFlu</td>
<td>45µg NanoFlu</td>
<td>45µg NanoFlu</td>
</tr>
<tr>
<td>A/Switzerland H3N2</td>
<td>A/Hong Kong H3N2</td>
<td>A/Singapore-NFIMH H3N2</td>
</tr>
<tr>
<td>180µg NanoFlu</td>
<td>180µg NanoFlu</td>
<td>180µg NanoFlu</td>
</tr>
<tr>
<td>IIV3-HD</td>
<td>IIV3-HD</td>
<td>IIV3-HD</td>
</tr>
</tbody>
</table>

Geometric Mean Fold Titer Rise (95% CI)

- **Vaccine Strain 2015-16 Historic Drift**
  - 45µg NanoFlu: 2.1
  - 180µg NanoFlu: 2.8
  - IIV3-HD: 2.5

- **Vaccine Strain 2016-17 and 17-18**
  - 45µg NanoFlu: 1.9
  - 180µg NanoFlu: 2.2
  - IIV3-HD: 2.3

- **Vaccine Strain 2018-19 Forward Drift**
  - 45µg NanoFlu: 2.8
  - 180µg NanoFlu: 3.5
  - IIV3-HD: 2.1

Ratio of Day 21 GMTs: 61% ↑ p=0.0002
Neutralization antibody responses (GMFRs) against egg-adapted vs. wild-type A/Singapore H3N2 viruses

Nanoflu induced improved neutralization antibody responses (GMFRs) against wild-type vs. egg-adapted A/Singapore H3N2 viruses underscoring the problem of egg-adaptive mutations

Neutralization antibody responses against wild-type circulating viruses are the most clinically relevant.
Avoidance of egg-adaptive antigenic changes leads to substantial improvements in vaccine-homologous A(H3N2) HAI antibody responses

Induction of immune responses against conserved HA head based epitopes expands cross-reactive HAI responses against a broad panel of A(H3N2) drift variants:
  - 28-38% increase in HAI against distant historic drifted viruses (2012-13, 2014-15)
  - 54% increase in HAI against recent historic drifted viruses
  - 64% increase in HAI against forward drifted virus, A/Singapore

Most substantial HAI antibody increases were observed against a “forward” drifted A(H3N2) virus, A/Singapore, offering a potential safeguard against the age-old problem of classical antigenic drift

Broad cross-reactivity to antigenically diverse co-circulating A(H3N2) viruses ensures that “one size fits all” regardless of geography

Next steps
  - Phase 2 in Fall 2018: quadrivalent formulation
  - Phase 3 anticipated in 2H 2019
Playing catch-up and does “one strain fit all”?
Rapid evolution and diversity of A(H3N2) viruses

Playing catch-up and does “one strain fit all”? Nanoflu has the potential to provide broader protection.

NanoFlu vaccine has potential to provide broader protection against antigenic drift.

Thank you