Magnitude and Durability of Anti-F IgG and Palivizumab-Competitive Antibody (PCA) Responses One Year Following Immunization with RSV F Nanoparticle Vaccine Adjuvanted with Aluminum Phosphate, or a Novel Adjuvant, Matrix-M™

RSV 2018 Symposium

Nov 1, 2018

Vivek Shinde, MD MPH
RSV F vaccine

- Novavax RSV F Vaccine is composed of a recombinant near full length F protein
  - Prefusogenic F trimers are associated with PS80 detergent micelles to form stable 40nm particles
  - RSV F Vaccine is thermodynamically stable, resists denaturation, and is not randomly aggregated.
  - For more details on structural and antigenic characterization see posters:
    - Poster #69 In-depth Analytical Characterization and Structural Modeling
    - Poster #70 Antigenic Characterization against a Broad Range of Neutralizing Monoclonal Antibodies
    - Poster #71 Physical and Antigenic Structure, Immunogenicity, and Protection
    - Poster #72 Feasibility Evaluation of Blow Fill Seal Process with Aluminum Adjuvanted Recombinant RSV F
    - Poster #73 Binding Kinetics of RSV F Vaccine to Palivizumab and Serum Polyclonal Antibody

- In 9 separate clinical trials in adults, Novavax’ RSV F Vaccine, formulated with or without Aluminum adjuvant, was found to have an acceptable safety profile and elicit robust RSV-specific antibody responses.
Unadjuvanted RSV F vaccine in older adults:
Experience and lessons through Phase 3

- Phase 2 trial demonstrated clinical efficacy (41% vs. RSV-ARD; 64% vs. RSV-msLRTD)
  - Placebo attack rate 4.9%, *single season*

- Phase 3 trial failed to meet efficacy endpoints
  - Placebo attack rate 1.9%, *single season*

- Spawned two major lines of investigation:
  1. Is the vaccine construct optimal and should an adjuvant/2-dose strategy be employed?
     - See 3 posters on construct listed in the previous slide; this talk will focus for the adjuvant effect and 2-dose strategy
  2. Was there an external factor leading to failure to meet endpoints?
     - And, was there a phase 3 signal worthy of additional clinical testing?

- Efficacy observed during periods of high population susceptibility/transmission (Phase 2), but not during periods of low susceptibility/transmission
  - Same phenomena observed in *single season* influenza vaccine trials

- Consistent evidence of efficacy against COPD hospitalizations RSV trials (Phase 2 and 3), suggest:
  - An under-recognized, under-studied, and unaddressed burden of RSV disease in COPD
  - Opportunity for an RSV vaccine to prevent COPD exacerbations to a degree that current pharmacotherapies cannot
Unadjuvanted RSV F vaccine in older adults:
Post-hoc efficacy signal in E201 / E301: COPD exacerbation hospitalizations

*Post-hoc* Analyses of Hospitalizations for **All Cause** acute exacerbation of COPD in E-201 and E-301 data from the **Safety** Database

<table>
<thead>
<tr>
<th>E301 Day 0-182</th>
<th>Placebo</th>
<th>Vaccine</th>
<th>VE%</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AECOPD hospitalization rate</td>
<td>23/5935 (0.39%)</td>
<td>9/5921 (0.15%)</td>
<td>60.8%</td>
<td>15.2—81.9</td>
<td>0.017</td>
</tr>
<tr>
<td>(all subjects)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AECOPD hospitalization rate</td>
<td>15/362 (4.1%)</td>
<td>9/403 (2.2%)</td>
<td>46.1%</td>
<td>-23—76.4</td>
<td>0.14</td>
</tr>
<tr>
<td>(Identified baseline COPD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| E 201 Day 0-182               |         |         |       |           |         |
| AECOPD hospitalization rate   | 4/801 (0.50%)   | 0/798 (0%)   | 100%  | NC        | NC      |
| (all subjects)                |         |         |       |           |         |
| AECOPD hospitalization rate   | 2/62 (3.2%)    | 0/58 (0%)    | 100%  | NC        | NC      |
| (Identified baseline COPD)    |         |         |       |           |         |
Unadjuvanted RSV F vaccine in older adults: Post-hoc efficacy signal in E201 / E301: COPD exacerbation hospitalizations

- RSV F vaccine effect occurs—as expected—during the RSV season
Unadjuvanted RSV F vaccine in older adults:
Experience and lessons through Phase 3

• Higher anti-RSV specific antibody titers were associated with less risk of RSV disease; “more antibody is better”

• However, largely overlapping antibody distributions between protected and unprotected individuals imply that:
  • There is no absolute protective cut-off titer in older adults
  • Available measures of anti-RSV specific antibodies may be relative (not absolute) correlates of protection in adults

• Phase 2 and 3 trials suggested that unadjuvanted RSV F vaccine can have efficacy in older adults, but needed enhancement of the immune response
  • Suggestion that repeat dosing (phase 2 re-immunization study) offers an avenue to improve efficacy
  • Classic and novel adjuvants were other obvious choices to consider moving forward
## Phase 2 (RSV-E-205)

**Evaluation of adjuvants and dose regimens with RSV F vaccine in older adults**

| **Rationale/aim** | ▪ Evaluate adjuvants and repeat dosing as potential avenues to enhance vaccine immunogenicity in older adults |
| **When** | ▪ Trial initiated in **Jan 2017** in Australia |
| **Design** | ▪ 300 healthy older adults (aged ≥60 years)  
▪ Randomized, observer-blinded, placebo-controlled, evaluation of RSV F **with and without** aluminum phosphate or our proprietary Matrix-M™ adjuvant; in one or two-dose regimens |
| **Objectives** | ▪ To ascertain whether adjuvantation or a two-dose primary regimen can alter the **quantity and quality** of the immune response to RSV F Vaccine in older adults  
▪ To identify one or a small number of regimens meriting further evaluation in additional safety and immunogenicity and eventual efficacy  
▪ To evaluate the **safety** of revised regimens and formulations of RSV F in older adults |
| **Endpoints** | ▪ Safety  
▪ RSV-specific immune responses by MN, anti-F IgG, PCA, and cell mediated immunity (CMI) |
Matrix-M™ adjuvant

- Potent saponin-based adjuvant
  - Purified fractions extracted from the bark of Quillaja saponaria Molina
  - Formulated with cholesterol and phospholipid, forming cage-like particles

- Shown to have the following properties in the context of various antigens:
  - Leads to enhancement of activated T cell, B cell, and APC populations in draining lymph nodes
  - Induction of functional, and broadly cross-reactive antibodies (Shinde et al, NEJM, 2018)
  - Induction of polyfunctional T cells, both CD4+ and CD8+
  - Antigen sparing in the context of pandemic influenza

- > 2,300 adults have been exposed to Matrix™-M in ongoing and complete clinical trials
  - Acceptable safety profile
**E-205: treatment groups**

[Focus on placebo, unadjuvanted formulation, and 4 treatment groups with best immune responses]

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Day 0</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Group</strong></td>
<td><strong>Subjects Per Group</strong></td>
<td><strong>RSV F Dose</strong></td>
</tr>
<tr>
<td>A</td>
<td>25</td>
<td>135 µg</td>
</tr>
<tr>
<td>B</td>
<td>25</td>
<td>95 µg</td>
</tr>
<tr>
<td>C</td>
<td>25</td>
<td>95 µg</td>
</tr>
<tr>
<td>D</td>
<td>25</td>
<td>120 µg</td>
</tr>
<tr>
<td>E</td>
<td>25</td>
<td>120 µg</td>
</tr>
<tr>
<td>F</td>
<td>25</td>
<td>135 µg</td>
</tr>
<tr>
<td>G</td>
<td>25</td>
<td>135 µg</td>
</tr>
<tr>
<td>H</td>
<td>25</td>
<td>65 µg</td>
</tr>
<tr>
<td>J</td>
<td>25</td>
<td>65 µg</td>
</tr>
<tr>
<td>K</td>
<td>25</td>
<td>35 µg</td>
</tr>
<tr>
<td>L</td>
<td>25</td>
<td>35 µg</td>
</tr>
<tr>
<td>M (Placebo)</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>300 Subjects</strong></td>
<td></td>
</tr>
</tbody>
</table>
E-205 Kinetics of **Anti-F IgG** in representative groups:

Adjuvant effect, 2nd dose effect, and durability of responses
E-205 Kinetics of Anti-F IgG in 135 µg unadjuvanted vs. 135 µg Matrix-M x2:
Substantial increases in peak and long-term responses

135 µg Matrix-M x 2 vs. 135 µg unadj
- 2x area under curve
- 2.5x peak @ Day 56
- 1.6x @ Day 385
E-205 Kinetics of **PCA** in representative groups:

Adjuvant effect, 2nd dose effect and durability of responses

![Graph showing PCA GMC levels over time for different groups.](image_url)
E-205 Kinetics of **PCA** in 135 µg unadjuvanted vs. 135 µg Matrix-M x2:

Substantial increases in peak and long-term responses

- 1.8x area under curve
- 1.9x peak @ Day 56
- 1.6x @ Day 385
E-205 RSV/A neutralizing antibodies in control and Matrix-M groups (ELISA-based method)

Sustained MN Response to Adjuvanted Vaccine
E205 Competitive Antibody Equivalents (CAE) detected by biolayer interferometry:

Polyclonal antibodies to pre-fusion and post-fusion epitopes

Competitive antibody equivalents (CAE) detected by biolayer interferometry using previously characterized mAbs to RSV F protein
E-205 Cellular immune responses:
Matrix-M enhances triple cytokine positive RSV F-specific CD4+ responses
E-205 conclusions

• With respect to safety, all adjuvanted formulations were clinically tolerable

• The totality of immune responses makes use of adjuvants and two-dose regimens desirable
  • Both adjuvants enhanced the **magnitude of peak** antibody responses
  • Only Matrix-M substantially **extended the long-term durability** of responses
  • **Two dose regimens** further enhanced the effects of adjuvants on peak and duration of responses
  • **T-cell immunity** was observed in all regimens, but was most notably enhanced by Matrix-M
  • High levels of antibodies competitive with site IIb (mota), site φ, and site IV antibodies were induced and enhanced by adjuvants

• 135 µg RSV F with Matrix-M, in a 2 dose regimen, outperformed all other formulations/regimens across a variety of humoral and cellular immune measures
  • Near doubling of peak responses and area under the curve as compared unadjuvanted formulation
  • One year responses 60% higher as compared to unadjuvanted formulation

• E205 data builds confidence in the continued development of **Matrix-M adjuvanted** RSV F vaccine in older adult, COPD, and other high-risk populations
Thank you