Development of Vaccines for Prevention of Respiratory Syncytial Virus (RSV) Disease in RSV-naïve Infants

Vaccines and Related Biological Products Advisory Committee Meeting
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Food and Drug Administration
Presentation Goals

• Provide an overview of RSV disease and prevention
• Review different RSV vaccine approaches and summarize immunologic mechanisms proposed to underlie vaccine-associated enhanced respiratory disease (ERD)
• Review recent workshops that addressed RSV vaccine development
• Discuss types of supportive preclinical and human data and the potential design of initial studies in RSV-naïve infants
RSV Disease and Prevention

- RSV infection greatly impacts health of infants and young children
- Treatment is largely supportive
- Passive immunization can confer protection against RSV disease
  - Respiratory Syncytial Virus Immune Globulin, Human [RSV-IVIG] (RespiGam)
  - Humanized Anti-RSV-F Monoclonal Antibody [Palivizumab] (Synagis)
  - Licensed “for the prevention of serious lower respiratory tract disease caused by RSV in children at high-risk of RSV disease”
RSV Vaccine Development

• Many products under development for active immunization

• Three main target populations
  – Adults ≥ 60-65 years of age
  – Pregnant women
  – Infants
Observations of Enhanced Respiratory Disease (ERD) in Infants

- Occurred in studies evaluating a formalin inactivated RSV (FI-RSV) vaccine in infants
- Increase in the proportion with severe RSV disease and in severity of illness in infants previously immunized with FI-RSV compared with controls
- Redirected vaccine development efforts towards first understanding mechanistic etiology of vaccine-associated ERD
Potential Mechanisms Underlying Vaccine-associated ERD

• Th2-dominant CD4⁺ T-helper cell cytokine responses
• Absence of CD8⁺ cytotoxic T lymphocyte (CTL) response
• Immune complex deposition in the lungs
• Low-affinity antibody response with minimal neutralizing activity
Potential RSV Antigen Targets for Vaccine Development

- Attachment Protein (G)
- Small Hydrophobic Protein (SH)
- Nucleoprotein (N)
- M2-1 (nonstructural)
- Fusion Protein (F)
- Phosphoprotein (P)
- Matrix protein (M)
- RNA Polymerase (L)
- (-) ss RNA
RSV Antigens Associated with Protection in Mice

<table>
<thead>
<tr>
<th>Protein</th>
<th>Location</th>
<th>B-Cell Epitopes</th>
<th>CD8+ CTL Epitopes</th>
</tr>
</thead>
<tbody>
<tr>
<td>F Fusion</td>
<td>Envelope</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>G Attachment</td>
<td>Envelope</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>N</td>
<td>Nucleocapsid</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>M2-1</td>
<td>Non structural</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Connors M et al., J Virol 1991
### Vaccine Characteristics and Potential Risk of ERD

<table>
<thead>
<tr>
<th>Immune Response</th>
<th>Whole Virus, Inactivated</th>
<th>Protein and Peptide Subunit</th>
<th>Gene-Based and Vectored</th>
<th>Live-Attenuated</th>
</tr>
</thead>
<tbody>
<tr>
<td>FI-RSV</td>
<td>FI-RSV</td>
<td>F, pre or post fusion</td>
<td>MVA</td>
<td>RSV engineered with attenuating mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- G protein</td>
<td>- Human or Chimpanzee Adenovirus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- G peptide</td>
<td>- Naked DNA/RNA</td>
<td></td>
</tr>
<tr>
<td>Neutralizing Antibody Response</td>
<td>Variable to low</td>
<td>Low to high</td>
<td>Low to high</td>
<td>Mucosal IgA and serum IgG</td>
</tr>
<tr>
<td>RSV-Specific CD8+ CTL</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Th1/Th2</td>
<td>Th2</td>
<td>Th2 &gt; Th1</td>
<td>Th1</td>
<td>Th1</td>
</tr>
<tr>
<td>ERD risk</td>
<td>Caused ERD in infants and toddlers</td>
<td>Some have shown ERD in animal models</td>
<td>Many have not shown ERD in animals</td>
<td>Tested in seronegative infants with no ERD observed so far</td>
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**Vaccines:**
- Whole Virus
  - Inactivated
- Protein and Peptide Subunit
- Gene-Based and Vectored
- Live-Attenuated

**Immune Responses:**
- Neutralizing Antibody Response
- RSV-Specific CD8+ CTL
- Th1/Th2
- ERD risk

**Th1/Th2:**
- Th1

**ERD Risk:**
- Caused ERD in infants and toddlers
- Some have shown ERD in animal models
- Many have not shown ERD in animals
- Tested in seronegative infants with no ERD observed so far
Cotton Rats Primed with Purified F Developed Alveolitis after RSV Challenge

- ERD seen after immunization with purified PreF or PostF, irrespective of adjuvant

Mock = supernatant from uninfected HEp-2 cells

Adapted from Schneider-Ohrum et al., J Virol, 2017
Cellular Components can Induce Alveolitis in the Cotton Rat Model of ERD

F = RSV F protein

Mock = supernatant from uninfected HEp-2 cells

Vaccine/Control Given Before RSV Challenge

Adapted from Shaw et al., Vaccine 2012
WHO Conference March 2015

“WHO Preferred Product Characteristics for RSV Vaccines” is a draft document that provides the following perspectives:

– Safety data in adults and RSV-experienced children 12 months to 5 years of age should precede evaluation of RSV-naïve infants

– Studies in RSV-naïve infants should extend over two RSV seasons for efficacy, cross-protection, and durability of response

– Case definitions proposed as endpoints for field trials for severe and very severe RSV lower respiratory tract infection using:
  • RT-PCR testing
  • SpO2
  • Pulse oximetry
  • Clinical signs of chest in-drawing (severe) vs. inability to feed or unresponsive to touch (very severe).
Key concepts included:

- No single animal model demonstrates all features of FI-RSV associated ERD in infants.
- Th2-biased immune responses following challenge of immunized animals are consistently associated with the ERD syndrome.
- A high-magnitude antibody response with poor neutralizing activity may be causally related to ERD.
- RSV-specific CD8+ T cells mediate virus clearance, but in the context of high viral loads on a background of low neutralizing antibodies can also contribute to pathology.
- Lung eosinophilia, while not causally related to ERD, is a marker of a Th2-type cytokine response and deserves careful consideration if present in vaccinated animals post challenge.
Use of Pre-clinical Models to Evaluate Candidate Vaccines

• Extrapolation from animal models that reproduce features of ERD might inform risk of ERD in humans

• Considerations when evaluating preclinical data
  – Animal model used
  – Vaccine dose (assessment may include dose de-escalation)
  – RSV challenge dose and timing relative to immunization
  – Establishing criteria for ERD
Clinical Studies in Adults

• Can assess reactogenicity of vaccine candidates, but not risk for ERD
• Human challenge studies in adults might help select promising vaccine candidates or identify correlates of protection
• Immune responses in adults represent boosting of pre-existing immunity and therefore may not predict a protective immune response in RSV-naïve infants
Clinical Studies in RSV-experienced Infants

• Can assess reactogenicity of vaccine
• Usefulness in assessing risk of ERD for RSV-naive subjects is uncertain
• Persistence of maternal antibody may inaccurately imply RSV experience, although less likely after 6 months of age
Considerations and Potential Approaches to Studies in RSV-naïve Infants

• Risk of ERD might be higher at younger ages
  – Studies in RSV-naïve infant subjects ≥ 6 months may help to predict risk of ERD in younger infants
  • ERD was observed in infants > 6 months of age, suggesting ERD can be detected in older children
  • RSV serology is confounded by maternal antibody in infants < 6 months of age

Considerations and Potential Approaches to Studies in RSV-naïve Infants

• Vaccine-associated ERD may not be clinically discernable from naturally-occurring severe RSV disease
  – Studies could evaluate the relative risk of severe RSV disease between vaccine recipients and controls

• Risk of ERD may increase as immunity wanes
  – May need to follow subjects past one RSV season (or until their first documented RSV infection)
  – Oldest FI-RSV-immunized infant developed severe RSV disease at 18 months
Summary

- Prevention of RSV disease in infants is an important public health need worldwide
- Observations of Fl-RSV vaccine-associated ERD in RSV-naïve infants have presented a challenge to development of safe and effective vaccines for infants
- Proposed immunologic mechanisms contributing to ERD include a Th2-dominant CD4+ T-cell response, immune complex deposition in the lungs, development of low-affinity antibodies, and lack of RSV-specific CTLs
Summary

- Animal models can mimic some features of ERD observed with FI-RSV, and are being used to assess ERD risk from candidate vaccines.
- Studies in adults and RSV-experienced (i.e., seropositive) children might provide support for the initial studies in RSV-naïve (seronegative) infants using an age de-escalation approach.
- Types of supportive data and study design may be product-specific.
Backup slides
# Preclinical Data Supporting Studies in RSV-naïve Infants

<table>
<thead>
<tr>
<th>Animal</th>
<th>Advantages</th>
<th>Disadvantages and Considerations</th>
</tr>
</thead>
</table>
| Murine     | • Low-cost  
            • Homogeneous  
            • Well-characterized genetics                                          | • Relatively resistant to RSV: high dose inoculation manifests mild disease                      |
| Cotton Rat | • Lung histopathology after challenge resembles histopathology seen in children given FI-RSV | • Vaccine dose must be optimized to allow sufficient viral replication in setting of low levels of vaccine-induced neutralizing antibodies |
## Preclinical Data Supporting Studies in RSV-naïve Infants

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<th>Advantages</th>
<th>Disadvantages and Considerations</th>
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<tr>
<td>Bovine Model</td>
<td>• Bovine RSV disease closely resembles human disease</td>
<td>• Logistically challenging and expensive</td>
</tr>
<tr>
<td></td>
<td>• FI-BRSV –associated ERD manifests in calves with close resemblance to human ERD</td>
<td>• Size of animals may compromise adequacy of histopathologic examination (skip lesions)</td>
</tr>
<tr>
<td></td>
<td>• Bovine and human RS viruses share close homology: potential to assess immunogenicity/effectiveness</td>
<td></td>
</tr>
<tr>
<td>Nonhuman Primates</td>
<td>• Pulmonary eosinophilia and IL-13 and IL-5+ T cells identified post RSV challenge FI-RSV-vaccinated macaques</td>
<td>• Studies typically small and expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Relatively RSV-infection resistant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Intratracheal administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Immunohistopathology of ERD not detected</td>
</tr>
</tbody>
</table>