RSV vaccines and passive immunization

R. Karron
SAGE
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Populations at risk of severe RSV disease

very young infants

older infants and toddlers

elderly
Goal for RSV immunization: prevention of infection?
Repeated RSV infections do not induce sterilizing immunity

![Graph showing percent of subjects over time of challenge (months)]
Goal for RSV vaccine development

• Safely induce sufficient immunity to protect against serious RSV infection: LRI and apnea

• Induction of sterilizing immunity (i.e. protection against URI) is not required (and may not be feasible)
Obstacles to successful RSV vaccine development

• Difficult to induce protective immunity in the very young infant
  – Suppression of the immune response by maternal Ab

• Heterogeneous at-risk populations require different vaccines
  – Newborns
  – Older infants and young children
  – Elderly

• Imperfect animal models; adult RSV challenge (reinfection) model does not recapitulate RSV infection in naïve infants

• Specter of enhanced disease
Potentiation of RSV LRI following formalin inactivated vaccine

Adapted from Kim et al. Am J Epidemiol 89:422-434, 1969
Implications of enhanced RSV disease for RSV vaccine development

- Vaccines for active immunization of RSV-naïve infants should induce neutralizing antibodies, CD4 and CD8 responses

- Different vaccines in development for maternal and infant immunization:
  - Non-replicating (subunit) RSV vaccines for maternal immunization
    • Also for other non-naïve populations (older children, elderly)
  - Replicating RSV vaccines (live-attenuated or vectored) for infant immunization
    • Safest alternatives for active immunization of RSV-naïve populations
    • Live-attenuated RSV candidate vaccines have been administered to hundreds of RSV-naïve children and have never been associated with enhanced disease.\(^1\)

\(^1\)Wright PF. Vaccine. 2007 Oct 16,25(42):7372-8
Populations at risk of severe RSV disease

Infants from birth until 3-6 months
- Maternal immunization
- RSV mAb

Infants and children >3 months
- Infant immunization
**RSV Vaccine Snapshot**

**62 candidates total; 16 in clinical trials**

<table>
<thead>
<tr>
<th><strong>LIVE-ATTENUATED</strong></th>
<th><strong>WHOLE-INACTIVATED</strong></th>
<th><strong>PARTICLE-BASED</strong></th>
<th><strong>PHASE 1</strong></th>
<th><strong>PHASE 2</strong></th>
<th><strong>PHASE 3</strong></th>
<th><strong>MARKET APPROVED</strong></th>
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<tbody>
<tr>
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<td><strong>GENE-BASED VECTORS</strong></td>
<td><strong>BIOCHEMICAL LITERATURE</strong></td>
<td><strong>COMBINATION/IMMUNOPROPHYLAXIS</strong></td>
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*http://sites.path.org/vaccinedevelopment/respiratory-syncytial-virus-rsv/*
Pediatric RSV vaccination:
Adenovirus vectored RSV F
Live-attenuated RSV; RSV/PIV3 vector
## GSK’s paediatric RSV vaccine candidate

<table>
<thead>
<tr>
<th>Paediatric</th>
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</thead>
<tbody>
<tr>
<td><strong>Global intent</strong></td>
</tr>
<tr>
<td><strong>Vaccination regimen</strong></td>
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<tr>
<td><strong>Vaccine Composition</strong></td>
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<td><strong>Stage of development</strong></td>
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Overview of the Pediatric Clinical Development

Phase 1: Ongoing
- Phase I 18-45 years Adults
- Safety (Immuno)

Phase 2: Planned
- Phase I/II 6-18 Mo S+ infants
- Safety (Immuno)
- Phase I/II 6-12 Mo S- infants
- Safety Immuno

Phase 3: Planned
- Phase II 6-12 Mo S- infants Safety immuno
- Phase I/II 2-3 Mo Infants
- Safety immuno Formulation selection
- Phase III 2-3Mo Infants
- Efficacy

All trials in pediatric population in scope of IDMC oversight

CONFIDENTIAL - GSK PROPRIETARY INFORMATION
RSV ‘junior’ vaccine

An adenovirus vector based vaccine (Ad 26 and Ad35; replication incompetent), expressing F antigen that aims to protect young infants against RSV, by eliciting high titer, potent neutralising antibodies and T cell immunity.

Ongoing:

- **FIH - two phase 1 studies evaluating homologous and heterologous prime boost regimens of Ad26 and Ad35**
  - RSV1001 (NCT02440035): n=48 (dosing completed)
    - Study to evaluate the Safety, Tolerability and Immunogenicity of Ad35 regimens boosted with Ad26 in Healthy Adult Volunteers
  - RSV1003 (NCT02561871): n=32 (fully enrolled, dosing ongoing)
    - Study to evaluate the Safety, Tolerability and Immunogenicity of Ad26 boosted with Ad35 in Healthy Adult Volunteers

**Ad26**

**Ad35**
RSV – planned studies

2017:

Phase 1/2 study in children

- Age de-escalation, to study safety, tolerability and immunogenicity
- Evaluating homologous vs heterologous prime boost regimens of Ad26 and Ad35
Live-attenuated RSV vaccines with M2-2 deletion

- RSV MEDI ΔM2-2 was developed by the Laboratory of Infectious Diseases, NIAID/NIH and MedImmune
- Deletion of the RSV M2-2 ORF results in decreased RNA replication & increased Ag expression when compared to the previous leading live-attenuated RSV vaccine candidate
- Deletion of M2-2 appears to ‘de-link’ virus replication and antibody response, and prime for a potent anamnestic response following natural infection with RSV

Current & upcoming clinical studies in NIAID program

Laboratory of Infectious Diseases/NIAID (Peter Collins, Ursula Buchholz, et al*)

1. Attenuated RSV strains
   - A number of gene deletion candidates in phase 1 studies in RSV seronegative infants and children in 2016-2017 to identify a lead candidate from the following:
     - A virus comparable to RSV MEDI ΔM2-2
     - Additional ΔM2-2 backbones to evaluate potential for increased immunogenicity
     - One or more backbones based on deletion of NS2 or NS1 (interferon antagonist) genes

2. Human parainfluenza type 3 virus vectors expressing RSV F protein
   - Bivalent RSV/HPIV3 vaccine (protection against both viruses)
   - Improved growth and stability to facilitate manufacture & distribution in LMIC
   - Expression of stabilized pre-fusion F protein enhances quality of RSV-neutralizing Ab-- potential to increase the quality of anamnestic responses
   - Clinical trial seed under development, clinical study in 2017

*Collaborators: Ruth Karron et al, CIR/JHU, Elizabeth McFarland, Coleen Cunningham et al, IMPAACT/NIAID, NICHD
Pediatric RSV immunization with mAb:

Palivizumab biosimilar
Extended half-life RSV F mAb MEDI8897
Biosimilar palivizumab – WHO and University of Utrecht

• Palivizumab off patent in 2015

• Plan to develop a ‘biosimilar’ of palivizumab and reduce costs through:
  – Using latest technologies (i.e. high expression cell line)
  – A novel development and financing plan:\(^1\)
    • Coordinated by the Utrecht Center of Excellence for Affordable Biotherapeutics for Public Health
    • Funded through a consortium of manufacturers
      – Agreement signed on 9 March 2016
  – Estimated price $US 250 per child for full 5 courses
  – First market authorization expected end 2017
  – Roll out the product in LMICs

MEDI8897: Passive RSV vaccine strategy using RSV F mAb

Characteristics

- Fully human, high potency IgG1 mAb derived from human B-cells
  - YTE half-life extension technology
- Targets site on RSV prefusion F
  - Neutralizes all RSV A and B clinical isolates tested
- Single fixed IM dose given; expected to protect up to 6 months
  - Given at birth or at onset of RSV season
  - Vaccine-like pricing

Program Status

- Phase 1a adult FTIH complete (N=136)
- Phase 1b/2a in 32-35 week gestational age infants (N=89); enrollment complete, follow-up ongoing
- Phase 2b clinical efficacy in 29-35 week gestational age infants planned for 2016 (N=1,500)
- FDA fast track designation granted, study endpoints agreed with EMA-PDCO, FDA
- Exploration of prequalification process has been initiated
MEDI8897 Clinical development overview

**Phase 1a FTIH (healthy adults)**
- Double-blind placebo controlled study (3:1) (N = 136)
- Evaluated multiple IV and IM dose levels
- Subjects followed for 1 year

**Safety**
- AEs: MEDI8897 62% vs placebo 63%
- 2 SAEs: Gun shot & appendicitis

**Pharmacokinetics**
- Bioavailability 87%
- Half-life extended to 85-117 days

**Anti-drug antibody**
- Incidence of ADA similar (MEDI8897 14% vs placebo 15%), titers were low, no observed impact on safety or PK

**Phase 1b/2a in 32-35 week GA infants**
- Double-blind placebo controlled study (4:1) in USA, SA, Chile (N=89)
- Three IM dose levels evaluated
- Subjects followed for 1 year

**Safety**
- Day 30 safety and tolerability profile reassuring

**Pharmacokinetics**
- Day 30 interim PK models support single 50mg intramuscular dose administration

**Anti-drug antibody**
- Day 30 incidence of ADA was low and balanced between groups, no observed impact on safety or PK
Maternal RSV vaccination:
RSV prefusion F vaccine
RSV postfusion F nanoparticle vaccine
### GSK’s maternal RSV vaccine candidate

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<thead>
<tr>
<th><strong>Global intent</strong></th>
<th>Active immunization of pregnant women during the 3rd trimester of pregnancy to prevent RSV-associated LRTI in infants</th>
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</thead>
</table>
| **Vaccination regimen** | • Single dose to boost pre-existing immune response  
• Immunization in the third trimester |
| **Vaccine Composition** | Recombinant subunit PreF antigen (Dosage TBD, with or without Alum) |
| **Stage of development** | Phase II: ongoing |
Overview of Maternal Clinical Development

Phase I
- Completed
  - 18-45 years Adults
  - Safety
  - Immuno

Phase II
- Ongoing
  - Non-pregnant women
  - Formulation fine-tuning
  - Pregnant women
  - Safety/immuno

Phase III
- Planned
  - Pregnant women
  - Efficacy

All trials in pregnant women in scope of IDMC oversight
Novavax RSV F Vaccine Clinical Development Program: Protection of Infants via Maternal Immunization

Prior to Phase II Maternal Immunization trial, confirmed
- Safety in repeat dose and repro toxicity studies
- Safety and efficacy in cotton rat challenge studies
- Transplacental antibody transfer in 3 animal models
- Acceptable safety profile of RSV F Vaccine in >1000 subjects
- Regulatory agency acceptance of study design

Prior to planned Phase III Maternal Immunization trial,
- Acceptable safety profile of RSV F Vaccine in expanded safety database in >2000 subjects, including third trimester pregnant women and other target populations
- Year 1 global regulatory agency input on study design obtained and trial initiated.
Novavax RSV F Nanoparticle Vaccine: Phase 2 safety, immunogenicity, and transplacental antibody transfer

- Well-tolerated
- High and sustained titers of RSV F IgG and palivizumab competing antibody (binding to postfusion RSV F in ELISA)

**Trial Overview**
- **Phase 2 trial** randomized, observer-blinded
- **50 pregnant women in 3rd trimester**
  - Singleton pregnancies
- **120µg dose** with aluminum adjuvant

**Goals**
- **Describe** the safety of the RSV F vaccine women and infants
- **Describe** the immunogenicity of the vaccine in the 3rd trimester
- **Characterize** antibody transfer and decay kinetics

**Method**
- **Detailed collection of third trimester safety endpoints**
- **Cord blood** and infant sera
- **Maternal and infant RSV surveillance** through RSV season
RSV F Vaccination to Protect Infants via Maternal Immunization: Global P3 Trial **Prepare™** launched 4Q 15

### Timeline

- Phase III trial initiated Dec 2015
- Group sequential design with enrollment 2 - 4 years

### Trial Objectives

- **Primary: Prevention** of RSV lower respiratory tract infection (LRTI) with hypoxemia in infants during the first 90 days of life
- **Secondary endpoints:** LRTI with severe hypoxemia, persistent efficacy to measure out to 120, 150, 180 days

### Trial Design

- **Pregnant women in 3rd trimester**
- 5,000 – 8,255 participants
- Randomized, placebo-controlled
- DSMB oversight and iterative futility analyses to ensure safety
- **Global sites**
  - Both hemispheres
Acknowledgements

- **GSK**
  - Ilse Dieussaert

- **Janssen**
  - Valerie Oriol Mathieu
  - Olga Popovic

- **MedImmune**
  - Filip Dubovsky

- **Novavax**
  - Allison August

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  - Peter Collins
  - Ursula Buchholz

- **PATH**
  - Deb Higgins
  - Carrie Trujillo

- **WHO**
  - Vasee Moorthy
  - Erin Sparrow