A review of the RSV vaccine landscape
Acknowledgements

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NIAID/NIH/LID
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  Ursula Buchholz
Obstacles to Successful RSV Vaccine Development

- Peak of severe pediatric disease in early infancy
  - suppression of the immune response by maternal Ab
- Heterogenous at-risk populations require different vaccines:
  - Newborns
  - Older infants and young children
  - Elderly
- Imperfect animal models; adult challenge model may be useful for elderly but not highly relevant for pediatric disease
- Specter of enhanced disease
Potentiation of RSV LRI following formalin inactivated vaccine

Adapted from Kim et al., Am J Epidemiol 89:422-434, 1969
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)
RSV Vaccine Landscape: 2004 (n=3)

**Preclinical**
- Live-Attenuated
  - Wyeth

**Phase I**
- LID/NIAID/NIH
  - Wyeth

**Phase II**
- LID/NIAID/NIH
  - Wyeth

**Phase III**
- LID/NIAID/NIH
  - Wyeth

**Market Approved**

**Subunit**
# RSV Vaccine Snapshot

## RSV Vaccine Development

### Clinical Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market Approved</th>
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**Updated:** March 10, 2015

Factors contributing to RSV vaccine development

1. Advances in structural biology and in large scale production of RSV F glycoprotein
Postfusion F has the palivizumab epitope, but prefusion F has the majority of neut epitopes recognized by human sera\(^1\)
Stabilization of antigenic site on conformationally authentic protein results in potent vaccine antigen

Postfusion F in 6-helix bundle conformation

Functional form of RSV F in pre-triggered conformation

Loss or preservation of neutralization sensitive site on the native F trimer

Candidate RSV vaccine is stabilized native F trimer

RSV Postfusion F Structure (JVI 2011)

RSV Prefusion F Structure (Science April 2013)

RSV Vaccine Design (Science November 2013)
# RSV F vaccines in clinical development

## Postfusion F

<table>
<thead>
<tr>
<th>Developer</th>
<th>Phase</th>
<th>Populations (tested)</th>
<th>Populations (target)</th>
<th>Adjuvant</th>
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<td>elderly, pregnant women, children 24-71 mos.</td>
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<td>18-45 y.o.</td>
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RSV F vaccines in clinical development

**Prefusion F**

<table>
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<td>NIH/VRC</td>
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Factors contributing to RSV vaccine development

1. Advances in structural biology and in large scale production of RSV F glycoprotein
2. Rational design of live-attenuated RSV vaccines
Rational vaccine design: stabilization of empirically-derived attenuating mutations

cps2

- Codon-stabilized version of the previously evaluated RSV 248/404/1030/ΔSH

- Phase I evaluation being completed in 51 RSV-seronegative infants and children (NCT1852266, NCT 1968083)
Rational vaccine design: attenuation based on gene function (I)

\( \Delta \text{NS2} \Delta 1313 \)

- Deletion of the NS2 gene (IFN antagonist) and 1313 codon in L gene
- Phase I evaluation: completely restricted in replication in RSV-seropositive children \( (n=15) \); currently being evaluated in RSV-seronegative children \( (n=60) \) NCT1893554
Rational vaccine design: attenuation based on gene function (II)

- M2-2 is an RNA regulatory factor
- Deletion of M2-2 results in:
  - decreased RNA replication
  - increased transcription and antigen expression\(^1\) (more Ag/virion)
- RSV Medi-ΔM2-2 is highly attenuated yet immunogenic in RSV-naïve infants and children

Factors contributing to RSV Vaccine Development

1. Advances in structural biology and in large scale production of RSV F glycoprotein
2. Rational design of live-attenuated RSV vaccines
3. New approaches to vectored vaccine development
RSV paediatric vaccine candidate: novel vector approach

ChAd & MVA encoding RSV F, N & M2-1 proteins

Open label dose escalation study in healthy adults (NCT01805921)

Experimental groups
1. PanAd3-RSV IM / MVA-RSV IM
2. PanAd3-RSV IM / PanAd3-RSV IM
3. PanAd3-RSV IN / MVA-RSV IM
4. PanAd3-RSV IN / PanAd3-RSV IM

Doses
PanAd3-RSV: Low $5 \times 10^9$ and High $5 \times 10^{10}$ vp
MVA-RSV: Low $1 \times 10^7$ and High $1 \times 10^8$ pfu

10 volunteers/group
(2 & 8 volunteers at low & high dose)

The vaccine candidates were well tolerated & immunogenic
Current clinical trials of RSV vaccines

Total=13

- live-attenuated
- live vectored
- RSV F subunit

Source: clinicaltrials.gov
MedI 18897: a vaccine-like mAb

- mAb directed at site 0 on RSV F
- YTE mutation extends half-life to several months
- Currently being evaluated in 32-34 wk GA infants <12 months old (NCT02290340)
Global priority populations for RSV vaccines: RSV-naïve infants and young children
Burden of Acute RSV Infection Extends Beyond Early Infancy (0-4 months)
>1 RSV vaccine type needed; >1 PPC

- **Maternal immunization**
  - Subunit and other nonreplicating vaccines
  - Alum or nonadjuvanted

- **Passive prophylaxis**
  - Next generation RSV F mAbs

- **Infant immunization**
  - Live vaccines (native virus and vectors)
Some clinical trial considerations for vaccines developed for protection of infants and RSV-naïve children
Clinical endpoints: Define appropriate parameters for a variety of clinical settings

- Hospitalization and medically-attended lower respiratory tract illness (MA-LRI) have been used as endpoints for trials of palivizumab and motavizumab in high-resource countries.

- Consider illness endpoints (RSV-LRI, RSV-hypoxemia) and facilities-based endpoints (RSV-hosp, RSV-ER visit, etc).
  - active vs passive case finding

www.savethechildren.org.uk
Consider potential efficacy determinants in low-resource settings

• In resource limited settings, RSV exposure, disease, and vaccine efficacy may be influenced by
  – Crowding
  – Limited access to water
  – Indoor air pollution

• Maternal illnesses that may affect transplacental transmission of antibody
  – HIV
  – Hypergammaglobulinemia
  – Placental malaria
Strengths and weaknesses of the global RSV vaccine portfolio

**RSV Vaccine Snapshot**

<table>
<thead>
<tr>
<th><strong>PRECLINICAL</strong></th>
<th><strong>PHASE 1</strong></th>
<th><strong>PHASE 2</strong></th>
<th><strong>PHASE 3</strong></th>
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| Intravacc | PIV-1/RSV | VaxGen | LIPI 
Vero | RSV |
| Delta-C RSV | PIV-1/RSV | VaxGen | LIPI 
Vero | RSV |
| **GENE-BASED VECTORS** | Bavarian Nordic | GenVec | RSV | MedImmune |
| AlphaVax | MVA | Adenovirus | RSV | LIPI 
Vero |
| Alphazyme | MVA | Adenovirus | RSV | LIPI 
Vero |
| AmVax | Emergent BioSolutions | Janssen Pharmaceutical | RSV | LIPI 
Vero |
| Sendai virus | MVA | Adenovirus | RSV | LIPI 
Vero |
| **NUCLEIC ACID** | CureVac | Inovio Pharmaceuticals | Novartis | Novartis |
| RNA | DNA | RNA | DNA | DNA |
| **WHOLE-INACTIVATED** | NanoBiis | Patentlife | Ruhr-Universität Bochum | Novovac |
| RSV | DNA | DNA | DNA | DNA |
| **PARTICLE-BASED** | AgiVax | Fraunhofer | Mynvax | NanoBiis |
| VLP | VLP | VLP | VLP | RSV Nanoparticle |
| Artificial Cell Technologies, Inc. | VLP | VLP | VLP | RSV Nanoparticle |
| Peptide microparticle | VLP | VLP | VLP | RSV Nanoparticle |
| Emory University | VLP | Virosome | VLP | RSV Nanoparticle |
| Mucos | BLP | VLP | VLP | RSV Nanoparticle |
| TechnoVax | VLP | VLP | VLP | RSV Nanoparticle |
| **SUBUNIT** | Immunovaccine | NIH/NIAID/VRC | Renoptys | GlaxoSmithKline |
| DPX-RSV | RSV pre-f proteins | RSV peptides | RSV F protein | RSV F protein |
| Instituto de Salud Carlos III | RSV peptides | RSV G protein | RSV protein | RSV protein |
| RSV F protein | RSV peptides | RSV G protein | RSV protein | RSV protein |
| **COMBINATION/OTHER** | Biomedical Research Models | Fudan University | MedImmune | MedImmune |
| Biopolymer protein vaccines | RSV peptides | RSV G protein | RSV protein | RSV protein |
| MedImmune | Anti-RSV | Anti-RSV | Anti-RSV | Anti-RSV |
| **UPATED: MARCH 10, 2015** | | | | |