Live-attenuated RSV vaccines for older infants and toddlers

Ruth Karron
ESWI 2024
Declaration of interests

Research funding from:

- US National Institutes of Health and Sanofi for evaluation of live-attenuated RSV vaccines

but the views presented are my own…. 
Victims of FI-RSV vaccine development

Ross Otto Hambrick 1965-1966
Victor King 1965-1966

https://undark.org/2023/10/09/rsv-vaccine-children-trials
The case for RSV vaccination of older infants and toddlers

- 33.1 million cases of RSV-ALRI
- ~3.6 million hospitalizations
- ~101,000 deaths

Substantial annual inpatient and outpatient burden

- ~80% > 6 months
- ~60% > 6 months
- ~54% ≥6 months

Shi T. et al, Lancet 390:946–958, 2 September 2017
The case for live-attenuated RSV vaccines for older infants and toddlers

• Induction of long-lasting immunity with potent memory responses
• Administered intranasally; infectious in the presence of passively acquired antibody
• Balanced humoral, cellular, mucosal immune responses, without markers of enhanced RSV disease in animal models
• Multiple strategies to shift the balance: enhance immunogenicity while maintaining or augmenting attenuation

Murphy et al, J Clin Micro, 1986
Connors et al, J Virol, 1992
Delgado et al, Nat Med, 2009
Acosta et al., CVI. 2015
Schneider-Ohrum et al., J. Virol. 2017
# RSV Vaccine and mAb Snapshot

<table>
<thead>
<tr>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>MARKET APPROVED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LIVE-ATTENUATED/CHIMERIC</strong></td>
<td><strong>LIVE-ATTENUATED/CHIMERIC</strong></td>
<td><strong>LIVE-ATTENUATED/CHIMERIC</strong></td>
<td><strong>LIVE-ATTENUATED/CHIMERIC</strong></td>
</tr>
<tr>
<td>Blue Lake</td>
<td>PIV5/RSV</td>
<td>Blue Lake</td>
<td>Meissa Vaccines</td>
</tr>
<tr>
<td>Codagenix,</td>
<td>Codagenix,</td>
<td>Meissa</td>
<td></td>
</tr>
<tr>
<td>UID/NIAID/NIH</td>
<td>UID/NIAID/NIH</td>
<td>Vaccines</td>
<td></td>
</tr>
<tr>
<td>RSV</td>
<td>RSV</td>
<td>RSV</td>
<td>RSV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PROTEIN-BASED</strong></th>
<th><strong>PROTEIN-BASED</strong></th>
<th><strong>PROTEIN-BASED</strong></th>
<th><strong>PROTEIN-BASED</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• PARTICLE</td>
<td>• PARTICLE</td>
<td>• PARTICLE</td>
<td>• PARTICLE</td>
</tr>
<tr>
<td>• SUBUNIT</td>
<td>• SUBUNIT</td>
<td>• SUBUNIT</td>
<td>• SUBUNIT</td>
</tr>
<tr>
<td>NIH/ NIAID/VRC</td>
<td>NIH/ NIAID/VRC</td>
<td>NIH/ NIAID/VRC</td>
<td>NIH/ NIAID/VRC</td>
</tr>
<tr>
<td>RSV F Protein</td>
<td>RSV F Protein</td>
<td>RSV F Protein</td>
<td>RSV F Protein</td>
</tr>
<tr>
<td>Virometix</td>
<td>Virometix</td>
<td>Virometix</td>
<td>Virometix</td>
</tr>
<tr>
<td>VLP</td>
<td>VLP</td>
<td>VLP</td>
<td>VLP</td>
</tr>
<tr>
<td>Advance</td>
<td>Advance</td>
<td>Advance</td>
<td>Advance</td>
</tr>
<tr>
<td>Vaccine Biotechnology</td>
<td>Vaccine Biotechnology</td>
<td>Vaccine Biotechnology</td>
<td>Vaccine Biotechnology</td>
</tr>
<tr>
<td>RSV G Protein</td>
<td>RSV F Protein</td>
<td>RSV F Protein</td>
<td>RSV F Protein</td>
</tr>
<tr>
<td>Daiichi Sankyo</td>
<td>Daiichi Sankyo</td>
<td>Daiichi Sankyo</td>
<td>Daiichi Sankyo</td>
</tr>
<tr>
<td>Protein</td>
<td>Protein</td>
<td>Protein</td>
<td>Protein</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>NUCLEIC ACID</strong></th>
<th><strong>NUCLEIC ACID</strong></th>
<th><strong>NUCLEIC ACID</strong></th>
<th><strong>NUCLEIC ACID</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanoﬁ</td>
<td>Sanoﬁ</td>
<td>Sanoﬁ</td>
<td>Sanoﬁ</td>
</tr>
<tr>
<td>RNA</td>
<td>RNA</td>
<td>RNA</td>
<td>RNA</td>
</tr>
<tr>
<td>Moderna</td>
<td>Moderna</td>
<td>Moderna</td>
<td>Moderna</td>
</tr>
<tr>
<td>RNA</td>
<td>RNA</td>
<td>RNA</td>
<td>RNA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>RECOMBINANT VECTORS</strong></th>
<th><strong>RECOMBINANT VECTORS</strong></th>
<th><strong>RECOMBINANT VECTORS</strong></th>
<th><strong>RECOMBINANT VECTORS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gates MRI</td>
<td>Trinomab Biotechnology</td>
<td>Merck</td>
<td>Astra Zeneca, Sanofi, Astra Zeneca, Sanoﬁ</td>
</tr>
<tr>
<td>Anti-F mAb</td>
<td>Anti-F mAb</td>
<td>Anti-F mAb</td>
<td>Nirsevimab, Palivilumab</td>
</tr>
</tbody>
</table>

**UPDated:** January 5, 2024

Indicates Change

[https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/](https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/)
BLB-201, PIV-5 vectored RSV F (Blue Lake Biotechnology)

- PIV-5 is the etiologic agent of kennel cough; some humans have PIV-5 antibodies but human PIV-5 illness has not been reported
- Phase 1 trial of BLB-201 \(^1\)
  - \(10^{7.5}\) pfu administered by nasal spray to adults aged 33 to 75 years
  - Mild rhinorrhea reported; 17% of participants shed vaccine virus
  - Neutralizing antibodies increased 1.5-fold, nasal IgA and T cell responses detected
- Phase 1/2a study of \(10^6\) and \(10^7\) pfu in children 18-59 months and 6-24 months of age is ongoing (NCT05655182)

Meissa MV-012-968 live-attenuated nasal spray RSV vaccine

- Contains codon-deoptimized genes (NS1, NS2) and a gene deletion
- Phase 1 dose-ranging study (n=79) in RSV-seronegative infants and toddlers showed that the vaccine was well-tolerated and immunogenic (NCT04909021)
- Phase 2/3 development anticipated
Live-attenuated RSV vaccines developed at LID, NIH using reverse genetics

A panel of rationally-designed candidates with precise attenuating mutations:

- **“Stabilized” attenuating point mutations**
  - mutations in L gene refractory to de-attenuation

- **Deletion of non-essential accessory proteins**
  - \( \Delta M2-2 \): Up-regulation of transcription and antigen expression to increase immunogenicity
  - \( \Delta NS1, \Delta NS2 \): Reduced viral suppression of host interferon and apoptosis responses; \( \Delta NS2 \) diminishes epithelial shedding and airway obstruction

- **Other approaches**
  - **Gene order rearrangements**: moving F and G to promoter proximal positions to enhance transcription and translation

Attenuation
Enhanced immunogenicity
Attenuation and enhanced immunogenicity

\( \text{RSV \( \Delta NS2/\Delta 1313/I1314L \)} \)

---

Biacchesi et al., 2004 (HMPV)
Le Nouen et al., PNAS 2014, 2017, 2021
Liesman R Clin Investm2014 May;124(5):2219-33
Recalibrating expectations:
RSV antibody levels achieved with live-attenuated RSV vaccines

- Priming with live-attenuated RSV results in modest primary RSV neut Ab responses (although comparable to primary wt RSV infection)
- Subsequent natural infection with wt RSV yields potent memory responses in the absence of medically-attended RSV illness

Preliminary suggestion of vaccine efficacy with live-attenuated vaccines

Post-hoc analysis: vaccines grouped by frequency of immune response:

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDIΔM2-2</td>
<td>95%</td>
</tr>
<tr>
<td>LIDΔM2-2</td>
<td>90%</td>
</tr>
<tr>
<td>ΔNS2/Δ1313/I1314L(10^6 dose)</td>
<td>80%</td>
</tr>
<tr>
<td>LIDΔM2-2/1030s</td>
<td>85%</td>
</tr>
<tr>
<td>D46/NS2/N/ΔM2-2-HindIII</td>
<td>95%</td>
</tr>
<tr>
<td>RSVcps2</td>
<td>59%</td>
</tr>
<tr>
<td>ΔNS2/Δ1313/I1314L(10^5 dose)</td>
<td>47%</td>
</tr>
<tr>
<td>LID/cp/ΔM2-2</td>
<td>45%</td>
</tr>
</tbody>
</table>

Total n= 239 (160 vaccinees, 79 placebo recipients)

5 “most promising” vaccine candidates

Karron et al., AJRCCM 2021
Proof of concept: efficacy against RSV-MAARI and RSV-MAALRI from pooled analysis

Total n=239 (160 V, 79 P)

Illness in placebo recipients
RSV-MAARI= 19%
RSV-MAALRI=7%

No child with ≥4 fold RSV neut Ab rise had RSV-MAALRI

4-fold rise in RSV neut Ab titer, rather than absolute titer, predicted protection
RSVt vaccine in clinical trials: Sanofi/NIH co-development

- ΔNS2:
  - attenuates virus and removes the risk of NS2 mediated epithelial sloughing/airway obstruction
  - may improve immunogenicity leading to effective viral clearance

- Δ1313/I1314L:
  - deletion of 1313 confers moderate temperature-sensitive phenotype; I1314L stabilizes this deletion

- RSV ΔNS2/Δ1313/I1314L:
  - well-tolerated and immunogenic in phase I/II trials in infants and children ages 4-24 months\textsuperscript{1,2}

Study design: Phase 1b/2 trial of RSVt vaccine

ClinicalTrials.gov Identifier: NCT04491877

FVFS, first visit, first subject; PFU, plaque forming unit; IA, interim analysis; LD, low dose; HD, high dose; vac, vaccination
Favorable safety profile; Transient rhinorrhoea and nasal congestion were common administration site reactions

Rhinorrhoea and nasal congestion occurred with similar frequency between the 2 dose levels; Rhinorrhoea was slightly less common in placebo recipients following vaccination 1

Safety Analysis Set. (all participants receiving at least one vaccine dose; cohort 4).

Summary of participants with solicited administration site reactions during the solicited period by grade. For vaccination 1, N=61 for RSV low dose, N=57 for RSV high dose, and N=61 for placebo. For vaccination 2, N=48 for RSV low dose, N=48 for RSV high dose, and N=54 for placebo.

Maximum intensity during solicited period shown
4-fold rise in neutralizing antibody titres after 2 vaccinations

RSV naive participants; cohort 4
RSVt Phase III (PEARL) study initiated February 2024: anticipated global footprint

NCT06252285
An alternative approach: bovine/human parainfluenza virus RSV preF

**RSV F DS-Cav1**

**HPIV3 glycoproteins**

**BPIV3 N, P, M, L proteins: host range restriction in primates**

- B/HPIV3 expressing RSV preF (DS-Cav1 or DS-Cav1-CT) as a dual HPIV3/RSV vaccine
- Potential advantages:
  - Protection against 2 important pediatric respiratory pathogens
  - May be particularly useful after a primary infection or in the presence of RSV Ab
  - In NHP studies:
    - not inhibited by preexisting RSV immunity
    - boosting with rB/HPIV3-RSV-pre-F yields significantly higher titers of RSV neut Ab compared to live-attenuated native RSV in preimmune animals
- Potential disadvantage: contains a single RSV protein
- Clinical evaluation of rB/HPIV3-RSV-pre-F anticipated in 2024

Liang et al., J Virol 2020
Some final thoughts

• Substantial burden of pediatric RSV disease exists beyond early infancy

• Live RSV vaccines currently in clinical development fall into 2 broad categories:
  • Native RSV attenuated by gene deletions, point mutations, codon deoptimization (NIH/Sanofi, Meissa)
  • Vectored RSV F with heterologous backbones (PIV-5 [Blue Lake Biotechnology]; B/HPIV3 [NIH])

• As with LAIV, products may be efficacious without a detectable CoP
  • Passive immunity cannot be used as a benchmark—priming is important!
  • Mechanisms of protection may differ between native RSV vaccines and vectored vaccines

• The next 3-5 years will be critical for live-attenuated RSV vaccine development
With thanks to:

LID, RNA Viruses Section
  Ursula Buchholz
  Cindy Luongo
  Cyril Le Nouen
  Shirin Munir
  Yumiko Matsuoka
  and team...

Medical Virology Section, LID
  Lesia Dropulic
  Jeffrey Cohen

DCR, OCRPRO
  John Tierney
  Mark Miller
  and team...

NIAID, VRC
  Li Ou
  Emily Phung
  Tracy Ruckwardt
  Baoshan Zhang
  Peter Kwong
  Barney Graham

University of Texas, Austin
  Jason McLellan

RSVPed
  Suzanne Woods
  Jocelyn San Mateo
  Kim Wanionek
  Jen Oliva
  Kristi Herbert
  Karen Loehr
  and team

IMPAACT
  Coleen Cunningham
  Elizabeth McFarland
  and team

University of Rochester Medical Center
  Mary Caserta
  Jennifer Nayak
  and team

Vanderbilt University Medical Center
  Natasha Halasa
  and team

Sanofi, Inc.
  Scott Gallichan
  Olobukola-Bukky Idoko
  Linong Zhang
  Haritha Adikarla
  Gustavo Dayan
  and the CRADA Team

The children and parents who participated in these studies
Extra slide
Live-attenuated RSV vaccines prime for strong anamnestic responses to wt RSV. Antibody responses are stable over time. Antibody titers to vaccines are comparable to those induced by primary RSV infection.

Can we boost primary RSV serum antibody titers to levels similar to anamnestic responses?

Karron et al., AJRCCM 2021