Arrinconando al VRS

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Global RSV disease burden

RSV kills more children aged <1 year than any other single pathogen except malaria

28–364 days of life
Variability in clinical presentation of RSV infections

URI, LRTI, lower respiratory tract infection; URI, upper respiratory infection.
How do we explain the variability in clinical presentations?

URI  Complex Interplay  LRTI Severe

Virus  Host

Age
Age and Disease Severity
Hospitalization Rates per Month of Age

RSV Hospitalization Rates per 1000 children

Do maternal antibodies influence disease severity?

If so, which specific antibodies are more relevant?
RSV: The Virus

RSV PreF and PostF Antigenic Sites

PreF, prefusion RSV F; PostF, postfusion RSV F
RSV G Induces Neutralizing Antibodies

Approximation by Will Ray

Courtesy of Mark Peeples
Higher maternal PreF antibodies and lower risk of severe RSV disease in infants

Serum maternal antibodies (1st trimester [9-12 weeks of gestation])

Risk of hospitalization for severe RSV Infection in first 3 months of age

Koivisto K, et al submitted
PreF are the most abundant antibodies in infants with acute Infection

Patients ≤4 months of age
n = 44; 40 Acute patients (circles)
Statistics: Kruskal-Wallis followed by Dunn’s Test to adjust for multiple comparisons
Serum IgG antibodies against RSV glycoproteins inversely correlate with age

\[ r = -0.73, \ p < 0.0001 \]

\( n = 65; \ 45 \) hospitalized patients and 20 outpatients

Spearman \( (r) \) correlation is indicated

Non-linear regression, one phase decay (shaded values)

IgG, immunoglobulin G

Patients with low severity scores had higher PreF- and G-specific antibodies.

Patients ≤6 months of age
n = 38 hospitalized patients
Statistics: Mann-Whitney, median with (IQR)
Are young infants capable of generating an effective antibody response to RSV?
Pre-F Ab concentrations acute, 1 month and 6 months follow-up

Garcia-Mauriño, C (in preparation)
RSV and the innate the immune system
Transcriptional profiles in children with RSV bronchiolitis

Training Set
Dallas, TX (n=59)

Test Set
Dallas, TX (n=49)

Mann-Whitney <0.01, Benjamini MTC x1.25-fold change

And.... what about age?
RSV-induced immune profiles by age group

**RSV Signature**
- Modules Over expressed (%): 53% (Red) vs 47% (Blue)
- Modules Under expressed (%): 36% (Red) vs 64% (Blue)

**RSV <6 months**
- Modules Over expressed (%): 71% (Red) vs 29% (Blue)

**RSV 6-24 months**
- Modules Over expressed (%): 36% (Red) vs 64% (Blue)

**Interferon modules**
- **< 6m**
  - M1.2: 50% (Red) vs 81% (Blue)
  - M3.4: 42% (Red) vs 68% (Blue)
  - M5.12: 52% (Red) vs 48% (Blue)

**Duration of supplemental O2**
- *r* = -0.65
- *P* < 0.0001

**Length of Hospital Stay**
- *r* = -0.52
- *P* < 0.0001

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RSV Immune responses: Age and disease severity

0–6 months

- Inpatients (n=10)
  - Age (months): 3.0 (2.0–4.9)
  - Males: 60%

- Outpatients (n=12)
  - Age (months): 4.5 (2.3–5.6)
  - Males: 67%

6–24 months

- Inpatients (n=14)
  - Age (months): 9.0 (7.1–11.0)
  - Males: 60%

- Outpatients (n=12)
  - Age (months): 8.6 (7.7–12.0)
  - Males: 67%

Is this relevant for healthy infants?
Infants aged <6 months show underexpression of interferon, inflammation and B cell genes, but overexpression of T cell genes.

<table>
<thead>
<tr>
<th>Innate Immune Response</th>
<th>0-3</th>
<th>3-6</th>
<th>6-9</th>
<th>9-12</th>
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<tbody>
<tr>
<td>(M1.2) Interferon</td>
<td>53</td>
<td>53</td>
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<td></td>
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<td>(M3.4) Interferon</td>
<td>45</td>
<td>40</td>
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<tr>
<td>(M5.12) Interferon</td>
<td>44</td>
<td>41</td>
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<tr>
<td>Monocytes</td>
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<tr>
<td>(M4.14) Monocytes</td>
<td>62</td>
<td>40</td>
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<tr>
<td>Neutrophils</td>
<td>21</td>
<td>13</td>
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</tr>
<tr>
<td>NK Cells</td>
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<tr>
<td>(M3.6) NK Cells</td>
<td>56</td>
<td>47</td>
<td>14</td>
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<td>(M3.2) NK Cells</td>
<td>30</td>
<td>24</td>
<td>10</td>
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<tr>
<td>(M4.2) NK Cells</td>
<td>66</td>
<td>47</td>
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<tr>
<td>(M4.6) NK Cells</td>
<td>70</td>
<td>46</td>
<td>30</td>
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<tr>
<td>(M4.13) NK Cells</td>
<td>34</td>
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<tr>
<td>(M5.1) NK Cells</td>
<td>49</td>
<td>35</td>
<td>18</td>
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<tr>
<td>Inflammation</td>
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<tr>
<th>Adaptive Immune Response</th>
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<th>6-9</th>
<th>9-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>(M4.1) T Cells</td>
<td>53</td>
<td>50</td>
<td>47</td>
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<td>(M4.15) T Cells</td>
<td>47</td>
<td>38</td>
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<td>B Cells</td>
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<tr>
<td>Plasma Cells</td>
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<td>(M4.10) Plasma Cells</td>
<td>26</td>
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<tr>
<td>(M4.11) Plasma Cells</td>
<td>60</td>
<td>55</td>
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</tbody>
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Overexpression

Underexpression

<10% of the genes differentially expressed
Preventing RSV
Maternal Vaccination

Prefusogenic F particle

Phase 3 and beyond: The RSV F nanoparticle vaccine for infants via maternal immunization

- Healthy pregnant women, at 28-36 weeks gestation
- Randomized 2:1 IM of RSV F nanoparticle vaccine or placebo
- Primary endpoint: 90 days
- Infants followed 364 days (safety)

https://novavax.com
RSV vaccination during pregnancy and effects in infants

n=4636

Subjects, %

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>RSV-F vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV LRTI</td>
<td>2.4% (35/1430)</td>
<td>1.5% (41/2765)</td>
</tr>
<tr>
<td>RR (97.5% CI)</td>
<td>39.4% [-1%-64%]</td>
<td></td>
</tr>
<tr>
<td>RSV Hypoxemia</td>
<td>1.0% (14/1430)</td>
<td>0.5% (14/2765)</td>
</tr>
<tr>
<td>(RR 95% CI)</td>
<td>48.3% [-8%-75%]</td>
<td></td>
</tr>
<tr>
<td>RSV Hospitalizations</td>
<td>3.7% (53/1430)</td>
<td>2.1% (57/2765)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>44.4% [19.6-61.5%]</td>
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</tbody>
</table>

PreF subunit vaccine
RSV 50% neutralization GMTs and GMFRs

Schmoele-Thoma B et al, IDWeek 2019
Active Immunization for children > 6 months of age
Efficacy of RSV live attenuated vaccines

A. RSV-MAARI

- Vaccinees (all): n=160
- Vaccinees (more promising): n=100
- Neut Responders (all): n=122
- Neut Responders (more promising): n=90

Point estimates and 95% CI*:

- Vaccine efficacy (%): 47% ± 67%
- Vaccine efficacy (%): 66% ± 67%

B. RSV-MAALRI

- Vaccine efficacy (%): 51% ± 88%
- Vaccine efficacy (%): 100% ± 100%

Karron et al AJRCCM September 2020
mRNA/lipid nanoparticle vaccine expressing RSV F variants

Cotton rat experimental model

(a) Neutralizing antibody titers

```
NT_{50} (GMT/95% CI)

mF  mDS-Cav1  RSV A2  None

RSV-B  RSV-A
```

(b) Protection against RSV challenge

```
pfu/μg Tissue

mF  mDS-Cav1  RSV A2  None

Lung LOD  Nose LOD

Lung Titers  Nose Titers
```

Espeseth et al NPJ Vaccines, 2020; 5:16
RSV PreF monoclonal antibodies

Graham B, Current Opinion of Immunol 2019; 24; 59: 57-64
Anti-RSV neutralizing mAbs

Palivizumab

Nirsevimab MK-1645

Prolonged half-life

Bind PreF neutralization

YTE
Nirsevimab serum concentrations time-profiles

Domachowske et al Pediatr Infect Dis J 2018;37:886
Single dose Nirsevimab for Prevention of RSV in Preterm Infants

- Randomized, Phase-2b double-blind, placebo-controlled study to evaluate the safety and efficacy of Nirsevimab in **1453 preterm infants** 29 – 35 weeks GA (Synagis-ineligible)

- **Primary endpoint**
  - Incidence of *medically attended LRTI* (inpatient and outpatient) caused by PCR confirmed RSV for 150 days after dosing

- **Secondary and exploratory endpoints**
  - Incidence of *hospitalizations* due to PCR-confirmed RSV for 150 days after dosing
  - Safety, PK, and ADA
  - Healthcare utilization and caregiver burden

Nirsevimab for prevention of RSV in preterm infants

Relative risk reduction; 95% CI

Griffin P, N Engl J Med 2020
Reinventing the role of mAbs for prevention of RSV

Palivizumab

MEDI8897
MK-1645
Summary

1. Young infants are at increased risk for severe RSV disease
2. Age and host response play major role in disease severity
3. RSV pre-F and G antibodies modulate disease severity
4. Infants demonstrate limited antibody responses to RSV
5. Interferon responses are inadequate in early life
6. Passive immunization best approach to prevent severe RSV infection
Two major strategies for passive immunization against RSV

Maternal vaccines (PreF) and Extended half-life mAbs