Once bitten, twice shy
The RSV vaccine story

Jim Buttery
Monash Children’s Hospital
Murdoch Childrens Research Institute
The Ritchie Centre
Department of Paediatrics, Monash University
RSV

Clinical picture

Epidemiology

Burden

History

Future
RSV

Paramyxovirus
RNA- stable antigenically

F- fusion protein
G protein- types A & B
<2yo
ALRI: (25-40%)
Bronchiolitis
Pneumonia

URTI

Asymptomatic
Clinical RSV

<2yo
ALRI: (25-40%)
Bronchiolitis
Pneumonia

older
Asymptomatic
URTI

URTI

Asymptomatic

High-risk:
Flu-like illness
Pneumonia
Global causes of child deaths*

- Pneumonia: 14% (4% is specifically RSV)
- Neonatal deaths: 41%
- Other non-communicable diseases: 4%
- Other infections: 9%
- Meningitis: 2%
- Pertussis: 2%
- AIDS: 2%
- Malaria: 8%
- Injury: 3%
- Measles: 1%
- Diarrhoea: 1%
- Preterm birth complications: 12%
- Birth asphyxia: 9%
- Sepsis: 6%
- Congenital abnormalities: 3%
- Other: 5%
- Tetanus: 1%

RSV burden

Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis


33.4 million cases RSV associated ALRI

3.4 million cases RSV associated severe ALRI

53,250-199,000 deaths

Lancet 2010; 375:1545-55
RSV epidemiology

Paediatric Seasonality of Detected Respiratory Pathogen

Courtesy Natasha Ching
RSV in adults

Adult Seasonality of Detected Respiratory Pathogen

Annually in the US, in adults 65 and older:

RSV infections: 2,400,000
Medical interventions: 900,000
Deaths: 14,000
Risk factors: RSV

< 6m (<2y)
Prematurity
Resp/cardiac disease
Crowding
Large families
School age siblings
Air pollution
Day care

DCC rooms:
50% children infected within 6 days of 1\textsuperscript{st} RSV case
(Chu et al J Clin Virol 2013)
Effect on transmission: Force of infection

Basic reproductive rate

Influenza: ~1.5

Rotavirus: ?

Measles: 13-16

RSV: 1.2-2.1

Varicella: 9-11
RSV vaccine history

1965-1967
Lower SES
RCT

RSV vaccine- NIH Lot 100
Formalin inactivated

Parainfluenza vaccine
Control (2 lots)
TABLE 5
RS virus infection and serious illness in comparable groups of infants receiving one or more injections of inactivated RS and parainfluenza vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Category of infants</th>
<th>No. and age of infants during designated time period of RS virus prevalence</th>
<th>Total No. infants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1965-1966</td>
<td>Age$ (mo.)</td>
</tr>
<tr>
<td></td>
<td>No. infants</td>
<td>Age$ (mo.)</td>
<td>No. infants</td>
</tr>
<tr>
<td>RS lot 100</td>
<td>At risk*</td>
<td>20</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>RS infection†</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Hospitalized</td>
<td>4</td>
<td>16 (80%)†</td>
</tr>
<tr>
<td>Para 1 lot 23</td>
<td></td>
<td>15.8</td>
<td>20</td>
</tr>
<tr>
<td>Trivalent parainfluenza lot 6279</td>
<td></td>
<td>8.4</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Hospitalized</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total parainfluenza</td>
<td>At risk*</td>
<td>20</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>RS infection†</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Hospitalized</td>
<td>1</td>
<td>1 (5%)†</td>
</tr>
</tbody>
</table>

2 deaths
Both in RSV arm
RESPIRATORY VIRUS IMMUNIZATION

*Age specific attack rates for hospitalized illness due to respiratory syncytial virus*

<table>
<thead>
<tr>
<th>Vaccine group</th>
<th>Total No. in age group at time of immunization (at risk)</th>
<th>Total hospitalized with RSV illness</th>
<th>Attack rate per 100 at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV</td>
<td>51</td>
<td>7*</td>
<td>13.7</td>
</tr>
<tr>
<td>Control (TPV)</td>
<td>65</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Control (non-vaccines)</td>
<td>116</td>
<td>1</td>
<td>0.88</td>
</tr>
</tbody>
</table>

6–11 Months

Military population Arizona 1001 infants
No deaths
So: what has changed?

• Better understanding immune response elicited by
  – Wild type RSV
  – Lot 100 FIV

• New design candidates
  – LAIV
  – Subunit vaccines
    • Esp F protein

• Approaches: maternal, elderly & older child
### RSV Vaccine Snapshot

#### Preclinical

<table>
<thead>
<tr>
<th>Live-Attenuated</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV</td>
<td>LID/NIAID/NIH</td>
<td>RSV AM2-2</td>
<td>RSV AM2 A1R3</td>
<td>Novavax RSV F Nanoparticle</td>
</tr>
<tr>
<td>RSV</td>
<td>Delta-G RSV</td>
<td>RSV AM2-2</td>
<td>RSV AM2 A1R3</td>
<td>Novavax RSV F Nanoparticle</td>
</tr>
<tr>
<td>RSV</td>
<td>LID/NIAID/NIH</td>
<td>RSV AM2-2</td>
<td>RSV AM2 A1R3</td>
<td>Novavax RSV F Nanoparticle</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Whole-Inactivated</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV</td>
<td>AgITVax</td>
<td>VLP</td>
<td>VLP</td>
<td>VLP</td>
<td>ClaroSmithKline RSV F Protein</td>
</tr>
<tr>
<td>RSV</td>
<td>Fraunhofer</td>
<td>VLP</td>
<td>VLP</td>
<td>VLP</td>
<td>ClaroSmithKline RSV F Protein</td>
</tr>
<tr>
<td>RSV</td>
<td>Mymetics</td>
<td>Virosome</td>
<td>VLP</td>
<td>VLP</td>
<td>ClaroSmithKline RSV F Protein</td>
</tr>
<tr>
<td>RSV</td>
<td>University of Massachusetts</td>
<td>VLP</td>
<td>VLP</td>
<td>VLP</td>
<td>ClaroSmithKline RSV F Protein</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Particle-Based</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV</td>
<td>AgITVax</td>
<td>VLP</td>
<td>VLP</td>
<td>VLP</td>
<td>ClaroSmithKline RSV F Protein</td>
</tr>
<tr>
<td>RSV</td>
<td>Fraunhofer</td>
<td>VLP</td>
<td>VLP</td>
<td>VLP</td>
<td>ClaroSmithKline RSV F Protein</td>
</tr>
<tr>
<td>RSV</td>
<td>Mymetics</td>
<td>Virosome</td>
<td>VLP</td>
<td>VLP</td>
<td>ClaroSmithKline RSV F Protein</td>
</tr>
<tr>
<td>RSV</td>
<td>University of Massachusetts</td>
<td>VLP</td>
<td>VLP</td>
<td>VLP</td>
<td>ClaroSmithKline RSV F Protein</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subunit</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV F protein</td>
<td>GlaxoSmithKline</td>
<td>RSV F protein</td>
<td>RSV F protein</td>
<td>RSV F protein</td>
<td>ClaroSmithKline RSV F Protein</td>
</tr>
<tr>
<td>RSV F protein</td>
<td>Janssen Pharmaceutical</td>
<td>RSV F protein</td>
<td>RSV F protein</td>
<td>RSV F protein</td>
<td>ClaroSmithKline RSV F Protein</td>
</tr>
<tr>
<td>RSV F protein</td>
<td>Innovax</td>
<td>RSV F protein</td>
<td>RSV F protein</td>
<td>RSV F protein</td>
<td>ClaroSmithKline RSV F Protein</td>
</tr>
<tr>
<td>RSV F protein</td>
<td>University of Saskatchewan</td>
<td>RSV F protein</td>
<td>RSV F protein</td>
<td>RSV F protein</td>
<td>ClaroSmithKline RSV F Protein</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nucleic Acid</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNA</td>
<td>CureVac</td>
<td>RNA</td>
<td>RNA</td>
<td>RNA</td>
<td>Immunovaccine DNA-RSV</td>
</tr>
<tr>
<td>DNA</td>
<td>GlaxoSmithKline</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
<td>Immunovaccine DNA-RSV</td>
</tr>
<tr>
<td>DNA</td>
<td>Invivo Pharmaceuticals</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
<td>Immunovaccine DNA-RSV</td>
</tr>
<tr>
<td>DNA</td>
<td>Ruhr-Universität Bochum</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
<td>Immunovaccine DNA-RSV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene-Based Vectors</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA</td>
<td>AlphaVac</td>
<td>MVA</td>
<td>MVA</td>
<td>MVA</td>
<td>Bavarian Nordic MVA</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Alphavirus</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Janssen Pharmaceutical Adenovirus</td>
</tr>
<tr>
<td>Sendai virus</td>
<td>AmVac</td>
<td>Sendai virus</td>
<td>Sendai virus</td>
<td>Sendai virus</td>
<td>Janssen Pharmaceutical Adenovirus</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>CanVac</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Janssen Pharmaceutical Adenovirus</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Ruhr-Universität Bochum</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Janssen Pharmaceutical Adenovirus</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Vanderbilt University</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Janssen Pharmaceutical Adenovirus</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Bayer</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Janssen Pharmaceutical Adenovirus</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Bavarian Nordic</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Janssen Pharmaceutical Adenovirus</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>ClaroSmithKline</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Janssen Pharmaceutical Adenovirus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combination/Immu-N-Prophylaxis</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA prime, particle boost</td>
<td>Bimedical Research Institute</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
<td>MedImmune Medi-8997 Anti-F mAb</td>
</tr>
<tr>
<td>DNA-protein combo</td>
<td>Fudan University</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
<td>MedImmune Medi-8997 Anti-F mAb</td>
</tr>
</tbody>
</table>

**Updated:** October 26, 2015

Current clinical trials of RSV vaccines

- Total=13
- live-attenuated
- live vectored
- RSV F subunit
2015

Implemented
OPV/IPV
MMR
Influenza
HAV
HBV
YF
Varicella
Rotavirus
JE
Rabies

Clinical trials
Dengue
RSV
Norovirus
HCV
Rhinovirus
HIV
Variables affecting impact

- Efficacy
- Coverage
- Schedule: Antenatal vs childhood
- Duration of protection
- Effect on transmission: nosocomial and community
- Replacement disease
Impact maternal flu immunisation

<6m hospitalisations 3 US states

Infants of vaccinated mothers were 45-48% less likely to have influenza hospitalizations

Conclusion

RSV major pathogen in infants and the elderly

1st vaccine trials in 60s a disaster and lesson

5 decades on reason for hope
Thank you