Perspectives on vaccination against respiratory syncytial virus

What makes the development of RSV vaccines challenging?

Oliver Wicht PhD,
Projectleader MD-RSV antibodies
RIVM, Centrum infektieziektenbestrijding

http://www.strategischprogramma.rivm.nl/gezondheid_afweer
RSV is a pleomorphic paramyxovirus

- Same family as measles virus, mumps virus, and metapneumovirus
- Vaccine is not available
- Pathogenesis varies from mild cold to bronchiolitis and pneumonia, rarely lethal
- Reinfections frequently occur throughout life, 5-20% of population per annum

RSV-mediated respiratory disease

- RSV infection by large droplets and contaminated surfaces
- Virus shedding: 3-5 days
- URT: 1-3 weeks
- Virus cleared
- Upper respiratory tract infection: Rhinorrhea, cough, common cold
RSV-mediated respiratory disease

RSV infection by large droplets and contaminated surfaces

Lower respiratory tract infection:
- Fever, malaise, headache, myalgia, sore throat, cough, dyspnea, rhinorrhea
- Otits, Sinositis, brochiolitis, pneumonia

Possible longer term effects:
- Airway hyperreactivity, wheezing, asthma
RSV-mediated respiratory disease

- RSV stays in the lungs, usually not systemic
  - Mucosal pathogens are hard to study because conditions are hard to mimick in cell culture

RSV infection by large droplets and contaminated surfaces

Lower respiratory tract infection:
- Fever, malaise, headache, myalgia, sore throat, cough, dyspnea, rhinorrhea
  → Otits, Sinositis, brochiolitis, pneumonia

Possible longer term effects:
- Airway hyperreactivity, wheezing, asthma

Virus cleared

3 - 5 days

1 - 3 weeks

4 - 8 months

Lower respiratory tract infection:
- Fever, malaise, headache, myalgia, sore throat, cough, dyspnea, rhinorrhea
  → Otits, Sinositis, brochiolitis, pneumonia

Possible longer term effects:
- Airway hyperreactivity, wheezing, asthma

Virus cleared
Newborns suffer from RSV infection

- Primary infections are usually symptomatic; broad range of severity
- Complications occur early in life, peak hospitalization at 2.5 months of age
- 90% of individuals had RSV one year after birth

Age at admission to hospital with RSV disease

Age at time of hospitalization for HRSV disease (months)

J Infect Dis 1999;180:41–49
Long term sequelae of severe RSV infection

- RSV bronchiolitis → increased risk of recurrent wheezing and asthma until early adulthood
- Common genetic predisposition for RSV infection and asthma
- RSV prevention trial (by monoclonal antibody) provided proof of the causal relationship between RSV infection and development of asthma (Simoes et al. J Allergy Clin Immunol 2010;126:256-262)

RSV incidence in NIVEL sentinel surveillance

- NIVEL sentinel network of general practitioners (~40 practices)
- Patients showing acute respiratory infections (ARI), among which influenza-like illness (ILI)
- Molecular diagnosis of infectious agents in respiratory samples

Indexed figure showing the seasonality of RSV occurrence in the Netherlands

Source: RIVM/IDS & EPI, NIVEL; courtesy Adam Meijer, RIVM/IDS
RSV-diagnosed patients suffering ARI or ILI as registered by NIVEL sentinel surveillance

Indexed figure showing the age distribution of RSV cases in the NIVEL cohorts

Source: RIVM/IDS & EPI, NIVEL; courtesy Adam Meijer, RIVM/IDS
RSV incidence amongst elderly

- GRIEP study amongst community dwelling, healthy adults ≥ 60 years of age
- 2500 individuals were monitored per season
- ~10% showed with influenza-like illness

Source: RIVM/IIV, GRIEP1-3, Josine van Beek

* Preliminary data
Public Health impact of RSV infections

- There is medical need for an RSV vaccine
  - Risks groups are more likely to benefit
  - Vaccination strategy depends on target group
  - Endpoint of vaccination trials has to be well defined

- Disease pathogenesis and immunity not well understood
Cellular immune response against RSV

- Remarkable influx of immune cells into the lungs during LRTI
- In contrast to other paramyxoviruses, RSV has extra proteins for immune evasion
- Type of CD4+ T-cell help impacts immunopathology
- Vaccines need to support humoral response by triggering the proper T-cell response without enhanced disease
Role of immunopathology during RSV disease

- Robust cellular response required for virus clearance
  - Th1 biased CD4+ T-cell response
  - robust CD8+ T-cell response
- Excessive inflammatory response in LRT
  - Excessive mucous production
  - Airway hyperreactivity
  - Tissue damage
  - Th2 biased CD4+ T-cell response associated with severe disease
Humoral immune response against RSV

- Single RSV serotype
- Infection results in systemic serum IgG and secretory IgA on mucosal epithelium
- Main targets for antibodies:
  - RSV fusion protein F (conserved)
  - RSV glycoprotein G (variable per subgroup RSV)
Nasal IgA protects from infection

- Protection of healthy adult volunteers against RSV challenge

Antibody response is weak and of short duration

- Antibody response after RSV infection by challenge of adults

Antibodies are prophylactically applied to high risk infants and protect against severe disease.

A multicenter, randomized, placebo-controlled trial in premature infants or children with bronchopulmonary dysplasia.

Vaccination against RSV

Risk groups – whom to vaccinate?
- Premature babies
- Infants under 2 years with chronic lung disease or heart problems
- Adults 65 years and older
- People with weakened immune systems, such as from HIV infection, organ transplants, or specific medical treatments like chemotherapy

Legacy
- 1960s formalin-inactivated RSV vaccine applied to newborns resulted in enhanced pathology upon natural RSV infection
- Ongoing safety concerns
Attenuation of disease by antibodies in early life

![Graph showing the attenuation of disease by antibodies in early life.](image-url)
Protection by vaccination early in life

- Placental transfer of maternal antibodies
- Maternal neutralizing antibodies in child
- Attenuation of disease by antibodies
- Vulnerable period

- Child’s own antibodies by vaccination
- Child’s own antibodies without vaccination
Maternal vaccination strategy

- Placental transfer of maternal antibodies
- Vaccination of mother during pregnancy
- Maternal neutralizing antibodies in child
- Child’s own antibodies by vaccination
- Child’s own antibodies without vaccination

Vulnerable period
What should a vaccine achieve?

**Block RSV infection**
- Does it require long lasting mucosal (IgA) response?
- Recurrent infections throughout life do not give protection
- Experimental reinfections of adults with the same RSV strain after 6 months

**Protect from severe disease**
- 50% efficacy or monoclonal antibodies in risk patients
- High concentrations of systemic IgG required?
- Severe disease occurs in newborns with high maternal antibody titers
- Unknown mechanism of protection

- No RSV disease = no asthma and wheezing?
## RSV Vaccine Snapshot

### Preclinical

<table>
<thead>
<tr>
<th>LIVE-ATTENUATED</th>
<th>WHOLE-INACTIVATED</th>
<th>PARTICLE-BASED</th>
<th>SUBUNIT</th>
<th>NUCLEIC ACID</th>
<th>GENE-BASED VECTORS</th>
<th>COMBINATION/IMMUNOPHYLAXIS</th>
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<tr>
<td>LID/NIAID/NIH (PIVI-3/RSV)</td>
<td>Fraunhofer (VLP)</td>
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<td>Janssen Pharmaceutical (RSV pre-F Protein)</td>
<td>GlaxoSmithKline (RNA)</td>
<td>Bavarian Nordic (MVA)</td>
<td>Fudan University (DNA + protein combo)</td>
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<td>Pontificia Universidad Catolica de Chile (BCG)</td>
<td>Meissa Vaccines (RSV)</td>
<td>Georgia State University (VLP)</td>
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<td>Ruhr-Universitat Bochum (VLP)</td>
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Vaccine concepts

Antibodies can block virus infection by stopping virus entry.

RSV fuses its membrane with the host cells to enter.
Refolding of the RSV F protein during virus entry

Antibodies against prefusion F should work well

Prefusion-specific antibodies like D25 (MedImmune, prophylactic antibody in pipeline)

Subunit vaccine candidates based on prefusion F

- Stabilization of prefusion F protein structure, recombinant protein expression
- Independent vaccine development by Janssen (Leiden), Mucosis (Groningen), and NIH (Bethesda, USA)
- Subunit vaccine concept works in naïve animals
  - McLellan et al. Science. 2013 Nov 1;342(6158):592-8
  - Krarup et el. Nat Commun. 2015 Sep 3;6:8143
- Prefusion F elicits prefusion-specific neutralizing antibodies

- Anti-prefusion F antibodies in human serum correlate with RSV neutralization
Prefusion epitopes are missing on formalin-inactivated RSV vaccine and RSV from preparations

Indexed figure showing the availability of prefusion F epitopes in FI-RSV vaccine preparations versus prefusion F protein

Potential reason for failure of formalin-inactivated RSV vaccination trial?

Source: Widjaja and de Haan, Utrecht University, manuscript in preparation
Can prefusion-specific maternal antibodies prevent disease?

- RSV-positive patient cohort at RadboudUMC <3 months of age
- Analysis of maternal antibodies of healthy control, hospitalized (moderate) and ICU admitted (severe) RSV cases

Indexed figures for detection of prefusion-F Specific antibodies in blood of newborns

→ Value of prefusion F vaccines and antibodies still unclear

Jans & Wicht et al. manuscript in preparation
Antibody functions beyond RSV neutralization?

Antibody-RSV immune complexes modulate innate immune signaling

Vissers et al. Cytokine. 2015 Dec;76(2):458-64.
Antibody-mediated enhancement of RSV infection - neutralizing versus enhancing characteristics -

Many antibodies → Insufficient amount of antibodies → No antibodies

→ neutralization
→ enhanced infection via antibody receptors
→ ‘normal’ infection
Summary

- RSV is a particular pathogen
  - A single serotype but frequent reinfections throughout life
  - Immune response can tip towards immunopathology
  - Predisposition for severe disease unclear
  - Infection is confined to the airways
  - Short lasting immune response – elaborate immune modulation (evasion?) by RSV
  - Antibodies can protect from disease to some degree
- Fundamental research enabled novel vaccine concepts that are being explored
Until then
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