Update on RSV vaccine pipeline

R. Karron
27 June 2019
# RSV vaccines for maternal immunization: PPC excerpts

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preferred Characteristic</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Efficacy</td>
<td>Greater than 70% vaccine efficacy against confirmed severe RSV disease in the offspring, from birth to age 4 months (and preferably more).</td>
<td>A vaccine with 50% vaccine efficacy against confirmed severe RSV disease in the offspring, from birth to age 3 months, may be considered as acceptable for use. Proposed priority study endpoint case definitions have been published (10). The dynamic of protection over time throughout infancy should be described, taking seasonality patterns into account. The vaccine efficacy against other endpoints of public health interest should also be evaluated, including: • non-severe RSV respiratory disease • recurrent wheezing, hyper-reactive airway disease and asthma • RSV-related morbidity in vaccinated women • reduction of antibiotic use in infants</td>
</tr>
<tr>
<td>Strain specificity</td>
<td>Vaccination protects against both RSV A and B subtypes.</td>
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### RSV vaccines for maternal immunization: PPC (2)

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<tr>
<td>Immunogenicity</td>
<td>Established correlate/surrogate of protection based on a validated assay measuring antibody levels in the mother and/or the neonate.</td>
<td>A detailed quantitative profiling of passively transferred antibodies, and relationship to timing of vaccination in pregnancy is desirable. Longevity of vaccine-induced maternal antibodies in infants should be characterized and the relationship to duration of protection should be investigated. The fine specificity of vaccine antigen neutralizing epitopes should be characterized, as they may have a significant influence on binding and functionality of the antibody induced. The generation of clinically relevant validated neutralization assay data, ideally using high-throughput formats, is an important goal. Quantitative assays measuring the ability of vaccine-induced antibodies to compete with monoclonal neutralizing antibodies (such as palivizumab or motavizumab) are interesting, but may not be reflective of all effector functions of vaccine-induced immunity, and should not replace the need to evaluate neutralization. The role of antibody transferred through breast-feeding should be investigated. The influence of maternal HIV infection and malaria in pregnancy should be evaluated.</td>
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GSK’s maternal immunisation RSV candidate vaccine is being developed to provide passive protection to the newborn\(^1\)

Purified recombinant F protein engineered to preferentially maintain its pre-fusion form:\(^1\)

- Administered as a single dose during the third trimester of pregnancy, boosting pre-existing maternal immunity\(^1\)
- Provides passive immunity to the newborn via placental transfer of anti-RSV antibodies\(^1\)

RSV, respiratory syncytial virus

Overview of clinical development for maternal RSV candidate vaccine


IDMC, Independent Data Monitoring Committee

Phase 1

Non-pregnant women1,2,3
Safety
Immunogenicity
Dose-ranging

Phase 2

First study in pregnant women4
Safety
Immunogenicity
Dose confirmation

Phase 3

Pregnant women5
Efficacy

All trials in pregnant women in scope of IDMC oversight

Phase 1 fully enrolled
Important features of Pfizer’s RSV vaccine candidate

VACCINE ANTIGEN

- Stabilized prefusion F with rigorously monitored conformation
- Sequence based on contemporary strains
- Elicits 50-fold higher NAb titers than postfusion F in NHPs
- Does not enhance respiratory pathology in cotton rats

INDICATIONS

- **Maternal**
  - Immunize pregnant women to prevent RSV-associated lower respiratory tract illness (LRTI) in infants
  - Aim to protect infants from birth to 4-6 months of age

- **Older adult**
  - Prevent RSV-associated moderate to severe LRTI in adults ≥ 60 years of age
  - May be administered annually concomitant with flu vaccine
Maternal phase 2 study: description and objectives

- Pregnant women 18 to 49 years of age
- Multiple formulations
- Respiratory disease surveillance
- To be initiated in 3Q 2019
- Pfizer’s RSV vaccine is being developed for maternal immunization globally

<table>
<thead>
<tr>
<th>Description</th>
<th>Phase 2 randomized, placebo controlled, observer-blind, dose-ranging</th>
</tr>
</thead>
</table>
| **Objectives** | **Primary**: Safety and tolerability mother and infant  
**Secondary**: Immunogenicity  
- RSV neutralizing antibody titers in cord blood and infants  
- To describe rates of RSV positive LRTI in the study population  
- Follow for 12 months |
GSK and Pfizer Maternal RSV vaccines in phase 1-2 development

• Contain stabilized versions of RSV F in the prefusion conformation
• Induce high levels of RSV neutralizing antibodies
• For both products, phase 2 trials in pregnant women scheduled to begin within the coming year
# RSV vaccines for pediatric immunization: PPC excerpts

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<th>Notes</th>
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<tr>
<td>Indication</td>
<td>Active immunization of infants, for prevention of RSV disease in infants and young children.</td>
<td>Preferred endpoint case definitions have been published (10).</td>
</tr>
<tr>
<td>Target population</td>
<td>Infants, for co-administration with existing vaccines from the Expanded Program on Immunization.</td>
<td>HIV infection and mild/moderate malnutrition should not be a contra-indication to vaccination.</td>
</tr>
<tr>
<td>Schedule</td>
<td>The vaccination regimen should provide the earliest protection and longest duration of protection possible.</td>
<td>The optimal age schedule will depend on whether a maternal RSV immunization or infant RSV monoclonal antibody program is already introduced, in which case the infant vaccination schedule should aim to extend protection, as maternally-derived or monoclonal antibody levels wane. The development plan should assess interference between maternally acquired/monoclonal antibodies and infant vaccine immunogenicity and protection. The optimal age will depend on a balance between immunogenicity and whether or not interference is seen between paediatric vaccination and pre-existing circulating antibodies. Some vaccines may be less prone to interference from pre-existing antibodies than others, either because of the nature of the platform itself or based upon the route of delivery (e.g. mucosal rather than parenteral).</td>
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### RSV vaccines for pediatric immunization: PPC (2)

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<tr>
<td>Vaccine platform and adjuvant requirement</td>
<td>A well characterized platform with existing favorable data on safety and immunogenicity in early life is preferred.</td>
<td>Adjuvant requirement should be investigated and justified if included.</td>
</tr>
<tr>
<td>Safety</td>
<td>Safety and reactogenicity at least as favourable as other WHO-recommended routine vaccines for use in the Expanded Program on Immunization. Safety profile demonstrates no or only mild, transient reactogenicity and no serious adverse events related to vaccination. No indication of ERD in vaccinated children.</td>
<td>In addition to typical toxicology evaluation of investigational pediatric vaccines, preclinical investigations should include the evaluation of the risk of post-vaccination ERD. Safety in children should first be investigated in RSV-experienced subjects, after thorough evaluation in older subjects. As ERD has historically been associated with vaccination of children without past RSV exposure, progression to younger infants and children with no past RSV infection who are seronegative at screening should be done under intense safety surveillance. Pandemic vaccination studies should include high quality medical oversight, with independent unblinded continuous safety data review, allowing detection of cases of RSV disease with features of enhanced severity, and early trial termination accordingly. A small number of seronegative infants only should be included initially, to allow for faster enrollment when enough evidence is accrued about the lack of post-vaccination ERD occurrence. This should be tailored to the available evidence about the level of risk, which may be lower for some vaccine platforms than others.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Greater than 10% vaccine efficacy against confirmed severe RSV disease over at least one year post-vaccination. Reduction in frequency and severity of RSV illnesses.</td>
<td>A vaccine with 50% vaccine efficacy against confirmed severe RSV, over at least one-year post-vaccination, may be considered as acceptable for use. Proposed priority study endpoint case definitions have been published (126). The dynamic of protection over time should be described, taking seasonality patterns into account. Protection over at least 2 years or successive RSV seasons, or more, would be preferred. The vaccine efficacy against other endpoints of public health interest should also be evaluated: • non-severe RSV respiratory disease, • hyper-reactive airway disease and recurrent wheezing in children, • reduction of antibiotic use. The demonstration of an effect of vaccination on RSV transmission, possible requiring booster doses, would be of great public health interest, but may be left for evaluation in specifically designed post-approval trials.</td>
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GSK’s paediatric candidate vaccine (ChAd155-RSV) uses a chimpanzee adenovirus vector to encode RSV proteins

Chimpanzee-derived adenovector (ChAd155)

**RSV proteins:**
- Fusion protein F
- Nucleocapside protein N
- Matrix protein M2.1

**ChAd155-RSV**
- Non-replicative
- F protein is a target for nAb production
- N and M2.1 proteins are a source of T-cell epitopes

nAb, neutralising antibody; RSV, respiratory syncytial virus

Overview of clinical development for paediatric RSV candidate vaccine

Phase I (ongoing)
- Adults aged 18–45 years
- Safety
- Immunogenicity

Phase II (ongoing)
- Age de-escalation from toddlers to target population
- Safety
- Immunogenicity

Phase III (planned)
- Infants aged 2–3 months
- Efficacy

All trials in paediatric population in scope of IDMC oversight

IDMC, Independent Data Monitoring Committee; RSV, respiratory syncytial virus

Overview of Clinical Development for Janssen RSV Junior Vaccine Ad26.RSV.preF

<table>
<thead>
<tr>
<th>Phase</th>
<th>RSV Status</th>
<th>Dose Schedule</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>JR2001</td>
<td>Phase 1/2</td>
<td>12-24 Mo</td>
<td>2 RSV seasons</td>
</tr>
<tr>
<td>JR2002</td>
<td>Phase 1/2</td>
<td>12-24 Mo</td>
<td>2 RSV seasons</td>
</tr>
<tr>
<td>JR2003</td>
<td>Phase 1/2</td>
<td>6-12 Mo</td>
<td>2 RSV seasons</td>
</tr>
<tr>
<td>JR2004</td>
<td>Phase 1/2</td>
<td>2-6 Mo</td>
<td>2 RSV seasons</td>
</tr>
<tr>
<td>JR3001</td>
<td>Phase 3</td>
<td>2-6 Mo</td>
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- **ongoing**
- **planned**

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Deletion of non-essential accessory proteins to yield improved phenotypes:

- **M2-2**: Up-regulation of antigen expression (ΔM2-2)

- **NS2**: Reduced viral suppression of host interferon responses (ΔNS1, ΔNS2)
Live-attenuated RSV vaccines in phase 1B/2 trials

Head-to-head comparison in RSV-naïve infants and children ages 6-24 mos:

ΔNS2/Δ1313/I1314L

6120/ΔNS2/1030S

ΔM2-2 (RSV 276)

ΔM2-2 (RSV 276)

NCT03916185
Pediatric RSV vaccines in phase I-II development

- Adenovirus vectored vaccines (GSK, Janssen) currently being evaluated in RSV-seronegative infants (GSK) and toddlers (Janssen)

With thanks to colleagues at...

• GSK
• Janssen
• Pfizer
• NIH/Sanofi Pasteur