OPTIONS FOR RSV PREVENTION
MATERNAL IMMUNIZATION

ADVAC ALUMNI MEETING AT ESPID SLOVENIA 2019

Flor M. Munoz, M.D.
Associate Professor
Pediatrics and Molecular Virology and Microbiology
Baylor College of Medicine
Texas Children’s Hospital
Houston, Texas
Disclosures

• Research Funding
  • National Institutes of Health - US
  • Centers for Disease Control and Prevention
  • Abt
  • Novavax
  • Janssen
  • Chimerix
  • Ansun
  • Biocryst
  • Alios
  • Regeneron
  • GAIA – Brighton Collaboration
  • National Vaccine Program Office
  • Bill and Melinda Gates Foundation

• DSMB Member
  • NIH
  • BioCSL – Seqirus
  • Moderna
  • Thrasher
  • PROPEL study

• Advisory role
  Novavax
  GSK
  Pfizer
Objectives

- RSV epidemiology and burden of disease in infants and pregnant women
- Rationale for maternal immunization with RSV vaccine
- Goals and challenges in the development of RSV vaccines for administration during pregnancy to protect young infants.
- Implementation Strategies
Respiratory Syncytial Virus

- **Neg sense, ssRNA Paramyxovirus**
- Two main types – A, B co-circulate
- 11 proteins, of which 2 are NS
- **Conserved F** (fusion – viral penetration, spread) and **variable G** (attachment) surface glycoproteins induce Neutralizing Ab

Peribronchiolar and interstitial lymphocytic infiltrates with airway trapping (**Bronchiolitis**)

[Image of RSV virus]

Multinucleated RSV **syncytium** in cell culture

[Image of RSV syncytium in cell culture]

[Link to figure title]

[Link to Nature article]
Features of Respiratory Syncytial Virus

• First described in 1957 (Chimpanzee coryza agent)
• Causes URI and LRTI – Bronchiolitis
• Co-circulation subgroups (A and B) winter outbreaks
• Illness burden and disease severity is greatest in infants, young children and elderly adults
• Recurrent infections occur throughout life and are milder except for people with chronic medical conditions
• Virus-specific serum neutralizing antibody protects against severe RSV LRTI
  • infection-induced
  • maternally derived
  • passively administered
Impact of RSV Disease in Children

• Most important cause of LRTI in infants and young children
• Nearly all children are infected at least once by age 2
• Recurrent infections common
• 30% to 40% of primary infections result in LRTI
• 2-3% of infected children require hospitalization – one of the most important causes of hospitalization in HIC
• >75% of RSV disease hospitalization occurs in full term, healthy infants.
• Higher (2x) mortality than influenza in infants
• Severe infection associated with subsequent reactive airways/asthma
RSV is a Major Global Pathogen
In Children under 5 years

2005 Estimates:
• 33.8 (19.3-46.2) million cases annually of RSV-ALRI
• 3.4 (2.8-4.3) million cases annually of severe RSV-ALRI (22% of all episodes)
• 55,000 to 199,000 deaths annually attributed to RSV
  • Most of the deaths in developing countries occur in young children

2015 Estimates in 132 developing countries:
• 33.1 (21.6-50.3) million cases annually of RSV-ALRI
• 3.2 (2.7-3.8) million hospitalizations in children <5 yr and 1.4 (1.2-1.7) million in <6 mo
• ~60,000 (48-75K) in-hospital deaths in children <5 yr and 27,000 (21-36K) in <6 mo attributed to RSV

Mortality estimates suggest RSV is an important cause of death in children
Overall mortality: ~120,000 (95,000 to 150,000)
99% of the deaths occur in developing countries
45% of deaths occur in infants < 6 months

Very young infants are most at risk for RSV-related death

- Case series hospital data from 23 countries
- **Median age** for RSV-related deaths in LMICs is **5 months**, with more than 40% occurring in under 3 months
- RSV deaths from community higher

Scheltema NM et al. Lancet Glob Health 2017
Growing evidence of the global burden of RSV

**Global Estimates**
- Hospitalized episodes
  - 3.3M (<5y)
  - 1.4M (<6m)
- Overall mortality
  - 118,200 (<5y)
  - 86,000 (<6m)

**PERCH**
- Most common cause of pneumonia
  - (36% in < 6 months and 8.1% among all fatalities)

**ANISA**
- Most prominent infectious pathogen in neonatal sepsis and pneumonia
  - (6.7% cases, 2.1% deaths)

**CHAMPS**
- RSV found in causal chain as a cause of death

**RSV GOLD**
- 58% of RSV deaths in LMICs are <6m
  - with > 40% occurring <3m

ANISA = Aetiology of Neonatal Infection in South Asia; PERCH = Pneumonia Etiology Research for Child Health; RSV GOLD = Respiratory Syncytial Virus GlObal Database; CHAMPS = Child Health and Mortality Prevention Surveillance Network.

MOST URGENT NEED IN RSV PREVENTION AND TREATMENT STRATEGIES IS: TO PROTECT YOUNG INFANTS

Source: www.jcpportraits.com
RSV in Children
Current Prevention Strategies

• No licensed vaccine for children or adults

• Passive Antibody
  • **RSV-Specific IgG** (RSV-IG or Respigam®)
  • **Monoclonal antibody** (Palivizumab or Synagis®)
    • Licensed 1998 US
    • Binds F protein of RSV preventing infection of host cell, replication and spread
    • Effective: Reduces mortality and severity of RSV disease
  • Restricted to:
    • Preterm infants < 29 weeks of gestation
    • Preterm infants with chronic lung disease (O2 requirement > 28 days)
    • Infants with hemodynamically significant/cyanotic congenital heart disease
  • Requires monthly IM administration
  • Protective levels need to be achieved *prior to* exposure
  • Most infants who are at risk for RSV (term) are excluded
  • Costly
Why don’t we have a RSV vaccine for children?

• Primary target population, the very young infant (0-4 months of age), has a suboptimal immune response to vaccination in part due to presence of maternal antibody

• Incomplete immunity to natural RSV infection, especially in younger patients

• Enhanced pulmonary disease (pneumonia)/death in very young seronegative infants receiving formalin-inactivated RSV vaccine in the 1960’s

• Subunit vaccines safe but not immunogenic enough

• Live attenuated vaccines administered intranasally pose challenges to balance between immunogenicity and reactogenicity
## FI-RSV Experience (Pfizer vaccine)

### Children 2 to 23 months of age

<table>
<thead>
<tr>
<th>RSV-outcome</th>
<th>Vaccinated group</th>
<th>Control group</th>
<th>Time between last dose and outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>pneumonia</td>
<td>9/13 (69%)</td>
<td>4/47 (9%)</td>
<td>15 to 236 days</td>
<td>Kapikian</td>
</tr>
<tr>
<td>hospitalization</td>
<td>9 cases</td>
<td>2 cases</td>
<td>Not provided</td>
<td>Chin</td>
</tr>
<tr>
<td>hospitalization</td>
<td>16/31 (52%)</td>
<td>1/40 (2.5%)</td>
<td>23 d to 11 mo</td>
<td>Kim</td>
</tr>
<tr>
<td>hospitalization</td>
<td>10/111 (9%)</td>
<td>2/173 (1.2%)</td>
<td>Not provided</td>
<td>Fulginiti</td>
</tr>
</tbody>
</table>

Kapikian et al, AJE 1969;89:405-421  
Chin et al, AJR 1969;89:449-463 (<1yr & 1-4 yrs: FI-RSV 43 & 99; FI-PIV 43 & 91)  
Kim et al, AJE 1969;89:422-433 (2 infants died at 14 and 16 months; vaccination started at 2 and 5 months, respectively; both received 3 doses)  
Fulginiti et al., AJE 1969;89:435-448
Rationale for Maternal Immunization to Protect Infants Against RSV

- Reduced incidence of RSV disease in neonates during the first several months after birth correlates with higher concentrations of RSV-specific maternal antibody.
- Passive anti-F IgG (e.g., Palivizumab) reduces incidence of severe disease.
- Adults (mothers) are primed from previous infections and vaccine will boost antibodies.
- RSV-specific IgG transfer from mothers to neonates is efficient.
- Potential protection from breast milk antibodies.
- Success of similar strategies for Tetanus, Pertussis, Influenza.
Factors that affect transplacental transfer of antibodies

- Gestational age at birth
- Interval vaccination to delivery
- Maternal IgG level
  - IgG1 \~ IgG3 > IgG4 > IgG2
- Placental abnormalities
- Infections (malaria, HIV)
- Other factors (maternal health, nutritional status, parity, etc)

Maternal IgG crosses the placenta by a selectivity and activity receptor-mediated transport system (hFcRn) (not IgM, IgA or IgE)
- Passage begins at ~ 17 wk, increases through term
- Cord/Maternal Ab correlation favors infant
- 40 wk: Fetal > Mat IgG
- Half life ~ 30-40 days
- High Ab \rightarrow longer protection
Goals of a Maternal Vaccination Program Against RSV

- Prevent infant death and hospitalization
- Prevent and/or reduce severity of lower respiratory illness in young infants
- Delay onset of first RSV infection in infants
- Reduce infection / transmission in the household and community
- Indirect benefits
  - Reduce secondary complications of RSV in infants - otitis media, bacterial infections
  - Reduce antibiotics usage for the treatment of ARI
  - Reduce virus-associated wheezing in the first decade of life
  - Improve maternal health and pregnancy outcomes (?)
RSV In Pregnancy

• Burden of RSV in pregnancy is mostly **unrecognized** (most OB providers do not test for respiratory viruses), but seems to be less frequent than rhinovirus/coronavirus and maybe more frequent than influenza

• Although most infections are likely **mild-moderate and self limited**, RSV can cause severe **lower respiratory tract illness in pregnant women**

• **Complications** of RSV infection in pregnancy include:
  • Maternal: Fever (uncommon), secondary bacterial infection, respiratory failure, preterm labor, emergent C-section
  • Infant: Preterm birth, low birth weight (?)

• Other effects: Physician visits, inappropriate antibiotics prescriptions, transmission within household
RSV in Pregnancy

- Burden of disease is unknown
- Clinical impact on pregnant women and outcomes of pregnancy unknown
- Several studies correlating maternal and prenatal factors with severity of bronchiolitis in infants
  - Eg. Maternal alcohol consumption, Cesarean section Risk
  - Maternal infection within 3 months prior to delivery Risk
- Literature review:
  - 1 report of clinical cases USA
  - 1 study each in Nepal, Mongolia, South Africa
  - PREVENT study
  - 1 study in Houston
  - Ongoing epidemiologic evaluations in context of vaccine trials
## Maternal Effects of RSV Infection during Pregnancy


<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, GA at Dx</strong></td>
<td>26 yr / 33 wk G1</td>
<td>27 yr / 34 wk G2P0</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>RSV</td>
<td>RSV and H1N1</td>
</tr>
<tr>
<td><strong>Diagnostic tool</strong></td>
<td>PCR - BAL</td>
<td>PCR – NP aspirate</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td>Bronchitis Pneumonia-VAP</td>
<td>Pneumonia</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Mechanical Vent 6 d C-section delivery at 34 weeks b/c LRTI. Hospitalization 14 d</td>
<td>Preterm labor and delivery at 34 weeks Mechanical Vent 1 d</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>5 d malaise, cough, wheezing, 1 d fever</td>
<td>5 d cough, congestion 3 d fever, chills</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Broad Atbx</td>
<td>Broad Atbx, steroids</td>
</tr>
<tr>
<td><strong>Underlying cond.</strong></td>
<td>Asthma Smoker</td>
<td>Asthma Smoker</td>
</tr>
<tr>
<td><strong>Exposures</strong></td>
<td>Young child URI</td>
<td>-</td>
</tr>
</tbody>
</table>
RSV infection in pregnancy: Clinical presentation and birth outcomes in Nepal - Chu et al. PLOS one March 2016

- Prospective, randomized trial of influenza immunization in pregnancy in rural Nepal, 2011-2014
- Enrollment and immunization in 2nd trimester (~ 17 weeks of gestation)
- Weekly home-based surveillance for febrile respiratory illness in mothers from enrollment until 180 days post-partum
- Mid nasal swabs during illness tested for RSV by PCR
- **Maternal illness = Fever** (> 38°C) plus at least one of cough, myalgia, sore throat, rhinorrhea
- Infant illness = any of – fever, cough, wheeze, difficult or rapid breathing, draining ear.
## RSV infection in pregnancy: Clinical presentation at birth outcomes in Nepal. Chu et al. PLOS one March 2016

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence RSV</td>
<td>14 (0.4%) RSV positive febrile illness episodes in 3693 women over 3554 person-years of surveillance 3.9/1000 person-years overall 11.8/1000 person-years between September and December</td>
</tr>
<tr>
<td>Morbidity</td>
<td>7/14 (50%) women sought medical care Median 2 (total 4) days of fever, myalgia, cough, rhinorrhea, sore throat  No deaths</td>
</tr>
<tr>
<td>Pregnancy effects</td>
<td>7/14 (50%) infected during pregnancy  All live births – median BW 3060 g [vs. 2790 g in women w/o RSV] 2 (29%) preterm births 34 and 36 weeks [vs. 469 (13%) in women w/o RSV]</td>
</tr>
<tr>
<td>Post-partum effects</td>
<td>7/14 (50%) infected post-partum  RSV was detected in 4 (47%) of their infants</td>
</tr>
<tr>
<td>Exposures</td>
<td>No difference in number of children in household, indoor cook stove or smoking between RSV pos and RSV Neg</td>
</tr>
<tr>
<td>Conclusion</td>
<td>RSV is uncommon cause of febrile respiratory illness in mothers during pregnancy and post-partum in Nepal</td>
</tr>
</tbody>
</table>
# Burden of RSV in Pregnant Women – Mongolia


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Study design**         | Prospective, observational, open cohort of 1260 unvaccinated pregnant women and their infants, 2013-2015  
**ILI and severe ARI** identified by bi-weekly call  
Flu and RSV point of care test |
| **Maternal Incidence rate** |  
ILI – 174 episodes in 160 PW or 11.8/1000 person days  
Severe ARI – 0.1 (0.0 – 0.4)/1000 person days  
Among 165 ILI cases tested:  
- 26 (15.8%) = influenza A (1.7 [1.5-1.9]/1000 person days)  
- 2 (1.2%) = influenza B (0.1 [0.1-0.2]/1000 person days)  
- 4 (2.4%) = RSV (0.3 [0.2-0.4]/1000 person days)  
- 2 women tested pos for both flu and RSV from separate ILI episodes in 2014/15 |
| **Illness**              | Testing within 5 days of onset  
Mean interval to resolution 8.1 days (3-20)  
No deaths |

• 2011-2012 **study of influenza vaccine efficacy in pregnant women**
• 1060 and 1056 HIV Neg; 194 HIV Pos
• **Incidence of RSV illness:**
  - HIV Neg 1.2 – 4.0 per 1000 person-months
  - HIV Pos: 3.4 per 1000
• Maternal RSV infection was associated with respiratory symptoms including cough (72.1%), rhinorrhea (39.5%), sore throat (37.2%), and headache (42%), but fever was absent.
• RSV infection during pregnancy was **not associated with adverse pregnancy outcomes**.
• Postpartum, RSV infection in mothers was associated with **concurrent infection** among 51.9% of **their infants** and, conversely, 29.8% of mothers investigated within 7 days of their infants having an RSV illness also tested positive for RSV.
RSV In Pregnancy – PREVENT* Study
Regan A, et al. RSV hospitalization in PW in four high income countries. CID May 2018

- 2010-2016 Hospitalizations for Acute Respiratory or Febrile Illness (ARFI) AND PCR testing for RSV
- Total population: 1,604,2016 pregnant women in US, Canada, Israel, Australia

RESULTS
- (0.9%) 15,287 ≥ 1 ARFI related hospitalization
- Only 6% (846/13,694 unique admissions for ARFI) were tested for RSV
- 2.5 % (21) POS for RSV (range: 1.9 – 3.1%); positivity by year: 0 to 4% (2013-14)
- 51% pos for influenza; < 1% pos for both RSV and influenza
- 63% tests and 67% detections in the 3rd trimester of pregnancy
- 38% women had pre-existing health condition (19% was asthma)
- Pneumonia was more common in RSV POS vs. neg women (38% vs. 19%, P=0.046)
- 48% of RSV POS women were admitted for ≥ 3 days
- No difference in preterm, SGA, and LBW births between RSV-pos and RSV-neg women.
- Among ARFI admissions where no delivery occurred, there was association between RSV-positivity and subsequent preterm birth (RSV-pos: 29% and RSV-neg: 15%; P=0.034).

*Pregnancy Influenza Vaccine Effectiveness Network (CDC-Abt:)*
RSV Pregnancy Houston. Hause A. ARI among Pregnant Women. JID May 2018

- Aim: Incidence and impact of RSV infection in pregnant women
- 2015-16 season (October – April)
- Cross sectional cohort of pregnant women receiving routine prenatal care at private OB practice
- Enrolled when healthy or ill
- Mid turbinate nasal swab for PCR viral diagnosis
- Symptom history and follow up for outcomes 2 weeks after enrolment if ill
- RSV identified by PCR in 10% of women, and attributed cause of ARI in 14% of women (PCR + serology)
# RSV Positive Patients

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of Enrollment</strong></td>
<td>Nov. 10</td>
<td>Nov. 16</td>
<td>Nov. 25</td>
<td>Dec. 12</td>
<td>Dec. 22</td>
<td>Mar. 31</td>
</tr>
<tr>
<td><strong>Maternal Age</strong></td>
<td>26 years</td>
<td>28 years</td>
<td>33 years</td>
<td>31 years</td>
<td>37 years</td>
<td>28 years</td>
</tr>
<tr>
<td><strong>Gestational Age</strong></td>
<td>39 weeks</td>
<td>24 weeks</td>
<td>37 weeks</td>
<td>15 weeks</td>
<td>26 weeks</td>
<td>34 weeks</td>
</tr>
<tr>
<td><strong>Days Post-Onset</strong></td>
<td>2 days</td>
<td>1 day</td>
<td>5 days</td>
<td>1 day</td>
<td>25 days</td>
<td>8 days</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Congestion</td>
<td>Congestion</td>
<td>Congestion</td>
<td>(\downarrow) Activity</td>
<td>Fever</td>
<td>Congestion</td>
</tr>
<tr>
<td></td>
<td>Sneezing</td>
<td>Sore throat</td>
<td>Sore throat</td>
<td>Appetite</td>
<td>Sore throat</td>
<td>Sore Throat</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>Cough</td>
<td>Cough</td>
<td>Appetite</td>
<td>Cough</td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sore throat</td>
<td>Chest pain</td>
<td>Short of breath</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Short of breath</td>
<td>Wheezing</td>
</tr>
<tr>
<td><strong>Duration of Illness</strong></td>
<td>11 days</td>
<td>7 days</td>
<td>18 days</td>
<td>9 days</td>
<td>30 days</td>
<td>34 days</td>
</tr>
</tbody>
</table>
RSV Vaccine for Maternal Immunization

- Which vaccine?
- Which antibodies?
- How much antibody is necessary to protect infants?
- What should outcomes in infants be?
- How is severe RSV defined? LRTI? Hypoxemia? Hospitalization? Death?
- How long will protection last?
- Role of breastmilk antibodies?
- What is acceptable safety/risk in mothers and infants?
- Risk for enhanced disease?
- Why maternal vaccination over infant vaccination or passive antibodies?
- What is the role of MI in the overall strategy of infant disease prevention?
MI: Which vaccine and which antibody?

- Non-live vaccine with or without adjuvants – one dose in 2-3rd trimester gest.
- F-Protein – Conformation dependent immunogenicity and structure based vaccine design
- Neutralizing antibodies, palivizumab competing antibodies (PCA), IgG – IgA
- Preserving neutralization-sensitive epitopes on functional form of F-protein essential for vaccine antigen design
RSV Vaccines in Development

**Historical**
- Recombinant or chimeric viruses
- WT or attenuated virus
- Whole-inactivated virus
- Postfusion F or G subunit

**New**
- Prefusion F subunit or SH pentamer
- Vectors
- Naked DNA or mRNA
- VLPs or virosomes
- Genetically modified and recombinant chimeric viruses

Eg: GSK/NIH/Pfizer vaccine
Eg: Novavax vaccine (pre-post-fusion epitopes)
Eg: GSK/Janssen vaccine (adenovirus vector)
Eg: Moderna vaccine

Source: B. Graham lecture ADVAC
MI: How much antibody?

<table>
<thead>
<tr>
<th>RSV Antibody Titer</th>
<th>Assay Method</th>
<th>Article</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RSV disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>652.6</td>
<td>Membrane Fluorescent Antibody Test</td>
<td>Ogilvie, J Med Vir 1981 7:263 Maternal Ab &amp; RSV</td>
</tr>
<tr>
<td>40.00 44.16</td>
<td>MFAT</td>
<td>Roca, J Med Vir 2002 67:616 IgG Mozambique</td>
</tr>
<tr>
<td>238.9</td>
<td>Neutralizing Ab</td>
<td>Piedra, Vaccine 2003 21:3479 Correlates of imm</td>
</tr>
<tr>
<td>538.0</td>
<td>Neutralizing Ab</td>
<td>Eick, Ped Inf Dis J 2008 27:207 Native Americans</td>
</tr>
<tr>
<td>1047</td>
<td>ELISA</td>
<td>Ochola, PLOS One 2009 4:e8088 Infants in Kenya</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fold-increase</th>
<th>Log2</th>
<th>Reciprocal NT titer</th>
<th>~months of protection</th>
</tr>
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<tbody>
<tr>
<td>32</td>
<td>13</td>
<td>8,000</td>
<td>7</td>
</tr>
<tr>
<td>16</td>
<td>12</td>
<td>4,000</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>2,000</td>
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</tr>
<tr>
<td>4</td>
<td>10</td>
<td>1,000</td>
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<td>9</td>
<td>500</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>250</td>
<td>2</td>
</tr>
<tr>
<td>0</td>
<td>7</td>
<td>125</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: B. Graham lecture ADVAC

A 2- to 4-fold lower concentration of RSV-specific antibody titers is seen in infants with RSV disease compared to infants with no disease.
PFP-2 Subunit RSV Vaccine in Pregnant Women

- 35 healthy women, 30-34 wk GA
- Vaccine was safe, well tolerated
- Vaccine response in mothers:
  - 95% with 4x-rise anti-F IgG ELISA vs. 6.6% placebo
  - Only 10% with 4x rise in Neut Ab
  - 75% by WB vs. 0 placebo
- Women with low antibody concentrations rose to higher, potentially protective levels (6.0 Log2)
- Efficient transplacental passage of IgG antibodies (>100%)
- Infant antibody higher than controls up to 6 months of age (half life 30-40 days)
- Ab in breast milk: Anti-F IgG and IgA > placebo at 2 and 6 months
- RSV infection in 2 infants of vaccine recipients and 4 placebo recipients (culture or serology). No enhanced infant RSV disease.

Serum and Breast milk IgG following RSV PFP-2 in Pregnant or Postpartum women


Glezen, WP, Vaccine 2003
Phase 2 clinical trial of investigational Pre-F RSV vaccine in non-pregnant women

**RSV F-020**

- **Australia**
  - N=500
  - Randomization 1:1:1
  - Visit 1: Visit 2: Visit 3: Visit 4: Follow-up
  - Time point: Day 0: Day 30: Day 60: Day 90: Day 360
  - Vaccination: Tdap control
  - Blood sampling for immunogenicity

- **US**
  - N=100
  - Randomization 1:1:1
  - Visit 1: Visit 2: Visit 3: Visit 4
  - Time point: Day 0: Day 7: Day 30
  - Vaccination: Tdap control
  - Blood sampling for safety

- **Czech Republic**

- **Germany**

- **Belgium**
  - N=100
  - Randomization 1:1:1
  - Visit 1: Visit 2: Visit 3
  - Time point: Day 0: Day 30
  - Vaccination: Tdap control
  - Blood sampling for safety

- **Additional Information**
  - Nonadjuvanted RSV vaccine containing 30 μg of Pref
  - Nonadjuvanted RSV vaccine containing 60 μg of Pref
  - Aluminium-adjuvanted RSV vaccine containing 60 μg of Pref

References:
Beran J, et al. JID, May, 2018; GSK Investigational vaccines: Purified Recombinant F-protein, prefusion, prepared in Chinese Hamster Ovary cells
All formulations of RSV-PreF boosted preexisting immune responses in 18–45-year old women with comparable immunogenicity. The RSV-PreF safety profile was similar to that of Tdap vaccine.
RSV F-nanoparticle aluminum adjuvanted vaccine protects women of childbearing age

A Phase 2 randomized, observer-blind, placebo-controlled, dose-ranging trial of aluminum-adjuvanted respiratory syncytial virus F particle vaccine formulations in healthy women of childbearing age

Allison August a, Gregory M. Glenn a, Elio Kpamegan b, Sonia P. Hickman c, Dewal Jani d, Hanxin Lu e, D. Ninel Thomas c, Insoo Wern g, P德m A. Piedra b, Torei C. Fries h, i

Serological determination of RSV infection before and after RSV season
RSF F-nanoparticle vaccine in Pregnant Women
Phase 2 study

Phase 2 - Antibody response in maternal participants
Anti-F IgG GMEU (95% CI)

Phase 2 – PCA response in maternal participants
PCA GMC (μg/mL)

120 μg RSV F Vaccine + 0.4 mg Aluminum as Phosphate Salt

RSV F-nanoparticle vaccine in Pregnant Women
Phase 2 study

2 Infants: Time from Vaccination to Delivery (Days)
Impacts Placental Antibody Transfer

<table>
<thead>
<tr>
<th>Assay</th>
<th>Source</th>
<th>Del. &lt; 30d post vacc., n=7*</th>
<th>Del. &gt; 30d post vacc., n=14</th>
<th>All n=21*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti F IgG</td>
<td>Cord</td>
<td>7,227</td>
<td>8,659</td>
<td>8,153</td>
</tr>
<tr>
<td></td>
<td>Mothers</td>
<td>12,979</td>
<td>6,993</td>
<td>8,594</td>
</tr>
<tr>
<td></td>
<td>Ratio</td>
<td>0.6</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>PCA</td>
<td>Cord</td>
<td>177</td>
<td>195</td>
<td>189</td>
</tr>
<tr>
<td></td>
<td>Mothers</td>
<td>303</td>
<td>178</td>
<td>213</td>
</tr>
<tr>
<td></td>
<td>Ratio</td>
<td>0.6</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>RSV/A</td>
<td>Cord</td>
<td>928</td>
<td>672</td>
<td>748</td>
</tr>
<tr>
<td></td>
<td>Mothers</td>
<td>1,448</td>
<td>580</td>
<td>786</td>
</tr>
<tr>
<td></td>
<td>Ratio</td>
<td>0.6</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>RSV/B</td>
<td>Cord</td>
<td>565</td>
<td>512</td>
<td>529</td>
</tr>
<tr>
<td></td>
<td>Mothers</td>
<td>724</td>
<td>410</td>
<td>495</td>
</tr>
<tr>
<td></td>
<td>Ratio</td>
<td>0.8</td>
<td>1.2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Important Findings:
- Maternal antibody peaks 14d after vaccination
- Period of placental transfer >30 days maximizes antibody titer in infants
- P3 recruitment window opened to 31 weeks to maximize antibody transfer

Source: J.Englund-ADVAC course

The RSV F-Nanoparticle Vaccine Phase 3 Trial in Pregnant Women

**Design**

**Randomized, Observer-Blind, Placebo-Controlled**

| **Number of Participants** | • 4,636 third trimester pregnant women randomized 2:1 (vaccine:placebo)  
• 87 clinical sites in 11 countries (northern and southern hemisphere) |
|----------------------------|---------------------------------------------------------------------|
| **Length of Study Participation** | • Mothers: up to 9 months  
• Infants: 1 year after delivery |
| **Dosing** | • 1 intramuscular (IM) Injection of RSV F vaccine or placebo at 28-36 weeks  
Estimated Gestational Age (EGA) |
| **Safety Assessment** | • Through 6 months post-partum in mothers  
• Through 1 year in infants |
| **Efficacy Assessment** | • Active/passive surveillance in mothers and infants  
• Confirmation of RSV infection by RT-PCR  
• Medically significant tachypnea or pulse oximetry (infants only)  
• Confirmation of LRTI (infants only) |

Determine the **efficacy** of maternal immunization with the RSV F vaccine against **medically significant RSV lower respiratory tract infection (LRTI)** through 90, 120, 150 and 180 days of life in infants.

Pre-post-fusion F-nanoparticle recombinant (baculovirus) vaccine produced in insect cells, adjuvanted with aluminum phosphate
Vaccine Immunogenicity and Transplacental Transfer of Antibodies: Palivizumab-Competitive Antibodies (PCA)

- **Seroresponse rate** in vaccinated mothers = 99.4%, ≥4-fold rise in 88.1%.
- Cord blood serum / maternal delivery serum = 104%; $T_{1/2} = 49.1$ days
- Anti-F IgG levels behave similarly
Vaccine Immunogenicity and Transplacental Transfer of Antibodies: Neutralizing Antibodies

Microneutralization Responses from Subset of Season 1 and 2 Subjects
**Efficacy Endpoints**

- **Primary endpoint (site only data*)**
  - Medically-significant RSV LRTI
    - RSV detected by RT-PCR and
    - At least one manifestation of LRTI, and
    - At least one of the following:
      - SpO2 <95% or,
      - Tachypnea (RR ≥70 bpm in infants 0-59 d or ≥60 bpm in infants ≥60 d)

- **Secondary endpoints (site only data*)**
  - RSV LRTI with hospitalization
  - RSV LRTI with severe hypoxemia, SpO2 <92 %

- **Exploratory efficacy endpoints (data from sites plus hospitalizations)**
  - Same as primary and secondary criteria
  - Referred to as “expanded data”

* Data collected by study personnel using standardized pulse oximeter and method of recording, physical exam by study staff and study PCR only
## Summary of Key Efficacy Findings

<table>
<thead>
<tr>
<th>Efficacy (%)</th>
<th>Time Interval</th>
<th>MS RSV LRTI</th>
<th>RSV LRTI hospitalizations</th>
<th>RSV LRTI w/severe hypoxemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>(97.52% CI and 95% CI for MS RSV LRTI primary endpoint at 90 days, all others 95% CI) Placebo, Vaccine cases³</td>
<td>0 to 90 days</td>
<td>39.4 (5.3, 61.2)²</td>
<td>44.4 (19.6, 61.5)</td>
<td>48.3 (-8.2, 75.3)</td>
</tr>
<tr>
<td></td>
<td>35/1430, 41/2765</td>
<td>53/1430, 57/2765</td>
<td>14/1430, 14/2765</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-1, 63.7)¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 to 180 days</td>
<td>26.6 (-7.8, 50.1)</td>
<td>40.4 (16.0, 57.7)</td>
<td>42.2 (-10.9, 69.9)</td>
</tr>
<tr>
<td></td>
<td>43/1430, 61/2765</td>
<td>59/1430, 68/2765</td>
<td>17/1430, 19/2765</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 to 90 days</td>
<td>40.9 (15.9, 58.5)</td>
<td>41.7 (16.7, 59.2)</td>
<td>59.6 (32.1, 76.0)</td>
</tr>
<tr>
<td></td>
<td>56/1430, 64/2765</td>
<td>55/1430, 62/2765</td>
<td>32/1430, 25/2765</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 to 180 days</td>
<td>26.5 (-0.6, 46.2)</td>
<td>35.6 (10.3, 53.7)</td>
<td>51.2 (21.9, 69.6)</td>
</tr>
<tr>
<td></td>
<td>64/1430, 91/2765</td>
<td>61/1430, 76/2765</td>
<td>35/1430, 33/2765</td>
<td></td>
</tr>
</tbody>
</table>

1. (97.5% CI); 2. (95.0% CI); 3. Per-protocol population
## Efficacy in World Bank High and Low/Middle Income Countries

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Location</th>
<th>Placebo (cases / N)</th>
<th>Vaccine (cases / N)</th>
<th>Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medically Significant RSV LRTI</strong></td>
<td>All sites</td>
<td>35/1430</td>
<td>41/2765</td>
<td><strong>39.4%</strong></td>
<td>5.3, 61.2</td>
</tr>
<tr>
<td></td>
<td>HIC</td>
<td>12/576</td>
<td>14/1079</td>
<td><strong>37.7%</strong></td>
<td>-33.3, 71.8</td>
</tr>
<tr>
<td></td>
<td>LMIC</td>
<td>23/854</td>
<td>27/1686</td>
<td><strong>40.2%</strong></td>
<td>-3.1, 65.7</td>
</tr>
<tr>
<td><strong>RSV LRTI with severe hypoxemia</strong></td>
<td>All sites</td>
<td>14/1430</td>
<td>14/2765</td>
<td><strong>48.3%</strong></td>
<td>-8.2, 75.3</td>
</tr>
<tr>
<td></td>
<td>HIC</td>
<td>5/576</td>
<td>5/1079</td>
<td><strong>46.6%</strong></td>
<td>-83.6, 84.5</td>
</tr>
<tr>
<td></td>
<td>LMIC</td>
<td>9/854</td>
<td>9/1686</td>
<td><strong>49.3%</strong></td>
<td>-27.1, 79.8</td>
</tr>
<tr>
<td><strong>RSV LRTI with hospitalization</strong></td>
<td>All sites</td>
<td>53/1430</td>
<td>57/2765</td>
<td><strong>44.4%</strong></td>
<td>19.6, 61.5</td>
</tr>
<tr>
<td></td>
<td>HIC</td>
<td>11/576</td>
<td>19/1079</td>
<td><strong>7.8%</strong></td>
<td>-92.4, 55.8</td>
</tr>
<tr>
<td></td>
<td>LMIC</td>
<td>42/854</td>
<td>38/1686</td>
<td><strong>54.2%</strong></td>
<td>-29.5, 70.2</td>
</tr>
</tbody>
</table>

Low/middle income (LMIC) = Bangladesh, South Africa, Mexico, and Philippines; High income countries (HIC) = US, Spain, UK, Argentina, Chile, Australia, New Zealand. Per-protocol analyses of primary and secondary endpoints.
## Impact of Immunization Timing on Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Gestational Age at Immunization</th>
<th>Interval from Immunization to Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;33 weeks</td>
<td>≥33 weeks</td>
</tr>
<tr>
<td>Transfer of anti-F IgG</td>
<td>138% (135, 141)</td>
<td>91% (88, 94)</td>
</tr>
<tr>
<td>Transfer of PCA</td>
<td>122% (119, 124)</td>
<td>83% (81, 86)</td>
</tr>
<tr>
<td>Transfer of RSV/A MN</td>
<td>118% (112, 125)</td>
<td>98% (93, 104)</td>
</tr>
<tr>
<td>Transfer of RSV/B MN</td>
<td>117% (111, 124)</td>
<td>97% (91, 103)</td>
</tr>
<tr>
<td>Efficacy vs. MS RSV LRTI*</td>
<td>41.4% (4.1, 64.2)</td>
<td>40.3% (0.9, 64.0)</td>
</tr>
<tr>
<td>Efficacy vs. RSV LRTI w/severe hypoxemia*</td>
<td>70.2% (37.6, 85.7)</td>
<td>44.0 (-18.4, 73.5)</td>
</tr>
<tr>
<td>Efficacy vs. RSV LRTI w/hospitalization*</td>
<td>53.5% (23.0, 71.9)</td>
<td>26.3% (9-23.1, 55.9)</td>
</tr>
</tbody>
</table>

*expanded dataset, 90 day data

Earlier gestational age at immunization (< 33 weeks) and longer interval between immunization and delivery (≥30 days) enhance transplacental antibody transfer and efficacy.
RSV F-Nanoparticle Vaccine Phase 3 RCT – My take

• First phase 3 clinical trial of RSV vaccine in pregnant women (*pregnancy indication*)
• **Global** participation, generating burden of disease and impact data
• Demonstrated the vaccine was **safe** for women and their infants (high standards/GA)
• Was **immunogenic** (neutralizing and PCA antibodies)
• Vaccine-induced antibody **transfer** was efficient favoring infant
• Determined that **gestational age** at immunization (< 33 weeks) and **interval** from vaccination to delivery (>30 days) **impact vaccine efficacy**
• Demonstrated challenges in selection and achievement of **efficacy outcomes**
• Demonstrated population based differences (HIC/US vs. LMIC)
• Showed **efficacy in prevention of severe RSV in most vulnerable period** (0-90 days) **in term infants**, where no alternative prevention strategy exists (40-50% reduction which is substantial given burden of disease)
• Final analyses ongoing – more lessons to be learned – the work continues
RSV Vaccine Design and Research in Pregnancy

FIGURE 2. Estimated RSV-ALRI hospitalization rates by narrow age bands, 2015

FIGURE 3. Estimated percent fatality of RSV-ALRI hospitalizations by narrow age bands, 2015

WHO Preferred Product Characteristics for Respiratory Syncytial Virus (RSV) Vaccines

PATH
J. Flemming

Munoz_2018
# Comparison of Deaths from MI-Preventable Diseases

According to GBD 2016 estimates, U5M is 5 million globally, including 2.1 million deaths in neonates. Amongst these, a total of 895,565 deaths were due to lower respiratory tract infection (LRI) and neonatal sepsis.

- **LRI** remains the leading cause of mortality in children U5 (652,572)
- **Neonatal sepsis** is ranked as the 8\(^{th}\) (from 10\(^{th}\) previous year) cause of death (242,992)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Stillbirths</th>
<th>Neonatal or other deaths related to maternal infection or non-immunity</th>
<th>Neonatal or infant cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group B Streptococcus</strong></td>
<td>57,000 (12,000-103,000)</td>
<td>90,000(^{a}) (36,000-169,000)</td>
<td>319,000 (119,000-417,000)</td>
</tr>
<tr>
<td><strong>Respiratory Syncytial Virus</strong></td>
<td>NA</td>
<td>86,000(^{b}) (69,000-109,000)</td>
<td>1.4 million</td>
</tr>
<tr>
<td><strong>Syphilis</strong></td>
<td>200,000</td>
<td>62,000(^{c})</td>
<td>102,000</td>
</tr>
<tr>
<td><strong>Tetanus</strong></td>
<td>NA</td>
<td>34,000(^{c}) (18,000-84,000)</td>
<td>1,996(^{cd})</td>
</tr>
</tbody>
</table>

\(^{a}\) Young infants (0-89 days); \(^{b}\) Overall <6 months (hospital + community; in-hospital alone, 27,300); \(^{c}\) Neonates (0-27 days); \(^{d}\) WHO Joint Reporting Form, 2016; NA not available.

Adapted from Seale A et al. CID 2017;65(S2):S200-19.
MI RSV-F Nanoparticle Vaccine
A Hierarchy of Efficacy by Severity of Disease

- 15.5% Infections
- 13.6% LRTI
- 6.1% LRTI w/ hypoxemia or tachypnea
- 3.9% Primary endpoint
- 3.8% LRTI Hospitalization
- 2.2% Severe hypoxemia

Observed vaccine efficacy rates:
- 11% Overall
- 15% LRTI
- 19% LRTI w/ hypoxemia or tachypnea
- 40.9% Primary endpoint
- 41.7% LRTI Hospitalization
- 59.6% Severe hypoxemia

1. Expanded data from sites and hospitalizations, through 90 days. * LB 95% CI >0
RSV Vaccine for Maternal Immunization – Key Lessons

• Understanding the burden and impact of disease
  • Mothers and infants (term, preterm, other comorbidities)
  • HIC and LMIC settings

• Diagnosis and Surveillance of RSV disease

• Safety
  • Vaccine associated adverse events vs Obstetric (background rates)
  • Vaccine enhanced disease upon natural infection under 2 years of age is NOT a significant consideration when vaccine is given to mother

• Efficacy Endpoints (eg. severe LRTI, hospitalization, death)

• Immunologic correlates of protection (may vary by vaccine and outcome)

Kaaijk et al. Human Vaccines & Immunotherapeutics 9:6, 1263–1267; June 2013
RSV Prevention: Implementation Strategies

1. Maternal + Infant vaccination at 2 – 6 months
2. Passive antibody + Infant vaccination
Maternal Vaccine vs. Infant Passive Antibodies

- Enhances natural immune mechanism of infant protection with mother as target
- Opportunities for implementation during ANC
- Requires administration in 2nd-3rd trimester and sufficient time from vaccination to delivery to achieve benefit.
- Benefits mostly term infants
- Affected by factors that alter antibody production and transplacental transfer in pregnant mothers (nutrition, co-infections, placental pathologies)
- Duration of protection short: 2-<6 mo
- Risks perceived vs. real
- Bridge until infant vaccination

- Enhances natural immune mechanism of infant protection with infant as target
- Requires administration early in life, and establishment of protection prior to exposure to RSV
- Multiple administrations needed to maintain protective levels
- However, this also ensures longer duration of protection
- Restricted to preterm infants, where most benefit is perceived, but term infants could benefit too.
- Cost and implementation challenges
- Prone to variable efficacy depending on “match” with RSV strains (escape mutants, variable epitopes/genotypes)
Thank you
ami Advancing Maternal Immunization
Vision—To improve infant health and survival

- AMI is a WHO/PATH collaboration, convening global, cross-sector experts to establish a framework for informing, coordinating, tracking, and contributing to global efforts to advance RSV maternal immunization.
- Key activities:
  - Identify evidence needs to enable efficient, well-informed global and country decisions and requirements for rapid launch and uptake of RSV maternal vaccines in LMICs
  - Assess evidence gaps and priorities, and articulate the way forward in a RSV maternal immunization roadmap
  - Develop a plan for meeting the full spectrum of decision-making, rapid launch, and uptake needs