IMPAACT 2000
A Companion Protocol to CIR Protocol Number: CIR 291

A Phase I Study of the Safety and Immunogenicity of Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine RSV LID ΔM2-2 in RSV-Seronegative Infants and Children
IMPAACT 2000

• **Study Overview**
  – Background and rationale
  – Study Objectives
  – Target Population
  – Study treatment
  – Inclusion/exclusion criteria
  – Timing of ordering vaccine
IMPAAACT 2000 Background

• Study is a 3-way collaboration
  – NIH Laboratory of Infectious Diseases (LID)
  – Johns Hopkins Center for Immunization Research (CIR)
  – IMPAAACT

• Collaboration began with P1096—an successful study in which a candidate parainfluenza vaccine (HPIV3) was studied
IMPAACT 2000 Background

• IMPAACT 2000 modeled after P1114 – study of another candidate attenuated RSV vaccine

• Protocol design based on CIR protocol which was already FDA approved; therefore, objectives, inclusion criteria, and safety monitoring have been kept similar, whenever possible

• Initial enrollment planned for prior to start of the RSV season (October 15)

• If not fully accrued, IMPAACT 2000 will resume enrollment April 1, 2015
## P1114/IMPAAACT 2000 timeline

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spring 2013</td>
<td>P1114 began development</td>
</tr>
<tr>
<td>Fall 2013</td>
<td>P1114 began enrollment, 4 sites</td>
</tr>
<tr>
<td>Spring 2014</td>
<td>P1114 continued enrollment, 2 sites added, 2 sites withdrawn</td>
</tr>
<tr>
<td>Spring 2014</td>
<td>IMPAAACT 2000 began development</td>
</tr>
<tr>
<td>July 28, 2014</td>
<td>Version 1.0 to sites</td>
</tr>
<tr>
<td>Fall 2014</td>
<td>IMPAAACT 2000/CIR 291 enrolling at 7 sites</td>
</tr>
</tbody>
</table>
IMPAACT 2000 sites

- 4001 Chicago Children’s
- 4601 Univ California San Diego
- 5038 Rush Univ. Cook County Hosp.
- 5048 Univ Southern California
- 5052 Univ of Colorado Denver
- 6501 St Jude/UTHSC
- 31779 Johns Hopkins CIR
- Spring 2015-may add additional site
IMPAACT 2000 sites

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IMPAACT 2000 - hypothesis

• Study hypothesis
  – RSV ΔM2-2, Delivered as nose drops to RSV-Seronegative infants and children ≥6 through <25 months of age, will be safe and immunogenic.
IMPAACT 2000--Objectives

• Primary Objectives

1. To determine the frequency of
   • vaccine-related adverse events (AEs) during Study Days 0 to 28
   • lower respiratory illness (LRI) during Study Day 0 to the Day 56 Visit.

2. To quantify the amount of vaccine virus shed by each recipient

3. To determine the number of vaccinated infants and children infected with RSV LID ΔM2-2

4. To characterize immune responses to the RSV LID ΔM2-2 vaccine, including quantification of the amount of RSV-neutralizing antibody and antibody to the RSV F glycoprotein induced by the vaccine
IMPAACT 2000--Objectives

• Secondary Objective
  – To characterize clinical and immune responses in vaccinated RSV-seronegative infants and children who experience subsequent natural infection with wild-type (wt) RSV.
### IMPAAACT 2000 Study Schema

- Double-blind, randomized, placebo-controlled study
- Will enroll 51 healthy RSV-seronegative infants and children ≥6 to <25 months of age

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Treatment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV seronegative infants and children ages ≥6 to &lt;25 months of age</td>
<td>34</td>
<td>Vaccine</td>
<td>$10^{5.0}$ PFU</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>Placebo</td>
<td>0 PFU</td>
</tr>
</tbody>
</table>

PFU = plaque forming units
IMPAACT 2000 study treatment

- One dose, intranasal
- Vaccine is LID RSV ΔM2-2 Vero Grown Virus Vaccine in Dulbecco’s MEM (DMEM) with 1X SPG (sucrose, 0.218 M; KH2PO4, 0.0038 M; K2HPO4, 0.0072 M; L-Glutamic Acid, 0.0054 M).
- Diluent and placebo are Leibovitz L-15 medium (a solution with amino acids, sugar and salt)
- First study of this vaccine in humans
- But, almost identical vaccine (Medi RSV ΔM2-2) has been in Phase 1 trials.
IMPAACT 2000 Study Schema

- Enrollment only occurs outside of RSV season; therefore, initial recruitment from September, 2014 until October 14, 2014
  - Evaluate the safety of the vaccine when there is no circulating wild-type RSV
- If note fully accrued, remaining children will be enrolled starting April 1, 2015
- Children followed intensely for 28 days, then less intensely until day 56
- Weekly contact during RSV season
IMPAACT 2000 Schedule

- **Screening:** 7-42 days
- **Nasal immunization:** day 0, 7, 14, 21, 28
- **Nasal wash:** Clinical assessment: inoculation plus 10 visits
- **Phone or email every day not seen**

**RSV SEASON SCHEDULE**

- **Pre-season**
  - Nov–Dec
  - Jan–Feb
  - March–April
  - Weekly phone contact or email
- **Blood draw**
- **RSV Season**
  - 56 days
- **Blood draw** (depends on time of enrollment)

**Notes:**
- **** Depends on time of enrollment
IMPAACT 2000--Objectives

You’re going to put what up my nose?!!

• Frequent nasal washes necessary to answer the primary objectives
  – Does the virus grow in the nares
  – How much virus grows
  – How long does the virus grow
IMPAACT 2000--Objectives

- Weekly calls for the whole winter?!!
- Needed to answer the secondary objective
  - Surveillance for more severe RSV infection
  - Safeguard necessary because of historical experience with an inactivated vaccine which caused worsened RSV
IMPAACT 2000 Target population

- Super baby

HEALTHY
IMPAACT 2000 inclusion criteria

• ≥6 months of age at the time of screening and <25 months at randomization

• The infant/child is in good health based on review of
  – the medical record, history, and physical examination
  – without evidence of chronic disease.
  – any questions regarding interpretation of this criterion should be forwarded to the team.
IMPAACT 2000 inclusion criteria

• Parents/guardians demonstrate their understanding of the study—**quiz optional but need to carefully assess understanding and document this.**

• Seronegative for RSV antibody- **tested at JHU lab,**
  – serum RSV-neutralizing antibody titer <1:40
  – no more than 42 days prior to scheduled inoculation.
IMPAACT 2000 inclusion criteria

• Height and weight > 5th percentile for age.
• **Received routine immunizations appropriate for age.**
• If born to an HIV-infected woman, non-breastfeeding with:
  – two negative HIV nucleic acid (RNA or DNA) tests OR
    • with both collected when ≥1 month of age
    • at least one collected when ≥4 months of age
    • no positive HIV nucleic acid (RNA or DNA) test or
  – two negative HIV antibody tests, both collected at ≥6 months of age.
IMPAACT 2000 exclusion criteria
22 exclusions!

- Slides are summary/paraphrase
- Refer to protocol for precise language
IMPAACT 2000 exclusion criteria

• Known or suspected HIV infection or impairment of immunological functions.
• Receipt of immunosuppressive therapy, including any systemic corticosteroids within 30 days of enrollment. Note: Cutaneous (topical) steroid treatment is not an exclusion.
• Transplant recipient
• Major congenital malformations
• Previous immunization with an RSV vaccine or anti-RSV antibody product
IMPAACT 2000 exclusion criteria

• Previous vaccine-associated anaphylactic or other severe adverse vaccine reaction.
• Known hypersensitivity to any study product component.
• Heart disease. Note: Subjects with cardiac abnormalities documented to be clinically insignificant and requiring no treatment may be enrolled.
• Lung disease, including any history of wheezing or reactive airway disease.
IMPAACT 2000 exclusion criteria--Rationale

• Preventing exposure to other vulnerable people
  – Most older children and adults immune
  – Older children and adults usually mild disease
  – Who do we need to protect
    • Young infants
    • Immunocompromised people
  – What period of time for protection
    • First 28 days
IMPAACT 2000 exclusion criteria

• Shares a daycare room with infants <6 mo of age
• Ok to enroll if parent/guardian will take child out of daycare for 28 days following inoculation.
• Ok to enroll if child is in daycare but will not share a room or other facilities with infants less than 6 months of age during the 28 days after inoculation are not excluded.
IMPAACT 2000 exclusion criteria

• Child lives with:
  – an infant who is less than 6 months of age
  – an immunocompromised individual, including, but not limited to:
    • CD4 T count <300/mcL for age ≥5yr
    • CD4 T percentage <15 for age <5yr
    • chemotherapy within the 12 months
    • **Reliable** verbal history of the CD4 count is acceptable
IMPAACT 2000 exclusion criteria

• Child lives with another child who is/will be enrolled in IMPAACT 2000 and there will be/has been an overlap in residency during the other child’s first 28 days of enrollment
  • This means:
    – one child per household can enroll
      Unless
    – A new child moves into the household after the first 28 days.
      • i.e. The new subject was never exposed to RSV vaccine/placebo
IMPAACT 2000 exclusion criteria

Any of the following events at the time of randomization (and inoculation):

• Fever (rectal temperature of ≥100.4°F (38°C))
• upper respiratory signs or symptoms (rhinorrhea, cough, or pharyngitis) or
• nasal congestion significant enough to interfere with successful inoculation, or
• otitis media.
IMPAACT 2000 exclusion criteria

• Vaccines prior to and after enrollment
  – >14 days for killed or rotavirus vaccines
  – > 28 days for live vaccine
• Receipt of immunoglobulin, any antibody products, or any blood products
  – May interfere with vaccine
  – May interfere with assessment of immune response
IMPAACT 2000 exclusion criteria

• Receipt of any of the following medications within 3 days of study enrollment:
  – systemic anti-infective agents
  – intranasal medications
  – other prescription medication except as listed
  – These are ok
    • gastroesophageal reflux
    • eye drops,
      • topical medications: steroids, antibiotics, antifungal
• Receipt of salicylate (aspirin) or salicylate-containing products within the past month.
• Remember—healthy!
IMPAACT 2000 exclusion criteria

• Born at less than 37 weeks gestation and less than 1 year of age at the time of enrollment.
  – Ex-premie who is now 1 year old and Healthy
• Meets criteria for failure to thrive within the six months prior to enrollment
• Suspected or documented developmental disorder, delay, or other developmental problem.
When can you order the vaccine?

- Place order on the day that you draw screening blood on your first potential participant