IMPAAACT 2011/2012/2013

Phase I Placebo-Controlled Study of the Infectivity, Safety and Immunogenicity of a Single Dose of a Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine, “xxxxxx”, Delivered as Nose Drops to RSV-Seronegative Infants 6 to 24 Months of Age

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Vaccine name</th>
<th>Protocol to sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>LID ΔM2-2 1030s</td>
<td>May 5, 2016</td>
</tr>
<tr>
<td>2012</td>
<td>LID cp ΔM2-2</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>RSV/NS2/N/ΔM2-2-AclI</td>
<td></td>
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</table>
• **Study Overview**
  
  – Background and rationale
  – Study Objectives
  – Target Population
  – Study treatment
  – Inclusion/exclusion criteria overview
  – FAQs
IMPAAACT 2011 Background

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

• Continuation of collaboration:
  – P1096-parainfluenza vaccine (HPIV3)
  – P1114 - RSV cps2 vaccine
  – IMPAAACT 2000 - LID RSV ΔM2-2
IMPAACT 2011 Background

• IMPAACT 2011 modeled after 2000

• Protocol design in parallel with the CIR protocol

• Open to accrual by June 5

• Goal—enroll by end of July

• Other protocols open later in summer

• Last day to enroll: October 14, prior to the RSV season
IMPAAACT 2011 Rationale

• Goal will be to rapidly evaluate the three vaccine candidates to determine which are most promising for further study based on:
  – Safety
  – Infectivity—vaccine virus shed in nose
  – Immunogenicity after vaccine—neutralizing Ab in blood
  – Immunogenicity and after RSV season—rise in neutralizing Ab in blood w/o reported RSV disease
IMPAACT 2011 - hypothesis

• Study hypothesis
  – RSV ΔM2-2 1030s will be safe and immunogenic in RSV-naive infants.
One dose, intranasal

Vaccine is LID RSV ΔM2-2 1030s

Diluent and placebo are Leibovitz L-15 medium (a solution with amino acids, sugar and salt)

First study of this vaccine in humans

But, more attenuated in vitro and non-human primates NHP than LID RSV ΔM2-2 studied in 2000
IMPAACT 2011 Study Schema

- Double-blind, randomized, placebo-controlled study
- Will enroll 33 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>
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</thead>
<tbody>
<tr>
<td>RSV seronegative infants and children ages ≥6 to &lt;25 months of age</td>
<td>22</td>
<td>Vaccine</td>
<td>$10^{5.0}$ PFU</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Placebo</td>
<td>0 PFU</td>
</tr>
</tbody>
</table>

PFU = plaque forming units
IMPAACT 2011 Study Schema

• Enrollment only occurs outside of RSV season
  – Evaluate the safety of the vaccine when there is no circulating wild-type RSV

• Children followed intensely for 28 days, then less intensely until day 56

• Weekly contact during RSV season
IMPAACT 2011 Schema

- Acute Phase—Day 0- Day 28 (midnight)
- Post-Acute Phase Day 29-Day 56 (midnight)
- “study hiatus”
- Pre-RSV Season Visit—October
- RSV Season Surveillance—Nov through March
- Post-RSV Season Visit—April
IMPAACT 2011 Schema

**ACUTE AND POST-ACUTE PHASE**

- Screening/blood collection within 42 days of enrollment
- Nasal wash
- Clinical assessment: inoculation plus 8 visits
- Phone or email contact
- Blood collection

**RSV SEASON SCHEDULE**

- Weekly phone contact or email
- Nasal wash if ill

**Timeline**

- Pre-season
- Nov
- Dec
- Jan
- Feb
- March
- April
- RSV Season
IMPAACT 2011—Primary Objectives

• Safety:
  – all AE through midnight of the 28th day following inoculation
  – SAE through midnight on the 56th day following inoculation

• Infectivity:
  – Peak titer of vaccine virus shed
  – Duration of virus shedding
  – Proportion of vaccinated infants participants infected with study vaccine

• Immunogenicity:
  – Antibody responses (Day 56) to the study vaccine
IMPAAACT 2011—Secondary Objectives

• Outcomes with wild-type (wt) RSV during the subsequent RSV season
  – Clinical symptoms if medically attended
  – Antibody responses

• Detailed characterization of the B cell response to vaccine
IMPAACT 2011--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

- Fewer than IMPAAACT 2000/P1114
IMPAACT 2011--Objectives

• Weekly calls for the whole winter?
• Needed to answer the secondary objective
  – Identify patients with RSV neutralizing Ab rises with wtRSV exposure with and without illness.
IMPAACT 2011 Target population

• Super baby

HEALTHY
IMPAACT 2011 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 2011 inclusion criteria

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

• Growing at a normal velocity for age

• Current height and weight
  – <1 year of age: above the 5th percentile
  – >1 year of age: above the 3rd percentile for age.
IMPAACT 2011 inclusion criteria

• 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 2011 exclusion criteria
24 exclusions!

- Slides are summary/paraphrase
- Refer to protocol for precise language
• Participant is
  – Not immunosuppressed
  – Not at risk of severe RSV
  – Healthy
  – Not ill at the time of inoculation
  – Has not received vaccine recently
• Participant contacts
  – Not immunosuppressed
  – Not at risk of severe RSV
  – Living with another child also on the vaccine study during the period of vaccine shedding
IMPAACT 2011 exclusion criteria

**Participant:** No immunosuppression or chronic illness

- HIV infection or impairment of immunological functions.
- Receipt of immunosuppressive therapy,
- Steroids within 28 days of enrollment
  - Systemic
  - nasal
  - inhaled.
  - Cutaneous allowed.
- Transplant recipient.

- Major congenital malformations (such as congenital cleft palate) or cytogenetic abnormalities.
- Heart disease. Unless clinically insignificant and requiring no treatment
- Lung disease, including any history of reactive airway disease or medically documented wheezing.
IMPAACT 2011 exclusion criteria

Participant: No history of treatment or response that might interfere with assessment on study

• Previous receipt of a licensed or investigational RSV vaccine (or placebo in the IMPAACT 2011 study) or
• previous receipt of anti-RSV product (such as ribavirin or RSV IG or RSV mAb).
• Previous anaphylaxis
• Adverse vaccine reaction Grade 3 or above.
• Known hypersensitivity to any study product component.
IMPAACT 2011 exclusion criteria

Contacts not at risk of severe RSV disease (during 28 days after inoculation)

• Infant who is less than 6 months of age (through Day 28).
  – At household
  – In shared daycare

• Another child who is, or is scheduled to be, enrolled in IMPAACT 2011, 2012 or 2013 AND there has been or will be an overlap in residency during that other child’s participation in the study’s Acute Phase (Days 0 to 28).

• Immunocompromised individual
IMPAACT 2011 exclusion criteria

Contacts living with HIV--immunosuppression

• > 6 years of age
  – CD4 T cell count <300 cells/mm$^3$.

• 1 year to <6 years
  – CD4 T cell percentage <25 or CD4 T count <750 cells/ mm$^3$
    (if both values are available, use the lower of the two).

• <1 year
  – CD4 T lymphocyte cell percentage <30 or CD4 T count <1000 cells/ mm$^3$
    (if both values are available, use the lower of the two).

• Verbal report is sufficient if confident !!!

• Measured within 6 months prior to enrollment
IMPAAACT 2011 exclusion criteria

Not ill at the time of inoculation:
- fever
- upper respiratory signs or symptoms
- nasal congestion significant enough to interfere
- otitis media.

Other vaccines that might interfere with assessment the time of inoculation
- killed vaccine or live-attenuated rotavirus vaccine within 14 days
- any live vaccine, other than rotavirus vaccine, within the 28 days
- another investigational vaccine or investigational drug within 28 days
- Receipt of immunoglobulin, any antibody products, or any blood products within the past 6 months
IMPAACT 2011 exclusion criteria

Medications within 3 days of study enrollment: need to be well at inoculation

- systemic antibacterial, antiviral, antifungal, antiparasitic, or antituberculous agents, whether for treatment or prophylaxis, or
- intranasal medications, or
- other prescription medication exceptions
  - Common meds not used for significant illness
- Receipt of salicylate (aspirin) within the past 28 days.
IMPAAACT 2011 exclusion criteria (last one!)

More criteria to assure not at risk of severe RSV

- Born at less than 34 weeks gestation.
- Born at less than 37 weeks gestation and less than 1 year of age at the time of enrollment.
- Failure to thrive within the six months prior to enrollment:
  - Developmental disorder, delay
  - Supplemental oxygen therapy ever in home setting
• Actually- lots of kids do meet these criteria!
Rapid Accrual for IMPAACT 2000 — 7 sites

<table>
<thead>
<tr>
<th>Month</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Sept 2014</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>October 2014</td>
<td>17</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>9</td>
<td>29</td>
</tr>
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IMPAACT 2011 sites

Prior 2000 sites

• 4001  Chicago Children’s
• 4601  Univ California San Diego
• 5048  Univ Southern California
• 5052  Univ of Colorado Denver
• 5083  Rush Univ. Cook County Hosp.
• 6501  St Jude/UTHSC
• 31779  Johns Hopkins CIR

New sites

• 5030  Emory Univ
• 5112  UCLA
• 5013  Jacobi Medical Center
• 5040  SUNY Stony Brook
• 5113  CHOP