RSV Vaccine Studies: IMPAACT 2018 and 2021 and JHU Center for Immunization Research (CIR) Companion Studies

Elizabeth (Betsy) McFarland, MD
June 2022

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Rationale For Live-Attenuated RSV Vaccines

- Live vaccines are free of the enhanced RSV disease associated with subunit/killed vaccines
- Intranasal: mucosal and systemic responses
- Innate, humoral, and cell-mediated
- All RSV antigens present
- RSV fusion (F) glycoprotein in its pre-fusion form- induces neutralizing antibody[1]
- Post-hoc, cross-protocol analysis found vaccinees with neutralizing antibody protected from RSV medically attended acute respiratory illness and LRI[2]

https://www.statnews.com/2018/09/03/flumist-vaccine-recommendations/

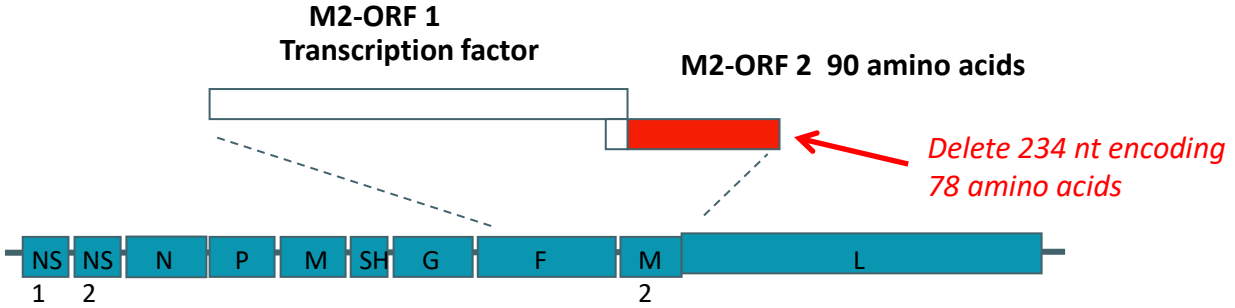
1. McFarland, et al, JID 2017; Buchholz et al, JID 2018; McFarland et al, JID 2020
2. Karron et al, Amer J Resp Crit Care Med 2021

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Attenuation Strategies For Live-Attenuated RSV Vaccines

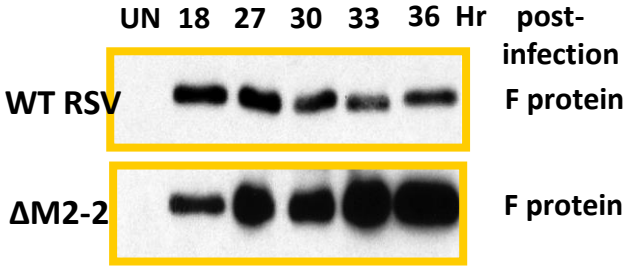
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

RSV with deleted ΔM2-2 gene



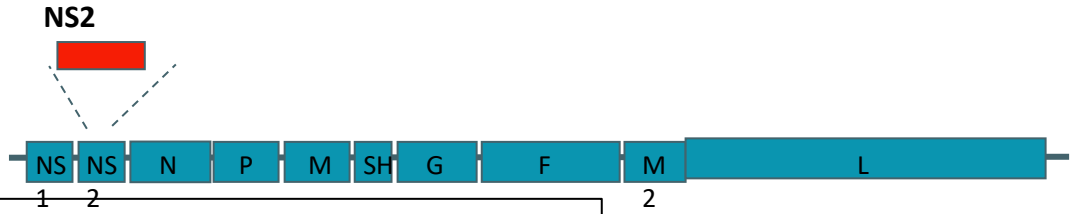
- RNA synthesis regulatory protein
  - RNA replication reduced
  - Viral gene transcription increased
  - Viral protein synthesis increased
- Gene deletion has been stable

Western blot (infected cell lysates) probed with anti-RSV F antibodies



IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

RSV attenuation strategies: ΔNS2

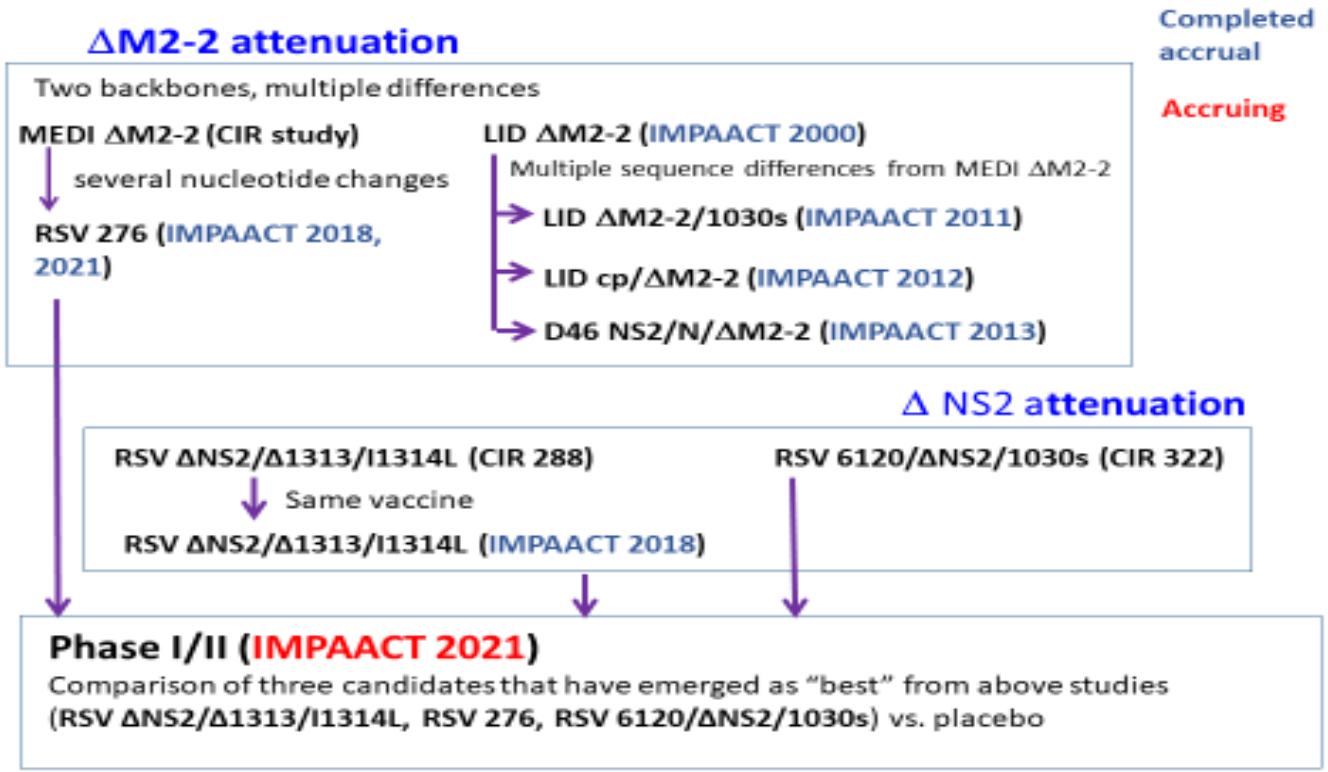


ΔNS2

NS2 functions:

- Viral antagonist of host interferon and apoptosis
- Promotes cell shedding that may contribute to airway obstruction
- Gene deletion has been stable

Overview of IMPAACT RSV Protocols



IMPAACT 2018: Randomized Phase I/II Study of Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated RSV Vaccines RSV ΔNS2/Δ1313/I1314L or RSV 276 or Placebo

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IMPAACT 2018 Vaccines

- **RSV ΔNS2/Δ1313/I1314L**
  - ΔNS2 – deletion of viral interferon antagonist
  - Δ1313 – deletion in viral polymerase – temperature sensitive
  - Highly promising at 10^6 infectious particles (PFU)
  - Additional clinical data needed
- **RSV 276**
  - Similar to MEDI ΔM2-2 (prior study with excellent immunogenicity and attenuation)

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

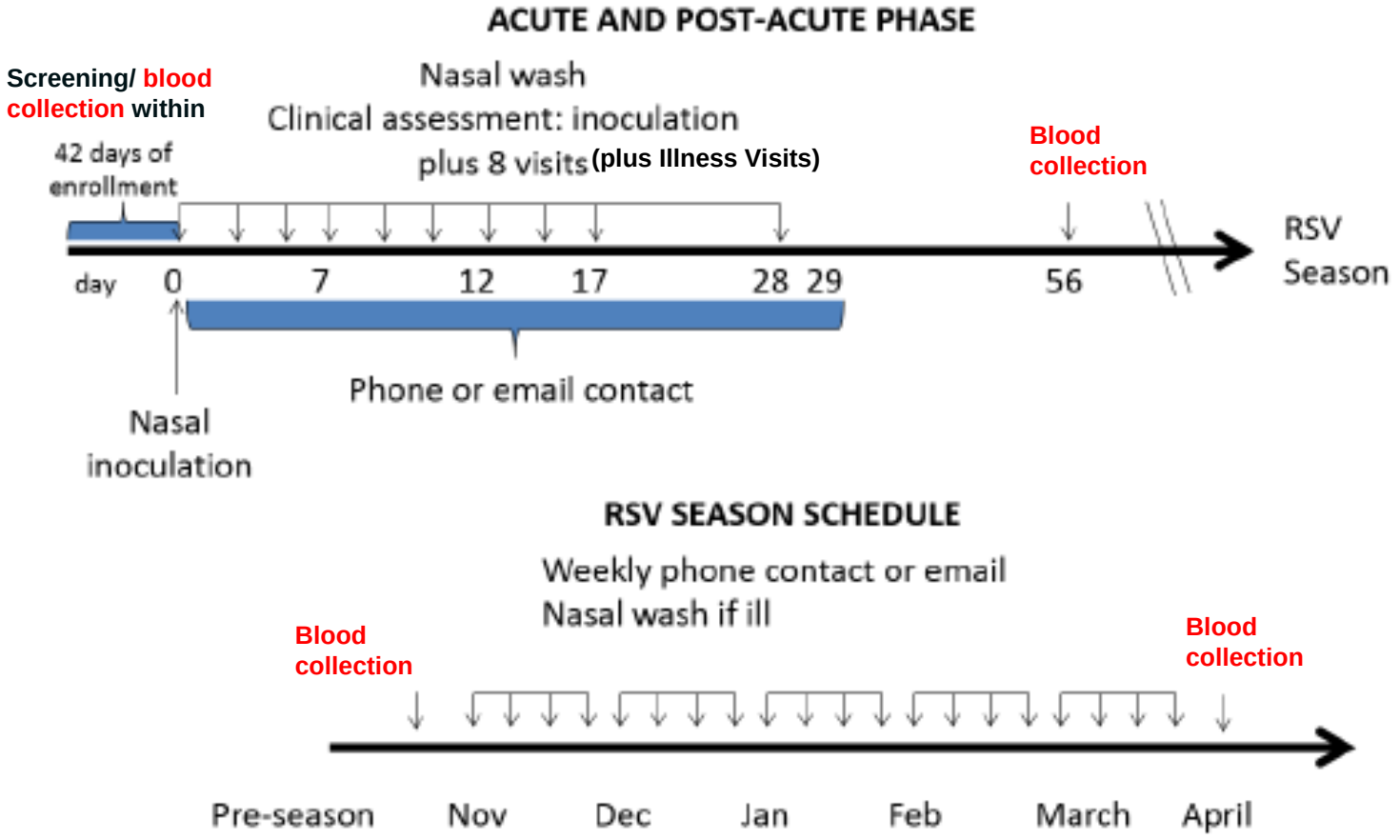
IMPAACT 2018 Study Design

- Phase 1, double-blind, randomized 2:2:1 (vaccine:vaccine:placebo)
- Eligibility- healthy 6 to 24-month-old children, RSV-seronegative, HIV-exposed, uninfected allowed

Target N	Product	Dose
32	RSV ΔNS2/Δ1313/I1314L Vaccine	10^6 PFU**
32	RSV 276 Vaccine	10^5 PFU**
16	Placebo	0

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IMPAACT 2018 Schedule of Evaluations



IMPAACT 2018 Baseline Characteristics

	RSV/ΔNS2/Δ1313/ I1314L Vaccine (n=25)	RSV/276 Vaccine (n=25)	Placebo (n=12)	Total (n= 62)
Female No. (%)	13 (52%)	7 (28%)	9 (75%)	29 (47%)
Age Median (IQR) Mos	13 (7, 14)	14 (10, 16)	9 (8, 15)	13 (8, 15)
HIV exposed No. (%)	8 (32%)	8 (32%)	4 (33%)	20 (32%)

All RSV-seronegative

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Fever, Cough and Respiratory Illness in 1st 28 Days after Inoculation

	RSV/ΔNS2/Δ1313/ I1314L Vaccine (n=25) No. (%)	RSV/276 Vaccine (n=25) No. (%)	Placebo (n=12) No. (%)
Fever	4 (16)	3 (13)	1 (8)
URI	16 (64)	18 (72)	5 (42)
LRI	0	0	0
Cough	3 (12)*	12 (48)*	2 (17)
Any fever or respiratory illness	16 (64)	21 (84)	7 (58)

* p = 0.012

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Fever, Cough and Respiratory Illness in 1st 28 Days after Inoculation

	RSV/ΔNS2/Δ1313/ I1314L Vaccine (n=25) No. (%)	RSV/276 Vaccine (n=25) No. (%)	Placebo (n=12) No. (%)
Fever	4 (16)	3 (13)	1 (8)
URI	16 (64)	18 (72)	5 (42)
LRI	0	0	0
Cough	3 (12)*	12 (48)*	2 (17)
Any fever or respiratory illness	16 (64)	21 (84)	7 (58)

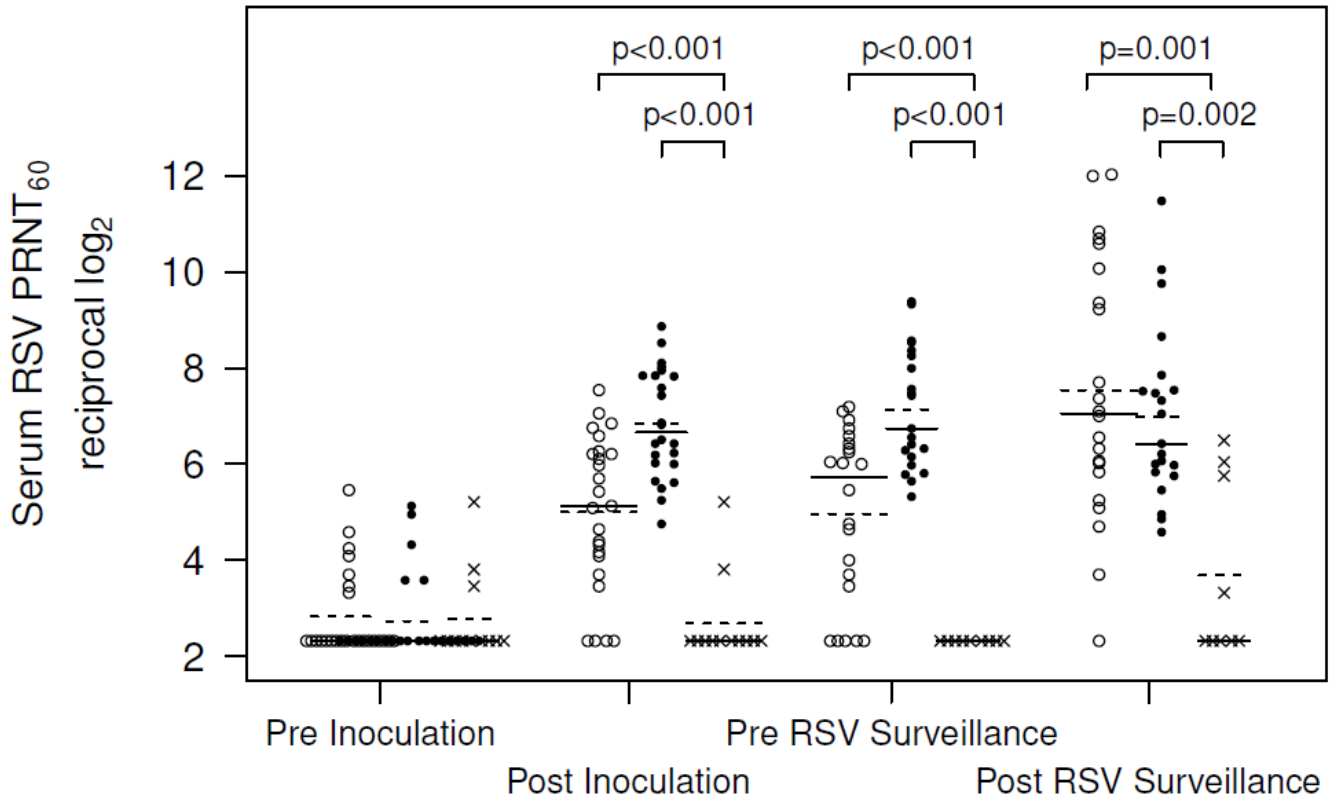
* p = 0.012

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Infectivity, Peak Viral Shedding and Immunogenicity

	RSV/ΔNS2/Δ1313/ I1314L Vaccine (n=25)	RSV/276 Vaccine (n=24)	Placebo (n=12)
Infectivity No. (%)	**22 (88)**	**23 (96)**	**0 (0)**
Peak viral shedding Median (IQR) RT-qPCR (Log10 cp/ml)	**5.1 (4.2, 5.4)**	**5.8 (5.2, 6.4)**	**1.7 (1.7, 1.7)**
Plaque Assay (PFU/ml)	**3.1 (1.8, 3.8)**	**3.2 (2.8, 4.0)**	**0.5 (0.5, 0.5)**
Antibody 4-fold rise	**15 (60)**	**22 (92)**	**0 (0)**

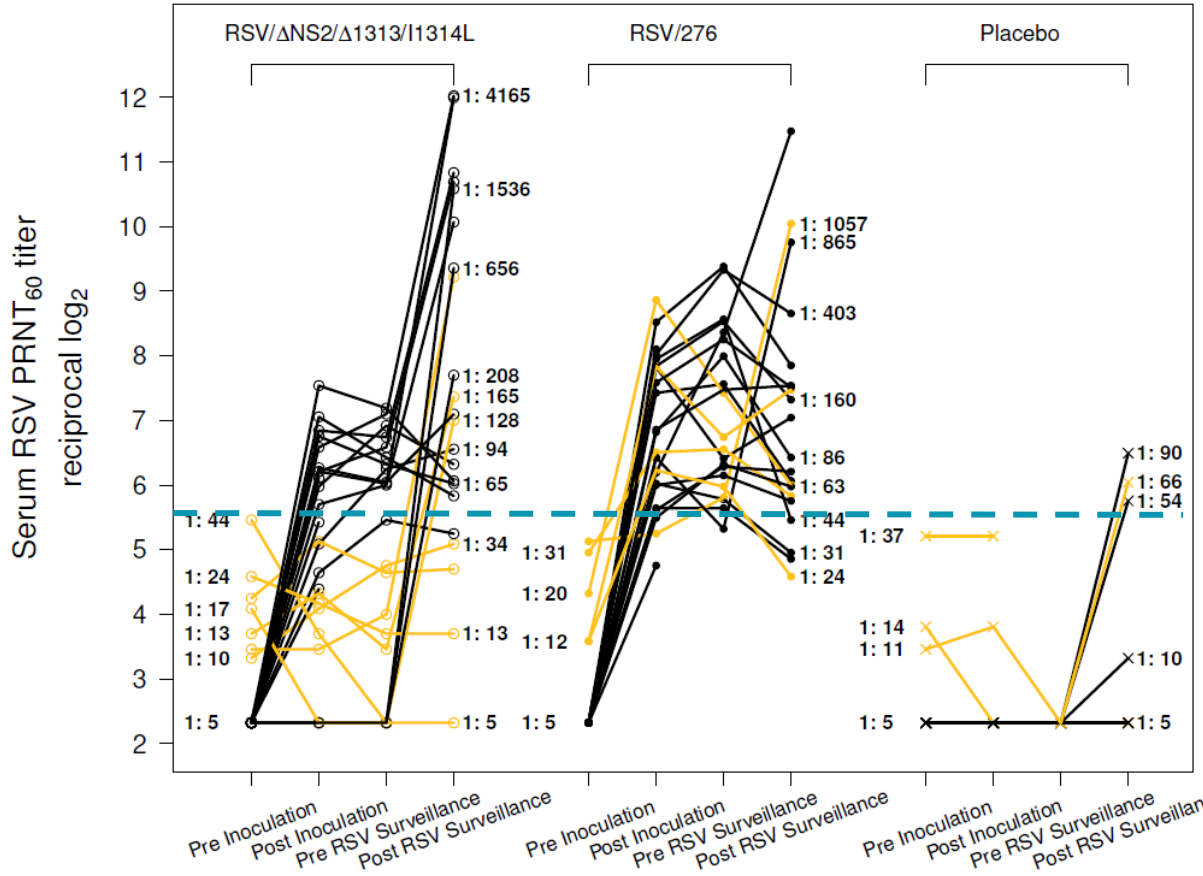
Serum Neutralizing Titers



○ = RSV ΔNS2
● = RSV276
X = placebo

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Individual Serum Neutralizing Antibody Titers – Effective of Pre-existing Anti-RSV Antibody



— **Black** = no detectable antibody at entry

— **Yellow** = low level detectable antibody at baseline

– – **Blue** dashed line = titer defined as RSV sero-negative for entry

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IMPAACT 2018 Conclusions

- Both vaccines with excellent infectivity in pediatric RSV vaccine target population
- Both well tolerated
- RSV276 with excess mild cough
- Both immunogenic and prime for anamnestic responses

Manuscript in press, JID 2022

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IMPAACT 2021: Randomized Phase I/II Study of Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated RSV Vaccines RSV ΔNS2/Δ1313/I1314L, RSV 6120/ΔNS2/1030s or RSV 276 or Placebo

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Vaccines in IMPAACT 2021

Arm 1: RSV ΔNS2/Δ1313/I1314L
Arm 2: RSV 276

} **Same vaccines in IMPAACT 2018**

Arm 3: RSV 6120/ΔNS2/1030s

- Attenuation elements: less attenuated and less temperature sensitive
  - Deletion of the RSV interferon antagonist NS2 (ΔNS2)
  - Genetically stable "1030s" attenuating point mutation [Y1321K(AAA) and S1313(TCA) mutation in L]

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IMPAACT 2021 Original Study Design

- Phase 1, double-blind, randomized 1:1:1:1 (vaccine:vaccine:vaccine:placebo)
- Eligibility: healthy 6- to 24-month-old children, RSV-seronegative; HIV-exposed, uninfected allowed

N	Product	Dose
40	RSV ΔNS2/Δ1313/I1314L Vaccine	10^6 PFU**
40	RSV 276 Vaccine	10^5 PFU**
40	RSV 6120/ΔNS2/1030s	10^5 PFU**
40	Placebo	0

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

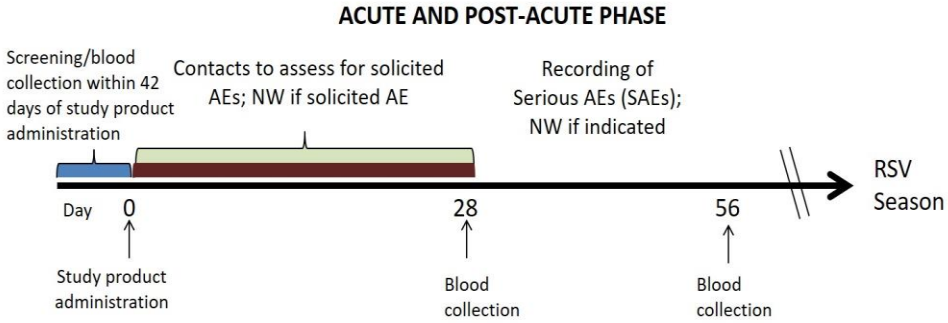
IMPAACT 2021 Design Changes Compared to Previous Studies

Version 1

- Scheduled in-person visits reduced from 14 to 5
- Nasal sample only with Illness Visit
- Elimination of Pre-RSV season blood draw
- Added blood collection at day 28 for comparison to day 56

COVID changes

- Nasal swab instead of nasal washes, now only occur if child is ill
- Telehealth allowed for mild URI



IMPAACT 2021 Version 2.0 – Changes After Analysis of IMPAACT 2018

- No further accrual to Arm 2, RSV 276 vaccine
- Randomizes 1:1:1 (vaccine:vaccine:placebo)
- Reduces enrollment target to n=130 from n=160.

N	Product	Dose
40	RSV ΔNS2/Δ1313/I1314L Vaccine	10^6 PFU**
~~40~~	~~RSV 276 Vaccine~~	~~10^5 PFU**~~
40	RSV 6120/ΔNS2/1030s	10^5 PFU**
40	Placebo	0

Accrual to IMPAACT 2021

- Opened to accrual in summer 2019
  - Study opened at 10 sites
    - 6 IMPAACT; 4 VTEU
  - N= 30 participants enrolled in June - Oct 2019
- No enrollments in 2020 and 2021 due to COVID
- Opened to accrual as Version 2.0 in April 2022
    - 8 of expected 13 sites open as of 27 June 2022
  - N= 10 participants enrolled as of 27 June 2022

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Blinded Safety Data for IMPAACT 2021

- Ad hoc DSMB reviews in November 2019
  - One Grade 2 LRI: “croup” x 1 day dx
    - DSMB recommended protocol to continue
  - Two Grade ≥3 fever
    - DSMB recommended protocol to continue
- No Serious Adverse Events (SAE)
- No unsolicited events Grade ≥3

IMPAACT 2021 Version 3.0 (Pending Implementation)

- Allows flexible enrollment periods based on local RSV incidence
- Eliminates requirement for negative SARS CoV2 test result at baseline

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Acknowledgments

IMPAACT 2018 and 2021 Protocol Teams

- Protocol Co-Chairs: Coleen Cunningham, Ruth Karron
- Protocol Vice Chairs: Elizabeth McFarland, Matthew Kelly, Amelia Thompson
- CRMs: Charlotte Perlowski, Jennifer Libous, Haley Brozik, Shane Reynolds
- DAIDS MOs: Dwight Yin, Patrick Jean-Philippe
- NICHD MO: Jack Moye, Jr
- DMID Program Officer: Sonnie Kim
- Pharmacists: Kelly Colsh, Azizza Davis, Lynette Purdue, Vivian Rexroad
- Investigators: Emmanuel Walter, Amanda Dempsey
- Statisticians: Petronella Muresan, Mark Giganti, Rachel Ketchum, Jane Lindsey
- Data Managers: Benjamin Johnston, Jared Kneebone, Kayla Denson, Linda Marillo
- Lab Data Managers: Frederic Bone, Andee Fox
- Lab Center Reps: Nicole Tobin, Sam Yi, Dale Dayton
- Lab Technologists: Paul Harding, Jason Rippe;
- Field Rep: Emily Barr
- Community Program Manager: Marcus Bryan
- Westat Reps: Aundria Charles, Scott Watson

JHU Center for Immunization Research

Ruth Karron
Elizabeth Schappell
Jennifer Oliva
Kimberli Wanionek

NIH NIAID Laboratory of Infectious Diseases

Peter Collins
Ulla Buchholz
Yumi Matsuoka
Cindy Luongo
Lijuan Yang

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Acknowledgments

IMPAACT sites

Ann & Robert Lurie Children's Hospital of Chicago*^
Baylor Texas Children's Hospital*^
Boston Medical Center*
Emory Univ School of Med^
Jacobi Medical Center, Bronx*^
Johns Hopkins University CIR*^
Rush University, Cook County*^
St. Jude Children's Research Ctr*
SUNY Stony Brook*^
Univ California Los Angeles*^
Univ California San Diego*^
Univ Colorado School of Med*^
Univ Southern California*^

* = IMPAACT 2018
^ = IMPAACT 2021

VTEU sites

St Louis Ctr for Vaccine Devel^
Duke University^
University of Maryland^
The Children's Mercy Hosp^
Cincinnati Children's Hosp^
University of Texas Med Branch^

Parents and infants for participating

NIH National Institute of Allergy and Infectious Diseases
Eunice Kennedy Shriver NICHD National Institute of Child Health & Human Development
SANOFI PASTEUR
IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

THANKS!

Questions?

You can find me at

- Betsy.mcfarland@cuanschutz.edu

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network