# Update on RSV vaccine and mAb development

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March 22, 2018

# Global burden of RSV in children U5 in 2015

- ~33.1 million cases of RSV-ALRI
  ~20% < 6 months
- ~3.2 million hospitalizations
  ~43% < 6 months
- ~27,300 in-hospital deaths
  ~47 % < 6 months

# Development of vaccines and mAbs for populations at risk

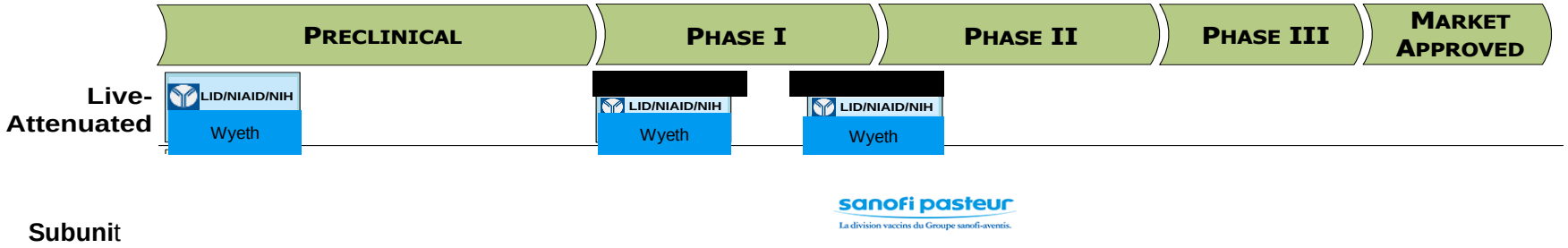
9 days...

**Maternal immunization with RSV F subunit**
**OR**
**Infant immunization with RSV F mAb**

9 months…

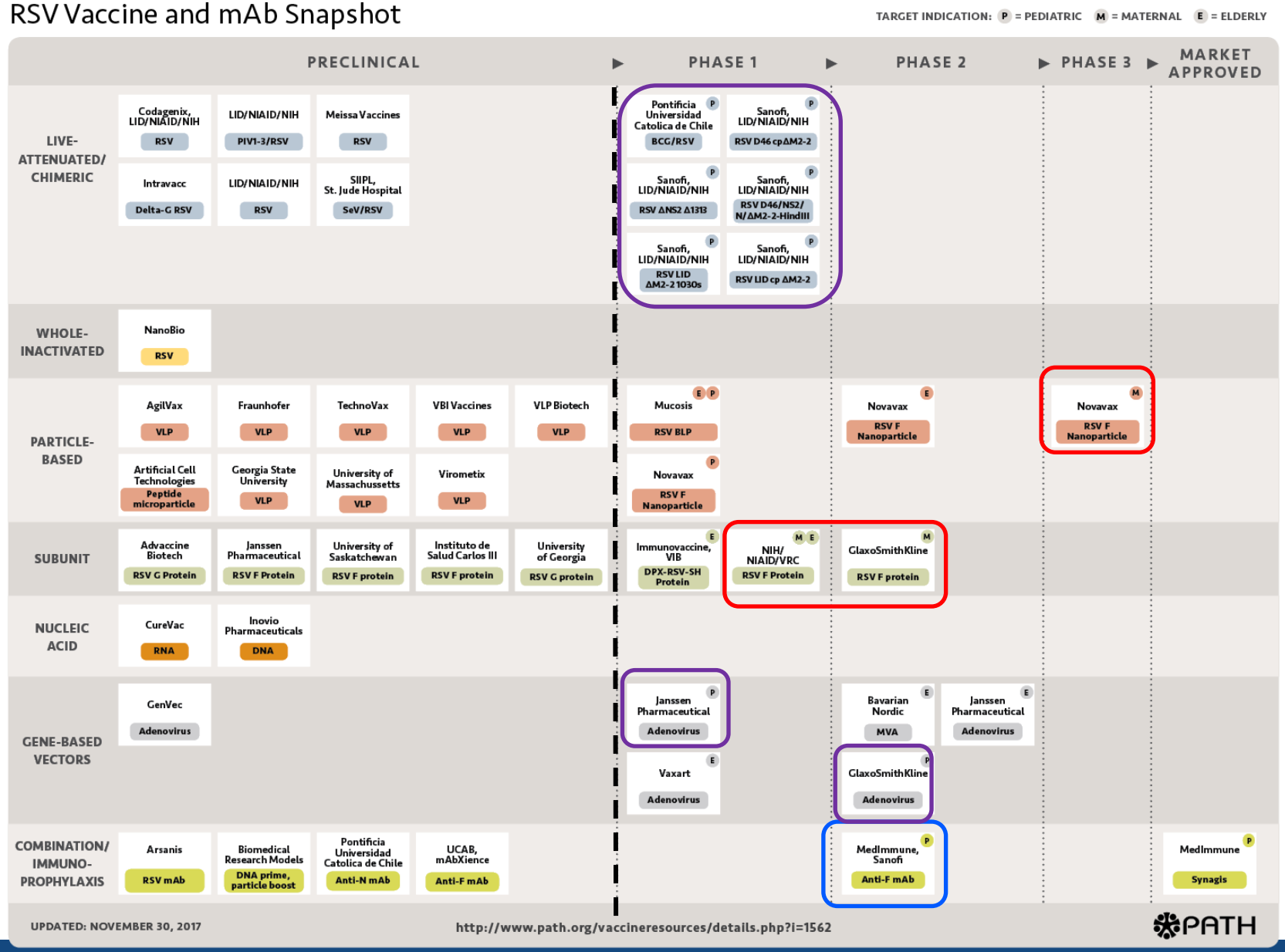
**Infant immunization with replicating vaccines (vectored or live-attenuated)**

# RSV Vaccine Technology Landscape 2002



# RSV Vaccines and Mab Technology Landscape 2018

## RSV Vaccine and mAb Snapshot




Maternal RSV F subunit

Infant RSV F mAb

Infant live-attenuated or vectored

# Novavax Phase 3 Trial of RSV postfusion F vaccine

Prepare™

| Timeline | Trial Objectives | Trial Design |
|---|---|---|
| • Phase III trial initiated Dec 2015<br>• Group sequential design with enrollment 2 - 4 years | • Primary: Prevention of RSV lower respiratory tract infection (LRTI) with hypoxemia in infants during the first 90 days of life<br>• Secondary endpoints: LRTI with severe hypoxemia, persistent efficacy to measure out to 120, 150, 180 days | • Pregnant women in 3rd trimester<br>• Healthy women without morbidities<br>• 5,000 – 8,255 participants planned<br>• Randomized, placebo-controlled<br>• DSMB oversight and iterative futility analyses to ensure safety |

# PREPARE trial: current status

- 80 sites in 11 countries
- Preliminary statistical analysis at ~30% enrollment (n=1307) showed ≥40% efficacy
- Interim analysis of ~4600 enrollees planned in January 2019
- BLA filing anticipated  4Q2019/ 1Q2020


First phase 3 maternal immunization trial– lessons for future trials?

# GSK RSV pre-F vaccine for maternal immunization

## Maternal immunization

- Primed population (pregnant women)
- 1 dose
- Ab response
- Infants up to 4-6 months

- PreF non-adjuvanted
- Phase 1: 2019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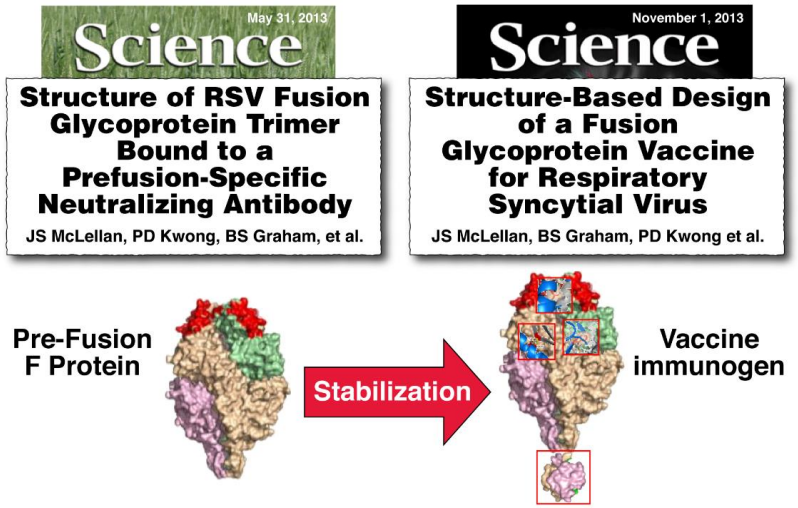
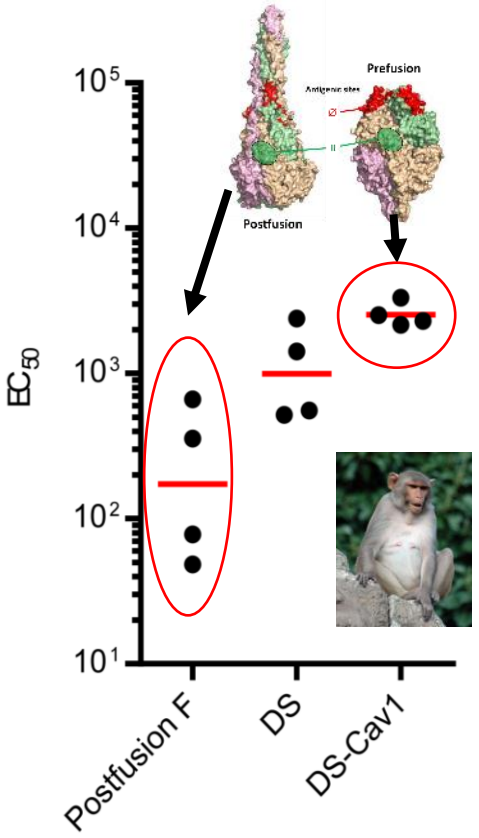
# VRC 317:
# Stabilizing Prefusion RSV F Improves Immunogenicity



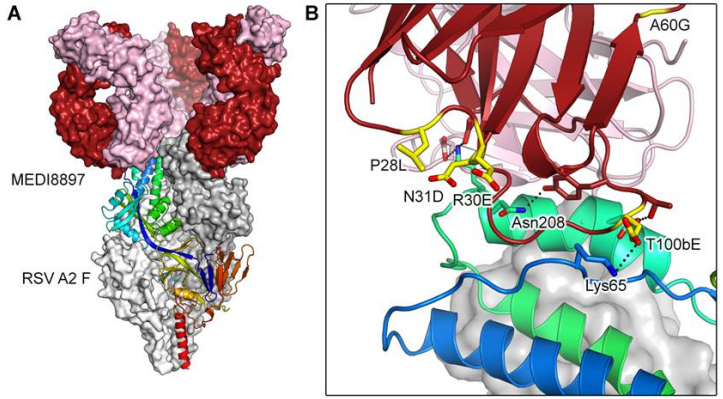




| VRC 317 Study Schema | | | | |
|---|---|---|---|---|
| **Group** | **Subjects** | **Dose** | **Day 0** | **Week 12** |
| 1 | 15 | 50 mcg | DS-Cav1 | DS-Cav1 |
| 2 | 15 | | DS-Cav1 + alum | DS-Cav1 + alum |
| 3 | 15 | 150 mcg | DS-Cav1 | DS-Cav1 |
| 4 | 15 | | DS-Cav1 + alum | DS-Cav1 + alum |
| 5 | 15 | 500 mcg | DS-Cav1 | DS-Cav1 |
| 6 | 15 | | DS-Cav1 + alum | DS-Cav1 + alum |
| Total | 90* | All DS-Cav1 vaccinations are administered with needle and syringe into the deltoid muscle. *Up to 100 subjects may be enrolled if needed to evaluate safety or immunogenicity. | | |

Preserving neutralization-sensitive epitopes on functional form of protein is essential for vaccine antigen design

# MEDI8897: An Extended Half-Life RSV Prefusion F mAb

- **Technology**
  - Fully human, high potency IgG1 mAb derived from human B-cells
  - YTE half-life extension technology
- **Highlights**
  - Immediate protection at dosing
  - Once per season dosing
  - Fixed IM dose (not weight based)
- **Clinical endpoint and target population**
  - Prevention of lower respiratory tract infection due to RSV
  - Preterm and term infants entering first RSV season
  - Children with CLD/CHD entering first and second RSV season
- **Program status**
  - Phase 1a adult FTIH complete (N=136)
  - Phase 1b/2a in 32-35 week gestational age preterm infants complete (N=89)
    - Well-tolerated; half-life ranged from 63-73 days
    - At 50 mg dose, 87%had levels above the target $EC_{90}$ level
  - Phase 2b clinical efficacy in 29-35 week gestational age preterm infants started Nov 2016 - enrollment complete (N=1,453); follow-up ongoing




Zhu et al Science Translational Medicine 2017

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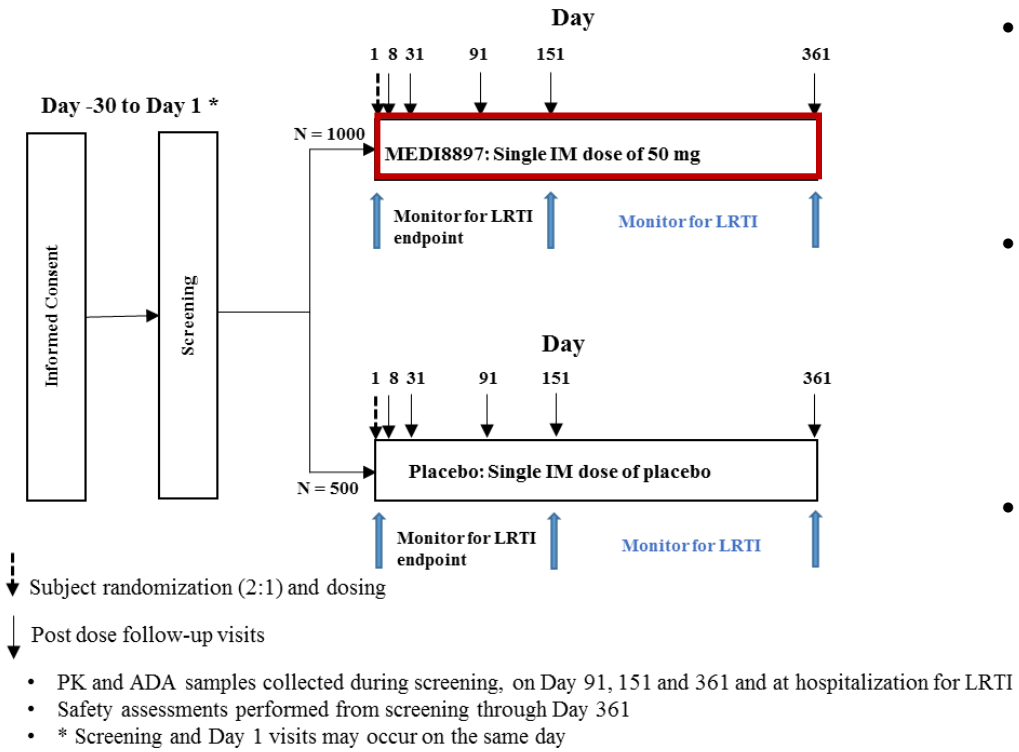
# MEDI 8897: Phase 2b Study Design

**Randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of MEDI8897 in healthy preterm infants**




- **Study population**
  - **1500 preterm infants 29 – 35 weeks gestational age** (Synagis-ineligible per guidelines) planned; **1453 enrolled**
- **Primary endpoint**
  - Incidence of **medically attended LRTI** (inpatient and outpatient) caused by RT-PCR confirmed RSV for 150 days after dosing
- **Key secondary and exploratory objectives**
  - Incidence of **hospitalizations** due to RT-PCR-confirmed RSV for 150 days after dosing
  - Safety, PK, and ADA
  - Assess healthcare utilization and caregiver burden

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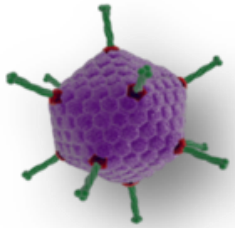
NCT02878330

# Janssen RSV vaccine based on Ad26.RSV.preF

## Vector



- Janssen platform technology (AdVac®)
- Replication-incompetent human serotype 26 adenovirus
- Large platform safety database
- Robust and sustained immune response
- Elicits Th1 response

## Antigen


- RSV fusion protein from the RSV A2 strain
- Wild-type F protein expressed in the prototype vaccine Ad26.RSV.FA2*
- **Optimised prefusion stabilised F protein expressed in the current vaccine Ad26.RSV.preF**
- FA2 and preF have only a 5 amino acid difference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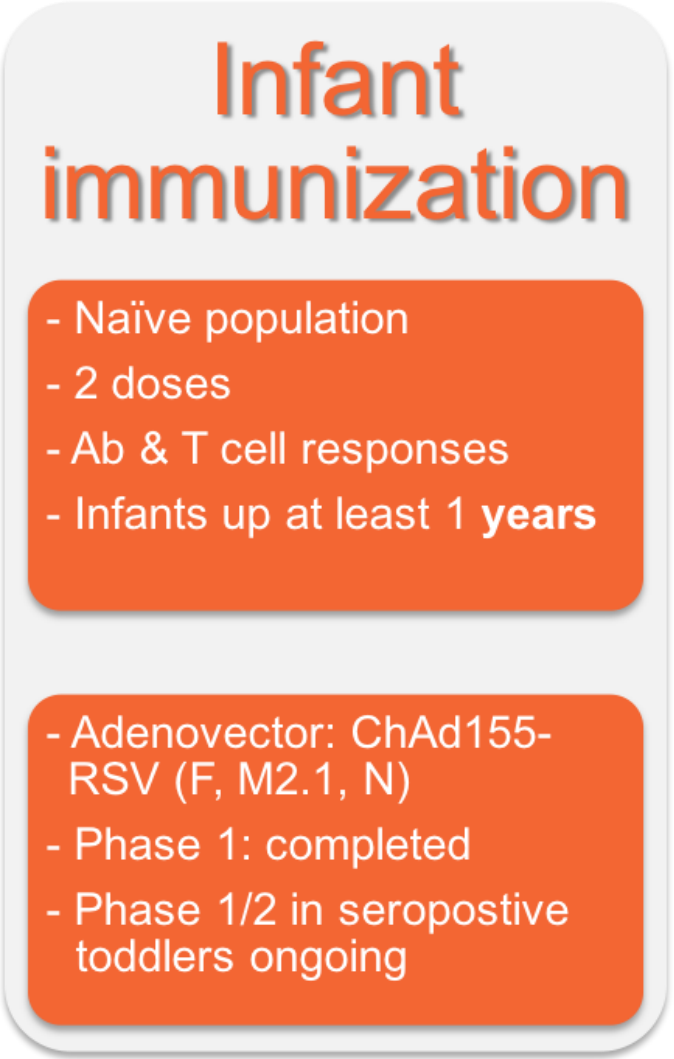
# Ad26 vector expressing the preF protein (Ad26.RSV.preF)

- Ad26.RSV.preF showed better immunogenicity compared to Ad26.RSV.FA2 in preclinical models
- A First-In–Human phase I study in healthy adult volunteers older than 60 years of age is ongoing (NCT02926430)

  interim Day 28 analysis:

  - Ad26.RSV.preF was safe and well tolerated in adults aged 60 years and older
  - Data suggest increased immunogenicity of Ad26.RSV.preF compared to Ad26.RSV.FA2
  - Ad26.RSV.preF induces preferentially preF specific antibodies with a low binding to neutralizing antibody ratio
- Janssen RSV vaccines based on Ad26 vector expressing the preF protein entered phase 2 studies in both pediatric and older adult populations

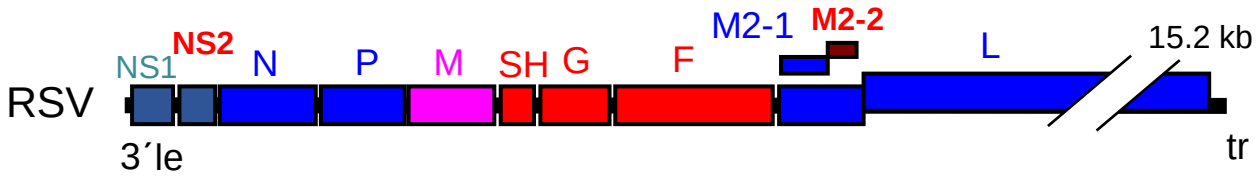
# GSK adenovirus vectored RSV vaccine for infant immunization



# Rational vaccine design for live-attenuated RSV

- Fully replication-competent viruses for intranasal administration
- Highly-defined attenuating mutations that can be combined as desired
- Deletion mutations and ”stabilized” point mutations refractory to de-attenuation.
- Deletion of non-essential accessory proteins may yield improved phenotypes:
  - Up-regulation of antigen expression (**ΔM2-2**).
  - Reduced viral suppression of host interferon, apoptosis responses (ΔNS1, **ΔNS2**).
- Evaluation in RSV-naïve infants and children ongoing

Labpratory of Infectious Diseases,
NIAID, NIH



# Preliminary evidence of efficacy against RSV-MAARI and RSV-MAALRI from postimmunization surveillance

| | RSV-MAARI | No RSV-MAARI | total |
|---|---|---|---|
| Placebo | 7 | 31 | 38 |
| Vaccinees | 4 | 76 | 80 |
| Total | 11 | 107 | 118 |

OR=0.23 (95% CI, 0.06 to 0.81), *P*=0.04
**VE= 73%** (95%CI, 13 to 92)

| | RSV-MAALRI | No RSV-MAALRI | total |
|---|---|---|---|
| Placebo | 3 | 35 | 38 |
| Vaccinees | 1 | 79 | 80 |
| Total | 4 | 114 | 118 |

OR=0.15 (95% CI, 0.00 to 1.08), *P*=0.09
**VE=84%** (95%CI, -47 to 98)

Phase I/II trial of 2 promising live-attenuated candidates (n=450 RSV seronegative infants and children) to begin Q3 2018

# Beyond efficacy: information needed to support global decision-making

- Vaccine/mAb-preventable disease burden (RSV LRI is common, so products with lower efficacy may still have high impact)

    - Precise estimates of efficacy and disease burden by month of life (0-6 months) to model impact of passive immunization strategies

- Vaccine effectiveness in pregnant women with morbidities

    - HIV, hypergammaglobulinemia, etc

- Seasonality (or lack thereof) in countries planning to introduce vaccine or mAb
- Health system capacity (ANC for maternal immunization;  birth dose for mAb)

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# Acknowledgements

**Laboratory of Infectious Diseases (NIAID/NIH)**
**IMPAACT/Sanofi Pasteur**
Peter Collins
Ursula Buchholz
Coleen Cunningham
Betsy McFarland
Scott Gallichan
Sanie Sesay

**GSK**
Ilse Dieussart

**Janssen**
Myra Widjojoatmodjo

**Vaccine Research Center, NIH**
Barney Graham

**Novavax**
Greg Glenn

**MedImmune/Sanofi Pasteur**
Pamela Griffin
Filip Dubovsky

Jose Melero