RSV vaccines and passive immunization

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April 2016

Populations at risk of severe RSV disease

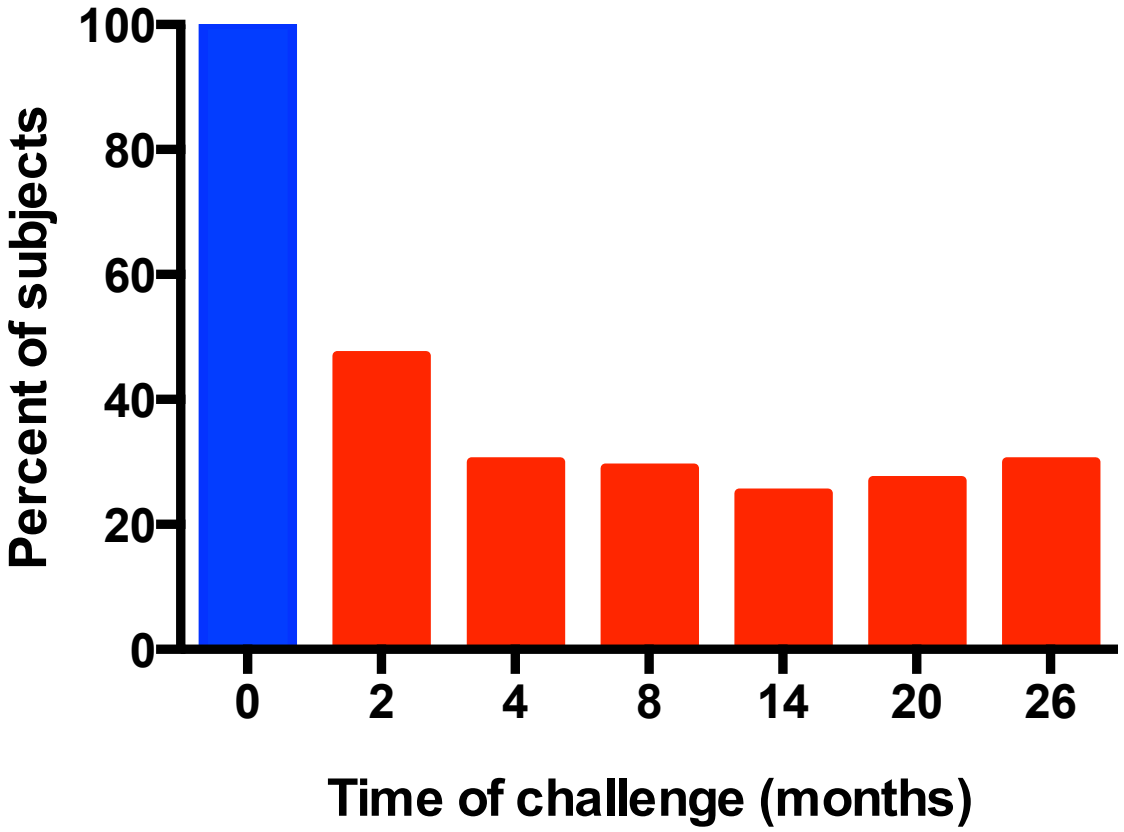
very young infants

older infants and toddlers

elderly

Goal for RSV immunization: prevention of infection?

Repeated RSV infections do not induce sterilizing immunity



Hall CB J Infect Dis 1991; 163:693-8

Goal for RSV vaccine development

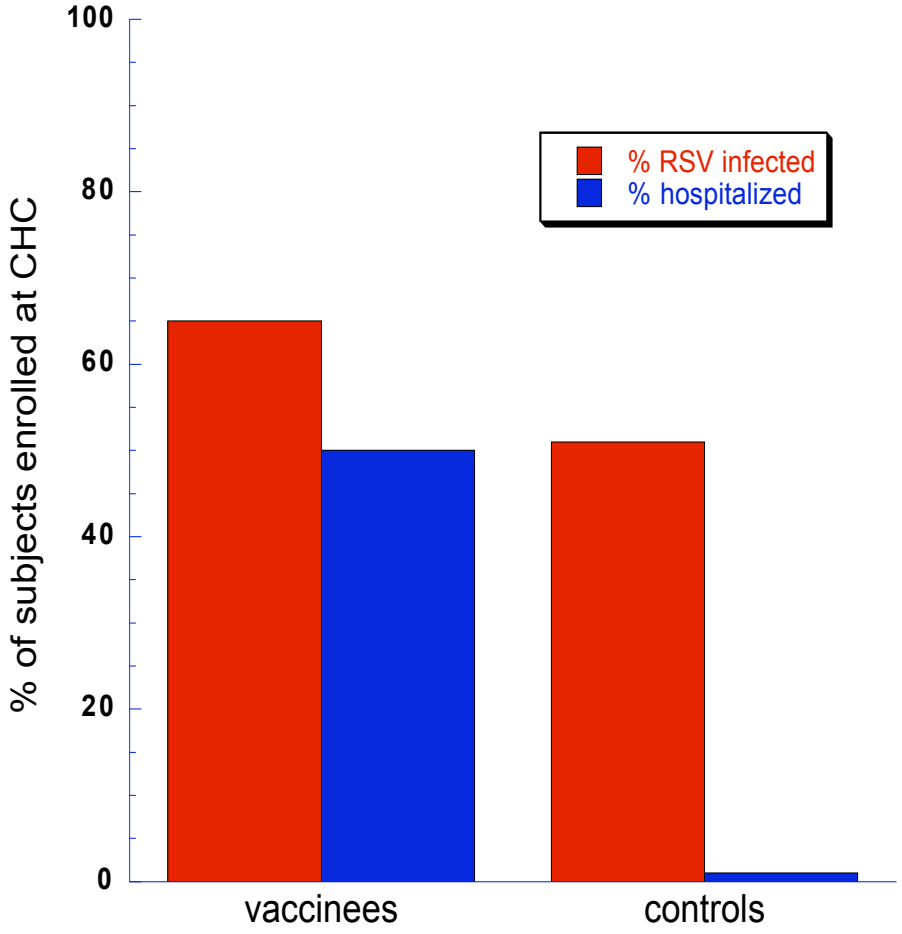
- Safely induce sufficient immunity to protect against serious RSV infection: LRI and apnea

- Induction of sterilizing immunity (i.e. protection against URI) is not required (and may not be feasible)

Obstacles to successful RSV vaccine development

- Difficult to induce protective immunity in the very young infant
  - Suppression of the immune response by maternal Ab
- Heterogeneous at-risk populations require different vaccines
  - Newborns
  - Older infants and young children
  - Elderly
- Imperfect animal models; adult RSV challenge (reinfection) model does not recapitulate RSV infection in naïve infants
- Specter of enhanced disease

Potentiation of RSV LRI following formalin inactivated vaccine



Adapted from Kim et al. Am J Epidemiol 89:422-434, 1969

Implications of enhanced RSV disease for RSV vaccine development

- Vaccines for active immunization of RSV-naïve infants should induce neutralizing antibodies, CD4 and CD8 responses

- Different vaccines in development for maternal and infant immunization:

  - Non-replicating (subunit) RSV vaccines for maternal immunization
    - Also for other non-naïve populations (older children, elderly)

  - Replicating RSV vaccines (live-attenuated or vectored) for infant immunization
    - Safest alternatives for active immunization of RSV-naïve populations
    - Live-attenuated RSV candidate vaccines have been administered to hundreds of RSV-naïve children and have never been associated with enhanced disease.[1]

[1]Wright PF. Vaccine. 2007 Oct 16,25(42):7372-8

Populations at risk of severe RSV disease

9 days

Infants from birth until 3-6 months

- Maternal immunization
- RSV mAb

9 months

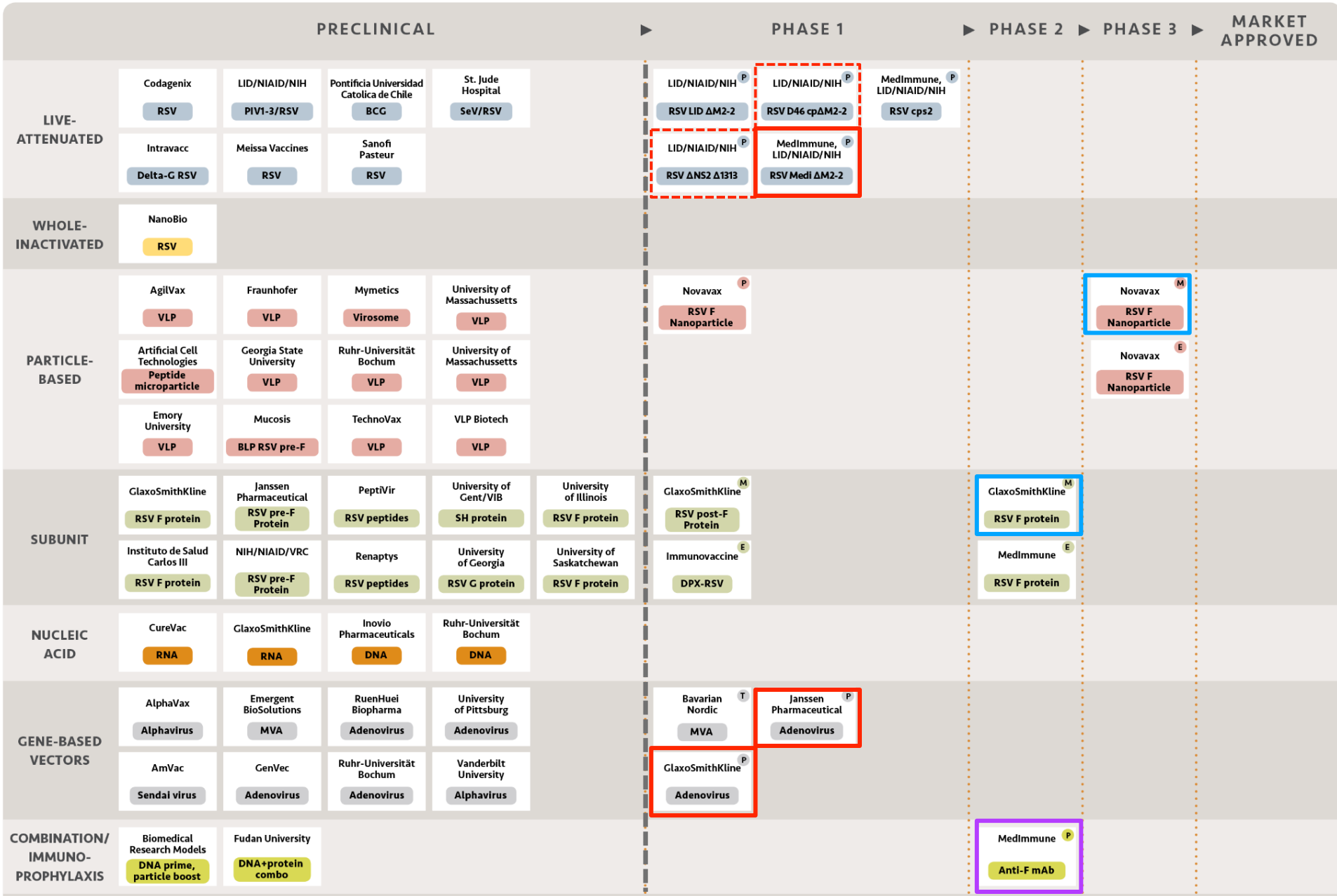
Infants and children >3 months

- Infant immunization

RSV Vaccine Snapshot

62 candidates total;16 in clinical trials

TARGET INDICATION: (P) = PEDIATRIC (M) = MATERNAL (E) = ELDERLY (T) = TBD



UPDATED: DECEMBER 15, 2015

http://sites.path.org/vaccinedevelopment/respiratory-syncytial-virus-rsv/

PATH

Pediatric RSV vaccination:

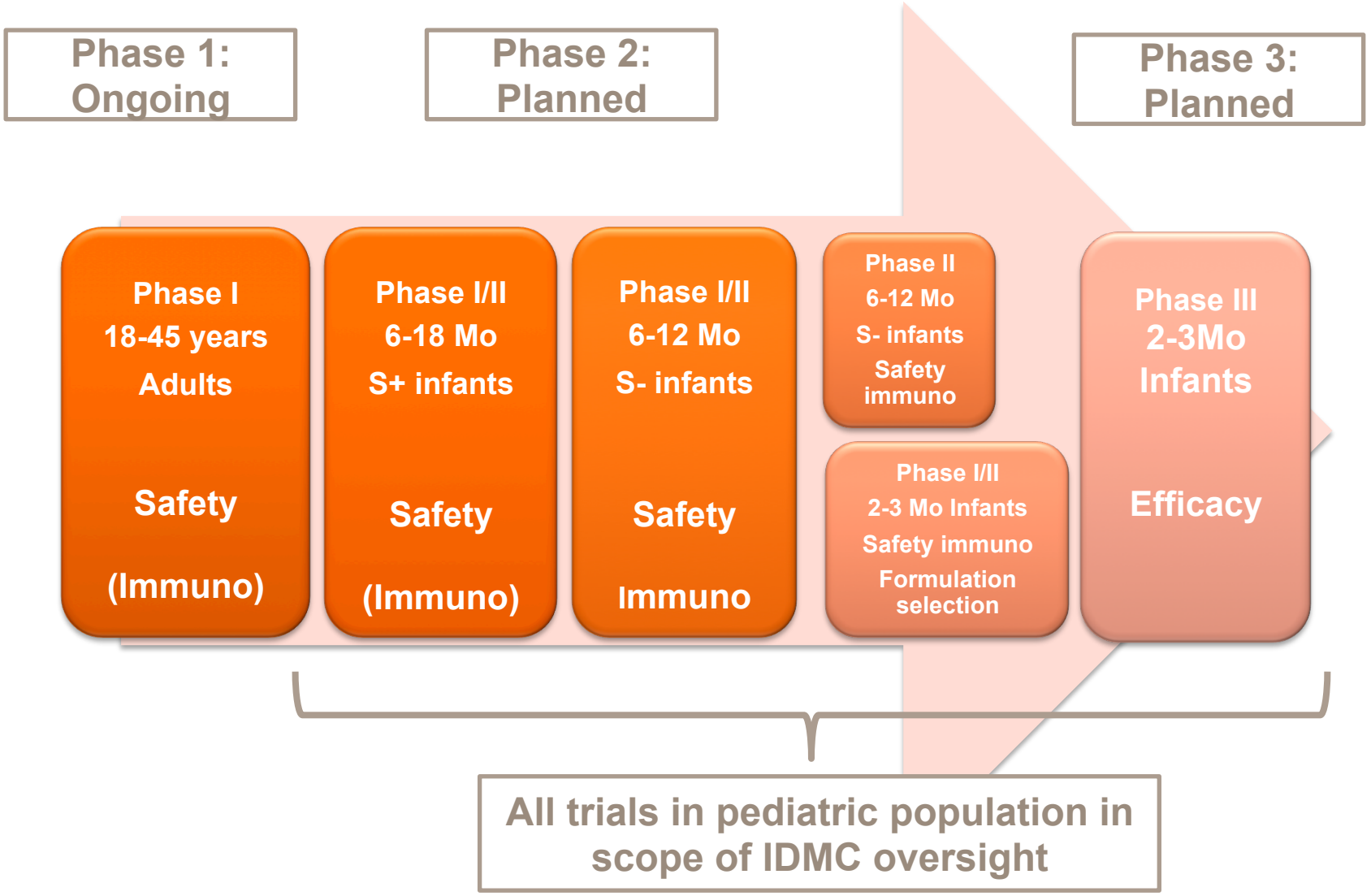
Adenovirus vectored RSV F

Live-attenuated RSV; RSV/PIV3 vector

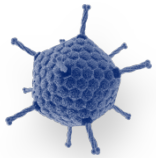
GSK's paediatric RSV vaccine candidate

	Paediatric
Global intent	Active immunization of infants for the prevention of RSV-associated LRTI
Vaccination regimen	• Two-dose regimen from 6 wks onwards (min 1 year protection) • Co-administration with routine paediatric vaccines
Vaccine Composition	Chimpanzee Adenovirus (ChAd155) encoding 3 antigens (F, N and M2.1)
Stage of development	Phase I: ongoing in adult

Overview of the Pediatric Clinical Development



RSV 'junior' vaccine

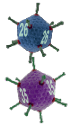


An adenovirus vector based vaccine (Ad 26 and Ad35; replication incompetent), expressing F antigen that aims to protect young infants against RSV, by eliciting high titer, potent neutralising antibodies and T cell immunity

Ongoing:

- FIH - two phase 1 studies evaluating homologous and heterologous prime boost regimens of Ad26 and Ad35

- RSV1001 (NCT02440035): n=48 (dosing completed)
  - Study to evaluate the Safety, Tolerability and Immunogenicity of Ad35 regimens boosted with Ad26 in Healthy Adult Volunteers
- RSV1003 (NCT02561871): n=32 (fully enrolled, dosing ongoing)
  - Study to evaluate the Safety, Tolerability and Immunogenicity of Ad26 boosted with Ad35 in Healthy Adult Volunteers



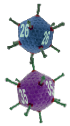
Ad26
Ad35

RSV – planned studies


2017:

Phase 1/2 study in children

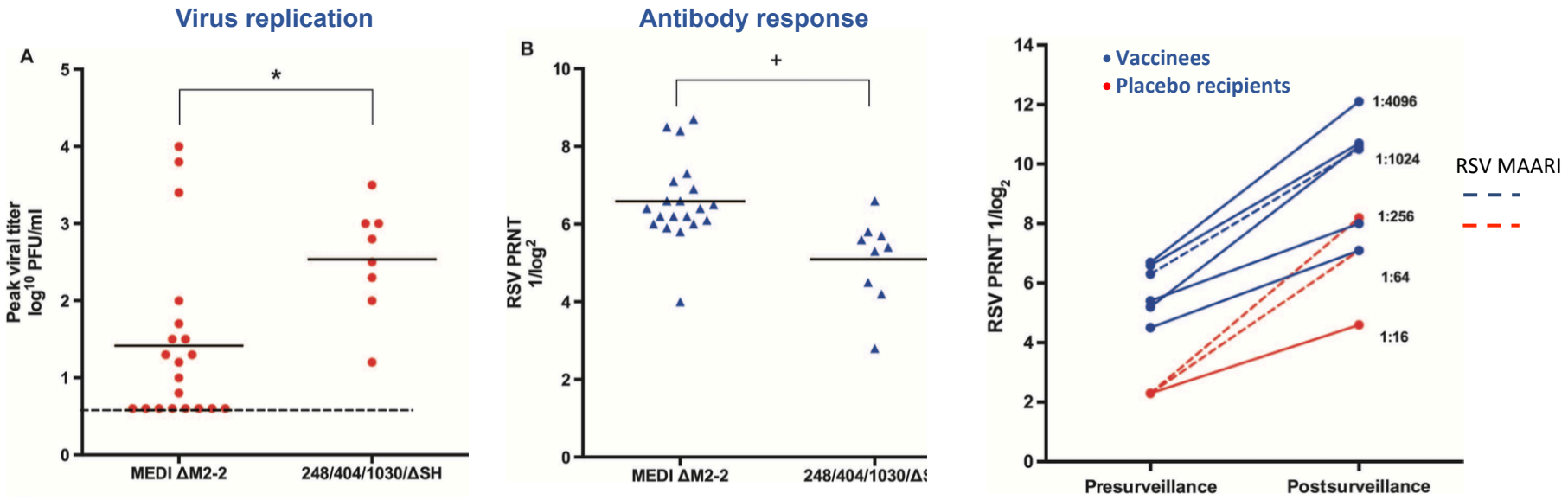
- Age de-escalation, to study safety, tolerability and immunogenicity
- Evaluating homologous vs heterologous prime boost regimens of Ad26 and Ad35



Live-attenuated RSV vaccines with M2-2 deletion

National Institute of Allergy and Infectious Diseases

- RSV MEDI ΔM2-2 was developed by the Laboratory of Infectious Diseases, NIAID/ NIH and MedImmune
- Deletion of the RSV M2-2 ORF results in decreased RNA replication & increased Ag expression when compared to the previous leading live-attenuated RSV vaccine candidate
- Deletion of M2-2 appears to 'de-link' virus replication and antibody response, and prime for a potent anamnestic response following natural infection with RSV



Karron R et al. Sci Transl Med. 2015 Nov 4;7(312):312ra175.

Current & upcoming clinical studies in NIAID program

National Institute of Allergy and Infectious Diseases

Laboratory of Infectious Diseases/NIAID (Peter Collins, Ursula Buchholz, et al*)

1. Attenuated RSV strains

- A number of gene deletion candidates in phase 1 studies in RSV seronegative infants and children in 2016-2017 to identify a lead candidate from the following:
  - A virus comparable to RSV MEDI ΔM2-2
  - Additional ΔM2-2 backbones to evaluate potential for increased immunogenicity
  - One or more backbones based on deletion of NS2 or NS1 (interferon antagonist) genes

2. Human parainfluenza type 3 virus vectors expressing RSV F protein

- Bivalent RSV/HPIV3 vaccine (protection against both viruses)
- Improved growth and stability to facilitate manufacture & distribution in LMIC
- Expression of stabilized pre-fusion F protein enhances quality of RSV-neutralizing Ab-- potential to increase the quality of anamnestic responses
- Clinical trial seed under development, clinical study in 2017

*Collaborators: Ruth Karron et al, CIR/JHU, Elizabeth McFarland, Coleen Cunningham et al, IMPAACT/NIAID, NICHD

Pediatric RSV immunization with mAb:

Palivizumab biosimilar

Extended half-life RSV F mAb MEDI8897

Biosimilar palivizumab – WHO and University of Utrecht

- Palivizumab off patent in 2015
- Plan to develop a 'biosimilar' of palivizumab and reduce costs through:
  - Using latest technologies (i.e. high expression cell line)
  - A novel development and financing plan[1]
    - Coordinated by the Utrecht Center of Excellence for Affordable Biotherapeutics for Public Health
    - Funded through a consortium of manufacturers
      - Agreement signed on 9 March 2016
  - Estimated price $US 250 per child for full 5 courses
  - First market authorization expected end 2017
  - Roll out the product in LMICs

World Health Organization

[1] http://www.uu.nl/en/news/first-consortium-of-local-manufacturers-to-make-affordable-biosimilars-available-for-low-income

MEDI8897: Passive RSV vaccine strategy using RSV F mAb

Characteristics

- Fully human, high potency IgG1 mAb derived from human B-cells
  - YTE half-life extension technology
- Targets site on RSV prefusion F
  - Neutralizes all RSV A and B clinical isolates tested
- Single fixed IM dose given; expected to protect up to 6 months
  - Given at birth or at onset of RSV season
  - Vaccine-like pricing

Program Status

- Phase 1a adult FTIH complete (N=136)
- Phase 1b/2a in 32-35 week gestational age infants (N=89); enrollment complete, follow-up ongoing
- Phase 2b clinical efficacy in 29-35 week gestational age infants planned for 2016 (N=1,500)
- FDA fast track designation granted, study endpoints agreed with EMA-PDCO, FDA
- Exploration of prequalification process has been initiated

MEDI8897 Clinical development overview

Phase 1a FTIH (healthy adults)

- Double-blind placebo controlled study (3:1) **(N = 136)**
- Evaluated multiple IV and IM dose levels
- Subjects followed for 1 year

Safety

- AEs: MEDI8897 62% vs placebo 63%
- 2 SAEs: Gun shot & appendicitis

Pharmacokinetics

- Bioavailability 87%
- Half-life extended to 85-117 days

Anti-drug antibody

- Incidence of ADA similar (MEDI8897 14% vs placebo 15%) , titers were low, no observed impact on safety or PK

Phase 1b/2a in 32-35 week GA infants

- Double-blind placebo controlled study (4:1) in USA, SA, Chile **(N=89)**
- Three IM dose levels evaluated
- Subjects followed for 1 year

Safety

- Day 30 safety and tolerability profile reassuring

Pharmacokinetics

- Day 30 interim PK models support single 50mg intramuscular dose administration

Anti-drug antibody

- Day 30 incidence of ADA was low and balanced between groups, no observed impact on safety or PK

Maternal RSV vaccination:

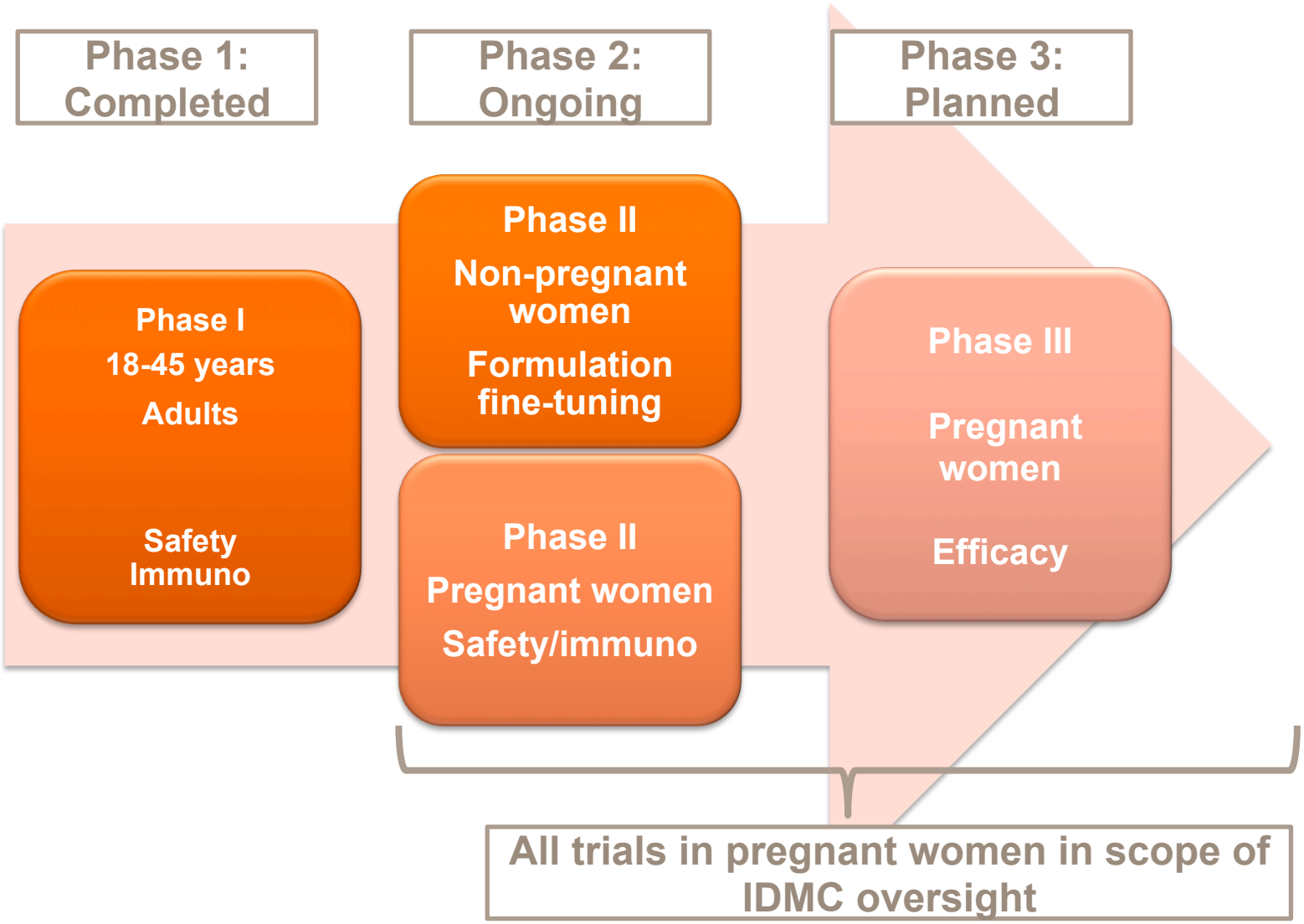
RSV prefusion F vaccine

RSV postfusion F nanoparticle vaccine

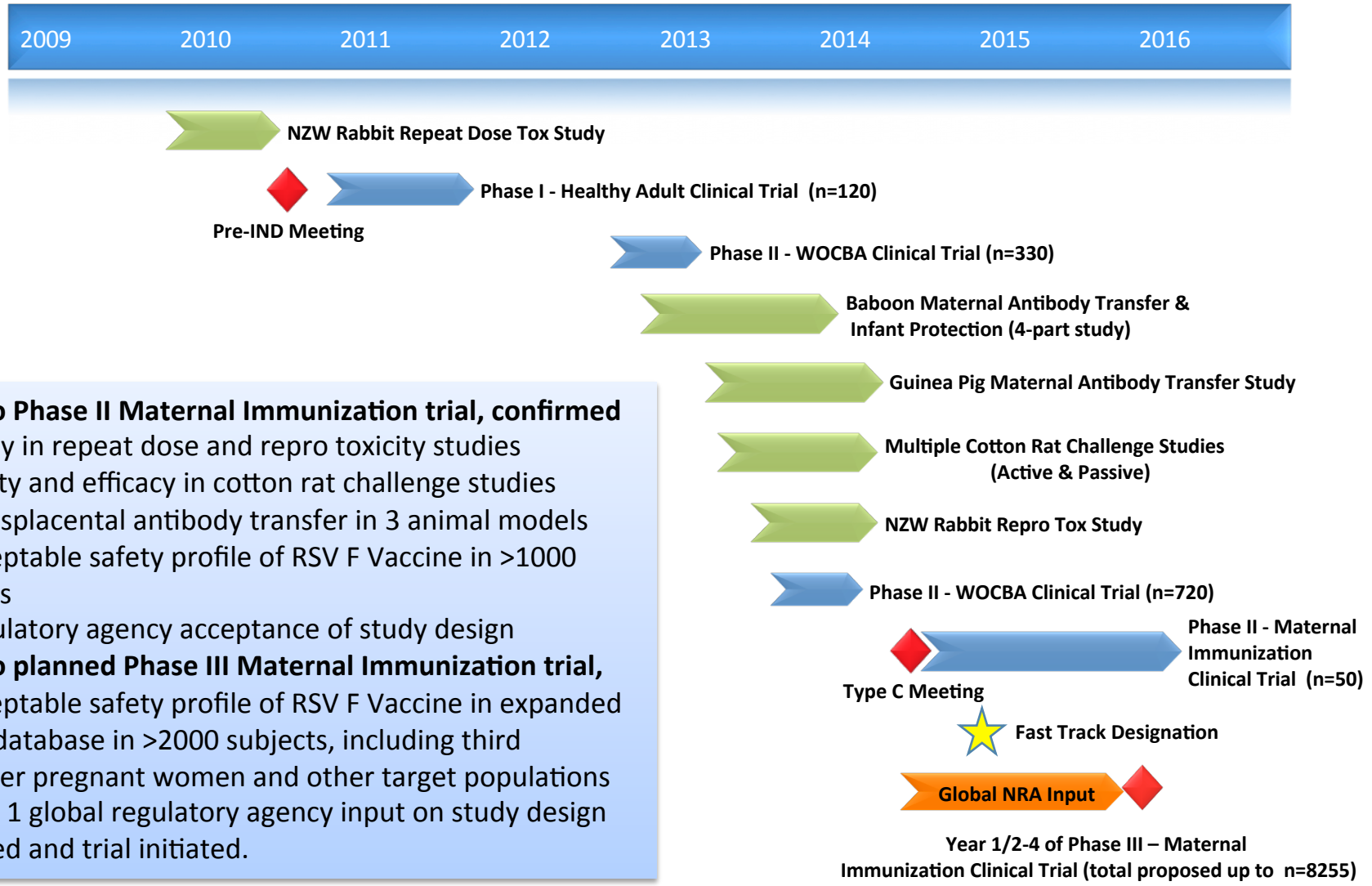
GSK's maternal RSV vaccine candidate

	Maternal
Global intent	Active immunization of pregnant women during the 3rd trimester of pregnancy to prevent RSV-associated LRTI in infants
Vaccination regimen	• Single dose to boost pre-existing immune response • Immunization in the third trimester
Vaccine Composition	Recombinant subunit PreF antigen (Dosage TBD, with or without Alum)
Stage of development	Phase II: ongoing

Overview of Maternal Clinical Development



Novavax RSV F Vaccine Clinical Development Program: Protection of Infants via Maternal Immunization



Prior to Phase II Maternal Immunization trial, confirmed

☑Safety in repeat dose and repro toxicity studies

☑ Safety and efficacy in cotton rat challenge studies

☑ Transplacental antibody transfer in 3 animal models

☑ Acceptable safety profile of RSV F Vaccine in >1000 subjects

☑ Regulatory agency acceptance of study design

Prior to planned Phase III Maternal Immunization trial,

☑ Acceptable safety profile of RSV F Vaccine in expanded safety database in >2000 subjects, including third trimester pregnant women and other target populations

☑ Year 1 global regulatory agency input on study design obtained and trial initiated.

Novavax RSV F Nanoparticle Vaccine: Phase 2 safety, immunogenicity, and transplacental antibody transfer

Protocol RSV-M-203

- Well-tolerated
- High and sustained titers of RSV F IgG and palivizumab competing antibody (binding to postfusion RSV F in ELISA)

Trial Overview

- **Phase 2 trial** randomized, observer-blinded
- **50 pregnant women in 3rd trimester**
  - Singleton pregnancies
- **120µg dose** with aluminum adjuvant

Goals

- **Describe** the safety of the RSV F vaccine women and infants
- **Describe** the immunogenicity of the vaccine in the 3rd trimester
- **Characterize** antibody transfer and decay kinetics

Method

- **Detailed collection of third trimester safety endpoints**
- **Cord blood** and infant sera
- **Maternal** and **infant RSV surveillance** through RSV season

RSV F Vaccination to Protect Infants via Maternal Immunization: Global P3 Trial **Prepare™** launched 4Q 15

Prepare™

Timeline

- Phase III trial initiated Dec 2015
- Group sequential design with enrollment 2 - 4 years

Trial Objectives

- **Primary: Prevention** of RSV lower respiratory tract infection (LRTI) with hypoxemia in infants during the first **90 days of life**
- **Secondary endpoints:** LRTI with severe hypoxemia, persistent efficacy to measure out to 120, 150, 180 days

Trial Design

- **Pregnant women in 3rd trimester**
- 5,000 – 8,255 participants
- Randomized, placebo-controlled
- DSMB oversight and iterative futility analyses to ensure safety
- **Global sites**
  - Both hemispheres

Acknowledgements

- **GSK**
  - Ilse Dieussaert
- **Janssen**
  - Valerie Oriol Mathieu
  - Olga Popovic
- **MedImmune**
  - Filip Dubovsky
- **Novavax**
  - Allison August
- **LID, NIAID/NIH**
  - Peter Collins
  - Ursula Buchholz
- **PATH**
  - Deb Higgins
  - Carrie Trujillo
- **WHO**
  - Vasee Moorthy
  - Erin Sparrow