Update on RSV Vaccine Development

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PDVAC 2016

Topics for review

RSV Epidemiology

- Burden of disease
- PERCH findings (preliminary)

RSV vaccines and mAbs in development

- Vaccines for the elderly
- Pediatric vaccines
- Pediatric mAbs
- Maternal vaccines to protect the infant

Research gaps and programmatic considerations

- related to licensure/registration
- related to implementation

RSV Global Burden Estimates (2005)

- 33.8 (95% CI, 193-46.2) million episodes of RSV LRI annually in children < 5 years (22% of all ALRI episodes)
- 3.4 million episodes requiring hospitalization
- 66,000-199,000 deaths in 2005, 99% in developing countries
- Updated estimates for RSV ALRI, severe ALRI (community based and hospitalized) and deaths presented to SAGE and publication by the RSV Global Epidemiology Network (RSV-GEN) expected this year

Lancet. 2010 May 1;375(9725):1545-55.

PERCH

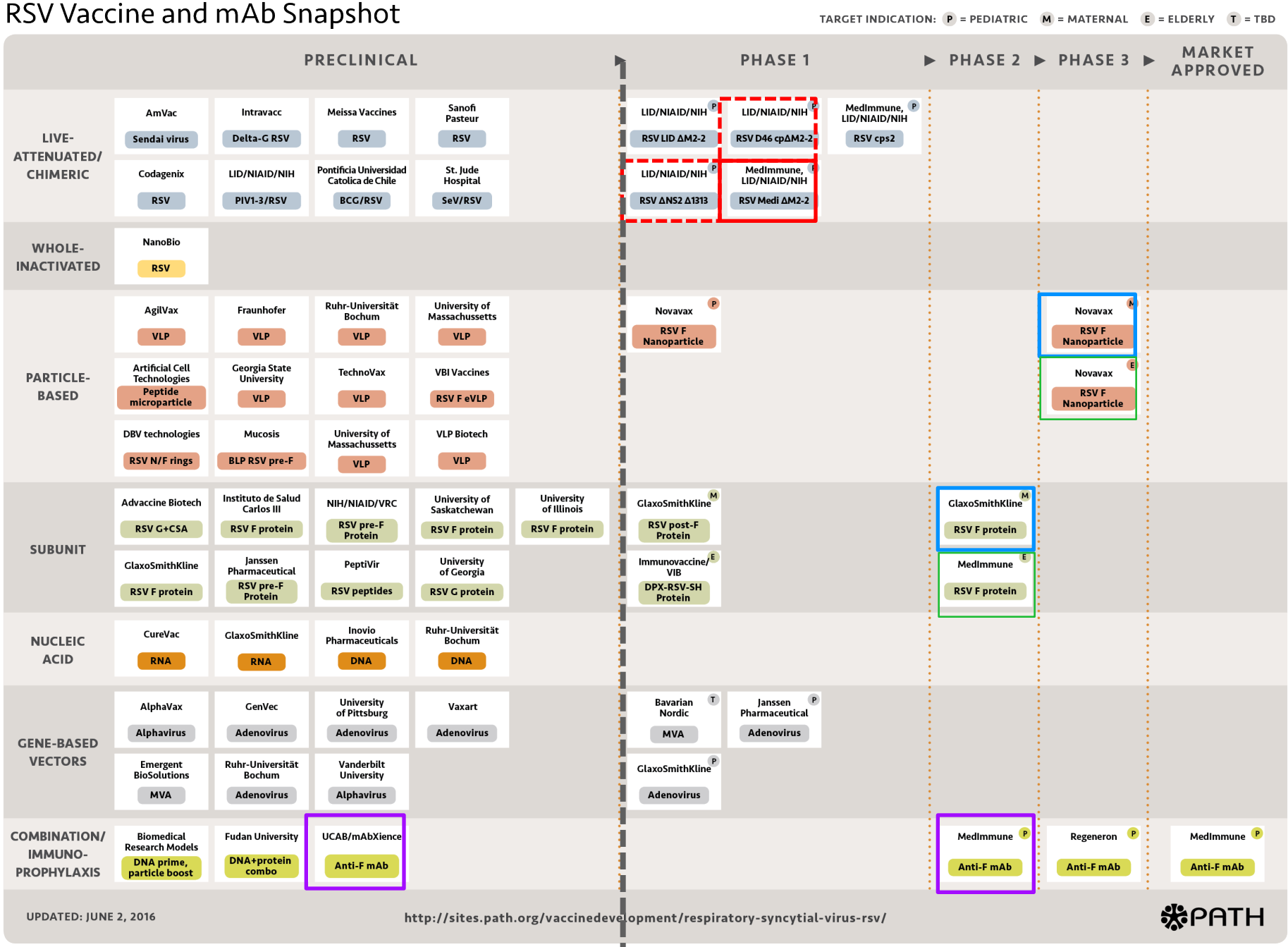
Pneumonia Etiology Research for Child Health

Pneumonia
Etiology
Research for
Child
Health

- A case-control study of hospitalized pneumonia
- 1-59 month old children
- Seven countries, nine sites in Africa and Asia
- Aims to improve the evidence-base for pneumonia prevention and treatment in developing countries

- Supported by Bill & Melinda Gates Foundation
- Based at Johns Hopkins Bloomberg School of Public Health

RSV Vaccine and mAb Snapshot



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

RSV Vaccines for the Elderly

- Two vaccines in late-stage clinical development
- Novavax (NCT02608502)
  - RSV postfusion F 135 mcg
  - Phase 3 Resolve trial in adults >60 yrs; fully enrolled Dec 2015 (n= 11,850)
  - Endpoints: 1^0 mod-severe RSV-LRTD*, 2^0 RSV-LRTD, any RSV- ARD
  - Results expected late 2016/early 2017
- MedImmune/Astra Zeneca (NCT02508194)
  - RSV soluble postfusion F with GLA (TLR4 agonist)
  - Phase 1 completed; phase 2b ongoing
  - Endpoint: any acute RSV respiratory illness
  - Estimated study completion date: April 2017
- Application for licensure likely to precede those for products to protect infants

Pediatric RSV vaccination:

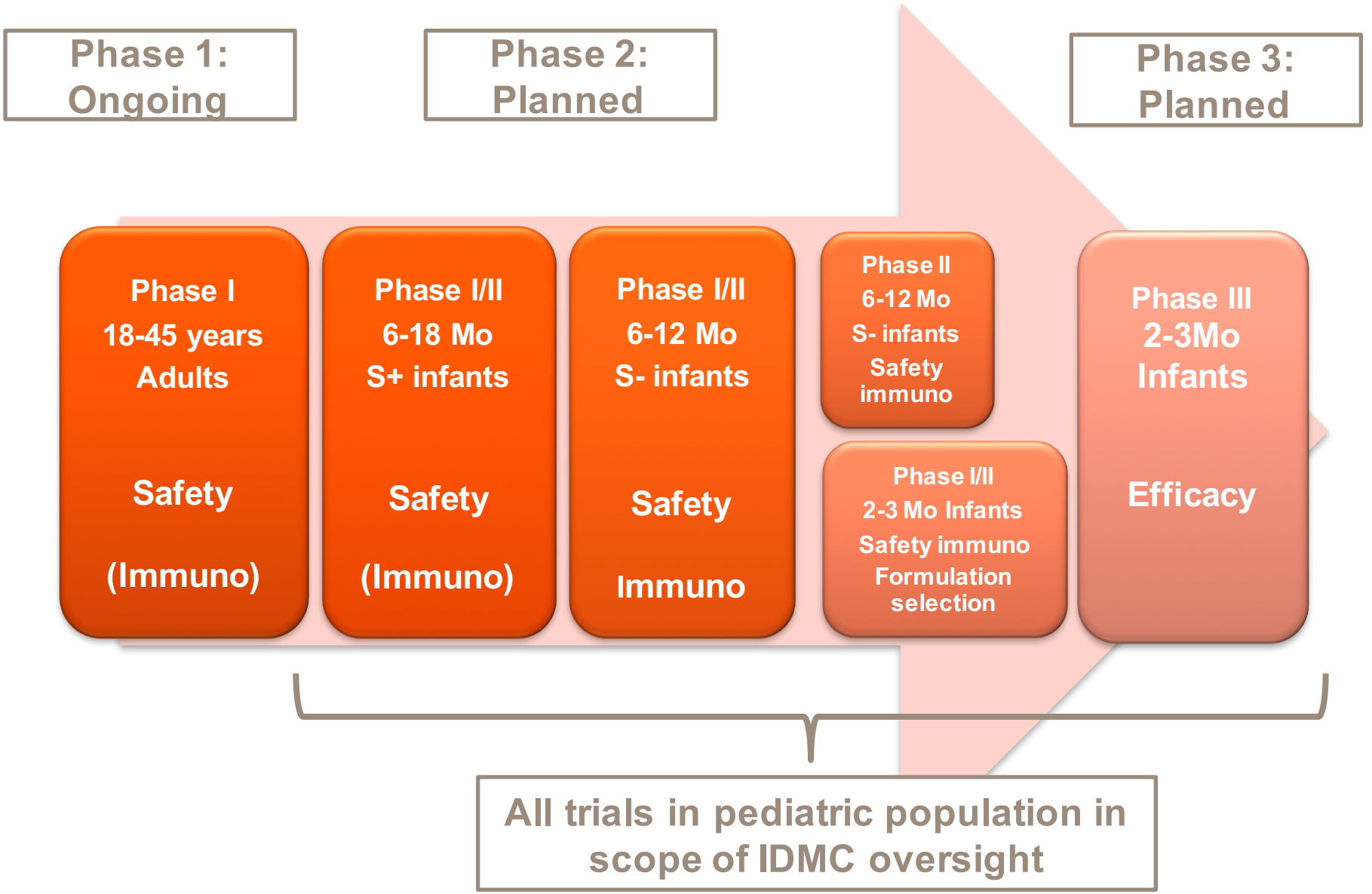
Adenovirus vectored RSV F

Live-attenuated RSV; RSV/PIV3 vector

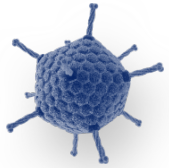
GSK's paediatric RSV vaccine candidate

	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

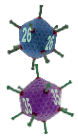


An adenovirus vector based vaccine (Ad 26 and Ad35; replication incompetent), expressing F antigen that aims to protect young infants against RSV, by eliciting high titer, potent neutralising antibodies and T cell immunity

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



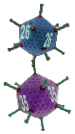
Ad26
Ad35

RSV – planned studies


2017:

Phase 1/2 study in children

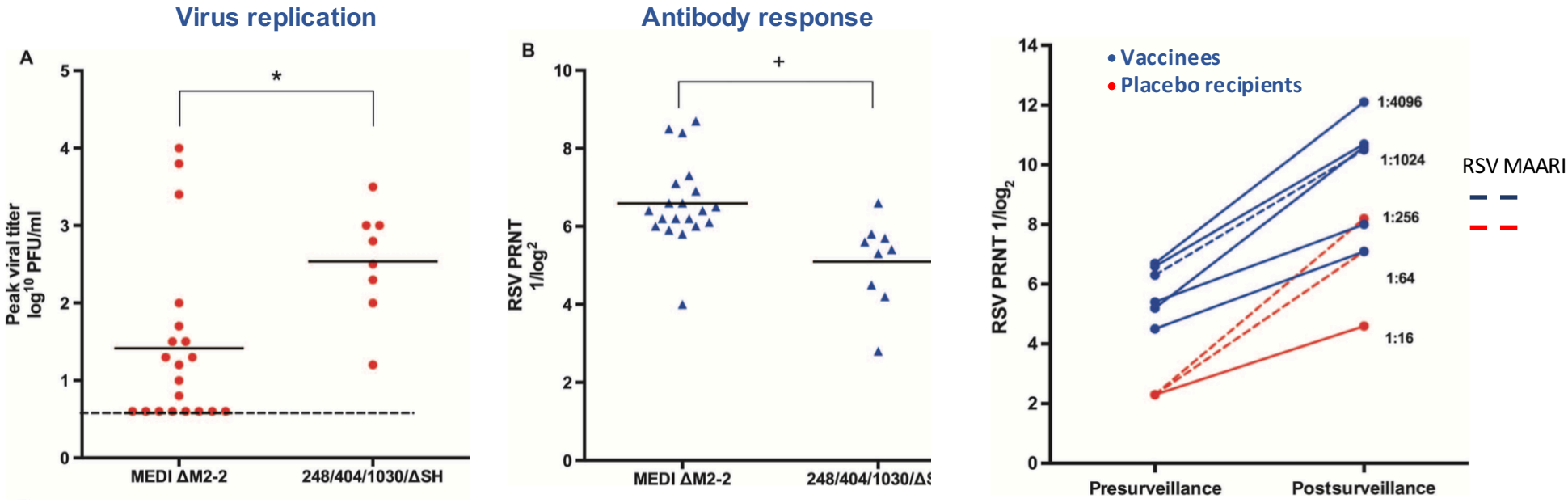
- Age de-escalation, to study safety, tolerability and immunogenicity
- Evaluating homologous vs heterologous prime boost regimens of Ad26 and Ad35



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:

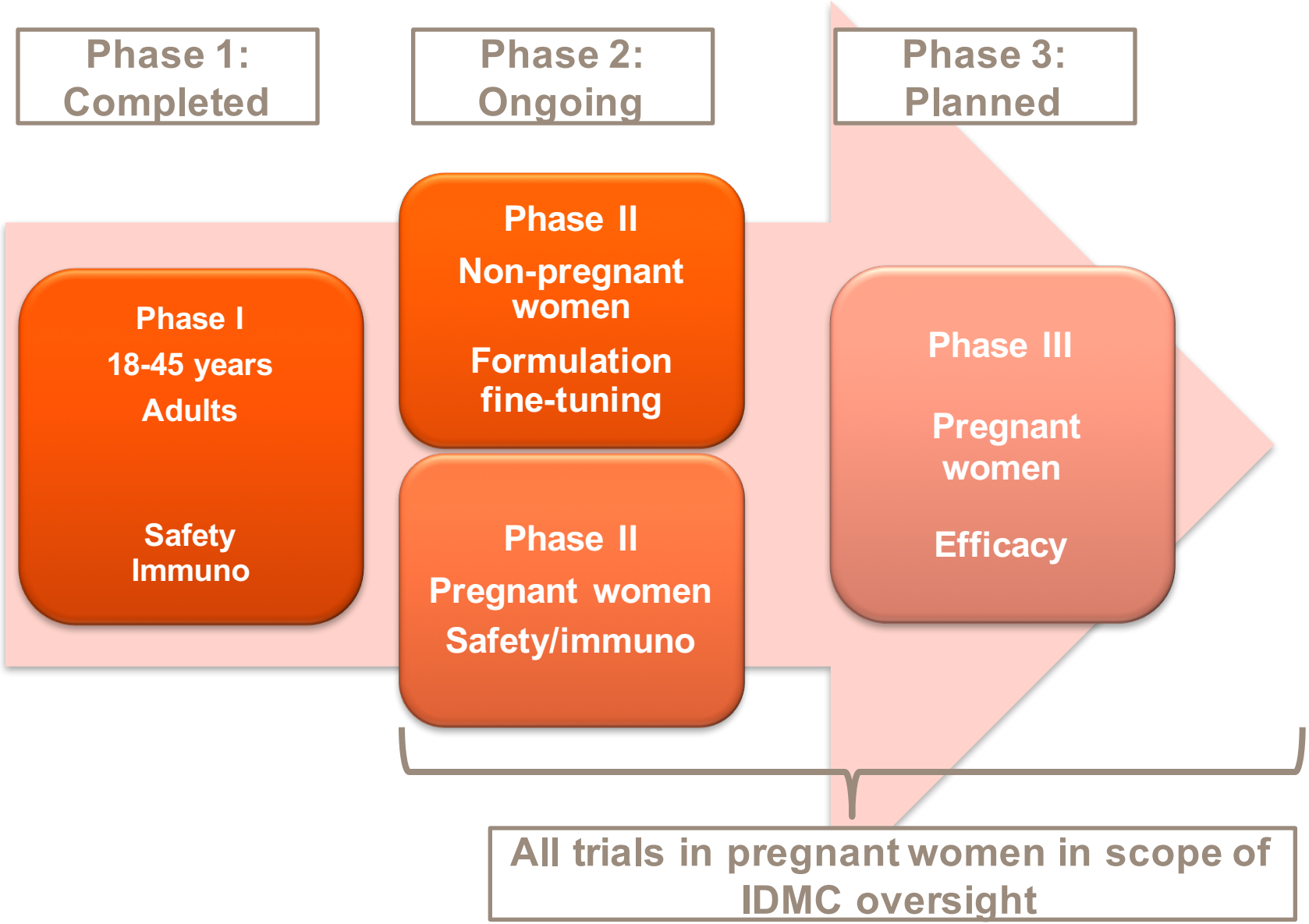
RSV prefusion F vaccine

RSV postfusion F nanoparticle vaccine

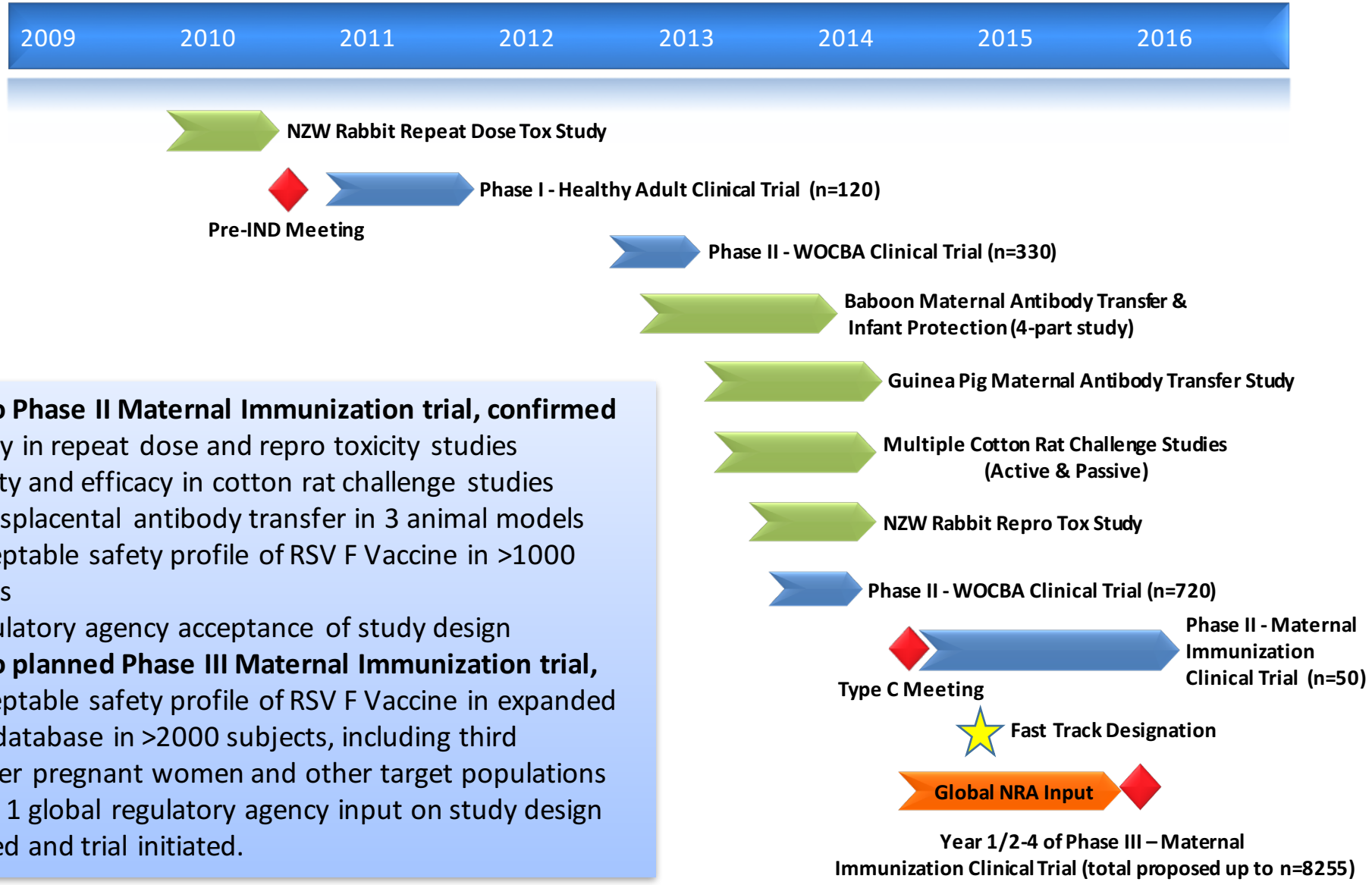
GSK's maternal RSV vaccine candidate

	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

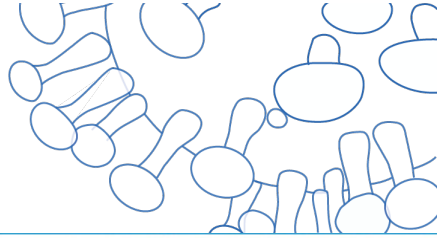
Goals

- **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

Research gaps related to licensure/registration

- Standardization of neutralizing antibody assays and exploration of RSV F competitive binding assays
- Case definitions

Severe RSV LRTI	Very Severe RSV LRTI
An infant or young child presenting to a health facility that is part of the case ascertainment system for the phase III trial who fulfills both the laboratory **AND** clinical criteria below: ***Laboratory criterion*** RSV infection as confirmed by a fit-for-purpose, fully validated PCR assay with high specificity and sufficient sensitivity on upper respiratory samples. ***Clinical criteria*** Respiratory Infection defined as Cough or Difficulty Breathing **AND** LRTI defined as FAST BREATHING by WHO criteria **OR** SpO2 < 95% **AND** ≥ 1 OF THE FOLLOWING FEATURES OF SEVERE DISEASE: **Pulse oximetry < 93%** **AND/OR** lower chest wall in-drawing	An infant or young child presenting to a health facility that is part of the case ascertainment system for the phase III trial who fulfills both the laboratory **AND** clinical criteria below: ***Laboratory criterion*** RSV infection as confirmed by a fit-for-purpose, fully validated PCR assay with high specificity and sufficient sensitivity on upper respiratory samples. ***Clinical criteria*** Respiratory Infection defined as Cough or Difficulty Breathing **AND** LRTI defined as FAST BREATHING by WHO criteria **OR** SpO2 < 95% **AND** ≥ 1 OF THE FOLLOWING FEATURES OF VERY SEVERE DISEASE: **Pulse oximetry < 90%** **AND/OR** Inability to feed **AND/OR** Failure to respond/unconscious

Maternal and Paediatric RSV programs

GSK's effort towards a case definition and severity scale

- Objective = to evaluate and standardize case definitions for LRTI and severe LRTI that can be used worldwide and are acceptable by both regulators and recommending bodies
- GSK proposed case definitions are currently being tested in a large epidemiological study (N = 2400) conducted in 8 different countries worldwide (HRC & LRC)

RTI	LRTI	Severe LRTI
Runny nose,	Child with RTI AND	Child with LRTI AND SaO2 < 92%*, OR
OR	SaO2 < 95%*, OR	Difficulty breathing leading to:
Blocked nose,	RR increase:	• Irritability/agitation, OR
OR	• > 60/min < 2m of age	• Lethargy/sleepiness, OR
Cough	• > 50/min 2-11m of age	• Lower chest wall indrawing, OR
	• > 40/min 12-24m of age	• Reduced/no vocalization, OR
		• Apnoea > 20 sec, OR
		• (Cyanosis), OR
		• Stop feeding well/dehydration

** Measured by oximeter.*
RR= Respiratory Rate; SaO2= Blood Oxygen Saturation; m = months; RTI = Respiratory Tract Infections; LRTI = Lower Respiratory Tract Infections

Case definitions

- Correlation with outcomes
- Feasibility
  - Standardization of pulse oximetry measurements
  - How to assess the very sick child immediately placed on oxygen
- The problem of the very young infant
  - May be hospitalized without severe/very severe LRI or hypoxemia (apnea, periodic breathing, concern for deterioration)

Challenges in planning long-term follow-up for RSV vaccine (mAb) trials

- Follow-up will occur after unblinding for primary efficacy endpoints
- Large numbers may be needed; may require pooling across studies
- Standardized outcome definitions will be needed
- Ability to measure outcomes that rely on pulmonary function testing will vary across sites

Available tools for evaluation of recurrent wheezing/asthma in children

36 MONTHS OF AGE: Recurrent wheezing outcome

Potential survey instruments

- Core asthma component from ISAAC questionnaire*^
- Other validated survey instruments

Potential physiologic assessments

- Forced oscillation technique (FOT)
- Spirometry.
- Airway resistance, Interrupter technique (Rint)

60 MONTHS OF AGE: Asthma outcome

Standard tools

- Core asthma component from ISAAC questionnaire*^
- Other validated survey instruments
- Spirometry and test of reversibility.

Potential tools to measure physiology and disease biomarkers

- Forced oscillation technique (FOT)
- Airway resistance, Interrupter technique (Rint)
- Fractional exhaled Nitric Oxide (FeNO)

* http://isaac.auckland.ac.nz/phases/phasethree/corequestionnaire_6-7.pdf

Caballero M et al, submitted for publication

Research gaps related to policy & implementation (LMIC focus)

- Age –stratified burden of acute RSV disease
  - Impact of vaccines on long-term wheezing outcomes
- Whether protection against severe disease occurs following a primary infection (data available for HIC)
- Community mortality
- Morbidity and mortality in pregnant women & elderly

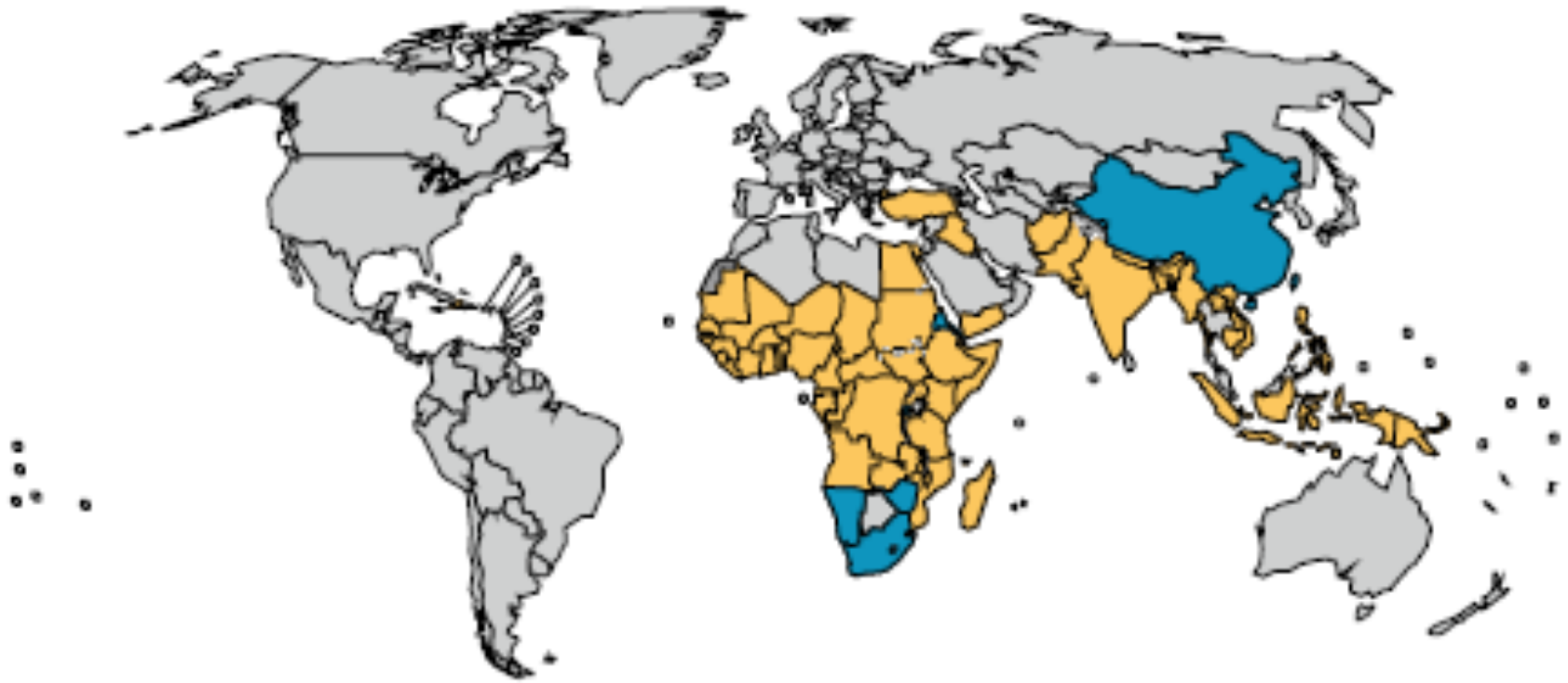
Cost-effectiveness and impact data

- Optimal methods to ensure timely maternal immunization

SAGE meeting, April 2016, http://www.who.int/wer/2016/wer9121.pdf?ua=1

Maternal and neonatal tetanus elimination has relied heavily on SIAs

Figure 4: 52 Member States that implemented TT SIAs between 1999 and 2014



Countries that achieved MNTE without TT SIAs during 1999–2014
Countries that initiated or expanded SIAs during 1999–2014
MNT eliminated before 2000

Map production: Immunization Vaccines and Biologicals (IVB), WHO.
Source: WHO-UNICEF database, February 2015.

The Quality-Coverage Gap in ANC: Demographic and Health Survey Data from 41 LMICs

Intervention	Abbreviation	Mean %	Upper %	Lower %
4 or more ANC visits	ANC4+	**57**	96	15
1st ANC visit before 4 months gestation	ANC<4mo	**55**	93	26
Iron-folic acid supplementation for 90+ days	IFA90+	**30**	78	2
Protected against tetanus	TT2+	**79**	97	47
Counseled on pregnancy danger signs	DSs	**58**	87	28
Blood pressure checked	BP	**91**	100	50
Urine specimen taken	Ur	**67**	98	12
HIV counseling and testing	HIV	**49**	88	5
At least 2 doses of sulfadoxine/pyramethamine for malaria prevention (where appropriate)	SP2+	**25**	74	1
Average		**60**		

Hodgins S. Glob Health Sci Pract. 2014

Summary

- RSV is a leading global cause of severe LRI in infants and young children
- Over 60 RSV vaccines and mAbs in development, with more than 15 in clinical development
- Research gaps related to product licensure/registration need to be addressed urgently, as products are already in phase 3 trials
- Research gaps related to policy and implementation will need to be addressed over the next 4-5 years, prior to product licensure/registration

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  - Site Teams
  - Pneumonia Methods WG
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