OPTIONS FOR RSV PREVENTION MATERNAL IMMUNIZATION

ADVAC ALUMNI MEETING AT ESPID SLOVENIA 2019

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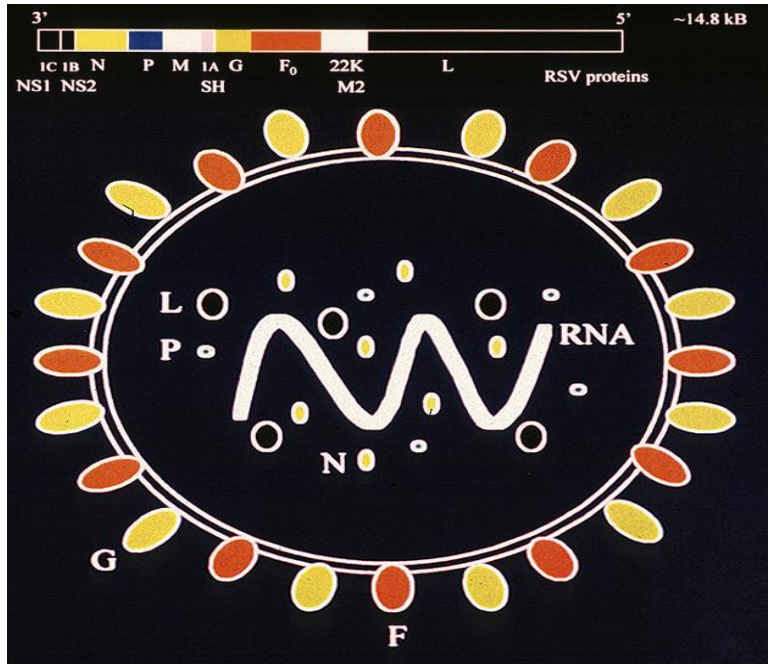
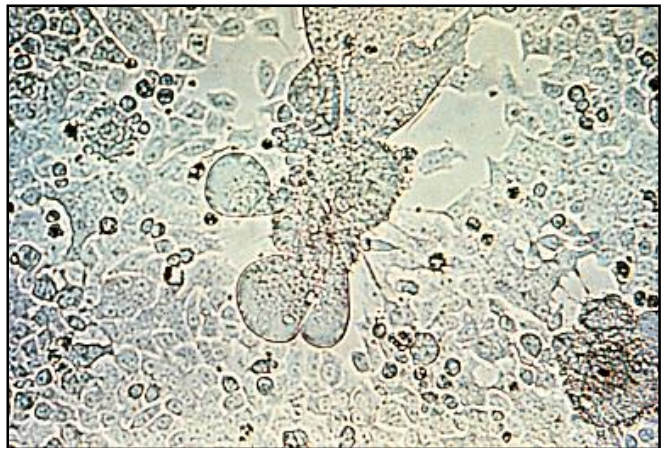
  Pfizer

Objectives

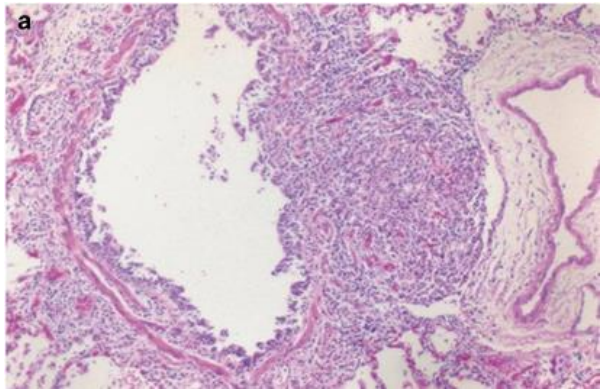
- RSV epidemiology and burden of disease in infants and pregnant women
- Rationale for maternal immunization with RSV vaccine
- Goals and challenges in the development of RSV vaccines for administration during pregnancy to protect young infants.
- Implementation Strategies

Respiratory Syncytial Virus





Multinucleated RSV **syncytium** in cell culture



Peribronchiolar and interstitial lymphocytic infiltrates with airway trapping (**Bronchiolitis**)

http://www.nature.com/modpathol/journal/v20/n1/fig_tab/3800725f3.html#figure-title

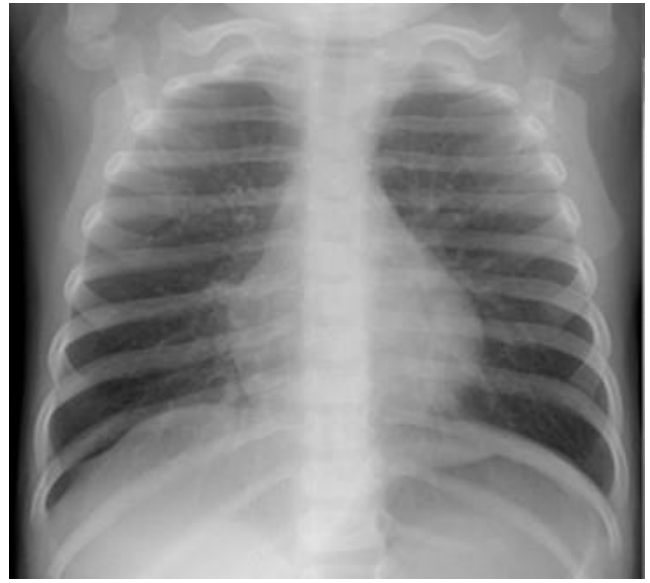
- Neg sense, **ssRNA Paramyxovirus**
- Two main types – **A, B co-circulate**
- 11 proteins, of which 2 are NS
- **Conserved F** (fusion – viral penetration, spread) and **variable G** (attachment) surface glycoproteins induce **Neutralizing Ab**

Features of Respiratory Syncytial Virus

- First described in 1957 (Chimpanzee coryza agent)
- Causes **URI and LRTI – Bronchiolitis**
- **Co-circulation subgroups (A and B) winter outbreaks**
- Illness burden and disease severity is greatest **in infants**, **young children** and **elderly adults**
- **Recurrent infections** occur throughout life and are milder except for people with chronic medical conditions
- **Virus-specific serum neutralizing antibody** protects against severe RSV LRTI
  - infection-induced
  - maternally derived
  - passively administered

Impact of RSV Disease in Children

- Most important cause of LRTI in infants and young children
- Nearly all children are infected at least once by age 2
- Recurrent infections common
- **30% to 40% of primary infections result in LRTI**
- **2-3% of infected children require hospitalization** – one of the most important causes of hospitalization in HIC
- **>75% of RSV disease hospitalization occurs in full term, healthy infants.**
- **Higher (2x) mortality than influenza in infants**
- **Severe infection associated with subsequent reactive airways/asthma**



RSV is a Major Global Pathogen
In Children under 5 years

2005 Estimates:

- **33.8** (19.3-46.2) **million cases** annually of **RSV-ALRI**
- **3.4** (2.8-4.3) **million cases** annually of ***severe* RSV-ALRI** (22% of all episodes)
- **55,000 to 199,000 deaths** annually attributed to RSV
  - Most of the deaths in developing countries occur in young children

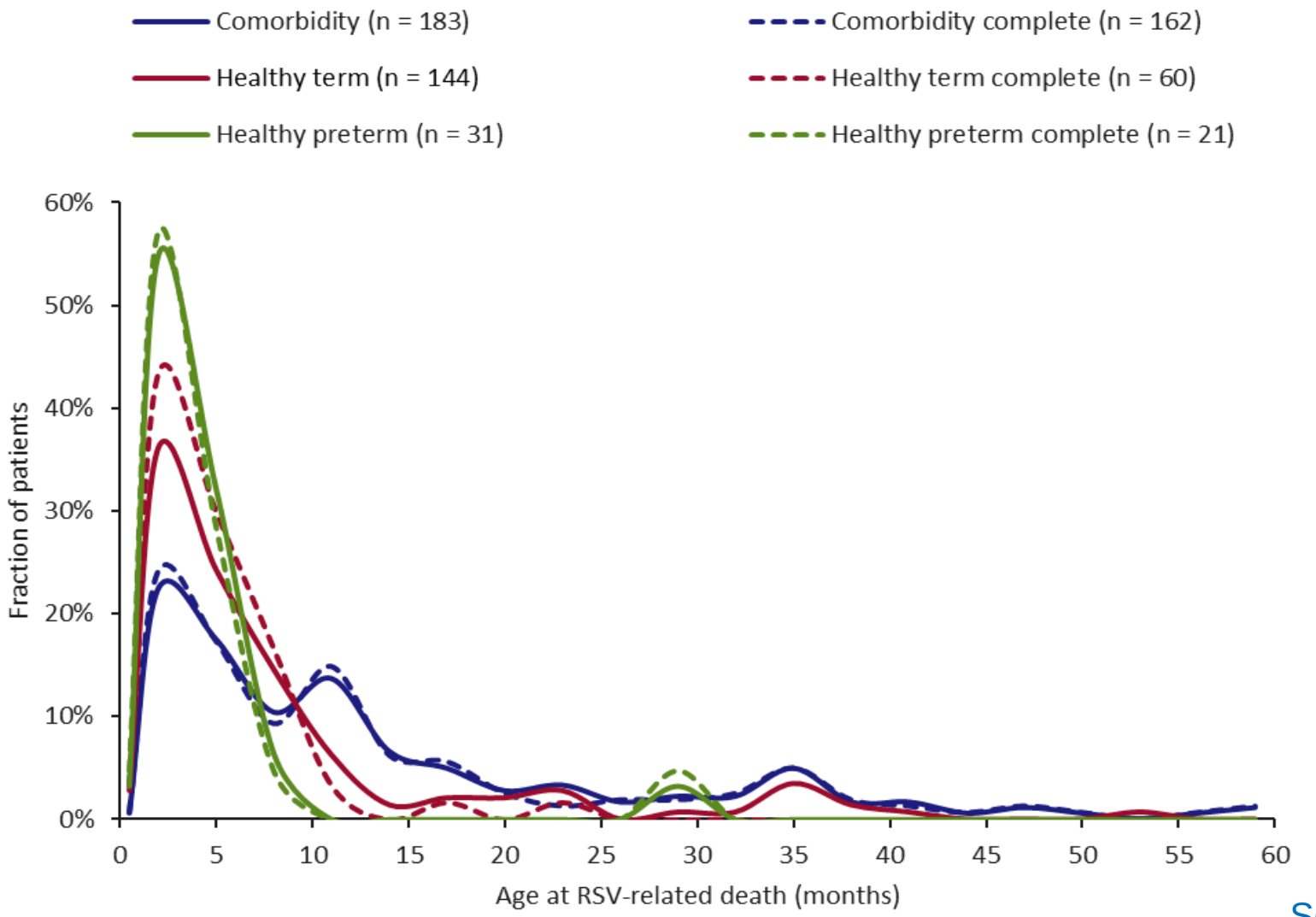
2015 Estimates in 132 developing countries:

- **33.1** (21.6-50.3) **million cases** annually of **RSV-ALRI**
- **3.2** (2.7-3.8) **million hospitalizations in children <5 yr** and **1.4 (1.2-1.7) million in <6 mo**
- **~60,000 (48-75K) in-hospital deaths in children <5 yr** and **27,000 (21-36K) in <6 mo** attributed to RSV

Mortality estimates suggest RSV is an important cause of death in children
Overall mortality: ~120,000 (95,000 to 150,000)
99% of the deaths occur in developing countries
45% of deaths occur in infants < 6 months

Nair H, et al., Lancet 2010;375:1545-55. and Shi T. et al. Lancet 2017;390:946-58

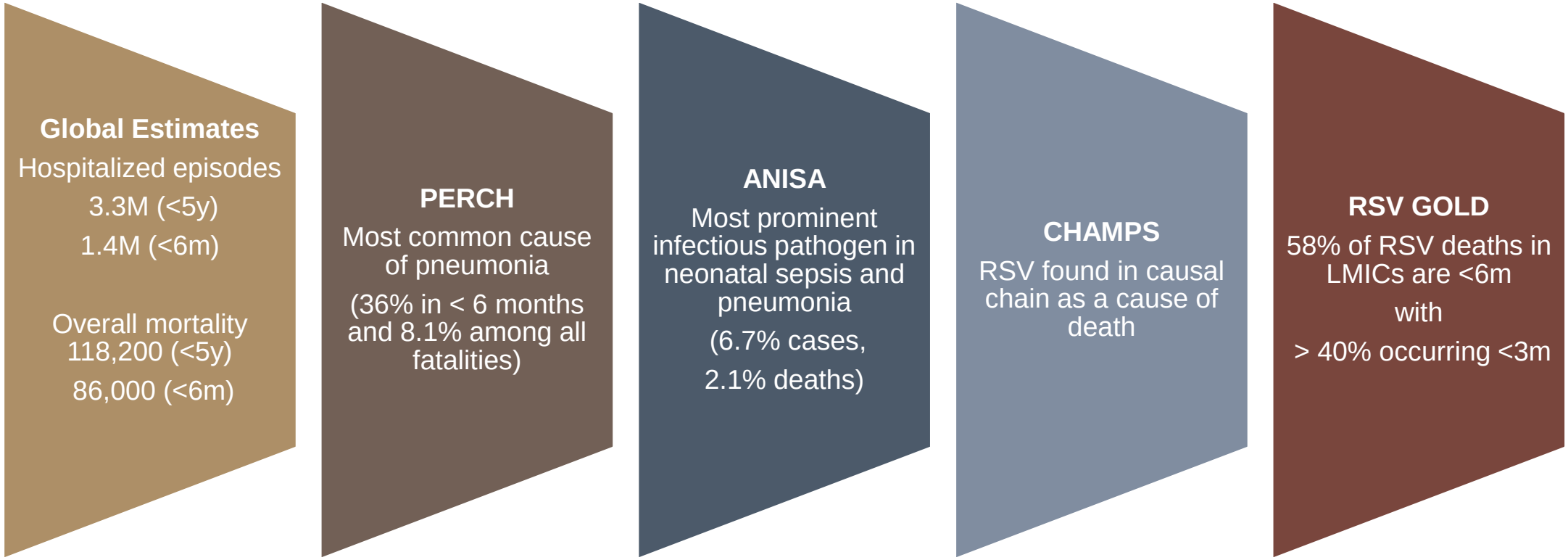
Very young infants are most at risk for RSV-related death



- Case series hospital data from 23 countries
- **Median age** for RSV-related deaths in LMICs is **5 months**, with **more than 40% occurring in under 3 months**
- RSV deaths from community higher

Scheltema NM et al. Lancet Glob Health 2017

Growing evidence of the global burden of RSV



ANISA = Aetiology of Neonatal Infection in South Asia; PERCH = Pneumonia Etiology Research for Child Health; RSV GOLD = Respiratory Syncytial Virus GlObaL Database; CHAMPS = Child Health and Mortality Prevention Surveillance Network.

Scheltema NM et al. *Lancet Glob Health* 2017; Shi T et al. *Lancet* 2017; Unpublished data, ANISA; Unpublished data, PERCH; Unpublished data, Harish Nair

MOST URGENT NEED IN RSV PREVENTION AND TREAMENT STRATEGIES IS: TO PROTECT YOUNG INFANTS

Source: www.jcpportraits.com

RSV in Children
Current Prevention Strategies

- **No licensed vaccine for children or adults**
- **Passive Antibody**
  - **RSV-Specific IgG** (RSV-IG or Respigam®)
  - **Monoclonal antibody** (Palivizumab or Synagis®)
    - Licensed 1998 US
    - Binds F protein of RSV preventing infection of host cell, replication and spread
    - Effective: Reduces mortality and severity of RSV disease
  - Restricted to:
    - Preterm infants < 29 weeks of gestation
    - Preterm infants with chronic lung disease (O2 requirement > 28 days)
    - Infants with hemodynamically significant/cyanotic congenital heart disease
  - Requires monthly IM administration
  - Protective levels need to be achieved *prior to* exposure
  - Most infants who are at risk for RSV (term) are excluded
  - Costly

Why don't we have a RSV vaccine for children?

- Primary target population, the very young infant (0-4 months of age), has a **suboptimal immune response to vaccination** in part due to presence of **maternal antibody**
- **Incomplete immunity to natural RSV infection**, especially in younger patients
- Enhanced pulmonary disease (pneumonia)/death in very young seronegative infants receiving **formalin-inactivated RSV vaccine in the 1960's**
- Subunit vaccines safe but not immunogenic enough
- Live attenuated vaccines administered intranasally pose challenges to balance between immunogenicity and reactogenicity

FI-RSV Experience (Pfizer vaccine)

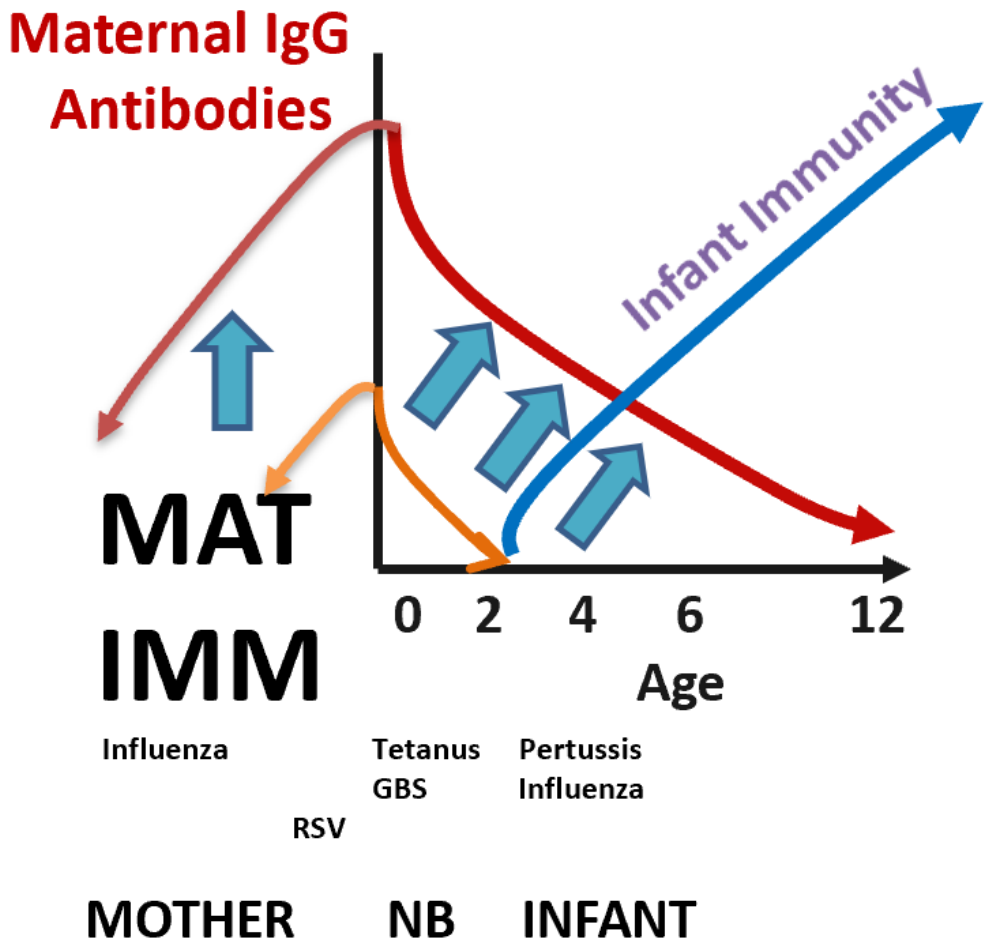
Children 2 to 23 months of age

RSV-outcome	Vaccinated group	Control group	Time between last dose and outcome	Reference
pneumonia	9/13 (69%)	4/47 (9%)	15 to 236 days	Kapikian
hospitalization	9 cases	2 cases	Not provided	Chin
hospitalization	16/31 (52%)	1/40 (2.5%)	23 d to 11 mo	Kim
hospitalization	10/111 (9%)	2/173 (1.2%)	Not provided	Fulginiti

Kapikian et al, AJE 1969;89:405-421
Chin et al,AJR 1969;89:449-463 (<1yr & 1-4 yrs: FI-RSV 43 & 99; FI-PIV 43 & 91)
Kim et al, AJE 1969;89:422-433 (2 infants died at 14 and 16 months; vaccination started at 2 and 5 months, respectively; both received 3 doses)
Fulginiti et al., AJE 1969;89:435-448

Rationale for Maternal Immunization to Protect Infants Against RSV

- Reduced incidence of RSV disease in neonates during the first several months after birth correlates with higher concentrations of RSV-specific maternal antibody.
- Passive anti-F IgG (e.g., Palivizumab) reduces incidence of severe disease.
- Adults (mothers) are primed from previous infections and vaccine will boost antibodies.
- RSV-specific IgG transfer from mothers to neonates is efficient.
- Potential protection from breast milk antibodies.
- Success of similar strategies for Tetanus, Pertussis, Influenza.



Factors that affect transplacental transfer of antibodies

- Gestational age at birth
- Interval vaccination to delivery

- Maternal IgG level
- IgG Subclass
  - IgG1 ~ IgG3 > IgG4> IgG2

- Placental abnormalities
- Infections (malaria, HIV)
- Other factors (maternal health, nutritional status, parity, etc)

- Maternal IgG crosses the placenta by a *selective* and *active* receptor-mediated transport system (hFcRn) (not IgM, IgA or IgE)
- Passage begins at ~ 17 wk, increases through term
- Cord/Maternal Ab correlation favors infant
- 40 wk: Fetal > Mat IgG
- Half life ~ 30-40 days
- High Ab → longer protection

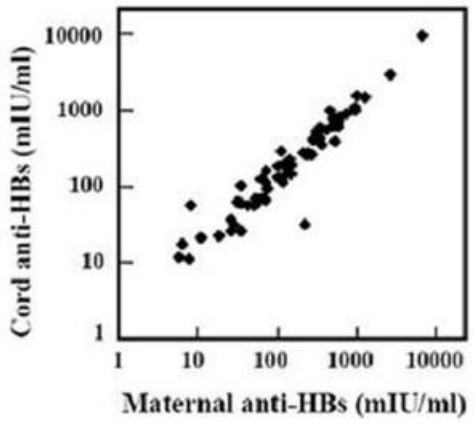
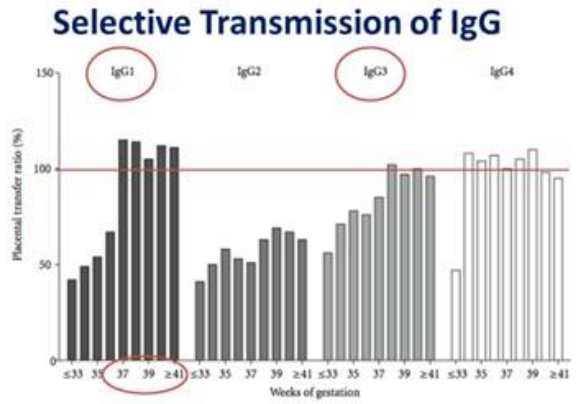


Figure 2. Correlation of transplacentally transferred anti-HB in infants with the maternal antibody (linear regressio analysis, $y = 1.393x - 37.286$, $r = 0.992$, $P < 0.001$, n = 63).



Palmeira, Clinical and Developmental Immunology, 2012, 1-13.

Goals of a Maternal Vaccination Program Against RSV

- Prevent infant death and hospitalization
- Prevent and/or reduce severity of lower respiratory illness in young infants
- Delay onset of first RSV infection in infants
- Reduce infection / transmission in the household and community
- Indirect benefits
  - Reduce secondary complications of RSV in infants - otitis media, bacterial infections
  - Reduce antibiotics usage for the treatment of ARI
  - Reduce virus-associated wheezing in the first decade of life
  - Improve maternal health and pregnancy outcomes (?)

RSV In Pregnancy

- Burden of RSV in pregnancy is mostly **unrecognized** (most OB providers do not test for respiratory viruses), but seems to be less frequent than rhinovirus/coronavirus and maybe more frequent than influenza
- Although most infections are likely **mild-moderate and self limited**, RSV can cause severe **lower respiratory tract illness in pregnant women**
- **Complications** of RSV infection in pregnancy include:
  - Maternal: Fever (uncommon), secondary bacterial infection, respiratory failure, preterm labor, emergent C-section
  - Infant: Preterm birth, low birth weight (?)
- Other effects: Physician visits, inappropriate antibiotics prescriptions, transmission within household

RSV in Pregnancy

- Burden of disease is unknown
- Clinical impact on pregnant women and outcomes of pregnancy unknown
- Several studies correlating maternal and prenatal factors with severity of bronchiolitis in infants
  - Eg. Maternal alcohol consumption, Cesarean section  Risk
  - Maternal infection within 3 months prior to delivery  Risk
- Literature review :
  - 1 report of clinical cases USA
  - 1 study each in Nepal, Mongolia, South Africa
  - PREVENT study
  - 1 study in Houston
  - Ongoing epidemiologic evaluations in context of vaccine trials

Maternal Effects of RSV Infection during Pregnancy

Wheeler, et al. Em Infect Dis, Nov 2015 – Duke – Winter 2014

	Case 1	Case 2	Case 3
Age, GA at Dx	26 yr / 33 wk G1	27 yr / 34 wk G2P0	21 yr / 32 wk G1
Infection	RSV	RSV and H1N1	RSV and GAStrep
Diagnostic tool	PCR - BAL	PCR – NP aspirate	PCR – NP aspirate
Disease	Bronchitis Pneumonia-VAP	Pneumonia	Pharyngitis
Complications	**Mechanical Vent 6 d** **C-section delivery at 34 weeks** b/c LRTI. **Hospitalization 14 d**	**Preterm labor and delivery at 34 weeks** **Mechanical Vent 1 d**	None Outpatient treatment Delivery at 39 weeks
Symptoms	5 d malaise, cough, wheezing,1 d fever	5 d cough, congestion 3 d fever, chills	3 d sore throat, congestion, fever
Treatment	Broad Atbx	Broad Atbx, steroids	Penicillin
Underlying cond.	Asthma Smoker	Asthma Smoker	Mild aortic coarctation Cognitive delay
Exposures	Young child URI	-	-

RSV infection in pregnancy: Clinical presentation and birth outcomes in Nepal. - Chu et al. PLOS one March 2016

- Prospective, randomized **trial of influenza** immunization in pregnancy in rural Nepal, 2011-2014
- Enrollment and immunization in 2nd trimester (~ 17 weeks of gestation)
- Weekly home-based surveillance for ***febrile*** **respiratory illness in mothers** from enrollment until 180 days post-partum
- Mid nasal swabs during illness tested for RSV by PCR
- **Maternal illness = Fever** (> 38^{o}C) *plus* at least one of cough, myalgia, sore throat, rhinorrhea
- Infant illness = any of – fever, cough, wheeze, difficult or rapid breathing, draining ear.

RSV infection in pregnancy: Clinical presentation at birth outcomes in Nepal. Chu et al. PLOS one March 2016

Outcome	Description
Incidence RSV	**14 (0.4%) RSV positive febrile illness episodes** in 3693 women over 3554 person-years of surveillance **3.9/1000 person-years overall** 11.8/1000 person-years between September and December
Morbidity	**7/14 (50%) women sought medical care** Median 2 (total 4) days of fever, myalgia, cough, rhinorrhea, sore throat No deaths
Pregnancy effects	**7/14 (50%) infected during pregnancy** All live births – median BW 3060 g [vs. 2790 g in women w/o RSV] **2 (29%) preterm births 34 and 36 weeks** [vs. 469 (13%) in women w/o RSV]
Post-partum effects	**7/14 (50%) infected post-partum** RSV was detected in 4 (47%) of their infants
Exposures	No difference in number of children in household, indoor cook stove or smoking between RSV pos and RSV Neg
Conclusion	**RSV is uncommon cause of febrile respiratory illness in mothers during pregnancy and post-partum in Nepal**

Burden of RSV in Pregnant Women – Mongolia

Chaw L, et al. PLOS One. Feb 2016

Outcome	Description
Study design	Prospective, observational, open cohort of 1260 unvaccinated pregnant women and their infants, 2013-2015 **ILI and severe ARI** identified by bi-weekly call Flu and RSV point of care test
Maternal Incidence rate	ILI – 174 episodes in 160 PW or 11.8/1000 person days Severe ARI – 0.1 (0.0 – 0.4)/ 1000 person days Among 165 ILI cases tested: - 26 (15.8%) = influenza A (1.7 [1.5-1.9]/1000 person days) - 2 (1.2%) = influenza B (0.1 [0.1-0.2]/1000 person days) - **4 (2.4%) = RSV (0.3 [0.2-0.4]/1000 person days)** - 2 women tested pos for both flu and RSV from separate ILI episodes in 2014/15
Illness	Testing within 5 days of onset Mean interval to resolution 8.1 days (3-20) No deaths

RSV in Pregnant and Post-partum Women South Africa. Madhi et al. Burden of RSV in SA HIV+/HIV- pregnant women. CID, 2018

- 2011-2012 **study of influenza vaccine efficacy in pregnant women**
- 1060 and 1056 HIV Neg; 194 HIV Pos
- **Incidence of RSV illness:**
  - **HIV Neg 1.2 – 4.0 per 1000 person-months**
  - **HIV Pos: 3.4 per 1000**
- Maternal RSV infection was associated with respiratory symptoms including cough (72.1%), rhinorrhea (39.5%), sore throat (37.2%), and headache (42%), but fever was absent.
- RSV infection during pregnancy was **not associated with adverse pregnancy outcomes**.
- Postpartum, RSV infection in mothers was associated with **concurrent infection** among 51.9% of **their infants** and, conversely, 29.8% of mothers investigated within 7 days of their infants having an RSV illness also tested positive for RSV.

RSV In Pregnancy – PREVENT* Study Regan A, et al. RSV hospitalization in PW in four high income countries. CID May 2018

- 2010-2016 **Hospitalizations** for Acute Respiratory or Febrile Illness (ARFI) AND PCR testing for RSV
- Total population: **1,604,2016 pregnant women in US, Canada, Israel, Australia**

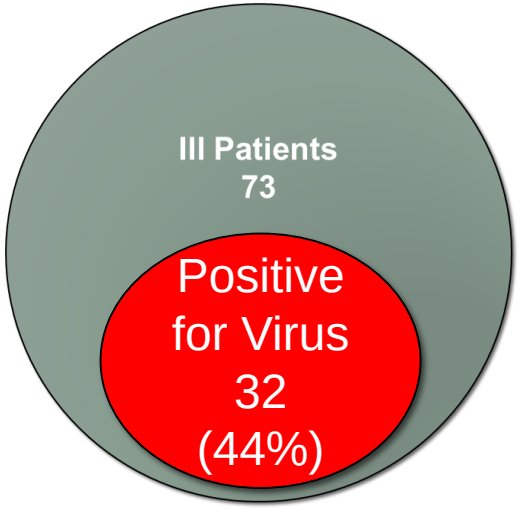
RESULTS

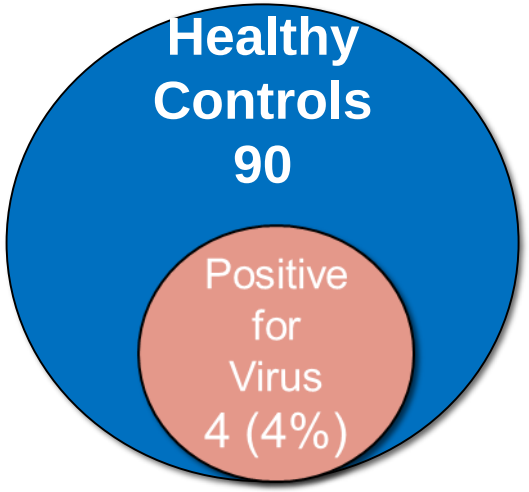
- **(0.9%)**15,287 **≥ 1 ARFI related hospitalization**
- **Only 6%** (846/13,694 unique admissions for ARFI) **were tested for RSV**
- **2.5 % (21) POS for RSV (range: 1.9 – 3.1%); positivity by year: 0 to 4% (2013-14)**
- 51% pos for influenza; < 1% pos for both RSV and influenza
- **63% tests and 67% detections in the 3rd trimester of pregnancy**
- **38% women had pre-existing health condition (**19% was asthma)
- **Pneumonia was more common in RSV POS vs. neg women** (38% vs. 19%, P=0.046)
- **48% of RSV POS women were admitted for ≥ 3 days**
- No difference in preterm, SGA, and LBW births between RSV-pos and RSV-neg women.
- Among ARFI admissions where no delivery occurred, **there was association between RSV-positivity and subsequent preterm birth** (RSV-pos: 29% and RSV-neg: 15%; P=0.034).

*Pregnancy Influenza Vaccine Effectiveness Network (CDC-Abt:)

RSV Pregnancy Houston. Hause A. ARI among Pregnant Women. JID May 2018

- Aim: Incidence and impact of RSV infection in pregnant women
- 2015-16 season (October – April)
- Cross sectional cohort of pregnant women receiving routine prenatal care at private OB practice
- Enrolled when healthy or ill
- Mid turbinate nasal swab for PCR viral diagnosis
- Symptom history and follow up for outcomes 2 weeks after enrolment if ill
- **RSV identified by PCR in 10% of women, and attributed cause of ARI in 14% of women (PCR + serology)**





RSV Positive Patients

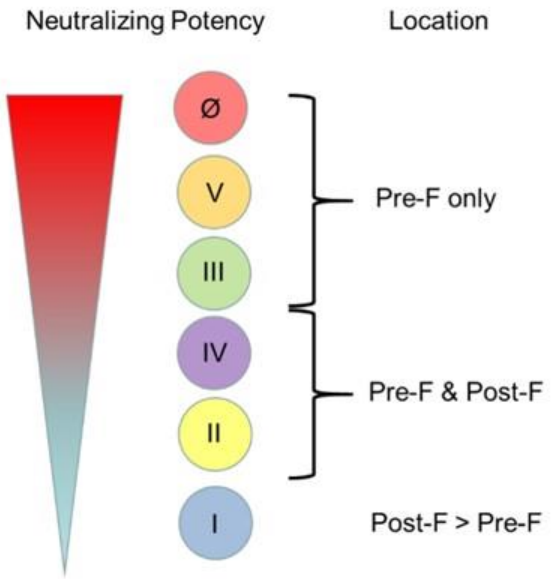
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Date of Enrollment	Nov. 10	Nov. 16	Nov. 25	Dec. 12	Dec. 22	Mar. 31
Maternal Age	26 years	28 years	33 years	31 years	37 years	28 years
Gestational Age	39 weeks	24 weeks	37 weeks	15 weeks	26 weeks	34 weeks
Days Post-Onset	2 days	1 day	5 days	1 day	25 days	8 days
Symptoms	Congestion Sneezing Cough	Congestion Sore throat Cough	Congestion Sore throat Cough	↓ Activity ↓ Appetite Sore throat	Fever ↓ Activity ↓ Appetite Congestion Sore throat Cough Chest pain Short of breath Wheezing	Congestion Sore Throat Cough Short of breath
Duration of Illness	11 days	7 days	18 days	9 days	30 days	34 days

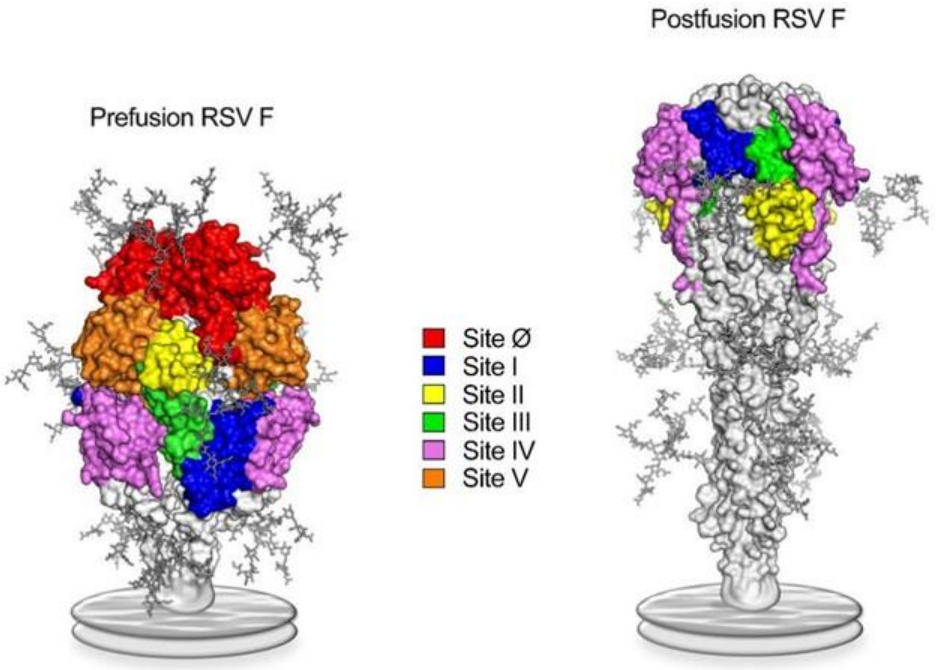
RSV Vaccine for Maternal Immunization

- Which vaccine?
- Which antibodies?
- How much antibody is necessary to protect infants?
- What should outcomes in infants be?
- How is severe RSV defined? LRTI? Hypoxemia? Hospitalization? Death?
- How long will protection last?
- Role of breastmilk antibodies?
- What is acceptable safety/risk in mothers and infants?
- Risk for enhanced disease?
- Why maternal vaccination over infant vaccination or passive antibodies?
- What is the role of MI in the overall strategy of infant disease prevention?

MI: Which vaccine and which antibody?

- Non-live vaccine with or without adjuvants – one dose in 2-3rd trimester gest.
- F-Protein – Conformation dependent immunogenicity and structure based vaccine design
- Neutralizing antibodies, palivizumab competing antibodies (PCA), IgG – IgA
- Preserving neutralization-sensitive epitopes on functional form of F-protein essential for vaccine antigen design

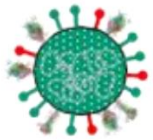




RSV Vaccines in Development

Historical

Recombinant or chimeric viruses



WT or attenuated virus

Whole-inactivated virus

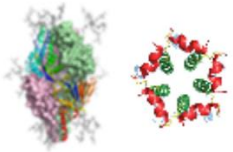
Postfusion F or G subunit

Eg: Lederle – Wyeth Connaught – Sanofi vaccines

Subunit F (F+G+M, FG, F+G) and G (BBG2Na) given to adults and children with pre-existing immunity (2-3 fold rise in NT; >10-20 fold rise in ELISA titers)

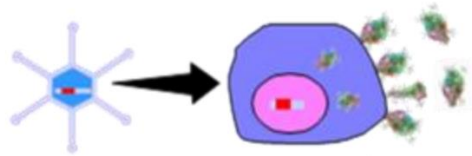
New

Prefusion F subunit or SH pentamer



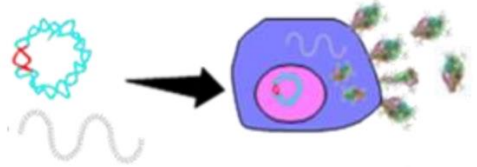
Eg: GSK/NIH/Pfizer
Eg: Novavax vaccine (pre-post-fusion epitopes)

Vectors



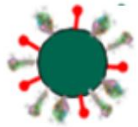
Eg: GSK/Janssen vaccine (adenovirus vector)

Naked DNA or mRNA

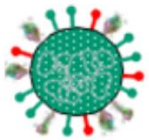


Eg: Moderna vaccine

VLPs or virosomes



Genetically modified and recombinant chimeric viruses



Source: B. Graham lecture ADVAC

MI: How much antibody?

RSV Antibody Titer		Assay Method	Article
No RSV disease	RSV disease		
652.6	198.1	Membrane Fluores-cent Antibody Test	Ogilvie, J Med Vir 1981 7:263 Maternal Ab & RSV
92	9.5	Neutralizing Ab	Glezen, J Ped 1981 98:708
40.00	11.08	MFAT	Roca, J Med Vir 2002 67:616 IgG Mozambique
44.16	11.37	Neutralizing Ab	
238.9	68.6	Neutralizing Ab	Piedra, Vaccine 2003 21:3479 Correlates of imm
538.0	392.1	Neutralizing Ab	Eick, Ped Inf Dis J 2008 27:207 Native Americans
1047	646	ELISA	Ochola, PLOS One 2009 4:e8088 Infants in Kenya

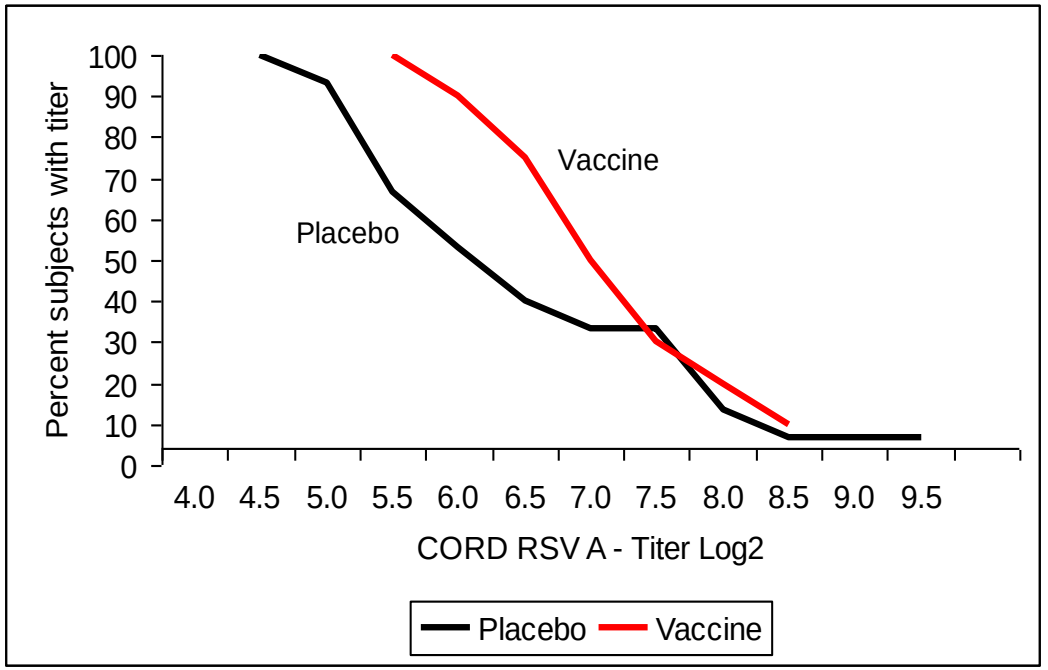
Fold-increase	Log2	reciprocal NT titer	~months of protection
32	13	8,000	7
16	12	4,000	6
8	11	2,000	5
4	10	1,000	4
2	9	500	3
1	8	250	2
0	7	125	1

Source: B. Graham lecture ADVAC

A 2- to 4-fold lower concentration of RSV-specific antibody titers is seen in infants with RSV disease compared to infants with no disease.

PFP-2 Subunit RSV Vaccine in Pregnant Women

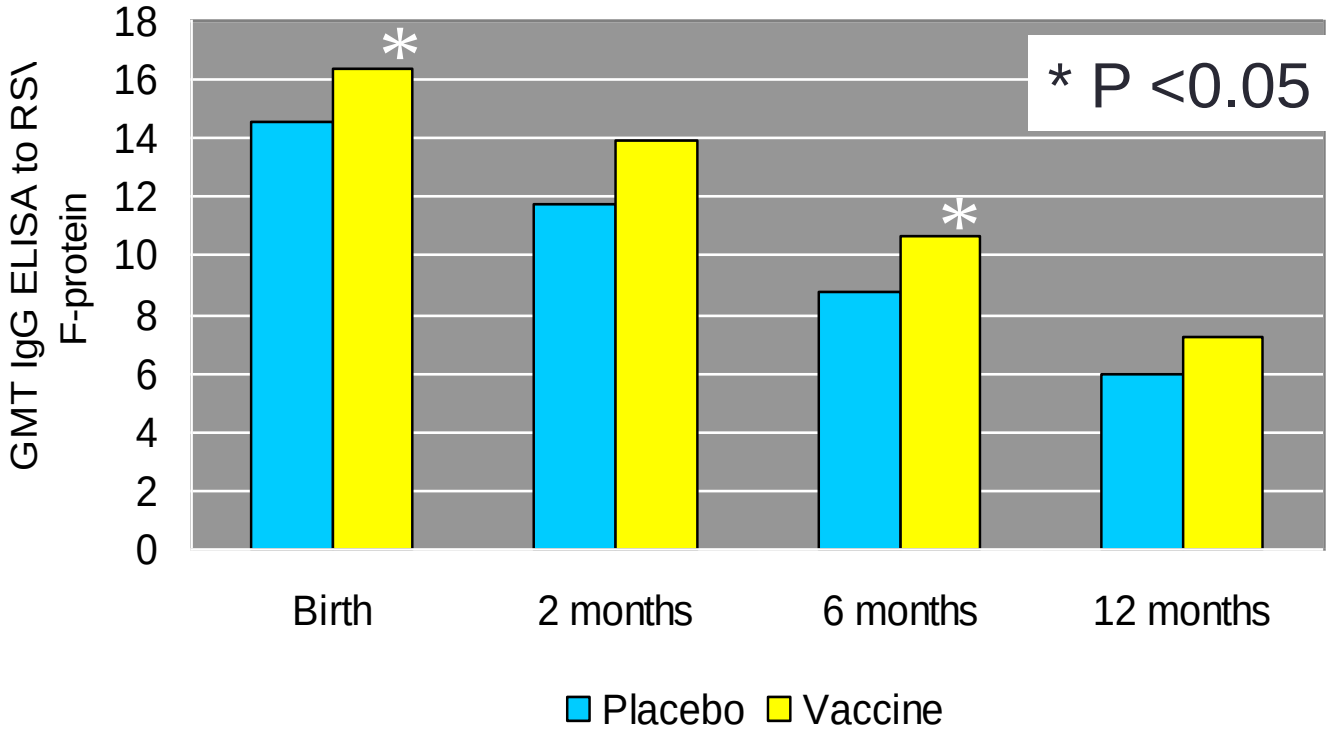
- 1999-2002, Houston, US
- 35 healthy women, 30-34 wk GA
- Vaccine was safe, well tolerated
- Vaccine response in mothers:
  - **95% with 4x-rise anti-F IgG ELISA** vs. 6.6% placebo
  - **Only 10% with 4x rise in Neut Ab**
  - 75% by WB vs. 0 placebo
- Women with low antibody concentrations rose to higher, potentially protective levels (6.0 Log2)



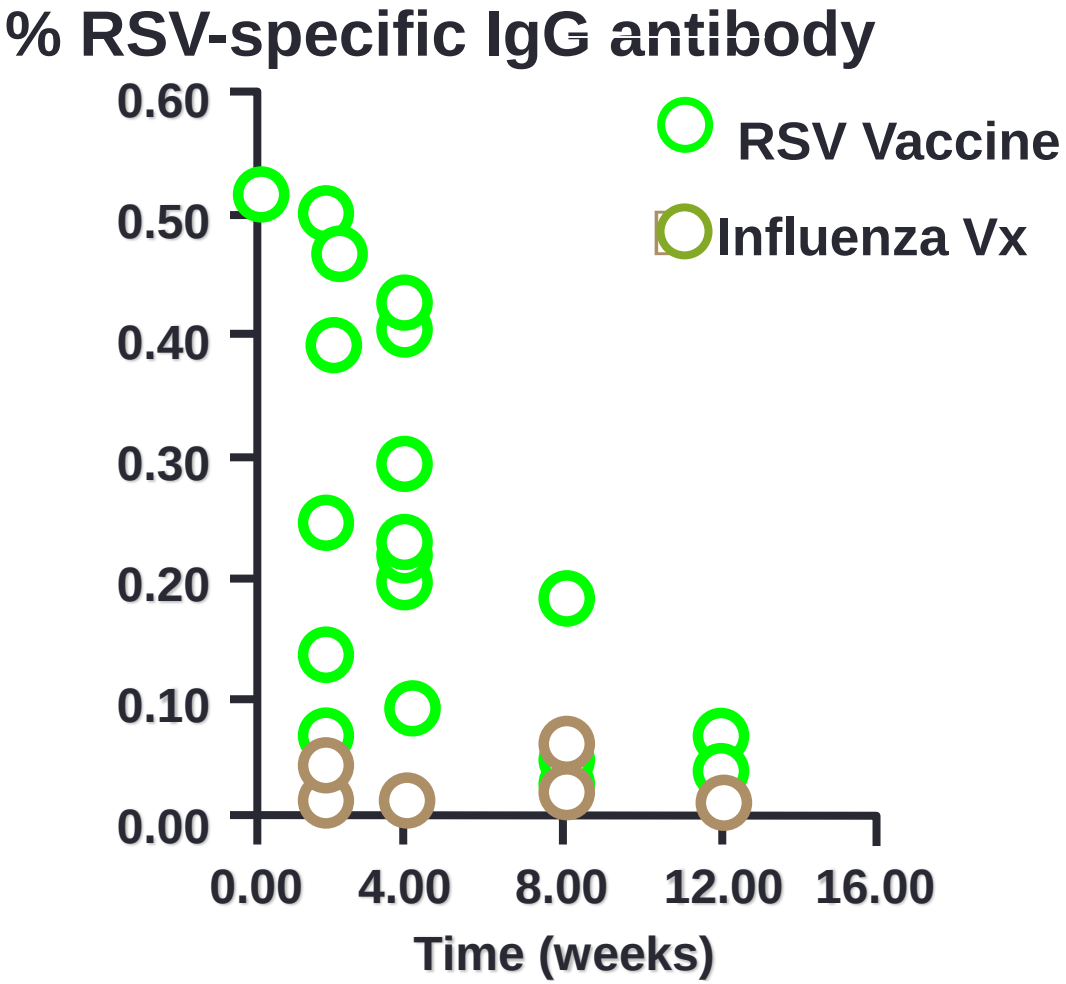
- Efficient transplacental passage of IgG antibodies (>100%)
- Infant antibody higher than controls up to 6 months of age (half life 30-40 days)
- **Ab in breast milk: Anti-F IgG and IgA** > placebo at 2 and 6 months
- **RSV infection** in 2 infants of vaccine recipients and 4 placebo recipients (culture or serology). **No enhanced infant RSV disease.**

Munoz, Piedra, Glezen. Vaccine 2003;21:3465

Serum and Breast milk IgG following RSV PFP-2 in Pregnant or Postpartum women



*Munoz, et al. Vaccine 2003

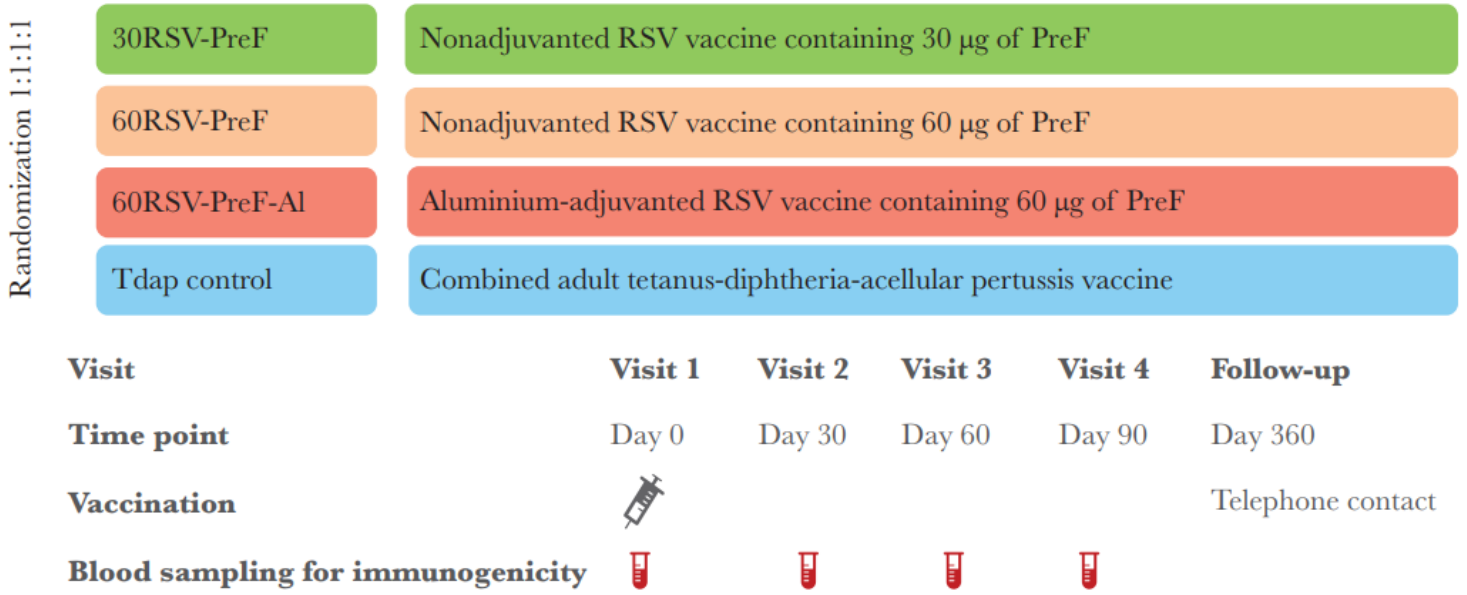


Glezen, WP, Vaccine 2003

Phase 2 clinical trial of investigational Pre-F RSV vaccine in non-pregnant women

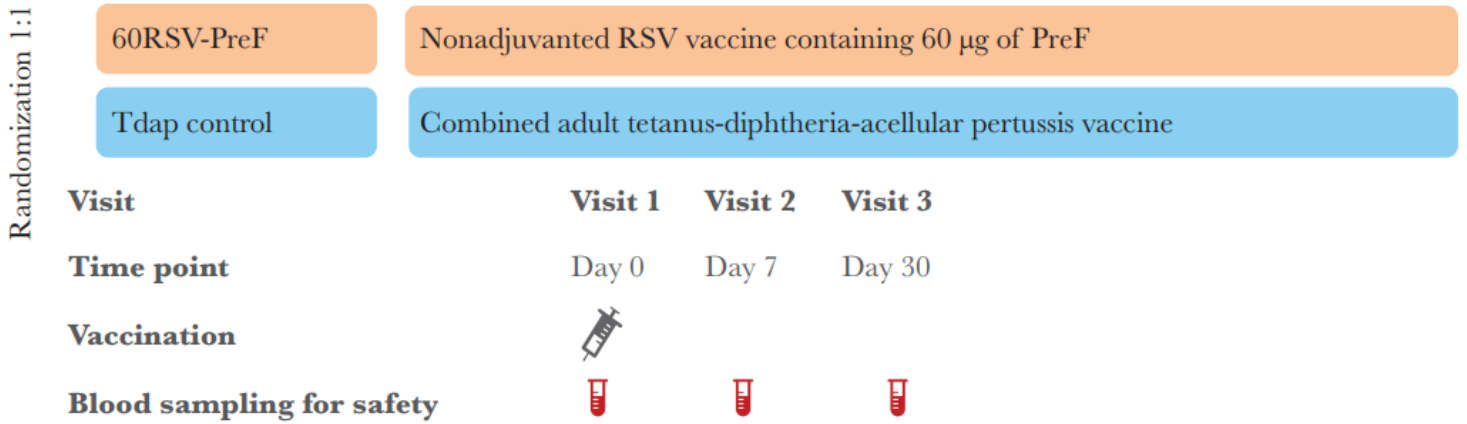
Australia
US
Czech Republic
Germany
N= 500

RSV F-020



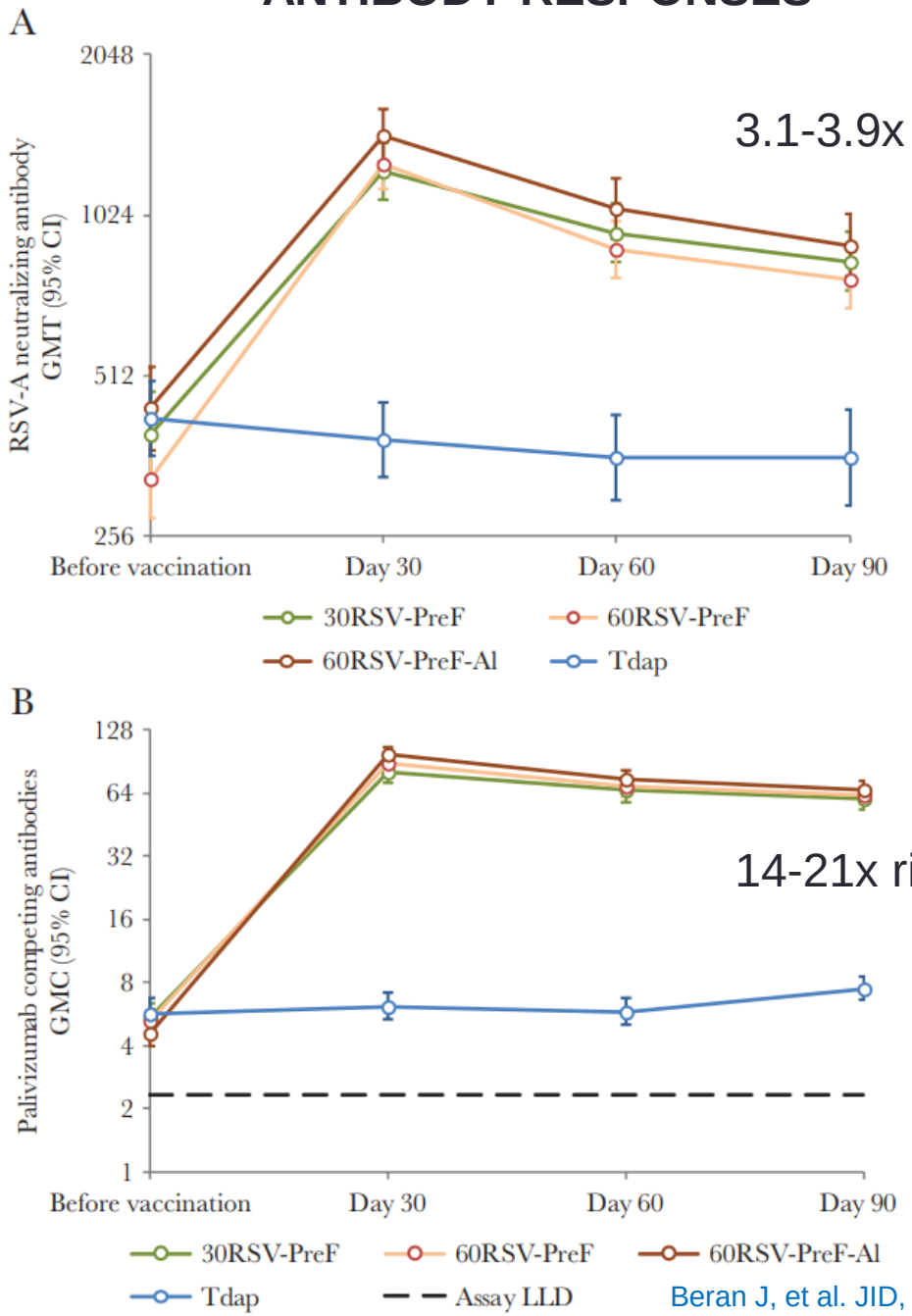
Belgium
N=100

RSV F-024

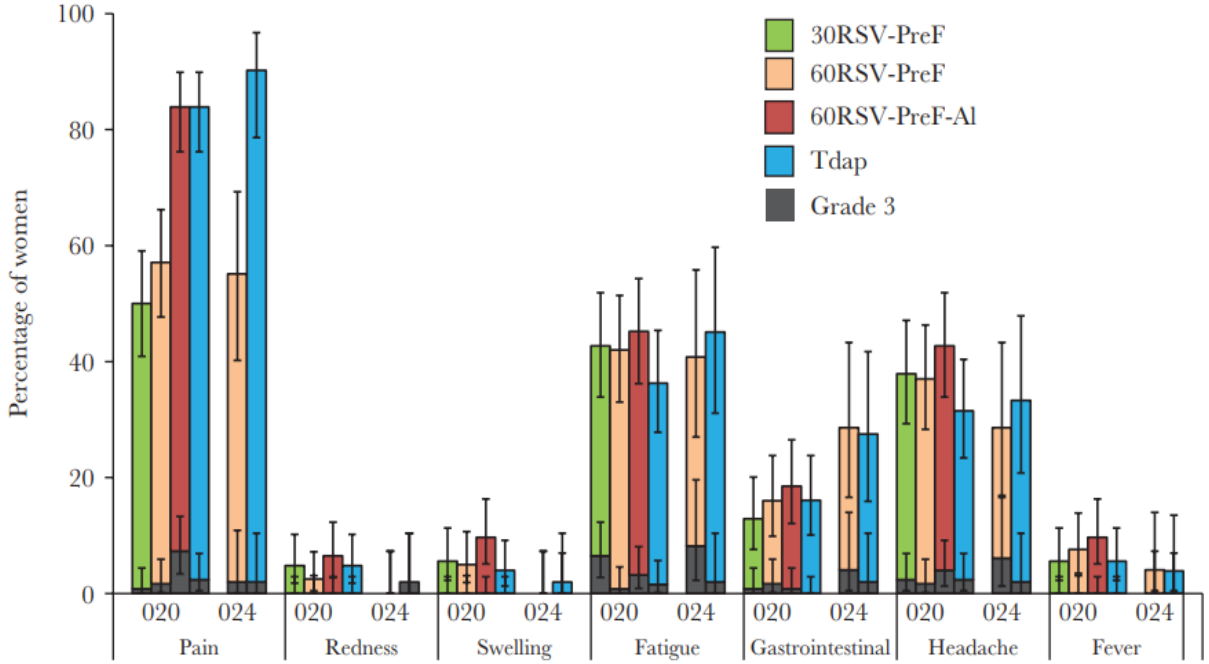


Beran J, et al. JID, May, 2018; GSK Investigational vaccines: Purified Recombinant F-protein, prefusion, prepared in Chinese Hamster Ovary cells

ANTIBODY RESPONSES



REACTOGENICITY



- All formulations of RSV-PreF boosted preexisting immune responses in 18–45-year old women with comparable immunogenicity.
- The RSV-PreF safety profile was similar to that of Tdap vaccine.

Beran J, et al. JID, May, 2018; GSK Investigational vaccines: Purified Recombinant F-protein, prefusion, prepared in CHO cells

RSV F-nanoparticle aluminum adjuvanted vaccine protects women of childbearing age

Vaccine 35 (2017) 3749–3759

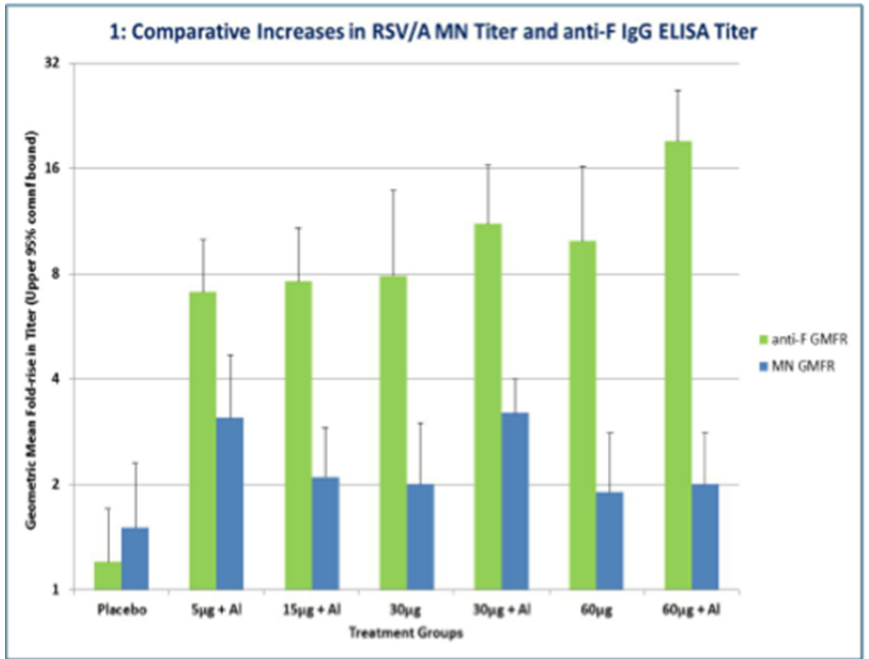
Contents lists available at ScienceDirect

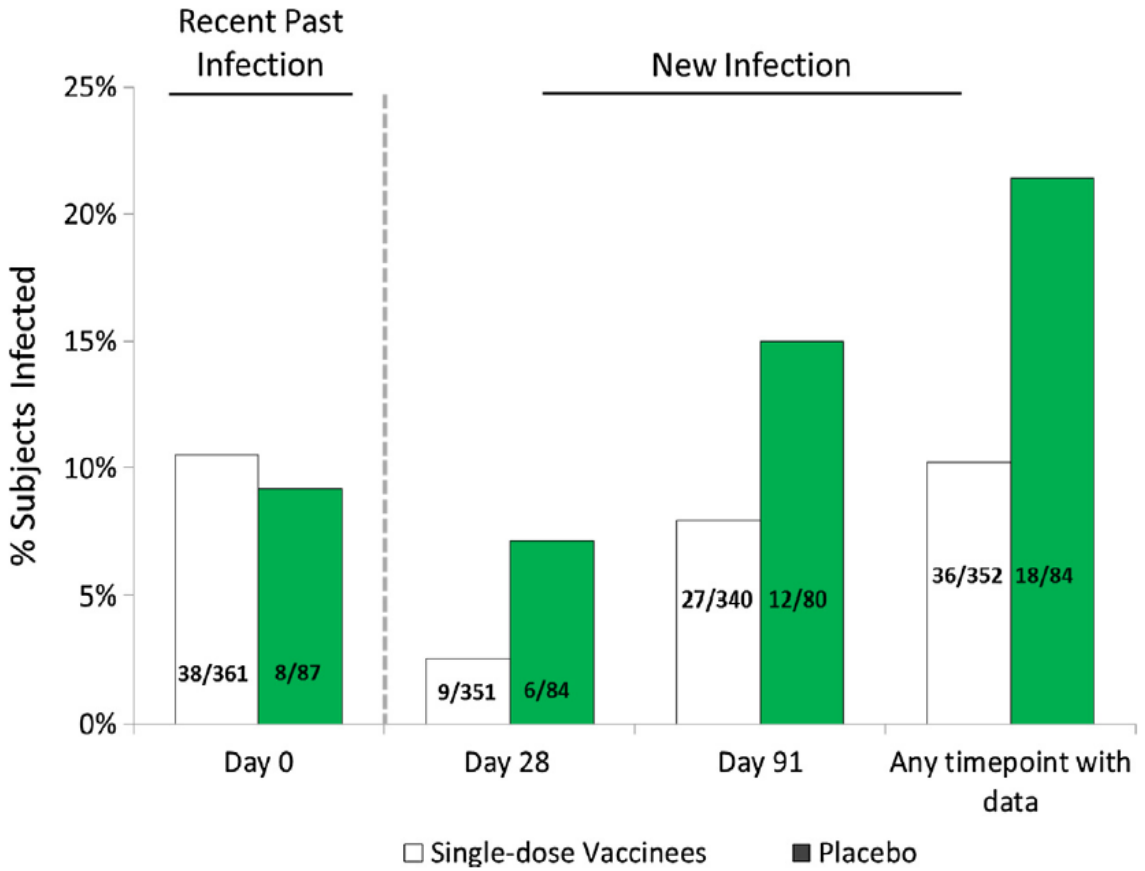
Vaccine

journal homepage: www.elsevier.com/locate/vaccine

A Phase 2 randomized, observer-blind, placebo-controlled, dose-ranging trial of aluminum-adjuvanted respiratory syncytial virus F particle vaccine formulations in healthy women of childbearing age

Allison August[a], Gregory M. Glenn[a], Eloi Kpamegan[a], Somia P. Hickman[a], Dewal Jani[a], Hanxin Lu[a], D. Nigel Thomas[a], Judy Wen[a], Pedro A. Piedra[b], Louis F. Fries[a,*]

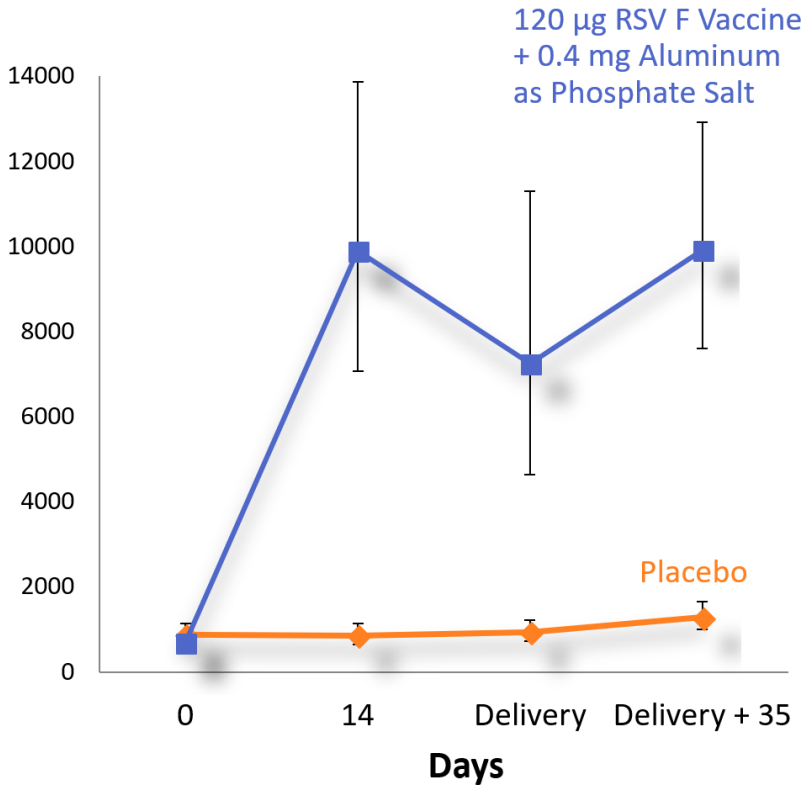




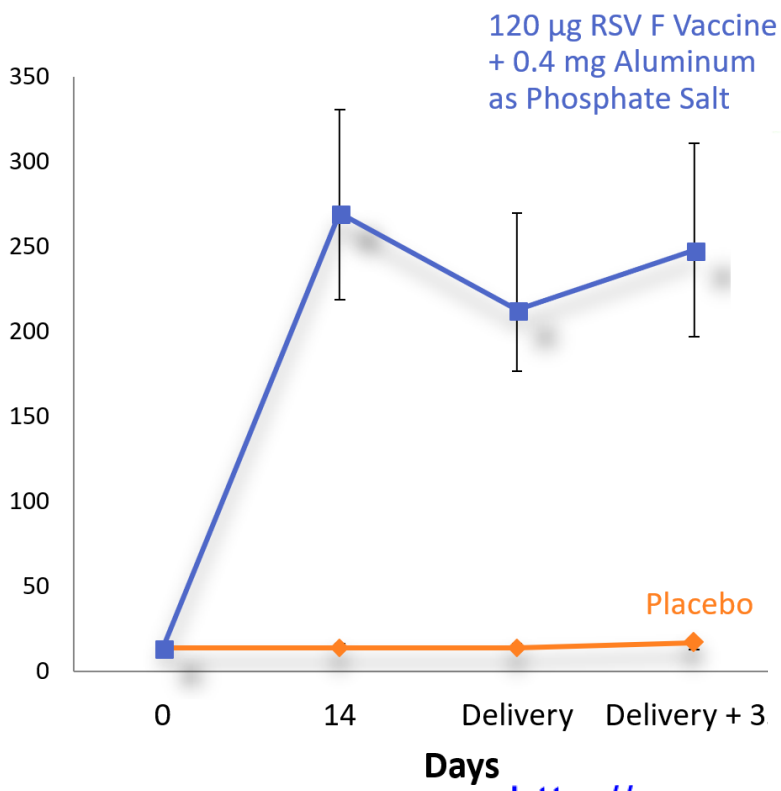
Serological determination of RSV infection before and after RSV season

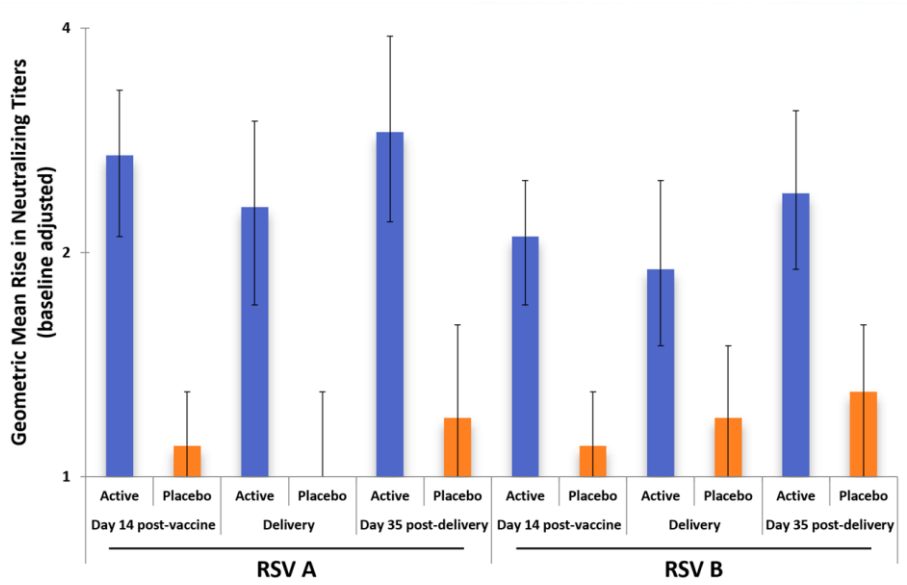
RSF F-nanoparticle vaccine in Pregnant Women Phase 2 study

Phase 2 - Antibody response in maternal participants
Anti-F IgG GMEU (95% CI)



Phase 2 – PCA response in maternal participants
PCA GMC (µg/mL)





http://novavax.com/presentation.show (accessed April 2018)

RSV F-nanoparticle vaccine in Pregnant Women Phase 2 study

›2 Infants: Time from Vaccination to Delivery (Days) Impacts Placental Antibody Transfer

Assay	Source	Del. < 30d post vacc., n=7*	Del. > 30d post vacc., n=14	All n=21*
Anti F IgG	Cord	7,227	8,659	8,153
	Mothers	12,979	6,993	8,594
	Ratio	**0.6**	**1.2**	**0.9**
PCA	Cord	177	195	189
	Mothers	303	178	213
	Ratio	**0.6**	**1.1**	**0.9**
RSV/A	Cord	928	672	748
	Mothers	1,448	580	786
	Ratio	**0.6**	**1.2**	**1.0**
RSV/B	Cord	565	512	529
	Mothers	724	410	495
	Ratio	**0.8**	**1.2**	**1.1**

GA = gestational age
Ad hoc analysis
*Excludes 1 mother/infant pair with delivery 5 days post-immunization, late pre-term delivery

Important Findings:

- Maternal antibody peaks 14d after vaccination
- Period of placental transfer >30 days maximizes antibody titer in infants
- P3 recruitment window opened to 31 weeks to maximize antibody transfer

*http://novavax.com/download/files/presentations/FIGO_7OCT2015_AA_P2_Data_10_14_15_FINAL(1).pdf

Source: J.Englund-ADVAC course

The RSV F-Nanoparticle Vaccine Phase 3 Trial in Pregnant Women

Primary objective

Determine the **efficacy** of maternal immunization with the RSV F vaccine against **medically significant RSV lower respiratory tract infection (LRTI)** through 90, 120, 150 and 180 days of life in infants.

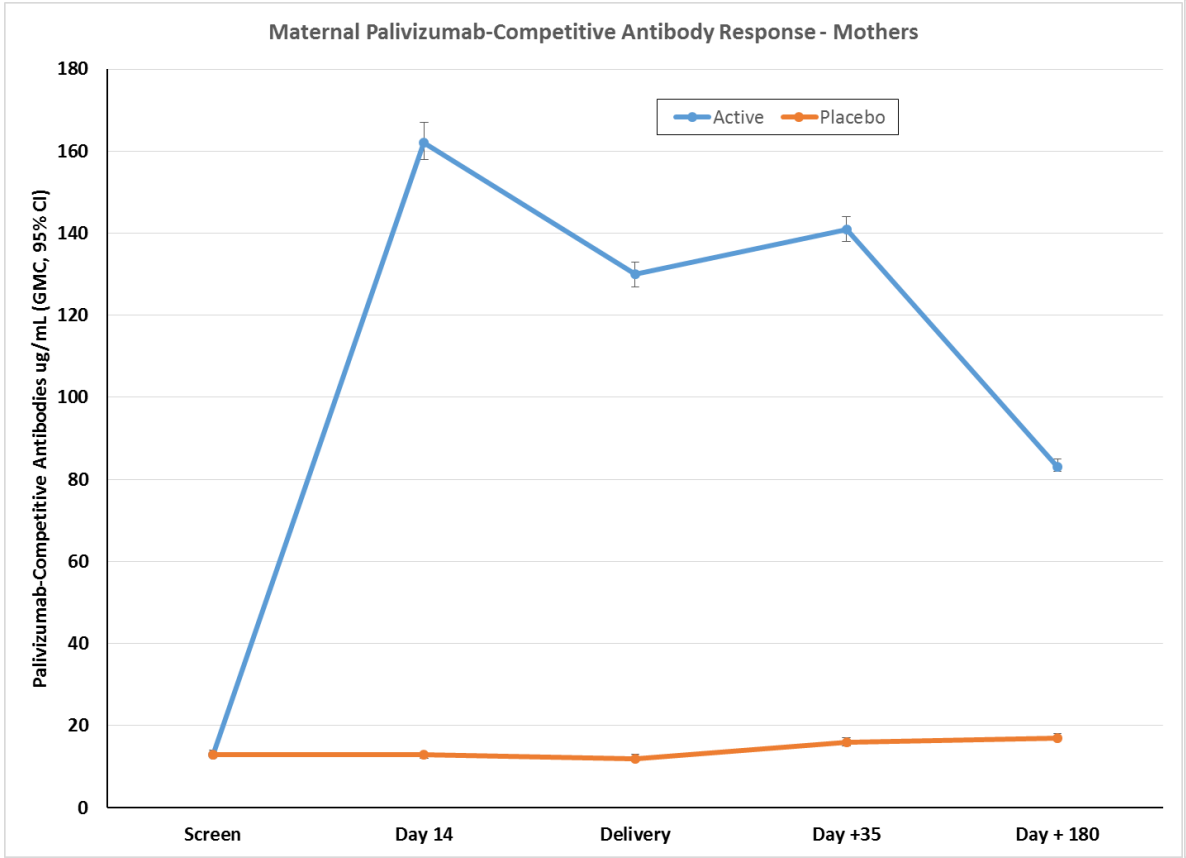
Design

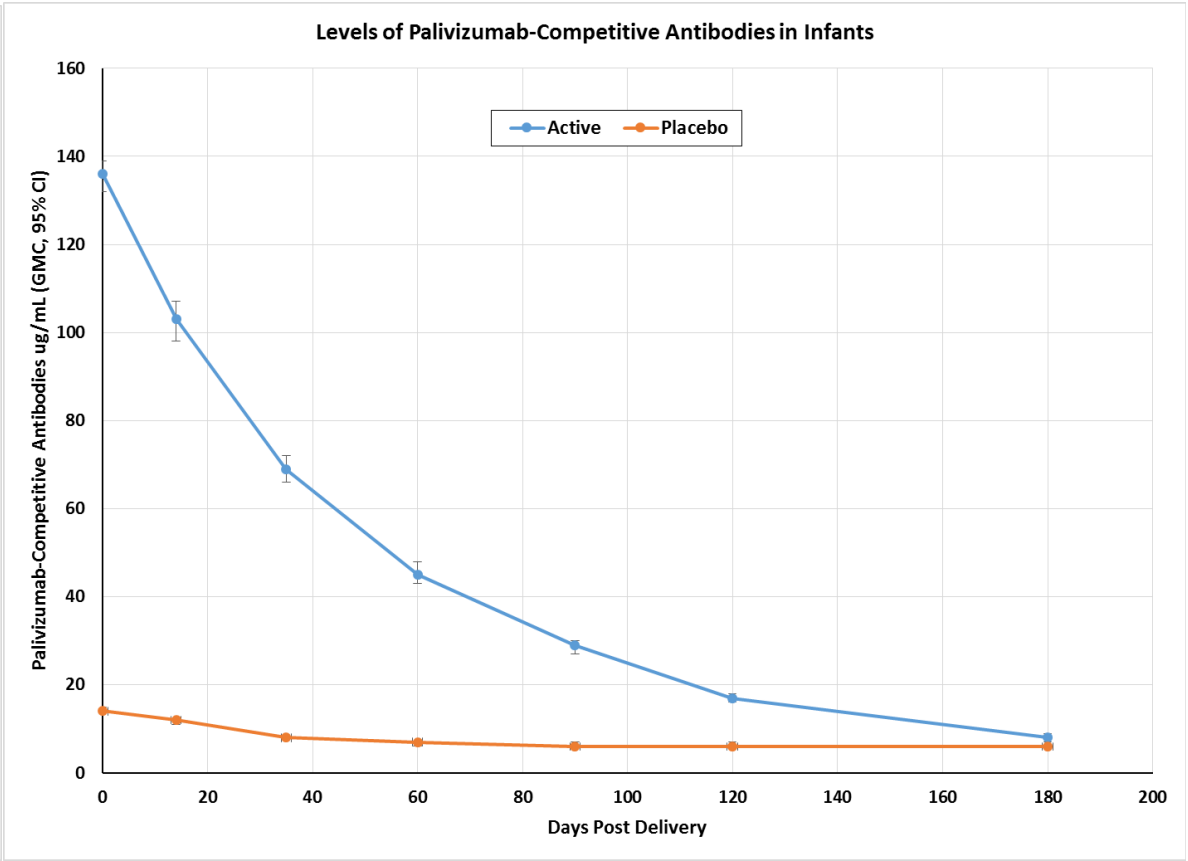
Randomized, Observer-Blind, Placebo-Controlled	
Number of Participants	• **4,636** third trimester pregnant women **randomized 2:1 (vaccine:placebo)** • **87 clinical sites in 11 countries (northern and southern hemisphere)**
Length of Study Participation	• Mothers: up to 9 months • Infants: 1 year after delivery
Dosing	• 1 intramuscular (IM) Injection of RSV F vaccine or placebo at **28-36 weeks** Estimated Gestational Age (EGA)
Safety Assessment	• Through 6 months post-partum in mothers • Through 1 year in infants

Efficacy Assessment	• **Active/passive surveillance in mothers and infants**
	  • Confirmation of RSV infection by RT-PCR
	  • Medically significant tachypnea or pulse oximetry (infants only)
	  • Confirmation of LRTI (infants only)

Pre-post-fusion F-nanoparticle recombinant (baculovirus) vaccine produced in insect cells, adjuvanted with aluminum phosphate

Vaccine Immunogenicity and Transplacental Transfer of Antibodies: Palivizumab-Competitive Antibodies (PCA)

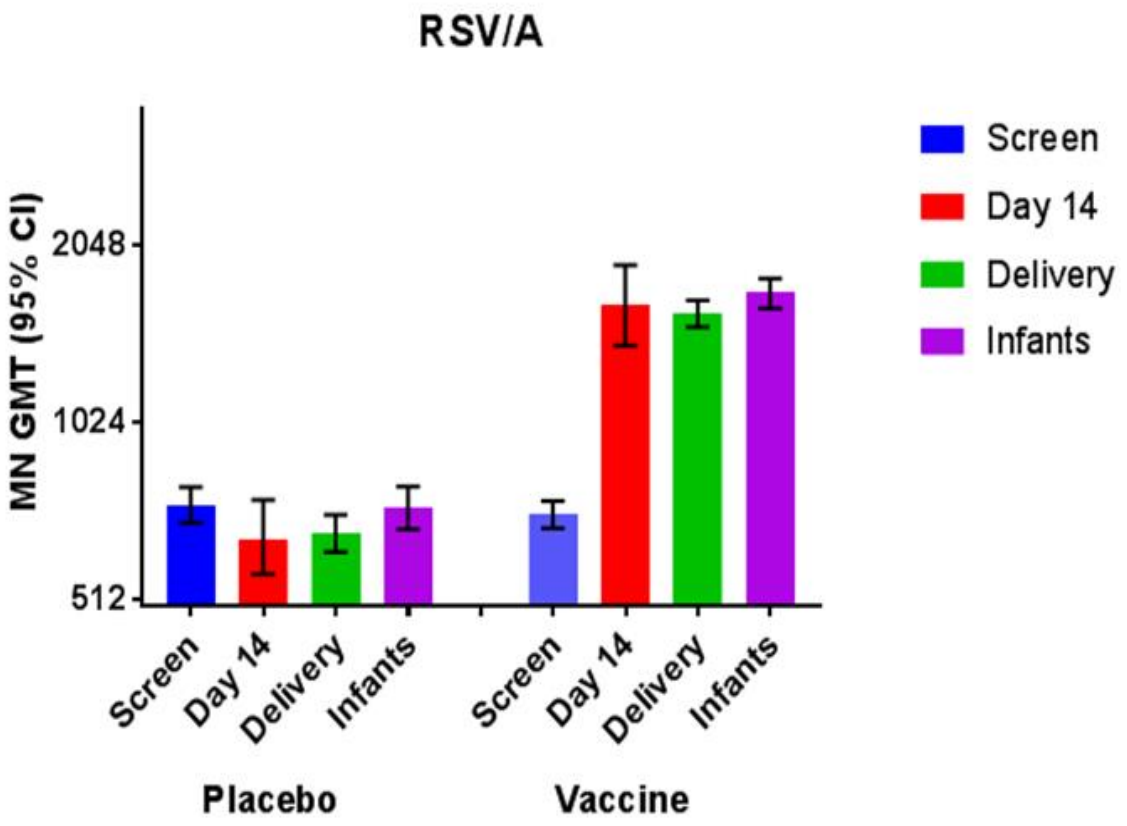


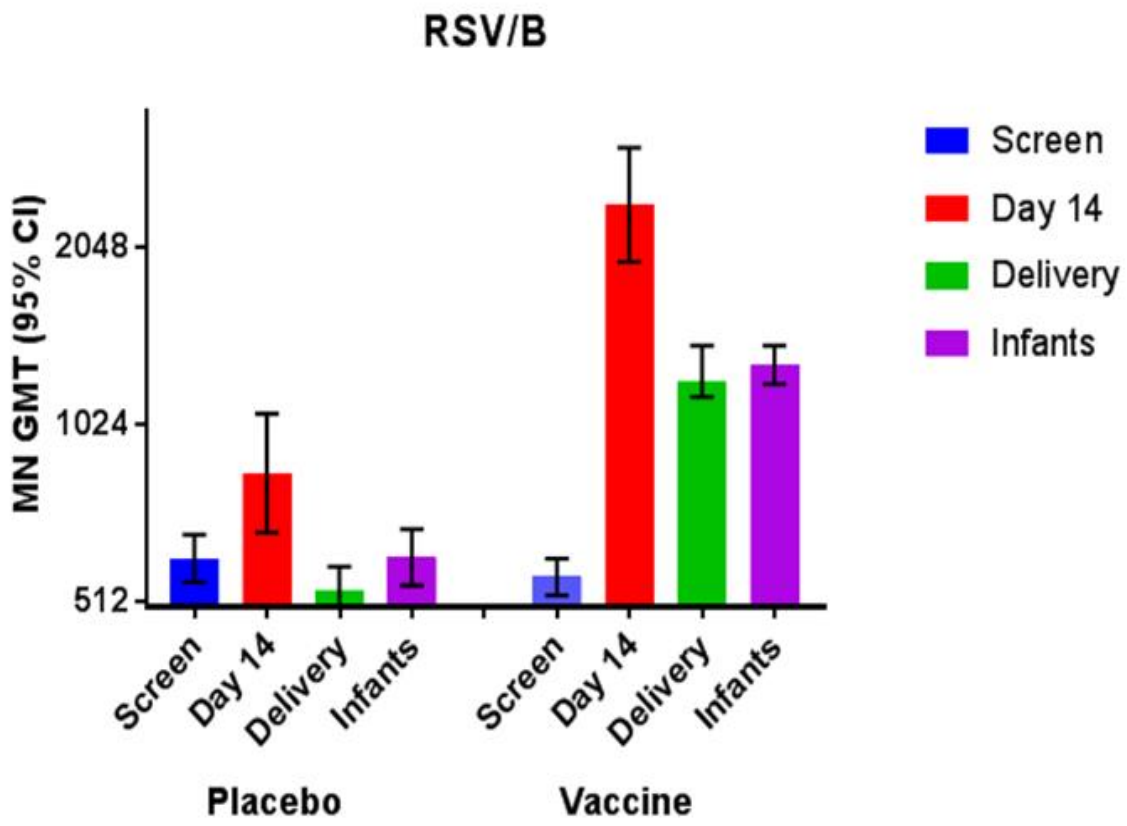


- **Seroresponse rate** in vaccinated mothers = 99.4%, ≥4-fold rise in 88.1%.
- Cord blood serum / maternal delivery serum = 104%; $T_{1/2}$ = 49.1 days
- Anti-F IgG levels behave similarly

Vaccine Immunogenicity and Transplacental Transfer of Antibodies: Neutralizing Antibodies

Microneutralization Responses from Subset of Season 1 and 2 Subjects





Efficacy Endpoints

https://www.whattoexpect.com/first-year/newborn-sleep.aspx

- **Primary endpoint (site only data*)**
  - **Medically-significant RSV LRTI**
    - RSV detected by **RT-PCR** and
    - At least one manifestation of **LRTI**, and
    - At least one of the following:
      - **SpO2 <95% or,**
      - **Tachypnea** (RR ≥70 bpm in infants 0-59 d or ≥60 bpm in infants ≥60 d)
- **Secondary endpoints (site only data*)**
  - RSV LRTI with **hospitalization**
  - RSV LRTI with **severe hypoxemia, SpO2 <92 %**
- **Exploratory efficacy endpoints (data from *sites plus hospitalizations)***
  - **Same as primary and secondary criteria**
  - Referred to as “expanded data”

* Data collected by study personnel using standardized pulse oximeter and method of recording, physical exam by study staff and study PCR only

Summary of Key Efficacy Findings

Efficacy (%) (97.52%CI and 95%CI for MS RSV LRTI primary endpoint at 90 days, all others 95%CI) Placebo, Vaccine cases[3]	Time Interval	MS RSV LRTI	RSV LRTI hospitalizations	RSV LRTI w/ severe hypoxemia
Primary and secondary RSV+ w/ Site data	**0 to 90 days**	**39.4** (-1, 63.7)[1] (5.3, 61.2)[2] 35/1430, 41/2765	**44.4** (19.6, 61.5) 53/1430, 57/2765	**48.3** (-8.2, 75.3) 14/1430, 14/2765
	0 to 180 days	**26.6** (-7.8, 50.1) 43/1430, 61/2765	**40.4** (16.0, 57.7) 59/1430, 68/2765	**42.2** (-10.9, 69.9) 17/1430, 19/2765
Pre-specified exploratory RSV+ w/expanded data	**0 to 90 days**	**40.9** (15.9, 58.5) 56/1430, 64/2765	**41.7** (16.7, 59.2) 55/1430, 62/2765	**59.6** (32.1, 76.0) 32/1430, 25/2765
	0 to 180 days	**26.5** (-0.6, 46.2) 64/1430, 91/2765	**35.6** (10.3, 53.7) 61/1430, 76/2765	**51.2** (21.9, 69.6) 35/1430, 33/2765

1. (97.5% CI); 2. (95.0% CI); 3. Per-protocol population

Efficacy in World Bank High and Low/Middle Income Countries

Endpoint	Location	Placebo (cases / N)	Vaccine (cases / N)	Efficacy	95% CI
Medically Significant RSV LRTI	**All sites**	35/1430	41/2765	**39.4%**	5.3, 61.2
	HIC	12/576	14/1079	**37.7%**	-33.3, 71.8
	LMIC	23/854	27/1686	**40.2%**	-3.1, 65.7
RSV LRTI with severe hypoxemia	**All sites**	14/1430	14/2765	**48.3%**	-8.2, 75.3
	HIC	5/576	5/1079	**46.6%**	-83.6, 84.5
	LMIC	9/854	9/1686	**49.3%**	-27.1, 79.8
RSV LRTI with hospitalization	**All sites**	53/1430	57/2765	**44.4%**	19.6, 61.5
	HIC	11/576	19/1079	**7.8%**	-92.4, 55.8
	LMIC	42/854	38/1686	**54.2%**	-29.5, 70.2

Low/middle income (**LMIC**) = Bangladesh, South Africa, Mexico, and Philippines;
High income countries (HIC) = US, Spain, UK, Argentina, Chile, Australia, New Zealand.
Per-protocol analyses of primary and secondary endpoints

Impact of Immunization Timing on Efficacy

	Gestational Age at Immunization		Interval from Immunization to Delivery	
	<33 weeks	≥33 weeks	14 to <30 days	≥30 days
Transfer of anti-F IgG	**138%** (135, 141)	91% (88, 94)	66% (63, 70)	**127%** (125, 130)
Transfer of PCA	**122%** (119, 124)	83% (81, 86)	63% (60, 66)	**113%** (111, 115)
Transfer of RSV/A MN	**118%** (112, 125)	98% (93, 104)	85% (77, 94)	**114%** (104, 119)
Transfer of RSV/B MN	**117%** (111, 124)	97% (91, 103)	87% (80, 96)	**112%** (107, 117)
Efficacy vs. MS RSV LRTI*	**41.4%** (4.1, 64.2)	40.3% (0.9, 64.0)	11.1% (-118.9, 63.9)	**45.5%** (19.9, 63.0)
Efficacy vs. RSV LRTI w/severe hypoxemia*	**70.2%** (37.6, 85.7)	44.0 (-18.4, 73.5)	-19.7% (-510.8, 76.6)	**65.1%** (38.8, 80.1)
Efficacy vs. RSV LRTI w/hospitalization*	**53.5%** (23.0, 71.9)	26.3% (9-23.1, 55.9)	-43.6% (-339.0, 53.0)	**48.7%** (24.7, 65.1)

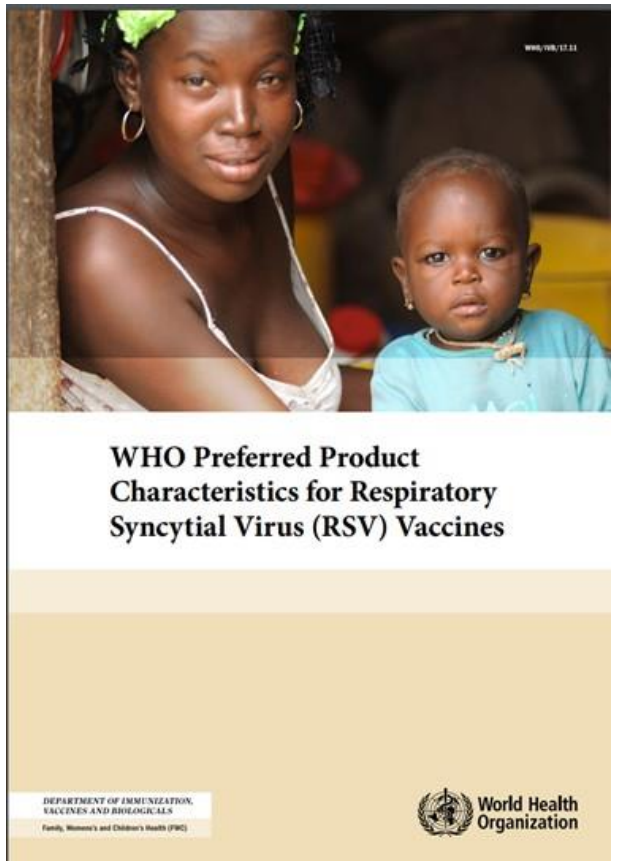
*expanded dataset, 90 day data

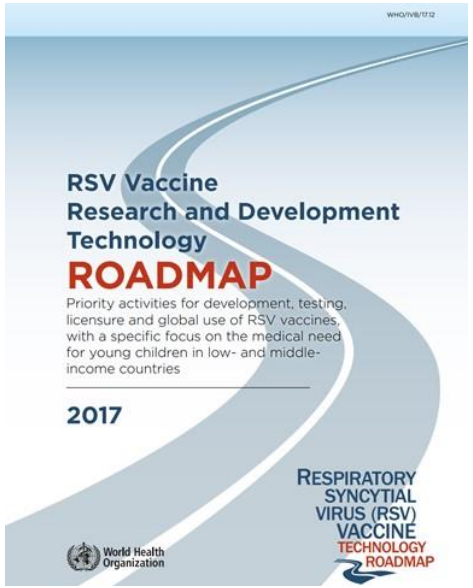
Earlier gestational age at immunization (< 33 weeks) and longer interval between immunization and delivery (≥30 days) enhance transplacental antibody transfer and efficacy

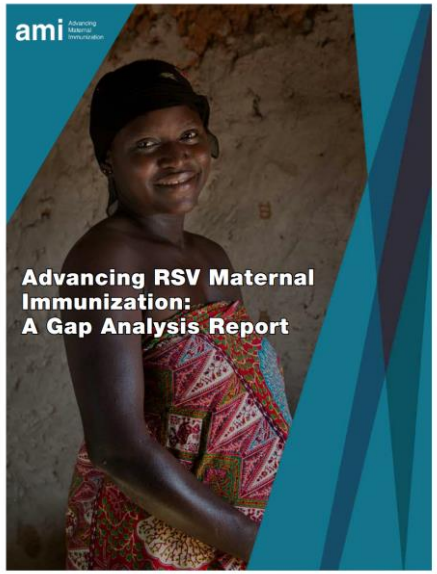
RSV F-Nanoparticle Vaccine Phase 3 RCT – My take

- First phase 3 clinical trial of RSV vaccine in pregnant women (**pregnancy indication**)
- **Global** participation, generating burden of disease and impact data
- Demonstrated the vaccine was **safe** for women and their infants (high standards/GA)
- Was **immunogenic** (neutralizing and PCA antibodies)
- Vaccine-induced antibody **transfer** was efficient favoring infant
- Determined that **gestational age** at immunization (< 33 weeks) and **interval** from vaccination to delivery (>30 days) **impact vaccine efficacy**
- Demonstrated challenges in selection and achievement of **efficacy outcomes**
- Demonstrated population based differences (HIC/US vs. LMIC)
- Showed **efficacy in prevention of severe RSV in most vulnerable period** (0-90 days) **in term infants**, where no alternative prevention strategy exists (40-50% reduction which is substantial given burden of disease)
- Final analyses ongoing – more lessons to be learned – the work continues

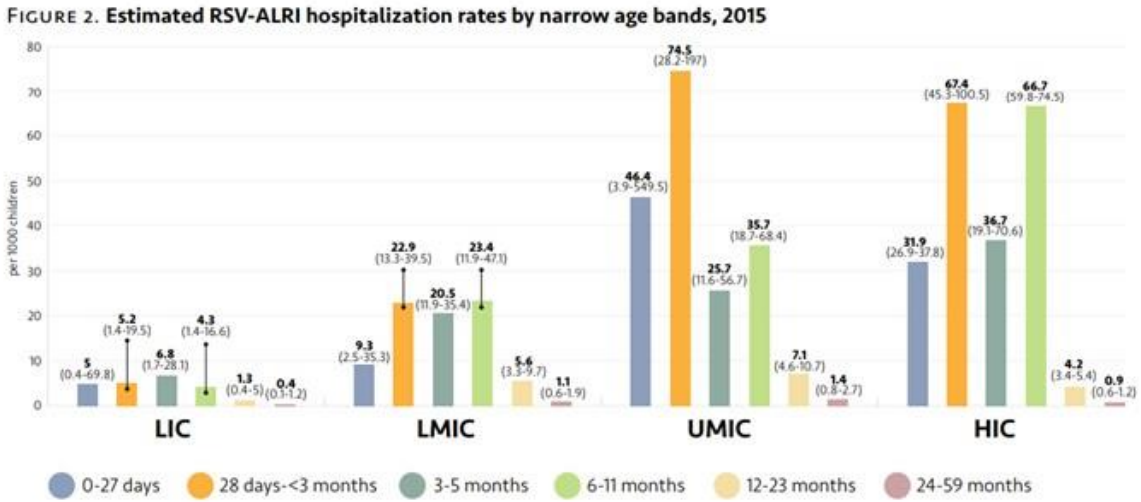
RSV Vaccine Design and Research in Pregnancy

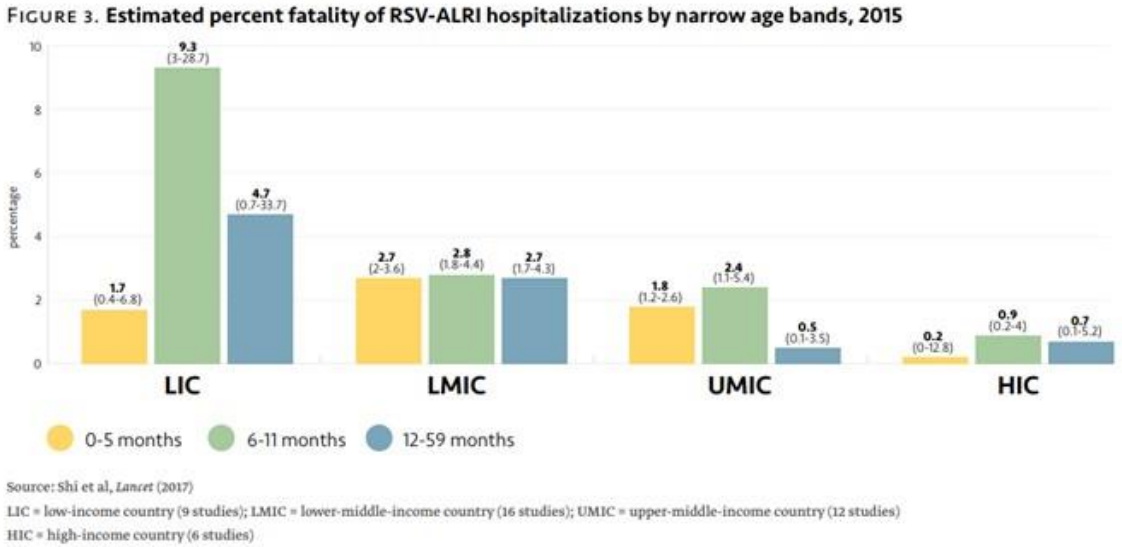






PATH
J. Flemming





Comparison of Deaths from MI-Preventable Diseases

According to GBD 2016 estimates, U5M is 5 million globally, including 2.1 million deaths in neonates. Amongst these, a total of 895,565 deaths were due to **lower respiratory tract infection (LRI) and neonatal sepsis**

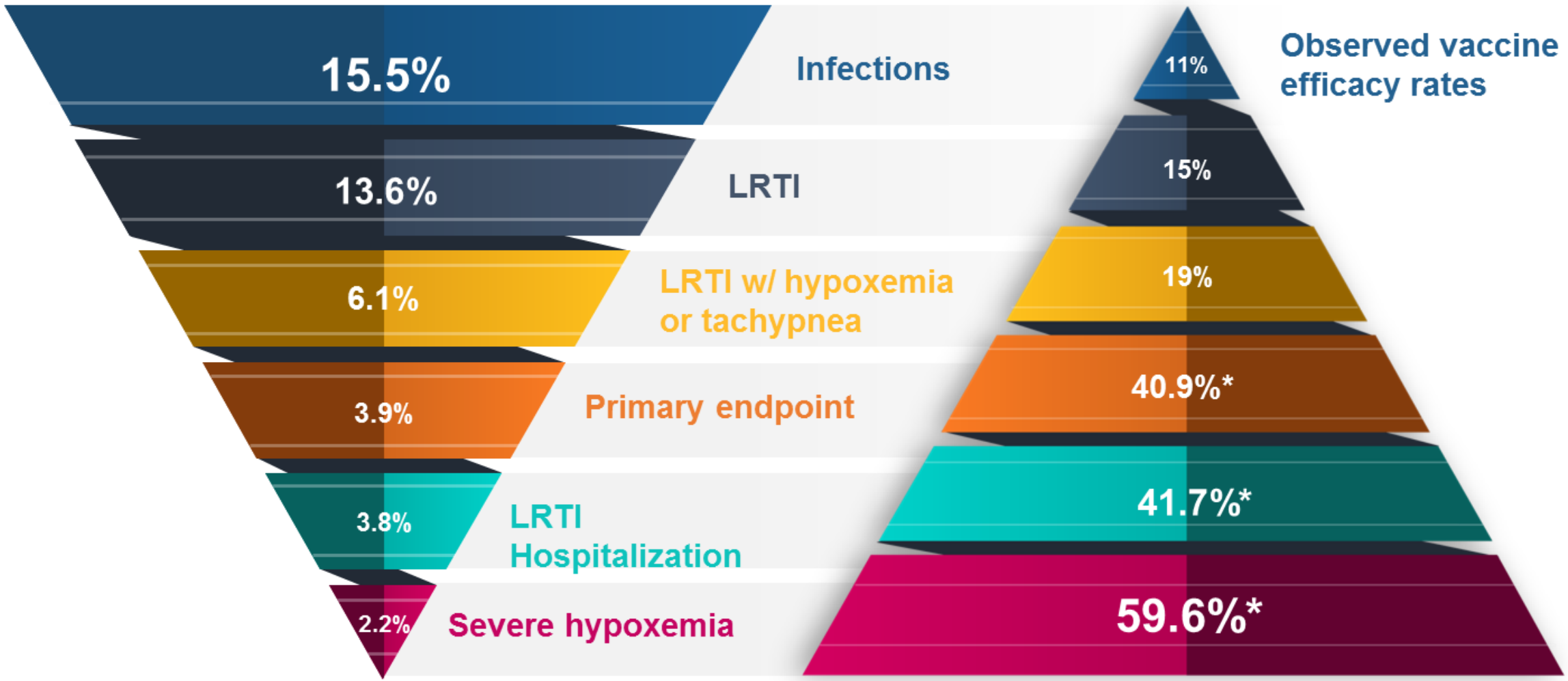
- **LRI** remains the leading cause of mortality in children U5 (**652,572**)
- **Neonatal sepsis** is ranked as the 8th (from 10th previous year) cause of death (**242,992**)

	OUTCOMES PER YEAR		
	Stillbirths	**Neonatal or other deaths related to maternal infection or non-immunity**	**Neonatal or infant cases**
Group B *Streptococcus*	57,000 (12,000- 103,000)	90,000[a] (36,000-169,000)	319,000 (119,000- 417,000)
Respiratory Syncytial Virus	NA	86,000[b] (69,000-109,000)	1.4 million
Syphilis	200,000	62,000[c]	102,000
Tetanus	NA	34,000 (18,000- 84,000)[c]	1,996[cd]

[a] Young infants (0-89 days); [b] Overall <6 months (hospital + community; in-hospital alone, 27,300); [c] Neonates (0-27 days); [d] WHO Joint Reporting Form, 2016; NA not available.

Adapted from Seale A et al. *CID* 2017;65(S2):S200-19.

MI RSV-F Nanoparticle Vaccine
A Hierarchy of Efficacy by Severity of Disease



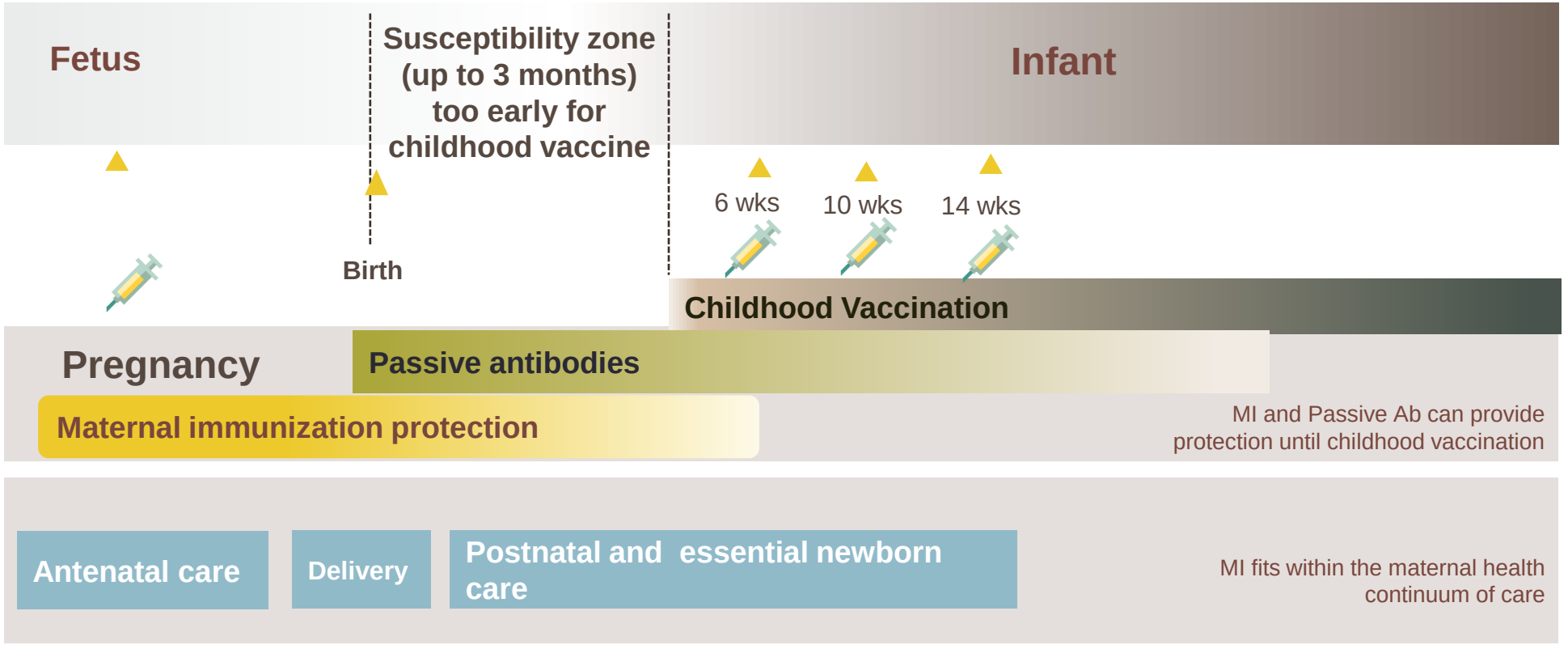
1. Expanded data from sites and hospitalizations, through 90 days, * LB 95%CI >0

RSV Vaccine for Maternal Immunization – Key Lessons

- Understanding the burden and impact of disease
  - Mothers and infants (term, preterm, other comorbidities)
  - HIC and LMIC settings
- Diagnosis and Surveillance of RSV disease
- Safety
  - Vaccine associated adverse events vs Obstetric (background rates)
  - Vaccine enhanced disease upon natural infection under 2 years of age is NOT a significant consideration when vaccine is given to mother
- Efficacy Endpoints (eg. severe LRTI, hospitalization, death)
- Immunologic correlates of protection (may vary by vaccine and outcome)

Nair et al. BMC Public Health 2011, 11(Suppl 3):S30; Poletti *et al. BMC Medicine* (2015) 13:49
Kaaijk et al. Human Vaccines & Immunotherapeutics 9:6, 1263–1267; June 2013

RSV Prevention: Implementation Strategies



1. Maternal + Infant vaccination at 2 – 6 months
2. Passive antibody + Infant vaccination

Maternal Newborn Child Health; Source: Every Newborn: An action plan to end preventable deaths (2013)

Maternal Vaccine vs. Infant Passive Antibodies

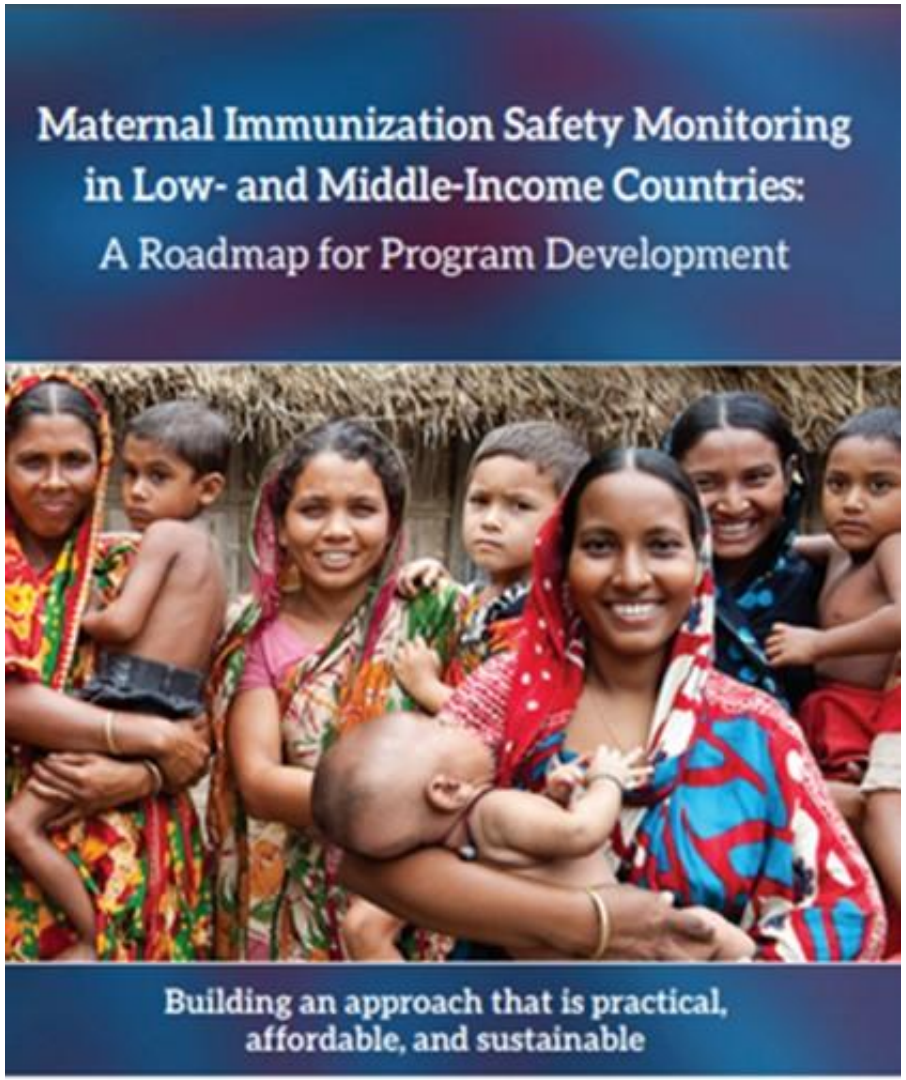
- Enhances natural immune mechanism of infant protection with mother as target
- Opportunities for implementation during ANC
- Requires administration in 2nd-3rd trimester and sufficient time from vaccination to delivery to achieve benefit.
- Benefits mostly **term** infants
- Affected by factors that alter antibody production and transplacental transfer in pregnant mothers (nutrition, co-infections, placental pathologies)
- Duration of **protection short**: 2-<6 mo
- Risks perceived vs. real
- Bridge until infant vaccination

- Enhances natural immune mechanism of infant protection with infant as target
- Requires administration early in life, and establishment of protection **prior to exposure to RSV**
- Multiple administrations needed to maintain protective levels
- However, this also ensures **longer duration of protection**
- Restricted to **preterm** infants, where most benefit is perceived, but term infants could benefit too.
- **Cost and implementation** challenges
- Prone to variable efficacy depending on “match” with RSV strains (escape mutants, variable epitopes/genotypes)

Thank you

Baylor College of Medicine

Texas Children's Hospital®



BILL & MELINDA GATES foundation

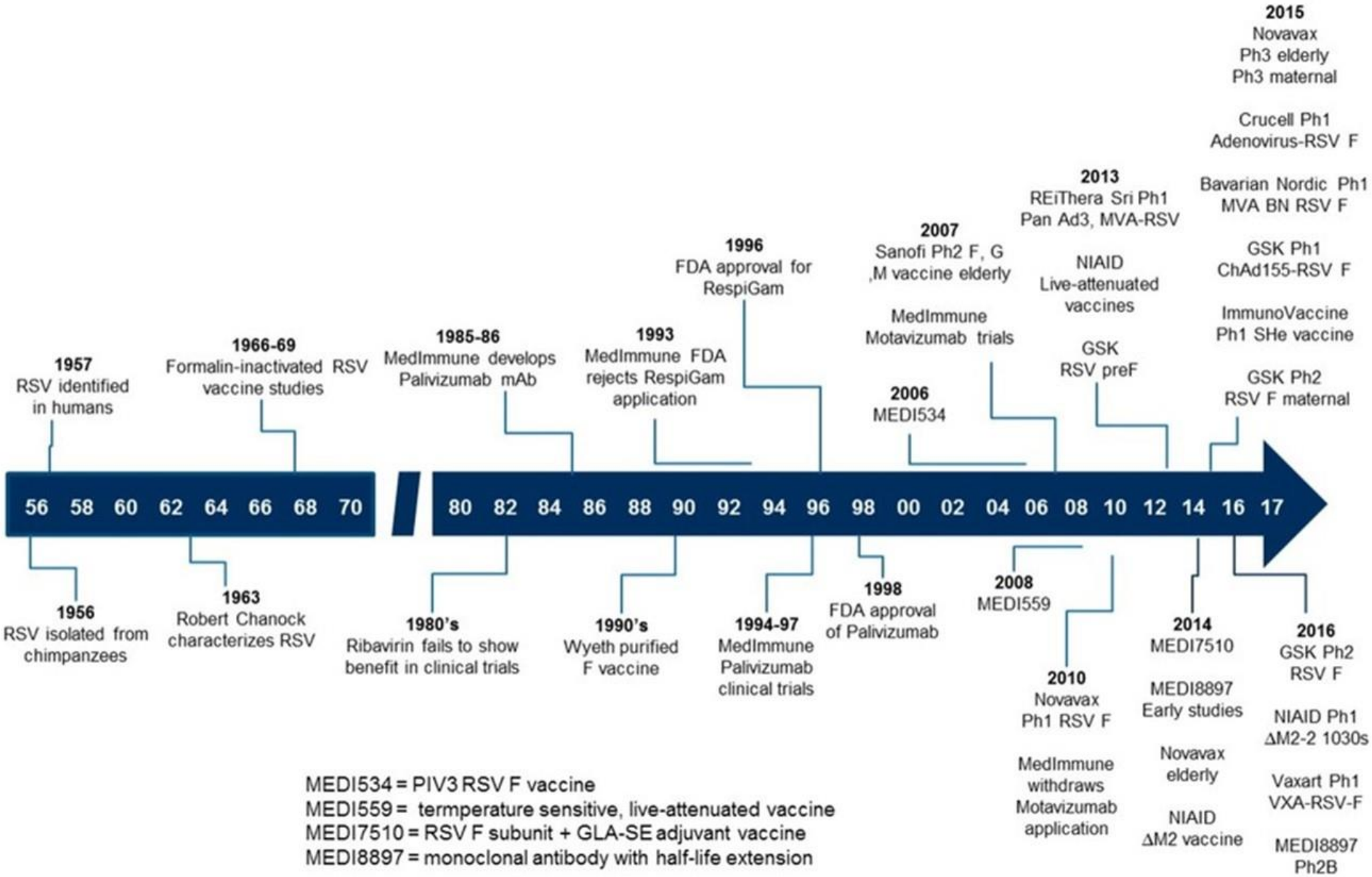
gapps

ami Advancing Maternal Immunization

Vision—To improve infant health and survival

- AMI is a WHO/PATH collaboration, convening global, cross-sector experts to establish a framework for informing, coordinating, tracking, and contributing to global efforts to advance RSV maternal immunization.
- Key activities:
  - **Identify evidence needs** to enable efficient, well-informed global and country decisions and requirements for rapid launch and uptake of RSV maternal vaccines in LMICs
  - **Assess evidence gaps** and priorities, and **articulate the way forward** in a **RSV maternal immunization roadmap**
  - **Develop a plan** for meeting the full spectrum of decision-making, rapid launch, and uptake needs

ami Advancing Maternal Immunization


1957
RSV identified in humans
1966-69
Formalin-inactivated RSV vaccine studies
1985-86
MedImmune develops Palivizumab mAb
1993
MedImmune FDA rejects RespiGam application
1996
FDA approval for RespiGam
2007
Sanofi Ph2 F, G ,M vaccine elderly
MedImmune Motavizumab trials
2006
MEDI534
2013
REiThera Sri Ph1 Pan Ad3, MVA-RSV
NIAID Live-attenuated vaccines
GSK RSV preF
2015
Novavax Ph3 elderly Ph3 maternal
Crucell Ph1 Adenovirus-RSV F
Bavarian Nordic Ph1 MVA BN RSV F
GSK Ph1 ChAd155-RSV F
ImmunoVaccine Ph1 SHe vaccine
GSK Ph2 RSV F maternal
56 58 60 62 64 66 68 70 80 82 84 86 88 90 92 94 96 98 00 02 04 06 08 10 12 14 16 17
1956
RSV isolated from chimpanzees
1963
Robert Chanock characterizes RSV
1980's
Ribavirin fails to show benefit in clinical trials
1990's
Wyeth purified F vaccine
1994-97
MedImmune Palivizumab clinical trials
1998
FDA approval of Palivizumab
2008
MEDI559
2010
Novavax Ph1 RSV F
MedImmune withdraws Motavizumab application
2014
MEDI7510
MEDI8897 Early studies
Novavax elderly
NIAID ΔM2 vaccine
2016
GSK Ph2 RSV F
NIAID Ph1 ΔM2-2 1030s
Vaxart Ph1 VXA-RSV-F
MEDI8897 Ph2B
MEDI534 = PIV3 RSV F vaccine
MEDI559 = termperature sensitive, live-attenuated vaccine
MEDI7510 = RSV F subunit + GLA-SE adjuvant vaccine
MEDI8897 = monoclonal antibody with half-life extension