Safety of Third Trimester Immunization with a Respiratory Syncytial Virus (RSV) F Protein Vaccine and Protection of Infants over the First 180 Days of Life Against All-Cause Lower Respiratory Tract Infection

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Disclosures

- Novavax
  - Site investigator for the study
  - Unpaid consultant for protocol design
- GlaxoSmithKline
  - Chair, Independent Data Monitoring Committee for RSV vaccine studies in pregnant women
- Pfizer
  - Chair, Independent Data Monitoring Committee for GBS vaccine studies in pregnant women

Lower Respiratory Tract Infection in Infants

- Acute lower respiratory tract infections (LRTI) are a major source of morbidity and mortality in infants and young children worldwide.[1]
- LRTI due to respiratory syncytial virus (RSV) is:
  - The second leading cause of infant death worldwide[2]; and
  - the leading cause of hospitalization in infants in the US, and especially serious from birth through 6 months of age.[3]
- Severe RSV LRTI in early infancy may increase risk for later respiratory morbidity, such as recurrent wheezing or asthma.[4]
- A second pneumovirus, human metapneumovirus (HMPV), also capable of causing severe illness, although less commonly than RSV.

1. Nair H. Lancet 2013; 381:1380
2. Losano R. Lancet. 2012; 380:2095
3. Leader S. J Pediatr. 2003;143:S127
4. Henderson J. Pediatr Allergy Immunol 2005; 16:386

Maternal Immunization to Address Infant LRTI

- Young age at infection is the most significant factor predicting severity of acute LRTI[1], probably due to:
  - Small caliber airways
  - Immature immune system
- Achieving timely immunity via active immunization in the first few months of life is challenging, but
- Immunization of pregnant women could provide protection to their infants in the first months of life via transplacental transfer of maternal antibody
  - Influenza, pertussis, and tetanus vaccines in pregnancy are successful precedents

1. Prasad N. Epidemiol Infect 2018; 146:1861

The RSV F Nanoparticle Vaccine Trial: Study Design

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	
	Participants	• **4,636** third trimester pregnant women **randomized 2:1 (vaccine:placebo) at 87 sites in 11 countries**
	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)

Demography of the Enrolled Women

- Inclusion/exclusion criteria dictated a **low-risk pregnancy** population
- **Age:** Global mean (SD) = 26 (5.2) yr; median = 26 yr
  - Approx. 2/3 of mothers in the 18 - <29 yr stratum, well-balanced
- **Race/Ethnicity:**
  - 30.1% white
  - 43.6% black/African
  - 26.2% all other
- **BMI:** Global mean (SD): 28.5 (5.1) Kg/M^2
- **Parity:** 34.2% primigravida, 95.8% with 3 or fewer prior pregnancies
- **Gestational age at vaccination:** global median = 32 weeks

Safety Outcomes

- **Short-term vaccine reactogenicity: 57% of vaccinees vs. 41.3% in placebo group,**
  - Primary drivers are mild injection site pain and swelling, <1% persists beyond 7 days
  - Minimal difference in systemic reactogenicity, no increase in fever in the 7 days post-treatment (1.2% vaccines vs. 1.6% placebo recipients).
- **NO notable differences in maternal safety outcome in terms of:**
  - All unsolicited AEs, or severe, related, or severe and related AEs
  - Medical attendance for AEs or serious AEs
- **98.8% vaccinees and 98.7% placebo recipients delivered live-born infants**
  - Prematurity: 5.8% of vaccine group and 6.1% of placebo delivered at < 37 weeks
  - Length, weight, FOC, 1 and 5 minute APGARS are essentially identical between treatment groups
- **No negative impact of maternal immunization on infants in terms of:**
  - All AEs, or severe or severe and related AEs over 180 days
  - Medical attendance over 180 days
  - Overall SAE profile

Pregnancy and Delivery Outcomes

Event type, n of subjects with event (%)	Placebo (N = 1582)	RSV F Vaccine (N = 3047)	Total (N = 4629)
New or worsened gestational diabetes	5 (0.3)	5 (0.2)	10 (0.2)
Gestational hypertension	68 (4.3)	141 (4.6)	209 (4.5)
Pre-eclampsia	42 (2.7)	72 (2.4)	114 (2.5)
Eclampsia	6 (0.4)	6 (0.2)	12 (0.3)
HELLP syndrome	1 (<0.1)	3 (<0.1)	4 (<0.1)
Premature rupture of membranes	35 (2.2)	75 (2.5)	110 (2.4)
Preterm birth	90 (5.7)	170 (5.6)	260 (5.6)
Stillbirth/foetal death	9 (0.6)	15 (0.5)	24 (0.5)
Third trimester hemorrhage, incl. placenta praevia	8 (0.5)	14 (0.5)	22 (0.5)
Placental abruption	7 (0.4)	12 (0.4)	19 (0.4)
Post-partum hemorrhage	30 (1.9)	49 (1.6)	79 (1.7)
Maternal fever or infection	17 (1.1)	17 (0.6)	34 (0.7)
Chorioamnionitis	17 (1.1)	25 (0.8)	42 (0.9)
C-sections			
Planned C-section, primary or repeat*	179 (11.4)	336 (11.1)	515 (11.2)
C-section after failed attempt at vaginal delivery*	66 (4.2)	123 (4.1)	189 (4.1)
Emergency C-section*	178 (11.3)	347 (11.4)	525 (11.4)

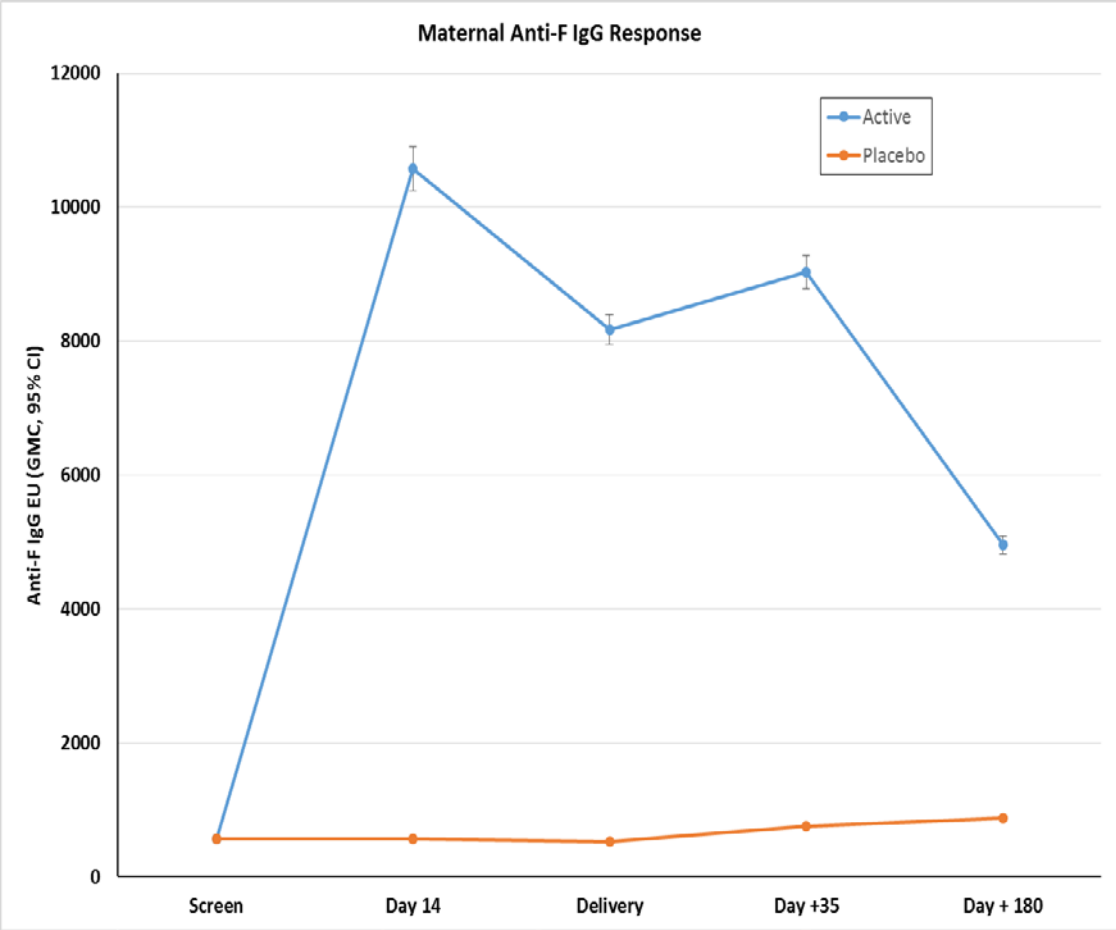
* Delivery outcome % based on 4603 women (1572 placebo, 3031 vaccine) with data

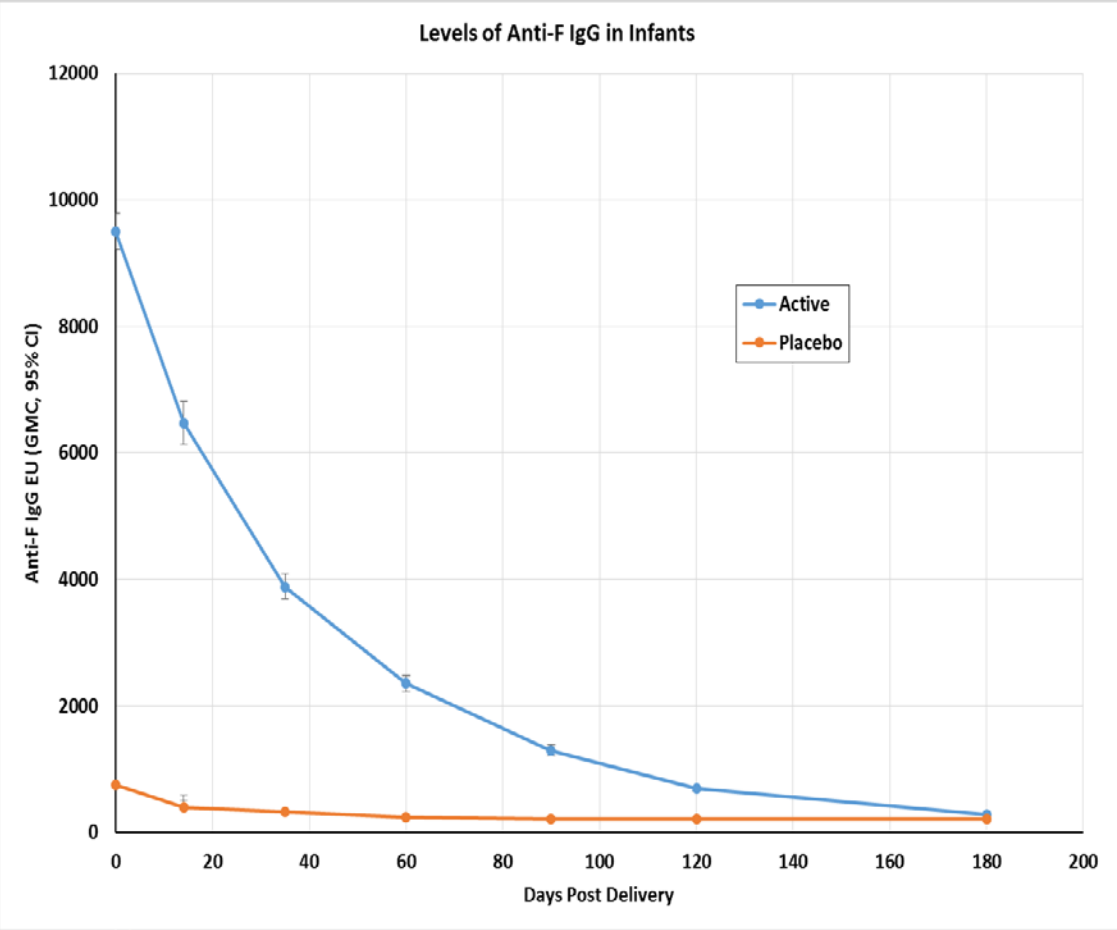
Infant Birth Outcomes

		Placebo (n = 1562)	RSV F Vaccine (n = 3010)	Total (n = 4572)
Male/female*		51.2%/48.5%	51.7%/48.2%	51.5%/48.3%
Gestational age (weeks) at delivery*	Mean (SD)	39.3 (1.58)	39.3 (1.49)	39.3 (1.52)
	Median	39.4	39.4	39.4
	≥37 weeks, n (%)	1459 (93.4)	2813 (93.5)	4272 (93.4)
	<37 weeks n (%)	96 (6.1)	175 (5.8)	271 (5.9)
Interval (days) from Immunization to Birth	Mean (SD)	51.3 (20.7)	51.9 (20.4)	51.7 (20.5)
	<14 days (n, %)	36 (2.3)	50 (1.7)	86 (1.9)
	< 30 days (n, %)	252 (16.1)	487 (16.2)	739 (16.2)
Length at birth (cm),	Mean (SD)	50.2 (3.1)	50.0 (2.9)	50.1 (3.0)
	Median	50.0	50.0	50.0
Weight at birth (kg)	Mean (SD)	3.20 (0.51)	3.21 (0.48)	3.20 (0.49)
	Median	3.20	3.20	3.20
FOC (cm)	Mean (SD)	34.2 (1.8)	34.2 (2.1)	34.2 (2.0)
APGAR	1 minute (median, 1st and 3rd quartile)	9 (8, 9)	9 (8, 9)	9 (8, 9)
	5 minute (median, 1st and 3rd quartile)	10 (9, 10)	10 (9, 10)	10 (9, 10)

* Approximately 0.2-0.6% of subjects missing data

Anti-RSV F Protein IgG: Screen through Day 180 After Delivery in Women and Infants





Seroresponse rates in vaccinees = 98.3%
4-fold rise in vaccinees = 91.9%

Geo. mn. cord serum/maternal serum 1.17 (1.19, 1.14)
$T_{1/2}$ = 38.3 days in active vaccine infants

Effect of Immunization Timing on Transplacental Antibody Transfer

	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)

*palivizumab-competitive antibody **microneutralization activity

- All classes of anti-RSV antibody measured were transferred significantly less efficiently when women were immunized after the 32nd week of gestation, or within 30 days of delivery.
- This same subset of women demonstrated a trend toward lower efficacy in the prevention of RSV LRTI.

Impact of Maternal Immunization on Medically-Significant LRTI through 90 Days of Life

- Medically-significant LRTI required lower tract findings, SpO_2 <95% or tachypnea ≥70bpm under 2 mos., ≥60bpm at ≥ 2mos.

	Per-Protocol			Intent-to-Treat		
	Placebo N = 1430	Vaccine N = 2765	Efficacy (95%CI)	Placebo N = 1547	Vaccine N = 2980	Efficacy (95%CI)
RSV medically-significant LRTI Days 0 to 90	35	41	39% (5, 61)	36	47	32% (-4, 56)
All pneumovirus medically-significant LRTI Days 0 to 90	39	44	42% (11, 62)	40	51	34% (0, 56)
All-cause medically-significant LRTI Days 0 to 90	100	148	24% (2, 40)	112	168	22% (2, 38)

- Primary endpoint, RSV medically-significant LRTI, had a 97.52% confidence lower bound of -1.0% and missed the protocol-specified success criterion.
- Clear impact on RSV and also all pneumovirus disease; all-cause effect is largely, but not entirely, driven by pneumovirus infections.

Impact of Maternal Immunization on LRTI with Severe Hypoxemia through 90 Days of Life

- Severe hypoxemia requires SpO_2 <92% or advanced O_2 support (high-flow nasal cannula, helium/oxygen, CPAP, mechanical ventilation.

	Per-Protocol			Intent-to-Treat		
	Placebo N = 1430	Vaccine N = 2765	Efficacy (95%CI)	Placebo N = 1547	Vaccine N = 2980	Efficacy (95%CI)
RSV LRTI with severe hypoxemia Days 0 to 90	14	14	48% (-8, 75)	14	15	44% (-15, 73)
All pneumovirus LRTI with severe hypoxemia Days 0 to 90	15	15	48% (-6, 75)	16	16	48% (-4, 74)
All-cause LRTI with severe hypoxemia Days 0 to 90	44	47	45% (17, 63)	49	51	46% (20, 63)

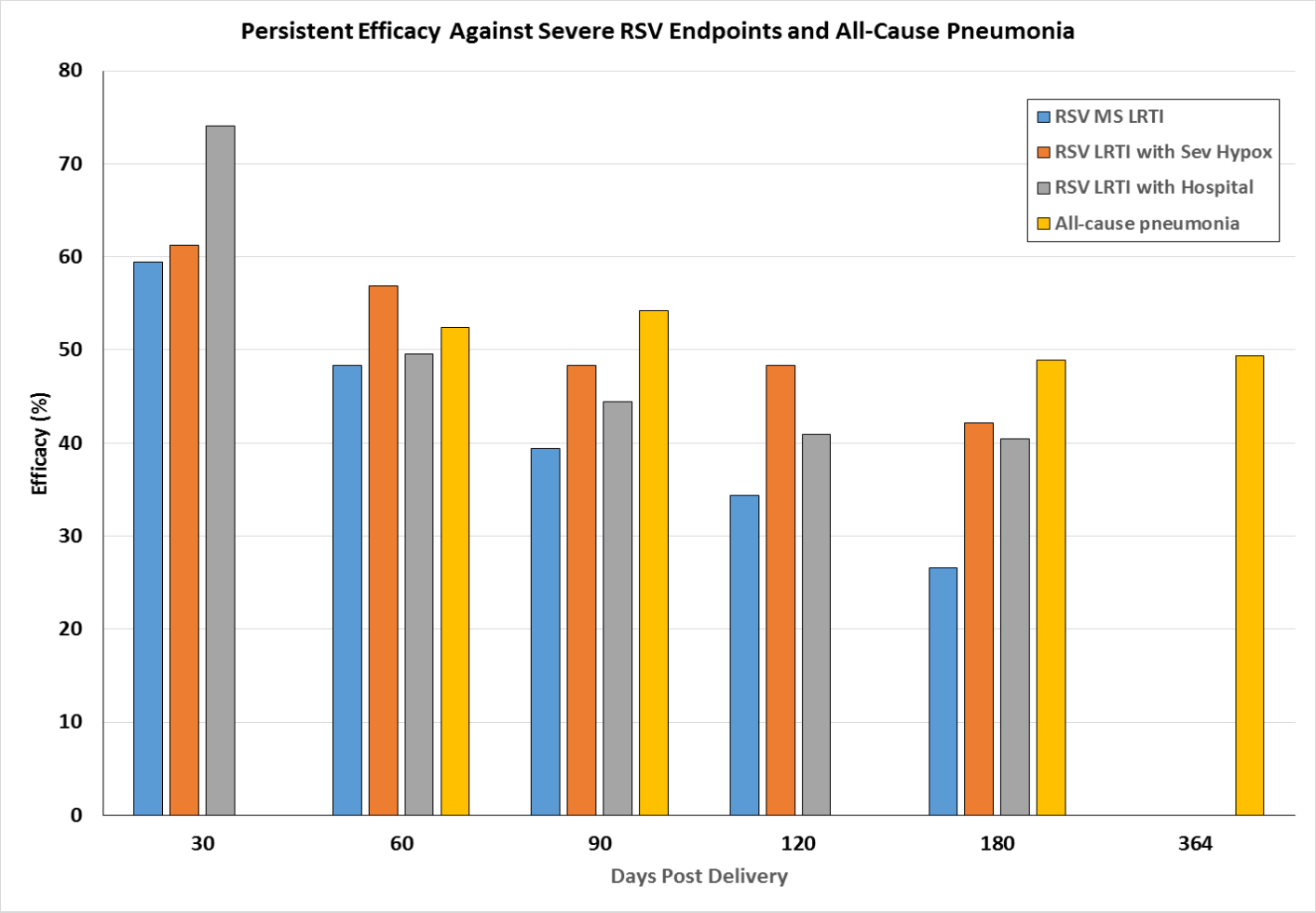
- Efficacy against more severe disease is superior to the milder, medically-significant endpoint.
- Contribution of HMPV to severe LRTI appears minimal. Interestingly, efficacy against LRTI with severe hypoxemia not shown to be due RSV or HMPV was still relatively high (43%).

Impact of Maternal Immunization on LRTI Precipitating Hospitalization through 90 Days of Life

	Per-Protocol			Intent-to-Treat		
	Placebo N = 1430	Vaccine N = 2765	Efficacy (95%CI)	Placebo N = 1547	Vaccine N = 2980	Efficacy (95%CI)
RSV LRTI with hospitalization Days 0 to 90	53	57	44% (20, 62)	60	60	48% (26, 64)
All pneumovirus LRTI with hospitalization Days 0 to 90	57	60	46% (22, 62)	67	63	51% (32, 65)
All-cause LRTI with hospitalization Days 0 to 90	86	118	29% (7, 46)	99	123	36% (17, 50)

- Efficacy against RSV or all pneumovirus LRTI with hospitalization is 44-51%;
- Efficacy against the economically significant outcome of all-cause hospitalization due to LRTI is noted, driven by the pneumovirus effect, with approximately one-third reduction in all-cause LRTI hospitalization.

Durable Efficacy Against More Severe Disease, Including All-cause Pneumonia



- Unsurprisingly, efficacy wanes as maternal antibody is cleared,
- Net efficacy against RSV LRTI with severe hypoxemia or hospitalization is relatively well-maintained (>40% through 180 days).
- An impact on all-cause clinical diagnoses of pneumonia is noted through the entire first year of life.

Impact of Maternal RSV Immunization on Pneumonia over One Year of Life

		Counts (%)			
Endpoint	Time Interval	Placebo (N = 1562)	Vaccine (N = 3010)	Efficacy	95% CI
Clinical pneumonia reported (All Cause)	0 to 90 days	51 (3.27)	45 (1.50)	54.2%	32.0, 69.2
	0 to 180 days	66 (4.23)	65 (2.16)	48.9%	28.4, 63.5
	0 to 364 days	80 (5.12)	78 (2.59)	49.4%	31.3, 62.7
Clinical pneumonia with CXR positive (All Cause)	0 to 90 days	33 (2.11)	24 (0.80)	62.3%	36.4, 77.6
	0 to 180 days	42 (2.69)	34 (1.13)	58.0%	34.2, 73.2
	0 to 364 days	47 (3.01)	39 (1.30)	56.9%	34.5, 71.7
Clinical pneumonia with positive CXR and RSV+ by PCR	0 to 90 days	21 (1.34)	11 (0.37)	72.8%	43.8, 86.9
	0 to 180 days	23 (1.47)	12 (0.40)	72.9%	45.7, 86.5
	0 to 364 days*	23 (1.47)	12 (0.40)	72.9%	45.7, 86.5

Data on all SAEs coded as "pneumonia," excepting "congenital pneumonia" in first 24 hours. Based on safety database as of 09 Jul 19.
*No active surveillance for RSV post day 180
**Pneumococcal vaccine NNV calculated from Cutts FT. Lancet 2005; 365:1139 and Palmu A. Vaccine 2018; 36:1826

- Clear *post-hoc* observation of efficacy against infant pneumonia through one year.
- Number-needed-to-vaccinate (NNV) to prevent one hospitalized case of pneumonia ~40, (All Cause).
- NNV for pneumococcal conjugate vaccines to prevent one case of clinical or x-ray confirmed all-cause pneumonia 47 to 185**

Conclusions (1)

- 4,636 maternal – infant pairs were studied across 3.5 years and 11 countries.
- The RSV F vaccine was well-tolerated by pregnant women.
- No meaningful changes in the overall safety profile were noted in the women or their infants through 180 days post-delivery.
  - 364 day safety follow-up is being completed in infants.
- Vaccine-induced RSV-specific antibodies were transferred from mother to the infant with >100% efficiency, but
- Immunization prior to 33 weeks gestation and ≥30 days prior to delivery resulted in clearly superior antibody transfer and a trend toward improved efficacy.

Conclusions (2)

- Observed efficacy of the vaccine strategy was 39.4% against the primary endpoint, medically-significant RSV LRTI, but…
- Observed efficacy was greater against more severe endpoints: RSV LRTI with severe hypoxemia and RSV LRTI with hospitalization.
- Efficacy against all pneumovirus disease is essentially identical to that against RSV, although HMPV adds relatively fewer cases to severe endpoints.
- Efficacy wanes over time, but net protection against LRTI with severe hypoxemia persists through 180 days of life.
- Efficacy against all-cause LRTI endpoints, as well as reduction in hospitalized all-cause pneumonia extending through 364 days, suggests that maternal immunization for prevention of early RSV LRTI could substantially modify these clinically- and economically-important outcomes.