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Creating Tomorrow's Vaccines Today

Progress Toward a Vaccine for Maternal Immunization to Prevent Respiratory Syncytial Virus (RSV) Lower Respiratory Tract Infection (LRTI) in Infants

October 2018

NASDAQ:NVAX

RSV clinical disease

RSV causes a predictable winter epidemic

Severe disease occurs at extremes of age and, in older adults, in high risk groups (congestive heart failure, COPD)

Infants:

- 65-70% of infants infected by RSV within first six months of life, ~100% by 2 years
- Approximately 15% are seen in medical offices or emergency departments
- 1-4% of all infants are hospitalized, predominantly in first six (6) months of life
- 80-85% of hospitalizations in *term, low-risk infants*

Downstream effects of significant RSV disease in infancy include an increased risk of recurrent wheezing, diagnosis of asthma, and hypothesized predisposition to COPD in later life.

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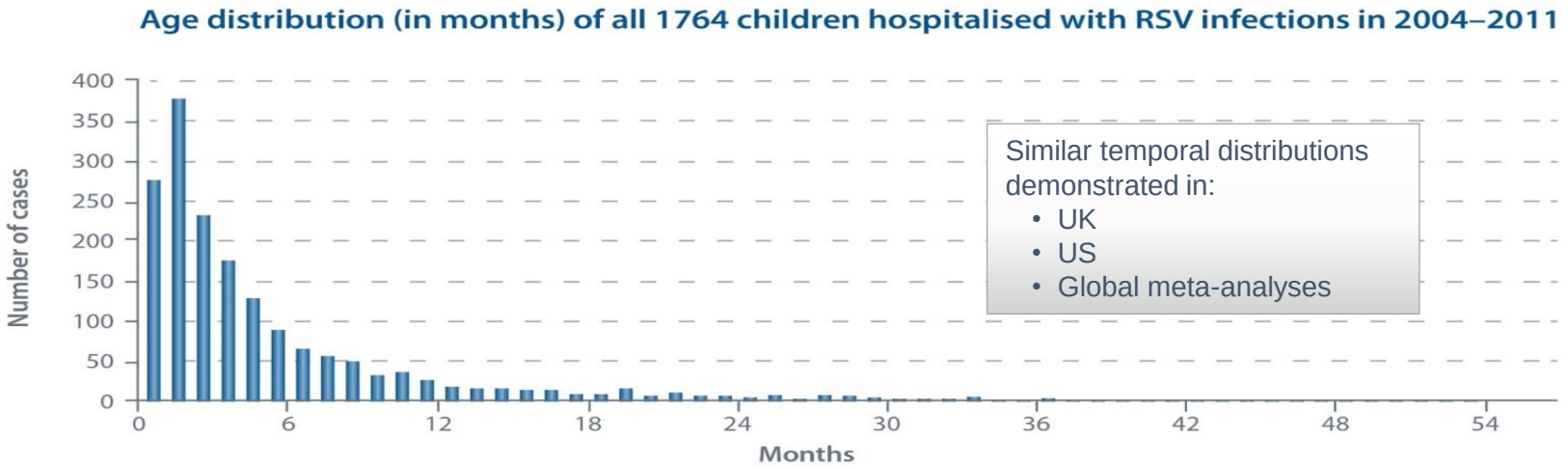
RSV hospital admissions in Sweden (children < 5 years old)



- 70% of hospitalizations occurred in the first 6 months of life
- Most infants needing hospitalization for RSV were full-term births (80%) with no known risk factors
- The individual risk of a newborn infant being hospitalized for RSV in the first year of life was 17.4 per 1000, a figure consistent with other industrialized countries
- Median hospital length of stay = 3 days (range 1 to 150 days)

Svensson C, et al. Acta Paediatri. 2015 Sep;104(9):922-6 / Hall CB. Pediatrics 2013;132:e341

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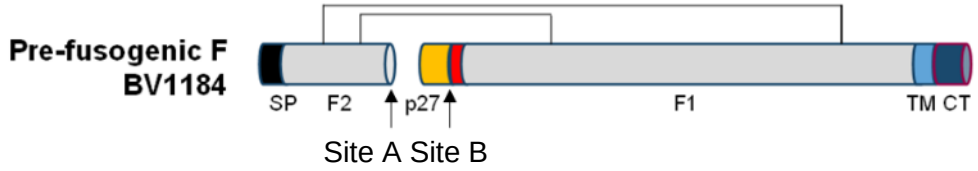
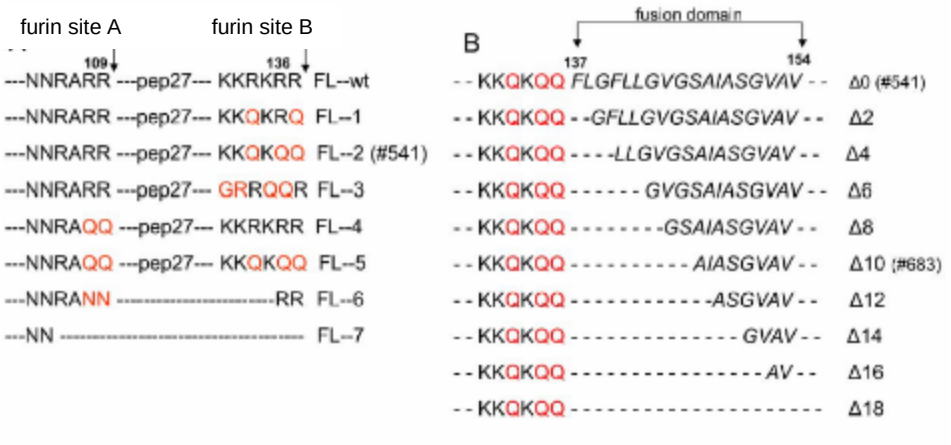
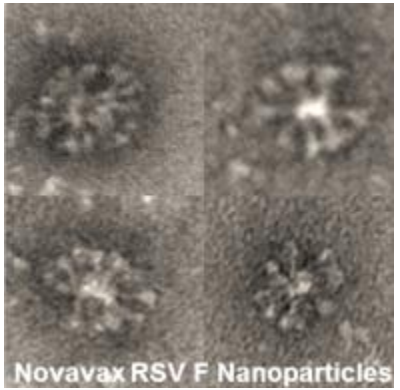
Novavax RSV F construct



Furin Site B mutation

Deletion 10aa fusion domain





Adapted from: Smith G, et al. PLoS ONE. Nov 30, 2012; 7(11): e50852

Key findings underpinning an RSV maternal immunization program

Source of evidence	Result
Experiments of nature	Higher levels of infant serum antibodies to RSV are inversely correlated with RSV disease severity or RSV hospitalization risk in infancy. (reviewed in Walsh et al. J Infect Dis 2018; 218:208-217)
Experiments of man	Tetanus, pertussis, and importantly, influenza vaccine given to the mother in pregnancy provide passive protection to the infant.

Pre-clinical data	• Rodents are protected against RSV replication in lungs and nose by:
	  • Active immunization with RSV F nanoparticle vaccine, or
	  • Passive administration of RSV F nanoparticle-induced antibodies.
	• Guinea pigs demonstrate efficient transplacental transfer of RSV F nanoparticle - induced antibodies to pups.
	• Olive baboon infants are protected against RSV challenge by immunization of mothers prior to delivery.

Clinical data	• Women of childbearing age immunized with RSV F show ~50% reduction **is** RSV seroconversion by Western blot across the transmission season • Pregnant women develop anti-F IgG and neutralizing antibodies and transfer them to their infants, with persistence $t_{1/2}$ 30-40 days

CDC: https://www.cdc.gov/flu/pdf/professionals/pregnant-women-letter_september-2017-2018.pdf / Raghunandan R, et al. Vaccine 2014;32:6485–92 / August A, et al. Vaccine. 2017 Jun 27;35(30):3749-3759 / Glen GM, et al. J Infect Dis 2016 ; 2016 Feb 1;213(3):411-22 2

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Clinical development synopsis to date – RSV F nanoparticle for maternal immunization

NVX.757.101

- Placebo-controlled, dose-escalating Phase 1 in 150 young adults
- No safety concerns, Al beneficial, dose response continues to 60µg F

NVX.757.201 (RSV-M-201)

- Placebo-controlled, dose/formulation finding Phase 2 in 330 women of childbearing age (WOCBA)
- Al clearly beneficial in neutralizing response, dose response continues to 90µg F

NVX.757.202 (RSV-M-202)

- Placebo-controlled, dose/regimen finding Phase 2 in 720 WOCBA
- Single dose at 120µg F superior to 60µg twice in antibody response AUC through 56 days, with acceptable safety. Al 0.4mg is optimal.

RSV-M-203

- Phase 2 placebo controlled safety and immunogenicity in 50 3rd trimester pregnant women.
- Immunogenicity similar to non-pregnant women, transplacental transfer of vaccine-induced antibodies shown, half-life in infants 35-45 days.
- No safety issues

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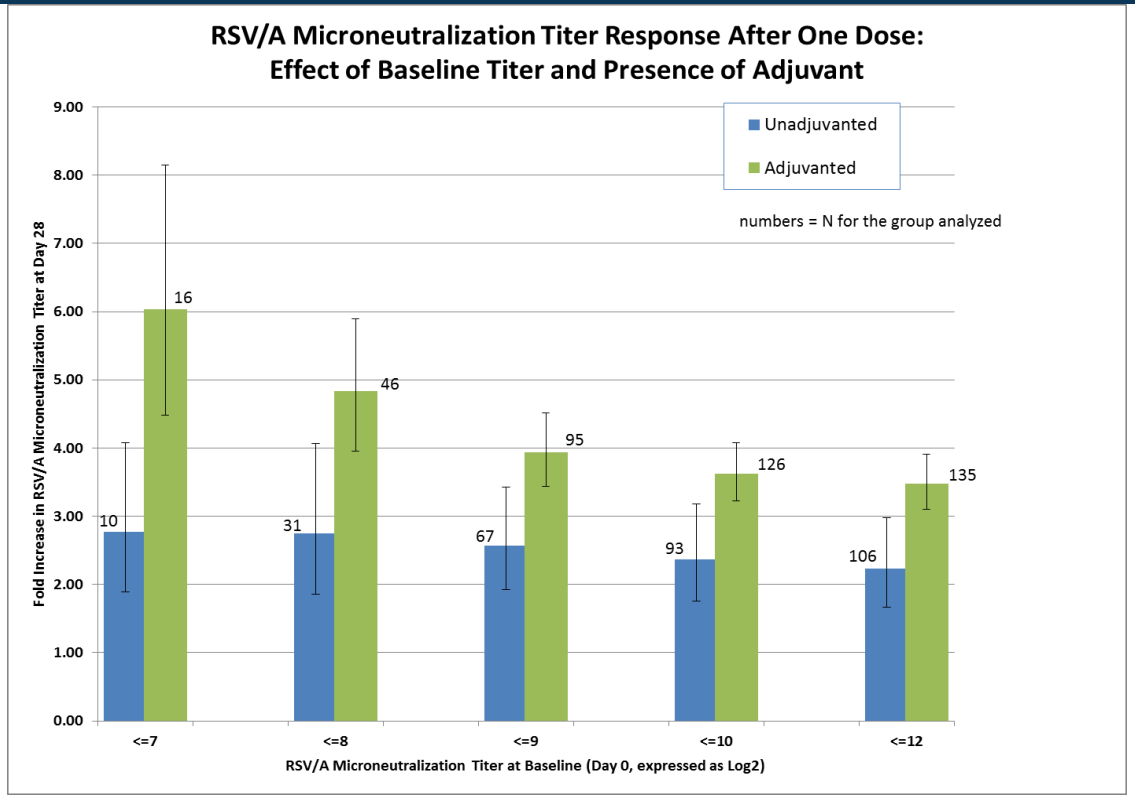
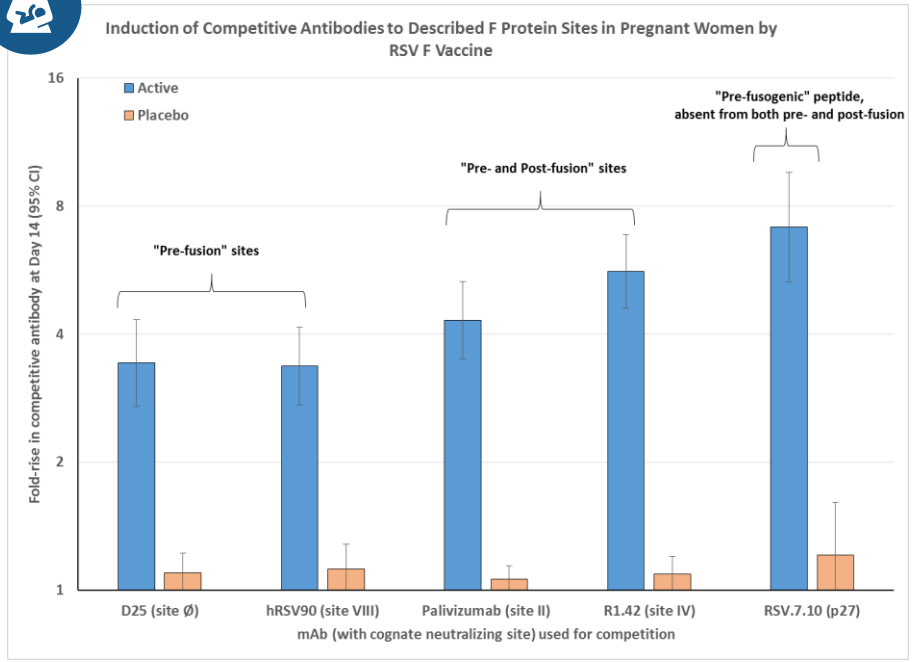
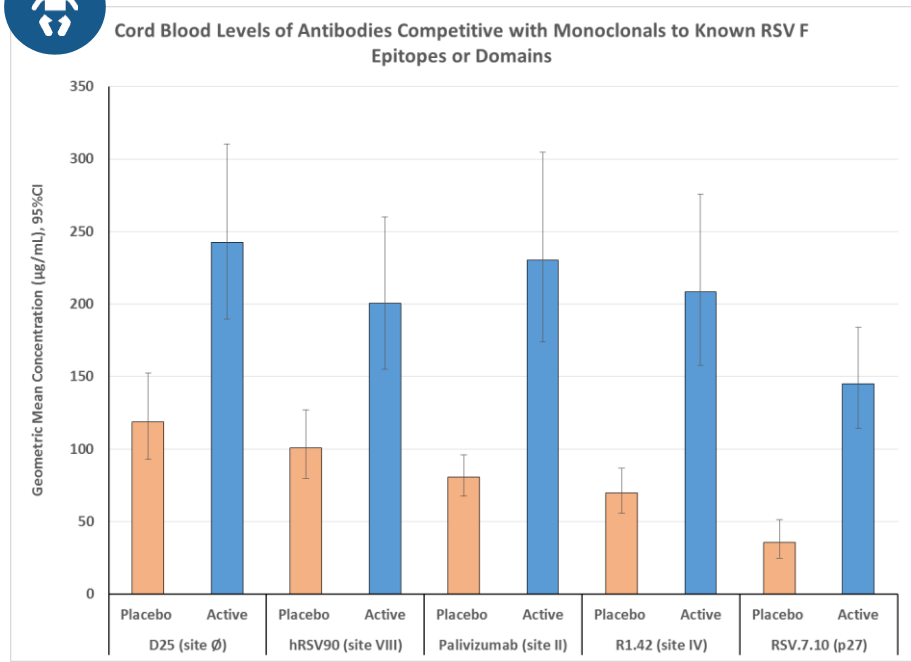
The basis for using aluminum



Adapted from: August A, et al. Vaccine. 2017 Jun 27;35(30):3749-3759

Induction and transfer of antibodies competing with monoclonal antibodies specific for known epitopes or domains





Competitive antibody equivalents (CAE) detected by biolayer interferometry using characterized mabs to RSV F protein.
Day 14 fold-rise in mothers (left panel) and comparative cord blood CAE (right panel).

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Phase 3 trial goals and design (RSV M-301)

THE Prepare™ TRIAL

Primary objective	Determine the efficacy of maternal immunization with the RSV F vaccine against medically significant symptomatic 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	• Minimum of 4,600 third trimester pregnant women and their infants
	Global study	• 87 sites in 11 countries
	Length of study participation	• Maternal participants: up to 9 months • Infant participants: 1 year after delivery
	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 • Ongoing DSMB oversight

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

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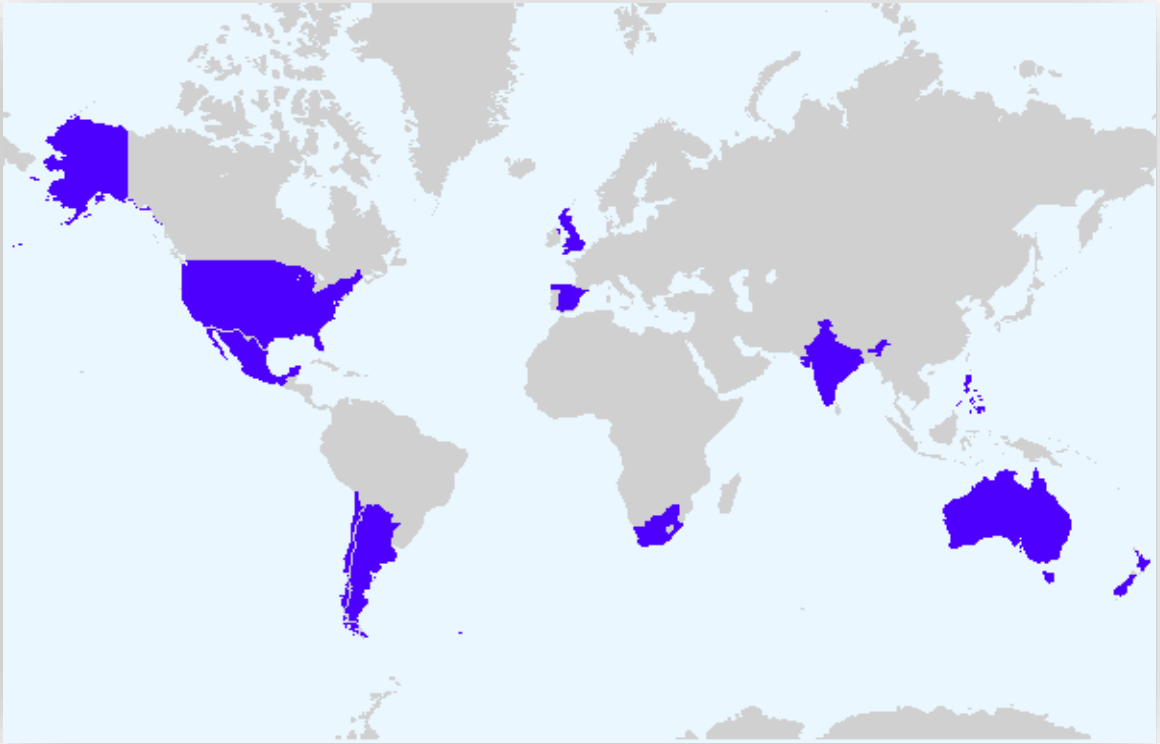
Global enrollment in the Prepare trial since 2015

Prepare™

Single protocol approved by 12 Regulatory Authorities

Enrollment at 87 sites in 11 countries



Seasonal enrollment (Northern & Southern Hemisphere) completed over 31 months

Total of 4,636 Maternal Subjects Enrolled

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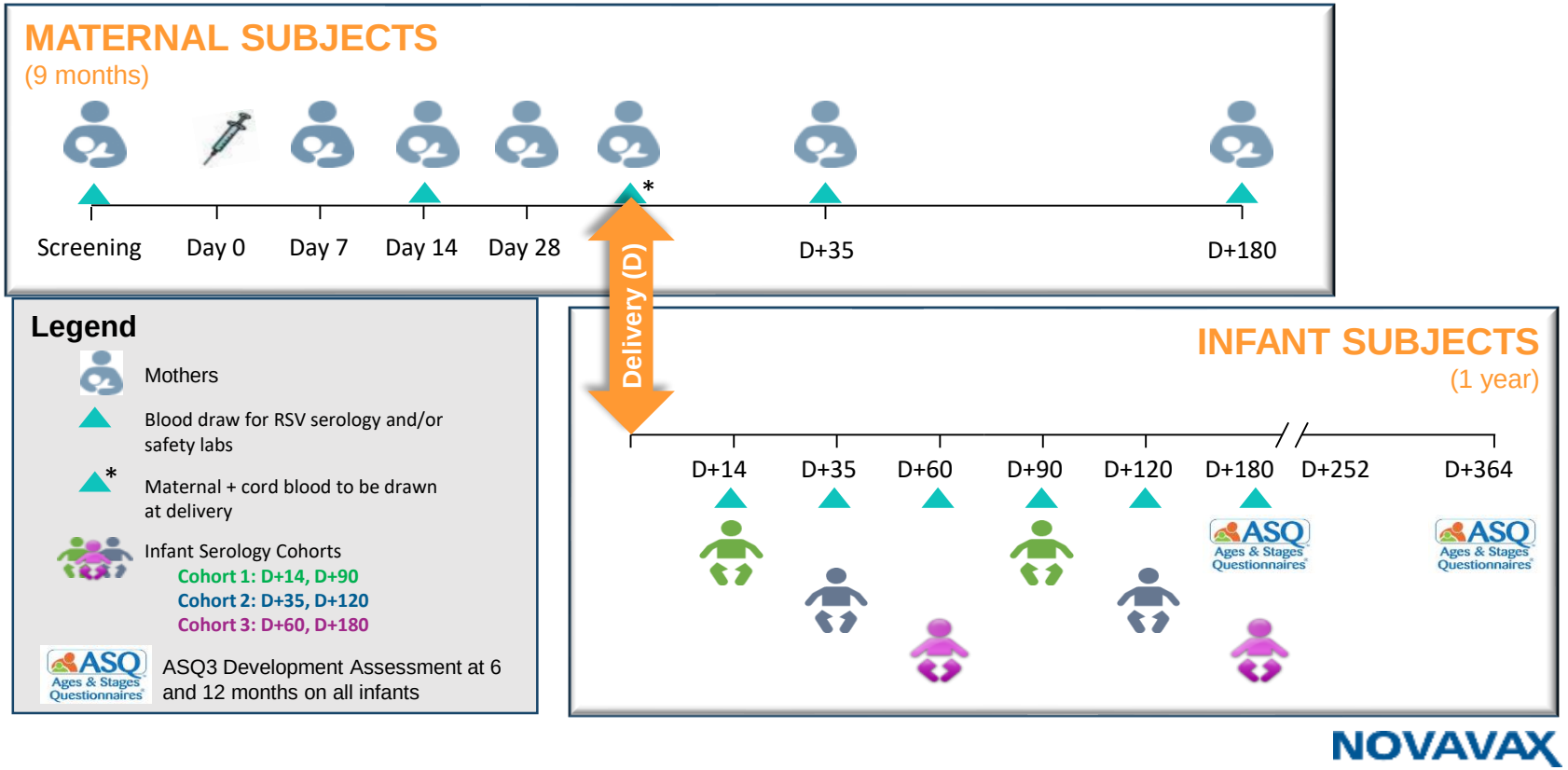
Trial participant visit schedule

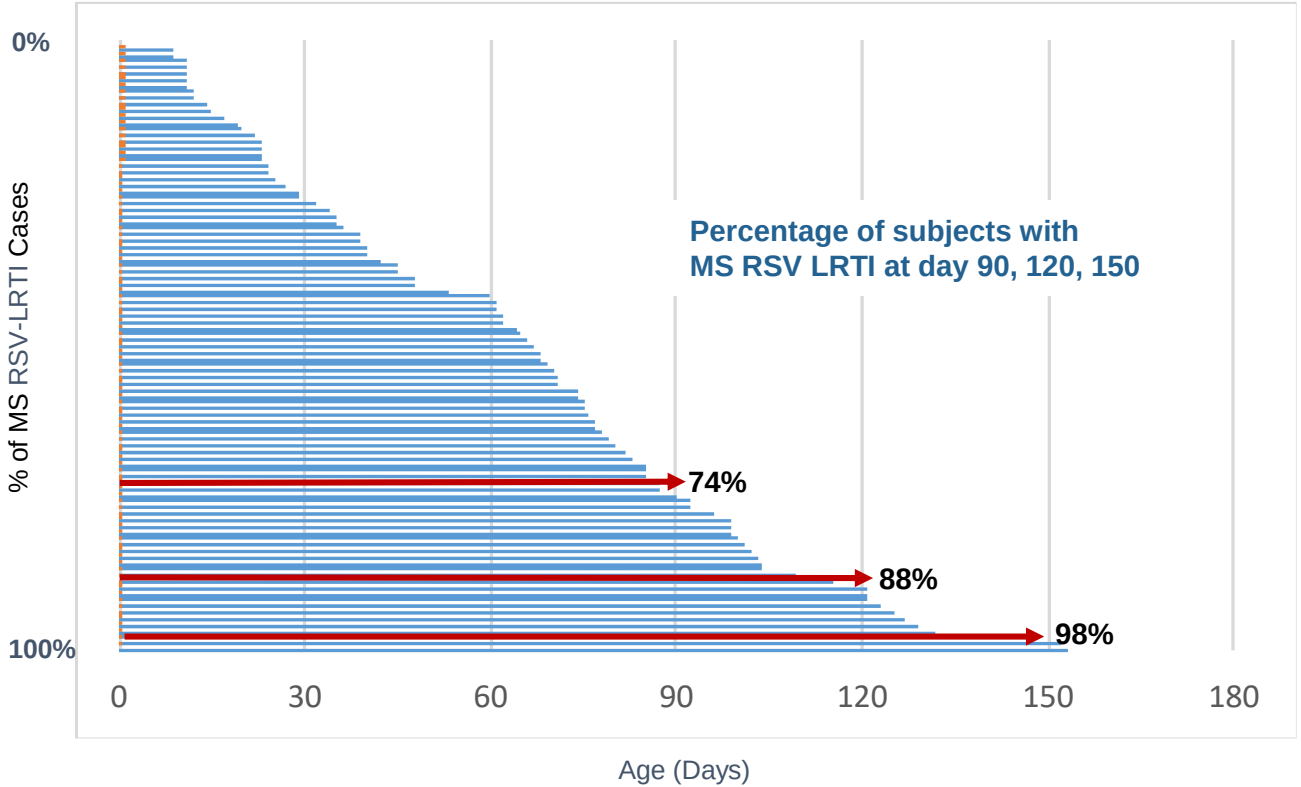


RSV illness ascertainment

To date:

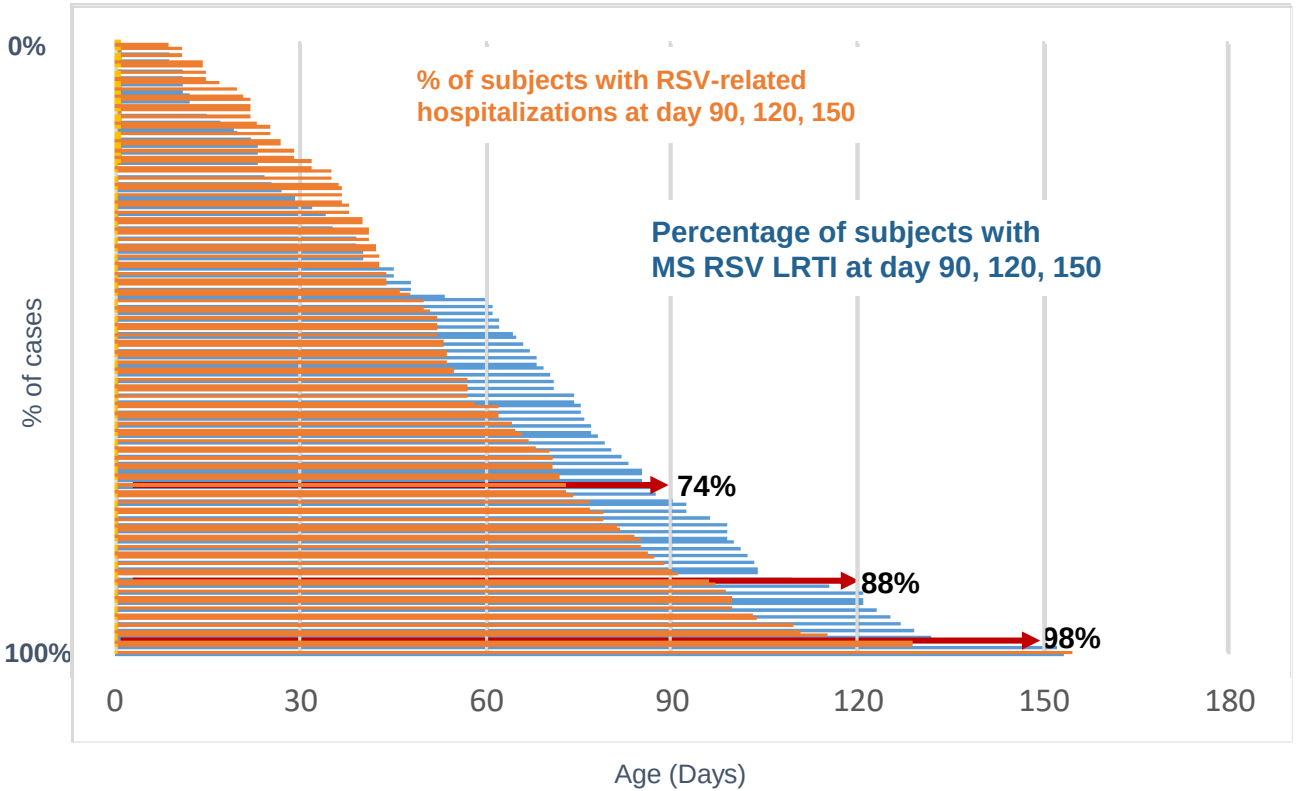
- 99.3% of live born infants have been the subject of active or passive surveillance contacts at least once.
- Parents report a respiratory illness in the first 180 days of life in 76% of infants.
  - 96% of these infants have been evaluated at least once with physical examination, pulse oximetry, and nasal swabbing for RT-PCR
- Approximately 57% of infants have physician-confirmed evidence of LRTI
- RSV has been detected in 21% of symptomatic infants; and
- RSV has been detected in approximately 5% of symptomatic mothers between enrollment and day 180 post-partum.

Medically significant disease is concentrated in the first 3 - 4 months of life: RSV M-301 surveillance



Medically significant RSV lower respiratory tract infection (MS RSV LRTI, primary endpoint) in this intensive surveillance setting in largely healthy, term infants is found primarily in infants <4 months of age.

RSV-related hospitalization is concentrated in the first 3 months of life: RSV M-301 surveillance



~90% of RSV-related hospitalization (orange lines) occurs within 90 days.

- Average age at hospitalization is 30 days < average age of MS-RSV-LRTI
  - 40-45% overlap between MS-LRTI and hospitalization
  - Not all MS-LRTI is hospitalized, even with hypoxemia
  - In the same venues, not all hospitalizations fulfill hypoxemia or tachypnea criteria
- From a combined medical and economic viewpoint, both endpoints deserve consideration.

RSV M-301 safety

Management of safety via DSMB:

- Multiple pre-planned serial futility analyses
- Iterative completely unblinded review of safety outcomes by an international DSMB of obstetricians and pediatricians, supported by an independent statistician

15 consecutive DSMB reviews: no advice to slow, pause, or alter protocol

2015 Brighton Collaboration list of pregnancy and peri-partum safety endpoints adopted as adverse events of special interest (AESI) and treated as serious adverse events (SAE).

- Overall blinded AESI rates are below global backgrounds; and
- AESI rates are similar to, or less than, published country-specific rates in the U.S. and South Africa, which together are responsible for ~76% of the data
- South African rates also compare favorably w/influenza vaccine trials

“Informational analysis” of RSV M-301 - 2017

Targeted a minimum efficacy threshold against the primary endpoint at day 90 of ~ 40%

Bayesian analysis, reflecting the underlying trial analysis plan, using a success criterion of a posterior probability ≥ 90% that the vaccine efficacy was ≥ 0% at the time of the analysis.

- This was selected to approximate a vaccine efficacy of ≥40% based on the sample size and event count at the time.

The DSMB statistician performed the analysis, the company remains blinded

The DSMB communicated that the analysis was positive Q4 2017

Based on the total case count of primary endpoints and the sample size, the point estimate of minimum vaccine efficacy was approximated:

- Assumed perfect randomization of 1,307 per-protocol infant subjects in the analysis
- VE at the time of the analysis was between 45 and100%.

Based on this, we plan to unblind for final analysis in Q1 2019.

What have we learned?

Pregnant women are open to vaccine trials that might benefit infants; fathers must be engaged and educated.

Social media are a major recruitment tool everywhere.

- Communications need to be carefully managed and subject to compulsive ethical review

A uniformly applied gestational age determination algorithm is key, and not simple to enforce across countries and cultures.

With careful planning and local epidemiology, it is possible to ensure the majority of infants are exposed to the RSV season.

You must be prepared to interact more than once with each illness episode to ensure capture of the clinical nadir.

The sickest infants will evade the study clinic; it is important to establish the broadest possible collaboration with local hospitals, so that endpoint data can be captured there.

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Thanks to:

- Our conscientious investigators and clinical site staff around the world
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