Magnitude and Durability of Anti-F IgG and Palivizumab-Competitive Antibody (PCA) Responses One Year Following Immunization with RSV F Nanoparticle Vaccine Adjuvanted with Aluminum Phosphate, or a Novel Adjuvant, Matrix-M™

RSV 2018 Symposium

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RSV F vaccine

- Novavax RSV F Vaccine is composed of a recombinant near full length F protein
  - Prefusogenic F trimers are associated with PS80 detergent micelles to form stable 40nm particles
  - RSV F Vaccine is thermodynamically stable, resists denaturation, and is not randomly aggregated.
  - For more details on structural and antigenic characterization see posters:
    - **Poster #69** In-depth Analytical Characterization and Structural Modeling
    - **Poster #70** Antigenic Characterization against a Broad Range of Neutralizing Monoclonal Antibodies
    - **Poster #71** Physical and Antigenic Structure, Immunogenicity, and Protection
    - **Poster #72** Feasibility Evaluation of Blow Fill Seal Process with Aluminum Adjuvanted Recombinant RSV F
    - **Poster #73** Binding Kinetics of RSV F Vaccine to Palivizumab and Serum Polyclonal Antibody

- In 9 separate clinical trials in adults, Novavax' RSV F Vaccine, formulated with or without Aluminum adjuvant, was found to have an acceptable safety profile and elicit robust RSV-specific antibody responses.

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Unadjuvanted RSV F vaccine in older adults:

Experience and lessons through Phase 3

- Phase 2 trial demonstrated clinical efficacy (**41%** vs. RSV-ARD; **64%** vs. RSV-msLRTD)
  - Placebo attack rate **4.9%**, *single season*
- Phase 3 trial failed to meet efficacy endpoints
  - Placebo attack rate **1.9%,** *single season*
- Spawned two major lines of investigation:
  1. Is the vaccine construct optimal and should an adjuvant/2-dose strategy be employed?

     See 3 posters on construct listed in the previous slide; this talk will focus for the adjuvant effect and 2-dose strategy

  2. Was there an external factor leading to failure to meet endpoints?

     And, was there a phase 3 signal worthy of additional clinical testing?
- Efficacy observed during periods of high population susceptibility/transmission (Phase 2), but not during periods of low susceptibility/ transmission
  - Same phenomena observed in *single season* influenza vaccine trials
- Consistent evidence of efficacy against COPD hospitalizations RSV trials (Phase 2 and 3), suggest:
  - An under-recognized, under-studied, and unaddressed burden of RSV disease in COPD
  - Opportunity for an RSV vaccine to prevent COPD exacerbations to a degree that current pharmacotherapies cannot

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Unadjuvanted RSV F vaccine in older adults:

Post-hoc efficacy signal in E201 / E301: COPD exacerbation hospitalizations

Post-hoc Analyses of Hospitalizations for **All Cause** acute exacerbation of COPD in E-201 and E-301 data from the **Safety** Database

E301 Day 0-182	Placebo	Vaccine	VE%	95% CI	p value
AECOPD hospitalization rate (all subjects)	23/5935 (0.39%)	9/5921 (0.15%)	60.8%	15.2—81.9	0.017
AECOPD hospitalization rate (Identified baseline COPD)	15/362 (4.1%)	9/403 (2.2%)	46.1%	-23—76.4	0.14
E 201 Day 0-182					
AECOPD hospitalization rate (all subjects)	4/801 (0.50%)	0/798 (0%)	100%	NC	NC
AECOPD hospitalization rate (Identified baseline COPD)	2/62 (3.2%)	0/58 (0%)	100%	NC	NC

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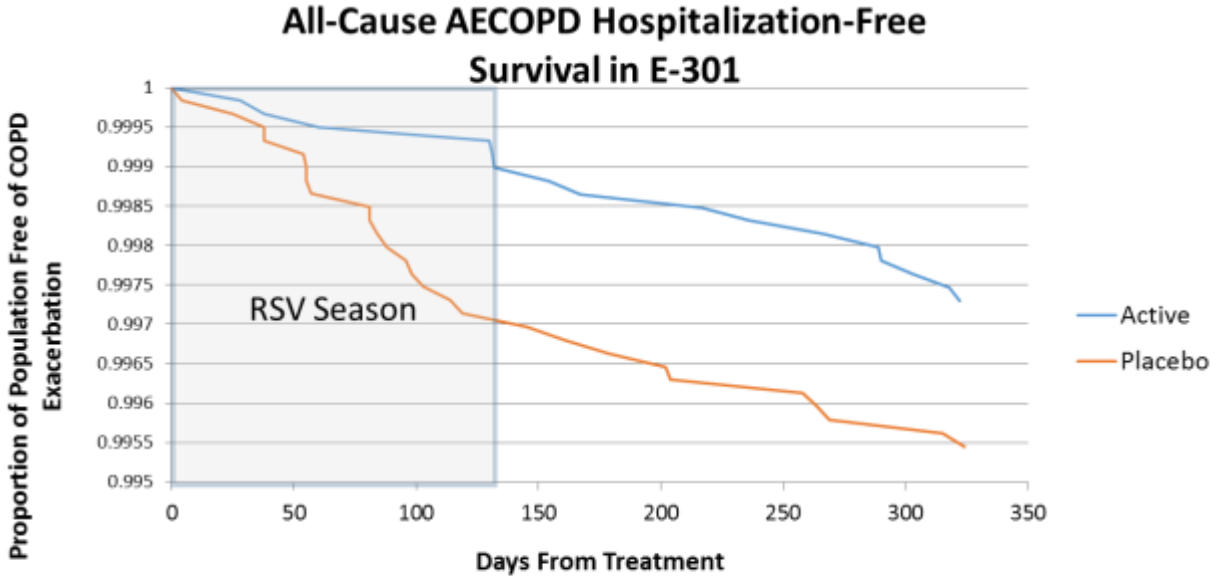
Unadjuvanted RSV F vaccine in older adults:

Post-hoc efficacy signal in E201 / E301: COPD exacerbation hospitalizations



- RSV F vaccine effect occurs—as expected—during the RSV season

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Unadjuvanted RSV F vaccine in older adults:

Experience and lessons through Phase 3

- Higher anti-RSV specific antibody titers were associated with less risk of RSV disease; “more antibody is better”

- However, largely overlapping antibody distributions between protected and unprotected individuals imply that:
  - There is no absolute protective cut-off titer in older adults
  - Available measures of anti-RSV specific antibodies may be relative (not absolute) correlates of protection in adults

- Phase 2 and 3 trials suggested that **unadjuvanted** RSV F vaccine can have efficacy in older adults, but needed enhancement of the immune response
  - Suggestion that repeat dosing (phase 2 re-immunization study) offers an avenue to improve efficacy
  - Classic and novel adjuvants were other obvious choices to consider moving forward

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Phase 2 (RSV-E-205)

Evaluation of adjuvants and dose regimens with RSV F vaccine in older adults

Rationale/aim	▪ **Evaluate adjuvants and repeat dosing as potential avenues to enhance vaccine immunogenicity in older adults**
When	▪ Trial initiated in **Jan 2017** in Australia
Design	▪ **300** healthy older adults (aged ≥60 years) ▪ Randomized, observer-blinded, placebo-controlled, evaluation of RSV F **with and without** aluminum phosphate **or** our proprietary Matrix-M™ adjuvant; in one or two-dose regimens
Objectives	▪ To ascertain whether adjuvantation or a two-dose primary regimen can alter the **quantity and quality** of the immune response to RSV F Vaccine in older adults ▪ To identify one or a small number of regimens meriting further evaluation in additional safety and immunogenicity and eventual efficacy ▪ To evaluate the **safety** of revised regimens and formulations of RSV F in older adults
Endpoints	▪ Safety ▪ RSV-specific immune responses by MN, anti-F IgG, PCA, and cell mediated immunity (CMI)

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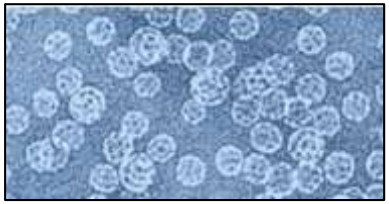
Matrix-M™ adjuvant

- Potent saponin-based adjuvant
  - Purified fractions extracted from the bark of Quillaja saponaria Molina
  - Formulated with cholesterol and phospholipid, forming cage-like particles



- Shown to have the following properties in the context of various antigens:
  - Leads to enhancement of activated T cell, B cell, and APC populations in draining lymph nodes
  - Induction of functional, and broadly cross-reactive antibodies (Shinde et al, NEJM, 2018)
  - Induction of polyfunctional T cells, both CD4+ and CD8+
  - Antigen sparing in the context of pandemic influenza

- > 2,300 adults have been exposed to Matrix™-M in ongoing and complete clinical trials
  - Acceptable safety profile

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E-205: treatment groups

[Focus on placebo, unadjuvanted formulation, and 4 treatment groups with best immune responses]

	Study Day	Day 0			Day 21		
Treatment Group	Subjects Per Group	RSV F Dose	Aluminum Dose	Matrix-M1 Dose	RSV F Dose	Aluminum Dose	Matrix-M1 Dose
A	25	135 µg	0	0	0	0	0
B	25	95 µg	0.3 mg	0	0	0	0
C	25	95 µg	0.3 mg	0	95 µg	0.3 mg	0
D	25	120 µg	0.4 mg	0	0	0	0
E	25	120 µg	0.4 mg	0	120 µg	0.4 mg	0
F	25	135 µg	0	50 µg	0	0	0
G	25	135 µg	0	50 µg	135 µg	0	50 µg
H	25	65 µg	0	50 µg	0	0	0
J	25	65 µg	0	50 µg	65 µg	0	50 µg
K	25	35 µg	0	50 µg	0	0	0
L	25	35 µg	0	50 µg	35 µg	0	50 µg
M (Placebo)	25	0	0	0	0	0	0
Total	300 Subjects						

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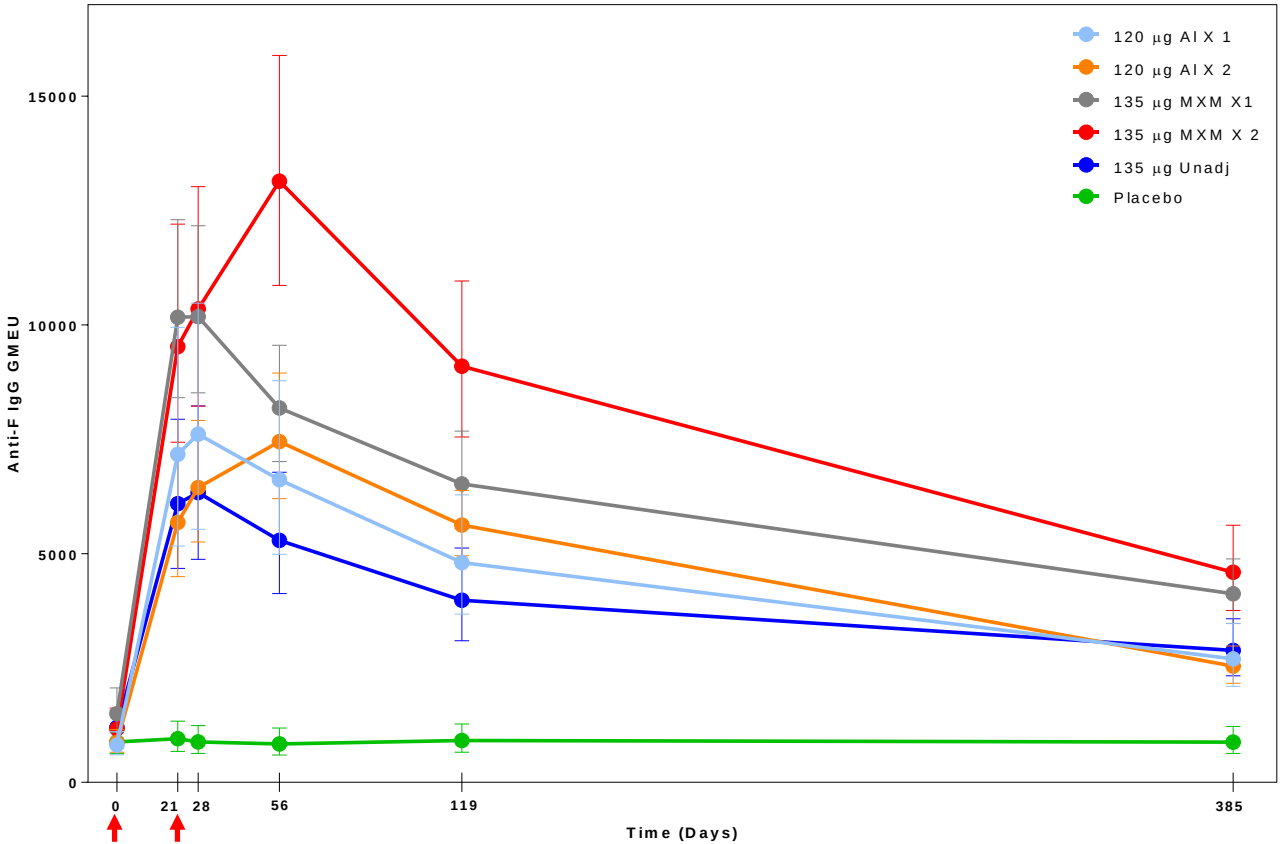
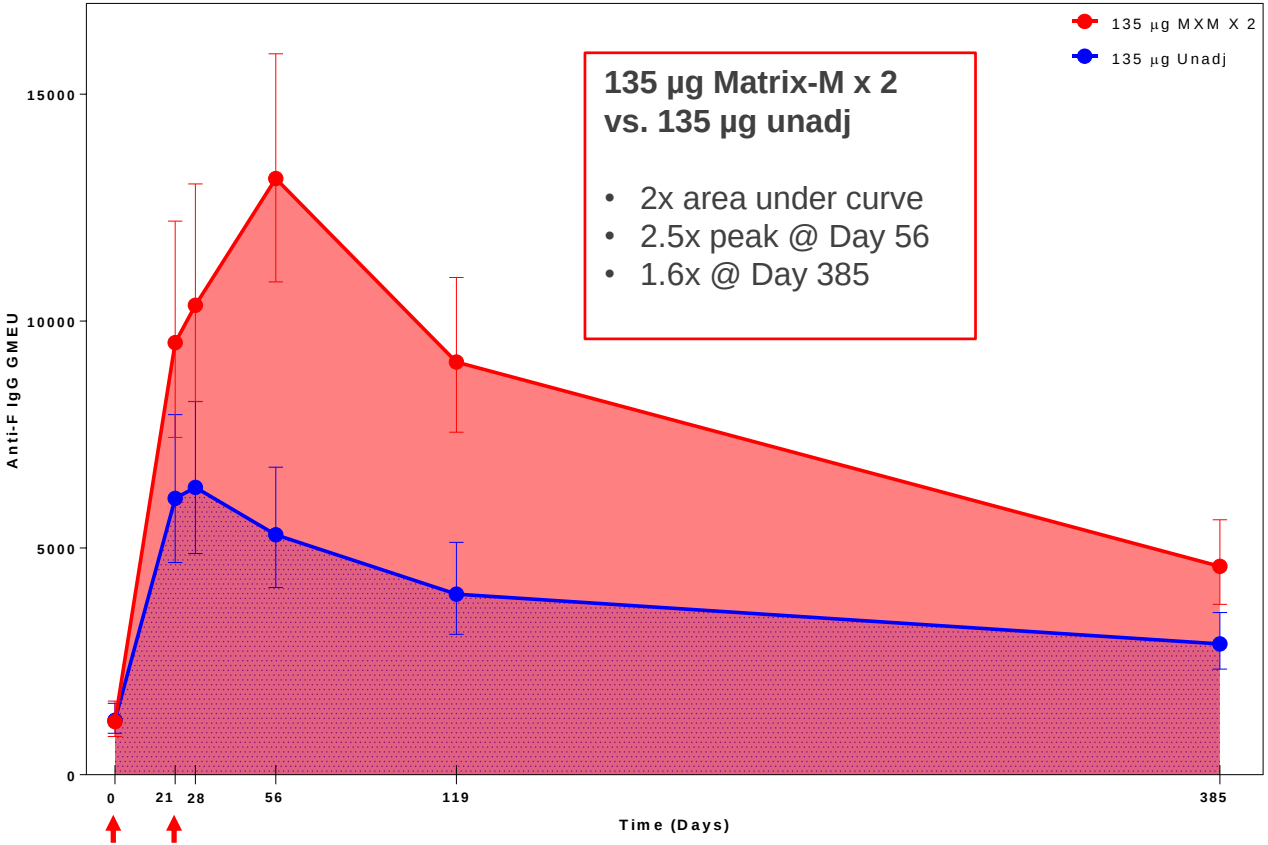
E-205 Kinetics of **Anti-F IgG** in representative groups:

Adjuvant effect, 2nd dose effect, and durability of responses



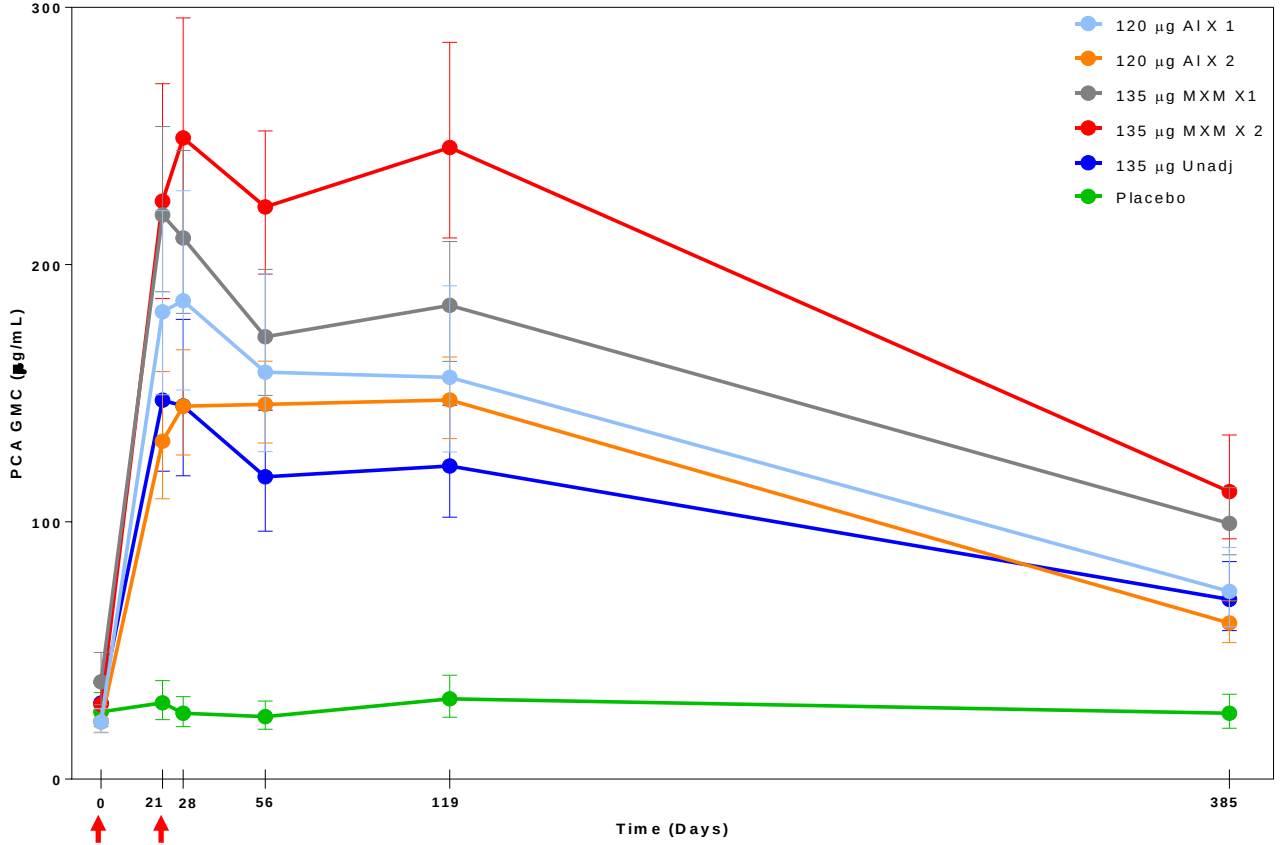
E-205 Kinetics of **Anti-F IgG** in 135 µg unadjuvanted vs. 135 µg Matrix-M x2:

Substantial increases in peak and long-term responses



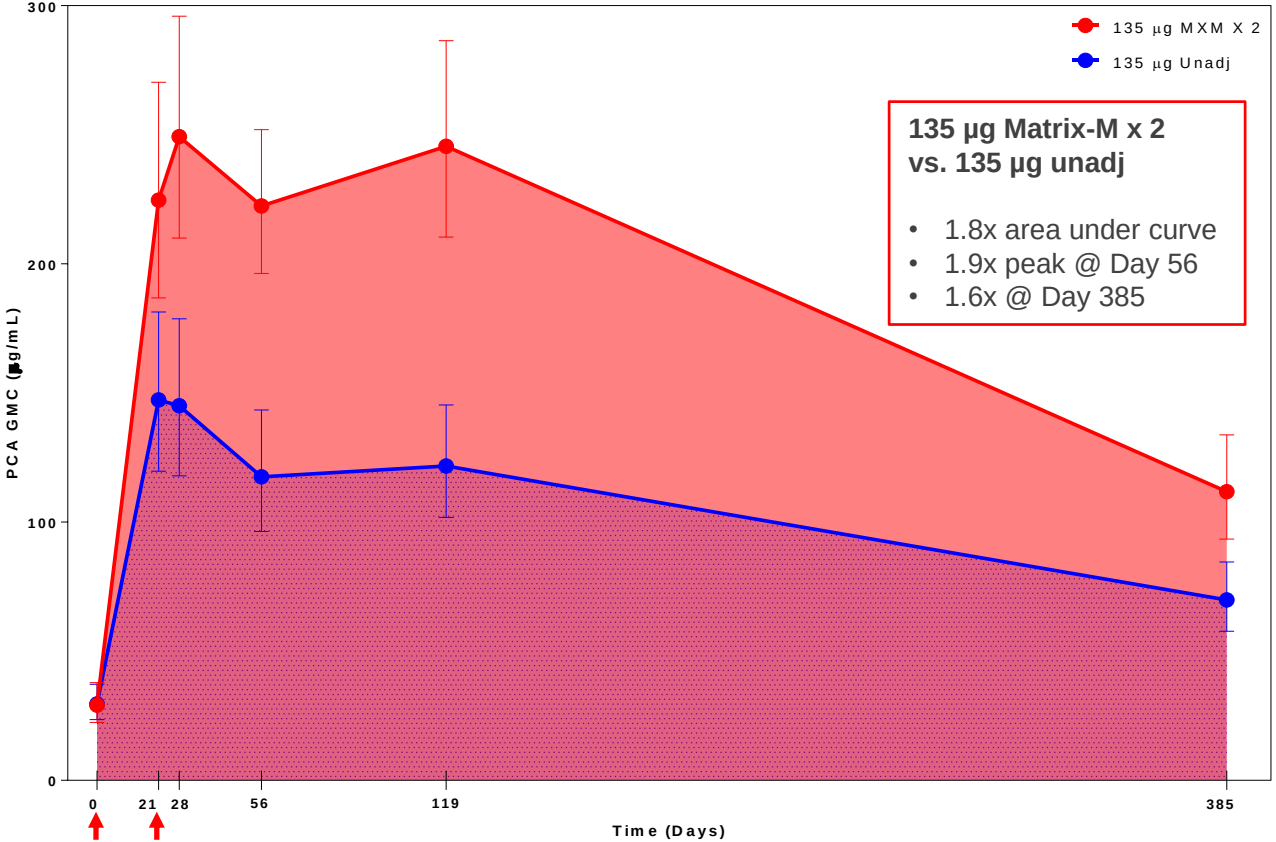
E-205 Kinetics of PCA in representative groups:

Adjuvant effect, 2nd dose effect and durability of responses

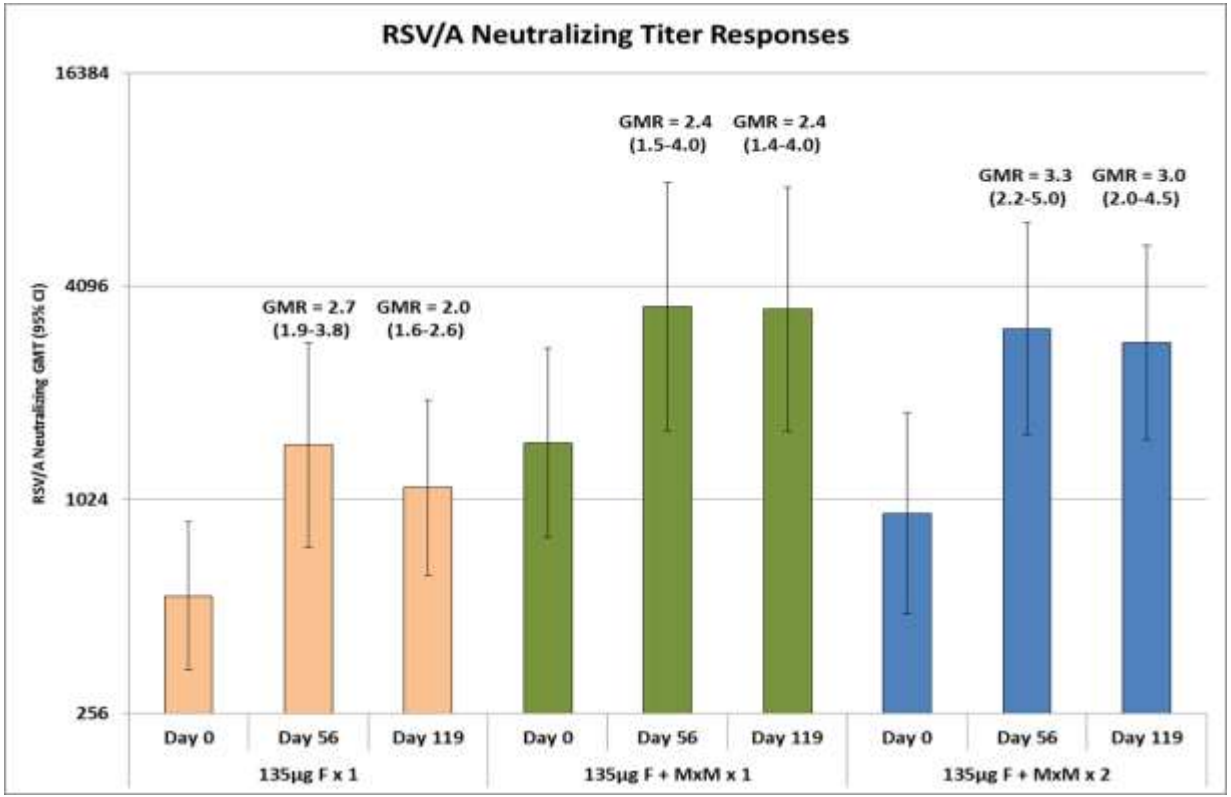


E-205 Kinetics of PCA in 135 µg unadjuvanted vs. 135 µg Matrix-M x2:

Substantial increases in peak and long-term responses



E-205 RSV/A neutralizing antibodies in control and Matrix-M groups (ELISA-based method)



Sustained MN Response to Adjuvanted Vaccine

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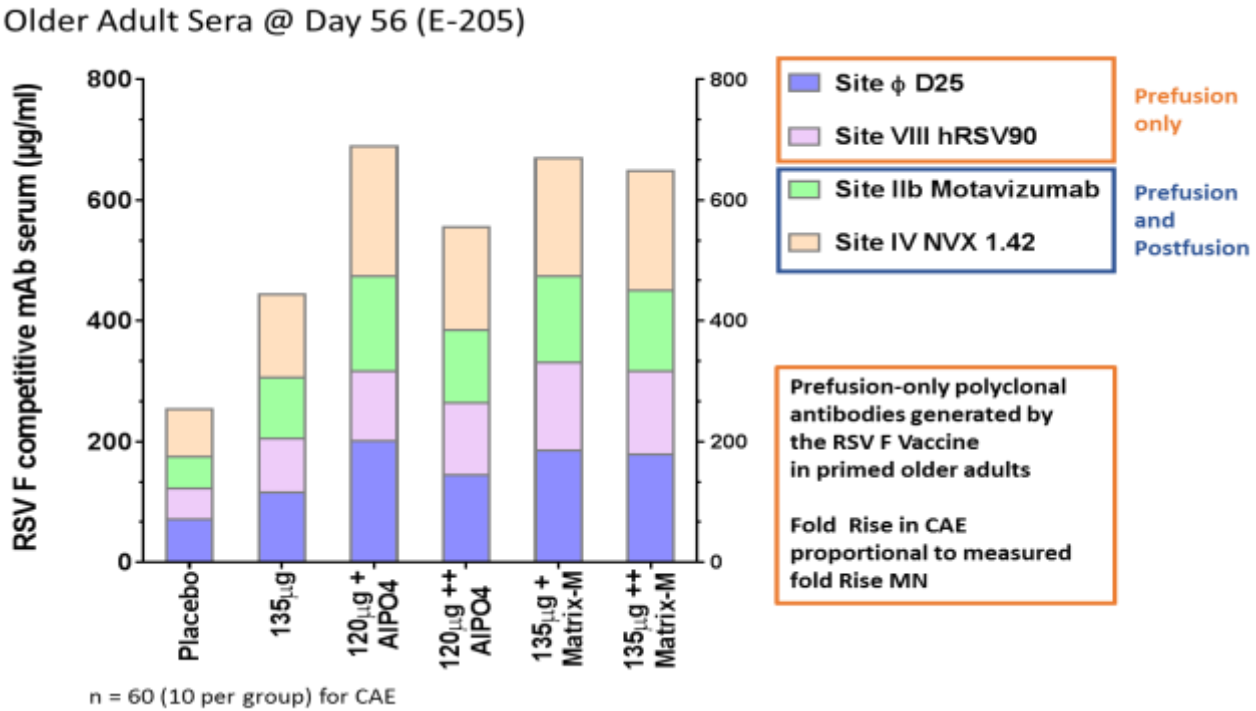
E205 Competitive Antibody Equivalents (CAE) detected by biolayer interferometry:

Polyclonal antibodies to pre-fusion and post-fusion epitopes



Competitive antibody equivalents (CAE) detected by biolayer interferometry using previously characterized mabs to RSV F protein

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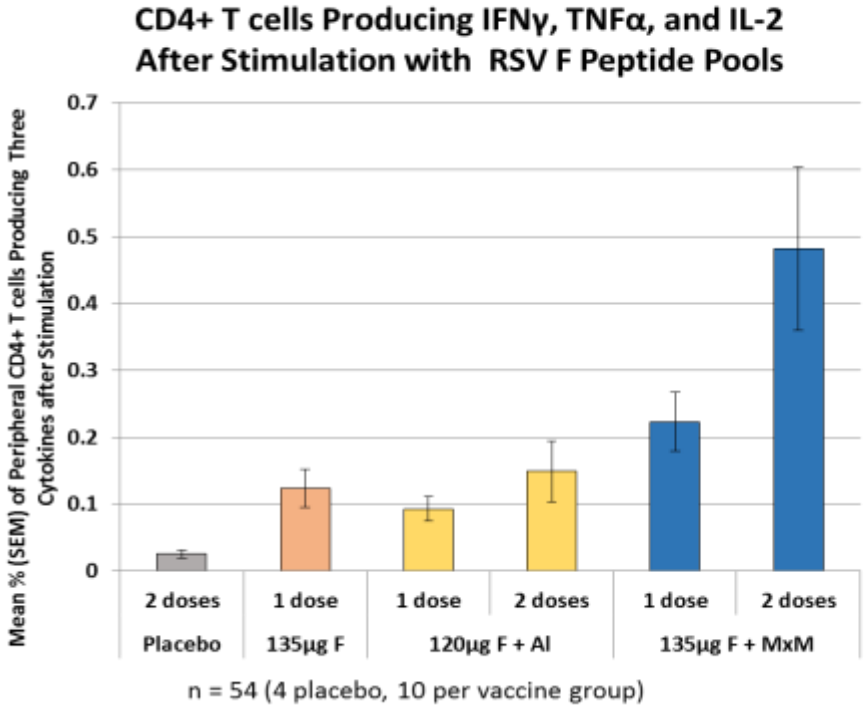
E-205 Cellular immune responses:

Matrix-M enhances triple cytokine positive RSV F-specific CD4+ responses

CD4⁺ T Cell Responses by Intracellular Staining



n = 54 (4 placebo, 10 per vaccine group)

Treatment	Doses	Day 0	Day 28
Placebo	2	0.026	0.014
135µg F	1	0.028	0.124
120µg F + Al	1	0.016	0.093
	2	0.011	0.218
135µg F + MxM	1	0.023	0.223
	2	0.022	0.482

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E-205 conclusions

- With respect to safety, all adjuvanted formulations were clinically tolerable

- The totality of immune responses makes use of adjuvants and two-dose regimens desirable
  - Both adjuvants enhanced the **magnitude of peak** antibody responses
  - Only Matrix-M substantially **extended the long-term durability** of responses
  - **Two dose regimens** further enhanced the effects of adjuvants on peak and duration of responses
  - **T-cell immunity** was observed in all regimens, but was most notably enhanced by Matrix-M
  - High levels of antibodies competitive with site IIb (mota), site ϕ, and site IV antibodies were induced and enhanced by adjuvants

- 135 µg RSV F with Matrix-M, in a 2 dose regimen, outperformed all other formulations/regimens across a variety of humoral and cellular immune measures
  - Near doubling of peak responses and area under the curve as compared unadjuvanted formulation
  - One year responses 60% higher as compared to unadjuvanted formulation

- E205 data builds confidence in the continued development of Matrix-M adjuvanted RSV F vaccine in older adult, COPD, and other high-risk populations

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Thank you
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