Covering the SARS-CoV-2 Antigenic Landscape: The COVAIL Trial and Beyond

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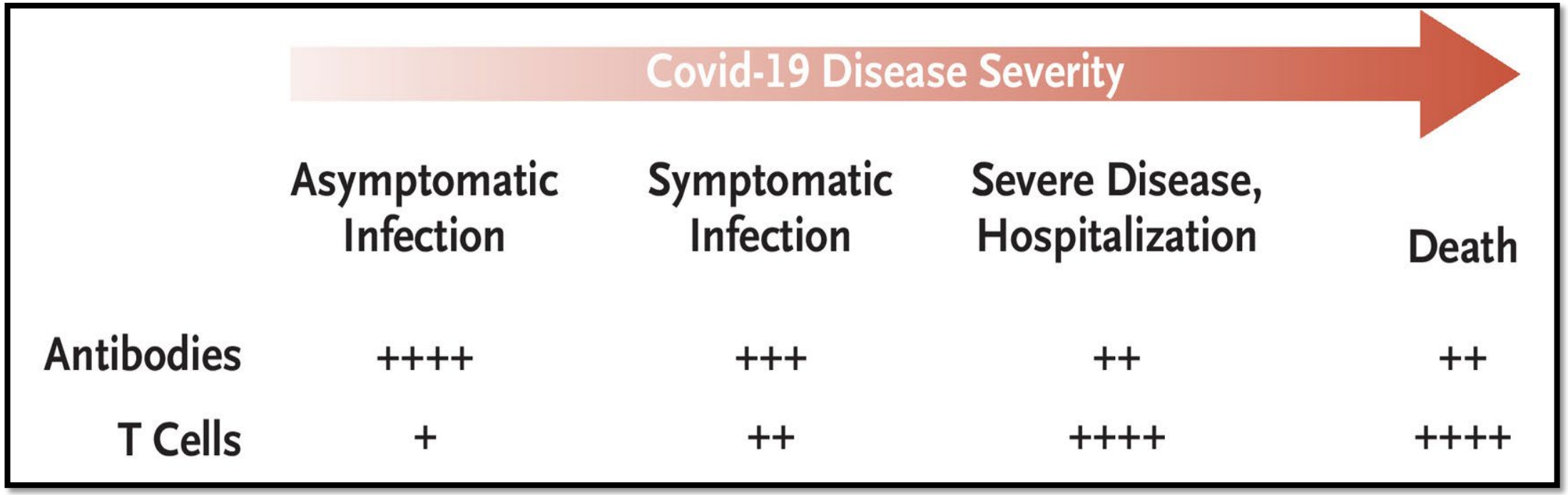
Disclosures

- No relevant conflicts of interest to disclose

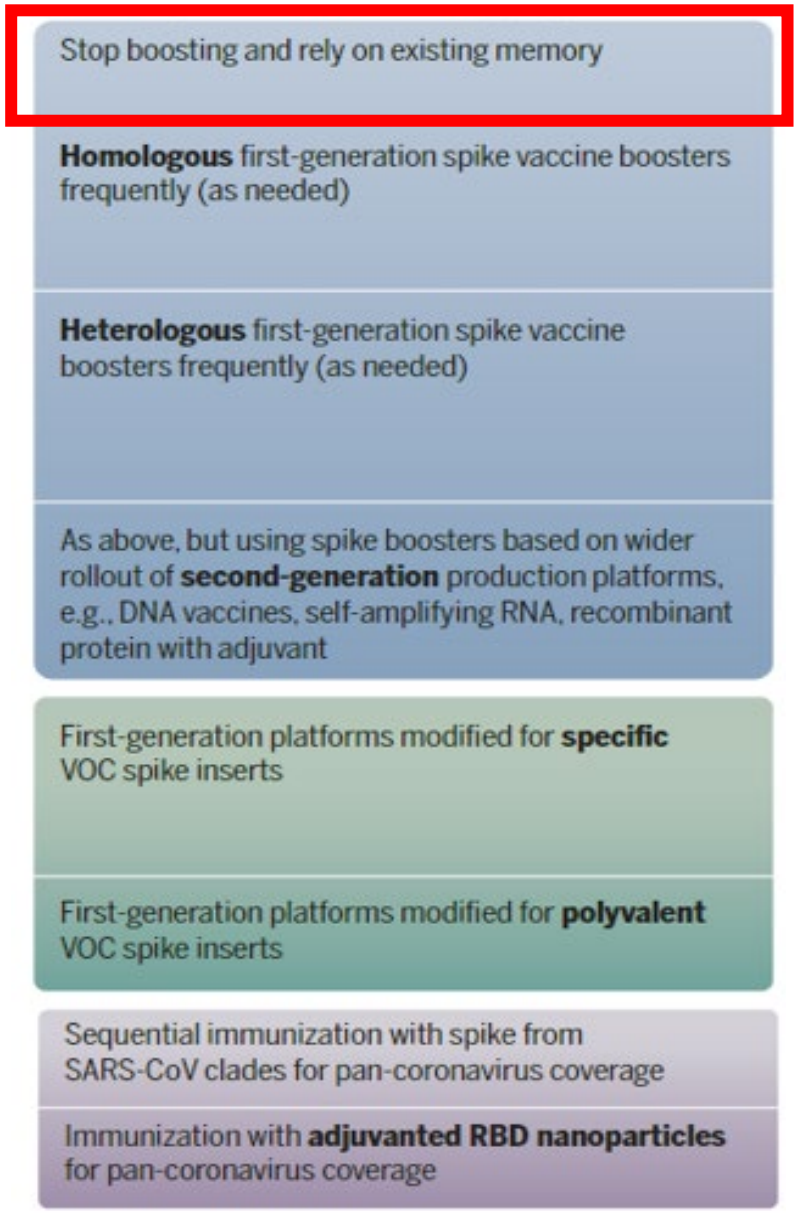
Background and Rationale

- Primary COVID19 vaccine regimens rapidly established immunity and protection against COVID19
- Over time, humoral immunity wanes resulting in risk for breakthrough infection
- **Emergence of variants of concern with different degrees of immune escape, challenge the effectiveness of pre-existing immunity from vaccine and infection.**



Barouch, DM. NEJM 2022; 387:1011-1020; DOI: 10.1056/NEJMra2206573

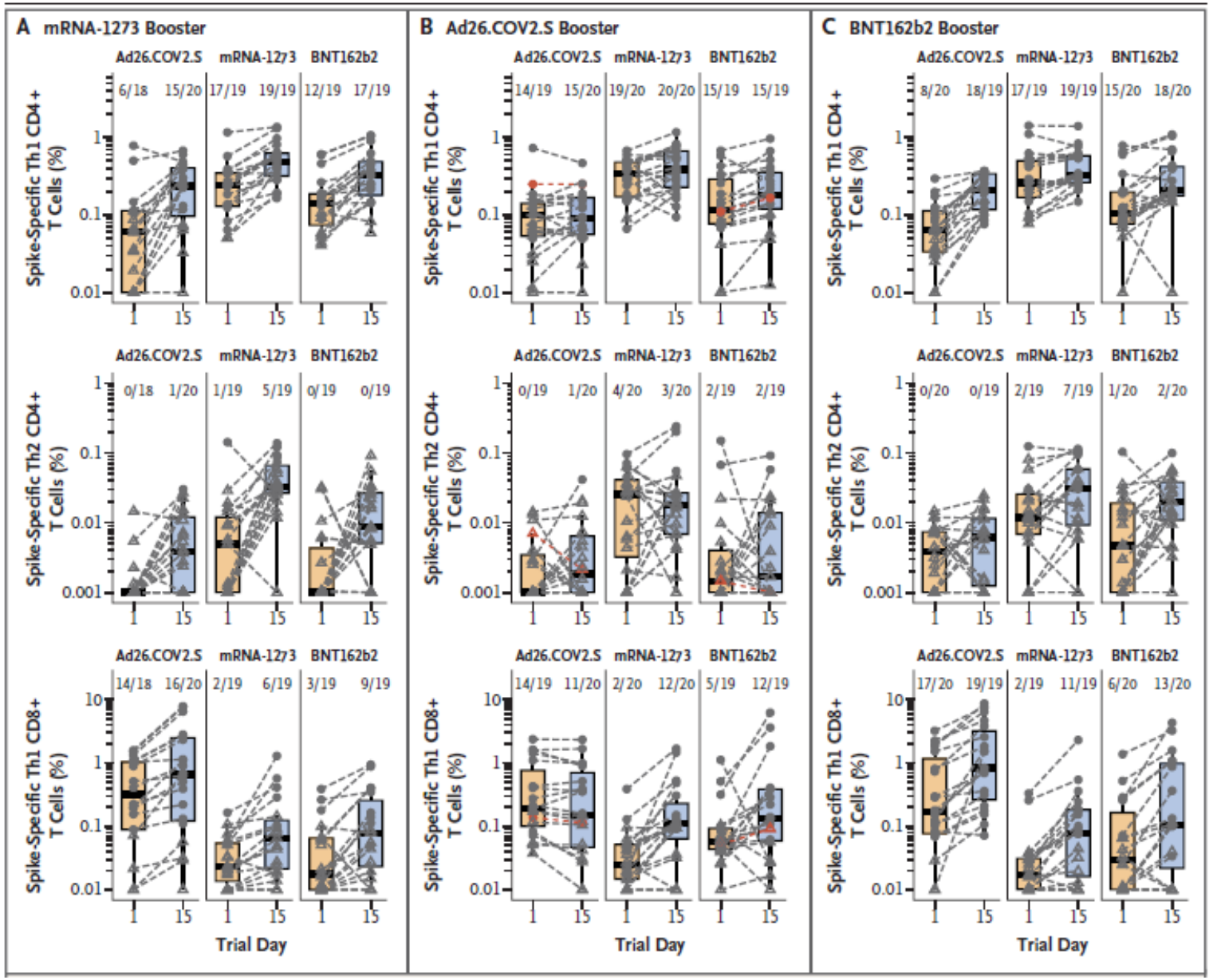
Future Approaches to Maintain or Improve Immunity to SARS-CoV-2



➢ Additional doses improves cellular responses after the primary series

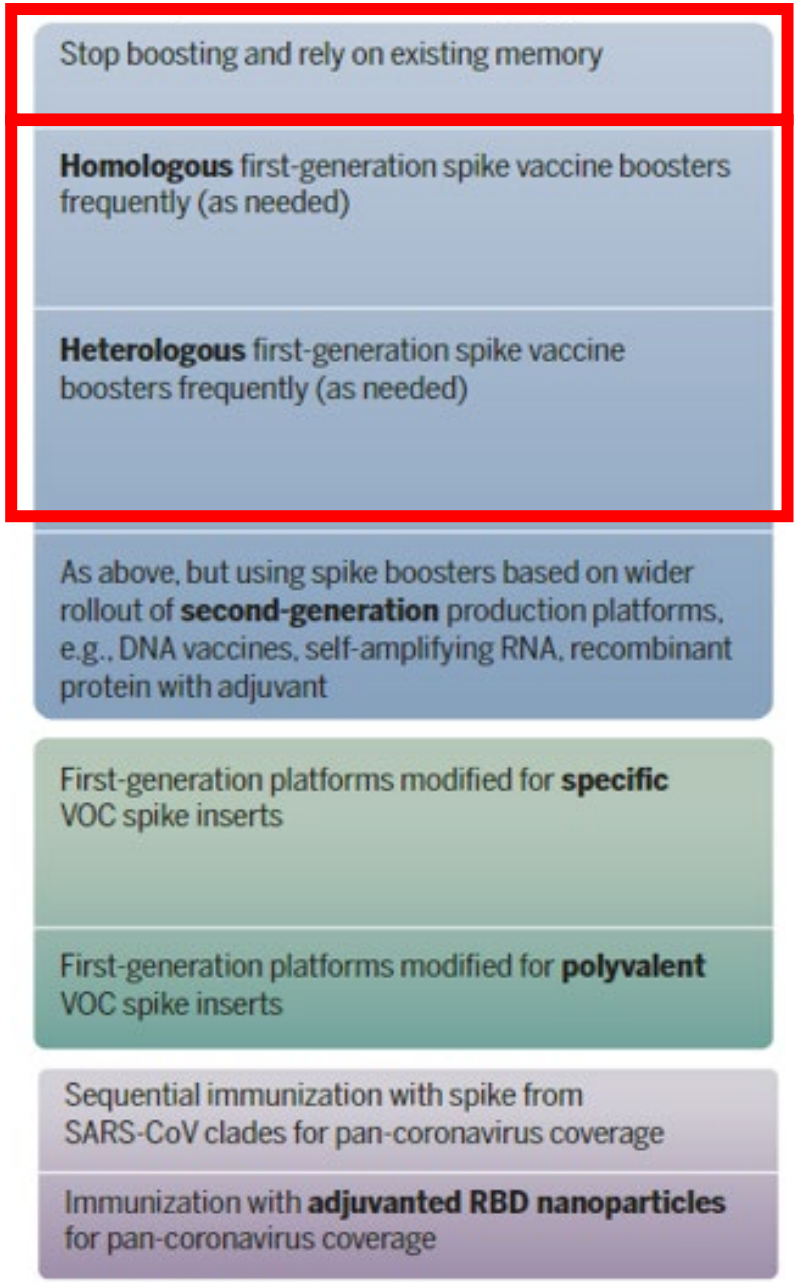
- SARS-CoV-2 spike-specific Th1 (interferon-γ, interleukin- 2, or both) CD4+ T cells responses increased at day 15 for all groups except for Ad26.COV2.S homologous prime-boost participants

- Booster immunization increased the response rate and amount of spike-specific CD8+ T cells in all groups, except for Ad26.COV2.S homologous prime-boost participants



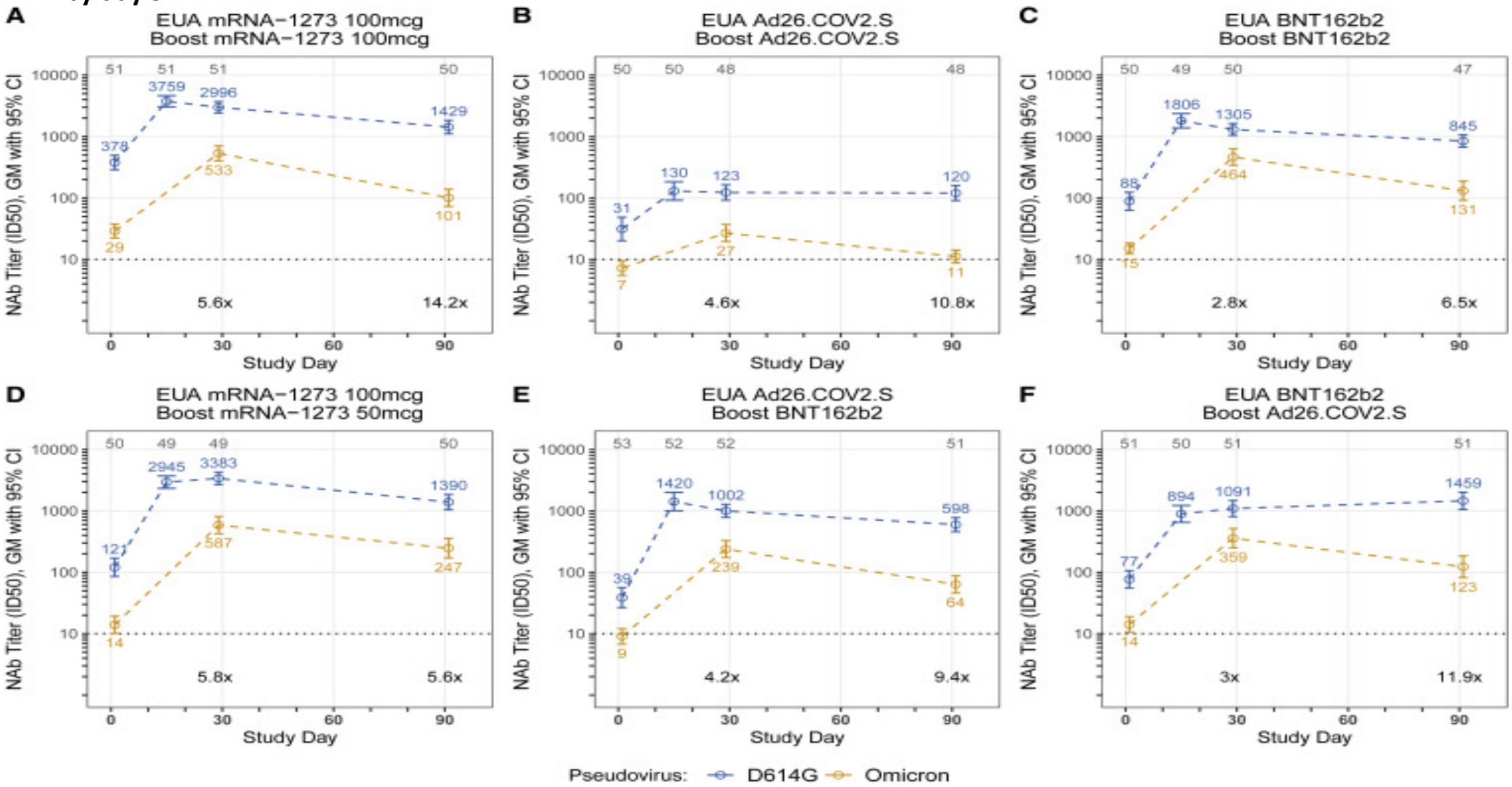
Atmar et al, NEJM, 2022 Mar 17;386(11):1046-1057

Future Approaches to Maintain or Improve Immunity to SARS-CoV-2



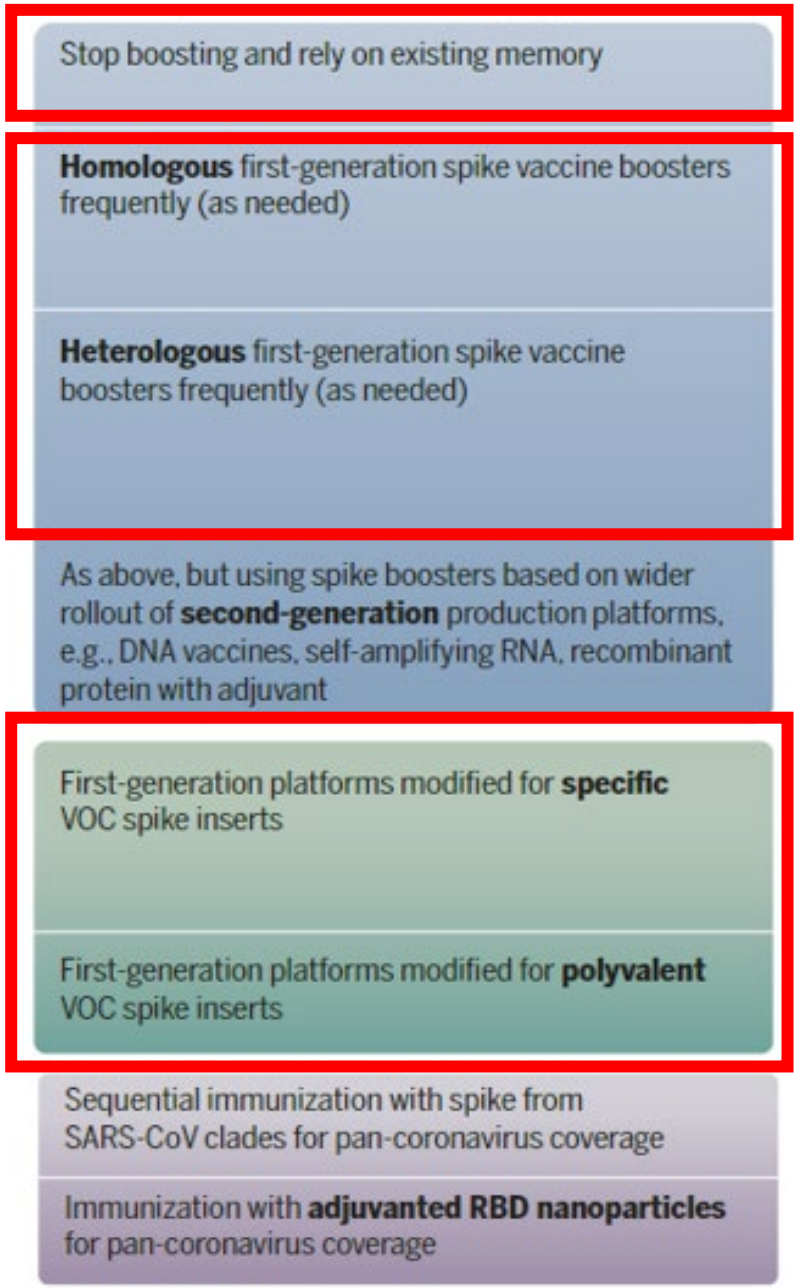
→ Immunity wanes and over time. There may be risks for severe disease with breakthrough infections and a third dose has been shown to improve both humoral and cellular responses.

- **We now know booster dose given as a third dose for most vaccines improved vaccine effectiveness against new variants in the short term but immunity is suboptimal with potentially a more rapid decay in GMT to Omicron BA.1 compared to D614G by day 91**



Lyke et al. Cell Reports Medicine 2022

Future Approaches to Maintain or Improve Immunity to SARS-CoV-2



→ Immunity wanes and over time. There may be risks for severe disease with breakthrough infections and a third dose has been shown to improve both humoral and cellular responses.

→ Immunity may be suboptimal against new and emerging variants potentiating risk for severe disease with breakthrough infections

→ **Would this strategy provide higher, more durable or more broadly cross-protective immune responses?**

→ **Can this strategy overcome the limitation of only protecting against the known antigenic space?**

COVID-19 VAriant Immunologic Landscape Trial (COVAIL Trial)

DMID Protocol Number: 22-0004

Rationale for COVAIL

How do we use vaccines with variant or wildtype spike antigens (monovalent, bivalent or multivalent) to expand and optimize immune coverage?

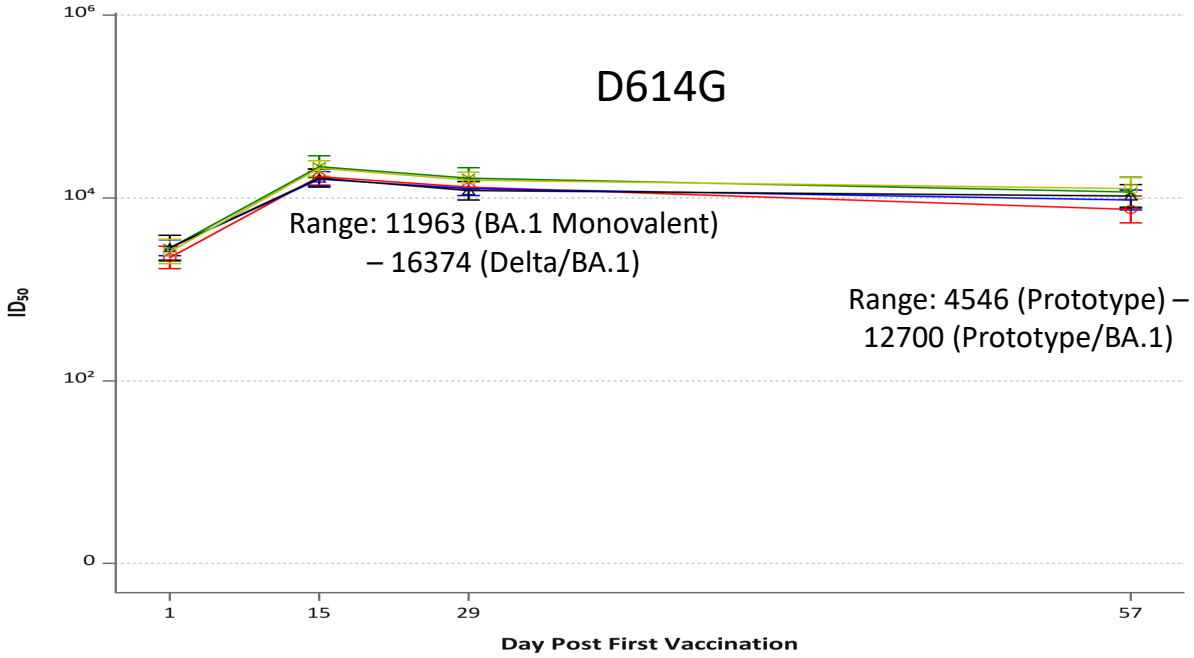
- Designed to look beyond Omicron and define how we can shift the immune response to cover new variants as they emerge

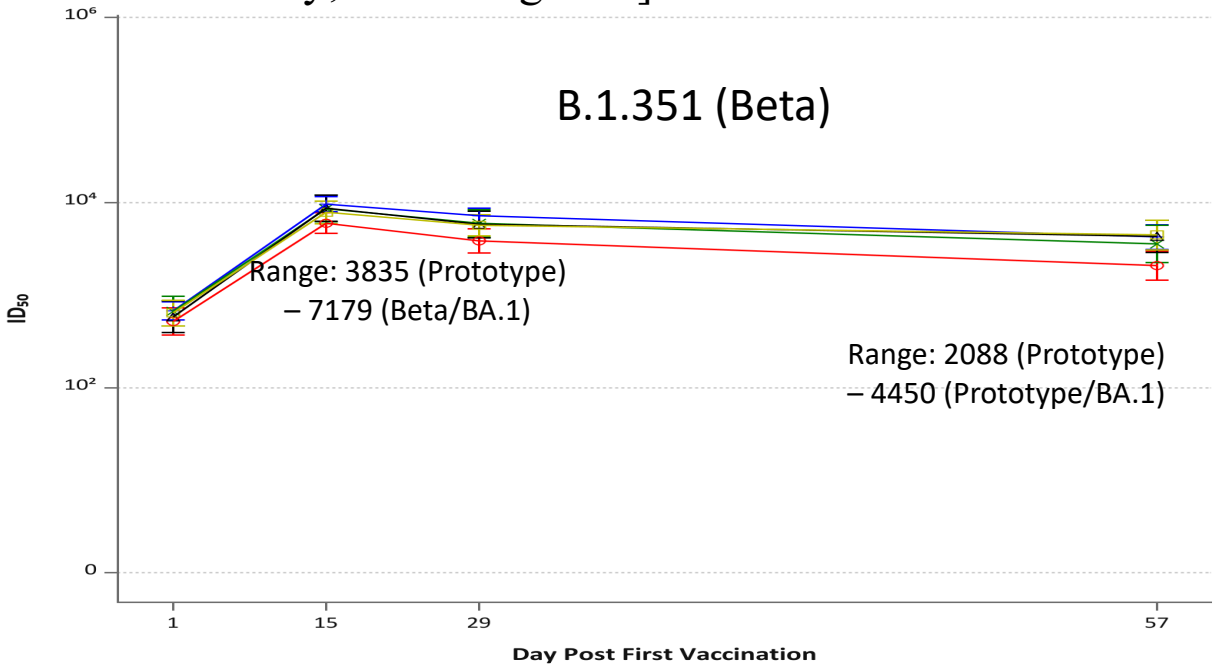
Covail Study Design

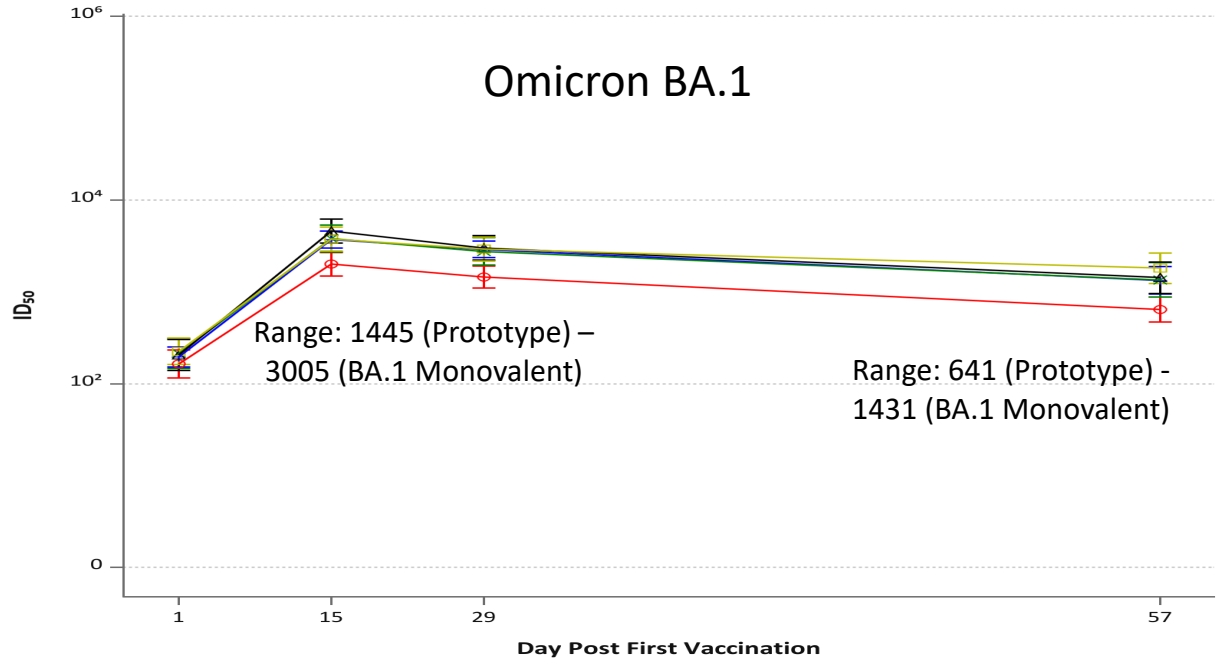
- **Population:**
  - Received any COVID-19 vaccine primary and boost
  - Homologous or heterologous
- **Two age strata:**
  - 18-54 years
  - ≥ 55 years
- **Two infection strata:**
  - Confirmed prior COVID-19 (>20%)

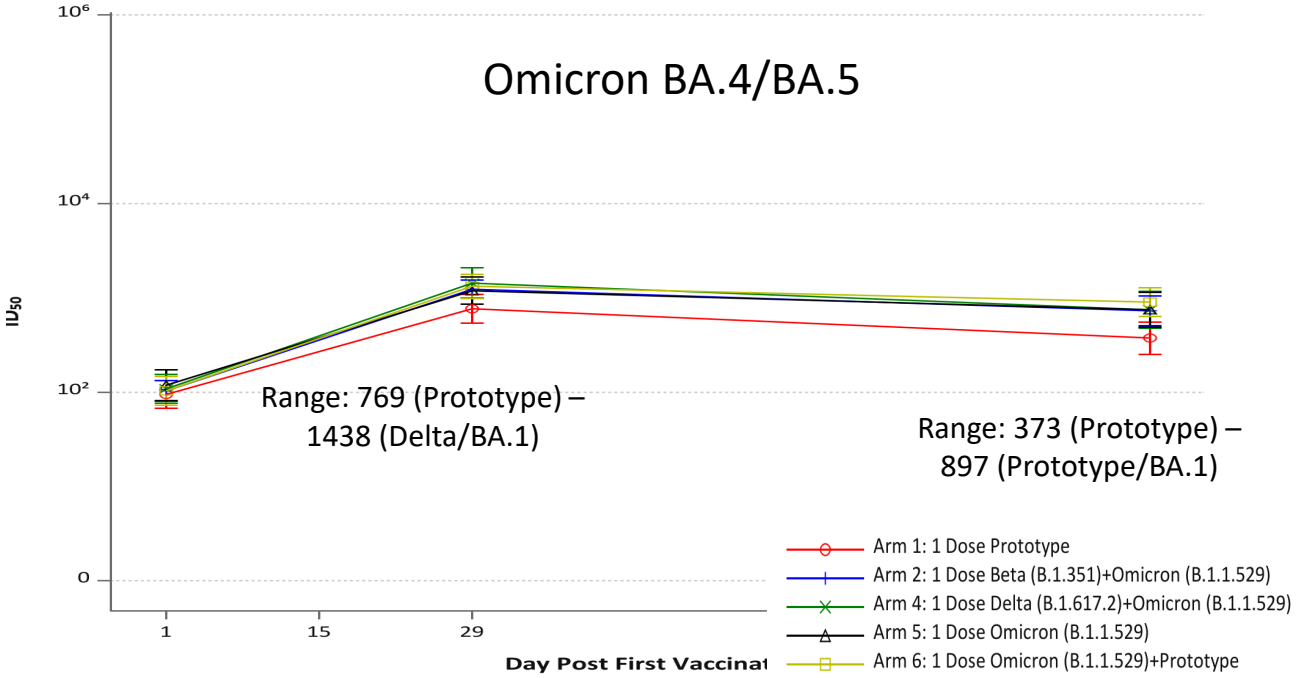
	Arms	Sample Size	Vaccine Candidate	Interval (weeks)	Dose	
Stage 1	1	100	Prototype	≥16	One dose	Moderna
	2	100	Beta + Omicron. BA.1	≥16	One dose	
	3	100	Beta + Omicron BA.1	≥16	Two Doses	
	4	100	Delta + Omicron BA.1	≥16	One dose	
	5	100	Omicron BA.1	≥16	One dose	
	6	100	Omicron +Prototype	≥16	One dose	
Stage 2	7	50	Wildtype (Prototype)	≥16	One dose	Pfizer
	8	50	Beta + Omicron BA.1	≥16	One dose	
	9	50	Omicron BA.1	≥16	One dose	
	10	50	Beta	≥16	One dose	
	11	50	Beta+Wildtype (Prototype)	≥16	One dose	
	12	50	Omicron BA.1 + Wildtype (Prototype)	≥16	One dose	
Stage 3	13	50	Prototype	≥16	One dose	Sanofi
	14	50	Beta	≥16	One dose	
	15	50	Beta + Prototype	≥16	One dose	
Stage 4	13	50	Wildtype + Omicron BA.1	≥16	One dose	Pfizer
	14	50	Wildtype + BA.4/BA.5	≥16	One dose	

Stage 1 COVAIL (Moderna): Monogram PsVN [Negative Infection History; N-Ab negative]



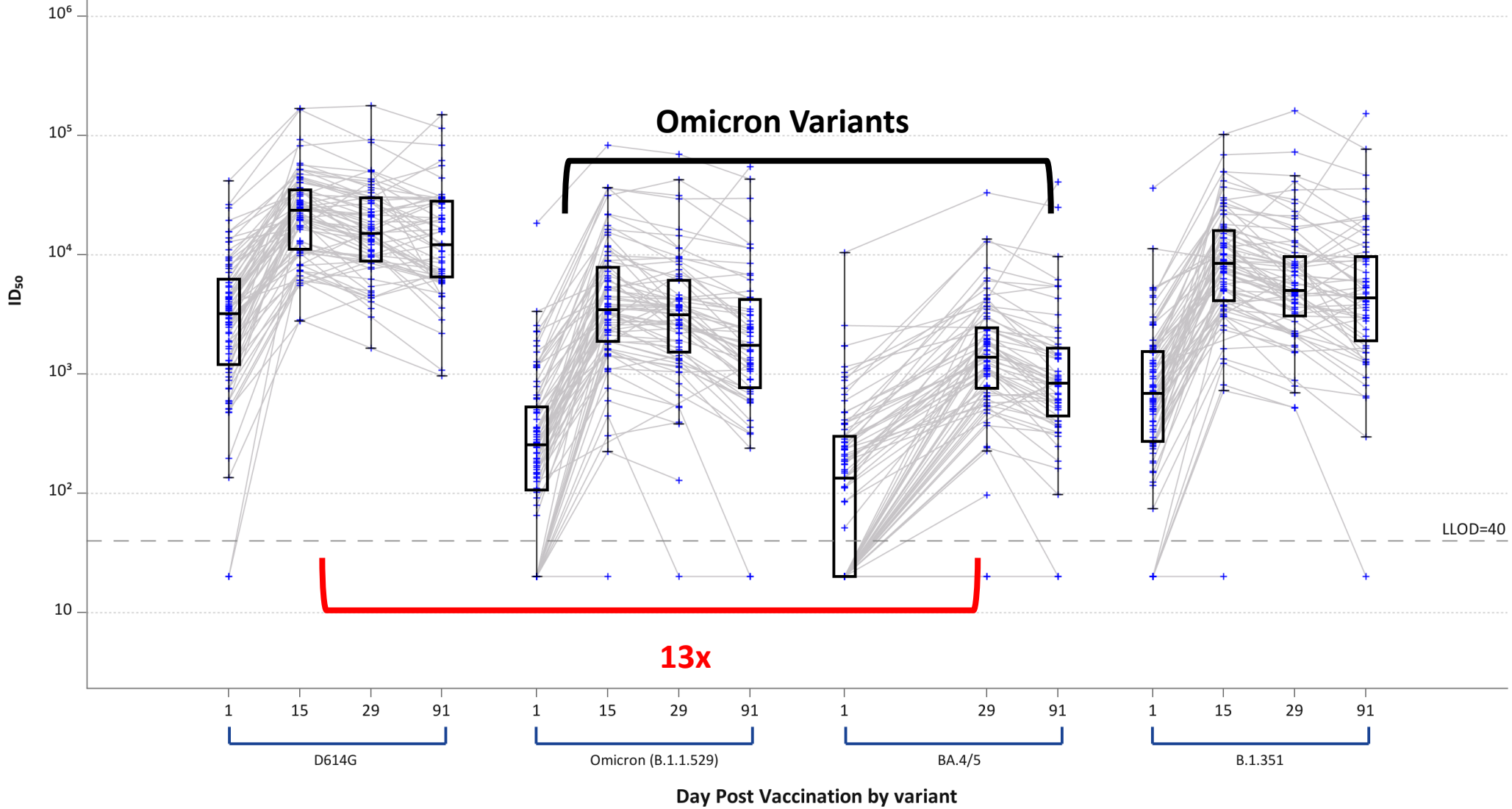






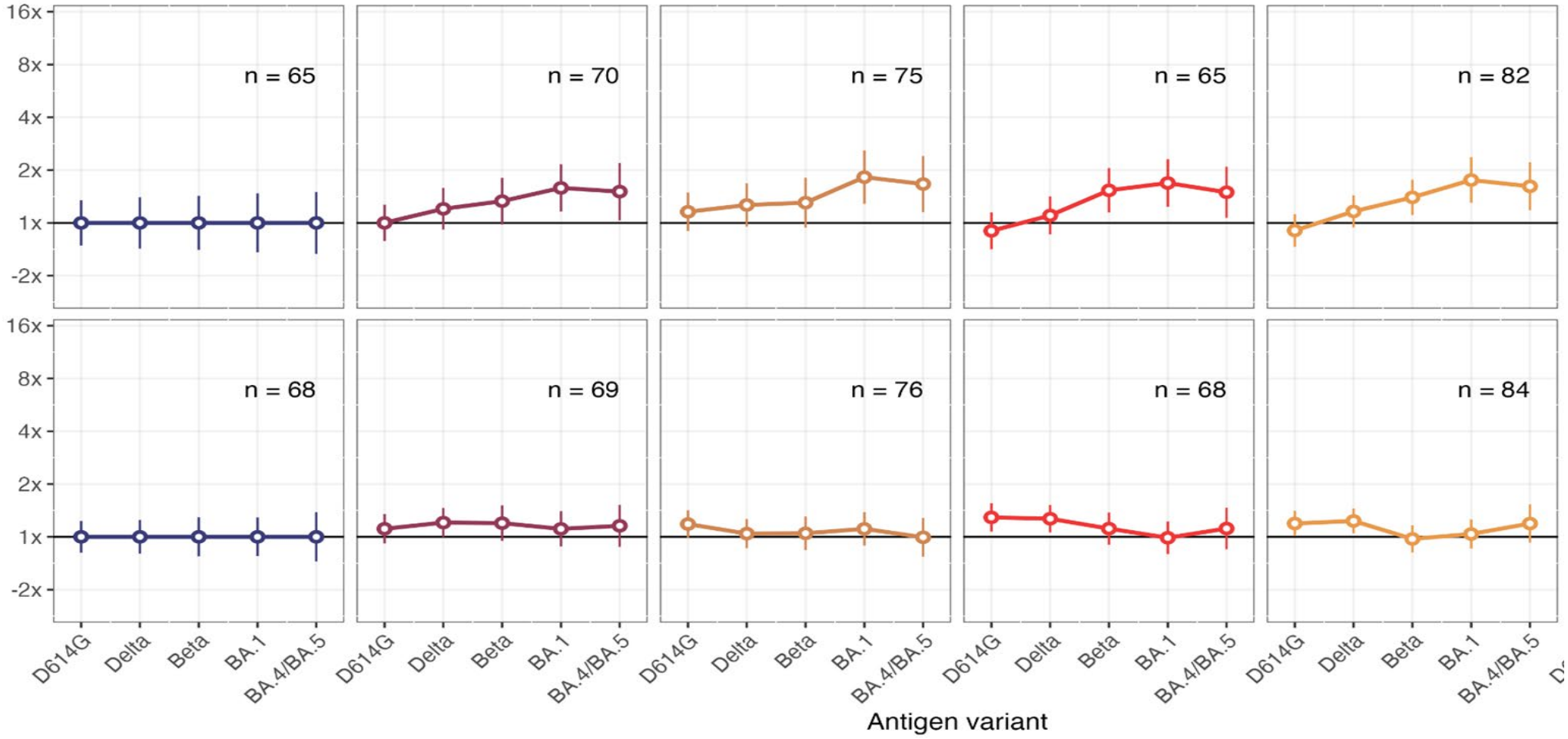
Prototype: Omicron BA.1 Bivalent Vaccine

GMFR	1.0	7.8	5.5	3.7	1.0	15.8	12.5	6.4	1.0	12.4	6.9	1.0	11.7	8.4	5.3
GMT	2586	21096	15590	12700	225	3747	2923	1805	103	1325	897	640	7814	5692	4450
GMR D614G	1.00	1.00	1.00	1.00	0.09	0.18	0.19	0.14	0.04	0.08	0.07	0.25	0.37	0.37	0.35
>LLOD	77	73	70	59	65	72	69	57	47	68	57	74	72	70	58
Total	79	73	70	59	79	73	70	59	79	70	59	79	73	70	59



Stage 1 COVAIL (Moderna): Ratio of GMFR Normalized to Prototype Baseline at Day 1, 29 and 91 [Negative Infection History; N-Ab negative]

Prototype | Prototype + Omicron BA.1 | Delta + Omicron BA.1 | Omicron BA.1 | Beta + Omicron BA.1



Ratio of GMFR from D1 to D91

Ratio of GMFR from D29 to D91

Stage 1: Adjusted Pseudovirus Neutralization Day 91 GMR ANCOVA Modeling: Overall

Note: Adjusted for baseline titers, age and prior infection. Confidence intervals are unadjusted at confidence level 97.5%.

Variant	Comparison to prototype	Estimate	Variant	Comparison to prototype	Estimate
D614G	Omicron BA.1 + Delta	1.31 (0.94 , 1.82)	Beta (B.1.351)	Omicron BA.1 + Delta	1.46 (1.01 , 2.11)
	Omicron BA.1	1.22 (0.88 , 1.68)		Omicron BA.1	1.97 (1.37 , 2.83)
	Omicron BA.1 + Prototype	1.4 (1.01 , 1.95)		Omicron BA.1 + Prototype	1.73 (1.19 , 2.51)
	Omicron BA.1 + Beta	1.2 (0.87 , 1.65)		Omicron BA.1 + Beta	1.92 (1.34 , 2.75)
Variant	**Comparison to prototype**	**Estimate**	**Variant**	**Comparison to prototype**	**Estimate**
Omicron BA.1 (B.1.1.529)	Omicron BA.1 + Delta	1.87 (1.27 , 2.76)	Omicron BA.4/BA.5	Omicron BA.1 + Delta	1.73 (1.17 , 2.57)
	Omicron BA.1	2.03 (1.39 , 2.97)		Omicron BA.1	1.72 (1.17 , 2.53)
	Omicron BA.1 + Prototype	2.2 (1.49 , 3.26)		Omicron BA.1 + Prototype	1.94 (1.3 , 2.88)
	Omicron BA.1 + Beta	2.26 (1.55 , 3.3)		Omicron BA.1 + Beta	2.1 (1.43 , 3.07)

Omicron BA.1 Neutralizing Antibody Titers Were Significantly Higher after 4th Dose with Omicron BA.1 Bivalent than mRNA-1273 (*Study 205, Per-Protocol Immunogenicity Set with No Prior Infection)*

	4th Dose	
	Prototype (mRNA-1273) N = 259	**Omicron BA.1 Bivalent (mRNA-1273.214)** (N = 335)
GMT Pre-booster, 95% CI	**330** (280, 388)	**298** (258, 343)
Estimated GMT at Day 29, 95% CI[1]	**1419** (1281, 1572)	**2470** (2256, 2704)
Seroresponse rate at Day 29 (pre-dose 1), 95% CI	**99.2%** (97.2, 99.9%)	**100%** (98.9, 100%)
Estimated GMT at Day 91, 95% CI[1]	**603** (535, 679)	**998** (898, 1107)
Seroresponse rate at Day 91 (pre-dose 1), 95% CI	**96.3%** (93.0-98.3%)	**98.5%** (96.4, 99.5%)
GMT Ratio[1] at Day 29 (Bivalent vs. Original), 97.5% CI	**1.74 (1.49, 2.04)**	
GMT Ratio[1] at Day 91 (Bivalent vs. Original), 97.5% CI	**1.66 (1.38, 1.99)**	

Success Criteria Met

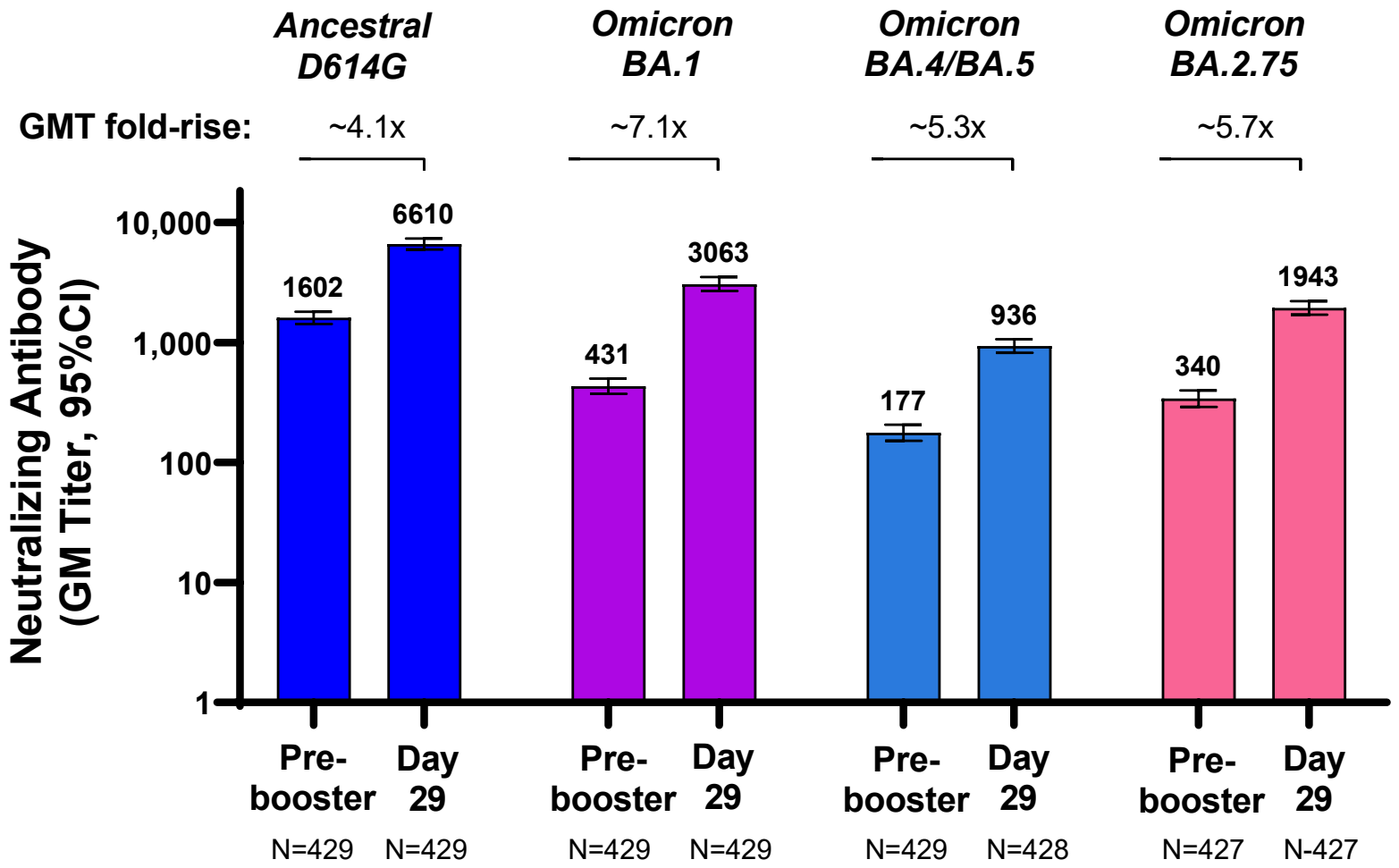
Superiority of GMTs: Lower 97.5% CI of GMT Ratio > 1.0

Non-inferiority of Seroresponse Rates: Lower 97.5% CI of difference > -10%

[1] Based on ANCOVA model adjusting for age group (<65, ≥65 years) and pre-booster titer

[2] Common risk difference and 97.5% CI were calculated by Miettinen-Nurminen method adjusted for age group (<65, ≥65 years)

Omicron BA.1 Bivalent Vaccine Exhibits Cross-Neutralization Across Multiple Omicron Variants



~5.3 – 7.1 fold increase in titers against Omicron variants following receipt of BA.1 Omicron Bivalent Booster (mRNA-1273.214)

Moderna Bivalent BA.4/BA.5 Booster Vaccine

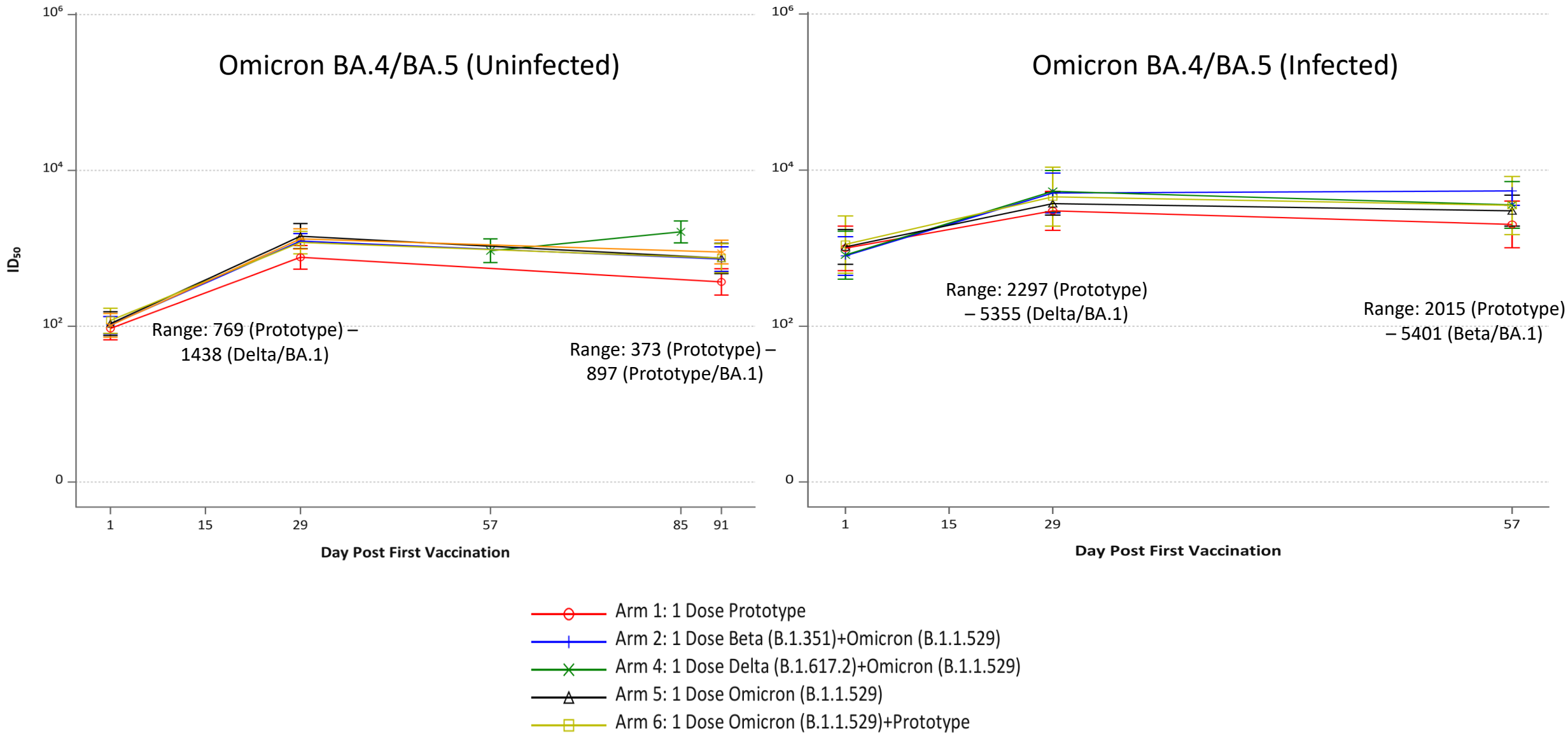
- Phase 2/3 study of a 50 µg booster dose of mRNA-1273.222 (Prototype + BA.4/BA.5) compared to a 50 µg booster dose of mRNA-1273 in previously vaccinated and boosted participants (ages 19-89 years)
- Participants received mRNA-1273.222 and mRNA-1273 approximately 9.5 months and 4.5 months after their most recent vaccination dose at different time periods

	Omicron BA.4/BA.5 Bivalent (mRNA-1273.222)
Day 29 GMT, 95% CI	4289 (95% CI: 3789.0, 4855.9)
Day 29 GMFR, 95% CI	15.1 (95% CI: 13.3, 17.1)
No Prior Infection Day 29 GMT, 95% CI	2325 (95% CI: 1321.2, 2812.7)
Day 29 GMFR, 95% CI	26.4 (95% CI: 22.0, 31.9)
Prior Infection Day 29 GMT, 95% CI	6965 (95% CI: 6043.7, 8025.4)
Day 29 GMFR, 95% CI	9.8 (95% CI: 8.4, 11.4)

- Results were consistent between participants aged 65 years and older and those aged 18 to 65
- Neutralization titers against BQ.1.1 were approximately 5-fold lower than to BA.4/BA.5

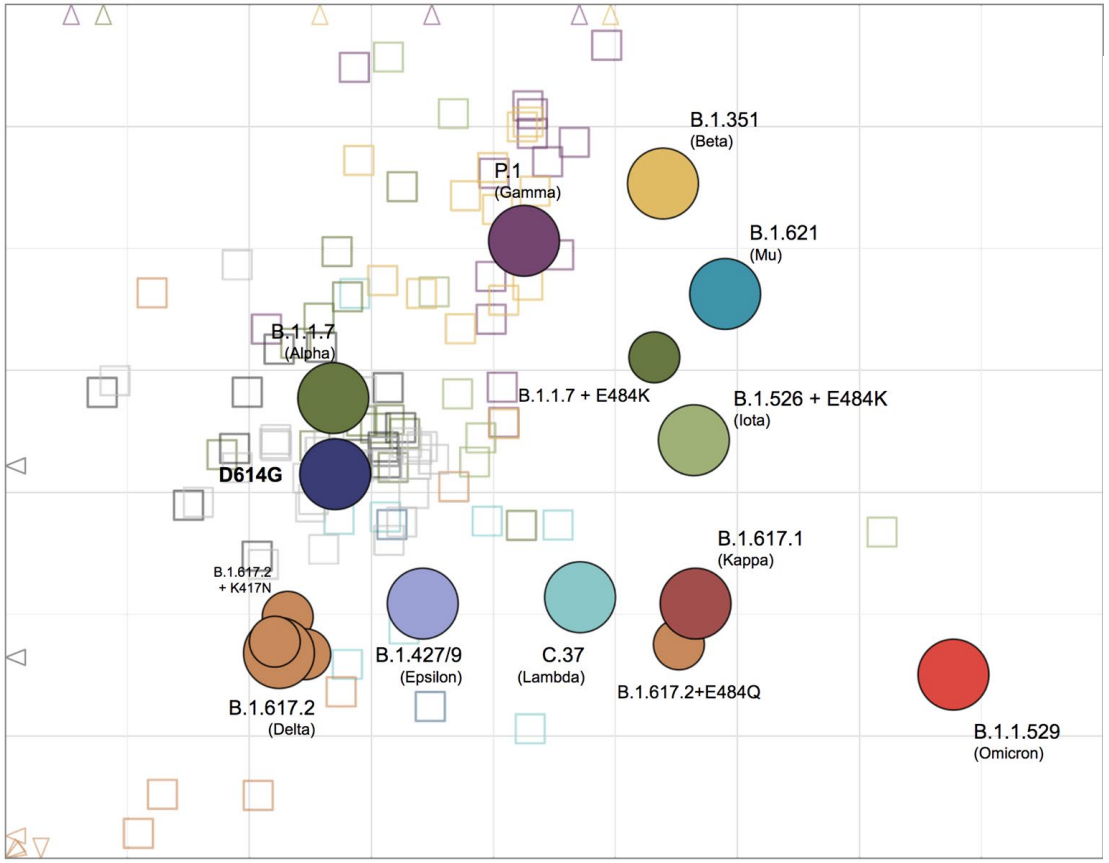
https://investors.modernatx.com/news/news-details/2022/Modernas-BA.4BA.5-Targeting-Bivalent-Booster-mRNA-1273.222-Meets-Primary-Endpoint-of-Superiority-Against-Omicron-Variants-Compared-to-Booster-Dose-of-mRNA-1273-in-Phase-23-Clinical-Trial/default.aspx

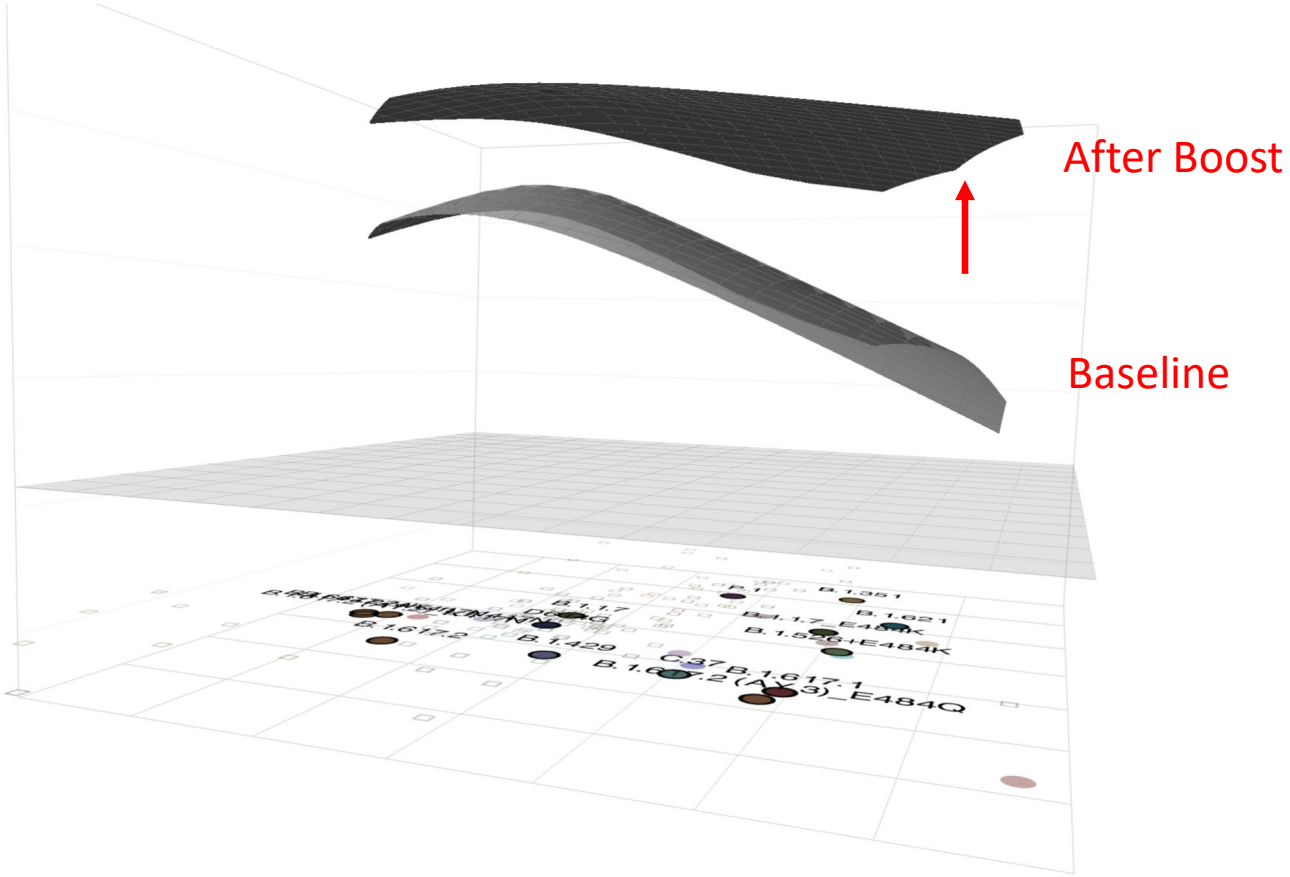
Stage 1 COVAIL (Moderna): Monogram PsVN BA.4/BA.5 GMT for Previously Infected vs. Uninfected



Antigenic Cartography

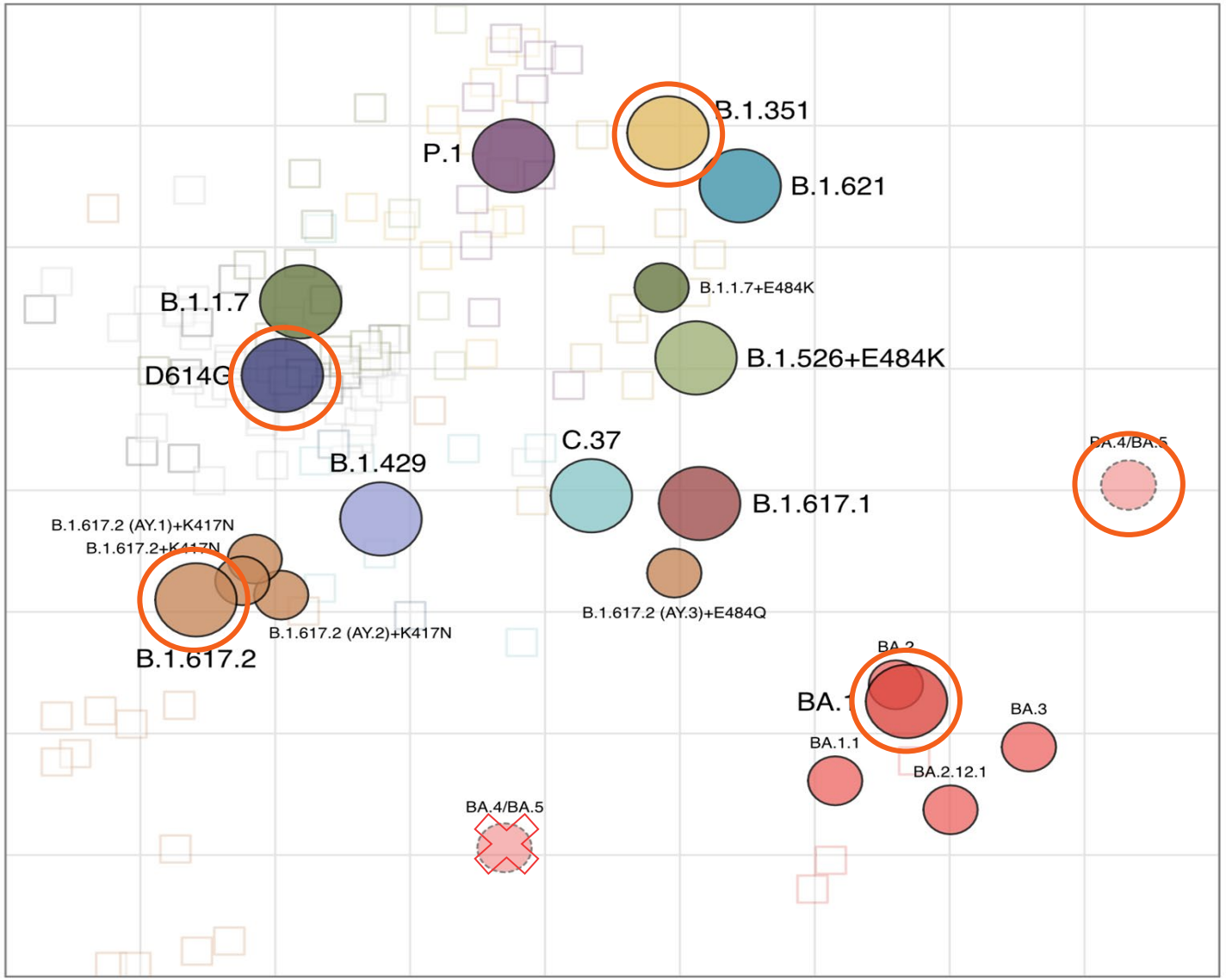
- **Utilize neutralization assays to map antibody responses and describe antigenic landscapes**
- Goal would be to produce a high titer lifted landscape which remains flat over time (durability)





Antigenic Cartograph Base Map

- Most recent Duke map as basis for antibody landscapes
- Two different optima for BA.4/BA.5, though right position is more likely



- **D1 (bottom) and D29 (top) GMT landscapes by Platform, Vaccine arm and Prior Infection Status at Baseline**

Non-Infected | **Infected**

Moderna

Pfizer

Sanofi

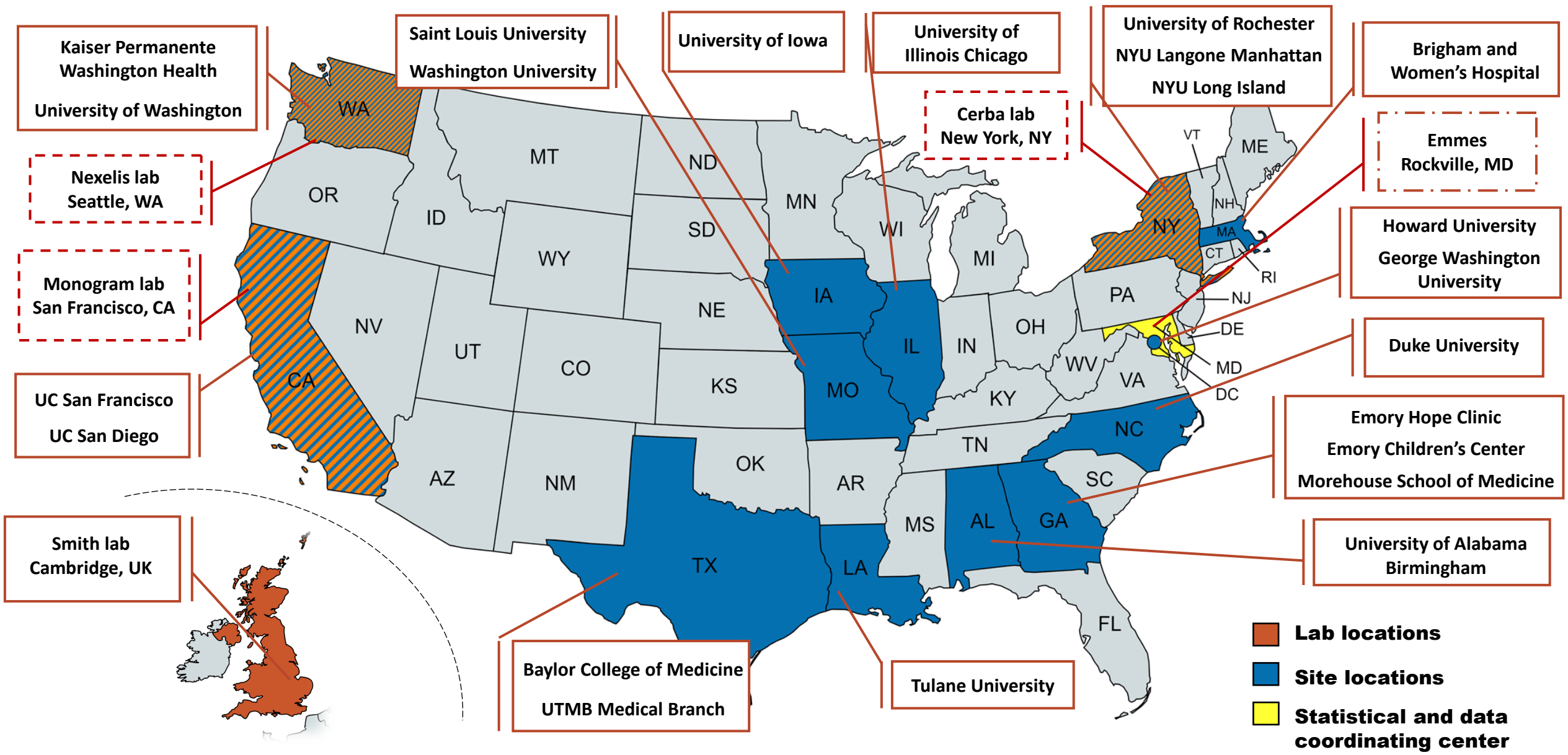
Conclusions

1. Bivalent vaccine combinations do appear to offer serologic advantage and flatten the antigenic landscape more than Prototype

2. Variant specific vaccines boost well to D614G and transition away from vaccines containing wildtype antigen may be possible for future generations of boosters

3. Hybrid Immunity may offer clues to a more broadly protective and durable immune response likely related to expansion of memory and cellular immunity

COVAIL Sites and Labs



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- **The Participants**

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