What's after Omicron?
Viral evolution and antigenic space

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4th INA-RESPOND Webinar: “Learning lessons from two years of the pandemic; Are we getting closer to the finish line?”
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Disclosures

John Beigel, M.D.

- Has no financial interest or relationships to disclose

For today

- Longitudinal data from NIAID's heterologous boost trial
  - Titers to Omicron after boost

- Why we likely need an additional booster
  - Why its not likely to be prototype vaccine
  - What we know about viral evolution
  - How we think about risk in certain antigenic areas
  - NIAID sponsored study to evaluate this

DMID 21-0012 Heterologous Boost "MixNMatch"

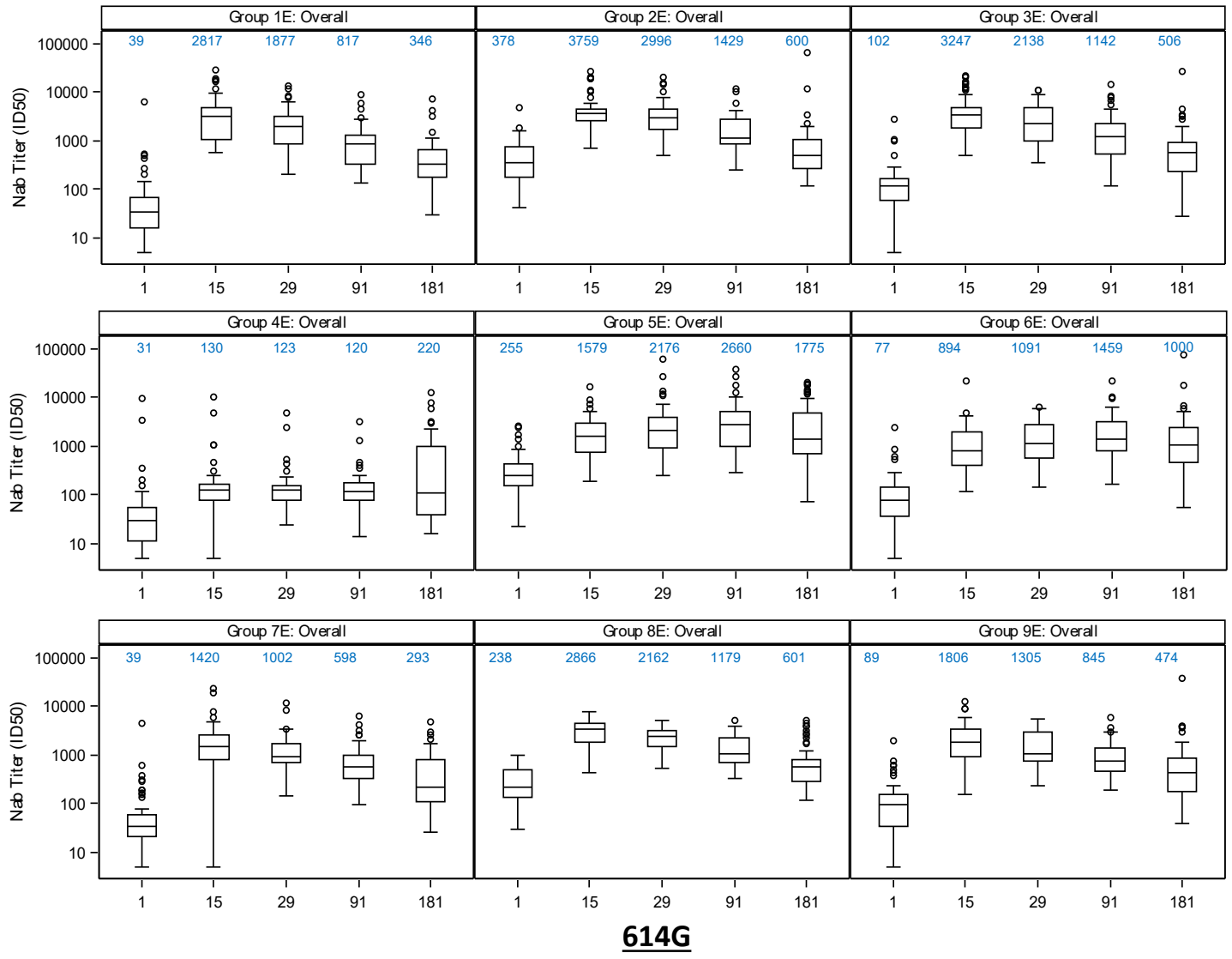
Booster vaccination: (Staged Enrollment)

	Group	Sample Size*	EUA Dosing Scheme	Interval (weeks)	Delayed Booster Vaccination	Strategy Tested
Moderna (100 mcg)	1E	50: 25 18-55 yr, 25 ≥56	Previously dosed Janssen	≥12	Moderna- mRNA-1273	 Same Strain Heterologous platform
	2E	50: 25 18-55 yr, 25 ≥56	Previously dosed Moderna	≥12		 Control - Same Strain & platform
	3E	50: 25 18-55 yr, 25 ≥56	Previously dosed Pfizer	≥12		 Same Strain Similar platform
Janssen ($5x10^{10}$ vp)	4E	50: 25 18-55 yr, 25 ≥56	Previously dosed Janssen	≥12	Janssen – Ad26.COV2.S	 Control - Same Strain & platform
	5E	50: 25 18-55 yr, 25 ≥56	Previously dosed Moderna	≥12		 Same Strain Heterologous platform
	6E	50: 25 18-55 yr, 25 ≥56	Previously dosed Pfizer	≥12		 Same Strain Heterologous platform
Pfizer (30 mcg)	7E	50: 25 18-55 yr, 25 ≥56	Previously dosed Janssen	≥12	Pfizer/BioNTech –BNT162b2	 Same Strain Heterologous platform
	8E	50: 25 18-55 yr, 25 ≥56	Previously dosed Moderna	≥12		 Same Strain Similar platform
	9E	50: 25 18-55 yr, 25 ≥56	Previously dosed Pfizer	≥12		 Control - Same Strain & platform
Moderna Bivalent 211 (100 mcg)	10E	50: 25 18-55 yr, 25 ≥56	Previously dosed Janssen	≥12	Moderna- mRNA-1273.211	 Variant Strain Heterologous platform
	11E	50: 25 18-55 yr, 25 ≥56	Previously dosed Pfizer	≥12		 Variant Strain Similar platform
Moderna (50 mcg)	12E	50: 25 18-55 yr, 25 ≥56	Previously dosed Janssen	≥12	Moderna- mRNA-1273	 Same Strain Heterologous platform
	13E	50: 25 18-55 yr, 25 ≥56	Previously dosed Moderna	≥12		 Control - Same Strain & platform
	14E	50: 25 18-55 yr, 25 ≥56	Previously dosed Pfizer	≥12		 Same Strain Similar platform
Novavax (currently enrolling)	15E	50: 25 18-55 yr, 25 ≥56	Previously dosed Janssen	≥12	Novavax	 Same Strain Heterologous platform
	16E	50: 25 18-55 yr, 25 ≥56	Previously dosed Moderna	≥12		 Same Strain Heterologous platform
	17E	50: 25 18-55 yr, 25 ≥56	Previously dosed Pfizer	≥12		 Same Strain Heterologous platform

21-0012 Heterologous Boost Trial

PRIMARY DOSE(S)

Ad26.COV2.S | **mRNA-1273** | **BNT162b2**



BOOSTER 3RD DOSE

Moderna (100 mcg)

Janssen ($5x10^{10}$ vp)

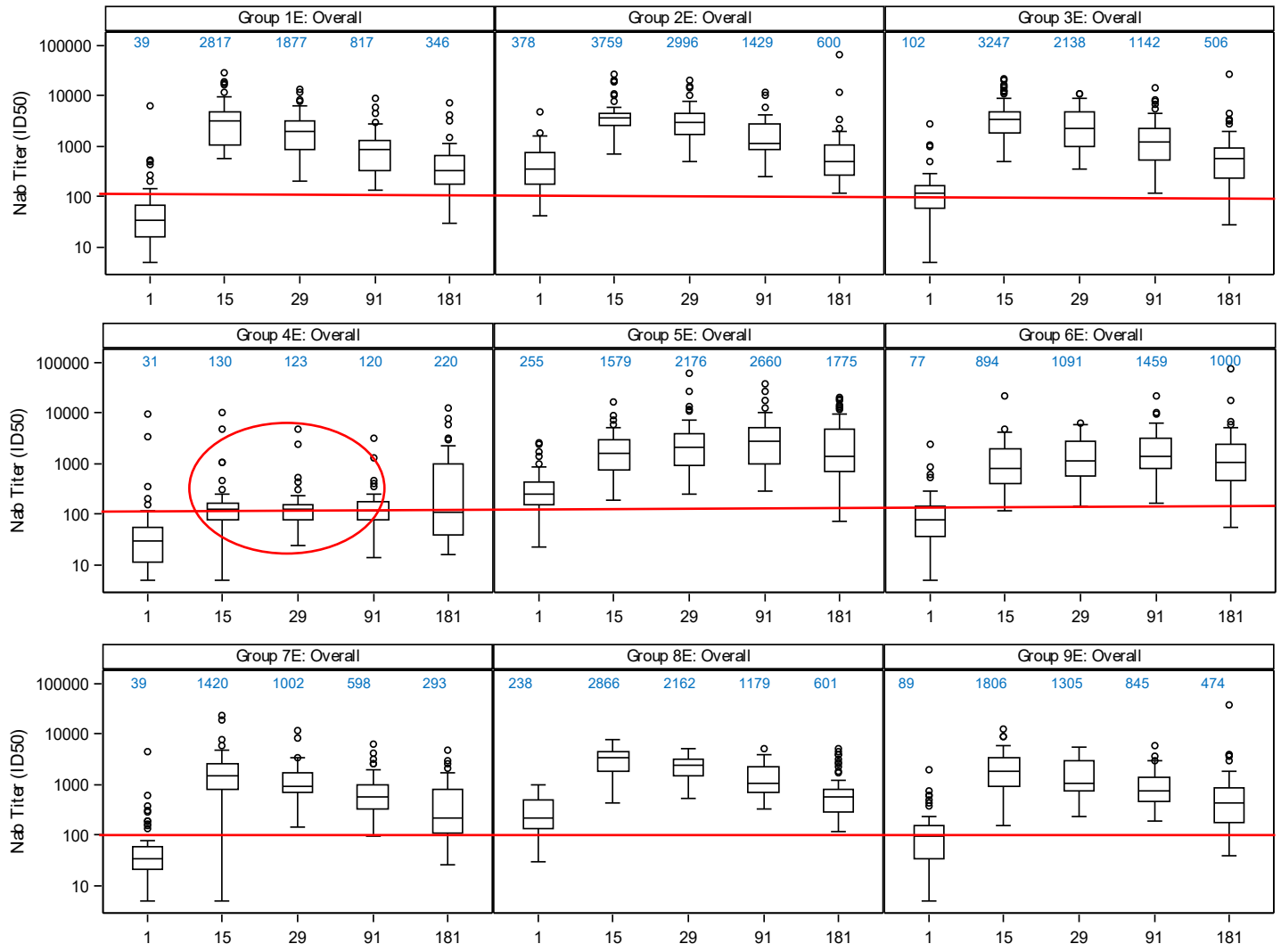
Pfizer (30 mcg)

614G

21-0012 Heterologous Boost Trial

PRIMARY DOSE(S)

Ad26.COV2.S | **mRNA-1273** | **BNT162b2**



BOOSTER 3RD DOSE

Moderna (100 mcg)

Janssen ($5x10^{10}$ vp)

Pfizer (30 mcg)

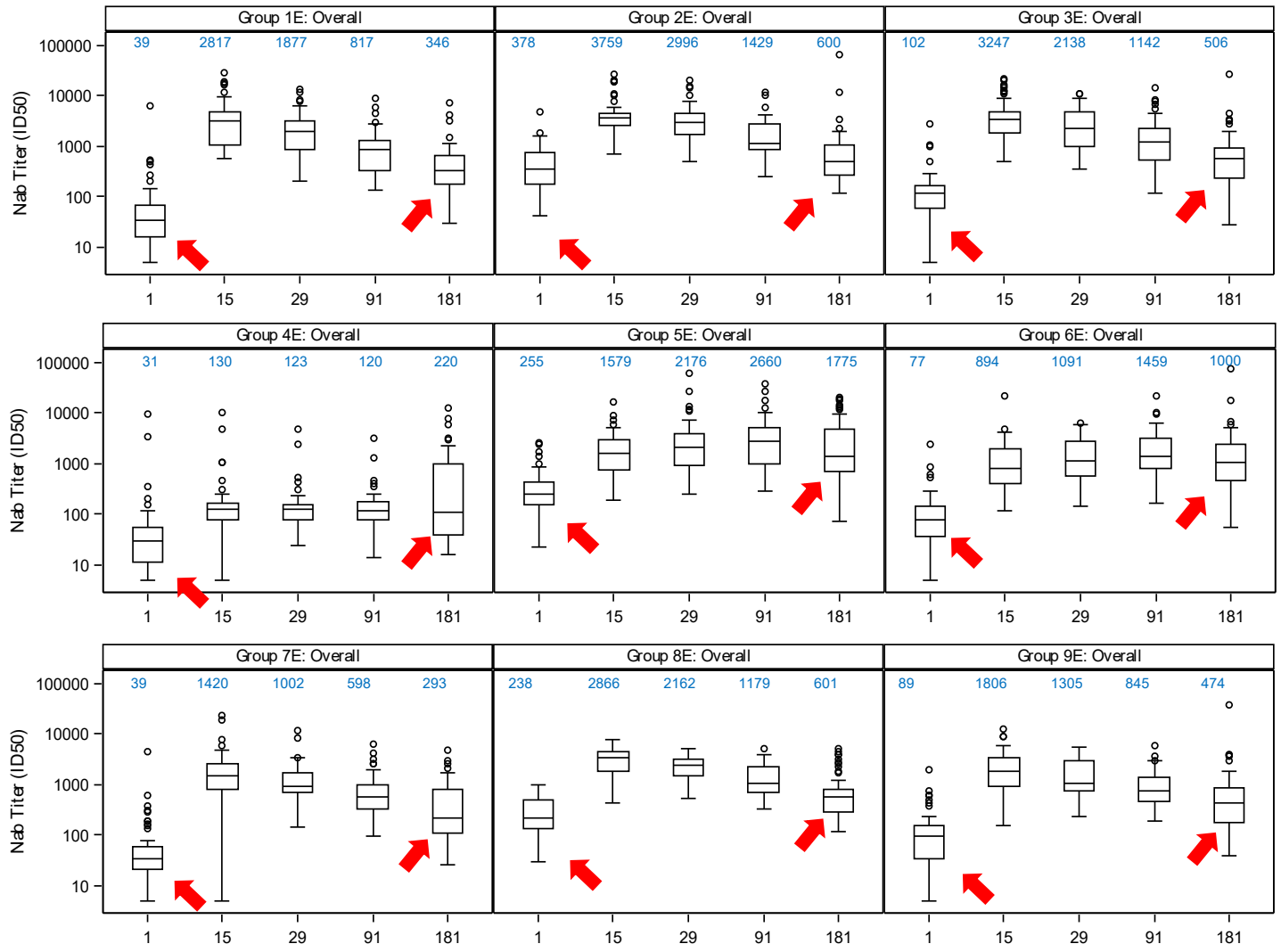
614G

Homologous or heterologous booster vaccines similarly increased titers to D614G (except Janssen boost Janssen)

21-0012 Heterologous Boost Trial

PRIMARY DOSE(S)

Ad26.COV2.S | **mRNA-1273** | **BNT162b2**



BOOSTER 3RD DOSE

Moderna (100 mcg)

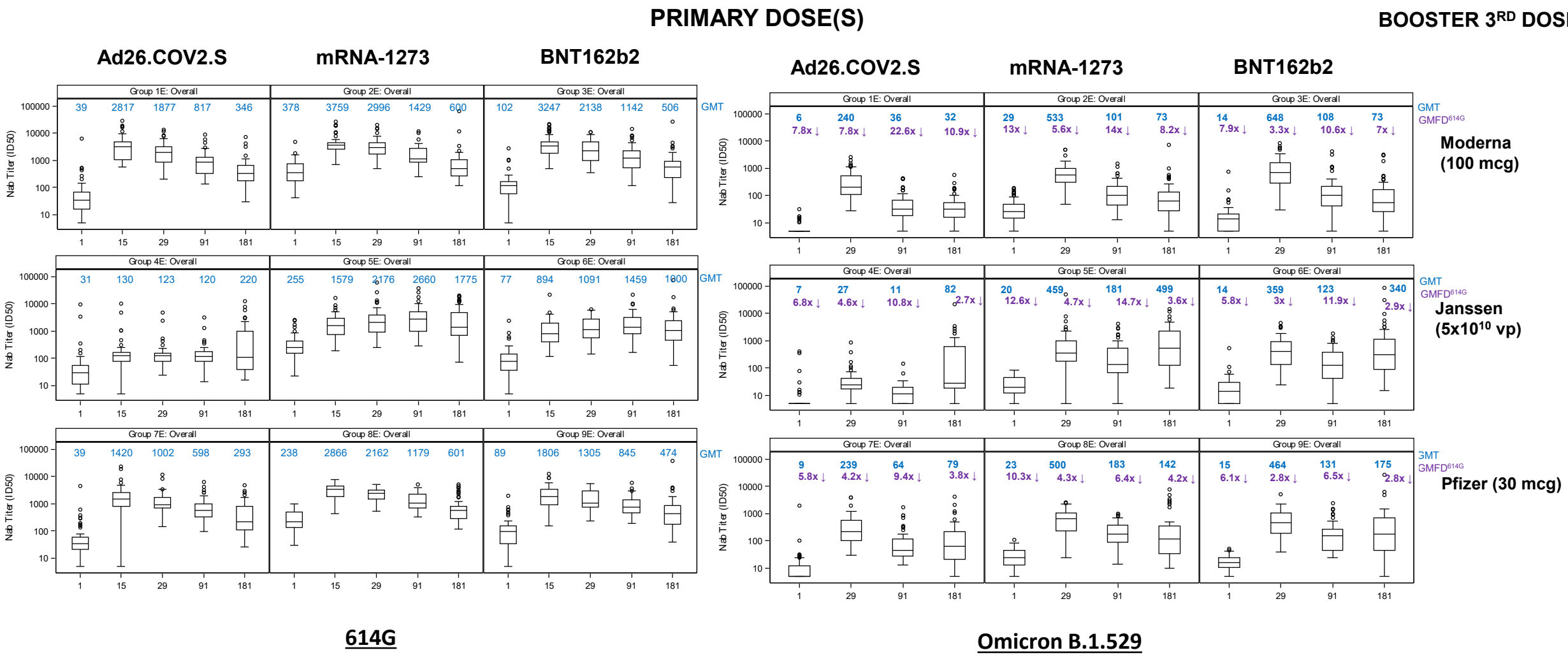
Janssen ($5x10^{10}$ vp)

Pfizer (30 mcg)

614G

Titers to D614G at 6 months after booster were higher than baseline (3.5 to 7 months after primary series) implying kinetics to D614G changed after booster

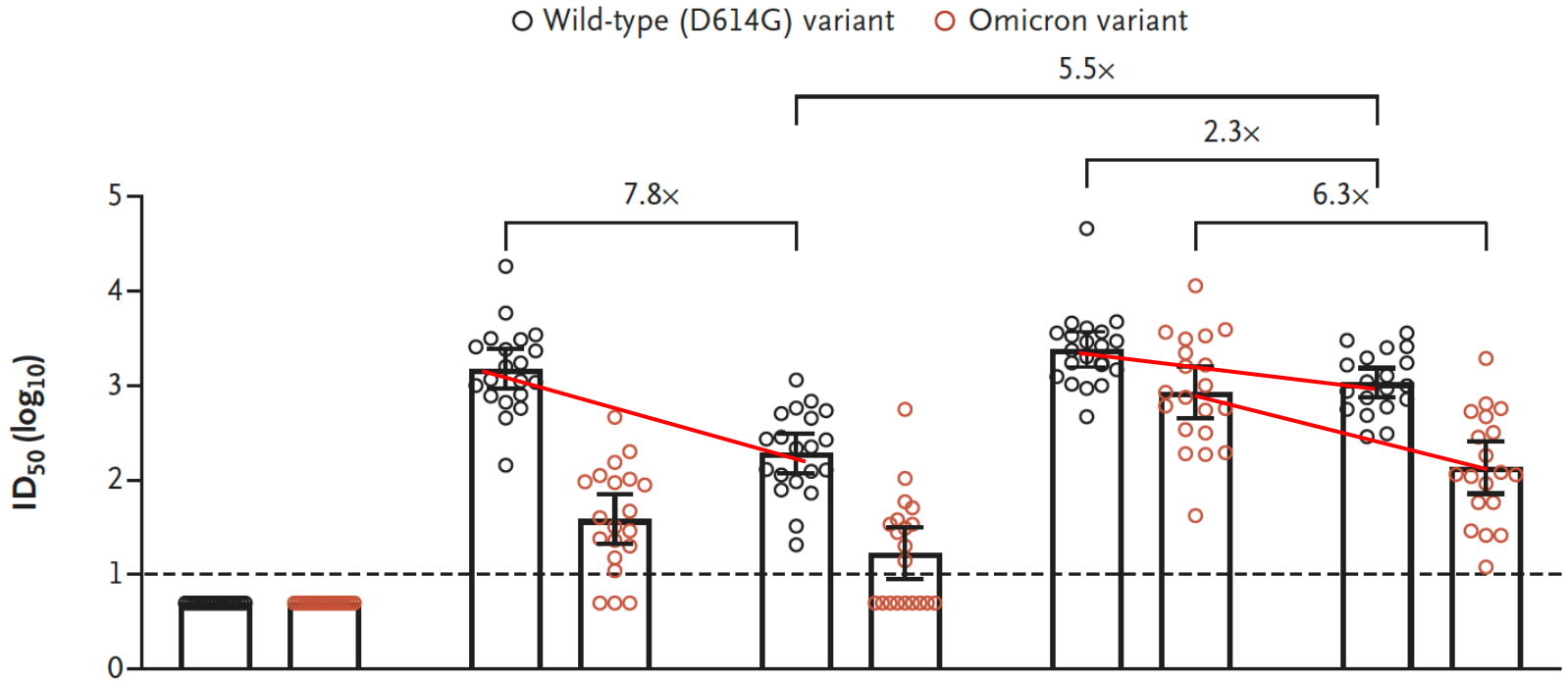
21-0012 Heterologous Boost Trial



The decrement in titers to Omicron decreases (closes the gap) after booster vaccines, but quickly increases (response to Omicron is not sustained)

Neutralizing antibody titers – after second dose and booster with Moderna mRNA-1273

A Neutralizing Antibody Titers over Time



Geometric Mean Titer	1496	43	193	23	2423	850	1067	136
Percentage of Participants with Detectable Neutralizing Antibodies	100	85	100	55	100	100	100	100

Pajon et al. NEJM 2022

- The booster vaccine:
  - Increased absolute titers to D614G
  - Changed the kinetics of titers to D614G over time

  - Increased titers to Omicron in the short term
    - Titers quickly decreased to < 100
    - Didn’t appear to change kinetics of titers

- Would this be better if we gave a variant booster vaccine?

DMID 21-0002 Variant Trial

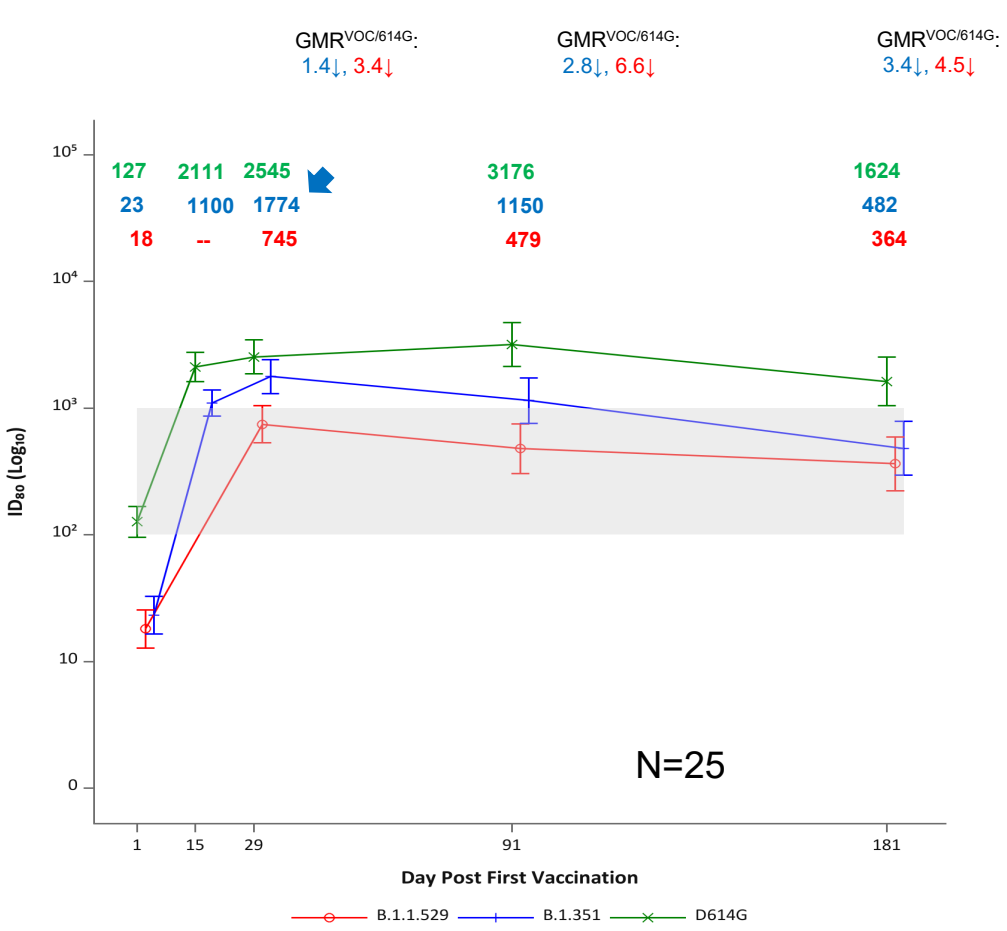
- ***9-11 months post-primary series (phase 1 mRNA-1273)***
- ***At the time, Beta was the variant we were most worried about***

Cohort 1
(N=48)
"Vaccinated" Subjects

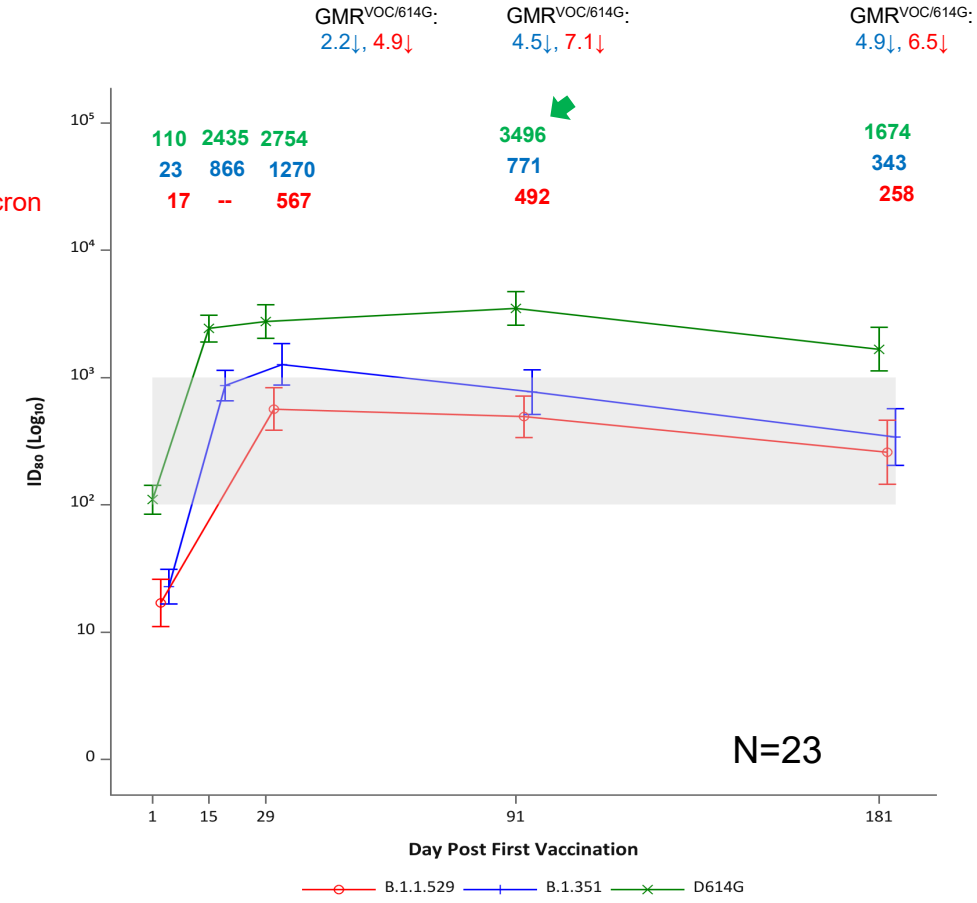
	Arm	Sample Size	Vaccination Product and Dose
N=25	**1A**	**~30**	**50 mcg mRNA-1273.351**
N=23	**1B**	~30	**25 mcg mRNA-1273 + 25 mcg mRNA-1273.351**

Boost at 9-11 months post D2

Cohort 1A Monovalent 351 Boost (50 μg)



Cohort 1B Bivalent Boost (Prototype/351; 50 μg)

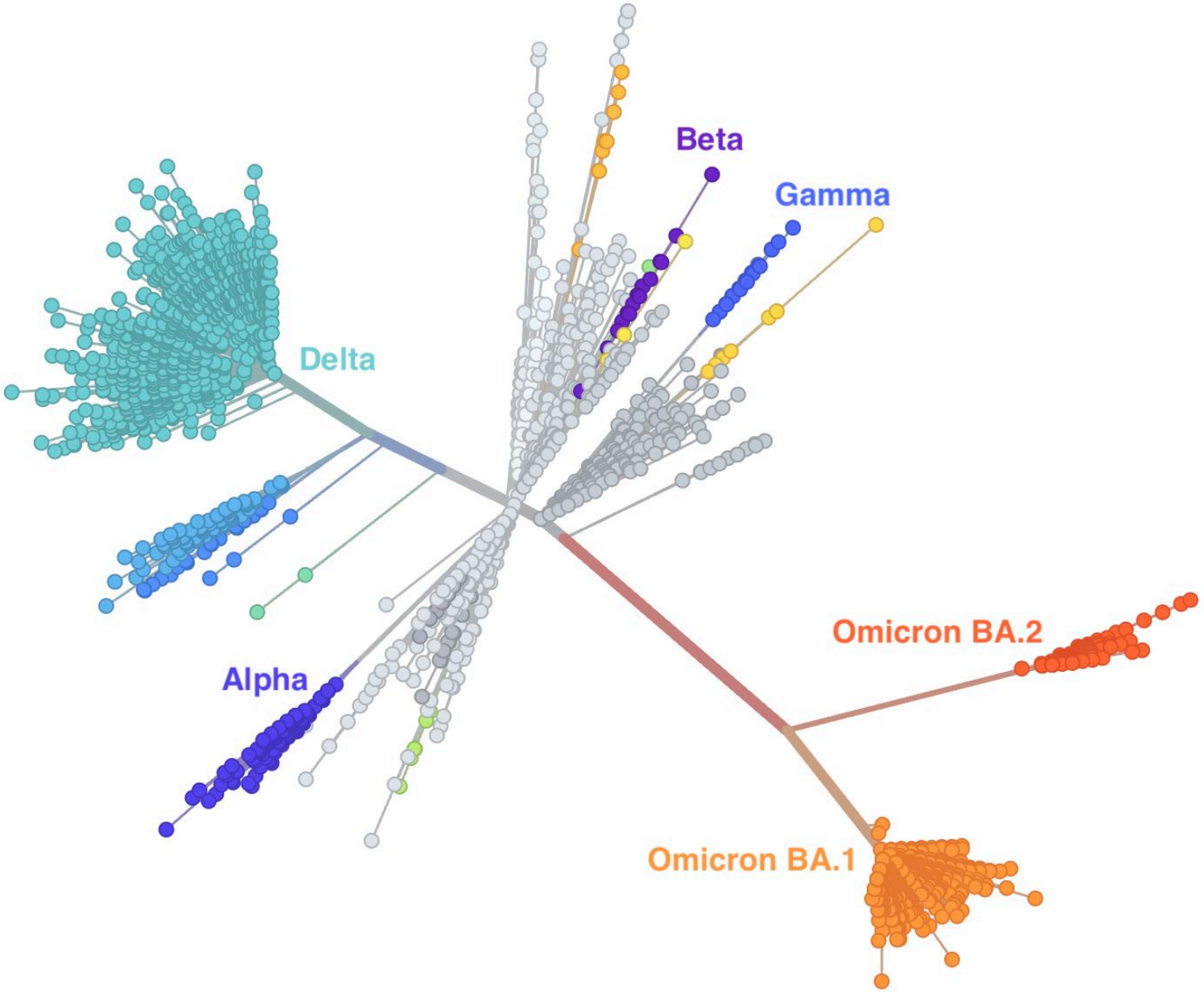


- Beta Monovalent or Bivalent Vaccines
  - Equivalent Boost to 614G
    - response to 614G peaks at D91 post-boost, and drops only ~2-fold by D181.
    - Boost with Prototype, peaks at D15, then begins to drop
  - Responses to the Beta > Omicron; both peak at D29 post-boost with GMTs dropping only ~3.7- and ~2-fold through D181, respectively.
  - Omicron GMTs appear to be sustained at higher levels through D181 compared to a boost with prototype (see Moderna and MixNMatch results).

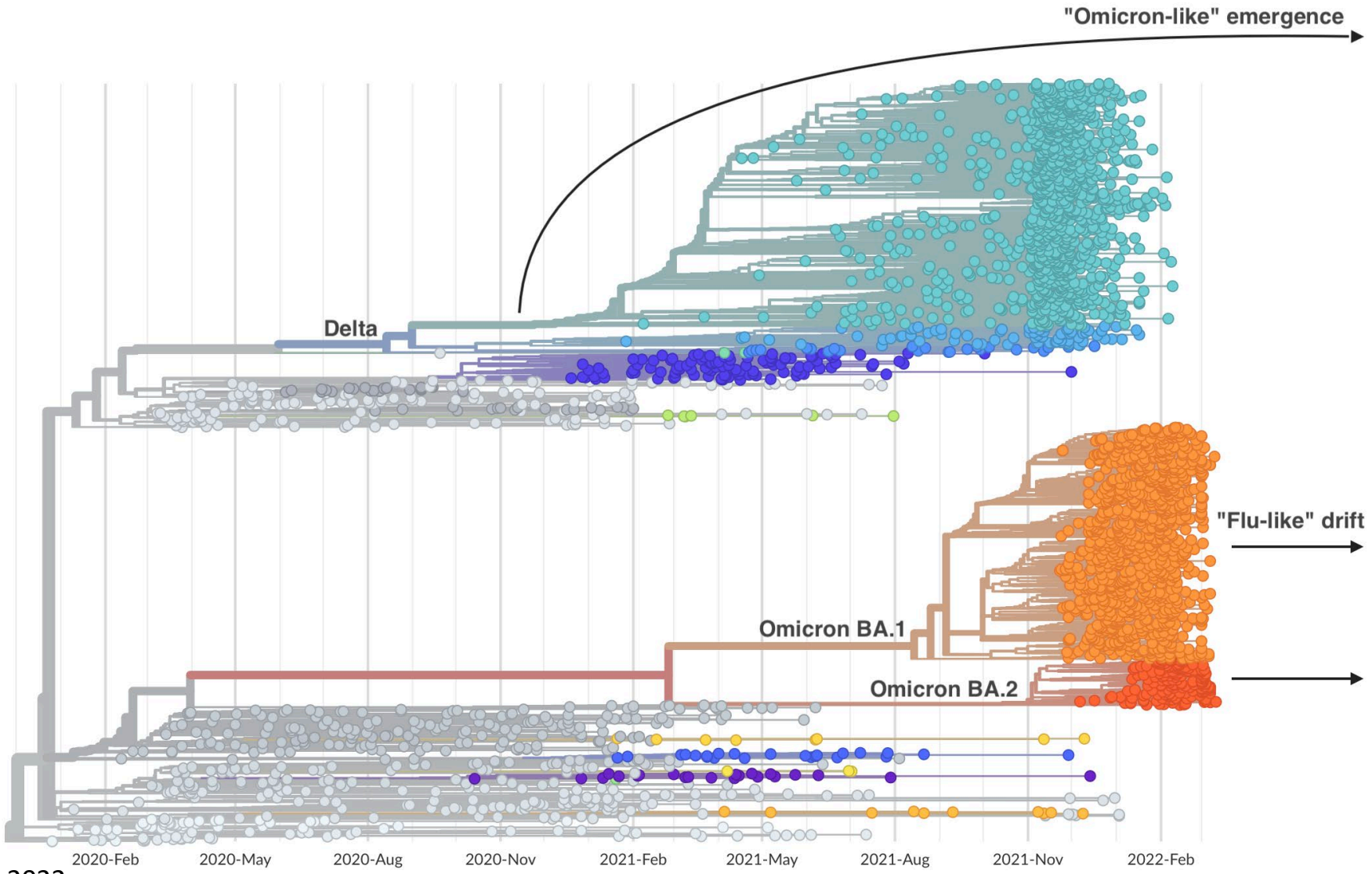
- Maybe variant vaccine boosters are better

- How do we pick?
  - Need to understand viral evolution
    - Especially the unknowns
  - Need to understand how out immune response covers different variants, including those that haven’t emerged yet
    - antigenic space

Genetic relationships of globally sampled SARS-CoV-2 to present



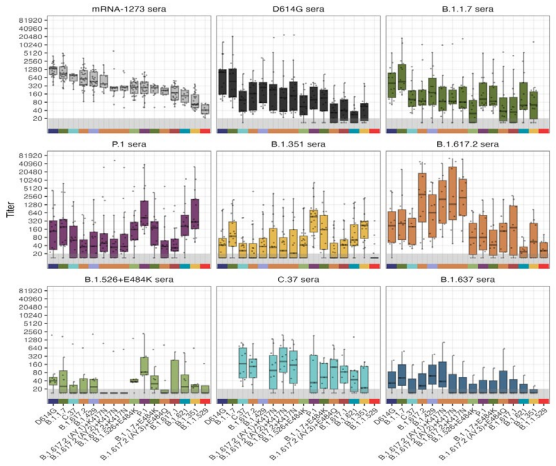
SARS-CoV-2 will continue to evolve to escape population immunity, though with multiple potential avenues

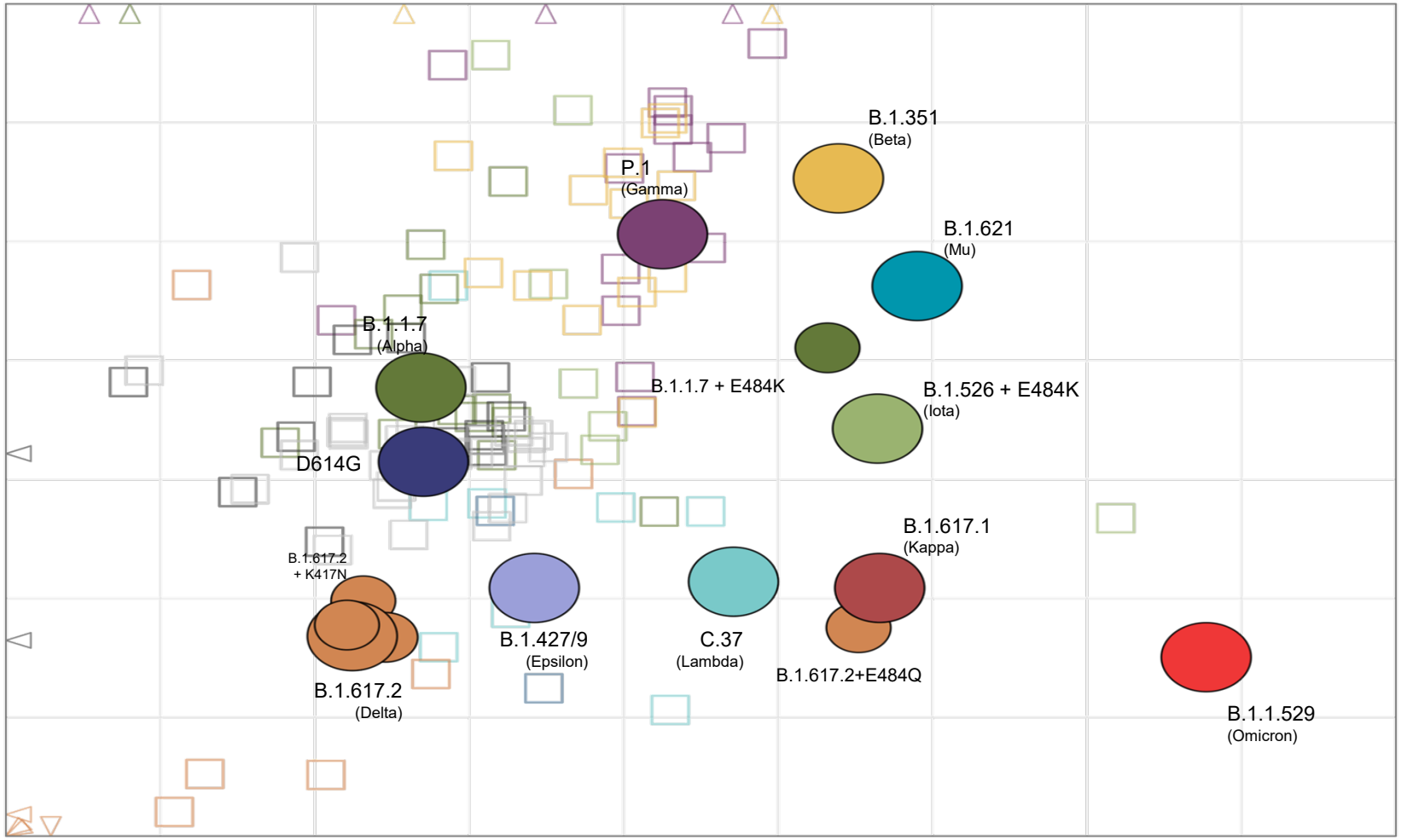


Bedford, VRBPAC April 6, 2022

Work by NIAID collaborators use neutralization assays coupled with antigenic cartography to describe antibody response.

- These maps are visualization tools for neutralization data to help understand antigenic spaces and risks.
- Antigenic cartography and antigenic landscapes are a common tool for strain selection for influenza.



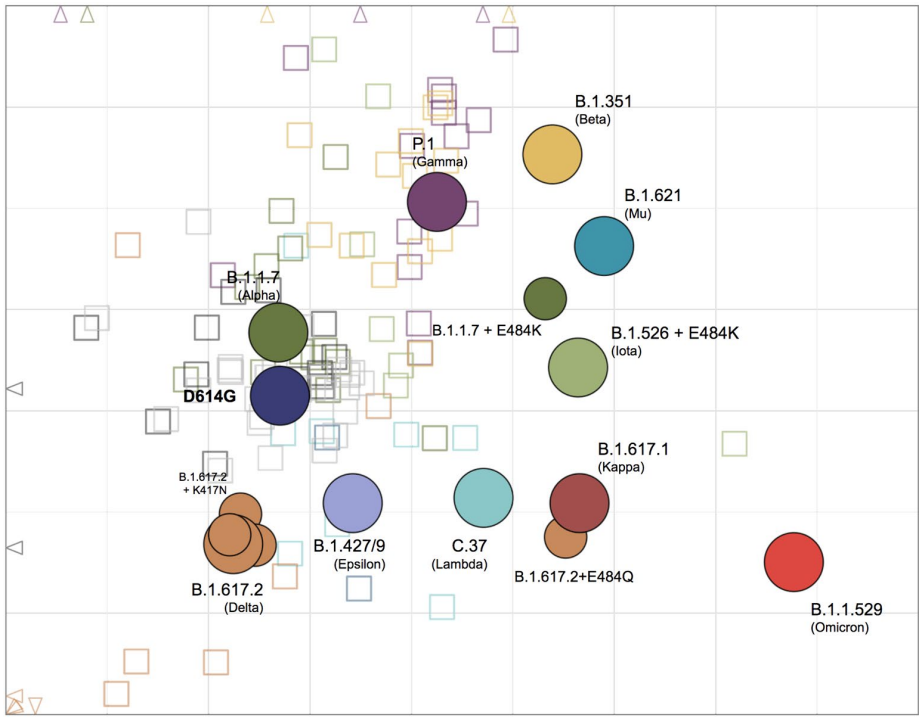


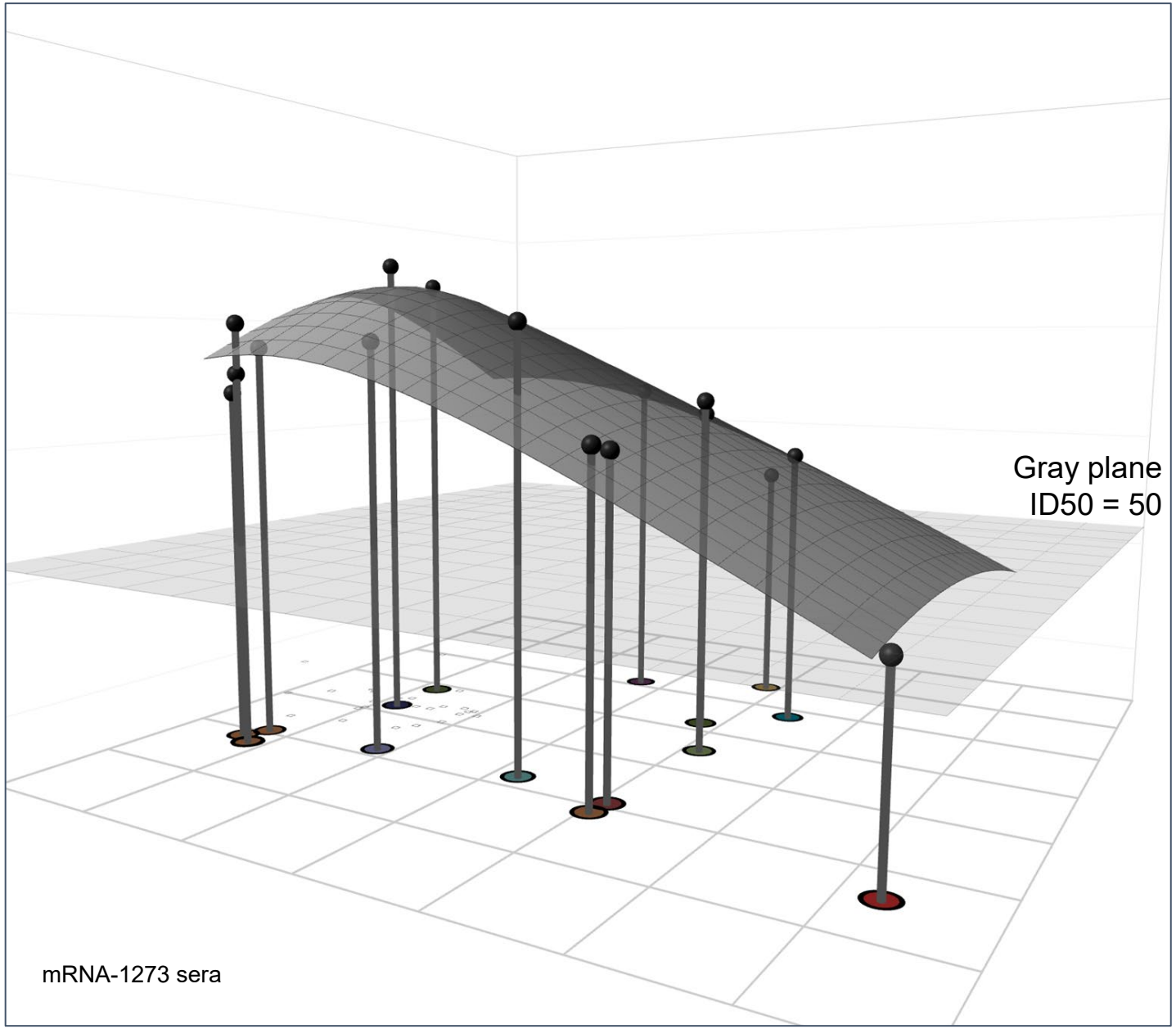
Samuel Wilks & Derek Smith (Cambridge)

PsVNA by Shen & Montefiori (Duke)

Map only reflects relative distance (dilutions) of antigens and serum

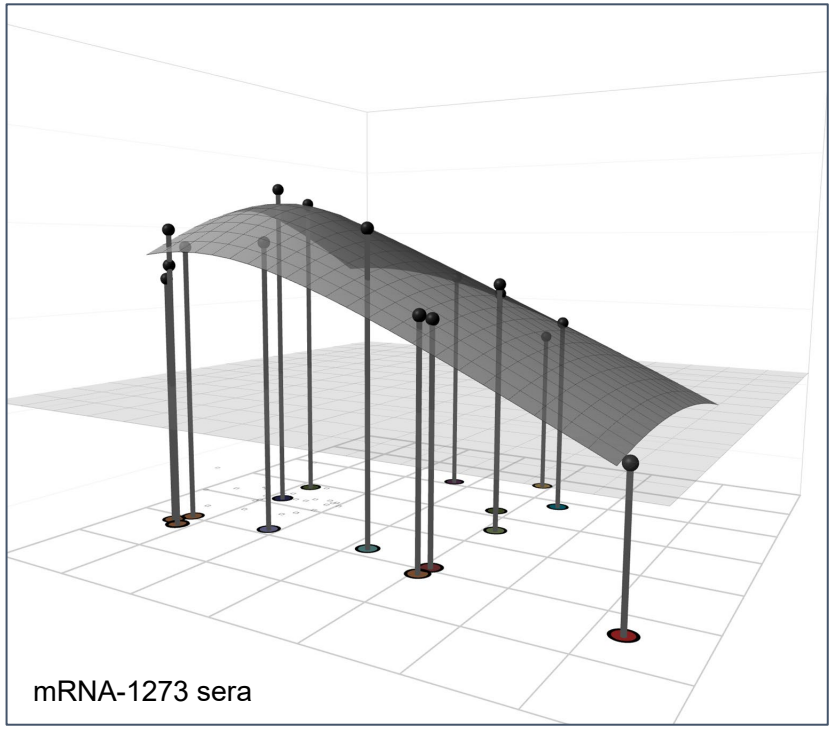
Landscape shows titers across variants in the map and shows areas of vulnerability

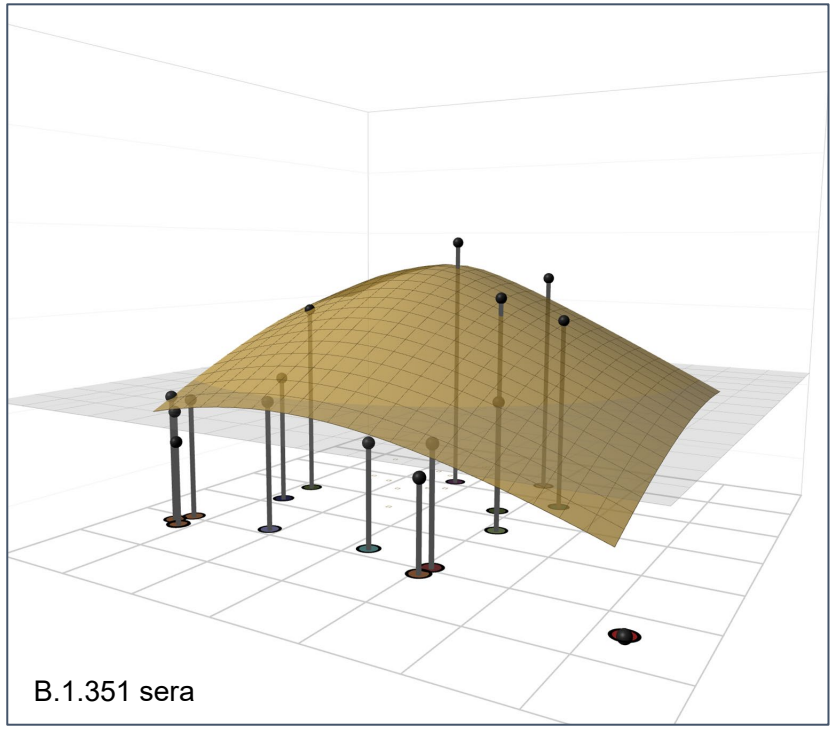


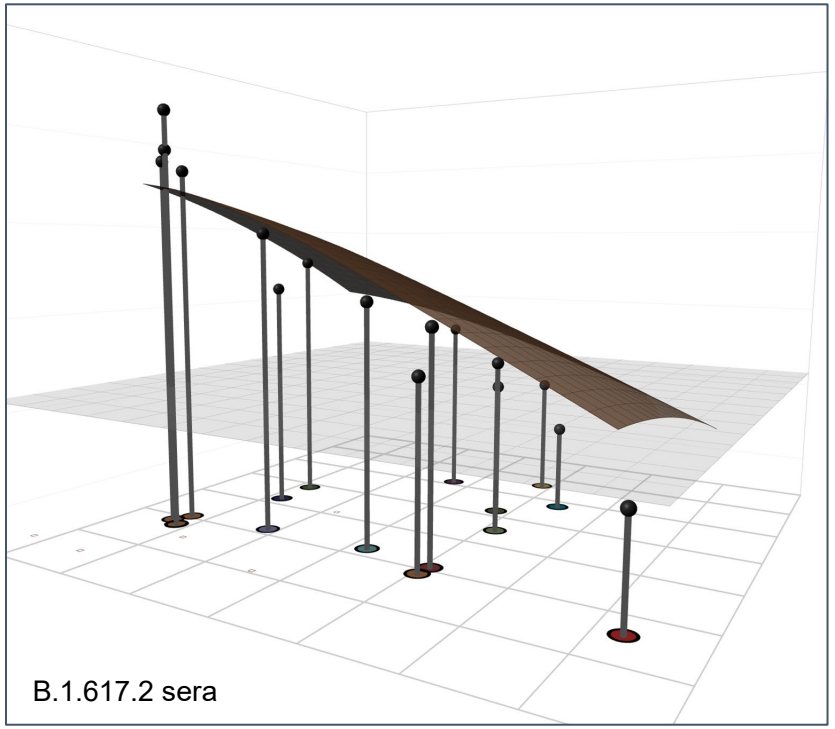


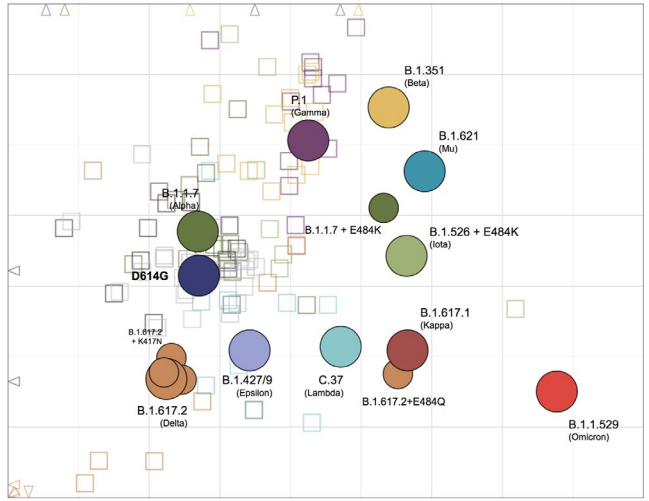
Derek Smith (Cambridge)

Infection by different strains give different antigenic landscapes



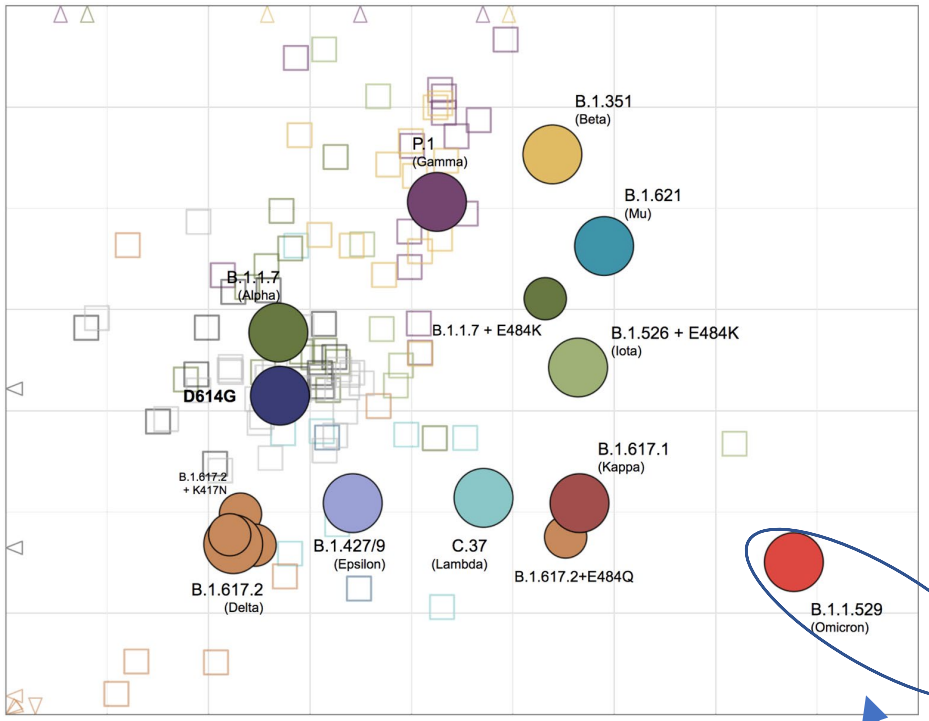


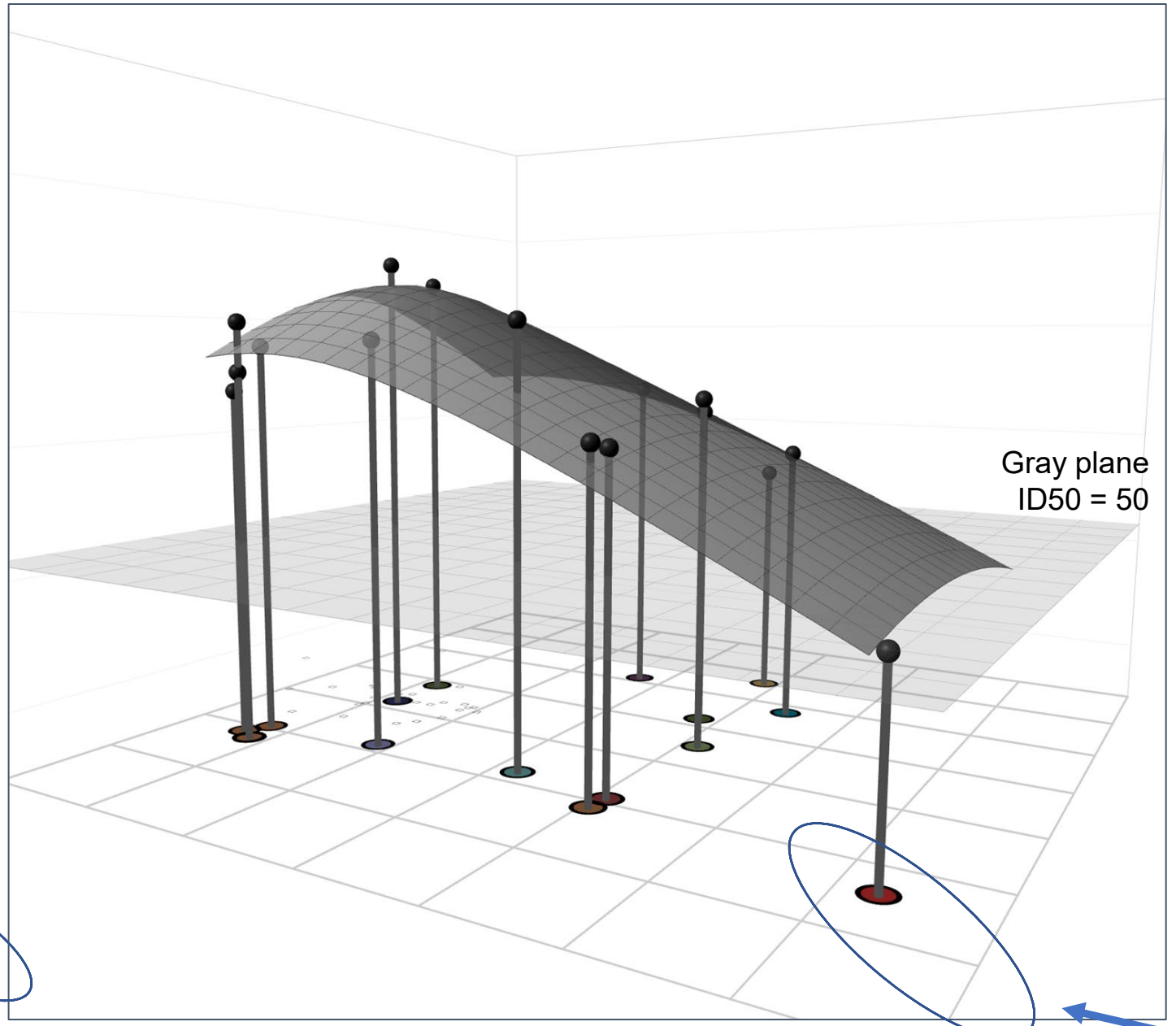




Derek Smith (Cambridge)

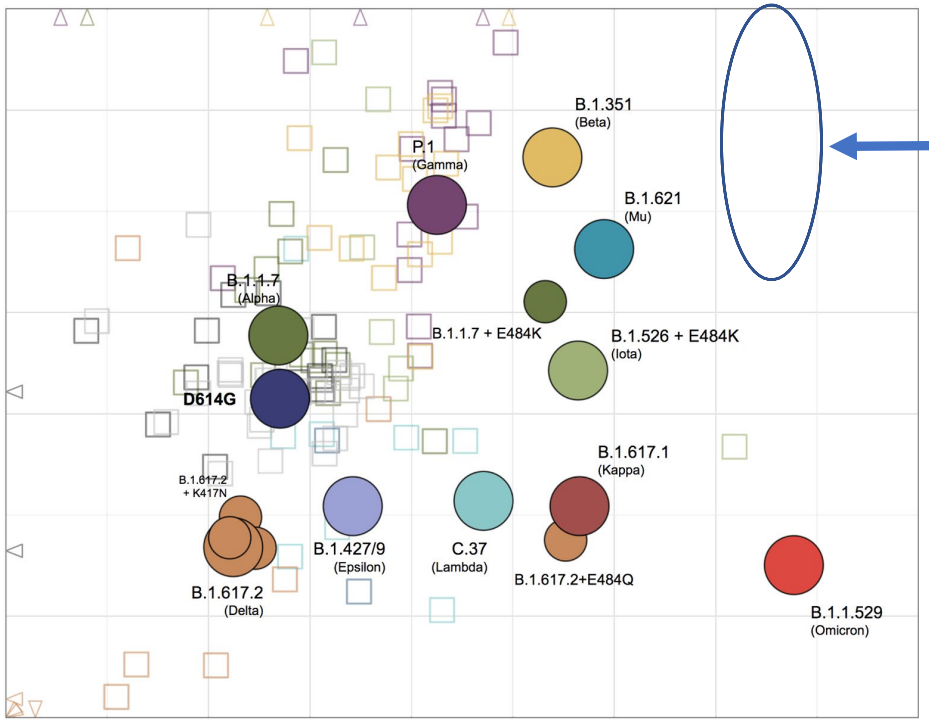
Targeting Omicron
-assumes an Omicron recurrence, or drift from Omicron

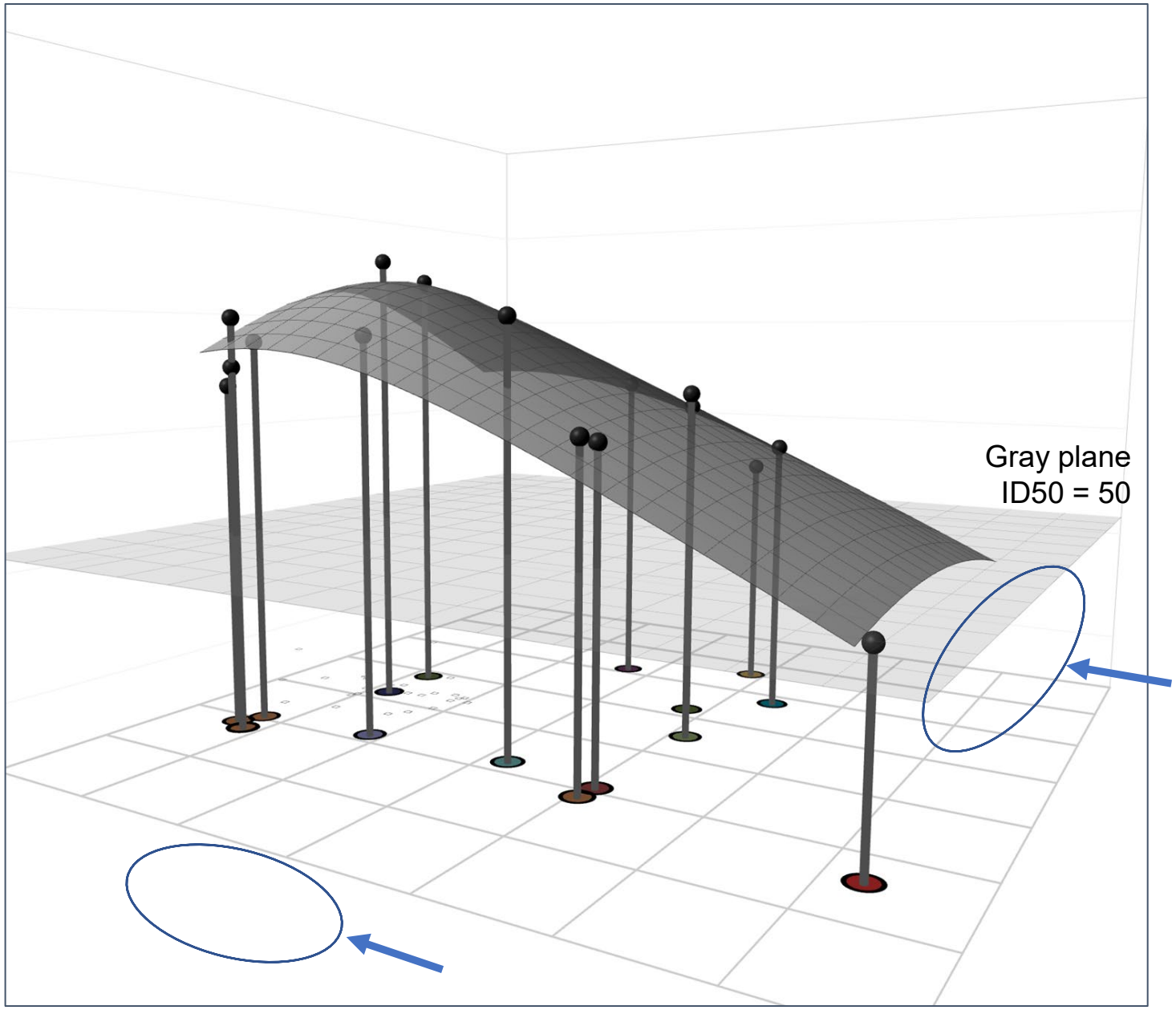




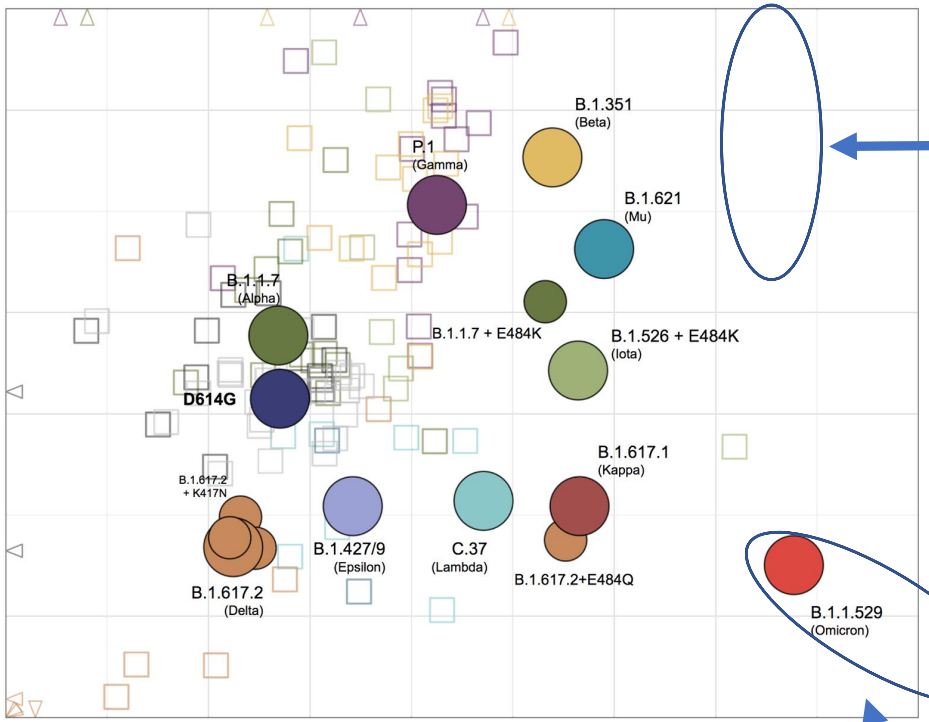
There may be other antigenic areas where the next variant may occur

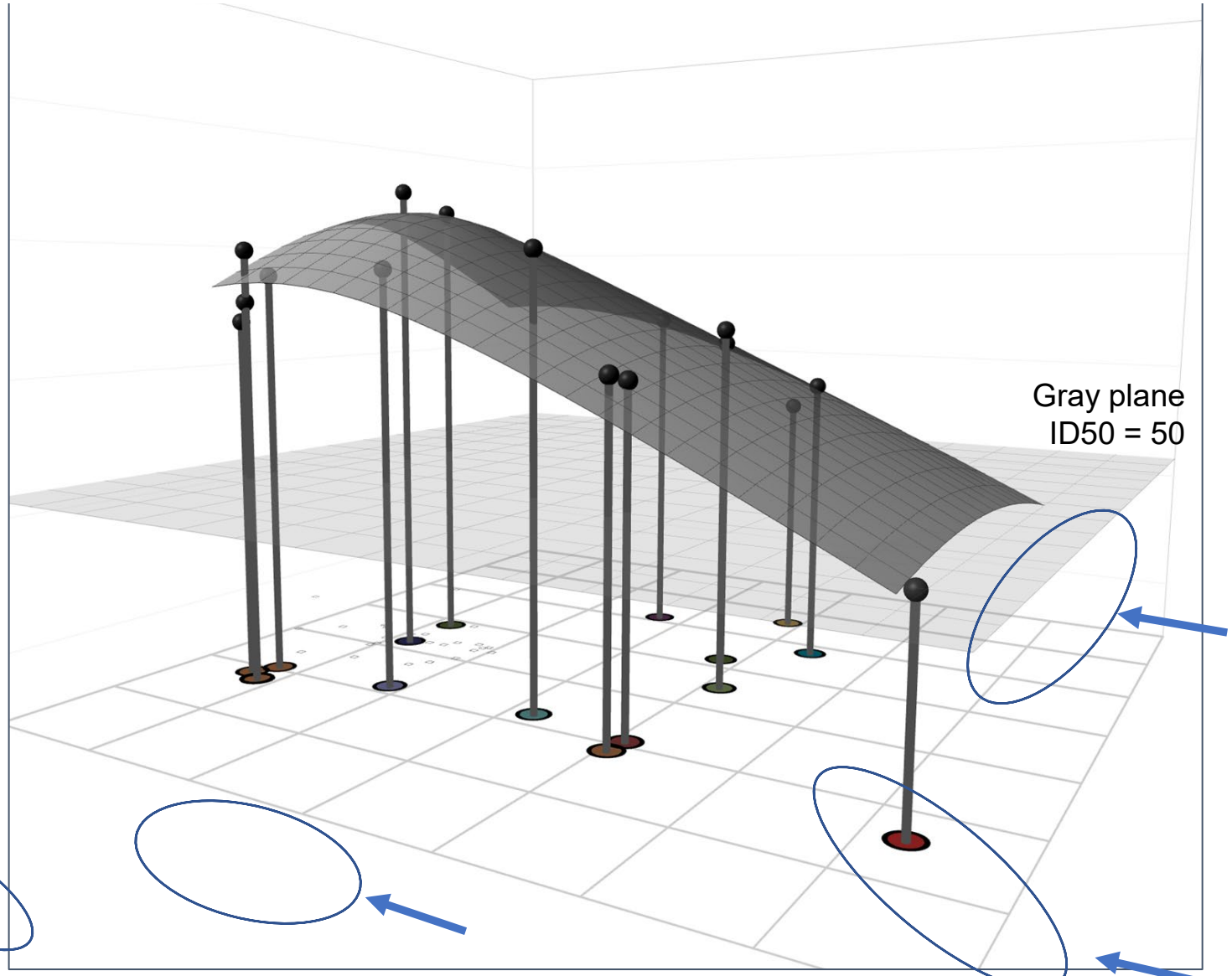
e.g., near beta or near delta
(distant from D614G and Omicron)





How do we use available variant vaccines to target these different antigenic spaces?





COVAIL Trial

COVID-19 Variant Immunologic Landscape Trial

Design:

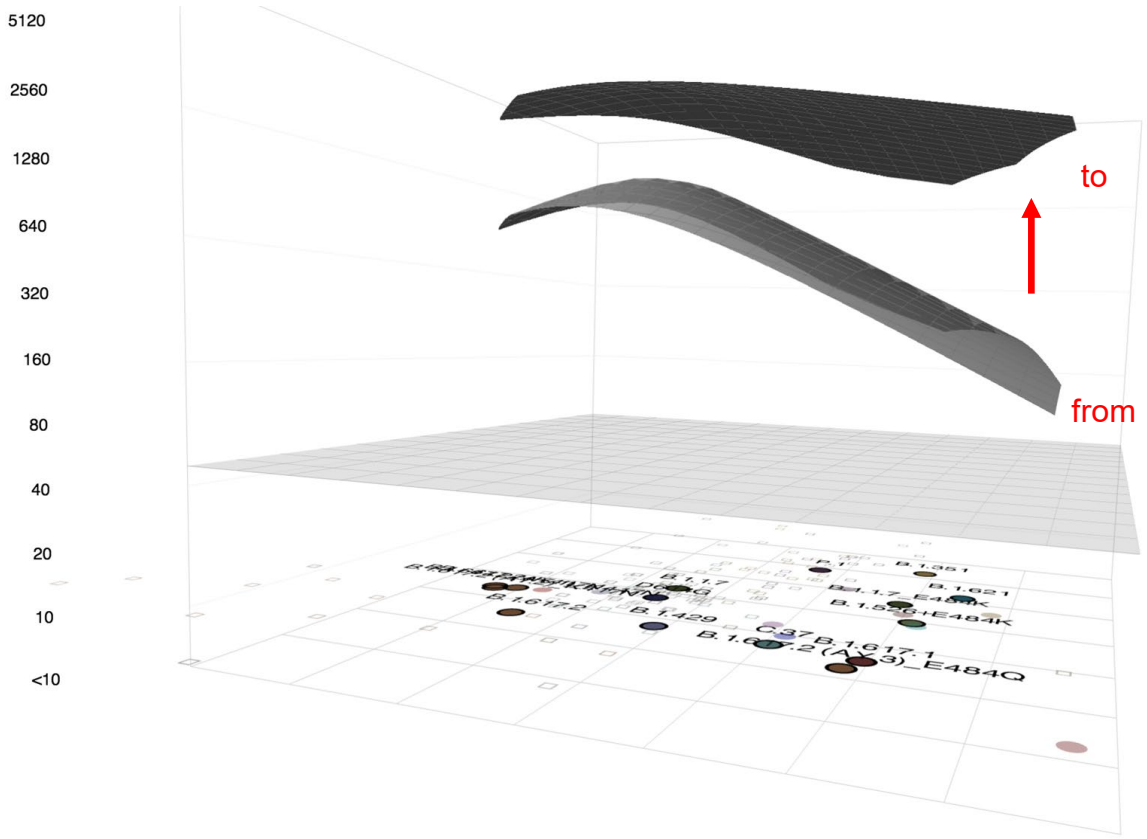
- Immunogenicity trial of second booster vaccine
- Evaluating the breadth of antibody response after different vaccine strains
  - monovalent and bivalent
  - prototype and variant
- Participants can have any combination of primary vaccine and booster (to reflect US population)

Timelines:

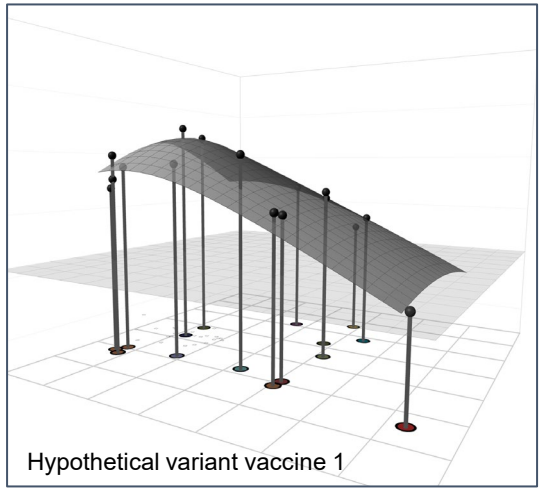
- Moderna stage finished enrollment May 6
  - Anticipate early (partial cohort) results in early June
- Pfizer began May 12
- Sanofi will begin early June

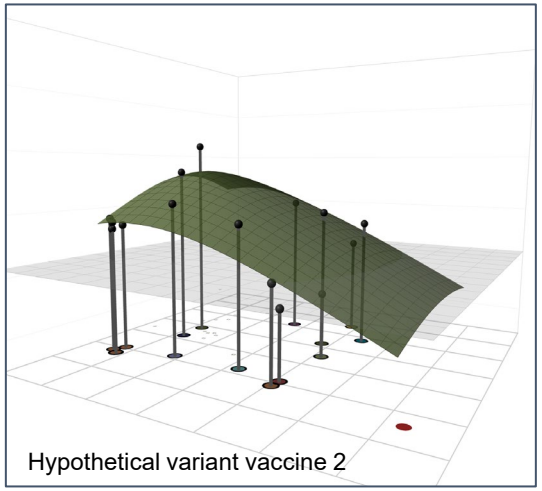
	Arms	Sample Size	Vaccine Candidate	Interval (weeks)	Dose	
Stage 1	1	100	Prototype	≥16	One dose	Moderna
	2	100	Beta + Omicron	≥16	One dose	
	3	100	Beta + Omicron	≥16	Two Doses	
	4	100	Delta + Omicron	≥16	One dose	
	5	100	Omicron	≥16	One dose	
	6	100	Omicron + Prototype	≥16	One dose	
Stage 2	7	50	Wildtype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

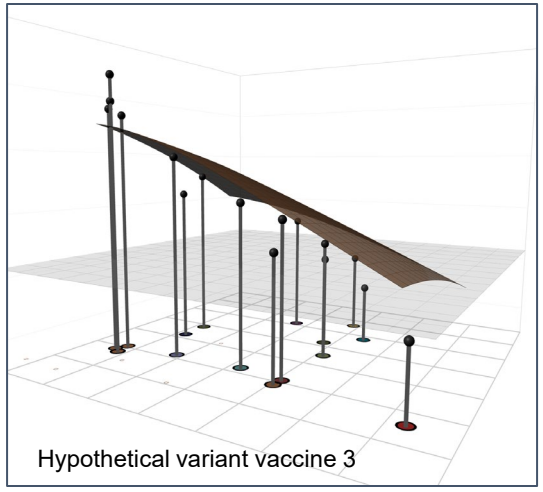
Early responses for any given variant vaccine may increase titers across landscape

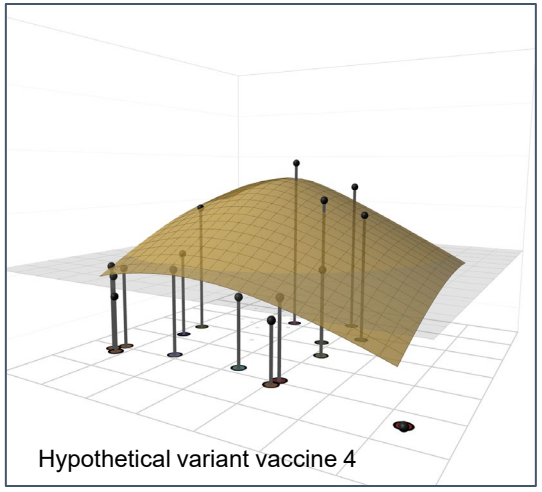


Later timepoints may show differential responses

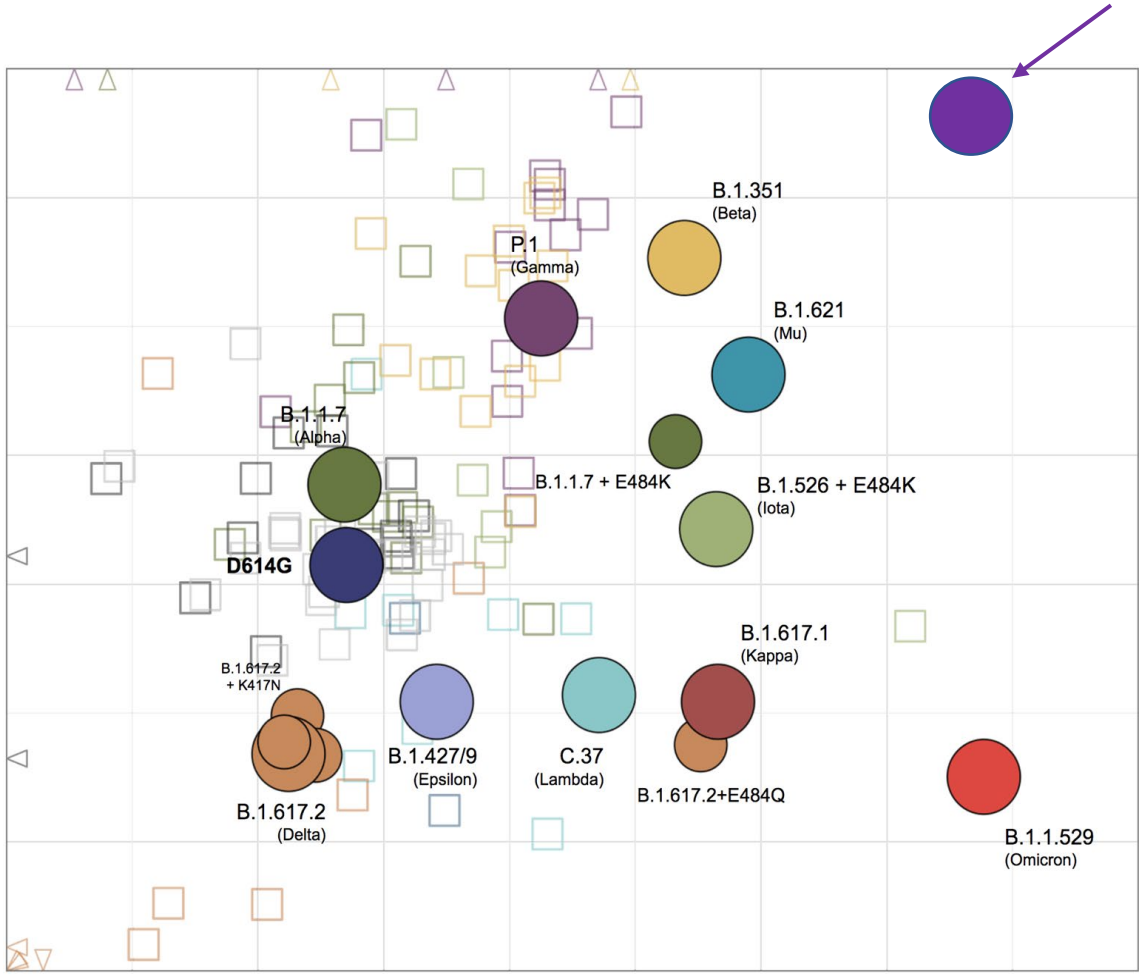


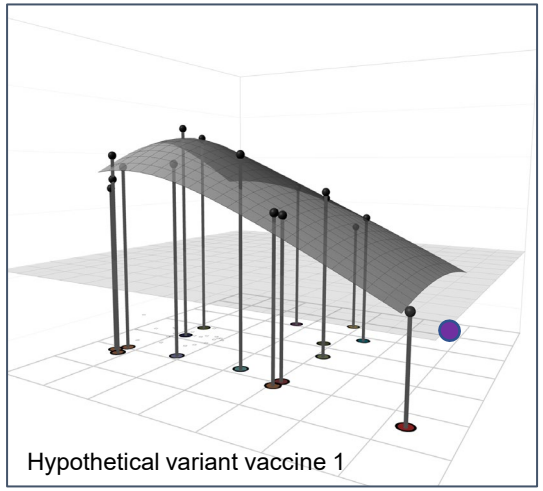


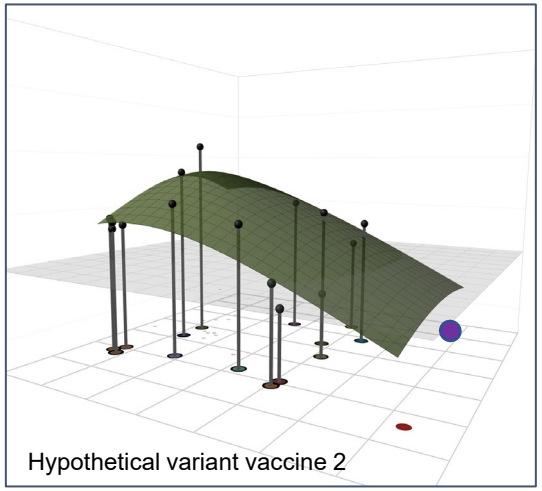


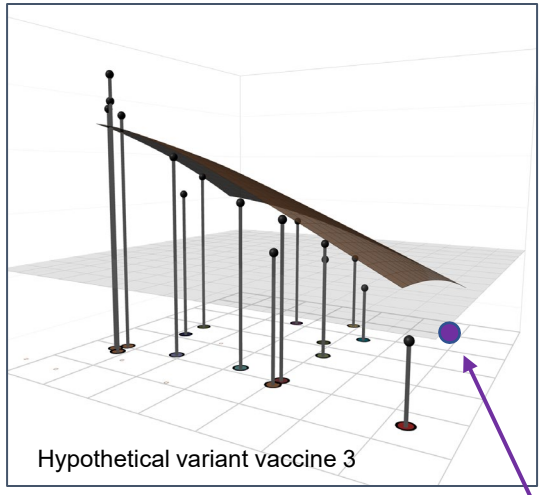


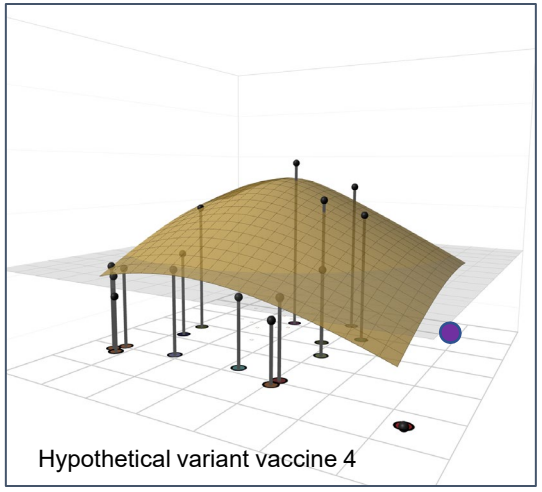
If (when) a new variant emerges, we can test serum to the new antigen
- will inform of vaccine options to use with previously tested variant vaccines











Conclusion

- There is likely to be continued evolution of the SARS-CoV-2 virus.
  - Evolution within Omicron BA.2, or
  - Another Omicron-like emergence event

- Ideally we learn to pick vaccine strains based on anticipated evolution.

- We need to understand how to use available vaccines (prototype and variant) to modify antibody responses and target different antigenic spaces.

Conclusion

- Anticipate a fall booster
  - Would anticipate it will include a SARS-CoV-2 variant
    - Alone or in combination
  - Picking the variant is difficult
    - Will want to cover Omicron and other variants that may emerge