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Evaluation of Next Generation COVID-19 Vaccines

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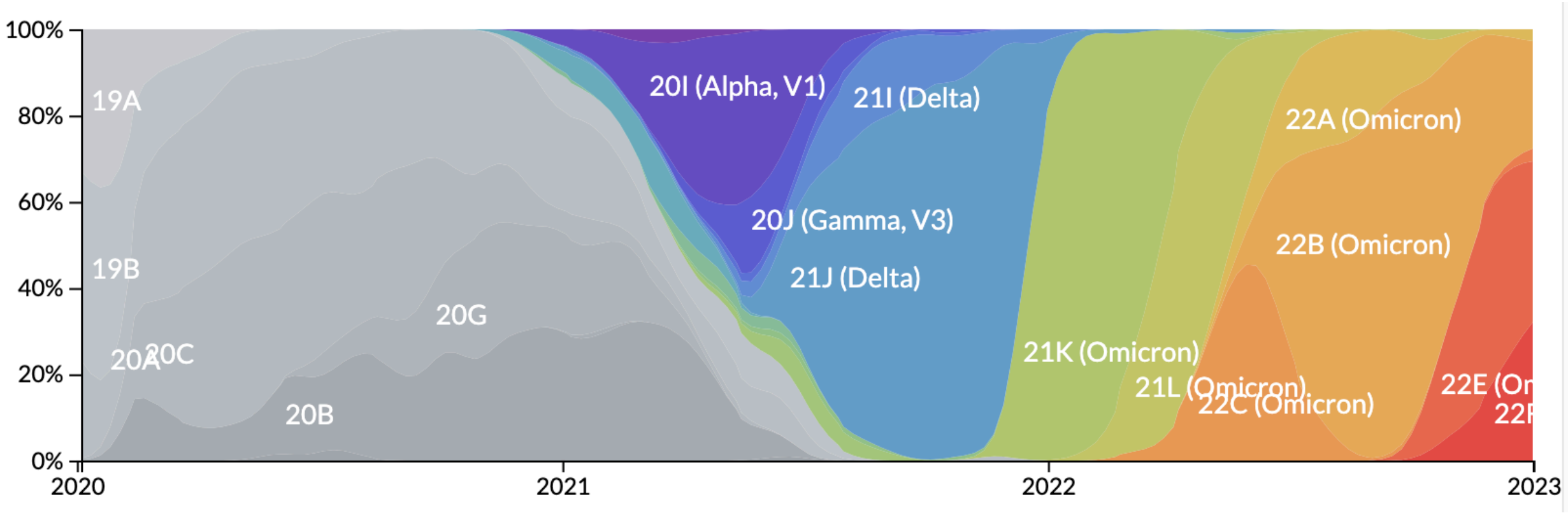
Disclosures

I have no direct financial relationships with any commercial interests

Within my household, there is an employee of the Vaccine Company

COVID-19 variants over time



To address this genetic evolution the FDA authorized bivalent boosters (prototype + BA.4/BA.5 Omicron variant) in 2022

Current strategy:
Using antigenically diverse vaccine strains

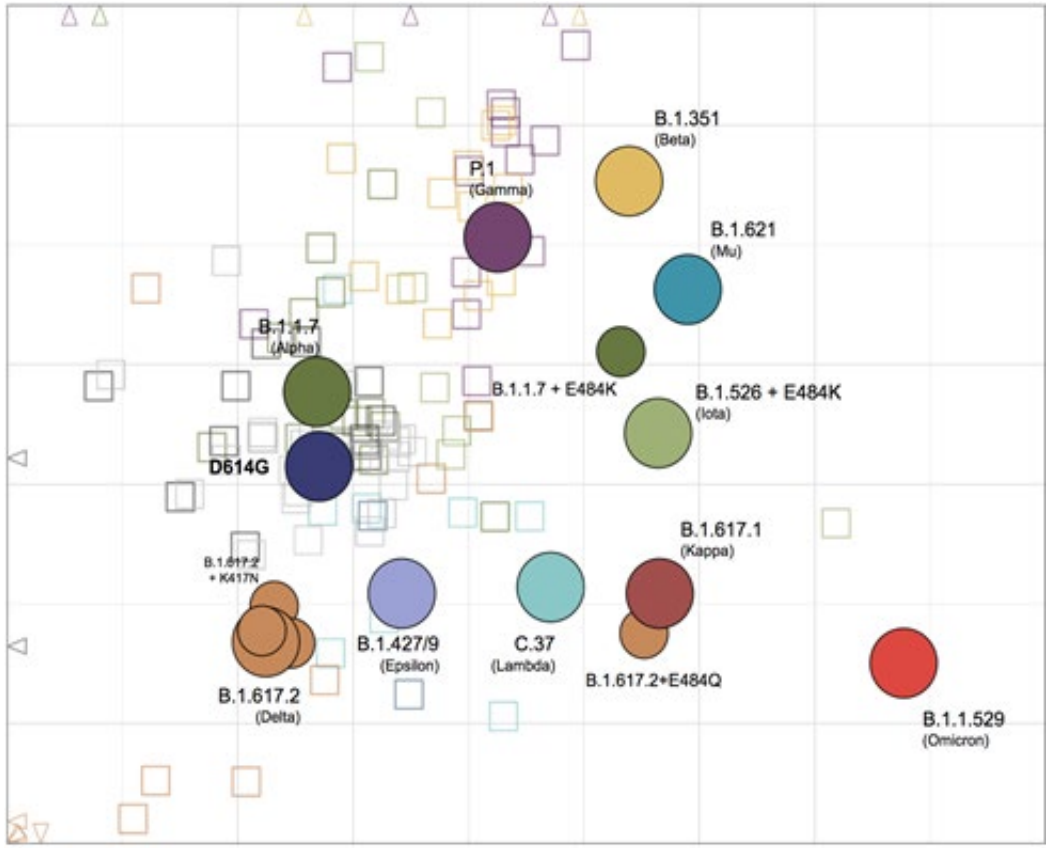
NIAID CoVAIL Trial

- **Population:**
  - Received any COVID-19 vaccine primary and boost
  - Homologous or heterologous
- **Two age strata:**
  - ≥ 18 years (same as for stage 1)
- **Two infection strata:**
  - Confirmed prior COVID-19 (>20%)
  - No known history of prior infection
- **Enrolled by stage, randomized to different variant vaccines (or prototype)**

	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 + BA.1	≥16	One dose	Pfizer
	14	50	Wildtype + BA.4/BA.5	≥16	One dose	

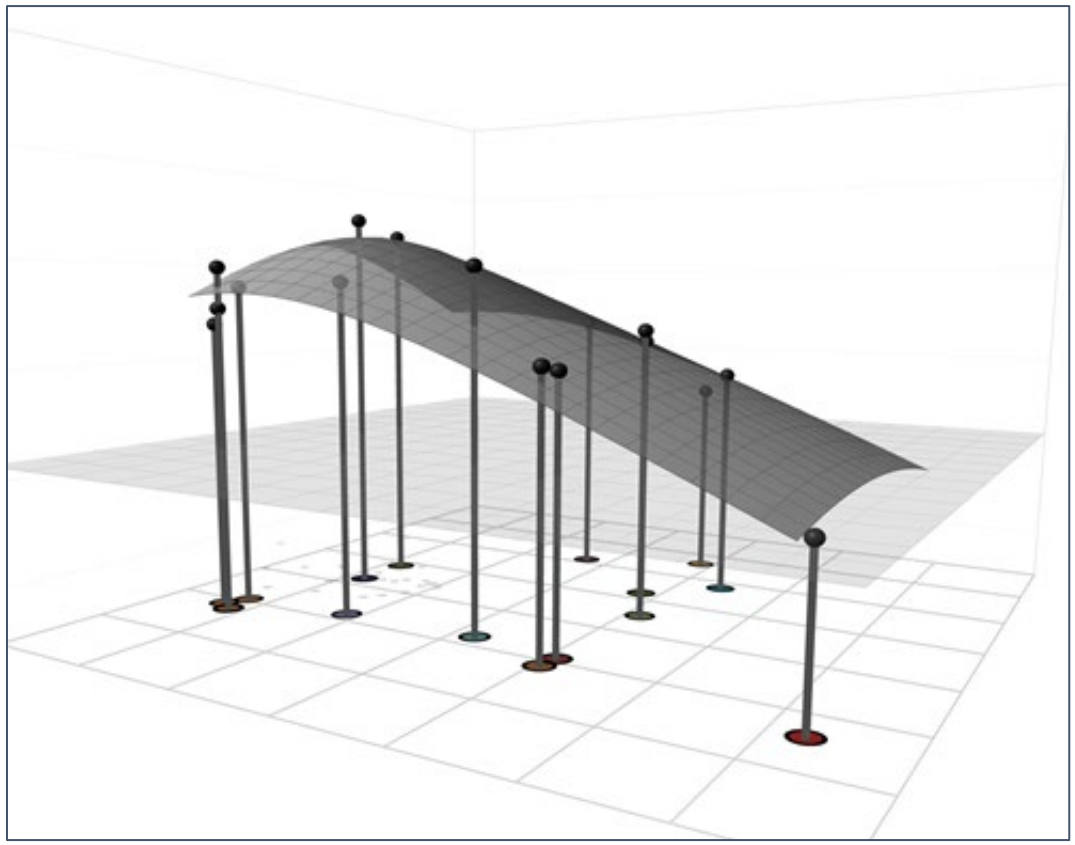
NCT05289037
Branche et al. www.medrxiv.org/content/10.1101/2022.07.12.22277336v1

Antigenic map reflects relative distance (dilutions) of antigens and serum



mRNA-1273 sera

Landscape shows titers across variants in the map

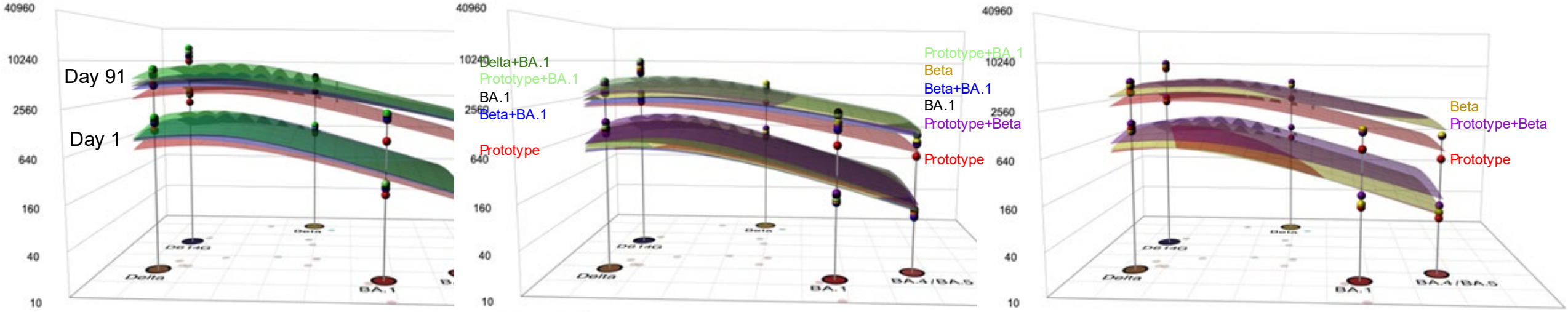


Variant antigens elicit modestly higher titers to variants of concern

Any booster, including prototype, improves antibody titers across all strains

Variant antigens elicit modestly higher titers compared to prototype for antigenically distant strains

- **Vaccines containing omicron were similar to those not containing omicron (except for prototype)**
- **Bivalent vaccines perform similar to monovalent variant vaccines**

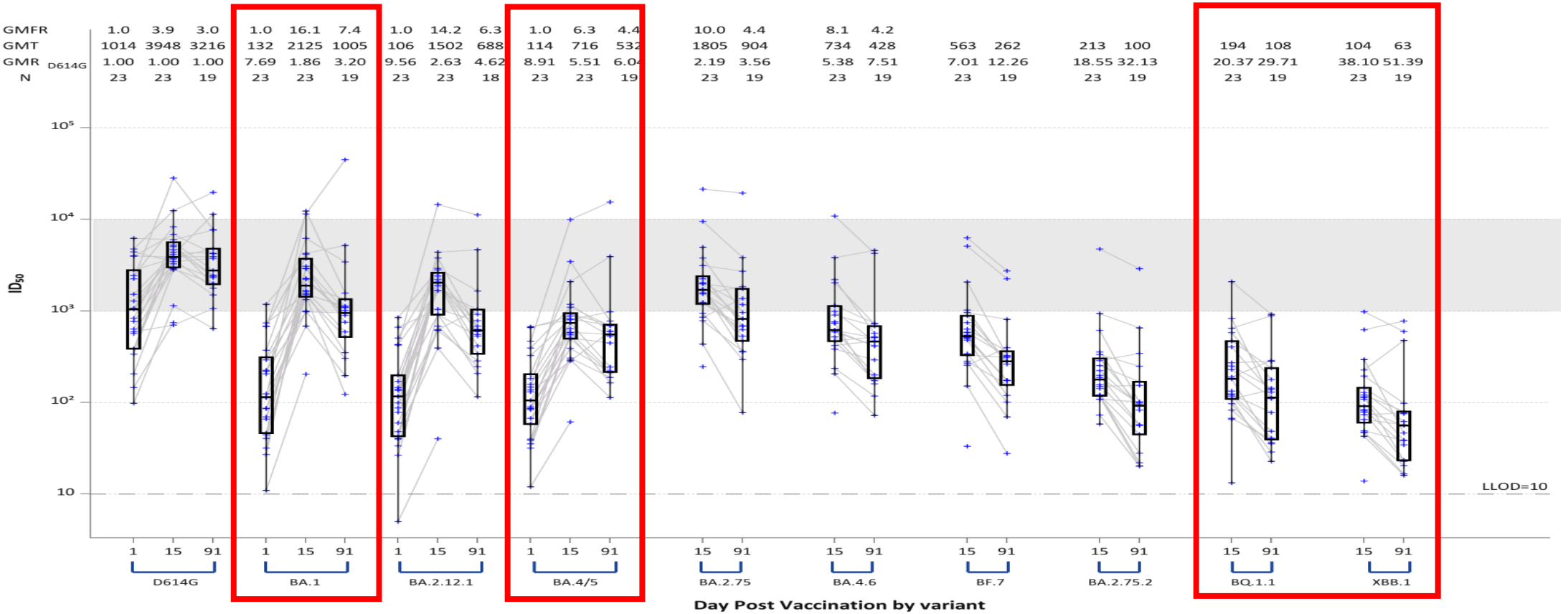


Moderna Pfizer Sanofi

NIAID COVAIL trial:
Day 1 and 91 antibody titer landscapes

Current vaccines elicit lower neutralizing antibody titers to newly emerging variants

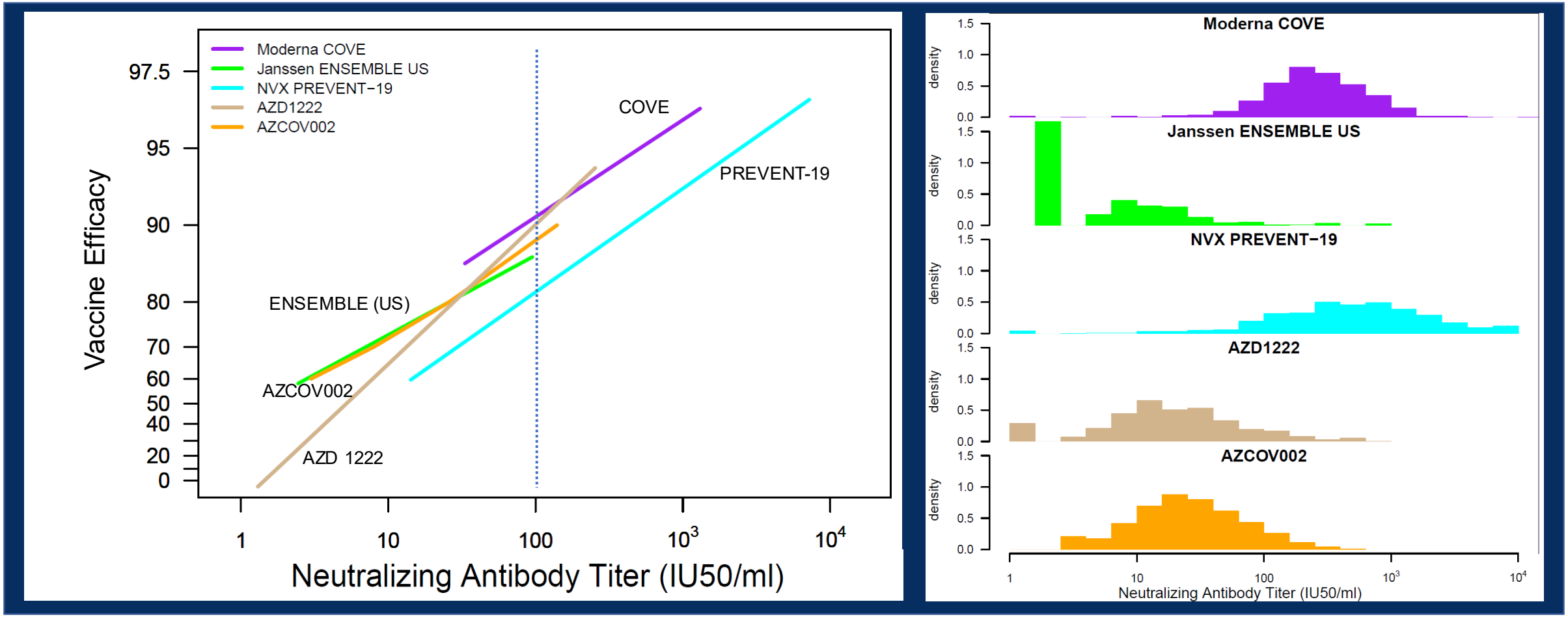
Moderna Omicron BA.1 + Prototype Vaccine (uninfected, enrolled March and April)



Variants that emerged within 9 months

NIAID COVAIL trial data, unpublished.

Correlates of Protection Analysis: Efficacy Decreases with Lower Neutralizing Antibody Titer



Gilbert et al. NEJM 2022
(updated by P Gilbert)

Better Protection Against Severe Disease

Cohort studies also support protection for asymptomatic disease

- Cohort studies suggest less pre-procedural asymptomatic infection in vaccinated individuals

Efficacy against asymptomatic disease is lower than symptomatic disease

	Per-protocol **population**		
	Placebo N=14164	mRNA-1273 N=14287	Estimated VE (95% CI)
Severe Covid-19 cases	106 (0.7)	2 (0)	**97.6** (92.4-99.2)
Symptomatic Covid-19	744 (5.3)	55 (0.4)	**93.2** (91.0-94.8)
Asymptomatic infection	498 (3.5)	214 (1.5)	**63.0** (56.6-68.5)

Tande et al. Clin Infect Dis, 2021
El Sahly et al, NEJM 2021

Protection Against Transmission is Modest

Limited data show:

- **Cohort studies suggest some protection against transmission**
  - e.g. within household
- **If a person is infected -> similar peak viral titers, less duration of shedding**
  - This may decrease transmission window
  - Definitive studies evaluating transmissibility after infection are lacking

Lyngse et al. Nat Comm, 2022
Hayek et al. Science 2022
Harris et al. NEJM 2021

Current Vaccines Remain Effective Against COVID-19, but …

Vaccine efficacy:

- Severe > Symptomatic >> Asymptomatic & Transmission

High titers are not sustained over long periods of time

The cross reactive antibody titers to new variants emerging within a year are marginal

- I.e., the antigenic landscape is not flattening enough to cover newly emerging strains with high titers

Next Generation SARS-CoV-2 Vaccines: Key Properties

- Enhanced breadth of protection (variant proof)
- Improved durability
- Enhanced ability to block infection/transmission

Next Generation Vaccines - Potential approaches

- **New antigens / constructs to generate broader response**
  - Conserved element
  - Mosaic
- **Induction of more durable immune response**
- **Targeting mucosal immunity**
  - E.g. intranasal or oral administration
  - Parenteral administration with more mucosal immunity

How Do We Advance Next Generation Vaccines?

- **For COVID-19 vaccine development under Operation Warp Speed, there was good data supporting which vaccines to advance**
  - Prior preclinical work supporting antibody role in minimizing severe disease
  - Prior work with vaccine platforms

- **For next generation candidates (especially mucosal), more data is needed:**
  - Which vaccines will increase breadth of protection, durability, and efficacy?
  - Which vaccines limit asymptomatic infection, and transmission?
    - What immune correlates are associated with protection for asymptomatic infection, and transmission?

Neutralizing antibody does not explain all of VE

Representative vaccine:

Trial/Marker	Direct VE (95% CI)	Indirect VE (95% CI)	Proportion Mediated (95% CI)
Moderna COVE D29 PsV ID50	56.0% (42.2, 66.5%)	83.2% (76.9, 87.8%)	68.5% (58.5, 78.4%)

Direct VE: VE through other pathways
Indirect VE: VE through neutralizing antibody titer
Proportion mediated: Proportion of overall VE mediated through neutralizing antibody

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	Placebo N=14164	mRNA-1273 N=14287	Estimated VE (95% CI)
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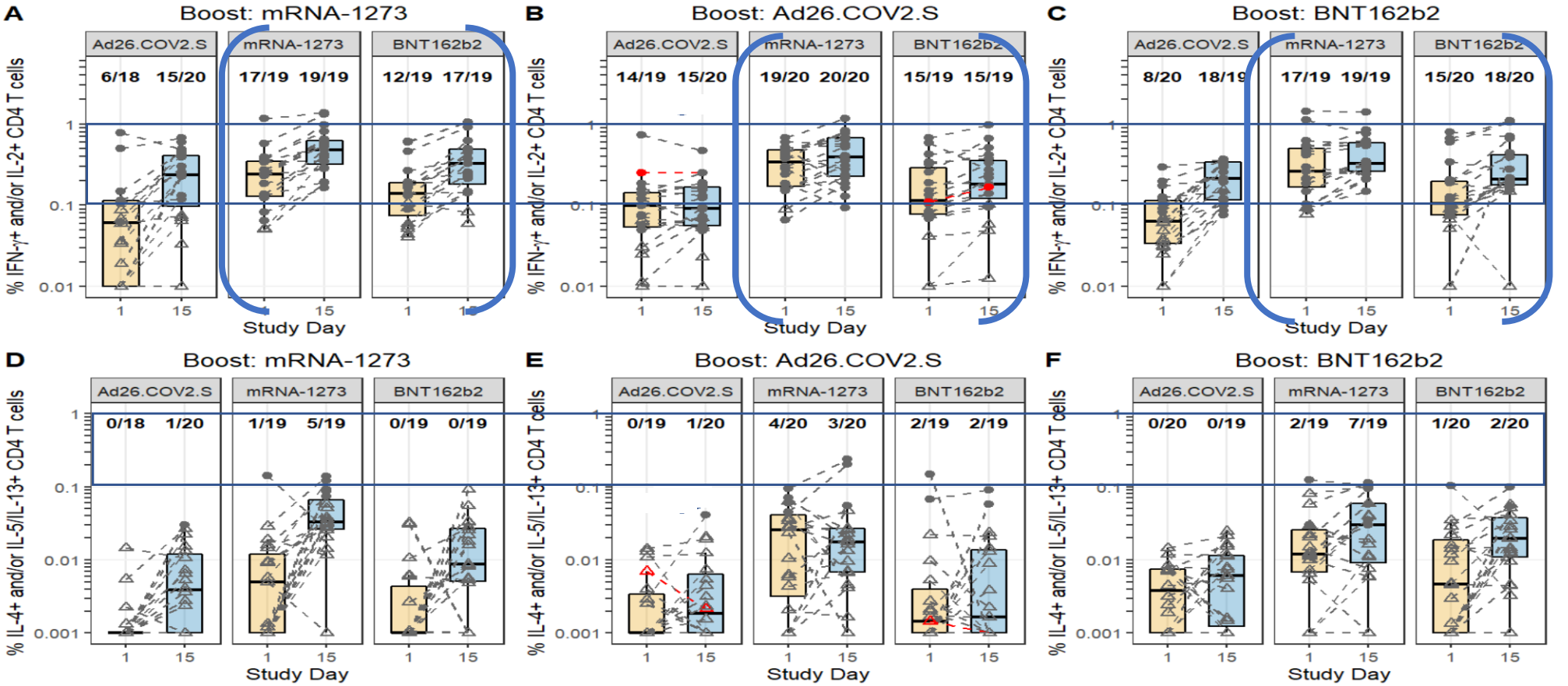
Neutralizing antibody likely does not contribute equally to VE for different outcomes

In addition to neutralizing antibodies, what other mediators may be contributing?

Different Vaccine Platforms Induce Different Cell Mediated Immunity



CD4⁺ Th1

(IFN□and/or IL-2)

At baseline:

- 49% Ad26.COV2.1
- 91% mRNA-1273
- 72% BNT162b2

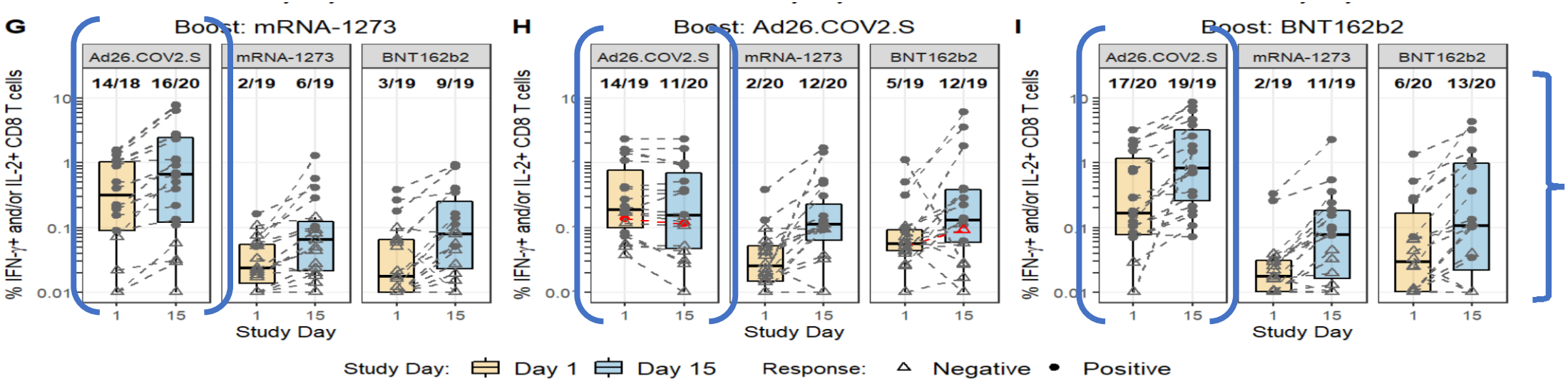
Post-boost:

- 81% Ad26.COV2.1
- 100 % mRNA-1273
- 86% BNT162b2

CD4⁺ Th2

- (IL-4⁺and/or IL-5, IL-13)
- Shaded region reflects magnitude of Th1 response
  - % of Th2 T cells 10 fold lower than % of Th1 T cells

Different Vaccine Platforms Induce Different Cell Mediated Immunity



CD8+ (IFN□and/or IL-2)

At baseline:
- 79% Ad26.COV2.1
- 10% mRNA-1273
- 24% BNT162b2

Post-boost:
- 78% Ad26.COV2.1
- 50 % mRNA-1273
- 59% BNT162b2

Atmar et al. NEJM 2022

Analyses Correlating Cell Mediated Immunity to Protection in Vaccine Trials are Ongoing

COVAIL trial

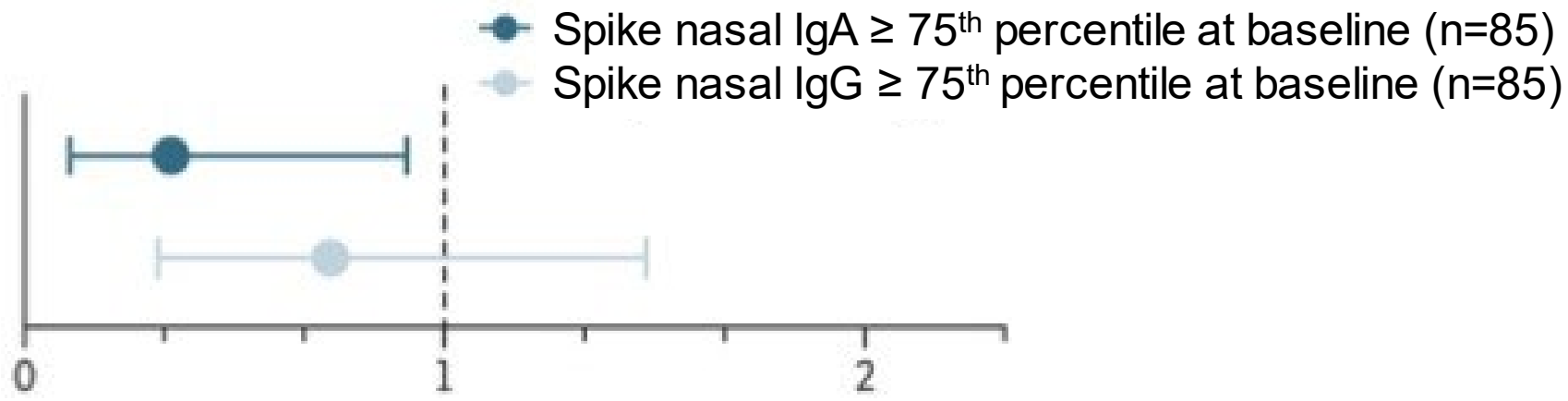
- Neutralizing antibody
- T-cell analysis on 70% of participants (ongoing)
  - Includes with and without prior infection history and intercurrent infections

COV2008 study with Janssen

- Primary vaccination with a single dose of Ad26.COV2.S or 2 doses of BNT162b2
- All participants boosted with Ad26.COV2.S ≥6 months post primary vaccination
- Assess 2-week post boost markers as CoR/CoP for COVID-19
  - Neutralizing and binding antibodies
  - T-cell responses (ICS)

Nasal IgA titers are related to protection…

Risk of Omicron breakthrough infection and effect on viral replication



…but we don't know:

- **If a vaccine changes the mucosal immune response**
- **If those changes are correlated with vaccine efficacy**
  - especially to the outcomes of transmission and asymptomatic infection

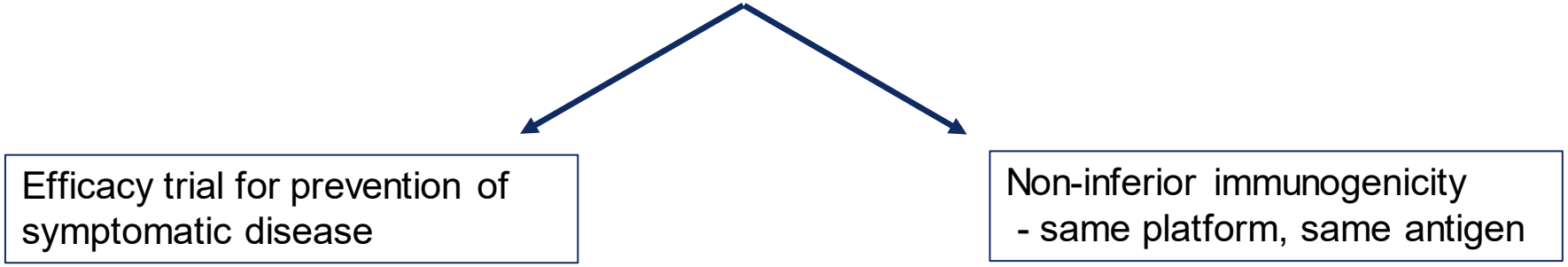
Havervall et al. NEJM 2022

What to Measure for Mucosal Vaccines?

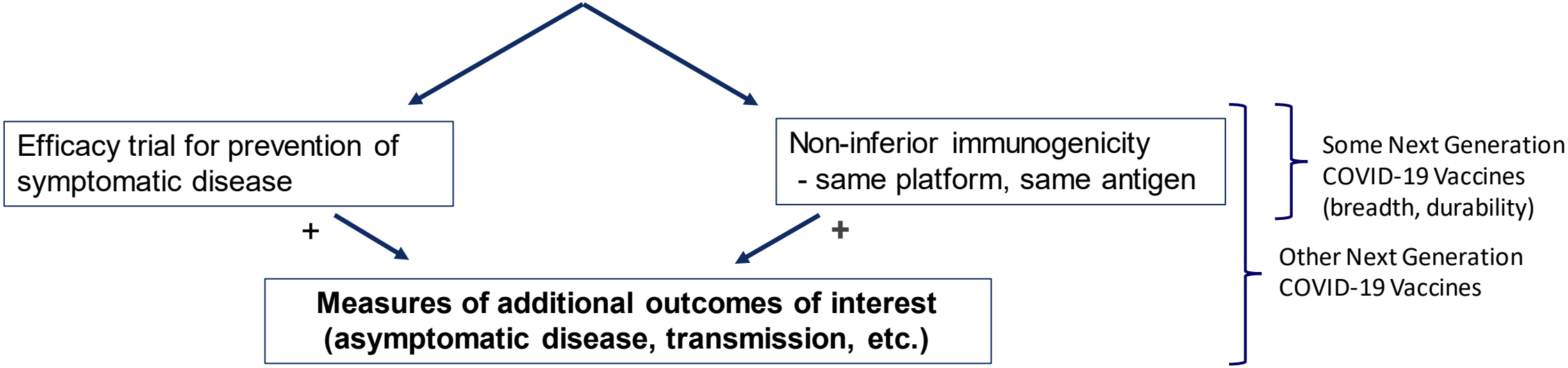
- Contributions from systemic vs mucosal?
- Mucosal antibodies or cellular responses (or both)?
- Nasal Or Salivary?
- IgA Or IgG?
- CD4 or CD8?

Sette and Crotty. Immunological Reviews 20222

Evaluation of Current Generation COVID-19 Vaccines



Evaluation of Next Generation COVID-19 Vaccines



To advance vaccines with these additional outcomes, we need to:

- Understand and identify immune markers related to outcomes of interest
  - E.g., the immune response necessary to impact transmission and asymptomatic infection
- Evaluate correlates of protection using these parameters
- Standardize sampling techniques
- Develop optimized/validated assays, performed in a way that allow comparisons

Conclusions

- **There is a public health need for next-generation vaccines**
- **Some next-generation vaccines can be advanced using data and assays similar to the pivotal trials…**
  - Broader protection against emerging variants
  - Increased durability
- **…but we also need to better understand the immune responses that protect against infection/transmission**
  - Those are the outcomes that are increasingly important
- **Together, this will allow identification of the most promising vaccine candidates to further decrease COVID-19 disease**