Vaccines and Related Biological Products Advisory Committee October 14-15, 2021 Meeting Presentation

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DMID 21-0012 - Heterologous Platform Boost Study

Mix and Match

Vaccines and Related Biological Products Advisory Committee
October 14-15, 2021

Kirsten E. Lyke, MD representing Mix and Match Study Team
University of Maryland, School of Medicine
Center for Vaccine Development and Global Health

Disclosures:

The speaker has received funding as co-Principal Investigator for Phase I studies involving the Pfizer COVID-19 vaccine. Additionally, the speaker receives grant funding from NIAID/IDCRC as co-Chair and site PI for the MixNMatch and as an investigator on the Moderna and Novavax Phase III studies

Kirsten E. Lyke, MD
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Heterologous Platform Boost Study: "*Mix and Match*"

3 vaccines are available under EUA in US

Key decisions to be made on late boost

- If boost needed?
- Whom to boost?
- When to administer boost?
- What to boost with?

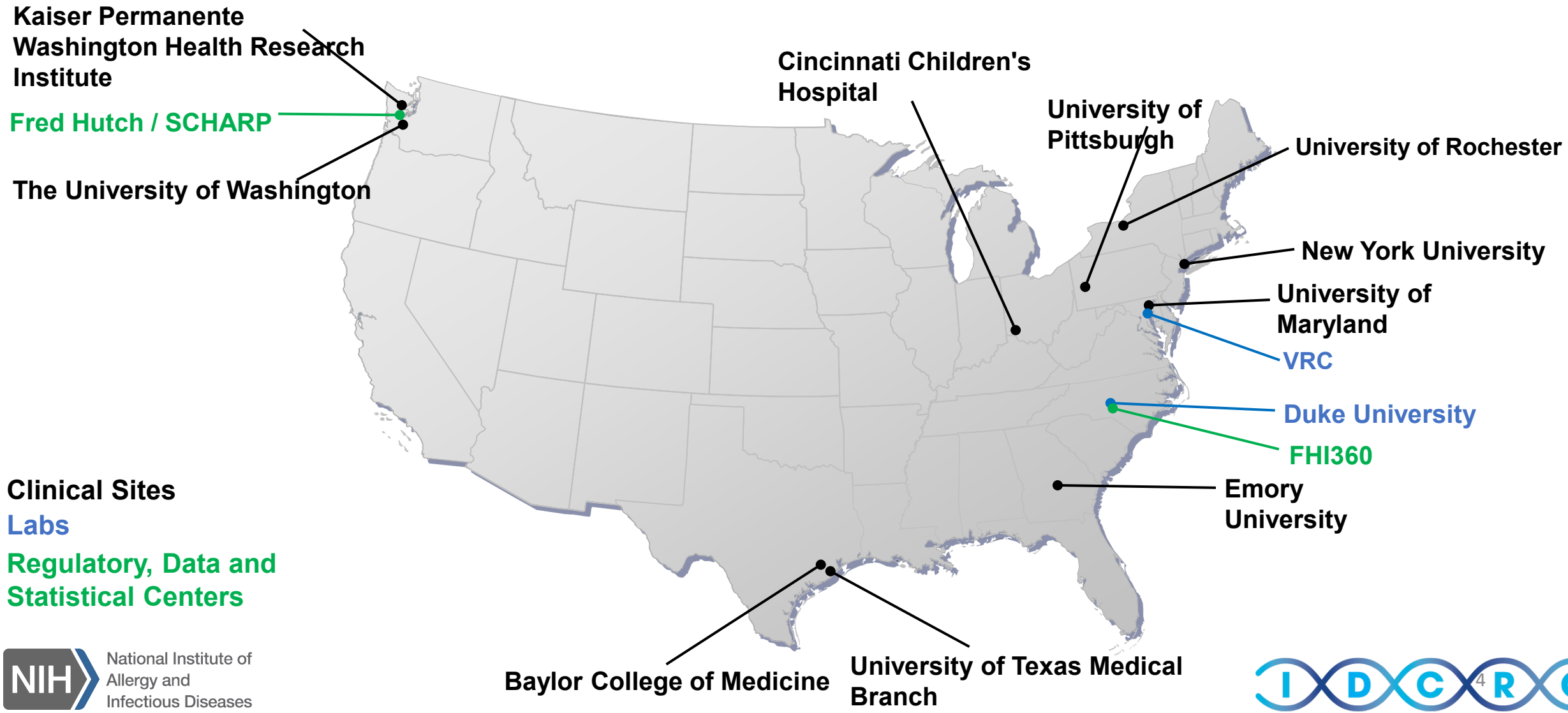
The data needed to make these decisions include:

- Correlates of protection
- Longevity of antibody response after primary vaccination
- Emergence of variants
- Breakthrough infections
- Safety and immunogenicity of boost – primarily homologous boost trials by companies
- **Understand how to use current vaccines to be used as a boost**
  - Can one vaccine be used as a boost to a different vaccine?
  - Is it safe to mix vaccines?
  - What happens to the immune response after booster vaccination?

This trial

The "Mix and Match" Study Team

Co-Chairs: Kirsten E. Lyke, MD and Robert L. Atmar, MD



Study Design

Volunteers received EUA/approved Covid-19 vaccine

- At least 12 weeks since the last vaccine dose
  - Timing driven by need to have data available for the fall
- Approximately 50 participants per group (primary vaccine + booster)
  - Sample size: ~25/age strata -18-55 years of age; ≥ 56 years of age
    - 99.5% probability of observing at least one AE with a true event rate of 10%
    - 63.6% probability of observing at least one AE with a true event rate of 2%
- Designed to inform public health decisions
  - Not powered or designed to compare between the groups

NIH NIAID

IDCRC Infectious Diseases Clinical Research Consortium

	Group	Sample Size*	EUA Vaccine	Interval (weeks)	Delayed Booster Vaccination	Strategy Tested
Booster Vaccination – Moderna (100 mcg)	1	50	**Previously dosed Janssen – Ad26.COV2-S**	≥12	Moderna- mRNA-1273	Same Strain Heterologous platform
	2	50	**Previously dosed Moderna – mRNA-1273**	≥12	Moderna- mRNA-1273	Control - Same Strain & platform
	3	50	**Previously dosed Pfizer/BioNTech –BNT162b2**	≥12	Moderna- mRNA-1273	Same Strain Similar platform
Booster Vaccination – Janssen ($5x10^{10}$ vp)	4	50	**Previously dosed Janssen – Ad26.COV2-S**	≥12	Janssen – Ad26.COV2.S	Control - Same Strain & platform
	5	50	**Previously dosed Moderna – mRNA-1273**	≥12	Janssen – Ad26.COV2.S	Same Strain Heterologous platform
	6	50	**Previously dosed Pfizer/BioNTech –BNT162b2**	≥12	Janssen – Ad26.COV2.S	Same Strain Heterologous platform
Booster Vaccination – Pfizer (30 mcg)	7	50	**Previously dosed Janssen – Ad26.COV2-S**	≥12	Pfizer/BioNTech – BNT162b2	Same Strain Heterologous platform
	8	50	**Previously dosed Moderna – mRNA-1273**	≥12	Pfizer/BioNTech-BNT162b2	Same Strain Similar platform
	9	50	**Previously dosed Pfizer/BioNTech –BNT162b2**	≥12	Pfizer/BioNTech – BNT162b2	Control - Same Strain & platform

Study Visits: Days 1, 8 (call), 15, 29, Months 3, 6, 12

Volunteer Characteristics

N = 458

2 Participants
- Group 4 (n = 1)
- Group 6 (n = 1)
- High N protein antibody (D1) suggestive of prior infection

1 Participant
- Group 5 (n = 1)
- Covid-19 Study Day 27

Table 1. Characteristics of the Participants at Enrollment

Group	1	2	3	4	5	6	7	8	9
Primary EUA Immunization Vaccine	Janssen Ad26.COV2-S 5x10¹⁰ vp	Moderna mRNA-1273 100-mcg	Pfizer/BioNTech BNT162b2 30-mcg	Janssen Ad26.COV2-S 5x10¹⁰ vp	Moderna mRNA-1273 100-mcg	Pfizer/BioNTech BNT162b2 30-mcg	Janssen Ad26.COV2-S 5x10¹⁰ vp	Moderna mRNA-1273 100-mcg	Pfizer/BioNTech BNT162b2 30-mcg
Booster	Moderna mRNA-1273 100-mcg			Janssen Ad26.COV2-S 5x10¹⁰ vp			Pfizer/BioNTech BNT162b2 30-mcg		
Total Number	53	51	50	50	49	51	53	51	50
Sex – no. (%)									
Female	26 (49.1)	32 (62.7)	29 (58.0)	27 (46.0)	16 (32.7)	23 (45.1)	29 (54.7)	26 (51.0)	23 (46.0)
Male	27 (50.9)	19 (37.3)	21 (42.0)	23 (54.0)	33 (67.3)	28 (54.9)	24 (45.3)	25 (49.0)	27 (54.0)
Age – years									
Mean (s.d.)	56.8 (14.5)	53.1 (16.2)	54.8 (17.4)	50.1 (13.9)	49.9 (16.8)	50.3 (15.4)	47.7 (14.5)	54.3 (16.8)	50.4 (17.9)
Range	24-81	24-76	22-85	24-77	20-75	20-76	22-74	23-75	19-80
Race – no. (%)									
Asian	4 (7.5)	5 (9.8)	4 (8.0)	3 (6.0)	5 (10.2)	6 (11.8)	1 (1.9)	2 (3.9)	1 (2.0)
Hawaiian or Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Black/African American	1 (1.9)	2 (3.9)	3 (6.0)	0 (0.0)	0 (0.0)	2(3.9)	0 (0.0)	2 (3.9)	1 (2.0)
White	46 (86.8)	41 (80.4)	43 (86.0)	44 (88.0)	43 (87.8)	40 (78.4)	50(94.3)	47 (92.2)	43 (86.0)
Multi-racial	1 (1.9)	3 (5.9)	0 (0.0)	3 (6.0)	1 (2.0)	2 (3.9)	1 (1.9)	0 (0.0)	4 (8.0)
Other	1 (1.9%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0%)	0 (0.0)	0 (0.0)	1 (2.0%)
Ethnicity – no (%)									
Non-Hispanic	49 (92.5)	46 (90.2)	47 (94.0)	47 (94.0)	49 (100.0)	48 (94.1)	51 (96.2)	49 (96.1)	45 (90.0)
Hispanic/Latino	4 (7.5)	4 (7.8)	3 (6.0)	2 (4.0)	0 (0.0)	3 (5.9)	2 (3.8)	2 (3.9)	5 (10.0)
Unknown/Not reported	0 (0.0)	1 (2.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Boost Interval weeks									
Mean (s.d.)	13.7 (1.0)	16.4 (1.9)	16.8 (2.2)	17.7 (2.0)	19.3 (4.2)	20.6 (5.8)	19.9 (2.5)	22.9 (4.6)	24.1 (5.2)
Range	12.0-15.9	12.4-20.0	12.0-20.9	13.9-21.0	12.6-26.0	12.3-41.3	10.9-23.0	12.6-28.7	14.3-31.9

Time from Vaccination to Boost (Weeks)[1]

Booster Vaccination

mRNA-1273

	Janssen 18-55	Janssen 56+	Moderna 18-55	Moderna 56+	Pfizer 18-55	Pfizer 56+	Total
N	21	32	26	25	25	25	154
Median	13.1	14.3	17.8	16.0	17.9	16.4	**15.4**
25th, 75th %tile	12.1, 14.0	13.3, 14.6	15.3, 18.7	15.0, 16.9	16.7, 19.1	14.6, 17.3	14.0, 17.3

Ad26.COV2.S

	Janssen 18-55	Janssen 56+	Moderna 18-55	Moderna 56+	Pfizer 18-55	Pfizer 56+	Total
N	26	24	24	25	25	26	150
Median	18.0	18.1	19.1	17.4	17.4	20.7	**18.4**
25th, 75th %tile	16.3, 19.3	16.8, 19.4	15.6, 23.9	16.1, 22.7	16.3, 25.1	16.4, 25.9	16.3, 21.0

BNT162b2

	Janssen 18-55	Janssen 56+	Moderna 18-55	Moderna 56+	Pfizer 18-55	Pfizer 56+	Total
N	31	22	22	29	24	26	154
Median	19.6	21.4	23.4	23.6	24.4	25.7	**21.5**
25th, 75th %tile	17.7, 21.1	20.1, 22.1	16.9, 26.9	19.9, 26.7	18.8, 28.4	20.7, 28.9	18.9, 26.0

Increasing interval with sequential, staged recruitment

Immunogenicity

Summary of Available Immunogenicity through D15/D29

Duke (Montefiori Lab): PsVN (ID50, ID80 and in IU_{50}/mL, IU_{80} /mL)

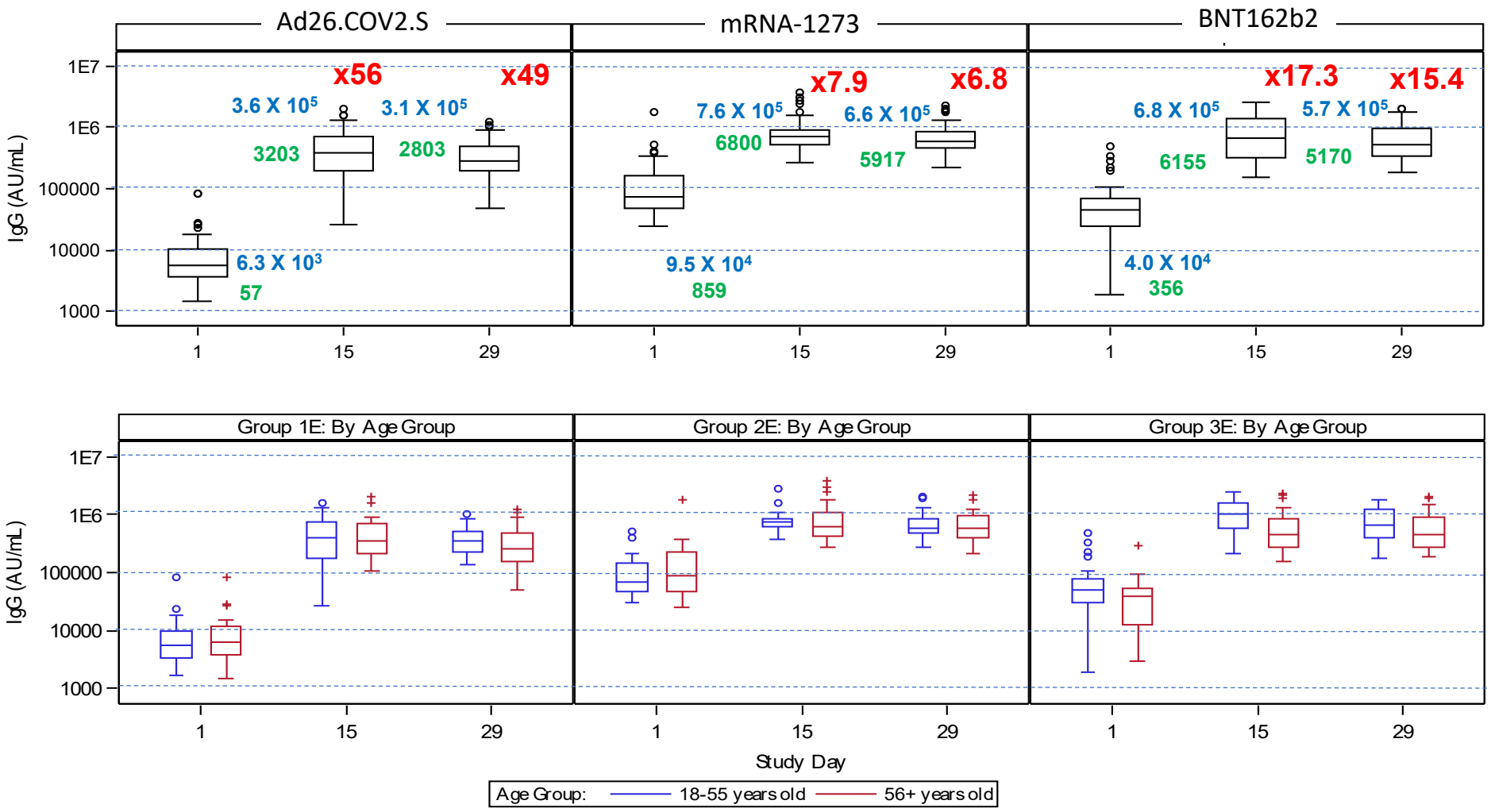
- D614G N=~450 (50/arm)
- VoCs N=60, 20/arm, 10/age group
  - Beta, Delta - In process

VRC (McDermott Lab): IgG Antibody Binding

- 4-plex (validated) (AU/mL)
  - S-2P (Wa-1 and Beta) N=~450 (~50/arm) (AU/mL)
    - S-2P Wa-1: Binding Antibody Units/mL (BAU/mL) (International Standard)
- 10-plex Fit for Purpose (FFP)
  - S-2P (Alpha, Beta, Gamma, Delta, Wa-1) (AUC/m)

Moderna mRNA-1273 Booster Vaccination with 100 mcg

IgG Serum Binding Antibody Response to S-2P-Wa-1 Antigen by 4-plex ECLIA V.2, by Group, Age and Timepoint: mRNA-1273 Booster Vaccination – through Day 29

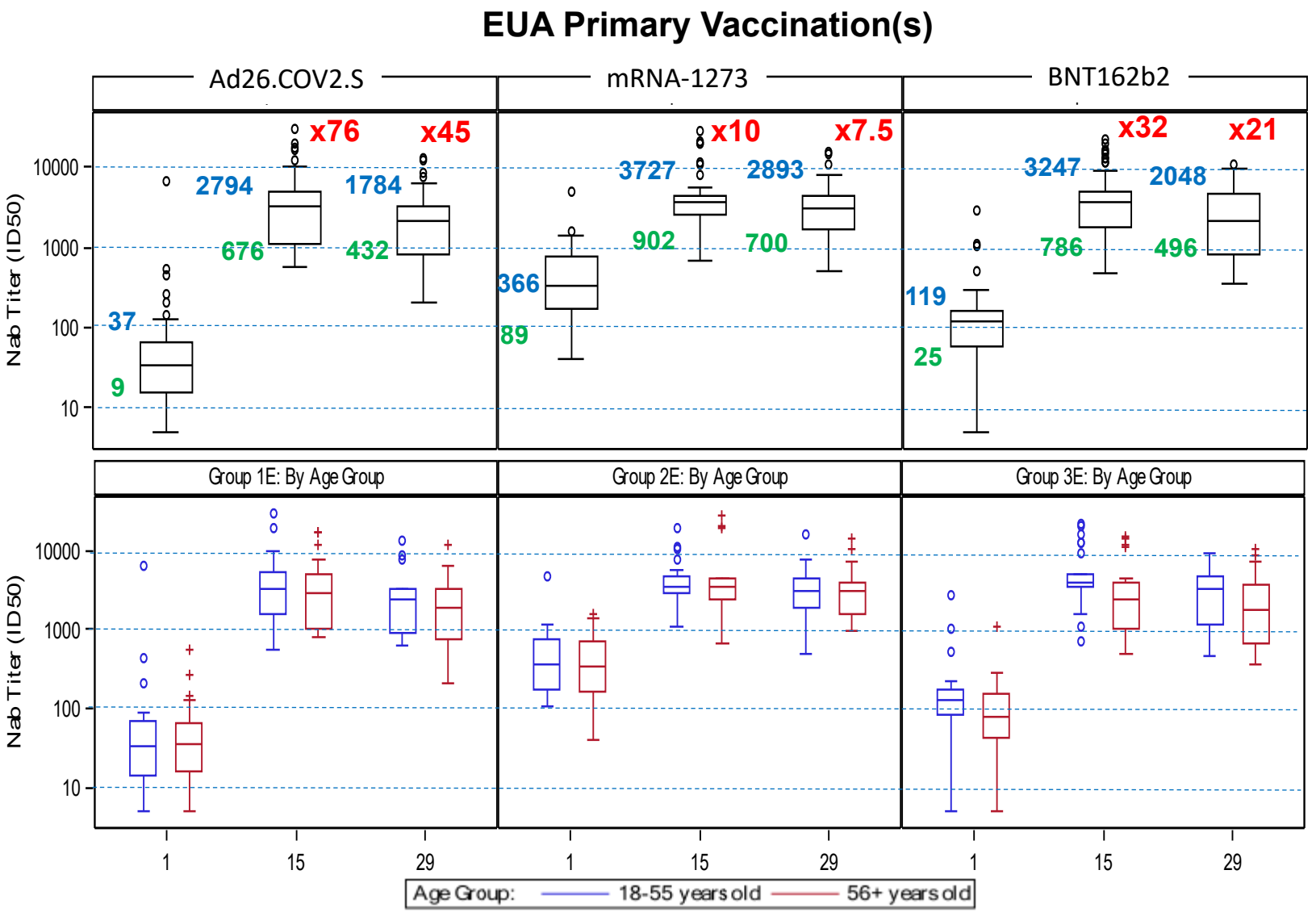


GMFR
GMT
GM BAU/mL

N=52 N=50 N=50

Pseudovirus Neutralization Antibody Titers to Spike D614G through D29 post-mRNA-1273 Boost (100 mcg)

ID50



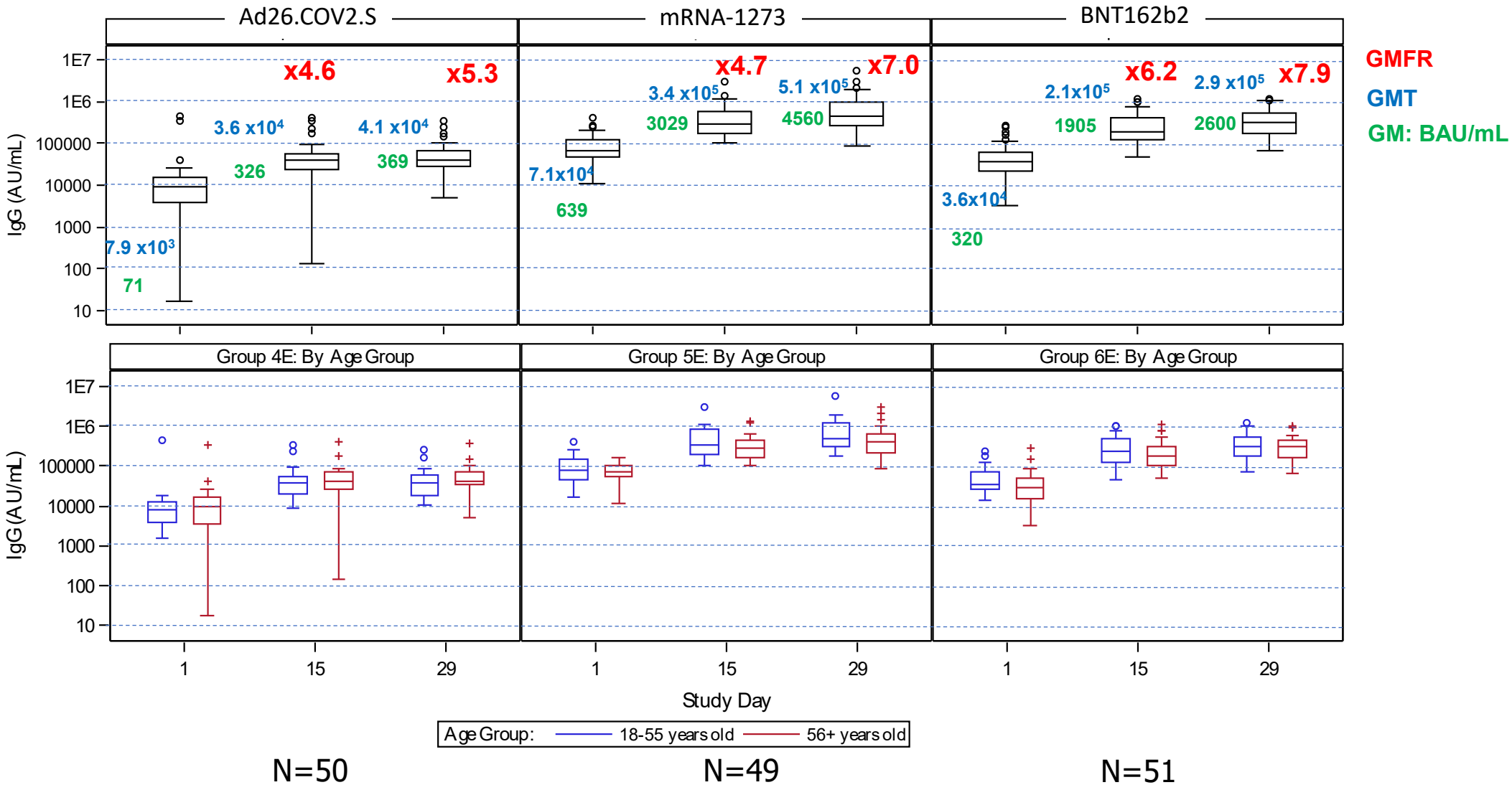
GMFR
GMT
GM IU50/mL

N=52 N=50 N=50

IU_{50}/mL = ID50 x 0.242

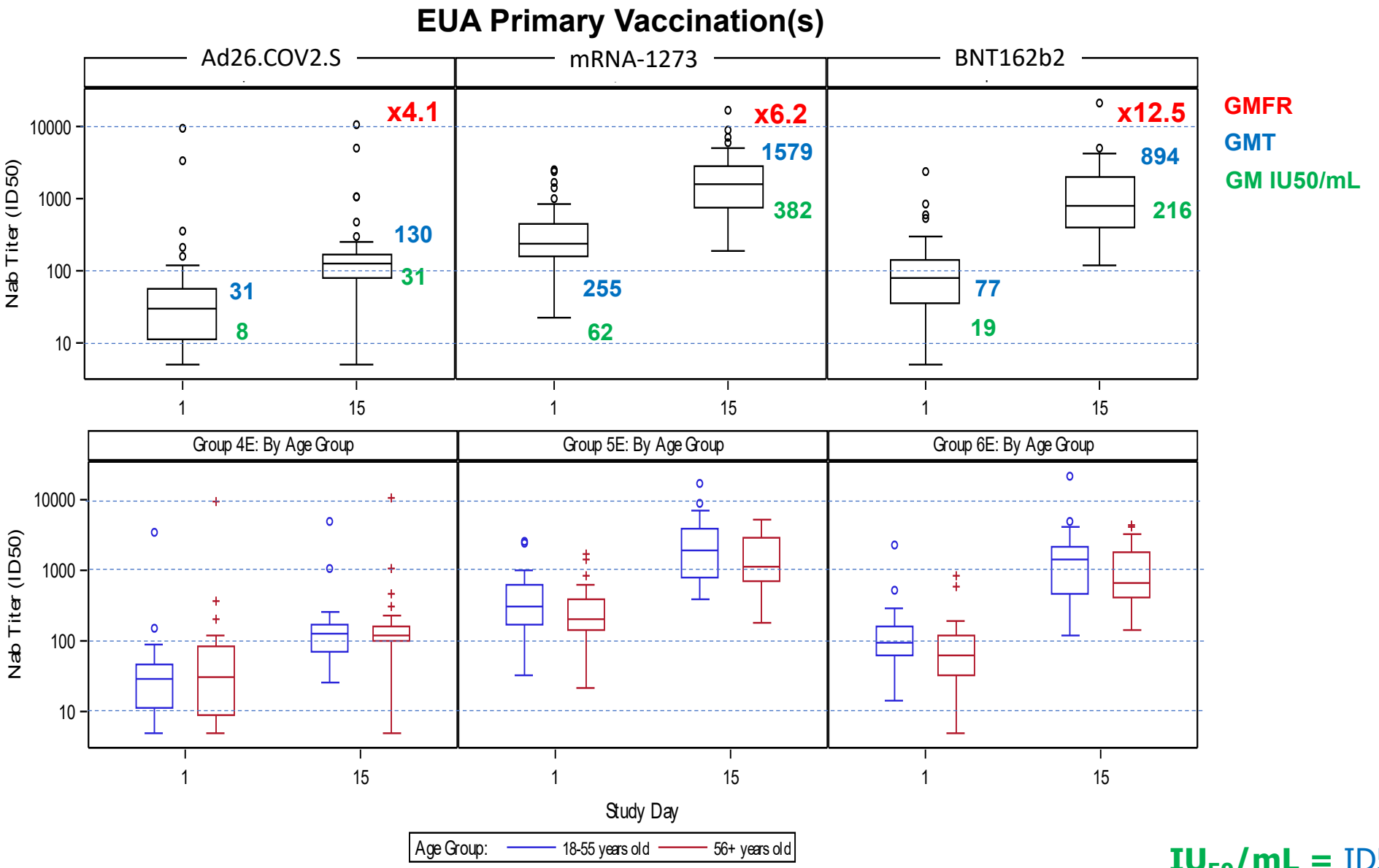
Janssen Ad26.COV2.S Booster Vaccination with $5x10^{10}$ vp

IgG Serum Binding Antibody Response to S-2P-Wa-1 Antigen by 4-plex ECLIA V.2, by Group, Age Group and Timepoint: Ad26.COV2.S Booster Vaccination – through Day 29



Pseudovirus Neutralization Antibody Titers to Spike D614G through 14 days post-Ad26.COV2.S Boost by Group (top) and Age (bottom), and Timepoint

ID50

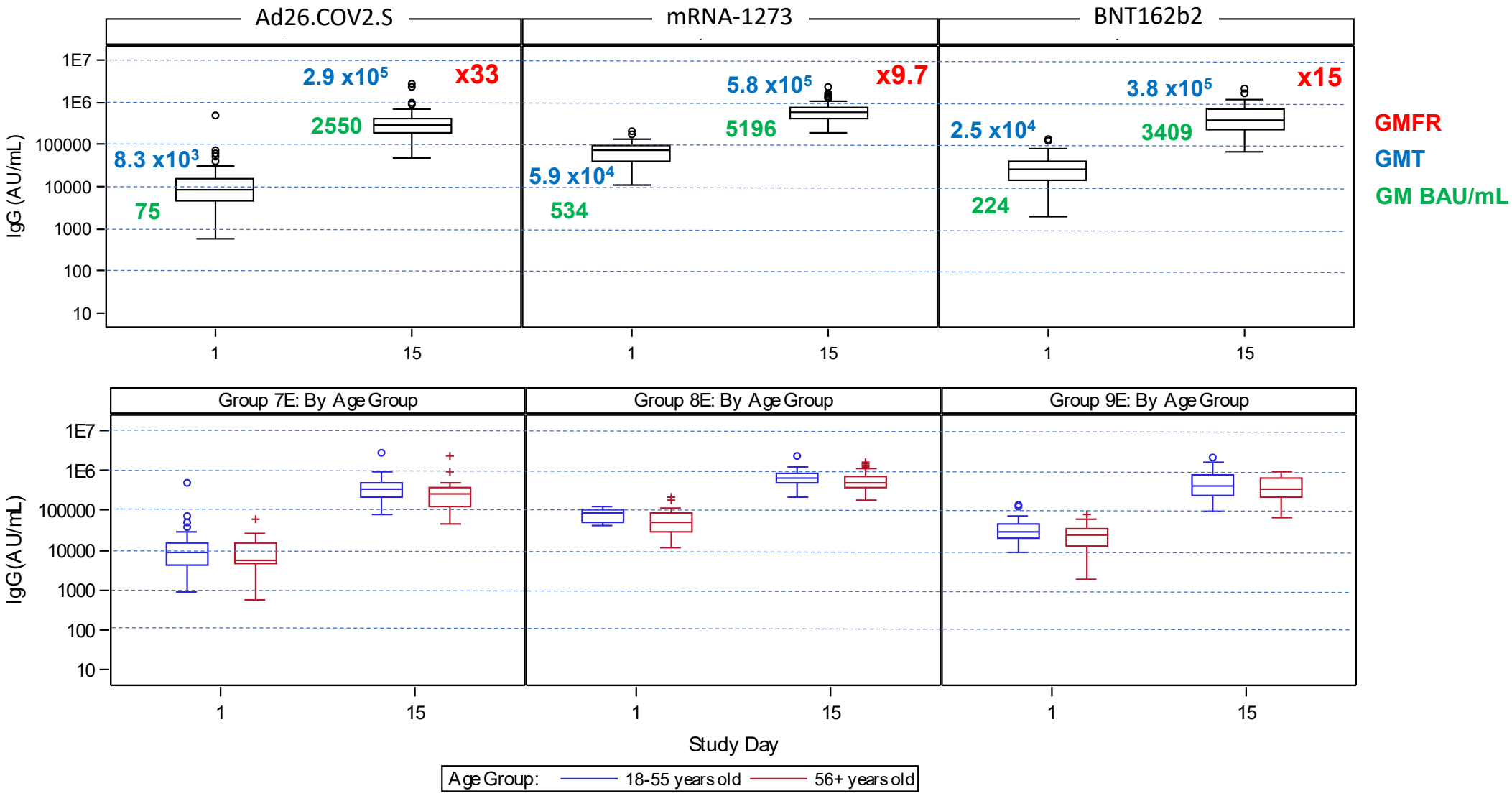


N=50 N=49 N=51

IU_{50}/mL = ID50 x 0.242

Pfizer/BioNTech Booster Vaccination with 30 mcg

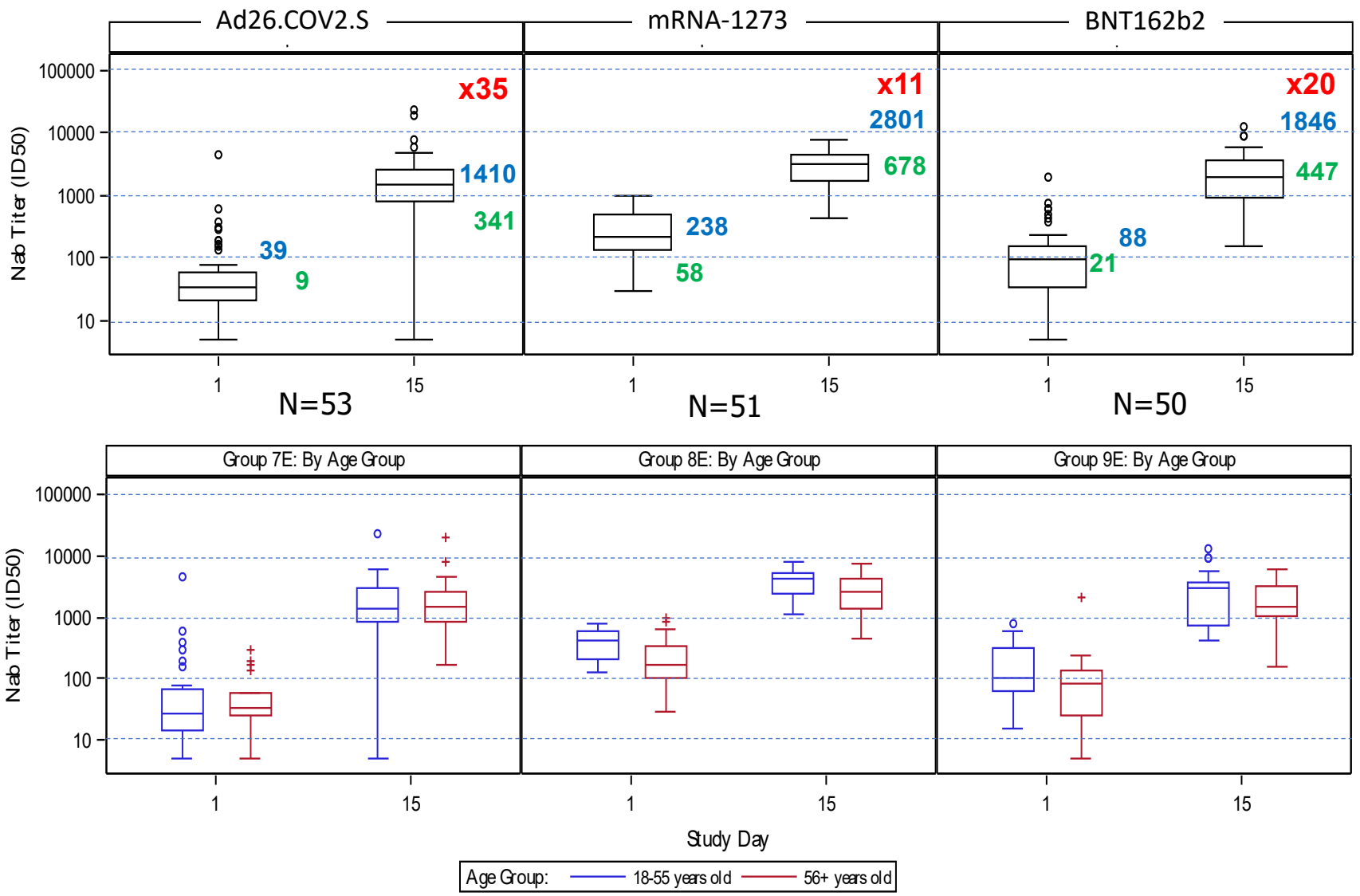
IgG Serum Binding Antibody Response to S-2P-Wa-1 Antigen by 4-plex ECLIA V.2, by Group, Age Group and Timepoint: BNT162b2 Booster Vaccination –Day 15



Pseudovirus Neutralization Antibody Titers to Spike D614G through 14 days post BNT162b2 Boost by Group (top) and Age (bottom), and Timepoint

EUA Primary Vaccination(s)

ID50

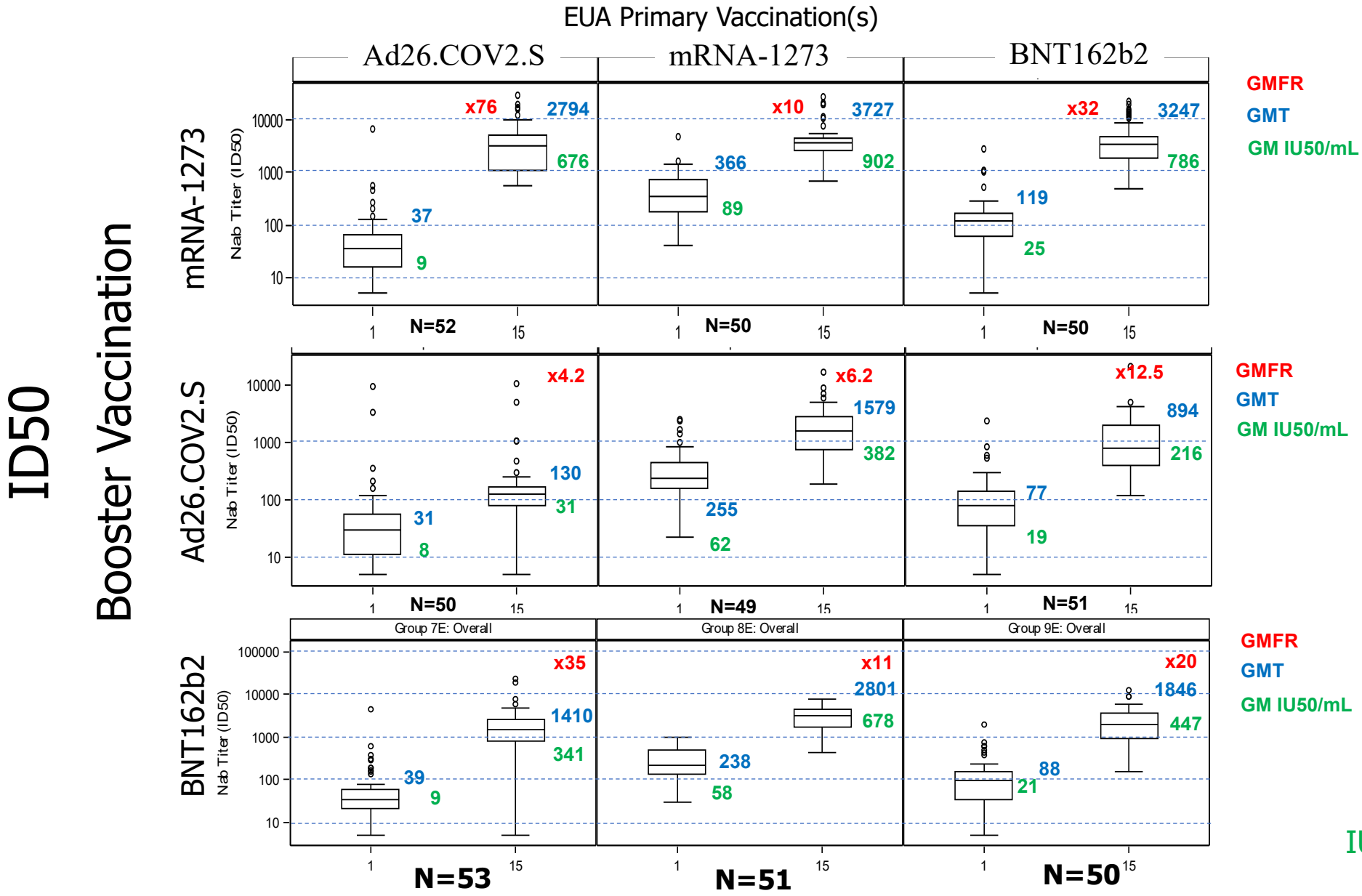


GMFR
GMT
GM IU50/mL

$IU_{50}/mL = ID50 \times 0.242$

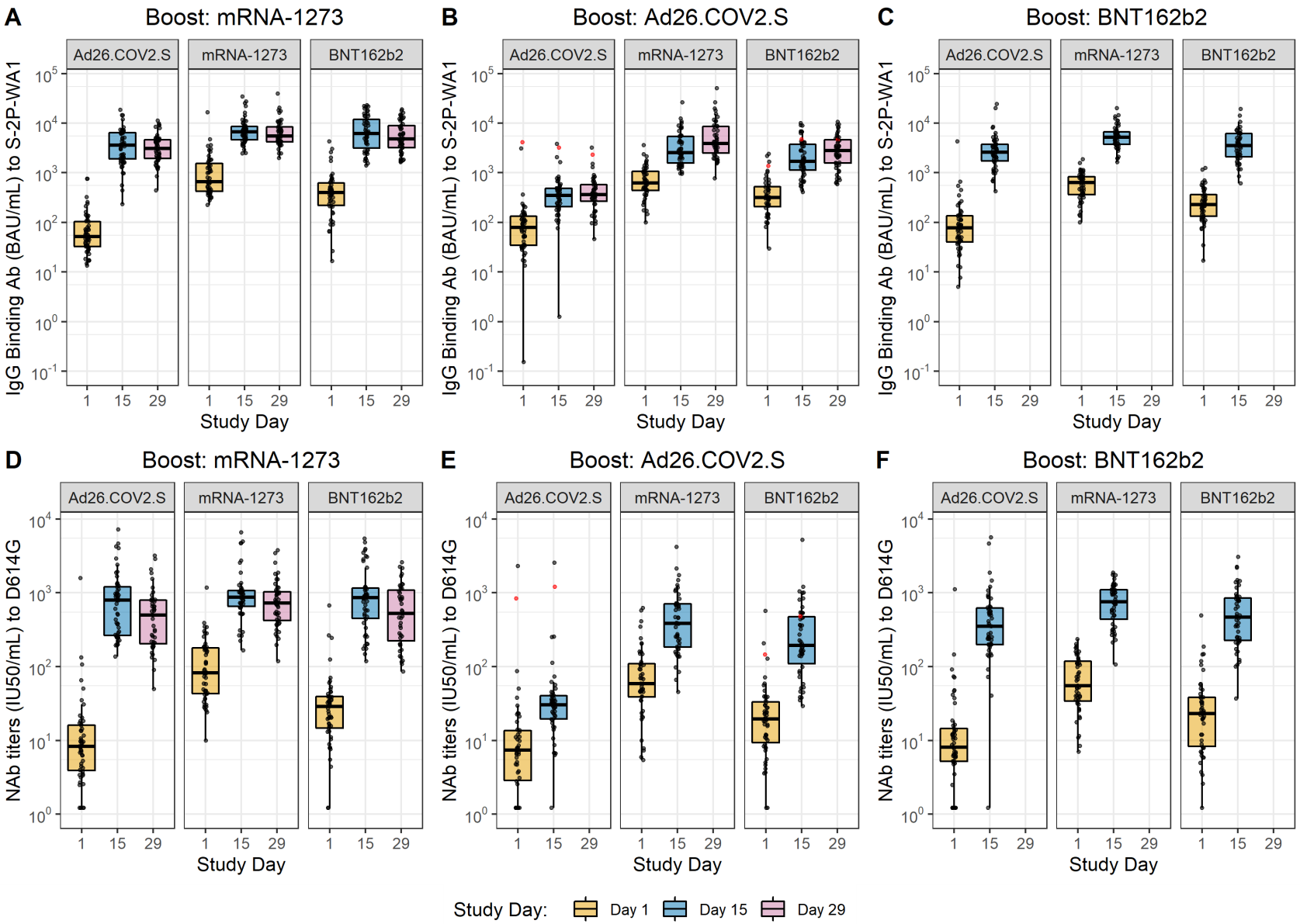
All Three Booster Vaccines

Pseudovirus Neutralization Antibody Titers to Spike D614G through 14 days post- mRNA-1273, Ad26.COV2.S and BNT162b2 Booster Vaccination by Group and Timepoint



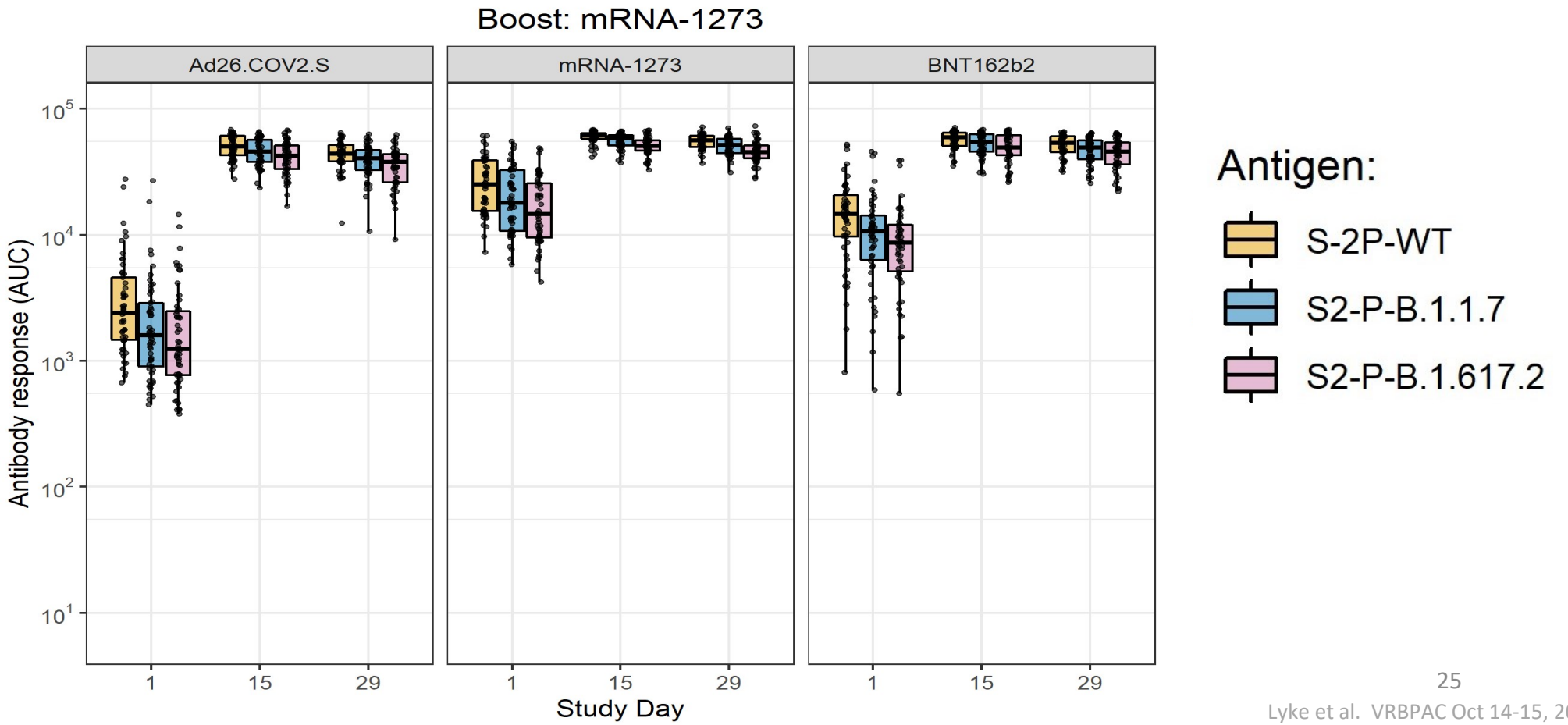
IU_{50}/mL = ID50 x 0.242

Immunogenicity of all three boosters - IgG binding Antibody and Neutralizing Antibody - Day 15/29

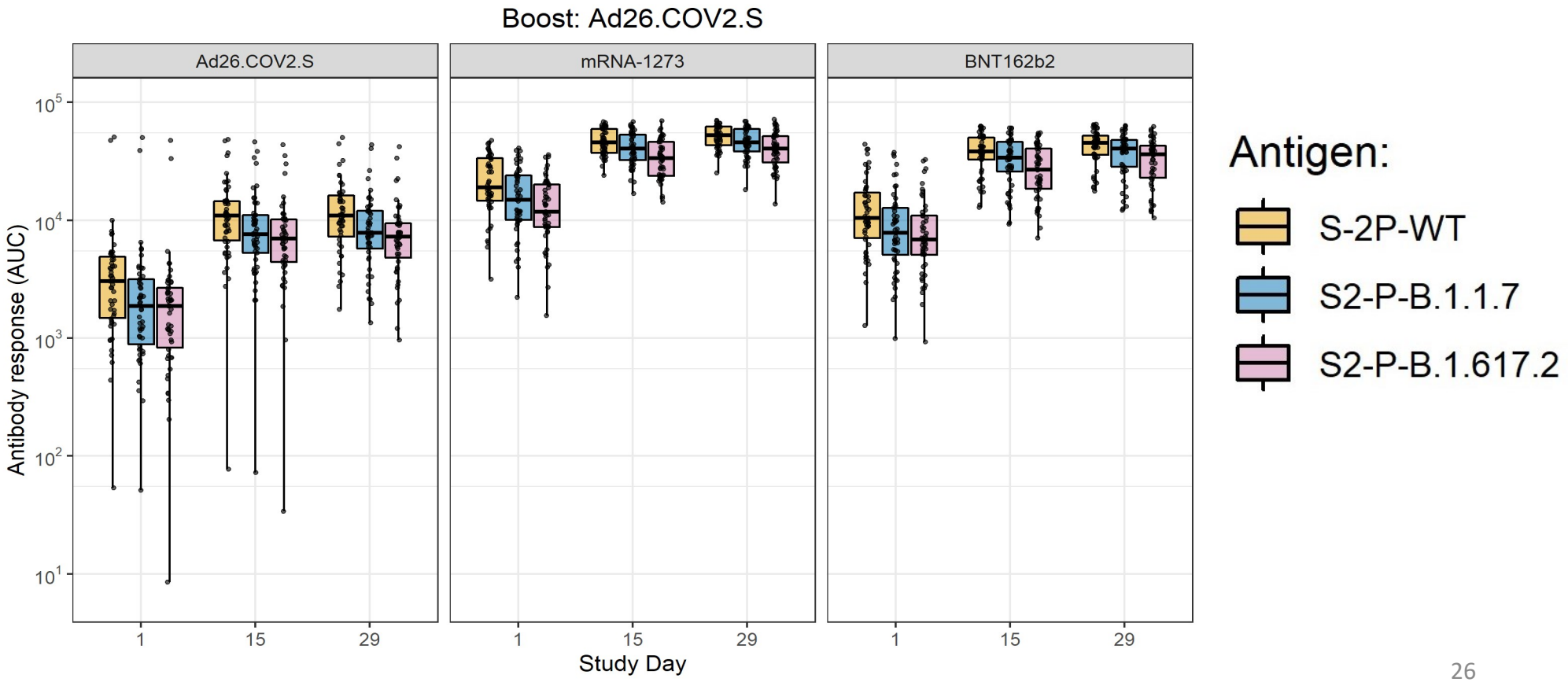


Immunogenicity – Variants of Concern

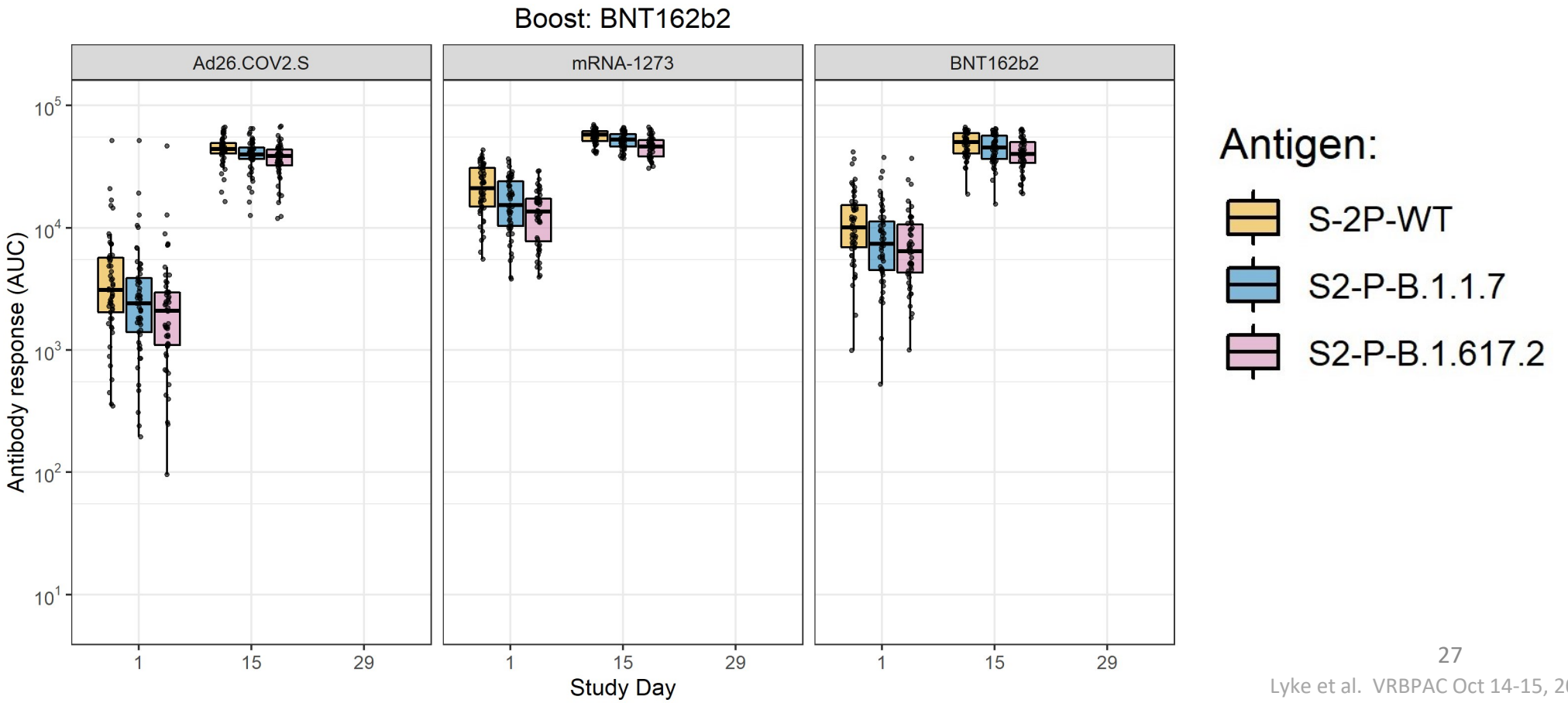
IgG Serum Binding Antibody Response to S-2P-Wa-1 (control), B.1.1.7 (alpha), and B.1.617.2 (delta) FFP 10-plex ECLIA, by Group and Timepoint - Results are reported as Area Under Curve (AUC) mRNA-1273 Booster Vaccination



IgG Serum Binding Antibody Response to S-2P-Wa-1 (control), B.1.1.7 (alpha), and B.1.617.2 (delta) FFP 10-plex ECLIA, by Group and Timepoint - Results are reported as Area Under Curve (AUC) Ad26.COV2.S Booster Vaccination



IgG Serum Binding Antibody Response to S-2P-Wa-1 (control), B.1.1.7 (alpha), and B.1.617.2 (delta) FFP 10-plex ECLIA, by Group and Timepoint - Results are reported as Area Under Curve (AUC) BNT162b2 Booster Vaccination



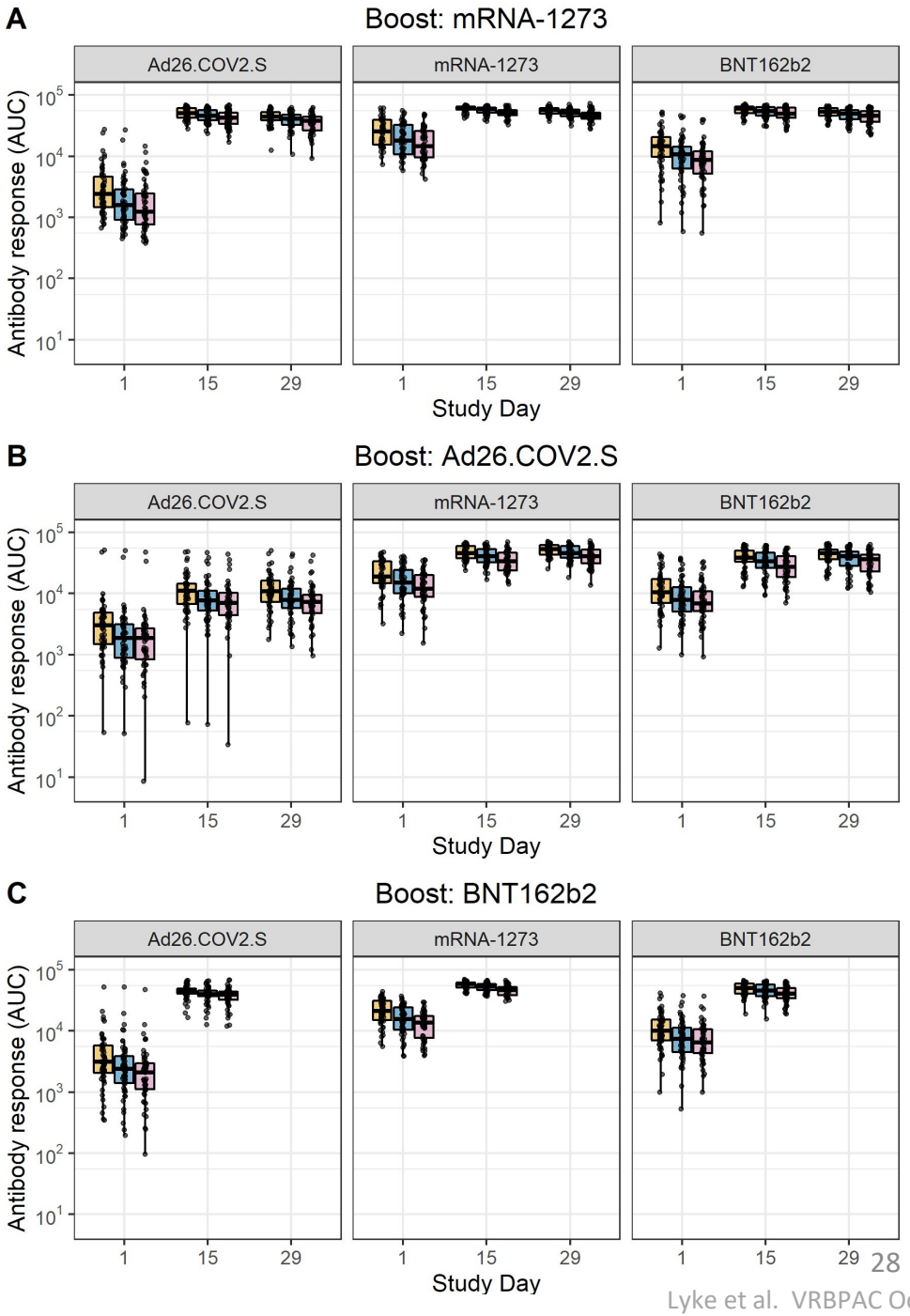
All 3 vaccines

IgG Serum Binding Antibody Response to
S-2P-Wa-1 (control), B.1.1.7 (alpha), and B.1.617.2 (delta)

FFP 10-plex ECLIA, by Group and Timepoint
Results are reported as Area Under Curve (AUC)

Antigen:

- S-2P-WT
- S2-P-B.1.1.7
- S2-P-B.1.617.2



Safety

- Two SAEs
  1. Acute renal failure due to rhabdomyolysis from a fall - Unrelated
     30 days after mRNA-1273 vaccination
  2. Acute cholecystitis - Unrelated
     24 days after Ad26.COV2.S vaccination.

- No pre-specified study-halting rules were met
- No new onset chronic medical conditions occurred (through study D29)
- One related AESI
  - Severe vomiting that led to a medically attended visit the day after vaccination: Ad26.COV2.S boost

Unsolicited AEs (deemed related to boost) of any severity grade

- mRNA-1273: 24/154 (15.6%)
- Ad26.COV2.S: 18/150 (12.0%)
- BNT162b2: 22/154 (14.3%)

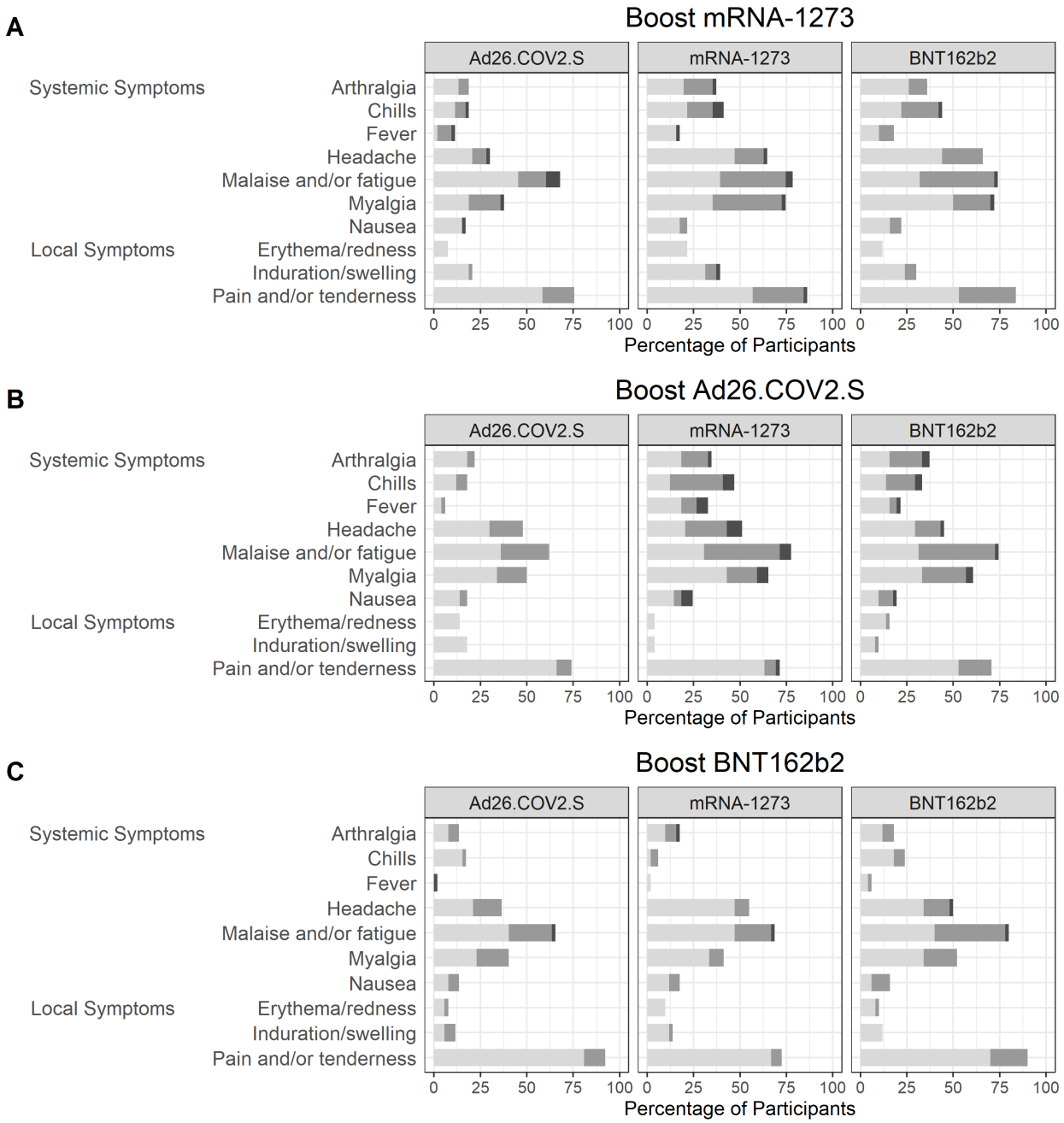
Most related AEs were Grade 1 or 2 severity

Four related Grade 3 AEs:

- Vomiting in one participant - mRNA-1273 booster group
- Vomiting in one participant - Ad26.COV2.S booster group
- Fatigue in one participant - Ad26.COV2.S booster group
- Insomnia in one participant - Ad26.COV2.S booster group

Booster Solicited AEs

Local and Systemic Reactogenicity – Day 8



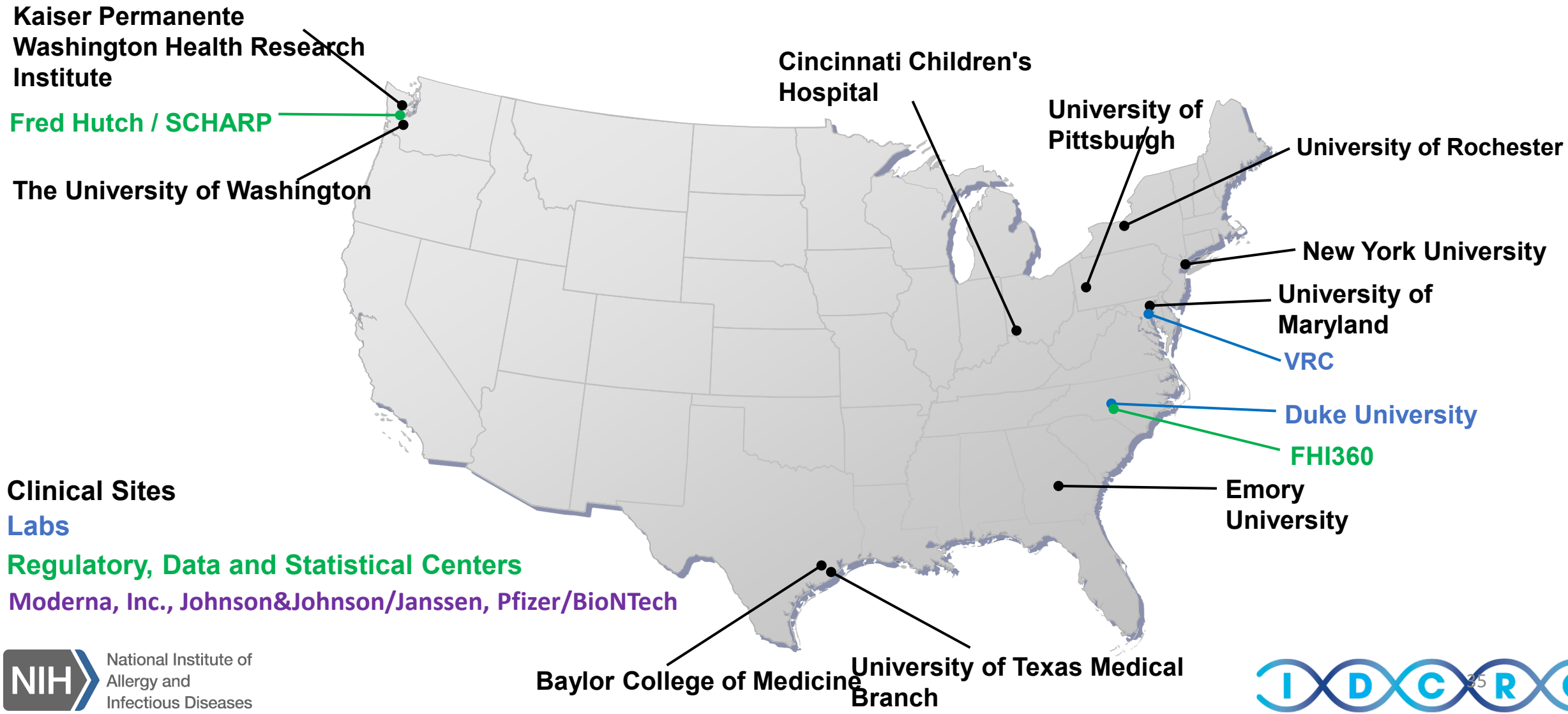
Limitations -

- Non-randomized, open label design
- Study not designed to compare between boosts
  - Didn't control for intervals between primary vaccine and boosts
- Correlates of protection are not completely elucidated.
- Correlates for severe disease and death are even less well understood.
- This is only antibody data.
  - Cellular immune responses are still being analyzed
- These data represent only early timepoints from the trial
  - Vaccines may differ in time to reach peak responses, and may have different durability of the responses

Conclusions -

1. Use of mRNA-1273, Ad26.COV2.S and BNT162b2 as booster vaccines led to anamnestic serologic responses in all 3 EUA-dose vaccine groups
2. For a given primary EUA Covid-19 vaccine, heterologous boosts elicited similar or higher serologic responses as compared to their respective homologous booster responses
3. mRNA vaccines resulted in higher antibody titers in the first 28 days after the boost
4. No safety concerns identified

The "MixNMatch" Study Team



Questions?