Booster Doses of Moderna COVID-19 Vaccines in Adults, Adolescents & Children

ACIP

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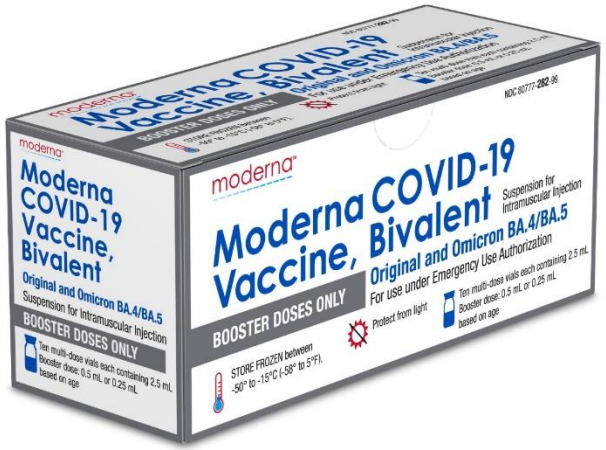
Indication for Use of Moderna COVID-19 Vaccine, Bivalent (Original And Omicron BA.4/BA.5)

EUA of Aug 31, 2022

Moderna COVID-19 Vaccine, Bivalent (Original And Omicron BA.4/BA.5) is authorized for use in individuals 18 years of age and older as a single booster dose administered at least 2 months after either:

- Completion of primary vaccination with any authorized or approved monovalent[1] COVID-19 vaccine, or
- Receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine.



[1] Monovalent refers to any authorized or approved COVID-19 vaccine that contains or encodes the spike protein of only the Original SARS-CoV-2.

Rationale for Variant-Containing Booster Vaccines

- Goals of variant-containing booster vaccines[1,2]
  - Retain neutralization for Original SARS-CoV-2
  - Stronger immune response against current variants
  - Broader cross-neutralization against future variants
  - Extend durability of protection

1. FDA Briefing Document for June 26, 2022 VRBPAC Meeting.
2. WHO Interim Statement on the Composition of Current COVID-19 Vaccines (June 17, 2022).

Moderna COVID-19 Investigational Variant-containing Vaccine Candidates Evaluated In Clinical Trials

- Extensive evaluation of 3 monovalent and 4 bivalent investigational variant vaccines in past year
  - >7,000 individuals boosted across all variant vaccine candidates
- Bivalent vaccine candidates include:

Beta-containing vaccine (mRNA-1273.211)	**25 µg** Original SARS-CoV-2	+	**25 µg** Beta Variant (B.1.351)
BA.1 Omicron-containing vaccine (mRNA-1273.214)	**25 µg** Original SARS-CoV-2	+	**25 µg** Omicron Variant (BA.1)
BA.4/BA.5 Omicron-containing vaccine (mRNA-1273.222)	**25 µg** Original SARS-CoV-2	+	**25 µg** Omicron Variant (BA.4/BA.5)

Clinical Studies of Booster Doses of Bivalent Vaccines in Adults

Clinical Studies with Moderna COVID-19 Investigational Bivalent Vaccine Candidates in Adults (≥ 18 Years of Age)

Bivalent Vaccine	Study (Part)	Dose	N	Median Follow-up
Beta (mRNA-1273.211)	205 (A)	3rd (1st booster)	300	245 days
BA.1 Omicron (mRNA-1273.214)	205 (G)	4th (2nd booster)	437	43 days
BA.4/BA.5 Omicron (mRNA- 1273.222)	205 (H)	4th (2nd booster)	512	Ongoing
		Total	1249	

- All participants previous received a primary series of mRNA-1273 (100 μg); participants in Parts G & H also previously received a 3rd dose (50 μg) of mRNA-1273
- Part G enrolled Mar 8-23, 2022; Part H enrolled Aug 10-23, 2022

Chalkias et al. *Research Squa*re 2022, doi: 10.21203/rs.3.rs-1555201/v1; in press *Nat Med*
Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703; in press *New Engl J Med*

Study of 4th Dose (2nd Booster) in Adults Using BA.1 Omicron Bivalent Vaccine (mRNA-1273.214) - Demographics and Baseline Characteristics

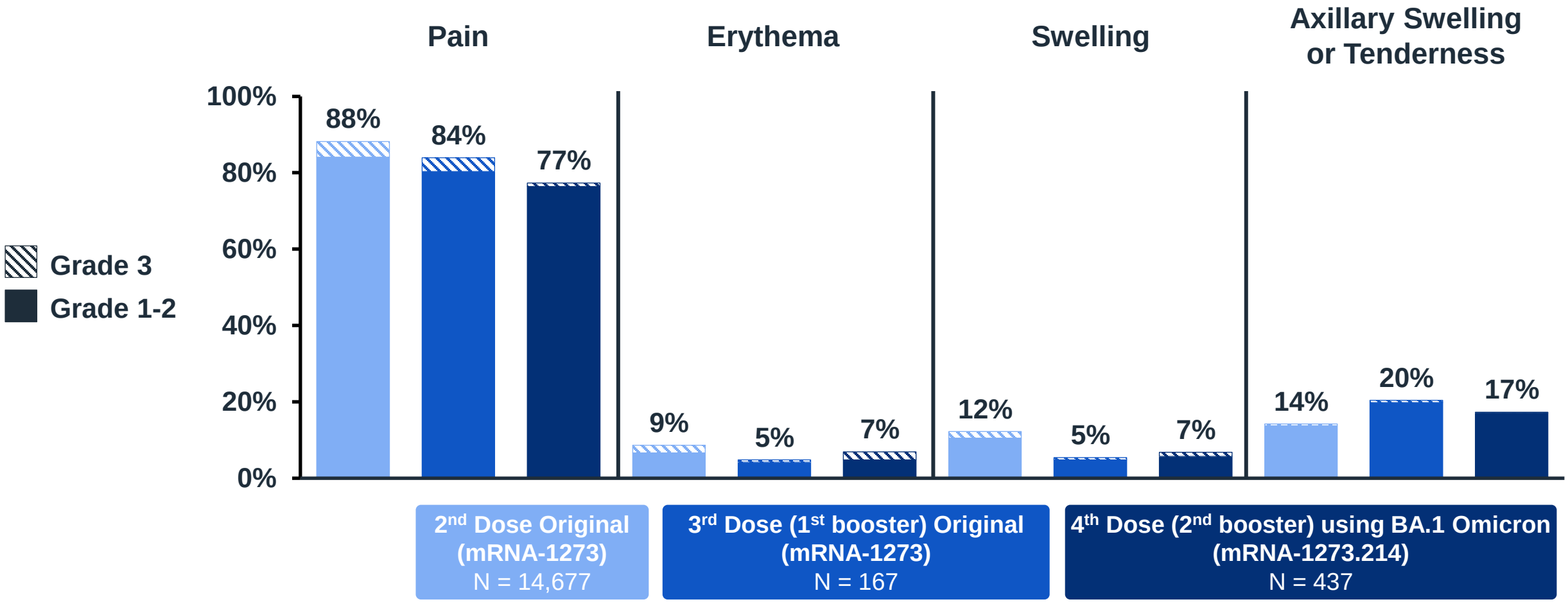
Study 205, Safety Set

Characteristic	4th Dose (2nd Booster) Original (mRNA-1273) N = 377	4th Dose (2nd Booster) BA.1 Omicron Bivalent (mRNA-1273.214) N = 437
Mean Age - Years (range)	**57.5** (20, 96)	**57.3** (20, 88)
≥ 65 years	**39.8%**	**39.8%**
Female	**50.7%**	**59.0%**
Non-White Race	**14.6%**	**12.8%**
Hispanic / Latino Ethnicity	**9.8%**	**10.5%**
Interval between 2nd and 3rd Dose (months) – median (range)	**8.0** (5.6, 14.4)	**8.0** (4.7, 15.0)
Interval between 3rd and 4th Dose (months) – median (range)	**4.4** (3.0, 10.2)	**4.5** (2.9, 13.4)
Prior SARS-CoV-2 Infection	**26.8%**	**22.0%**

Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703; in press *New Engl J Med*

Local Reactogenicity of BA.1 Omicron Bivalent (mRNA-1273.214) as 4th Dose Similar to 2nd Dose of Primary Series and 3rd Dose of Original (mRNA-1273) in Adults

Study 205, Safety Set

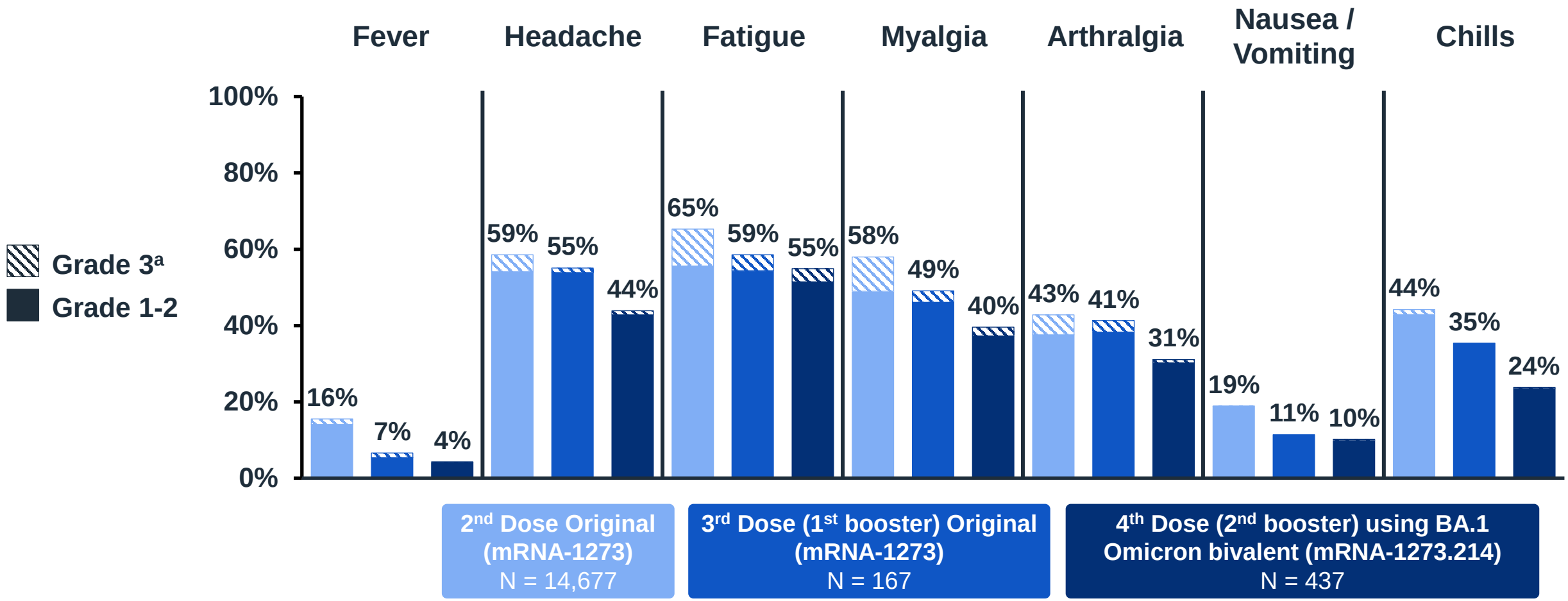


Solicited local adverse reactions within 7 days after injection. No Grade 4 events reported.

2nd dose mRNA-1273 (Baden et al, *NEJM* 2021); 3rd dose mRNA-1273 (Choi et al, *Nat Med* 2022); 4th dose mRNA-1273.214 (Chalkias et al. *medRxiv* 2022; in press *New Engl J Med*).

Systemic Reactogenicity of BA.1 Omicron Bivalent (mRNA-1273.214) as 4th Dose Generally Lower than 2nd Dose of Primary Series and 3rd Dose of mRNA-1273 in Adults

Study 205, Safety Set



Solicited systemic adverse reactions within 7 days after injection. a) Grade 4 systemic reactions only with 2nd dose of mRNA-1273 (<0.1%).

2nd dose mRNA-1273 (Baden et al, *NEJM*, 2021); 3rd dose mRNA-1273 (Choi et al, *Nat Med*, 2022); 4th dose mRNA-1273.214 (Chalkias et al. *medRxiv*, 2022; in press *New Engl J Med*).

Similar Overall Safety Profile of BA.1 Omicron Bivalent (mRNA-1273.214) and Original mRNA-1273 as 4th Dose (2nd Booster)

Study 205, Safety Set

n (%)

Unsolicited AEs within 28 Days After Any Injection	Original (mRNA-1273) N = 377	BA.1 Omicron Bivalent (mRNA-1273.214) N = 437
Any AE	78 (20.7%)	81 (18.5%)
SAE	1 (0.3%)	2 (0.5%)
Fatal AE	0	0
Medically Attended AE	52 (13.8%)	43 (9.8%)
AE Leading to Discontinuation from Study	0	0
Severe AE	3 (0.8%)	4 (0.9%)

Omicron BA.1 Neutralizing Titers Were Significantly Higher Following 4th Dose (2nd Booster) Using Omicron BA.1 Bivalent (mRNA-1273.214) than with mRNA-1273

Study 205, Per-Protocol Immunogenicity Set with No Prior Infection

	4th Dose (2nd Booster)	
Parameter	Original (mRNA-1273) N = 260	Omicron BA.1 Bivalent (mRNA-1273.214) (N = 334)
GMT Pre-booster	**332**	**298**
95% CI	(282, 391)	(259, 343)
GMT at Day 29[1]	**1421**	**2480**
95% CI	(1283, 1574)	(2264, 2716)
GMT Ratio[1] (Bivalent vs Original)	**1.75**	
97.5% CI	(1.49, 2.04)	
Seroresponse rate at Day 29	**99.2%**	**100%**
95% CI	(97.2, 99.9)	(98.9, 100)
Difference in seroresponse rates[2]	**1.5**	
97.5% CI	(-1.1, 4.0)	

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)**

Chalkias et al. medRxiv 2022, doi: 10.1101/2022.06.24.22276703 – in press *New Engl J Med*

Original Strain (D614G) Neutralizing Titers Were Higher Following 4th Dose (2nd Booster) Using Omicron BA.1 Bivalent (mRNA-1273.214) than with mRNA-1273

Study 205, Per-Protocol Immunogenicity Set with No Prior Infection

	4th Dose (2nd Booster)	
Parameter	Original (mRNA-1273) N = 260	Omicron BA.1 Bivalent (mRNA-1273.214) (N = 334)
GMT Pre-booster	**1521**	**1267**
95% CI	(1353, 1710)	(1120, 1432)
GMT at Day 29[1]	**5287**	**6422**
95% CI	(4887, 5719)	(5990, 6886)
GMT Ratio[1] (Bivalent vs Original)	**1.22**	
97.5% CI	(1.08,1.37)	
Seroresponse rate at Day 29	**100%**	**100%**
95% CI	(98.9, 100)	(98.6, 100)
Difference in seroresponse rates[2]	**0**	
97.5% CI		

Success Criteria Met

Non-inferiority of GMTs: Lower 97.5% CI of GMT Ratio ≥ 0.67

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

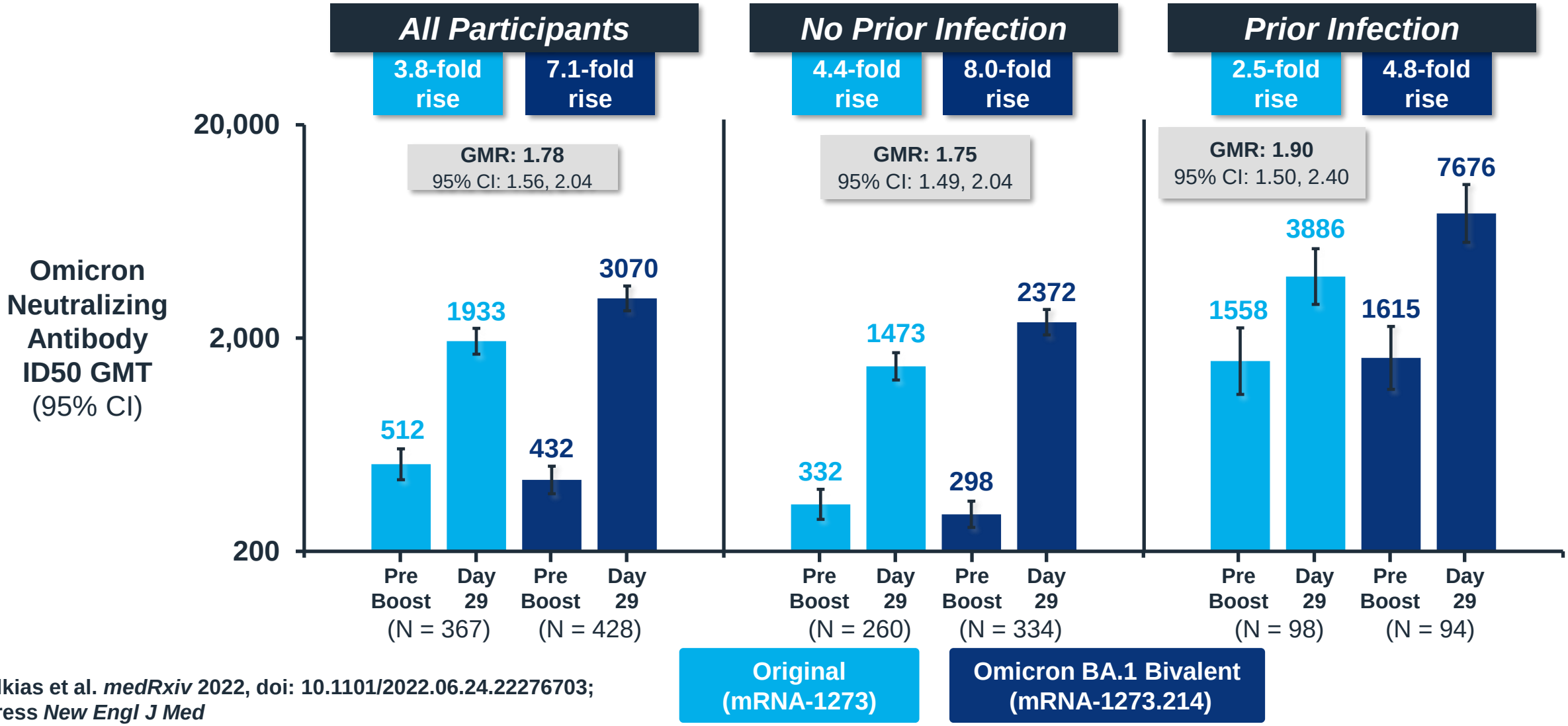
[1] **Based on ANCOVA model adjusting for age group (<65, ≥65 years) and pre-booster titer**

[2] **Common risk difference and 97.5% CI (Miettinen-Nurminen) cannot be calculated when SRR in both group is 100%, absolute difference is reported.**

Chalkias et al. medRxiv 2022, doi: 10.1101/2022.06.24.22276703 – in press *New Engl J Med*

Omicron BA.1 Neutralizing Titers After 4th Dose (2nd Booster) Significantly Higher with BA.1 Omicron Bivalent (mRNA-1273.214) than mRNA-1273 in Adults

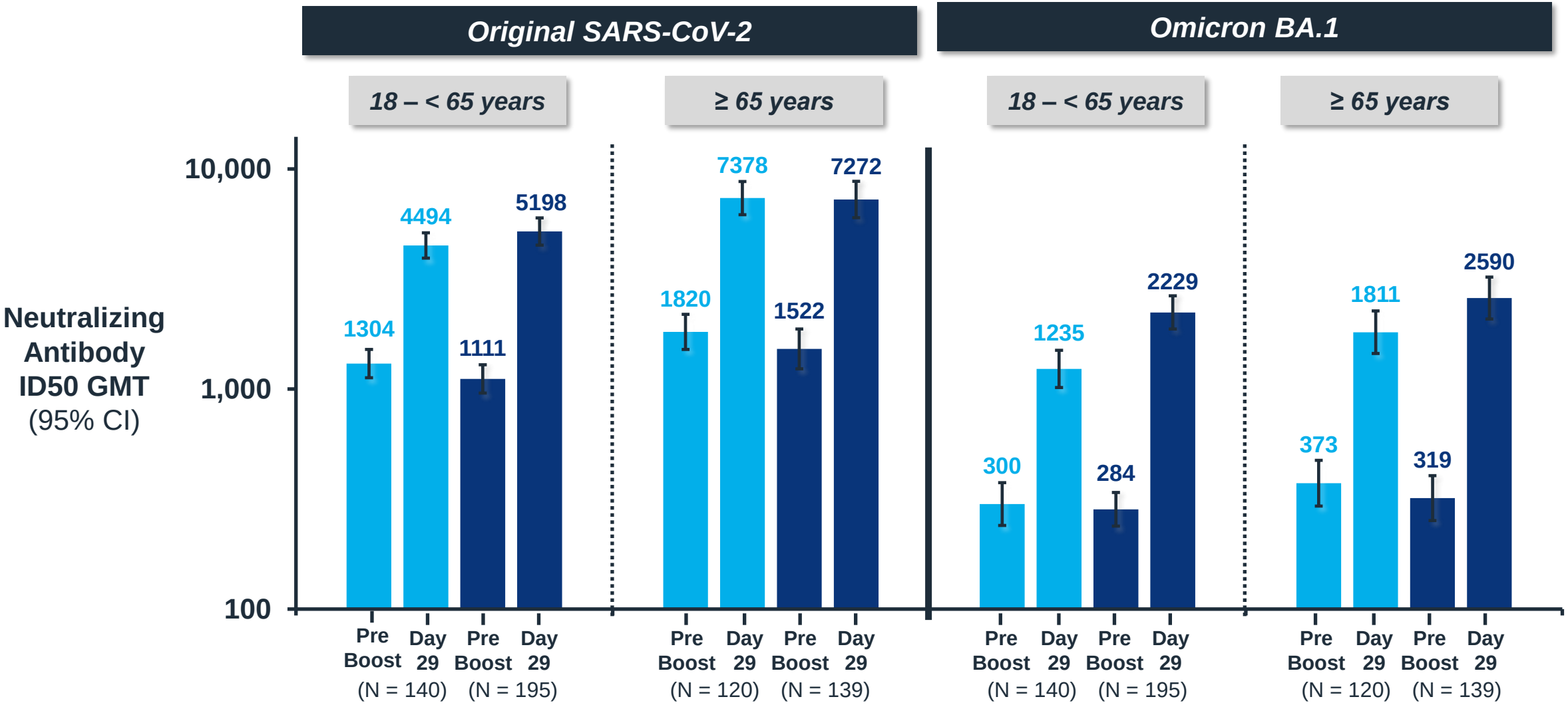
Study 205, Per-Protocol Immunogenicity Set



Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703; in press *New Engl J Med*

Omicron BA.1 and Original Strain (D614G) Neutralizing Titers After 4th Dose (2nd Booster) of BA.1 Omicron Bivalent Were Consistent in Persons ≥65 Years of Age

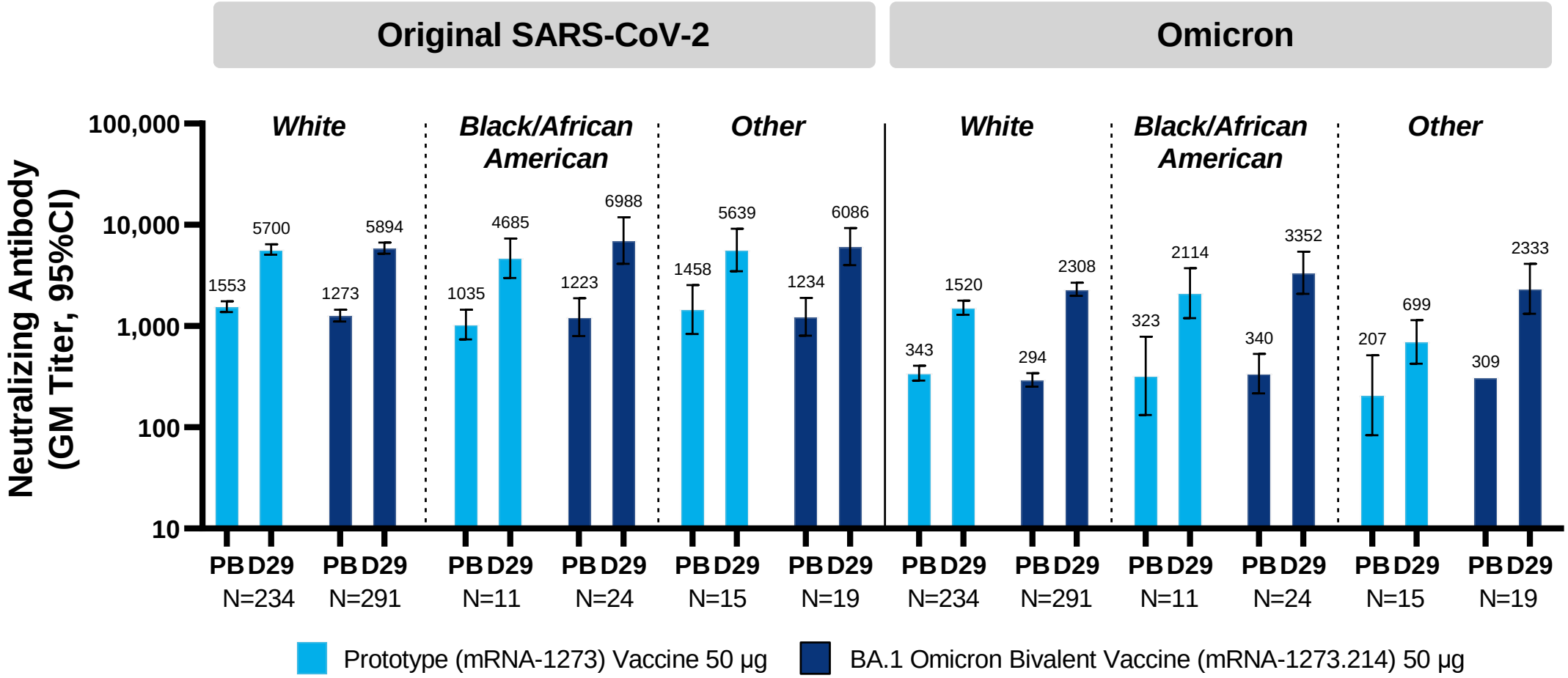
Study 205, Per-Protocol Immunogenicity Set with No Prior Infection



VRBPAC, June 28, 2022 https://www.fda.gov/media/159492/download

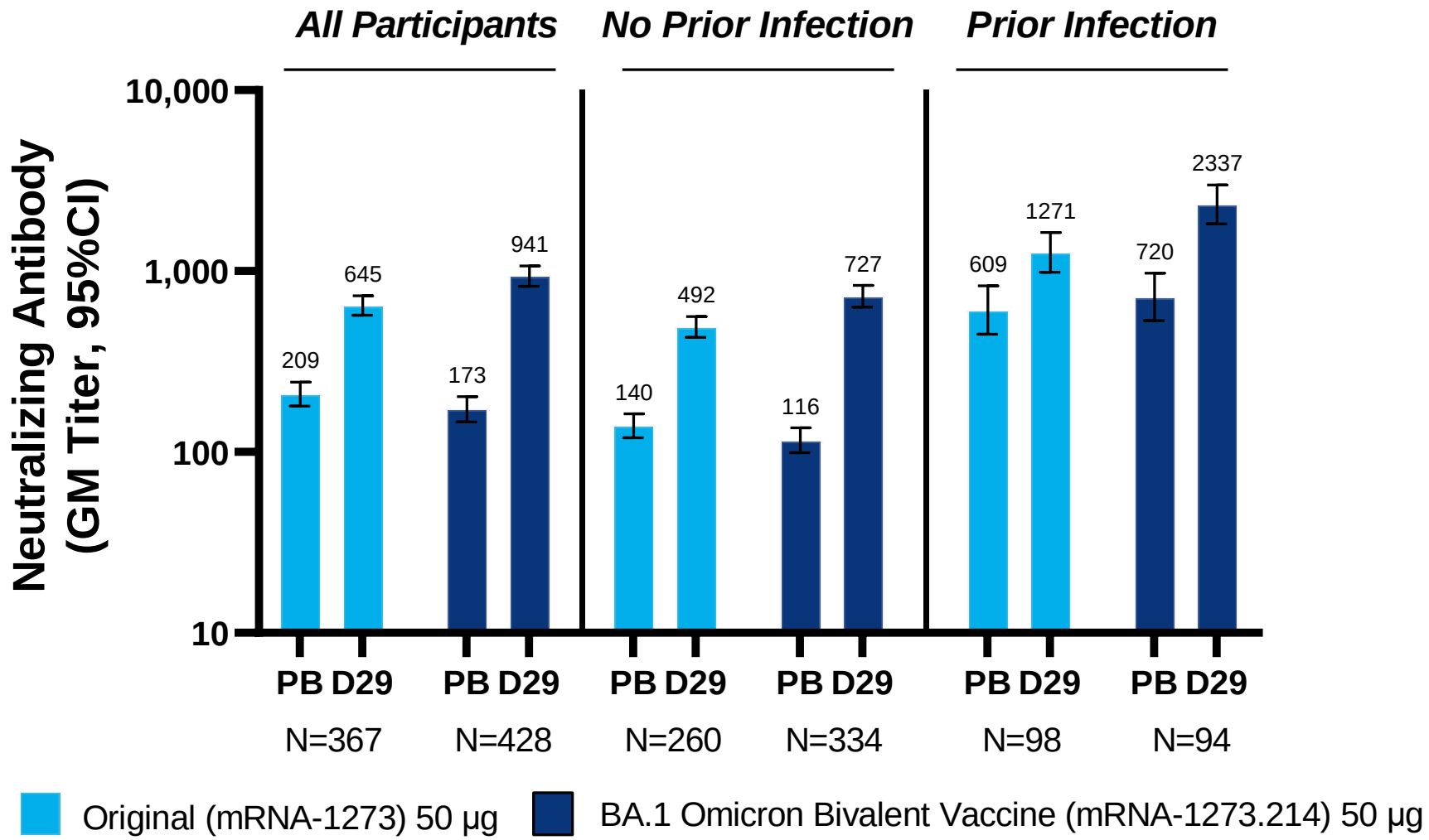
Omicron B.1 and Original Strain (D614G) Neutralizing Antibodies After 4th Dose (2nd Booster) Comparable Across Racial Groups

Study 205, Per-Protocol Immunogenicity Set with No Prior Infection



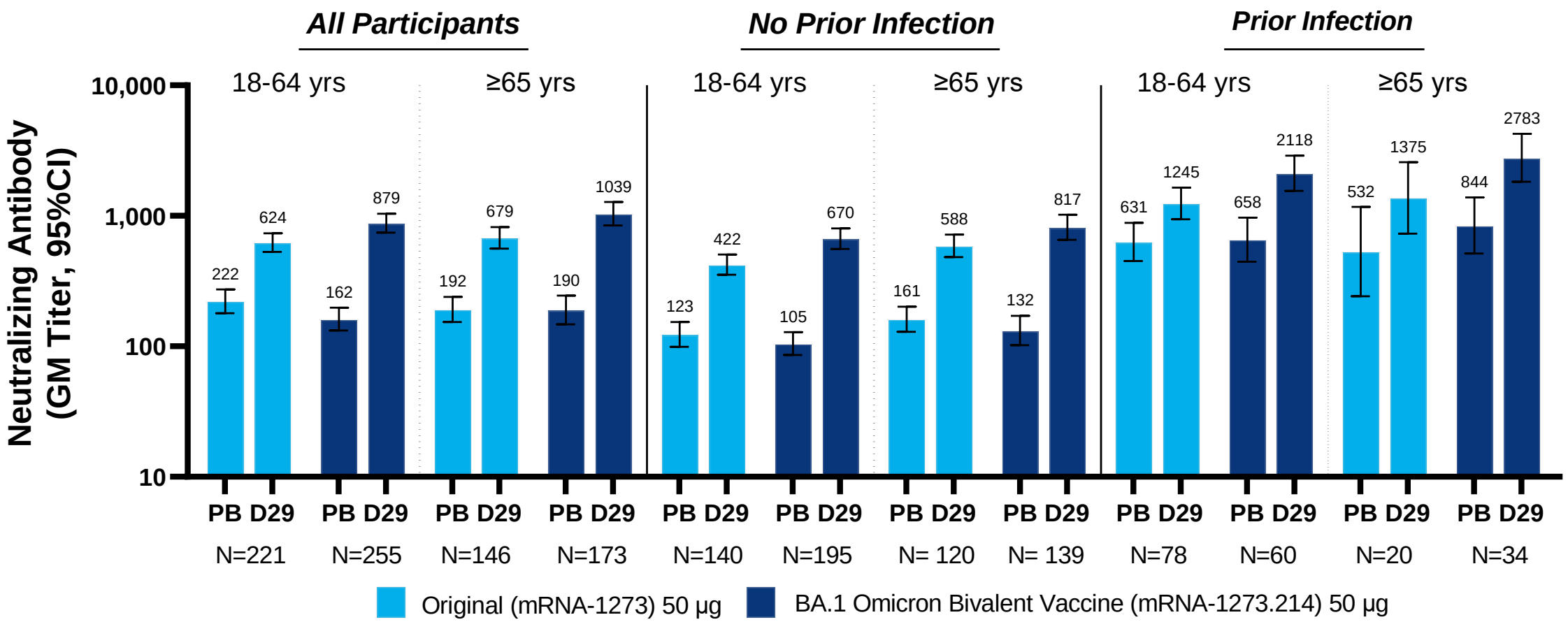
Pre-booster (**PB**), Day 29 post-boost (**D29**)

4th Dose (2nd Booster) with BA.1 Omicron Bivalent Booster (mRNA-1273.214) Resulted in Higher Neutralizing Antibody Titers against Omicron BA.4 & BA.5 than mRNA-1273 in Adults



Pre-booster (**PB**), Day 29 post-boost (**D29**)

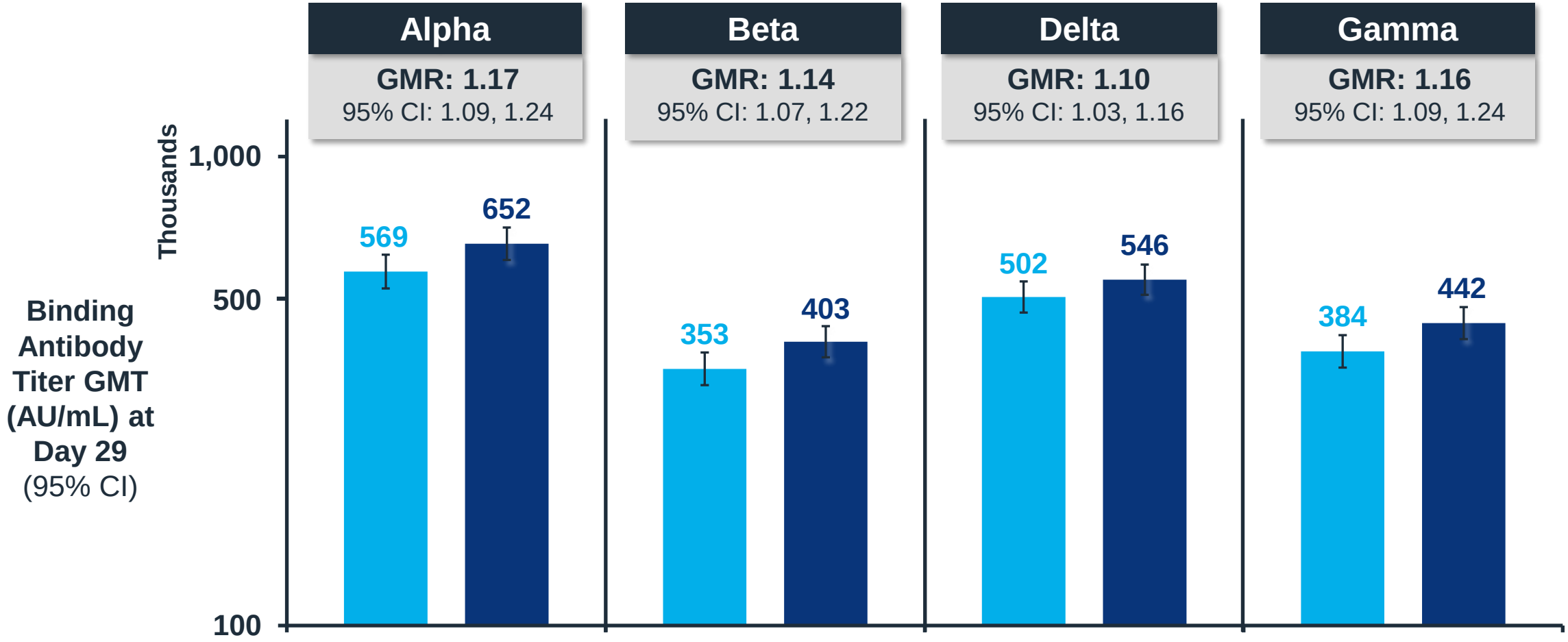
4th Dose (2nd Booster) with BA.1 Omicron Bivalent Booster (mRNA-1273.214) Resulted in Higher Neutralizing Antibody Titers against Omicron BA.4/BA.5 Across Age Groups, Including ≥65 Year Olds, than mRNA-1273



Pre-booster (**PB**), Day 29 post-boost (**D29**)

Binding Antibody Titers Against VOCs Are Significantly Higher after 4th Dose (2nd Booster) with BA.1 Omicron Bivalent (mRNA-1273.214) than mRNA-1273 in Adults

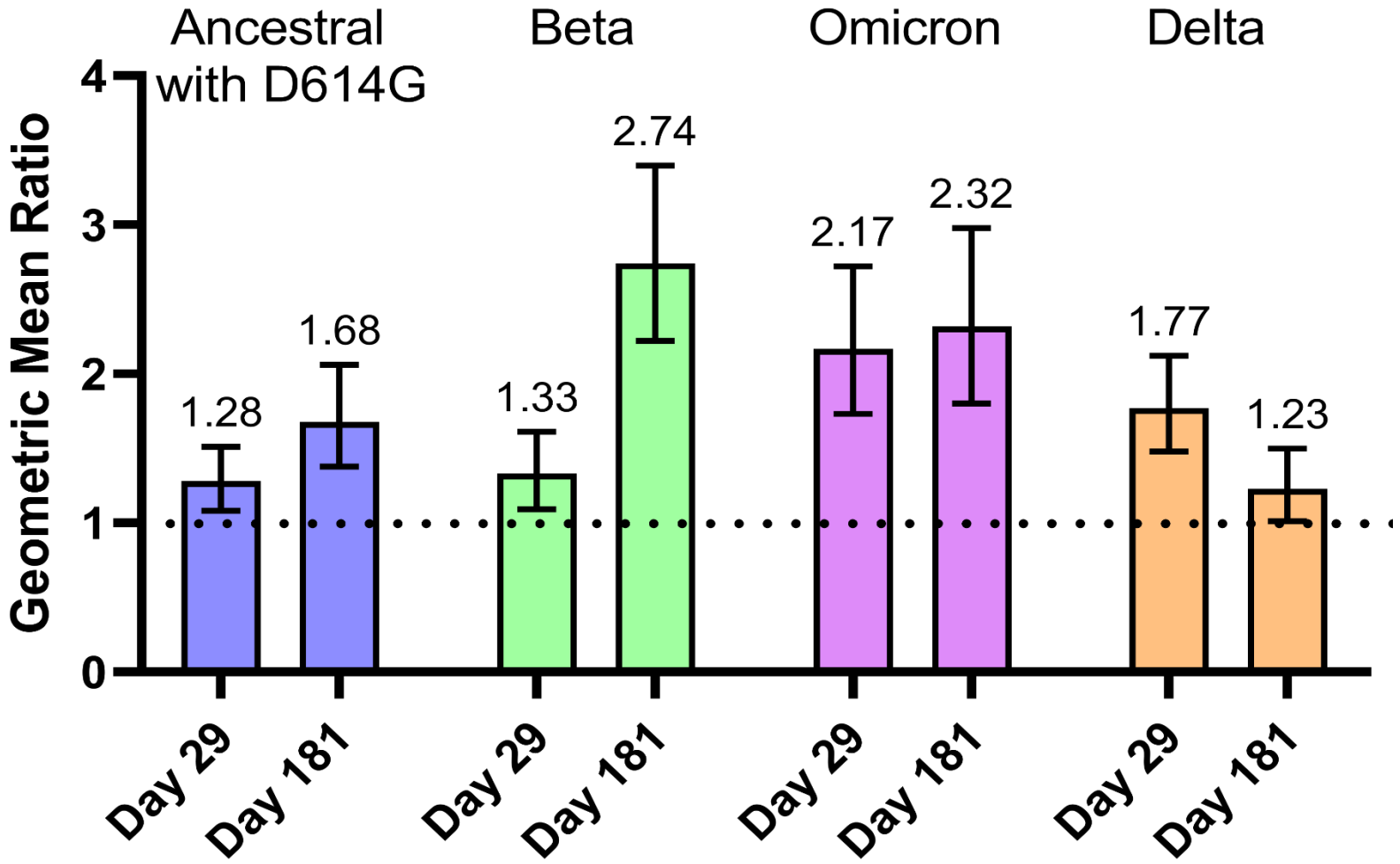
Study 205, Per-Protocol Immunogenicity Set



GMR – ratio of GMT of BA.1 Omicron bivalent/GMT of mRNA-1273 at day 29
VOC – Variant of Concern
Meso Scale Discovery (MSD) Assay. Nominal alpha = 0.05.
mRNA-1273 N = 350-351; mRNA-1273.214 N = 398-402

Bivalent Beta Vaccine (mRNA-1273.211) as 3rd Dose Elicited Higher Neutralizing Antibody Responses in Adults through 6 Months Compared to mRNA-1273

Study 205 Part A & Study 201 Part B, Per-Protocol Immunogenicity Set, No Prior Infection



Geometric Mean Ratio – GMT of bivalent beta vaccine (mRNA.1273.211)/GMT of original mRNA-1273 vaccine ofvramRNA-1273 N = 149; Bivalent Beta vaccine (mRNA-1273.211) N = 295

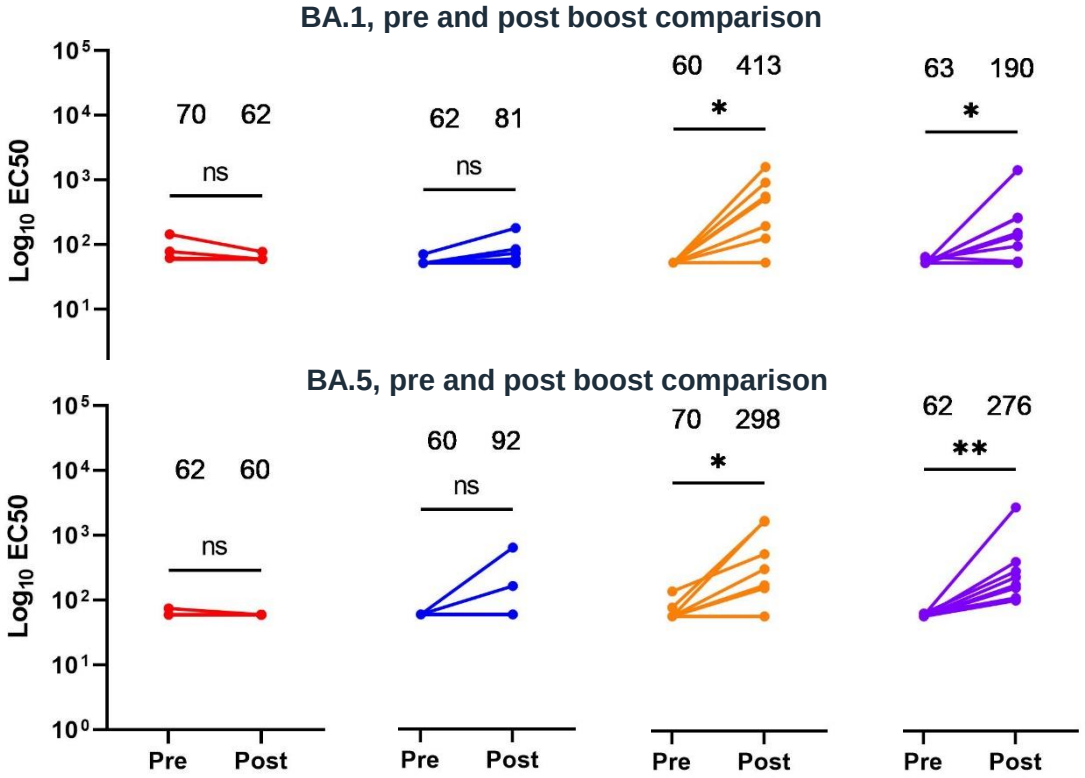
Chalkias et al. *Research Square* 2022, doi: 10.21203/rs.3.rs-1555201/v1– in press *Nature Medicine*

Pre-Clinical Studies of Booster Doses of Bivalent BA.4/5-Containing Vaccine (mRNA-1273.222) in Mice

Increased Immunogenicity after Booster Dose of the BA.1 & BA.4/BA.5 Omicron Bivalent Vaccines (mRNA-1273.214 & mRNA-1273.222) in Mice

- K18 hACE2 mice previously vaccinated with primary series of mRNA-1273 (n = 8-10 per group)
- Boosted with Original (mRNA-1273), BA.1 Omicron Bivalent (mRNA-1273.214), or BA.4/BA.5 Bivalent (mRNA-1273.222
- ~31 weeks between primary series & booster
- Low 0.25 µg dose used to allow for differences between dose regimens to be captured

Neutralization (before and 4 weeks after booster)



- PBS
- mRNA-1273
- mRNA-1273.214
- mRNA-1273.222

ns – not significant
*** p <0.05**
**** p <0.01**

PBS = 1273 primary series + PBS booster

BA.1 neuts:
- **7- and 3-fold increase from bivalent vaccines**

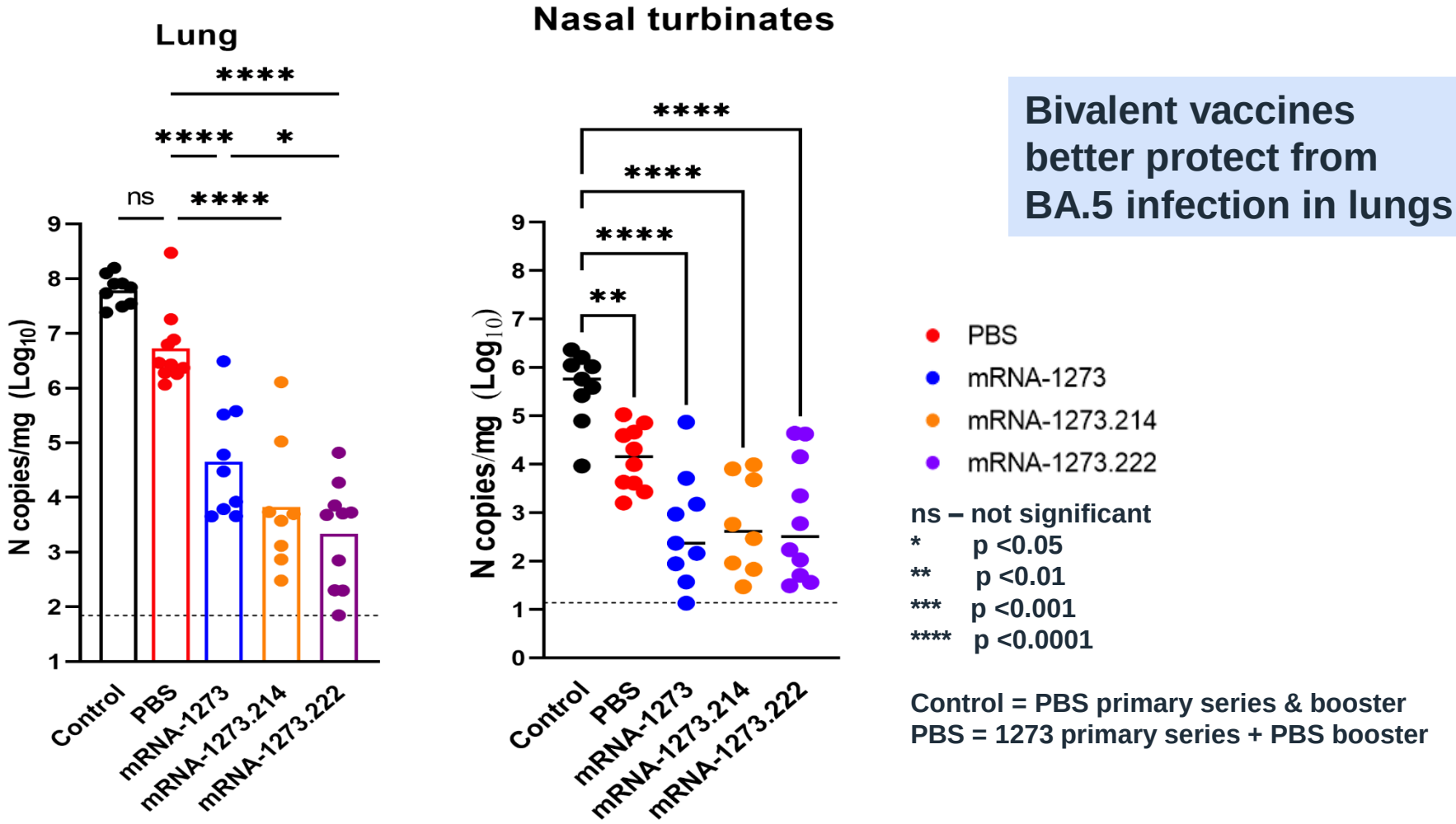
BA.5 neuts:
- **4.2- and 4.5-fold increase from bivalent vaccines**

Limited boost from mRNA-1273

Scheaffer et al, manuscript under preparation

Increased Protection from BA.5 Challenge after Booster Dose of BA.4/BA.5 & BA.1 Omicron Vaccines (mRNA-1273.214 & mRNA-1273.222) in Mice

- Mice challenged with 10^4 PFU of BA.5 virus 4 weeks after booster dose



Bivalent vaccines better protect from BA.5 infection in lungs

ns – not significant
*** p <0.05**
**** p <0.01**
***** p <0.001**
****** p <0.0001**

Control = PBS primary series & booster
PBS = 1273 primary series + PBS booster

Scheaffer et al, manuscript under preparation

Ongoing Studies of Booster Doses in Adolescents and Children, 6 Months - 17 Years of Age

Studies of Booster Dose of Original (mRNA-1273) Vaccine in Adolescents & Children, 6 - 17 Years

Studies 203 & 204

- 3rd dose (1st booster) administered after completion of primary series

Study	Age	Booster Dose	Months between 2nd Dose & Booster (range)	N
203	12-17 years	50 μg	10.4 (9.0, 13.9)	1346
204	6-11 years	25 μg	7.4 (4.1, 12.4)	1294

- Submission of data to the FDA is ongoing

Ongoing Study of BA.1 Omicron Bivalent Vaccine (mRNA-1273.214) Primary Series & Booster Dose in Infants & Children, 6 Months - 5 Years

Study 306

- Open-label, Phase 3 study to evaluate safety & immunogenicity

Part	History	Vaccine Series	Vaccine Dose	N	Status
1	Vaccine naive	2-dose primary series	25 μg	480 (320 2-5 years; 160 6-23 months)	Enrollment ongoing
2	Previously received primary series	1 booster dose	10 μg	480 (320 2-5 years; 160 6-23 months)	2-5 year olds fully enrolled Enrollment ongoing for 6-23 month olds

Summary of Moderna COVID-19 Vaccine Booster Program

Safety

- Vaccine boosters generally well tolerated in adults ≥18 years
- Local and systemic reactogenicity of BA.1 Omicron bivalent as 4th dose similar to or lower than 2nd dose of primary series & 3rd dose of original vaccine (mRNA-1273) in adults
- No new safety concerns identified

Immunogenicity

- Pre-specified immunogenicity objectives met for booster doses in adults
- BA.1 Omicron bivalent in adults demonstrated:
  - Superior responses against BA.1 Omicron compared to Original mRNA-1273 booster in subjects who were antibody negative pre-booster
  - Significantly higher neutralizing GMT against both BA.4/BA.5 Omicron & Original (D614G) in subjects who were anti-N negative pre-booster
  - Significantly higher binding titers against Alpha, Beta, Delta and Gamma, confirming a broad immune response regardless of VOC
  - Consistent immunogenicity across all ages (including ≥65 year olds)
- Beta-containing bivalent in adults demonstrated improved durability of neutralizing antibodies against VOC through 6 months compared to the original vaccine
- Studies of BA.4/BA.5 Omicron bivalent booster in adults & BA.1 Omicron bivalent booster in children 6 months - 5 years ongoing

THANK YOU to Our Study Collaborators, Investigators, and Participants

- *All investigators*
- *Study site personnel*
- *Most importantly, the individuals who participated in these trials and their families*