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# Moderna COVID-19 Variant Vaccines

Moderna, Inc.

June 15, 2023

Vaccines and Related Biological Products Advisory Committee

# Introduction

**Rituparna Das, MD, PhD**

Vice President, Clinical Development

Therapeutic Area Head, Respiratory Vaccines

Moderna, Inc.

# Moderna Continues to Prepare and Evaluate New COVID-19 Vaccines as SARS-CoV-2 Variants Emerge

## Moderna's Ongoing Commitment

- Monitor emerging Variants of Concern
- Develop new candidate vaccines
- Generate preclinical and clinical data accordingly
- Ensure manufacturing capabilities to rapidly respond to public health needs
- Prepared to supply new variant-containing vaccine as recommended

## Recent Research Activities

- Authorized bivalent BA.4/5 vaccine
  - Assessed real-world effectiveness
  - Evaluated cross neutralization against emerging XBB variants
- Investigational XBB-containing vaccines
  - Developed at risk
  - Generated preclinical and clinical data

# Effectiveness of Authorized Bivalent (Original + BA.4/5) COVID-19 Vaccine

Kaiser Permanente Southern California  
*Study 901*

# Methods

## *Study 901 - Kaiser Permanente Southern California Effectiveness Study*

### Study Design

- Matched cohort design
- 3 groups of adults  $\geq 18$  years (1:2:1 ratio)
  - Individuals who received  $\geq 2$  doses of any mRNA vaccine + Moderna BA.4/5 booster
  - Individuals who received  $\geq 2$  doses of any mRNA vaccine only
  - Unvaccinated individuals
- Matched on age, sex, race/ethnicity, and the index date

### Study Period

- Moderna BA.4/5 bivalent vaccine administered 8/31/2022-12/31/2022
- Follow-up through 1/31/2023

Index date for bivalent booster group: Date of receipt of bivalent dose

Index date for monovalent & unvaccinated groups: Date assigned to match bivalent booster group within age/sex/race risk set

Tseng et al., *MedRxiv*, 2023

# Comparisons for Vaccine Effectiveness

*Study 901 - Kaiser Permanente Southern California Effectiveness Study*

## Original Vaccine Cohort

Individuals who received  $\geq 2$  original mRNA vaccine doses only

**N = 580,584**

## Bivalent Vaccine Cohort

Individuals who received  $\geq 2$  original mRNA vaccine doses + Moderna BA.4/5 bivalent vaccine

**N = 290,292**

## Unvaccinated Cohort

Individuals who never received COVID-19 vaccine

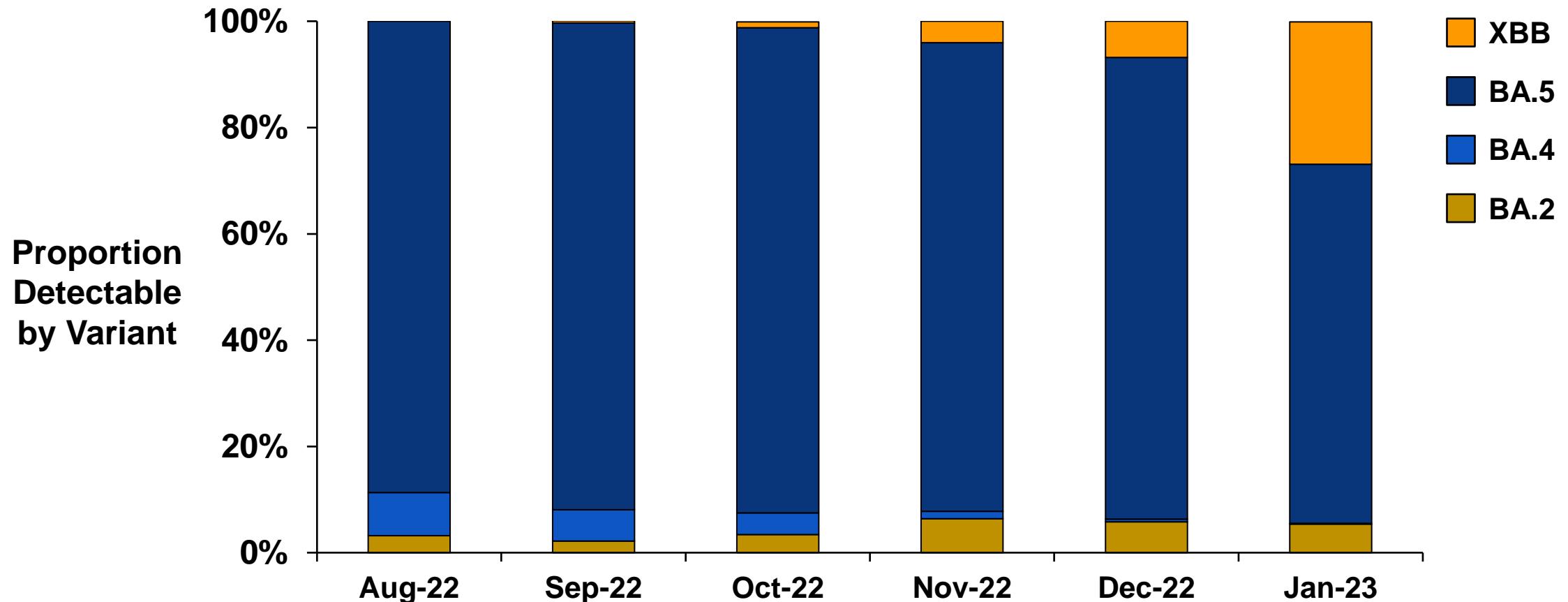
**N = 204,655**

**Relative Vaccine Effectiveness (rVE)**

**Absolute Vaccine Effectiveness (VE)**

# SARS-CoV-2 Variant Distribution, Aug 2022 – Jan 2023 (N = 26,993 samples)

*Study 901 - Kaiser Permanente Southern California Effectiveness Study*



Kaiser – unpublished data

71% of XBB isolates in Jan 2023 were XBB.1.5

# Study Population - Baseline Characteristics

Aug 31, 2022 – Jan 31, 2023

*Study 901 - Kaiser Permanente Southern California Effectiveness Study*

Baseline Characteristic	Original Vaccine Cohort N = 580,584	Moderna BA.4/5 Bivalent Cohort N = 290,292	Unvaccinated Cohort N = 204,655
Median Age – Years (Q1, Q3)	61 (46, 72)	62 (46, 72)	53 (40, 66)
Non-White Race	61%	61%	58%
Number of Original mRNA vaccine doses prior to index date			
2 doses	24%	5%	N/A
3 doses	49%	49%	N/A
≥ 4 doses	27%	46%	N/A
Median Days (Q1, Q3) since last non-bivalent vaccine dose	312 (189, 384)	260 (173, 343)	N/A

# Effectiveness of Moderna BA.4/5 Bivalent mRNA Vaccine

## Aug 31, 2022 – Jan 31, 2023

### Study 901 - Kaiser Permanente Southern California Effectiveness Study

#### COVID-19 Outcomes

##### Relative Vaccine Effectiveness

(compared with individuals who had  $\geq 2$  original vaccine doses)  
**N = 290,292 bivalent receipts & 580,584 controls**

##### Absolute Vaccine Effectiveness

(compared with individuals not vaccinated with any COVID-19 vaccine)  
**N = 290,292 bivalent receipts & 204,655 controls**

**Hospitalization (Chart confirmed)**

**70% (64%, 75%)**

**83% (79%, 86%)**

**COVID-19 In-Hospital Deaths**

**83% (64%, 92%)**

**90% (78%, 95%)**

**ED and Urgent Care**

**55% (51%, 59%)**

**55% (50%, 60%)**

**Bivalent BA.4/5 booster provides additional protection against hospitalizations, ED, and urgent care visits**

# **Variant Monitoring, Risk Assessment, and Preclinical Assessment of Investigational New Variant Vaccines**

**Darin Edwards, PhD**

Executive Director

COVID-19 Program Lead

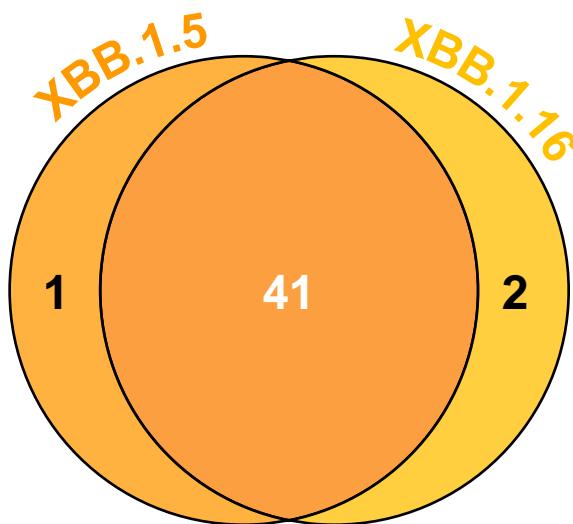
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# Moderna Continuously Prepares New Candidate Vaccines Against Emerging Variants

- Continuous epidemiological monitoring and risk assessment of variants
  - Identify variants that contain immune evading mutations versus authorized vaccines and increased growth dynamics regionally or globally
  - Group antigenically similar sub-lineages in our selection (sub-family matching)
  - Select variants for further study based on global and regional coverage
- At-risk candidate vaccine manufacturing preparation and preclinical evaluations begin in parallel
- These activities allow for expedited delivery of updated vaccines, if requested
- XBB sublineage is dominant globally
  - Now focused our efforts on XBB-containing vaccines

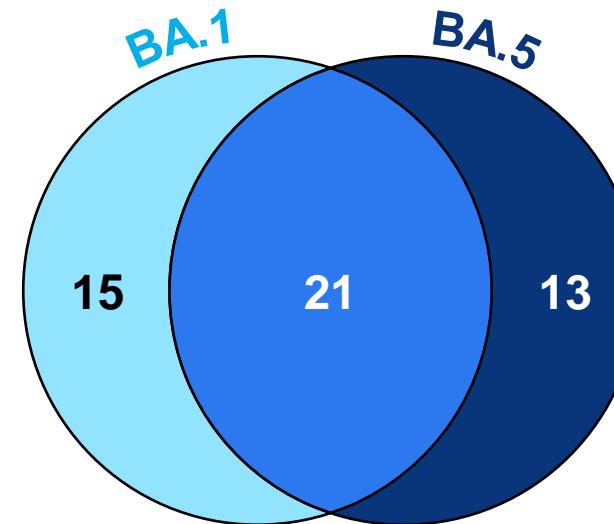
# Antigenic Differences Between Variants Drive Selection Strategy

**XBB.1.5 vs. XBB.1.16**  
(Current)



$$1 + 2 = 3 \text{ mutations}$$

**BA.1 vs. BA.5**  
(Past)

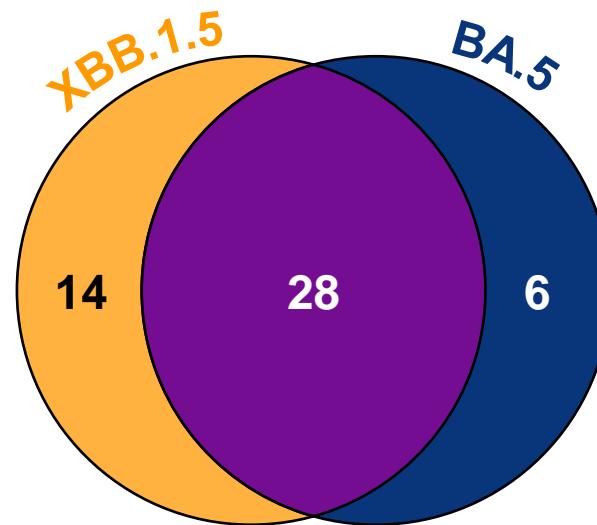


$$15 + 13 = 28 \text{ mutations}$$

- More unique spike mutations when comparing BA.1 and BA.5 than XBB.1.5 and XBB.1.16
- Analysis provides further support to grouping variants into “sub-families” where antigenic distance is minimal and not predicted to be impactful
- BA.1 and BA.5 would NOT have been grouped together into a common sub-family

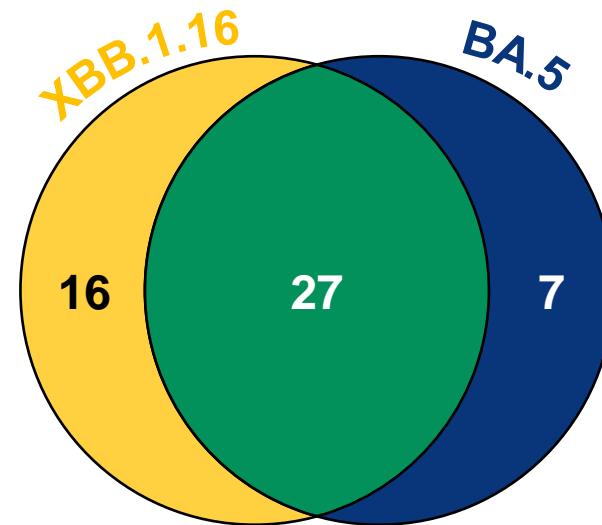
# XBB Subvariants Have Significant Antigenic Differences Compared to BA.5 Variant

XBB.1.5 vs. BA.5



$$14 + 6 = 20 \text{ mutations}$$

XBB.1.16 vs. BA.5



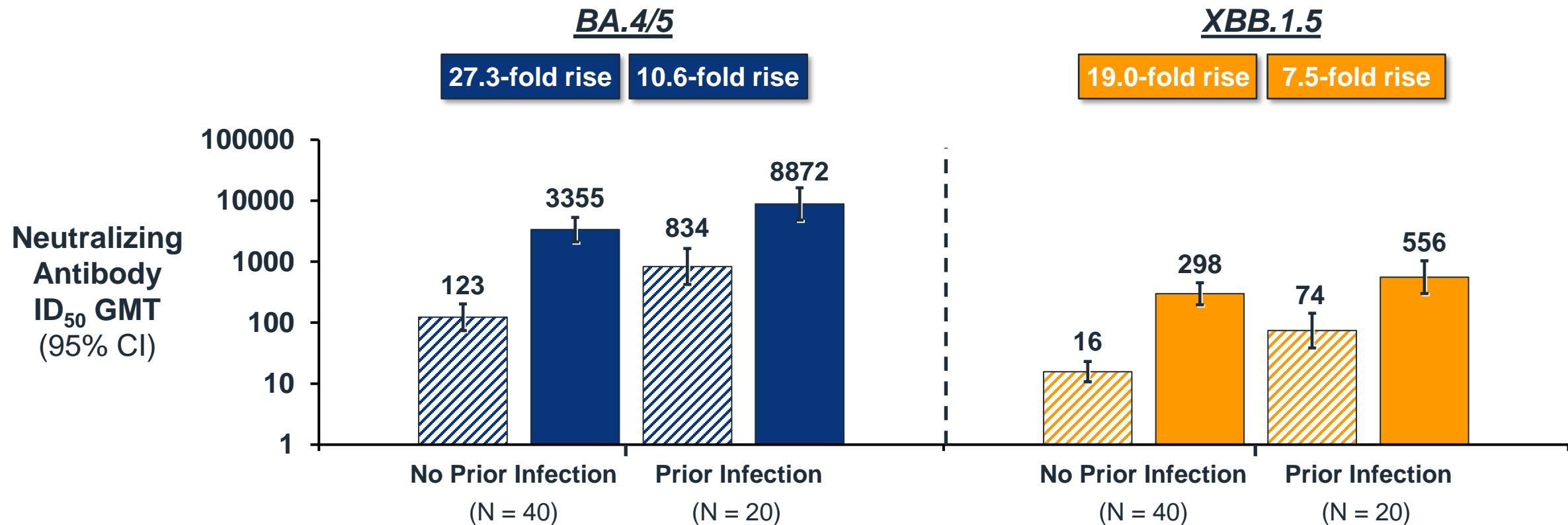
$$16 + 7 = 23 \text{ mutations}$$

Antigenic differences between XBB subvariants and BA.5 suggest an updated vaccine composition may be needed

# Cross-Neutralization at Day 29 Following Omicron BA.4/5 Bivalent Booster

## Study 205H, Per-Protocol Immunogenicity Set

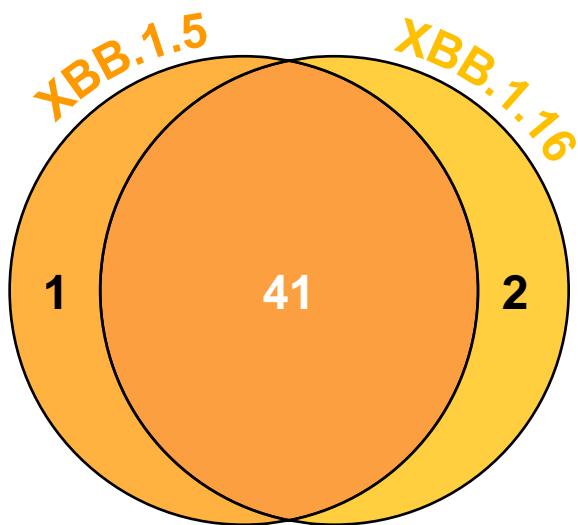
▨ Pre-Boost ■ 29 Days Post Boost



Neutralization capacity of currently authorized BA.4/5 vaccine considerably less against XBB.1.5

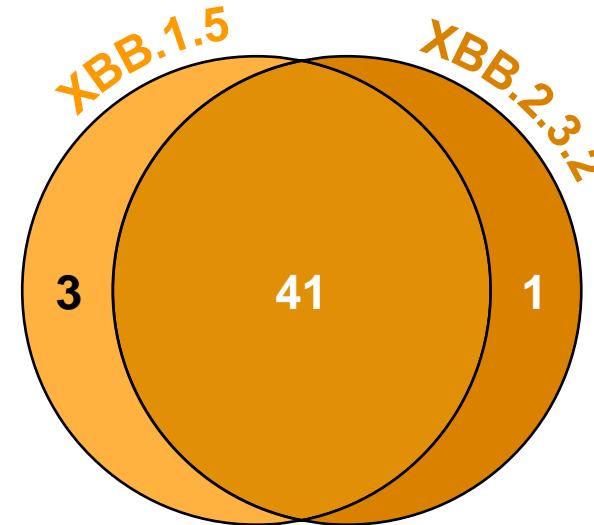
# Minimal Antigenic Differences Between Circulating XBB Variants (XBB.1.5, XBB.1.16, and XBB.2.3.2)

XBB.1.5 vs. XBB.1.16



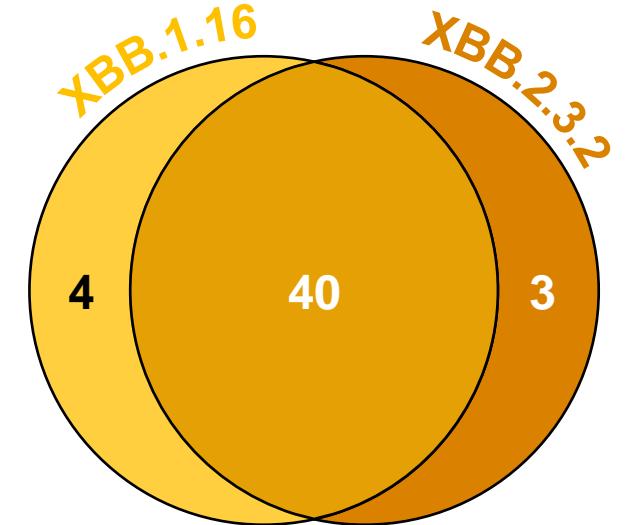
$$1 + 2 = 3 \text{ mutations}$$

XBB.1.5 vs. XBB.2.3.2



$$3 + 1 = 4 \text{ mutations}$$

XBB.1.16 vs. XBB.2.3.2



$$4 + 3 = 7 \text{ mutations}$$

XBB-containing vaccines will likely perform similarly; cross-neutralization is unlikely to be significantly impacted

# Overview of Preclinical Studies to Assess Investigational XBB-Containing Vaccines

# Preclinical Studies Conducted with XBB.1.5 and XBB.1.16-Containing Vaccine Candidates

Studies to compare investigational XBB sub-variant containing vaccine formulations in mice:

## Primary Series

*Antigen naïve mice*

**Monovalent and Bivalent  
XBB.1.5-Containing Vaccines**  
*Complete*

**Monovalent and Bivalent  
XBB.1.16-Containing Vaccine**  
*Ongoing*

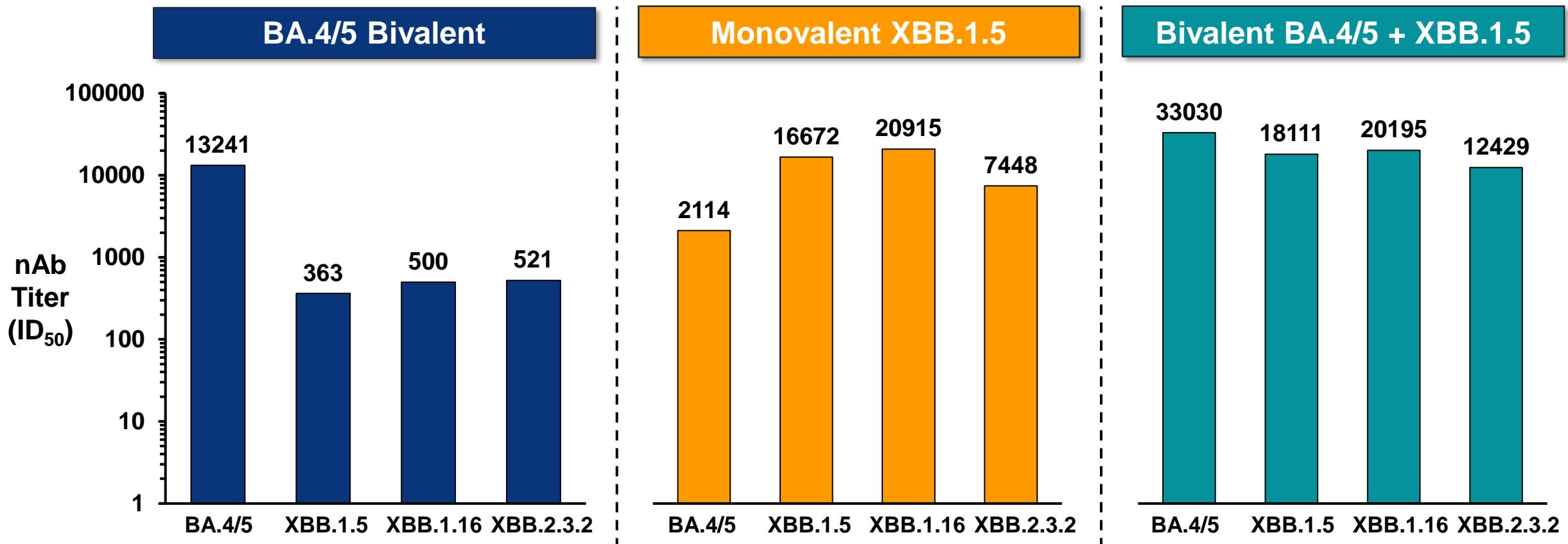
## Booster (3rd) Dose

*Mice previously immunized with a  
2-dose primary series of mRNA-1273*

**Monovalent and Bivalent  
XBB.1.5-Containing Vaccines**  
*Complete*

**Monovalent and Bivalent  
XBB.1.16-Containing Vaccines**  
*Complete*

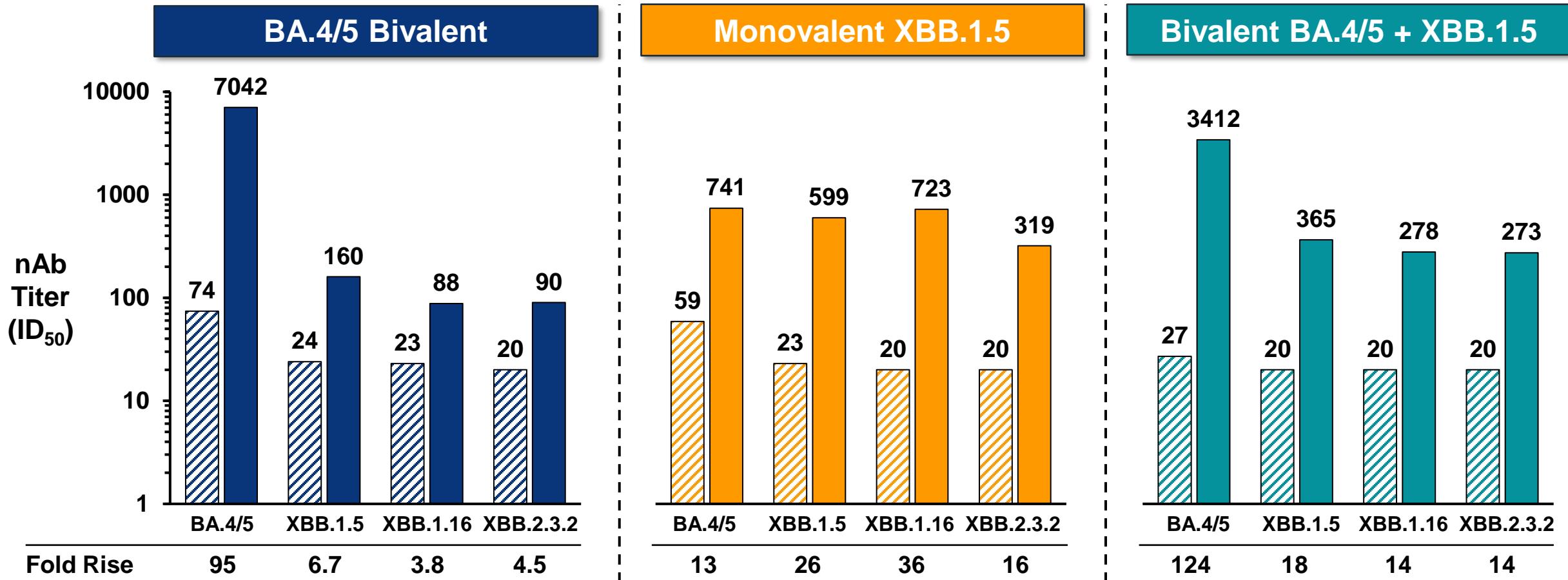
# Neutralizing Antibody Titers in Mice 14 Days after Primary Series of XBB.1.5-Containing Vaccines



Monovalent and bivalent XBB.1.5-containing vaccines effectively drive neutralization of XBB subvariant viruses

# Neutralizing Antibody Titers in Mice 14 Days after Booster (3<sup>rd</sup>) Dose of XBB.1.5-Containing Vaccines

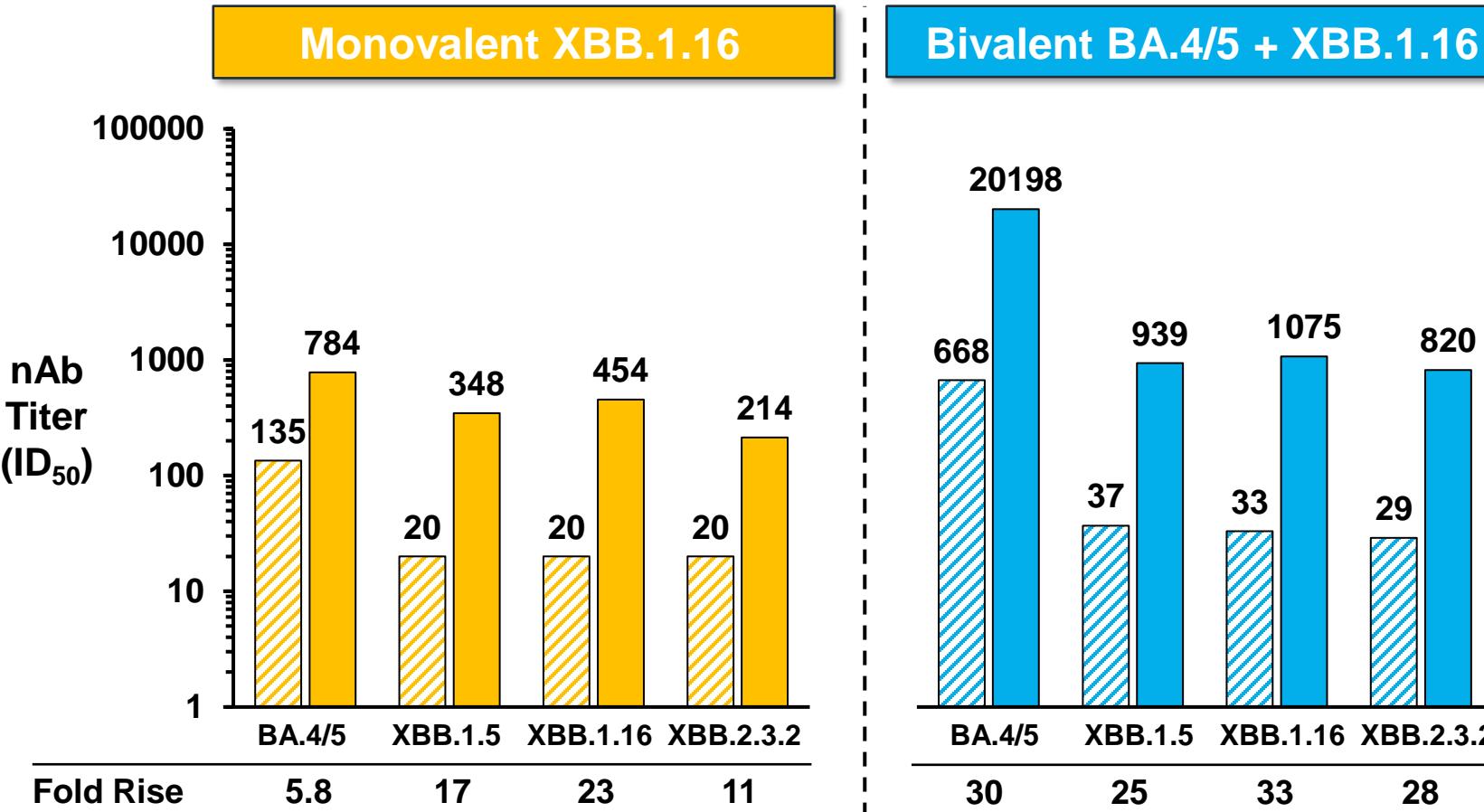
▨ Pre-Boost ■ 14 Days Post Boost



Monovalent and bivalent XBB.1.5-containing vaccines effectively increase neutralization of XBB sub-variant viruses

# Neutralizing Antibody Titers in Mice 14 Days after Booster (3<sup>rd</sup>) Dose of XBB.1.16-Containing Vaccines

▨ Pre-Boost   ■ 14 Days Post Boost



Pre-boost differences between groups likely lead to higher post-boost titers with bivalent vaccine

Monovalent and bivalent XBB.1.16 containing vaccines effectively increase neutralization of XBB sub-variant viruses

## Summary of Pre-Clinical Data

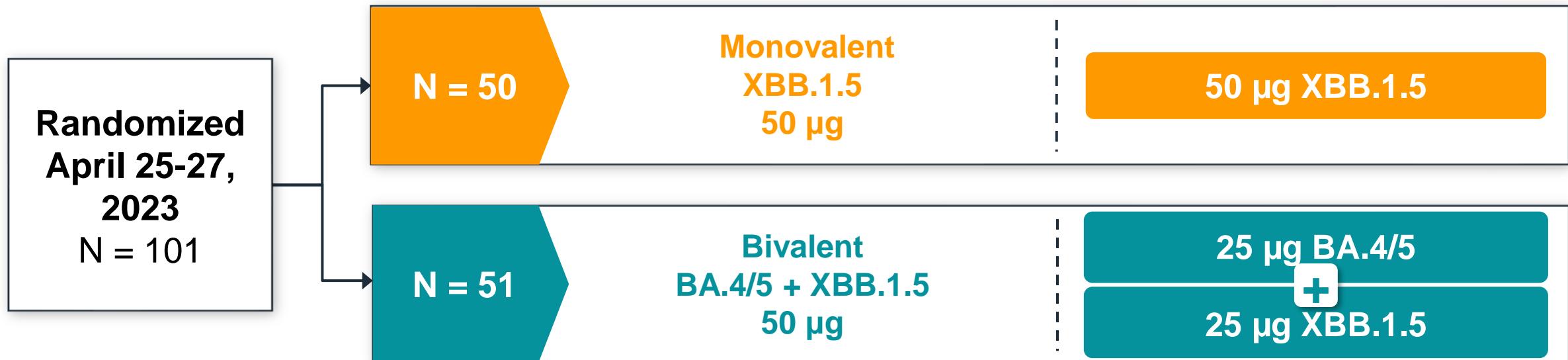
- Preclinical data suggest that an XBB-containing vaccine is more immunogenic against currently circulating XBB variants
- Minimal antigenic differences seen across the XBB sub-family
- Cross-neutralization across XBB sub lineage for both XBB-containing vaccines was demonstrated

# **Clinical Trial of Investigational XBB.1.5 Variant-Containing Vaccines**

**Rituparna Das, MD, PhD**

# Phase 2/3 Randomized Safety and Immunogenicity Study of XBB.1.5-Containing Booster in Adults $\geq 18$ Years

## Study 205J, 5<sup>th</sup> Dose (3<sup>rd</sup> Booster)



- All participants previously received 4 doses of vaccine:
  - Original vaccine primary series + booster
  - Any mRNA BA.4/5 booster  $\geq 3$  months prior to enrollment
- All analyses are descriptive

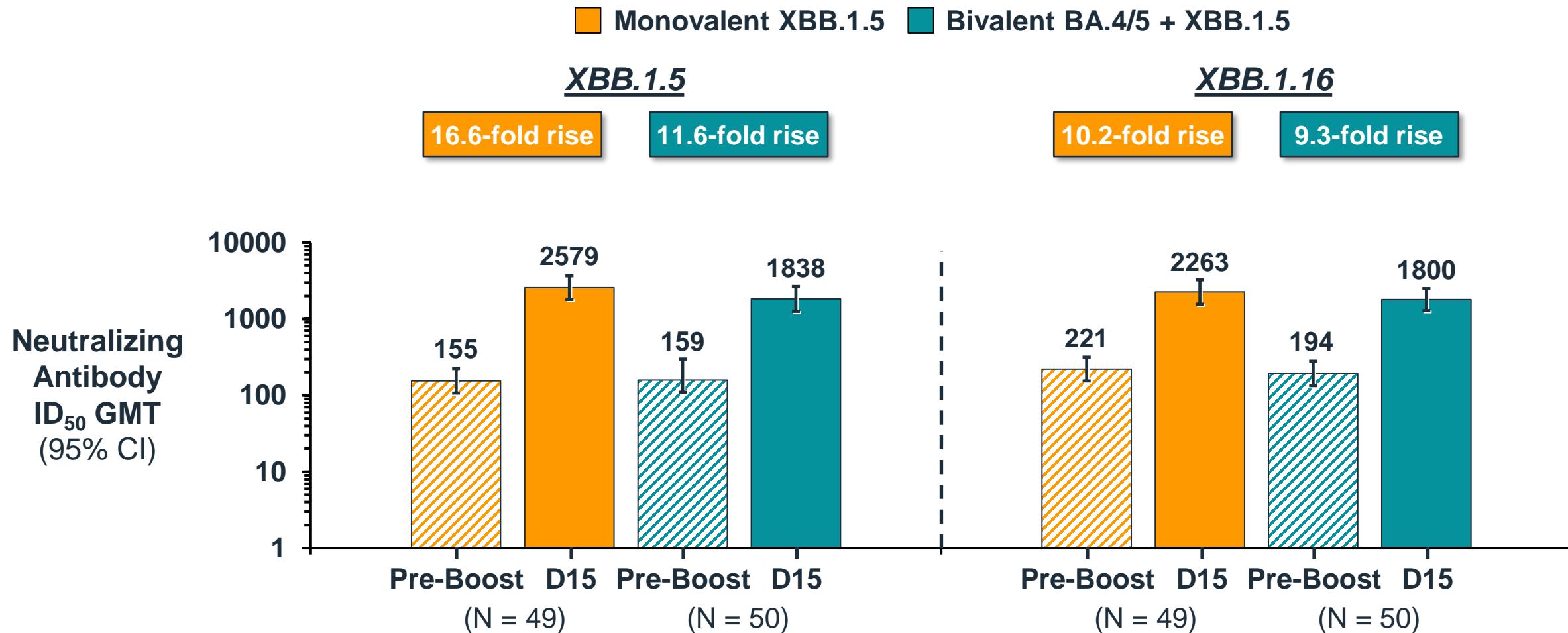
# Demographics and Baseline Characteristics

Study 205J, 5<sup>th</sup> Dose (3<sup>rd</sup> Booster)

Characteristic	5 <sup>th</sup> Dose (3 <sup>rd</sup> Booster)	
	Monovalent XBB.1.5 N = 50	Bivalent BA.4/5 + XBB.1.5 N = 51
<b>Mean Age – Years</b>	51.6	48.4
<b>Median Age – Years (range)</b>	55 (21, 84)	48 (24, 82)
<b>≥ 65 years</b>	11 (22.0%)	7 (13.7%)
<b>% Female</b>	30 (60.0%)	31 (60.8%)
<b>Non-White Race</b>	5 (10.0%)	10 (19.6%)
<b>Months between 2<sup>nd</sup> and 3<sup>rd</sup> Dose, median (Q1, Q3)</b>	8.2 (7.8, 9.8)	9.2 (7.8, 12.2)
<b>Months between 3<sup>rd</sup> and 4<sup>th</sup> Dose, median (Q1, Q3)</b>	9.8 (8.3, 10.3)	9.2 (8.2, 10.3)
<b>Months between 4<sup>th</sup> and 5<sup>th</sup> Dose, median (Q1, Q3)</b>	8.2 (8.1, 8.3)	8.3 (8.1, 8.4)
<b>Prior SARS-CoV-2 Infection</b>	34 (68.0%)	40 (78.4%)

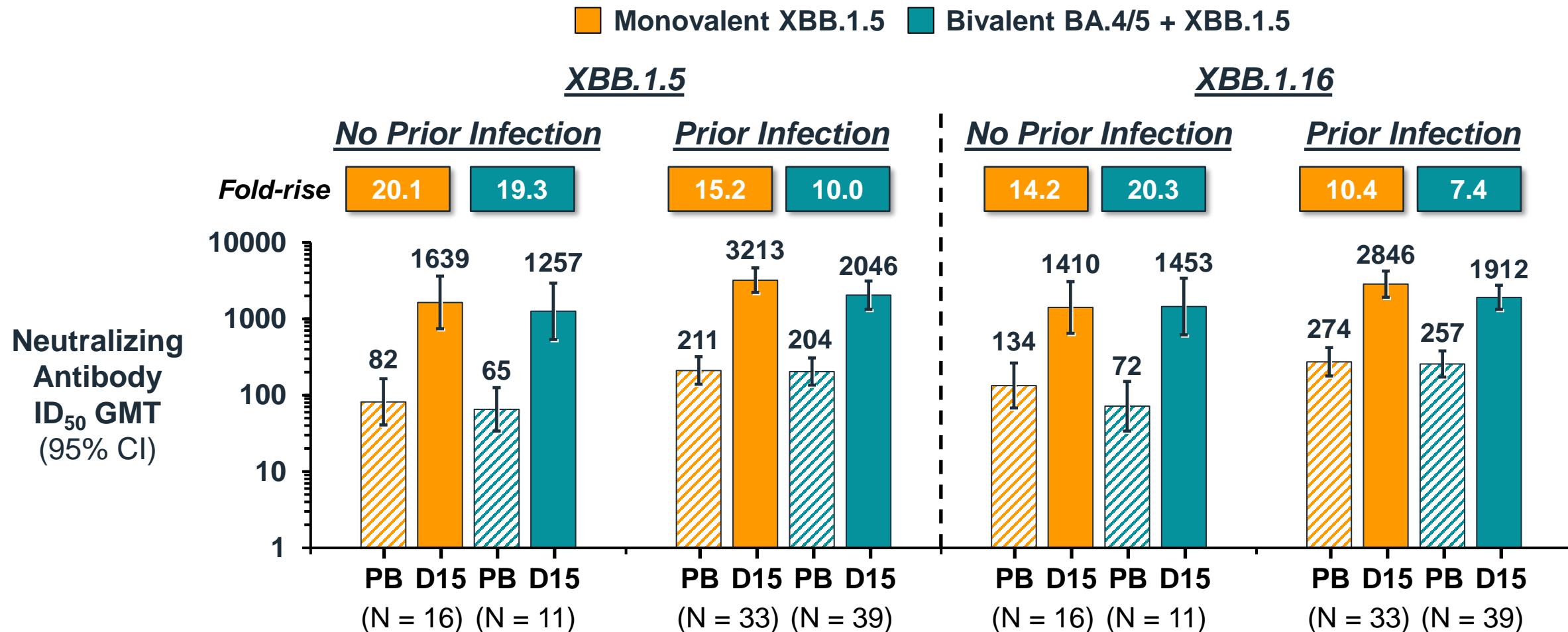
# XBB.1.5 and XBB.1.16 Neutralizing Antibodies After 5<sup>th</sup> Dose (3<sup>rd</sup> Booster) of XBB-Containing Vaccines in Adults

*Study 205J, Per-Protocol Immunogenicity Set – All Participants*



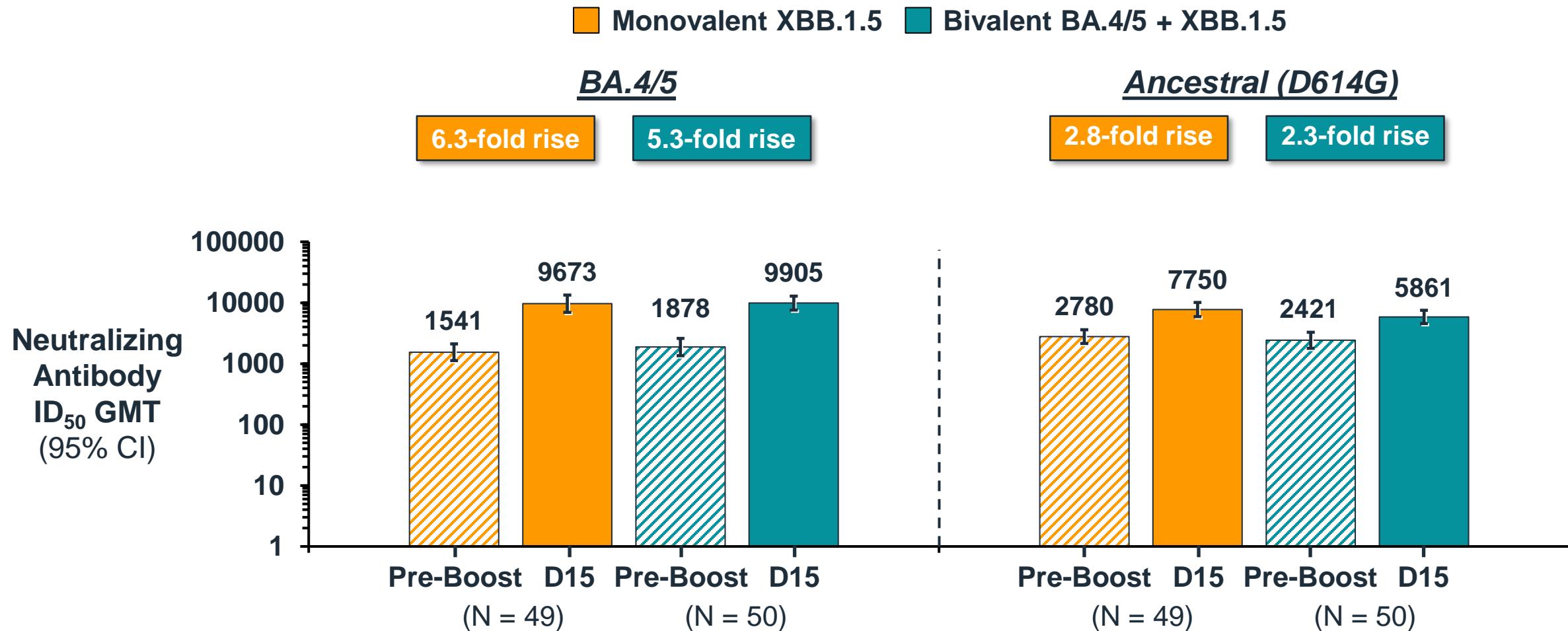
# XBB.1.5 and XBB.1.16 Neutralizing Antibodies After 5<sup>th</sup> Dose (3<sup>rd</sup> Booster) of XBB-Containing Vaccines in Adults

*Study 205J, Per-Protocol Immunogenicity Set – By Prior Infection Status*



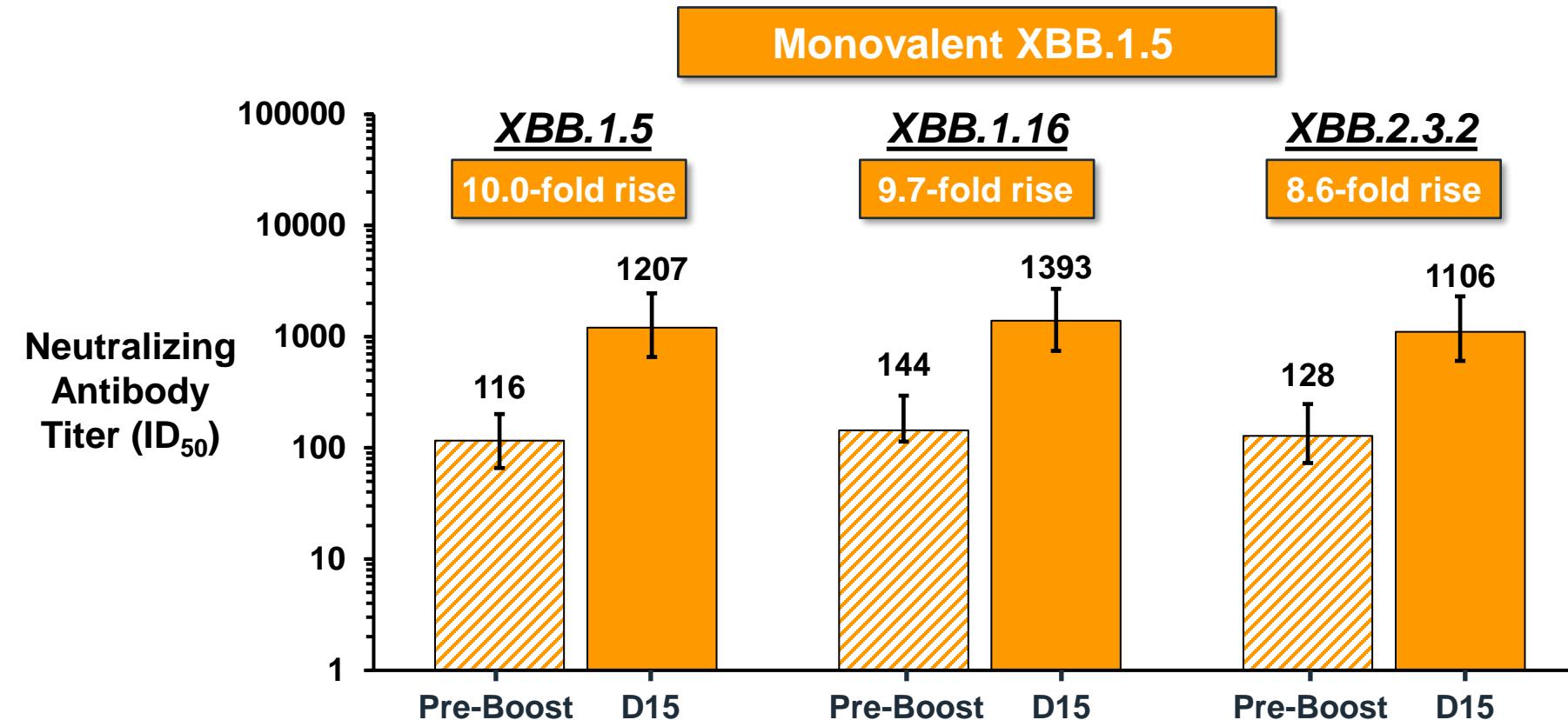
# BA.4/5 and Ancestral (D614G) Neutralizing Antibodies After 5<sup>th</sup> Dose (3<sup>rd</sup> Booster) of XBB-Containing Vaccines in Adults

*Study 205J, Per-Protocol Immunogenicity Set – All Participants*



# XBB.1.5, XBB.1.16, and XBB.2.3.2 Neutralizing Antibodies After 5<sup>th</sup> Dose (3<sup>rd</sup> Booster) of Monovalent XBB.1.5 Vaccine in Adults

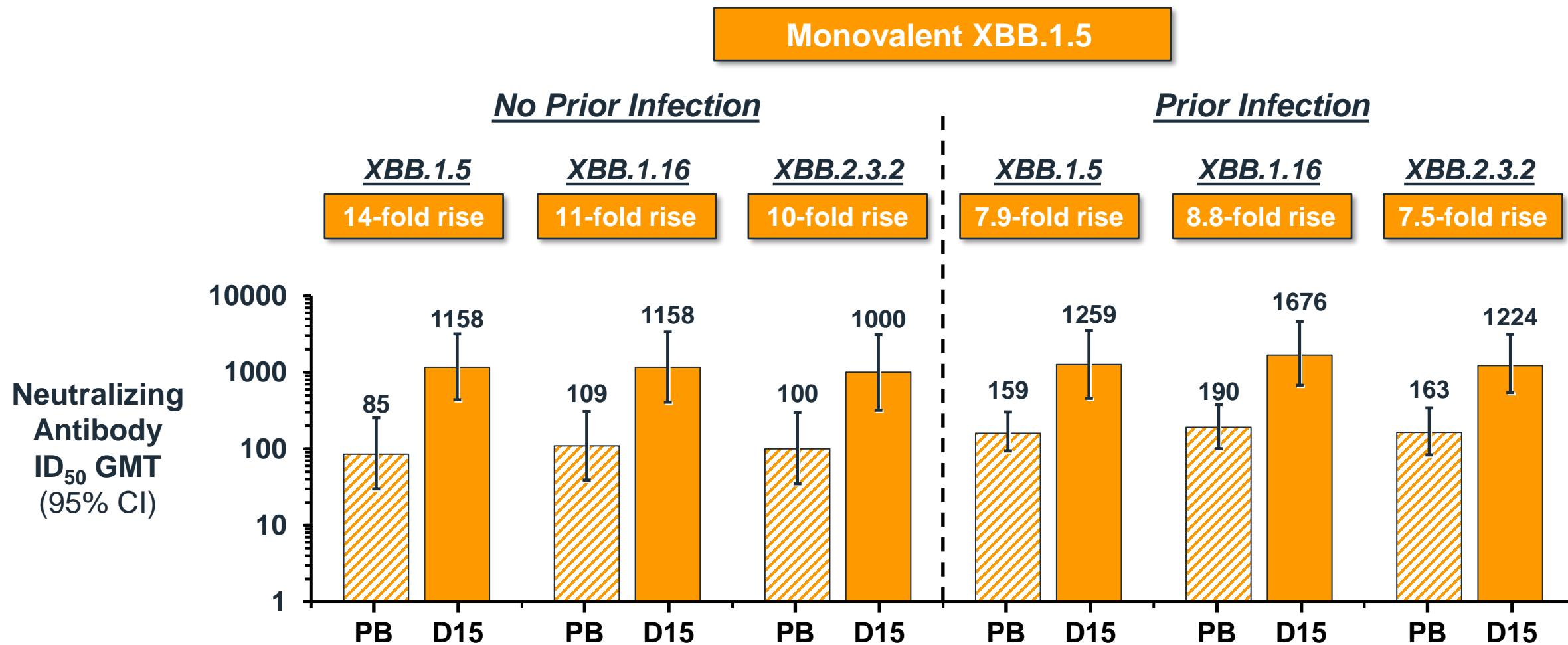
Study 205J, Subset Analysis (N = 20)



Similar neutralization of XBB.1.5, XBB.1.16, and XBB.2.3.2 sub-variants measured in this subset analysis

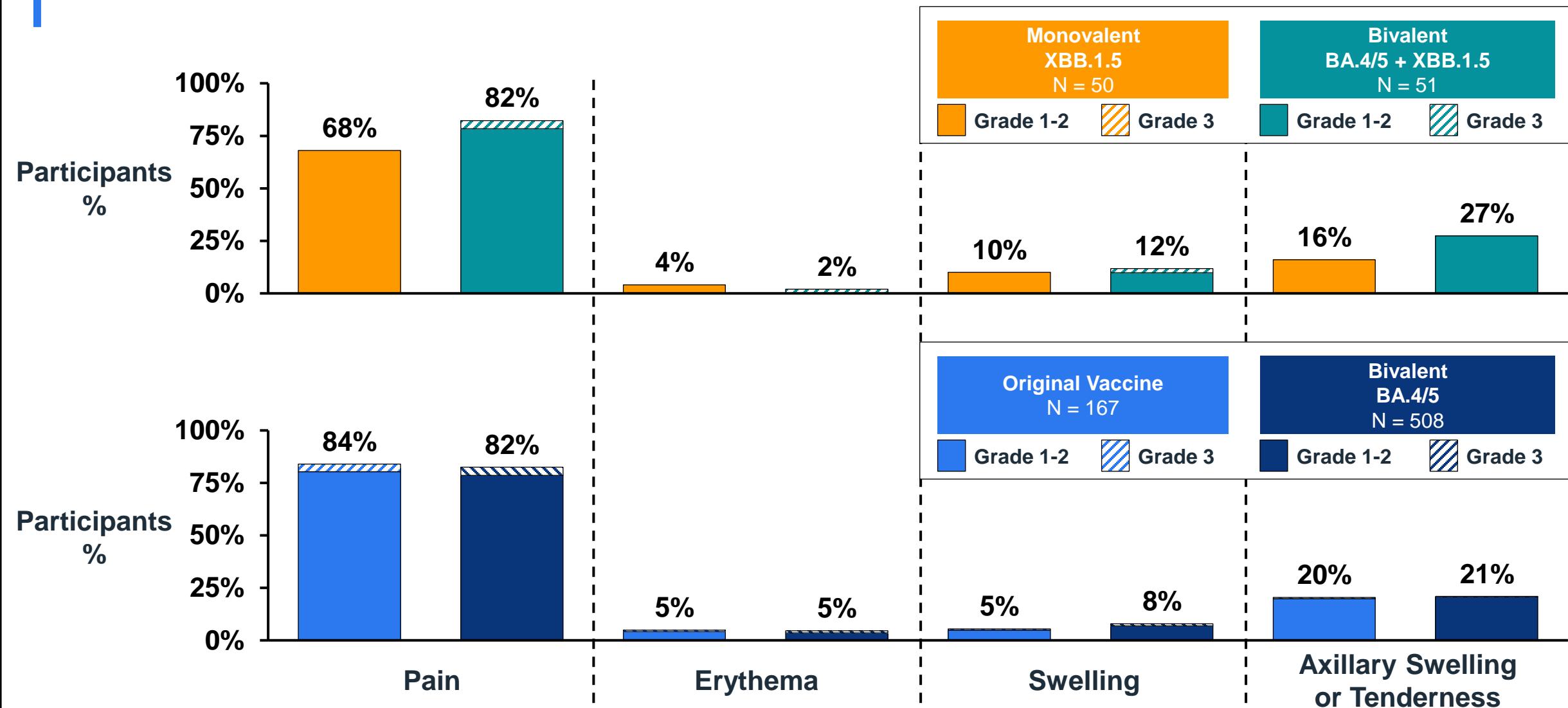
# XBB.1.5, XBB.1.16, and XBB.2.3.2 Neutralizing Antibodies After 5<sup>th</sup> Dose (3<sup>rd</sup> Booster) of XBB-Containing Vaccines in Adults

*Study 205J, Subset Analysis (N=10 With Prior Infection, N=10 Without Prior Infection)*



# Local Reactions Following Booster Doses in Adults

## Study 205J and Study 205H, Solicited Safety Set

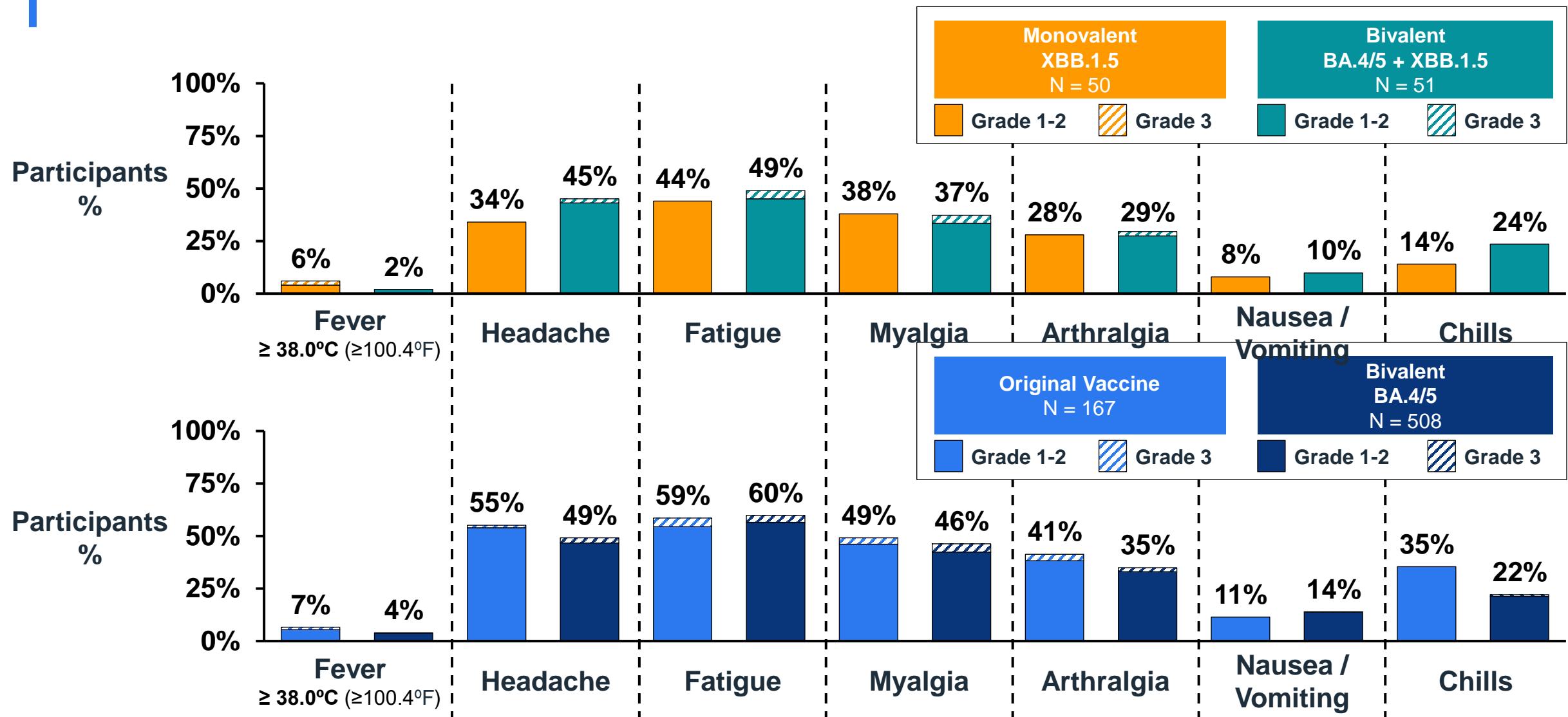


Within 7 days of injection; No Grade 4 events reported

Chalkias et al., medRxiv, 2022, Chu et al, Nat Med 28:1041, 2022

# Systemic Reactions Following Booster Doses in Adults

## Study 205J and Study 205H, Solicited Safety Set



# Conclusions

Rituparna Das, MD, PhD

# Summary

## Kaiser Real World Effectiveness Study

- BA.4/5 booster effective against COVID-19 when BA.5 was the predominant circulating strain

## Preclinical and Clinical Studies of XBB-containing Vaccines

- Antigenic similarities in XBB-variants support grouping of the XBB viruses
- Pre-clinical data suggest an XBB-containing vaccine is more immunogenic against currently circulating XBB variants than the authorized BA.4/5 vaccine
- Clinical data demonstrate that XBB.1.5-containing vaccines robustly elicit neutralizing antibodies against XBB variants
- Safety profile of XBB-containing vaccines consistent with previously authorized vaccines

## Moderna's Vaccine Preparedness

- Moderna is prepared to supply a new variant-containing vaccine for Fall 2023 as recommended by FDA

# **THANK YOU to Our Study Collaborators, Investigators, and Participants**

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