Pfizer/BioNTech COVID-19 Omicron-Modified Vaccine Options

Vaccines and Related Biological Products Advisory Committee

June 28, 2022

Presentation Outline

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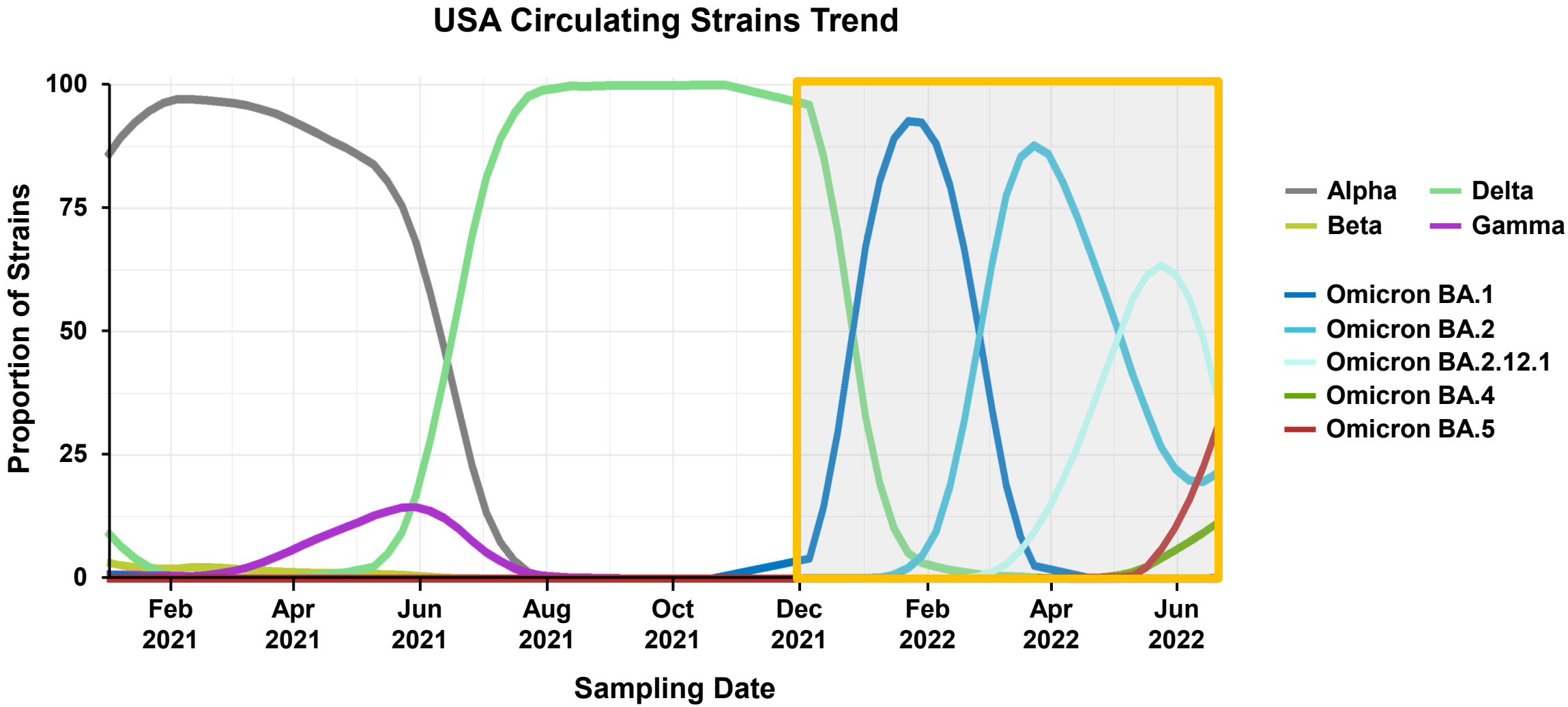
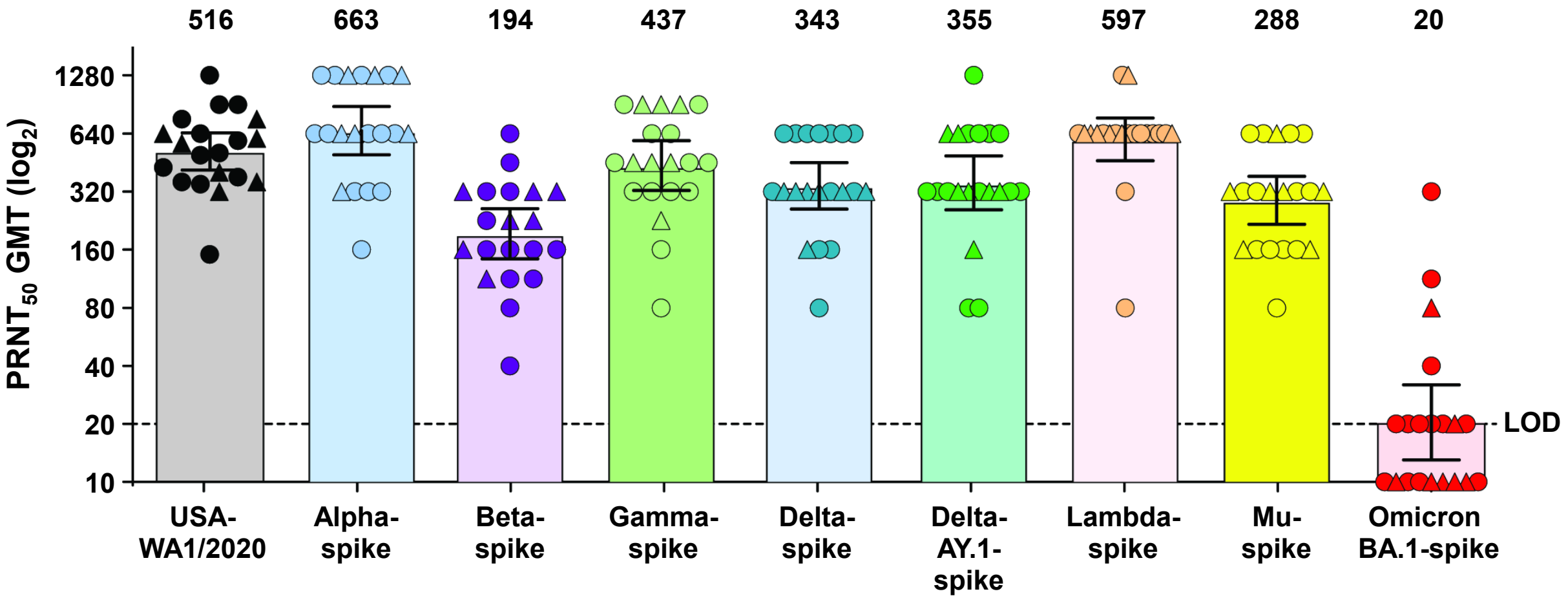
- **Immunogenicity and safety of Omicron variant-modified vaccines as a booster or primary series to support variant modified EUA**
- **Considerations for future vaccine updates**

SARS-CoV-2 Epidemiology Changes Quickly



GISAID data as of June 24, 2022

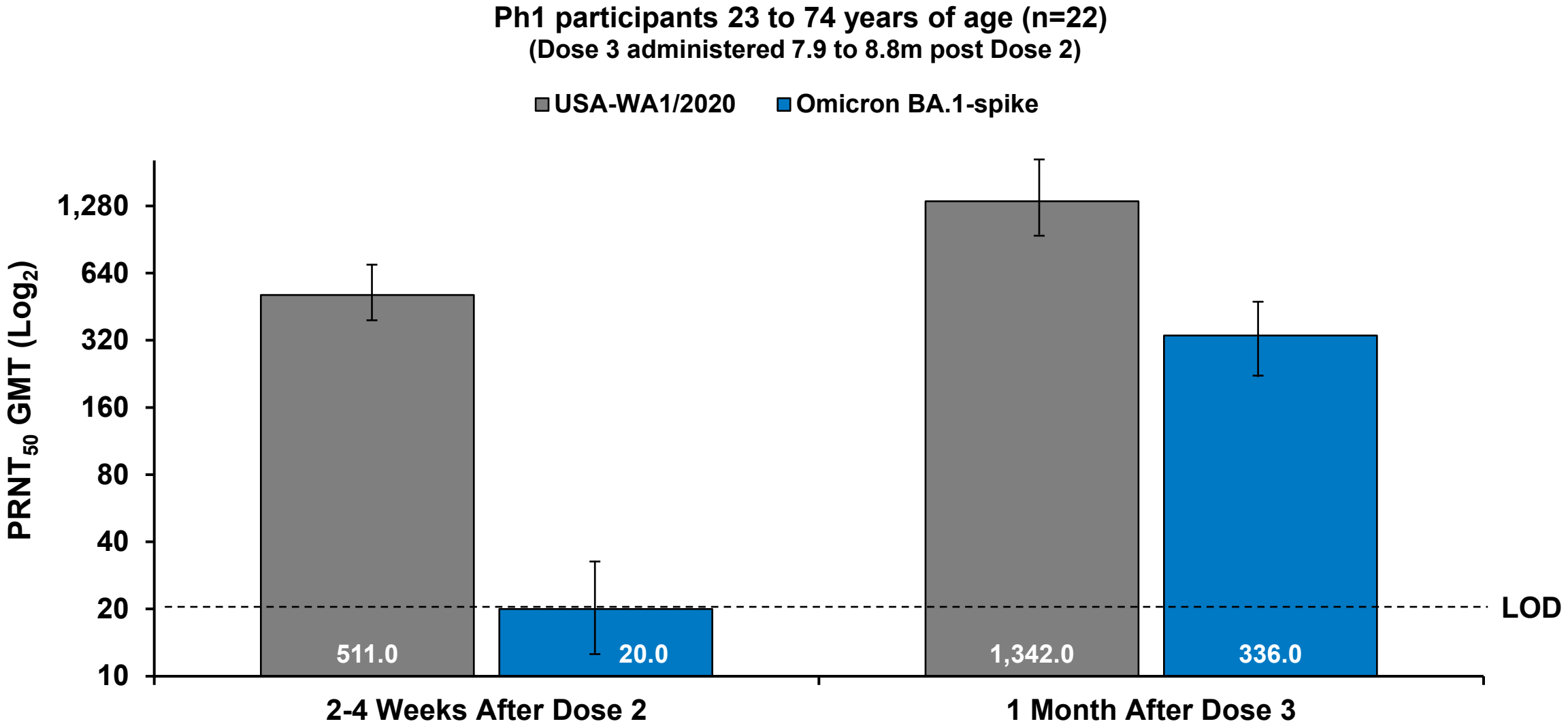
BNT162b2-Elicited Sera (1M Post Second Dose) Efficiently Neutralize SARS-CoV-2 Variants of Concern, Except Omicron



1. *Cell Host & Microbe*, 30:485 (2022) (https://doi.org/10.1016/j.chom.2022.02.015)
2. *N Engl J Med*, 385:472 (2021) (https://doi.org/10.1056/NEJMc2106083)
3. *N Engl J Med*, 384:1466 (2021) (https://doi.org/10.1056/NEJMc2102017)

PRNT, plaque reduction neutralization test; LOD, limit of detection

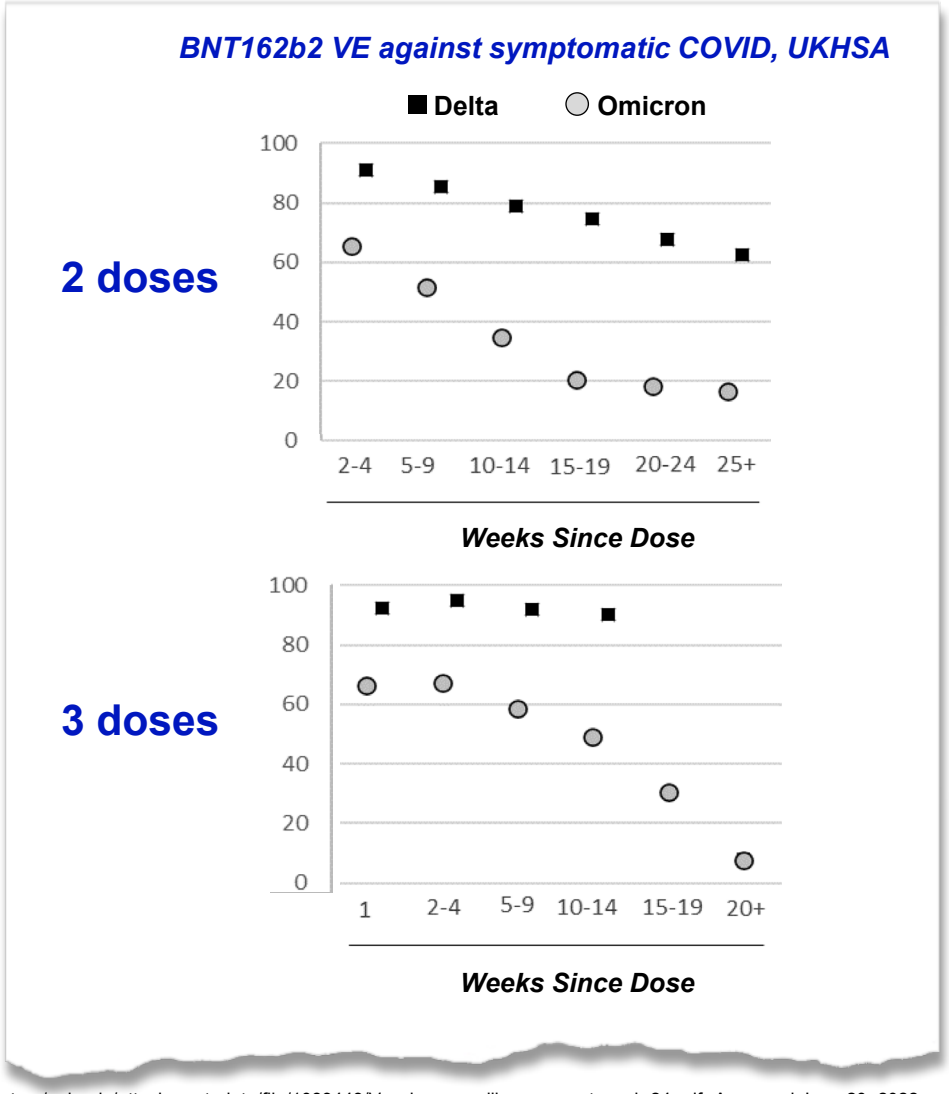
Third Dose of BNT162b2 Substantially Boosts Neutralization Titers and Expands Breadth Against Omicron BA.1



Recombinant SARS-CoV-2 with variant spike coding sequences on a common, USA-WA1/2020 genetic background.
PRNT, plaque reduction neutralization test; LLOD, Lower Limit of Detection. bioRxiv preprint doi: https://doi.org/10.1101/2022.01.21.476344.

Effectiveness and Duration of Protection against Omicron Lineages and Emerging Variants Unknown

- **Vaccine efficacy against COVID-19 is lower and wanes faster for Omicron (figure)[1]**
  - Adapted vaccines can help slow virus circulation and emergence of VOCs
- **Vaccines have been effective against severe Omicron illness,[1,2] however…**
  - Waning against Omicron hospitalization observed >9m after second dose[3]
  - Duration of protection >6m post-boost is unknown

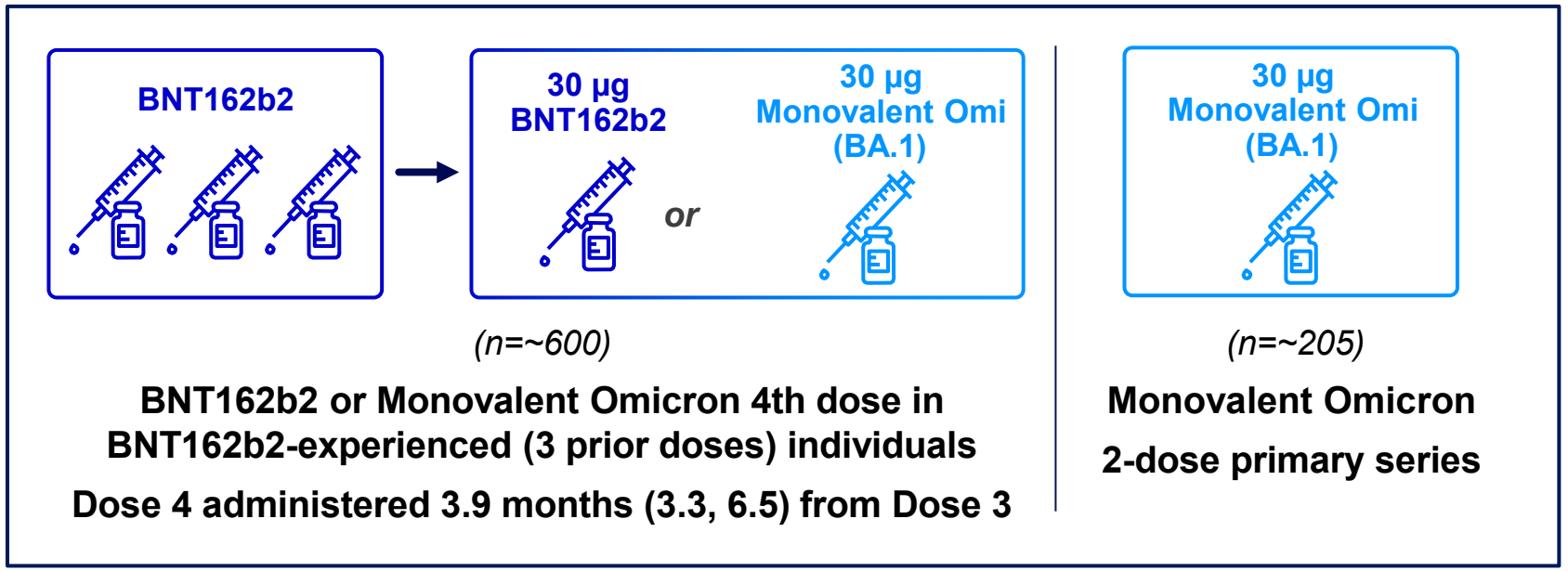


1. UK Health Security Agency. COVID-19 vaccine surveillance report: week 24. 16 June 2022. Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1083443/Vaccine-surveillance-report-week-24.pdf. Accessed June 20, 2022.
2. Tartof S et al. Immunocompromise and durability of BNT162b2 vaccine against severe outcomes due to omicron and delta variants. *Lancet Respir Med*. 2022 May 6:S2213-2600(22)00170-9. doi: 10.1016/S2213-2600(22)00170-9.
3. Tartof S et al. Durability of BNT162b2 vaccine against hospital and emergency department admissions due to the omicron and delta variants in a large health system in the USA: a test-negative case-control study. *Lancet Respir Med*. 2022 Apr 22:S2213-2600(22)00101-1. doi: 10.1016/S2213-2600(22)00101-1

Clinical Study For Monovalent Omicron-modified Vaccine Booster and Primary Series

18-55y Participants

C4591031 Substudy D evaluates safety and immunogenicity in ~1,420 participants



EUA Guidance

- **Omicron neutralization:**
  - **GMR Simple Superiority:** the lower bound of the 95% confidence interval for the GMR is >1
  - **Seroresponse Noninferiority:** the lower bound of the 95% confidence interval for the percentage difference is greater than -5
- **Reference strain neutralization:**
  - **Descriptive analyses:** comparison of geometric mean neutralizing titers for reference strain (USA-WA1/2020)

GMR, geometric mean ratio

Monovalent Omicron-modified Vaccine (OMI 30 µg) as 4th Dose Booster Met Simple Superiority for Omicron Neutralizing Antibody Response

18-55y Participants

Participants WITHOUT Evidence of Infection up to 1 Month After First Study Vaccination

	GMR		Seroresponse Difference from Prototype Vaccine	
	BNT162b2 OMI (30 µg) / BNT162b2 (30 µg)		Difference in % BNT162b2 OMI (30 µg) - BNT162b2 (30 µg)	
Assay	GMR (95% CI)	Met Superiority (Y/N)	% (95% CI)	Met Non-inferiority (Y/N)
SARS-CoV-2 neutralization assay – Omicron BA.1 NT50 (titer)	1.75 (1.39, 2.22)	Y	23 (11.1, 34.3)	Y

GMR Simple Superiority Criterion: the lower bound of the 95% confidence interval for the GMR is >1
Seroresponse Noninferiority Criterion: the lower bound of the 95% confidence interval for the percentage difference is greater than -5

n = 132, BNT162b2 OMI; n=141 BNT162b2
Omicron BA.1 NT50 measured using validated 384-well assay

Monovalent Omicron-modified Vaccine (OMI 30 µg) Reference Strain Neutralizing Antibody Response Similar to Prototype Vaccine as 4th Dose Booster

18-55y Participants

Participants WITHOUT Evidence of Infection up to 1 Month After First Study Vaccination

Assay	BNT162b2 OMI (30 µg) n=207		BNT162b2 (30 µg) n=227		BNT162b2 OMI (30 µg)/ BNT162b2 (30 µg)
	GMT (95% CI)	GMFR (95% CI)	GMT (95% CI)	GMFR (95% CI)	GMR (95% CI)
SARS-CoV-2 neutralization assay – reference strain - NT50 (titer)	11997.1 (10553.5, 13638.3)	2.7 (2.4, 3.0)	12009.9 (10744.3, 13424.6)	3.0 (2.7, 3.3)	1.00 (0.84, 1.18)

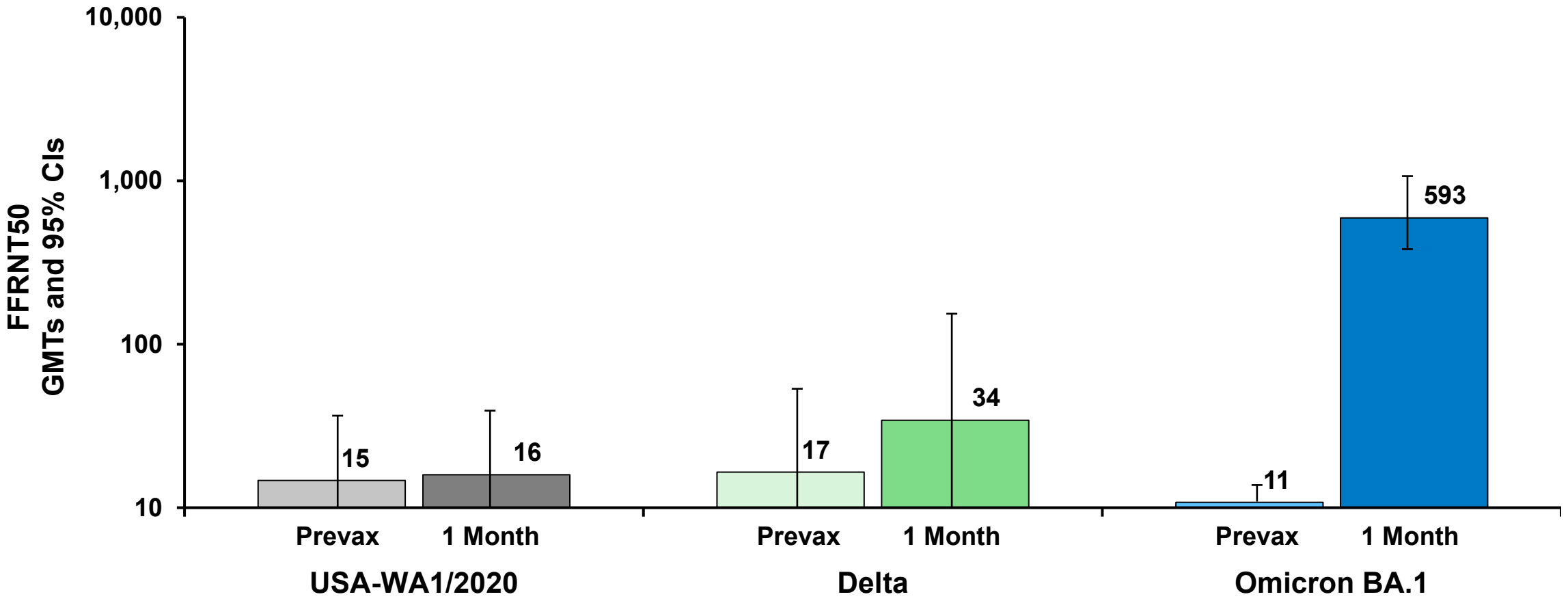
Descriptive analyses: comparison of geometric mean neutralizing titers for reference strain

Reference strain NT50 measured using validated 384-well assay

In Naïve Individuals, Omicron Monovalent Vaccine Elicits a Predominantly Omicron-specific Response

30 µg Dose, Evaluable Immunogenicity Population – Sentinel Group

Participants WITHOUT Evidence of Infection up to 1 Month After Dose 2

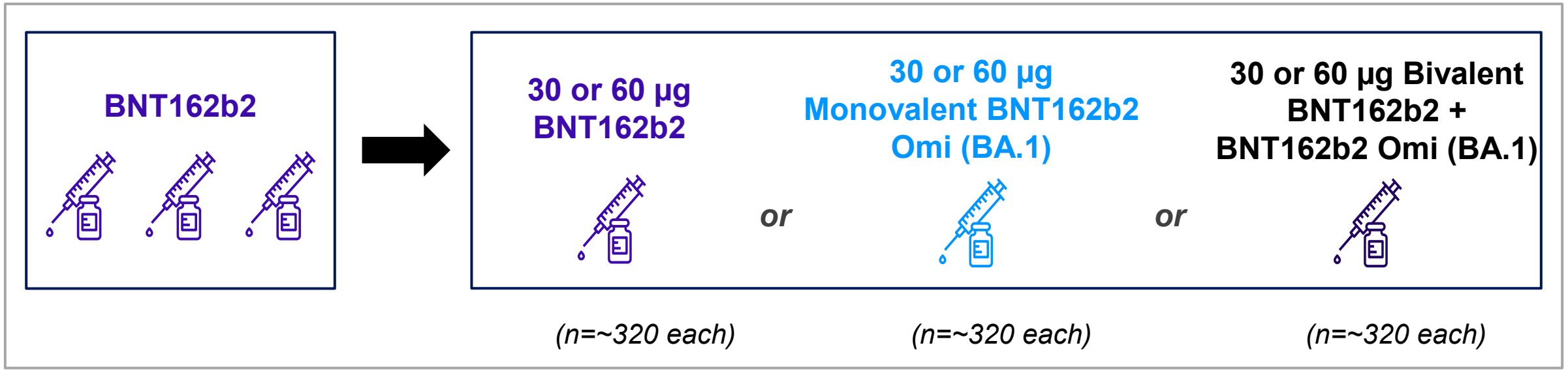


FFRNT, fluorescent focus reduction neutralization test
N=9 for all groups without evidence of infection up to 1 month after dose 2 shown out of total N=30 sentinel cohort

Clinical Study to Evaluate Monovalent and Bivalent Omicron-modified Vaccines in Vaccine-experienced Participants

>55y Participants

C4591031 Substudy E Evaluates Safety & Immunogenicity in ~1920 participants >55 Years



Dose 4 administered a median of 6.3 months (4.7, 12.9) from Dose 3

Monovalent BNT162b2 Omi (BA.1) 60 µg (N~330), bivalent BNT162b2 + BNT162b2 Omi (BA.1) 30 µg (N~180) and 60 µg (N~480) also being evaluated in participants 18-55 years of age

Omicron BA.1 GMR Consistent with Simple Superiority Criterion for Omicron-modified Vaccines

>55y Participants

Participants WITHOUT Evidence of Infection up to 1 Month After the Study Vaccination

Assay	Vaccine Groups	n	GMT (95% CI) 1M Post-Dose	Vaccine Group / BNT162b2 30 µg	
				GMR (95% CI)	Met Superiority (Y/N)*
SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titer)	BNT162b2 30 µg	163	455.8 (365.9, 567.6)		
	BNT162b2 OMI 30 µg	169	1014.5 (825.6, 1246.7)	2.23 (1.65, 3.00)	Y
	BNT162b2 OMI 60 µg	174	1435.2 (1208.1, 1704.8)	3.15 (2.38, 4.16)	Y
	Bivalent OMI 30 µg[1]	178	711.0 (588.3, 859.2)	1.56 (1.17, 2.08)	Y
	Bivalent OMI 60 µg[2]	175	900.1 (726.3, 1115.6)	1.97 (1.45, 2.68)	Y

GMR Simple superiority criterion: the lower bound of 95% confidence interval for GMR is >1.0

*Multiple hypotheses are to be evaluated in sequential order for alpha control. Declaration of OMI 30 mcg simple superiority pending outcome of additional hypotheses

Omicron BA.1 NT50 measured using validated 384-well assay

Omicron BA.1 GMR Consistent with Super Superiority Criterion for Monovalent Omicron-modified Vaccine

>55y Participants

Participants WITHOUT Evidence of Infection up to 1 Month After the Study Vaccination

Assay	Vaccine Groups	n	GMT (95% CI) 1M Post-Dose	Vaccine Group / BNT162b2 30 µg	
				GMR (95% CI)	Met Superiority (Y/N)*
SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titer)	BNT162b2 30 µg	163	455.8 (365.9, 567.6)		
	BNT162b2 OMI 30 µg	169	1014.5 (825.6, 1246.7)	2.23 (1.65, 3.00)	Y
	BNT162b2 OMI 60 µg	174	1435.2 (1208.1, 1704.8)	3.15 (2.38, 4.16)	Y
	Bivalent OMI 30 µg[1]	178	711.0 (588.3, 859.2)	1.56 (1.17, 2.08)	Y
	Bivalent OMI 60 µg[2]	175	900.1 (726.3, 1115.6)	1.97 (1.45, 2.68)	Y

GMR Super superiority criterion: the lower bound of 95% confidence interval for GMR is >1.5

*Multiple hypotheses are to be evaluated in sequential order for alpha control. Declaration of super superiority pending outcome of additional hypotheses

Omicron BA.1 NT50 measured using validated 384-well assay

Omicron BA.1 Seroresponse Rate Exceeds Noninferiority Criterion for Omicron-containing Vaccines

>55y Participants

Participants WITHOUT Evidence of Infection up to 1 Month After the Study Vaccination

Assay	Vaccine Groups	N	n (%)	(95% CI) 1M Post-Dose	Seroresponse Difference in % Vaccine Group – BNT162b2 30 µg % (95% CI)	Met Non-inferiority (Y/N)*
SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titer)	BNT162b2 30 µg	149	85 (57.0)	(48.7, 65.1)		
	BNT162b2 OMI 30 µg	163	125 (76.7)	(69.4, 82.9)	19.6 (9.3, 29.7)	Y
	BNT162b2 OMI 60 µg	166	143 (86.1)	(79.9, 91.0)	29.1 (19.4, 38.5)	Y
	Bivalent OMI 30 µg[1]	169	121 (71.6)	(64.2, 78.3)	14.6 (4.0, 24.9)	Y
	Bivalent OMI 60 µg[2]	162	110 (67.9)	(60.1, 75.0)	10.9 (0.1, 21.4)	Y

Non-inferiority criterion: the lower bound of 95% confidence interval for interval for the percentage difference is >-5

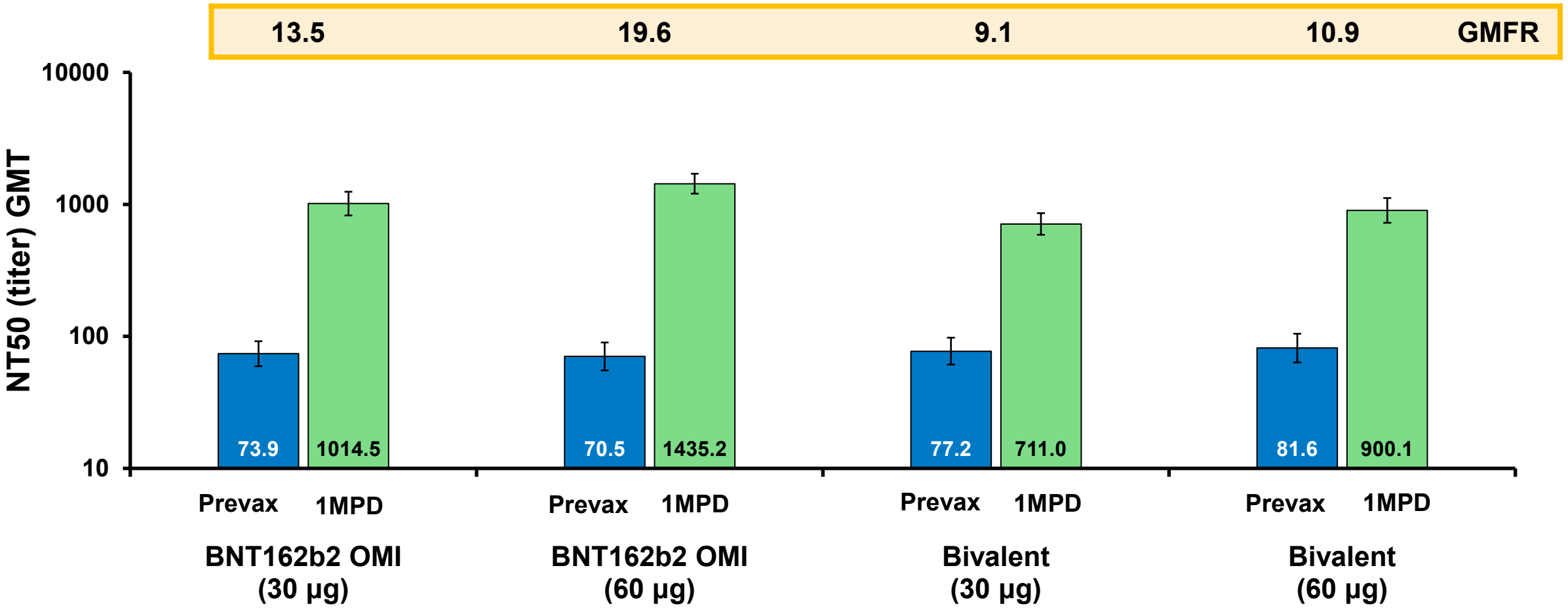
*Multiple hypotheses are to be evaluated in sequential order for alpha control. Declaration of OMI 30 mcg noninferiority pending outcome of additional hypotheses.

Omicron BA.1 NT50 measured using validated 384-well assay

Omicron BA.1 Neutralization Activity Substantially Increased with Omicron-modified Vaccines as 4th Dose Booster

>55y Participants

>55 Year Olds Without Evidence of Prior Infection
Median Time from Dose 3 to Study Vaccination: 6.3 Months (4.7, 12.9)



Omicron BA.1 NT50 measured using validated 384-well assay

Reference Strain Geometric Mean Titers Boosted in All Groups

>55y Participants, Sentinel Cohort (Evaluable Immunogenicity Population)

Participants WITHOUT Evidence of Infection up to 1 Month After the Study Vaccination

	Vaccine Group (as Randomized) GMT (95% CI)					
	BNT162b2 (30 µg) n=17	BNT162b2 (60 µg) n=20	BNT162b2 OMI (30 µg) n=17	BNT162b2 OMI (60 µg) n=18	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) n=12	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) n=18
SARS-CoV-2 FFRNT – reference strain - NT50 (titer)						
Prevax	208.6 (106.9, 406.9)	255.5 (127.0, 513.8)	221.7 (119.8, 410.3)	226.3 (114.7, 446.3)	369.7 (232.4, 588.2)	172.8 (105.2, 283.9)
Month 1	1810.2 (946.3, 3462.7)	1718.5 (1174.6, 2514.1)	962.2 (520.3, 1779.4)	1522.2 (809.2, 2863.4)	2560.0 (1492.8, 4390.3)	1522.2 (1071.6, 2162.2)
GMFR	8.7 (5.5, 13.8)	6.7 (4.3, 10.4)	4.3 (2.5, 7.7)	6.7 (3.5, 12.8)	6.9 (4.1, 11.7)	8.8 (6.3, 12.2)

FFRNT, fluorescent focus reduction neutralization test

Reactogenicity Profile of Variant Vaccines Overall Similar to Prototype BNT162b2 Vaccine

- **18-55y participants:** Monovalent Omicron-modified vaccine (30-µg) showed a similar local reaction and systemic event profile as the prototype vaccine (30-µg)

- **>55y participants:** Monovalent and Bivalent Omicron-modified vaccines (30-µg) showed a similar local reaction and systemic event profile as the prototype vaccine
  - 60-µg dose level - Mild to moderate injection site pain, fatigue and muscle pain were more common compared to 30-µg

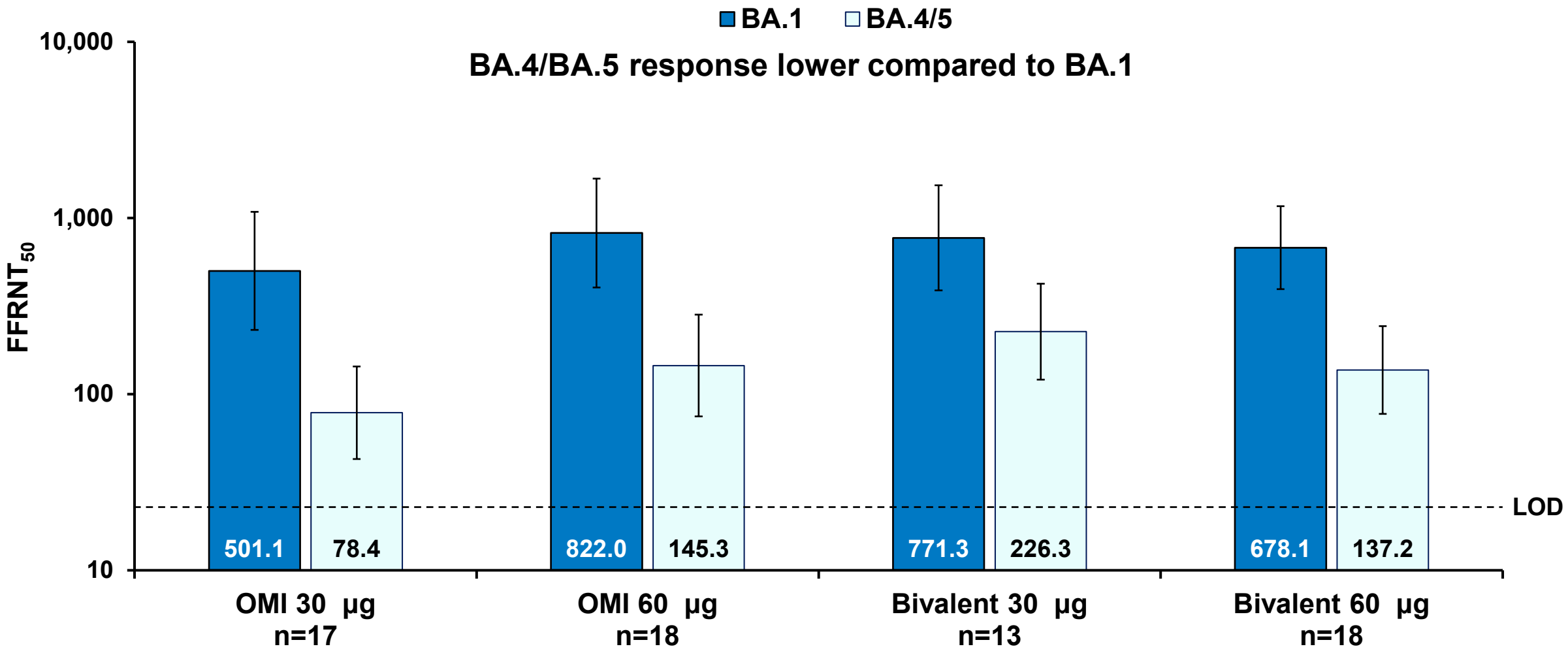
Omicron-containing Modified Variant Vaccine Summary

- **Neutralizing responses for Omicron-containing vaccines are consistent with regulatory criteria:**
  - Simple superiority for GMR and non-inferiority for seroresponse (monovalent and bivalent vaccines)
  - ‘Super’ superiority for GMR (monovalent vaccines)
- **Reactogenicity profile of variant vaccines overall similar to prototype BNT162b2 vaccine**

Omicron-containing Modified Variant Vaccines as 4th Dose Elicit Improved Omicron Neutralization Response

>55y Participants Sentinel Cohort, 30 and 60 µg Dose

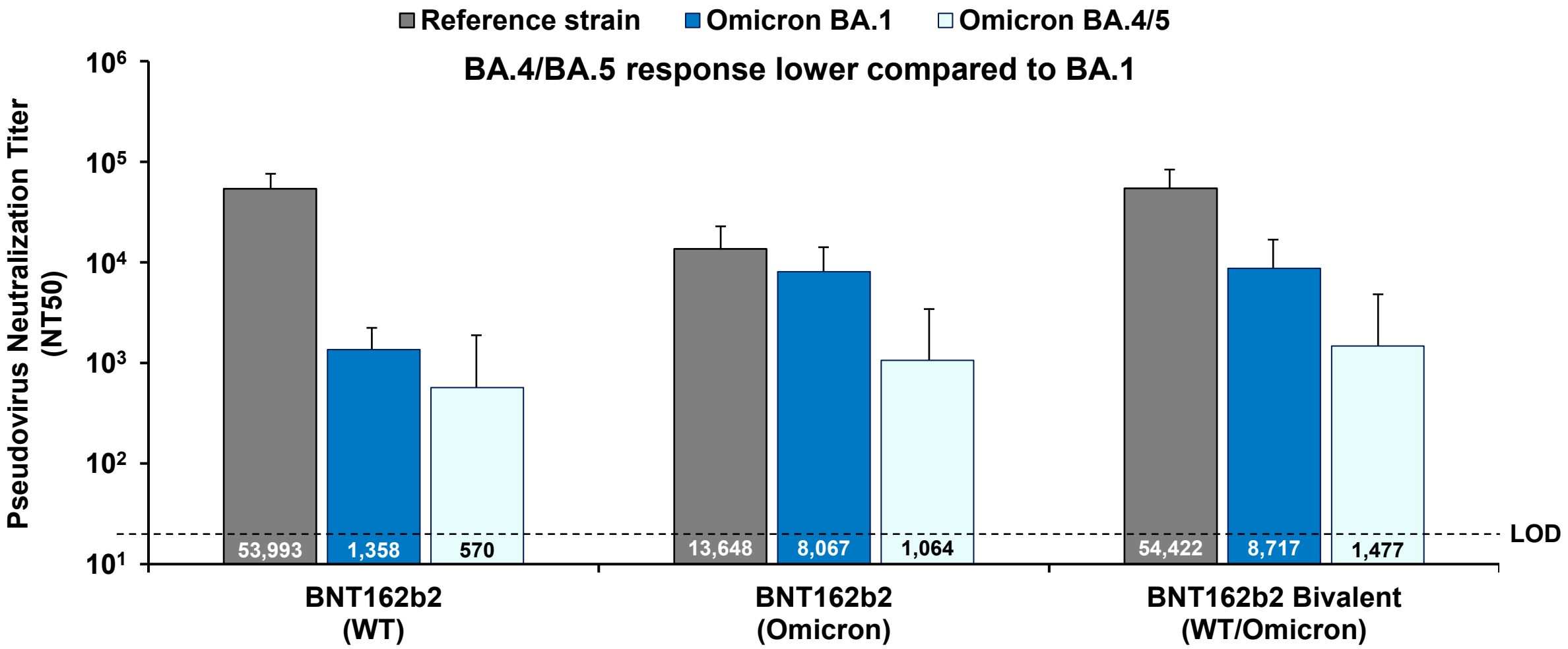
Participants WITHOUT Evidence of Infection up to 1 Month After First Study Vaccination



FFRNT, fluorescent foci reduction neutralization test; LOD, Limit of Detection

Similar to Clinical Data, Omicron Monovalent and Bivalent Booster in Mice Increases Omicron Neutralization Response; Continued Trend for Reduced BA.4/BA.5 Neutralization Compared to BA.1

1M Post 3rd Dose Booster Following 2 Doses of BNT162b2

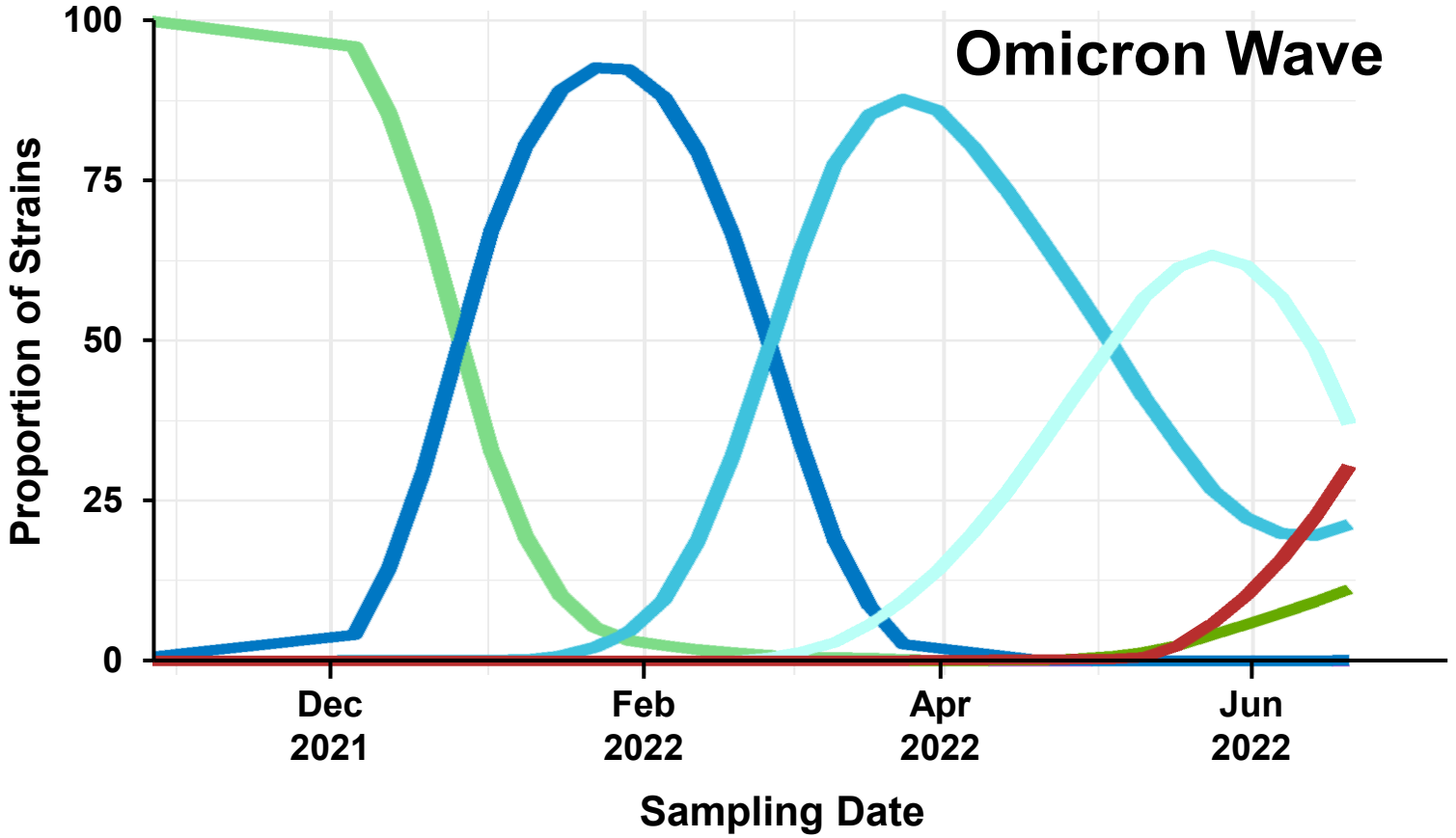


Pseudovirus neutralization assay; LOD, Limit of Detection; Reference strain, Wuhan-Hu-1

SARS-CoV-2 Epidemiology Changes Quickly – Vaccine Updates Need to Adapt with the Pace of the Virus

Variant Vaccine Update Pathway

Clinical (current)	~8 months
Pre-clinical/CMC (proposed)	~3 months



USA Circulating Strains

- Delta
- Omicron BA.1
- Omicron BA.2
- Omicron BA.2.12.1
- Omicron BA.4
- Omicron BA.5

GISAID data as of June 24, 2022

Conclusions

EUA criteria met for Omicron-containing vaccines for both monovalent and bivalent as booster

- **Extensive clinical experience for variant-modified vaccines demonstrating safety and effectiveness**
- **Request permissiveness to update if needed to address BA.4/BA.5, or other future variant, based on preclinical effectiveness data, together with appropriate CMC data for updated vaccine**

Pfizer/BioNTech COVID-19 Vaccine and Candidate Variant-modified Vaccine

Vaccines and Related Biological Products Advisory Committee

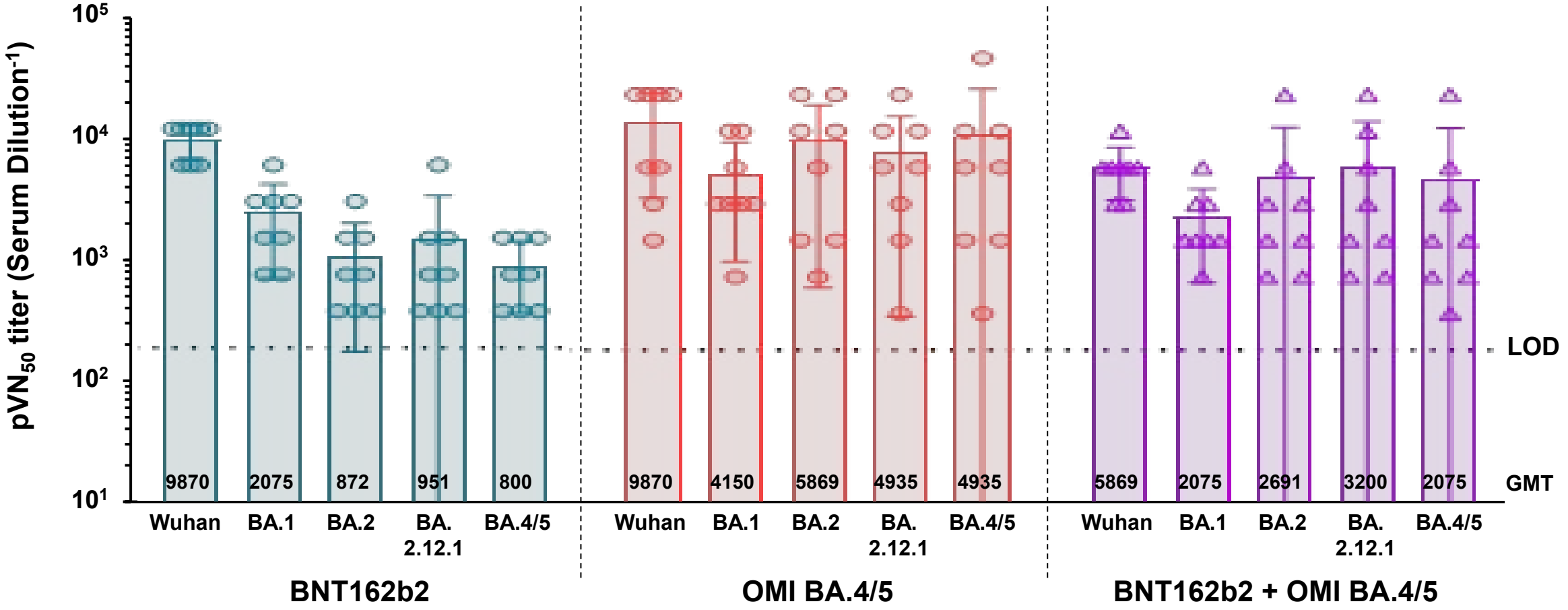
June 28, 2022

CC-23

Backup Slides Shown

Omicron BA.4/5 Monovalent and Bivalent Boosters in Mice Substantially Increase Omicron Neutralization Responses to all Omicron Variants Including BA.4/5 and Reference Strain

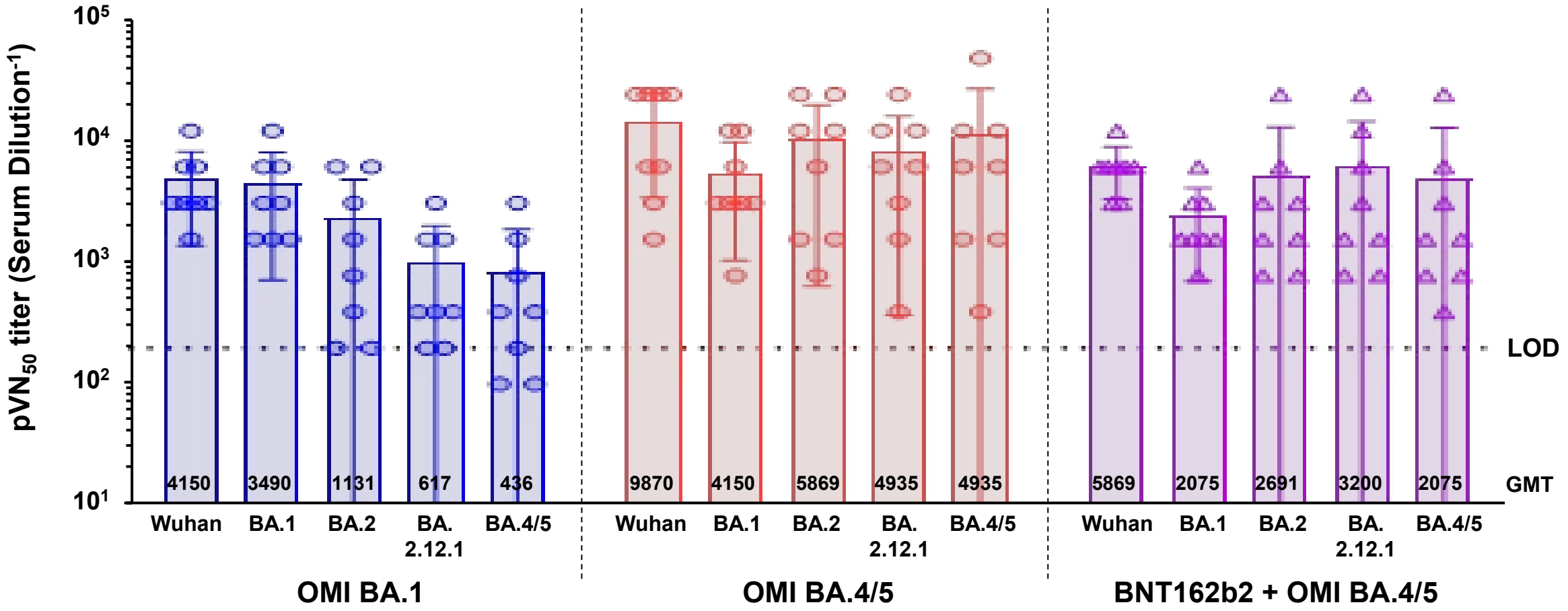
Compared to BNT162b2 Neutralizing BA.4/5 titers increase by ~6.2 fold [mono BA.4/5] or ~2.6 fold (bivalent BA.4/5)



N=8 mice Balb/c mice. Mice preimmunized with 2 doses of BNT162b2; boosters given at day 104
Pseudovirus neutralization assay; LOD, Limit of Detection

Omicron BA.4/5 Monovalent and Bivalent Boosters in Mice Substantially Increase Omicron Neutralization Responses to all Omicron Variants Including BA.4/5 and Reference Strain

Compared to Monovalent OMI BA.1, BA.4/5 neutralizing titers increase by ~11.3 fold [mono BA.4/5] or ~4.8 fold (bivalent BA.4/5)



N=8 mice Balb/c mice. Mice preimmunized with 2 doses of BNT162b2; boosters given at day 104
Pseudovirus neutralization assay; LOD, Limit of Detection