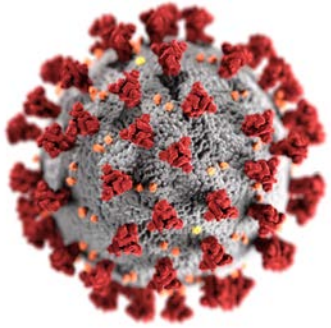
The twist and turns of COVID-19 pandemic: antibody-mediated immunity against SARS-CoV-2 variants

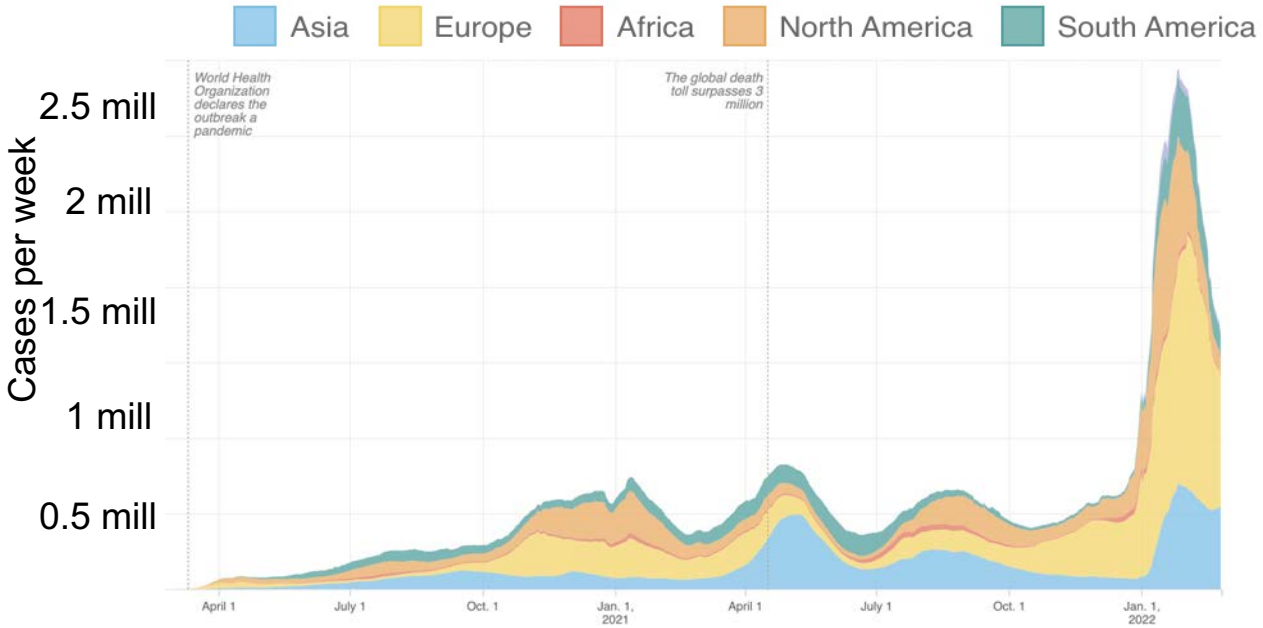
Los Angeles City Health Commission Special Meeting

Fikadu G. Tafesse, PhD
Oregon Health & Science University



February 28, 2022

COVID-19: Global pandemic



Global

USA

Coronavirus World Map: Tracking The Spread Of The Outbreak : Goats and Soda : NPR. https://www.npr.org/sections/goatsandsoda/2020/03/30/822491838/coronavirus-world-map-tracking-the-spread-of-the-outbreak.

John Hopkins University COVID-19 Dashboard https://coronavirus.jhu.edu/map.html

Humoral immune responses elicited by natural infection and/or vaccination: paths to super-immunity?

SARS-CoV-2 variants contain numerous spike mutations

Cohorts description

Convalescent serum donors

Characteristic	Total ($N = 50$)
Median age - year (range)	56 (1-88)
Sex - no. (%)	
Female	29 (58)
Male	21 (42)
Symptomatic - no. (%)	
No	4 (8)
Yes	46 (92)
Hospitalized - no. (%)	
No	34 (68)
Yes	16 (32)
Admitted to ICU (subset of hospitalized) - no. (%)	
No	12 (22.2)
Yes	5 (9.25)
Median time between first positive COVID-19 PCR test and sample collection - days (range)	188.5 (1-302)

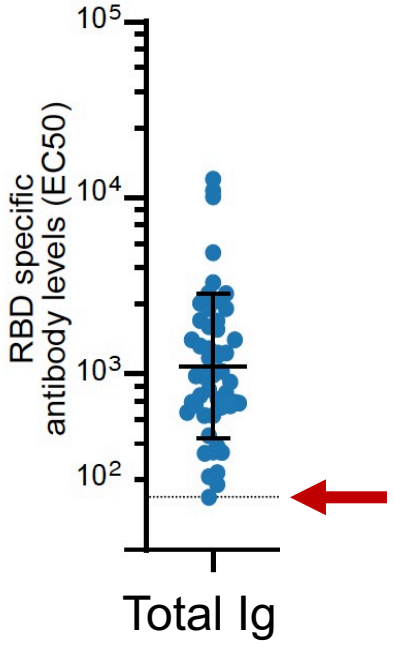
BNT162b2/Pfizer vaccinated donors

Characteristic	Total ($N = 51$)
Median age - year (range)	50 (21-82)
Sex - no. (%)	
Female	28 (54.9)
Male	23 (45.1)
Median time between vaccine doses - days (range)	21 (20-22)
Median time between second dose and sample collection - days (range)	14 (14-15)

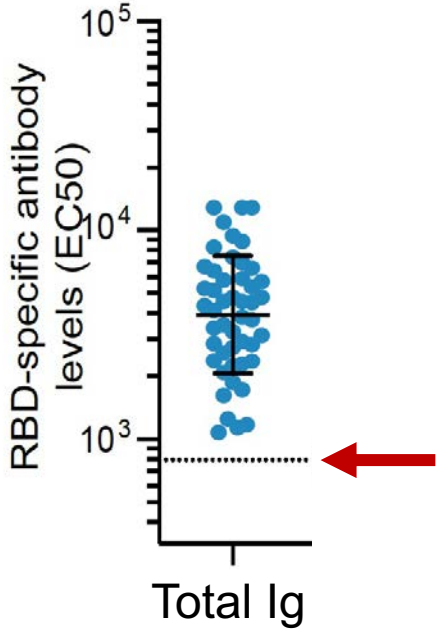
While vaccination induces robust antibody responses, natural infection is highly variable

Antibody levels (ELISA)

Natural infection



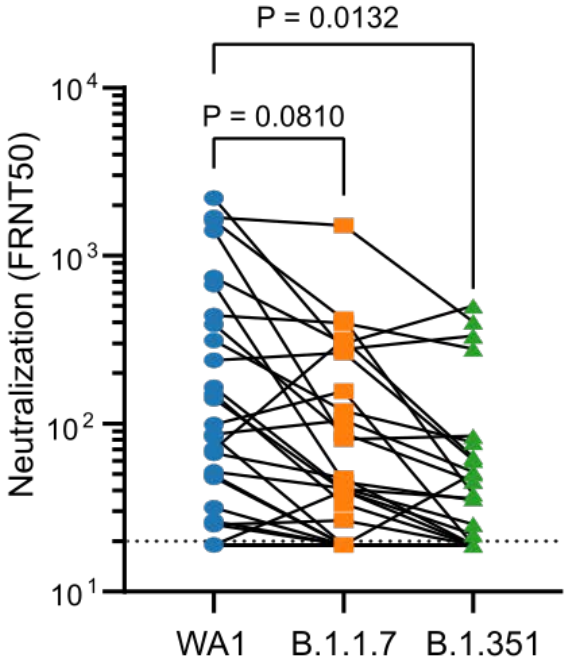
Pfizer Vaccine



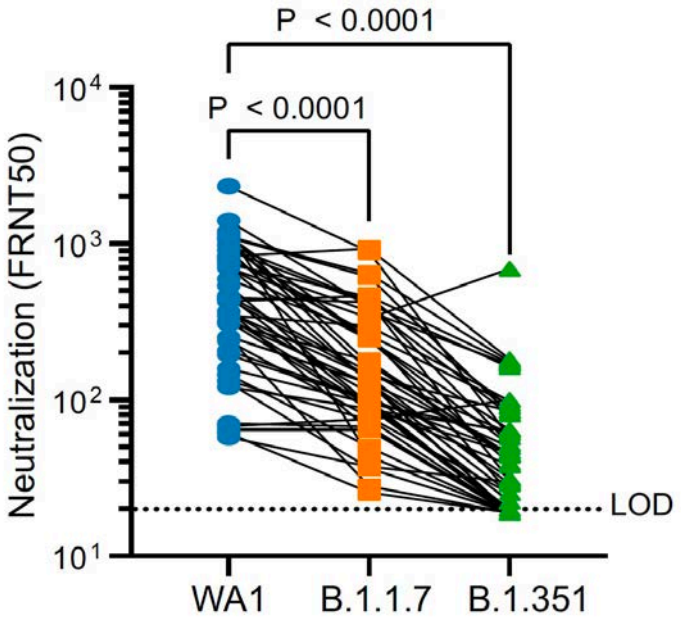
Bates et al., Nature Communications, 2021

Neutralization- FRNT50 (live SARS-CoV-2 variants)

Natural infection



Vaccine

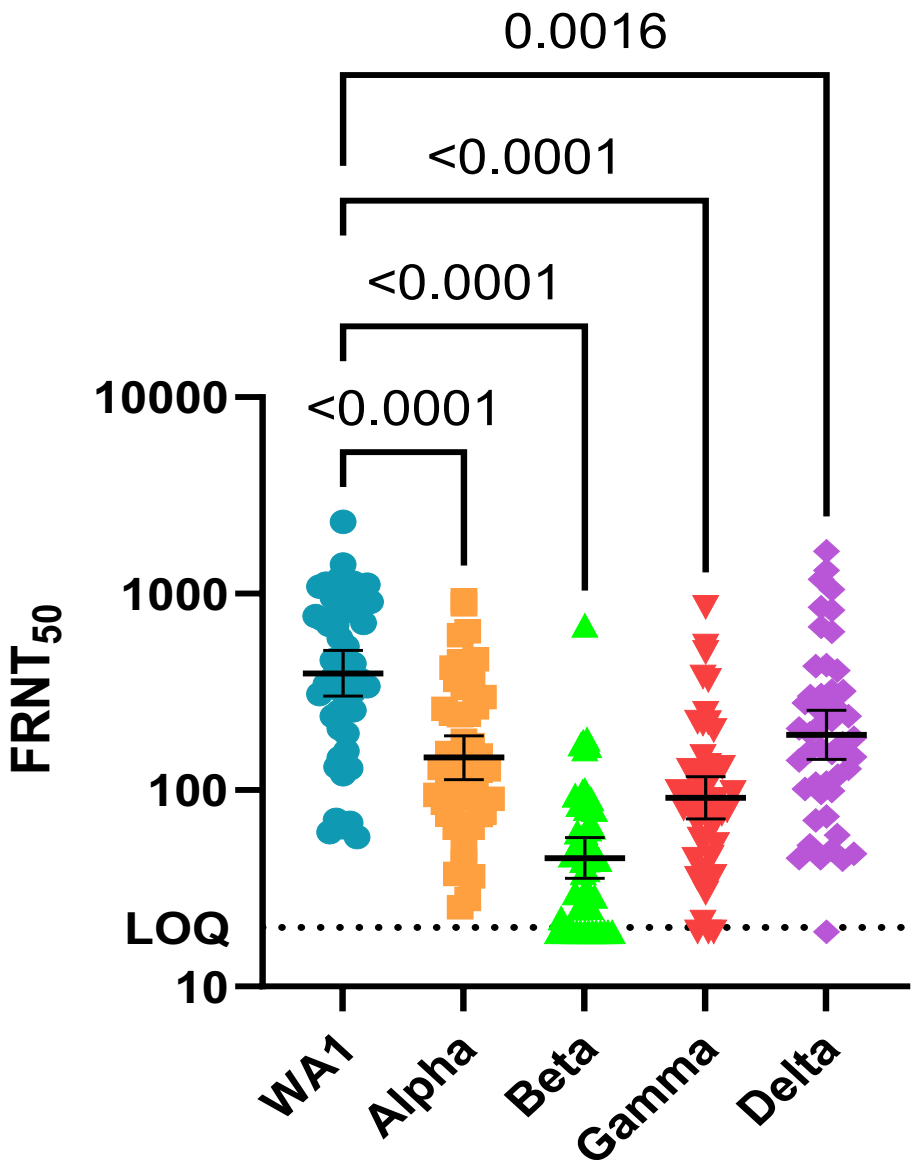


Original (Wuhan- WA1)
Alpha (B.1.1.7)
Beta (B.1.351)

Many COVID-19 patient sera fell below the limit of detection (LOD): WA1, 43%; Alpha (B.1.1.7), 54%; Beta (B.1.351), 64%

Bates et al., Nature Communications, 2021

Neutralization against variants of concern (vaccine cohort)



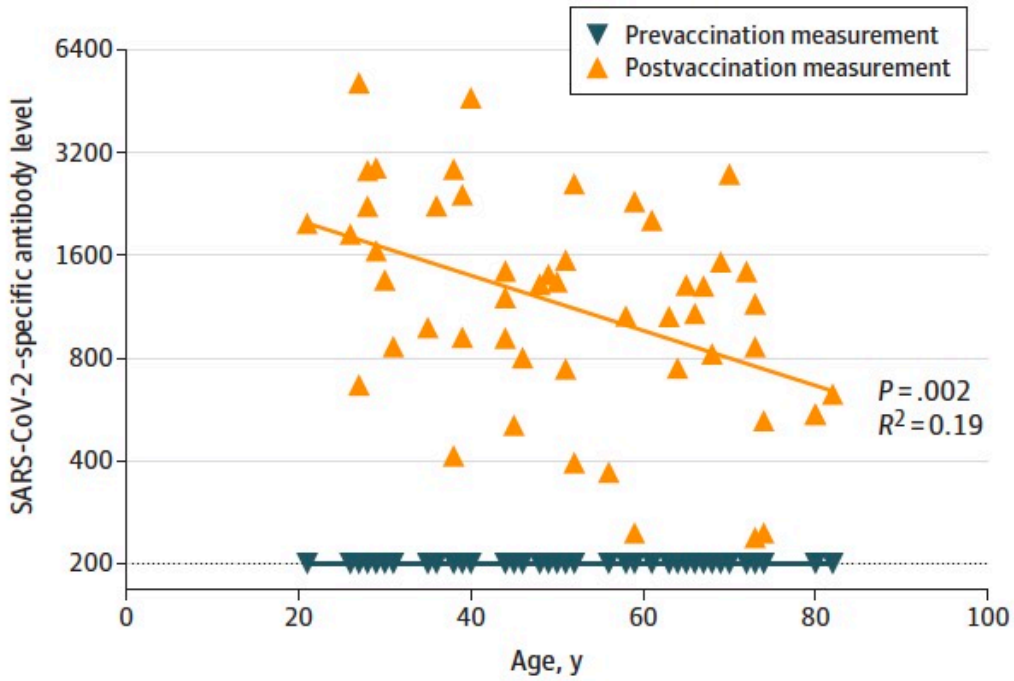
Variant

WA1	Alpha	Beta	Gamma	Delta
392.5	146.3	45.16	91.41	191.3
1x	**-2.6x**	**-9x**	**-4x**	**-2x**

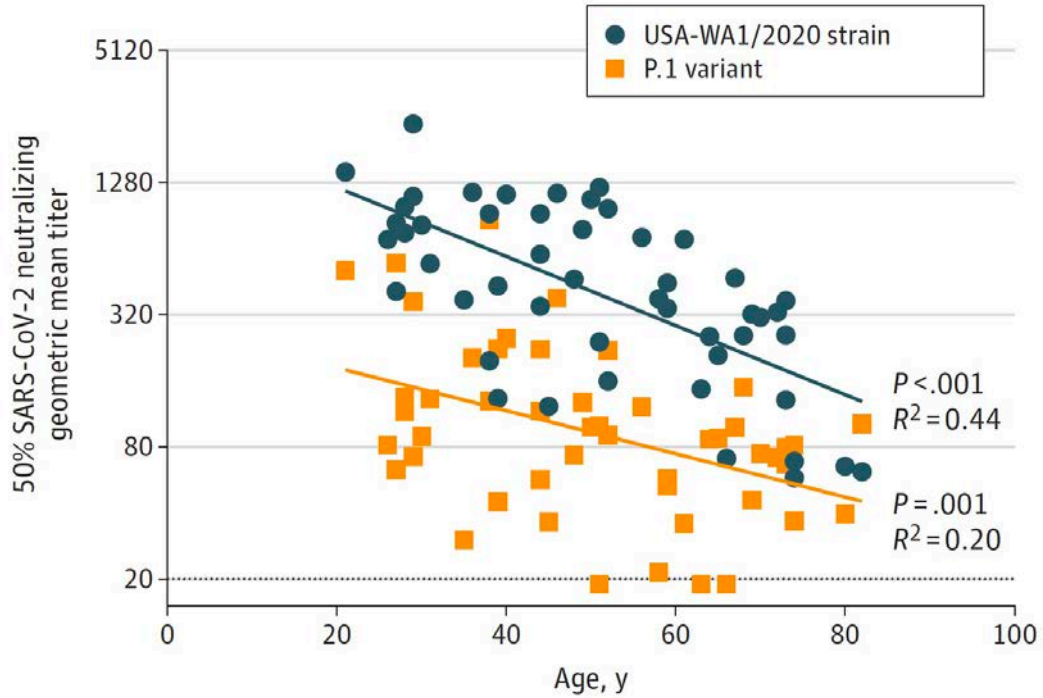
Bates et al., Nature Communications, 2021
Bates et al., JAMA, 2021

Age-dependent antibody and neutralization responses

Antibody levels



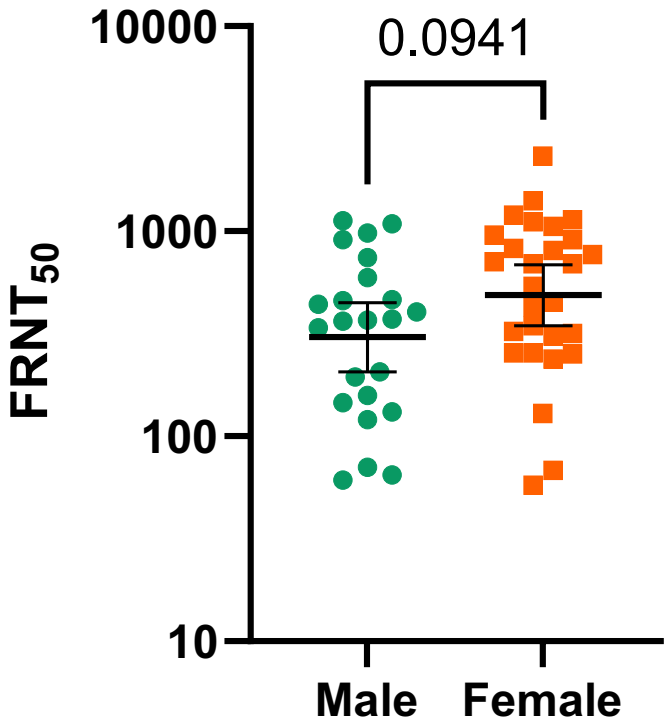
Neutralization



20s vs 70s: ~7x

Bates et al., JAMA, 2021

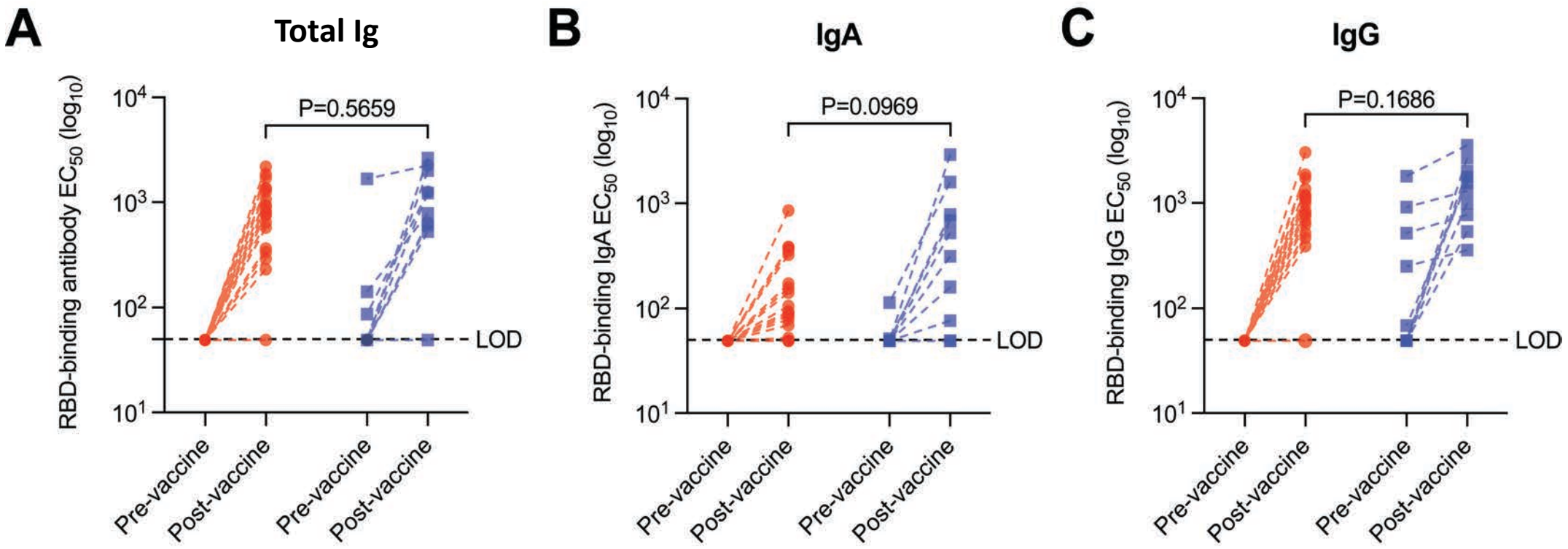
Sex vs neutralization in vaccine response



Bates et al., Nature Communications, 2021

Vaccination after natural infection

Antibody levels (ELISA)



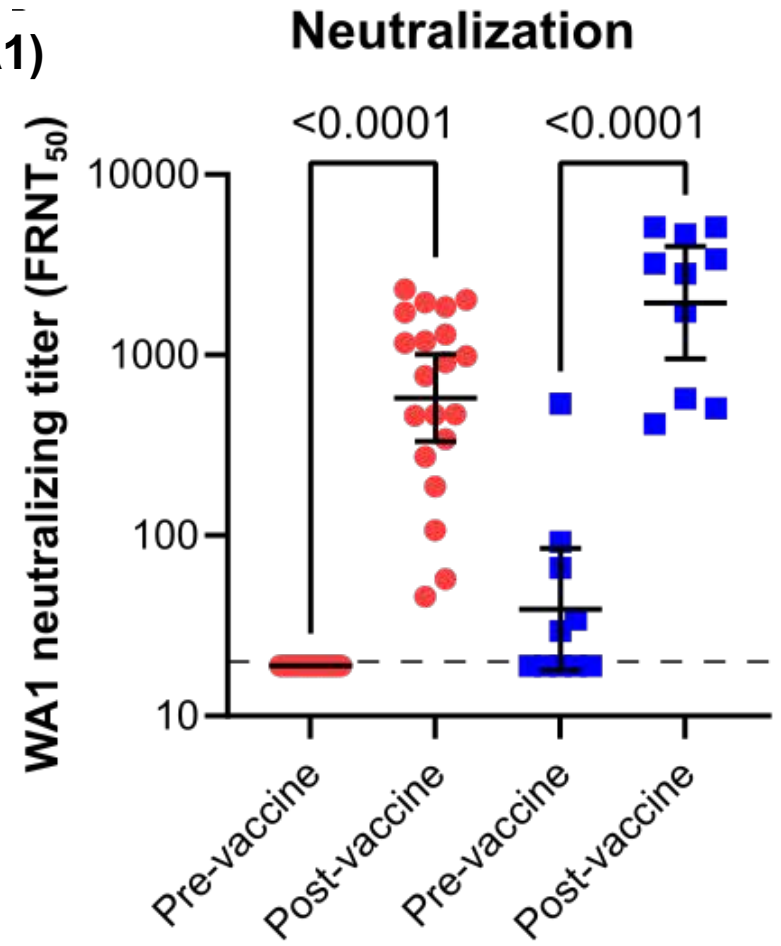
No history of infection

Previously infected

Hans et al., bioRxiv, 2021

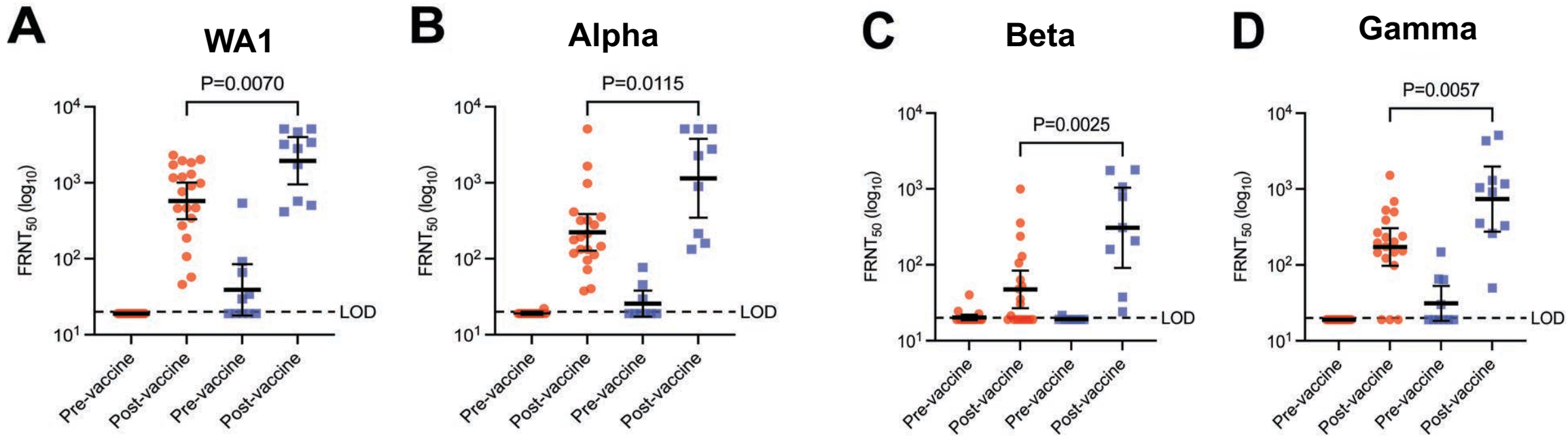
Vaccination after natural infection significantly improves neutralization

Original strain (Wuhan- WA1)



Hans et al., bioRxiv, 2021

Vaccination after natural infection significantly improves cross-variant neutralization



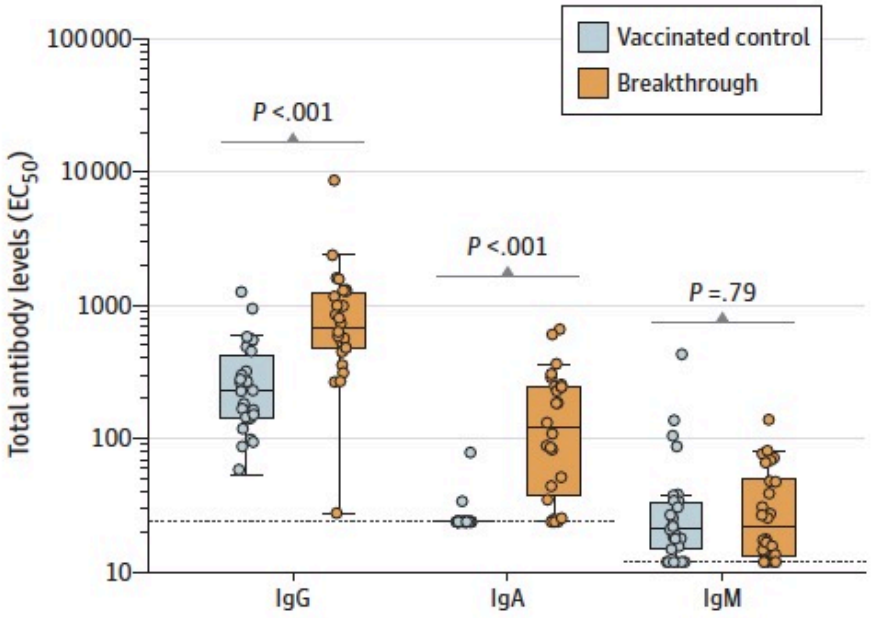
No history of infection

Previously infected

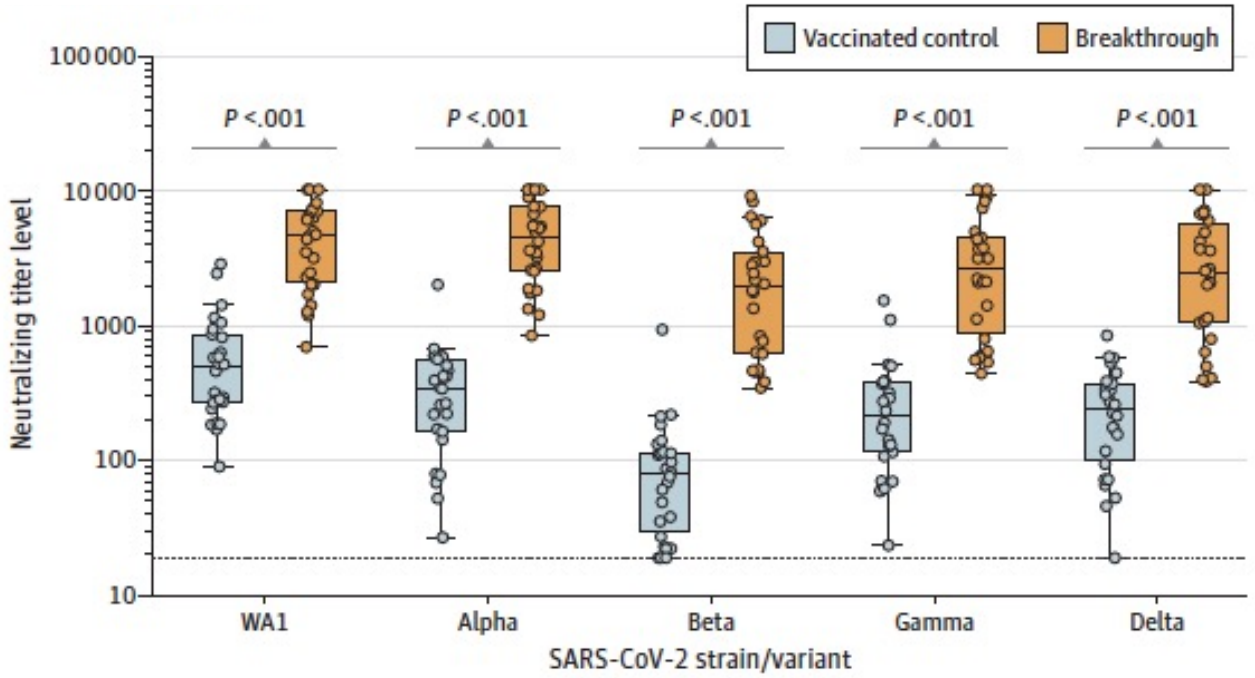
Hans et al., bioRxiv, 2021

Breakthrough infections provide enhanced response

Anti-spike RBD antibodies



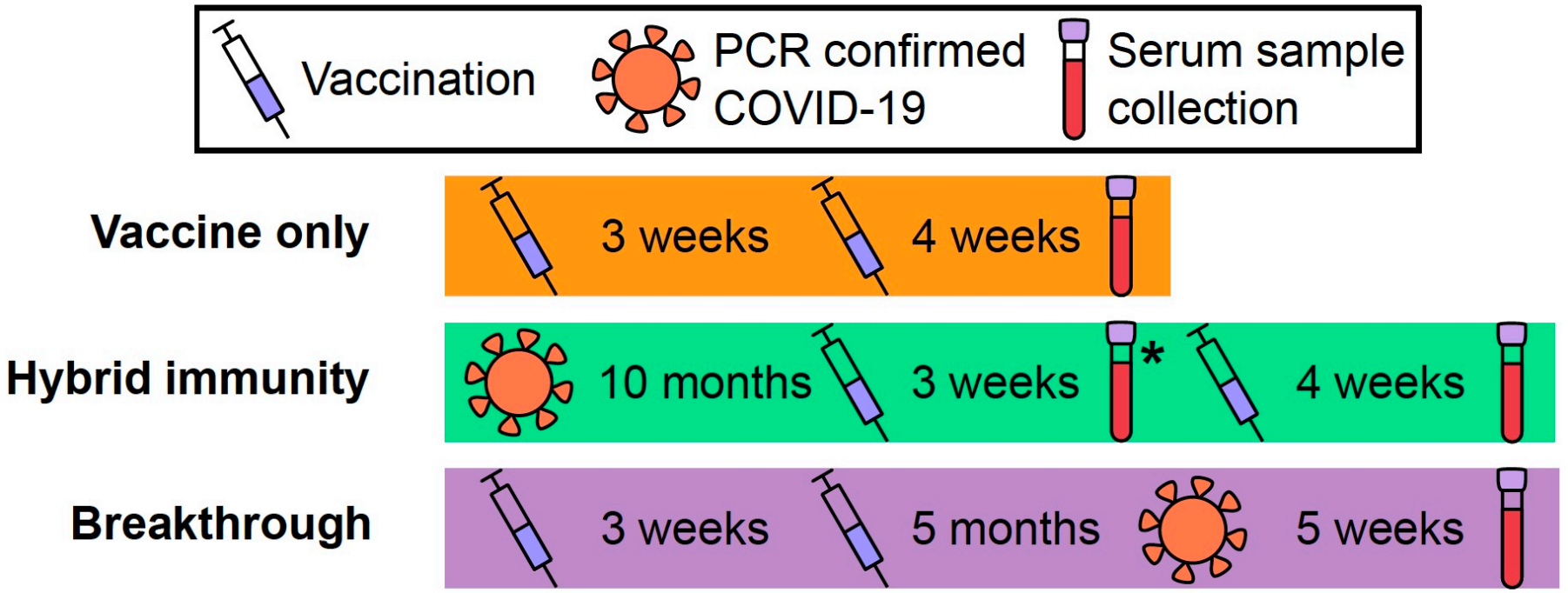
Neutralizing titer



Bates et al., JAMA 2022

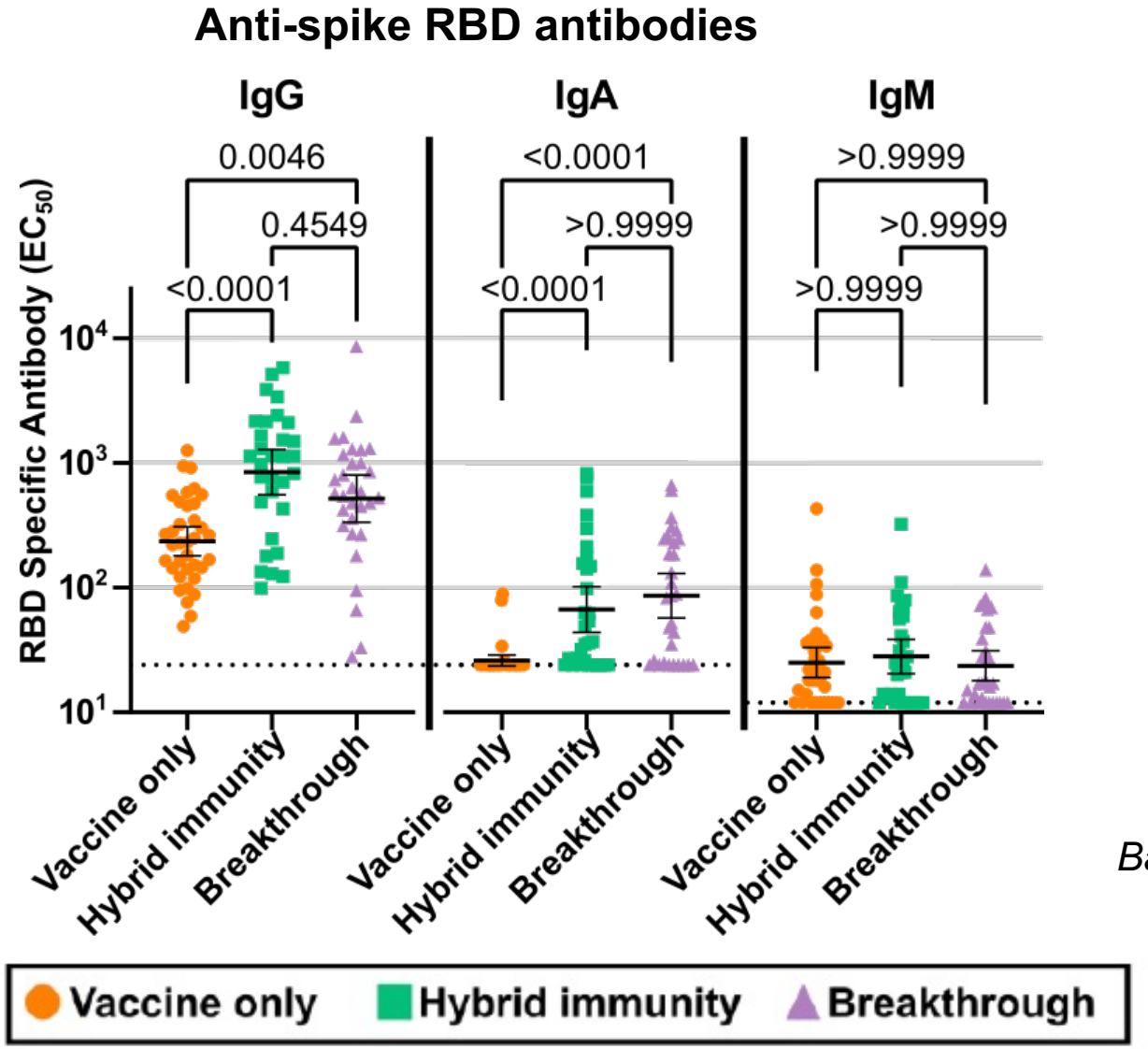
Vaccination before/after infection: does the order matter?

Study design



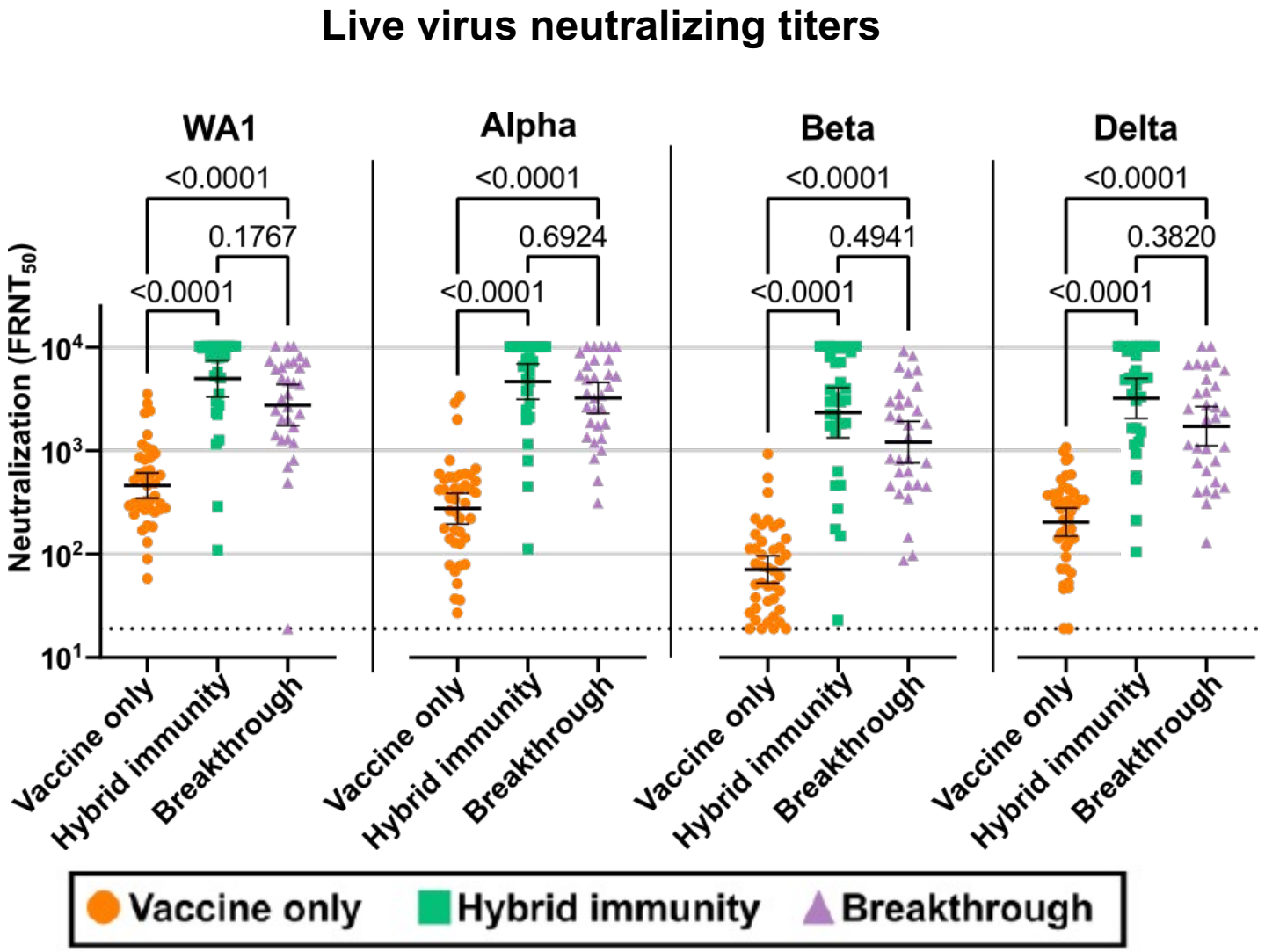
*6 hybrid immunity participants provided samples after only 1 vaccine dose

Let’s compare infection before/after vaccination: two paths to enhanced immunity



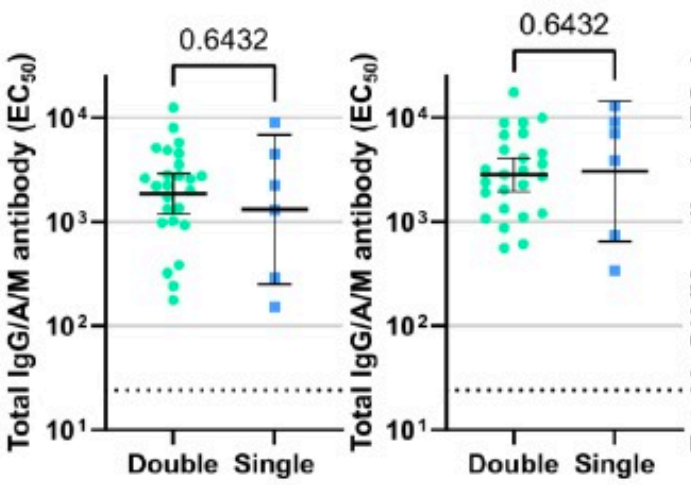
Bates et al., Science Immunology, 2022

Let’s compare infection before/after vaccination: two paths to enhanced immunity



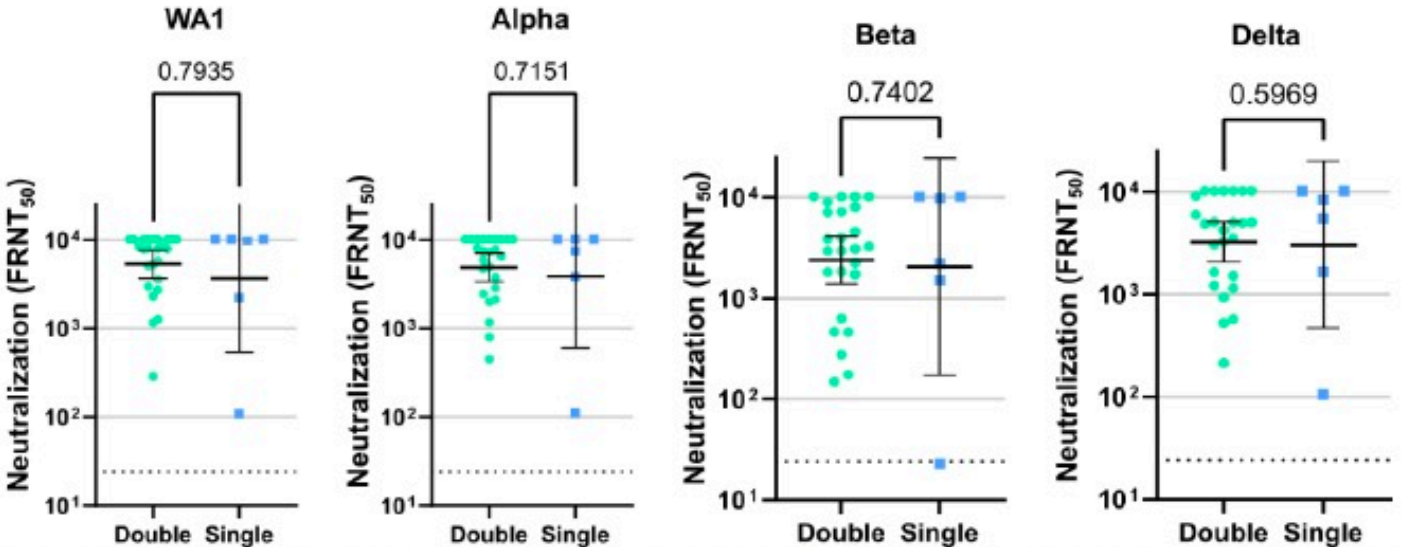
Hybrid immunity: one vs double dose

Anti-spike (RBD or full-length) antibodies

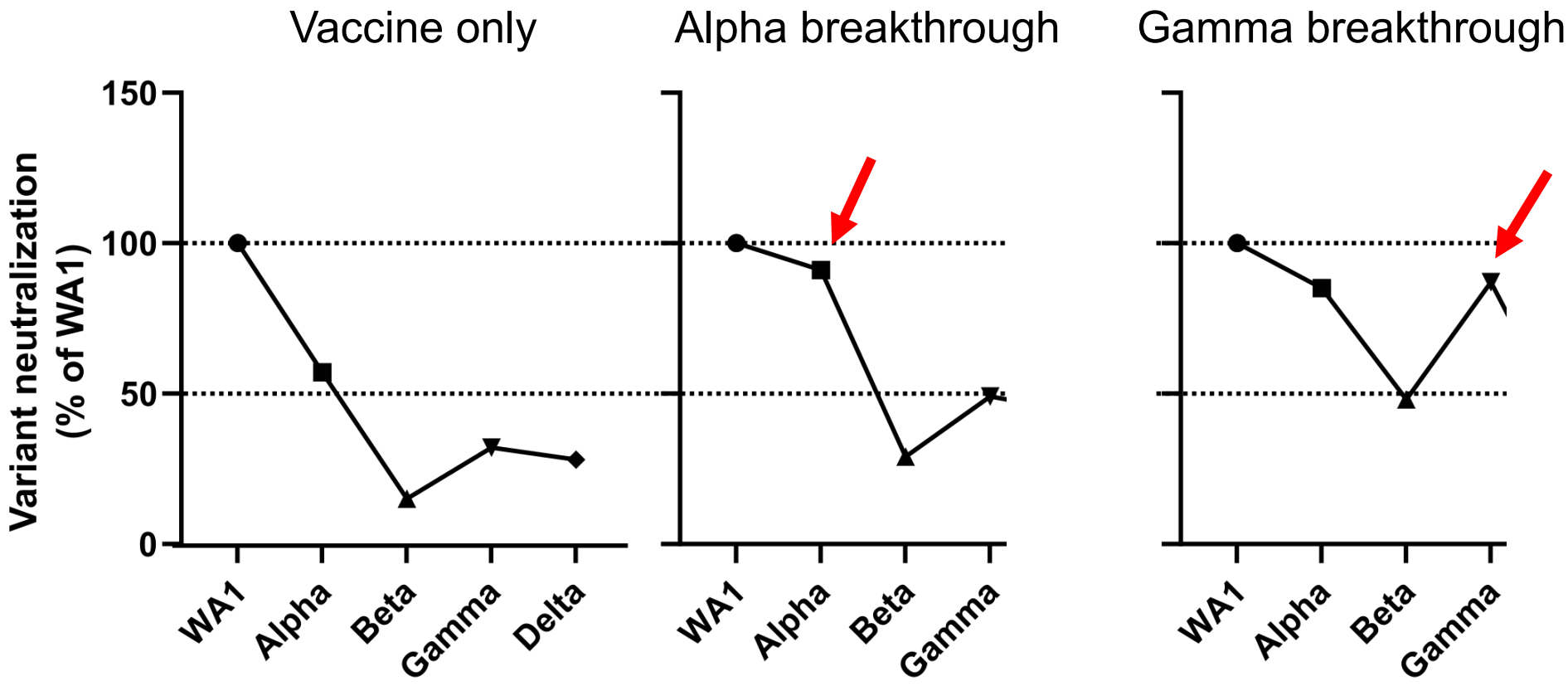


Bates et al., Science Immunology, 2022

Live virus neutralizing titers

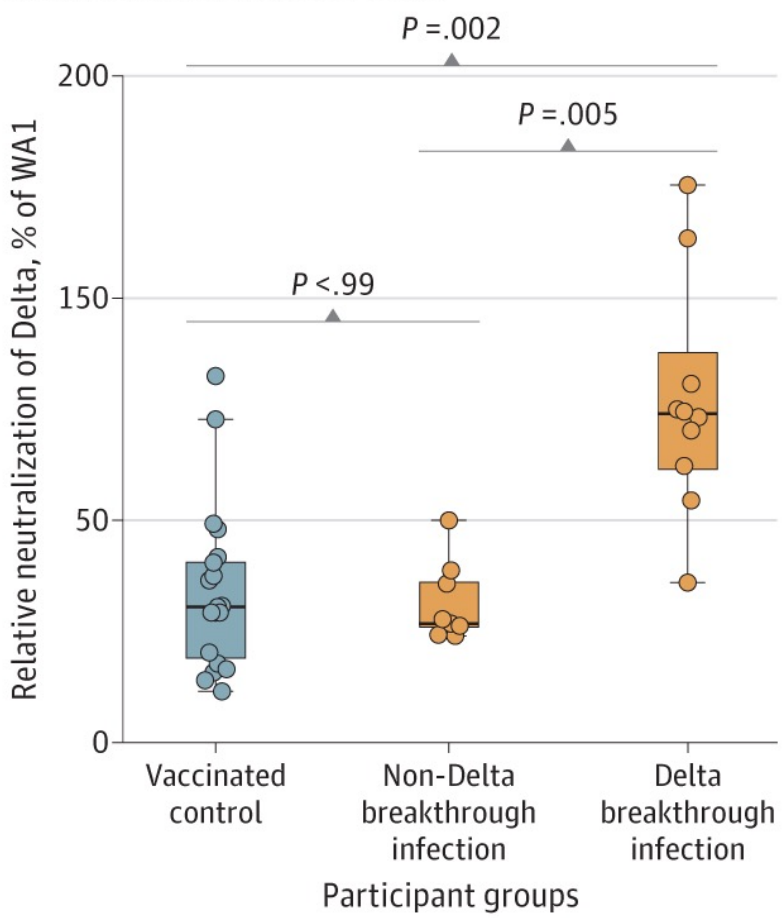


Variant specific enhanced responses by breakthrough



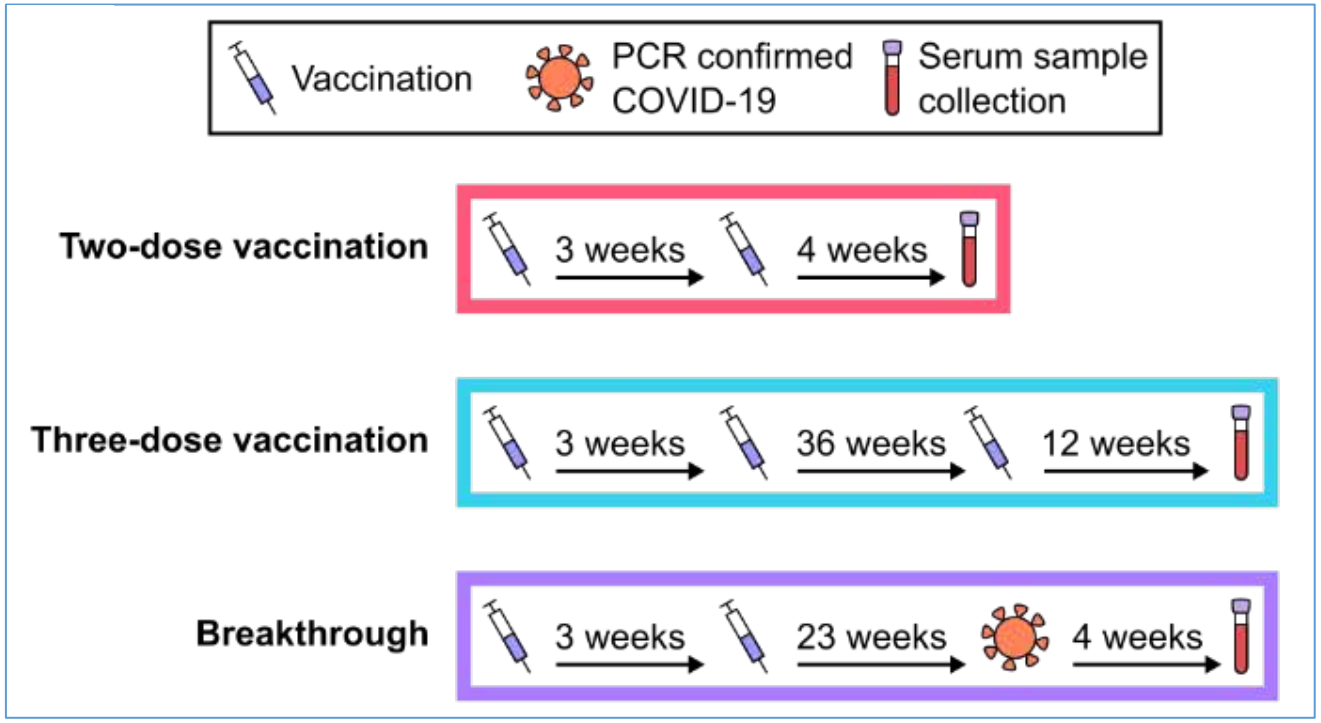
Variant specific enhanced responses by breakthrough

Relative neutralization of Delta by Delta breakthroughs

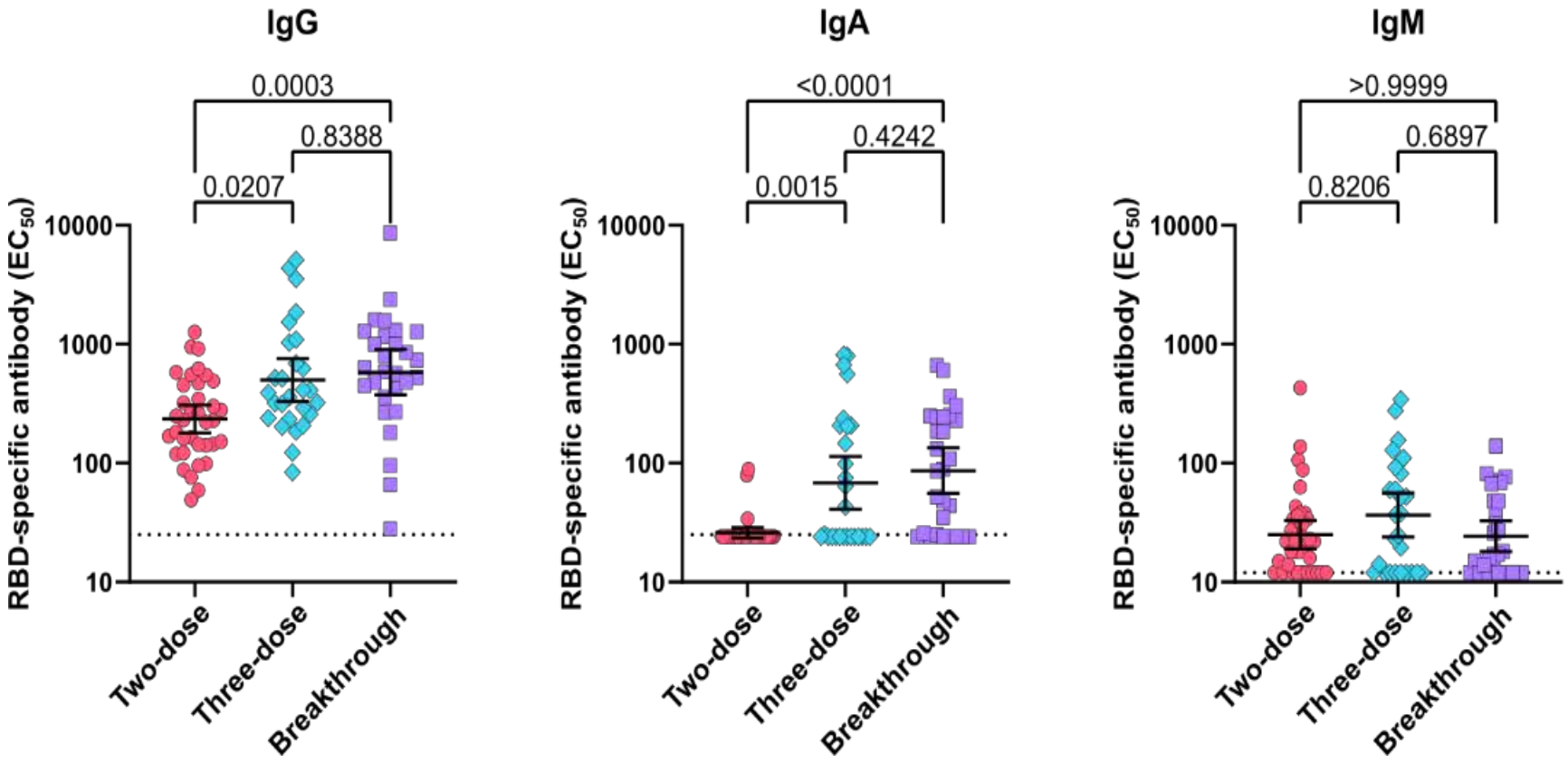


What about three-dose vaccination vs breakthroughs?

Study design



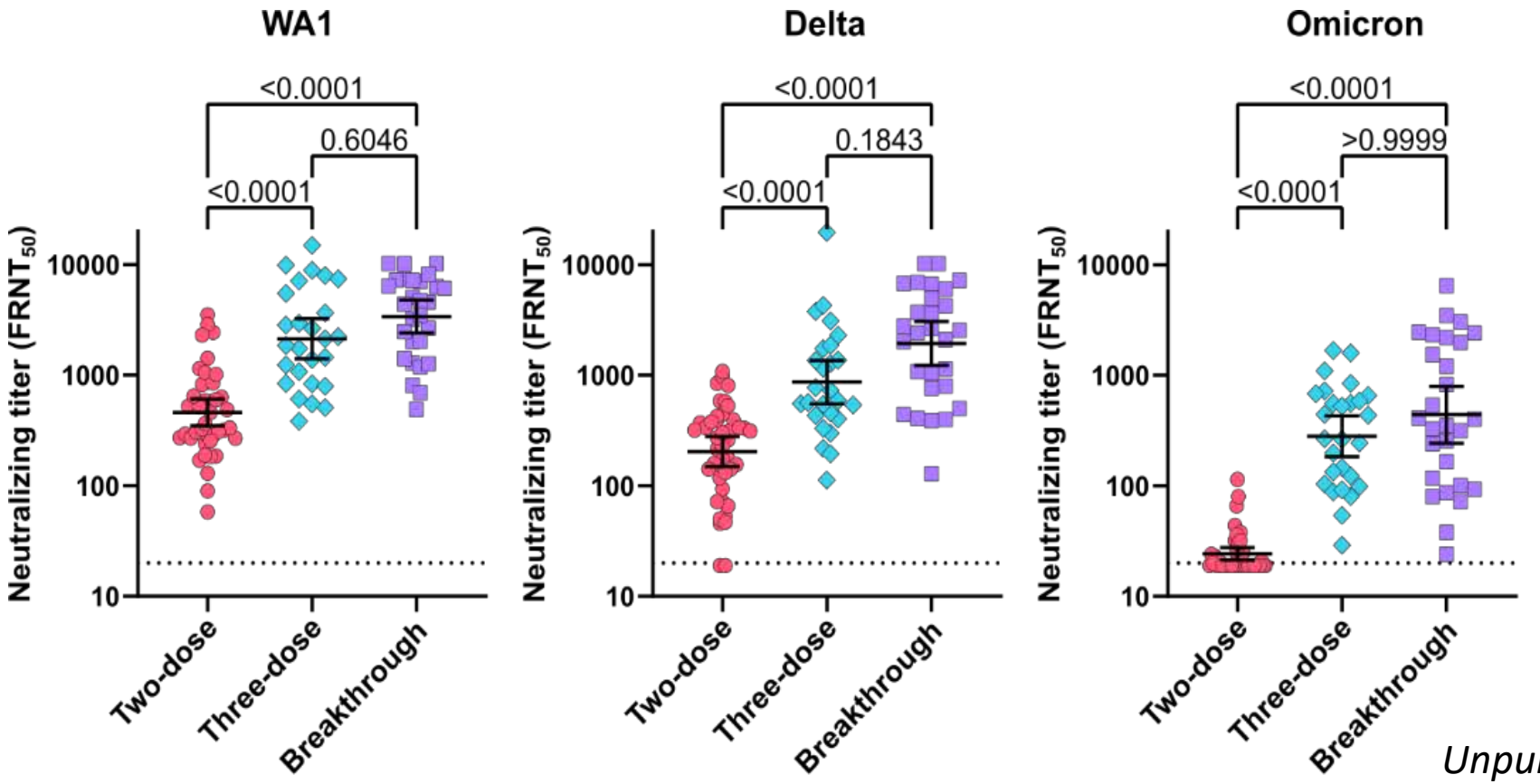
Third-dose vaccination improves antibody responses



Unpublished data

Third-dose vaccination improves Omicron neutralization

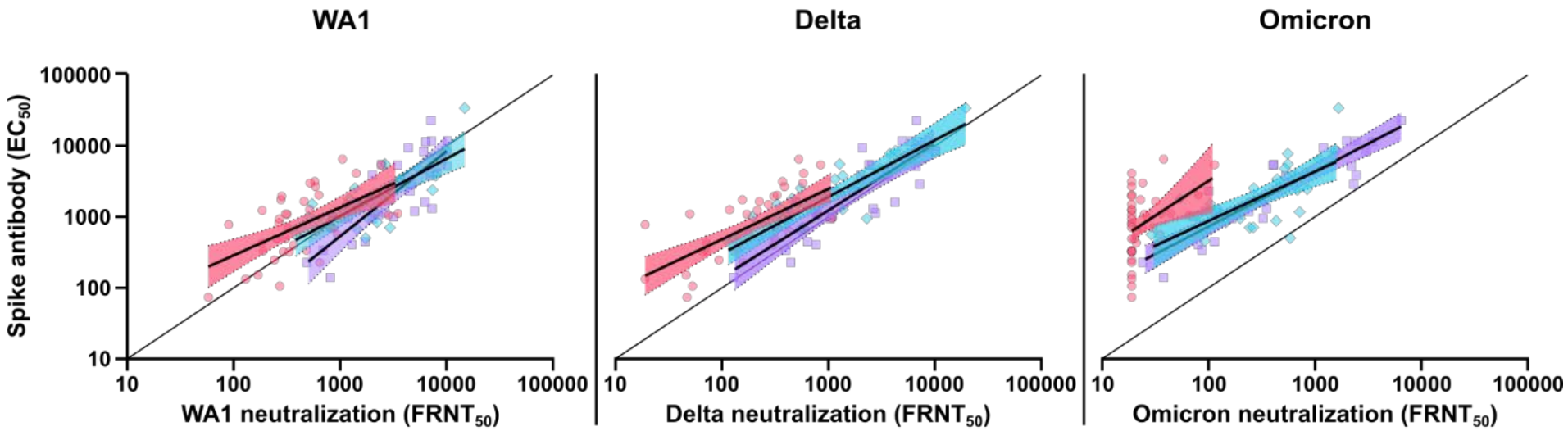
Live virus neutralizing titers



Unpublished data

Third-dose vaccination improves antibody responses

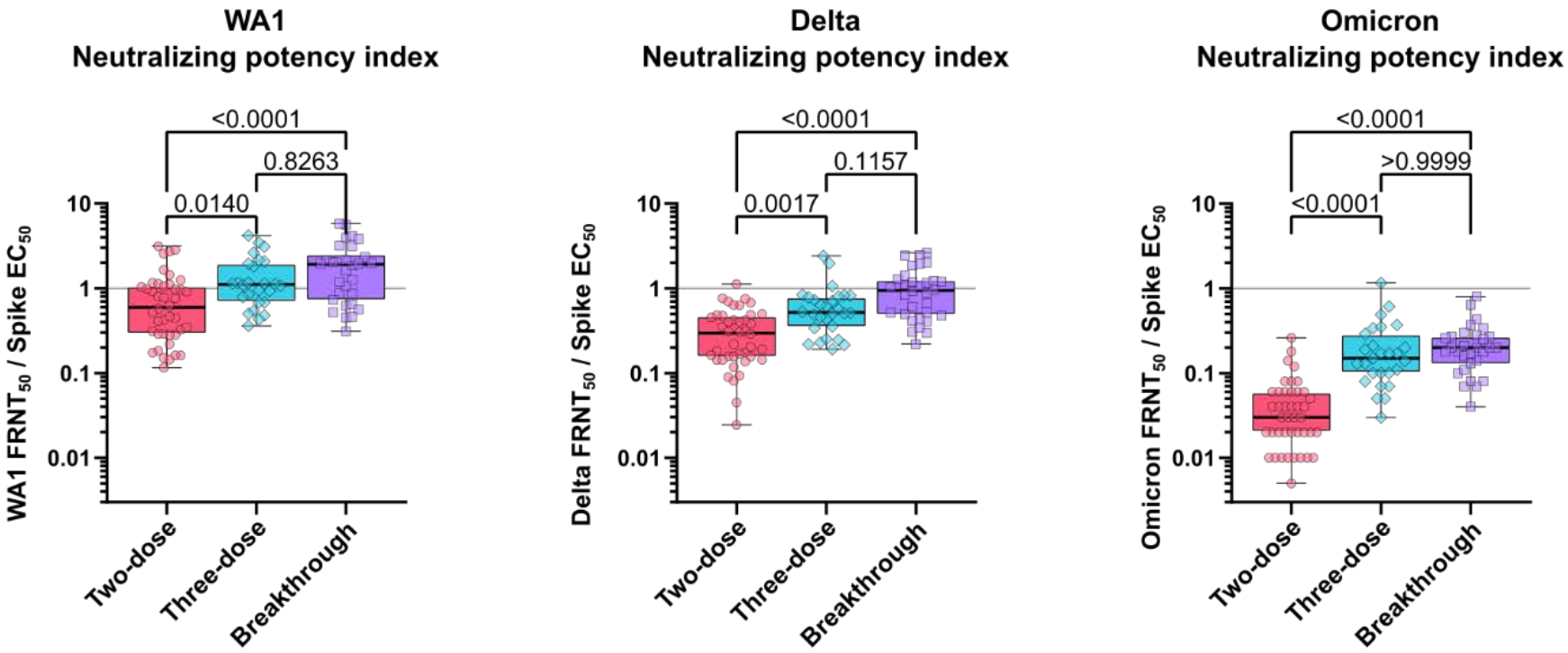
Correlation of full-length spike-binding antibody EC_{50} with $FRNT_{50}$



Group		ρ	P		ρ	P		ρ	P
Two-dose	WA1	0.5431	0.0002	Delta	0.6618	<0.0001	Omicron	0.3304	0.0326
Three-dose	WA1	0.7121	<0.0001	Delta	0.7538	<0.0001	Omicron	0.6557	0.0002
Breakthrough	WA1	0.7672	<0.0001	Delta	0.8028	<0.0001	Omicron	0.8803	<0.0001

Unpublished data

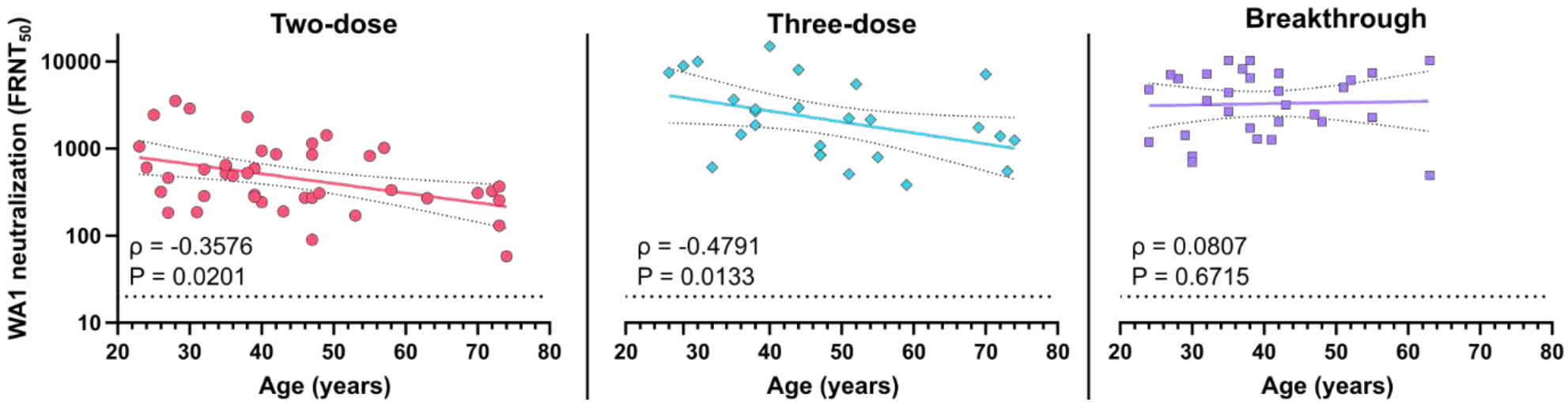
Third-dose vaccination improves antibody potency



Neutralizing potency index: the ratio of neutralizing titer ($FRNT_{50}$) to spike binding EC_{50} values

Unpublished data

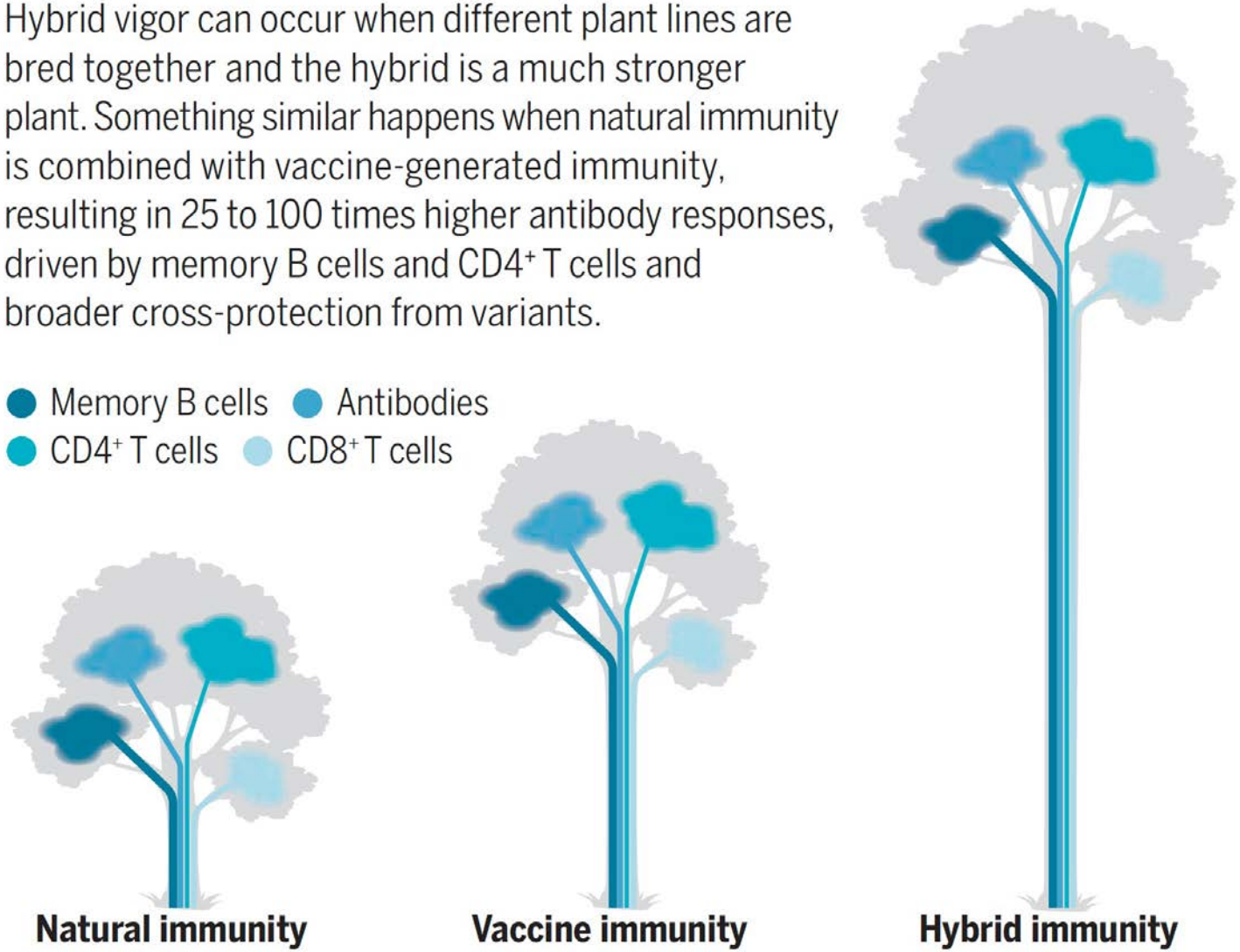
Third-dose vaccination vs age



Unpublished data

Hybrid vigor immunity with COVID-19 vaccines

Hybrid vigor can occur when different plant lines are bred together and the hybrid is a much stronger plant. Something similar happens when natural immunity is combined with vaccine-generated immunity, resulting in 25 to 100 times higher antibody responses, driven by memory B cells and $CD4^+$ T cells and broader cross-protection from variants.



Crotty, *Science* 2021

Conclusions

- Getting vaccinated leads to more neutralizing antibodies than natural infection
- The response to natural infection is highly variable
- Age-dependent response of antibody/neutralizations
- A combination of vaccination and natural infection gives the greatest response

Acknowledgements

Study participants

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OHSU COVID-19
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(Drs. Andrew Adey,
Benjamin Bimber, Brian
O'Roak)

MMI faculty

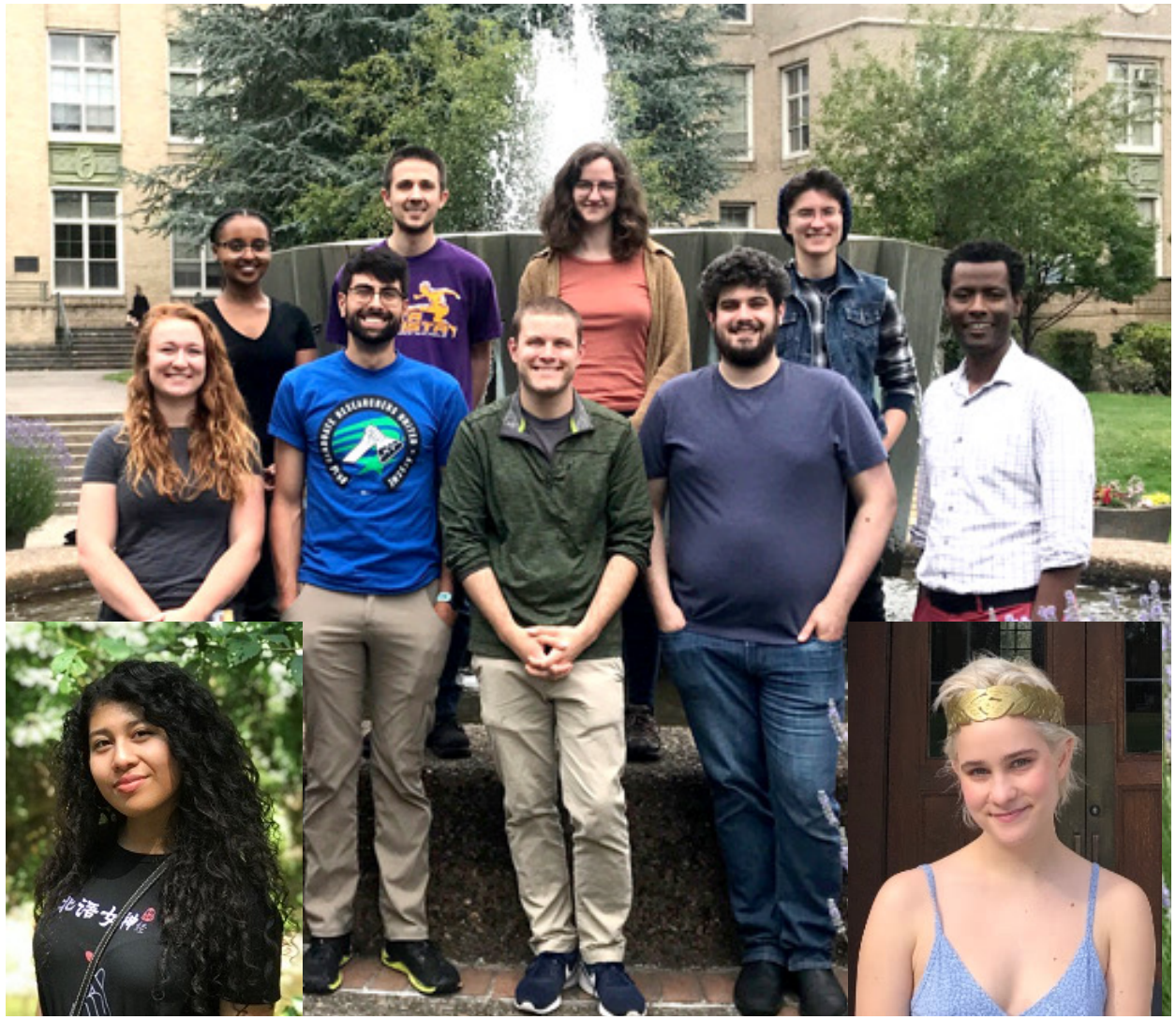
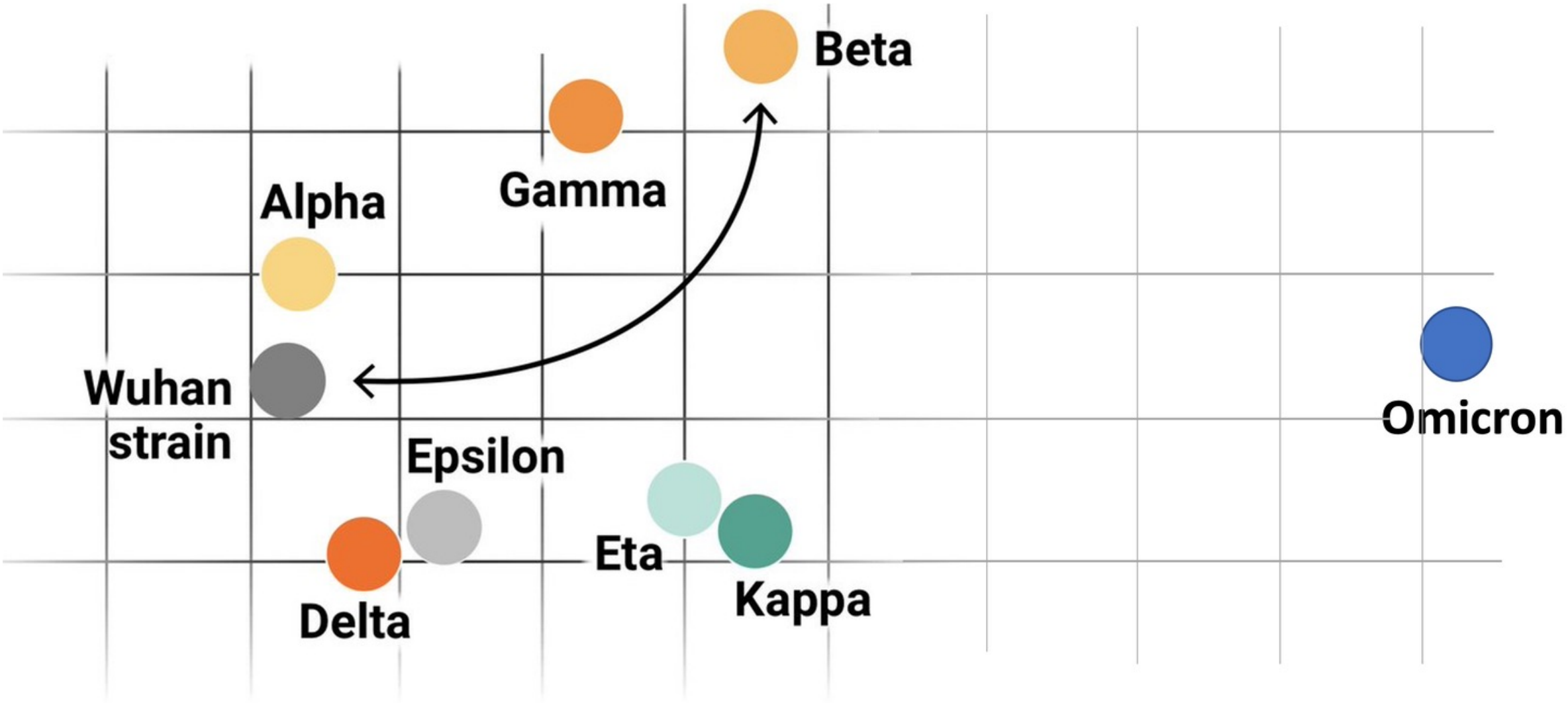


Table 1. Effectiveness of Previous Infection with SARS-CoV-2 against Symptomatic Reinfection, According to Variant.*

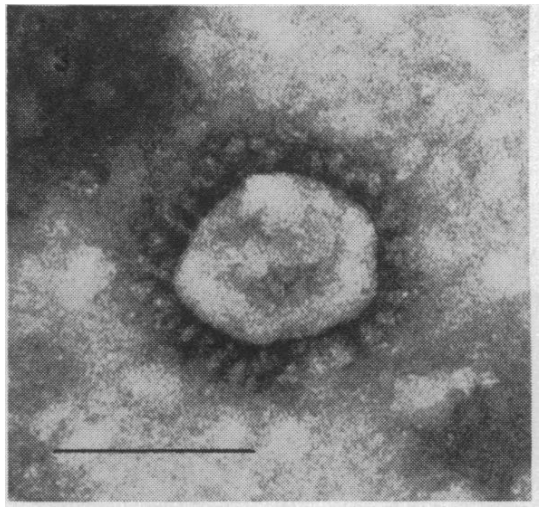
Type of Analysis and Variant	Cases (PCR-Positive)		Controls (PCR-Negative)		Effectiveness (95% CI)†
	Previous Infection	No Previous Infection	Previous Infection	No Previous Infection	
	number of patients				*percent*
Effectiveness against symptomatic infection					
Primary analysis‡					
Alpha	2	334	94	1548	90.2 (60.2 to 97.6)
Beta	14	1322	450	6084	85.7 (75.8 to 91.7)
Delta	23	2153	1154	8782	92.0 (87.9 to 94.7)
Omicron	412	5284	1620	9053	56.0 (50.6 to 60.9)

Altarawneh et al., NEJM 2022 (study from Qatar)



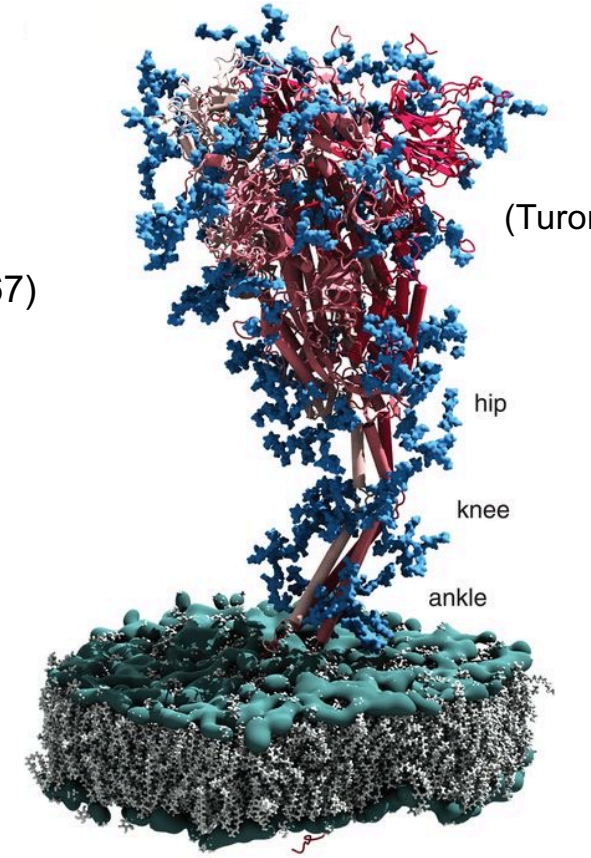
Kai Kupferschmidt, Science 2022

An abridged history of coronaviruses



Almeida JD, Tyrrell, DAJ (1967)

McIntosh et al., 1967



(Turoňová et al., 2020)