Need for a pan-sarbecovirus vaccine?

What are the challenges

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Janssen Pharmaceuticals of Johnson & Johnson
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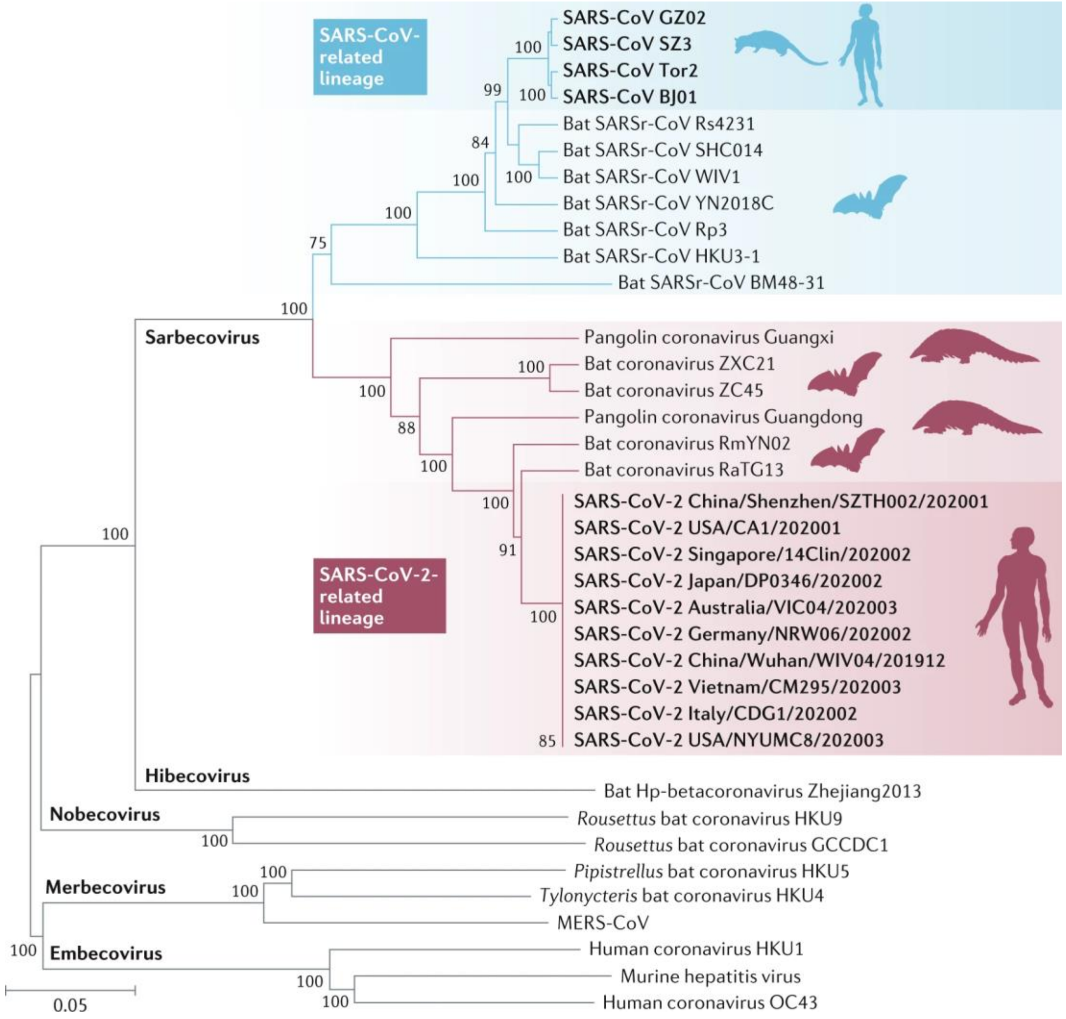
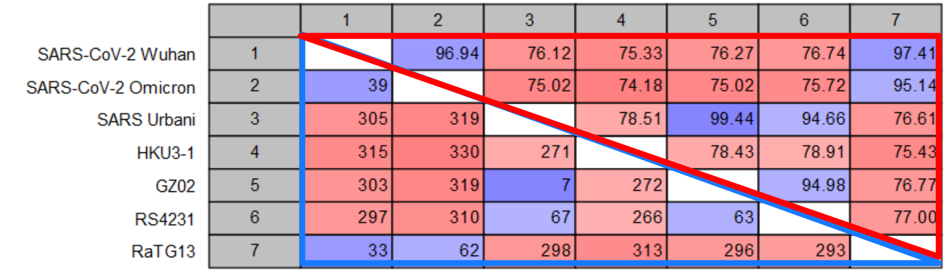
Sarbecovirus phylogenetic relationships



https://www.nature.com/articles/s41579-020-00459-7

Complete spike

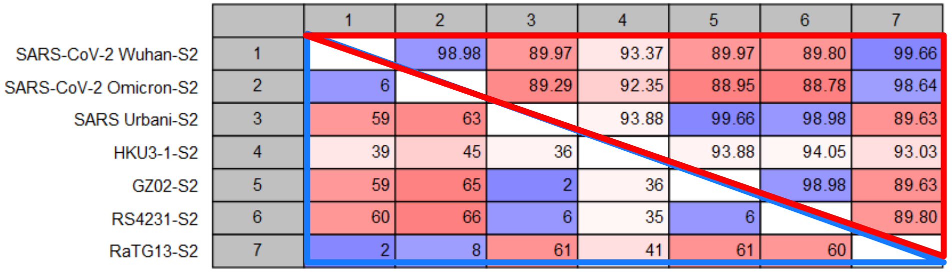


% identity

		1	2	3	4	5	6	7
SARS-CoV-2 Wuhan	1		96.94	76.12	75.33	76.27	76.74	97.41
SARS-CoV-2 Omicron	2	39		75.02	74.18	75.02	75.72	95.14
SARS Urbani	3	305	319		78.51	99.44	94.66	76.61
HKU3-1	4	315	330	271		78.43	78.91	75.43
GZ02	5	303	319	7	272		94.98	76.77
RS4231	6	297	310	67	266	63		77.00
RaTG13	7	33	62	298	313	296	293	

Differences

S2 domain



% identity

		1	2	3	4	5	6	7
SARS-CoV-2 Wuhan-S2	1		98.98	89.97	93.37	89.97	89.80	99.66
SARS-CoV-2 Omicron-S2	2	6		89.29	92.35	88.95	88.78	98.64
SARS Urbani-S2	3	59	63		93.88	99.66	98.98	89.63
HKU3-1-S2	4	39	45	36		93.88	94.05	93.03
GZ02-S2	5	59	65	2	36		98.98	89.63
RS4231-S2	6	60	66	6	35	6		89.80
RaTG13-S2	7	2	8	61	41	61	60	

Differences

- ➢ Relatively low sequence conservation in S1
- ➢ High sequence conservation in S2

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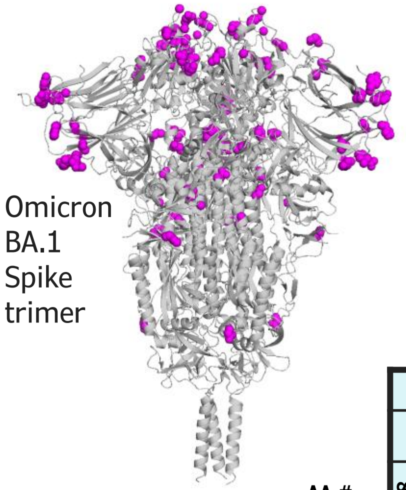
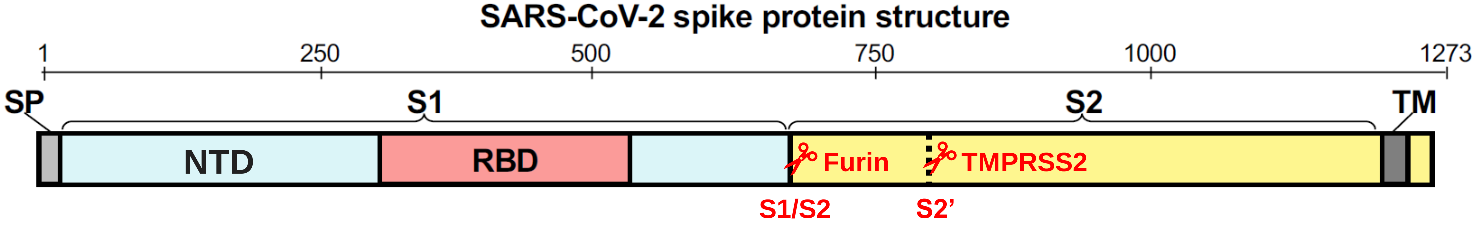
SARS-CoV-2 [S] variants of concern and interest



Omicron BA.1 Spike trimer



		S1 subunit (14-685)																																																				S2 subunit (686-1273)												
		NTD (14-305)																												RBD (319-541)																																						
	AA #	18	19	20	24	25	26	27	67	69	70	80	95	138	142	143	144	145	156	157	158	190	211	212	213	i214	215	242	243	244	339	371	373	375	376	405	408	417	440	446	452	477	478	484	493	496	498	501	505	547	570	614	655	679	681	701	716	764	796	856	950	954	969	981	982	1027	1118	1176
	Wuhan-Hu-1	L	T	T	L	P	P	A	A	H	V	D	T	D	G	V	Y	V	E	F	R	R	N	L	V		D	L	A	L	G	S	S	S	T	D	R	K	N	G	L	S	T	E	Q	G	Q	N	Y	T	A	D	H	N	P	A	T	N	D	N	D	Q	N	L	S	T	D	V
	B.1	.	.	.	.	.	.		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Alpha	**B.1.1.7**	.	.	.	.	.	.		.	–	–	.	.	.	.	.	–	.	.	.	.	.	.	.	.		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	D	G	.	.	H	.	I	.	.	.	.	.	.	.	A	.	H	.
Zeta	**P.2**	.	.	.	.	.	.		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F
Beta	**B.1.351**	.	.	.	.	.	.		.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.		G	–	–	–	.	.	.	.	.	.	.	N	.	.	.	.	.	K	.	.	.	Y	.	.	.	G	.	.	.	V	.	.	.	.	.	.	.	.	.	.	.	.
Gamma	**P.1**	F	.	N	.	.	S		.	.	.	.	.	Y	.	.	.	.	.	.	.	S	.	.	.		.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	K	.	.	.	Y	.	.	.	G	Y	.	.	.	.	.	.	.	.	.	.	.	.	I	.	F
Delta	**B.1.617.2**	.	R	.	.	.	.		.	.	.	.	.	.	D	.	.	.	G	–	–	.	.	.	.		.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	K	.	.	.	.	.	.	.	.	G	.	.	R	.	.	.	.	.	N	.	.	.	.	.	.	.
Omicron	**BA.1**	.	.	.	.	.	.		V	–	–	.	I	.	D	–	–	–	.	.	.	.	–	I	.	EPE	.	.	.	.	D	L	P	F	.	.	.	N	K	S	.	N	K	A	R	S	R	Y	H	K	.	G	Y	K	H	.	.	K	Y	K	.	H	K	F	.	.	.	.
Omicron	**BA.2**	.	I	–	–	–	.	S	.	.	.	.	.	.	D	.	.	.	.	.	.	.	.	.	G		.	.	.	.	D	F	P	F	A	N	S	N	K	.	.	N	K	A	R	.	R	Y	H	.	.	G	Y	K	H	.	.	K	Y	.	.	H	K	.	.	.	.	.

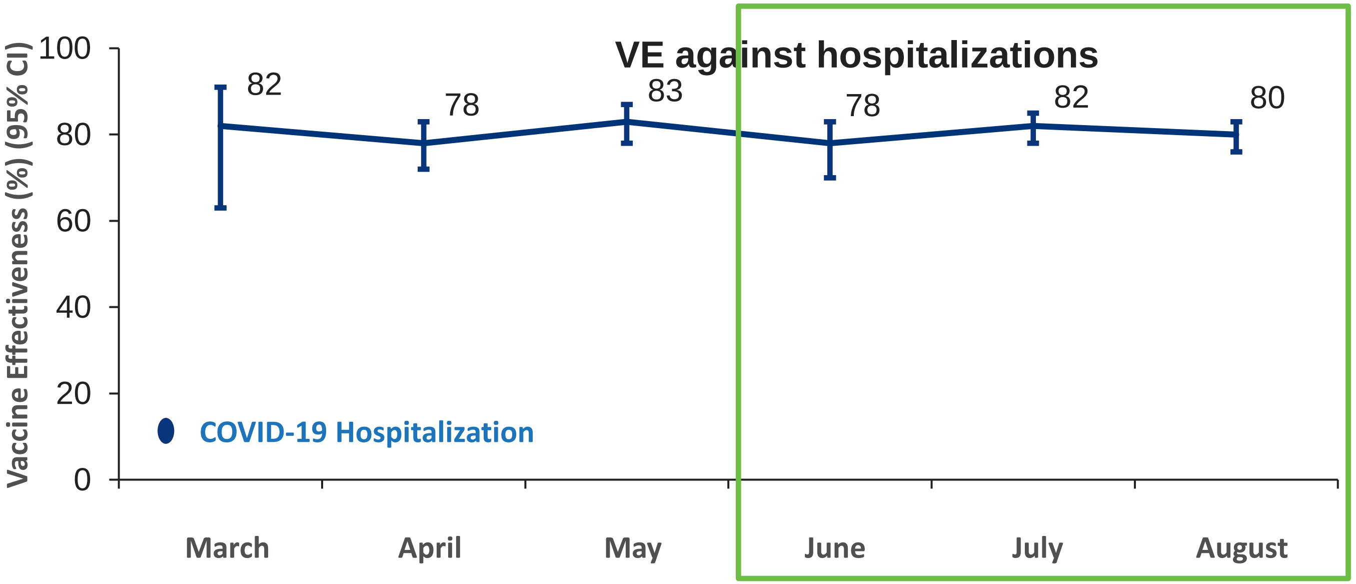
. equal to B.1 Wuhan-Hu-1 sequence – deletion N potential new N-glycosylation site i insertion

Figure 1: Spike protein schematic structure and alignment of substitutions in SARS-CoV-2 variants. S, Spike protein; NTD, N-terminal domain; RBD, receptor binding domain; SP, signaling peptide; TM, transmembrane domain; AA, amino acid.

Figure adapted from: Jongeneelen *et al.* BioRXIV preprint, doi: https://doi.org/10.1101/2021.07.01.450707
Source of field isolates sequence information: www.GISAID.org

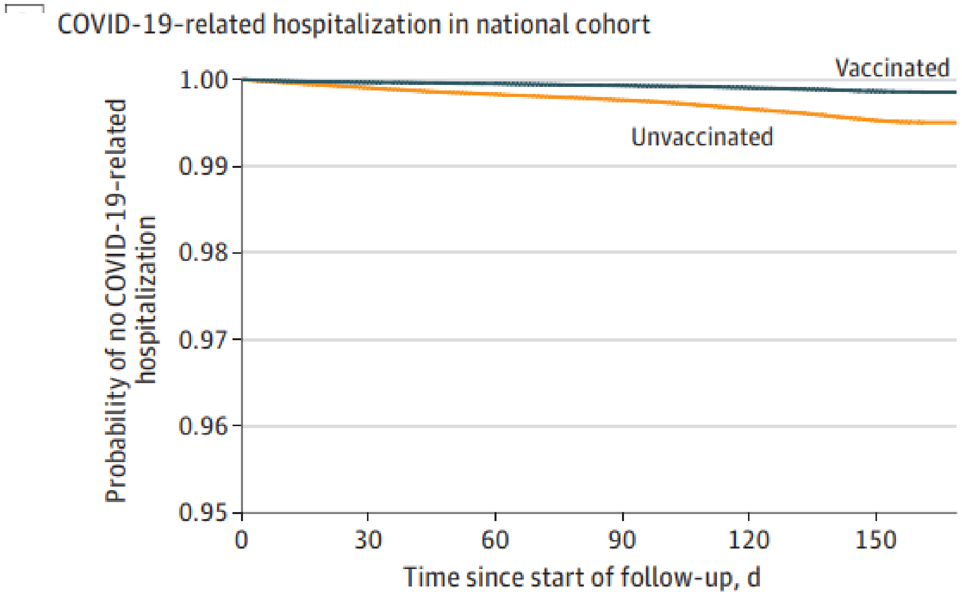
Analysis of Large US Health Claims Database (Health Verity) Supports Durable Protection of a Single Dose of the Janssen COVID-19 Vaccine against COVID-19 Related Hospitalizations

Stable month-over-month vaccine effectiveness including when Delta emerged to when it became dominant



Prevalence of Delta in U.S.[1]	0%	4%	15%	34%	87%	97%

Time-to-event analyses suggests durable vaccine effectiveness during 183 days after vaccination



No. at risk						
Unvaccinated	1645397	1460511	1338512	1154525	898761	339016
Vaccinated	422034	408262	391913	349800	284267	115538

Corrected vaccine effectiveness estimates are presented in this slide – Month-over-Month uncorrected vaccine effectiveness estimates are 68%-75% for COVID-19 related Hospitalization

Published in part in Polinski JM et al. JAMA Netw Open. 2022 Mar 1;5(3):e222959.

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Sisonke 2 Study (COV3021)

Background

- Sisonke 2 enrolled 227,310 HCW who had received an initial single dose of the Janssen COVID-19 vaccine from Nov 8 to Dec 17, 2021
- Enrollment started just **before** the onset of the Omicron driven 4th wave in South Africa affording an opportunity to evaluate early VE against the Omicron variant

Objective

- To evaluate early VE in preventing hospital admissions of a homologous boost of Janssen COVID-19 vaccine when administered 6-9 months after primary vaccination with the Janssen COVID-19 vaccine in HCW

HCW, healthcare workers; VE, vaccine effectiveness; VOC, variant of concern; PCR, polymerase chain reaction.

Gray G et al. Available from:
https://www.medrxiv.org/content/10.1101/2021.12.28.21268436v1
Accessed 5 January 2022

Sisonke 2 Study (COV3021)

Results

- These data demonstrate a **homologous boost** with the Janssen COVID-19 vaccine (Ad26.COV2.S) given to HCW 6-9 months after the initial vaccination with the Janssen COVID-19 vaccine is **highly protective against hospital admissions during the Omicron wave**

National Data	Vaccine Effectiveness for hospitalization	95% CI	Median follow up time in days since last dose (IQR)
Ad26.COV.2 booster (0-13 days)	**63%**	**31-81**	**8** (5-11)
Ad26.COV.2 booster (14-27 days)	**84%**	**67-92**	**20** (17-24)
Ad26.COV.2 booster (1-2 months)	**85%**	**54-95**	**32** (29-34)
Gauteng (Epicenter)			
Ad26.COV.2 booster (0-13 days)	**93%**	**47-99**	**8** (5-10)
Ad26.COV.2 booster (14-27 days)	**81%**	**49-93**	**20** (17-23)

VE, vaccine effectiveness; HCW, health care workers; CI, confidence interval; IQR, interquartile range.

Gray G et al. Available from:
https://www.medrxiv.org/content/10.1101/2021.12.28.21268436v1
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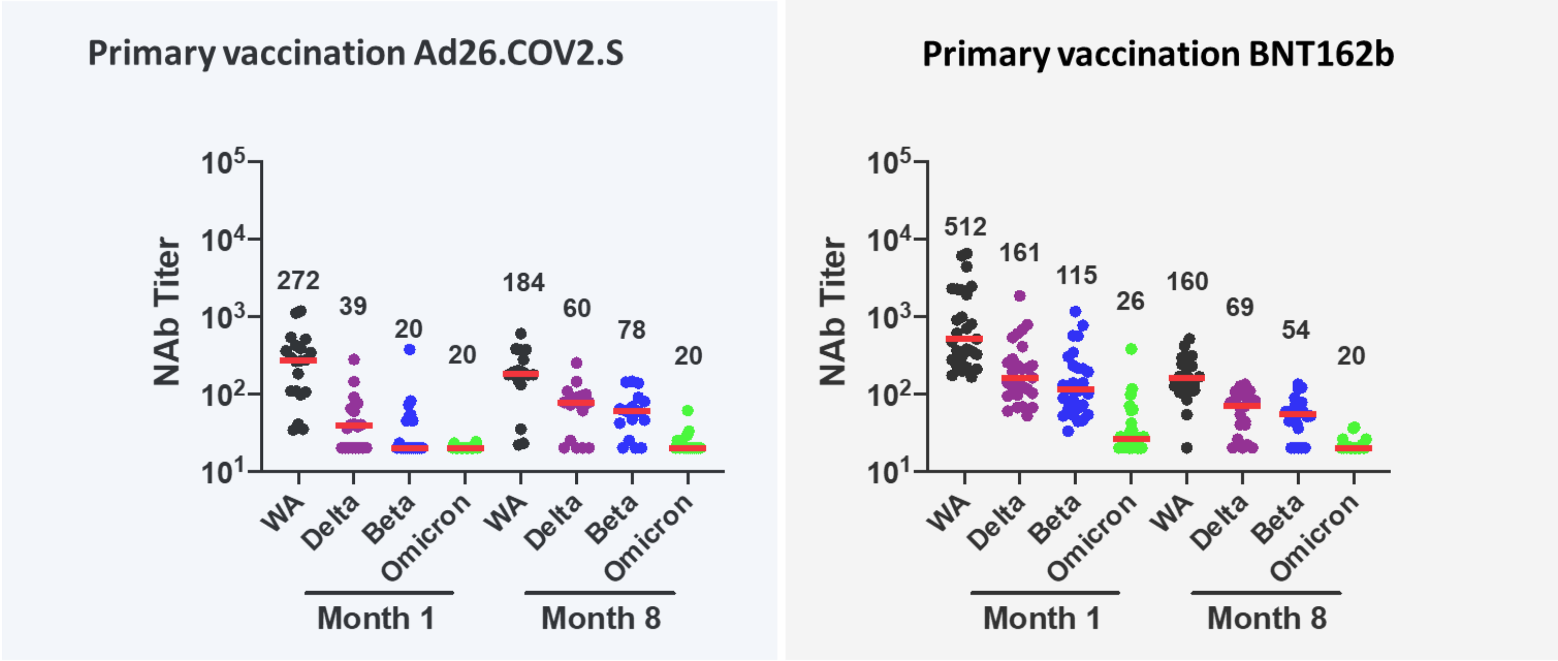
Covid-19 Vaccine-Elicited Neutralizing Antibody Responses Are Markedly Reduced to Omicron

Neutralizing antibody titers (psVNA)

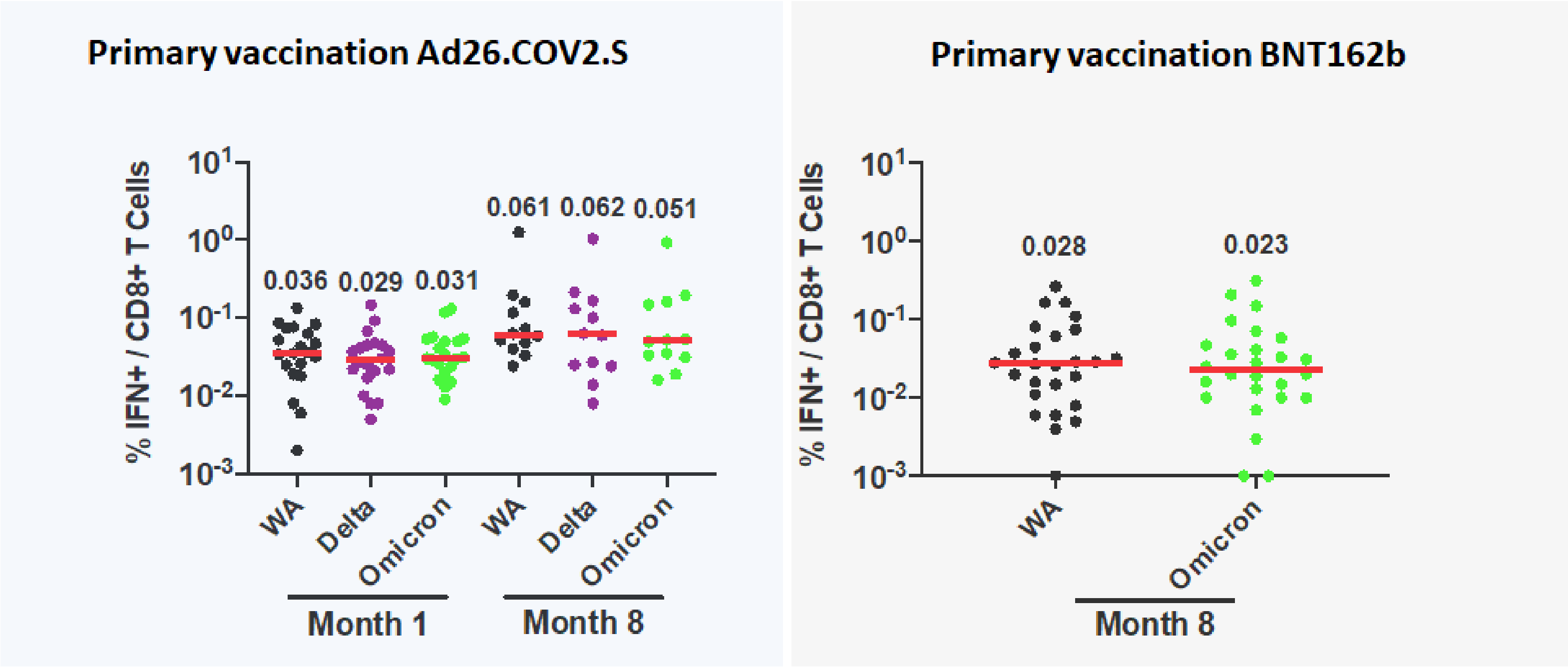


Time Following Initial Immunization

Liu et al., medRxiv 2022

T-Cell Responses elicited by primary vaccination with Covid-19 vaccines are Highly Cross-Reactive to Omicron

CD8+ T-cells



Time Following Initial Immunization

Liu *et al.*, medRxiv 2022

Challenges in the development of a pan-Sarbecovirus vaccine

- Vaccine that elicits potent, broad, durable humoral and cellular immunity

- High vaccine mediated protection against severe disease or even infection

- Demonstration of breadth and duration of vaccine efficacy in humans in absence of multiple circulating (distant) sarbeco viruses

  - Licensure through:
    - Animal rule?
    - Human challenge model?

- Will pan-sarbecovirus vaccines provide sufficient protection in comparison to targeted vaccines based on rapid response platforms?

- Safety

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