Hybrid immunity against SARS-CoV-2 elicits cross-variant ADCC

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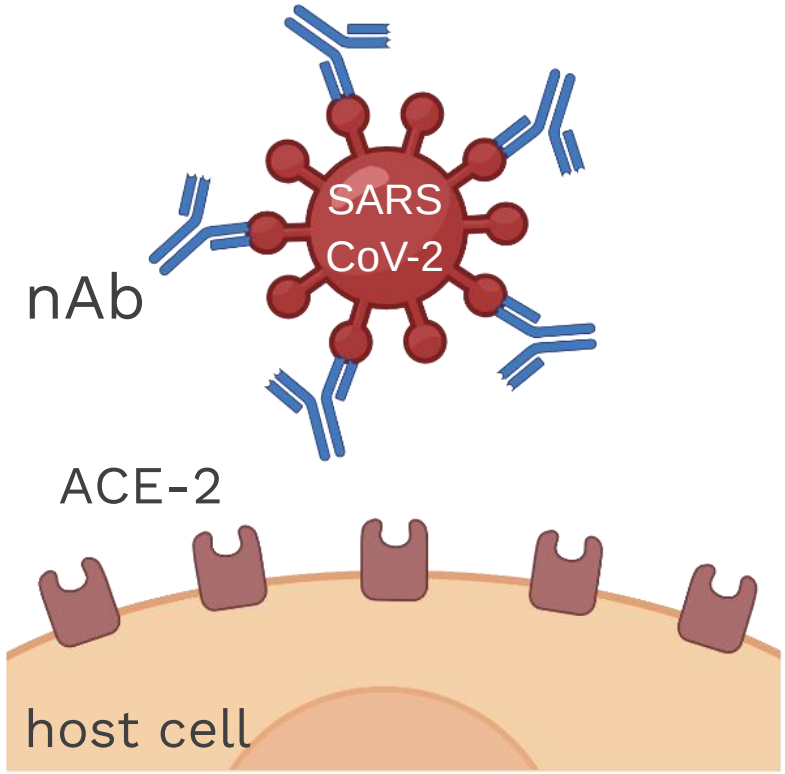
Disclaimer

I have no COIs to declare related to this study.



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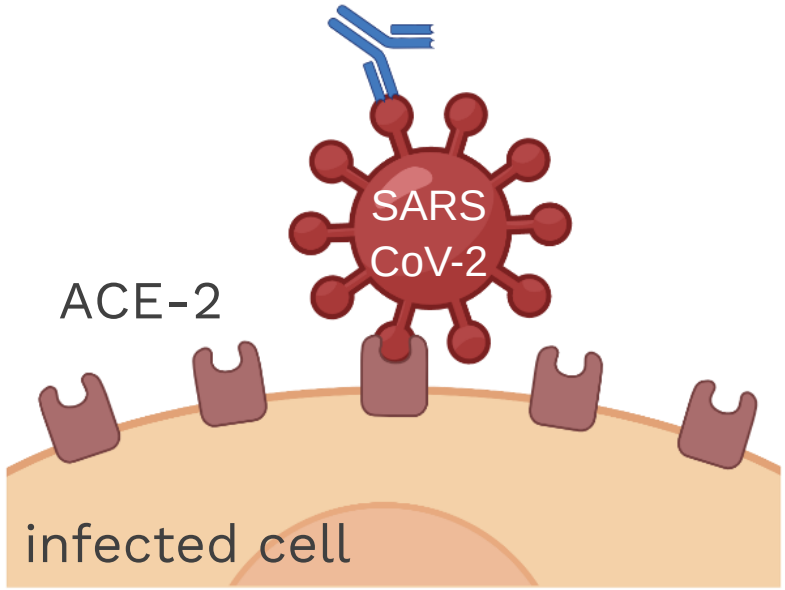
SARS-CoV-2 variants escape antibody neutralization



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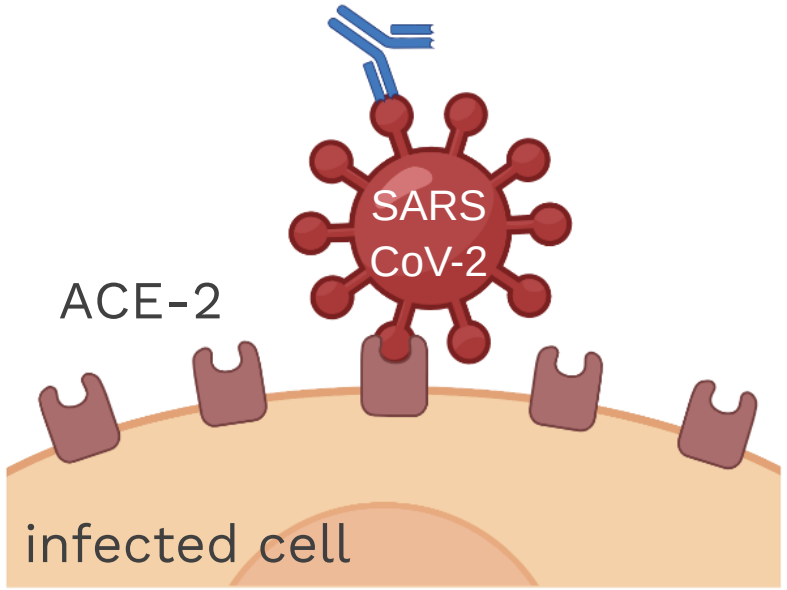
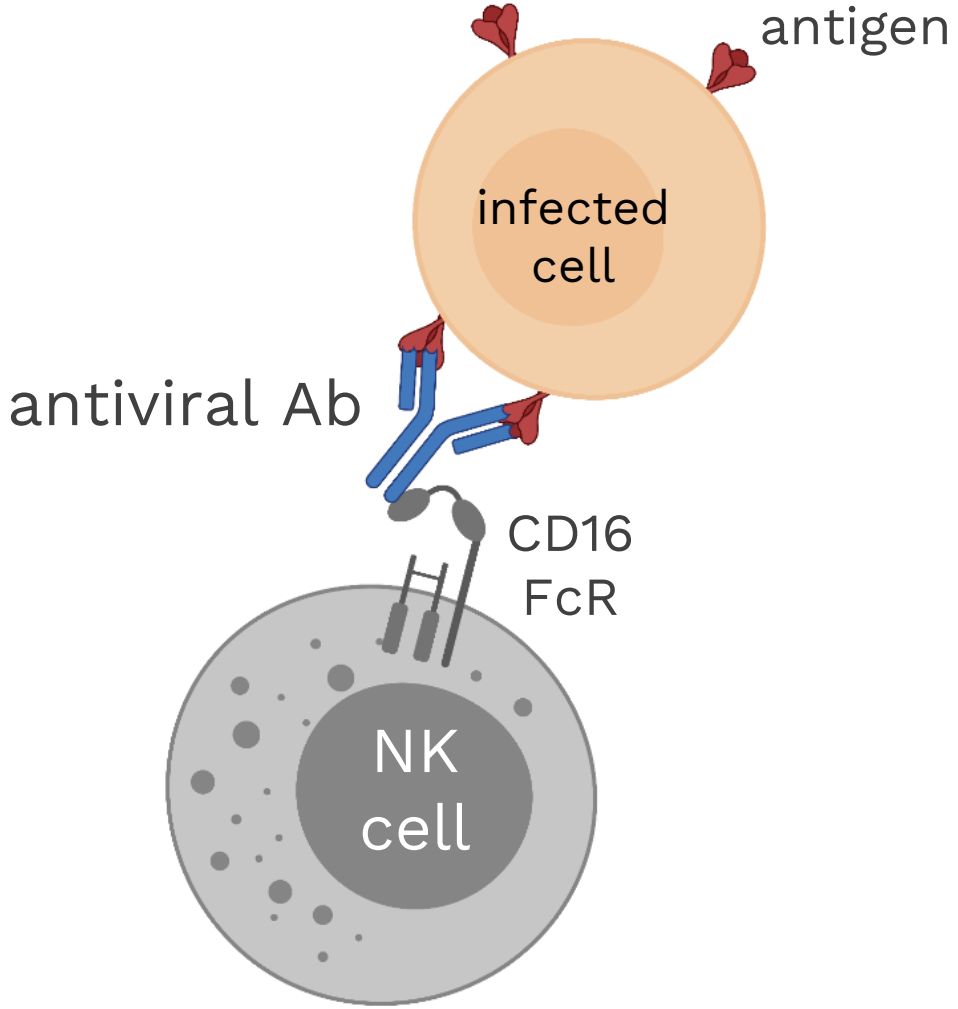
FcR-dependent mechanisms control cell-associated virus





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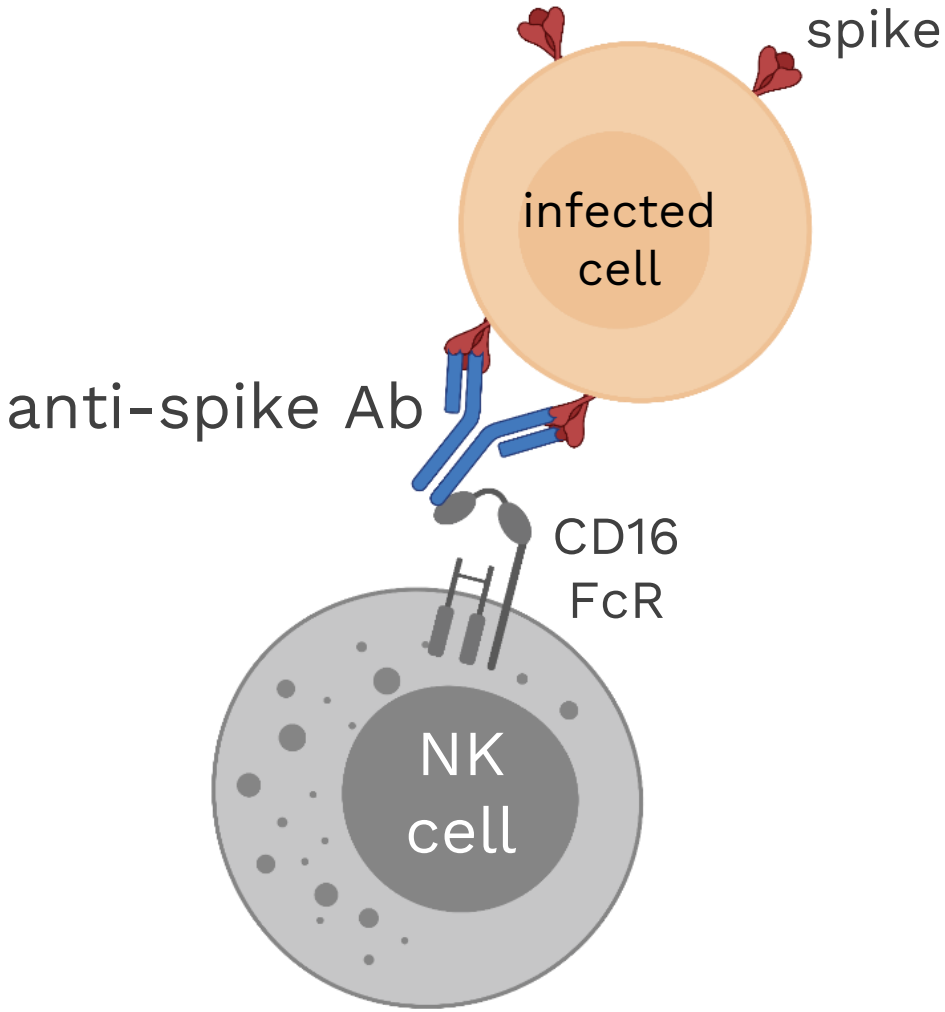
Antibody Dependent Cell-mediated Cytotoxicity



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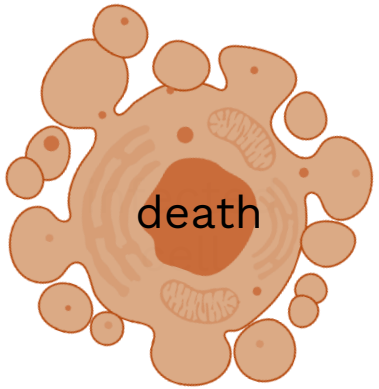
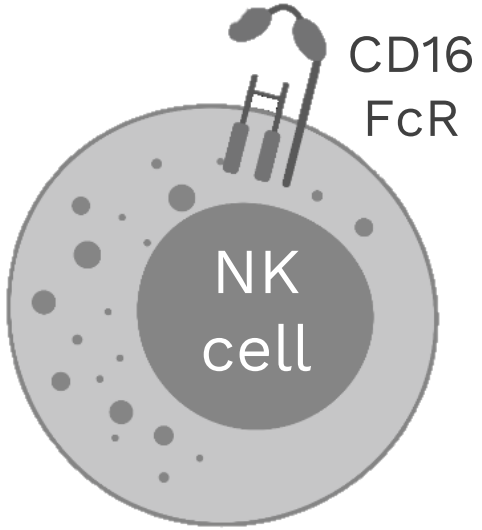
Antibody Dependent Cell-mediated Cytotoxicity





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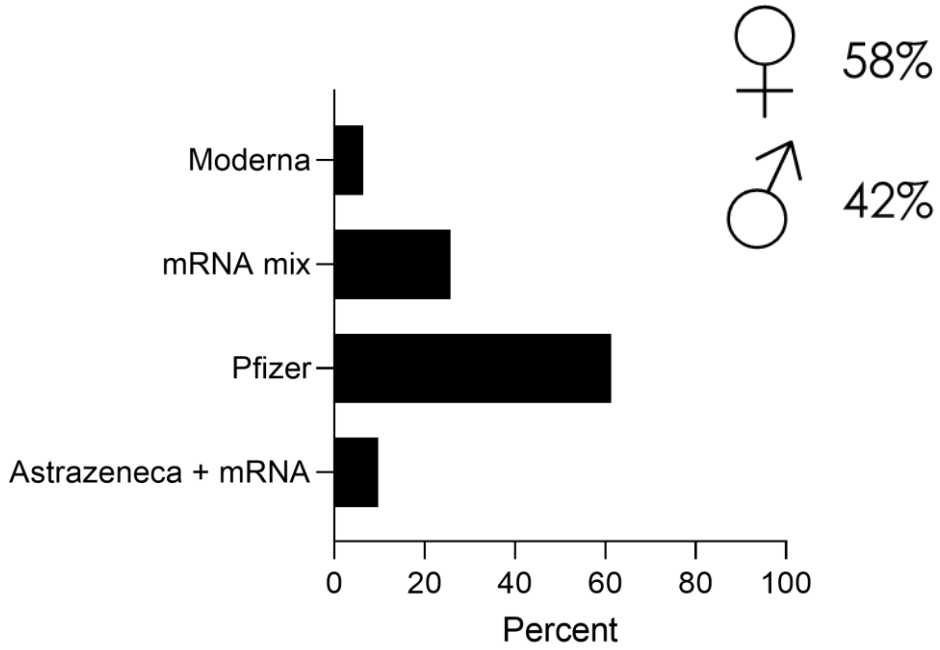
Study Cohort

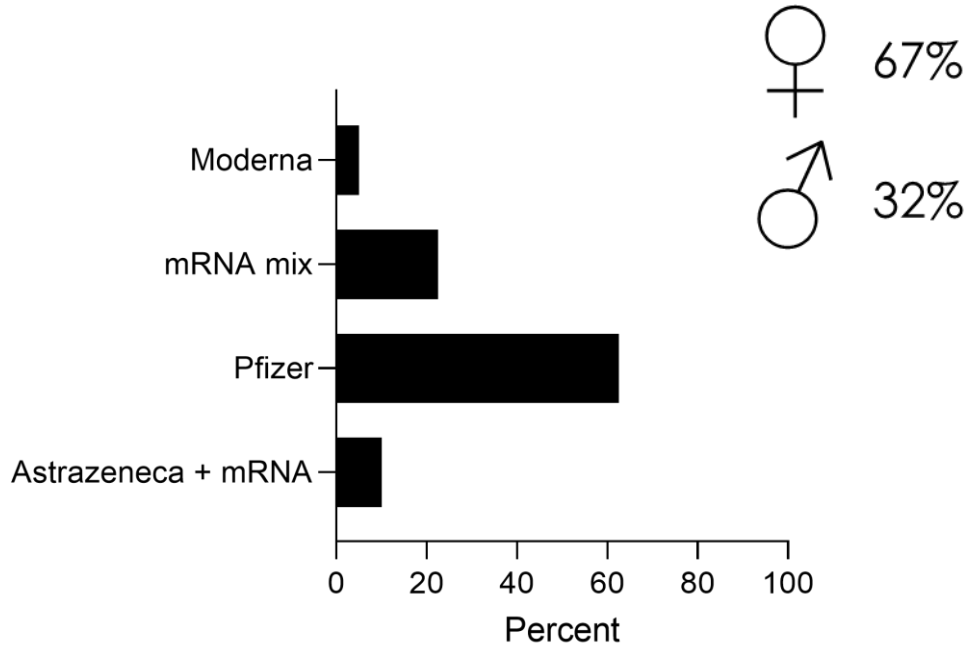
Hybrid Immunity (n = 31)

Mean Age: 60 ± 15.2 years



Vaccinees (n = 40)

Mean Age: 53.8 ± 14.3 years



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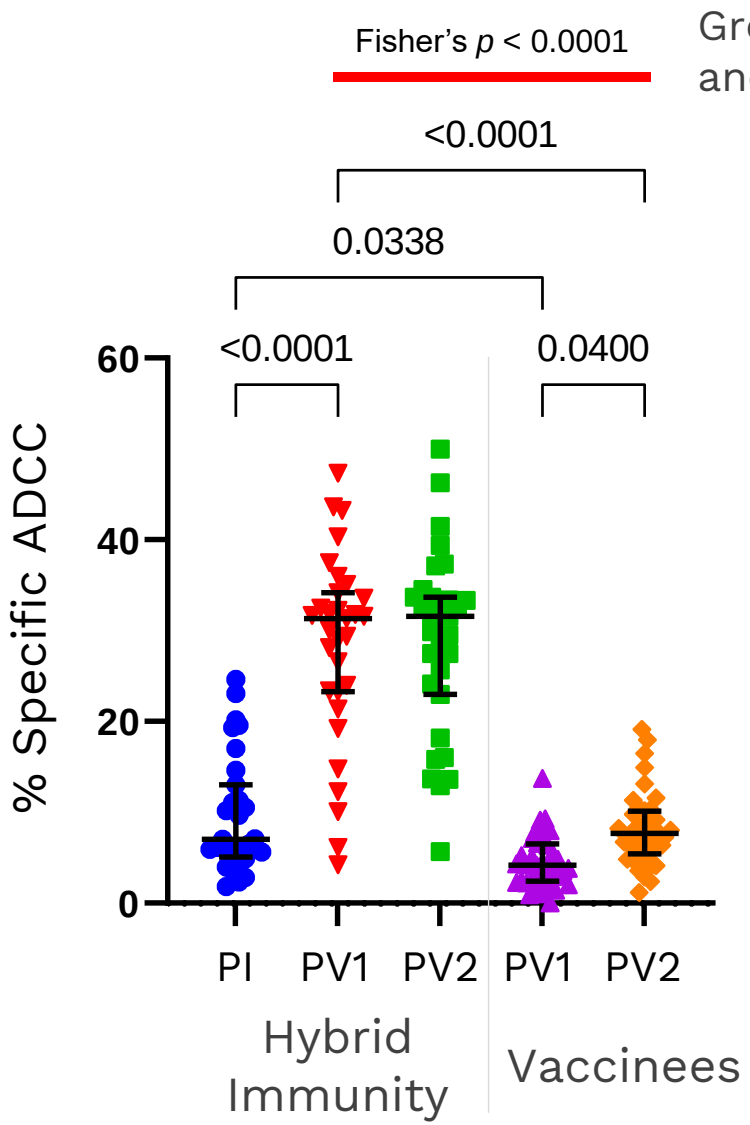
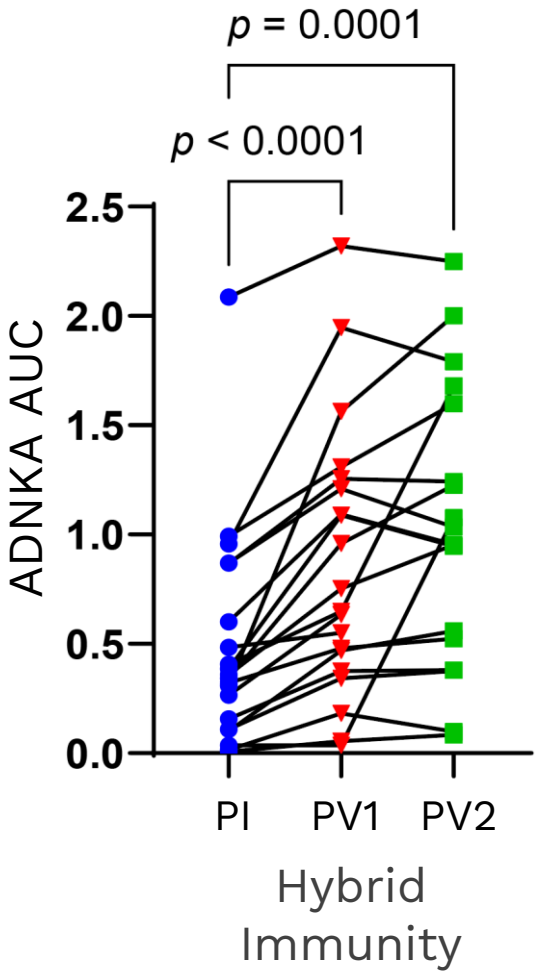
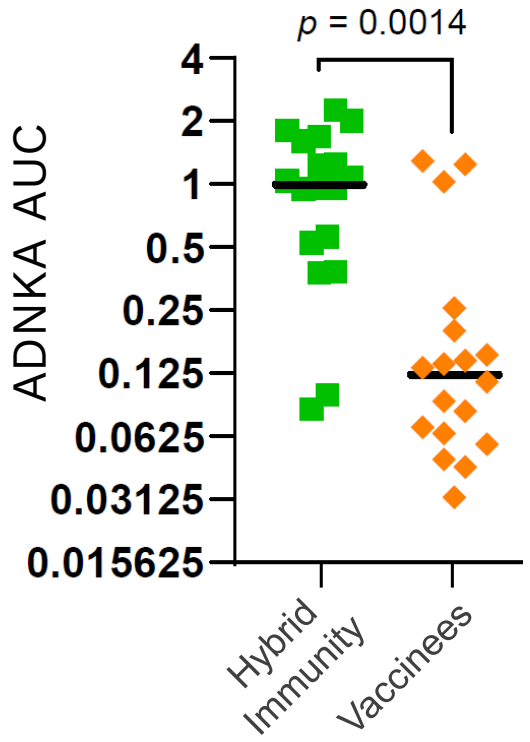
Robust ADCC with hybrid immunity

Greater likelihood of robust ADCC after infection and one vaccination than after two vaccinations







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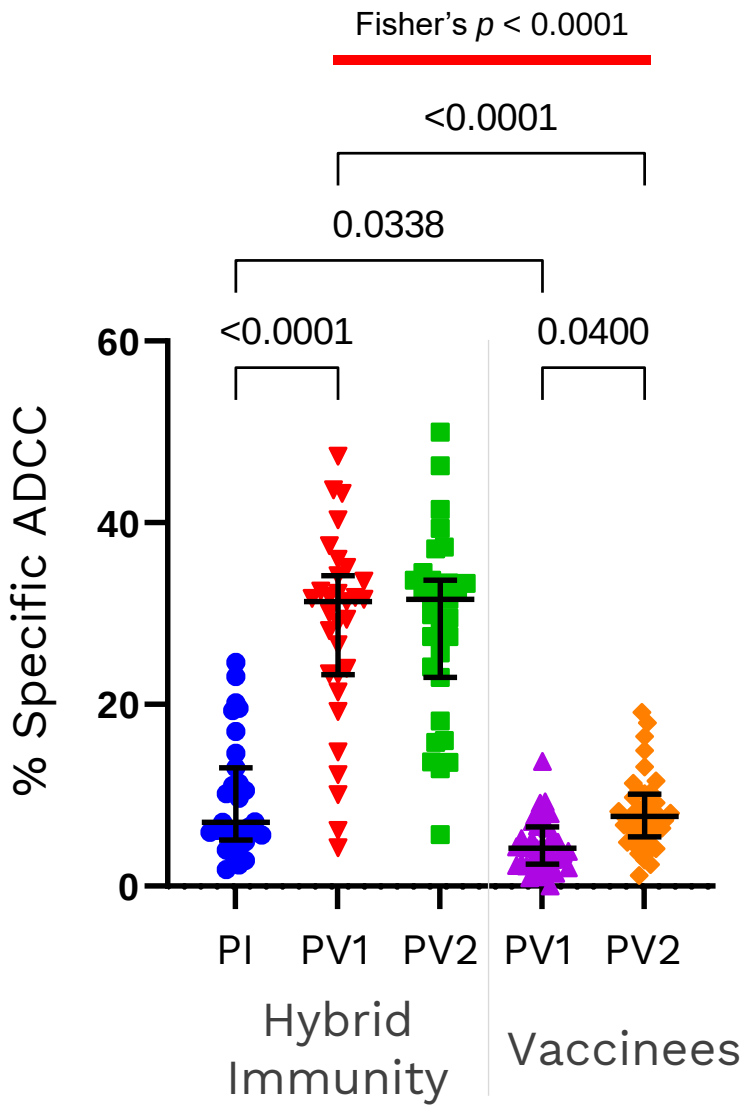
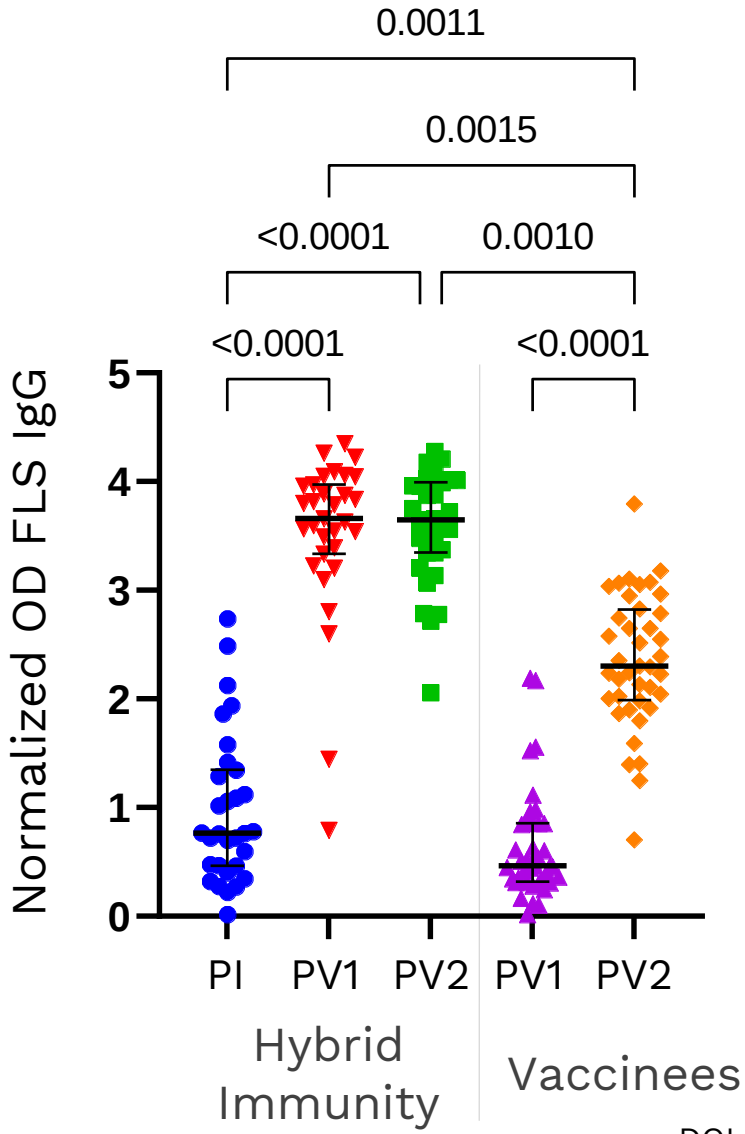
Robust ADCC mirrors FLS IgG levels, but…





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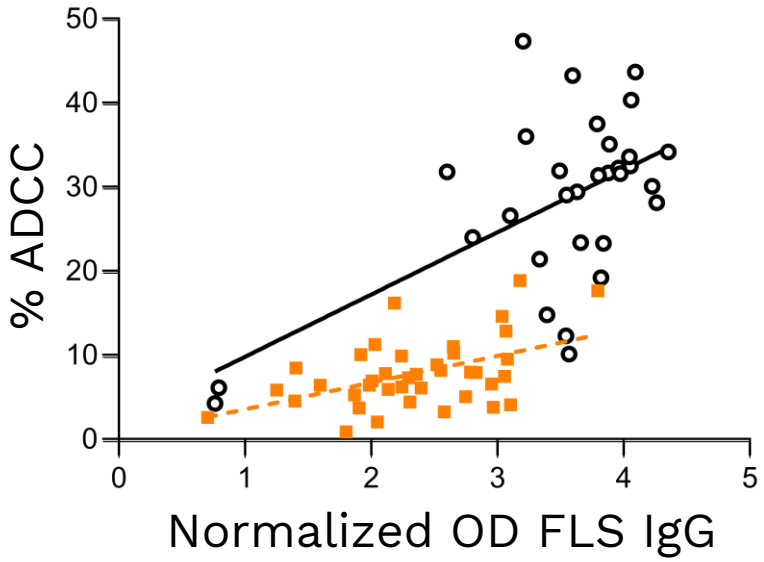
… quantity is not the whole story

- Hybrid PV1 (n = 31)
- Vaccinees PV2 (n = 40)

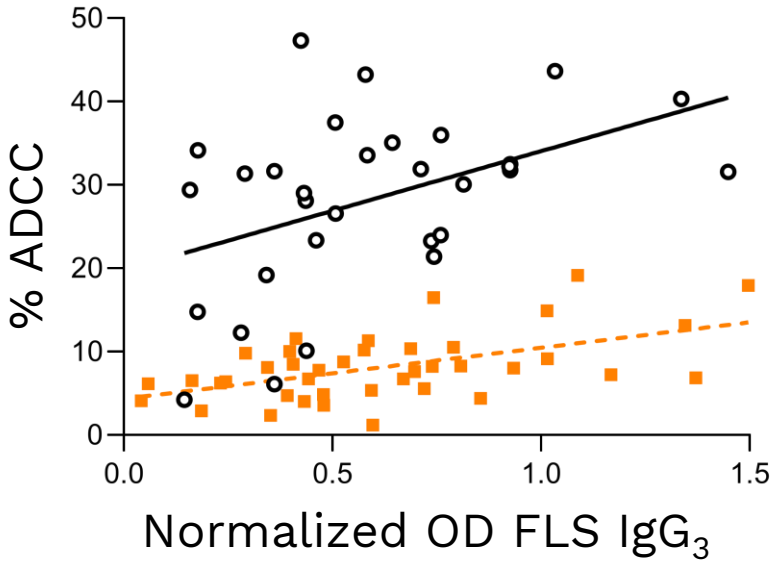
FLS IgG



r = 0.4077
p = 0.0228

r = 0.3919
p = 0.0124

FLS IgG_3



r = 0.4422
p = 0.0103

r = 0.4662
p = 0.0024

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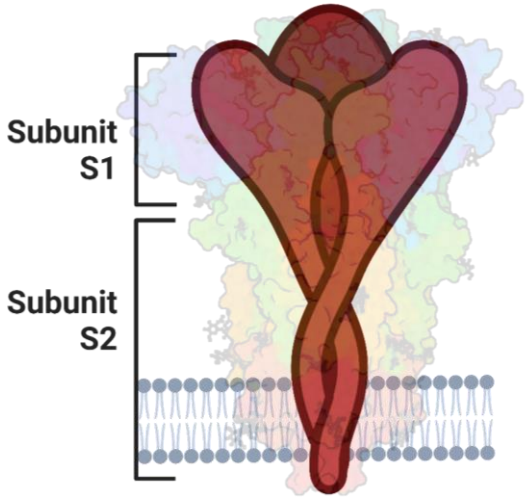
Which antibodies elicit robust spike-directed ADCC?

- S2 is relatively conserved



- S1 mutations contribute to breakthrough infection

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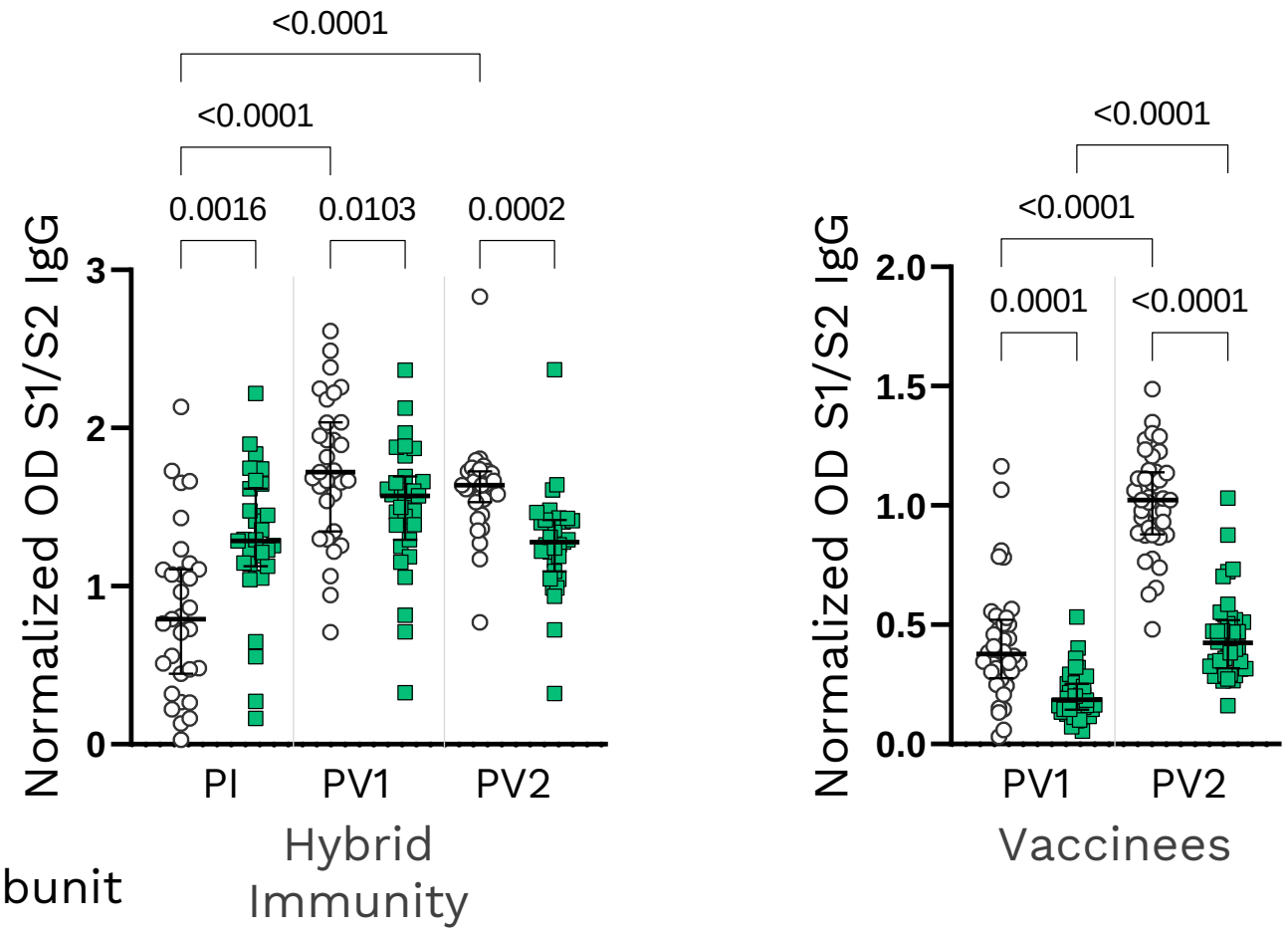
Infection favours anti-S2 antibodies, vaccination skews towards anti-S1



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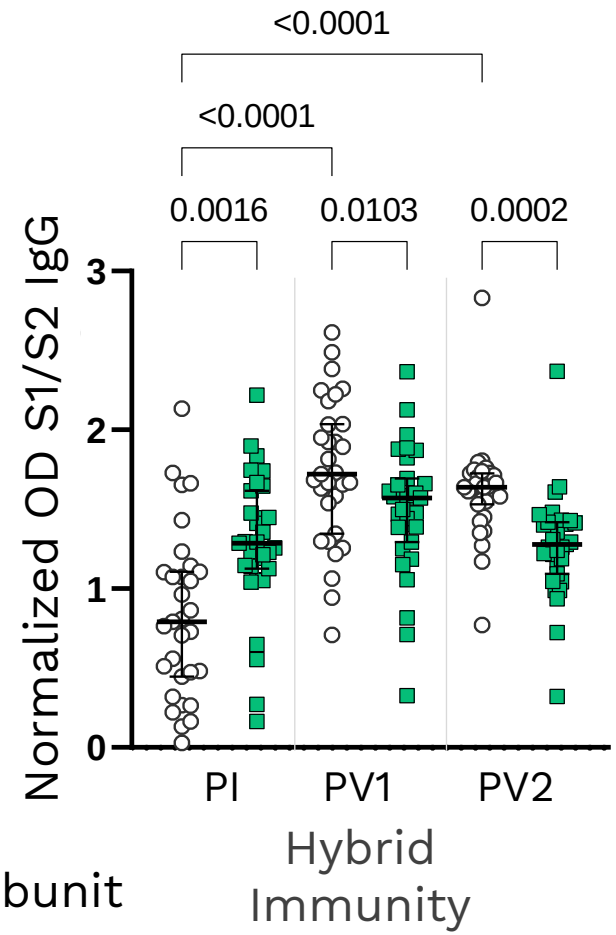
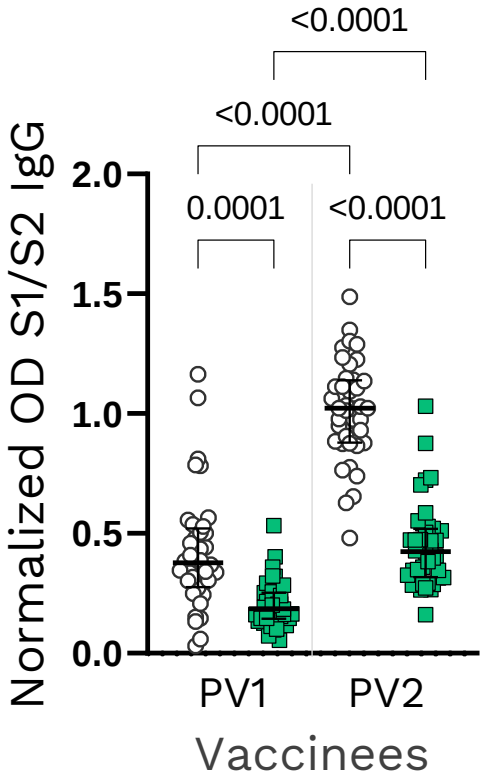
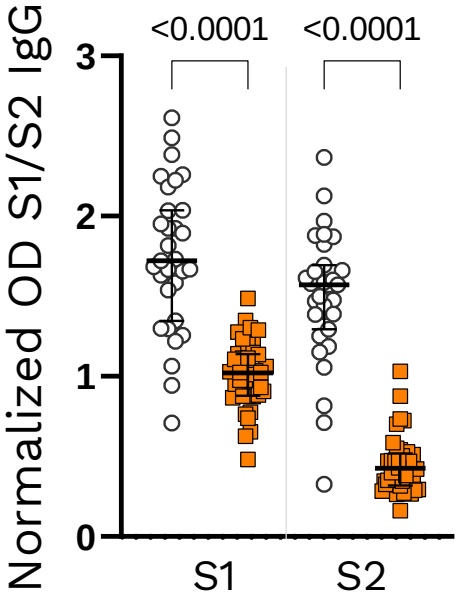
Hybrid immunity offers the best of both







S1 subunit

S2 subunit

Hybrid PV1 (n = 31)

Vaccinee PV2 (n = 40)

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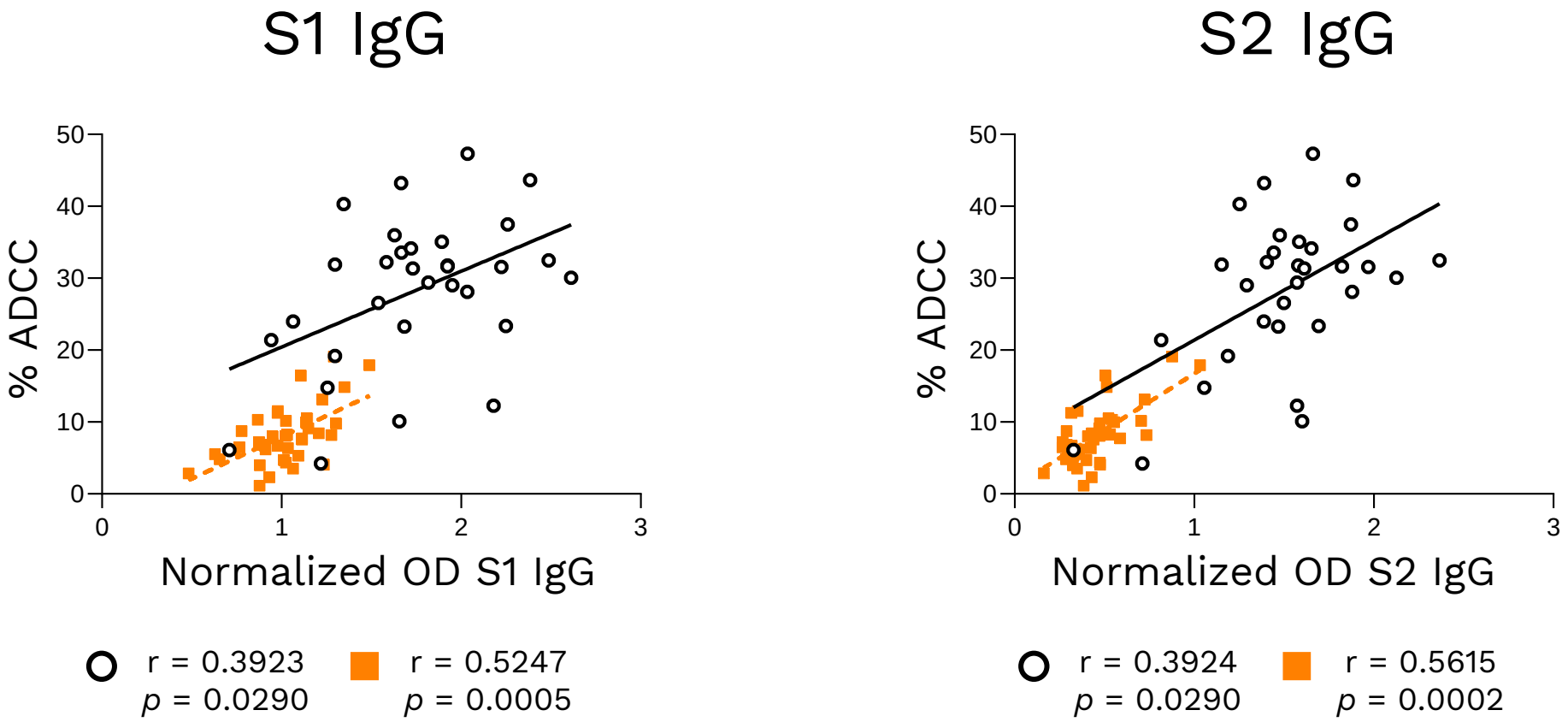
Anti-S1 and S2 antibody levels correlate with ADCC

- Hybrid PV1 (n = 31)
- Vaccinees PV2 (n = 40)



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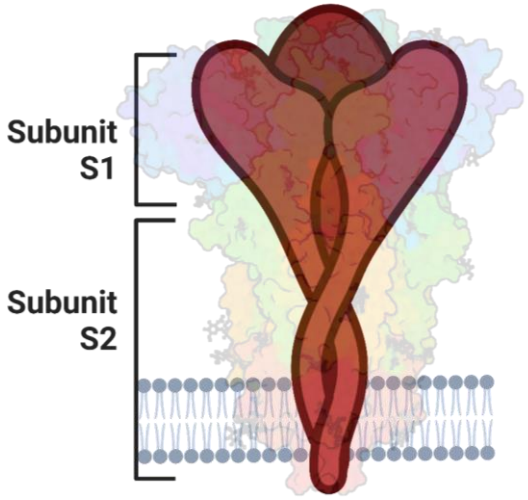
Where are the ADCC determinants distributed within spike?



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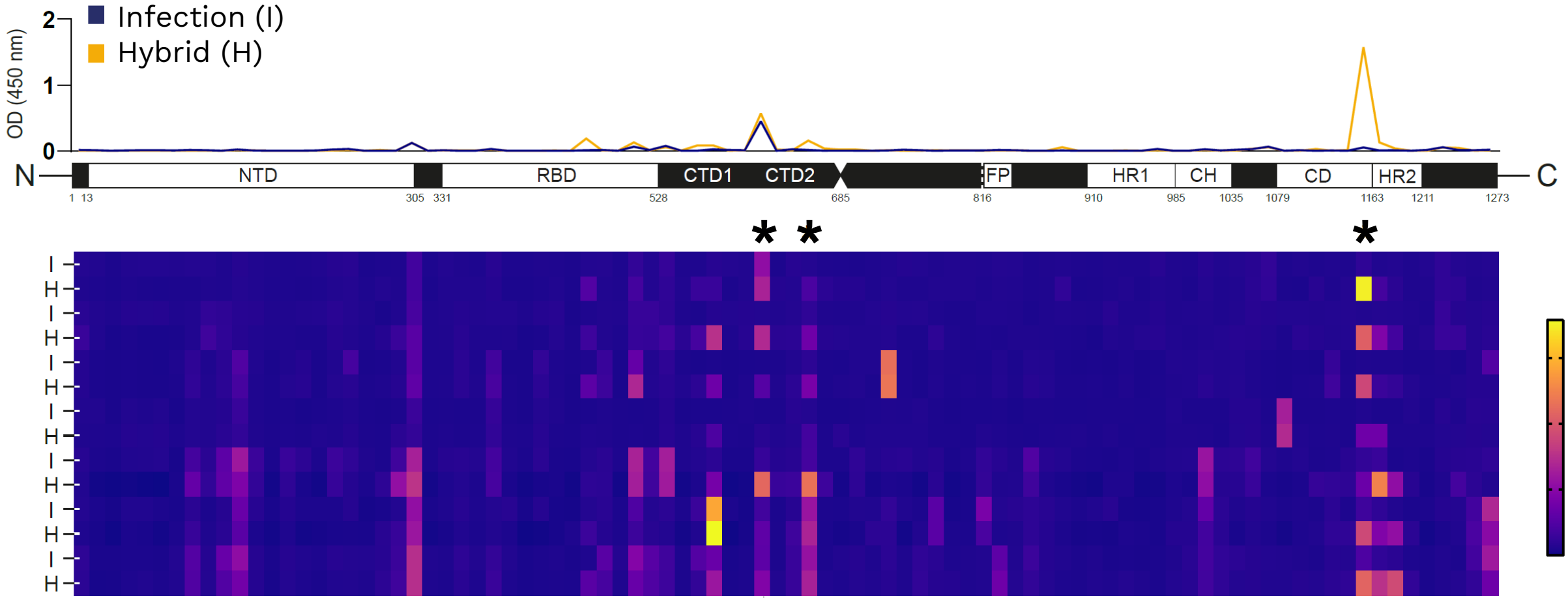
Robust ADCC corresponds with reactivity against three linear epitopes within spike



I = Infection; H = Hybrid

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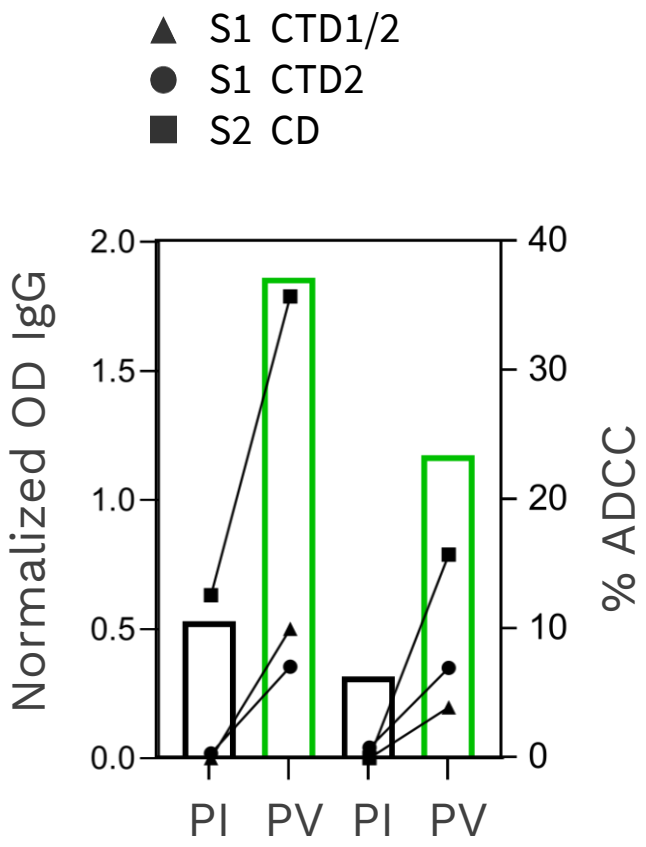
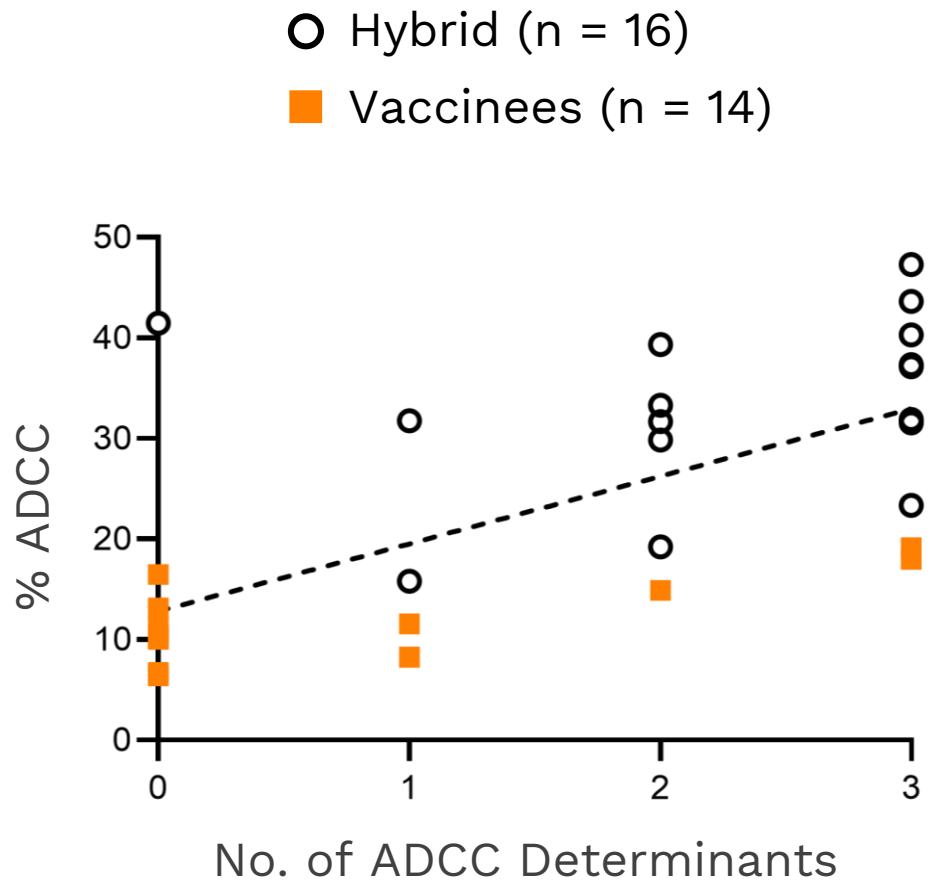
Robust ADCC corresponds with reactivity against three linear epitopes within spike





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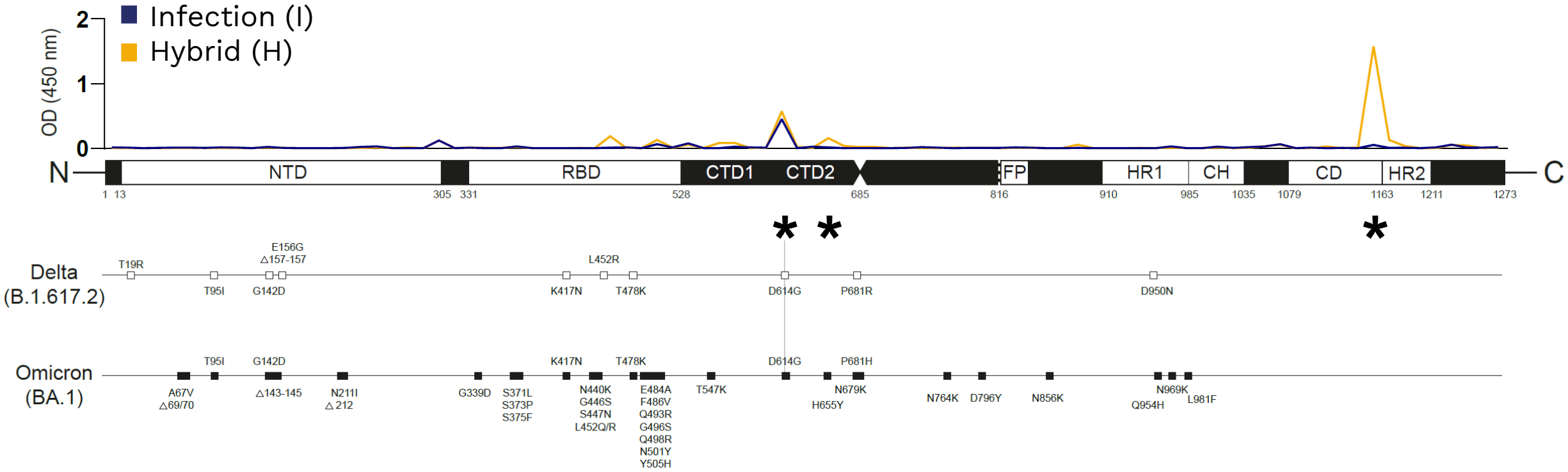
Key ADCC determinants lie outside of heavily mutated sites in variants



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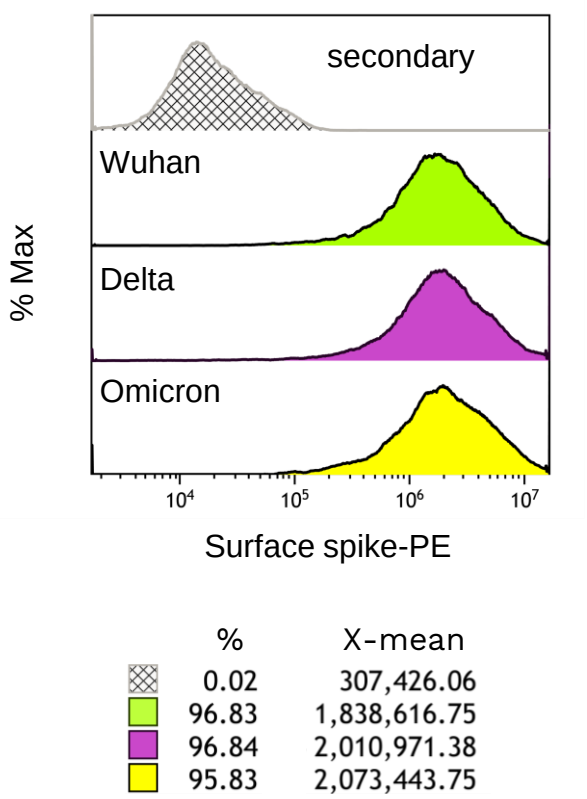
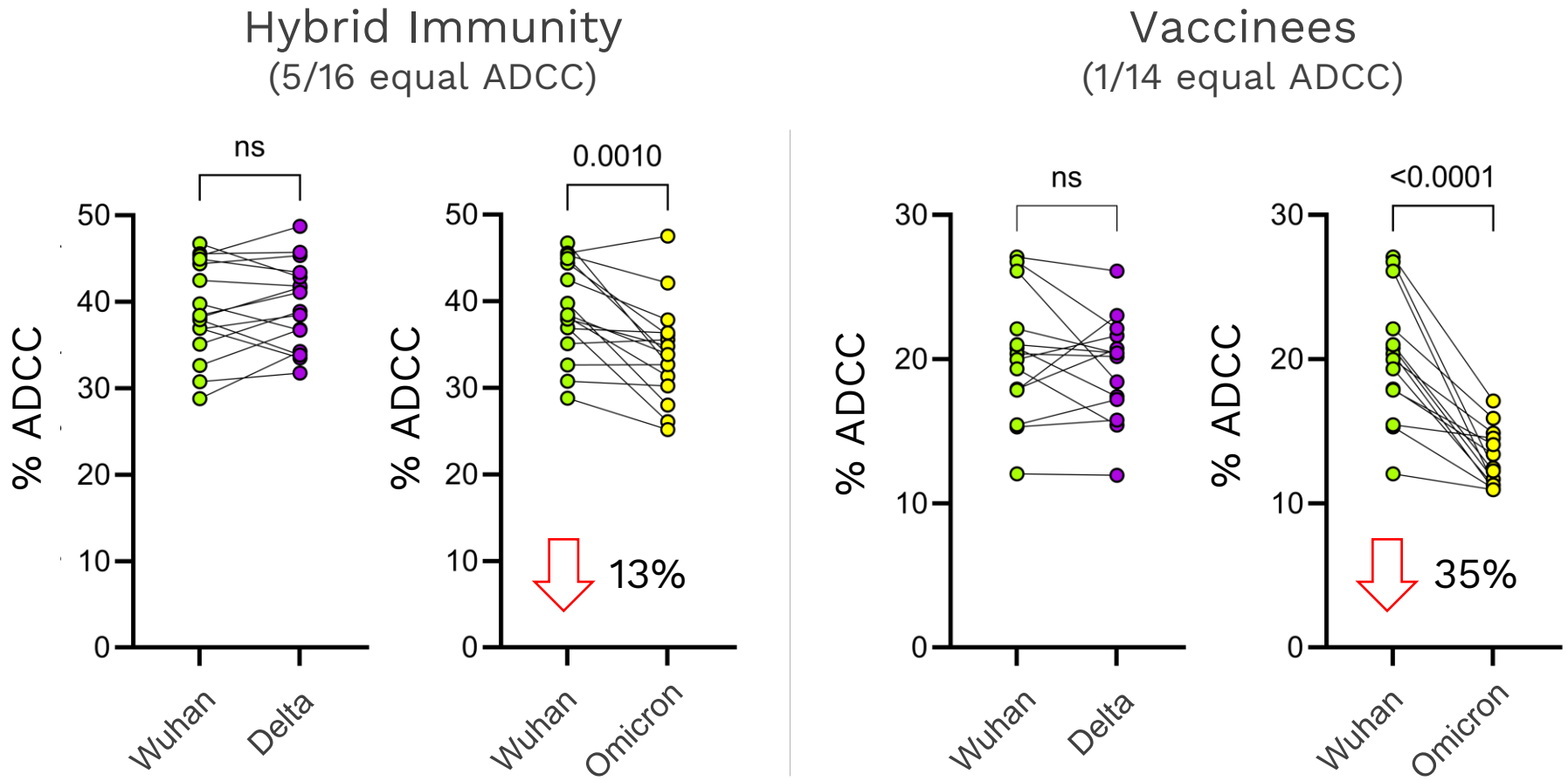
Does ADCC span variants?

nextstrain.org

Hybrid immunity elicits ADCC across variants





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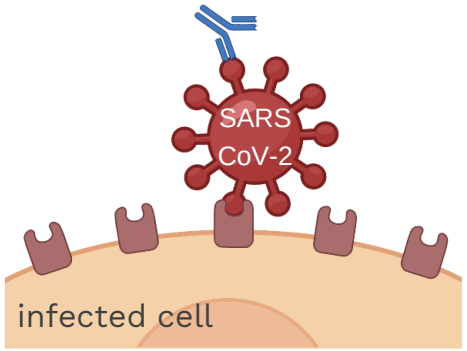
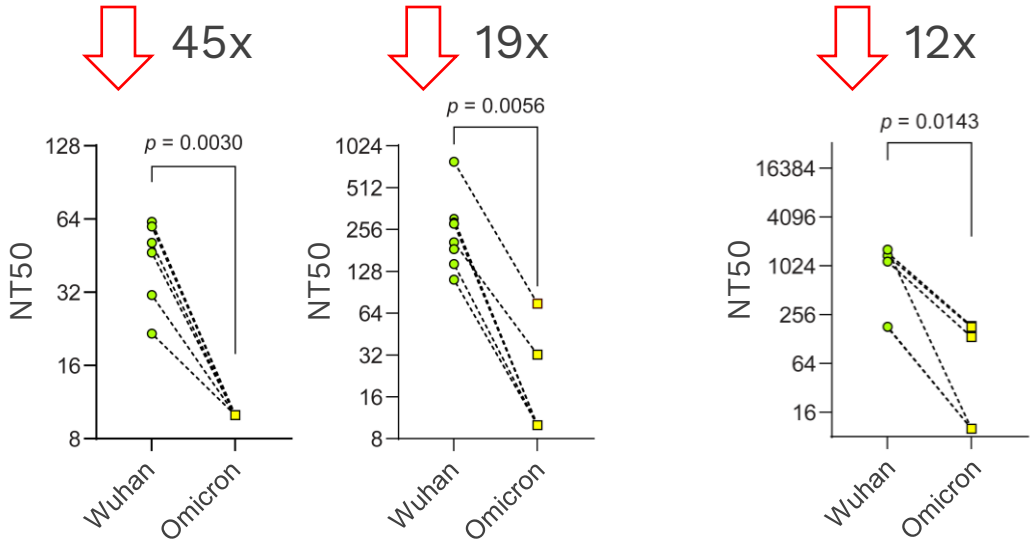
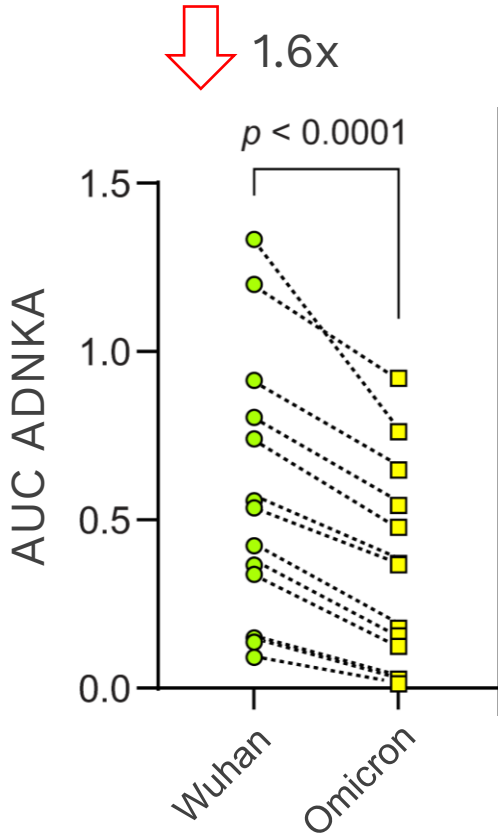
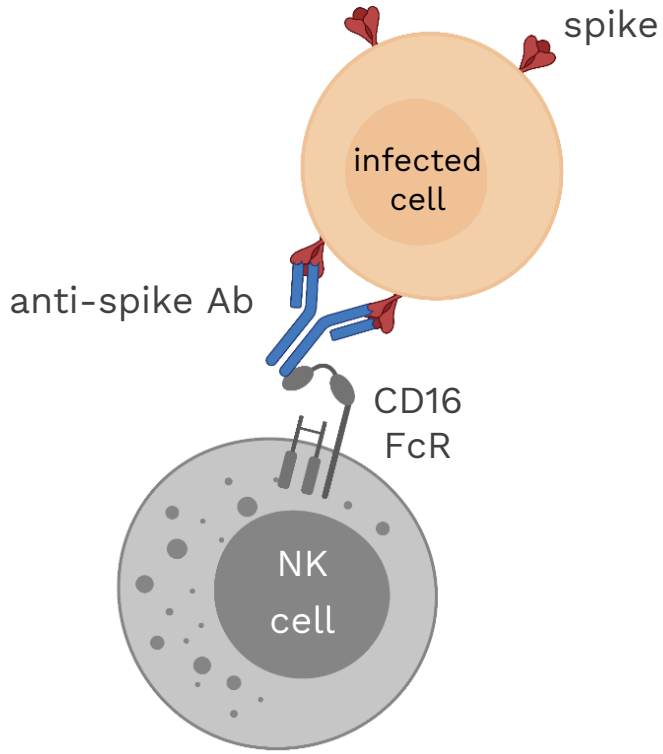
ADCC is preserved against variants, neutralization is not





Az (Vaccinees) Pf Hybrid Immunity





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Final Thoughts

- Hybrid immunity generates anti-S1 and S2 antibodies with the strength & breadth to elicit robust ADCC.
- Since ADCC determinants are distributed throughout spike, escape of any single epitope may not substantially impact ADCC.
- Vaccine strategies should not focus only on the RBD since enhancing neutralizing antibody production may occur at the expense of ADCC.

Acknowledgements

Prof Michael Grant
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Keeley Barnable

Prof Richard Stanton
Dr Kirsten Bentley
Dr Ceri Fielding

Prof Eddie Wang

NL COVID Cohort

Debbie Harnum (RN, BN)
Study Participants

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Public Health Agency of Canada
Agence de la santé publique du Canada

Lessons Learned

- Difficulties associated with short-term funding – PhD candidate
- Shortage of personnel
- Streamline research for urgency
- Research Ethics Protocol – blood draw schedule modifications with changes to PH guidelines
- Regularly reporting antibody titre results helped retain participants

Study Cohort

		Hybrid n = 31	Vaccinee n = 40
Symptoms n (%)	Asymptomatic	4 (12.9)	N/A
	Mild	8 (25.8)	
	Moderate	14 (45.2)	
	Severe	5 (16.1)	
	Mean DPI/DPSI ± SD*	250.4 ± 103.2	
	Median Age (IQR)	63 (53-73)	55 (40-66)
	Mean Age ± SD	60 ± 15.2	53.8 ± 14.3
	Female n (%)	18 (58)	27 (67.5)
	Male n (%)	13 (42)	13 (32.5)
Vaccine 1	ChAdOx1-S n (%)	3 (9.7)	4 (10)
	Pfizer-BioNTech n (%)	26 (83.9)	34 (85)
	Moderna n (%)	2 (6.4)	2 (5)
	Mean DPV1 ± SD*	58 ± 14.8	61 ± 15.4
Vaccine 2	Pfizer-BioNTech n (%)	20 (64.5)	26 (65)
	Moderna n (%)	11 (35.5)	14 (35)
	Mean DPV2 ± SD*	71.2 ± 21.1	72 ± 17.7
	Mean Days Between Vaccination ± SD	71.3 ± 16.8	75.5 ± 16

**Days post infection/days post symptom onset (DPI/DPSO); days post first vaccination (DPV1); days post second vaccination (DPV2). Mild = few symptoms < 7 days; moderate = multiple symptoms > 7 days; severe = hospitalised.*

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