Insights from dengue vaccines

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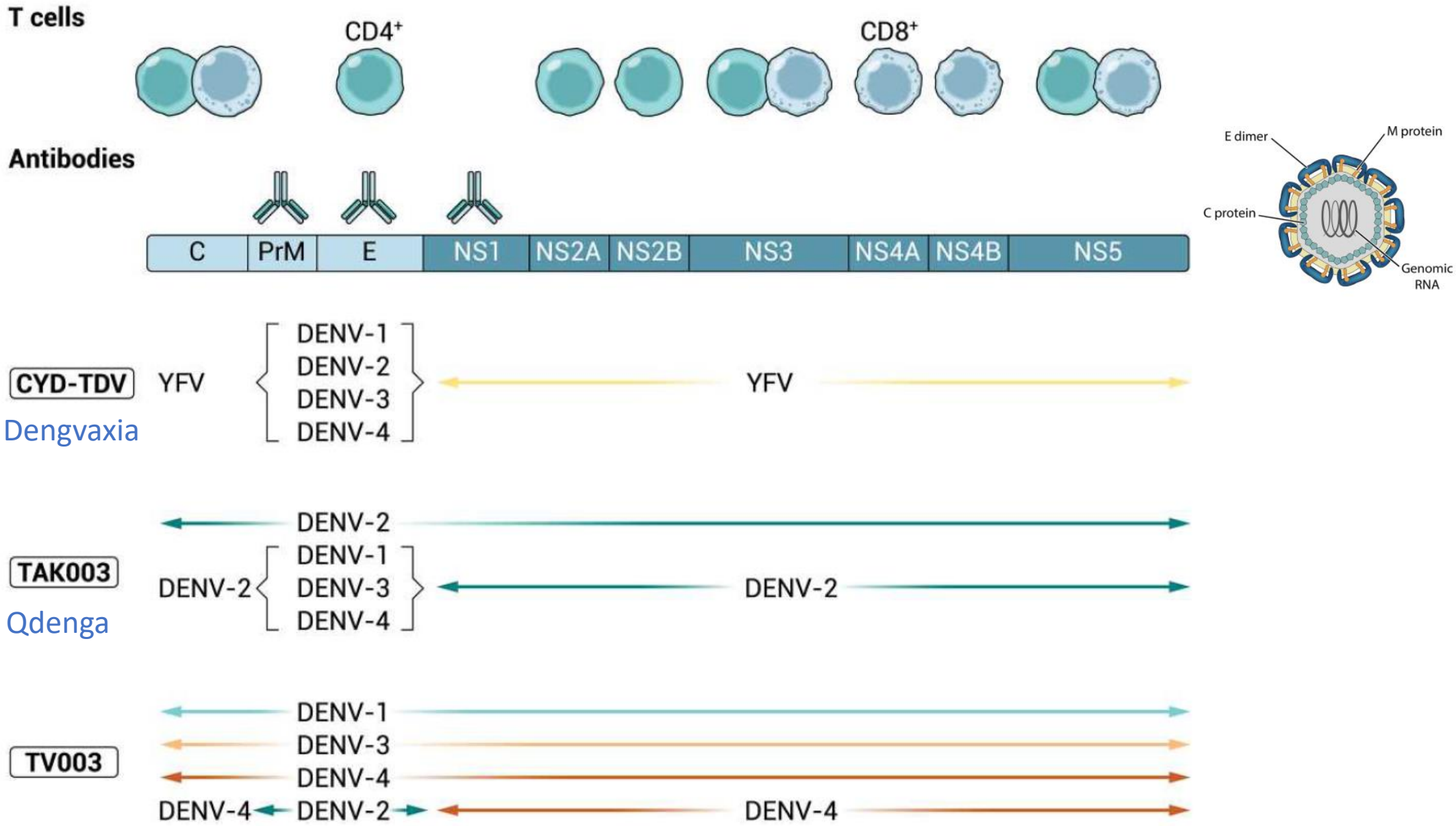
Updates on clinical phase dengue vaccines/candidates

Vaccine	Type	Stage	Efficacy outcome	Status
Dengvaxia (Sanofi Pasteur	Chimeric	Licensed in several countries	• Efficacious only in seropositive at baseline	Use in those with prior dengue infection (PDI)
TAK003 (Takeda)	LAV/Chimeric	Licensed in several countries	• Efficacious in both seropositive and overall seronegative • No efficacy against DENV3 in seronegatives • Too few cases to conclude on DENV4	No conclusive evidence of risk in those without PDI
TV003 (NIH/Butantan/Merck)	LAV/Chimeric	Completed Phase 3	• Efficacious for both seropositive and seronegative • Data limited to DENV-1 and -2	Phase 3 trials in Asia starting
TDEN (GSK/WRAIR)	Inactivated	Phase 1	Poor immunogenicity	Stopped
V180 (Merck)	Subunit	Phase 1	Poor immunogenicity	Stopped
D1ME100 (US Navy)	DNA	Phase 1	?	Likely stopped



Ooi and Kalimuddin, Sci Transl Med 2023

Efficacy of the 3 live attenuated vaccines

	CYD-TDV (CYD14) (*32*)	CYD-TDV (CYD15) (*33*)	TAK003 (*35, 36*)	TV003 (*38*)
Primary end point*:				
VCD (%)	56.5	60.8	80.2	79.6
Other efficacy end points:				
Hospitalized VCD (%)	67.2	80.3	90.4†	NA

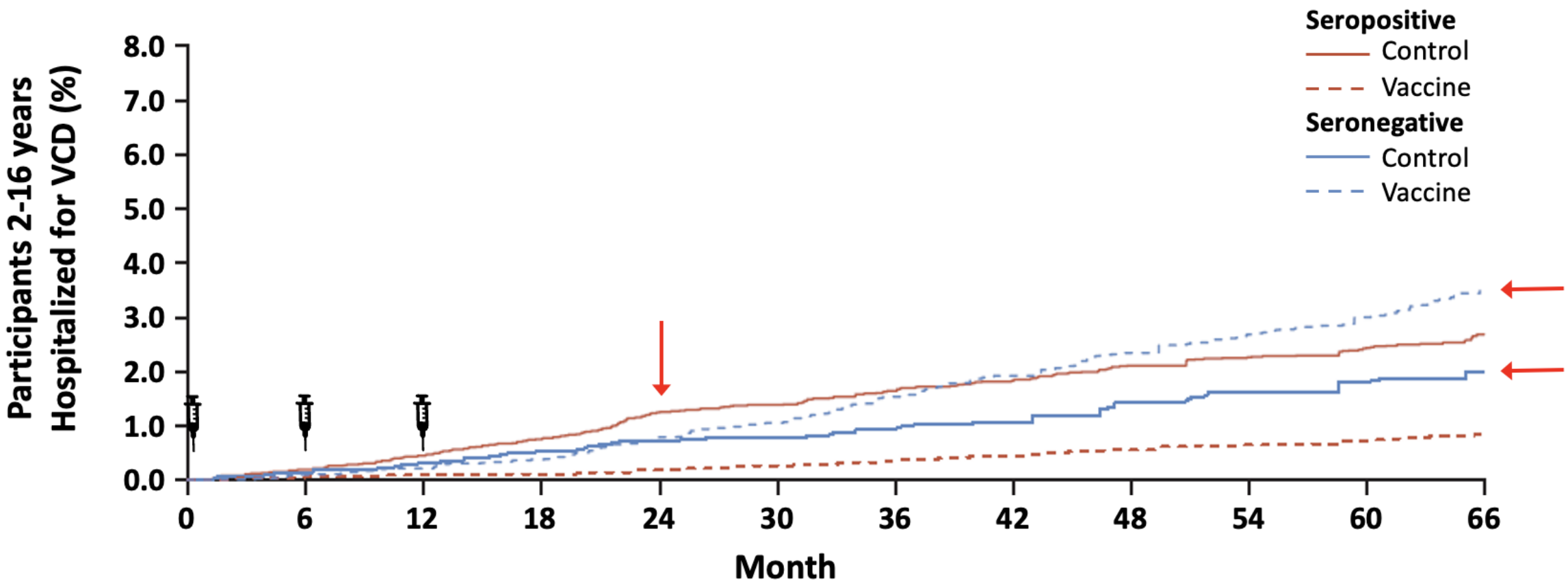
Ooi and Kalimuddin, Sci Transl Med 2023

Efficacy by DENV type

	CYD-TDV (CYD14) (*32*)	CYD-TDV (CYD15) (*33*)	TAK003 (*35, 36*)	TV003 (*38*)
VCD by DENV type				
DENV-1 (%)	50.0	50.3	73.7	89.5
DENV-2 (%)	35.0‡	42.3	97.7	69.6
DENV-3 (%)	78.4	74.0	62.6	NA
DENV-4 (%)	75.3	77.7	63.2‡	NA

Ooi and Kalimuddin, Sci Transl Med 2023

CYD-TDV in those without prior DENV infection



Sridhar et al, NEJM 2018

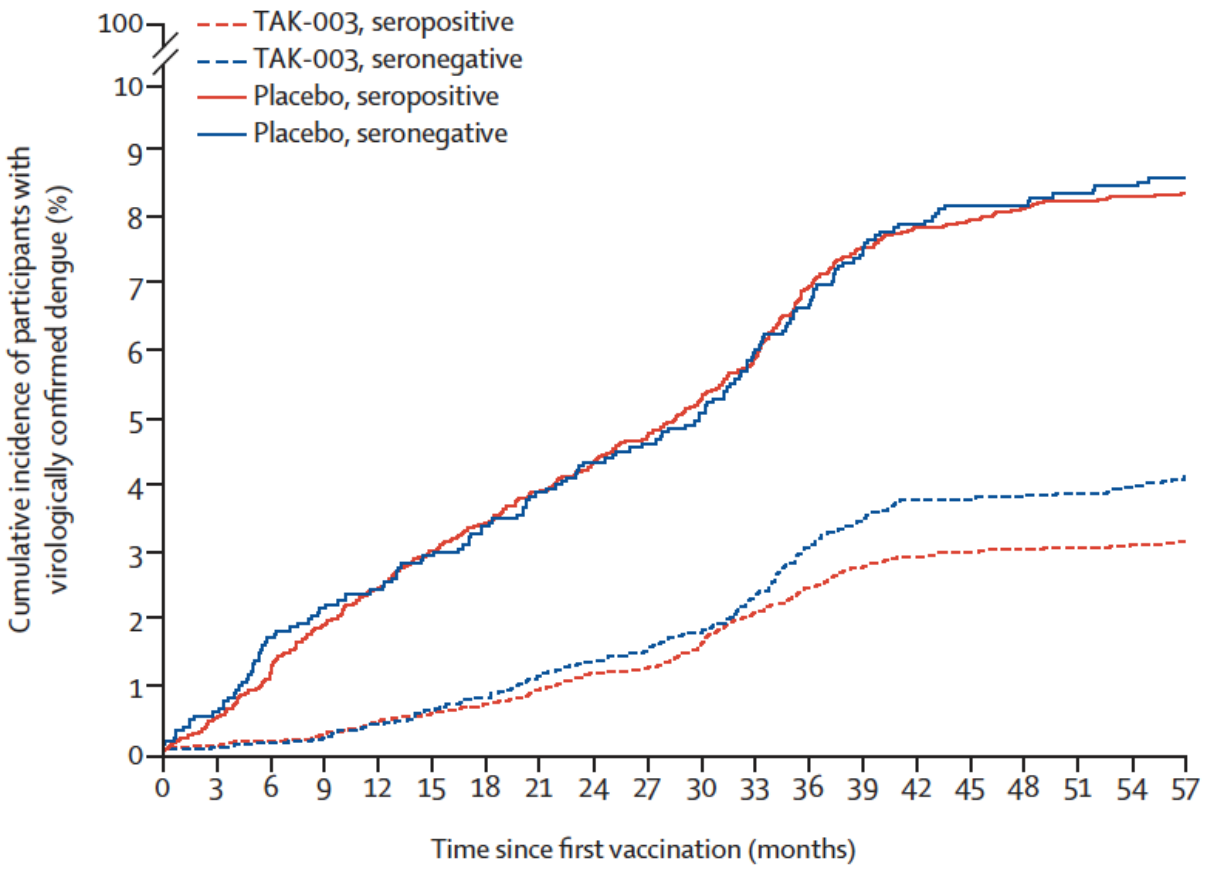
Efficacy by baseline serostatus & DENV type

Ooi and Kalimuddin, Sci Transl Med 2023

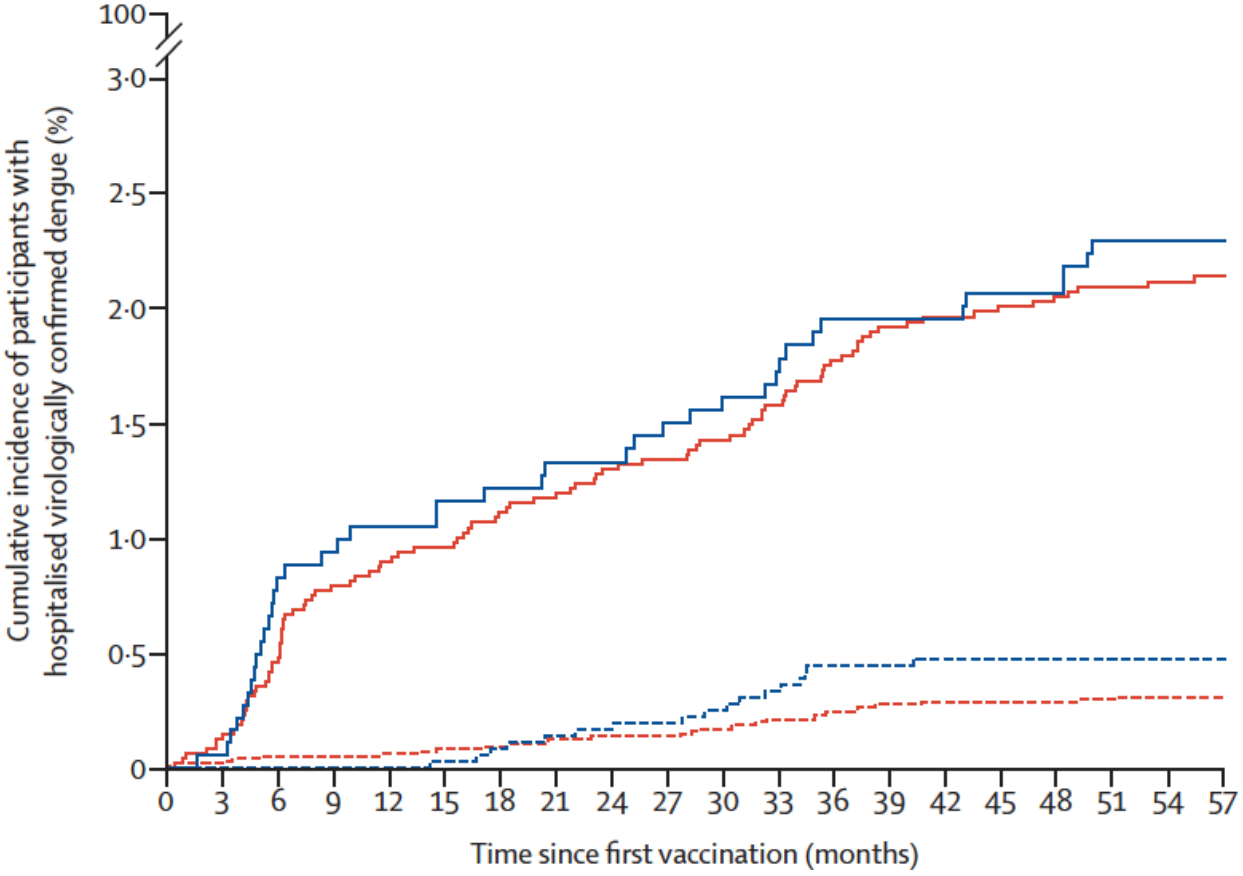
	CYD-TDV (CYD14) (*32*)	CYD-TDV (CYD15) (*33*)	TAK003 (*35, 36*)	TV003 (*38*)
VCD by baseline serostatus and DENV type				
Negative (overall) (%)	35.5‡	43.2‡	66.2	73.5
DENV-1 (%)	ND	ND	67.8	85.5
DENV-2 (%)	ND	ND	98.1	57.9
DENV-3 (%)	ND	ND	–68.2‡	NA
DENV-4 (%)	ND	ND	NA	NA
Positive (overall) (%)	74.3	83.7	76.1	89.2
DENV-1 (%)	ND	ND	72.0	96.8
DENV-2 (%)	ND	ND	93.7	83.6
DENV-3 (%)	ND	ND	61.8	NA
DENV-4 (%)	ND	ND	61.2‡	NA

Takeda's TAK003 vaccine efficacy over 54-months

Virologically-confirmed dengue



Hospitalized dengue



Tricou et al, Lancet Global Health 2024

Lessons from current dengue vaccines

Each DENV has unique immunity thresholds

Neutralising antibodies are important but don’t ignore T cells

Protection against DENV2 requires high nAb titers

6 DENV1 cases vs 13 PCR neg contacts

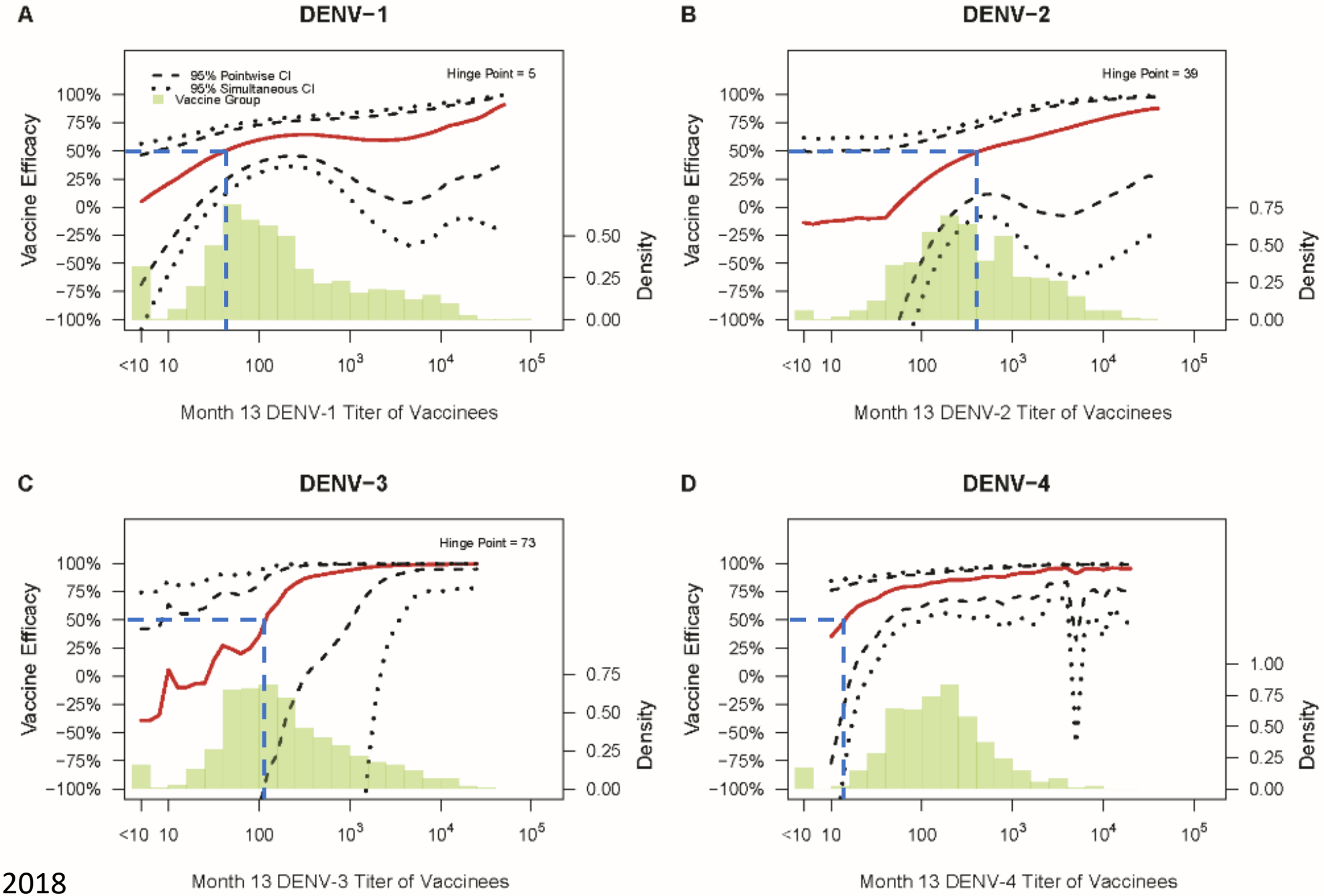
6 DENV4 cases vs 9 PCR neg contacts

5 DENV2 cases vs 10 PCR neg contacts

NT cutoff status[a]	PCR negative, no.	PCR positive, no.
	All serotypes combined	
Homotypic NT <11	13	14
Homotypic NT ≥11	19	3
	DENV-1	
DENV-1 NT <11	7	6
DENV-1 NT ≥11	6	0
	DENV-4	
DENV-4 NT <16	3	6
DENV-4 NT ≥16	6	0
	DENV-2	
DENV-2 NT <323	4	5
DENV-2 NT ≥323	6	0

Buddhari et al, PLoS Negl Trop Dis 2014

DENV-2 requires the highest neutralizing antibody titers for protection (CYD14 trial)



Moodie et al, J Infect Dis 2018

Balanced type-specific nAbs for protection?

JOURNAL ARTICLE

Immunogenicity of a Live Dengue Vaccine (TAK-003) FREE

Aravinda de Silva ✉, Laura White Author Notes

The Journal of Infectious Diseases, Volume 227, Issue 1, 1 January 2023, Pages 163–164, https://doi.org/10.1093/infdis/jiac424

Published: 26 October 2022 **Article history ▼**

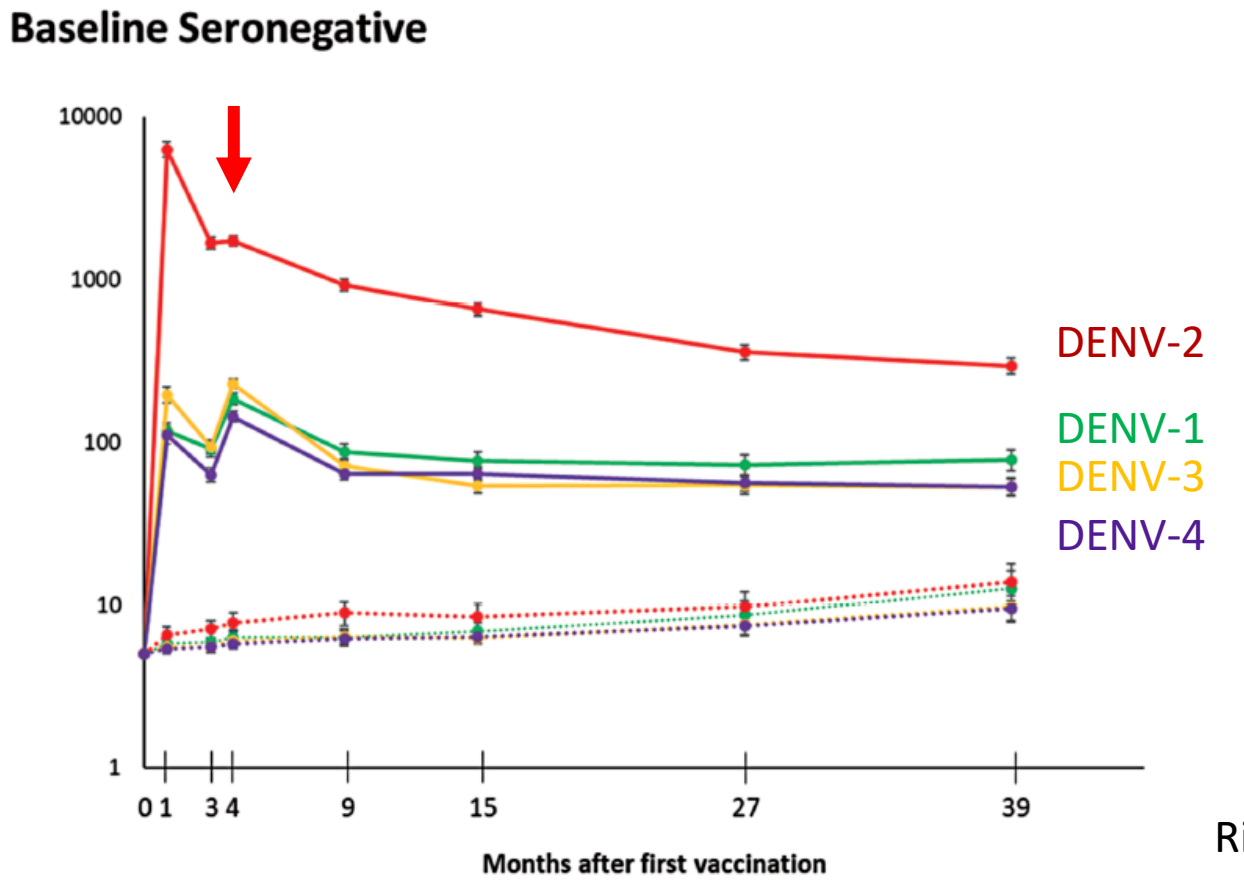
Primary DENV infection → Lasting type-specific immunity → Type-specific nAbs

Secondary DENV infection → Mostly asymptomatic 3rd & 4th infection → Cross-reactive nAbs

Okowlski et al, J Infect Dis 2013

Dejnirattisai et al, Nat Immunol 2015

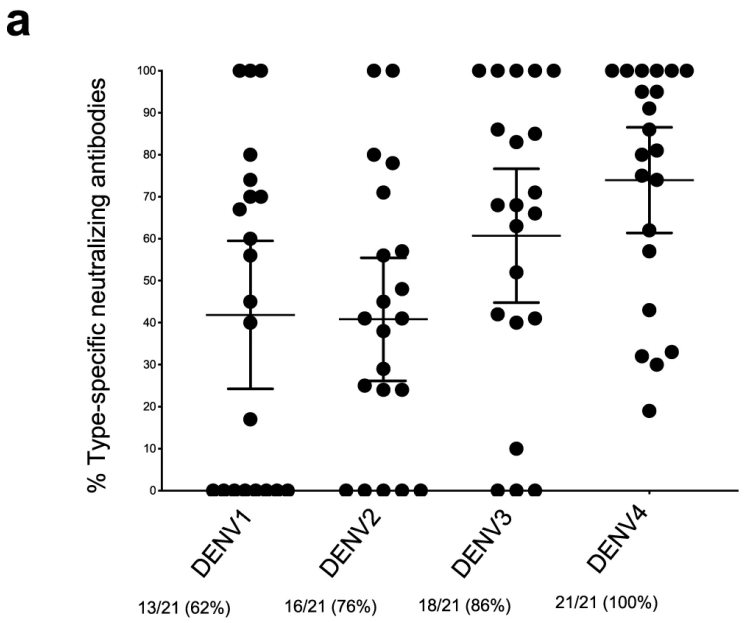
Secondary DENV-1, -3 and -4 infection with 2nd TAK003 dose?

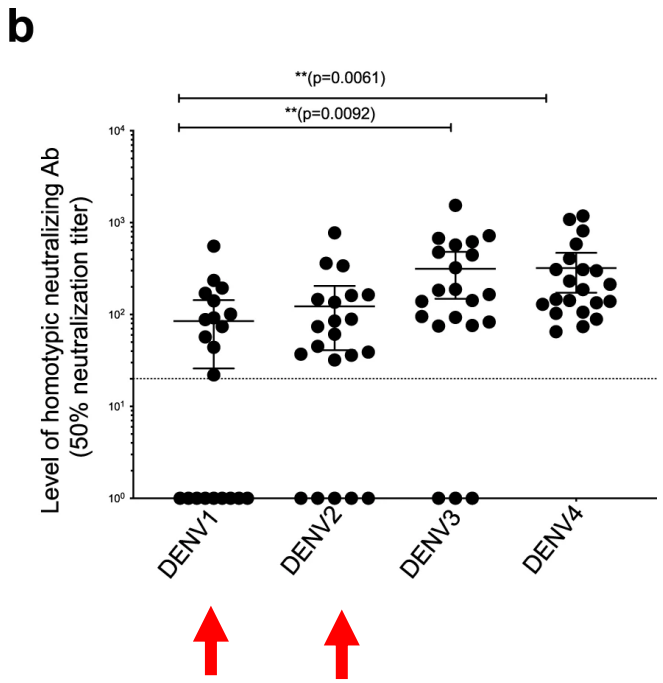


Rivera et al, Clin Infect Dis 2022

NAbs from TAK003 vaccination should reflect post-secondary DENV infection serology

Lower DENV-2 specific efficacy in seronegatives despite comparable type-specific neutralizing antibodies



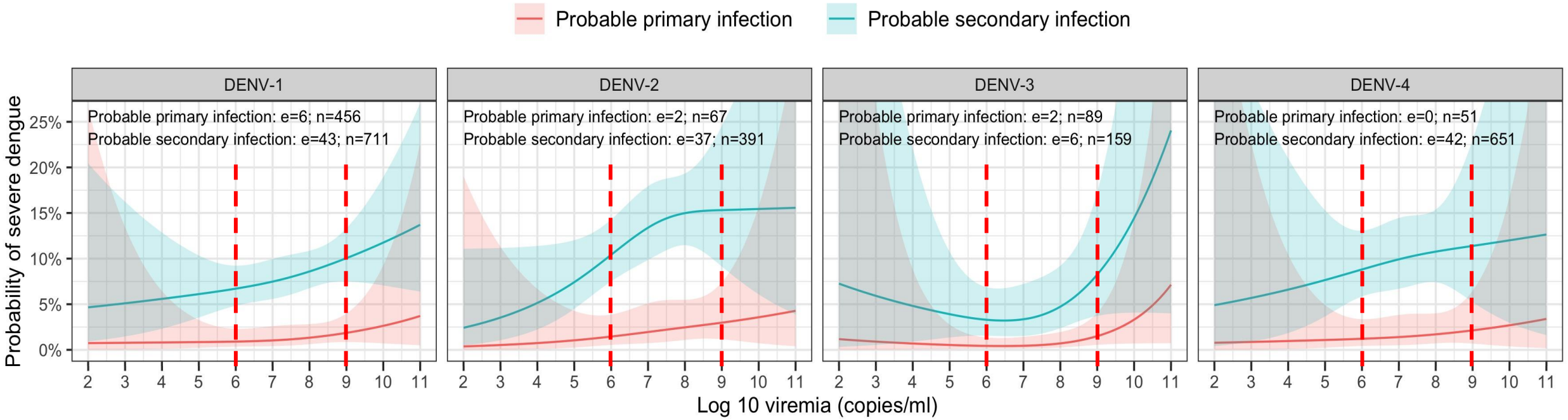


DENV-1	
Regardless of serostatus	89.5 (78.7 to 95.0)
With previous exposure	96.8 (81.0 to 99.8)
Without previous exposure	85.6 (69.1 to 94.0)
DENV-2	
Regardless of serostatus	69.6 (50.8 to 81.5)
With previous exposure	83.7 (63.1 to 93.5)
Without previous exposure	57.9 (20.8 to 78.1)

Nivarthi et al, Nat Commun 2021

Kallas et al, New Engl J Med 2024

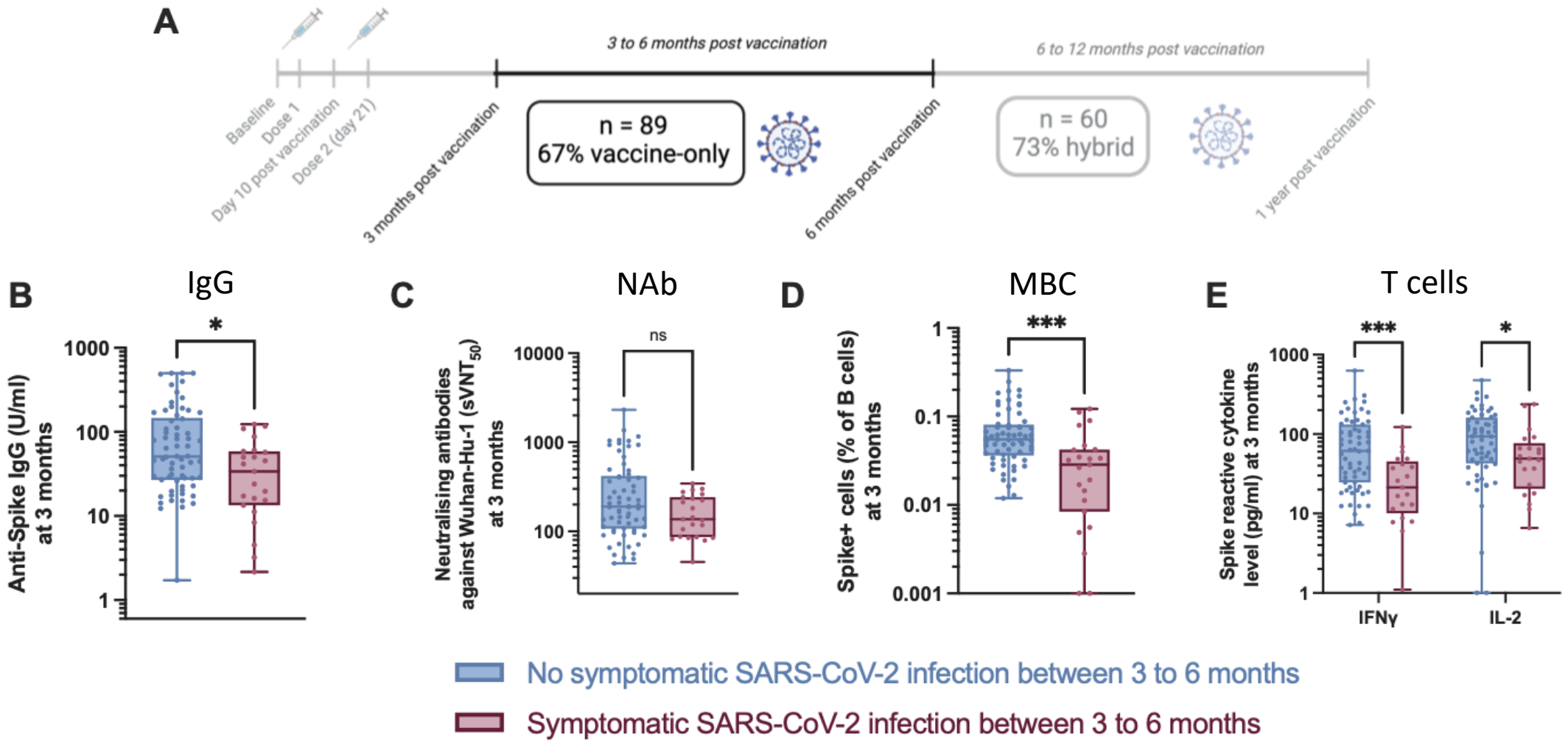
Secondary DENV2 shows greatest increase in risk of severe dengue



Vuong et al, Clin Infect Dis 2021

Can mRNA overcome challenges met by live attenuated vaccines?

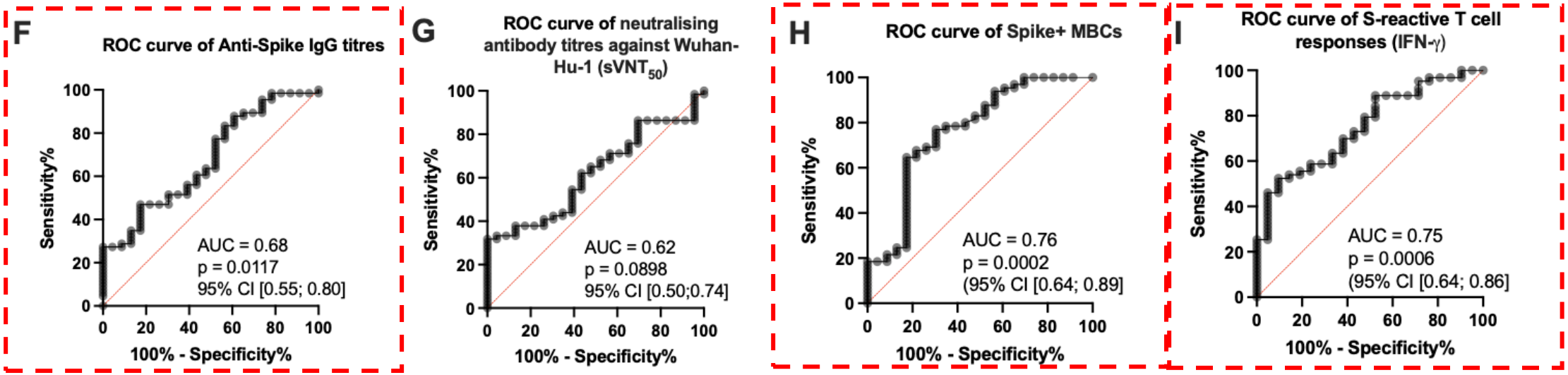
Higher total IgG, MBC and T cells protect against infection before hybrid immunity



Zhong et al, Nat Med, in press

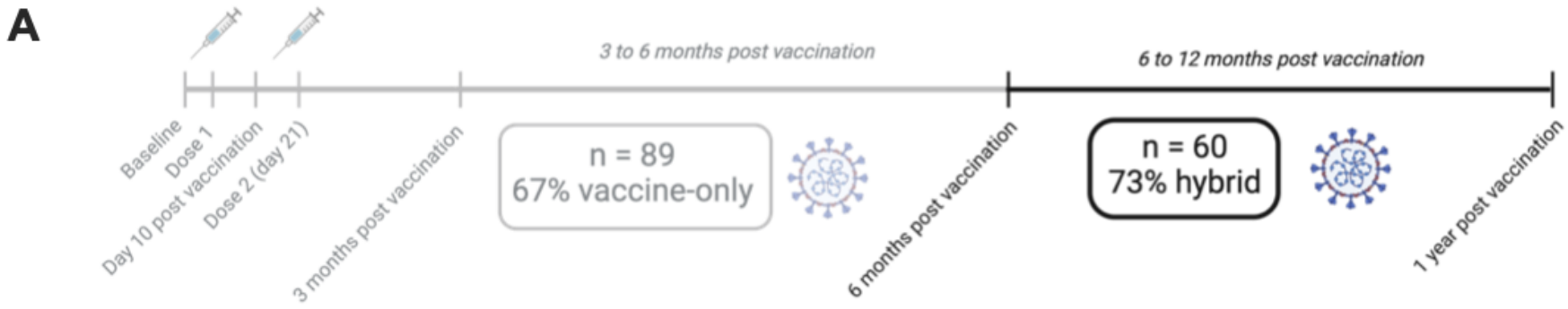
T cell levels predict protection against COVID-19

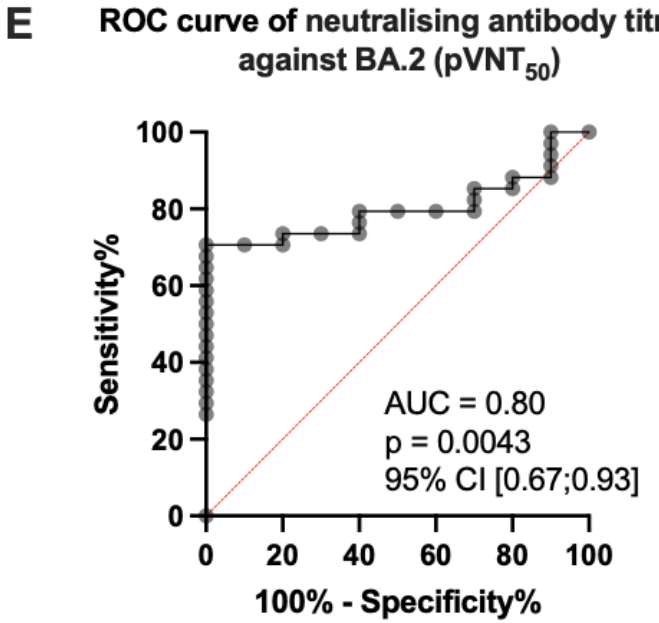
Zhong et al, Nat Med, in press

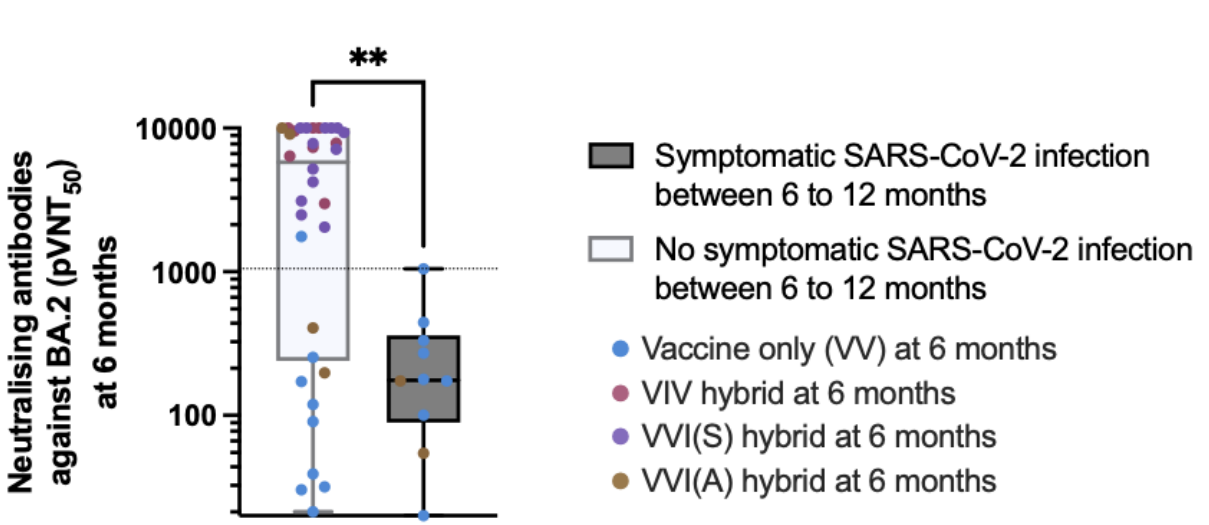


Parameter	Odds Ratio	95% Confidence Interval	p-value
Anti-S IgG	0.66	0.13, 3.95	0.600
Wuhan-Hu-1 $sVNT_{50}$	1.76	0.12, 33.26	0.700
BA.2 $pVNT_{50}$	0.41	0.12, 1.22	0.130
IFN-γ	0.16	0.03, 0.66	0.020
S+ MBC	0.00	0.00, 0.04	0.057
(Intercept)	78.81	0.48, 31401.80	0.11

Post-hybrid immunity is dominated by nAbs



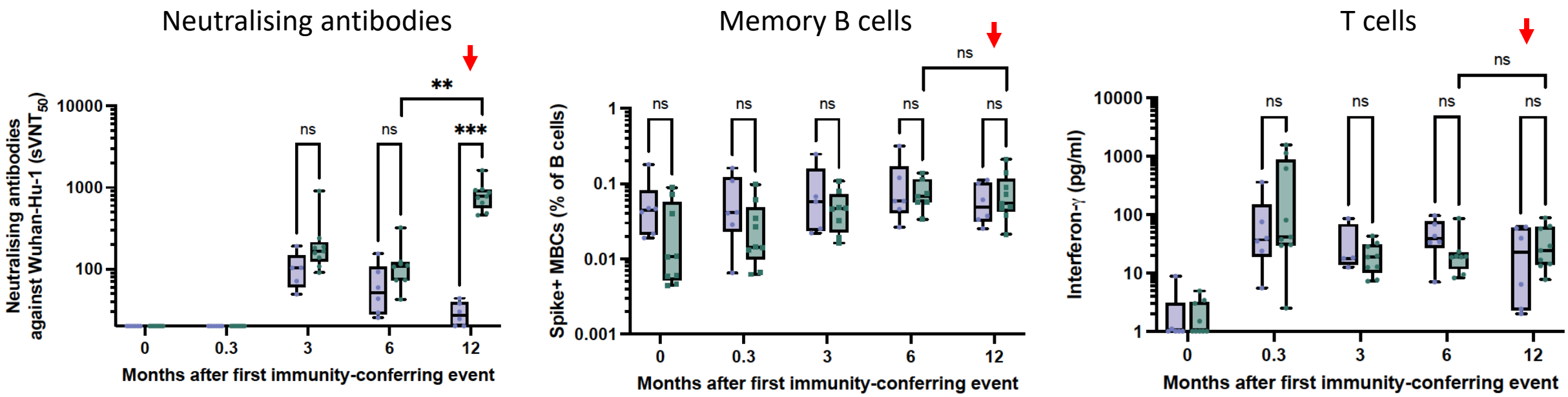




Zhong et al, Nat Med, in press

NAb titers but not MBCs and T cells wane

↓ 3rd booster mRNA vaccination



NAb titers wane; no waning of MBCs and T cell levels

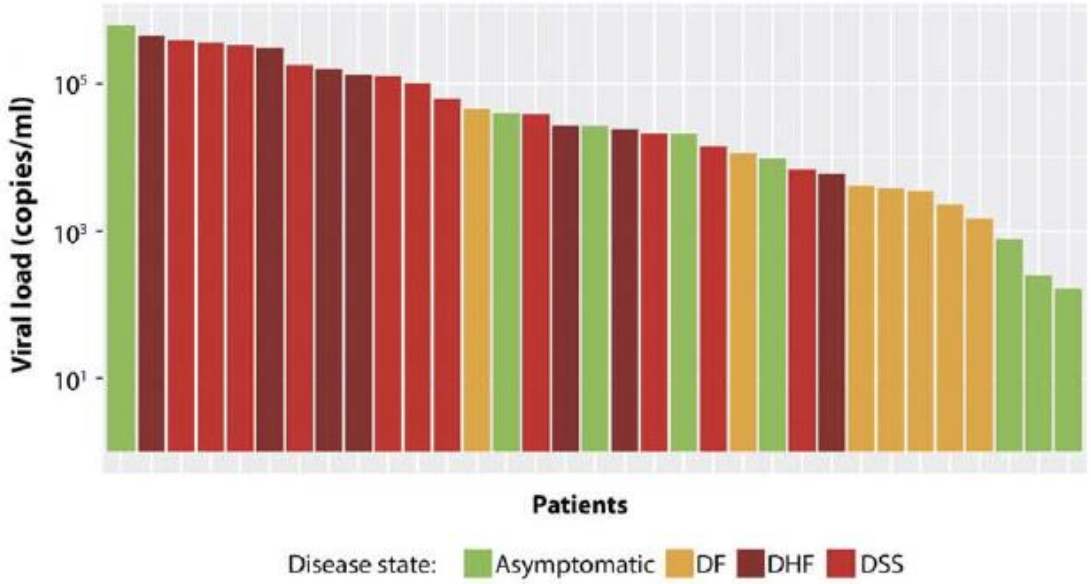
Zhong et al, Nat Med, in press

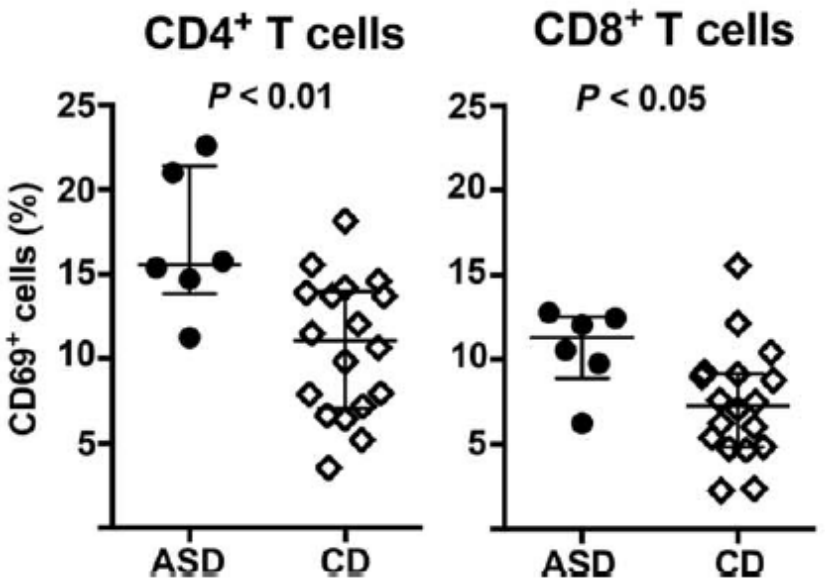
Do T cells protect against dengue?

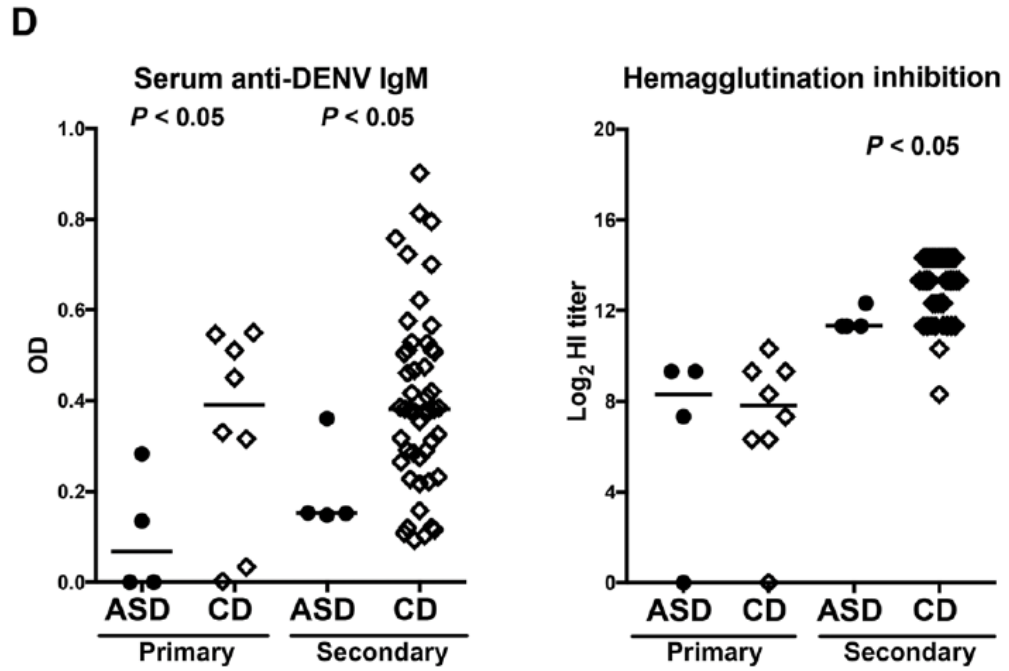
Increased T cell activation in asymptomatic DENV infection

Simon-Loriere et al, Sci Transl Med 2017

ASD: Asymptomatic dengue
CD: Clinical dengue







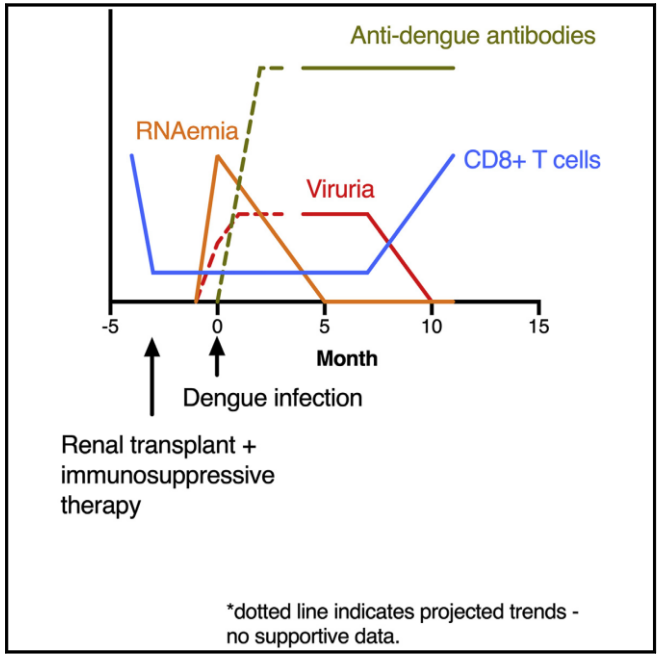
T cells - not antibodies - terminate DENV infection

Cell Host & Microbe

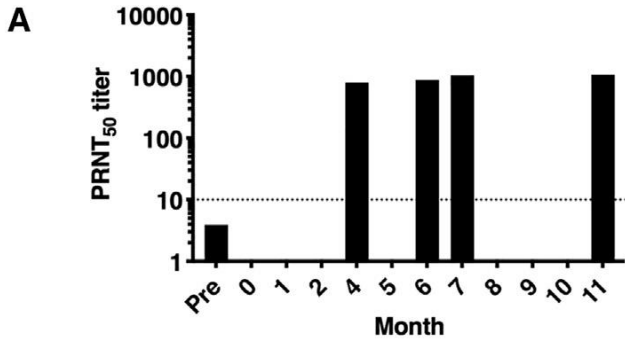
Persistent Dengue Infection in an Immunosuppressed Patient Reveals the Roles of Humoral and Cellular Immune Responses in Virus Clearance

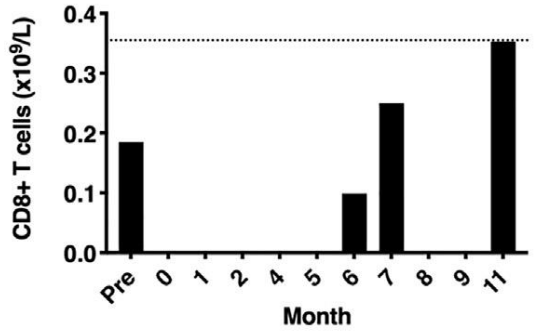
Kar-Hui Ng,[1,2,9,*] Summer Lixin Zhang,[3] Hwee Cheng Tan,[3] Swee Sen Kwek,[3] October Michael Sessions,[3,4] Chang-Yien Chan,[1] Isaac Desheng Liu,[2] Chun Kiat Lee,[5] Paul Ananth Tambyah,[6] Eng Eong Ooi,[3,4,7,8] and Hui-Kim Yap[1,2,8]

Graphical Abstract



Renal Tx patient
DENV-3 infection





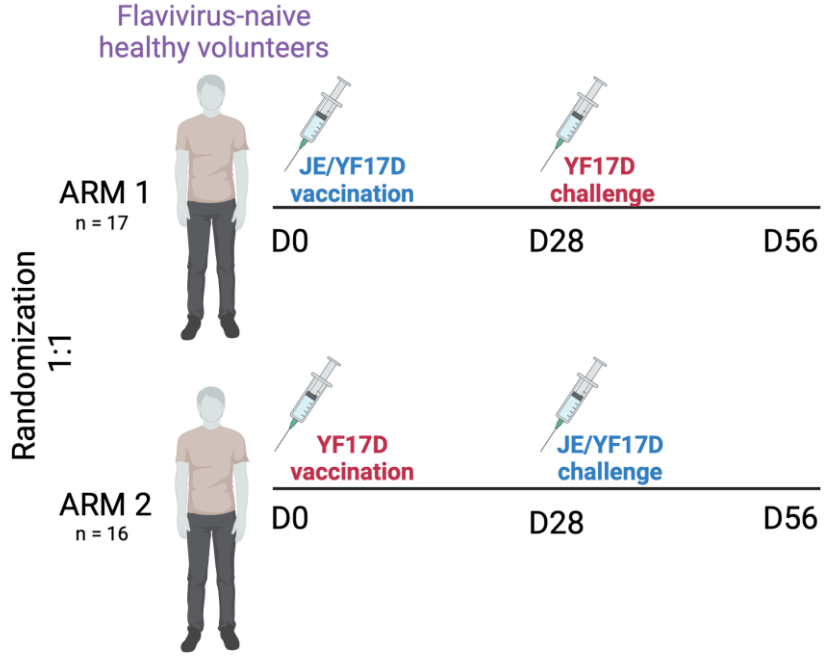
F

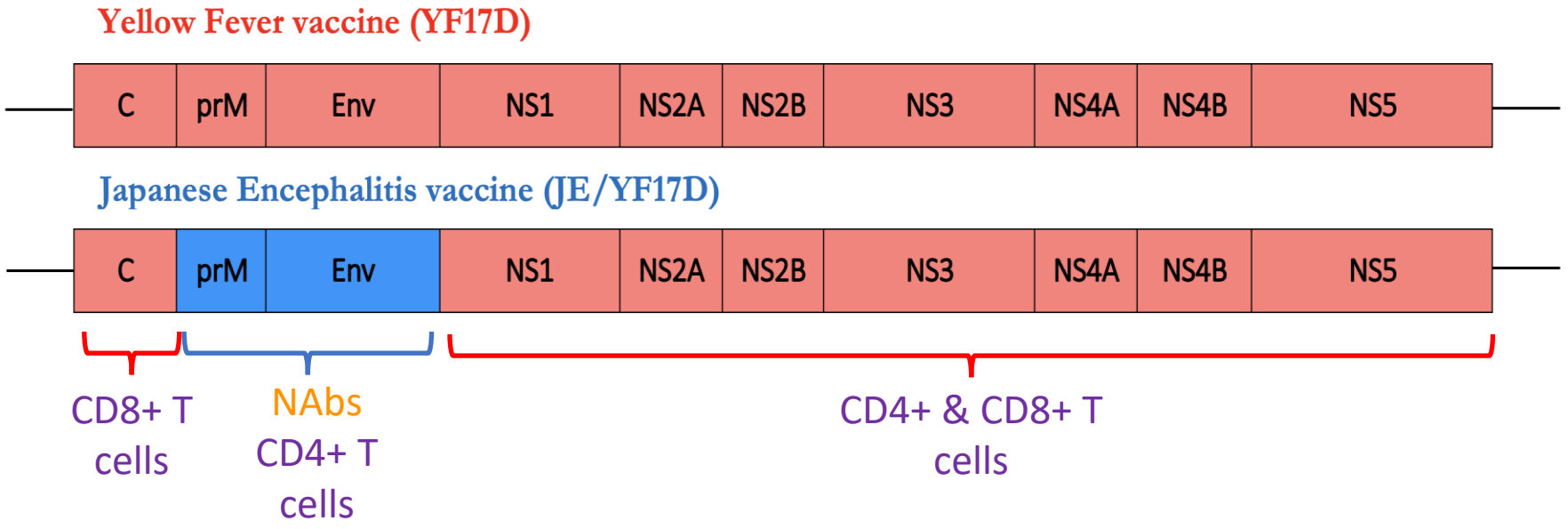
DENV RT-PCR (serum)	o + + + + o - - o o o
Virus isolation (serum)	o o o o - o o - o o o
Virus isolation (urine)	o o o o + o o + o + o
DENV RT-PCR (podocytes)	o o o o o o + + - o -

What T cells are needed?

Flavivirus vaccination and heterologous challenge

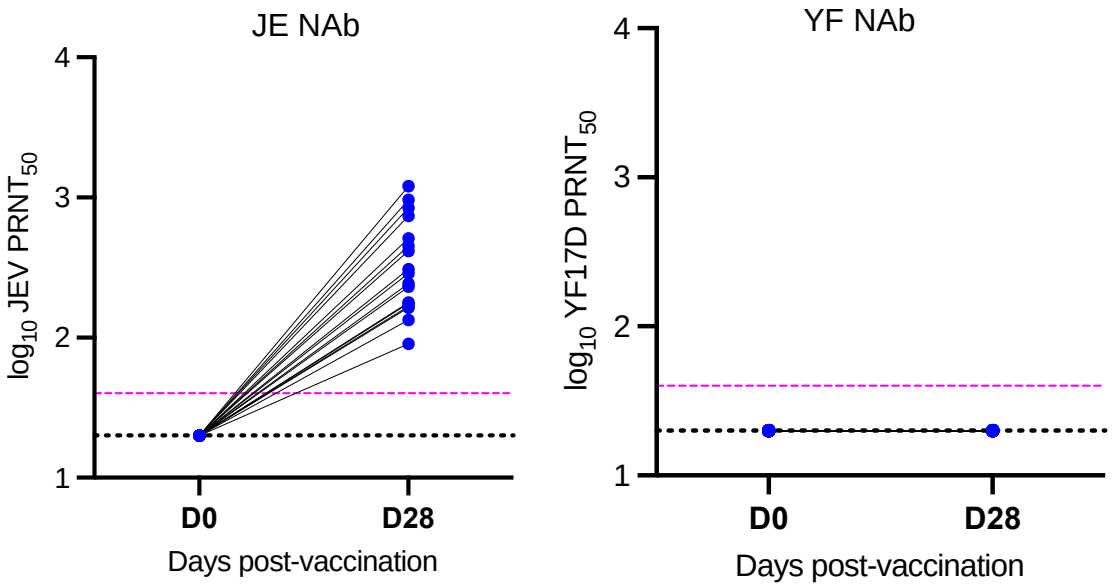
Kalimuddin et al, manuscript in preparation



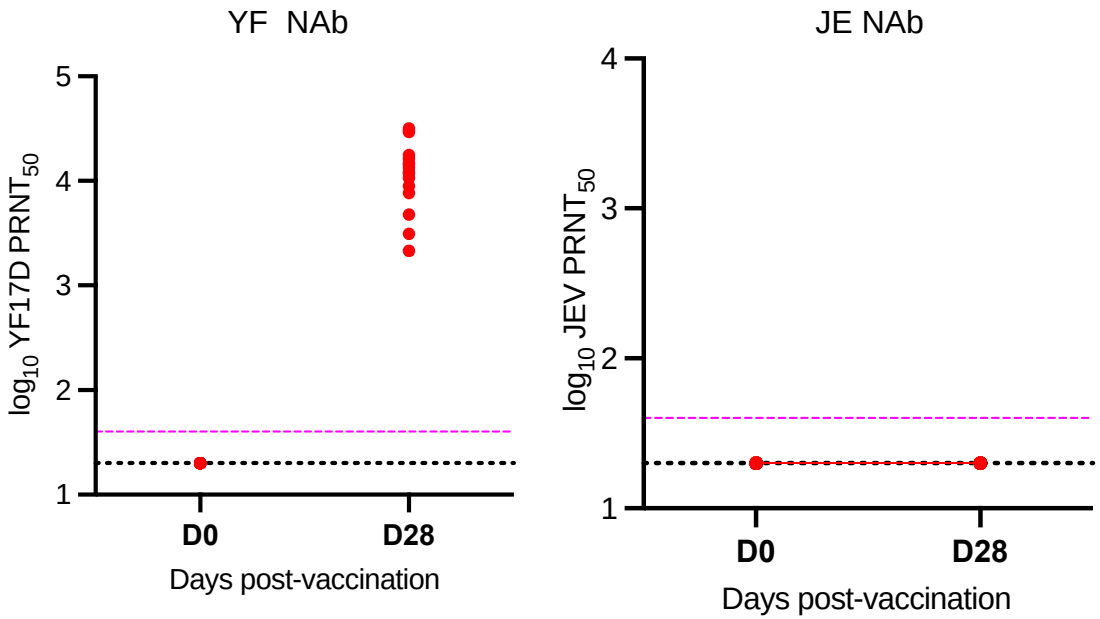


YF17D and JE/YF17D vaccinees all seroconvert
No cross-neutralization

JE/YF17D vaccination

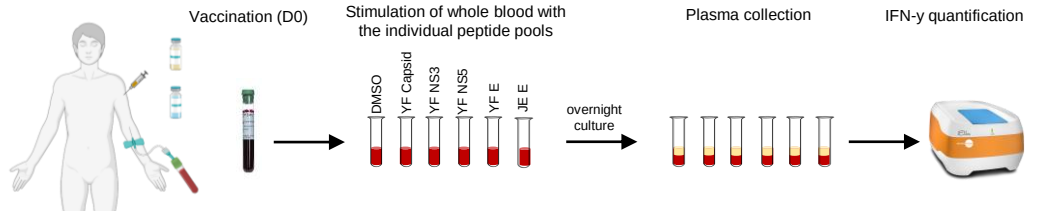


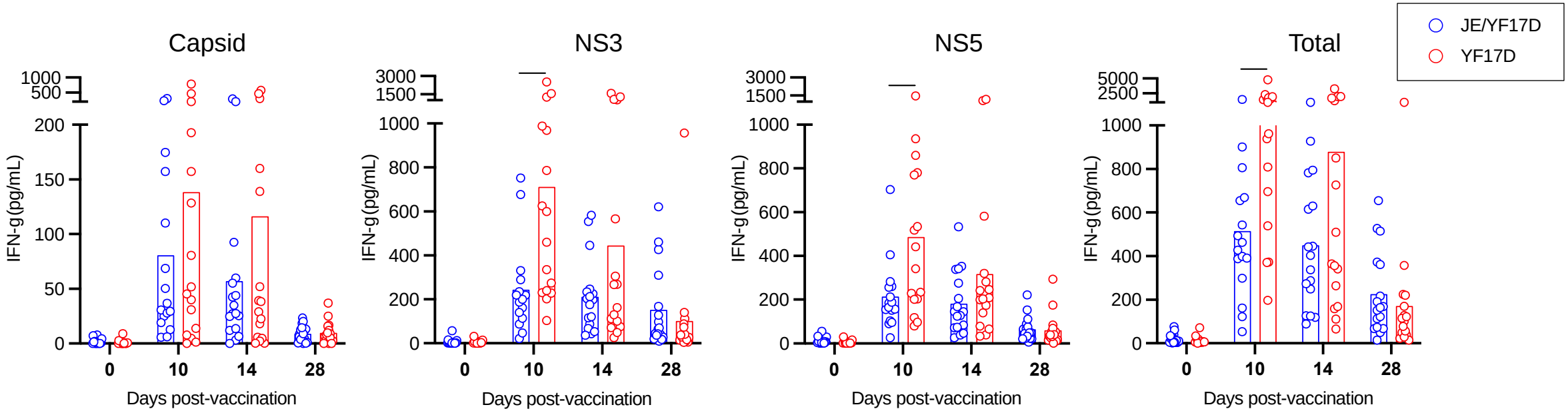
YF17D vaccination

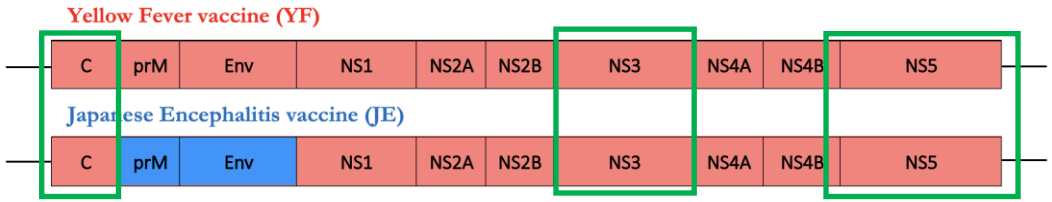


Kalimuddin et al, manuscript in preparation

YF17D induces stronger antigen-specific T cell responses compared to JE/YF17D





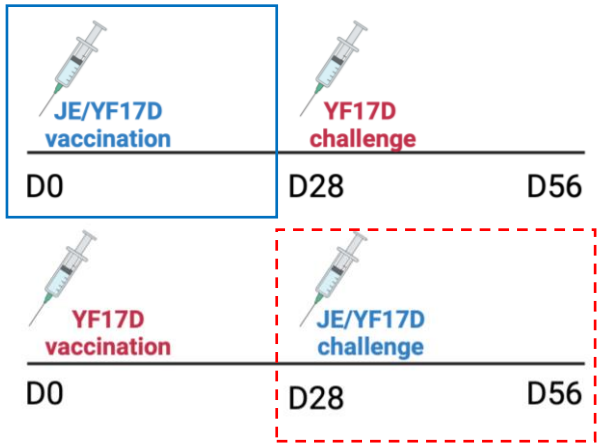


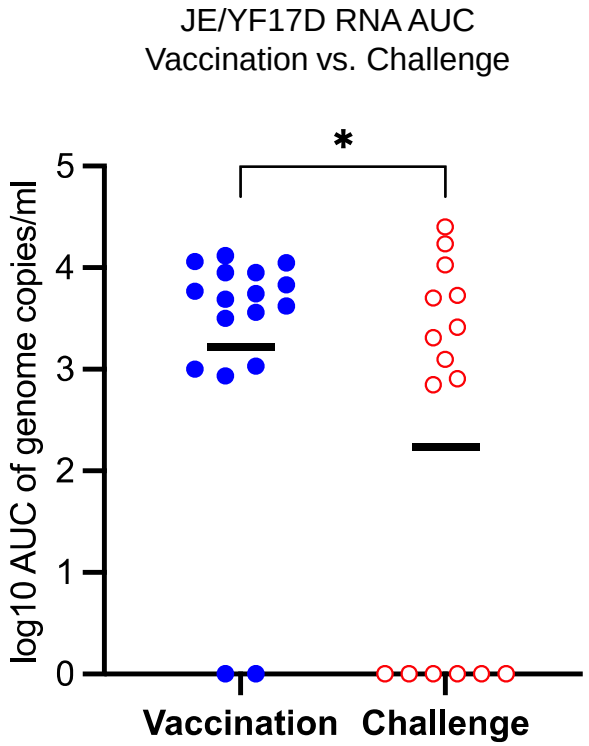
A priori hypothesis

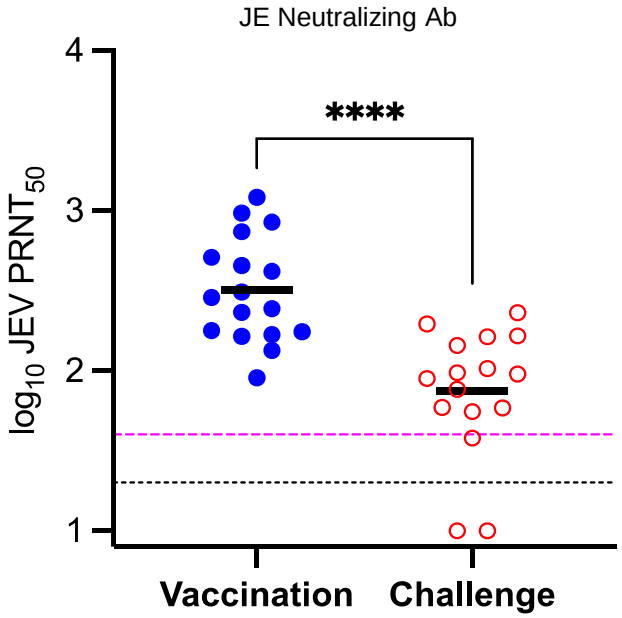
Higher T cell response from YF17D vaccination will reduce chimeric JE/YF17D viremia

YF17D vaccination and JE/YF17D challenge

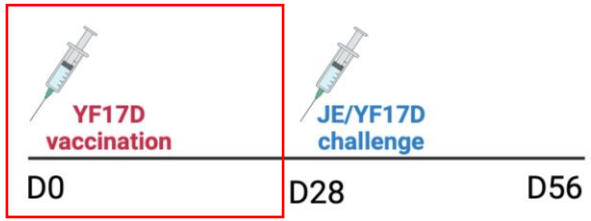
Primary outcome: Reduction of JE/YF17D viremia at challenge vs vaccination



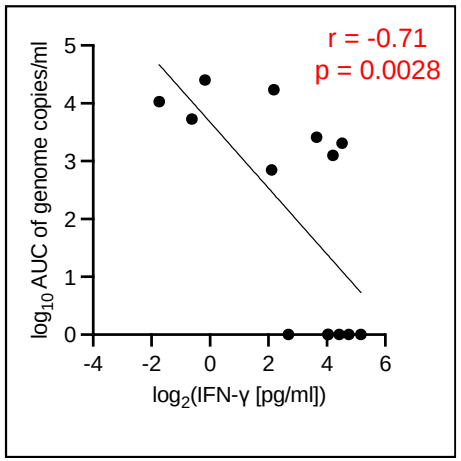


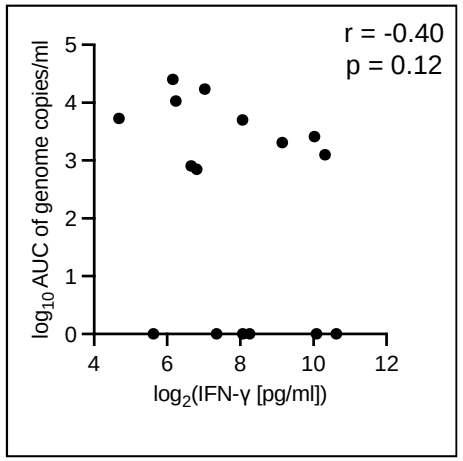


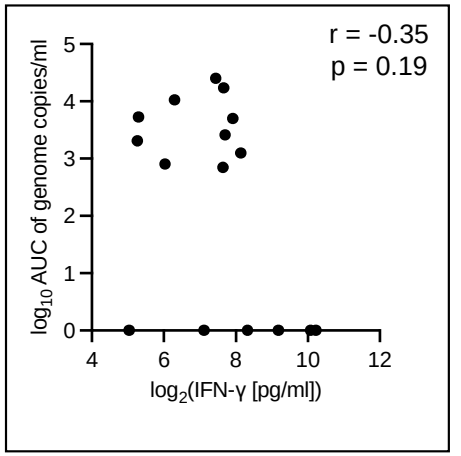
High YF17D-induced T cell responses control JE/YF17D challenge infection

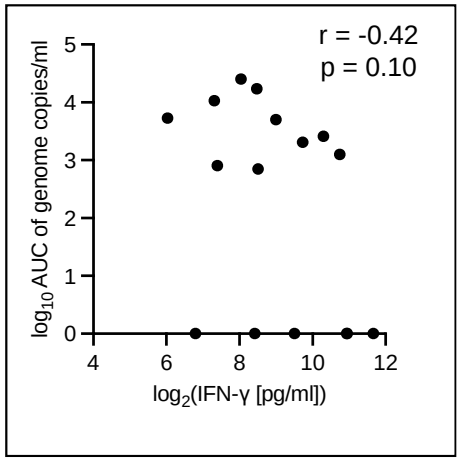


Day 14
(Pre-JE/YF17D challenge)

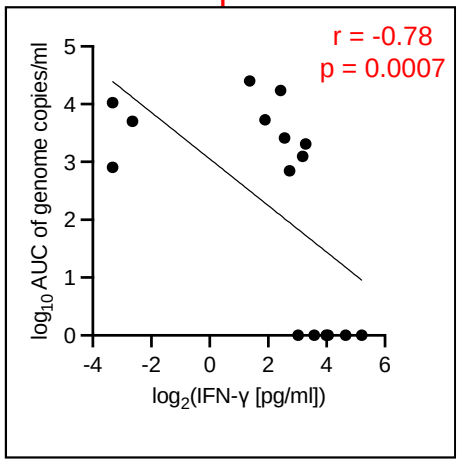


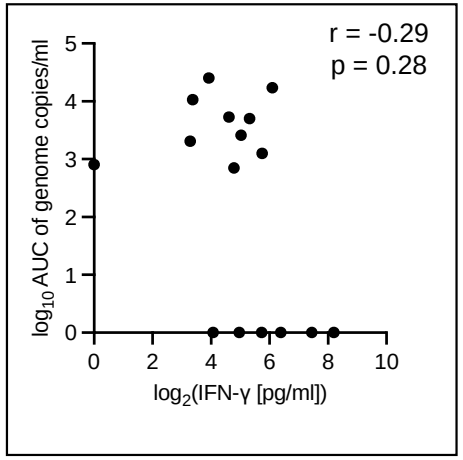


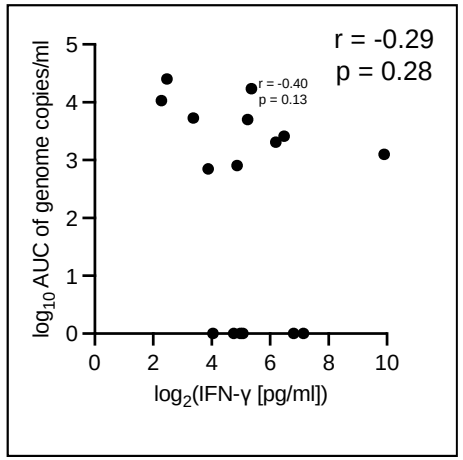


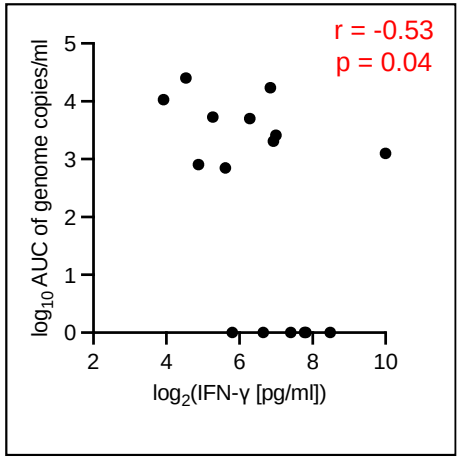


Day 28
(Day of JE/YF17D challenge)

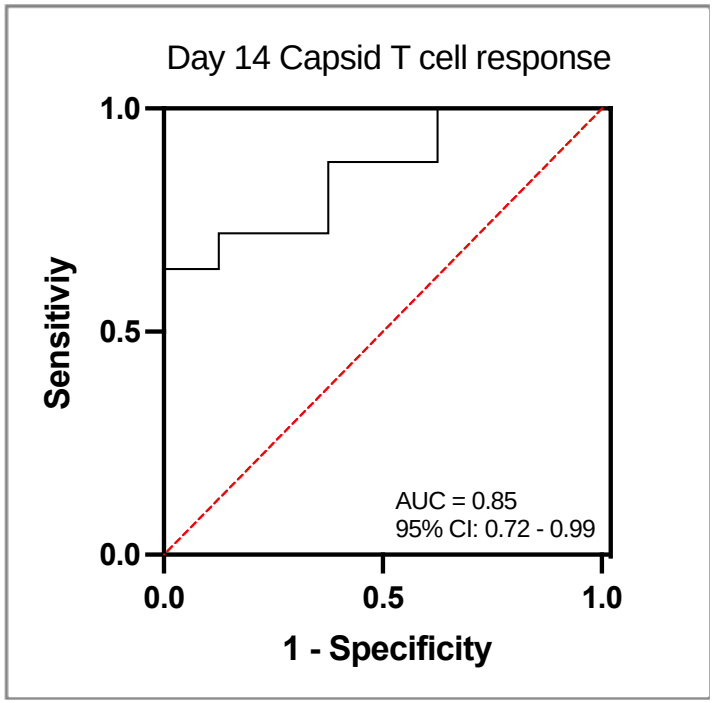


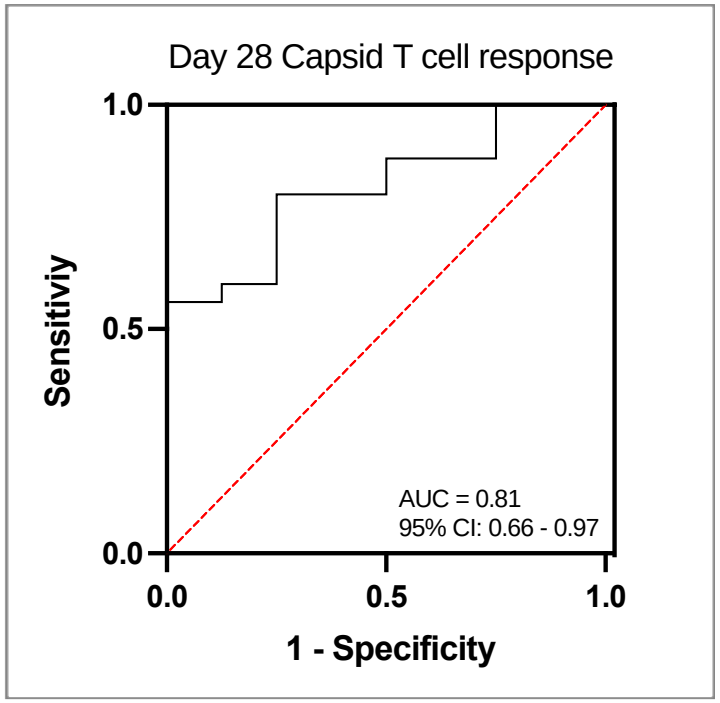






Vaccine-induced Capsid-specific T cell response predict challenge infection outcome





Day 14 capsid-specific T cell response of $\geq$ 38.8 pg/ml IFN-γ can differentiate between viremia and aviremia

Sensitivity: 72%, Specificity: 87.5%, LR:5.76.

Summary

- DENV1-4 are not monolithic
- Each DENV has a different immunity threshold
- T cells protect
- New vaccines
  - B and T cell immunity
  - Choice of T cell epitopes
- Heterologous prime-boost approach to full protection?

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