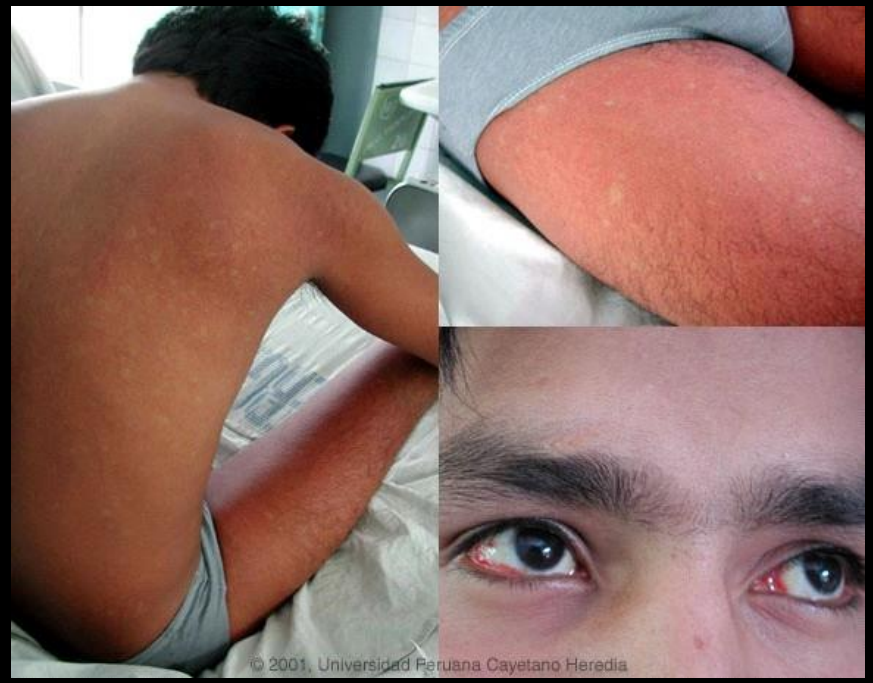
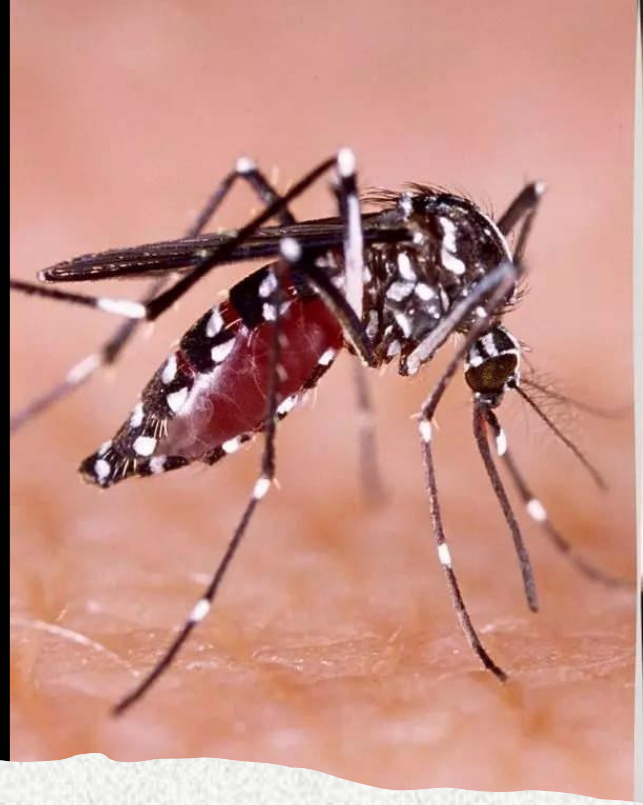
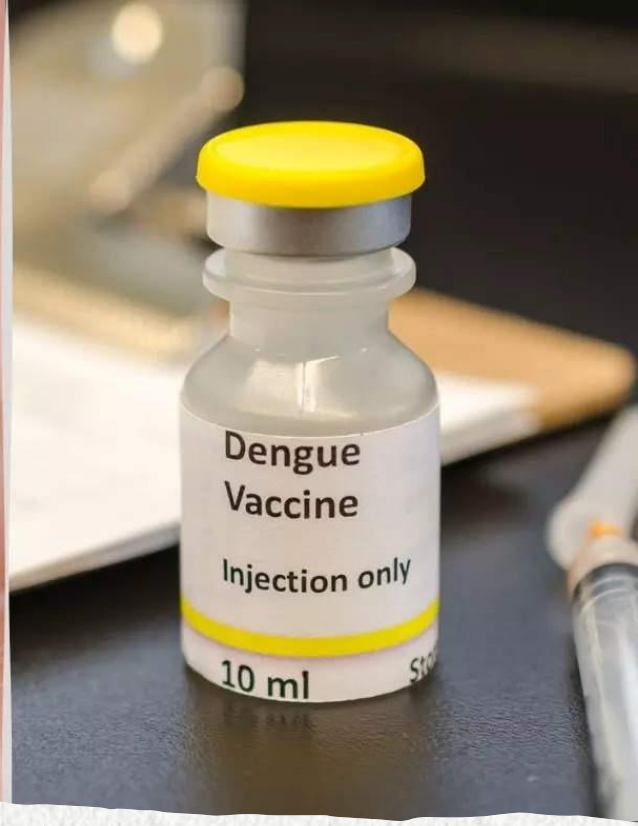






Clinical trial design and policy expectations for dengue vaccines

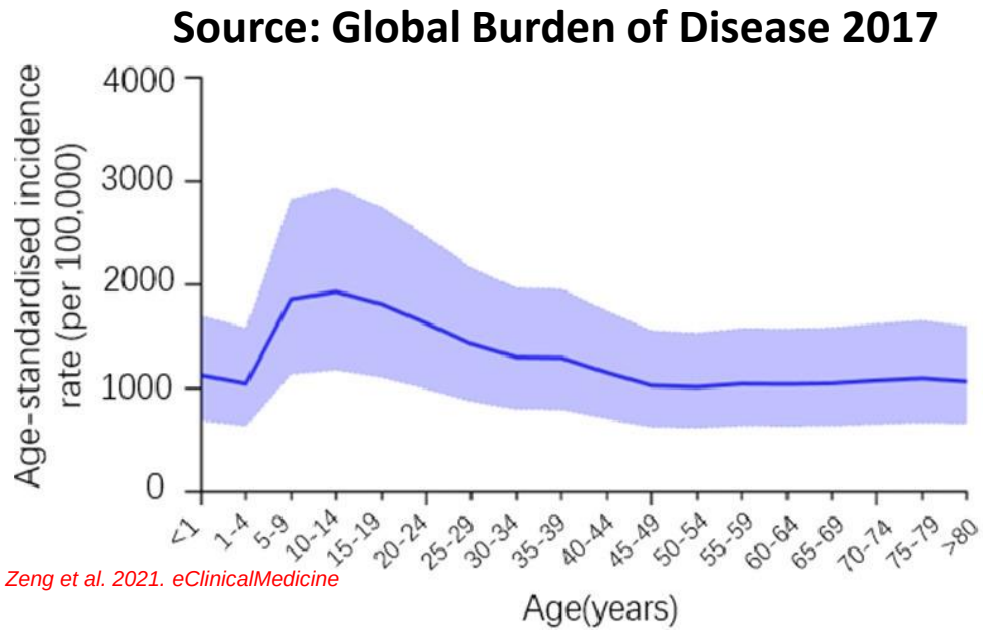
Annelies Wilder-Smith MD PhD

WHO, IVB, Team Lead Vaccine Development

WHO technical lead: SAGE WG Dengue Vaccines

Honorary Professor of Emerging Infectious Diseases, London School of Hygiene and Tropical Medicine

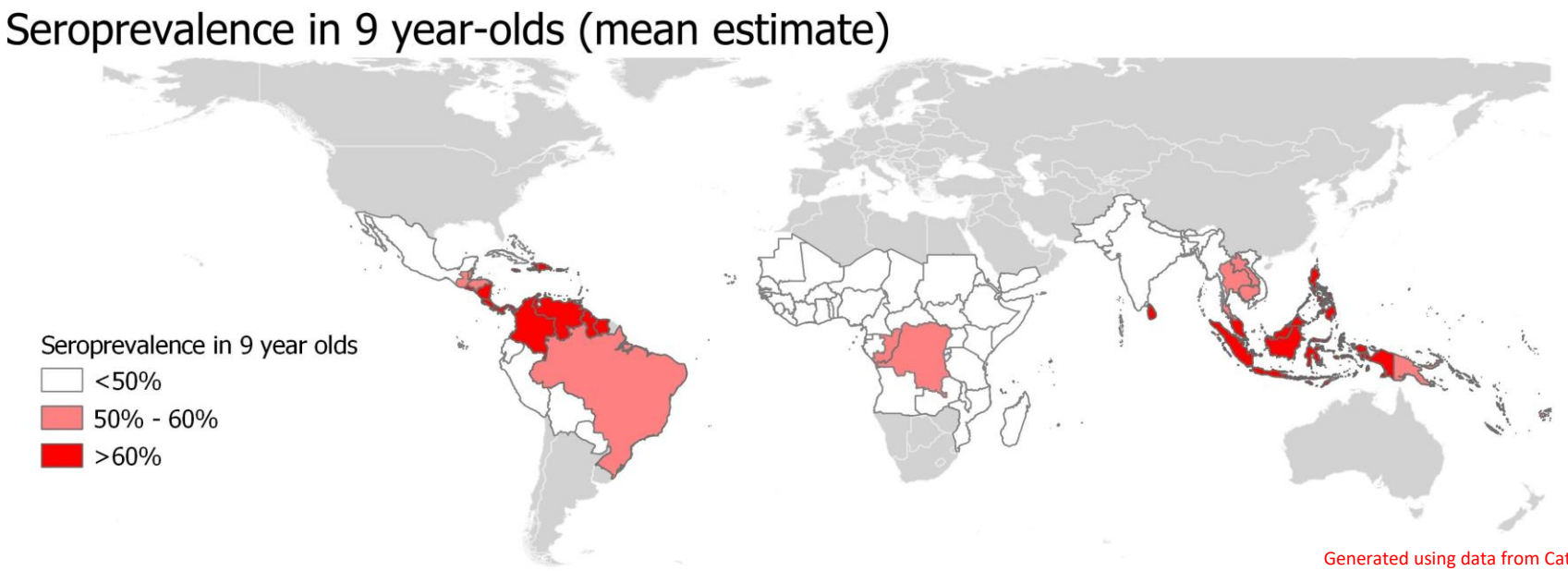
Age-dependent dengue transmission trends



Zeng et al. 2021. eClinicalMedicine

Globally, incidence peaks between 5 and 14 years of age.

Seroprevalence in 9-year olds: a good proxy for high transmission and endemic settings.

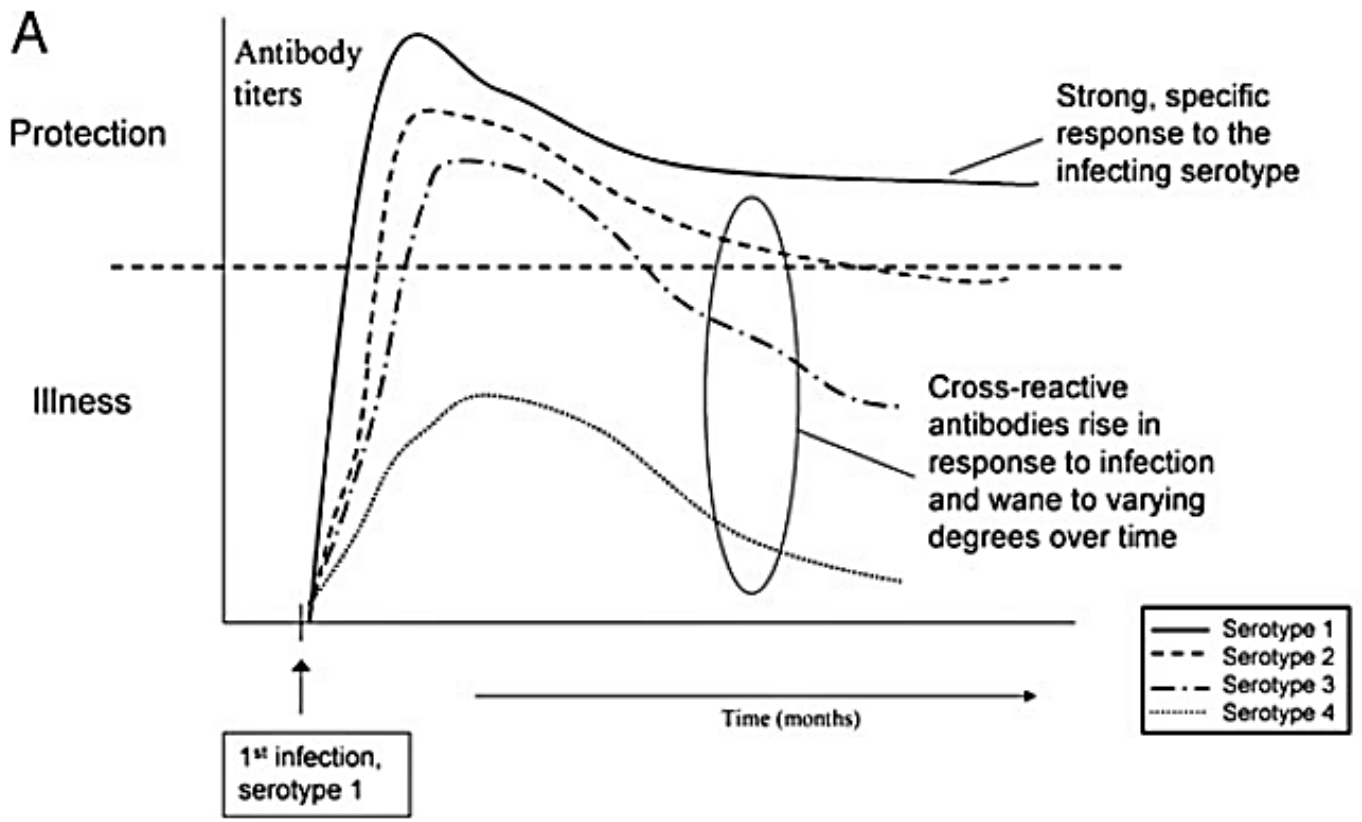


Generated using data from Cattarino et al. 2020. Science Trans. Med.

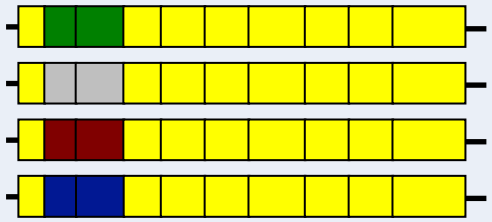
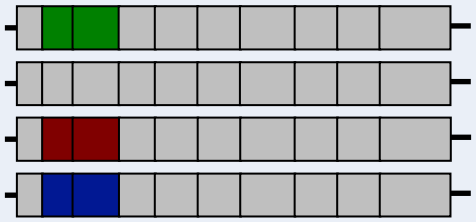
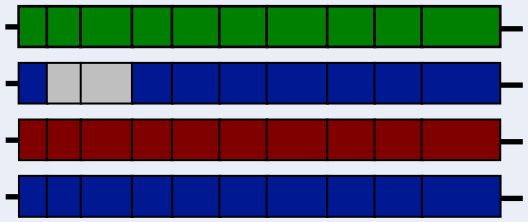
Policy expectations

- A dengue vaccine that meets the public health needs:
- Efficacious and safe regardless of dengue serostatus
- Balanced efficacy against all four serotypes
- Long duration
- Ideally single dose
- Age indication: Infants, children and adolescents (for most endemic countries); without upper age limit (for low endemic countries and for travellers)

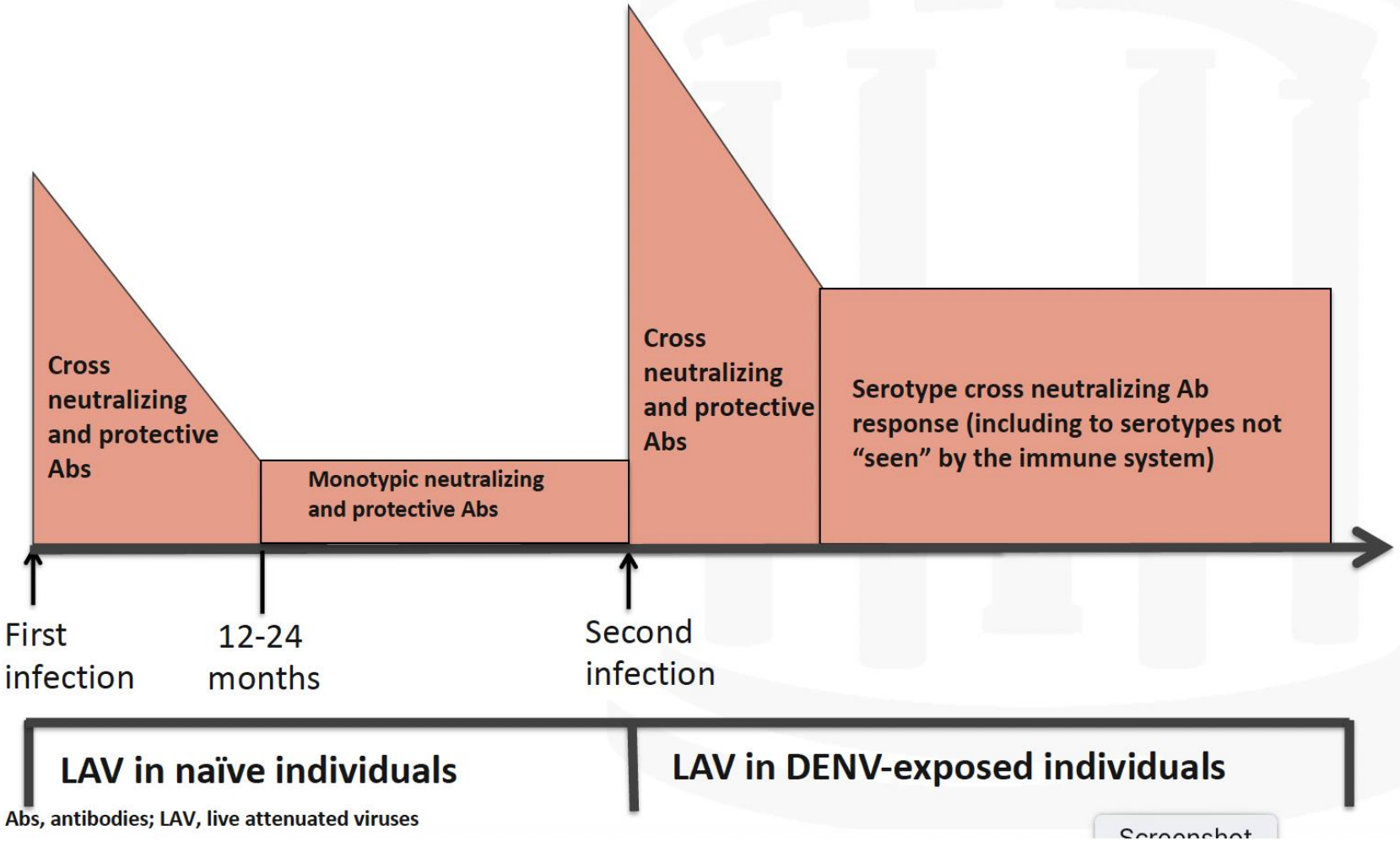
Immunological interaction between the 4 serotypes



Three dengue vaccine candidates, all are tetravalent and live attenuated; differences in the backbone and extent of chimerization

	Dengvaxia (Sanofi Pasteur)	TAK-003 (Takeda)	TV003/TV005 (NIH/Butantan/Merck)
Status	Licensed	Licensed	Phase 3
# Doses	3 doses over 12 months (0, 6, 12)	2 doses (0, 3 months)	Single dose
Indicated age	9 - 45	Phase 3 age range 4 - 16	Phase 3 age range 2 - 59
Other	Requires documented previous DENV infection	?	?
Construct			
Dengue proteins	8	16	32

Neutralizing/protective antibody responses following DENV infection and vaccination



Abs, antibodies; LAV, live attenuated viruses

Serostatus-driven vaccine performance

- Dengvaxia
- Seropositive persons. efficacious and safe, especially serotype 4
- Seronegative persons: increased risk of severe dengue in seronegative persons:
  - RR 2-3
- a “pre-vaccination screening strategy” is the recommended strategy, in which only dengue-seropositive persons are vaccinated.
- Age 6-45
- Low vaccine uptake due to the costs and complexities of the “test-and vaccinate” policy

- Qdenga TAK-003
- Seropositive persons: efficacious and safe, especially serotype 2
- Seronegative persons: efficacious against serotypes 1 and 2. Absence of efficacy in serotypes 3 and 4
- Safety risk cannot be excluded with the available data
- WHO recommendation: use in settings with high dengue transmission intensity only, eg seroprevalence > 60%, age 6-16
- No pre-vaccination screening

Viremia following a single dose of Butantan/Merck`s TV003 vaccine

The percentage of subjects with detectable viremia by PCR after a single dose in flavivirus-naïve subjects				
	DENV-1	**DENV-2**	**DENV-3**	**DENV-4**
CYD, Day 7 (n=12)[1]	0	0	17	**50**
CYD, Day 7 (n=84)[2]	0	2	0	**30**
CYD (n=25)[3]	0	4	0	**52**
CYD (n=95)[4]	7.4	0	12.6	**44.2**
TAK (n=74)[5]	0	68.9	0	0
TV003 (n=36)[6]	**63.9**	**69.4**	**52.8**	**52.8**

1. Qiao et, 2011, viremia only measured on day 7 & 14, but cumulative viremia was not reported
2. Poo, et al, 2011, viremia only measured on day 7 & 14, but cumulative viremia was not reported
3. Dayan, et al, 2013; CYD 5:5:5:5 formulation. Viremia measured only by RT-PCR
4. Torresi, et al 2017; CYD lot-to-lot consistency trial. Viremia measured on days 6, 8, 10, 14, & 20
5. Rupp et al 2015; Viremia measured on days 7, 9, 11, 14, &17
6. Russell et al, ASTMH 2019, Merck V181. Viremia collected on days 7 & 12 only

Vaccine

Volume 36, Issue 24, 7 June 2018, Pages 3411-3417

WHO Report

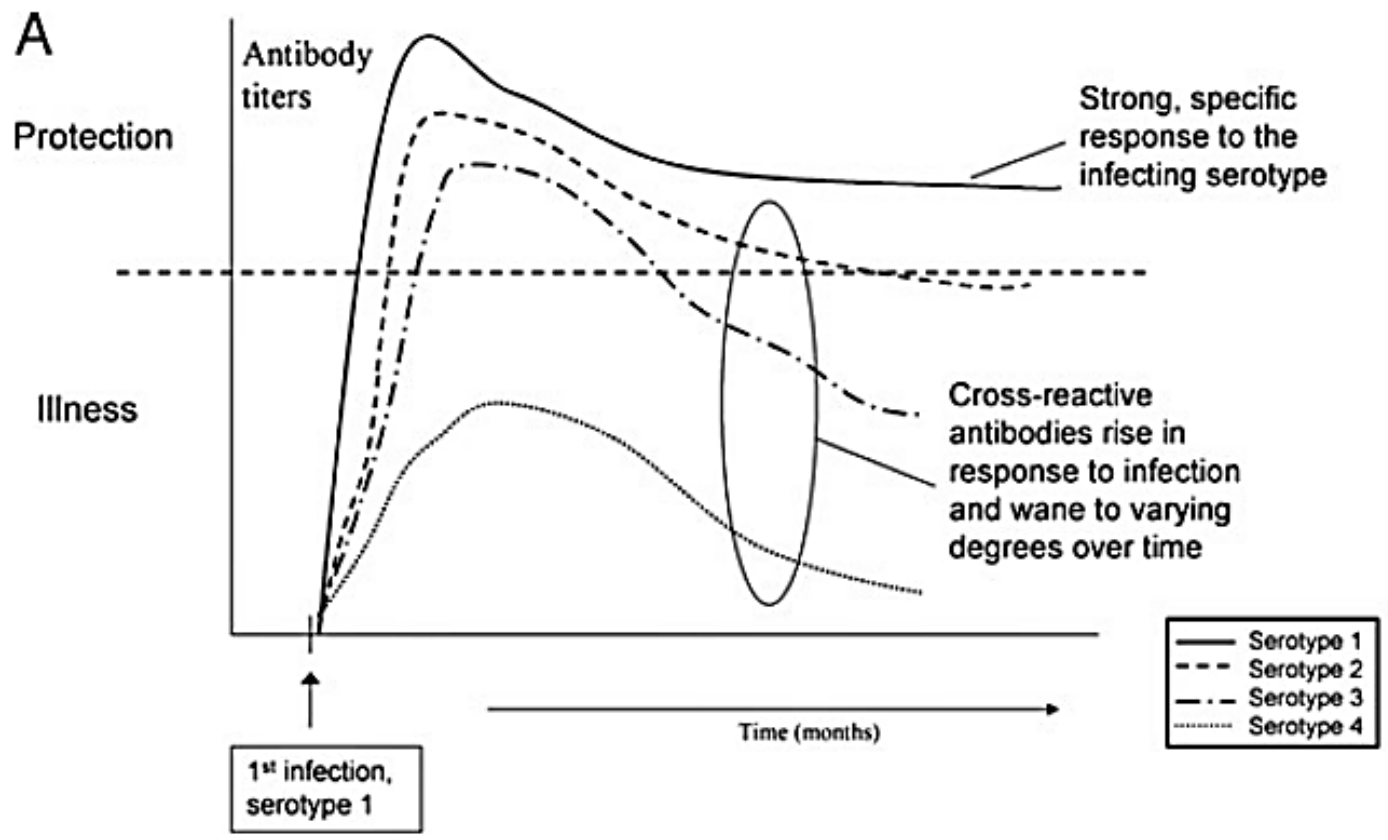
Clinical development and regulatory points for consideration for second-generation live attenuated dengue vaccines

Kirsten S. Vannice [a 1], Annelies Wilder-Smith [a b 1], Alan D.T. Barrett [c 1], Kalinka Carrijo [d 1], Marco Cavaleri [e 1], Aravinda de Silva [f 1], Anna P. Durbin [g 1], Tim Endy [h 1], Eva Harris [i 1], Bruce L. Innis [j 1], Leah C. Katzelnick [i 1], Peter G. Smith [k 1], Wellington Sun [l 1], Stephen J. Thomas [h 1], Joachim Hombach [a 1]

PRNT

Current assays do not distinguish between type-specific antibodies, transient heterotypic antibody, and long-lasting heterotypic antibody.

Serotype-specific assays need to be used.



Vaccine infectivity and interference

- Vaccine infectivity:
- Demonstrating replication for each of the four vaccine viruses, when administered as a live tetravalent vaccine, is highly desirable given the potential risk of interferences.

- Interference:
- Antibody depletion assays to determine whether type-specific responses were generated for each of the four serotypes

Immunobridging

Lack of immune correlates for protection

Lack of immune correlates for enhancement

Whilst for some flavivirus vaccines (eg JE, yellow fever etc), immunobridging has been accepted, RCT Phase 3 trials are still required for dengue

Human Challenge Studies

CAN PROVIDE INITIAL PROOF-OF-CONCEPT THAT A VACCINE MAY HAVE POTENTIAL FOR CLINICAL BENEFIT

WAS DONE FOR THE NIH TETRAVALENT VACCINE

CHALLENGE SHOULD BE DONE >12 MONTHS

BUT GREATER CONFIDENCE IS REQUIRED IN DENGUE CHIM PERFORMANCE: HIGHLY ATTENUATED CHALLENGE VIRUS VS DISEASE-CAUSING VIRUS

Clinical trial design requirements

- Baseline samples needed to determine baseline serostatus
- A-priori plans to stratify by serostatus, serotype and clinical endpoints
- Active surveillance
- Duration 3-5 years
- An extended follow-up period will allow for additional power to look at secondary analyses, eg VE by infecting serotype
- Multi-country trial over several seasons to ensure that all 4 serotypes are captured

Thank you

Dengvaxia: post-hoc results from the Phase 3 trials: Cumulative incidence of hospitalised dengue by serostatus

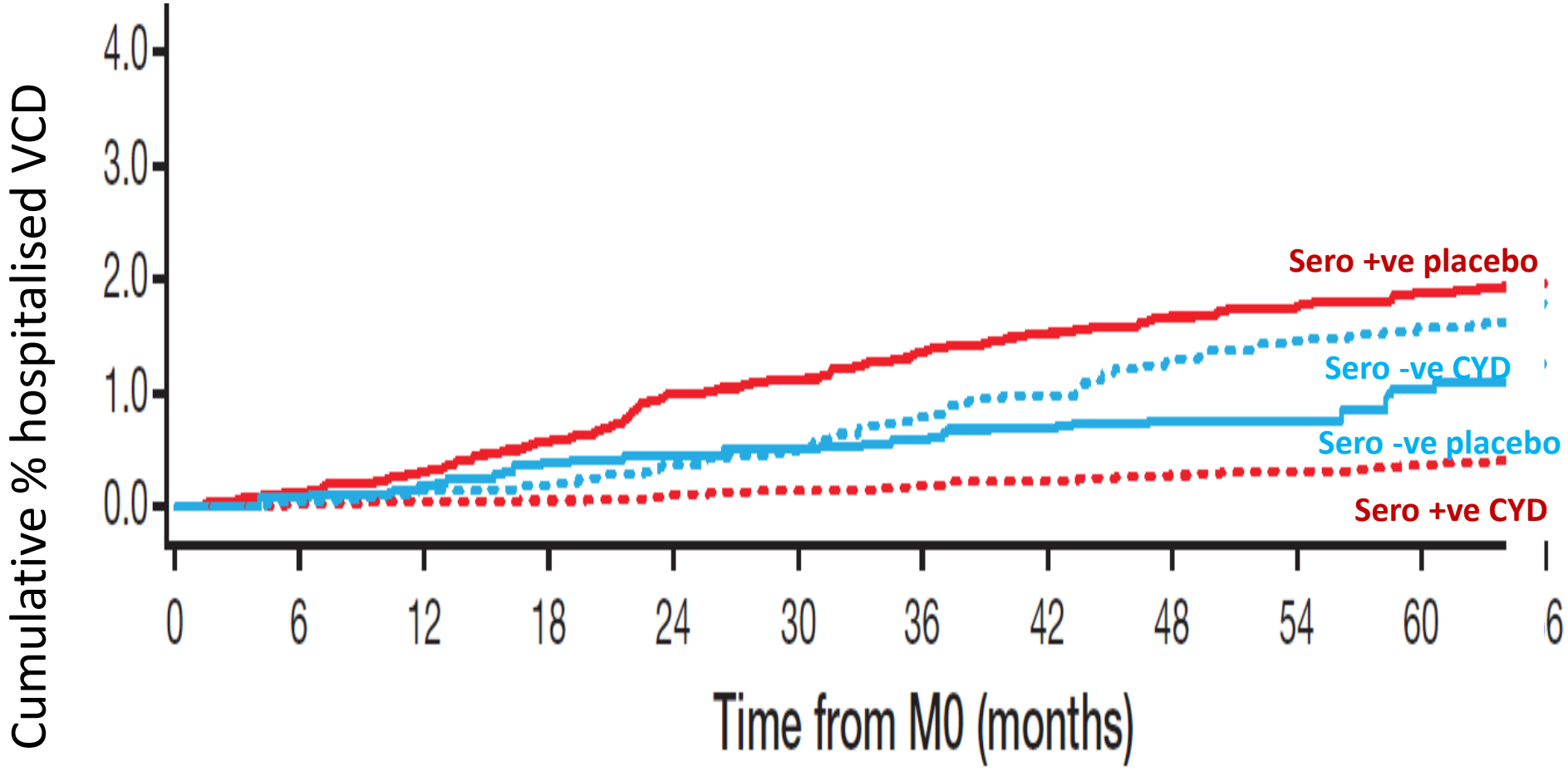
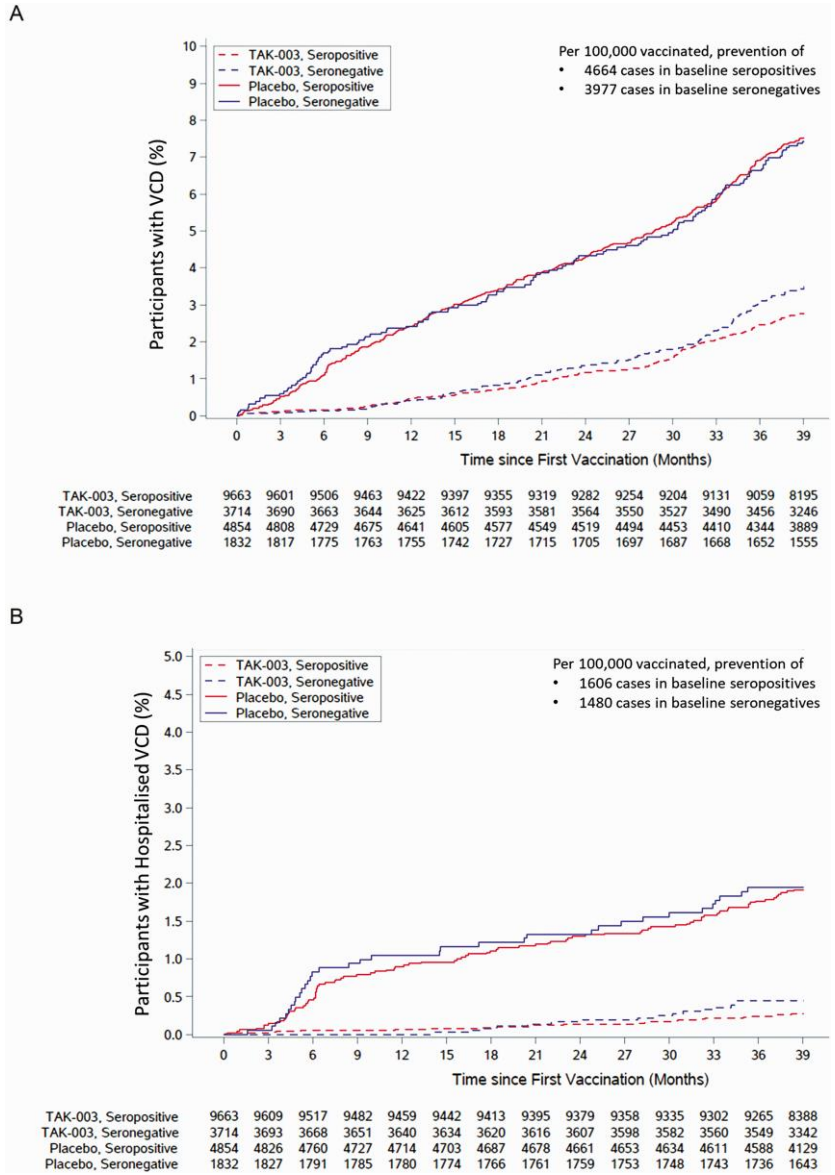


Figure 3. Cumulative incidence of (A) virologically confirmed dengue (VCD) cases and (B) hospitalized VCD cases



Clin Infect Dis, Volume 75, Issue 1, 1 July 2022, Pages 107–117, https://doi.org/10.1093/cid/ciab864

Risk of severe dengue associated with secondary versus primary infections

Cumulative incidence (CI) of severe dengue per 1000 unvaccinated children in the Phase 3 trial CYD-TDV			RR
	Seronegative	**Seropositive**	
2–8 years old			
Multiple imputations methods, months 0–60	3.64	11.6	3.19
9–16 years old			
Multiple imputations methods, months 0–60	1.74	4.80	2.76
2–16 years old			
Multiple imputations methods, months 0–60	2.52	6.09	2.42