UPDATE ON DENGUE VACCINATION

THE PROS & THE CONS

Hôpitaux Universitaires Genève
MÉDECINE TROPICALE ET HUMANITAIRE

Joint Annual Meeting 2023 ¦ SSI ¦ SSHH ¦ SSTTM ¦ 15.09.2023

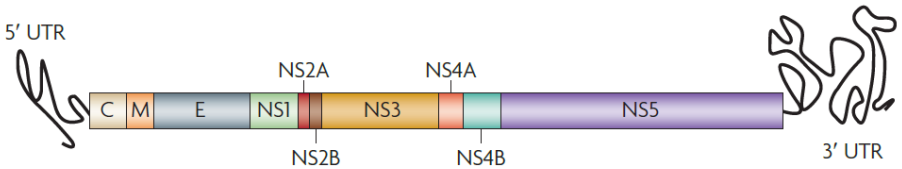
Dr G. Eperon, SMTH, HUG

Dengue Fever

Virology | Epidemiology | Clinical & management | Public health measures

Vaccines

- Flavivirus (YF, JE, TBE, WNV…)
  - single stranded RNA (ssRNA)
  - 3 structural proteins (C; M; E) & 7 non-structural proteins (NS1…)



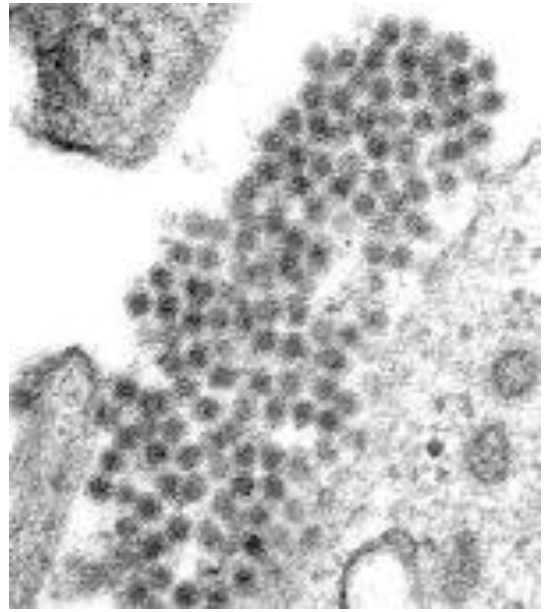
Guzman M.G, *et al*. Nature Reviews Microbiology 2010 doi:10.1038/nrmicro2460

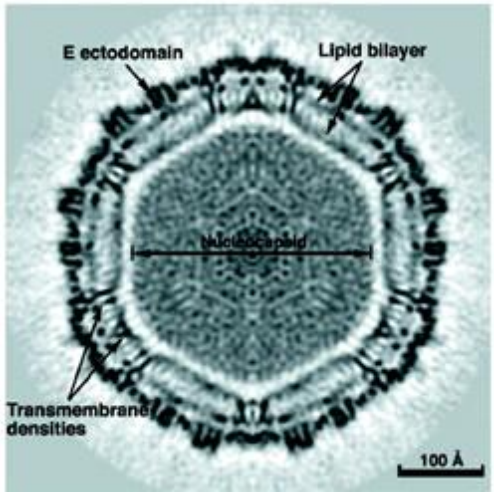
  - 4 related but distinct serotypes (DENV-1, DENV-2, DENV-3, DENV-4)
    - genetic variation (shares ~65% of the genome)
    - Production of antibodies (Abs) :
      - homotypic (mainly E protein)

      &
      - heterotypic (mainly precursor M protein) antibodies (Abs)

        → ADE (antibody-dependent enhancement) phenomenon
  - In the blood: presence of mature & immature DENV

- Vector:
  - mosquitoes : Aedes aegypti & A. albopictus





Zhang et al., 2003,

Schmidt A.C, NEJM 2010

Tsai WY, et al. Front Microbiol 2017

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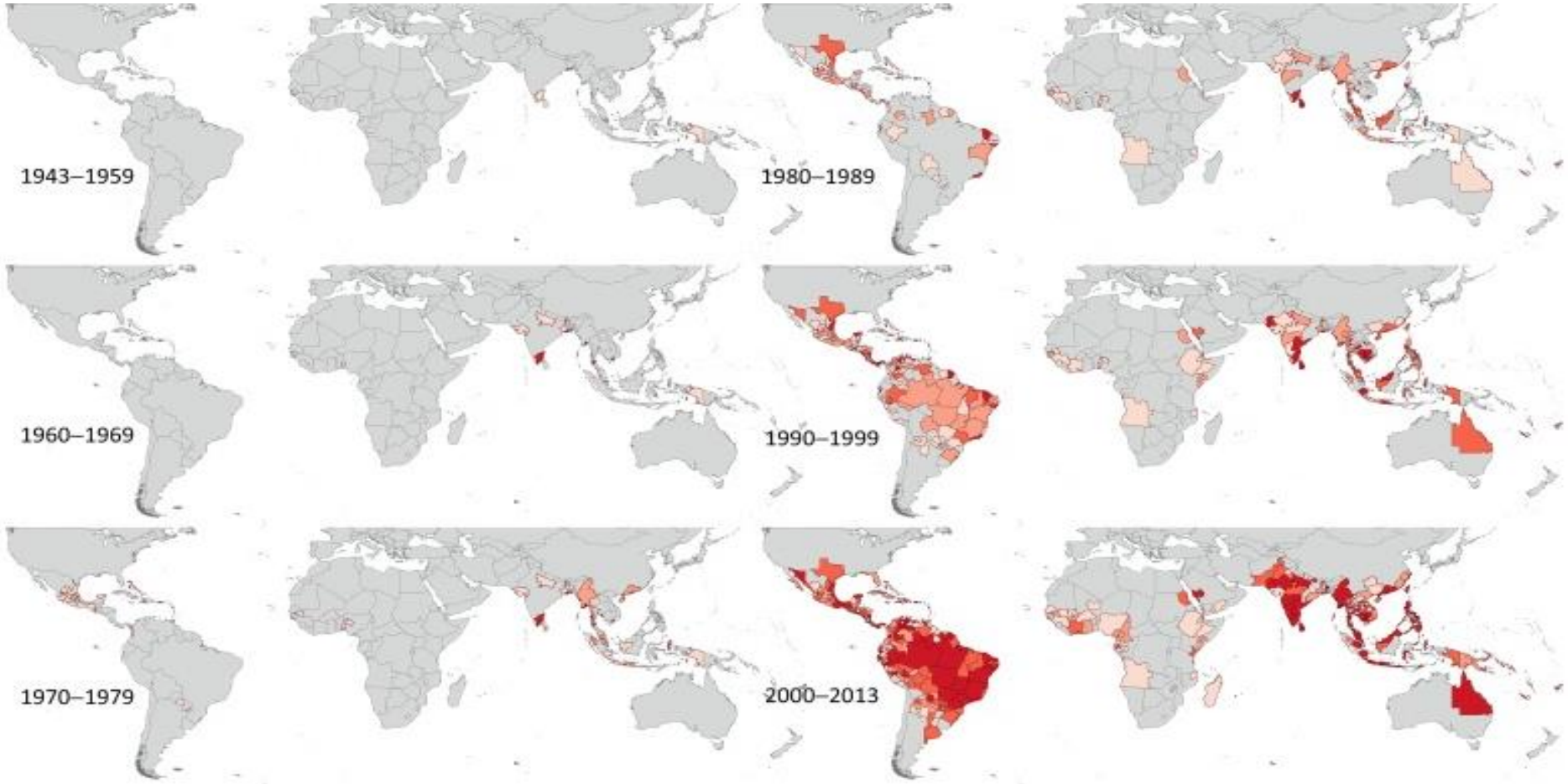

DENV Co-circulation. Cumulative number of DENV types reported by decade since 1943.

Messina J, et al. Trends Microbiol 2014

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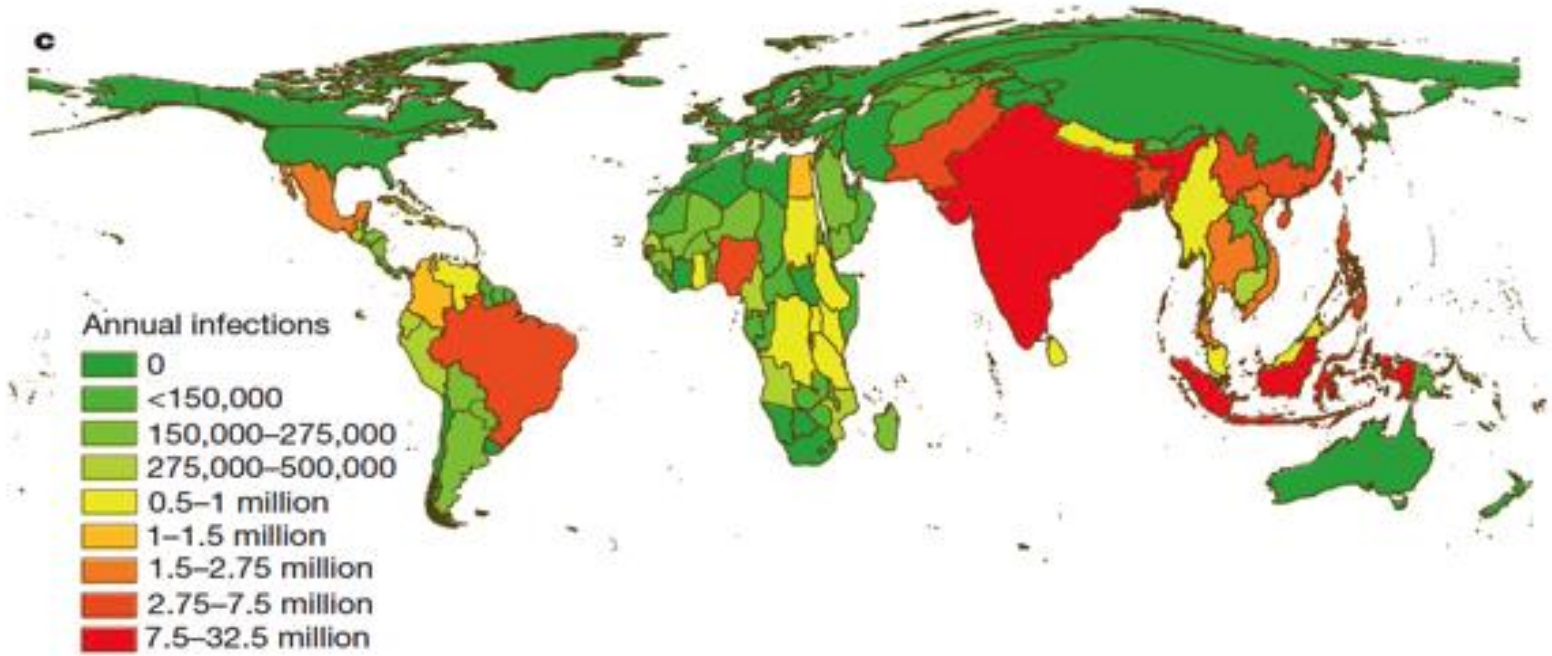


Table 1 | Estimated burden of dengue in 2010, by continent

	Apparent	Inapparent
	Millions (credible interval)	Millions (credible interval)
Africa	15.7 (10.5–22.5)	48.4 (34.3–65.2)
Asia	66.8 (47.0–94.4)	204.4 (151.8–273.0)
Americas	13.3 (9.5–18.5)	40.5 (30.5–53.3)
Oceania	0.18 (0.11–0.28)	0.55 (0.35–0.82)
Global	96 (67.1–135.6)	293.9 (217.0–392.3)

Acknowledgement to Pr A. Wilder-Smith

Bhatt et al, Nature 2013. doi:10.1038/nature12060

- Asymptomatic : ~ 50 – 80%

- Self-limiting febrile illness (~95% of symptomatic)
  - fever
  - myalgia & arthralgia : 50-70% (of symptomatic), sometimes « severe»: «break-bone disease »
  - rash
  - hyperesthesia, dysesthesia
  - leukopenia, thrombopenia

- Severe dengue (~2-5% of symptomatic)
  → need hospitalization
  → role of NS1 («viral toxin»)
  → ADE (antibody-dependent enhancement) phenomenon

- Case fatality rate (CFR) : 0.1 – 1% (CFR) (~ 5'000 – 50'000 deaths/year)
  - Risk factor: children & elderly (>65 y.o.)

- Main cause of hospitalization and deaths for children in Asia

- No specific treatment → only symptomatic treatment & supportive measures

OMS, 2006;
Thomas et al. J Clin Virol 2010
Flasche et al, PLoS Med.2016
Halstead S, et al, JTM 2019;
Halstead SB, et al Lancet Child Adolesc Health 2019
Zeng Z. et al. eClinical medicine 2021

Cumulative overall Vaccine efficacy (VE)

Dengvaxia® vs Qdenga®

cVE Dengvaxia® M25	SE-Asia	Latin America
	55%	65%

cVE Qdenga®	M12	M18	M39	M54
	80%	73%	62%	61%

Capeding MR et al. Lancet 2014; 384:1358-65
Villar L et al. N Engl J Med 2015; 372:113-23

Biswal S, et al. NEJM 2019
Biswal S, et al. Lancet 2020
Rivera L. et al CID 2022
Sponsor's Summary of Product Characteristics 2022

Expertenkomitee für Reisemedizin
Comité d'experts pour la médecine des voyages
Comitato di esperti per la medicina di viaggio
Expert committee for travel medicine

Swiss ECTM recommandations – 2023 (draft)

- vaccination with Dengvaxia® or Qdenga® is **not recommended** in travellers with no prior dengue fever.

- vaccination with Qdenga® **can be considered** in travellers (≥4 years old) :
  - with previous dengue infection : confirmed previous Dengue (PCR, Ag or raise of IgM) OR clinical history & IgG+

  AND
  - who are planning a long-term stay (>4 weeks) or multiple trips to an endemic region.

- given the existing cross-reactions with other flaviviruses or their vaccines, particularly in patients living outside endemic DF areas, **serology alone without a compatible anamnesis should be interpreted with caution**,

WHY?

- Be aware of lack of knowledge about :
  - the duration of protection

  and
  - the need for a booster in a population living in a non-endemic area & unable to rely on a "natural booster"

→ risk-benefit ratio of such a vaccination MUST be taken in consideration

Dengue Fever

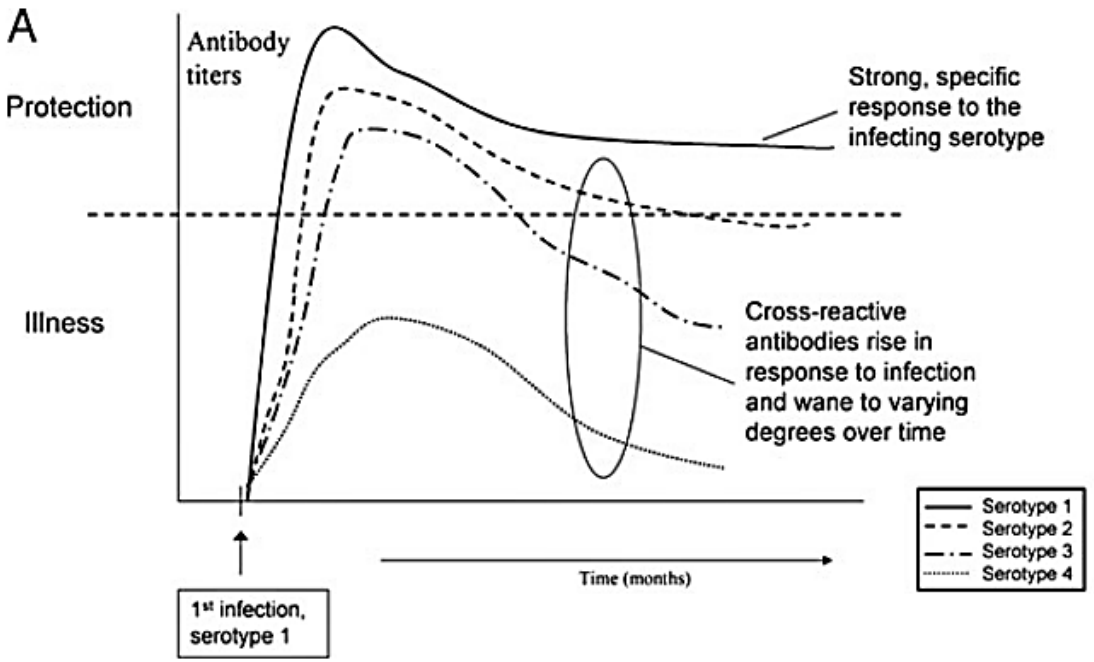
Vaccines

Immunology Development CYD-TDV TAK-003 Others Travellers?

humoral cellular

- Homotypic neutralizing-Abs:
  - vs anti-envelope protein & NS
  - serologically specific
  - Life-long immunity; *probable sterilizing immunity*
- Cross-neutralizing Abs
  - nAbs cross-reaction among serotypes, only ~12 months
- heterotypic NON-neutralizing Abs
  - vs anti-precursor membrane protein
  - cross-reaction among serotypes → Cause of ADE phenomenon
- heterotypic NS Abs?
  - vs NS protein : role in inhibition of NS-1 toxic effect
  - cross-reaction among serotypes nAbs? or only protection against complication?

  → ADE phenomenon = ?, theoretically no



Anderson *et al.* J Inf Dis. 2014
Sharma M, et al. JID 2020
Guy B, et al Vaccines 2020
Kirkpatrick et al, Sci Trans Med 2017

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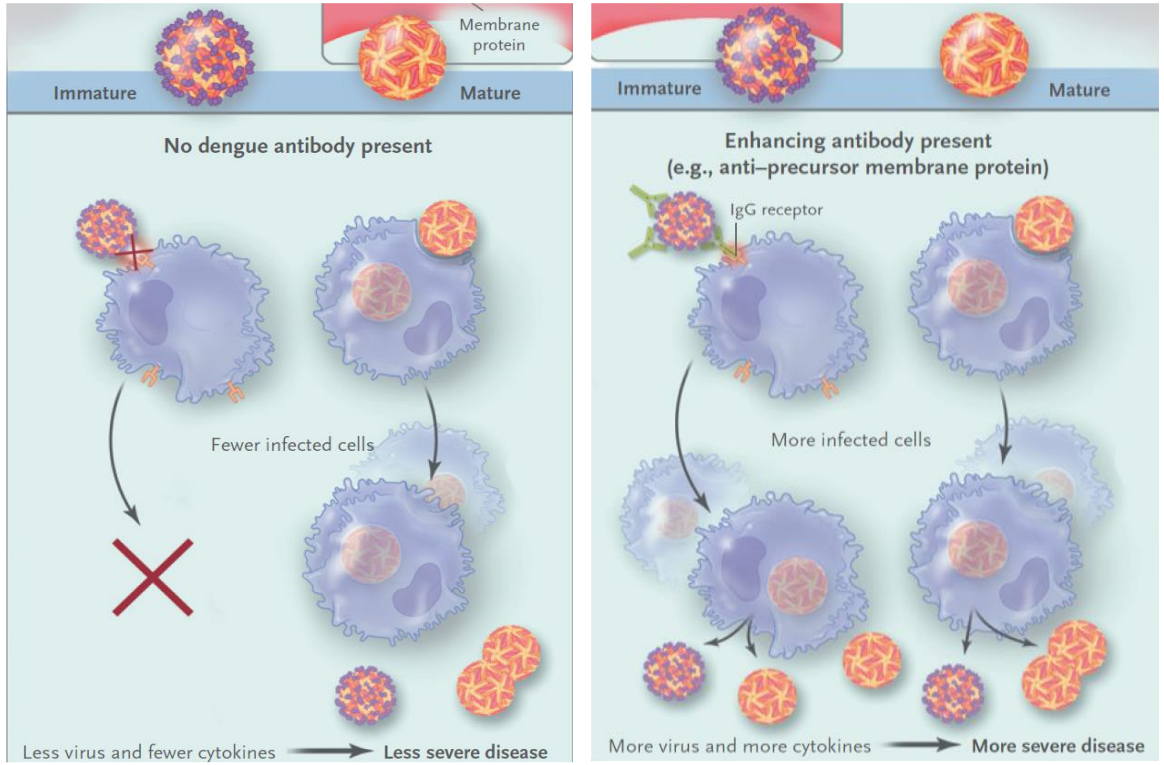
Vaccines

Immunology Development CYD-TDV TAK-003 Others Travellers?

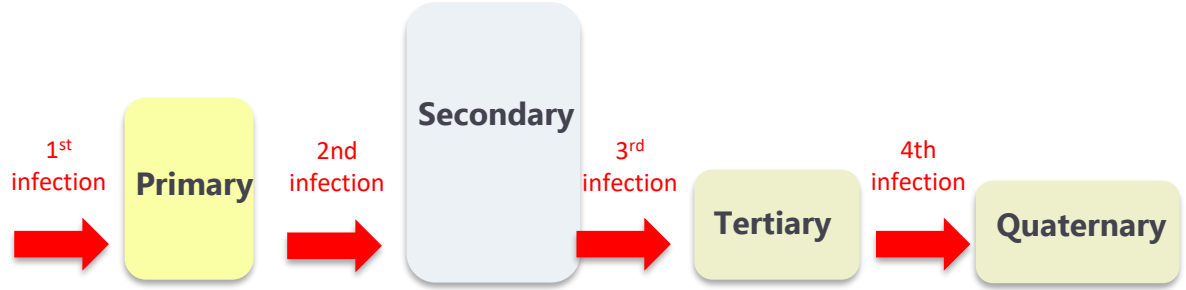
humoral cellular

- antibody-dependent enhancement (ADE)
  - mature virus infect mononuclear cells through clathrin-mediated endocytosis
  - immature virus = noninfectious
  - However, in the presence of non-neutralizing anti–precursor membrane protein Abs:
    → immature virus infect IgG receptor–bearing cells
    - ↗ replication
    - ↗ infected cells
    - (↗ cytokines)
    - ↗ *free* NS1 circulation (≈ viral-toxin)

    → more severe disease (capillary-leak)



- → the vaccine should induce long lasting and equal seroprotection vs all 4 serotypes



Severe Dengue ~ 0.1-1% ~ 5%

Schmidt A.C, NEJM 2010
Flasche et al, PLoS Med.2016
Halstead S, et al Lancet Child Adolesc Health 2019, 3:734-41

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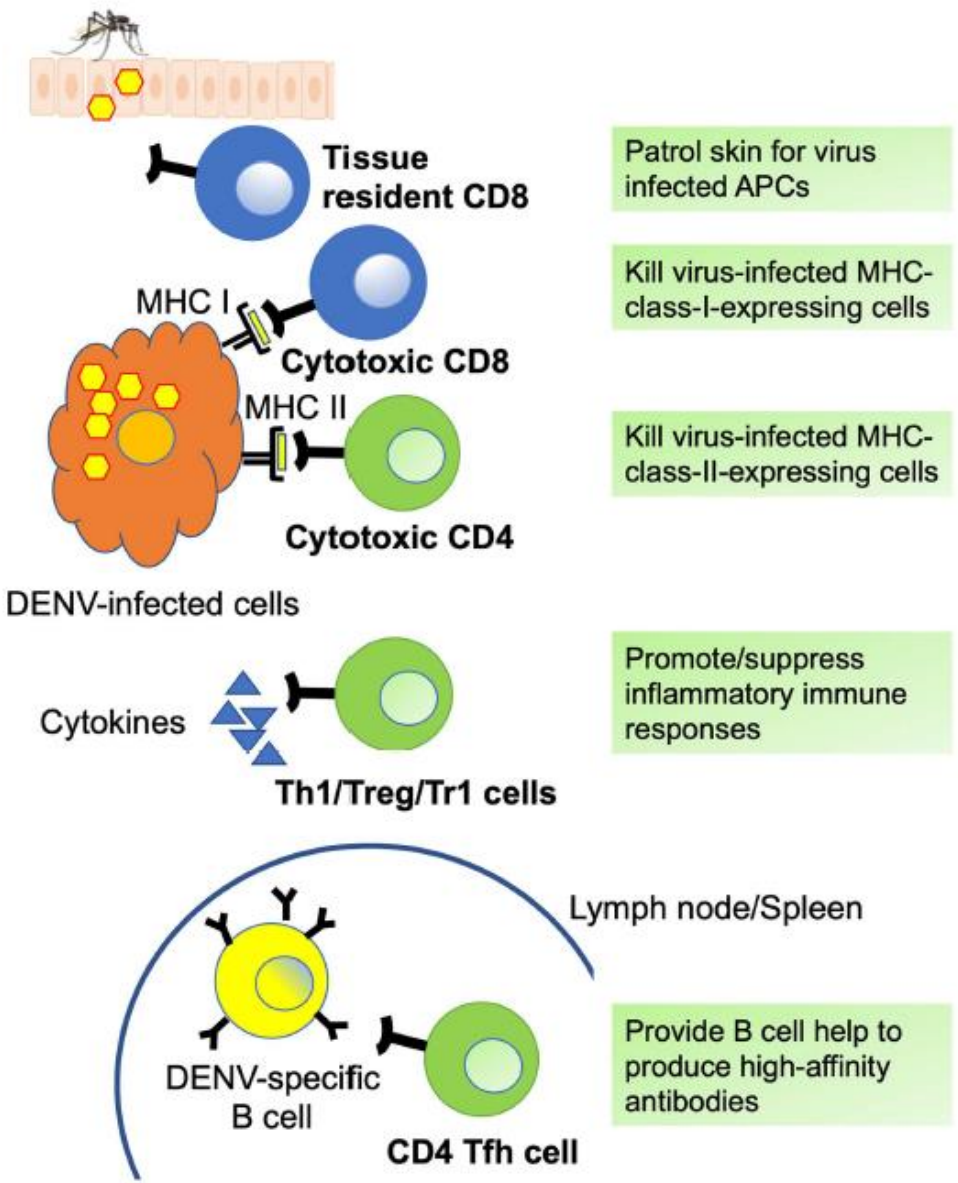
humoral cellular



CD8 response importance for viral clearance

(8/12 subjects with detectable viremia did not achieve viremia detectable by culture)

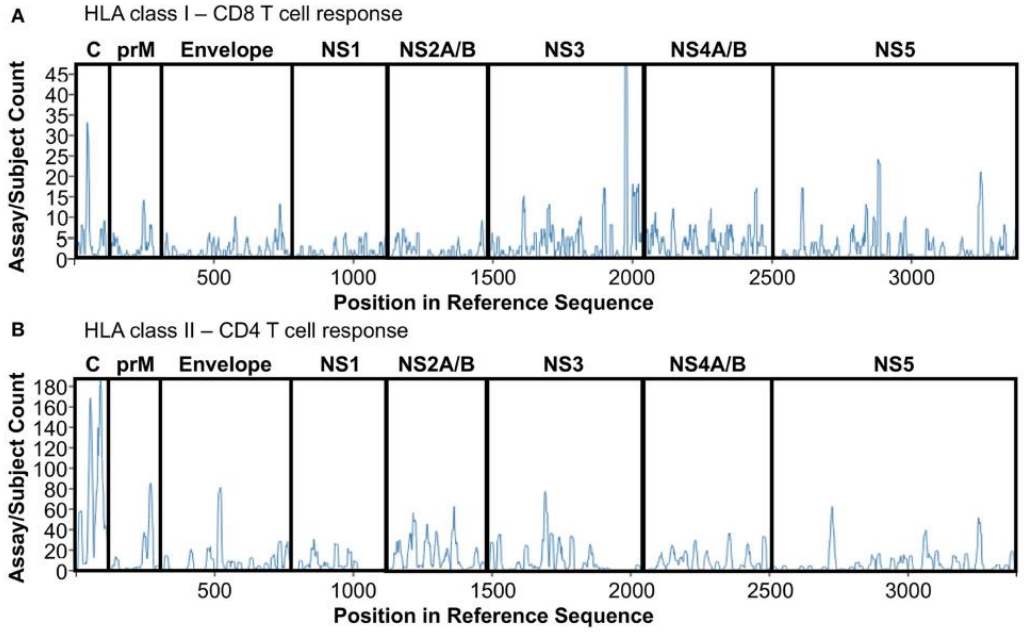
CD8 & CD4 response has been shown to be (partially?) protective against severe disease…

…not sufficient to prevent disease *(non-sterilizing immunity?)*

Tian Y, et al. Front Immunol. 2019 doi: 10.3389/fimmu.2019.02125
Kirkpatrick et al, Sci Trans Med 2017

- Majority of CD8 epitopes located in the NS proteins
- Little variations in NS epitopes among serotypes

  → “original antigenic sin”(≈ ADE for cellular immunity) **seems not** present



High majority (81%) of DENV CD8 epitopes are located in the NS proteins
High majority of DENV CD4 epitopes are located in the C(apsid)

Weiskopf D, PNAS 2013 doi: 10.1073/pnas.1305227110.
Tian Y, et al. Front Immunol. 2019 doi: 10.3389/fimmu.2019.02125
Dung NTP, et al. J of Immunol 2010, 184: 7821-7
Waickman AT, et al. Front in Immunol 2019

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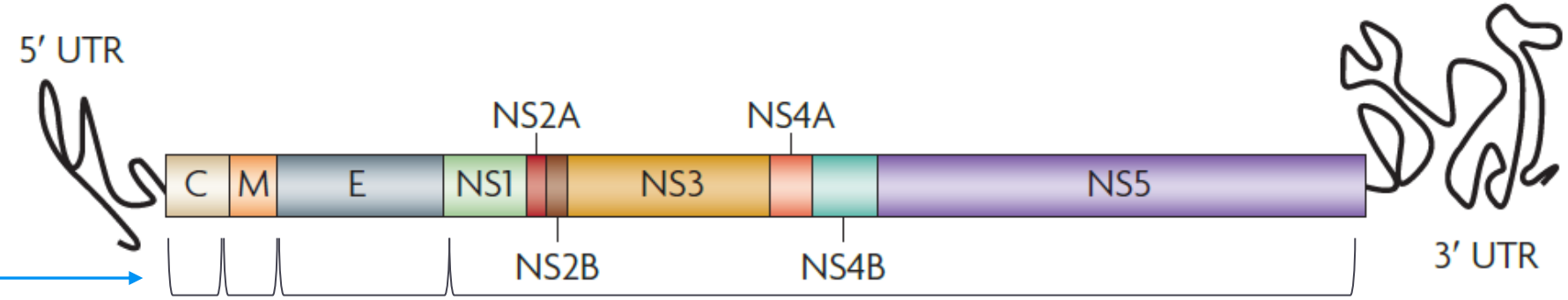

humoral Immunity

- heterotypic Abs ≈ NON-neutralizing Abs, cross-reaction, ADE
- homotypic Abs ≈ neutralizing Abs (NAbs), life-long immunity
- heterotypic Abs vs NS protein ?

cellular immunity

- CD8 the NS proteins
- CD4 in the C(apsid)

"There is general agreement that DENV vaccines should ideally **induce [immunity]** to **each of the 4 serotypes simultaneously**… would also reduce or eliminate the risk of … antibody-dependent-enhancement…"

WHO Technical Report Series, 2011. Annex 2 2011

- **animal models not available**…

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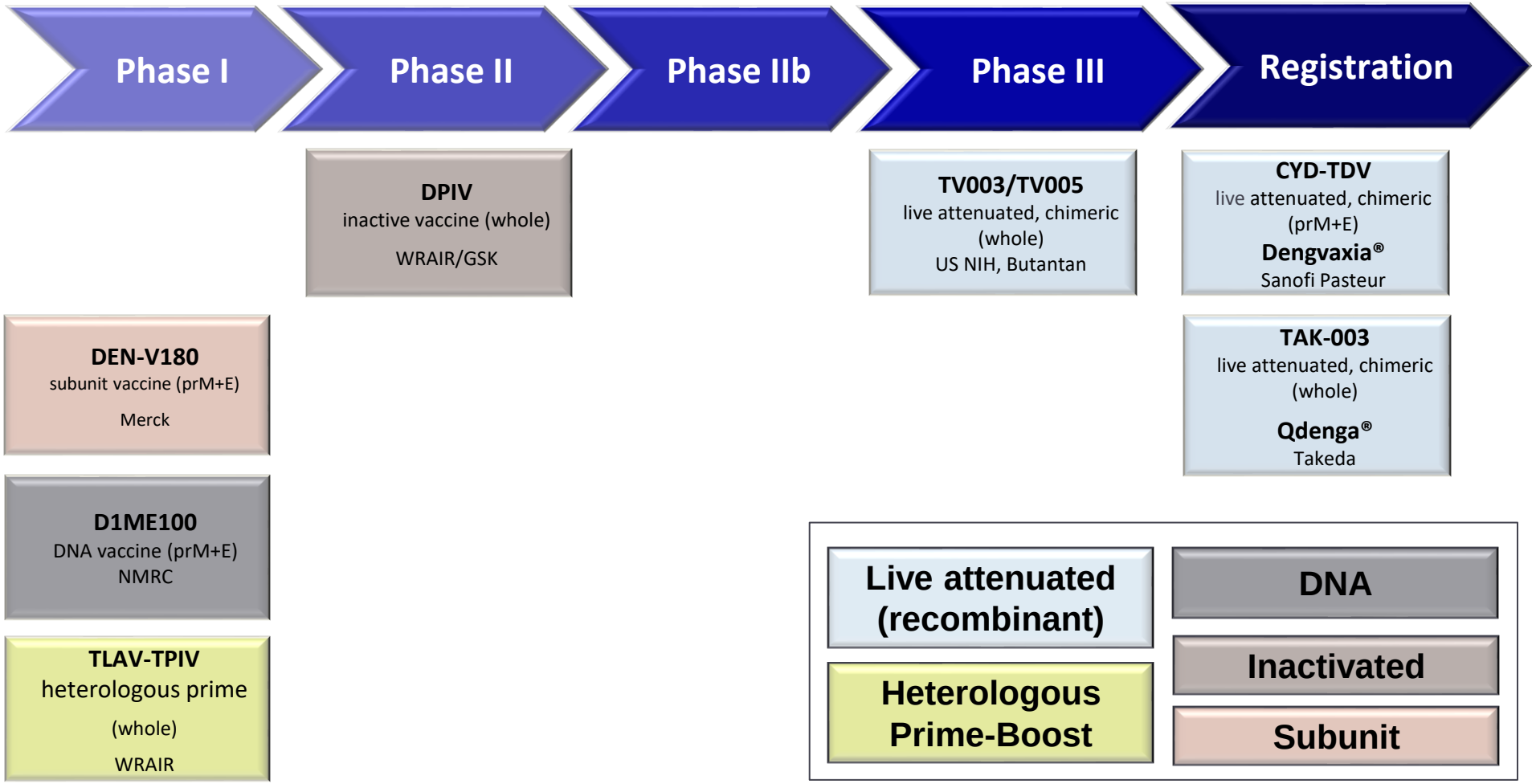

NIH: National Health Institute, NMRC: Naval Medical Research Center, WRAIR: Walter Reed Army Institute of Research

Acknowledgement to Pr A. Wilder-Smith

Prompetchara E, et al. APJAI 2019
Halstead SB, et al Lancet Child Adolesc Health 2019, 3:734-41
WHO 2020 *http://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/*

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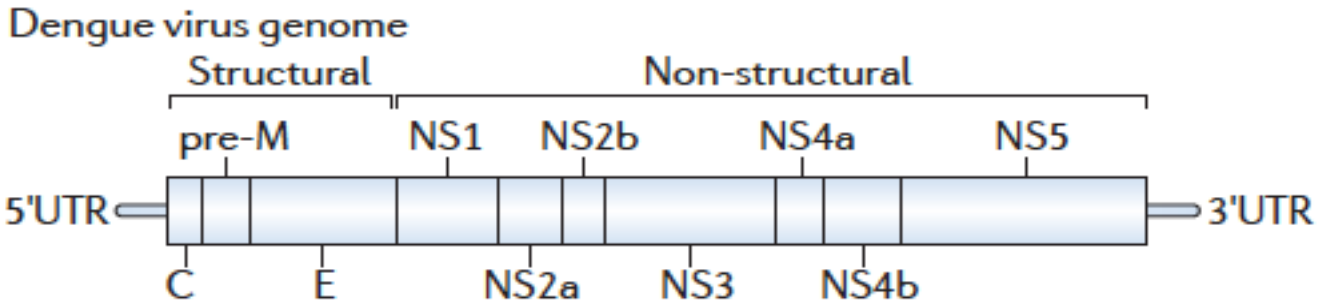
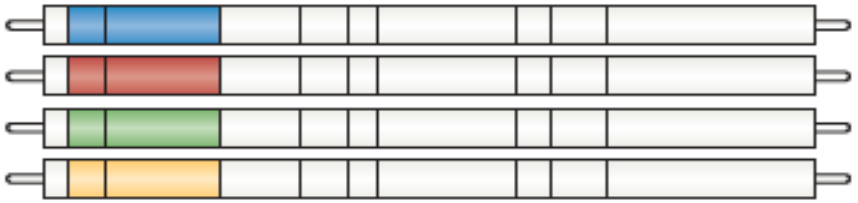
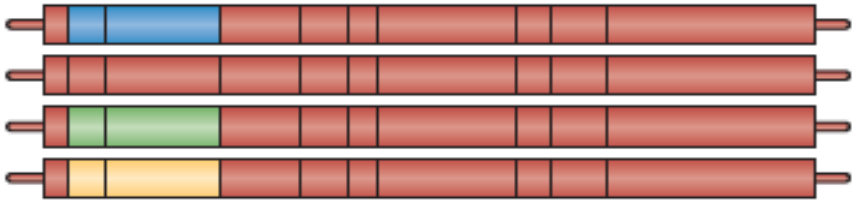


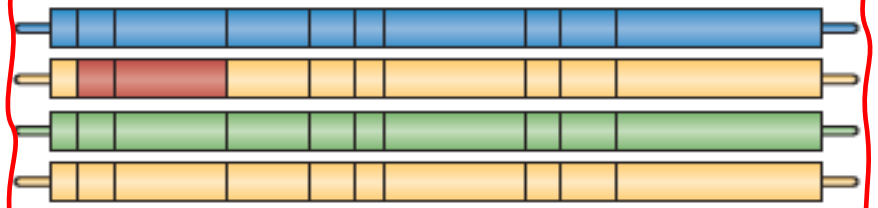
Sanofi Pasteur Dengvaxia®



Takeda (Qdenga®)



TV003 - Butantan



Merck (subunit)

DNA or heterologous viral vectors (various)

DENV-1 genome
DENV-2 genome
DENV-3 genome
DENV-4 genome
Yellow fever virus genome

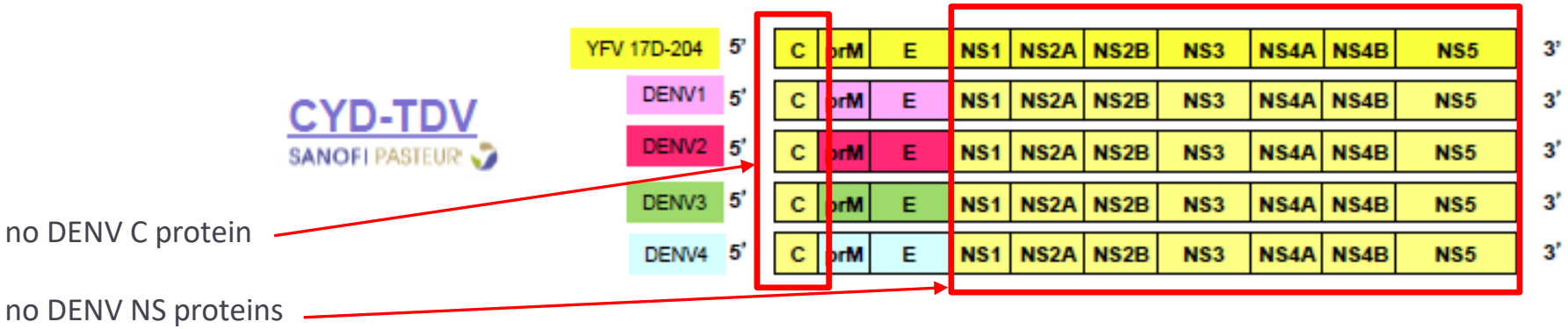
Rothman AL et al. Nat Rev Immunol 2011
Halstead SB, et al Lancet Child Adolesc Health 2019, 3:734-41

Acknowledgement to Dr A. Neumayr

- Dengvaxia® : Chimerivax Dengue tetravalent vaccine

- Sanofi – Pasteur
- Live attenuated

- Backbone of Yellow fever vaccine + genes for E & prM → 4 chimeric



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Immunology Development CYD-TDV TAK-003 Others Travellers?

Dengvaxia®

Table 2: Efficacy of CYD-TDV vaccination against symptomatic, virologically-confirmed dengue due to any serotype

	Vaccine group (N=6848)			Control group (N=3424)			Vaccine efficacy (% [95% CI])
	Cases* (n)	Person-years at risk†	Incidence density‡ (95% CI)	Cases (n)	Person-years at risk	Incidence density (95% CI)	
Primary analysis (per-protocol)§	117	6526	1·8 (1·5–2·1)	133	3227	4·1 (3·5–4·9)	56·5% (43·8–66·4)
Intention-to-treat analysis¶	286	13571	2·1 (1·9–2·4)	309	6623	4·7 (4·2–5·2)	54·8% (46·8–61·7)

Capeding MR et al. Lancet 2014; 384:1358-65

- age 2- 14 y.o.
- seroprevalence at D0 = 68%

Outcome at M13-M25

- ↘ severe dengue: 80,8% (95% CI: 43-95)
- ↘ hospitalization: 67.2% (95% CI: 50.3-78.6)

- safety vaccine groupe = placebo group
  1 acute disseminated encephalomyelitis (vaccine group)

Table 2. Vaccine Efficacy against Any Serotype of Dengue.

Analysis	Vaccine Group			Control Group			Vaccine Efficacy (95% CI)
	Cases/ Events*	Person-Yr at Risk†	Incidence Density (95% CI)‡	Cases/ Events*	Person-Yr at Risk†	Incidence Density (95% CI)‡	
	no.		*no./100 person-yr*	*no.*		*no./100 person-yr*	%
Per-protocol analysis	176/176	11,793	1.5 (1.3–1.7)	221/221	5,809	3.8 (3.3–4.7)	60.8 (52.0–68.0)
Intention-to-treat analysis	277/280§	26,883	1.0 (0.9–1.2)	385/388§	13,204	2.9 (2.6–3.3)	64.7 (58.7–69.8)

Villar L et al. N Engl J Med 2015; 372:113-23

- age 9- 16 y.o.
- seroprevalence at D0 = 79%

- ↘ severe dengue: 95.5% (95% CI: 68.8-99)
- ↘ hospitalization: 80.3% (95% CI: 64.7-89.5)

- safety vaccine groupe = placebo group

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	Vaccine group (N=6848)			Control group (N=3424)			Vaccine efficacy (% [95% CI])
	Cases* (n)	Person-years at risk†	Incidence density‡ (95% CI)	Cases (n)	Person-years at risk	Incidence density (95% CI)	
Efficacy against VCD, more than 28 days after third injection in all participants who had received three injections							
Serotype 1	51	6548	0·8 (0·6 to 1·0)	50	3210	1·6 (1·2 to 2·0)	50·0% (24·6 to 66·8)
Serotype 2	38	6561	0·6 (0·4 to 0·8)	29	3253	0·9 (0·6 to 1·3)	35·0% (−9·2 to 61·0)
Serotype 3	10	6613	0·2 (0·1 to 0·3)	23	3281	0·7 (0·4 to 1·1)	78·4% (52·9 to 90·8)
Serotype 4	17	6605	0·3 (0·2 to 0·4)	34	3265	1·0 (0·7 to 1·5)	75·3% (54·5 to 87·0)

Capeding MR et al. Lancet 2014; 384:1358-65

Variable	Vaccine Group			Control Group			Vaccine Efficacy (95% CI)
	Cases	Person-Yr at Risk	Incidence Density (95% CI)	Cases	Person-Yr at Risk	Incidence Density (95% CI)	
	no.		*no./100 person-yr*	*no.*		*no./100 person-yr*	%
Modified per-protocol analysis*							
Serotype 1	66	12,478	0.5 (0.4–0.7)	66	6,196	1.1 (0.8–1.4)	50.3 (29.1–65.2)
Serotype 2	58	12,495	0.5 (0.4–0.6)	50	6,219	0.8 (0.6–1.1)	42.3 (14.0–61.1)
Serotype 3	43	12,514	0.3 (0.2–0.5)	82	6,213	1.3 (1.1–1.6)	74.0 (61.9–82.4)
Serotype 4	18	12,522	0.1 (0.1–0.2)	40	6,206	0.6 (0.5–0.9)	77.7 (60.2–88.0)

Villar L et al. N Engl J Med 2015; 372:113-23

Table published in the «appendix»

Dengvaxia®

Table 1: Exploratory analysis of vaccine efficacy by age strata, baseline dengue seropositivity, and country; analyses are intention-to-treat

		Vaccine group			Control group			
		Cases (n)	Person-years at risk	Incidence Density (95% CI)	Cases (n)	Person-years at risk	Incidence Density (95% CI)	Vaccine efficacy % (95% CI)
Age strata (N)								
2 to 5 years	(2483)	120	3219	3·7 (3·1; 4·4)	89	1584	5·6 (4·5; 6·9)	33·7 (11·7; 50·0)
6 to 11 years	(5463)	137	7229	1·9 (1·6; 2·2)	165	3524	4·7 (4·0; 5·4)	59·5 (48·9; 68·0)
12 to 14 years	(2329)	29	3123	0·9 (0·6; 1·3)	55	1515	3·6 (2·7; 4·7)	74·4 (59·2; 84·3)
Dengue seropositivity at baseline in the subset (N)								
Seropositive*	(1340)	18	1811	1·0 (0·6; 1·6)	34	880	3·9 (2·7; 5·4)	74·3 (53·2; 86·3)
Seronegative	(643)	23	838	2·7 (1·7; 4·1)	18	423	4·3 (2·5; 6·6)	35·5 (−26·8; 66·7)

Capeding MR et al. Lancet 2014; 384:1358-65

Table S2: Exploratory analyses of vaccine efficacy by age and by baseline dengue serostatus, and between doses

	Vaccine group			Control group			
	Cases (n)	Person-years at risk	Incidence density (95% CI)	Cases (n)	Person-years at risk	Incidence density (95% CI)	Vaccine efficacy % (95% CI)
Dengue serostatus at baseline							
Seropositive[1]	8	2,116	0.4 (0.2–0.7)	23	994	2.3 (1.5–3.5)	83.7 (62.2–93.7)
Seronegative	9	500	1.8 (0.8–3.4)	9	284	3.2 (1.5–5.9)	43.2 (-61.5–80.0)

Villar L et al. N Engl J Med 2015; 372:113-23

Dengue Fever

Vaccines

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Vaccination contre la dengue : le fiasco de Sanofi

Le laboratoire français est-il allé trop vite ? Après le décès de plusieurs enfants aux Philippines, l'industriel a dû interrompre brutalement sa campagne contre cette maladie tropicale.

LE MONDE SCIENCE ET TECHNO | 06.03.2018 à 06h33 • Mis à jour le 06.03.2018 à 12h02 |

Par Lise Barnéoud et **Chloé Hecketsweiler**

- WHO 21.04.2016:
  - Sub-group analysis : hospitalization risk

	CYD14 (2-5 years)		
Time Period (Follow up)	CYD group cases	Control group cases	RR (95%CI)
Year 1 (Active)	8	6	**0.64** (0.20-2.32)
Year 2 (Active)	9	7	**0.64** (0.21-2.02)
Year 3 (Hospital)	15	1	**7.45 (1.15-313.80)**
Year 4 (Hospital)	20	7	**1.42** (0.58-3.99)
Year 5 (Hospital/SEP)	6	2	**1.49** (0.27-15.15)

Acknowledgement to Pr A. Wilder-Smith

Capeding MR et al. Lancet 2014; 384:1358-65

  - ↗↗ hospitalizations RR 7,45 (IC à 95%: 1,15 – 313,80)

Dengue Fever

Vaccine efficacy against symptomatic virologically confirmed dengue in the 25 months after dose 1

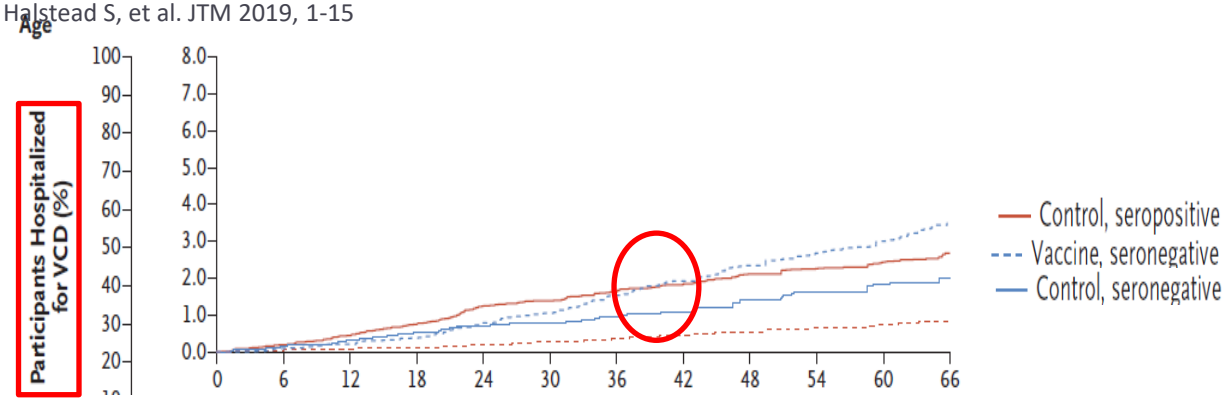
(2-16 year-olds)

Sero-status at dose 1	Vaccine efficacy	95% confidence interval
Sero-positive	**72%**	58%, 82%
Sero-negative	**32%**	-9%, 58%

Table 2. RR of severe dengue in seronegative compared with seropositive children; data derived from the placebo group in the Phase 3 trials of the CYD-TDV dengue vaccine[96]

			RR
Cumulative incidence (CI) of severe dengue per 1000 unvaccinated children in the Phase 3 trial CYD-TDV 2–16 years old			
Multiple imputations methods, months 0–60	2.52	6.09	2.42

Halstead S, et al. JTM 2019, 1-15



S. Sridhar et al. NEJM 2018 379(4): 327-40 DOI:10.1056/NEJMoa1800820

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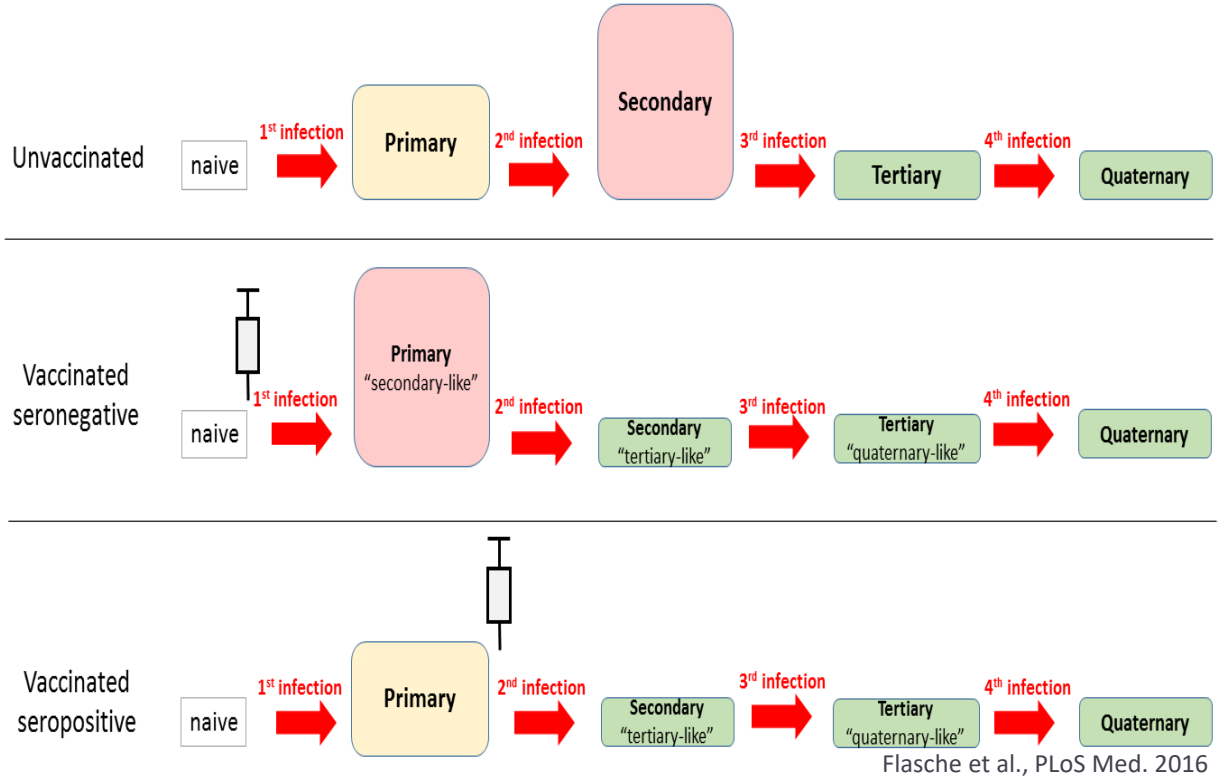

Flasche et al., PLoS Med. 2016

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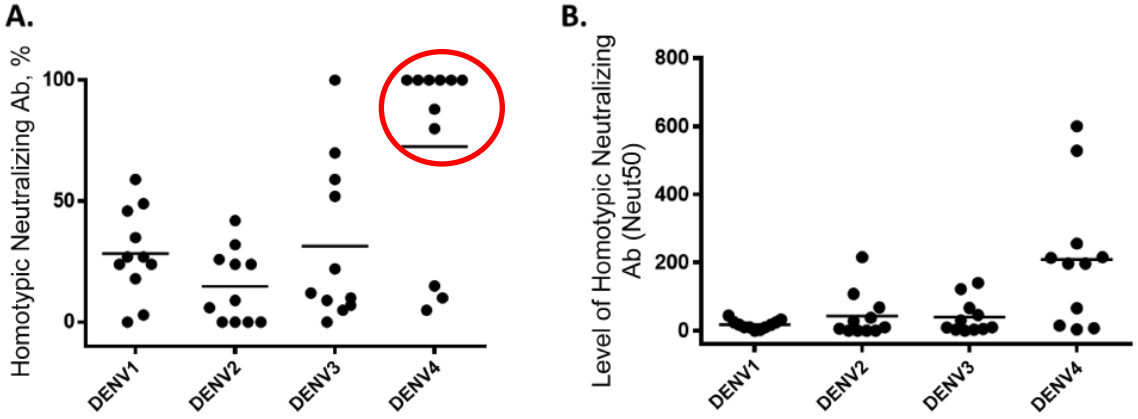
Vaccines

Immunology Development CYD-TDV TAK-003 Others Travellers?

Percentage of subjects with detectable viremia by PCR after 1st dose in flavirus-naïve subjects				
	DENV-1	DENV-2	DENV-3	DENV-4
CYD (n=95)[1]	7.4	0	12.6	44.2

Torresi et al, JID2017



S. Henein et al. JID 2017

primarily a **DENV4 vaccine**
by viremia AND homotypic Ab measurment

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

7 SEPTEMBER 2018, 93th YEAR / 7 SEPTEMBRE 2018, 93e ANNÉE
No 36, 2018, 93, 457–476
http://www.who.int/wer

Contents

457 Dengue vaccine: WHO position paper – September

Dengue vaccine: WHO position paper – September 2018

Note de synthèse de l'OMS sur le vaccin contre la dengue – septembre 2018

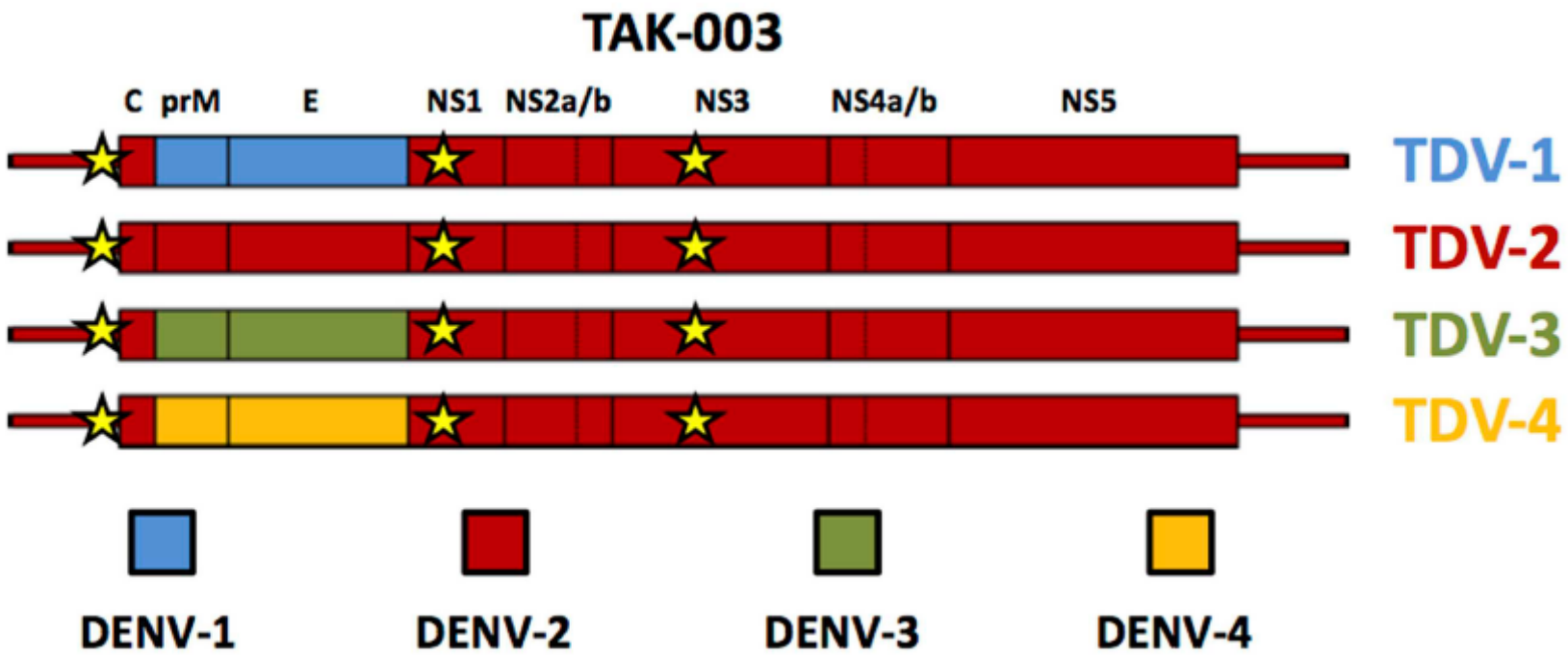
Pre-Vaccination Screening

Strategic Advisory Group of Experts on Immunization (**SAGE, WHO) 07.09.2018:**

… a "**pre-vaccination screening strategy**" is the recommended strategy, in which **only dengue-seropositive persons are vaccinated**

Whether there are age-specific effects, independent of serostatus, is the subject of ongoing research. Currently, the vaccine **should be used within** the indicated age range, which is typically **9 to 45 years of age**.

- TAK-003(Qdenga®) :



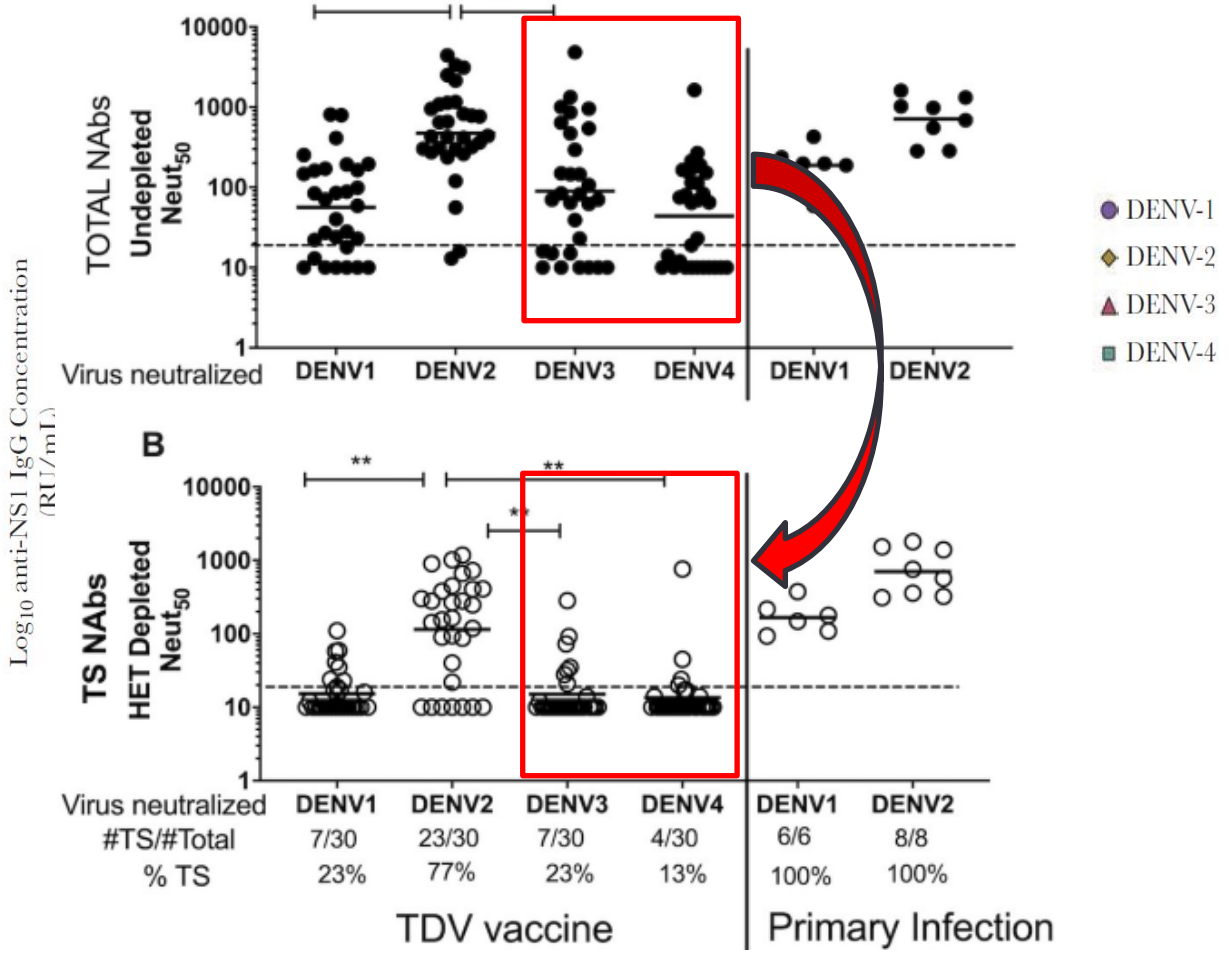
Waickman AT, et al. Front in Immunol 2019

Dengue Fever

Vaccines

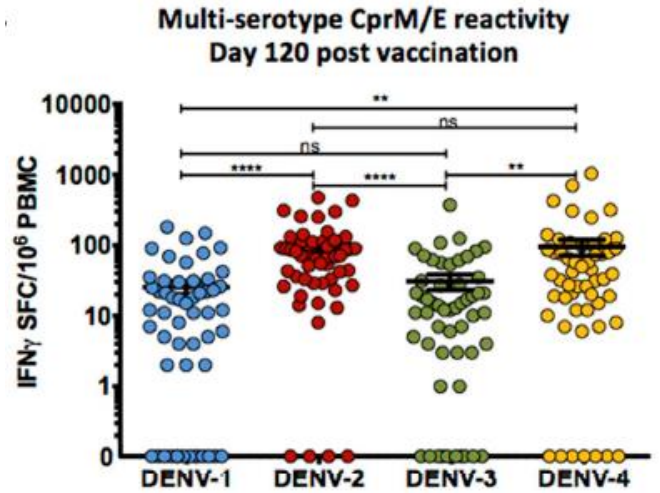
Immunology Development CYD-TDV TAK-003 Others Travellers?

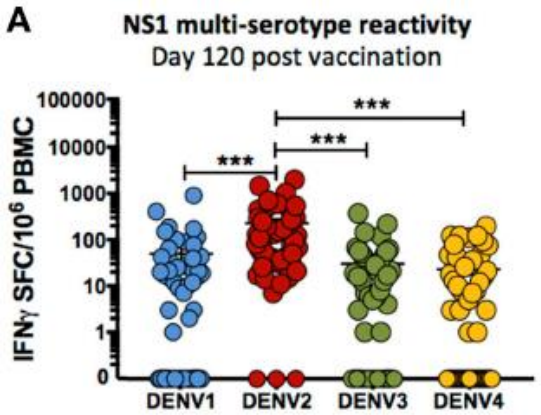
- humoral immunity vs
  - Strct (E+M) prot & NS prot (DENV-2 NS-1 specific)
  - anti-NS1 cross reaction but not complete inhibition NS1-toxin effect (endothelial hyperpermability)
  - Geometric mean titres
    - high in all serotypes, but higher in DENV-2
    - Persistent for 48 months
    - DENV-3 & DENV-4 mainly heterotypic nAbs

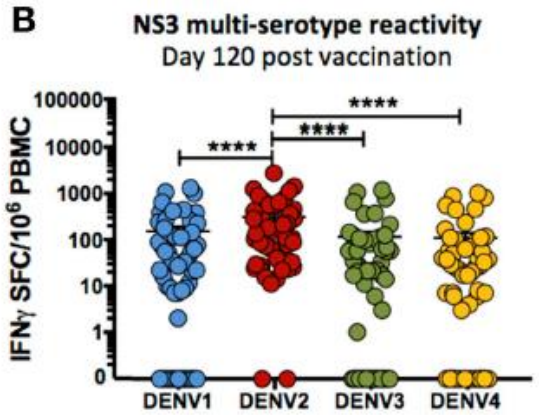


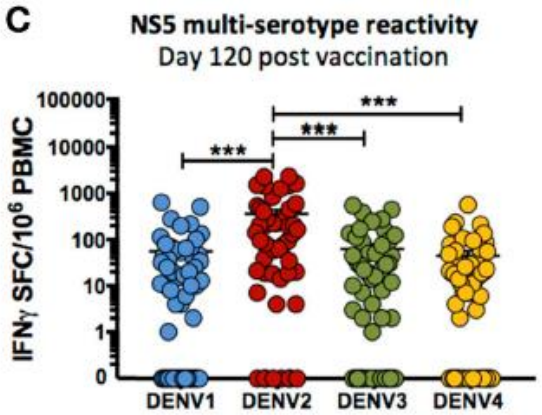
Sharma M, et al. JID 2020
Tricou V, et al. Lancet 2020
White L, et al. PLoS NTD 2021

- cellular immunity (at least 4 months) :
  - CD8 cross-immunity vs NS1-5
    - DENV-1,-3,-4 lower than specific DENV-2
    - no cross-immunity for DENV-1 NS1
    - individual-to-individual variation









Waickman AT, et al. Front in Immunol 2019

Dengue Fever

Vaccines

Immunology Development CYD-TDV TAK-003 Others Travellers?

- Brazil, Colombia, Dominican Republic, Nicaragua, Panama
- Philippines, Thailand,
- Sri Lanka

- Sponsor: Takeda Vaccines
- phase 3 study → 54 months after 2nd dose

- 20’099 participants, age 4- 16 y.o.
- seroprevalence at D0 = 72.3% (heterogenity from locations)
- 18’260 completed 4-4.5 year after 2nd dose

Outcome at **M12-18-39-54**

- ↘ cases (virogical confirmed Dengue= VCD)

Cumulative Vaccine efficacy	M12	M18	M39	M54
	80%	73%	62%	61%

- ↘ hospitalization : cVE (M54) : 84%

- safety vaccine group = placebo group

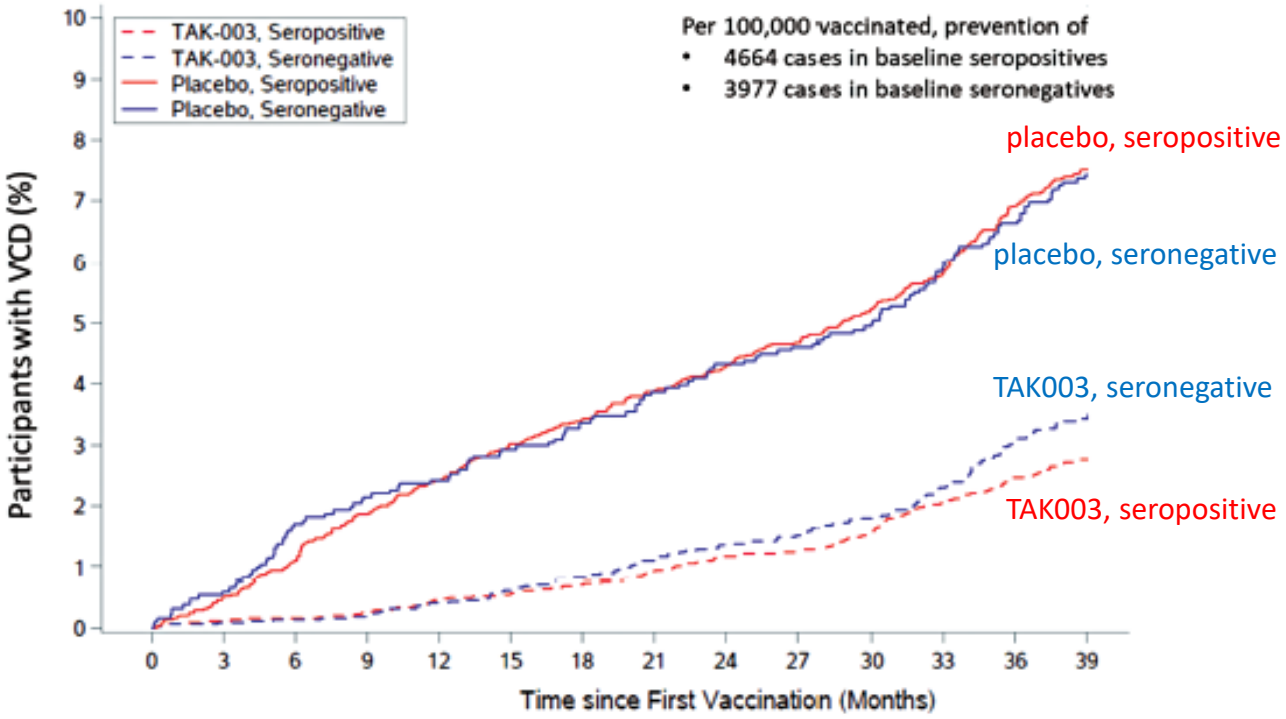
Biswal S, et al. NEJM 2019
Biswal S, et al. Lancet 2020
Rivera L. et al CID 2022
Sponsor’s Summary of Product Characteristics 2022

Dengue Fever

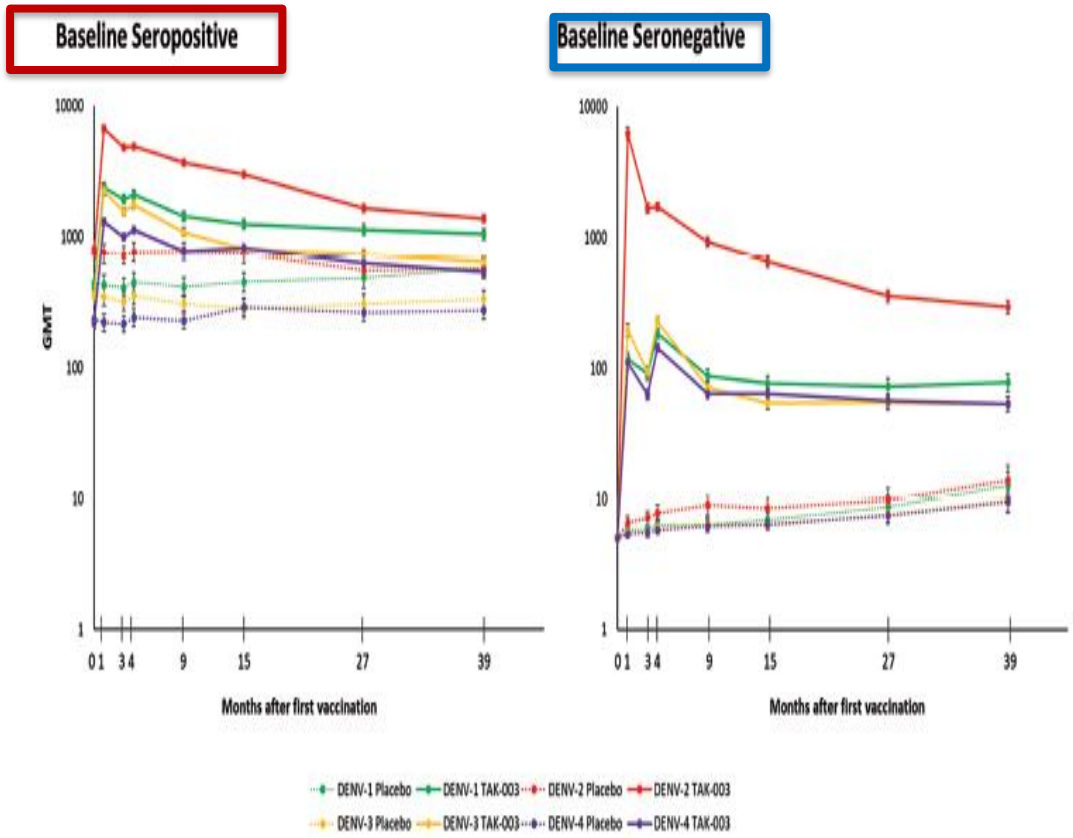
Vaccines

Immunology Development CYD-TDV TAK-003 Others Travellers?

VCD = virogical confirmed Dengue



VCD = virogical confirmed Dengue



Rivera L. et al CID 2022

Dengue Fever

Vaccines

Immunology Development CYD-TDV TAK-003 Others Travellers?

Cumulative efficacy for virogically confirmed Dengue (VCD) at M54

Overall VE

61.2% (56.0, 65.8%)

VE in Seropositives

64.2% (58.4, 69.2%)

VE in Seropositives by Serotype

DENV-1	**56.1%**	**(44.6, 65.2%)**
DENV-2	**80.4%**	**(73.1, 85.7%)**
DENV-3	**52.3%**	**(36.7, 64.0%)**
DENV-4	**70.6%**	**(39.9, 85.6%)**

VE in Seronegatives

53.5% (41.6–62.9%)

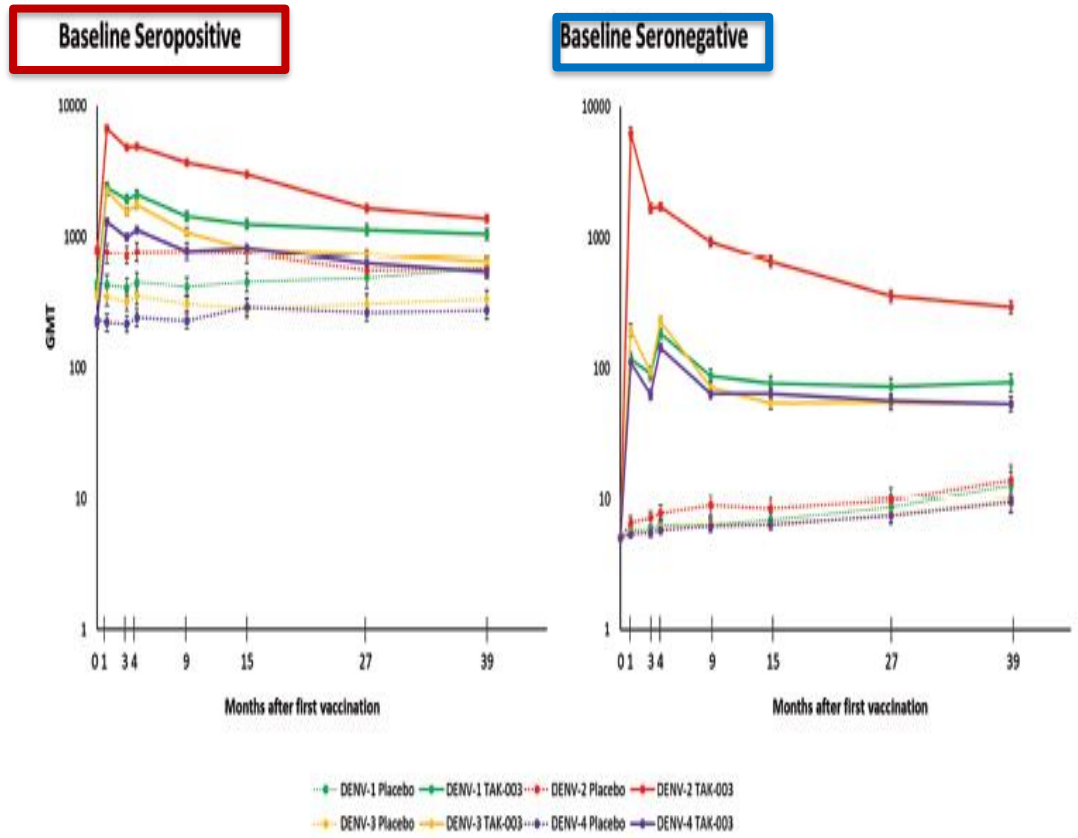
VE in Seronegatives by Serotype

DENV-1	**45.4%**	**(26.1, 59.7%)**
DENV-2	**88.1%**	**(78.6, 93.3%)**
DENV-3	-15.5%	(-108.2, 35.9%)
DENV-4	-105.6%	(-628.7, 42.0%)

*57 months after first dose; significant results bolded. Number for seropositive placebo participants 4,855 and vaccine 9,666; Seronegative placebo 1,832 and vaccine 3,714.

Unpublished data presented by Takeda to ACIP WG

VCD = virogical confirmed Dengue



Sponsor's Summary of Product Characteristics 2022

Rivera L. et al CID 2022

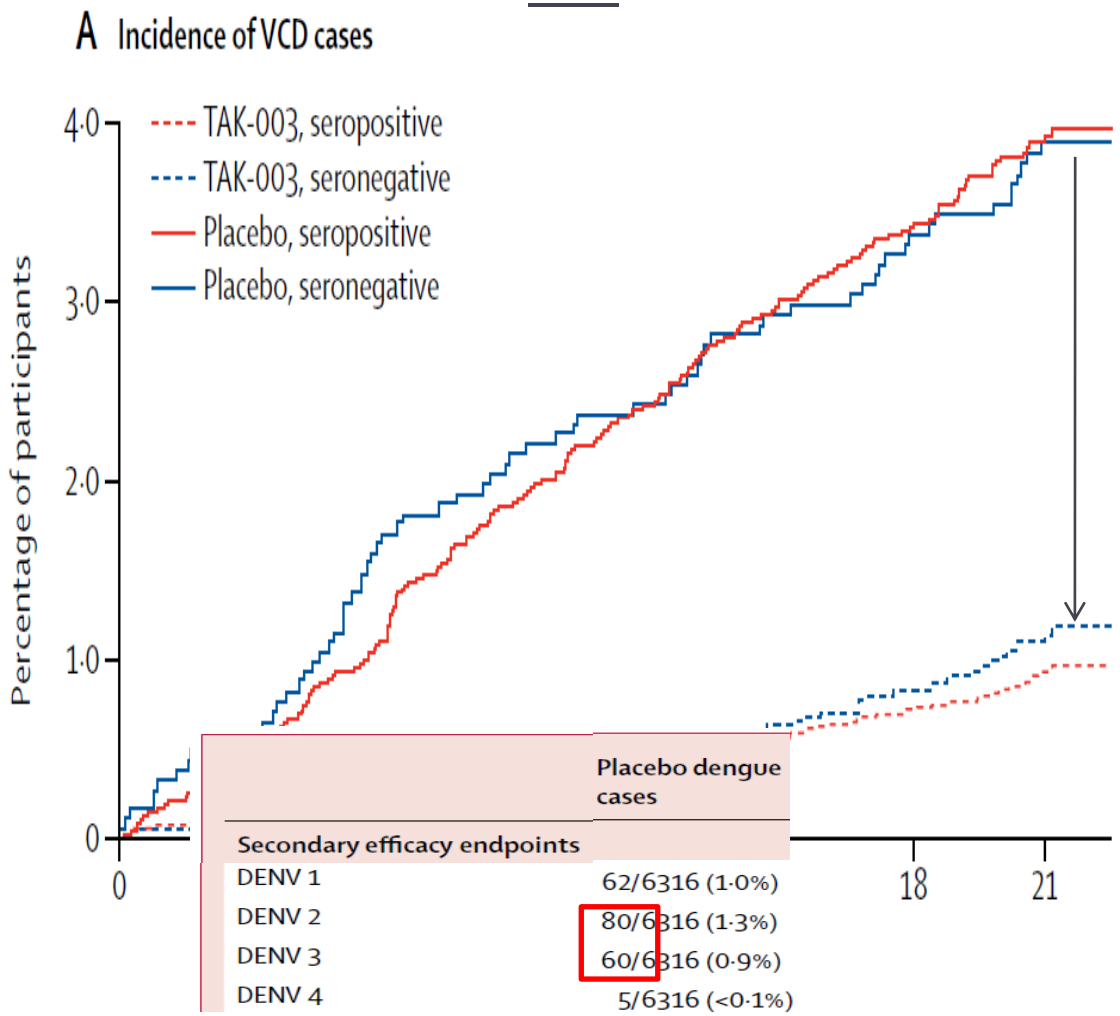
Dengue Fever

Vaccines

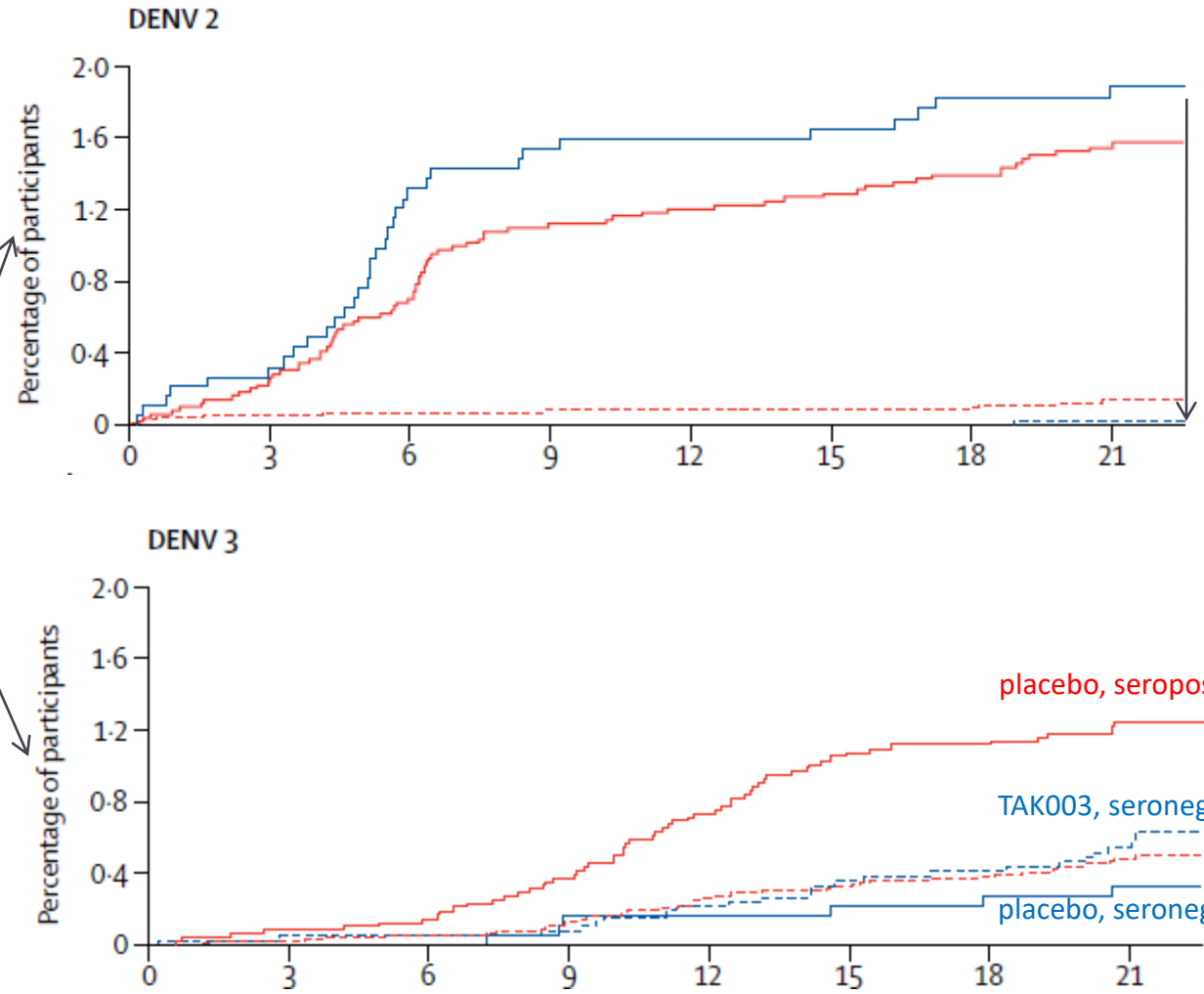
Immunology Development CYD-TDV TAK-003 Others Travellers?

VCD = virogical confirmed Dengue

M18



Secondary efficacy endpoints	Placebo dengue cases
DENV 1	62/6316 (1·0%)
DENV 2	80/6316 (1·3%)
DENV 3	60/6316 (0·9%)
DENV 4	5/6316 (<0·1%)

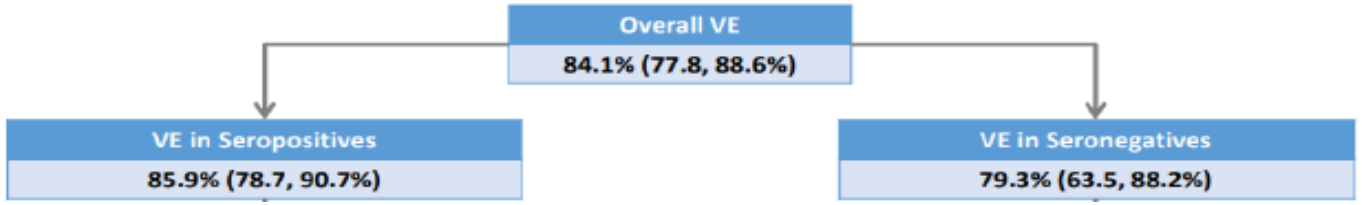


Warning: ~40% of placebo VCD are DENV-2

→ possible overestimation of overall VE

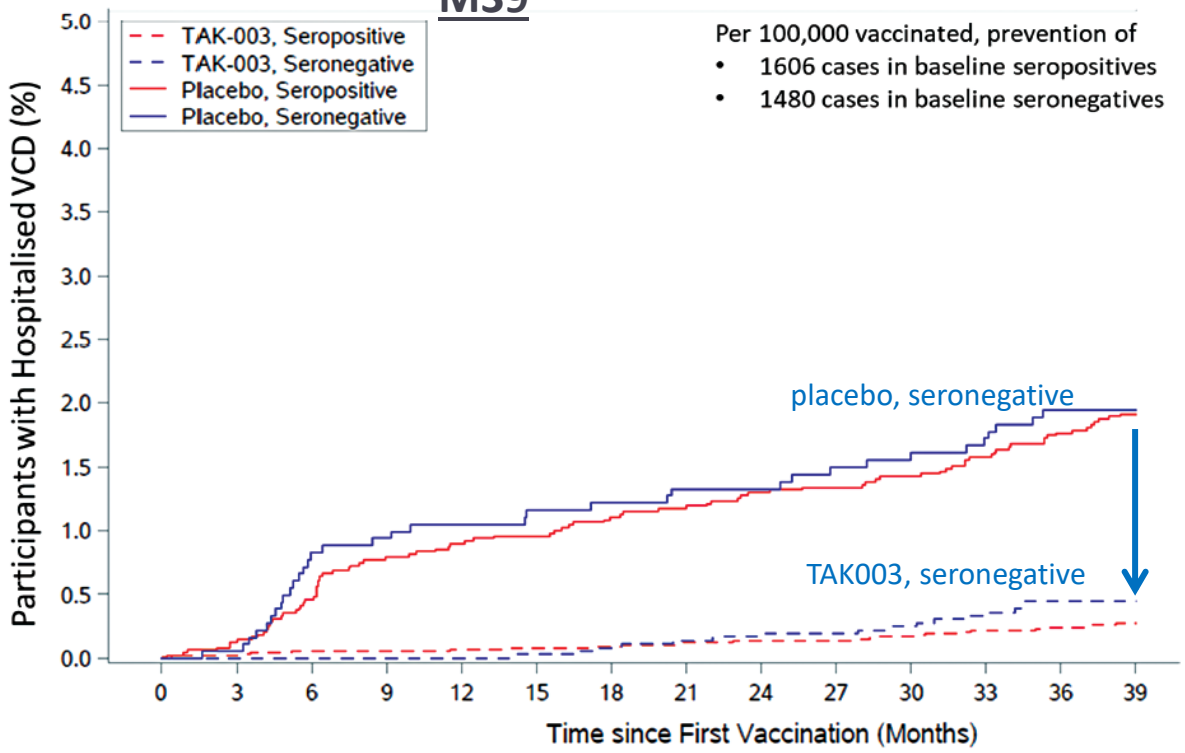
Biswal S, et al. Lancet 2020

Cumulative efficacy for hospitalisation at M54

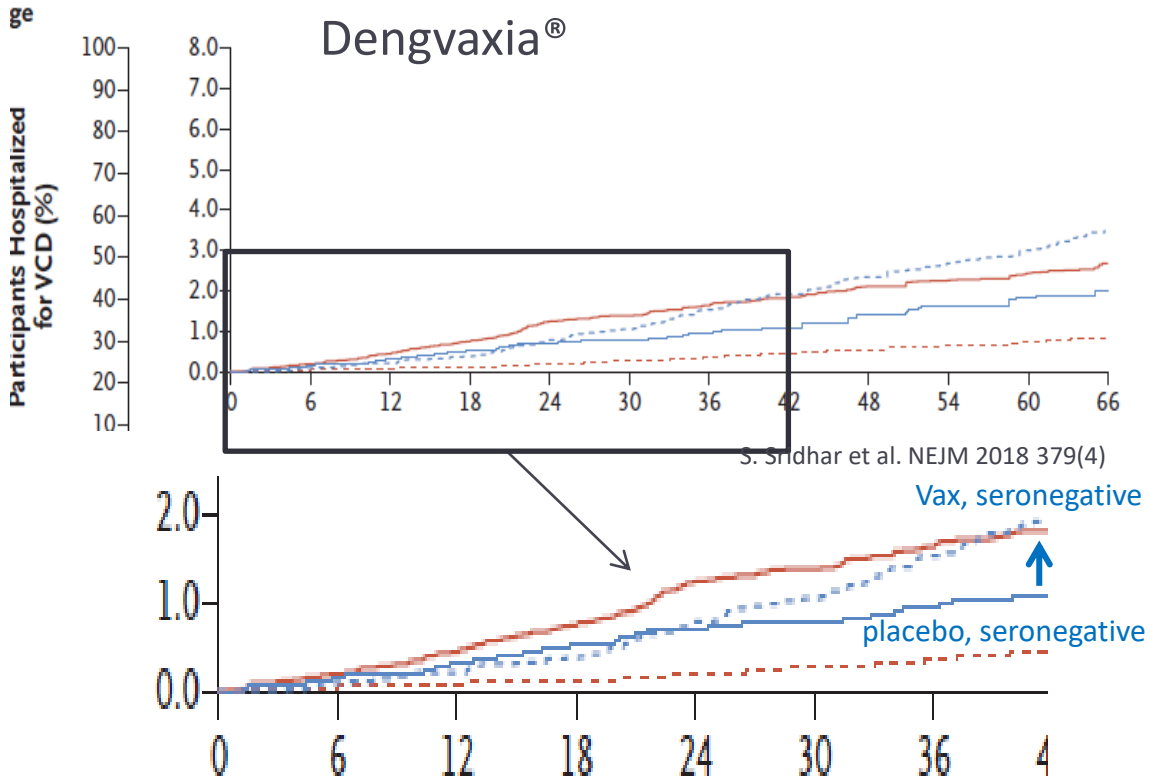


TAK-003(Qdenga®) hospitalisation

M39



Dengvaxia®



Biswal S, et al. Lancet 2020
Rivera L. et al CID 2022

Dengue Fever

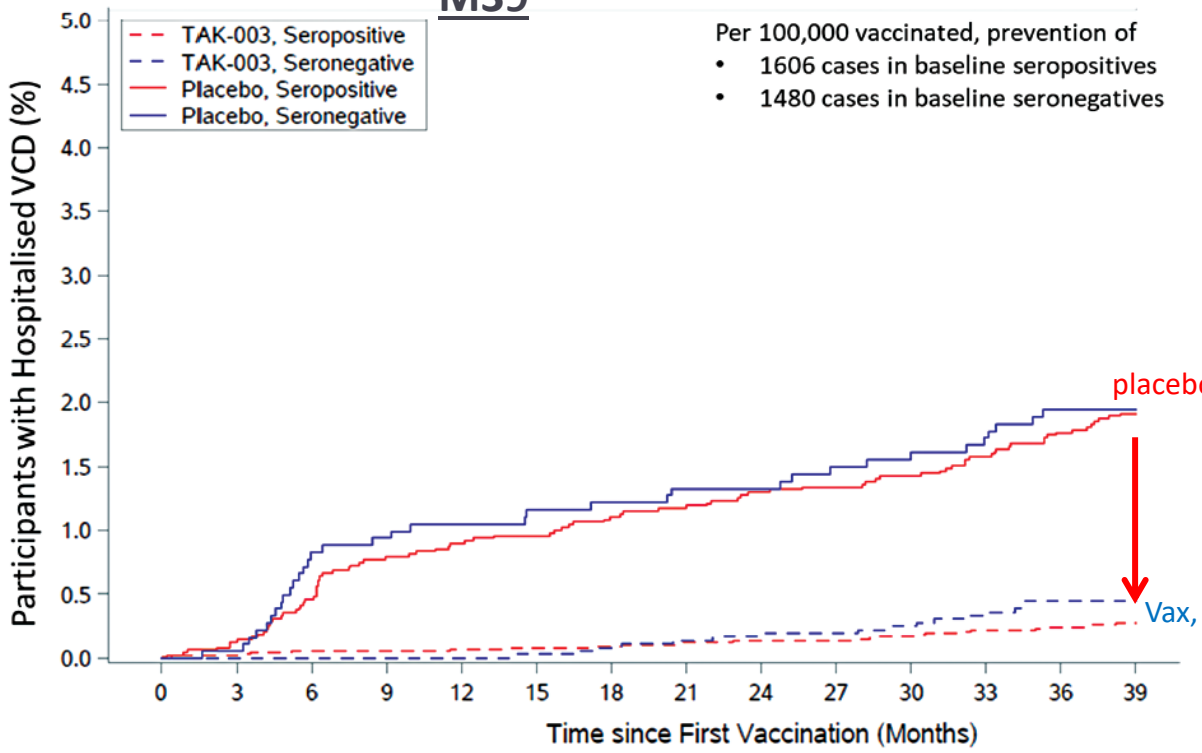
Vaccines

Immunology Development CYD-TDV TAK-003 Others Travellers?

TAK-003(Qdenga®)

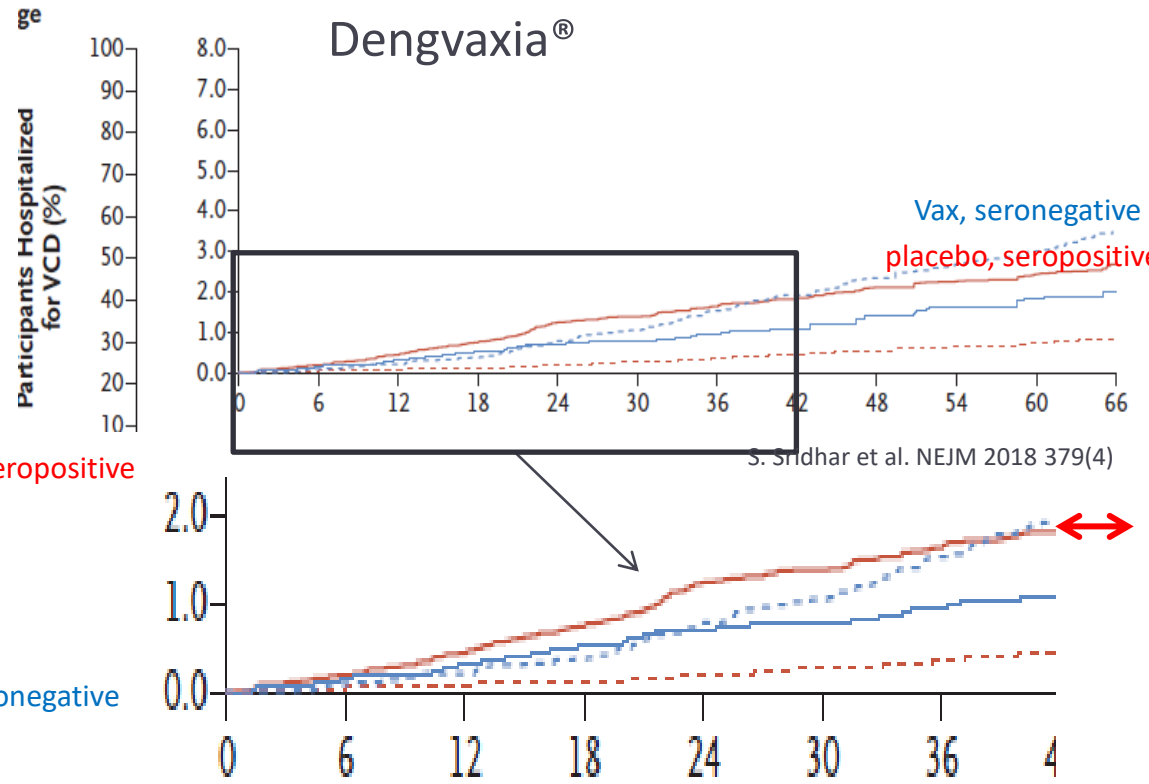
hospitalisation

M39



		Placebo sero+	TAK-003 sero-
Overall hospitalisation	M39	91/4854 (1.9%)	16/3714 (0.4%)
	M54	*101/4854 (2.1%)*	*17/3714 (0.5%)*

Dengvaxia®



Biswal S, et al. Lancet 2020
Rivera L. et al CID 2022

Cumulative efficacy for hospitalisation at M54

Overall VE

84.1% (77.8, 88.6%)

VE in Seropositives

85.9% (78.7, 90.7%)

VE in Seropositives by Serotype

DENV-1	**66.8% (37.4, 82.3%)**
DENV-2	**95.8% (89.6, 98.3%)**
DENV-3	**74.0% (38.6, 89.0%)**
DENV-4	**100% (NE, NE)†**

VE in Seronegatives

79.3% (63.5, 88.2%)

VE in Seronegatives by Serotype

DENV-1	**78.4%**	**(43.9, 91.7%)**
DENV-2	**100%**	**(NE, NE)§**
DENV-3	-87.9%	(-573.4, 47.6%)¶
DENV-4	100 %	(NE, NE)**

§DENV-2 Placebo events: 23 TAK-003 events: 0
¶DENV-3 Placebo events: 3 TAK-003 events: 11
**DENV-4 Placebo events: 1 TAK-003 events: 0

Unpublished data presented by Takeda to ACIP WG

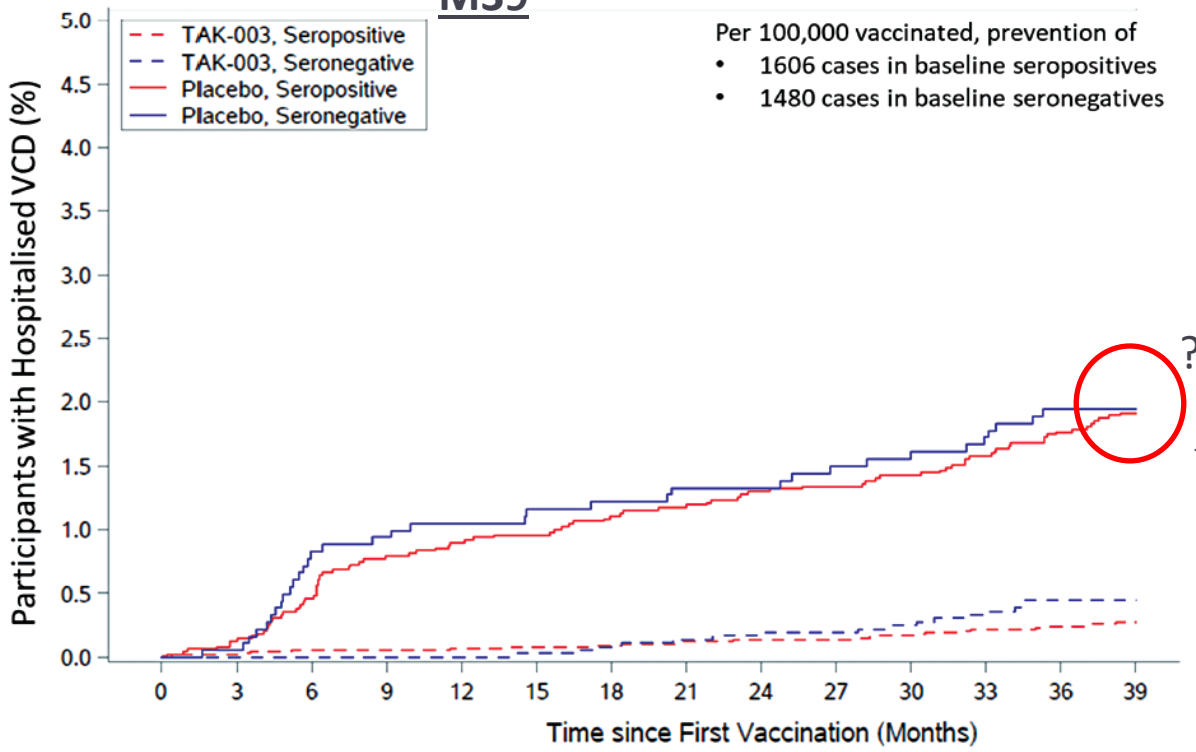
		Placebo sero+	TAK-003 sero-
Overall hospitalisation	M39	91/4854 (1.9%)	16/3714 (0.4%)
	M54	*101/4854 (2.1%)*	*17/3714 (0.5%)*
DENV-3 hospitalisation	*M54*	*15/4854 (0.3%)*	*11/3714 (0.3%)*

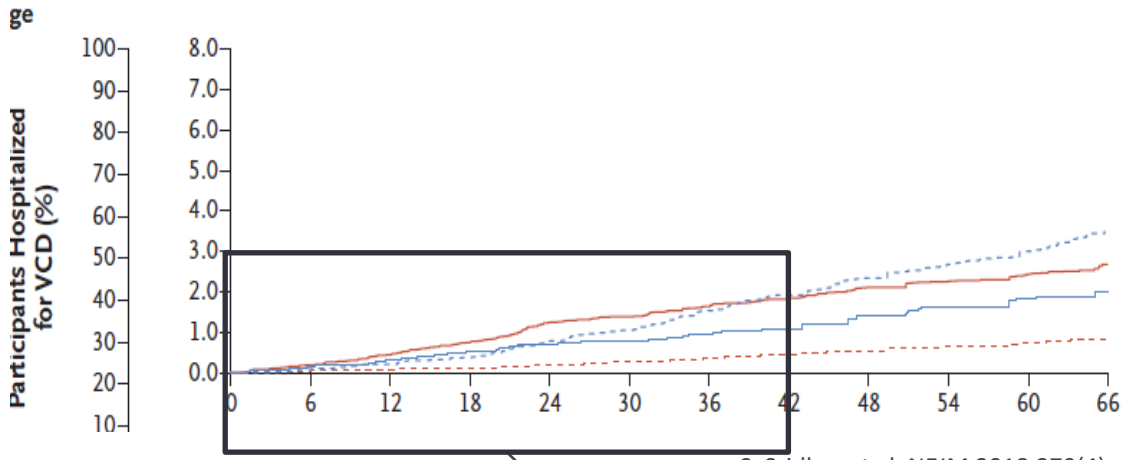
↔

Sponsor's Summary of Product Characteristics 2022

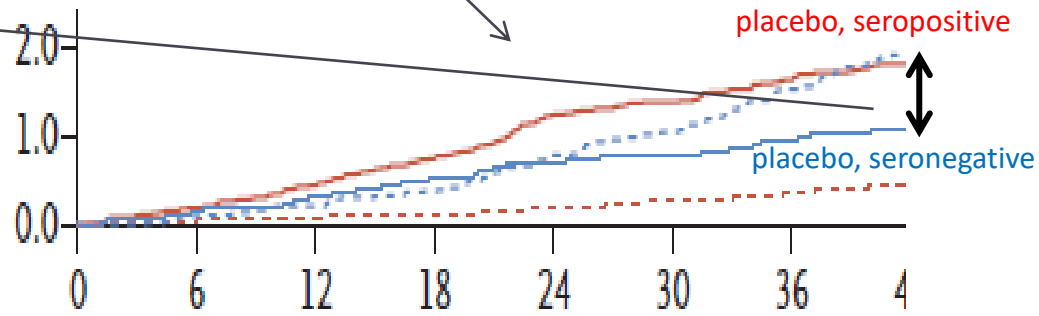
TAK-003(Qdenga®) hospitalisation

M39





S. Sridhar et al. NEJM 2018 379(4)



no hospitalisation difference between sero+ vs sero- placebo in Qdenga® study:

- Bias : Hospitalisation ≠ severity ?
- Coinfection with multiple serotypes ? *but does not seem link to severity…* *[Senarathne U.T.N, et al. Epidemiology and Infection 2020]*

Biswal S, et al. Lancet 2020
Rivera L. et al CID 2022

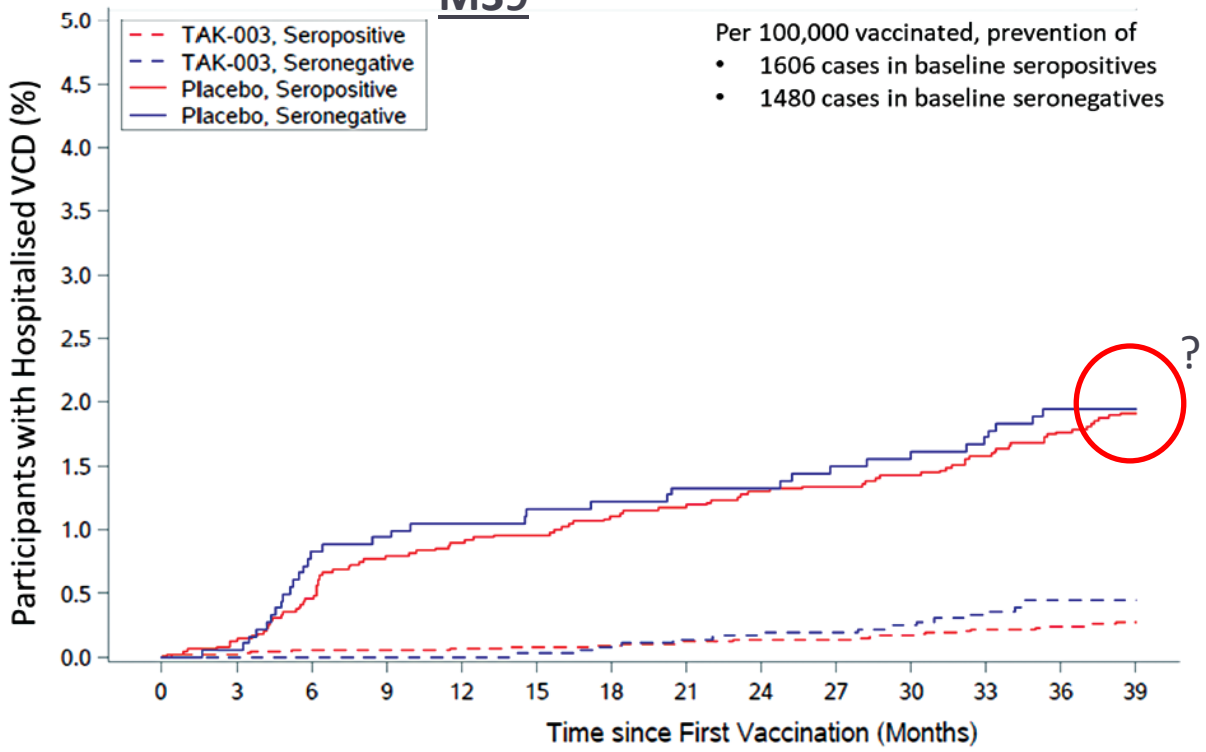
Dengue Fever

Vaccines

Immunology Development CYD-TDV TAK-003 Others Travellers?

TAK-003(Qdenga®) hospitalisation

M39



Subgroup	Placeb (n=6,68	TAK-003 (n=13,380)	VE (95% CI)
Number of cases by severity (per 100 person years) M54			
DHF (WHO 1997 criteria)			
Seronegative	2 (<0.1)	4 (<0.1)	-3.4 (-464.7, 81.1)
Seropositive*	13 (<0.1)	5 (<0.1)	80.9 (46.3, 93.2)

data provided by Takeda®

…too small to conclude anything. Underpowered?

no hospitalisation difference between sero+ vs sero- placebo for Qdenga®:

- Bias : Hospitalisation ≠ severity ?
- Coinfection with multiple serotypes ? *but does not seem link to severity…*

Biswal S, et al. Lancet 2020
Rivera L. et al CID 2022

Dengue Fever

Vaccines

Immunology Development CYD-TDV TAK-003 Others Travellers?

Qdenga®

- licensed by EMA & others countries…
- submitted to Swissmedic in April 2023
  - 1st report : mid-september 2023
  - approval ? : august 2024

- Voluntary withdraw from FDA (july 2023)
  - Data collection issues (missing lab data in minority of patients with fever during follow-up?, follow-up visit missing?)
  - efficacy or safety not transmitted…

- Strategic Advisory Group of Experts on Immunization (SAGE), WHO
  - meeting : 25.9.23
  - Official publication: end 2023?

Healthcare & Pharmaceuticals | Approvals | Regulatory | Public Health

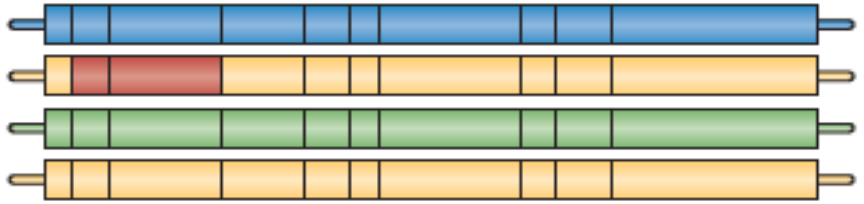
Takeda withdraws US application for dengue vaccine candidate

Reuters

July 11, 2023 5:32 PM GMT+2 · Updated a month ago

- TV003 (Butantan):
  - Phase 3 ongoing
  - Whole DFV backbone
    - humoral immunity: Strct (E+M) prot & NS prot (DENV-1-3-4 NS-1 specific)
    - cellular immunity: NS epitopes for NS1-5 (DENV-1-3-4)

TV003 - Butantan



Percentage of subjects with detectable viremia by PCR or culture after 1st dose in flavirus-naïve subjects				
	DENV-1	DENV-2	DENV-3	DENV-4
CYD (n=95)[1]	7.4	0	12.6	44.2
TAK (n=74)[2]	0	68.9	0	0
TV003 (n=80)[3]	63.9	97.2	69.4	52.6

VE TV003 (>24 months)	overall	Sero-	Sero+
DENV-1	89.5%	85.5%	96.8%
DENV-2	69.6%	57.9%	83.6%
DENV-3/4	n.a.	n.a.	n.a.

Halstead SB, et al Lancet Child Adolesc Health 2019, 3:734-41
[1]Torresi et al, JID2017
[2]Rupp et al, 2015
[3] Russel et al, Human Vacc & Immuno 2022
Thomas S. npj vacc 2023

Dengue Fever

Vaccines

- "Much more frequent than many of the other travel-associated vaccine-preventable disease"

→ ~1-5% travellers in dengue-endemic countries…

2.4% after 1 month travel; 6.9% after 6 months travel

but

only ~17% of secondary infection DF in Europe

rarely cause death in travelers

- Dengvaxia®
  - i.m. ; M0-M6-M12 (booster?) (however, short-term efficacy after one dose is as high as after 3 doses)
  - 1st dose: (3-)6 months after acute infection
  - NOT licensed in Switzerland, but :
    - 2015: licensed in Mexico ~~& Philippines~~
    - 2018: EMA-approval : 6-45 y.o. seropositive
    - 2019: FDA-approval: 6-16 y.o. seropositive & living in endemic areas
      - BUT low seroprevalence in travellers…

- Qdenga® (TAK-003) and others
  - s.c.; M0-M3 (booster?)
  - 1st dose 2 weeks before trip, then 2nd later might be possible…

  - NOT (yet?) licensed in Switzerland, but :
    - 2022: licensed in Indonesia & Brazil
    - 2022: EMA-approval : > 4 y.o. … BUT different recommendations according to national societies
    - 2023: voluntary withdraw for FDA-approval…

    - ECTM 2023: possible in DF prior infected travelers and long trip…

Wilder-Smith A, JTM 2019
Wilder-Smith A, Bundesgesundheitsbl 2020
Wilder-Smith A, CISTM18

Expertenkomitee für Reisemedizin
Comité d'experts pour la médecine des voyages
Comitato di esperti per la medicina di viaggio
Expert committee for travel medicine

Swiss ECTM recommandations – 2023 (draft)

- vaccination with Dengvaxia® or Qdenga® is **not recommended** in travellers with no prior dengue fever.

- vaccination with Qdenga® **can be considered** in travellers (≥4 years old) :
  - with previous dengue infection : confirmed previous Dengue (PCR, Ag or raise of IgM) OR clinical history & IgG+

  AND
  - who are planning a long-term stay (>4 weeks) or multiple trips to an endemic region.

- given the existing cross-reactions with other flaviviruses or their vaccines, particularly in patients living outside endemic DF areas, **serology alone without a compatible anamnesis should be interpreted with caution**,

- Be aware of lack of knowledge about :
  - the duration of protection

  and
  - the need for a booster in a population living in a non-endemic area & unable to rely on a "natural booster"

→ risk-benefit ratio of such a vaccination MUST be taken in consideration

THANK YOU FOR YOUR ATTENTION!

ANY QUESTIONS?

NO? GREAT!
BYE.