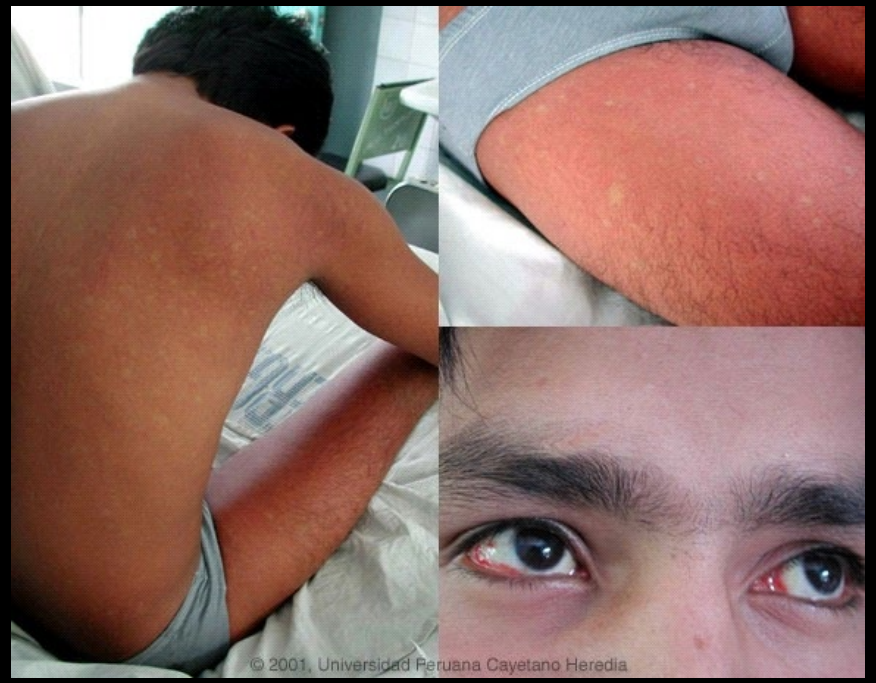
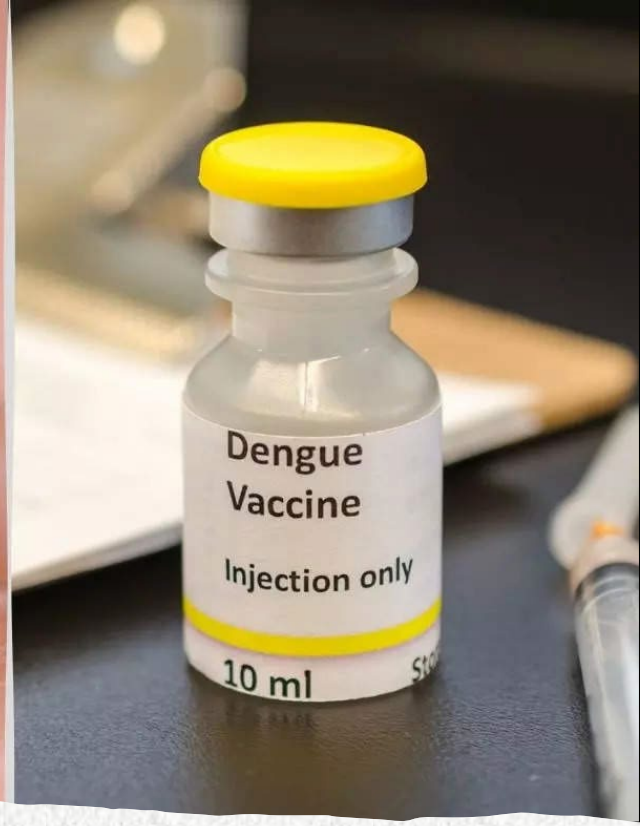




Dengue vaccines

- Annelies Wilder-Smith MD PhD
- WHO, IVB-PDR
- WHO focal point: SAGE WG Dengue Vaccines
- Honorary Professor of Emerging Infectious Diseases, London School of Hygiene and Tropical Medicine

Dengue burden

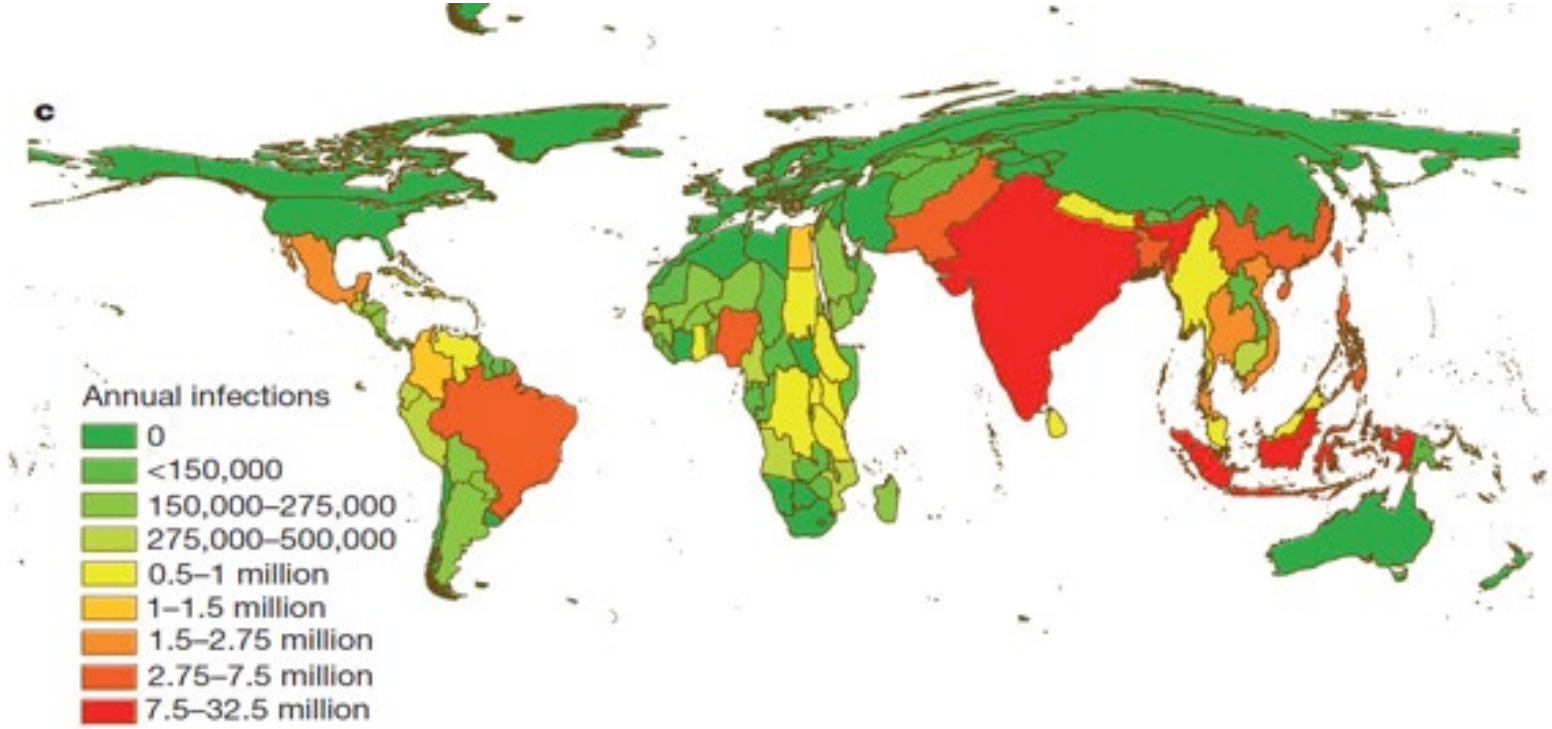
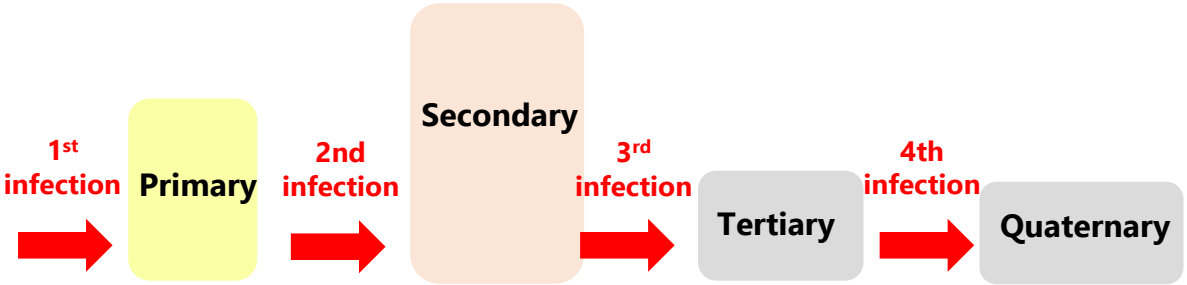


Table 1 | Estimated burden of dengue in 2010, by continent

	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)

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

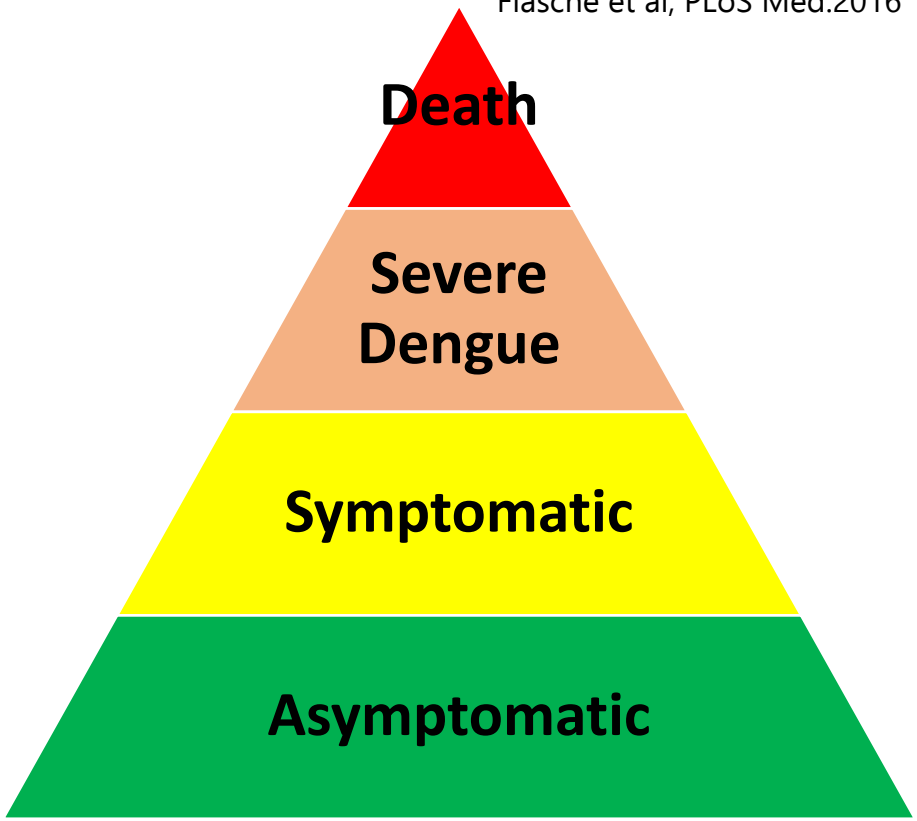
Dengue



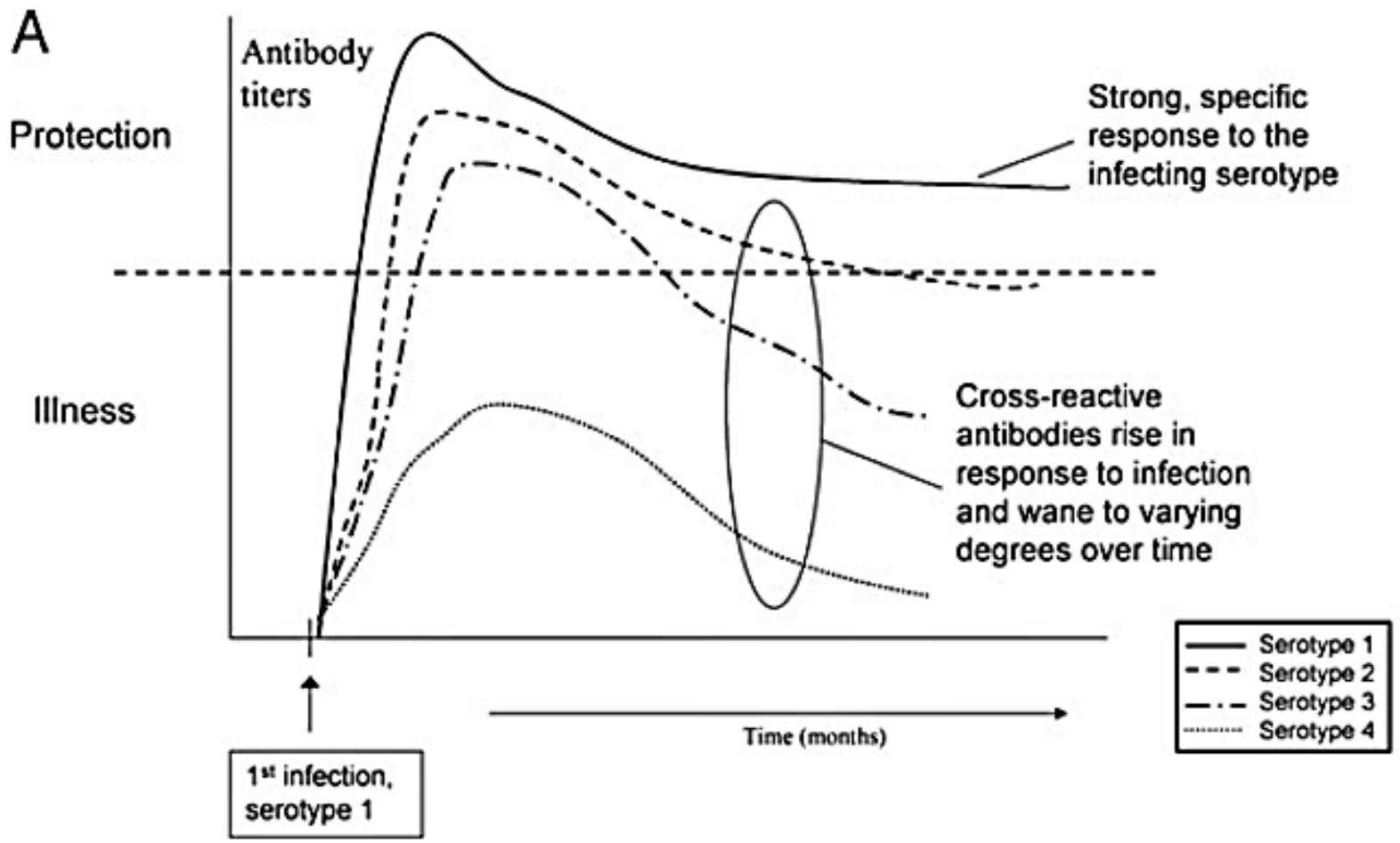
- Four antigenically distinct serotypes (DENV1-4)

- Clinical spectrum:
  - 80% asymptomatic
  - Self-limiting febrile illness
  - Secondary infections are associated with higher risk of more severe dengue
  - Severe dengue (~2-4% of symptomatic)
  - CFR 0.1—1%

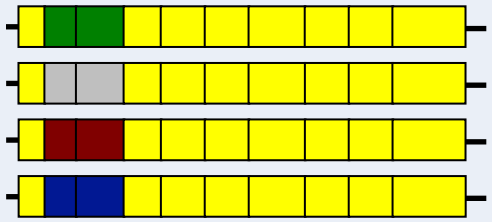
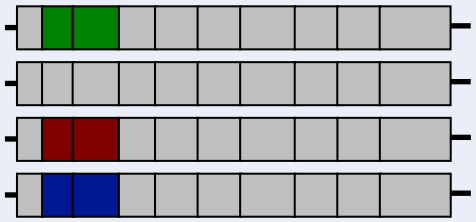
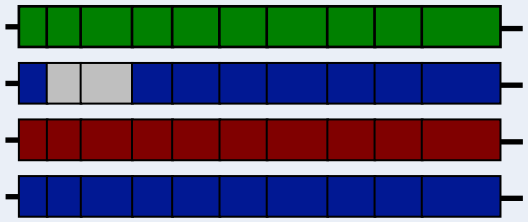
Flasche et al, PLoS Med.2016

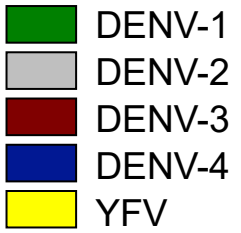


Immunological interaction between the 4 serotypes

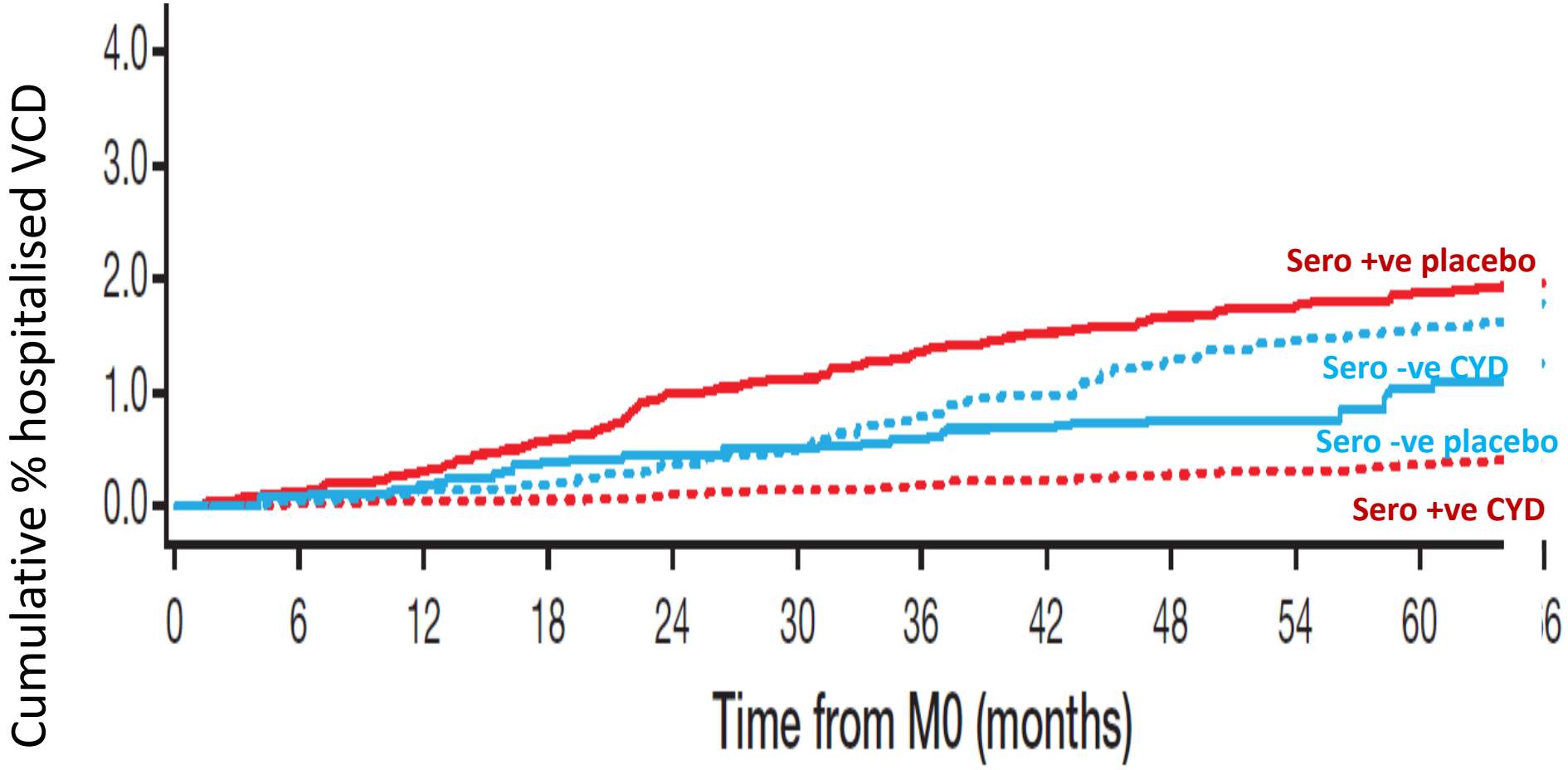


Three dengue vaccine candidates, all are tetravalent and live attenuated; differences in the backbone and extent of chimerization

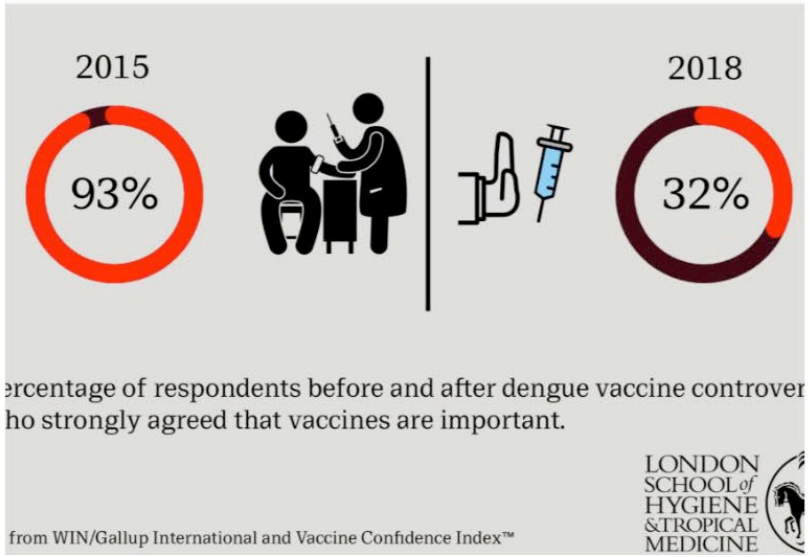
	Dengvaxia (Sanofi Pasteur)	TDV (Takeda)	TV003/TV005 (NIH/Butantan)
Status	Licensed	Licensed	Phase 3
# Doses	3 doses over 12 months (0, 6, 12)	2 doses (0, 3 months)	Single dose
Indicated age	9 - 45	Phase 3 age range 4 - 16	Phase 3 age range 2 - 59
Other	Requires documented previous DENV infection	?	?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



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



Dramatic drop in vaccine confidence in the Philippines



Public health net benefit of Dengvaxia

Impact for vaccinated subjects over 10 years (direct protection only)

Results for a vaccinated cohort of 1,000,000 vaccinees

Prevented number of hospitalisations over 10 years*

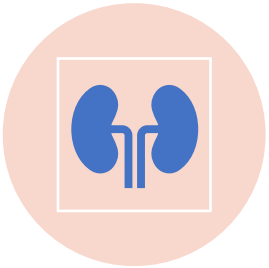
	Endemic setting	Hospitalisations		
		Sero+	Sero-	All
Very high	90%	6419 [5713;7101]	348 [82;992]	6767 [5795;8093]
	80%	6535 [5834;7116]	-7 [-436;612]	6528 [5398;7728]
High	70%	5611 [5219;6332]	-572 [-874;-287]	5039 [4344;6045]
	60%	4303 [3833;5148]	-1484 [-1740;-698]	2820 [2093;4450]
Moderate	50%	2978 [2724;3181]	-2039 [-2224;-1758]	939 [500;1423]
	40%	2243 [2124;2484]	-1904 [-2337;-1314]	340 [-213;1170]
Low	30%	143 [115;219]	-217 [-290;-188]	-74 [-176;31]
	20%	74 [43;80]	-231 [-701;-122]	-157 [-658;-42]
Very low	10%	9 [6;11]	-57 [-89;-44]	-48 [-83;-33]

Viremia following a single dose of CYD-Dengvaxia

The percentage of subjects with detectable viremia by culture (% 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)	0 (0)	0 (17)	**8 (50)**
CYD, Day 7 (n=84)[2]	0 (0)	1 (2)	0 (0)	**2.1 (30)**
CYD (n=25)[3]	(0)	(4)	(0)	**(52)**
CYD (n=95)[4]	(7.4)	(0)	(12.6)	**(44.2)**

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

Summary: CYD-TDV vaccine (Dengvaxia) serostatus dependent performance



Dengvaxia is efficacious and safe in seropositive persons: 72-80% against dengue of any severity; >90% against severe dengue

Dengvaxia increases the risk of severe dengue in seronegative persons: RR 2-3

What is the best use of the first licensed dengue vaccine?

Pre-Vaccination Screening Strategy

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

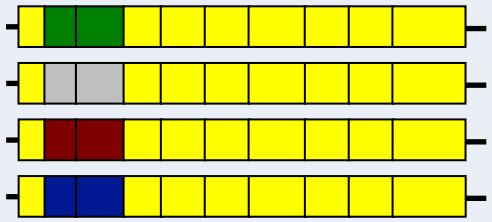
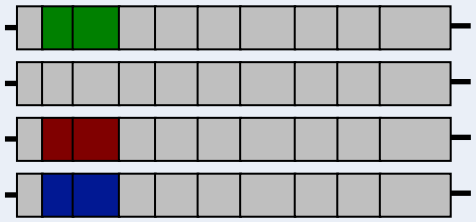
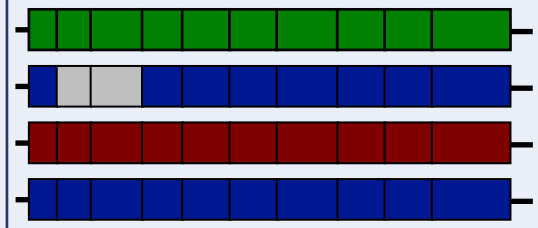
Contents

Dengue vaccine: WHO position paper – September 2018

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

- For countries considering vaccination as part of their dengue control program, a "pre-vaccination screening strategy" is the recommended strategy, in which only dengue-seropositive persons are vaccinated

Takeda TAK-003: now licensed by EMA, MHRA, Brazil and Indonesia. First introducing country is Indonesia.

	Dengvaxia (Sanofi Pasteur)	TAK-003 (Takeda)	TV003/TV005 (NIH/Butantan)
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

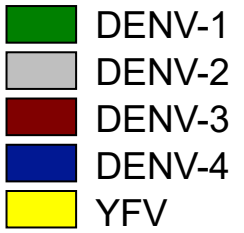
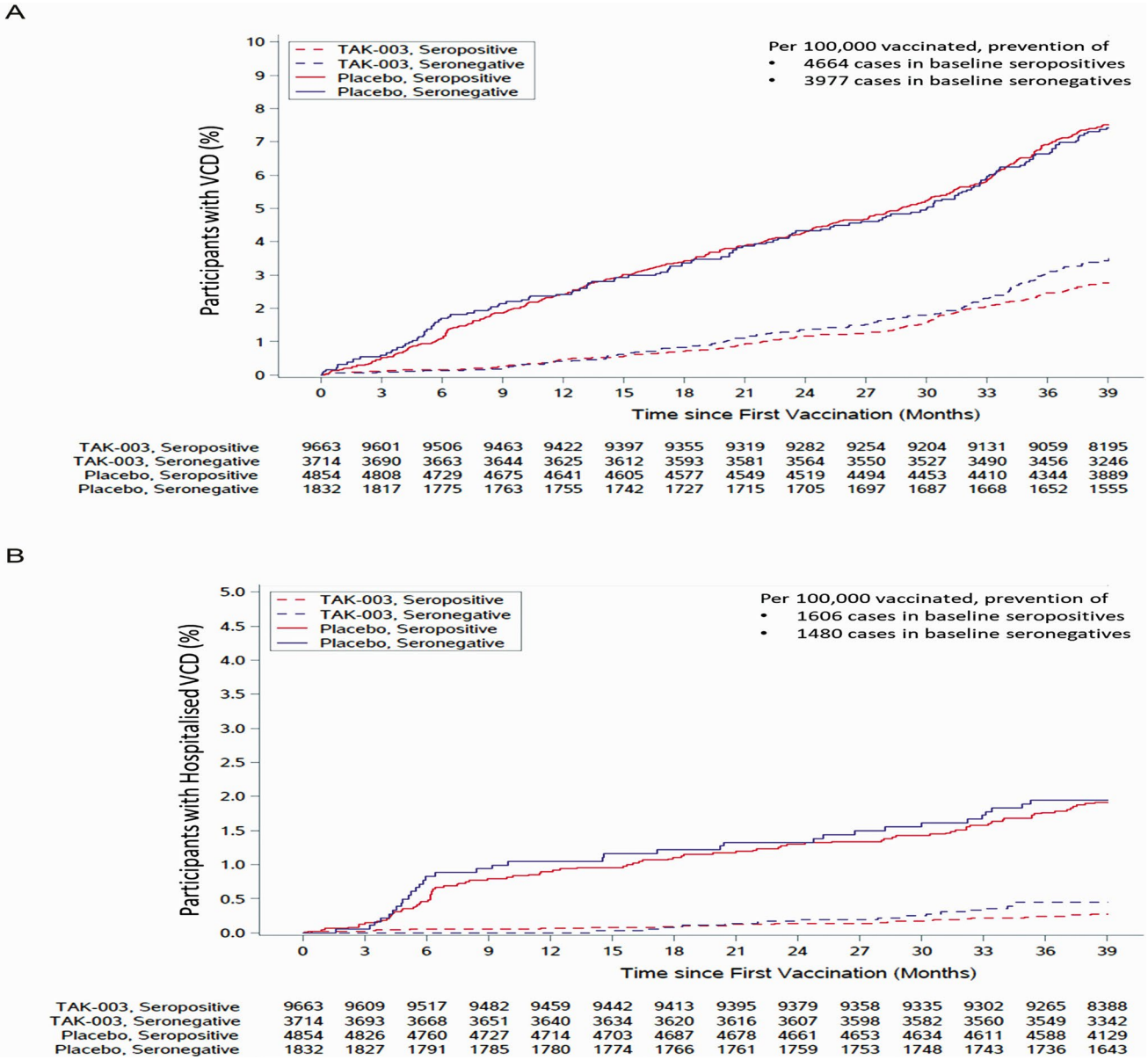


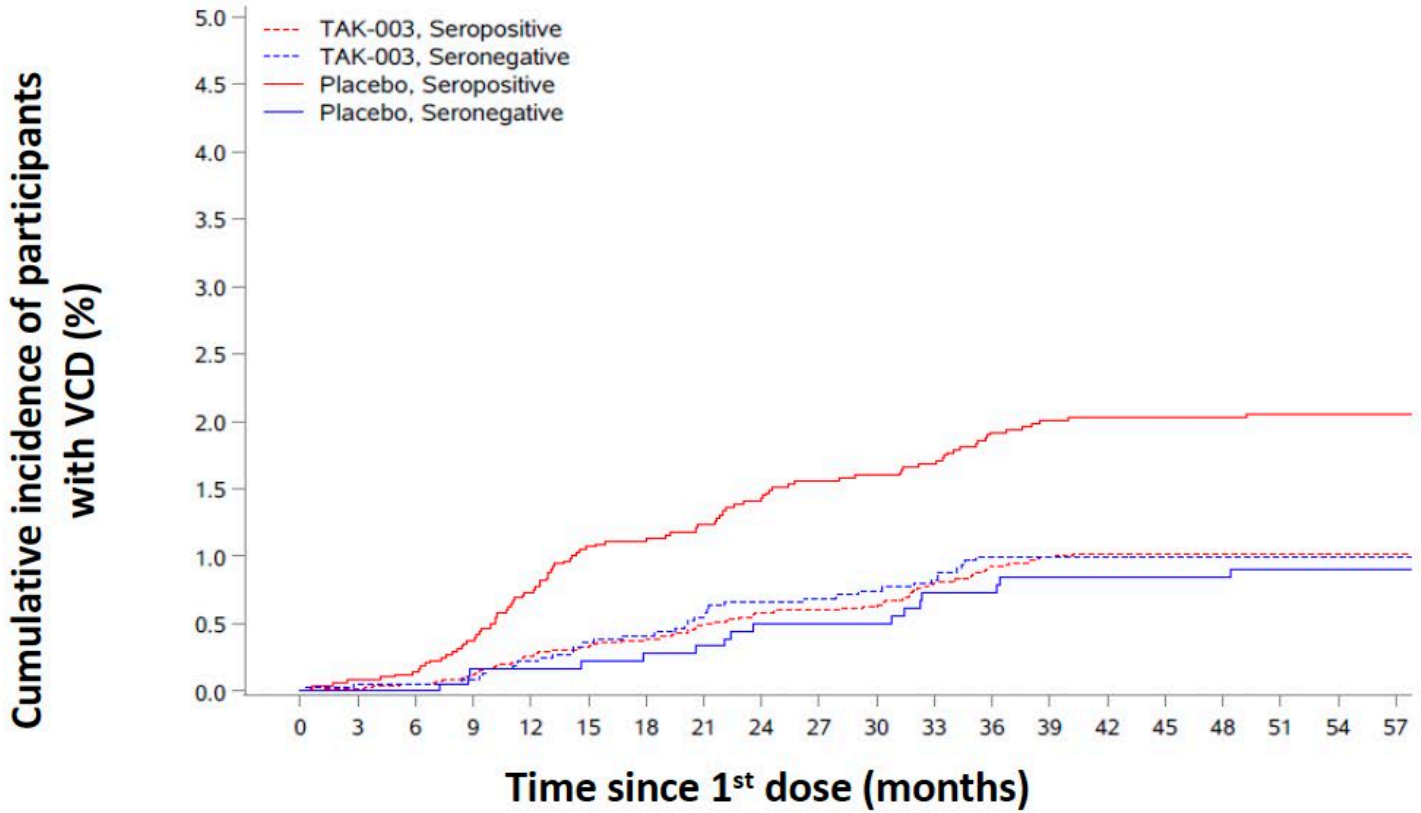
Figure 3. Cumulative incidence of (A) virologically confirmed dengue (VCD) cases and (B) hospitalized VCD cases



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

Cumulative incidence of VCD over ~ 57 months after 1st dose

Subgroup analysis by baseline seropositivity status and serotype (safety set) - **DENV-3**



Safety set data and truncated at 57 months after 1st dose. Seronegative at baseline: Seronegative to all four dengue serotypes; seropositive at baseline: Reciprocal neutralizing titer ≥10 for one or more DENV serotypes.
DENV, dengue virus; VCD, virologically confirmed dengue.
Takeda. Data on file. 2022.

Viremia following a single dose of CYD & Takeda vaccines

The percentage of subjects with detectable viremia by culture (% 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)	0 (0)	0 (17)	**8 (50)**
CYD, Day 7 (n=84)[2]	0 (0)	1 (2)	0 (0)	**2.1 (30)**
CYD (n=25)[3]	(0)	(4)	(0)	**(52)**
CYD (n=95)[4]	(7.4)	(0)	(12.6)	**(44.2)**
TAK (n=74)[5]	(0.0)	**(68.9)**	(0.0)	(0.0)

1. Qiao et al, 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

TAK-003: VE by clinical outcome, serostatus and serotype at 57 months

Clinical outcome	VE overall	VE in seropositives	VE in seronegatives
Virologically confirmed disease	61.2% (56.0, 65.8%)	64.2% (58.4, 69.2%)	53.5% (41.6, 62.9%)
Serotype 1		56.1% (44.6,65.2%)	45.4% (26.1,59.7%)
Serotype 2		80.4% (73.1, 85.7%)	88.1% (78.6, 93.3%)
Serotype 3		52.3% (36.7, 64.0%)	-15.5% (-108.2; 35.9%)
Serotype 4		70.6% (39.9, 85.6%)	-105.6% (-628.7, 42.0%)
Hospitalized dengue	84.1% (77.8, 88.6%)	85.9% (78.7, 90.7%)	79.3% (63.5, 88.2%)
Serotype 1		66.8% (37.4, 82.3%)	78.4% (43.9, 91.7%)
Serotype 2		95.8% (89.6, 98.3)	100% (NE, NE) (23 vs 0 events)
Serotype 3		74.0% (38.6, 89.0%)	-87.9% (-573.4, 47.6%)
Serotype 4		(NE, NE)	(NE, NE) (1 vs 0 events)
Severe dengue	70.2% (-24.7; 92.9%)	90.2% (16.4, 98.9%)	-999.0% (NE, NE)(0 vs 2 events)

TAK-003 dengue vaccine

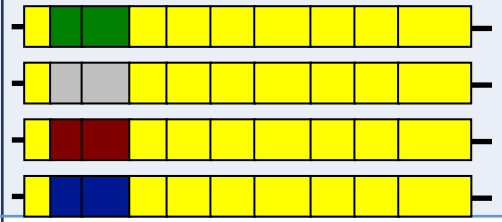
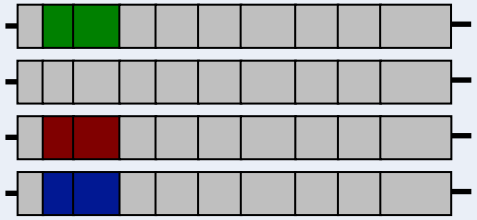
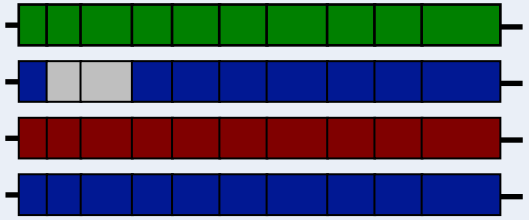
Good efficacy against serotypes 2 and 1, higher in seropositives.

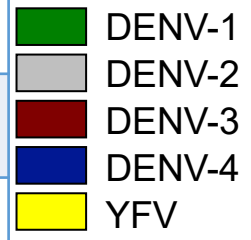
No efficacy against serotype 3 in those who are baseline seronegative

Data insufficient to rule out a safety risk in seronegative individuals exposed to serotype 3.

Scarcity of serotype 4 circulation does not allow for any conclusions

TV003/TV005:
Interim results recently released; complete Phase 3 trial results still pending

	Dengvaxia (Sanofi Pasteur)	TDV (Takeda)	TV003/TV005 (NIH/Butantan)
Status	Licensed	Licensed	Phase 3 (2 year data web-posted)
# 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



Viremia following a single dose of Butantan`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

	Dengvaxia (Sanofi Pasteur)	TDV (Takeda)	TV003/TV005 (NIH/Butantan)
Status	Licensed	Licensed	Phase 3 ongoing; interim analyses at 2 years (data cut-off July 2021)
# Doses	3 doses (0, 6, 12 months)	2 doses (0, 3 months)	Single dose
Age range in Ph3 trials	2 - 16	4 - 16	2 - 59
Number of subjects	18,835 in 10 countries	19,024 in 8 countries	16,162 in 1 country
Overall VE against VCD by 2 years	60.8% (52.0-68.0)	72.7% (67.1 -77.3)	79.6% (70.0-89.3)
VE by serostatus	Seropositive: 83.7% (62.2 - 92.7) Seronegative: 43.4% (-61.5 -80)	Seropositive: 74.8% (68.6-79.8) Seronegative: 67.0% (53.6-76.5)	Seropositive: 89.2% (77.6-95.6) Seronegative: 73.6% (57.6-83.7)
Remarks	Increased risk of severe dengue from month 30 onwards in seronegatives	Evidence of “no efficacy” or “negative efficacy” in seronegatives exposed to serotype3. Serotype 4: insufficient data	No data for serotypes 3 and 4 (data cut-off 13 July 2021)
WHO SAGE recommendations	Requires pre-vaccination screening	?	?

Conclusions

- Dengvaxia requires pre-vaccination screening; uptake has been minimal
- TAK-003 was recently licensed in various countries. First introducing country: Indonesia.
- SAGE will provide policy recommendations on TAK-003 in September 2023
- NIH-Butantan-Merck vaccine: promising high-level data from Phase 3 trial results released but not yet published; to-date unknown regulatory timelines. No VE data for serotypes 3 and 4.
- It is unlikely that a “perfect” dengue vaccine will be available soon and trade-offs need to be considered requiring pro-active communication