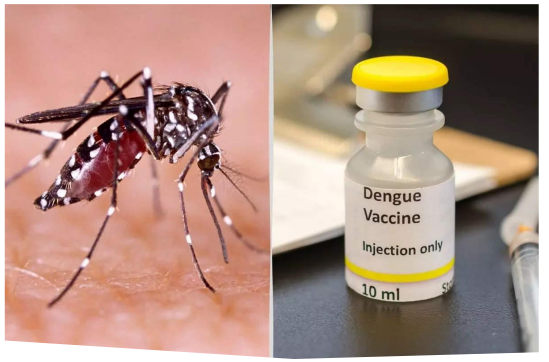
Prof Annelies Wilder-Smith

IMMUNISATION COALITION

A WHO perspective on dengue vaccines

6:15 pm



Epidemiology

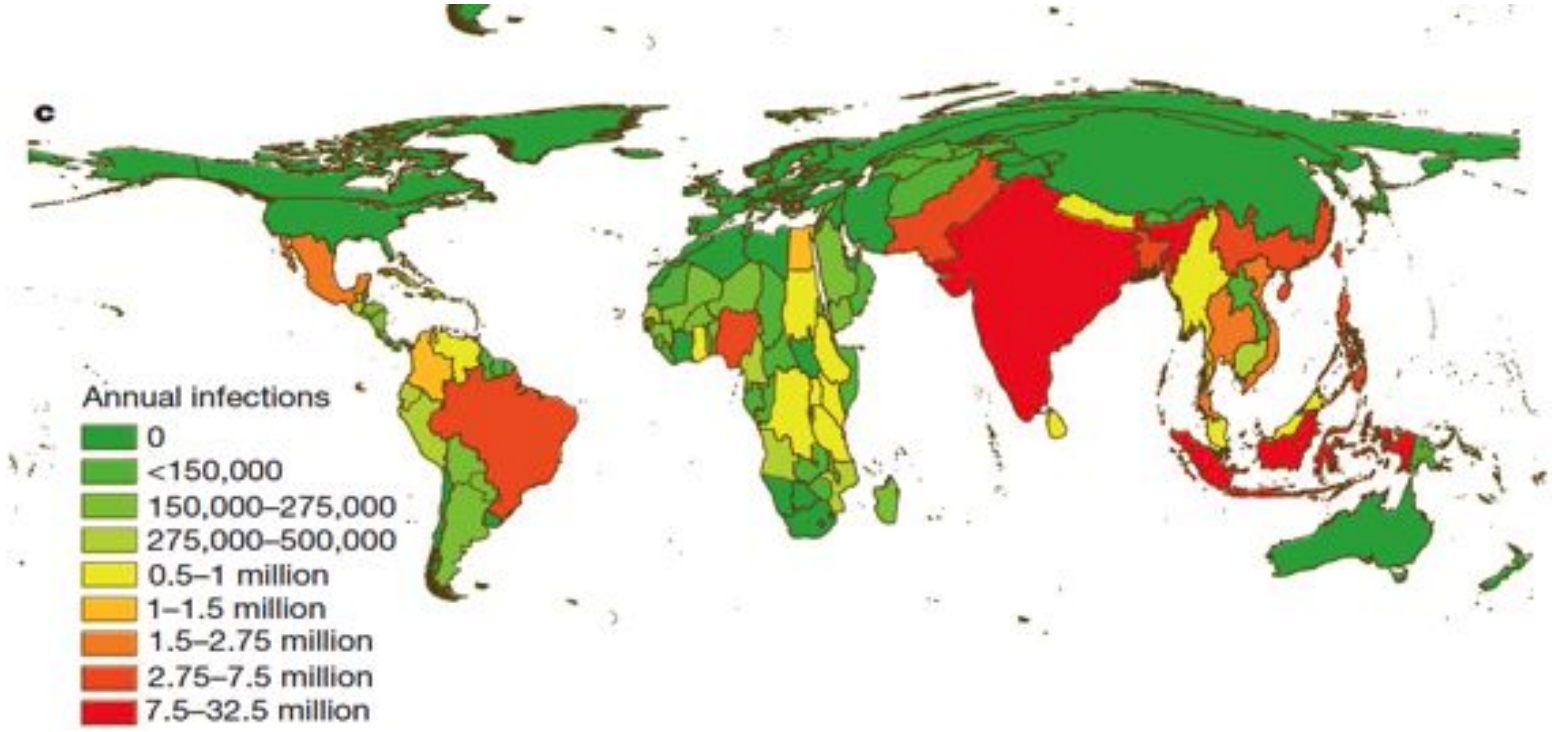
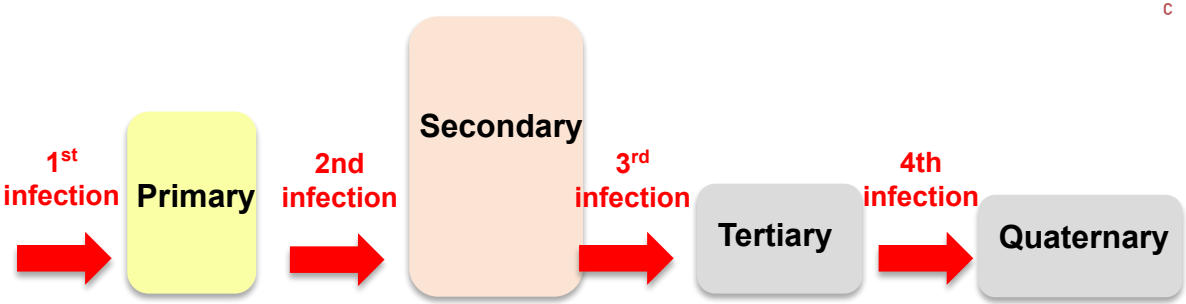


Table 1 | Estimated burden of dengue in 2010, by continent

	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)

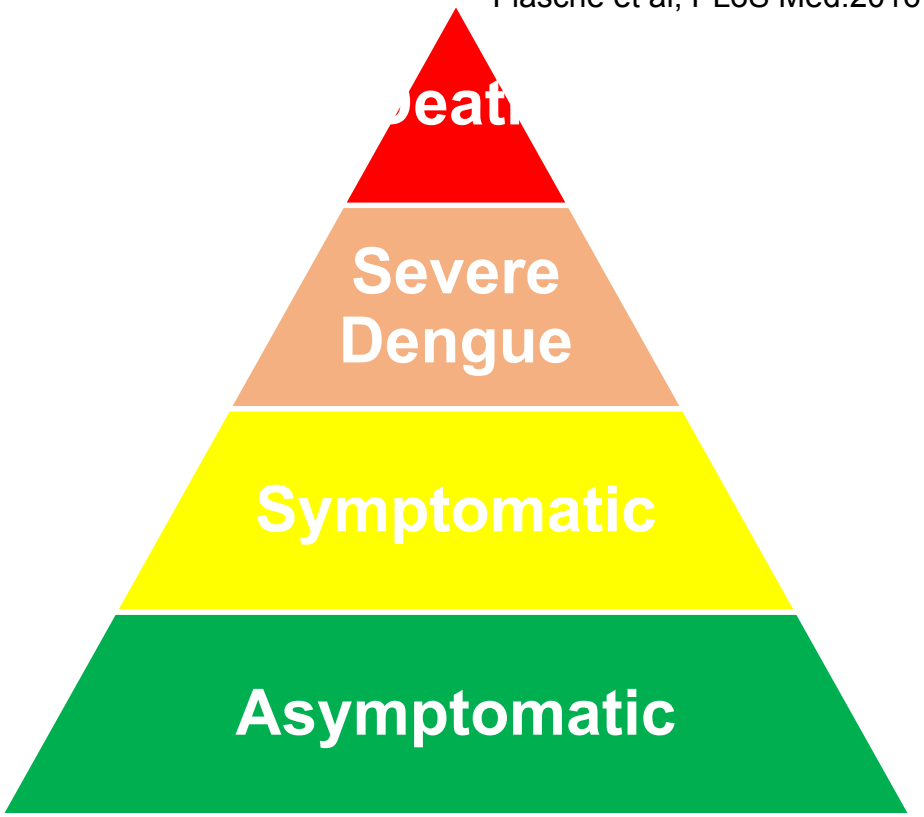
Dengue



Flasche et al, PLoS Med.2016

- Four antigenically distinct serotypes (DENV1-4)

- Clinical spectrum:
  - 80% asymptomatic
  - Self-limiting febrile illness
  - Secondary infections have a **RR 2-3** to develop severe dengue compared to primary infection
  - **Not every secondary infection leads to severe dengue: 2-4%**
  - CFR < 0.4% (during epidemic situations 10x higher)



Dengue

WHO listed dengue as one of the top 10 global health threats

400% increase over the past two decades

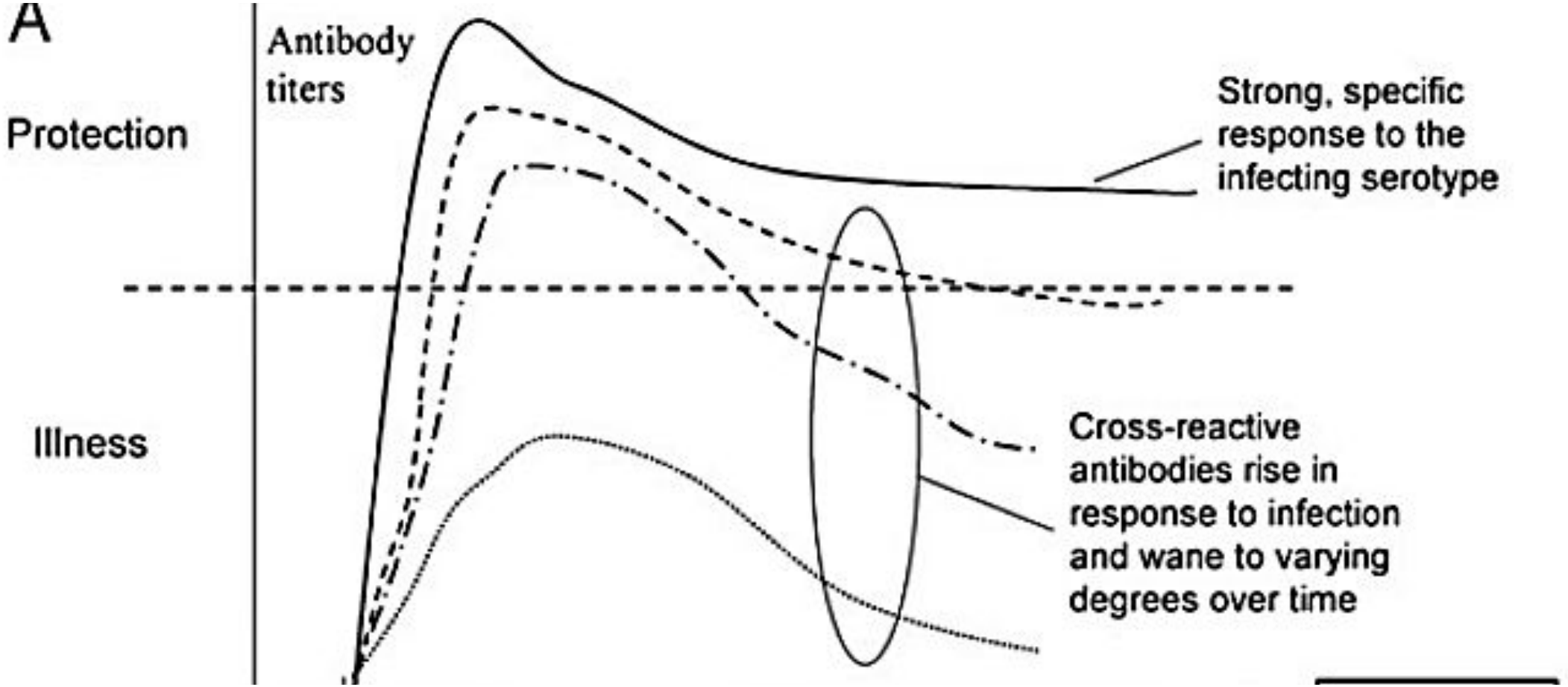
Increasing frequency and magnitude of outbreaks due to urbanization and population densities

Increasing geographic range due to global warming and mobility

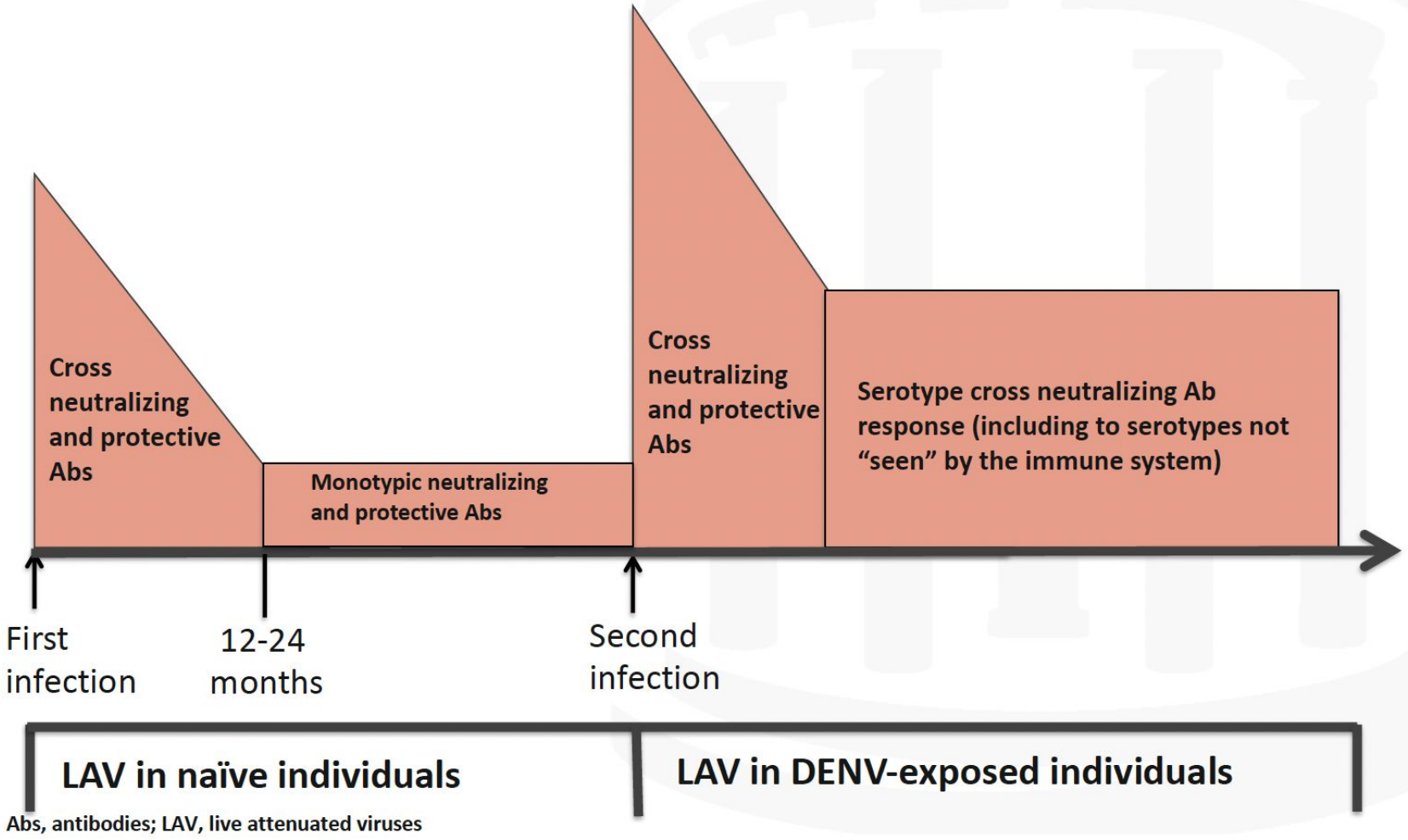
Why did it take so long to get a dengue vaccine?

Why is it so difficult to develop a dengue vaccine?

Immunological interaction between the four serotypes between the 4 serotypes

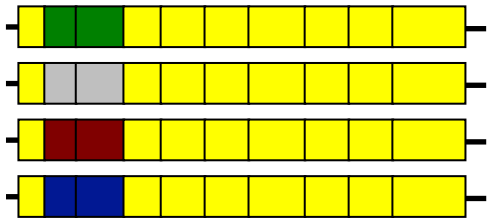
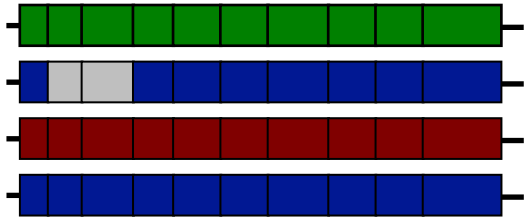


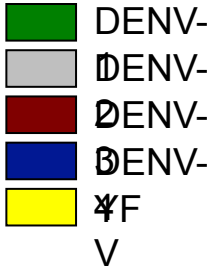
Neutralizing/protective antibody responses following DENV infection and vaccination



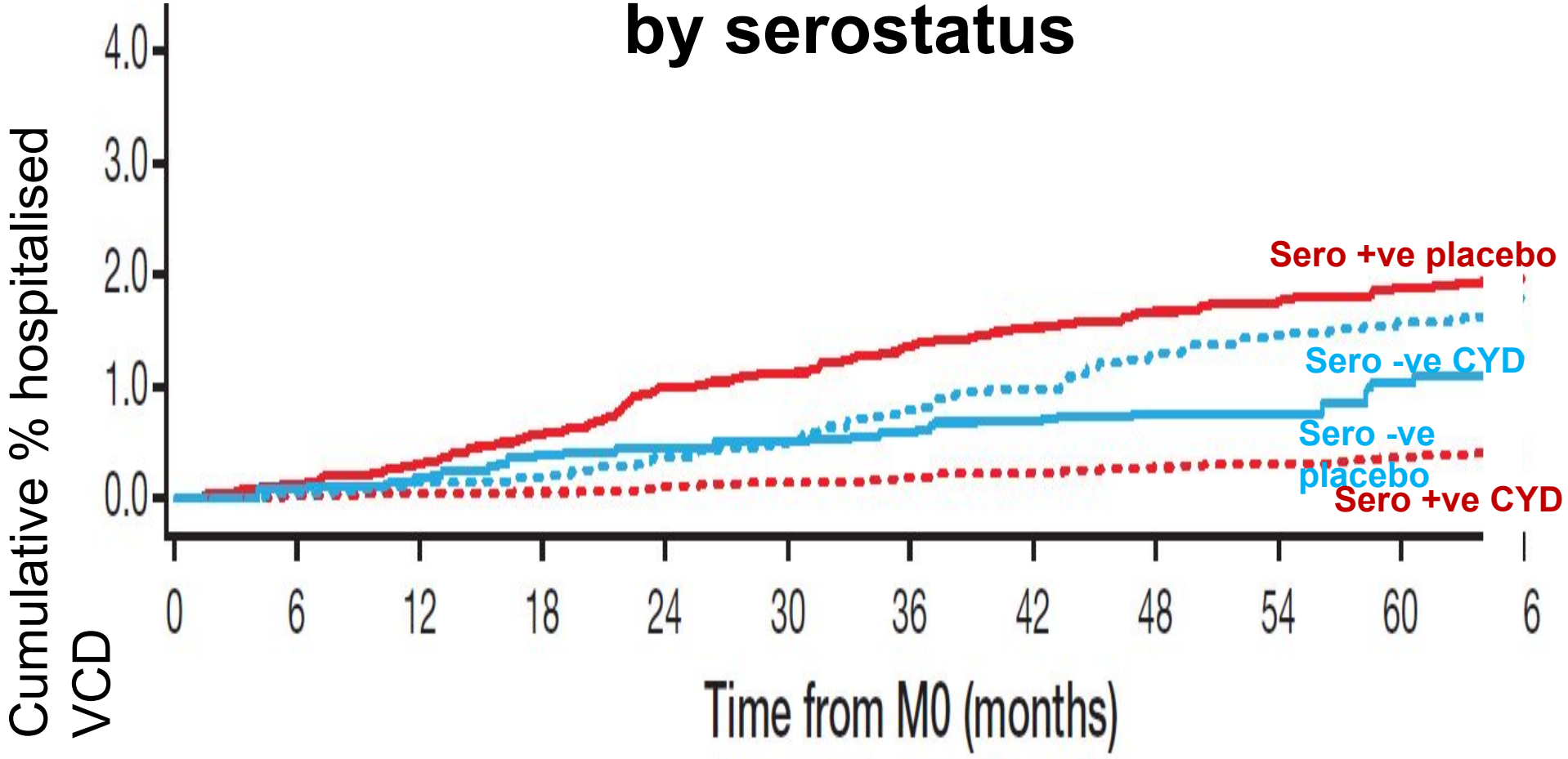
Abs, antibodies; LAV, live attenuated viruses

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 (NIH/Butantan/Merck)
Status	Licensed in 2015	Licensed in 2022	Phase 3
# Doses	3 doses (0, 6, 12)	2 doses (0, 3 months)	Single dose
Construct			
Dengue proteins	8	16	32



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



Serostatus-driven vaccine performance
Dengvaxia CYD-TDV

IMMUNISATION COALITION

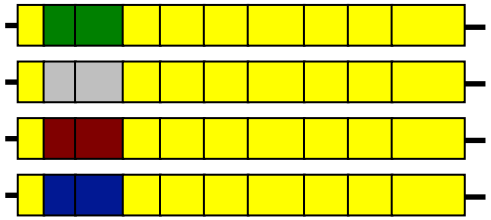
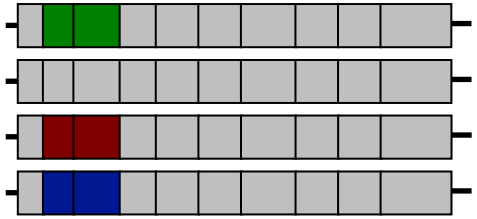
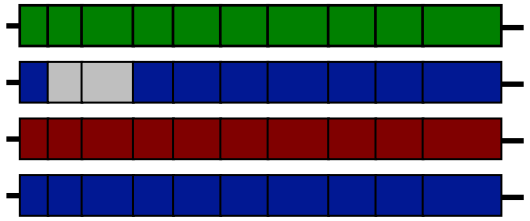
- Dengvaxia is efficacious and safe in seropositive persons:
  - VE 72-80% against dengue of any severity; >90% against severe dengue
- Dengvaxia increases the risk of severe dengue in seronegative persons:
  - RR 2-3
- Population-level benefit is high, but sub-population at risk is identifiable.
- A “pre-vaccination screening strategy” is the recommended strategy, in which only dengue-seropositive persons are vaccinated.
- Low vaccine uptake due to the costs and complexities of the

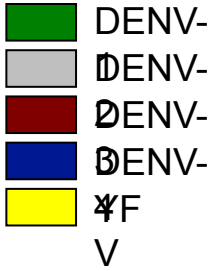
Viremia following a single dose of CYD-Dengvaxia

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

Takeda TAK-003: now licensed by EMA, MHRA, Brazil and Indonesia. First introducing country is Indonesia. After EMA approval, many European countries are using TAK-003 in travelers

	Dengvaxia (Sanofi Pasteur)	TAK-003 (Takeda)	TV003 (NIH/Butantan/Merck)
Status	Licensed in 2015	Licensed by EMA Dec 2022	Phase 3
# Doses	3 doses over 12 months (0, 6, 12)	2 doses (0, 3 months)	Single dose
Age range in Phase 3 trials	2-16	4 - 16	2 - 59
Policy recommendations	Requires documented previous DENV infection	?	?
Construct			
Dengue proteins	8	16	32

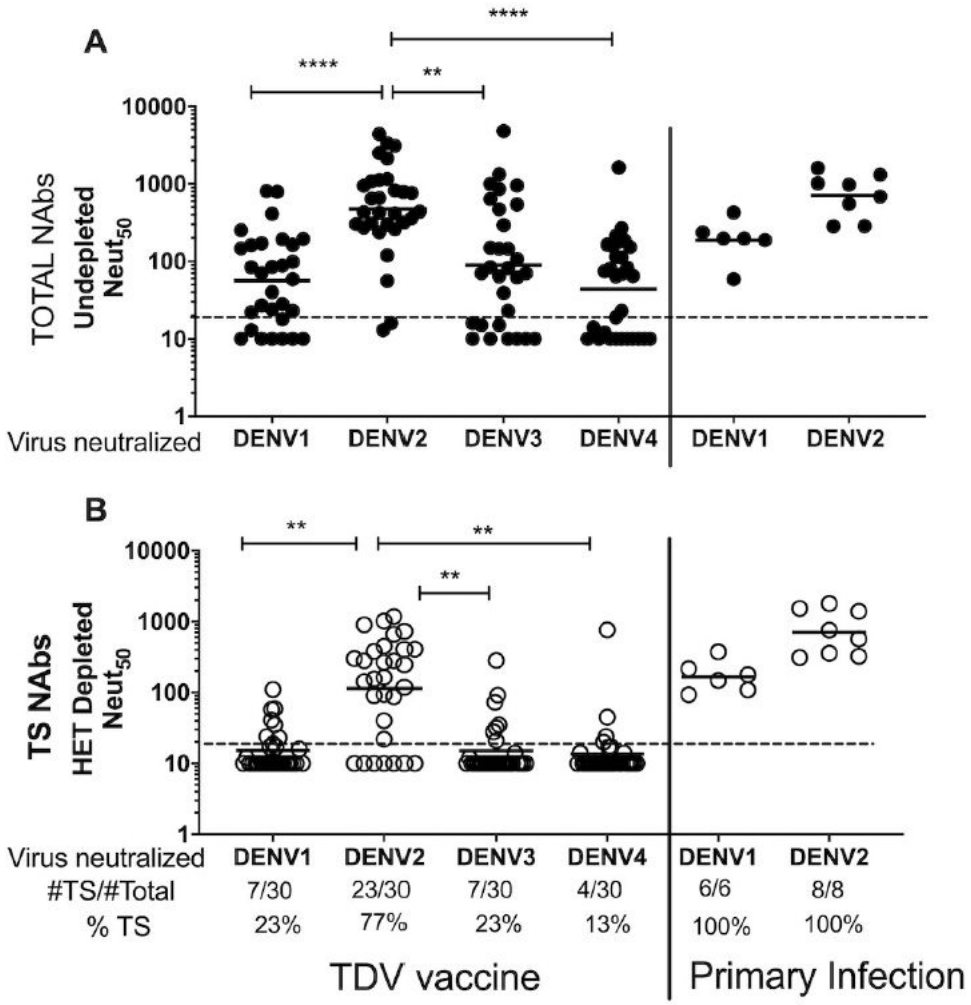


Viremia following a single dose of TAK-003 versus CYD Dengvaxia

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)**
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

Neutralizing antibodies, overall and type-specific



RESEARCH ARTICLE

Defining levels of dengue virus serotype-specific neutralizing antibodies induced by a live attenuated tetravalent dengue vaccine (TAK-003)

Laura J. White[1]*, Ellen F. Young[2], Mark J. Stoops[1], Sandra R. Henein[1], Elizabeth C. Adams[1], Ralph S. Baric[1,2], Aravinda M. de Silva[1]

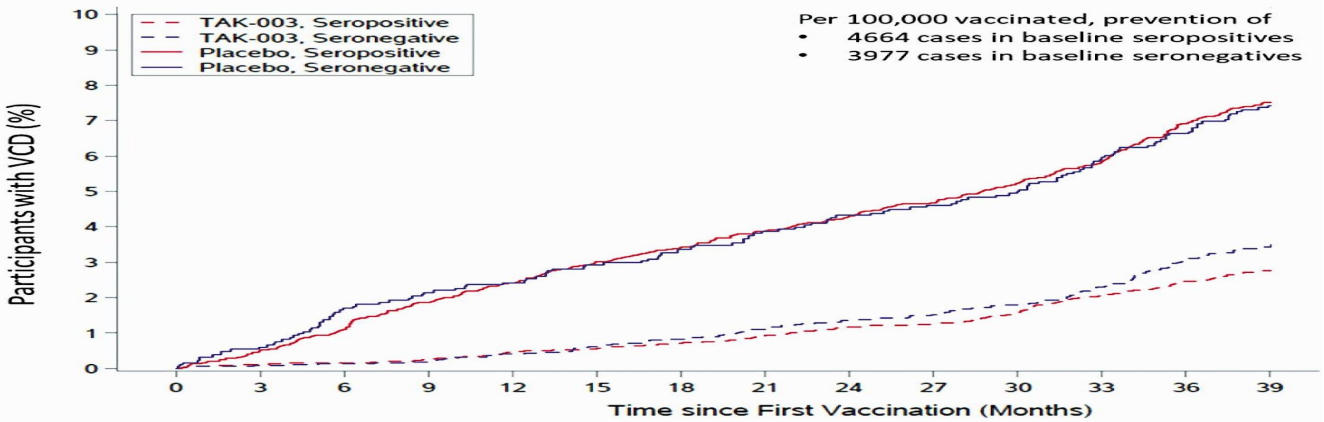
1 Department of Microbiology and Immunology, The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, United States of America, **2** Department of Epidemiology, The University of North Carolina at Chapel Hill School of Public Health, Chapel Hill, NC, United States of America

PLOS Neglected Tropical Diseases | https://doi.org/10.1371/journal.pntd.0009258 March 12, 2021

Cumulative incidence of (A) virologically confirmed dengue (VCD) and (B) hospitalized VCD

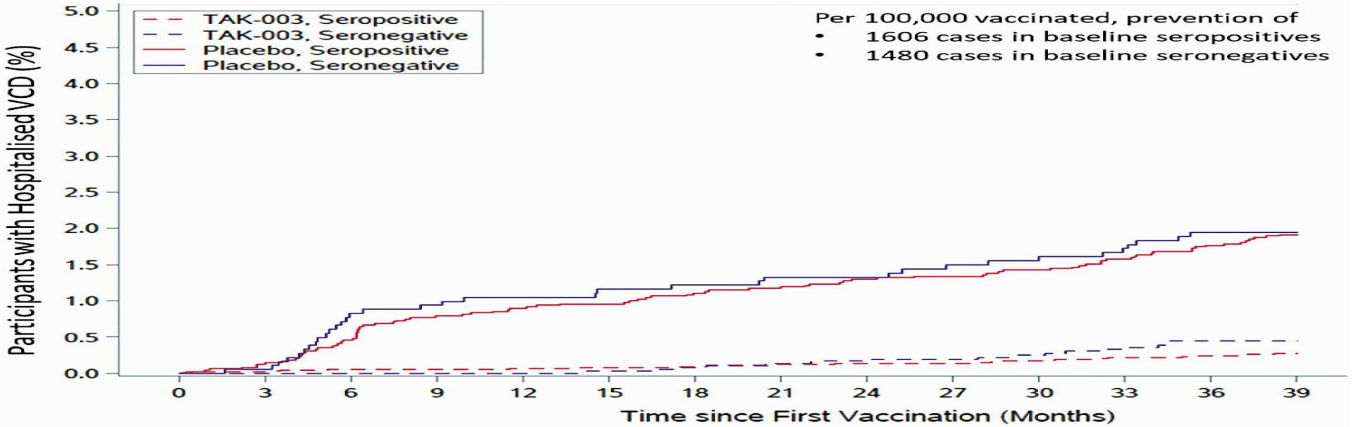
IMMUNISATION COALITION

A



TAK-003, Seropositive	9663	9601	9506	9463	9422	9397	9355	9319	9282	9254	9204	9131	9059	8195
TAK-003, Seronegative	3714	3690	3663	3644	3625	3612	3593	3581	3564	3550	3527	3490	3456	3246
Placebo, Seropositive	4854	4808	4729	4675	4641	4605	4577	4549	4519	4494	4453	4410	4344	3889
Placebo, Seronegative	1832	1817	1775	1763	1755	1742	1727	1715	1705	1697	1687	1668	1652	1555

B



TAK-003, Seropositive	9663	9609	9517	9482	9459	9442	9413	9395	9379	9358	9335	9302	9265	8388
TAK-003, Seronegative	3714	3693	3668	3651	3640	3634	3620	3616	3607	3598	3582	3560	3549	3342
Placebo, Seropositive	4854	4826	4760	4727	4714	4703	4687	4678	4661	4653	4634	4611	4588	4129
Placebo, Seronegative	1832	1827	1791	1785	1780	1774	1766	1761	1759	1753	1748	1743	1736	1643

TAK-003 Phase 3 trial

IMMUNISATION COALITION

- Design: double-blind RCT, randomized to TAK-003 or placebo in a 2:1 ratio
- Age range: 4-16 years
- Safety set included 20,071 participants, 28% were seronegative at baseline
- Sites: conducted in 5 countries in Latin America and 3 countries in Asia
- Duration: approximately 5 years

- **Primary endpoint:** virologically confirmed dengue (VCD)

Stratified by serostatus
Stratified by serotypes
Stratified by year
Stratified by age

- **Secondary endpoints:**
- Hospitalization for dengue
- Dengue haemorrhagic fever (DHF)
- Trial-specific severe dengue definition

For the purpose of today: 54 months cumulative data across all age groups, stratified by serostatus and serotypes and clinical endpoints

Vaccine Efficacy* — Outcome: **Virologically Confirmed Dengue**

Overall VE

61.2% (56.0, 65.8%)

VE in Seropositives

64.2% (58.4, 69.2%)

VE in Seronegatives

53.5% (41.6–62.9%)

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 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%)

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

Unpublished data presented by Takeda to ACIP WC

Vaccine Efficacy* Outcome: **Hospitalization**

Overall VE

84.1% (77.8, 88.6%)

VE in Seropositives

85.9% (78.7, 90.7%)

VE in Seronegatives

79.3% (63.5, 88.2%)

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 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-4 Placebo events: 3 TAK-003 events: 0

[§]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

months after first dose, significant results **bolded**. Number for seropositive placebo

Key take home messages

IMMUNISATION COALITION

Seropositive persons:

Protects against VCD, hospitalizations and severe dengue for all 4 serotypes

Seronegative persons:

Serotypes 1 and 2: Protects against VCD and hospitalizations for DENV-1 and 2

Serotype 3:
Does NOT protect against VCD and hospitalizations for DENV-3

Serotype 4:
Does NOT protect against VCD for DENV-4
Only one DENV-4 hospitalization; limits VE assessment

WHO SAGE Working Group considerations

Communication of an uncertain risk is difficult.

The public is sensitized to the potential risk due to the Dengvaxia story.

Transparency is needed.

SAGE WG considered a full range of policy options and narrowed down the options to recommending the use in high dengue transmission settings only without pre-vaccination screening

Rationale for use in high dengue transmission settings only

IMMUNISATION COALITION

- Highest public health impact
- Mitigate any potential individual risk
- Most cost-effective use of finite vaccine supplies
- Targeted roll-out allows time for communication strategies and advocacy
- Will enable more precise risk estimates in seronegative persons, thereby enabling a broader recommendation in the near future

Seroprevalence

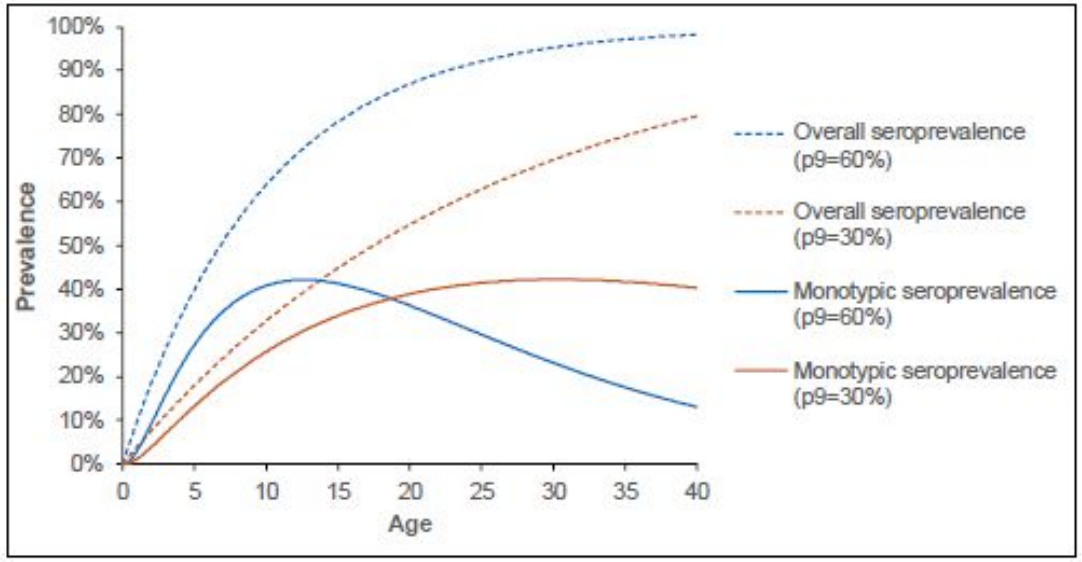
IMMUNISATION COALITION

- Proportion of seropositive persons in the population
- Seroprevalence is correlated with force of infection
- The higher the force of infection, the younger the mean age of peak incidence
- Seroprevalence by a certain age is therefore not just the proportion of seropositive persons; it reflects the transmission intensity and therefore the interval between infections
- Seroprevalence of 60% and above by age 9 is a proxy for high dengue transmission intensity

Target age for programmatic use of TAK-003

WHO recommends that the vaccine is introduced for children aged 6 to 16 years in settings with high dengue transmission intensity.

Within this age range, the vaccine should optimally be introduced about 1-2 years prior to the age-specific peak incidence of dengue related hospital admissions, but considerations such as programmatic alignment with the administration of other school-based vaccination strategies (i.e. HPV vaccines) can also be taken into account.



Special populations

Pregnant and lactating persons

Although development and reproductive toxicology studies in animals and follow-up of pregnancy outcomes in pregnant women who were inadvertently vaccinated did not indicate any safety concerns, data are insufficient to make recommendations for vaccination in pregnancy.

Until such data become available, TAK-003 is not recommended in pregnant women and women of childbearing potential should avoid pregnancy for at least 1 month following vaccination.

Immunocompromised persons

TAK-003 is a live attenuated vaccine. TAK-003 is contraindicated in persons with immunocompromising conditions

Until the efficacy-risk profile in seronegative persons for DENV3 and DENV4 has been more precisely assessed, WHO does not recommend the programmatic use of this vaccine in low to moderate dengue transmission settings

What about travellers as most travellers are adults and seronegative?

Travellers

IMMUNISATION COALITION

- Persons living in non-endemic countries who have previously been infected with any of the four dengue virus serotypes as a result of travel to dengue-endemic countries may benefit from TAK-003 vaccination to prevent a secondary (and hence potentially more severe) dengue infection when travelling again to dengue-endemic countries.

- Frequent travellers, long-term travellers, migrants and long-term expatriates have a higher likelihood of having had a dengue infection in the past (and may therefore be seropositive) compared to first-time or short-term travellers.

- There is lower benefit of TAK-003 in travellers who have never experienced a dengue infection (and are therefore seronegative) compared to travellers who have had a dengue infection in the past.

- Travellers need to be informed that the vaccine does not confer protection against DENV3 and DENV4 in seronegative vaccinees and that there is a theoretical risk of severe dengue if seronegative persons are exposed to DENV3 and DENV4, a risk which currently cannot be ruled out with the available data.

IMMUNISATION
COALITION

Thank you

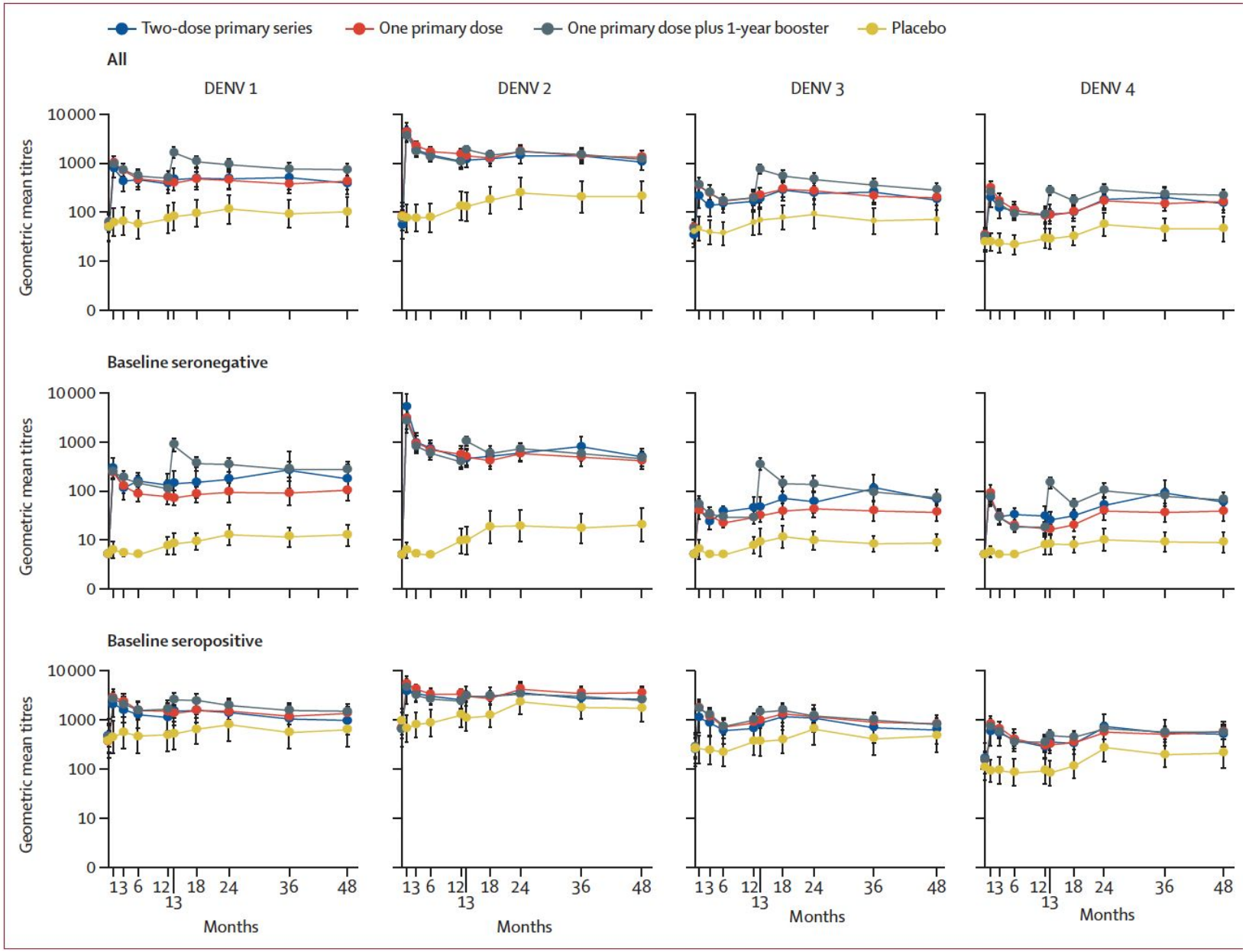


Figure 2: Geometric mean titres against each serotype at study assessment timepoints for all participants by baseline serostatus in the per-protocol subset

Safety and immunogenicity of a tetravalent dengue vaccine in children aged 2–17 years: a randomised, placebo-controlled, phase 2 trial

Vianney Tricou, Xavier Sáez-Llorens, Delia Yu, Luis Rivera, José Jimeno, Ana Cecilia Villarreal, Epiphany Dato, Onix Saldaña de Suman, Nathali Montenegro, Rodrigo DeAntonio, Sonia Mazara, Maria Vargas, Debbie Mendoza, Martina Rauscher, Manja Brose, Inge Lefevre, Suely Tuboi, Astrid Borkowski, Derek Wallace

Lancet 2020

https://doi.org/10.1016/

Immunogenicity results show that two doses are required in seronegative persons to achieve higher GMT

Presented as oral communication at CISTM on 22 May 2023:

VE 14 days to 3 months after first dose is similar to VE after 3 months

	Dengvaxia (Sanofi Pasteur)	TAK-003(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 seronegative vaccinees	No efficacy for seronegative persons exposed to serotype 3 and 4. Negative point estimates with wide confidence intervals	No data for serotypes 3 and 4 (data cut-off 13 July 2021)
WHO recommendations	Requires pre-vaccination screening	?	?

Co-administration with other vaccines?

Yellow fever vaccine: concomitant and sequential administration: non-inferiority criteria met. Tricou et al. PloS NTD 2023

Hepatitis A vaccine: non-inferiority criteria met: Tricou et al. Vaccine 2023