Dengue Vaccines

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September 5, 2018

Deliberations of the Strategic Advisory Group of Experts on Immunization on the use of CYD-TDV dengue vaccine

Annelies Wilder-Smith, Joachim Hombach, Neil Ferguson, Michael Selgelid, Kate O`Brien, Kirsten Vannice, Alan Barrett, Elizabeth Ferdinand, Stefan Flasche, Maria Guzman, Hillegonde Maria Novaes, Lee-Ching Ng, Peter G Smith, Piyanit Tharmaphornpilas, In-Kyu Yoon, Alejandro Cravioto, Jeremy Farrar, Terry M Nolan

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

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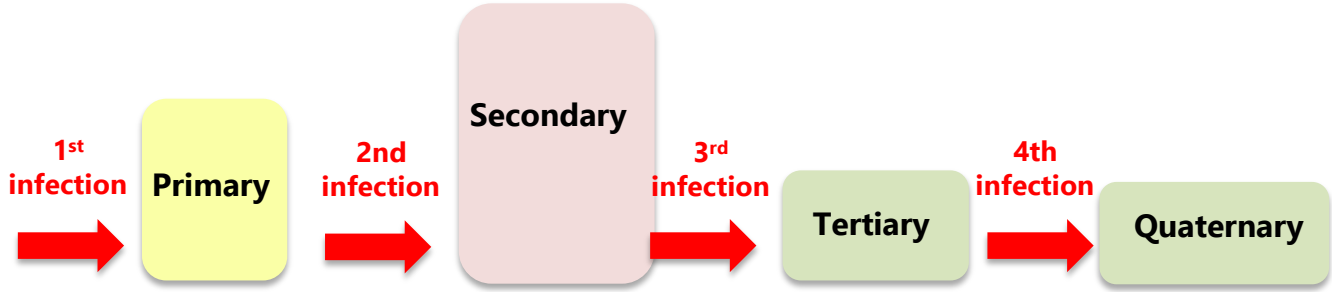
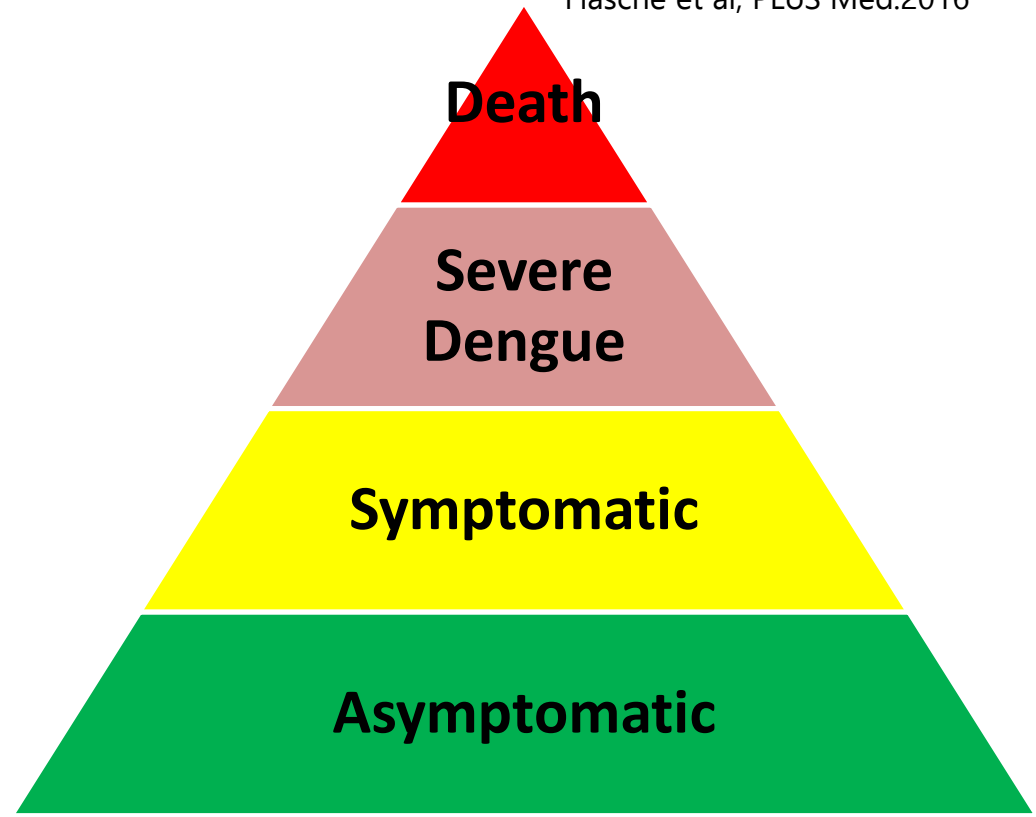
Note de synthèse de l'OMS sur le vaccin contre la dengue – septembre 2018

Dengue



- Four antigenically distinct serotypes (DENV1-4)
- 50-100 million cases every year
- Clinical spectrum:
  - 80% asymptomatic
  - Self-limiting febrile illness
  - Severe dengue (~2-4% of symptomatic)
  - Secondary infections are associated with higher risk of more severe dengue
  - CFR 0.1—1%

Flasche et al, PLoS Med.2016

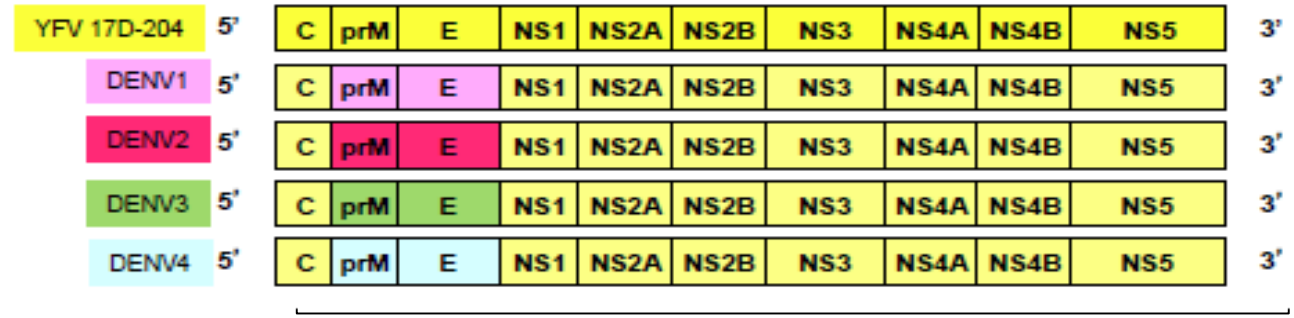


Dengue Vaccine

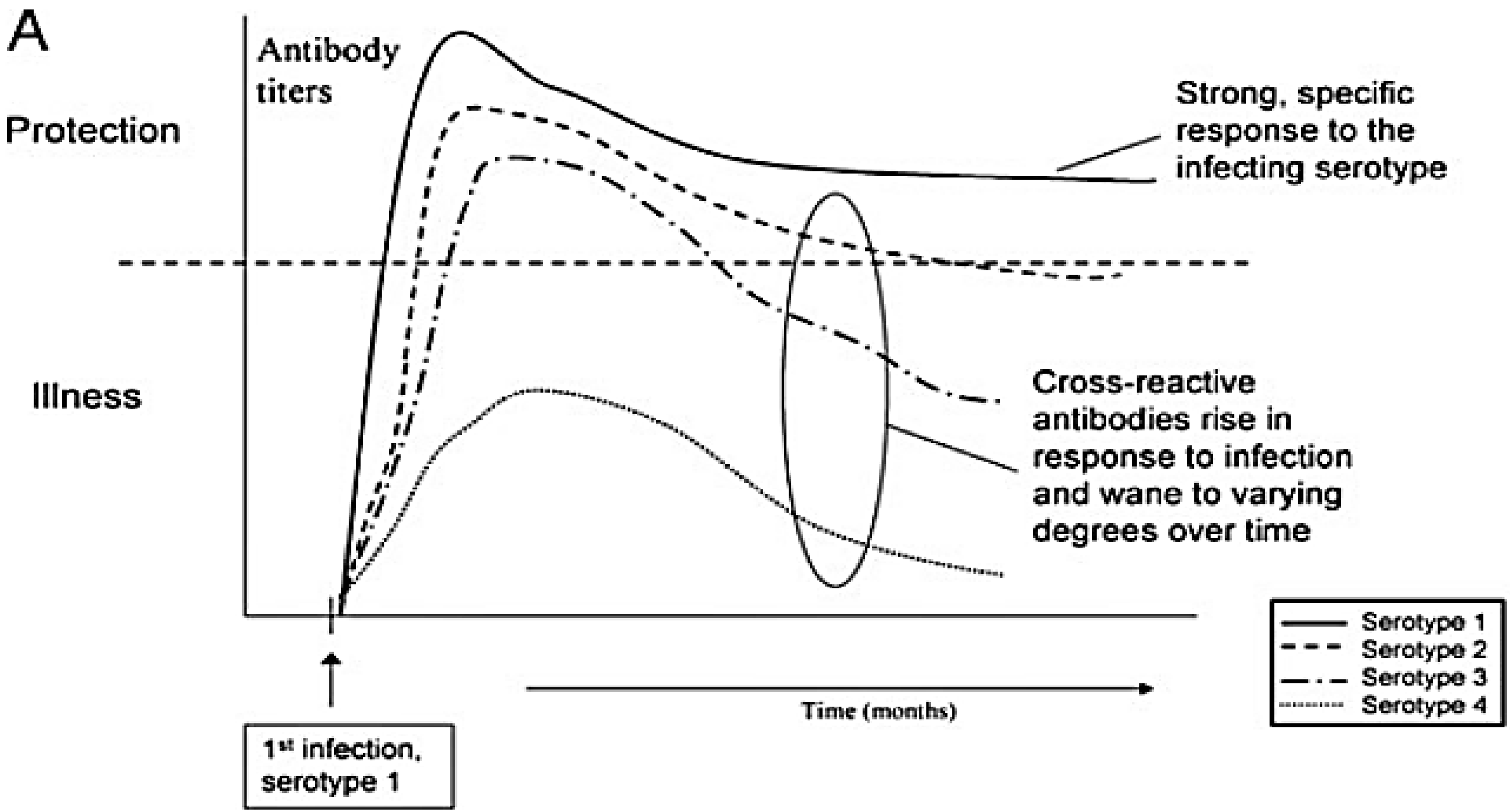
(http://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/)

Phase I	Phase II	Phase IIb	Phase III	Registration
DPIV GlaxoSmithKline, Biomanguinhos, WRAIR			TV003/TV005 US National Institutes of Health[1] Butantan	CYD-TDV Dengvaxia™ Sanofi Pasteur
DEN-80E Merck			DENVax Takeda	
TVDV Naval Medical Research Center				
TLAV-TPIV WRAIR				

CYD-TDV
SANOFI PASTEUR



Homotypic and heterotypic antibodies



Anderson et al, A Shorter Time Interval Between First and Second Dengue Infections Is Associated With Protection From Clinical Illness in a School-based Cohort in Thailand. J Inf Dis. 2014

Phase II randomized controlled trial in Singapore

Yee Sin Leo,[1] Annelies Wilder-Smith,[2,3] Sophia Archuleta,[2,3] Lynette P. Shek,[4] Chia Yin Chong,[5] Hoe Nam Leong,[6] Chian Yong Low,[6] May-Lin Helen Oh,[7] Alain Bouckenooghe,[8] T. Anh Wartel[8,*] and Denis Crevat[10]

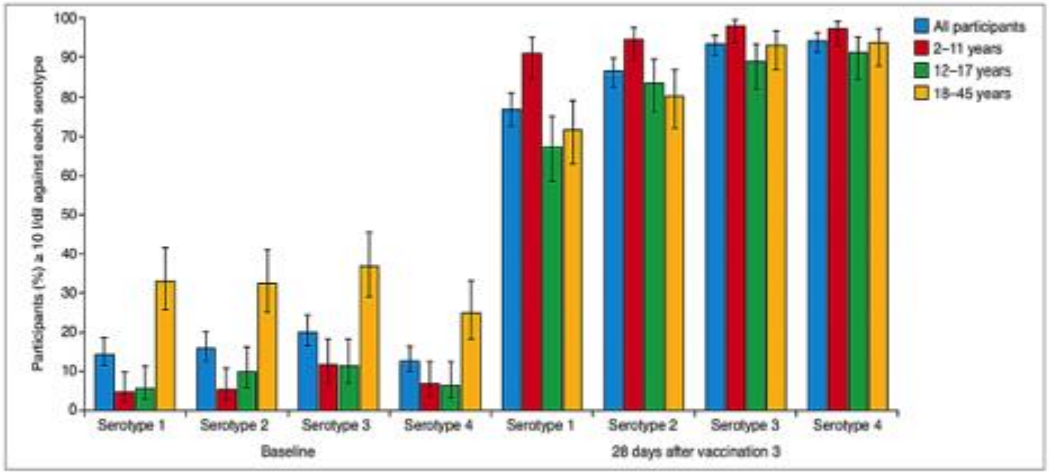


Figure 3. Seropositivity rates (percentage of participants $PRNT_{50}$ titer ≥ 10 1/dil) against each of the four dengue virus serotypes (1, 2, 3 and 4) at baseline and 28 d after the third vaccination in all participants and in each of the three age groups.

- **Vaccine efficacy varied by :**
  - **Serotype (serotype 4 and 3)**
  - **Serostatus (seropositive)**
  - **Severity of disease (more severe)**
  - **Age (older age)**

NEJM 2015

Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease

S.R. Hadinegoro, J.L. Arredondo-García, M.R. Capeding, C. Deseda, T. Chotpitayasunondh, R. Dietze,

WHO recommendations for settings with seroprevalence > 70% (April 2016)

- Licensed for age 9 and above
- Public Health benefit– Vaccine preventable disease incidence, seropositivity drives efficacy
- Safety benefit – high proportion of seropositives; seronegatives will have a higher or equal risk of secondary infections through natural exposure than potential vaccine induced secondary-like infections

Press release from Sanofi, 29 Nov 2017

November 29, 2017

Sanofi updates information on dengue vaccine

- New analysis of long-term Dengvaxia® data found differences in vaccine performance based on prior dengue infection
- Company will ask regulators to update product label to reflect new information

PARIS, FRANCE – November 29, 2017 – Sanofi will ask health authorities to update information provided to physicians and patients on its dengue vaccine Dengvaxia® in countries where it is approved. The request is based on a new analysis of long-term clinical trial data, which found differences in vaccine performance based on prior dengue infection.

Based on up to six years of clinical data, the new analysis evaluated long-term safety and efficacy of Dengvaxia in people who had been infected with dengue prior to vaccination and those who had not. The analysis confirmed that Dengvaxia provides persistent protective benefit against dengue fever in those who had prior infection. For those not previously infected by dengue virus, however, the analysis found that in the longer term, more cases of severe disease could occur following vaccination upon a subsequent dengue infection.

"These findings highlight the complex nature of dengue infection. We are working with health authorities to ensure that prescribers, vaccinators and patients are fully informed of the new findings, with the goal of enhancing the impact of Dengvaxia in dengue-endemic countries," said Dr. Su-Peing Ng, Global Medical Head, Sanofi Pasteur.

About half of the world's population lives in countries where four serotypes of dengue virus are in circulation. Every year an estimated 390 million dengue infections are reported. People can be infected with dengue up to four times in their lifetime and they can get severely ill after any of these infections. Surveillance data from some endemic countries indicate that between 70 and 90 percent of people will have been exposed to dengue at least once by the time they reach adolescence. There are many factors that can lead to severe dengue infection. However, the highest risk of getting more severe disease has been observed in people infected for the second time by a different dengue virus.

Dengvaxia is currently indicated in most of the countries for individuals 9 years of age and older living in a dengue-endemic area. In this indicated population, Dengvaxia has been shown to prevent 93 percent of severe disease and 80 percent of hospitalizations due to dengue over the 25 month phase of the large-scale clinical studies conducted in 10 countries in Latin America and Asia where dengue is widespread.

Proposed Label Update

Based on the new analysis, Sanofi will propose that national regulatory agencies update the prescribing information, known as the label in many countries, requesting that healthcare professionals assess the likelihood of prior dengue infection in an individual before vaccinating. Vaccination should only be recommended when the potential benefits outweigh the potential risks (in countries with high burden of dengue disease). For individuals who have not been previously infected by dengue virus, vaccination should not be recommended.

The Sanofi label proposal will be reviewed by national regulatory agencies in each of the countries where the vaccine is registered or under registration. Following their review, each agency might amend the company proposed label.

…analysis found that in the longer term, more cases of severe disease occur following vaccination upon a subsequent dengue infection…..

- *For individuals who have not been previously infected by dengue virus, vaccination should not be recommended*.


KAGAWARAN NG KALUSUGAN
DEPARTMENT OF HEALTH
ILIGTAS sa PANGANIB ANG 750,000 BATANG BINAKUNAHAN NG DENGVAXIA!
GABRIELA METRO MANILA
PAANO NA ANG AMING MGA ANAK?
-GABRIELA CALOOCAN
SERBISYO SA KALUSUGAN! HUWAG GAWING NEGOSYO!
-ANAKBAYAN CALOOCAN

News analysis

Politics comes into play in dengue vaccine scare

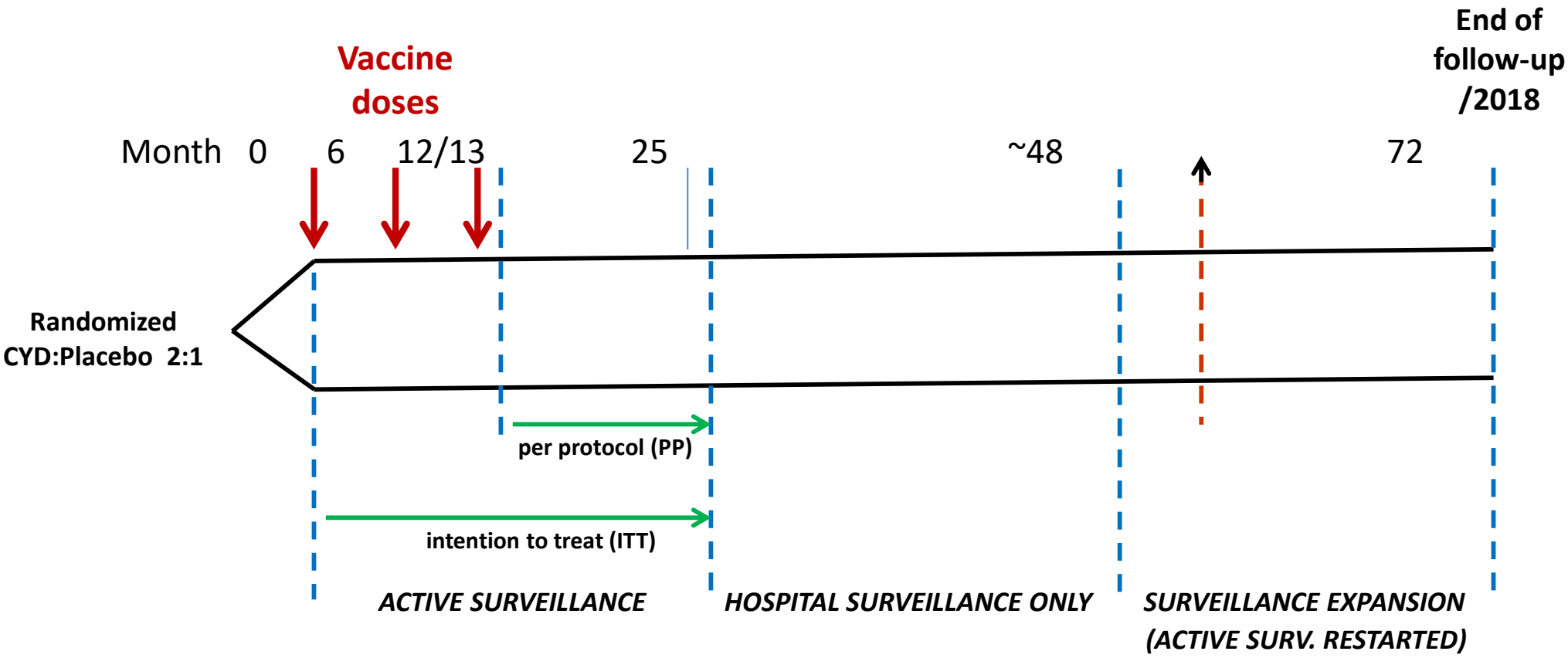
Raul Dancel
Philippines Correspondent

Philippines defied experts' advice in pursuing dengue immunisation...

Parents of vaccine ‘victim’ seek justice

Philippines Suspends Dengue Shots After Drug Firm’s Warning

How did Sanofi Pasteur determine serostatus-dependent performance?



Sridhar et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. N Engl J Med. 2018 Jul 26;379(4):327-340

Vaccine efficacy against symptomatic VCD in the 25 months after dose 1

(2-16 year-olds - MI method)

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

Sridhar et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. N Engl J Med. 2018 Jul 26;379(4):327-340

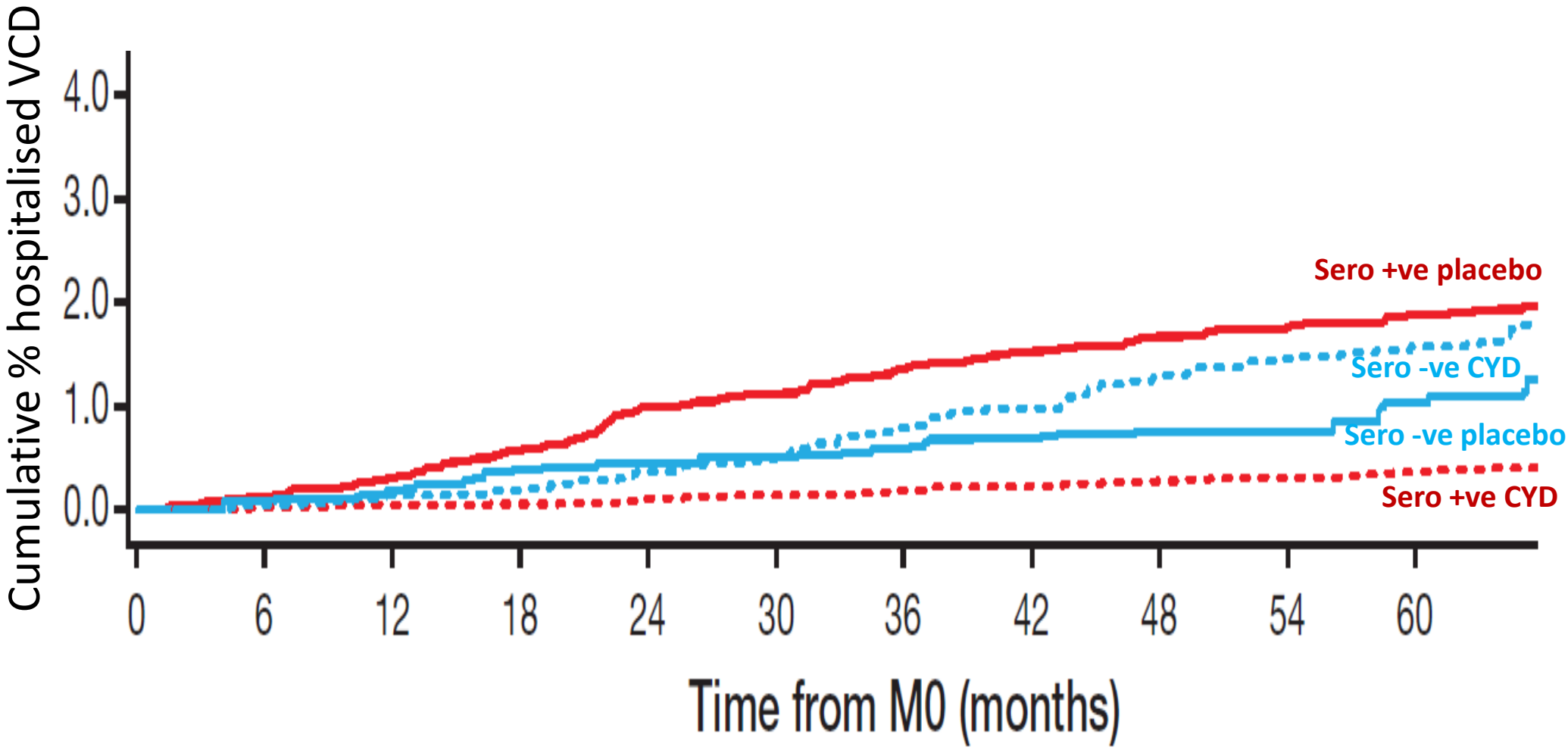
Relative risk of severe VCD comparing vaccinated to controls in the 66 months after dose 1

(2-16 year-olds - MI method)

Sero-status at dose 1	Relative risk (CYD:Control)	95% confidence interval
Sero-positive	**0.28**	0.15, 0.52
Sero-negative	**3.00**	1.10, 8.15

Sridhar et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. N Engl J Med. 2018 Jul 26;379(4):327-340

Time to hospitalized VCD – MI method - age 9-16 years



How do we explain the CYD-TDV observations?

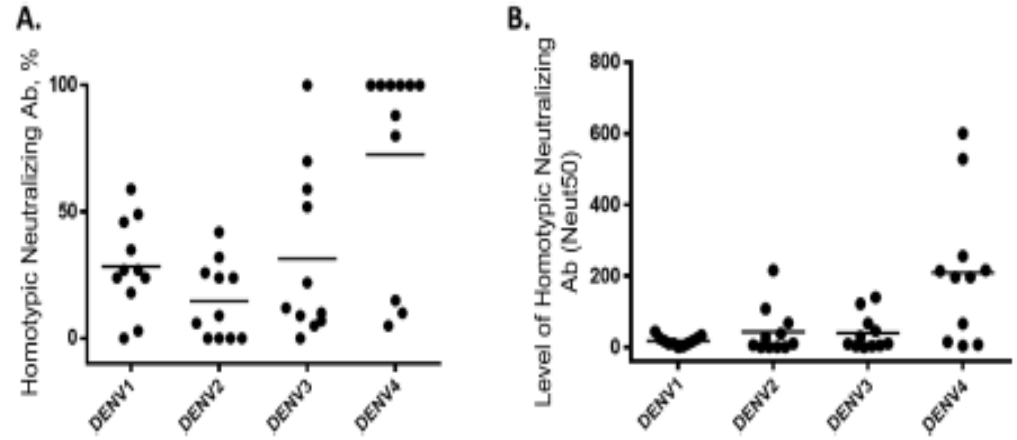
Viremia induced by CYD-TDV

	Percentage of subjects with detectable viremia by culture after a single dose (% by RT-PCR) 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

Homotypic vs heterotypic antibody response in CYD-TDV (Dengvaxia): depletion assays

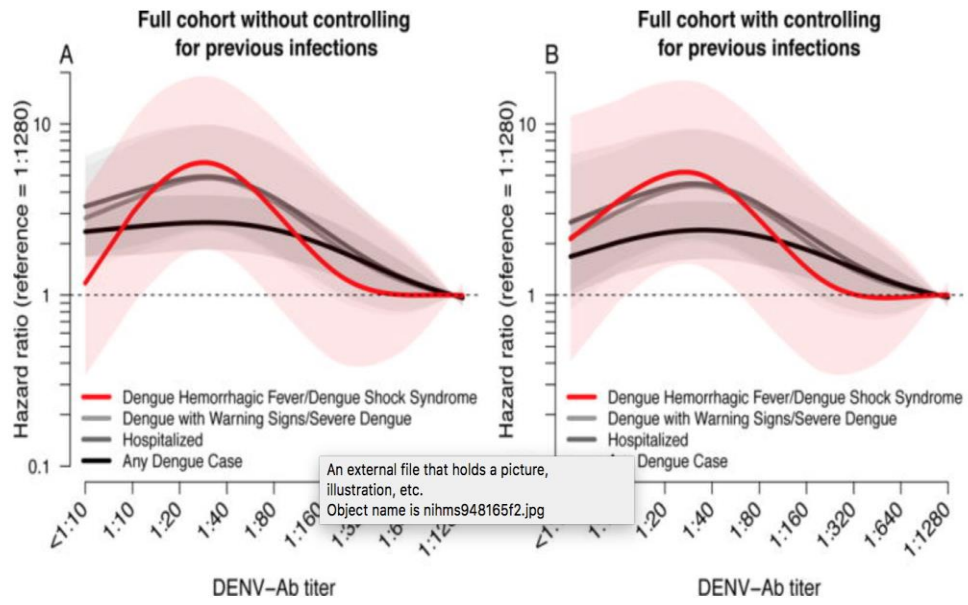
- *Samples were depleted of serotype specific antibodies to determine proportion of cross-reactive response*
- Serotype specific antibodies dominated the DENV-4 response (CYD-4 most often detected post-vaccination)
- Cross-reactive antibodies dominated the DENV-2 response



Henein et al, JID 2017

Level of antibodies determine the risk and protection

Fig. 2



Continuous hazard ratio curves for severe dengue disease or any dengue case by pre-existing DENV-Ab titer for the Pediatric Dengue Cohort. Cox proportional hazard models were fit without (**A**) or with (**B**) control for number of previous infections. Models were also adjusted for sex, epidemic season, and age.

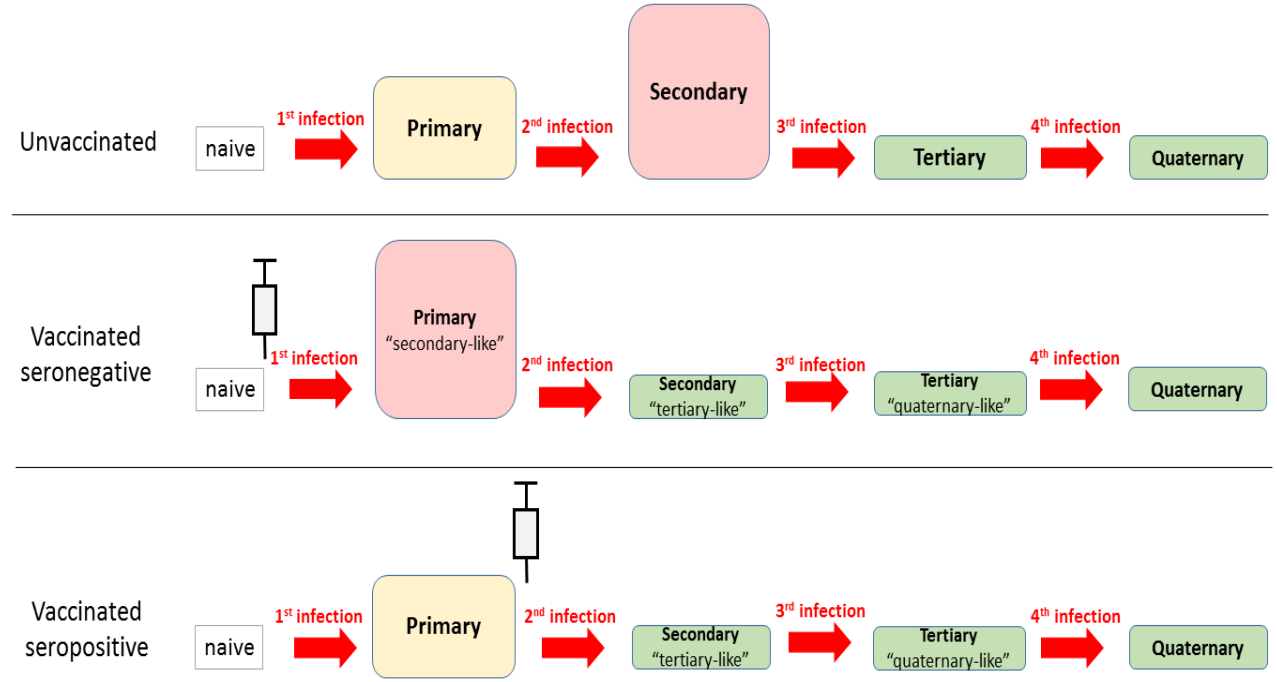
Binding Abs were associated with both clinical risk and protection at different levels

- Nicaragua cohort
- iELISA binding Abs to E fusion loop & prM
- Pre-existing anti-DENV **Abs 1:21 -1:80**, DHF/DSS hazard was **7.64 fold higher**
- Anti-DENV **Abs < 1:21 , dengue naïve,** had hazard of 1.6
- **anti-DENV Abs> 1:1280** had hazard of **1.5**

Katzelnick L et al. Antibody-dependent enhancement of severe dengue diseases in human. Science. 2017 Nov 17

Explanatory hypothesis for excess cases in seronegative trial participants:
"Silent infection" mode of action

- Vaccination primes the immune system similarly to infection:
  1. Temporary high degree of cross-immunity in at least seronegative recipients
  2. Seronegative recipients have secondary-like breakthrough infection once cross-immunity wanes
  3. Seropositive recipients have tertiary-like breakthrough infection once cross-immunity wane



Ferguson et al., Science 2016; Flasche et al., PLoS Med. 2016

Summary: CYD-TDV vaccine

Serostatus dependent performance

- Dengvaxia is efficacious and safe in seropositive persons
- Dengvaxia increases the risk of severe dengue in seronegative persons

How to best use the first licensed dengue vaccine?

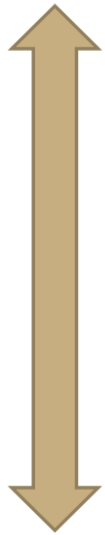
Public health net benefit of Dengvaxia

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



Ethical Dilemma

70% seroprevalence:

Every 1 excess case of hospitalized dengue in vaccinated seronegatives would be offset by 7 hospitalized cases prevented in vaccinated seropositives

85% dengue seroprevalence:

Every 1 excess case of hospitalized dengue in vaccinated seronegatives would be offset by 18 cases prevented in vaccinated seropositive persons

SAGE Working Group Considerations

A number of dimensions:

- Population benefit versus individual risk
- Ethical considerations
- Risk perceptions and communication
- Screening tests versus serosurveys
- Programmatic issues
- Vaccine coverage estimates

Came down to an evaluation of:

Population Seroprevalence Criteria without Screening	***Pre-Vaccination Screening***

1. Benefits and Harm

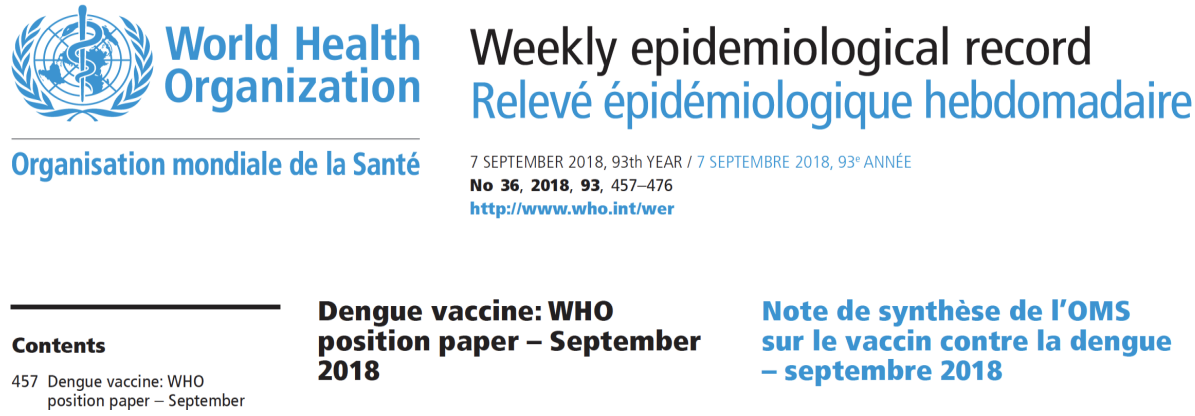
Population Seroprevalence Criteria without Screening	***Pre-Vaccination Screening***
BENEFIT Overall substantial population benefit in areas with high seroprevalence predicted.	**BENEFIT** Maximizing the benefit (high efficacy and good safety) in seropositive while avoiding harm in correctly identified seronegatives.
HARM An identifiable subset of the population will be put at increased risk of severe dengue, at least in the short to medium term.	**HARM** Some seronegative individuals will be put at increased risk of severe dengue if vaccinated due to a false positive screening test result.

2. Risk

Population Seroprevalence Criteria without Screening	***Pre-Vaccination Screening***
• If vaccine is introduced in a setting with 80% seroprevalence, 20% of the vaccinated population will be put at risk. • Loss in vaccine confidence (dengue vaccines and possibly other vaccines). • Inability of vaccinees to know own serostatus may lead to increased vaccine hesitancy.	• Risk of false positive test: seronegative individuals will be misclassified as seropositive • In a setting with 80% seroprevalence and a test with 98% specificity, 0.4% of the population would be unintentionally vaccinated.

Pre-Vaccination Screening Strategy

- 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



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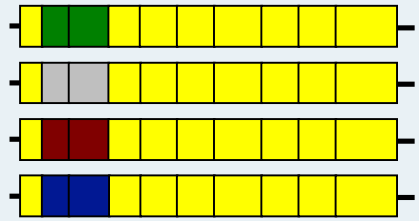
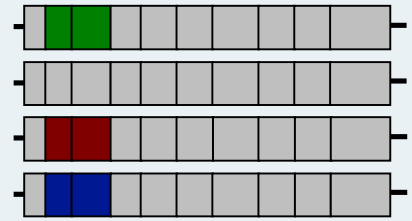
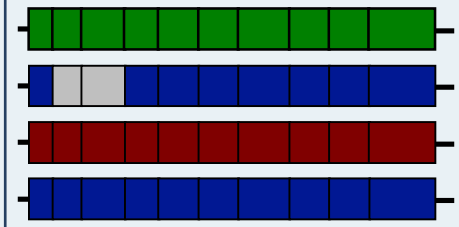
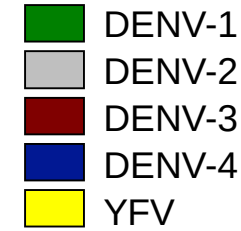
Dengue vaccine: WHO position paper – September 2018

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

Second-generation dengue vaccines

	Dengvaxia (Sanofi Pasteur)	TDV (Takeda)	TV003 (Butantan)
Status	**Licensed**	**Phase 3**	**Phase 3**
# Doses	3 doses over 12 months (0, 6, 12)	2 doses 3 months apart	1 dose
Indicated age	9 - 45	Phase 3: age range 4 - <16[1]	Phase 3: age range 2 - 59[2]
Construct			
# DENV proteins	8	16	32



1. NCT02747927
2. NCT02406729

Lessons learnt

Conclusions	Action taken by second generation dengue vaccines
Baseline blood samples from all trial participants	x
A priori plans for analyses by baseline serostatus	x
Observation time 5 years after last dose	x
Document viremia for all 4 serotypes in a tetravalent formulation	x
Do not rely on PRNT, use depletion assays Consider CHIM	X Done for NIH candidate

What about travellers?

JOURNAL of TRAVEL MEDICINE

International Society of Travel Medicine
Established 1991
Promoting healthy travel worldwide

Journal of Travel Medicine, 2018, 1–3
doi: 10.1093/jtm/tay057
Perspective

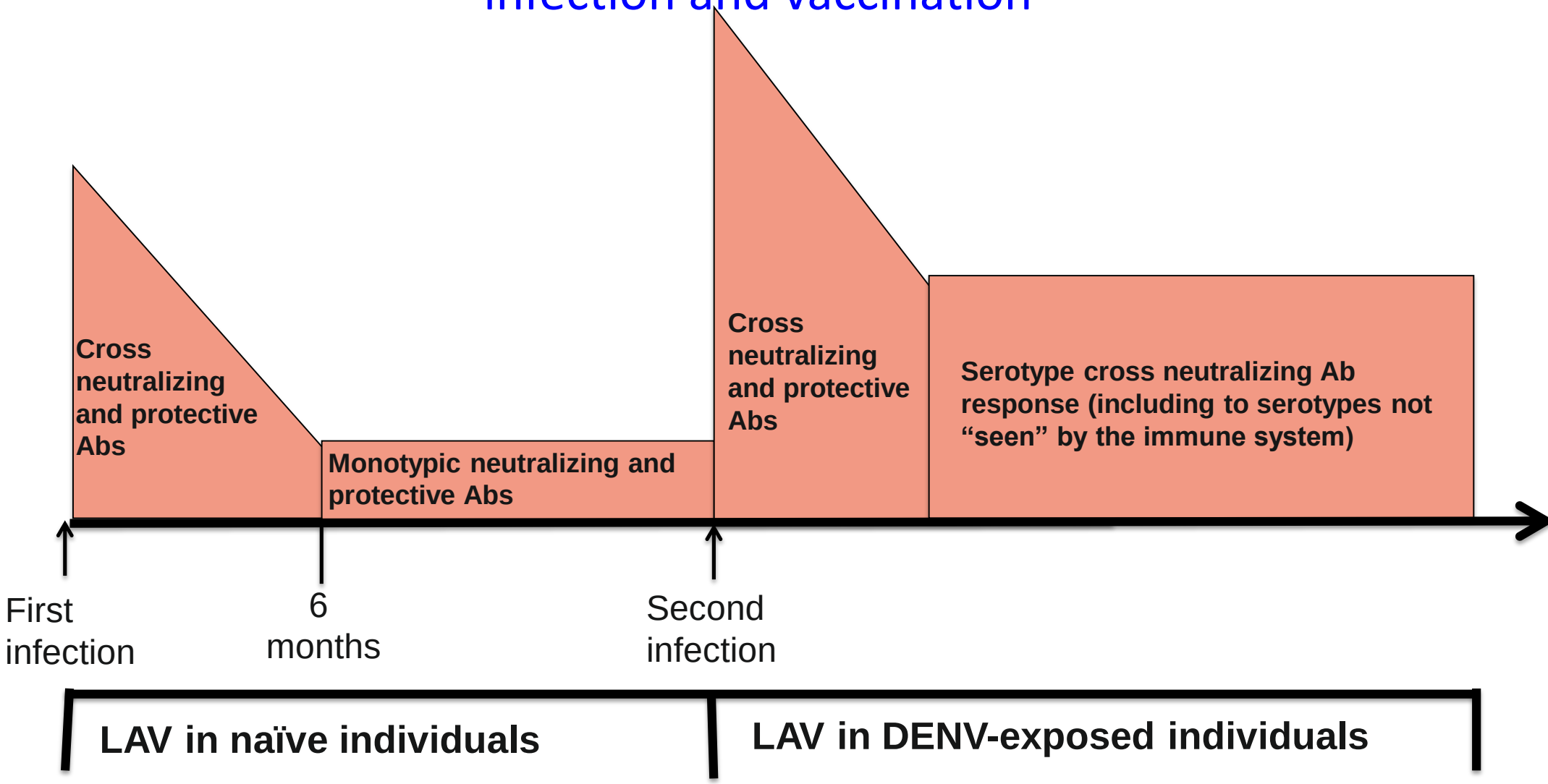
Perspective

Serostatus-dependent performance of the first licensed dengue vaccine: implications for travellers

Annelies Wilder-Smith, MD, PhD*

Low seroprevalence in travellers
Not licensed in most non-dengue endemic countries
3 doses (however, short-term efficacy after one dose is as high as after 3 doses)

Neutralizing/protective antibody responses following DENV infection and vaccination



Abs, antibodies; LAV, live attenuated viruses