The Dengue Vaccine Landscape

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Dengue Vaccine Initiative (DVI)

John Hopkins University School of Public Health

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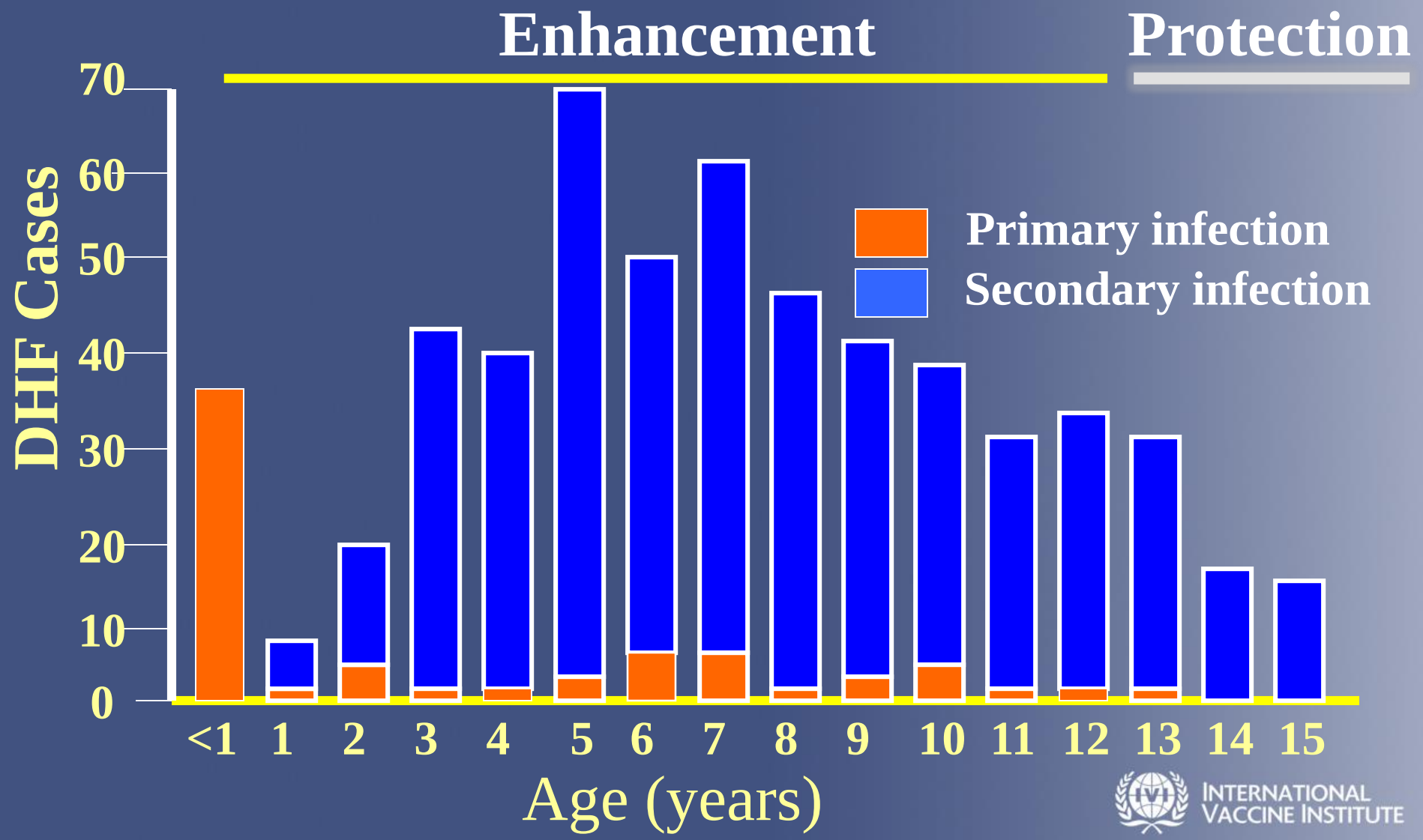
Mission – To accelerate the development and consideration of vaccines to prevent dengue

Background: Dengue

- Most common global vector-borne viral infection
- Caused by dengue virus within flavivirus genus (others include YFV, JEV, WNV, ZIKV, etc.)
- Four known antigenic serotypes (DENV-1, -2, -3, -4)
- Clinically presents as asymptomatic/ subclinical/ mild infection, non-specific febrile illness, DF, DHF/ DSS, “severe” dengue

Immune enhancement

Halstead SB, Nimmannitya S, Cohen SN.
Yale J Biol Med. 1970 Apr;42(5):311-28.



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Substantial challenges exist in developing dengue vaccine

- Mainly due to existence of four serotypes that interact with each other in significant and (currently) unpredictable ways
  - Protection
  - Enhancement
  - Interference

Substantial challenges exist

- Vaccination can theoretical lead to risk of enhancement
  - Prior natural infection could cause enhancement during live virus vaccination to cause disease
  - Suboptimal vaccination could enhance subsequent natural infection to cause disease
  - Theoretical risk has led to vaccination strategy of inducing **simultaneous tetravalent homotypic immunity**
    - May not reflect cumulative natural immunity from sequential infection

Substantial challenges exist

- Interference
  - Different serotypes in tetravalent live vaccine compete with each other
  - Pre-existing natural immunity to DENV could interfere with immune response to live vaccine
  - Pre-existing natural immunity to DENV could be boosted by vaccine (but could be suboptimal)

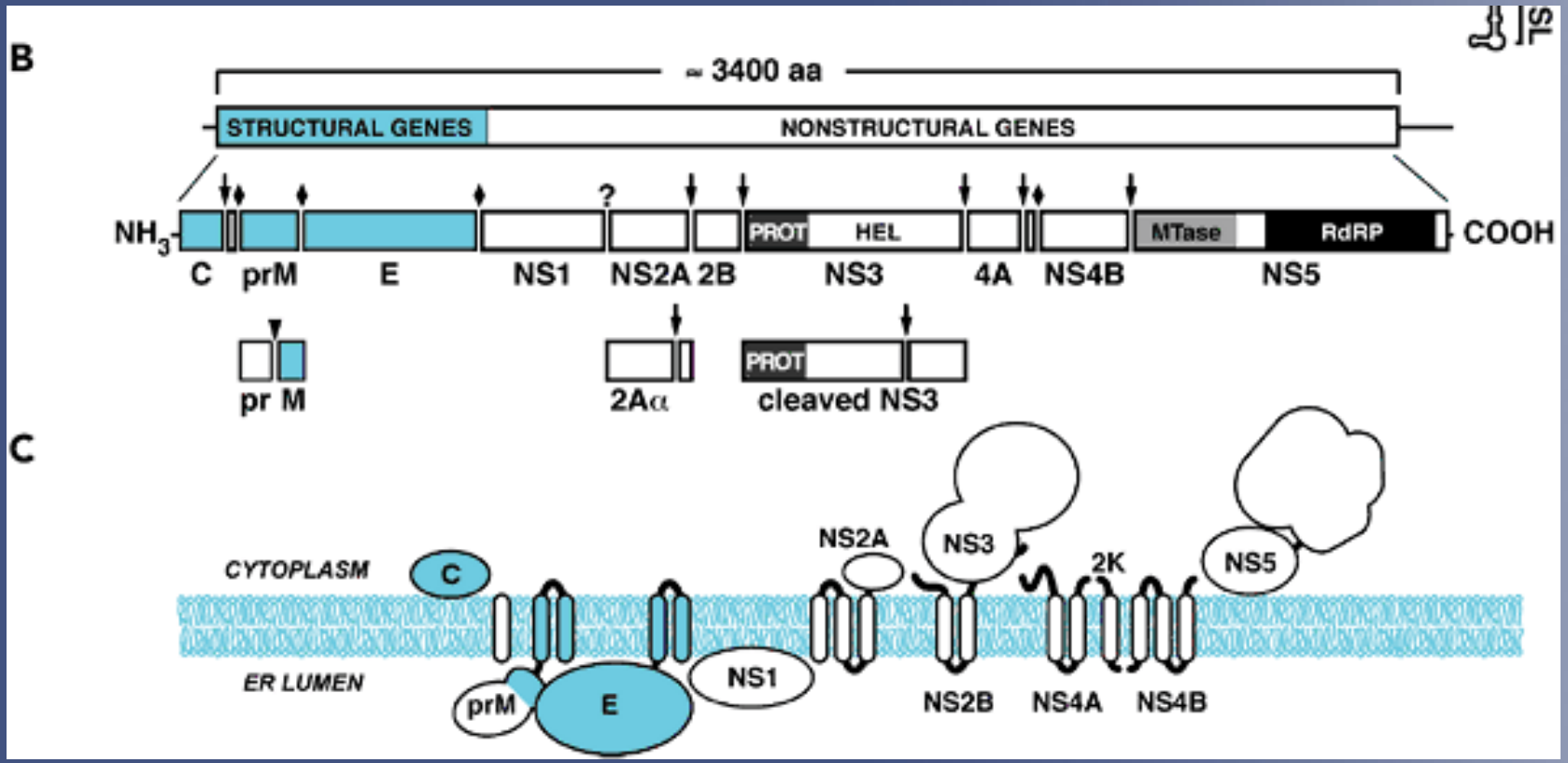
Substantial challenges exist

- Biological assays to measure immune response are imprecise and of unclear clinical relevance
  - No current lab measurement is correlate of protection or risk
- No valid animal model
  - Monkeys have viremia but lower than humans and no disease
  - Immunodeficient mouse models have been developed but have limitations

Good news: Vaccine is feasible

- Natural immunity exists
  - Serotype-specific infection confers long-term protection against disease with that serotype
    - Basis for tetravalent vaccination strategy
  - Short-term (2 months to 2-3 years) protection against other serotypes
  - Sequential natural infection with 2 serotypes may confer protection against disease by other serotypes
    - Not many DHF cases from known 3rd or 4th infections
    - 3rd or 4th infections more likely to be subclinical than symptomatic
    - Different from homotypic immunity by tetravalent vaccination

Dengue virus genome



- Positive sense, single stranded, 11kb RNA virus
- 3 structural (prM/M, E, C) and 7 non-structural proteins

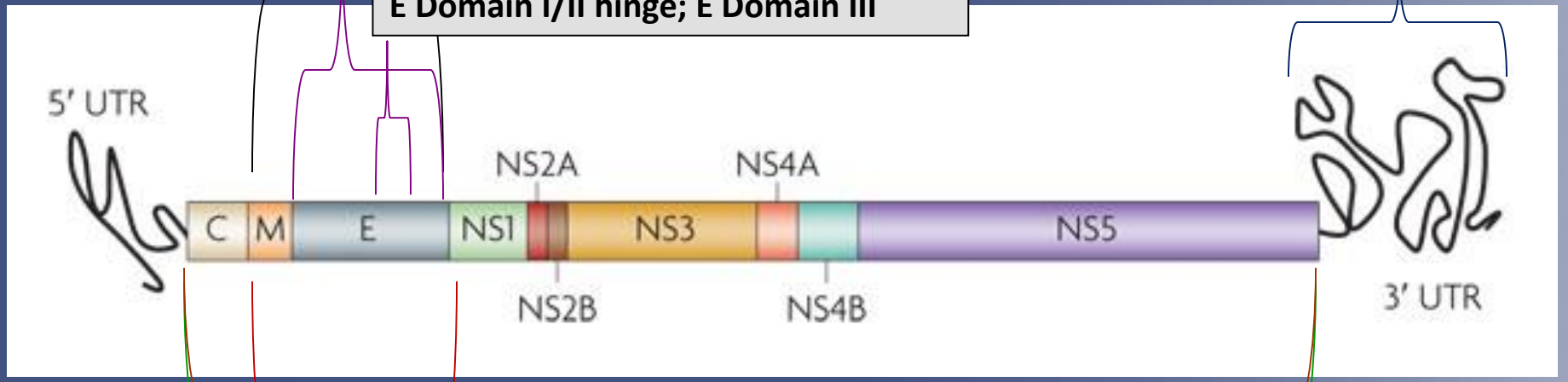
Dengue vaccine design strategies

DNA (prM + E) + adjuvant

E recombinant
Expressed in Drosophila cells

Directed mutagenesis
Chimeras

E Domain I/II hinge; E Domain III



Virus-like particles

YF 17D backbone
DENV-1,-2,-3,-4 prM and E

PIV + adjuvant
Purified, formalin-inactivated

DENV-2 PDK-53 backbone
DENV-1,-3,-4 prM and E

Possible importance of conformational epitopes

- Human mAbs to complex quaternary epitopes derived from dengue patients are strongly neutralizing
  - Human mAbs with **serotype-specific strongly neutralizing** activity bind 3 adjacent E protein regions
  - Human mAbs with **serotype cross-reactive strongly neutralizing** activity bind parts of EDII (including fusion loop) on one side, and EDI and EDIII on other side of dimer (i.e., E-dimer dependent epitope)
  - ?Role in homotypic and heterotypic protection

Vaccines in active human clinical trials

Category	Sponsor	Vaccine name	Approach	Phase
Live attenuated with or without chimera	Sanofi Pasteur	CYD-TDV	Yellow fever 17D backbone and YF-DENV chimera	III
	Takeda	TDV	DENV-2 PDK-53 backbone and DENV-DENV chimera	II; soon III
	US NIH/ Butantan/ Others	TV003/TV005	Direct mutagenesis and DENV-2/4 chimera	II; soon III
Protein subunit	Merck	V180	DENV 80% E protein recombinant + adj	I
Inactivated whole virus	US Army/GSK	TDENV-PIV	Formalin inactivated + adj	I
DNA	US Navy	TVDV	Plasmid DNA + adj	I
Heterologous prime-boost	US Army	TDENV LAV TDENV PIV	Live attenuated/ inactivated whole	I

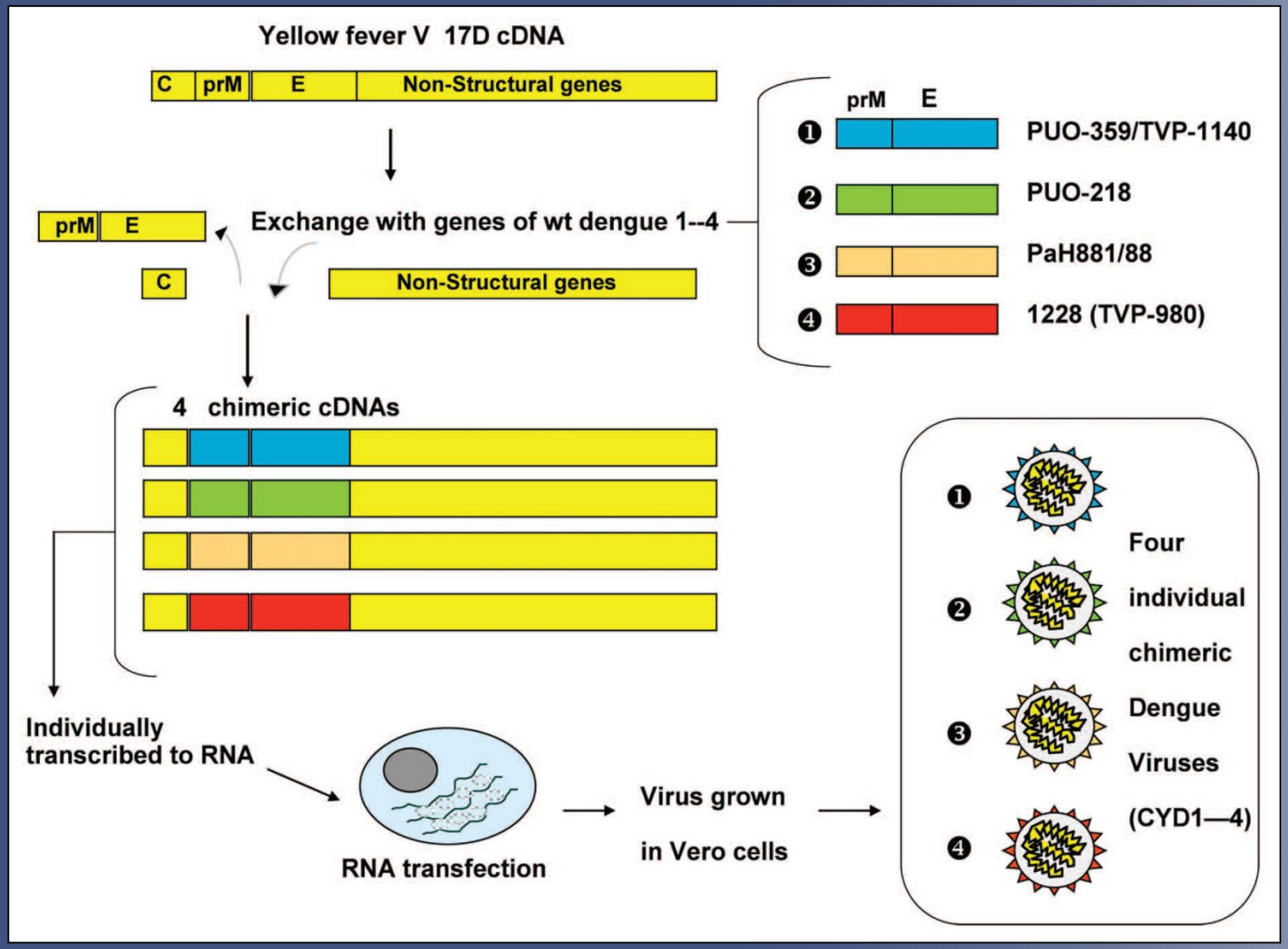
Vaccines in preclinical development (NHPs)

Table 1
Active dengue vaccine candidates in preclinical development that have been evaluated in NHP models.

Vannice et al. Vaccine. 2015 Sep 28.

Technological approach	Vaccine developer	Antigen	Valency under evaluation or evaluated in NHP
Recombinant subunit vaccines	IPK/CIGB	EDIII-p64k fusion proteins and EDIII-capsid fusion proteins expressed in *E. coli*	Monovalent
	VaxInnate	Bivalent 80E-STF2 fusion proteins expressed in baculovirus/insect cells	Tetravalent
	NHRI	Tetravalent consensus EDIII protein expressed in *E. coli*	Tetravalent
DNA vaccines	NMRC	Tetravalent "shuffled" prM/E expressed from plasmid vector	Tetravalent
	CDC	prM/E expressed from plasmid vector	Tetravalent
VLP Vaccines	ICGEB	EDIII-HBsAg VLPs or ectoE-based VLPs expressed in *P. pastoris*	Tetravalent
Virus-vectored vaccines	Themis Bioscience/Institut Pasteur	Tetravalent EDIII and DENV-1 ectoM expressed from live-attenuated measles virus vector	Tetravalent
	Global Vaccines	E85 expressed from single-cycle VEE virus vector	Tetravalent
Purified inactivated virus vaccines	NMRC	Psoralen-inactivated DENV	Monovalent
	WRAIR/GSK/FIOCRUZ	Purified inactivated DENV	Tetravalent
	Global Vaccines	Inactivated virus (+VEE-particle adjuvant)	Tetravalent
Live attenuated virus vaccines	Chiang Mai University/Mahidol University/NSTDA/BioNet-Asia	DEN/DEN chimeric viruses	Monovalent
	Arbovax	DEN host range mutations	Tetravalent
	Beijing Institute of Microbiology and Epidemiology	DEN-SA 14 14 2	Monovalent
	Novartis Institute for Tropical Diseases/Agency for Science, Technology and Research, Singapore	DEN targeted mutation (2′-*O*-methyltransferase mutant)	Bivalent
Heterologous prime-boost approaches	NMRC/WRAIR	Purified inactivated DENV or plasmid vector expressing prM/E (prime) and live attenuated DENV (boost)	Tetravalent
Simultaneous administration	FIOCRUZ	DENV prM/E expressed from live attenuated chimeric YF 17D/DEN virus with DNA vaccine	Monovalent

Sanofi Pasteur's CYD-TDV



Human Vaccines 6:9, 696-705; September 2010; © 2010 Landes Bioscience

Sanofi Pasteur phase 2b and 3 trials

Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial

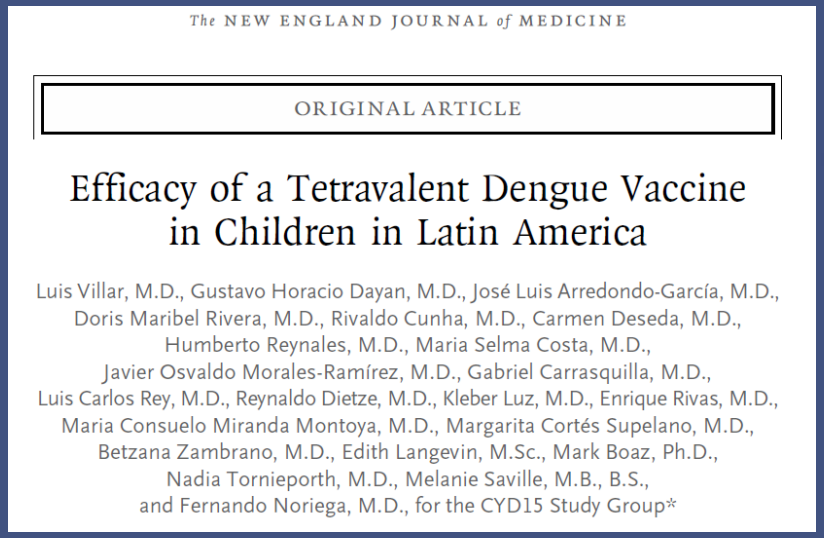
Arunee Sabchareon, Derek Wallace, Chukiat Sirivichayakul, Kriengsak Limkittikul, Pornthep Chanthavanich, Saravudh Suvannadabba, Vithaya Jiwariyavej, Wut Dulyachai, Krisana Pengsaa, T Anh Wartel, Annick Moureau, Melanie Saville, Alain Bouckenooghe, Simonetta Viviani, Nadia G Tornieporth, Jean Lang

Sabchareon A et al. Lancet. 2012 Nov 3;380(9853)..

Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial

*Maria Rosario Capeding, Ngoc Huu Tran, Sri Rezeki S Hadinegoro, Hussain Imam HJ Muhammad Ismail, Tawee Chotpitayasunondh, Mary Noreen Chua, Chan Quang Luong, Kusnandi Rusmil, Dewa Nyoman Wirawan, Revathy Nallusamy, Punnee Pitisuttithum, Usa Thisyakorn, In-Kyu Yoon, Diane van der Vliet, Edith Langevin, Thelma Laot, Yanee Hutagalung, Carina Frago, Mark Boaz, T Anh Wartel, Nadia G Tornieporth, Melanie Saville, Alain Bouckenooghe, and the CYD14 Study Group**

Capeding MR et al. Lancet. 2014 Oct 11;384(9951).



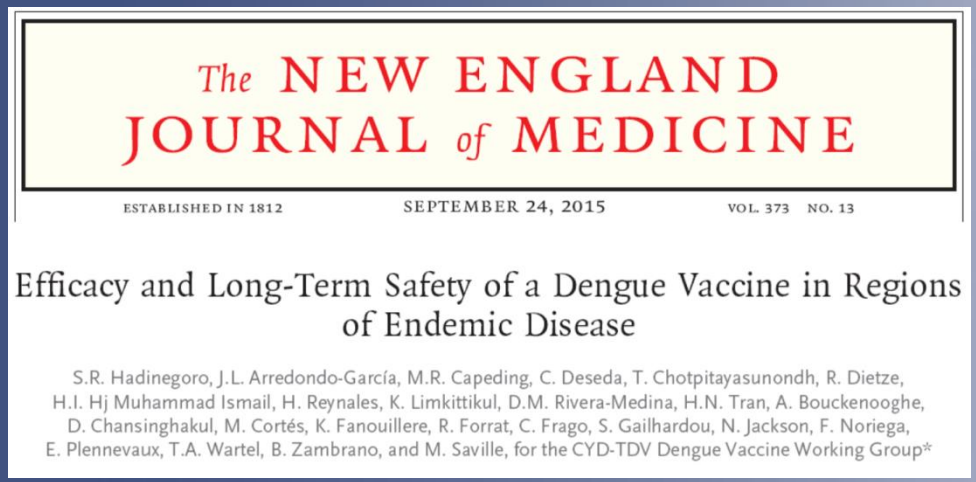
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

Luis Villar, M.D., Gustavo Horacio Dayan, M.D., José Luis Arredondo-García, M.D., Doris Maribel Rivera, M.D., Rivaldo Cunha, M.D., Carmen Deseda, M.D., Humberto Reynales, M.D., Maria Selma Costa, M.D., Javier Osvaldo Morales-Ramírez, M.D., Gabriel Carrasquilla, M.D., Luis Carlos Rey, M.D., Reynaldo Dietze, M.D., Kleber Luz, M.D., Enrique Rivas, M.D., Maria Consuelo Miranda Montoya, M.D., Margarita Cortés Supelano, M.D., Betzana Zambrano, M.D., Edith Langevin, M.Sc., Mark Boaz, Ph.D., Nadia Tornieporth, M.D., Melanie Saville, M.B., B.S., and Fernando Noriega, M.D., for the CYD15 Study Group*

Villar L et al. NEJM. 2014 Nov 3.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 24, 2015 VOL. 373 NO. 13

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, H.I. Hj Muhammad Ismail, H. Reynales, K. Limkittikul, D.M. Rivera-Medina, H.N. Tran, A. Bouckenooghe, D. Chansinghakul, M. Cortés, K. Fanouillere, R. Forrat, C. Frago, S. Gailhardou, N. Jackson, F. Noriega, E. Plennevaux, T.A. Wartel, B. Zambrano, and M. Saville, for the CYD-TDV Dengue Vaccine Working Group*

Hadinegoro SR et al. NEJM. 2015 Sep 24;373(13).

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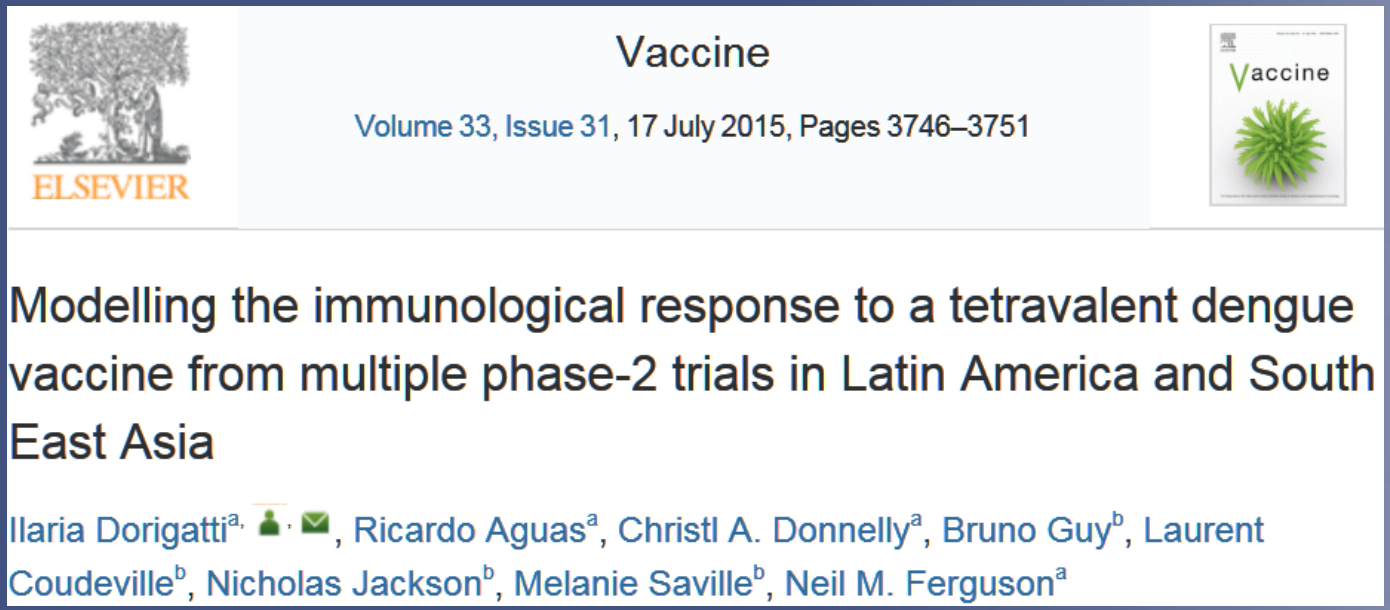
Summary of Sanofi phase 2b and 3 trials

- Serotype-specific efficacy:
  - Poor efficacy against DENV-2
  - Marginal efficacy against DENV-1
  - Good efficacy against DENV-3 and 4
  - Immunogenicity by PRNT of unclear clinical relevance
- Better efficacy against severe dengue
- Poor efficacy in very young children and dengue naïve subjects
- Efficacy apparent after dose 1 in primed subjects
- Increased risk in very young children during 3rd year

What happened?

- Interference by other vaccine serotypes blunted response to DENV-2 (e.g., DENV-4)



Vaccine

Volume 33, Issue 31, 17 July 2015, Pages 3746–3751

Modelling the immunological response to a tetravalent dengue vaccine from multiple phase-2 trials in Latin America and South East Asia

Ilaria Dorigatti[a], Ricardo Aguas[a], Christl A. Donnelly[a], Bruno Guy[b], Laurent Coudeville[b], Nicholas Jackson[b], Melanie Saville[b], Neil M. Ferguson[a]

Dorigatti et al. Vaccine. 2015 Jul 17;33(31):3746-51

Balanced PRNT titers after 3 doses, but DENV-4 immunodominant after first dose

What happened?

- Traditional neutralizing antibody titers to DENV-2 may have been too low
  - So formulation had insufficient DENV-2 component or too much interference from other serotypes

OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Dengue Virus Neutralizing Antibody Levels Associated with Protection from Infection in Thai Cluster Studies

Darunee Buddhari[1]*, Jared Aldstadt[2], Timothy P. Endy[3], Anon Srikiatkhachorn[4], Butsaya Thaisomboonsuk[1], Chonticha Klungthong[1], Ananda Nisalak[1], Benjawan Khuntirat[1], Richard G. Jarman[5], Stefan Fernandez[1], Stephen J. Thomas[5], Thomas W. Scott[6,7], Alan L. Rothman[8], In-Kyu Yoon[1]

Buddhari et al. PLoS NTD. 2014 Oct 16;8(10):e3230.

DENV PRNT titer cutoffs for risk of infection:

- **DENV-1 = 11**
- **DENV-2 = 323**
- **DENV-4 = 16**

What happened?

- Vaccine did not elicit sufficient T cell response to dengue antigens, which could have been important for protection
  - T cell response is mostly to NS proteins which were YF 17D, not DENV
- Chimeric vaccines “look different” to immune system
  - Potential importance of conformational epitopes

Why was there a safety signal?

- Possible immune enhancement in youngest children maybe due to:
  - Immature immune system with poor immune response and/or quicker waning immunity
  - Immature physiology predisposing to DHF in combination with other factors
  - Vaccination served as artificially-induced “primary” infection in dengue naïve subjects leading to earlier secondary infection
- ?Risk in older dengue naïve subjects

Submission for licensure

- Given efficacy profile and no observed safety signal in post-hoc analysis in older children, Sanofi Pasteur has submitted the dossier for licensure in multiple dengue endemic countries in Asia and Lat Am for those 9 years of age or older
  - "Reverse" regulatory strategy

Importance of different epidemiology

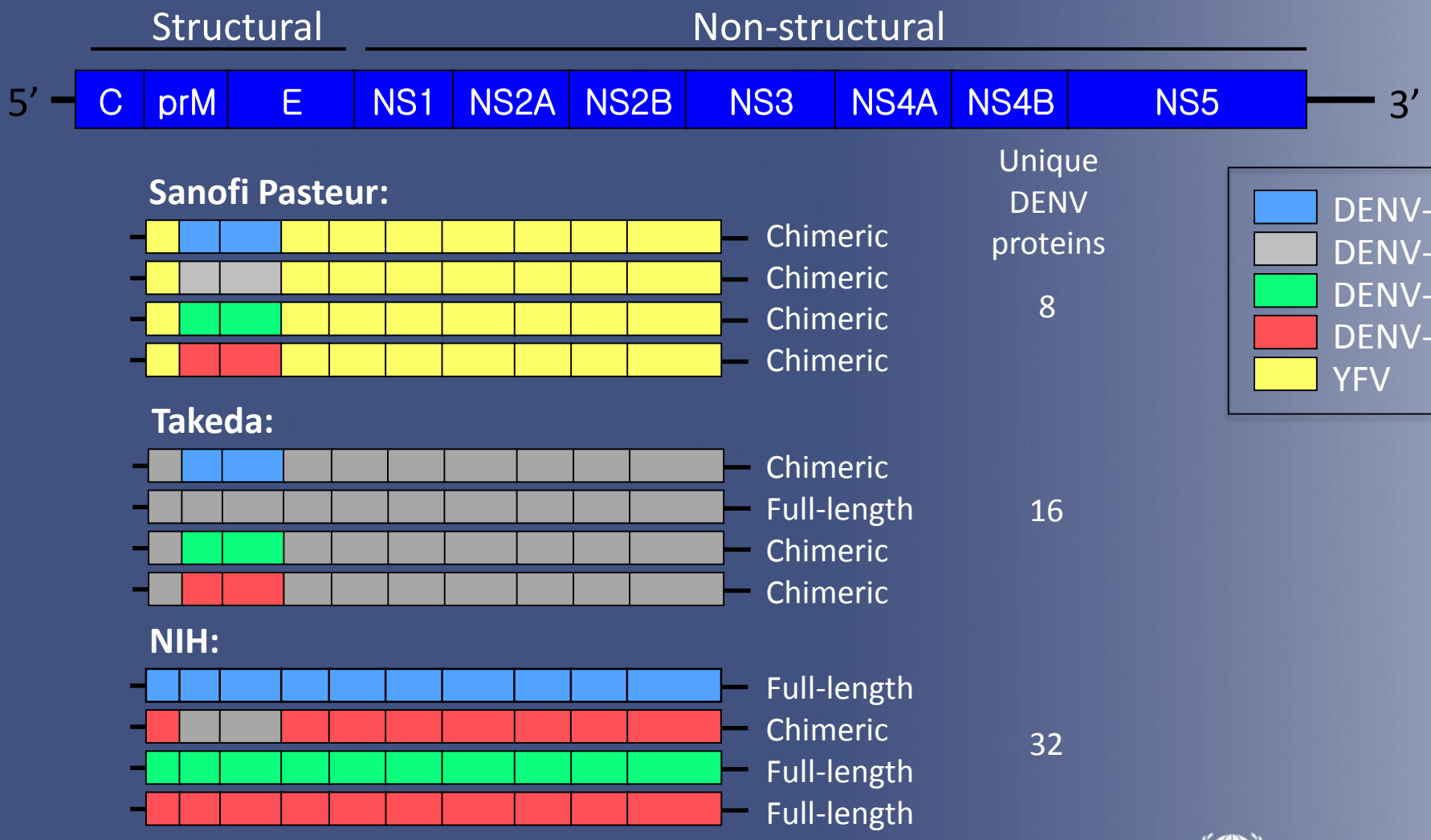
- Any potential introduction needs to be well planned

E.g., Effect of background dengue epidemiology on efficacy: Colombia compared with Mexico in Phase 3 trial in LatAm

Country	N randomized to receive vaccine (V) or placebo control (C)				Baseline dengue seropositivity rate[1]	Incidence density (ID) and infecting serotype of virologically-confirmed dengue in the control group (ITT)[2]							Vaccine Efficacy, (ITT)[3]	
	Overall		Subset											
	V	C	V	C	%	ID	(95%CI)	ST1	ST2	ST3	ST4	ND	%	(95% CI)
All	13920	6949	1334	666	79.4	2.9	(2.6–3.2)	109	84	106	83	14	64.7	(58.7–69.8)
Brazil	2370	1178	202	98	73.5	3.7	(2.9–4.6)	9	0	0	72	0	77.5	(66.5–85.1)
Colombia	6497	3246	613	308	92.2	2.7	(2.3–3.1)	58	33	67	9	2	67.5	(58.3–74.7)
Honduras	1866	933	200	100	85.7	4.0	(3.2–5.0)	6	20	39	0	9	71.1	(57.0–80.7)
Mexico	2312	1152	219	108	53.1	2.5	(1.9–3.2)	25	30	0	1	2	31.3	(1.3–51.9)
Puerto Rico	875	440	100	52	56.2	1.6	(0.8–2.6)	11	1	0	1	1	57.6	(-2.5–82.8)

Implications for other vaccine candidates

3 most advanced dengue vaccine candidates



Implications for other vaccine candidates

- Impact of interference
- Role of non-structural proteins
- Role of conformational epitopes
- Serotype-specific vs serotype-cross protective epitopes
  - Is tetravalent vaccination to elicit tetravalent homotypic immunity the only viable strategy?
- Durability of immunity
- Meaning of traditional immunogenicity measures during development
  - Role of human infection models for vaccine down-selection
  - Pursuit of correlates of protection and risk
- Regulatory implications

Summary

- Many challenges exist to dengue vaccine development and introduction, but it is feasible
- Sanofi Pasteur vaccine efficacy trials had mixed results
  - Some disappointing (e.g., DENV-2)
  - Some promising (e.g., severe dengue)
  - Some questions remain (e.g., safety, durability)
- A robust pipeline of vaccine candidates are in development; two may soon enter phase 3 trials

Thank you