Current status of dengue vaccine development

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SAGE/Immunization Meeting
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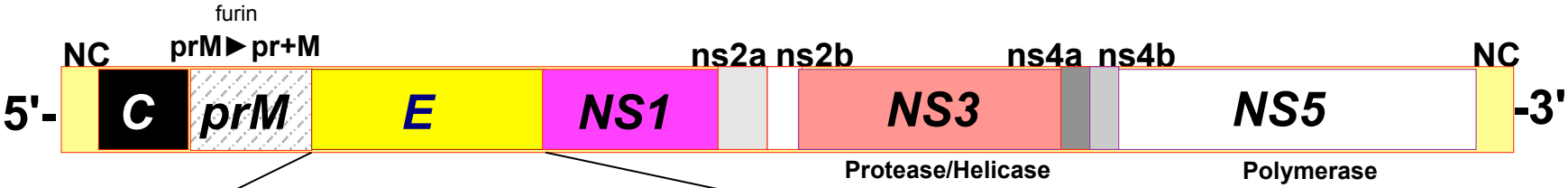
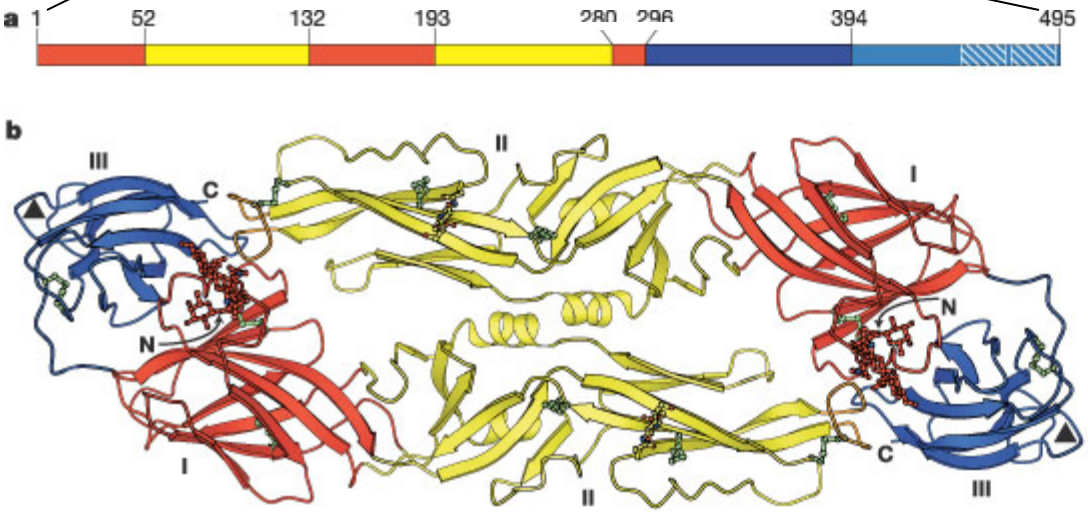
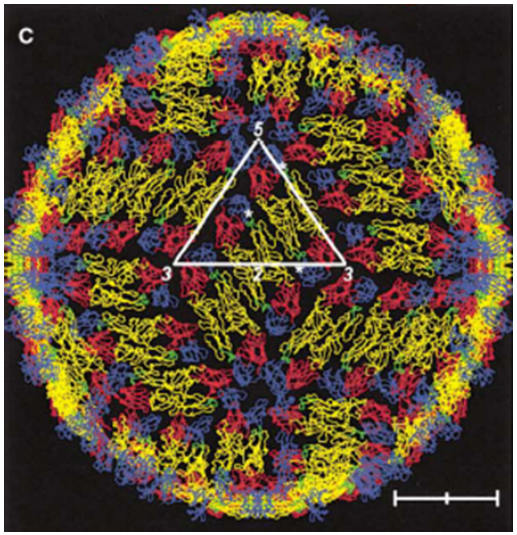
National Center for Emerging and Zoonotic Infectious Diseases
Division of Vector-Borne Diseases, Arboviral Diseases Branch

Flavivirus structure



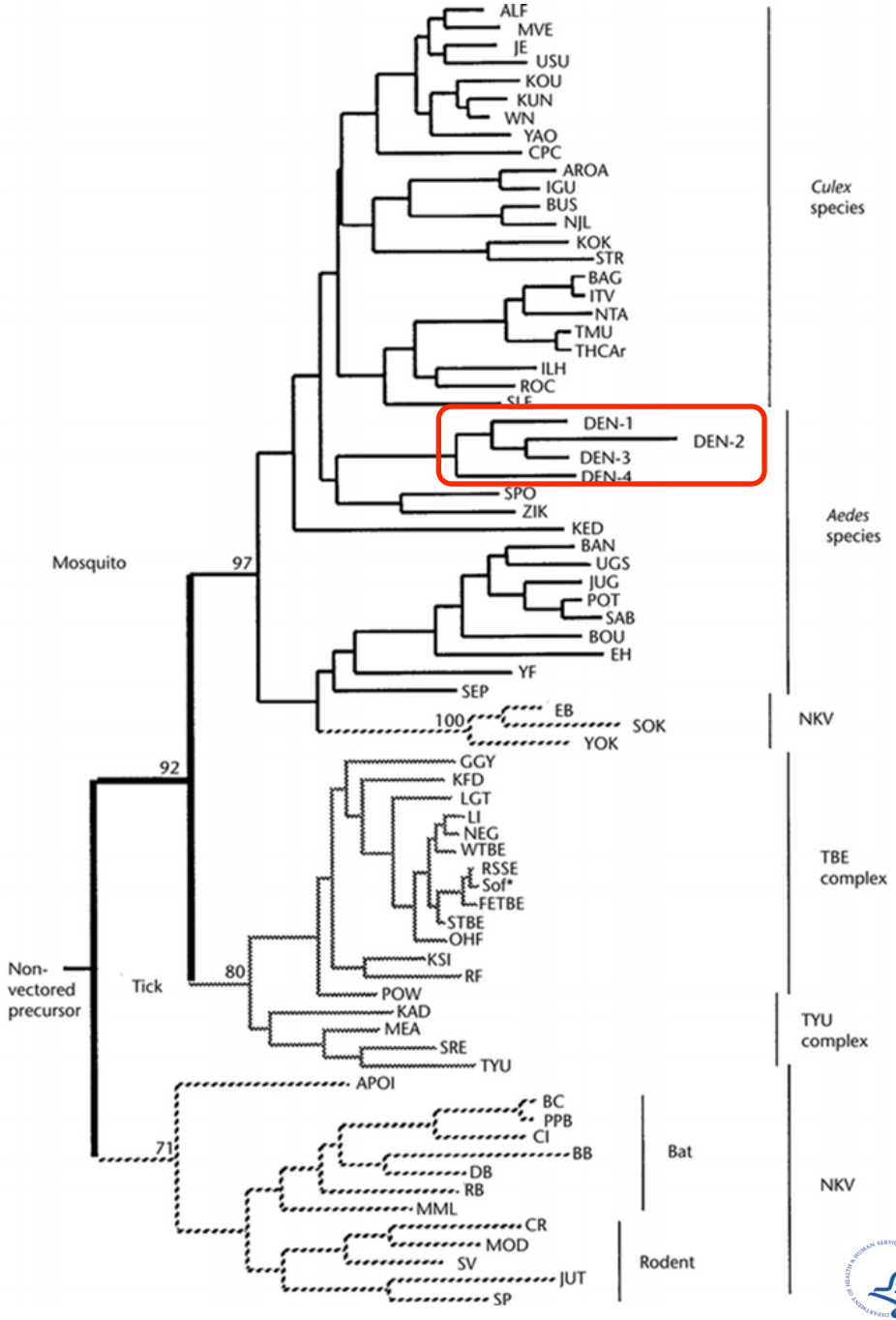




- E glycoprotein biology
  - Major virion surface protein
  - Induces virus-neutralizing/protective antibody
  - Involved in virus attachment
  - Mediates virus-specific membrane fusion
- NS-proteins (NS3) elicits cytotoxic T-cell response

Kuhn *et al.*, 2002

Flavivirus phylogeny based on the gene sequence of NS5



Unique challenges for DENV vaccine

- Infection by one DENV serotype confers lasting protection only against re-infection with the homotypic DENV serotype.

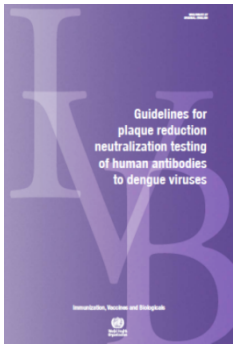
- A secondary heterotypic infection is associated with an increased risk of severe disease (immune enhancement, IE). Because of this WHO recommends longer vaccinee follow-up as vaccine immunity wanes.

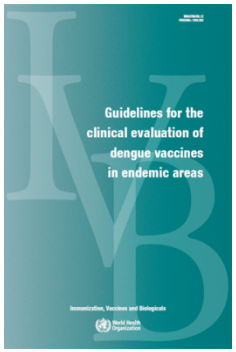
- Tetravalent vaccines are aimed at providing long-term protection against all four serotypes at once, thus reducing IE risk, but complicating serological analyses of vaccinees and breakthrough cases.

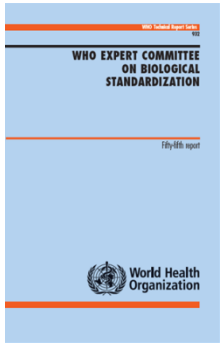
- Lack of adequate animal disease models makes it difficult to identify correlates of protection that will likely come only from clinical trial results.

WHO guidance and selected reports related to DENV vaccine development

- Long-term safety assessment of live attenuated tetravalent dengue vaccines: Deliberations from a WHO technical consultation (Vaccine, in press 2013)
- Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live, attenuated) (update of TRS932, in press).
- Next generation dengue vaccines (Vaccine *29*:7276-7, 2011).
- Dengue modelling (WHO/IVB/11.02).
- Cell-mediated immunity in dengue vaccine development (Vaccine *27*:355-368, 2008).
- Guidelines for the evaluation of dengue vaccines in endemic areas (WHO/IVB/08.12).
- Guidelines for plaque reduction neutralization testing of human antibodies to dengue viruses (WHO/IVB/07.07, and Viral Immunology *21*:123-132, 2008).
- Immune correlates of protection induced by dengue vaccines (Vaccine *25*:4130-4139, 2007).







World Health Organization

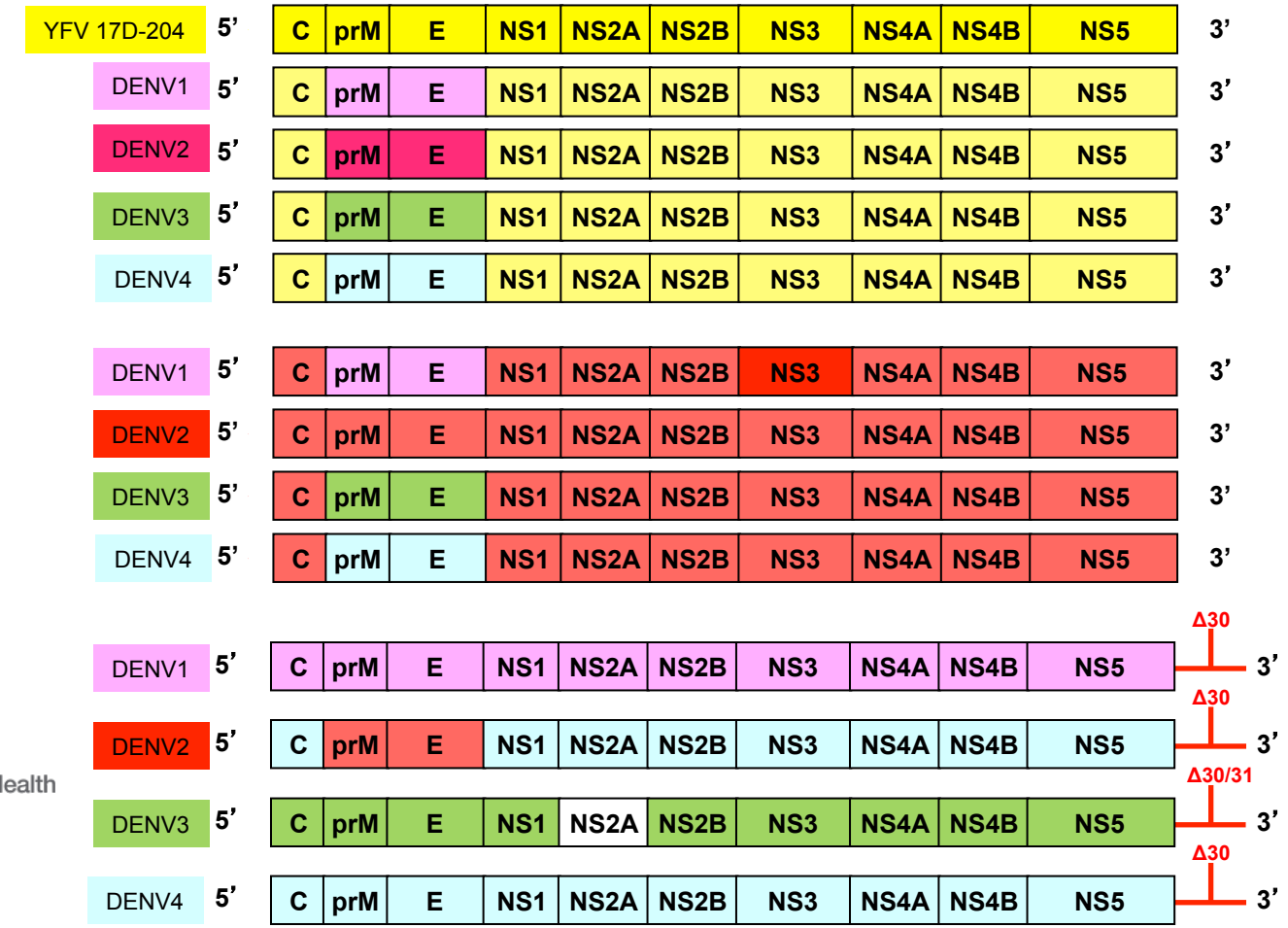
Tetravalent live-attenuated vaccines (LAVs) in human clinical trials

The first DENV LAVs were developed by Mahidol University (Thailand/SP) and WRAIR. These vaccines were abandoned.

CYD-TDV
SANOFI PASTEUR

DENVax
inviragen

TV003
NIH National Institutes of Health
Turning Discovery Into Health



CDC

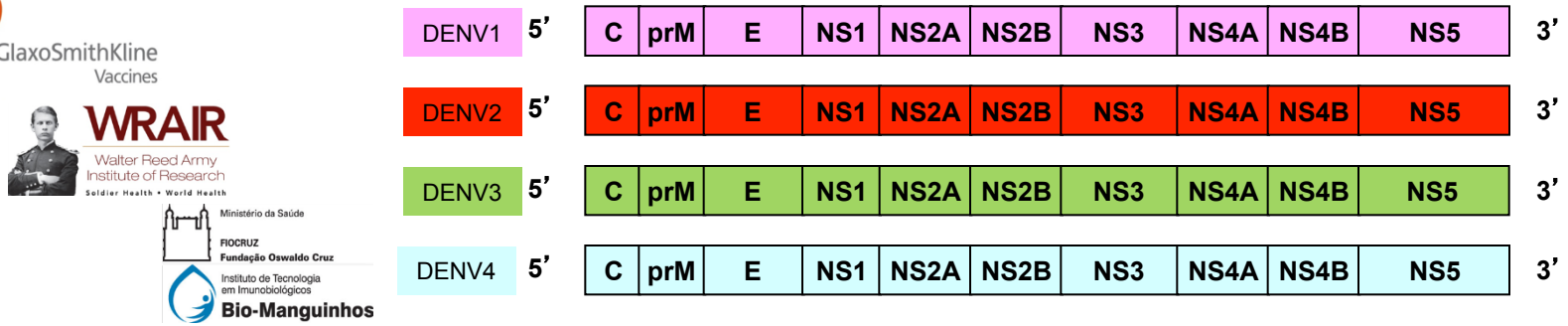
Tetravalent inactivated or subunit vaccines in human clinical trials

DPIV

GlaxoSmithKline Vaccines

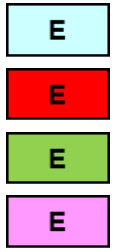
WRAIR Walter Reed Army Institute of Research

Ministério da Saúde FIOCRUZ Fundação Oswaldo Cruz Instituto de Tecnologia em Imunobiológicos Bio-Manguinhos



80% E-proteins

MERCK Be well



CDC

Global DENV vaccine pipeline

Phase I	Phase II	Phase IIb	Phase III
	CYD-TDV	CYD-TDV	CYD-TDV
DENVax	DENVax		
TV003	TV003		
DPIV			
80% E-proteins			

Large scale CYD-TDV safety and efficacy trials

- 2009: First Phase IIb Efficacy study initiated in Thailand / Ratchaburi / 1 site
- 2011: Phase III Large Scale Efficacy trials initiated in Asia and LatAm/ 33 sites

Phase III Efficacy Latin America

- **Countries:** Colombia, Mexico, Honduras, Puerto Rico, and Brazil
- **Age group:** 9-16 years
- **Sample Size:** 20,875

Phase III Efficacy Asian

- **Countries:** Thailand, Indonesia, Malaysia, Viet Nam, Philippines
- **Age group:** 2-14 years
- **Sample Size:** 10,278

Phase IIb Efficacy study Thaïland

- **Country:** Thailand
- **Age group:** 4-11 years
- **Sample size:** 4,002

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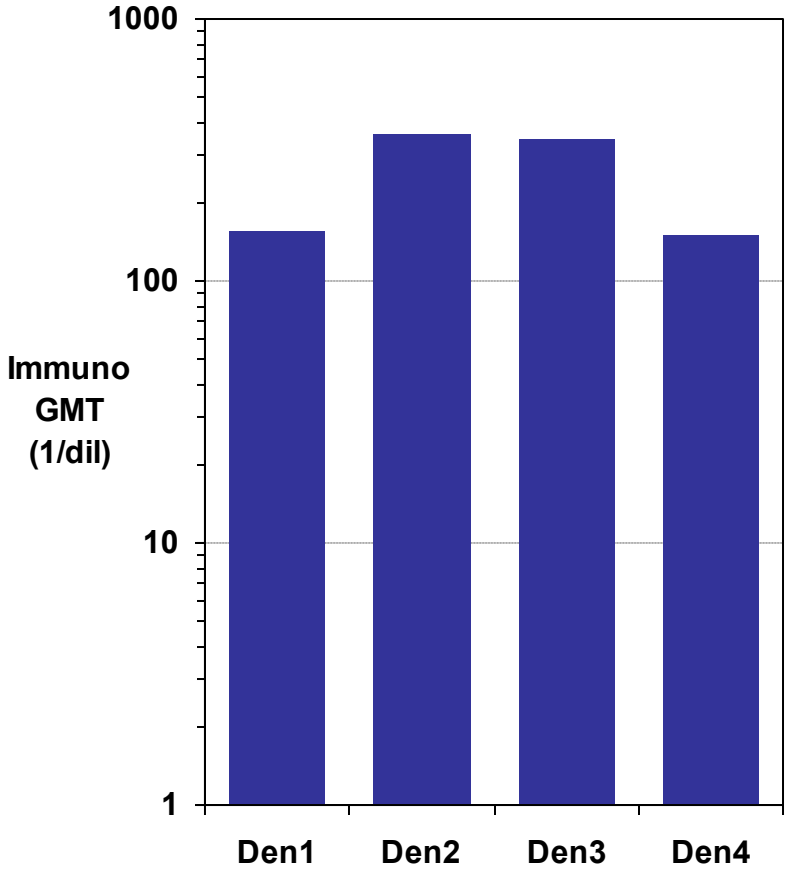
WHO advisory group summary of initial Phase IIb trial of CYD-TDV DENV vaccine

Sabchareon *et al*., Lancet 2012

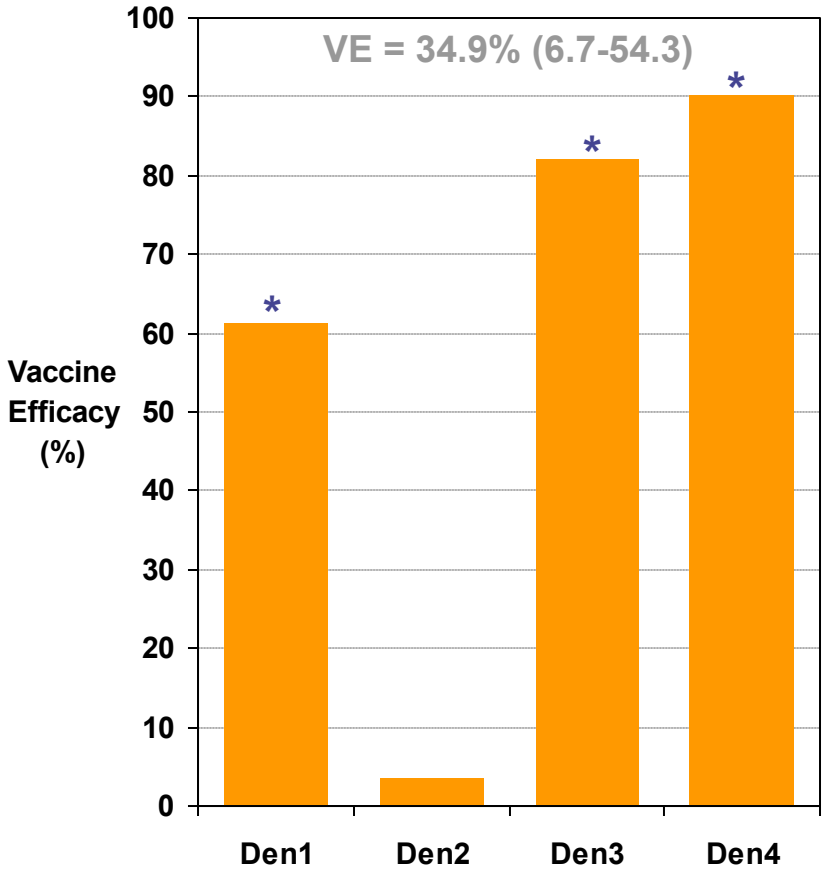
- The safety profile of CYD-TDV is satisfactory - up to 25 months after the first vaccine dose.
- The overall efficacy is 30.2% (95% confidence interval: -13.4% to 56.6%) and is not statistically significant - therefore tetravalent vaccine efficacy remains inconclusive.
- Efficacy estimates for DENV1, 3, and 4 were statistically significant after at least one vaccine dose, but not after three doses. Larger data sets are needed to confirm these observations.
- Phase III data will be critical for evaluating CYD-TDV performance and efficacy against disease caused by any or all of the four DENV serotypes.

Phase IIb results – 0, 6, 12 month regimen
Immunogenicity vs vaccine efficacy- intention to treat (ITT)

Immuno subset PD3 ($PRNT_{50}$) n=300



ITT, After at least one dose, n=134
(DENV1=32, DENV2=79, DENV3= 15, DENV4 = 6)



* = Lower bound of 95% CI is > 0

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Phase I tetravalent NIH vaccine results
Safety and Immunogenicity

TV-003
DEN1Δ30
DEN2/4Δ30
DEN3Δ30/31
DEN4Δ30

- Single subcutaneous dose (10^3 pfu each serotype)
- Flavivirus-naïve adult subjects
- No serious adverse events
- Remarkably few reported symptoms
  - 55% of subjects had asymptomatic, faint rash
- Very low vaccine viremia
- Up to 36% of vaccinees had peak antibody titers after day 56

		% seroconverted ($PRNT_{50} \geq 10$)				Mean titer (GMT) ($PRNT_{50} \geq 10$)			
Vaccine	N	DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4
TV-003	38	92	76	97	100	63	40	85	151

After just ONE dose:

74% of subjects had tetravalent antibody response
95% of subjects had at least a trivalent response

After SECOND dose:

No detectable vaccine replication. No vaccine rash
91% of subjects had tetravalent antibody response

NIH National Institutes of Health
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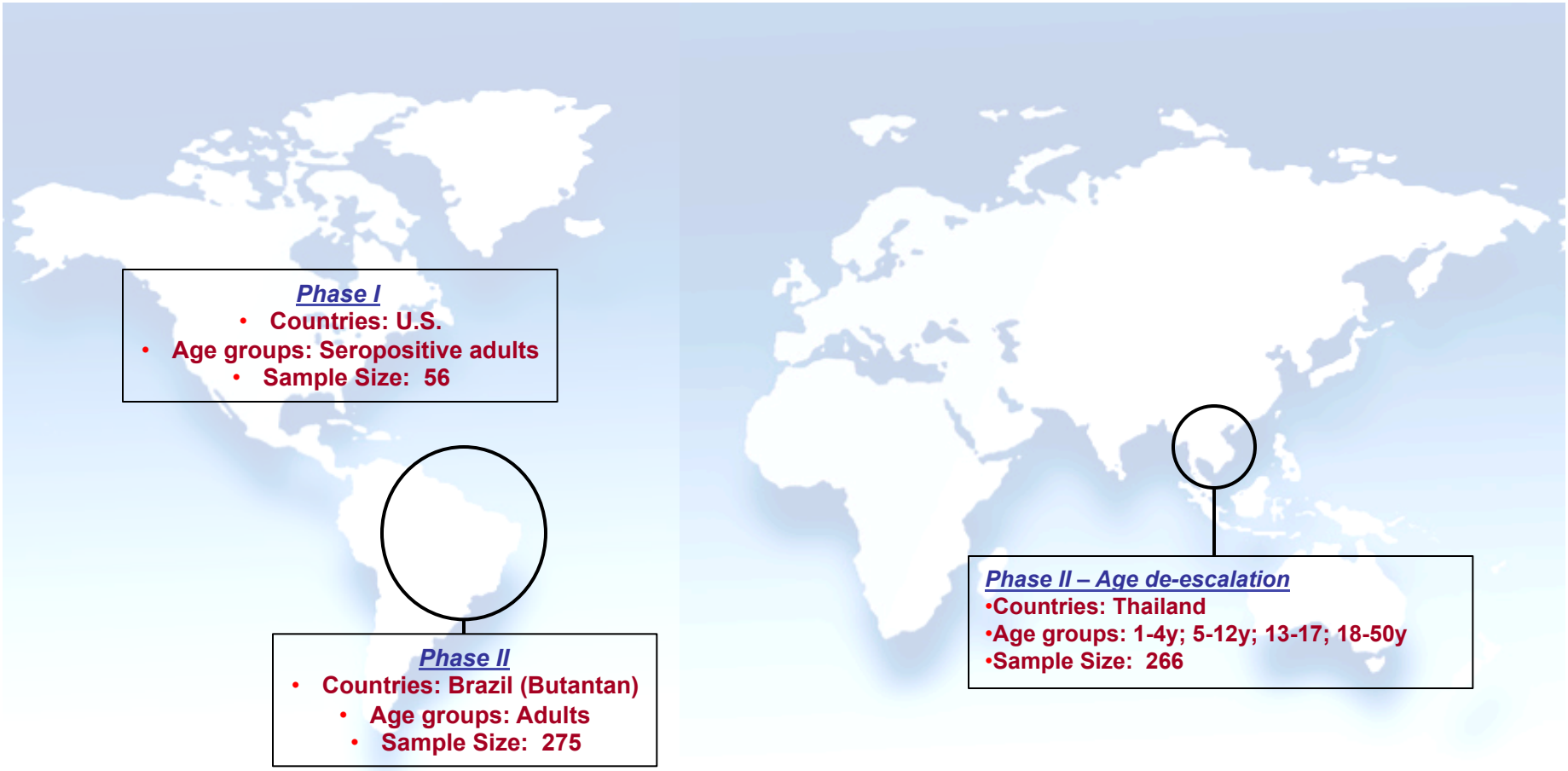
Ongoing NIH TV-003 vaccine trials

Licensing partners: Butantan Foundation, Sao Paulo, Brazil; Biological E Ltd, Hyderabad, India; Panacea Biotec, New Delhi, India; Vabiotech, Hanoi, Vietnam; GSK (inactivated vaccine application)



Phase II dosing – Bangkok, T=0 and 6 months; Brazil, T=0 only

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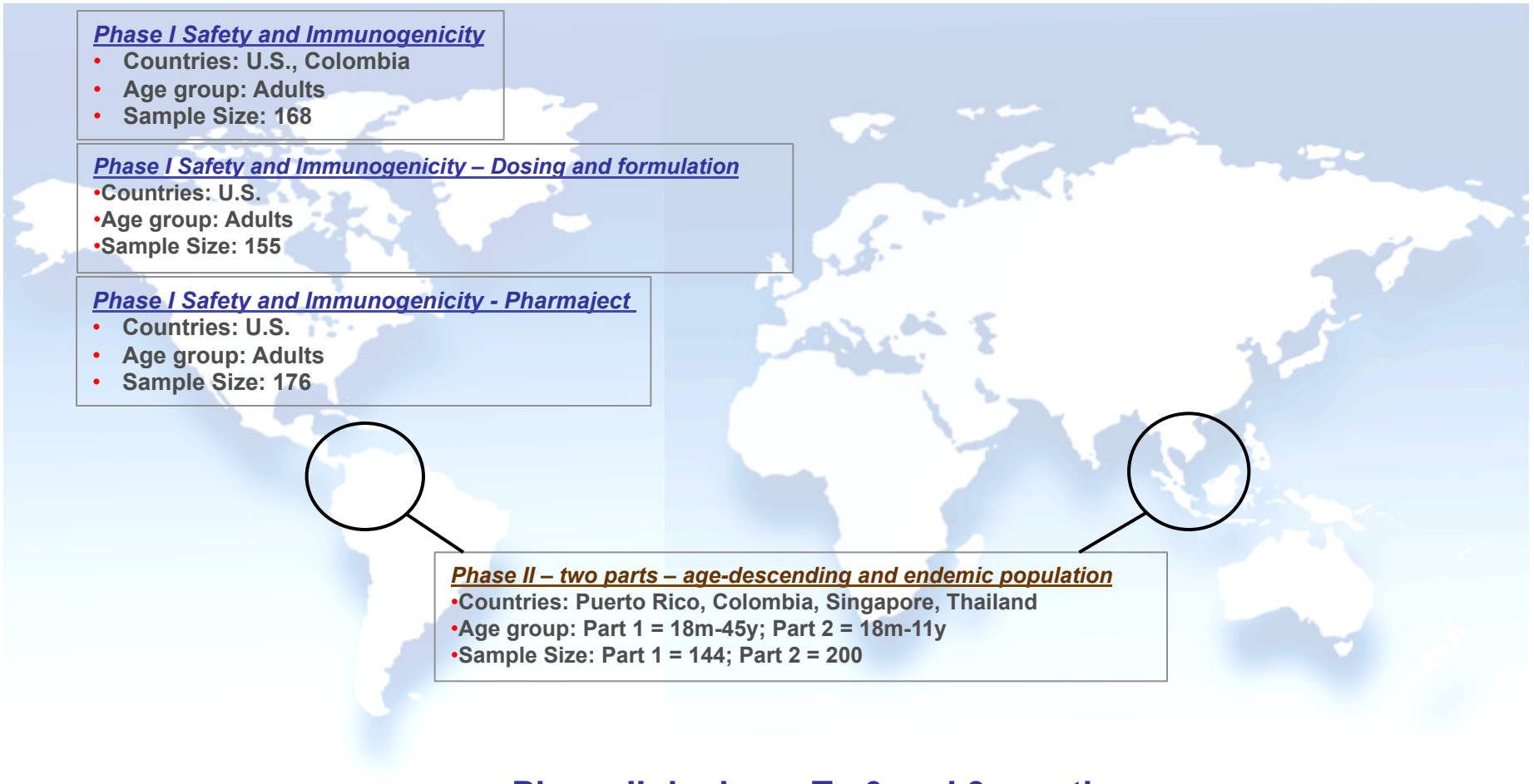
Ongoing or planned Inviragen DENVax trials

Phase I studies – 2010, 2012, 2013; Phase II studies – 2011, 2013; Phase IIb studies – 2014 (n~5000)



Phase II dosing – T= 0 and 3 months

inviragen

DENV vaccines in Phase I clinical trials

MERCK – E proteins

- Flavivirus-negative, healthy, young adults, Australia
- Tetravalent: DEN1-80E, DEN2-80E, DEN3-80E, DEN4-80E, formulated with/without adjuvants
- Safety assessed throughout the study and immunogenicity based on virus neutralizing antibody responses - Seroconversion rates and GMTs of responses for each serotype, 28 days post-dose 3

GSK/WRAIR/Fiocruz - DPIV

- Two doses of DPIV (Vero), combined with alum or GSK adjuvant system, given 4 weeks apart, for rapid onset of durable protection
- Joint vaccine development in a public-private partnership including WRAIR (U.S. Army), Fiocruz (MoH Brazil) and GSK Vaccines
- Two Phase I studies using WRAIR manufactured antigen are ongoing in the U.S. and Puerto Rico. Goal is to select best adjuvant (AS01 vs. AS03 vs. alum) in 2013.

Summary

- Vaccination for dengue is different than other flaviviruses
  - Four distinct but related serotypes of DENV
  - Possibility of antibody-dependent enhancement (ADE) leading to severe dengue disease (*e.g.*, DHF/DSS)
- Five DENV vaccines in human clinical trials and all are tetravalent formulations
  - Phase I/II results do not suggest vaccine-related severe adverse events (SAEs)
- Sanofi-Pasteur is in the lead, however first protection results were surprising
  - Follow-up science to decipher results
  - Phase III data will be critical to appraise vaccine performance
  - More thought about expectations
- All LAV vaccines are constructed differently, so each will yield unique data, *e.g.*, contribution of NS proteins to efficacy
- Inactivated whole virus vaccine approach has worked for other flaviviruses – so why not dengue?
- Second generation vaccines are in development - *e.g.*, DNA, VLP, EDIII, and virus vectored (adenovirus, alphavirus (VEEV), measles, and WNV

Acknowledgements

- Beth-Ann Coller - Merck
- Jean Lang and Jean-Antoine Zinsou – Sanofi Pasteur
- Alex Schmidt - GSK
- Dan Stinchcomb and Aurelia Haller – Inviragen
- Steve Whitehead – U.S. NIH

Licensing partners:

- Butantan Foundation, Sao Paulo, Brazil
- Biological E Ltd, Hyderabad, India
- Panacea Biotec, New Delhi, India
- Vabiotech, Hanoi, Vietnam
- GSK (inactivated vaccine application)

Ongoing studies:

- Evaluate vaccine in flavivirus-seropositive adults (N = 56)
- Targeted challenge of vaccinees with DEN2Δ30 virus
- Phase II age de-escalation studies in Bangkok (N=266)
  - Adults (18 – 50 years)
  - Adolescents (13 – 17 years)
  - Older children (5 – 12 years)
  - Younger children (1 – 4 years)
- Phase II study in Sao Paulo (Butantan Institute) (N = 275)

Inviragen - DENVax

Study Number	Sites	Purpose	Subject Number	Route & Dose	Start Date
INV-DEN-101 Phase 1	US	Safety, Immunogenicity	72	SC & ID Low and High dose	Jul-10
INV-DEN-102 Phase 1	Columbia (non-endemic)	Safety, Immunogenicity	96	SC & ID Low and high dose	Oct-10
INV-DEN-203 Phase 2*	Puerto Rico, Columbia, Singapore, Thailand (endemic areas)	Part 1 - age descending study (18m - 45y) Part 2 - expansion of 18m - 11y children	Part 1 -144 Part 2 -200	SC High dose	Nov-11 Feb-13
INV-DEN-104 Phase 1	US	Safety, Immunogenicity Part 1 - Test various dose schedules Part 2 – Test new vaccine formulation Part 3 – test 1/10 diluted HD vaccine	~155	SC High dose new High Dose #2 formulation containing increased DENVax-4 HD and HD#2 diluted 1/10	 Aug-12 4Q2012 Not yet started
INV-DEN-103 Phase 1	US	Safety, Immunogenicity, compare needle to PharmaJet	96	ID Low dose	March-13
INV-DEN-105 Phase 1	US	Safety, Immunogenicity, compare IM vs SC administration using needle-free PharmaJet injector	80	IM Low dose	Feb-13

*Two doses on day 0 and day 90 for the current phase 2.

Merck Dengue Vaccine: Ongoing Phase 1 Clinical Program

- **Overall objective:** To evaluate recombinant vaccine for safety and immunogenicity
- **Design:** randomized, blinded, placebo-controlled trial
- **Trial population:** Flavivirus-negative, healthy, young adults
- **Trial site:** Australia
- **Vaccine formulations:**
  - Tetravalent: DEN1-80E, DEN2-80E, DEN3-80E, DEN4-80E
  - Formulated with/without adjuvants
- **Key endpoints:**
  - Safety – assessed throughout the study
  - Immunogenicity based on virus neutralizing antibody responses:
    - Seroconversion rates for each serotype, 28 days post-dose 3
    - GMTs of responses for each serotype, 28 days post-dose 3

Collaborative Development of a Dengue Purified Inactivated Virus (DPIV)

- Vaccine composition: whole dengue virus grown in Vero, inactivated, adjuvanted
- TPP: Two doses of DPIV, combined with alum or GSK adjuvant system, given 4 weeks apart, for rapid onset of durable protection
- Joint vaccine development in a public-private partnership including WRAIR (U.S. Army), Fiocruz (MoH Brazil) and GSK Vaccines
- Highly immunogenic in non-human primates; protection against viremia following challenge
- Two Phase I safety / immunogenicity studies using WRAIR manufactured antigen are ongoing in the U.S. and Puerto Rico (NCT01666652 & NCT01702857). Goal is to select best adjuvant (AS01 vs. AS03 vs. alum) in 2013.
- Prospective epi cohort studies: ongoing in Brazil and planned for additional countries in Asia and the Americas

WRAIR
Walter Reed Army Institute of Research
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Instituto de Tecnologia em Imunobiológicos
Bio-Manguinhos

gsk GlaxoSmithKline Vaccines

Other DENV vaccines in preclinical development

From WHO Consultation on next generation dengue vaccine 2010

Approach	Developers	DENV antigens
Rec. subunit	ICGEB, IPK, VaxInnate	EDIII
DNA	CDC, Inovio, Kobe University, NMRC	EDIII or prM/E
VLP	Cytos, ICGEB, Kobe University	EDIII or prM/E
Virus-vectored	GenPhar (AV), Themis (MV), UNC (VEE), UTMB (WNV)	EDIII or prM/E

Schmitz et al., Vaccine 2011

Recommendations to WHO on dengue vaccines by Advisory Committee

- Continue close scrutiny of ongoing vaccine trial results.
- Strongly encourage sharing of all information on the results of vaccines trials with WHO.
- Strongly encourage appropriate specimen collection to assure valid analyses of pre-existing immunity, post-vaccination immune-responses, viremias, and vaccine-induced T-cell responses in vaccine breakthrough cases. In order to get appropriate sample sizes to power analyses, consider recommending collection of specimens from later stages of clinical testing, e.g., Phase III trials.
- Continue to encourage development of other live-attenuated vaccines and second generation DENV vaccines e.g., killed vaccines, sub-unit vaccines, and prime-boost strategies.
- Encourage long-term safety follow-up as outlined in WHO safety guidelines.
- Continue convening regular informational general meetings for subject matter experts, industry, and other stakeholders to be informed of the status of vaccine development and implementation.
- Consider the development of a human/DENV challenge model which would be of use for vaccine development and enhance other areas of dengue diagnostics/treatment/pathogenesis/immunity. Such a model could employ partially attenuated challenge viruses that have been developed in the course of vaccine development research as outlined in the 2008 WHO Guidelines for Evaluation of Dengue Vaccines in Endemic Areas.

Further research questions on dengue vaccines

- Virus neutralization assays
- Antibody reactivities
- Chimeric vaccines
- Cellular responses
- Efficacy trial design
- Viral genetics and variation