

Butantan: Developing a Dengue Vaccine for Brazil

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Outline

Description of Dengue

The virus

The disease

Epidemiology of Dengue

Worldwide

South America and Brazil

Vaccine to Prevent Dengue

Butantan's Development of Dengue Vaccine

Collaborators:

Butantan

Dr. Isaias Raw

Dr. Neusa Frazatti Gallina

Dr. Alex Precioso

NIAID

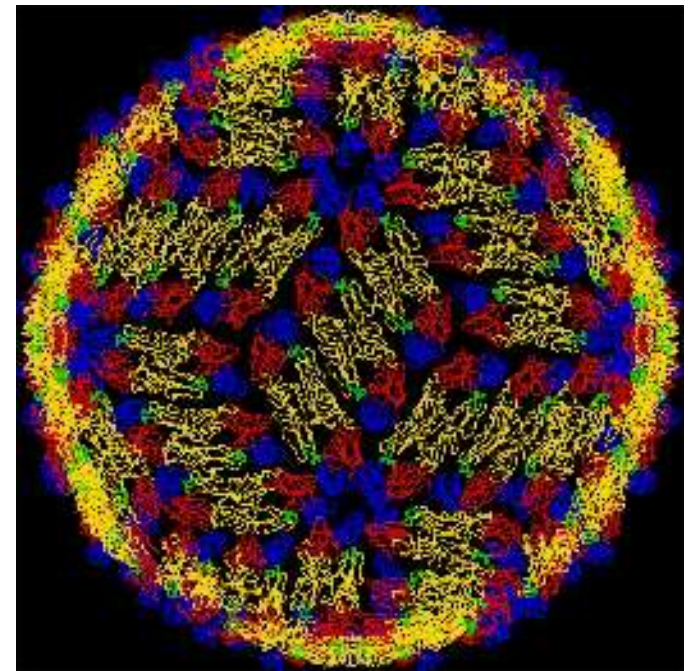
Dr. Steve Whitehead

Johns Hopkins

Dr. Anna Durbin

Dengue virus type 1-4

- Mosquito-borne RNA virus
- Single-stranded positive sense



Source: Kuhn, et al. Cell. 2002 Mar 8;108(5):717

E protein:

Domain I: red

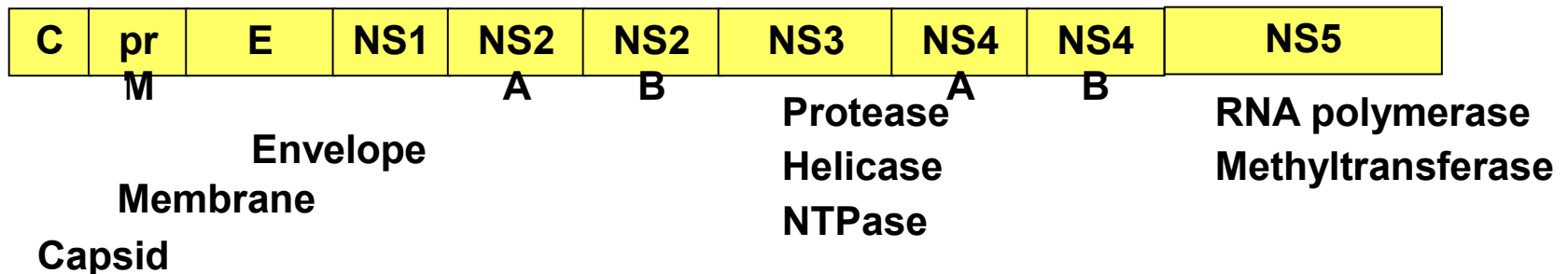
Domain II: yellow

Domain III: blue

Fusion pep: green

Structural

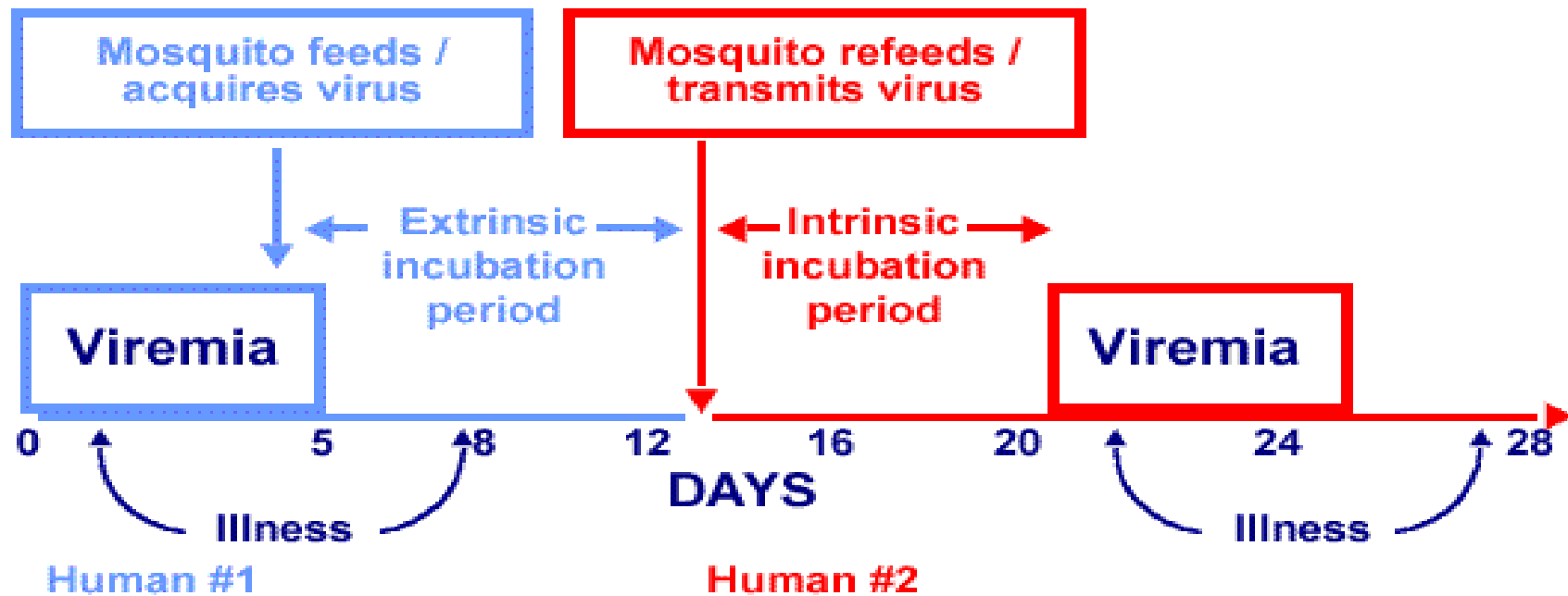
Non-structural



Aedes aegypti



Dengue Virus Transmission



Dengue rash



Hemorrhagic Dengue



<http://denguefeverpictures.com/>

New Estimates of the Burden of Dengue

Table 1. New Estimates of the Burden of Dengue

Disease	Symptomatic Cases	Deaths	Estimated Countries Affected
Dengue	36 million	21,000	124
Yellow Fever	200,000	30,000	>42
Japanese Encephalitis	50,000	>10,000	>10
Malaria	500 million	>1 million	>105

* Adapted from: E. Callaway. Dengue fever climbs the social ladder. Nature 2007; 448:734-735.

Dengue Endemic Areas

2011



Increasing incidence of dengue – South America

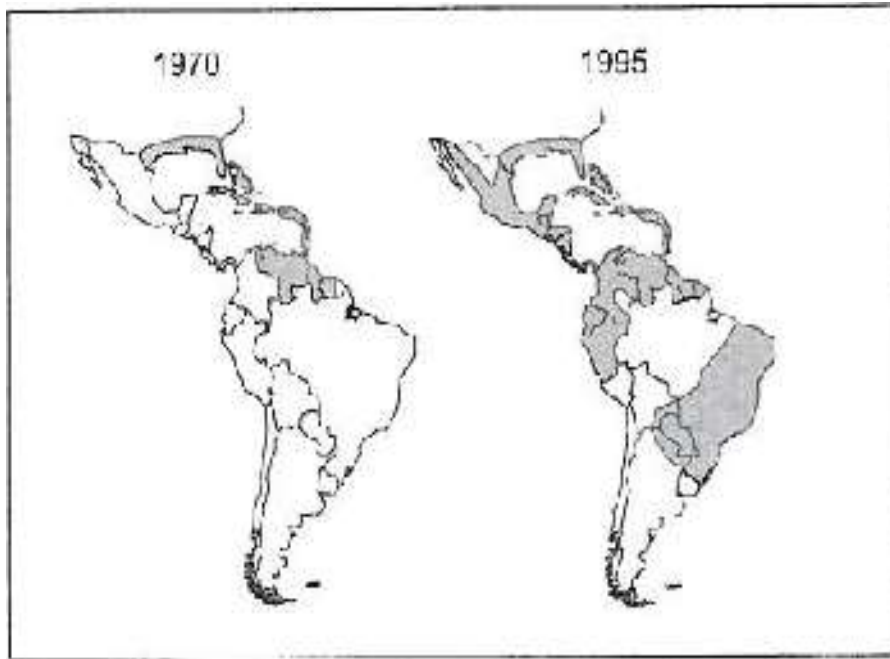


Figure 1. Distribution of *Aedes aegypti* (shaded areas) in the Americas in 1970, at the end of the mosquito eradication program, and in 1995.

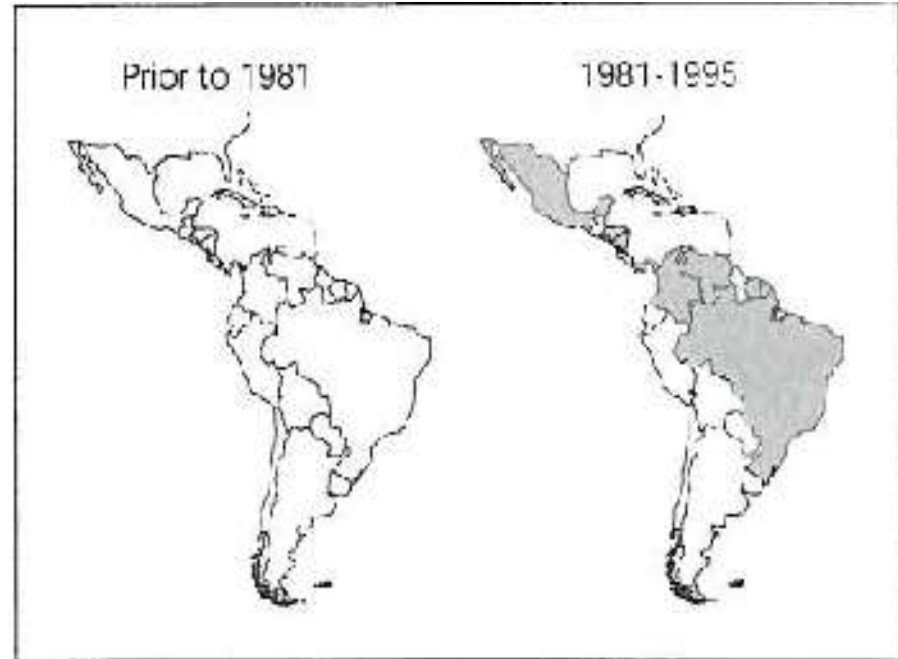


Figure 2. American countries with laboratory-confirmed hemorrhagic fever (shaded areas), prior to 1981 and from 1981 to 1995.

Amazonas registra primeiro caso de dengue tipo 4 no Estado

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Mais de 26 mil casos de dengue são registrados em 2011



Opportunities for Dengue Control

- Decrease Mosquito Population/Bites
 - Remove breeding sites
 - Window screens, etc.
- Vaccine

Dengue Vaccines

- Virology: Four serotypes
- Candidate vaccines in development
- Butantan vaccine
 - Production
 - Clinical testing
- Conclusions

Four Dengue Virus Serotypes

- Each serotype provides specific lifetime immunity, and short-term cross- immunity
- All serotypes can cause severe and fatal disease

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Late Stage Dengue Vaccines

<u>Company</u>	<u>Phase</u>	<u>Study site(s)</u>	<u>Expected Licensure</u>
Sanofi	IIB/III	Thailand	? 2015
Butantan	I	Brazil	? 2016
Inviragen	I	US/Columbia	?

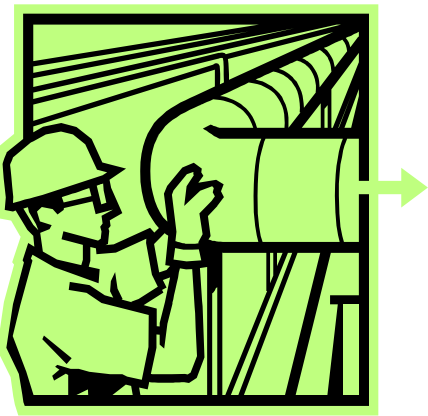
NIAID Candidate Vaccine



Lessons learned from other flavivirus vaccines

Virus	Existing vaccine?	Serotypes
Yellow fever	Yes	1
Japanese encephalitis	Yes	1
West Nile	Yes (veterinary)	1
Tick-borne encephalitis	Yes	1
Dengue	No	4

Development of a four component dengue vaccine is as much work as developing the previous four flavivirus vaccines!



Development of the NIAID Dengue Vaccine

1. Identify attenuated vaccine candidates
2. Preclinical testing:
 - Genome sequence
 - Attenuated replication in suckling mice brain
 - Attenuated replication in Huh-7 SCID mice
 - Attenuated replication in rhesus macaques
 - Restricted infectivity / replication in mosquitoes
3. Manufacture safety tested lot in Vero cells
4. Prepare IND application
5. Phase I / II testing in human subjects
 - monovalent
 - tetravalent
6. Licensure to industry

Human Studies in the US

Summary of U.S. Clinical Trials

	<u>DEN1</u>	<u>DEN2</u>	<u>DEN3</u>	<u>DEN4</u>	<u>Total</u>
Number of Studies	3	3	3	5	17
Formulations	1	1	3	2	7
Volunteers	114	71	112	183	480

Licensing partners of NIH Vaccine

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

Instituto Butantan, Sao Paulo



- Founded in 1901
- Largest producer of vaccines in Latin America
 - 150 million doses/yr
- Research and Development
 - rotavirus
 - dengue
 - pertussis-MPLA



leptospirosis
influenza
rabies-VERO cell

Butantan Dengue Vaccine

Initially Developed at US NIH

Licensed to Butantan	2007
Production studies (NIH vaccine)	2010
Butantan production (DEN1,2 and 4)	2010
(DEN 3)	2011
ANVISA approval for Phase I (expected)	Nov 2011
Phase 1 (100 volunteers) plan to start	Dec 2011

Advancing to Licensure

<u>Phase of Testing</u>	<u>Primary Measurements</u>
Phase I	Safety
Phase II	Safety and immune response
Phase III	Protection

Phase I Testing in Brazil

Expected Start: Dec 2011

- Vaccine: rDEN1 Δ 30, rDEN2/4 Δ 30, **rDEN3 Δ 30/31**, rDEN4 Δ 30
- Volunteers: 100 (80 vaccine, 20 placebo)
- Doses: Two doses, 6 months apart
- Endpoints: Safety, immunogenicity

Safety Issues with Dengue Vaccines

- Adequate attenuation: ? Side effects
- With viremia: ? Transmission to others
- If incomplete immunity: ? possible enhanced disease upon re-exposure.

Conclusions

- Dengue a huge and increasing public health problem
- Several candidate vaccine in pipeline
- Butantan leading the way
- First efficacy trial soon
- Optimism for a vaccine

V

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