School of Medicine
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Arbovirus vaccines: Dengue, Zika vaccines - Advances and challenges.

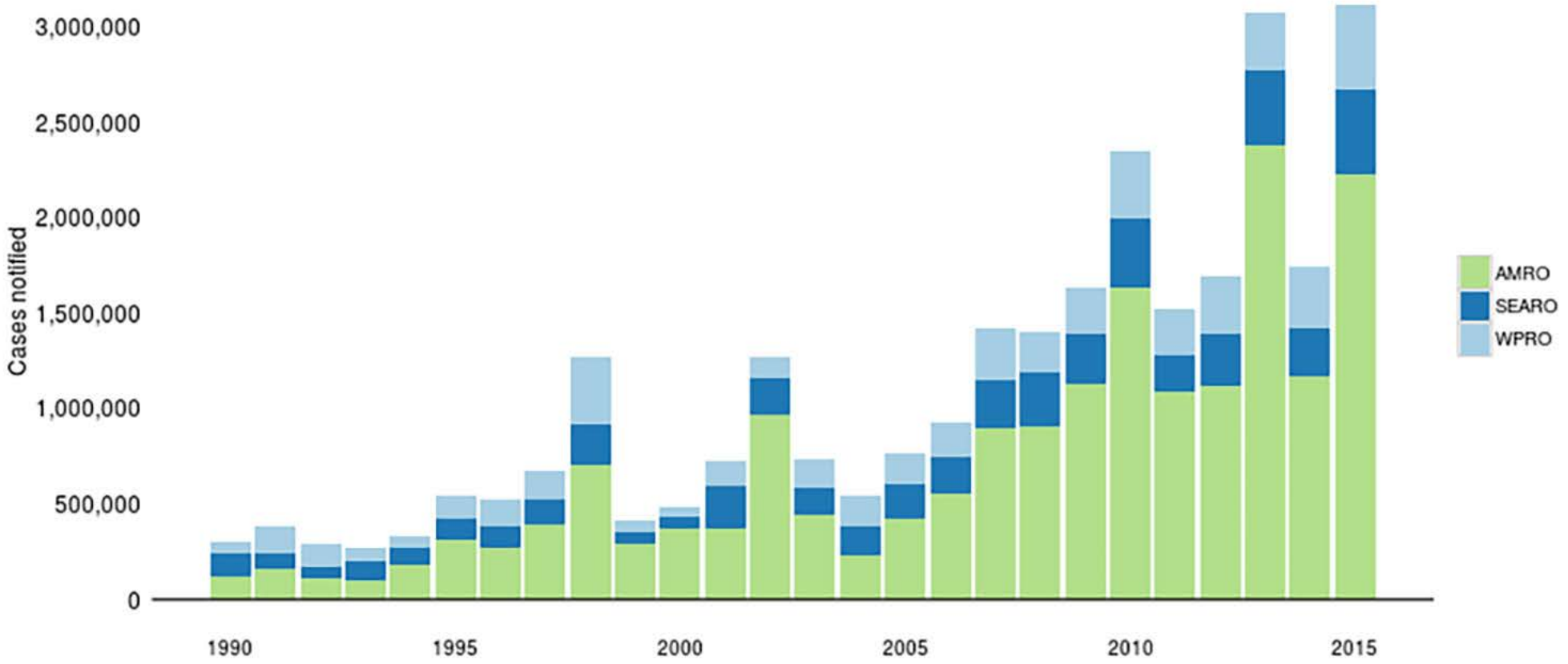
Edwin J. Asturias MD

Associate Professor of Pediatrics and
Pediatric Infectious Diseases

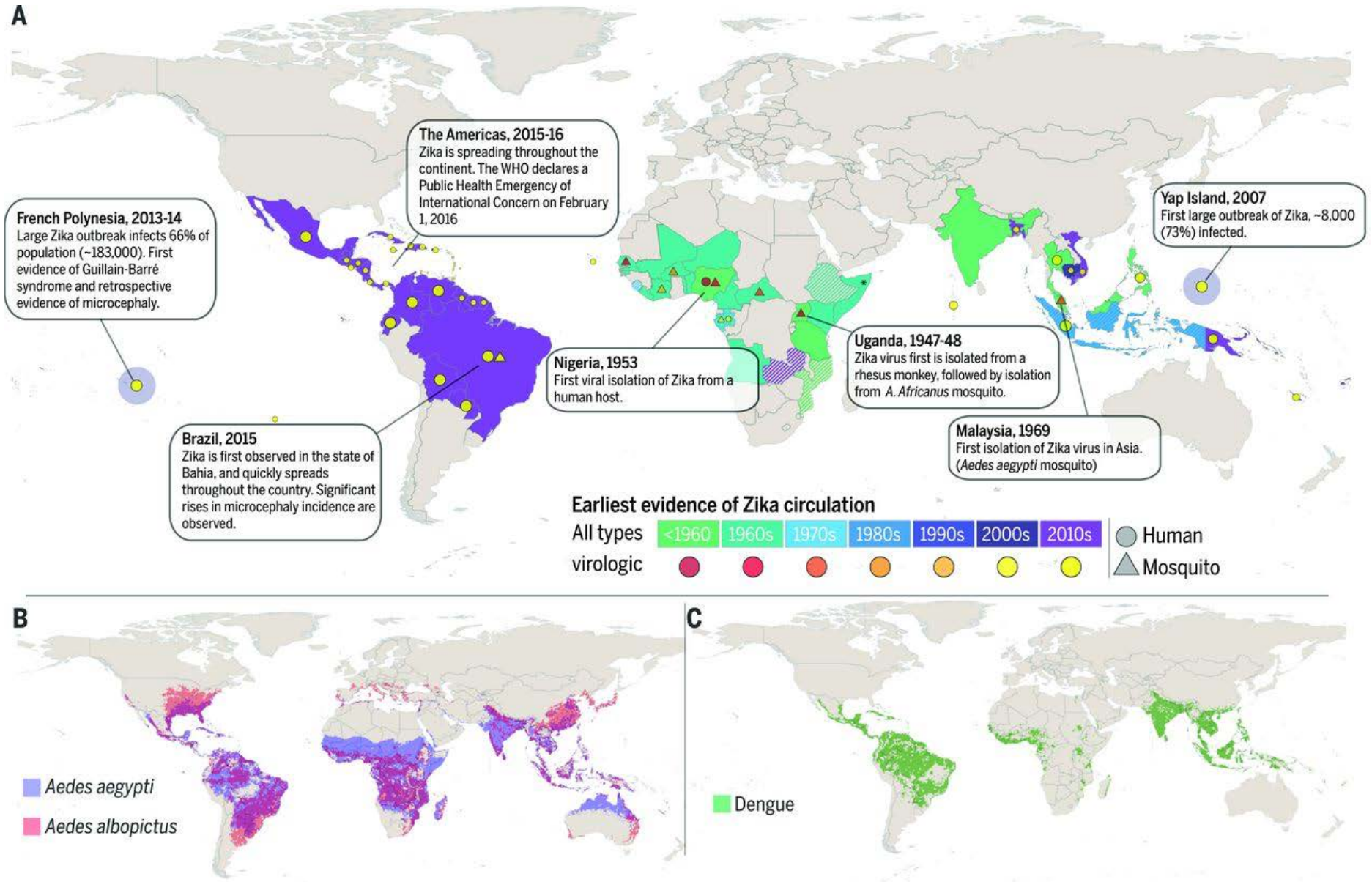
Director for Latin America

Dengue: the most common arboviral infection worldwide

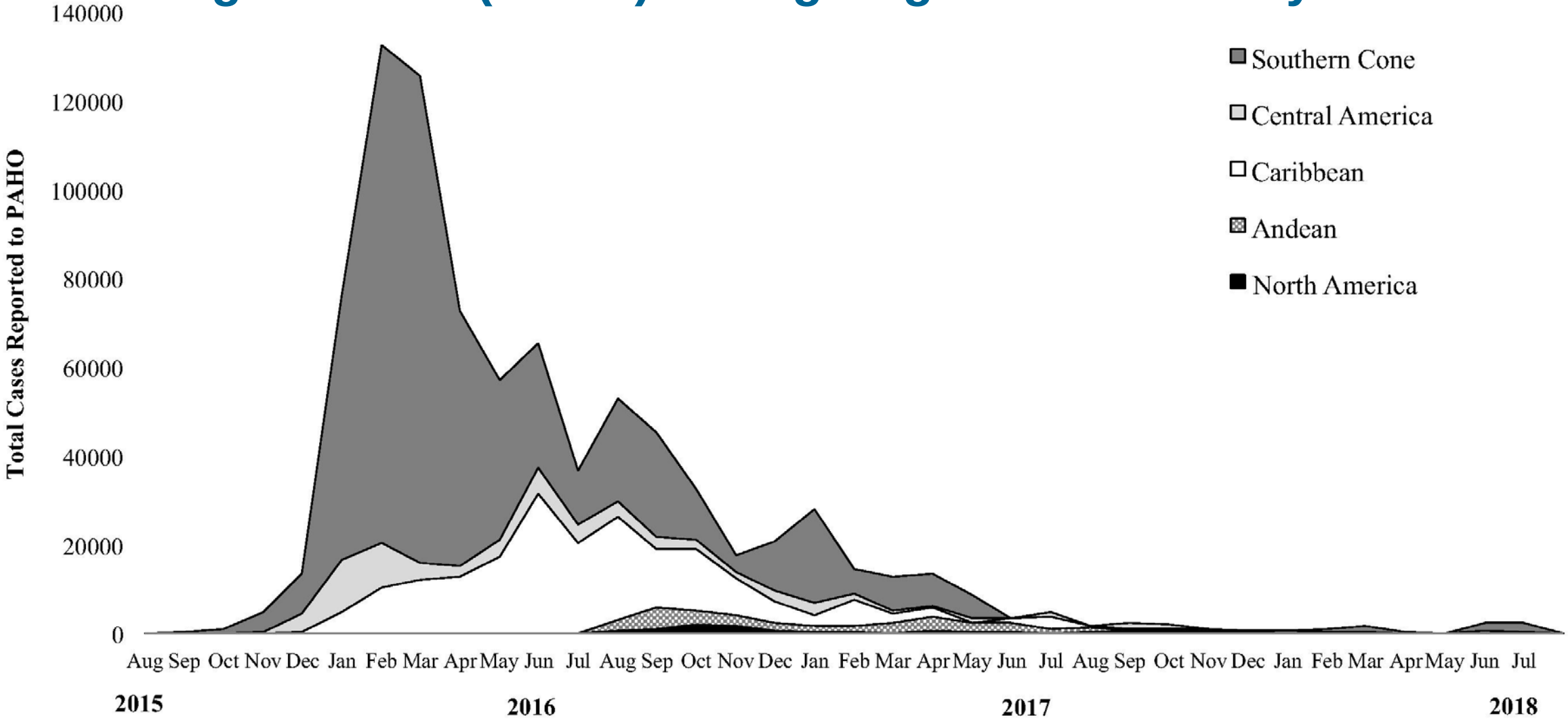
- **390 million dengue infections per year**
- 96 million (67–136 million) manifest **clinically**
- **75%** reduction in 2016



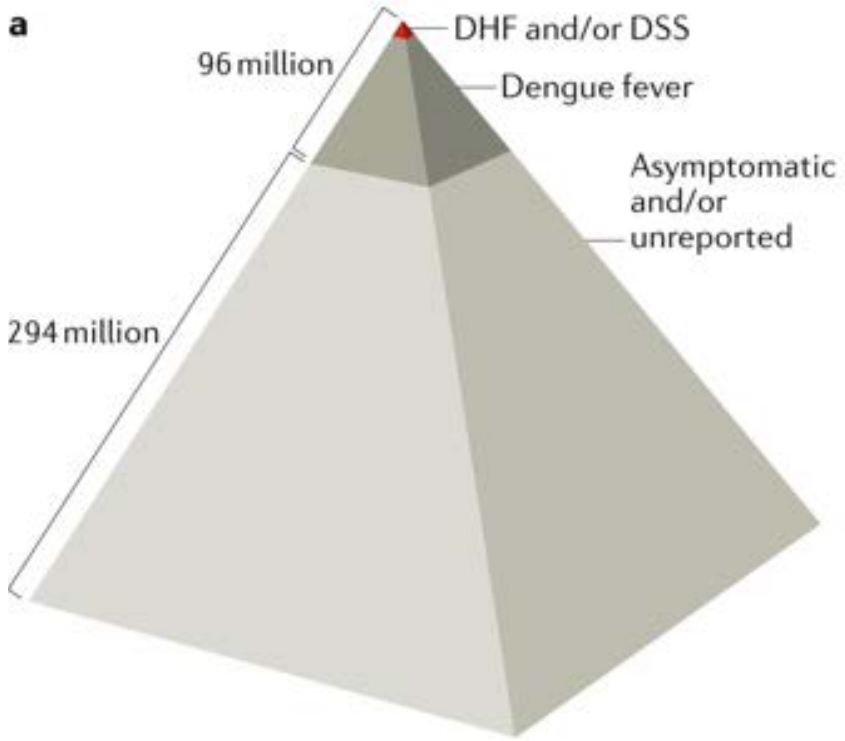
Zika infection and outbreaks 1947-2017



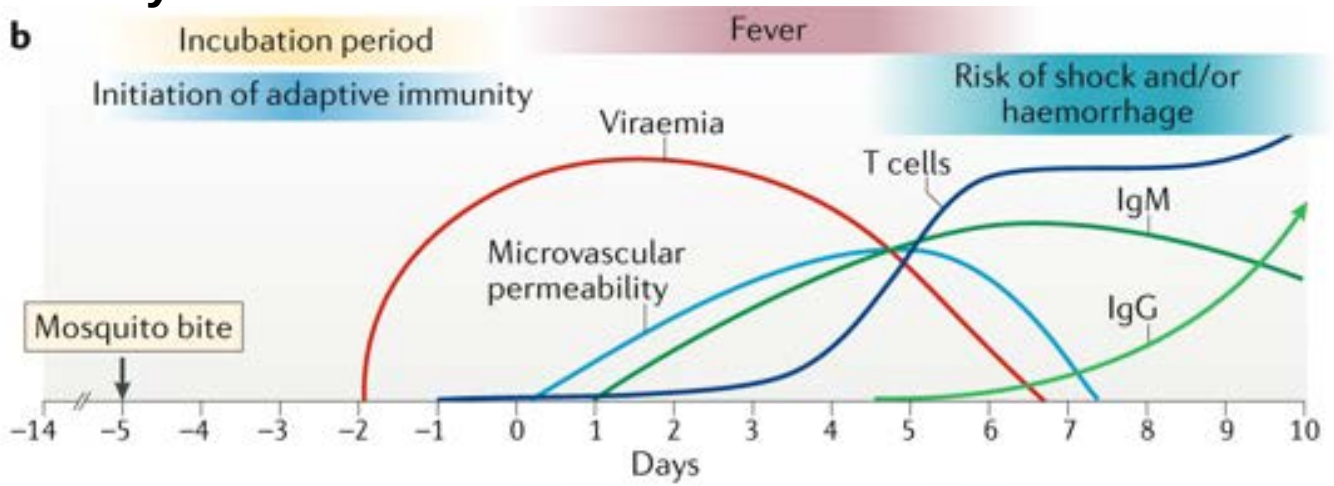
Monthly Zika illness case counts reported to the Pan American Health Organization (PAHO) during August 2015 to July 2018

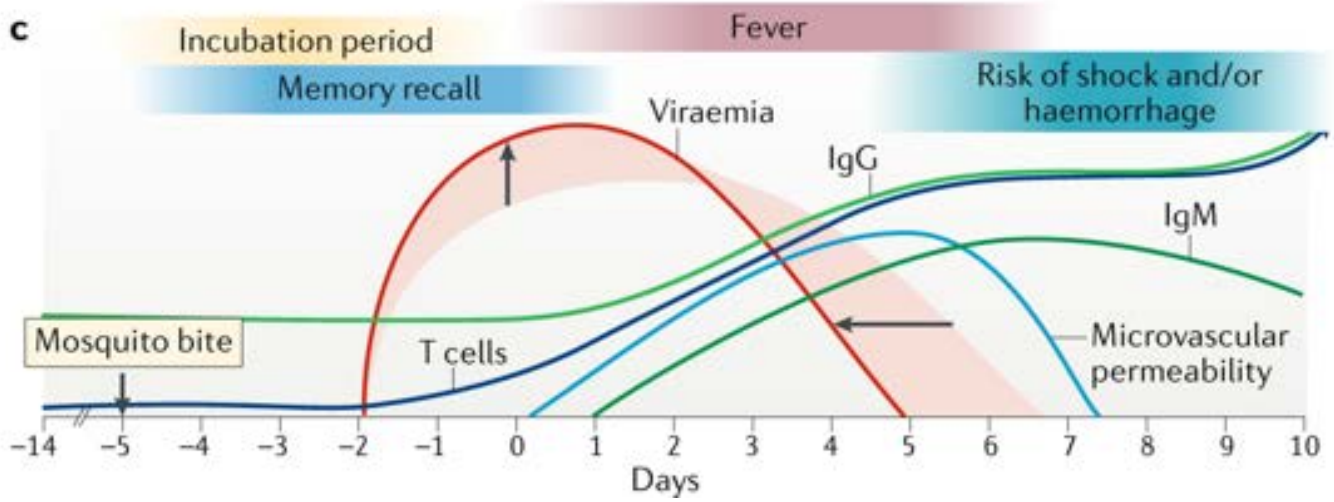


Dengue and its adaptive immunity



Primary DENV infection

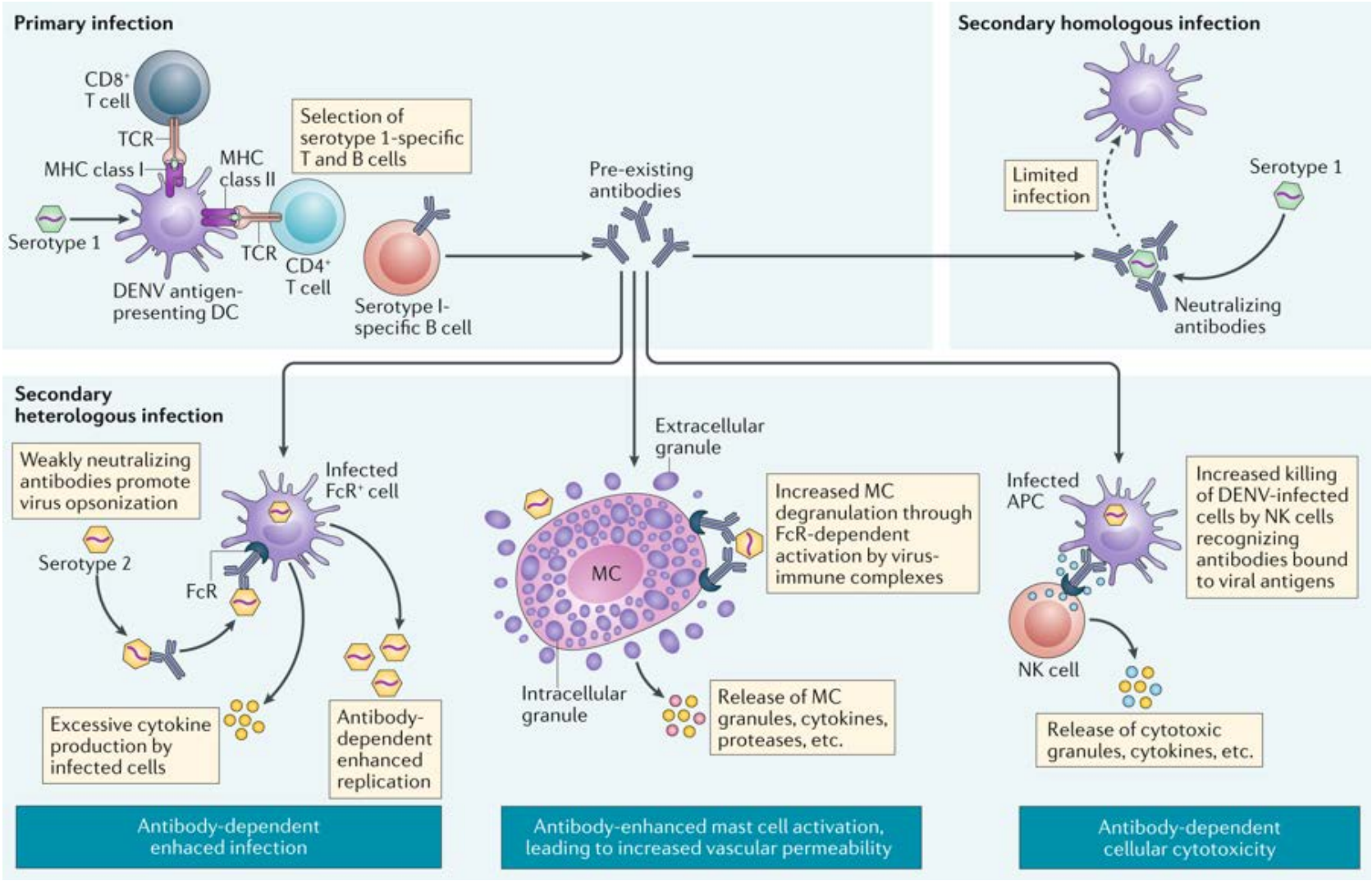




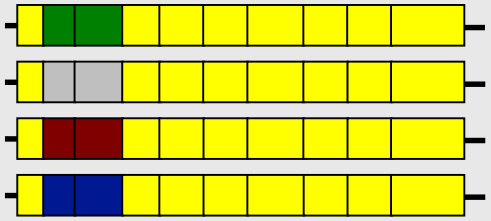
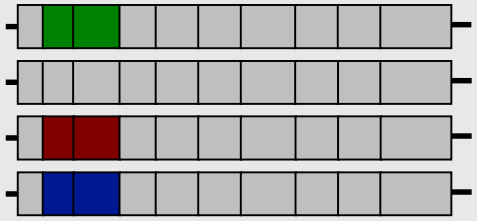
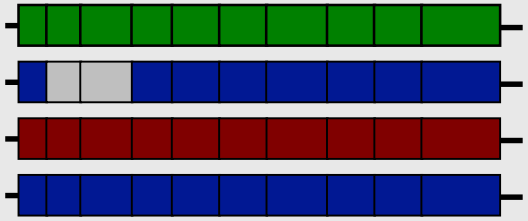
Secondary heterologous DENV infection

Dengue: critical issues for vaccine development

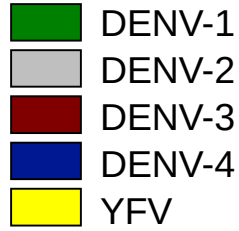
- Four DENV serotypes all capable of causing the full spectrum of disease (***need for a tetravalent vaccine***)
- Life-long **homotypic protection** afforded after infection but only short term (few months) heterotypic protection is afforded
- ***Secondary infection with a different serotype is strongly associated with severe disease***



Current Live attenuated dengue vaccines

	Dengvaxia (Sanofi Pasteur)	TDV (Takeda)	TV003 (NIH/Butantan)
Status	Licensed	Phase 3	Phase 3
# Doses	3 doses over 12 months (0, 6, 12)	2 doses (0, 3 months)	Single dose
Indicated age	9 - 45	Phase 3 age range 4 - <16[1]	Phase 3 age range 2 - 59[2]
Other	Seropositive to dengue	?	?
Construct			

1. NCT02747927
2. NCT02406729



Courtesy of Anna Durbin, JHSPH

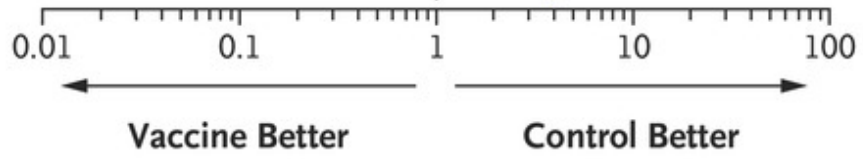
Efficacy[1] of CYD-TDV

Trial	Region	Vaccine recipients enrolled	Age	Overall Efficacy (95% CI)	Efficacy, hospitalization	Efficacy, severe disease
CYD23[2]	Thailand	2,669	4-11	**30.2 (-13.4-56.6)**	Not reported	Not reported
CYD14[3]	SE Asia	6,851	2-14	56.5 (43.8-66.4)	**67%**	**80%**
CYD15[4]	Latin America	13,920	9-16	60.8 (52.0-68.0)	**80%**	**91.7%**

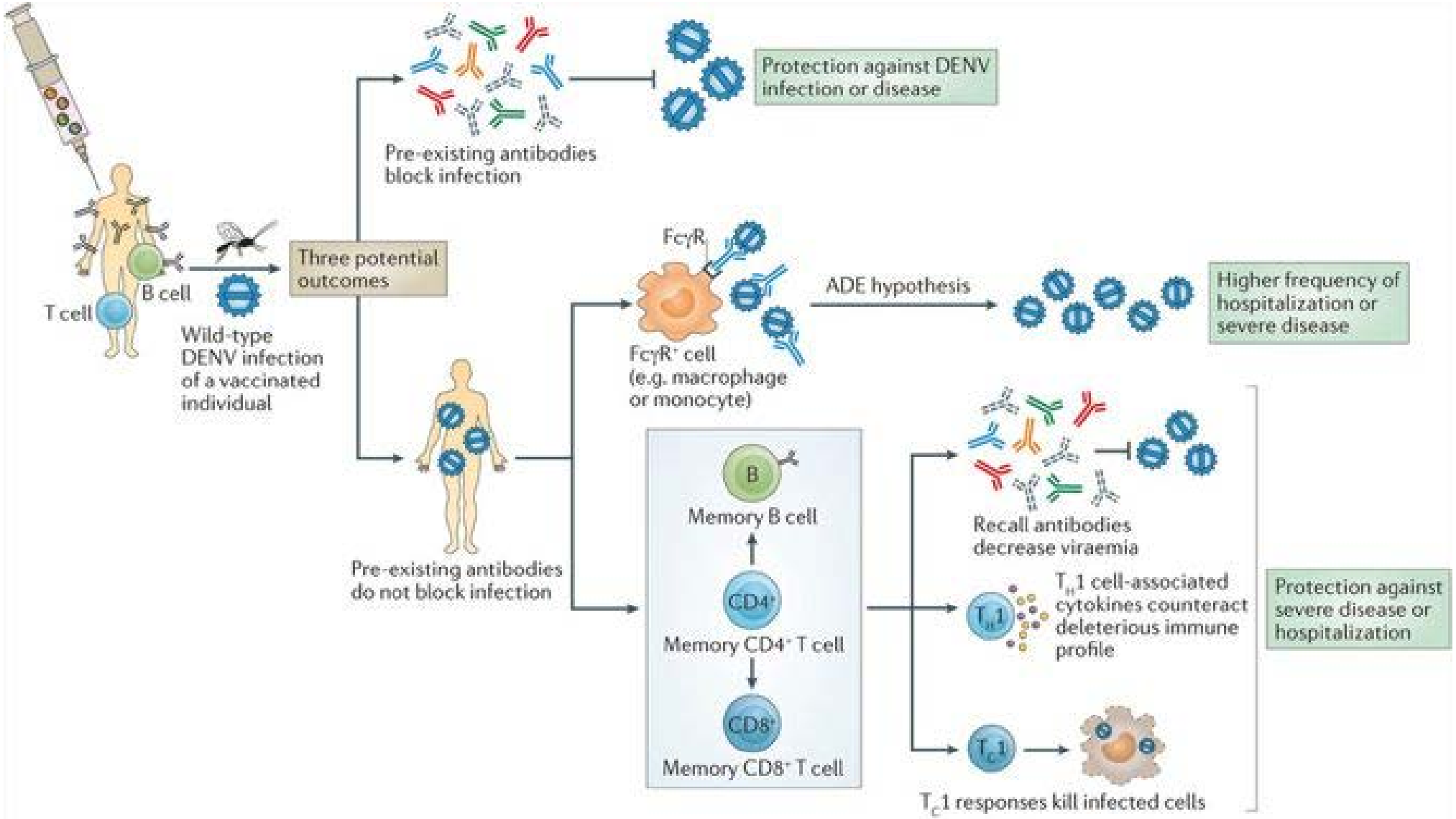
1. Per protocol analysis. Period of primary efficacy evaluation was > 28 days after the third dose to month 25 (12 month period)
2. Sabchareon, The Lancet, 2012
3. Capeding et al, The Lancet, 2014
4. Villar et al, NEJM, 2014

Risk of Hospitalization for confirmed Dengue and of Severe VCD in subjects 2 to 16 Years of Age in Asia and Latin America (Dengvaxia Phase III)

Serostatus, End Point, and Method	Vaccine Group	Control Group	Relative Risk or Hazard Ratio (95% CI)
	no./total no.		
Seropositive			
Hospitalization for VCD			
MI, month 0 onward	152.4/1816.1	227.5/886.2	0.32 (0.23–0.45)
TMLE, month 0 onward	99.2/1742.3	199.5/846.7	0.25 (0.12–0.53)
NS1, T9, month 13 onward	124/1750	175/822	0.34 (0.26–0.43)
Severe VCD			
MI, month 0 onward	35.1/1816.1	53.4/886.2	0.31 (0.17–0.58)
TMLE, month 0 onward	28.2/1742.3	49.9/846.7	0.27 (0.15–0.48)
NS1, T9, month 13 onward	31/1750	44/822	0.33 (0.21–0.53)
Seronegative			
Hospitalization for VCD			
MI, month 0 onward	201.6/567.9	62.5/307.8	1.75 (1.14–2.70)
TMLE, month 0 onward	244.0/547.2	65.5/296.8	2.10 (0.94–4.70)
NS1, T9, month 13 onward	187/512	53/272	1.89 (1.35–2.65)
Severe VCD			
MI, month 0 onward	44.9/567.9	8.6/307.8	2.87 (1.09–7.61)
TMLE, month 0 onward	44.6/547.2	9.3/296.8	2.62 (1.03–6.70)
NS1, T9, month 13 onward	37/512	5/272	3.93 (1.53–10.10)



Sridhar S. N Engl J Med 2018; 379:327-340



The Dengvaxia Sanofi vaccine ”safety issue”

Nature Reviews | Microbiology

Updated SAGE-WHO review of Dengvaxia

- Overall population level benefit of vaccination remains favorable, ***but the vaccine performs differently in seropositive versus seronegative individuals***.
- There is an increased risk of hospitalized and severe dengue in seronegative individuals starting about 30 months after the first dose.
- In areas of 70% dengue seroprevalence, over a 5-year follow-up:
  - For every **4 severe cases prevented** in seropositive, there would be **one excess severe case in seronegative per 1,000 vaccinees**;
  - For every **13 hospitalizations** prevented in seropositive vaccinees, there would be **1 excess hospitalization in seronegative** vaccinees per 1,000 vaccinees.

TDV summary (Takeda vaccine)

- Similar GMTs achieved with different regimens
- Better multi-valent seroconversion frequencies with 2 dose regimen in dengue-naïve
- RR of dengue = 0.29 in those who received TDV compared with placebo
- Current formulation in Phase 3 clinical trial in Asia and Latin America (dosing: 0 & 3 months)

	Total 1794	Grp 1 n=200	Grp 2 n=398	Grp 3 N=998	Grp 4 N=198
Confirmed dengue cases	**30**	4	3	14	9
Serotype recovered					
	DEN-1	DEN-2	DEN-3	DEN-4	Unk
# cases	10	11	5	3	1

All participants were monitored for episodes of febrile illness throughout the study. Within 5 days of fever or febrile illness suspected to be due to dengue infection, blood samples were collected and analyzed for the presence of dengue by RT-PCR or NS1 ELISA

Saez-Llorens Lancet ID 2017

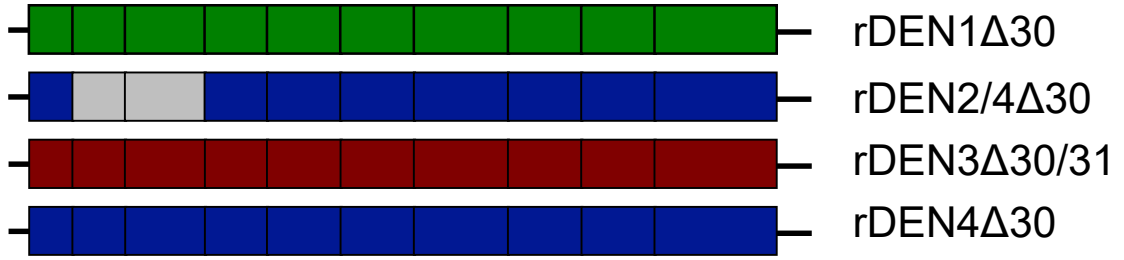
Takeda's Dengue Vaccine Candidate Meets Primary Endpoint in Pivotal Phase 3 Efficacy Trial

January 29, 2019

Cambridge, Mass., and Osaka, Japan, January 29, 2019 – Takeda Pharmaceutical Company Limited [**TSE:4502 / NYSE:TAK**] ("Takeda") today announced that the **pivotal Phase 3 trial of its dengue vaccine candidate met the primary efficacy endpoint.** This first analysis of the **Tetravalent Immunization against Dengue Efficacy Study (TIDES)** trial showed that the company's investigational live-attenuated tetravalent dengue vaccine (TAK-003) was efficacious in preventing dengue fever caused by any of the four serotypes of the virus.

TV003/TV005 – NIH/Butantan vaccine

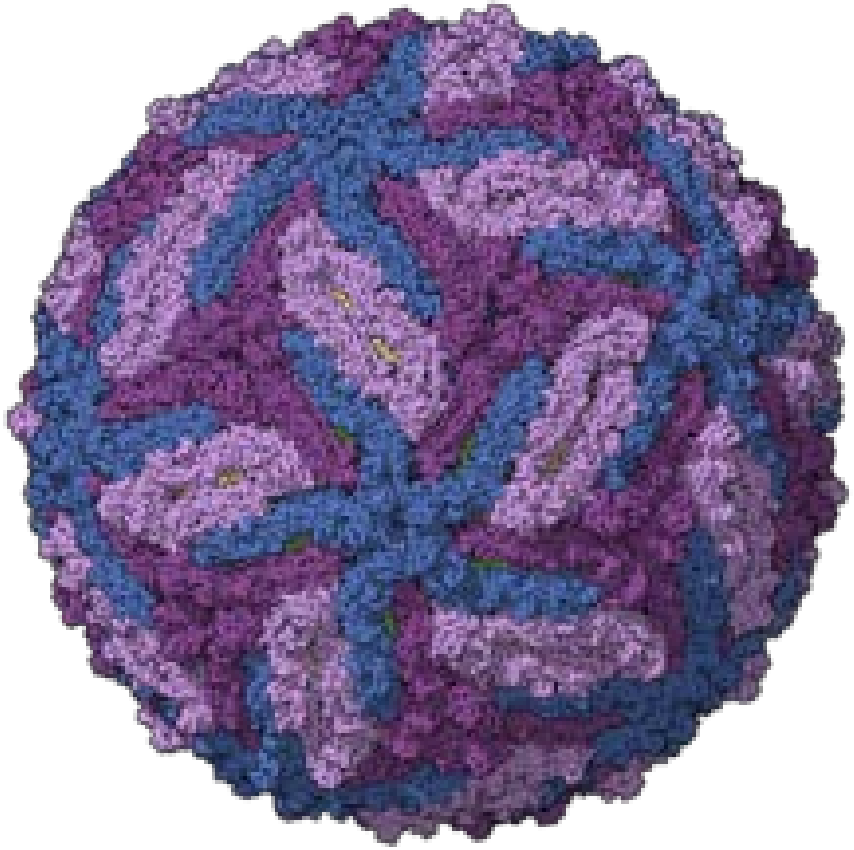
- Attenuated by deletions in 3´ UTR (3 components) and chimerization (1 component)
  - Contains 32 dengue proteins
- TV003 contains 3 $\log_{10}$ PFU of each monovalent component, TV005 contains a 10-fold higher dose of rDEN2/4Δ30
- Asymptomatic rash most common vaccine-associated adverse event (correlated with tetravalent antibody response)
- Viremia detected in ~65% vaccinees (all 4 components detected)
  - HID_{50} of each component is ≤ 10 PFU

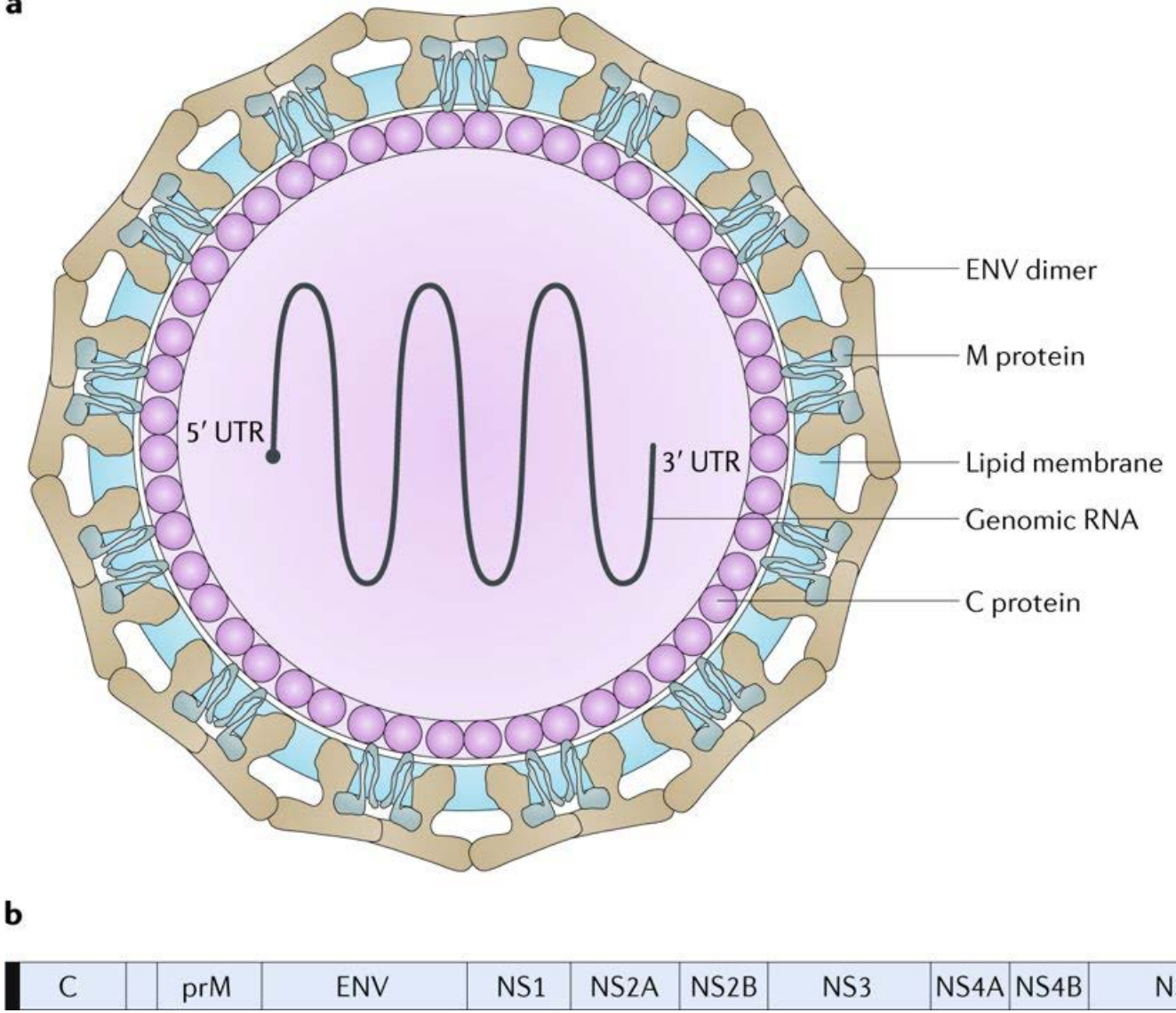


Current status and challenges of Dengue vaccines

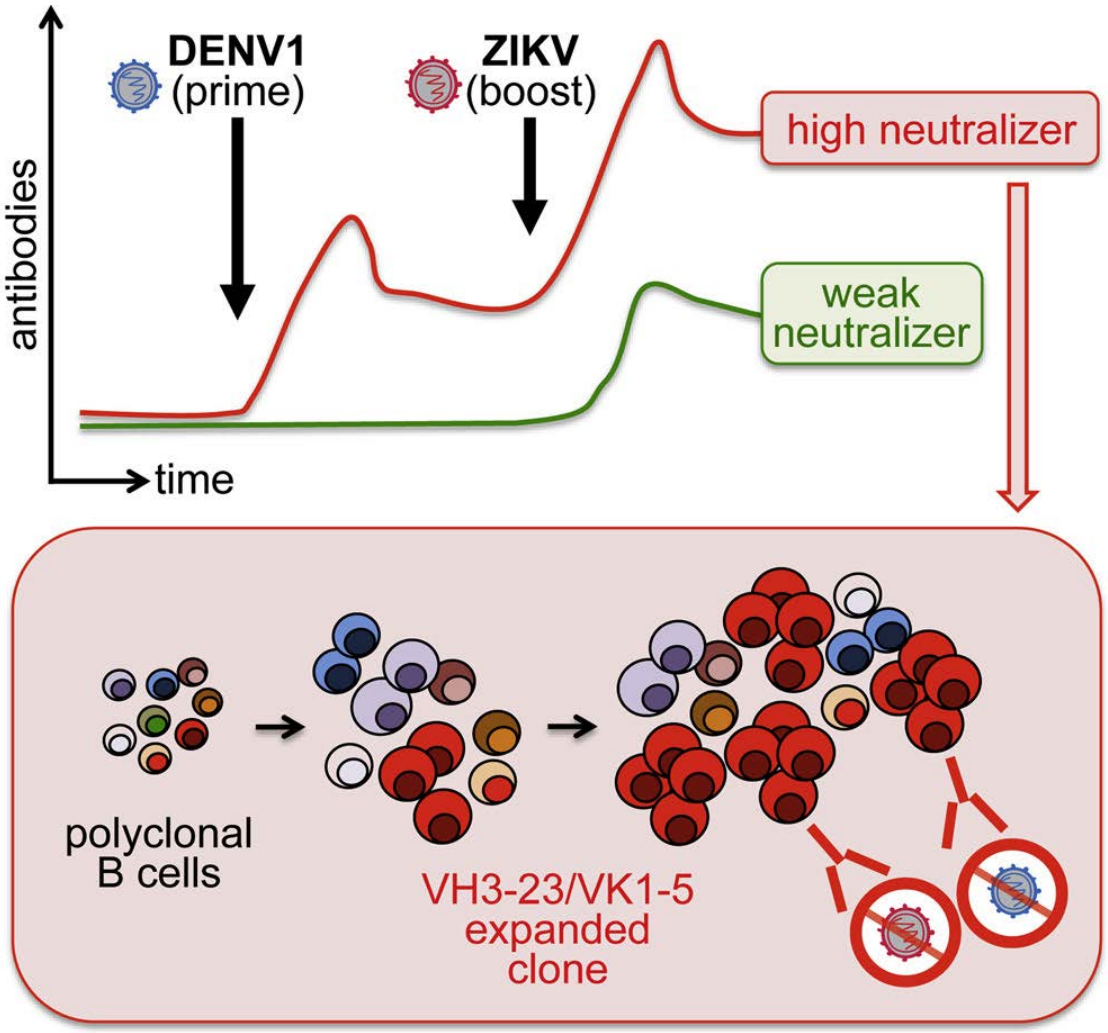
- Dengvaxia just approved by FDA – ACIP to discuss its use in endemic US territories
- First vaccine to potentially need a **rapid diagnostic test** before administration (major challenge ahead)
- Takeda vaccine results to be denuded soon, will the **safety signal** be also an issue? Long term data needed
- NIH-Butantan - very low dengue incidence in Latin America 2017 & 2018 delaying efficacy results

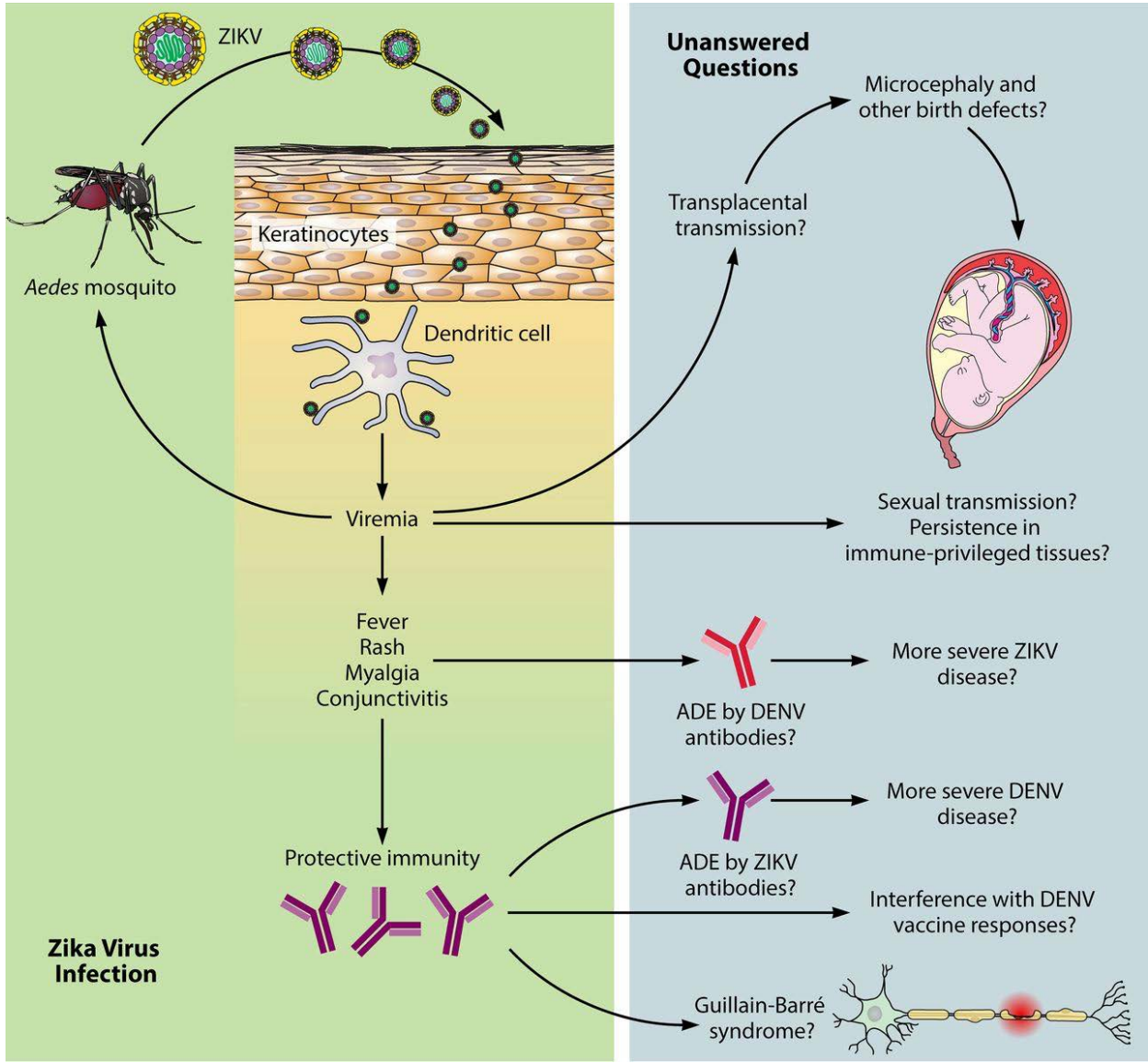
Zika virus structure[a]





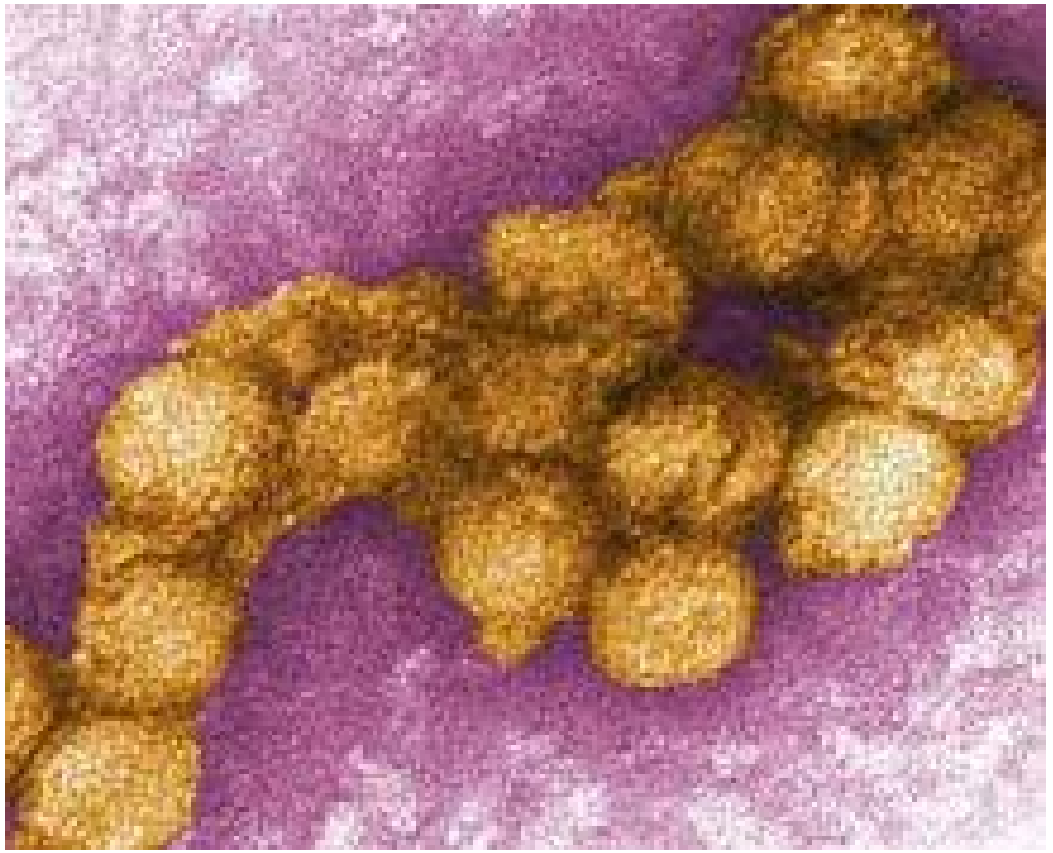
Zika immunity and dengue



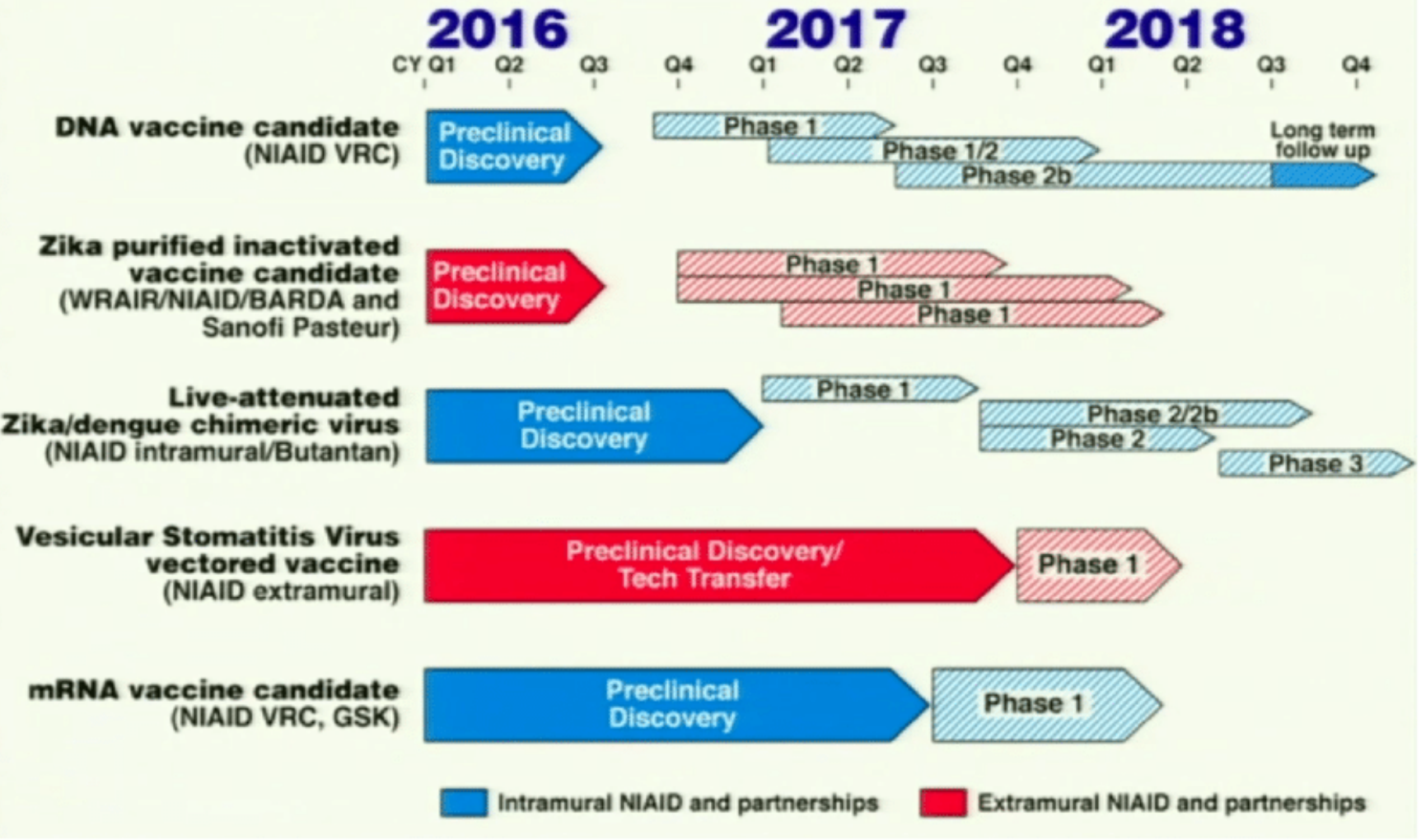


Experience with other Flavivirus Vaccines

- **Yellow Fever Vaccine *(live-attenuated)***
  - Effective against 7 genotypes
  - Protective titer ≥1:10
  - High efficacy rates
- **JEV and TBE Vaccines *(inactivated virus)***
  - Protective titer ≥1:10
  - High efficacy rates
- **Dengue Vaccines *(live recombinant and chimeric)***
  - Protective titer undefined
  - Variable efficacy
- **Investigational WNV vaccines**
  - Multiple platforms have been tested
  - Correlate of protection undefined
- **E protein is primary target for neutralizing antibody**



Zika Vaccine Development Timeline

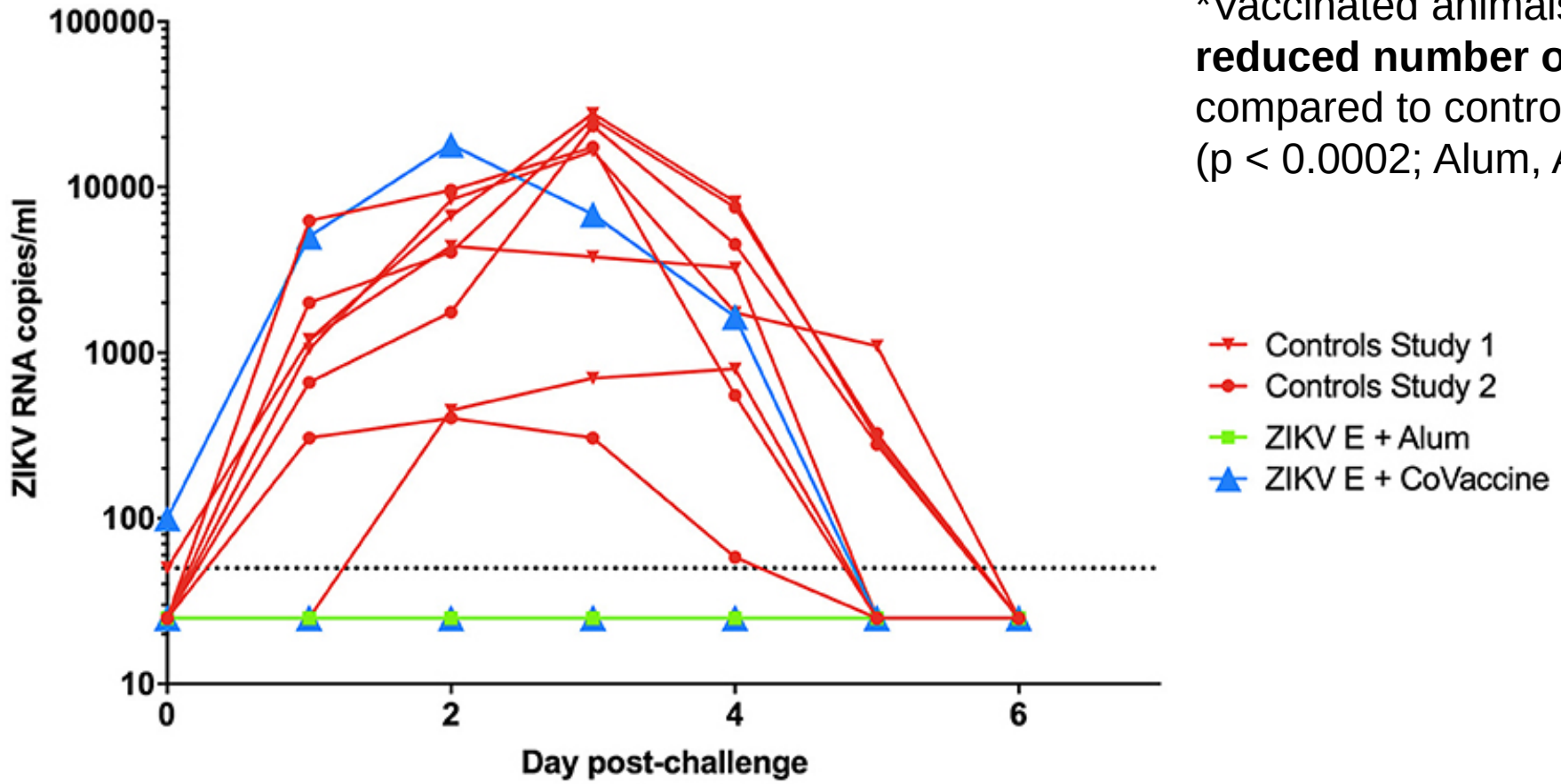


ZIKV Vaccine Evaluation

Concept	Vaccine	Antigens	Developer
Whole-inactivated virus	Formalin-inactivated	All	Takeda, Walter Reed, Sanofi Pasteur, Valneva
Replicating virus	Chimeric Dengue	prM-E	NIAID
	Live-attenuated	All	UTMB by mutation, Codagenix by codon-deoptimization
	Chimeric Yellow Fever	prM-E	Sanofi Pasteur
Nucleic acid Gene delivery	DNA plasmids	M-E	Beth Israel
	DNA plasmids	prM-E	NIAID, Inovio
	mRNA	prM-E	Moderna, UPenn
	Self-amplifying RNA	prM-E	GlaxoSmithKline
Vector Gene delivery	VSV Vector	prM-E	Harvard
	Adenovirus Vector	M-E	Beth Israel (J&J)
	Measles Vector	prM-E	Institut Pasteur (with Themis)

Vaccine	Antigen	Induction of NAbs	Short-term protection in mice	Immunocompetence	Short-term protection in monkeys	Long-term protection in monkeys	Advanced to clinical trial	Refs
ZPIV	NA	Yes	Yes	Competent	100%	79%	Phase I	66,67,– 68
DNA	prM-ENV	Yes	Yes	Competent	100%	29%	Phase II	66,67,68,–69
Ad	prM-ENV	Yes	Yes	Competent	100%	100%	Phase I	67, 68, 70
				Competent/ deficient				
mRNA	prM-ENV	Yes	Yes	Competent/ deficient	100%	NR	Phase I/II	53, 54
				Competent				
MVA	NS1	Yes	Yes	Competent	NR	NR	Phase I	72
MV	prM-ENV	Yes	NR	NR	NR	NR	Phase I	59
ZIKV-LAV	NA	Yes	Yes	Competent	NR	NR	NA	73,74,– 75
				Deficient				
				Competent/ deficient				

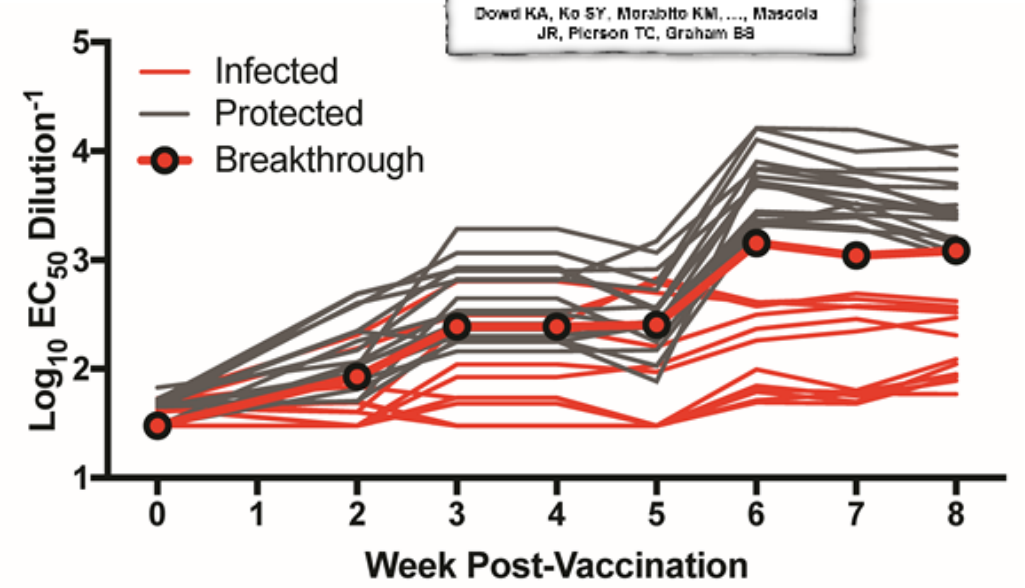
Viremia in vaccinated and control cynomolgus macaques challenged with ZIKV



*Vaccinated animals had a significantly **reduced number of viremic days** compared to control animals ($p < 0.0002$; Alum, Alhydrogel® 85).

Medina LO et al Front. Immunol., 2018 | https://doi.org/10.3389/fimmu.2018.02464

ZIKV DNA Vaccine-Induced Antibody and Protection



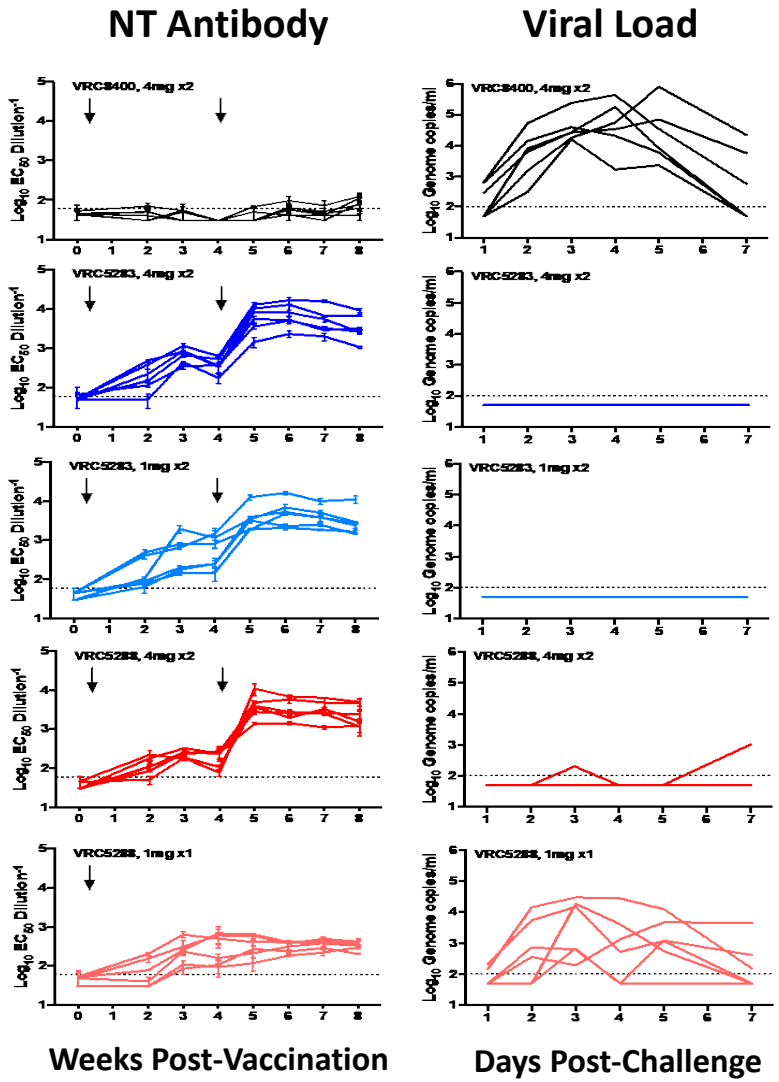
VRC8400 control

VRC5283 4mg X2

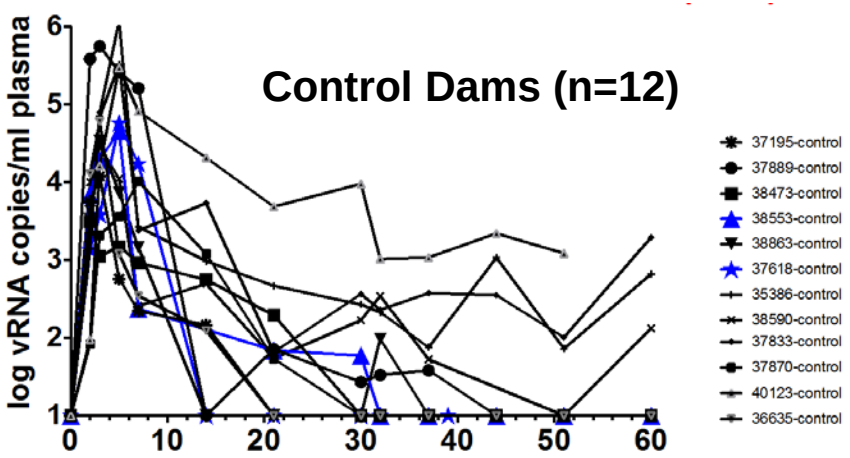
VRC5283 1mg X2

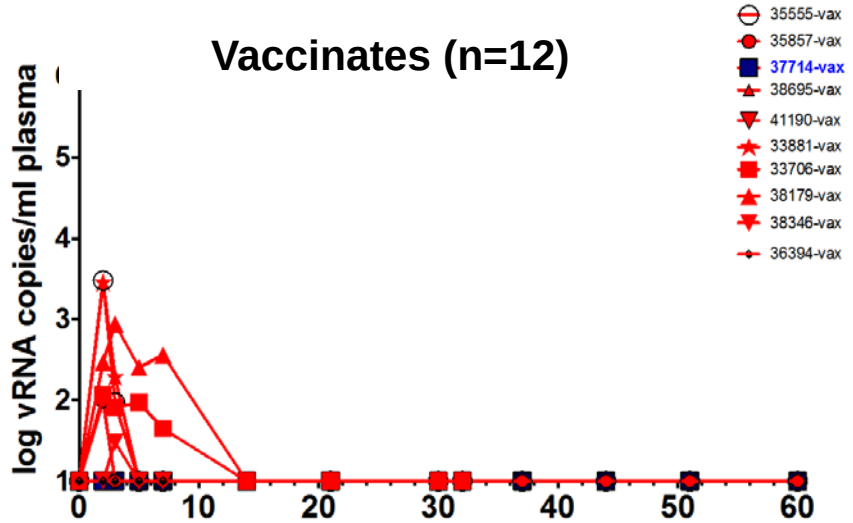
VRC5288 4mg X2

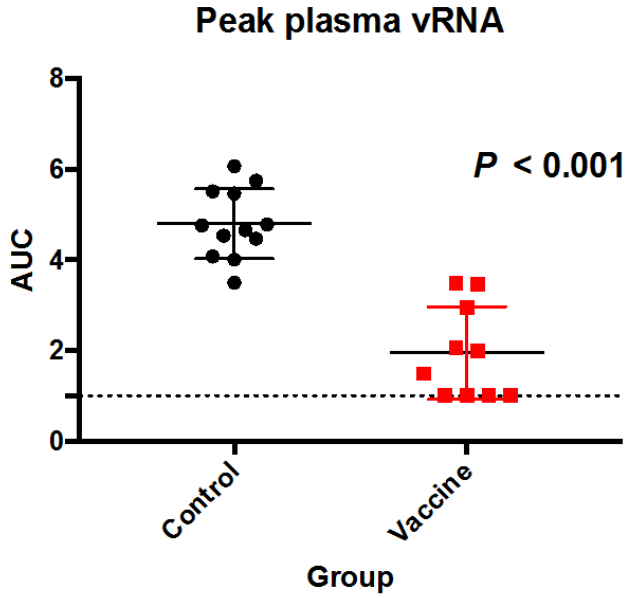
VRC5288 1mg X1

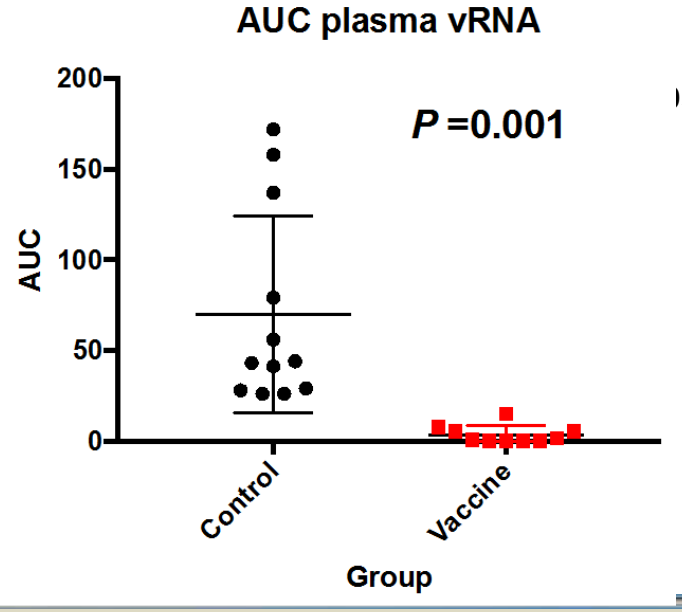


Plasma viremia after challenge at gestational day 30









ost-Challenge

Data from
Koen Von Rompay
UC Davis

ZIKV DNA Vaccine Development

2013 2014 2015 2016 2017

Zika Virus Outbreak ?

2013 - 2014
Zika virus outbreak French Polynesia

May 2015
1st reports of Zika infection in Brazil

Feb 2016
Zika virus spread to over 20 countries in Western hemisphere

Feb 10, 2016
Pre-IND

Apr 24, 2016
DNA Vaccine Sequence Selected

July 2016
Product Release

July 21, 2016
IND Submission

Aug 2, 2016
First vaccination VRC 319 (Phase 1)

Dec 12, 2016
First vaccination VRC 320 (Phase 1)

July 2015
Alerted to Zika problem (doenca misteriosa) by Brazilian physician

Dec 2015
Reagents designed to explore potential for Zika vaccine development

Jan 2016
Initial ZIKV constructs received

May 23, 2016
IRB Review

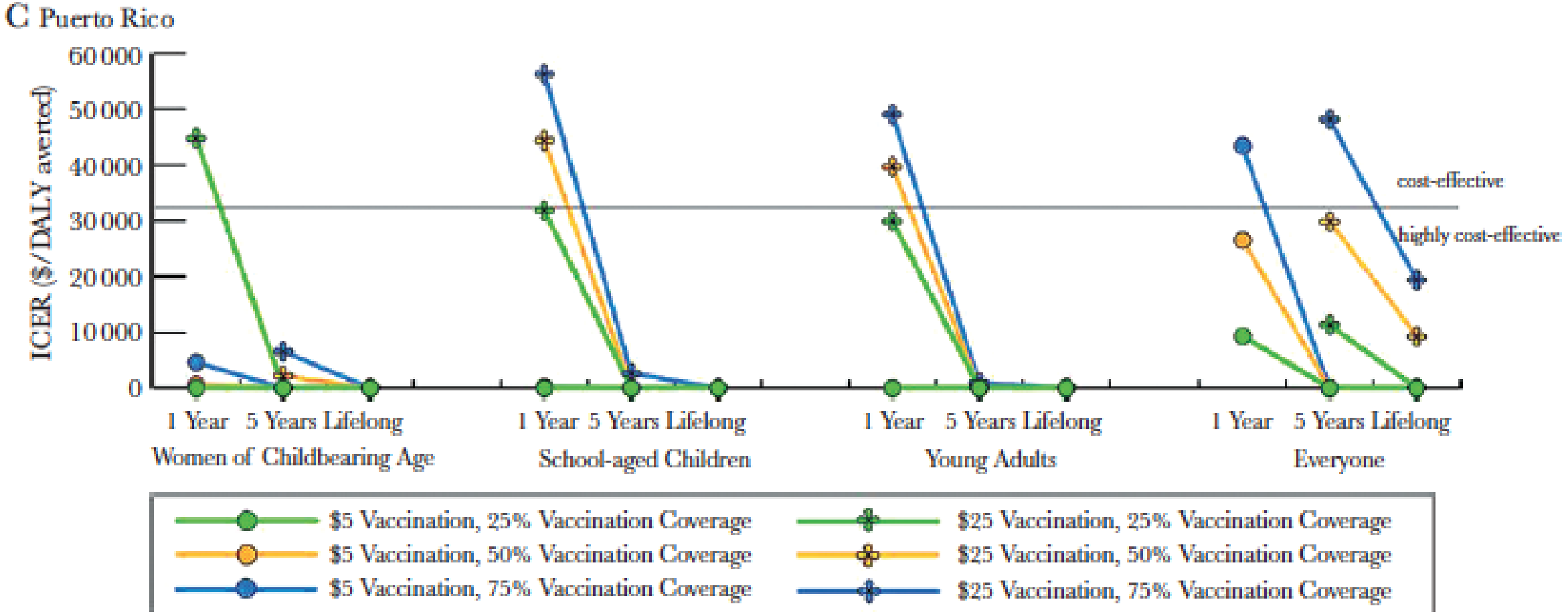
June 2016
Drug Product Manufacturing

Oct 14, 2016
Preclinical data published

Mar 30, 2017
First vaccination In Phase 2a/2b

Projected Date

Estimated cost-effectiveness of a Zika vaccine according to target populations



Challenges ahead for Zika vaccines

- **Neutralizing antibodies** are likely to be an important immune marker of protection;
- WHO **standardization and validation of assays** are critical for appropriate assessment of the immune response to Zika vaccine
- **Passive transfer studies** in animals showing protection against disease, infection, and CZS with human sera useful approximation
- **Clinical disease endpoint efficacy** studies may be challenging or even infeasible given the current epidemiology of ZIKV;
- **Post-licensure studies** will be required for all approved ZIKV vaccines: the specific studies will depend on the regulatory pathway, the indication, and vaccine characteristics.