A, B, C, D, E do Virus Zika
Fundação Oswaldo Cruz
Centro de Pesquisa Aggeu Magalhães

Research Resources of the U.S. National Institutes of Health in Addressing Zika Virus Disease and Microcephaly

David M. Morens, M.D.

Senior Advisor to the Director

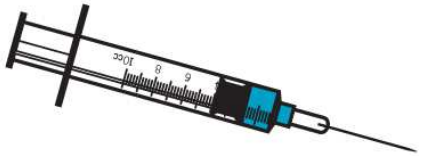
National Institute of Allergy and Infectious Diseases

National Institutes of Health

National Institute of Allergy and Infectious Diseases

NIAID Biomedical Research Response

- Epidemiology and Natural History
- Basic Research
- Research on Vector Control
- Diagnostics
- Countermeasures: Vaccines and Therapeutics

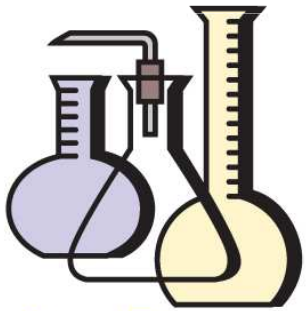


Vaccines

Therapeutics

Diagnostics

NIH Countermeasure Research and Development



Basic Research

Clinical Research

Resources for Researchers/ Industry to Advance Product Development

Biomedical Research Response: Epidemiology and Natural History

- Epidemiology and natural history
  - Symptomatic vs. asymptomatic
  - Frequency of sequelae
- Pathogenesis of microcephaly

EPIDEMIOLOGICAL STUDIES

EPIDEMIOLOGIC STUDIES

- 8 Clinical Trial sites in Brasil (NICHD)
- Prospective study in Brasil (Yale)
- Natural history population study in Nicaragua (UC Berkeley)
- Natural history population study in Brasil (U Alabama; UC Berkeley)
- Planned prospective maternal study (NICHD)

EPIDEMIOLOGIC STUDIES

- Transfusion recipient study (NHLBI)
- Zika pathogenesis in pregnant primates (U Wisconsin)
- Mouse model on Zika intrauterine infection (Utah State)
- Plan for Zika in Pregnancy clinical network in region; multiple sites (NIAID/NICHD)
- Mouse model (Wash U; CDC)

Biomedical Research Response: Diagnostics

- **CDC** – Diagnostic and Reference Laboratory in Arbovirus Diseases Branch
- RT-PCR assay for Zika, Dengue and Chikungunya
- Antibody assay for acute infection that will not cross-react with other flaviviruses

Biomedical Research Response: Vector Control

- Vector competence: Ability of mosquitoes other than *Aedes aegypti* to carry and transmit Zika virus
- Novel insecticides
- Novel vector control methods

DIAGNOSTICS/VECTOR CONTROL

Zika Diagnostics

- ELISA Development (LVD)
- Improved Nt Assay (LVD)
- Improved PCR probes (LID)
- Multiplex RT PCR
  (Columbia; UC Berkeley; MIT)
- New rapid gene coding (Columbia)
- Generation of Zika MAbs (Wash U; CDC)

Vector Control

- Wolbachia studies (corporate)
- vector competence/insecticide resistance (Yale)
- Insecticide/repellant research (UC Riverside)
- Larvacide-treated adult male mosquitoes (corporate)

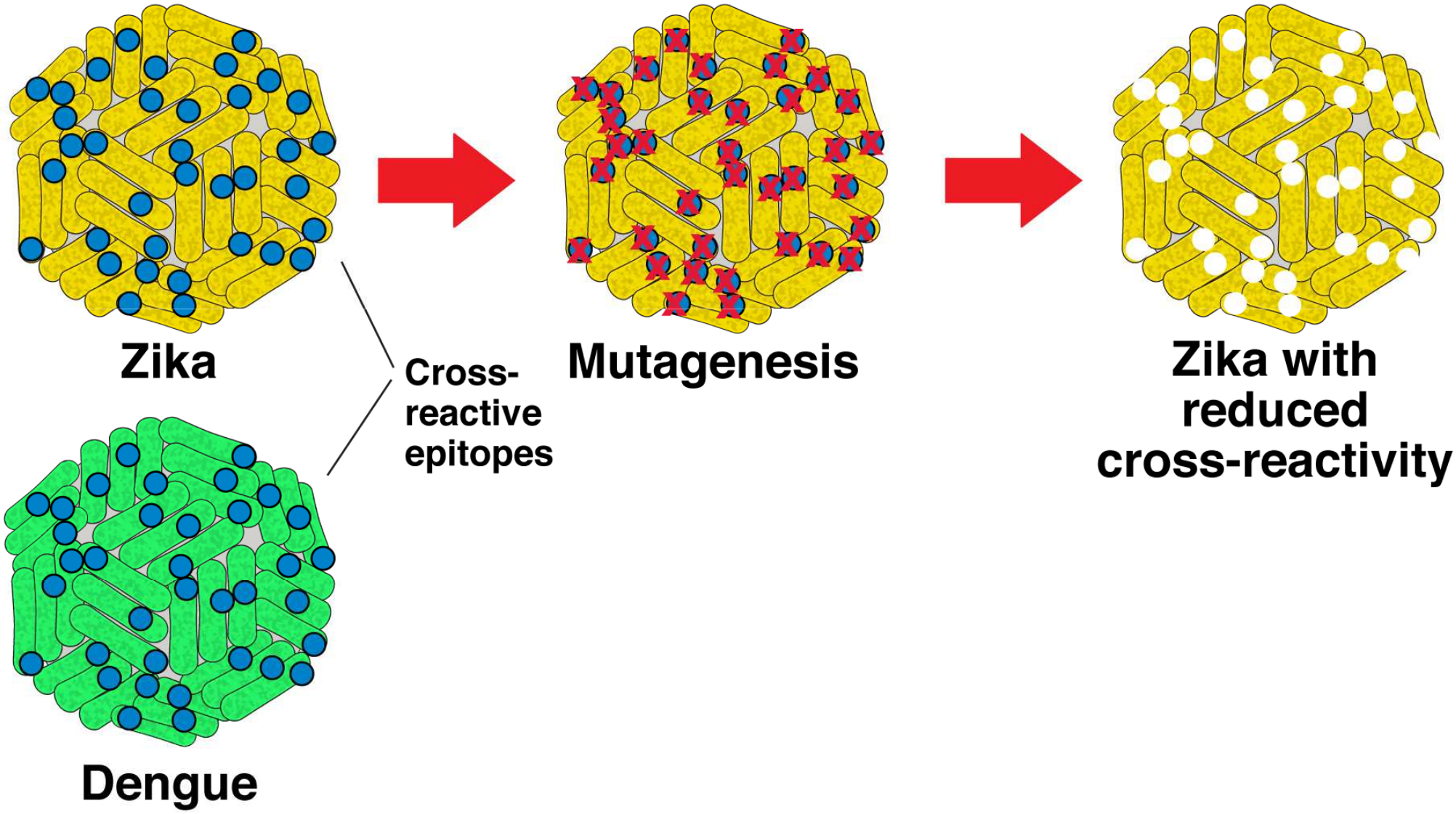
Biomedical Research Response: Countermeasures – Therapeutics

- Developed *in vitro* antiviral screening assay
- Testing compounds with known activity against other flaviviruses
- Broad screening of compounds without known anti-flavivirus activity
- "Targeted" antiviral approach – similar to HIV and Hepatitis C

Biomedical Research Response: Countermeasures – Vaccines

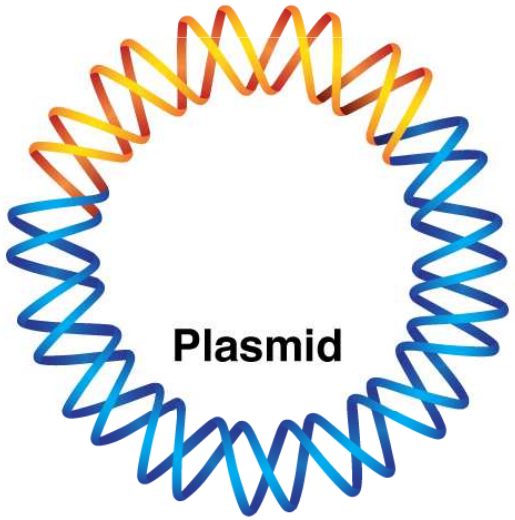
- DNA vaccine – success with West Nile Virus
- Live-attenuated vaccine (for non-obstetric population) – success with dengue

Developing Improved Diagnostics Through Mutagenesis

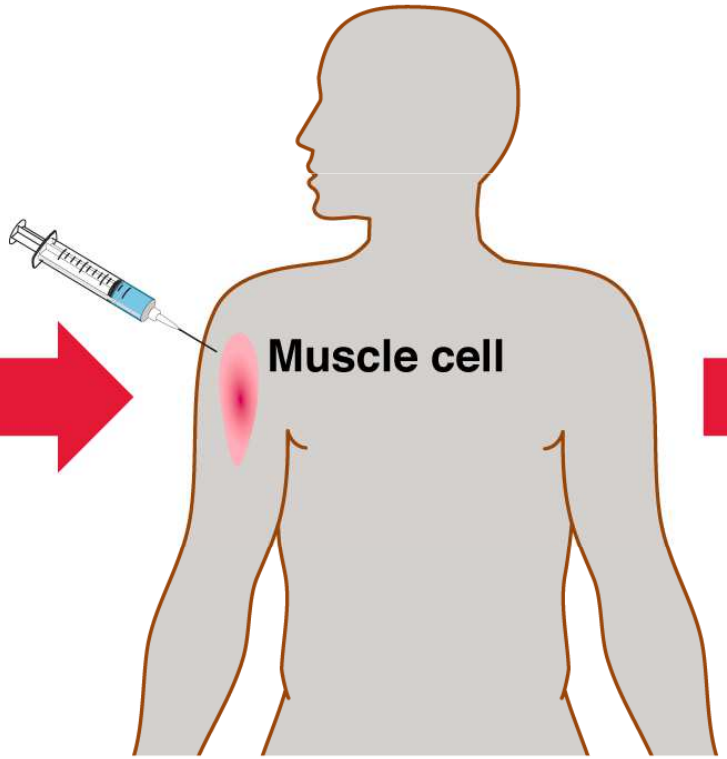


DNA Vaccine Approach

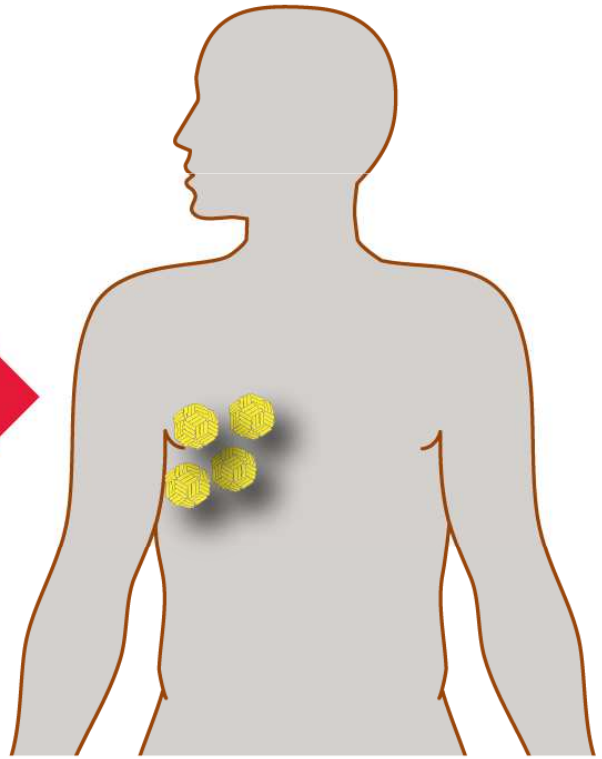
Gene encoding surface protein from Zika virus



Inject DNA containing Zika gene



Body's cells produce virus-like particles, the basis of the vaccine



TREATMENT/VACCINES

TREATMENT

- Antiviral screening (Utah)
- Rodent model for therapeutics testing (Utah State)
- Therapeutic MAbs (Rockefeller)

VACCINE DEVELOPMENT

- Zika LAV chimera on DEN4 backbone (LID)
- DNA to VLP vaccine (VRC)
- VSV-expressing Zika E (Harvard)

Biomedical Research Response: Basic Science

- Molecular Virology: a) elucidate viral structure; b) compare viruses from different outbreaks
- Pathogenesis of disease
- Studies on immune response (innate and adaptive)
- Establish animal models

OTHER GRANTS/MEETINGS

OTHER GRANTS AWARDED

- Basic research; improved PCR; serological assays, phylogenetic analyses; vector fitness; mosquito transmission (UTMB)
- Molecular structure (LID; Purdue)
- Cloning multiple strains (UNC)
- Study primary human trophoblasts (NICHD)
- Immune response to Zika (LV)
- Zika fitness, emergence, evolution (U Colorado)
- ADE (Wash U)
- Metabolomics /biosignature studies (UNC)

MEETINGS/WORKSHOPS

- 16 Feb NAM Research Priorities
- 18 Feb R21 Grants, rapid funding opportunity
- 28-29 Workshop w/ BARDA

END

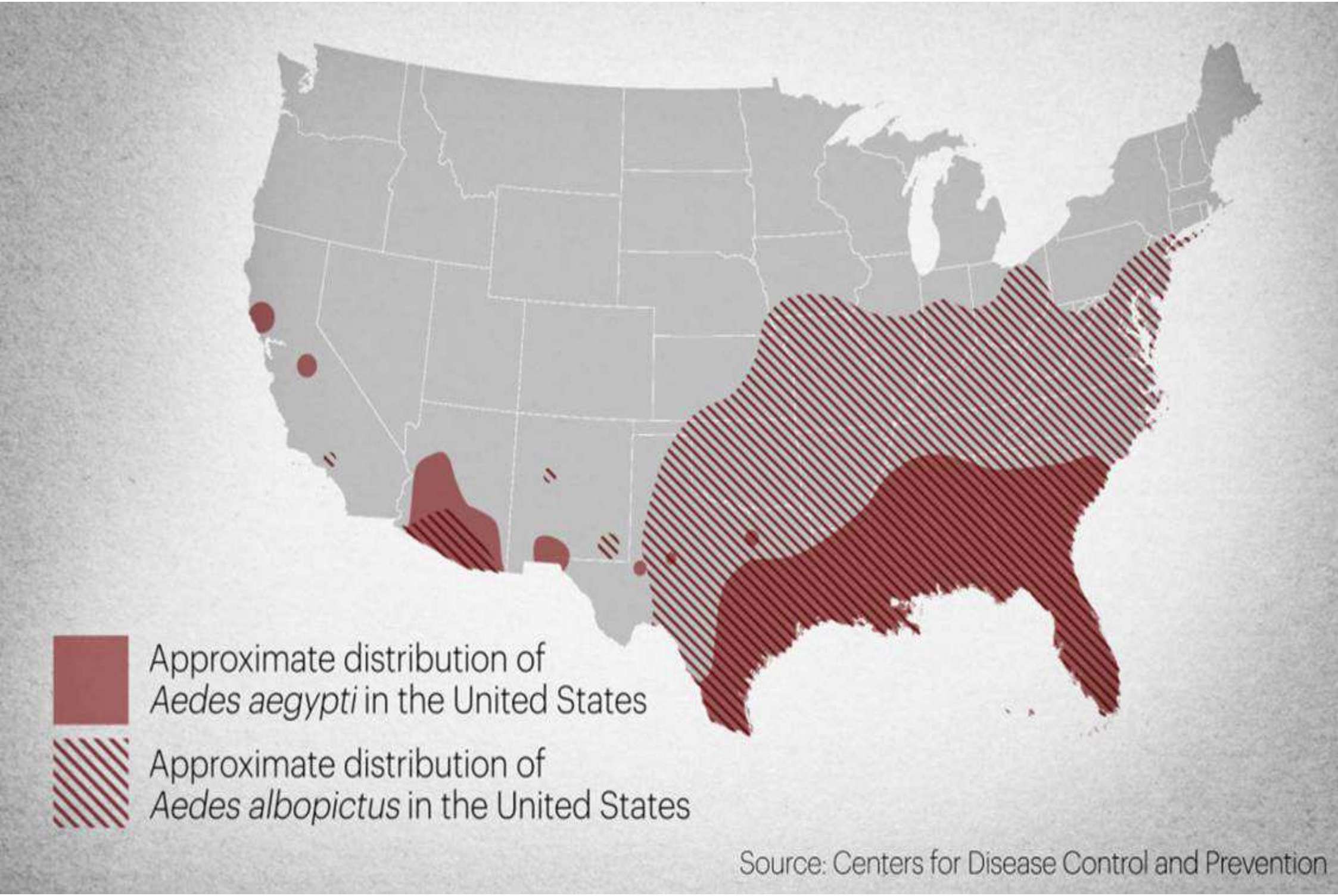
The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

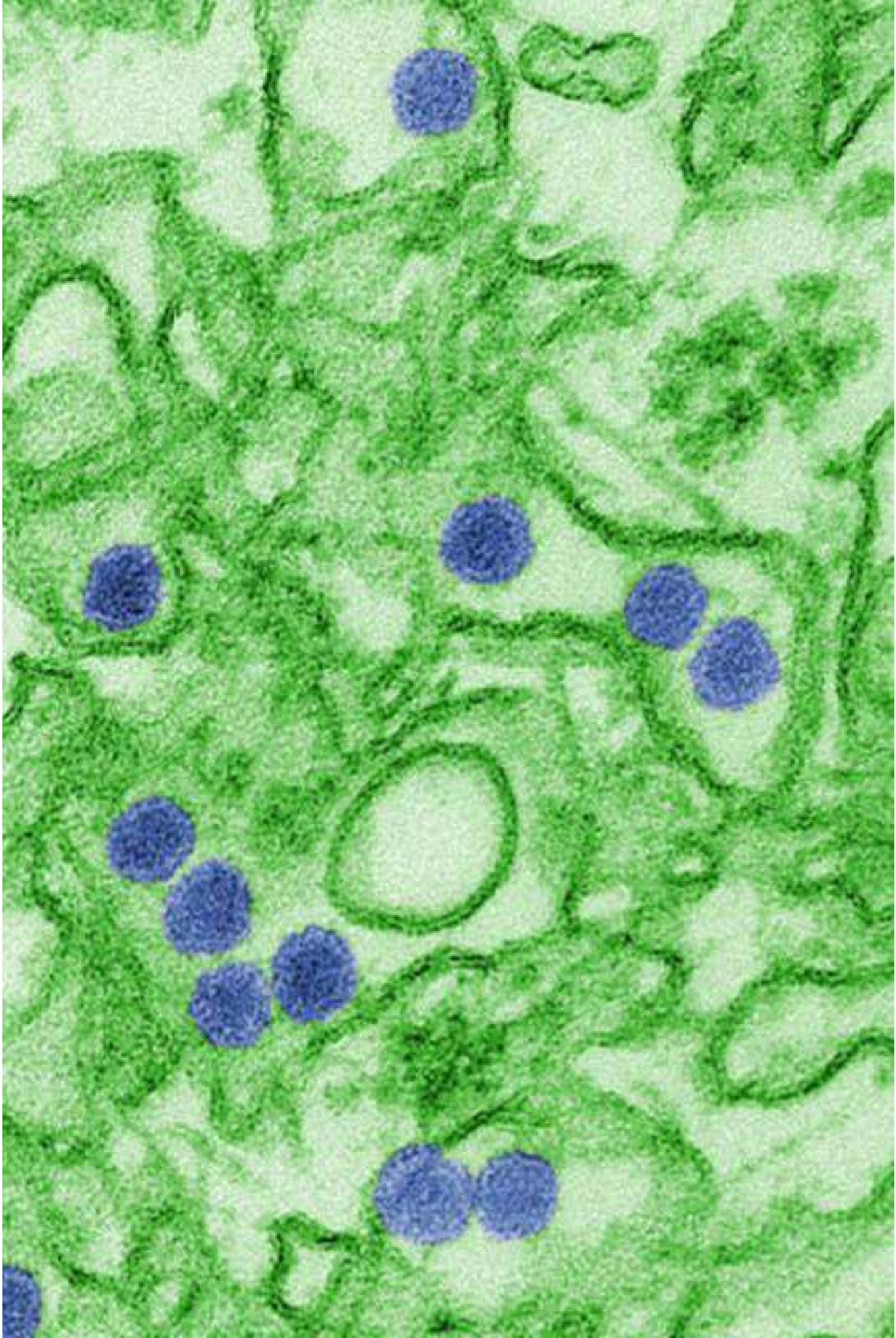
published online January 13, 2016

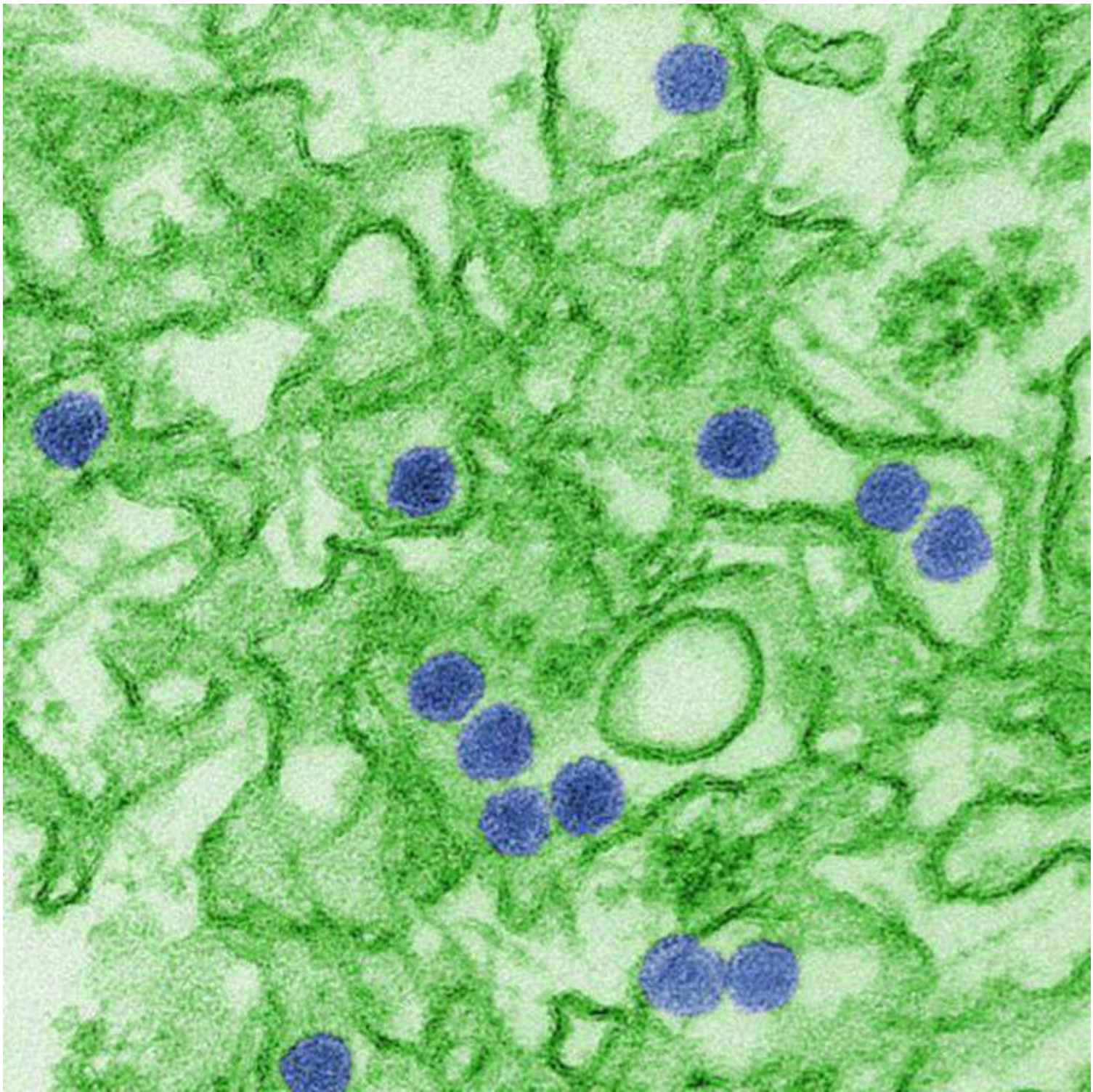
Zika Virus in the Americas — Yet Another Arbovirus Threat

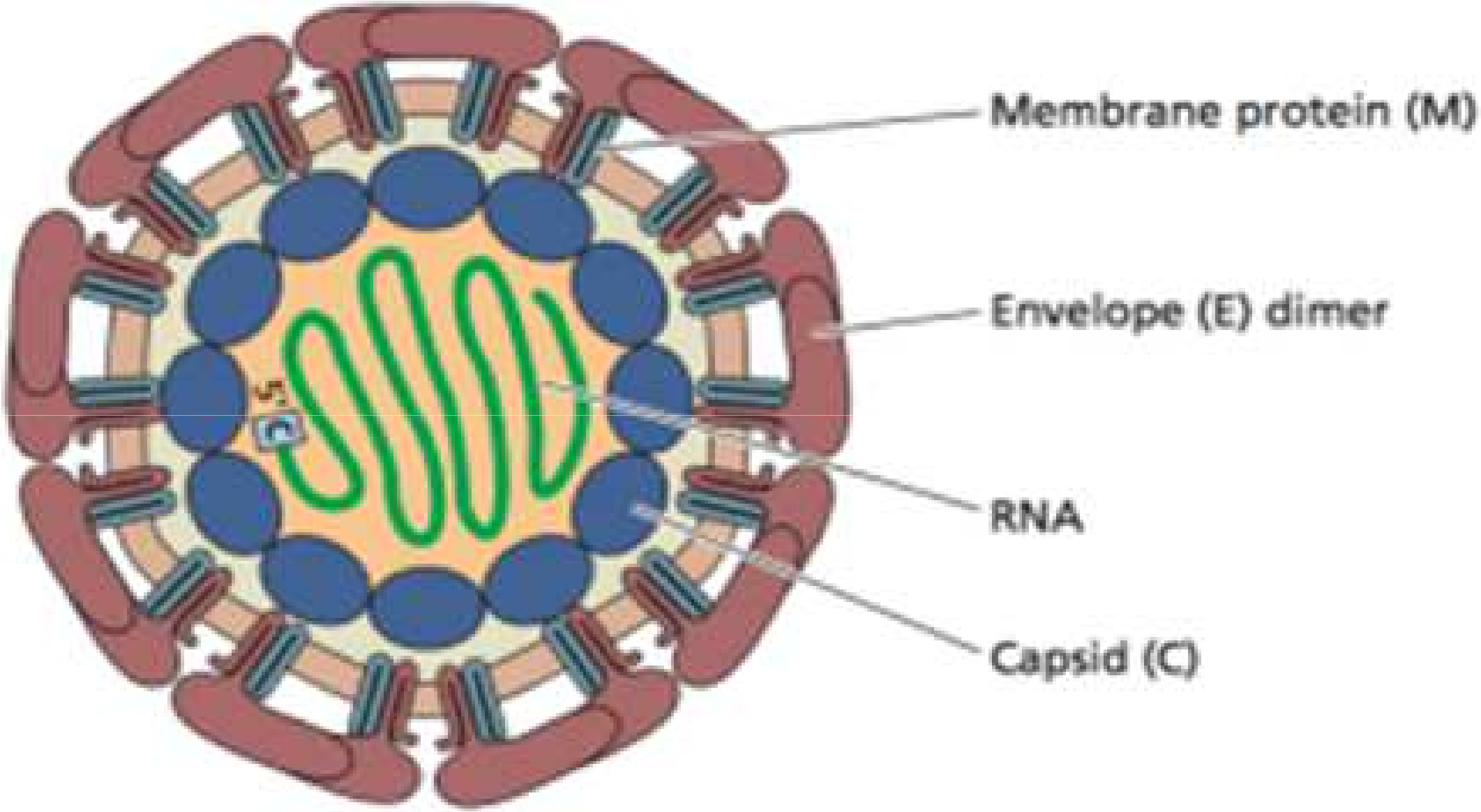
AS Fauci and DM Morens


Approximate distribution of
Aedes aegypti in the United States
Approximate distribution of
Aedes albopictus in the United States
Source: Centers for Disease Control and Prevention

Aedes aegypti






Membrane protein (M)
Envelope (E) dimer
RNA
Capsid (C)

- Zika background
- Current outbreak in Caribbean and Latin America
- Zika and the USA
- Role of research and development
  - Diagnostics
  - Vaccines
  - Therapeutics

Attenuated Virus Approach to Flavivirus Vaccines

SANOFI PASTEUR

December 28, 2015

Press Release

Dengvaxia® First Dengue Vaccine Approved in Brazil

"Brazil has granted regulatory approval to Dengvaxia… which was also approved in Mexico and the Philippines earlier this month"

NIH National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

U.S. Department of Health and Human Services
NIH News
National Institutes of Health

National Institute of Allergy and Infectious Diseases (NIAID)

January 14, 2016

Dengue Vaccine Enters Phase 3 Trial in Brazil

Investigational Vaccine to Prevent "Breakbone Fever" Developed at NIH

May 15, , 2011
Volume 203
Number 10

The Journal of Infectious Diseases

A West Nile Virus DNA Vaccine Utilizing a Modified Promoter Induces Neutralizing Antibody in Younger and Older Healthy Adults in a Phase I Clinical Trial

JE Ledgerwood, BS Graham, et al., VRC 303 Study Team

- Safe and well-tolerated; elicited neutralizing antibody and T-cell responses in majority of subjects.

Biomedical Research Response: Countermeasures – Vaccines

- DNA vaccine – success with West Nile Virus (NIAID)
- Live-attenuated vaccine (for non-obstetric population) – success with dengue alone (NIAID)

dengue/Zika chimeric

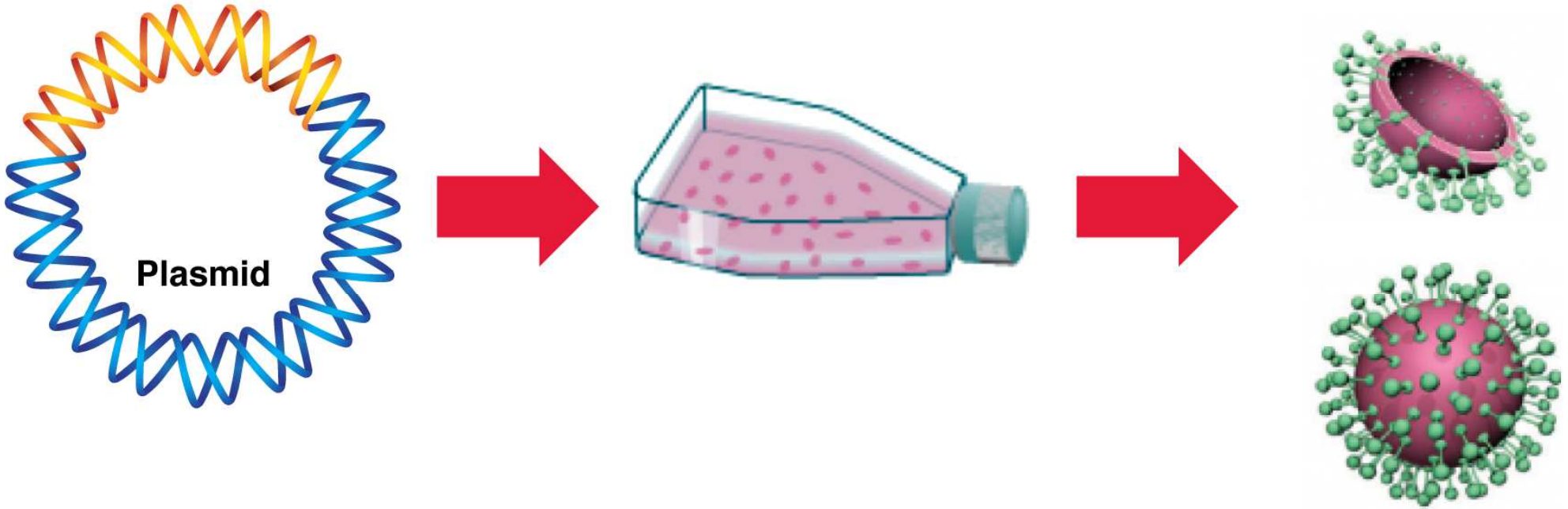
- Whole particle inactivated [redacted] vaccine (NIAID/BARDA)
- Vesicular-stomatitis-virus (VSV) vectored vaccine (Harvard)

DNA Vaccine Approach

Gene encoding surface protein from Zika virus

Express gene in cells

Gene product forms virus-like particles, the basis of the vaccine



Vaccination for Congenital Infections: Lessons from Rubella

- Congenital Rubella Syndrome (CRS): Infants born with blindness, deafness, heart defects, often microcephaly
- Between 1964-1965, 50,000 pregnant women in U.S. exposed to Rubella
  - 20,000 infants born with CRS
- With MMR vaccine, CRS has all but disappeared

National Library of Medicine

Vaccine Development Pathway

1. Identify which part of the virus is immunogenic
2. Design product candidates that deliver that protein(s) into a human
   - Inactivated virus
   - Subunit proteins / peptides
   - Virus like particles
   - Live attenuated virus or chimeric virus
   - Vectored expression
   - DNA / RNA launched expression
3. Characterize / evaluate in the appropriate animal models
4. Prepare clinical lot material
5. Test, test, test. And then test some more.
   - Phase I Safety & immunogenicity
   - Phase II Expanded safety & immunogenicity. Dosing. Age.
   - Phase III Expanded safety and efficacy
6. Scale up manufacture / Regulatory approval
7. Launch / market vaccine
   - Phase IV Post-licensure monitoring

Phil Russell

Vaccine Development Pathway

1. Identify which part of the virus is immunogenic — ✓
2. Design product candidates that deliver that protein(s) into a human — **4 mos.**
   - Inactivated virus
   - Subunit proteins / peptides
   - Virus like particles
   - Live attenuated virus or chimeric virus
   - Vectored expression
   - DNA / RNA launched expression
3. Characterize / evaluate in the appropriate animal models — **4 mos.**
4. Prepare clinical lot material — **4 mos.**
5. Test, test, test. And then test some more.
   - Phase I Safety & immunogenicity — **8 mos.**
   - Phase II Expanded safety & immunogenicity. Dosing. Age. — **8 mos.**
   - Phase III Expanded safety and efficacy — **14 mos.**
6. Scale up manufacture / Regulatory approval — **4 mos.**
7. ~~Launch / market vaccine~~
   - ~~Phase IV Post-licensure monitoring~~

46 mos.

ZIKV Vaccine Approaches

Inactivated	PaxVax, CA, USA NewLink Genetics, MA, USA GSK, USA/Belgium Bharat Biotech, India WRAIR / NIAID / BARDA, USA
Subunit / Peptide	Protein Sciences, CT, USA Hawaii Biotech, HI, USA Bharat Biotech, India Replikins, MA, USA
Live	NIAID-LID / Instituto Butantan, USA/Brazil UTMB / Instituto Evandro Chagas, USA/Brazil Sanofi Pasteur, France
Vectored	Jenner Institute (Chimp adenovirus), UK Harvard University (VSV), MA, USA Themis Bioscience (Measles), Austria
DNA / RNA	NIAID-VRC (Biojector needle-free), USA Inovio Pharmaceuticals (Electroporation), PA, USA GSK (RNA), USA/Belgium

ZIKV Vaccine Questions/Concerns

1. Who to vaccinate?
    - Special populations – Pregnant women, immunocompromised
    - Serological background

2. When to vaccinate?
    - Age
    - Doses
    - Durability

3. Safety?
    - Replicating vs. non-replicating vaccines
    - Neurovirulence
    - Guillain–Barré syndrome
    - Adjuvants

The NIAID Dengue Vaccine

- Live attenuated
- Tetravalent

- Single dose
- Tested in over 1600 subjects (Phase 1 & 2) in 3 countries
- Phase III efficacy study currently underway in Brazil
- Economical to produce

Second generation vaccines?

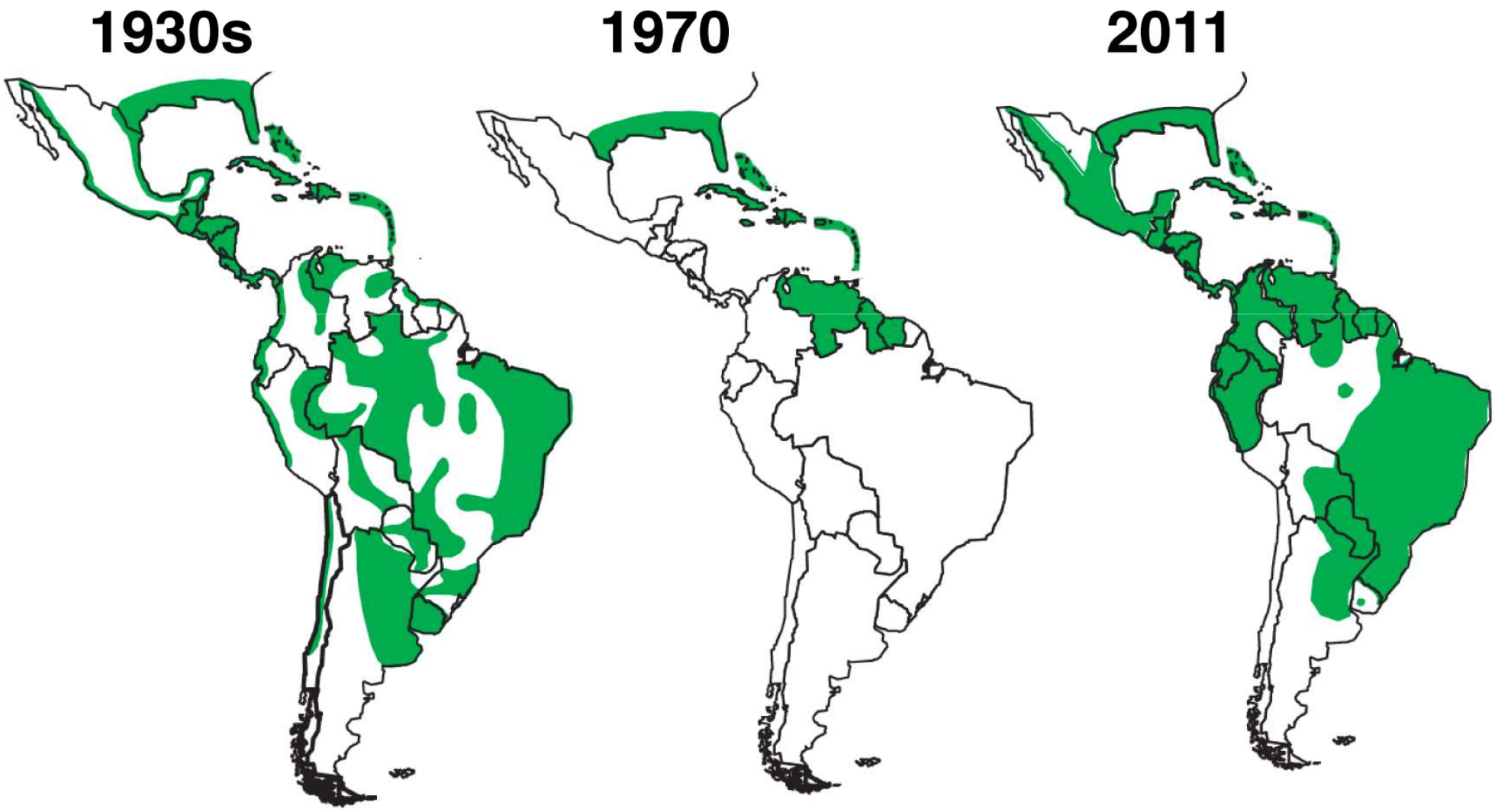
Pentavalent-Z (the Americas):

Pentavalent-J (Southeast Asia):

Pentavalent-U (??):

Usutu virus

Aedes aegypti Vector Control in the Age of DDT



Source: *Tropical Medicine and Health* Vol. 39 No. 4 Supplement, 2011

Biomedical Research Response: Epidemiology and Natural History

- **Epidemiology and natural history**
  - **Symptomatic vs. asymptomatic**
  - **Frequency of sequelae**
  - Cohort studies to determine incidence of adverse pregnancy outcomes in Zika-infected pregnant women
- **Pathogenesis of microcephaly**

Strategies for ZIKV Vaccine Development

Stephen Whitehead, 24 Feb 2016
Laboratory of Infectious Diseases

Public Health Interventions

1. Treatment and care centers
2. Vaccines
3. Therapeutics / Antivirals / Antiserum-Antibodies
4. Vector control and mosquito repellents
5. Travel restrictions, screenings, quarantines
6. Birth control
7. Condom use
8. Blood supply / donor screening
9. Others?

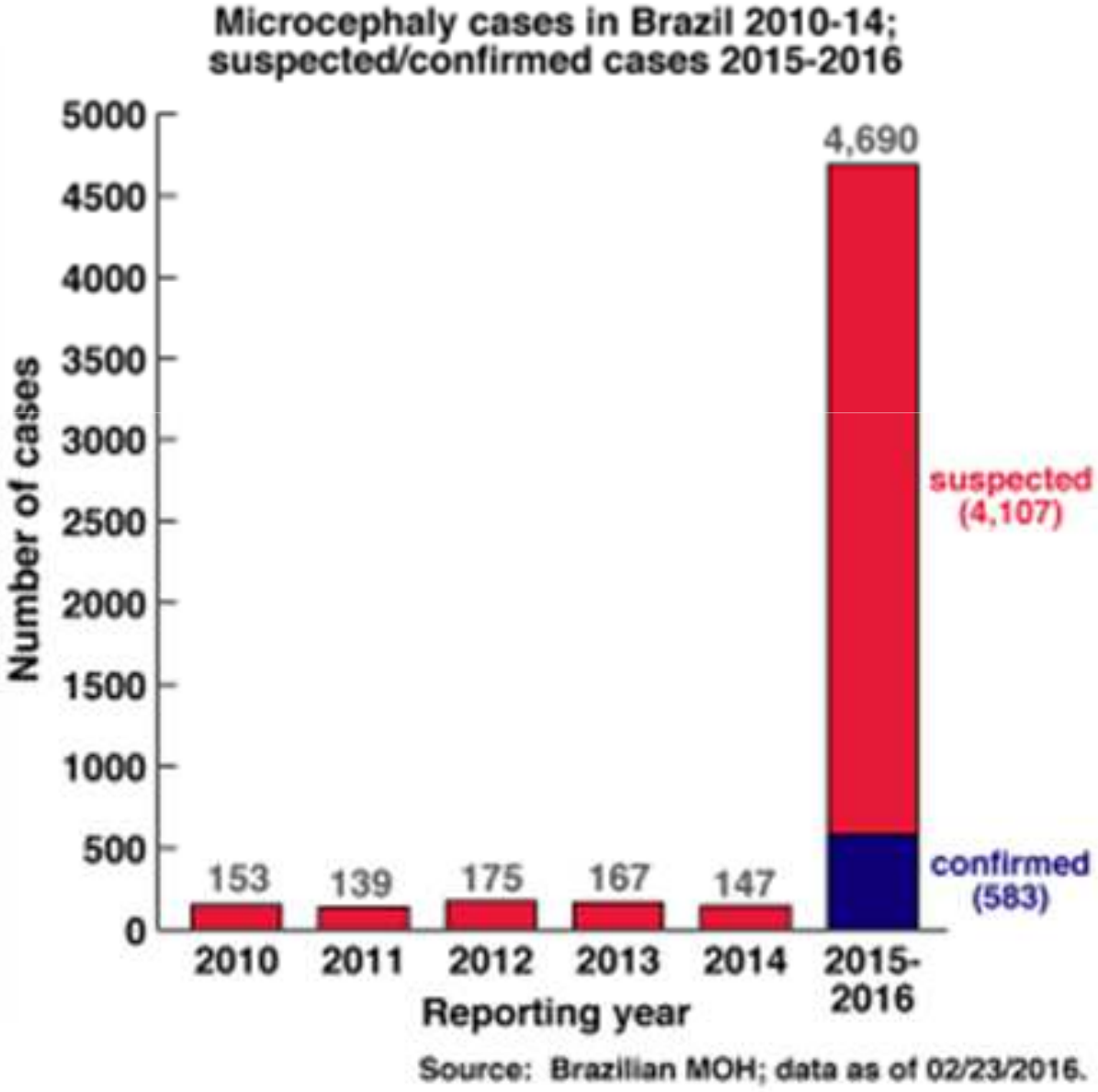
Zika as a Potential Cause of Microcephaly

Associated Press

November 30, 2015

Brazil Links Mosquito-Borne Zika Virus to Microcephaly Birth Defect

Nine states with Zika infections see surge in babies born with small heads




BRAZIL
Political Map
VENEZUELA
GUYANA
SURINAME
FRENCH GUIANA
COLOMBIA
PERU
BOLIVIA
CHILE
PARAGUAY
ARGENTINA
URUGUAY
PACIFIC OCEAN
ATLANTIC OCEAN
ATLANTIC OCEAN
Boa Vista
RORAIMA
AMAPA
Macapá
Belém
São Luís
Manaus
AMAZONAS
PARA
MARANHAO
Teresina
Fortaleza
CEARA
RIO GRANDE DO NORTE
Natal
João Pessoa
PARAIBA
Recife
PERNAMBUCO
ALAGOAS
Maceió
SERGIPE
Aracaju
PIAUI
ACRE
Rio Branco
Porto Velho
RONDONIA
Palmas
TOCANTINS
BAHIA
Salvador
MATO GROSSO
DISTRIT OF EDERAL
BRASÍLIA
Cuiabá
GOIAS
Goiânia
MINAS GERAIS
Belo Horizonte
ESPIRITO SANTO
Vitoria
MATO GROSSO DO SUL
Campo Grande
SAO PAULO
RIO DE JANEIRO
Rio de janeiro
São Paulo
PARANA
Curitiba
SANTA CATARINA
Florianópolis
RIO GRANDE DO SUL
Porto Alegre
LEGEND
International Boundary
State Boundary
National Capital
State Capital
0 200 400KM
0 200 Miles
Copyright © 2015 www.mapsofworld.com
(Updated on 14th April, 2015)


BRAZIL
VENEZUELA
GUYANA
SURINAME
FRENCH GUIANA (FR)
COLOMBIA
NORTH ATLANTIC OCEAN
Equator
Pico da Neblina 2,994 m
Boa Vista
Guiana Highlands
Macapa
Belem
São Luís
Parnaíba
Fortaleza
AMAZON BASIN
Manaus
Santarém
Teresina
Imperatriz
Natal
João Pessoa
Campas Catinga
Recife
Porto Velho
Rio Branco
Palmas
Juazeiro
Maceió
Aracaju
Feira de Santana
Salvador
PERU
Chapada dos Guimarães
BRASÍLIA
Anápolis
Goiânia
Cuiaba
Itabuna
BOLIVIA
Montes Claros
BRAZILIAN HIGHLANDS
Belo Horizonte
Pico da Bandeira 2,892 m
Campo Grande
Divinópolis
Victória
Juiz de Fora
PACIFIC OCEAN
CHILE
PARAGUAY
Maringá
Marilia
Sao Paulo
Santos
Carnaval
Jardim Botânico
Rio de Janeiro
Christ the Redeemer
Harbour of Rio de Janeiro
Agulhas Negras
Tropic of Capricorn
Itaipu Dam
Iguazu Falls
Curitiba
Joinville
Florianópolis
Passo Fundo
ARGENTINA
Santa Maria
Porto Alegre
Bagé
Rio Grande
URUGUAY
SOUTH ATLANTIC OCEAN
Amazon
Negro
Japura
Jurua
Madeira
Paru
Iriri
Teles Pires
Juruena
Xingu
Araguaia
Tocantins
Gurupi
Parnaiba
São Francisco
Guaporé
Abuna
Paraná
Paraguay
Iguaçu
60° W
50° W
40° W
30° W
0°
10° S
20° S
30° S
0 375 575 Km
0 200 375 Miles
LEGEND
Country Boundary
Major Road
River
Major City
Sea Port
Country Capital
Airport
Point of Interest
Lake
Mt. Peak
Copyright © 2013 www.mapsofworld.com
(Updated on 18th January, 2013)


BRASIL
AMAZONAS
RORAIMA
PARÁ
AMAPÁ
MARANHÃO
PIAUÍ
CEARÁ
RIO GRANDE DO NORTE
PARAÍBA
PERNAMBUCO
ALAGOAS
SERGIPE
BAHIA
TOCANTINS
GOIÁS
BRASÍLIA
MINAS GERAIS
ESPÍRITO SANTO
RIO DE JANEIRO
SÃO PAULO
PARANÁ
MATO GROSSO
MATO GROSSO DO SUL
RONDÔNIA
ACRE
GUIANA
GUIANA FRANCESA
SURINAME
VENEZUELA
COLÔMBIA
PERU
BOLÍVIA
PARAGUAI
CHILE
OCEANO ATLÂNTICO
OCEANO PACÍFICO
Manaus
Belém
São Luís
Fortaleza
Natal
João Pessoa
Recife
Maceió
Aracaju
Salvador
Palmas
Teresina
Cuiabá
Campo Grande
Goiânia
Belo Horizonte
Vitória
São Paulo
Rio de Janeiro
Curitiba
Porto Alegre
Florianópolis
Porto Velho
Rio Branco
Boa Vista
Macapá
Equador
0°
-10°
-20°