Zika Virus Outbreak and NIAID Research Response

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Zika Virus

- Single stranded, enveloped RNA Virus
- Family *Flaviviridae*, Genus *Flavivirus*
- Closely related to dengue, yellow fever, Japanese encephalitis and West Nile viruses
- Transmitted to humans primarily by *Aedes* species mosquitoes

Source: CDC
Symptoms of Zika Virus Infection

- 4 in 5 individuals asymptomatic

Incubation: 3-12 days

Mild symptoms: 2-7 days

- Rash
- Headache/Malaise
- Non-purulent conjunctivitis/Conjunctival hyperemia
- Elevated body temperature (Above 99°F)
- Arthralgia/Myalgia
- Peripheral edema/gastrointestinal disturbance have also been observed

Source: BMJ.com, 2/2016
Zika Virus.
I. Isolations and Serological Specificity

GW Dick, SF Kitchen, AJ Haddow

Virus first isolated from a monkey in the Zika forest of Uganda in 1947
Zika Virus: A Report on Three Cases of Human Infection During an Epidemic of Jaundice in Nigeria

FN MacNamara

March, 1954
Vol. 48 No. 2

First human cases reported in Nigeria in 1952
Zika Virus Spread, 1947-2016

1952: First human cases described

1947: Discovered in Uganda

1977-78: Pakistan, Malaysia, Indonesia

2007: Yap, Micronesia

2013: French Polynesia

2015: Brazil

Source: Lancaster University
Countries and Territories with Active Zika Virus Transmission – April 2016

44 countries/territories (35 in the Americas/Caribbean)

Source: CDC, April 29, 2016
Marked Increase in Microcephaly Cases in Brazil

Associated Press
November 30, 2015

Brazil Links Mosquito-Borne Zika Virus to Microcephaly Birth Defect

Microcephaly cases in Brazil 2010-14; suspected/confirmed cases 2015-2016

Number of cases

153  139  175  167  147  4,851


suspected* (3,580)
1,271 confirmed (203 confirmed as Zika-positive)

*does not include 2,492 cases investigated and discarded

Source: Brazilian MOH; data as of 5/4/2016.
Microcephaly

- An occipitofrontal circumference at least 2 standard deviations below the mean (definitions differ)
- Associated with reduced life expectancy and abnormal neurocognitive development
- Major etiologies include:
  - Genetic anomalies
  - Fetal alcohol syndrome
  - Other maternal factors (malnutrition, endocrine disorders)
  - Maternal infections (including cytomegalovirus, toxoplasmosis, rubella)
  - Zika

AS Fauci/NIAID
Microcephaly Attributed to Zika

Normal infant brain and head size

Microcephaly, Colombia 2015

AS Fauci/NIAID

Images: LatinAmericanScience.org
Neonatal Manifestations of Congenital Zika Virus Infection

- Microcephaly
- Intracerebral calcifications (mostly periventricular)
- Hearing loss
- Vision abnormalities
- Lissencephaly
- Pachygyria
- Ventricular enlargement
- Arthrogryposis
- Muscular atrophy

Neurological Disease Caused by Zika

- Guillain-Barré Syndrome
  - Acute, immune-mediated neuropathy

- Acute Myelitis
  - Spinal cord inflammation

- Meningoencephalitis
NIAID Research Response

- Leveraging existing Program on Flaviviruses to rapidly start research on Zika

- Since January 2016, over 40 projects initiated to:
  - Understand basic biology/structure/evolution of virus and competence of the mosquito vectors
  - Develop vaccines, diagnostics, therapeutics and vector control strategies
  - Elucidate the mechanism of pathogenesis and congenital infection
Developing Improved Diagnostics Through Mutagenesis

Zika → Cross-reactive epitopes → Mutagenesis → Zika with reduced cross-reactivity

The 3.8 Å resolution cryo-EM structure of Zika virus

Devika Sirohi, Zhenguo Chen, Lei Sun, Thomas Klose, Theodore C. Pierson, Michael G. Rossmann, Richard J. Kuhn

March 31, 2016

Cite as: Sirohi et al., Science 10.1126/science.aaf5316 (2016).

AS Fauci/NIAID
Antiviral Screening Program

- Developed Zika in vitro screening assay
- Tested 87 antiviral compounds with known activity against other flaviviruses
  - 14 have high to moderate activity against Zika virus
- Promising drug candidates are being further tested in Zika mouse model
  - BCX4430 found to protect immune-deficient mice infected with Zika virus
- Collaborating with NCATS and Gates Foundation to develop high throughput screening assay to screen existing libraries of approved drugs
Zika Vaccine Development Timeline

2016

DNA vaccine candidate
(NIAID VRC)

Preclinical Discovery

2017

Whole-particle inactivated virus
(NIAID/WRAIR/BARDA and corporate partner)

Preclinical Discovery

Phase 1

Live-attenuated Zika chimera
(NIAID intramural/Butantan)

Preclinical Discovery

Phase 1

Vesicular Stomatitis Virus vectored vaccine
(NIAID extramural)

Preclinical Discovery/ Tech Transfer

Phase 1

mRNA vaccine candidate
(NIAID VRC)

Preclinical Discovery

Phase 1

2018

Long term follow up

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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 – genetically modified mosquitoes; *Wolbachia*-infected mosquitoes
Pathogenesis Studies

- Natural history, cohort studies in pregnant and non-pregnant population
  - Role of existing flavivirus immunity
  - Role of asymptomatic infections in congenital disease
  - Viral loads/dynamics in different bodily fluids (transmission)
  - Long term observational studies in babies born from Zika-infected mothers

- Development of animal models
  - Mice
  - Hamsters
  - NHPs (Dave O’ Connor)