Zika Virus

Not your daddy's arbovirus (hopefully)

Michael Libman MD
J.D. MacLean Centre for Tropical Diseases
McGill University

NO CONFLICT OF INTEREST TO DECLARE
(EXCEPT ON CATMAT GUIDELINES COMMITTEE)

U.S. officials: The more we know about Zika, the scarier it is

BREAKING NEWS

Zika 'spreading explosively'

'Level of alarm is extremely high' about virus, WHO leader says

Photos | 5 things you need to know | The children of Zika | Opinion: How to stop it | Map: Tracking the virus

HEALTH ZIKA

What Every Woman Needs to Know About Zika

TIME

Alexandra Sifferlin @acsifferlin April 22, 2016

The New York Times

Zika Is Coming

By PETER J. HOTEZ APRIL 8, 2016

The Washington Post

HUFFPOST HEALTHY LIVING

An Illustrated Guide To The Zika Outbreak

The virus is suspected of causing birth defects and a rare autoimmune disorder.

Zika virus Full coverage of the outbreak

CANADA

TRENDING RIP Prince | Ghosts of Vietnam | NDP | Attawapiskat | Bosma | Jays | Trump

Seven B.C. residents, including two pregnant women, test positive for Zika virus that causes birth defects

NP Pamela Fayerman, Postmedia News | April 19, 2016 8:47 AM ET

More from Postmedia News

Thanks: Ling Yuan Kong

TRANSACTIONS OF THE ROYAL SOCIETY OF
TROPICAL MEDICINE AND HYGIENE.
Vol. 46. No. 5. September, 1952.

COMMUNICATIONS

ZIKA VIRUS

(I). ISOLATIONS AND SEROLOGICAL SPECIFICITY

BY

G. W. A. DICK,

The National Institute for Medical Research, London

S. F. KITCHEN,

Formerly staff member of the Division of Medicine and Public Health, The Rockefeller Foundation, New York, U.S.A.

AND

A. J. HADDOW,

Formerly staff member of International Health Division, The Rockefeller Foundation, New York, U.S.A.

(*From the Virus Research Institute, Entebbe, Uganda.*)

TRANSACTIONS OF THE ROYAL SOCIETY OF
TROPICAL MEDICINE AND HYGIENE.
Vol. 50. No. 5. September, 1956.

Virus inoculated via mouse brain suspension to a 34 year old European male: fever, headache 3.5 days after inoculation

ZIKA VIRUS INFECTION EXPERIMENTALLY INDUCED IN A HUMAN VOLUNTEER

BY

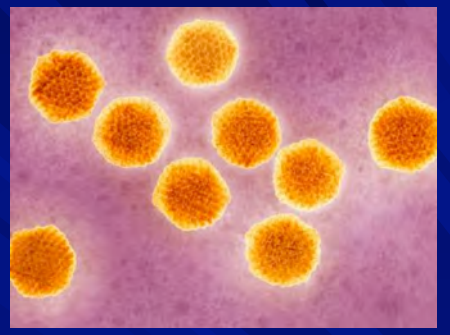
W. G. C. BEARCROFT*

West African Council for Medical Research Laboratories, Lagos, Nigeria.

Outline

- Where is Zika?
- Transmission modes – what do we know
- Manifestations, Diagnosis – quick recap
- Risk assessment
- Recommendations - Guidelines

Zika Virus



- Single stranded RNA virus of *Flavivirus* genus
- Closely related to dengue, West Nile, yellow fever, and Japanese encephalitis viruses
- Arbovirus: arthropod-borne virus
- Primary vector - *Ae. aegypti* but several other *Aedes* spp. and *Culex* spp. capable of transmission (in laboratory)
  - –Strain dependent

Two Distinct Zika Lineages – Only One Serotype

- African
- Asian
  - All strains have identical surface antigens
  - Antibodies elicited after infection with Asian lineage potently inhibit both lineages *in vitro*
  - Sequence homology 90% (primer problems)

- Dowd K et al. Cell Reports 2016
- Enfissi A et al Lancet 2016

Epidemiology

Discovered in Zika Forest, Uganda 1947

Epidemiology

- First human case diagnosed 1962-3 in Uganda
- Serosurveys – neutralizing antibodies in East and West Africa, India, and SE Asia
  - Late 1940s to late 1990s
- Outbreaks in Yap, Micronesia in 2007
  - First cases outside Asia/Africa, first outbreak
  - French Polynesia 2013, Easter Island 2014
- Brazil early 2015 then spread in the Americas
  - Chen & Hamer. Ann Int Med 2016
  - Musso & Gubler. Clin Microbiol Rev July 2016

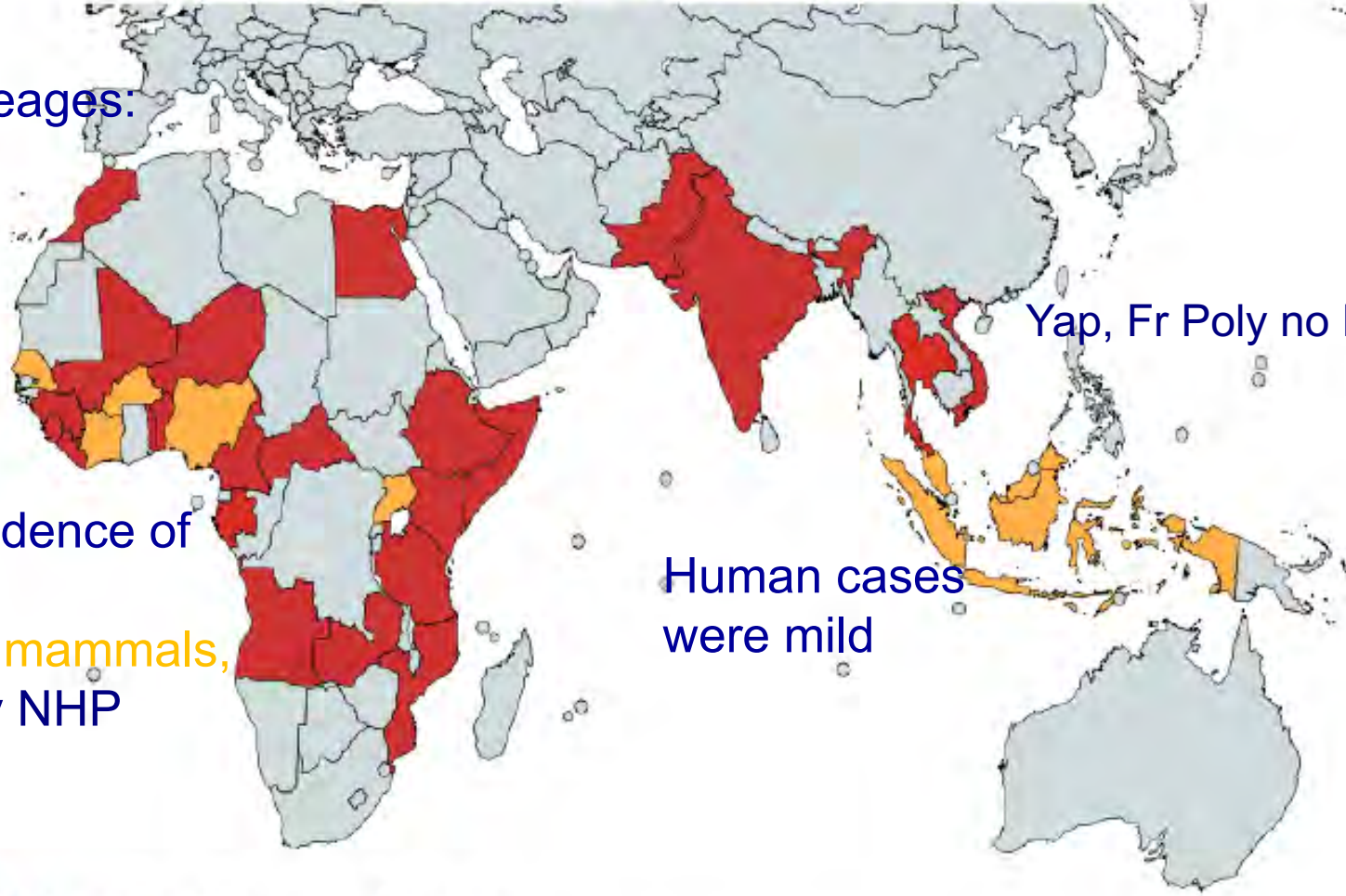
Serologic Evidence of ZIKV Distribution until 2007

Two lineages:
African
Asian

Yap, Fr Poly no NHP

Sero evidence of ZIKV
multiple mammals,
viro only NHP

Human cases were mild



Serologic evidence
Virus detection or confirmed human case

Pan American Health Organization

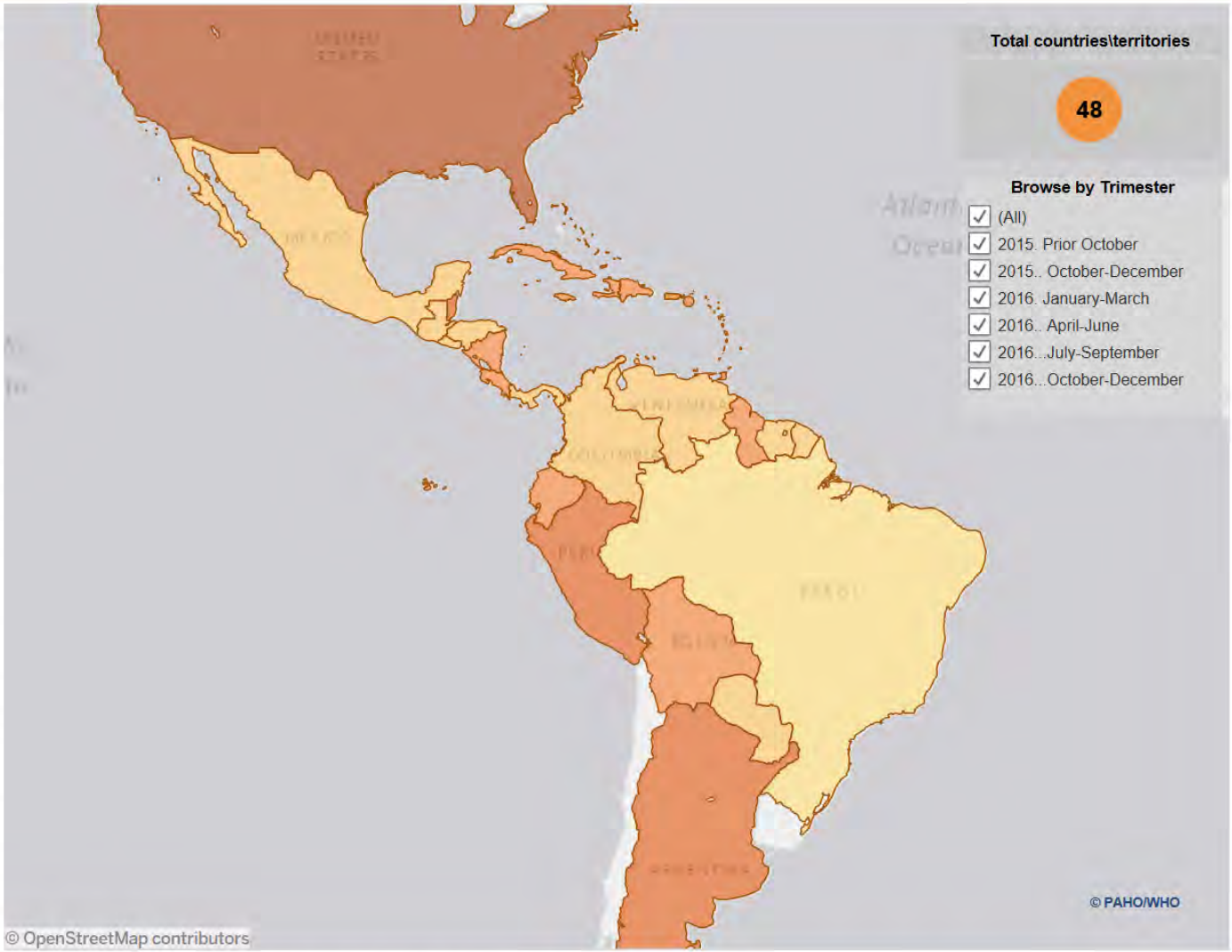
World Health Organization
Regional Office for the Americas

Countries and territories of the Americas with confirmed autochthonous cases of Zika virus (vector-borne transmission), 2015-2017

Data as of 27 April 2017 2:00 PM EST

Country name

- Anguilla
- Antigua and Barbuda
- Argentina
- Aruba
- Bahamas
- Barbados
- Belize
- Bolivia
- Bonaire, St. Eustatius and Sa..
- Brazil
- British Virgin Islands
- Cayman Islands
- Colombia
- Costa Rica
- Cuba
- Curacao
- Dominica
- Dominican Republic
- Ecuador
- El Salvador
- French Guiana
- Grenada
- Guadeloupe
- Guatemala
- Guyana
- Haiti
- Honduras
- Jamaica
- Martinique
- Mexico
- Montserrat
- Nicaragua
- Panama
- Paraguay
- Peru
- Puerto Rico
- Saint Barthelemy
- Saint Kitts and Nevis
- Saint Lucia
- Saint Martin
- Saint Vincent and the Grenadi.
- Sint Maarten
- Suriname
- Trinidad and Tobago
- Turks and Caicos Islands
- United States of America
- United States Virgin Islands
- Venezuela



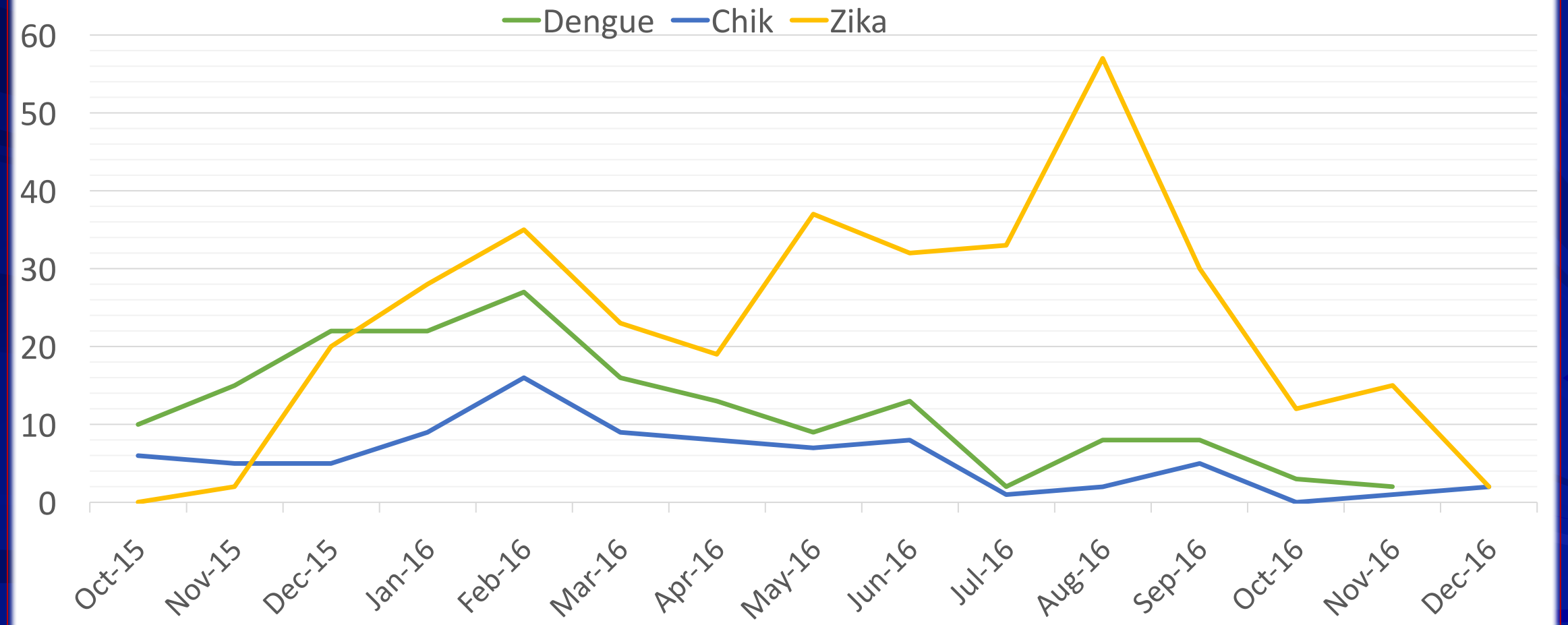
Source: Cases reported by the IHR National Focal Points to the WHO IHR Regional Contact Point for the Americas and through the Ministry of Health websites, 2017.

Note: Further information regarding subnational geographic distribution of Zika virus cases is available on the Ministry of Health websites. For more details on country totals please visit Cumulative Cases table at

Map Production: PAHO Health Emergencies Department (PHE) / Health Emergency Information & Risk Assessment (HIM); 2017 Updated as of 27 April 2017. Washington, D.C.

Suggested citation: Pan American Health Organization / World Health Organization. ***Countries and territories of the Americas with confirmed autochthonous cases of Zika virus (vector-borne transmission), 2015-2017***. Washington, D.C.

GeoSentinel Epi Curves



Why has Zika emerged now?

- Naïve populations in South Pacific amplified virus and facilitated spread via global mobility
- Abundance of competent vectors in the Americas
- Antibody-dependent enhancement in a heavily dengue-exposed population
- Mutational change (‘Asia strain’) - enhanced viral infectivity of *Aedes* vectors
- Mutational change – higher human viremia and improved transmission efficiency

Probable Sentinel Cases

- 2012: Indonesia (diagnosed in Australia)
  - Kwong JC et al. AJTMH 2013
- 2014: the Philippines (dx in Germany)
  - – First case since 2012 for this country
- 2013: Thailand (dx in Canada)
  - – Serological data in Thailand from the 1950s
    - Fonseca C et al. AJTMH 2014
- 2015: Vietnam (dx in Israel)
  - – Serological data in Vietnam from the 1950s
    - Pond WL. Trans R Soc Trop Med Hyg 1963

Sentinel Cases

- 2010: Cameroon (diagnosed retrospectively in Belgium)
  - Only reported case in Cameroon since 2010
- 2015: Kirabati (dx in New Zealand)
  - First known report
- April 2016: East Timor (dx in Germany)
  - First known report although only probable

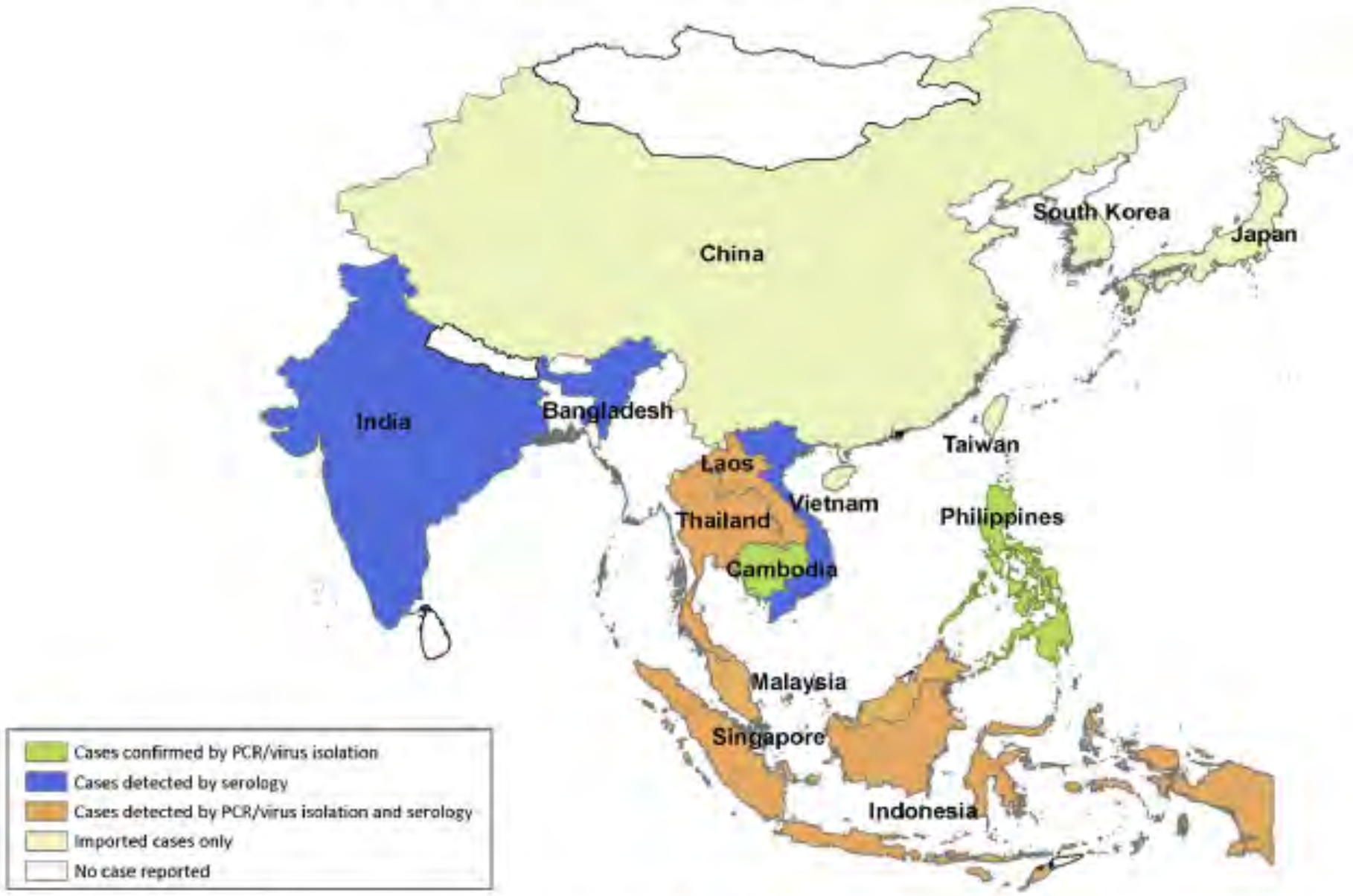


Figure 2. Map of Asian countries in which Zika virus circulation has been reported up to September 1, 2016.

Transmission – Other Modes

Proven:

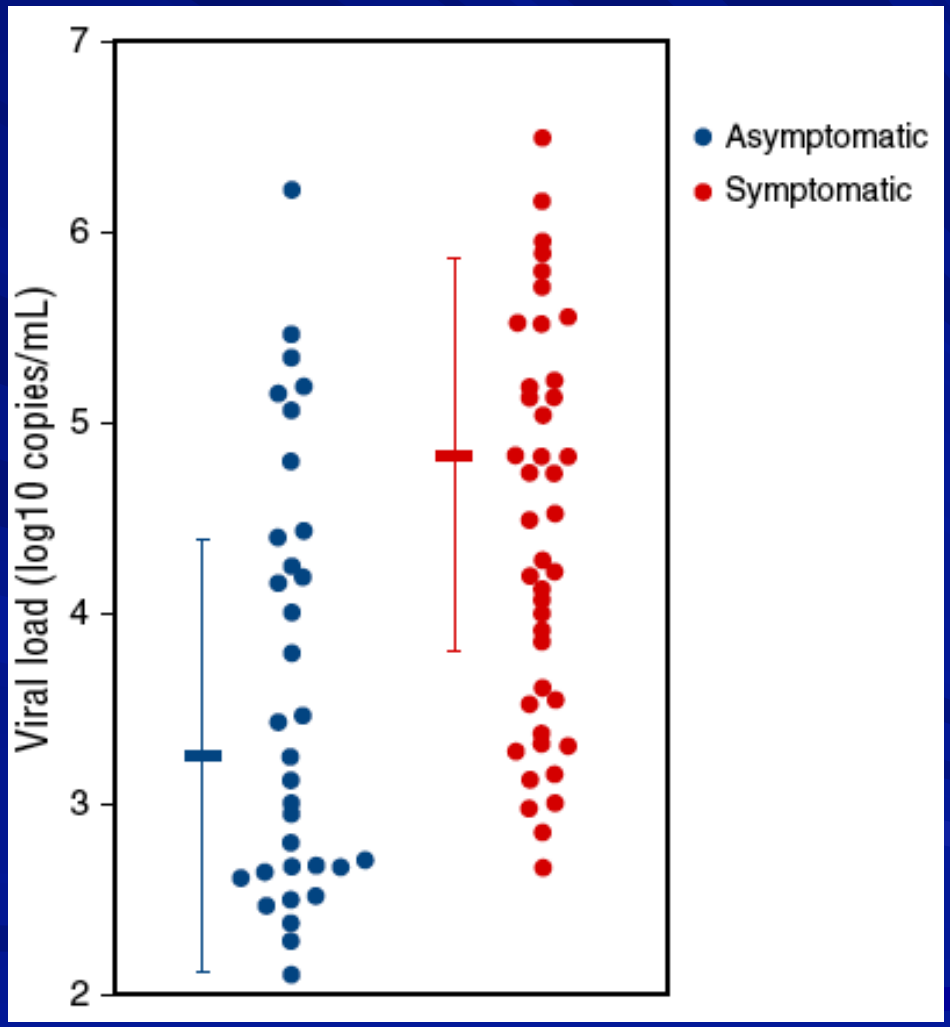
- Sexual
  - Male to female; male to male; female to male
- Blood products
  - Documented in Brazil and French Polynesia

Theoretically possible, with serious implications:

- Breast milk (Colt PLOS NTD april 2017)
  - 3 cases, 1 culture pos (VL 850k/ml) day 4 postpartum
  - No clear transmission to child by milk
- Saliva or tears
- Transplantation

Transmission – Transfusion

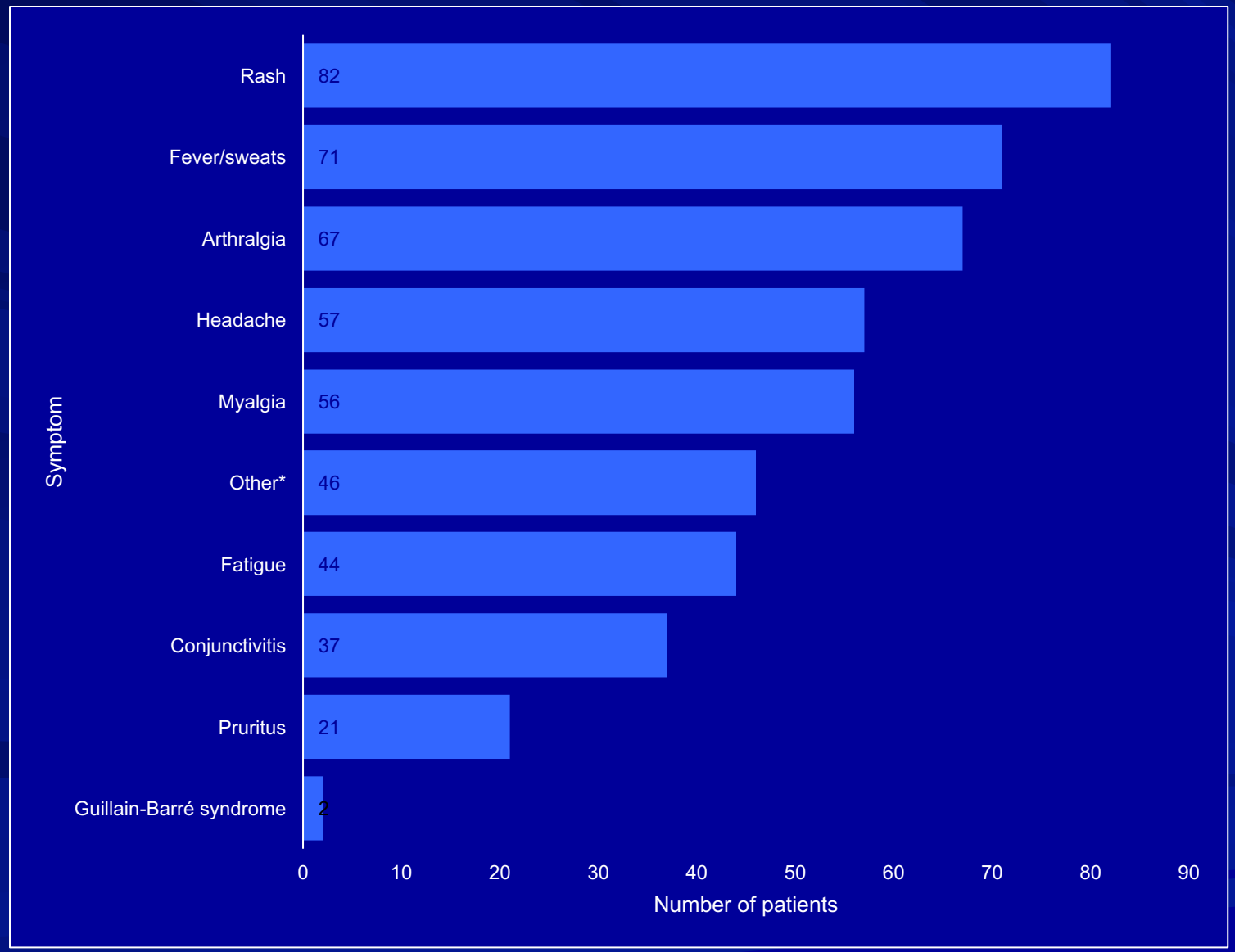
- Martinique January to June 2016
  - Screened 4129 blood donations
  - 1.84% positive by nucleic acid testing
- Contacted donors to determine whether they were or became symptomatic
  - Mean $\log_{10}$ RNA higher if symptomatic (P = .0013)
  - Symt:asympt 1:1
    - Gallian P et al. Blood 2017



Sexual Transmission

- Preliminary semen carriage studies:
  - Up to 188 days by PCR. Mean 34, CI 28-41
  - Unpublished intermittent shedding upto 1 yr (ECDC)
  - Replication competent Zika in semen for 69 days
    - But RNA virus: likely real
- High viral load in semen (and urine)
- Rarely hematospermia or microhematospermia
- Viral shedding in vaginal secretions to 14 days and in cervical mucus to day 11 post-symptom onset
- Time from sexual contact to symptom onset 8-21 days
  - Hamer DH et al. Curr Infect Dis Rep 2017
  - Russell K et al. Clin Infect Dis 2016
  - Paz-Bailey NEJM 2017

Clinical symptoms and signs in 93 patients with Zika virus disease acquired in the Americas



Hamer DH et al. GeoSentinel case series Ann Int Med 2016

rash

o

esy of

v,

land,

Maculopapular rash after travel to Haiti

Maculopapular rash after travel to Haiti

Zika rash

Photo courtesy of Marc Shaw, Auckland, NZ

Less Common Signs

- Joint swelling
- GI: diarrhea, nausea, vomiting
- Paraesthesias
- Retro-orbital pain
- Pharyngitis
- Dysgeusia
- Subcutaneous hematomas
- Epididymitis

Substantial Clinical Overlap Among Common Arboviruses

Feature	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Arthralgia/ arthritis	++	+	+++
Conjunctivitis	++	-	-
Myalgia	+	++	+
Headache	+	++	++
Hemorrhage	Rare	+/-	-
Shock	-	+	-

Co-infection Data for 346 Nicaragua Children Waggoner JJ et al. CID 2016

ZCD Assay Result	Number, n (% of all Samples)
Positive	263 (76.0)
Monoinfections	*192 (55.5)*
ZIKV	47 (13.6)
CHIKV	91 (26.3)
DENV[a]	54 (15.6)
Coinfections	*71 (20.5)*
ZIKV-CHIKV	16 (4.6)
ZIKV-DENV[a]	6 (1.7)
CHIKV-DENV[a]	43 (12.4)
ZIKV-CHIKV-DENV[a]	6 (1.7)
Negative	83 (24.0)

Abbreviations: CHIKV, chikungunya virus; DENV, dengue virus; ZCD, multiplex real-time reverse-transcription polymerase chain reaction for the detection and differentiation of ZIKV, CHIKV, and DENV; ZIKV, Zika virus.

[a] Serotypes of 109 DENV-positive samples: DENV-2, 107; DENV-1, 1; DENV-4, 1.

Zika Neurological Complications

- Congenital Zika syndrome
  - Fetal brain disruption sequence
  - In vitro: Asian strain only
    - $ZIKV^{AF}$ –monkey adapted
      - Cugola, Nature 2016
- Guillain-Barré syndrome (GBS)
- Meningoencephalitis
- Acute myelitis
- Hearing loss
- Posterior uveitis

So – what's our advice?
Risk assessment

- Risk of CZS if infected (USA registry)
  - Approx 5% (51/1297 pregnancies)
    - 10% if lab confirmed (24/250),
    - 15% 1st trimester (9/60)
  - 30x higher than baseline
  - 1/5 risk of 1st trimester rubella
- Risk of GBS
  - About 1/4000 cases (cf Campylobacter)
  - Maybe faster, milder
  - Acute motor axon type

MMWR April 7 2017, Song BH, J neuroimmunol 2017

When is the risk?

- 1st trimester – consistently shows highest risk
  - Peri-conception: theoretically low risk, but not supported by epi data
  - Placental persistence
- All pregnancy
  - Interrupted brain development at any stage
  - May seem normal at delivery
  - Should be imaged
- After delivery??
  - Low inoculum, more intact BBB

Risk assessment
Where are travelers getting Zika?

Region of Travel	Canada (n=482)[a]	Country visits from Canada over two years[b]	United States (n=2,382)[c]	England (n=295)[d]
Carribbean	65% (313)	7,328,800	65% (1,545)	73% (215)
South America and Central America	19% (92)	2,921,800	27% (658)	23% (68)
N America	9%[e] (43)	4,330,800[g]	5% (111)	2% (6)
Cumulative % from the Americas	99.6%		99%	98.6%
Asia	0.4%[f] (2)	5,395,800	<1% (11)	1.7%[i] (4)
Oceania	0% (0)	390,200[h]		
Sub-Saharan Africa	0% (0)	1,237,600	0% (0)	0% (0)

Many numbers are estimates extrapolated from multiple sources, not official

WHO Classifications of Zika Transmission

- Category 1:
  - Countries with a reported outbreak from 2015 onwards
  - e.g. Angola, Brazil, Maldives, USA
- Category 2:
  - Countries with evidence of transmission before 2015 and ongoing transmission
  - e.g. Haiti, Viet Nam

WHO/CDC Classifications of Zika Transmission

- Category 3:
  - Countries with evidence of local mosquito-borne Zika infections in or before 2015, but without documentation of cases since, or outbreak terminated (interrupted transmission) (potential future transmission?)
  - e.g. Easter Island, French Polynesia
- Category 4:
  - Established competent vector, no known transmission
  - e.g. most of Africa, Uruguay, various islands

CDC Recommendations for pregnant women

- Category 1 (plus Haiti, not USA): Travel health notice
  - do not travel
- Category 2, some cat 4
  - (38 countries,incl most of Africa, Asia)
  - Should not travel
  - Includes most of the tropical world
- Sexual transmission precautions for all
- Based on uncertainty in risk
- Implications for insurance, personal ??

How can we estimate the risk?

- Asia:
  - 1 zika case / 2.5 million trips
  - So really 1/250,000 (1/5 symptomatic-say 1/10)
  - Risk of CZS 1/2,500,000 (6% - say 10%)
  - Maybe 1/250,000 (10-fold under estimate)
- S/C America, Caribbean = 100x higher
- Compare:
  - Risk of maternal death – 1/5000 live births
  - Risk of death by MVA – 1/7000/year (x40 in Africa)
  - Baseline risk of major malformation 1-3/100
  - Baseline risk of “Zika-like” malformation 3/1000

Other types of pregnancy risk

- Risk of congenital rubella syndrome:
  - 65-85% in 1st 2 months of gestation
  - Major screening and vaccination programs
- Congenital CMV syndrome:
  - 50% of primary infections, 1/400 pregnancies
  - No program
- CATMAT: >1/10,000 = travel advisory during pregnancy
  - So Category 1 + Haiti

CATMAT

- Pregnancy
  - Cat 1: avoid travel
  - Cat 2: moderate risk, 3-4 low risk
  - Cat 2-4: consider postponing, caution for malaria, discuss with couple, values/preference/risk tolerance
- Sexual contact: Cat 1 = usual avoidance rec's
  - Cat 2-4: avoidance measures not routinely recommended, but discuss

ECDC

- Make modifications of WHO cat's
  - Subdivide cat 1 countries into regions when possible
  - Cat 2+ = areas of cat 2 with "new documented intense transmission" (>10 cases/3 mo, or cases in >1 region)
    - Eg Vietnam, Philippines
  - 4a: no transmission, but border cat 2
- 1, 2+ = high, 2=mod, 3, 4a=low, 4=very low
  - No specific recommendations

Big questions

- Why is Brazil CZS rate >> USA? (29% vs 6%)
  - USA registry based
    - Maybe more severe entered registry
    - Maybe cases occurring outside of registry
  - Outcomes detection systems/methods
    - few infants PCR+, some IgM-, imaging erratic, multiple outcomes
  - Demographic/genetic differences (age)
  - Co-morbidities, exposure to cofactors (dengue?)
  - Not viral strain
  - USA rates higher than French Polynesia (1%)

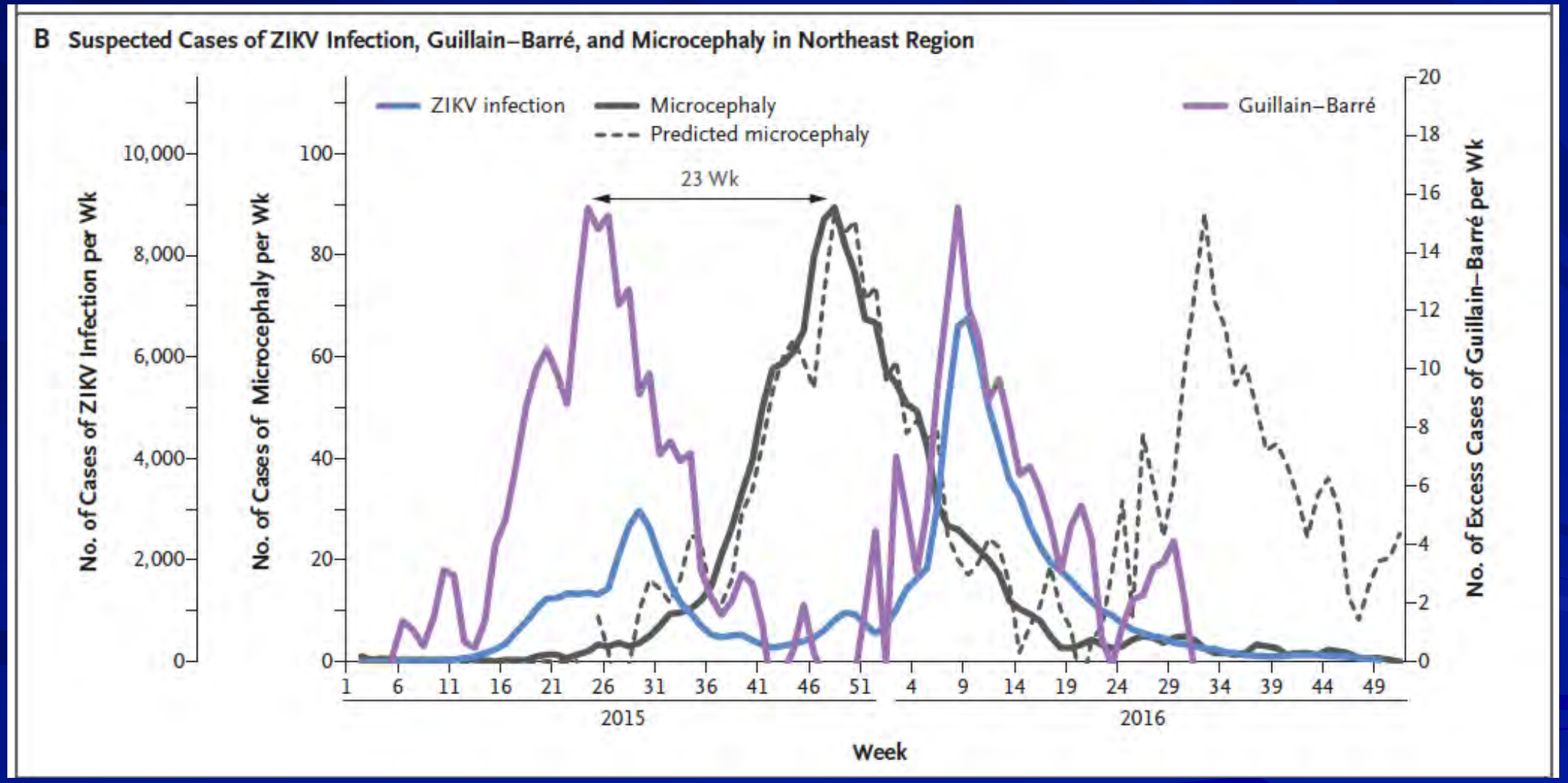
Big questions

- Is epidemic peaking?
  - In South America, still waves of outbreaks, but less than 2016
    - Argentina this austral summer
  - Central America: moving north through the summer
    - USA? Hawaii? Australia?
  - Caribbean: Very slow in Martinique, Guadeloupe, St Martin, French Guiana
  - French Polynesia: outbreak terminated at 50% seroprevalence
    - New Caledonia 12%
      - Aubry M EID 2017, Musso CMR 2016

What about late term or post partum exposure

- Subtle imaging changes?
- Subtle cognitive changes?
  - Cf toxoplasma

Where is the epidemic going?



De Oliveira WK NEJM 2017