ZIKA, DENGUE, CHIKUNGUNYA – TRAVELERS BEWARE!

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Disclosures

- No disclosures

- Acknowledgement:

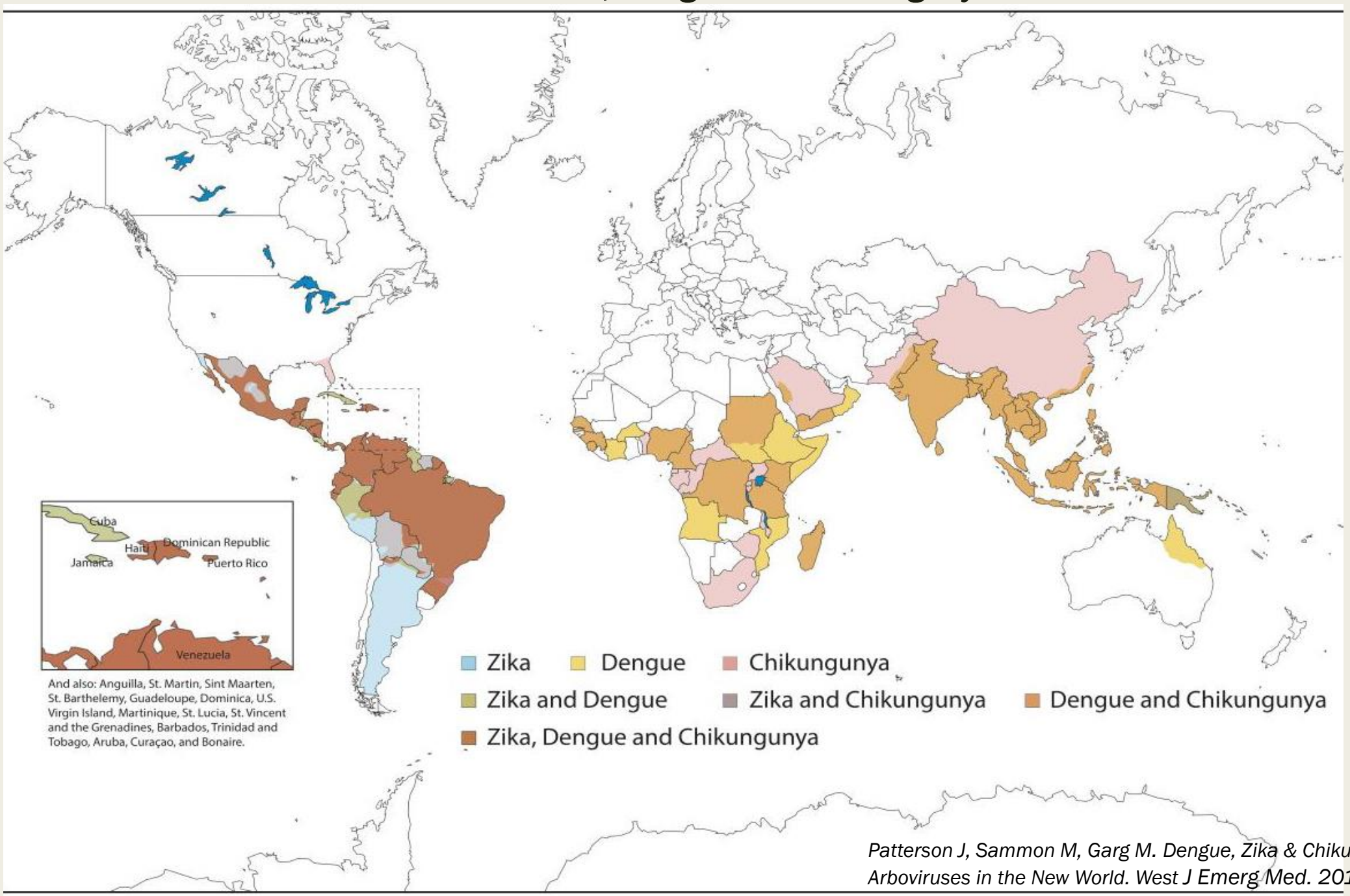
New and emerging information along with Zika updates at ID Week, October 2016 and PAS, May 2017:

  - *Sonja Rasmussen, MD, MS, Director of Public Health Info & Dissemination; Ed/Chief of MMWR, Centers for Disease Control and Prevention, Atlanta, GA*
  - *Lyle Peterson, MD, MPH, Division of Vector-Borne Disease, National Ctr for Emerging and Zoonotic Infectious Diseases, CDC, Ft Collins, CO*

Learning Objectives

- Compare presentations in patients infected with Dengue, Chikungunya and Zika
- Discuss clinical manifestations and laboratory findings in older children and adults with Zika Virus infection
- Recognize manifestations of Congenital Zika Virus infection
- Discuss diagnostic testing for pregnant women and infants with suspected Zika Virus exposure or infection

Global Distribution of Zika, Dengue and Chikungunya Viral Infections



Patterson J, Sammon M, Garg M. Dengue, Zika & Chikungunya: Emerging Arboviruses in the New World. West J Emerg Med. 2016; 17: 671–679

Dengue Virus

- Arbovirus
  - transmitted by *Aedes* mosquito
- Genus: Flavivirus
- Single stranded RNA
- 4 Types
  - DEN-1
  - DEN-2
  - DEN-3
  - DEN-4

Epidemiology

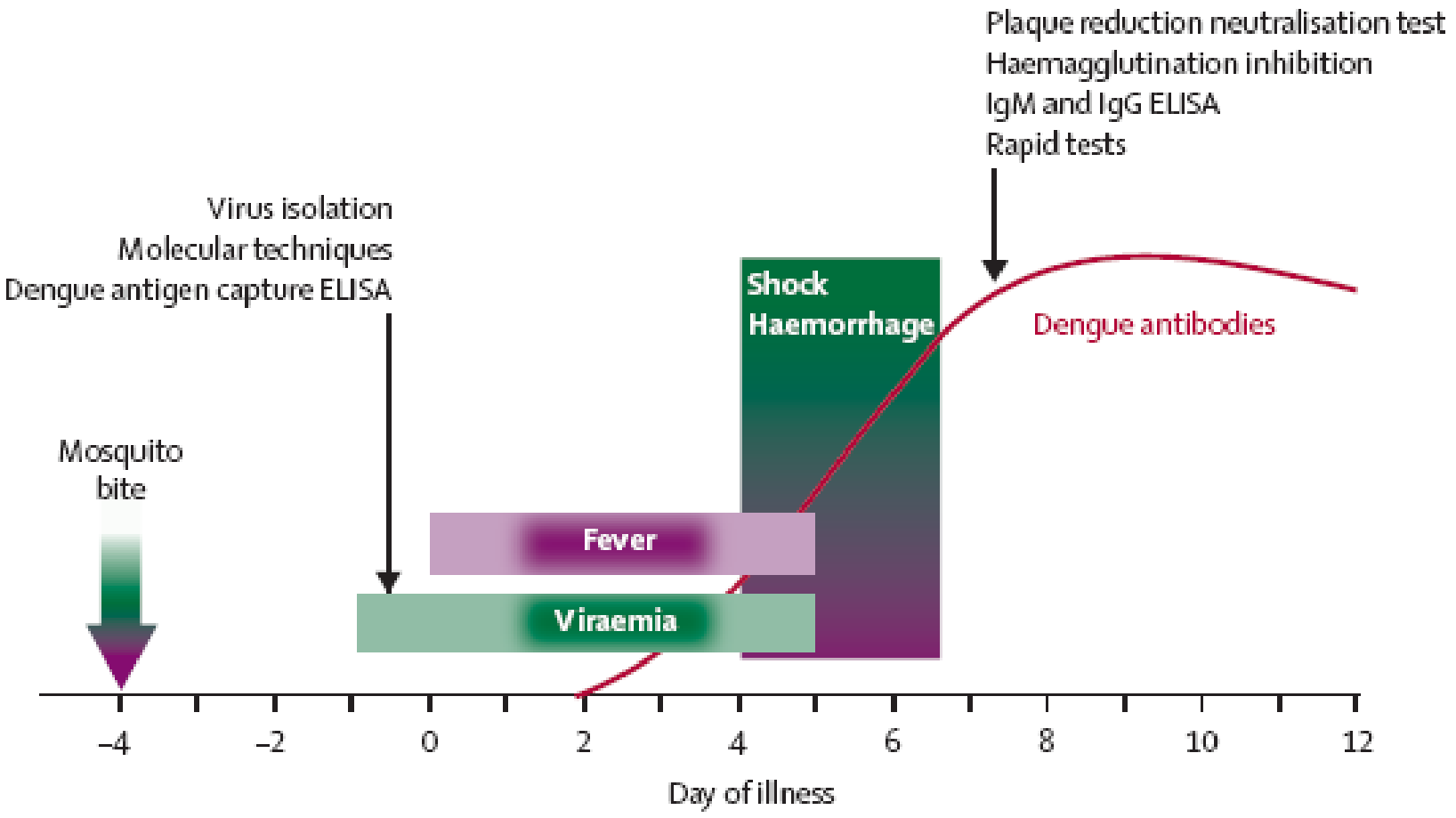
- ~ 20 million cases/year
  - Symptomatic & asymptomatic
- ~ 24,000 deaths/year

Clinical Syndromes

- Asymptomatic
- Dengue fever
- Dengue hemorrhagic fever
- Dengue shock syndrome

Center for Disease Control, Atlanta, USA.

Dengue



Lancet 2007; 370: 1644–52

Three Phases of Dengue: Incubation, Febrile and Recovery

Dengue Time Frame

Phase	Incubation	Febrile Phase						Critical Phase		Recovery phase
Time frame	3-14 days	3-7 days						1-2 days		3-5 days
Symptoms	None	Fever is present						Fever resolves		
		>Myalgias >Rash >Petechiae >Tourniquet test >Leukopenia >Mild bleeding					Warning signs may occur	>Capillary leak >Shock >Severe hemorrhage >Severe organ involvement		> Fluid Reabsorption >Diuresis
Testing						DENV IGM				
		DENV NS1 DENV PCR								
Day of illness	0	1	2	3	4	5	6+	7	8	9	10+

Figure 3

Three distinct phases of dengue infection have been described: incubation, febrile, and recovery. The critical phase, when patients may become unstable, typically occurs after defervescence of the

Patterson J, Sammon M, Garg M: Dengue, Zika and Chikungunya: Emerging Arboviruses in the New World. West J Emerg Med. 2016; 17: 671–679

Dengue: Treatment

- Supportive care
  - Replace plasma volume
  - Coagulation factors

- No ASA or NSAIDs

Chikungunya

- **Chikungunya** – means *“that which bends up”, referring* to the characteristic symptom of arthralgia
- presents as a more benign dengue-like syndrome:
  - *abrupt onset of fever*
  - *arthralgia*
  - *maculopapular rash*
  - *leukopenia*

DENGUE

RED SPOTS OR PATCHES ON THE SKIN

RESTLESSNESS

LOSS OF APPETITE

BLEEDING FROM GUMS OR NOSE

JOINT PAIN

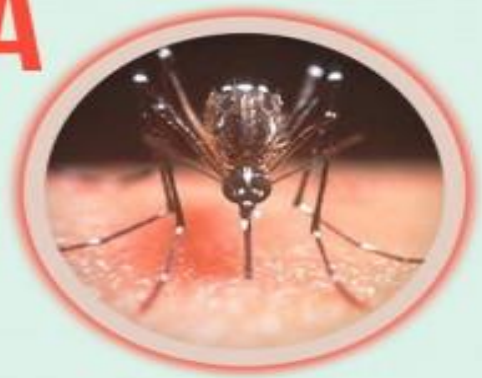
HEADACHES

HIGH FEVER

PAIN BEHIND EYES

NAUSEA AND VOMITING

CHIKUNGUNYA



HEADACHES

SEVERE JOINT PAIN MAINLY IN THE ARMS AND LEGS

MUSCLE PAIN

RED SPOTS OR PATCHES ON THE SKIN

HIGH FEVER

ZIKA

JOINT AND MUSCLE PAINS

BACK PAIN

MILD FEVER

HEADACHES

RED EYES

RED AND WHITE PATCHY SKIN RASH

Comparison of Clinical Features in Zika, Dengue and Chikungunya Viral Infections

Features	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	–	–
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Hemorrhage	–	++	–
Shock	–	+	–

Reproduced from: Centers for Disease Control and Prevention. Zika

Chikungunya and Dengue in Children: Distinguishing Clinical Findings – occur with Different Frequency

Manifestation	Chikungunya (32 Cases)		Dengue* (32 Cases)		Significance
	Number†	Percent	Number†	Percent	
Maculopapular rash	19/32	59.4	16/132	12.1	$p < .001$
Conjunctival injection	15/27	55.6	20/61	32.8	$.05 > p < .01$
Myalgias, arthralgias	8/20	40.0	9/75	12.0	$.05 > p < .01$

Textbook of Pediatric Infectious Diseases 2014. Ed Feigin and Cherry

Chikungunya and Dengue in Children: Comparison of Frequency of Clinical Findings

	Hospitalized				Outpatient			
	Chikungunya (32 Cases)		Dengue (142 Cases)*		Chikungunya (17 Cases)		Primary Dengue (27 Cases)*	
Day of Illness	No.	%	No.†	%	No.	%	No.	%
Headache	13/19	68	37/83	45	2	12	4	15
Injected pharynx	28/31	90	121/125	97	12	71	27	100
Enanthem	3/27	11	7/84	8	0	24	0	22
Rhinitis	3/31	6	6/47	13	4	6	6	41
Cough	7/30	22	17/79	22	1	35	11	56
Vomiting	19/32	59	73/126	58	6	6	15	15
Constipation	12/30	40	16/30	53	0	18	4	4
Diarrhea	5/32	16	5/78	6	1		1	7
Abdominal pain	6/19	32	38/76	50	3		2	
Lymphadenopathy	8/26	31	32/79	41				
Restlessness	10/30	33	17/79	22				

Chikungunya and Dengue in Children: Comparison of Frequency of Clinical Findings

	Chikungunya				Primary Dengue		Secondary Dengue	
	Outpatients (17 Cases)		Inpatients (32 Cases)		Outpatients (27 Cases)		Inpatients (135 Cases)	
Day of Illness	No.*	%	No.	%	No.	%	No.	%
Positive tourniquet test result	3/17	18.0	24/31	77.4	4/27	14.8	94/112	83.9
Petechiae, scattered	0/17	0	10/32	31.2	4/27	7.4	60/129	46.5
Petechial rash	0/17	0	0/32	0	2/27	7.4	13/129	10.1
Maculopapular rash	0/17	0	19/32	59.4	1/27	3.7	16/132	12.1
Epistaxis	0/17	0	4/32	12.5	0/27	0	20/106	18.9
Gum bleeding			0/32	0			2/135	1.5
Melena, hematemesis			0/32	0			14/119	11.8

ZIKA


Zika virus spreading 'explosively'
» Global health emergency may be declared on Monday
» Up to 4 million people could be infected in the Americas this year, doctors predict
» World wakes up to threat from infection, with 'strongly suspected' link to birth defects
alamy stock photo


6
National
Couples travelling to Zika zone told: use condoms for a month
Alert to people returning from 23 affected countries
Public health regulators urge use of contraception
Haroon Siddique and agencies
Couples returning from countries in South and Central America affected by the mosquito-borne Zika virus should not try for a baby for a month, according to official advice issued yesterday.
alamy stock photo
www.alamy.com - FEKM17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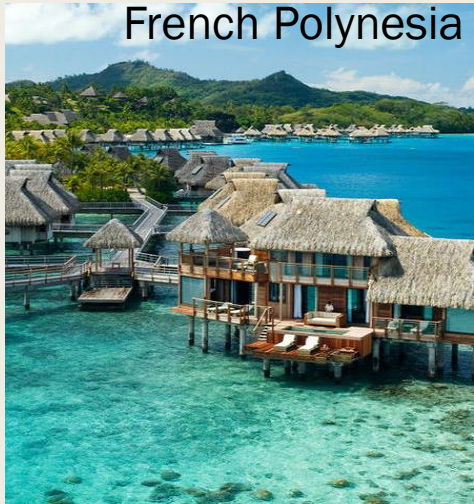
ZIKA SPREADS WORLDWIDE
EXPLOSIVE PANDEMIC EXPECTED
LEVEL 2 TRAVEL ALERT ISSUED
PRESIDENTIAL AUTHORITY COMES INTO PLAY

Zika Virus identification and Spread

- Arbovirus
- Flavivirus family
  - *ssRNA enveloped virus; both African and Asian genotypes of virus*
  - *Closely related to Dengue, WNV, Japanese encephalitis, Yellow fever virus*
- 1947 – first isolated from a macaque in the Zika Forest (Uganda)
- 1953 – ZV recognized as cause of human illness in Jegeria
- Before 2007 - only 14 sporadic human cases reported in Africa & southeast Asia
- 2007 - large outbreak of ZV disease on Yap Island in Pacific
  - *Attack rate 73%; 20% symptomatic*
  - *2/3rds on island seroconverted*
- 2013-14 - large outbreak in French Polynesia

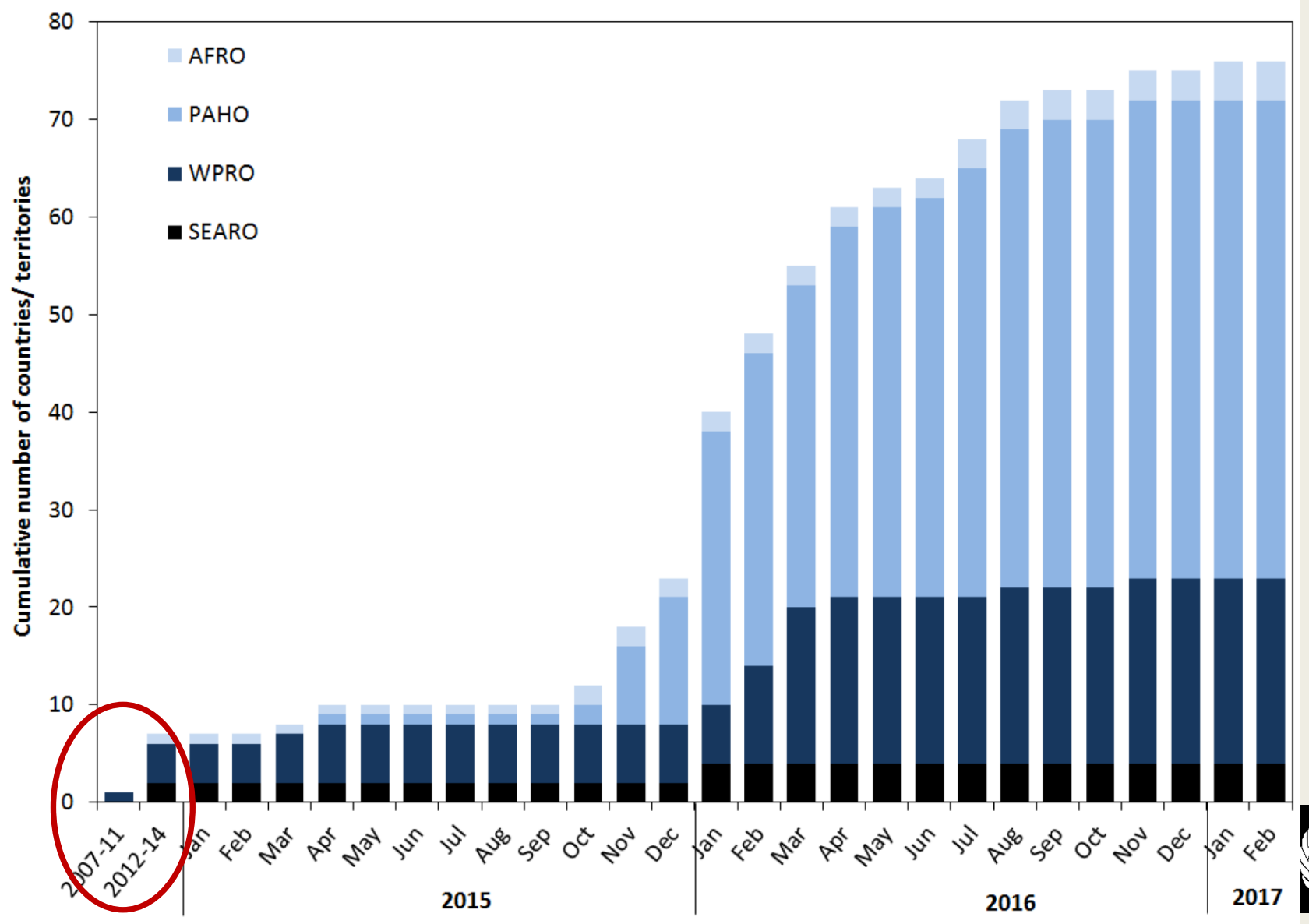


NEJM april 13, 2016

Zika Virus identification and Spread

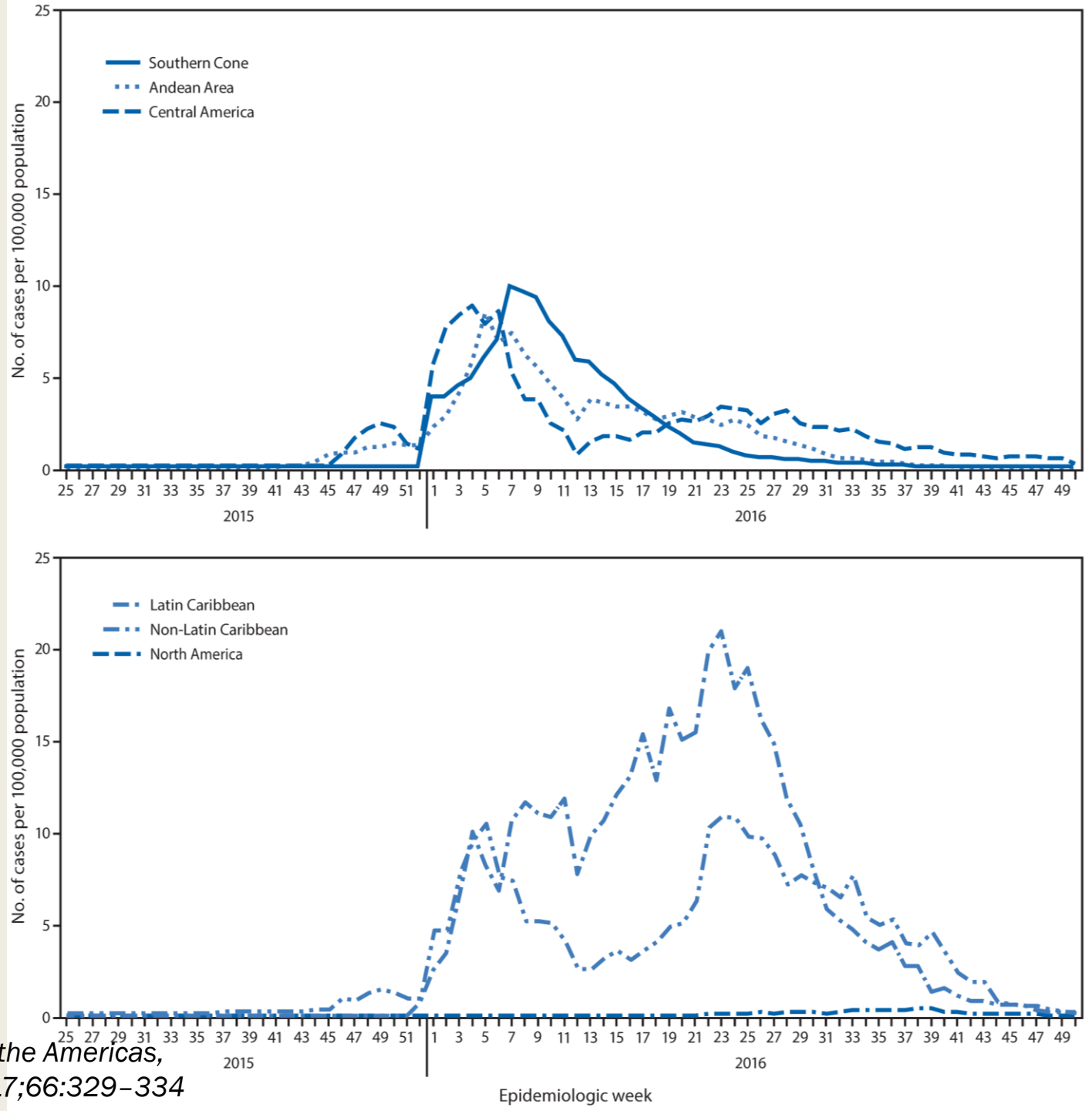
- 76 countries and territories have reported mosquito-borne Zika virus transmission since 2007
  - *70 report ZV in or after 2015*
- March 2015 – ZV (Asian genotype) identified in the Americas, in Brazil
  - *Before 2015, there were no reports of Zika disease in the Americas*
- Sept 2015 - increased number of infants with microcephaly noted in NE Brazil
- Early 2016 - increased microcephaly observed retrospectively in French Polynesia, following 2013-14 outbreak
- **January 15, 2016 - CDC issued interim travel guidance for pregnant women**
  - *Recommended they avoid travel to areas with ongoing ZV transmission based on concern for neonatal birth defects*

Cumulative # of countries and territories reporting mosquito-borne ZV transmission for the 1st time by year (2007–2014), and by month from 1/1/15 to 2/1/17



World Health Organization

Zika Virus Disease in the Caribbean, May 2015- Dec 2016



Ikejezie J, Shapiro CN, Kim J, et al. Zika Virus Transmission — Region of the Americas, May 15, 2015–December 15, 2016. MMWR Morb Mortal Wkly Rep 2017;66:329–334

Zika Virus Routes of Transmission

- First mosquito-borne virus transmitted sexually and first major cause of congenital birth defects in years (since rubella).
- **Routes of transmission:**
  - *Aedes sp. Mosquitoes*
    - *Aedes aegypti* and *Aedes albopticus*
  - *Intrauterine*
  - *Perinatal – 2 cases who did well*
  - *Percutaneoous*
  - *Sexual*
    - long duration in semen, documented up to 188 dys post illness onset but usually <60 days
    - higher titer in semen vs. serum
    - reported transmission from infected travelers to non-traveler partners within 20 days
  - *Laboratory exposure*
  - *Blood Transfusion (probable)*

Aedes species Mosquitoes

- Efficient mosquitoes; Day and nighttime biters
  - *Peak feeding during day, often bites indoors, can feast on multiple humans per feed*
- Found in the US– northern not permanent in north but possibly spread intermittently with travel…
- Same mosquitoes transmit the following viruses:
  - *Dengue*
  - *Yellow fever*
  - *Chikungunya*
  - *Zika*
- All 4 can have Enzootic cycle and urban epidemic spread
- Urban epidemic spread - humans infect mosquitoes
- Humans can serve as amplifying host – can spread by travel
  - *Humans thought to develop lifelong immunity, herd immunity important*

Vector Surveillance Maps for *Aedes aegypti* and *Aedes albopticus, 4/2015*

Figure 2a

A.aegypti

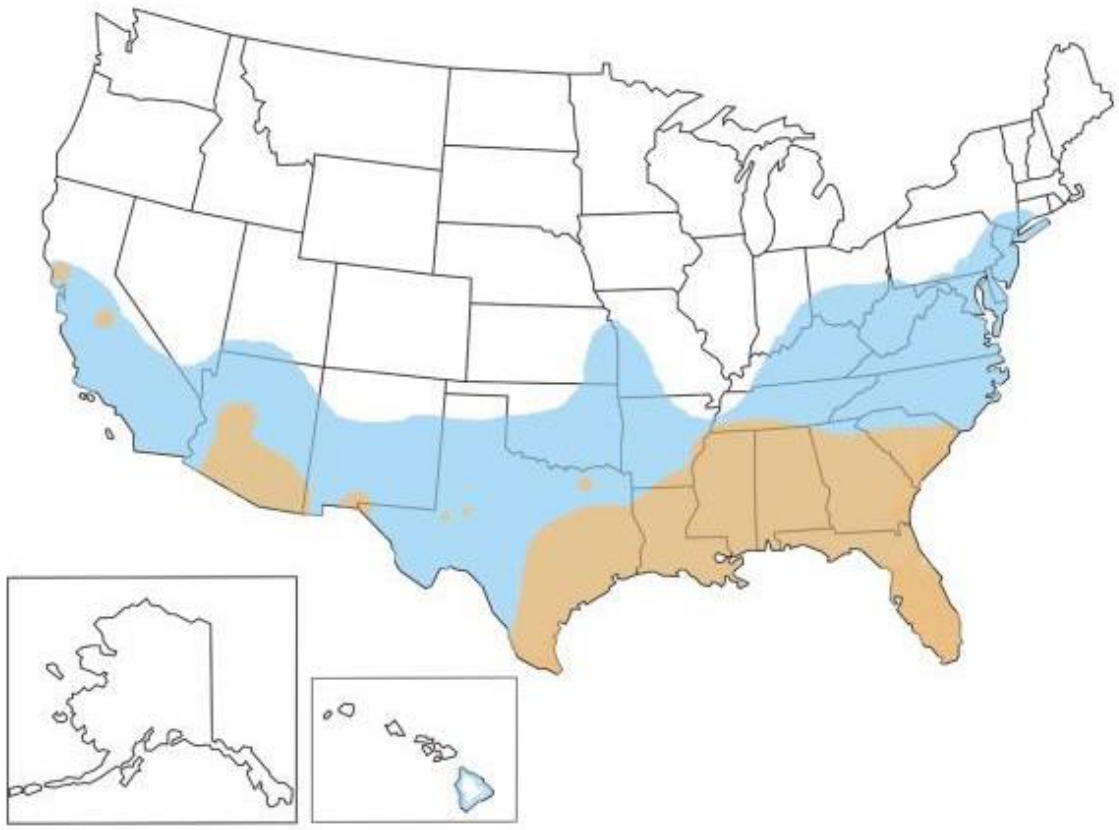
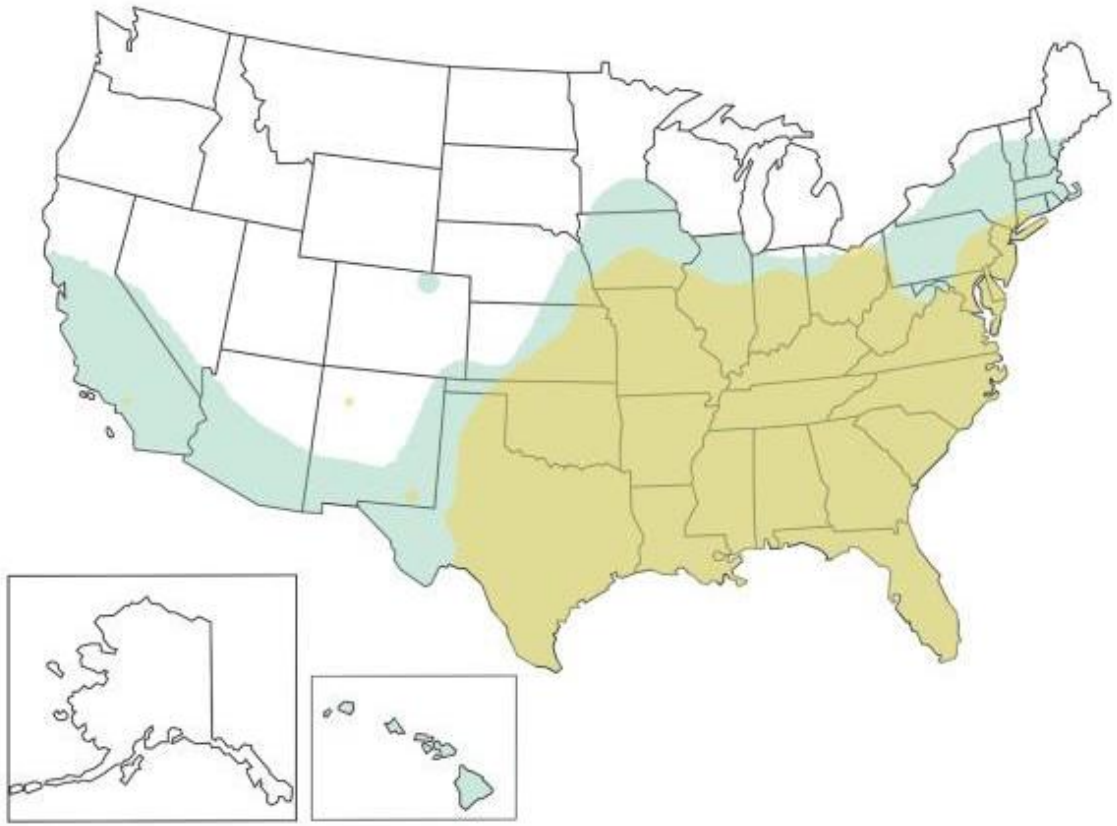


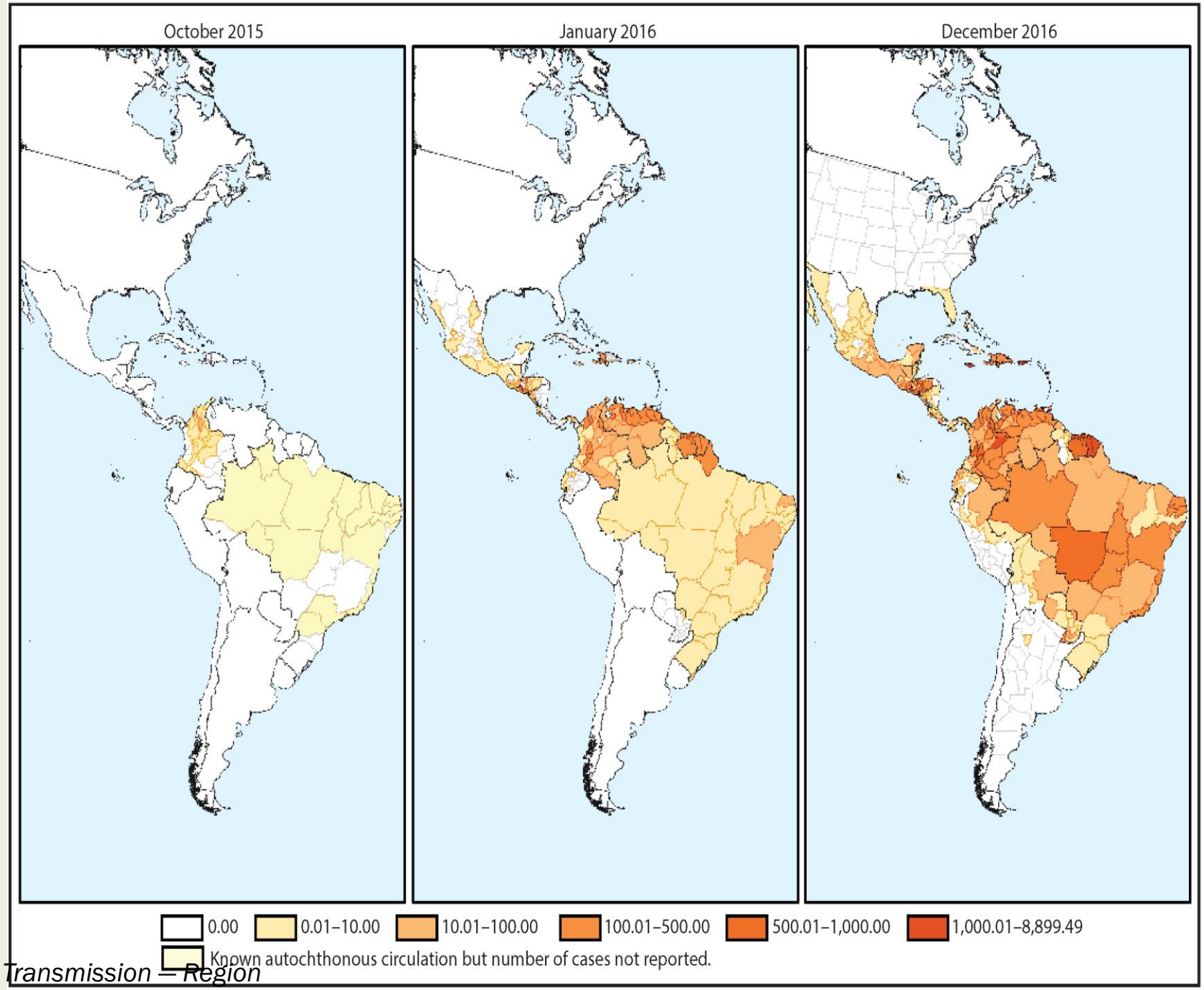
Figure 2b

A.albopictus



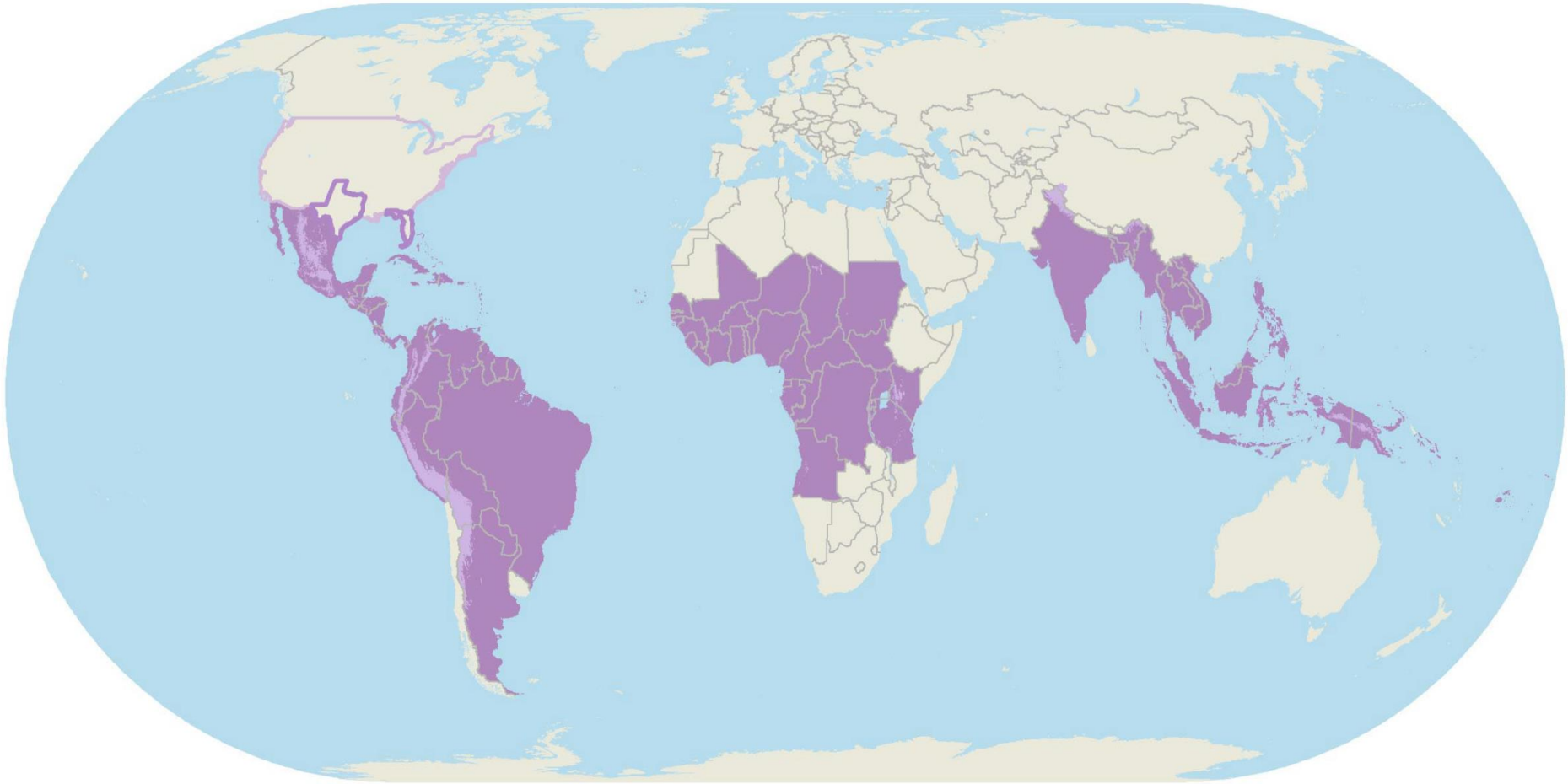
Patterson J, Sammon M, Garg M. Dengue, Zika and Chikungunya: Emerging Arboviruses in the New World. West J Emerg Med. 2016; 17: 671–679

Cumulative suspected & confirmed cases of ZV disease per 1000,000 in the Americas



Ikejezie J, Shapiro CN, Kim J, et al. Zika Virus Transmission — Region of the Americas, May 15, 2015–December 15, 2016. MMWR 2017;66:329

World Map of Areas with Risk of Zika



United States areas

- State Reporting Zika
- No Known Zika

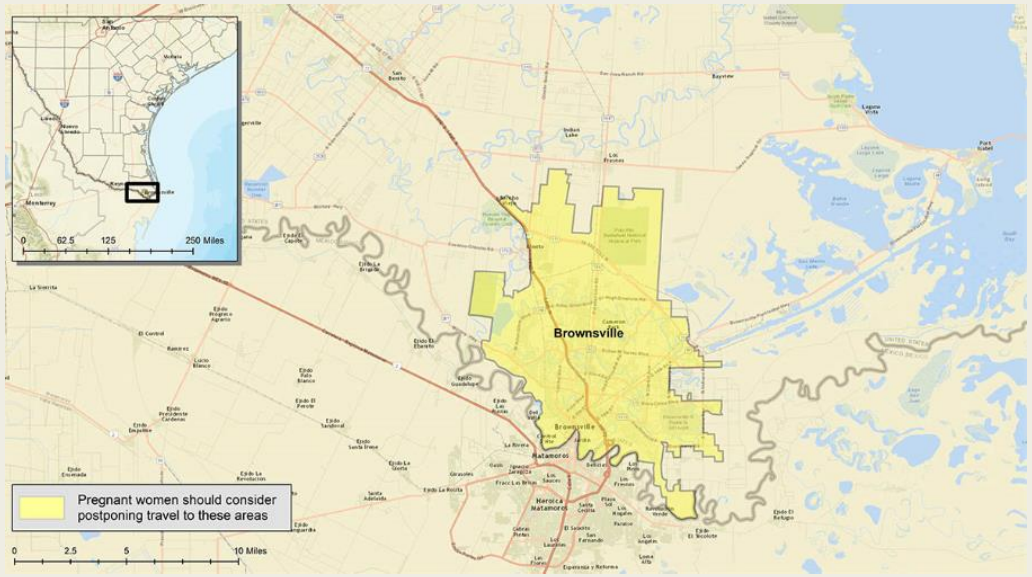
International areas

- Area with risk of Zika
- Area with minimal risk of Zika
- No Known Zika

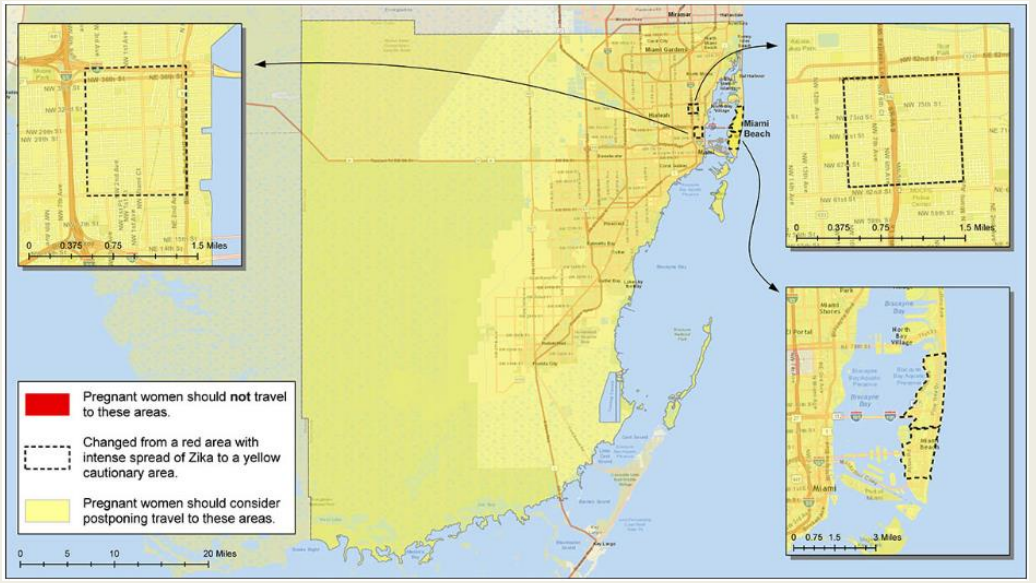
CDC June 2017

Zika in the United States

- Local mosquito-borne spread of Zika virus identified in Miami-Dade County, Florida, and Brownsville, Texas
- Pregnant women should consider postponing travel to all parts of these areas



Brownsville, Texas

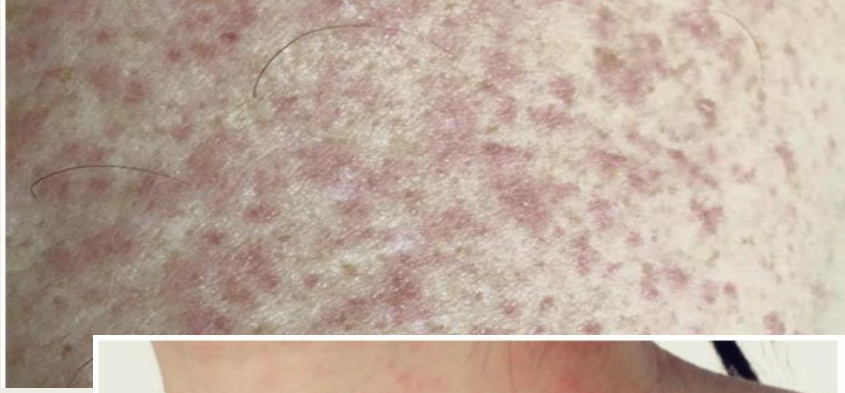


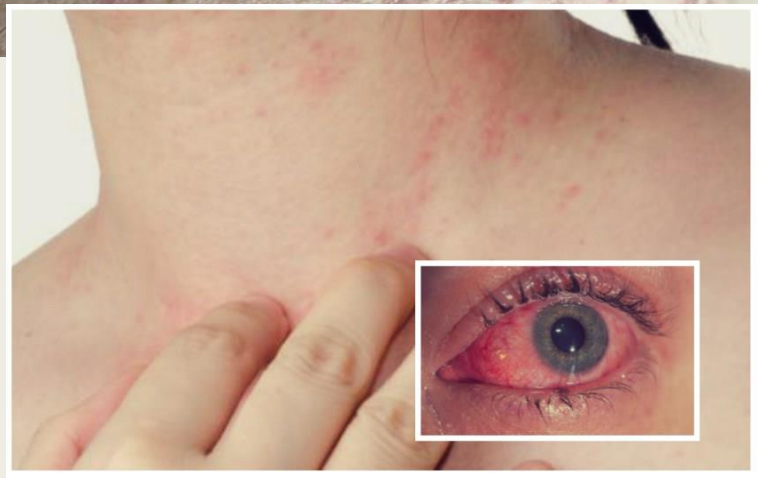
Miami-Dade County, Florida

Zika Virus: Clinical Manifestations

- Median incubation period ~6 days
- Usually a mild or asymptomatic infection (~80%)
  - *Can be asxic and viremic*
  - *Symptomatic – duration several days to a week*
- Approx 20% sxic and usually have a mile clinical illness
- Severe disease uncommon unless already co-morbid conditions or thrombocytopenia
  - Fatalities rare
- Symptoms last several days to a week

Zika Virus: Clinical Manifestations





- Most common signs and symptoms:
  - *Rash,* –90% Maculopapular, often pruritic
    - lasts ~1 week
  - *Fever* - 65%, usually low grade
  - Arthritis or arthralgia, 65%
  - *Conjunctivitis,* Non-purulent 55%
  - *Headache*
  - *Muscle pain, myalgia*
  - *Some with thrombocytopenia*

- Once infected, likely protected from future infections (if like other viral infections)

- Neurological disease: GBS ~1:5000 infections with GBS reported in the UK; multiple reports
  - *other syndromes – encephalitis, ADEM, anterior myelitis, ocular abnormalities, hearing loss*
  - *6 – 7 dys to onset of GBS, ~1/3rd required mechl ventilation; 80 – 90+% incr CSF protein*

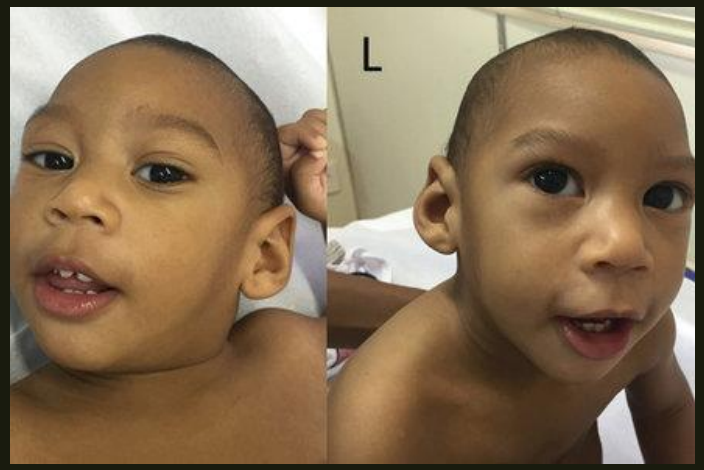
Patterson J, Sammon M, Garg M. Dengue, Zika and Chikungunya. West J Emerg Med. 2016; 17: 671

Zika Virus Disease: Clinical Management

- Supportive symptomatic treatment
  - *Rest*
  - *Hydration*
  - *No NSAIDs or ASA until Dengue ruled out*
  - *Acetaminophen prn fever and/or pain*

- Prevent mosquito bites during 1st week of illness to avoid transmission to others through mosquito

- No vaccine or specific antiviral
  - *Vaccines currently under study*



March 13, 2017

Zika Warning Issued Over Sperm Banks in the Miami Area

CONGENITAL ZIKA SYNDROME (CZS)

April 4, 2017

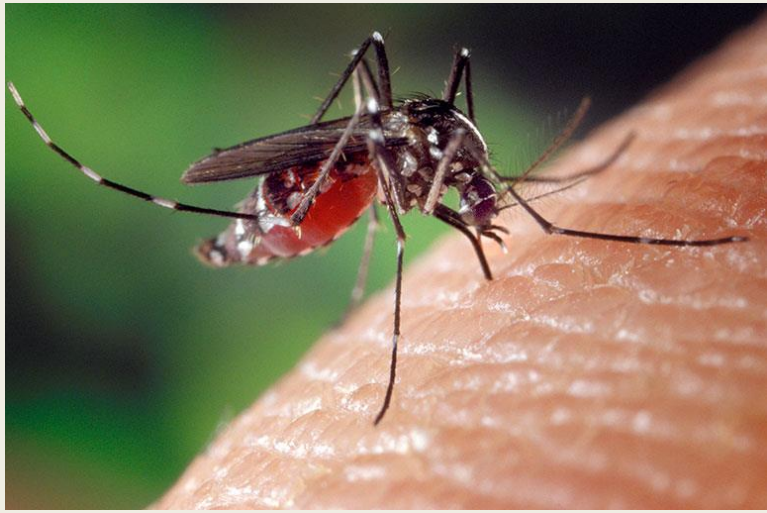
One in 10 Pregnant Women With Zika in U.S. Have Babies With Birth Defects by PAM BELLUCK

Birth Defects Rise Twentyfold in Mothers With Zika, C.D.C. Says

By DONALD G. McNEIL Jr.MARCH 2, 2017

- *First major infectious disease linked to birth defects to be discovered in more than a half century*

- *“…the last time an infectious pathogen (rubella virus) caused an epidemic of congenital defects was more than 50 years ago…”*
  - *NEJM 4/13/16*



- *“Never before in history has there been a situation where a bite from a mosquito could result in a devastating malformation”*
  - *Tom Frieden, Director of CDC / Fortune 2016*

- US Zika Pregnancy Registry
  - *Lab evidence of ZV infection during Pregnancy*
    - US 1,762 women
      - *58 of 1367 delivered with birth defects, 7 pregnancy losses*
    - US territories 3,592 women

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Zika Virus and Birth Defects — Reviewing the Evidence for Causality

Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H.,
Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.

SUMMARY

The Zika virus has spread rapidly in the Americas since its first identification in Brazil in early 2015. Prenatal Zika virus infection has been linked to adverse pregnancy and birth outcomes, most notably microcephaly and other serious brain anomalies. To determine whether Zika virus infection during pregnancy causes these birth outcomes. Addressing these questions will improve our ability to reduce the burden of the effects of Zika virus infection during pregnancy.

POTENTIAL RELATIONSHIP BETWEEN ZIKA VIRUS INFECTION AND BIRTH DEFECTS

- Based on available evidence and use of “criteria specific for evaluation of potential teratogens and the Bradford Hill criteria, we suggest that sufficient evidence has accumulated to infer a causal relations between prenatal ZV infection and microcephaly and other severe brain anomalies.”

N Engl J of Med 374;20;1981. May 19, 2016

Congenital Zika Syndrome

- Recognized pattern of congenital anomalies associated with ZV infection during pregnancy, including:
  - *Microcephaly*
  - *Intracranial calcifications*
  - *Other brain anomalies, such as thin cerebral cortex with subcortical calcifications, absent corpus callosum, hydrocephalus, hydranencephaly, flattened head shape*
- CZS also linked to:
  - *ocular anomalies*
    - structural and anterior eye abnormalities
    - optic nerve dysplasia and pallor
    - macular scarring, pigmentary retinal mottling
  - *hearing loss, limb abnormalities & congenital contractures (arthrogryposis), impaired growth, developmental disabilities, preterm birth, seizures, swallowing issues, cortical blindness, hypertonia*
- + IHC for ZV in aborted fetal tissues

Microcephaly associated with maternal ZV infection

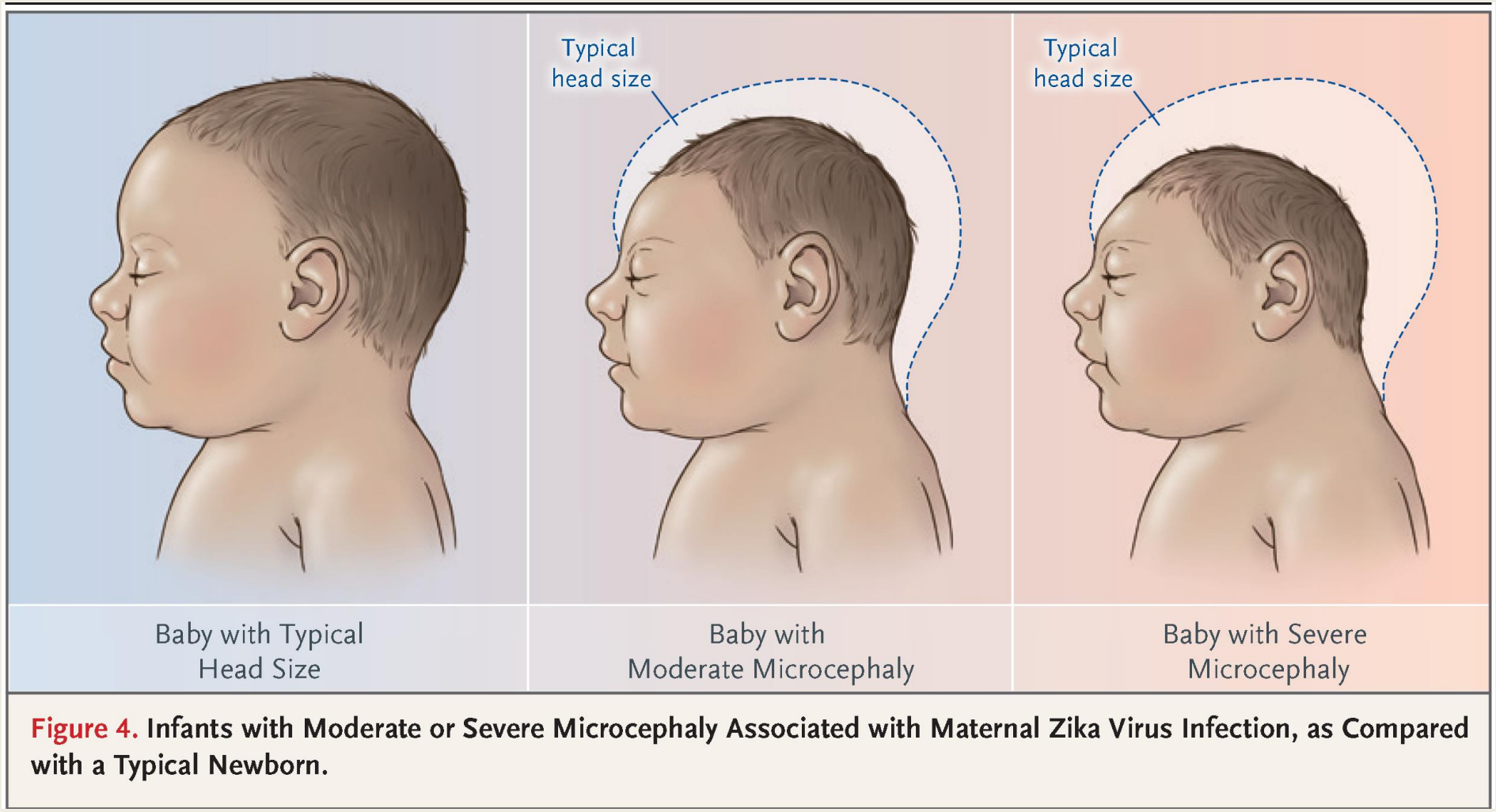


Figure 4. Infants with Moderate or Severe Microcephaly Associated with Maternal Zika Virus Infection, as Compared with a Typical Newborn.

Petersen LR, Jamieson DJ, Powers AM, et al. Zika Virus. NEJM 2016;374:1552-63

Congenital ZV Syndrome

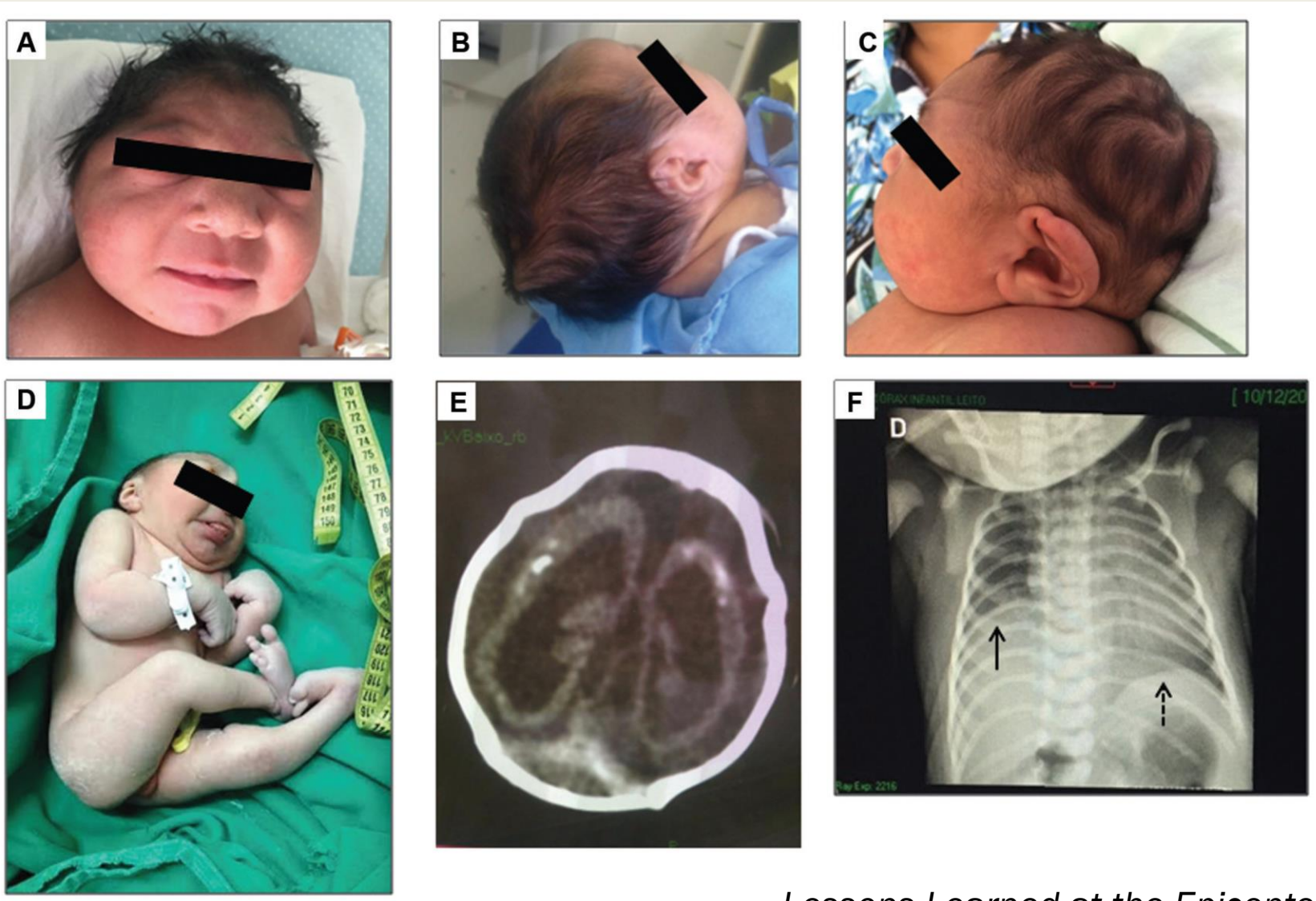


Figure 4. Clinical features and imaging findings of infants with congenital Zika syndrome. *A*, Craniofacial disproportion. *B*, Pointed occiput. *C*, Redundant scalp skin. *D*, Arthrogryposis. *E*, Cerebral calcifications in computed tomography scan. *F*, Right diaphragmatic paralysis (bold arrow).

Lessons Learned at the Epicenter of Brazil's Congenital Zika Epidemic: Evidence From 87 Confirmed Cases
Meneses JdA, Ishigami,AC, Mello LM, et al. CID 2017;64:1302

Microcephaly

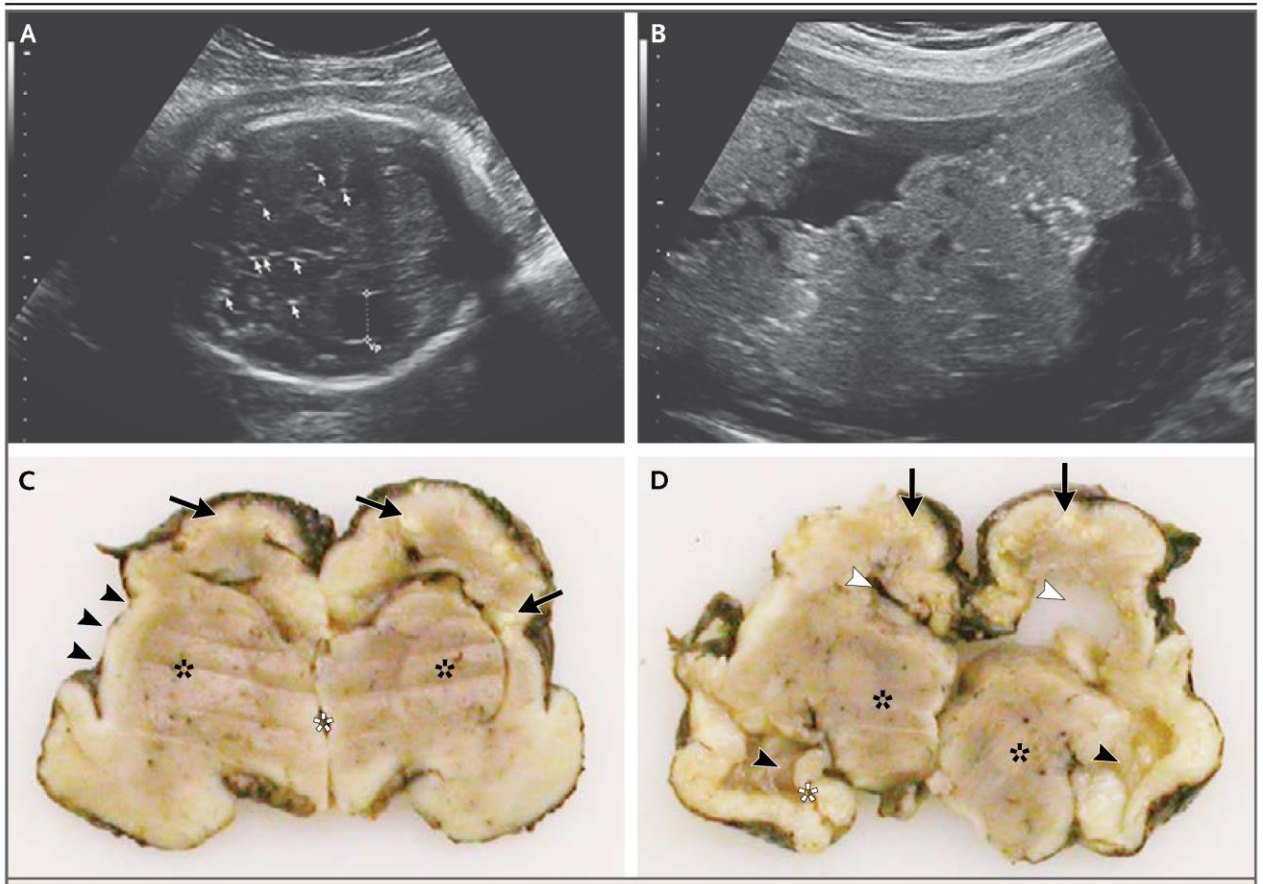


Figure 1. Prenatal Ultrasonographic Images and Photographs of Coronal Slices of Brain.

Panel A shows numerous calcifications in various parts of the brain (some marked with arrows) and the dilated occipital horn of the lateral ventricle (Vp, marked with a measurement bar) as seen on transverse ultrasonography. Panel B shows numerous calcifications in the placenta. Panel C shows multifocal cortical and subcortical white calcifications (arrows) and almost complete loss of gyration of the cortex. The basal ganglia are developed but poorly delineated (black asterisks), and the sylvian fissures are widely open on both sides (arrowheads on the left). The third ventricle is not dilated (white asterisk). Panel D shows dilated body of the lateral ventricles (white arrowheads); the left is collapsed. Temporal horns of the lateral ventricles (black arrowheads) are also dilated. The thalami (black asterisks) and the left hippocampus (white asterisk) are well developed, whereas the contralateral structure is not recognizable owing to autolysis.

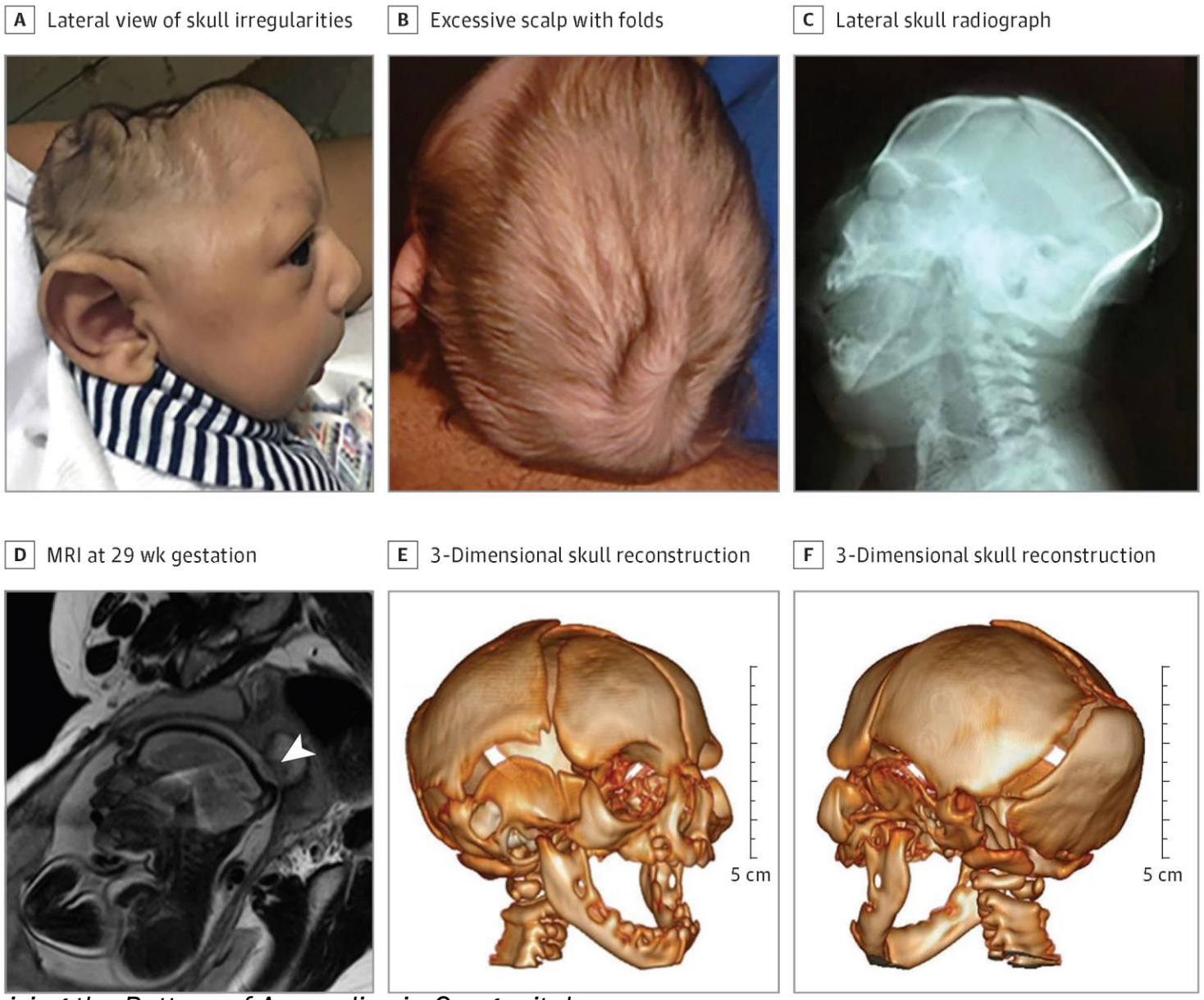
Zika Virus Associated with Microcephaly
Jernej Mlakar, Misa Korva, Nataša Tul, Mara Popović et al. n engl j med 374:10:951

Fetal Brain Disruption Sequence (FBDS)

- 1984 described by Russell, et al – due to vascular event
- Rare phenotype before Zika; ~20 case reports
- Cases of CZS with FBDS – had been rare to see
- Destruction of CNS and disruption of brain development
  - *results in severe microcephaly (most >3SD less than mean)*
  - *partial collapse of fetal skull,*
  - *occipital bone prominence,*
  - *scalp rugae*
  - *neurological impairment*

Fetal brain disruption sequence

Figure 1. Cranial Morphology Supporting Fetal Brain Disruption Sequence Phenotype in Congenital Zika Syndrome



A, Lateral view of an infant with congenital Zika virus infection. Note the severe decrease in cranial vault, irregularity of the skull, and scalp rugae. B, Typical scalp folds or rugae in a 3-month-old infant with presumed congenital Zika virus infection. C, Lateral skull radiograph in a newborn showing partial collapse of the cranial bones with prominent occiput. D, Fetal magnetic resonance image (MRI) showing same phenotype at 29 weeks' gestation. The white arrowhead indicates occipital area. E and F, 3-Dimensional skull reconstruction in a 3-month-old infant showing downward displacement of the frontal and parietal bones while the occipital bone appears stable.

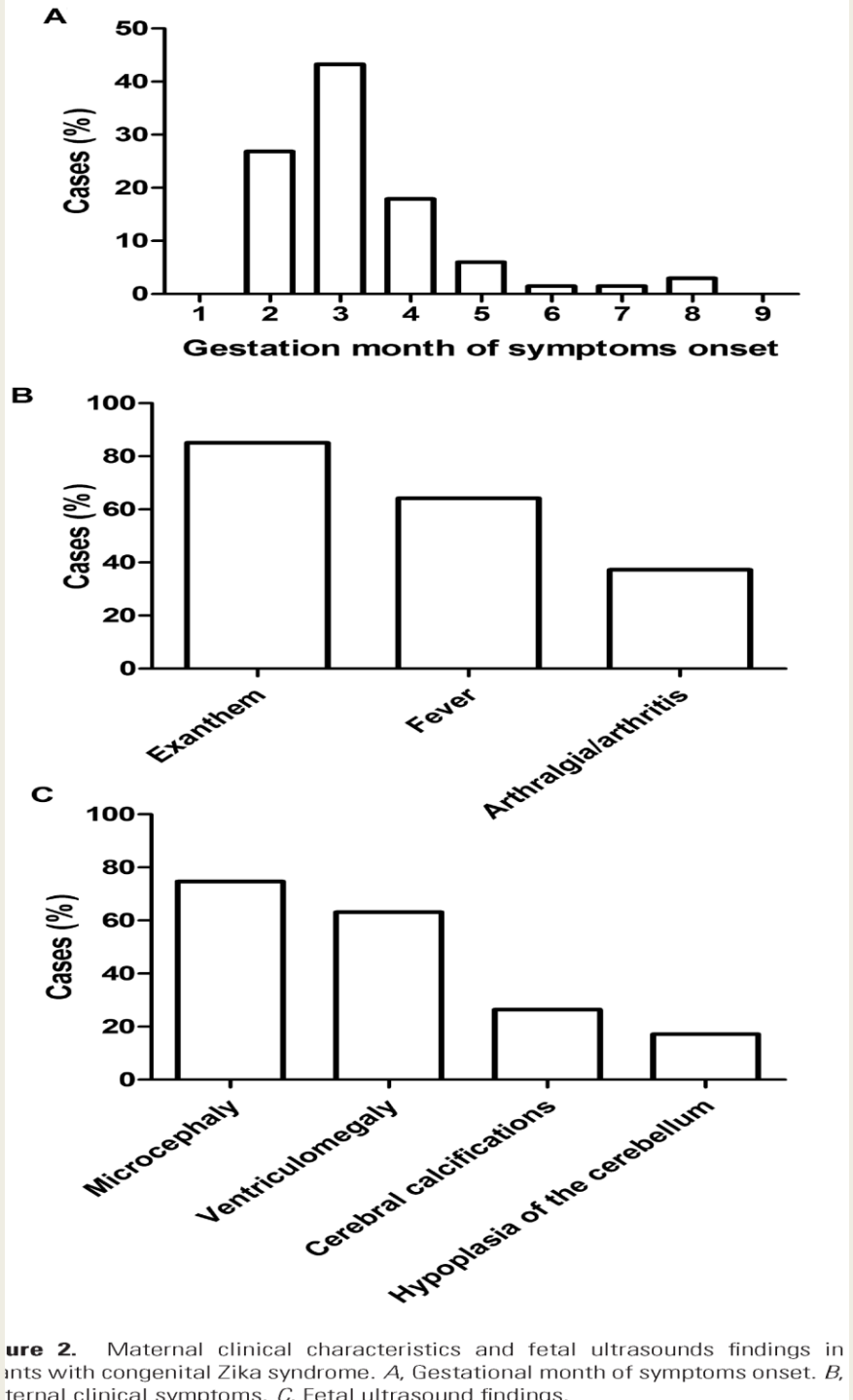
Moore CA, Staples JE, et al. Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians. JAMA Pediatr. 2017;171:288-295

Timing of Transmission during Pregnancy and Risk of CZS

- Timing of prenatal ZV Infection
  - *Highest risk for severe microcephaly appears to be first trimester*
  - *Bazil reported 55% of infants infected in 1st trimester*
  - *However, women with exposure during 1st, 2nd & 3rd trimesters have delivered infants with abnormalities*
    - Transmission occurs in all trimesters
- Estimated risk 1 - 15% of microcephaly in 1st trimester
  - *Modeling based on Bahia, Brazil outbreak*
    - vs 1% modelling in French Polynesia outbreak
  - *Risk felt to be negligible in 2nd and 3rd trimesters*
- Unclear what spectrum of disease is, in those w/o overt disease

July 7 2016 NEJM 2016;375:1-4

Mother infant pairs with congen ZV infection: Maternal characteristics and Fetal US, brazil



ure 2. Maternal clinical characteristics and fetal ultrasounds findings in
nts with congenital Zika syndrome. *A*, Gestational month of symptoms onset. *B*,
ternal clinical symptoms. *C*, Fetal ultrasound findings.

Clinical Infectious Diseases CID 2017;64(10):1302–8
Lessons Learned at the Epicenter of Brazil's Congenital Zika Epidemic: Evidence From 87 Confirmed Cases
Meneses JdA, Ishigami,AC, Mello LM, et al

Box. Birth Defects Potentially Related to Zika Virus Infection During Pregnancy and Monitored by the US Zika Pregnancy Registry for Enhanced Surveillance

Brain Abnormalities With and Without Microcephaly

Confirmed or possible congenital microcephaly[a]

Intracranial calcifications

Cerebral atrophy

Abnormal cortical formation (eg, polymicrogyria, lissencephaly, pachygyria, schizencephaly, gray matter heterotopia)

Corpus callosum abnormalities

Cerebellar abnormalities

Porencephaly

Hydranencephaly

Ventriculomegaly/hydrocephaly (excluding "mild" ventriculomegaly without other brain abnormalities)

Fetal brain disruption sequence (collapsed skull, overlapping sutures, prominent occipital bone, scalp rugae)

Other major brain abnormalities including intraventricular hemorrhage in utero (excluding postnatal intraventricular hemorrhage)

Neural Tube Defects and Other Early Brain Malformations

Neural tube defects including anencephaly, acrania, encephalocele, spina bifida

Holoprosencephaly (arhinencephaly)

Eye Abnormalities

Microphthalmia/anophthalmia

Coloboma

Cataract

Intraocular calcifications

Chorioretinal anomalies involving the macula (eg, chorioretinal atrophy and scarring, macular pallor, gross pigmentary mottling and retinal hemorrhage; excluding retinopathy of prematurity)

Optic nerve atrophy, pallor, and other optic nerve abnormalities

Consequences of Central Nervous System Dysfunction

Congenital contractures (eg, arthrogryposis, clubfoot, congenital hip dysplasia) with associated brain abnormalities

Congenital deafness documented by postnatal audiological testing

[a] Live births: measured head circumference (adjusted for gestational age and sex) less than the third percentile at birth or, if not measured at birth, within first 2 weeks of life. Pregnancy loss: prenatal head circumference more than 3 SDs below the mean based on ultrasound or postnatal head circumference less than the third percentile. Birth measurements are evaluated using the Intergrowth-21st standards (http://intergrowth21.ndog.ox.ac.uk/) based on measurements within 24 hours of birth.

Baseline Prevalence of Birth Defects Observed with Zika

- Used data from birth defects surveillance systems in Massachusetts, North Carolina, and Atlanta, Georgia, during pre-Zika outbreak years (2013–2014)
- Prevalence of Zika-related birth defects before Zika outbreak in the Americas:

  3 out of every 1,000 births

- Proportion of infants with birth defects among completed pregnancies with confirmed Zika infection (2016):

  24 out of every 250 completed pregnancies

Estimated

30-fold increase

in Zika-related birth defects in pregnancies with confirmed Zika infection compared with pre-Zika years

Cragan JD, Mai CT, Petersen EE, et al. Baseline Prevalence of Birth Defects Associated with Congenital Zika Virus Infection — Massachusetts, North Carolina, and Atlanta, Georgia, 2013–2014. MMWR Morb Mortal Wkly Rep 2017;66:219–222. DOI: http://dx.doi.org/10.15585/mmwr.mm6608a4

Reynolds MR, Jones AM, Petersen EE, et al. Vital Signs: Update on Zika Virus–Associated Birth Defects and Evaluation of All U.S. Infants with Congenital Zika Virus Exposure — U.S. Zika Pregnancy Registry, 2016. MMWR Morb Mortal Wkly Rep 2017;66:366-373.

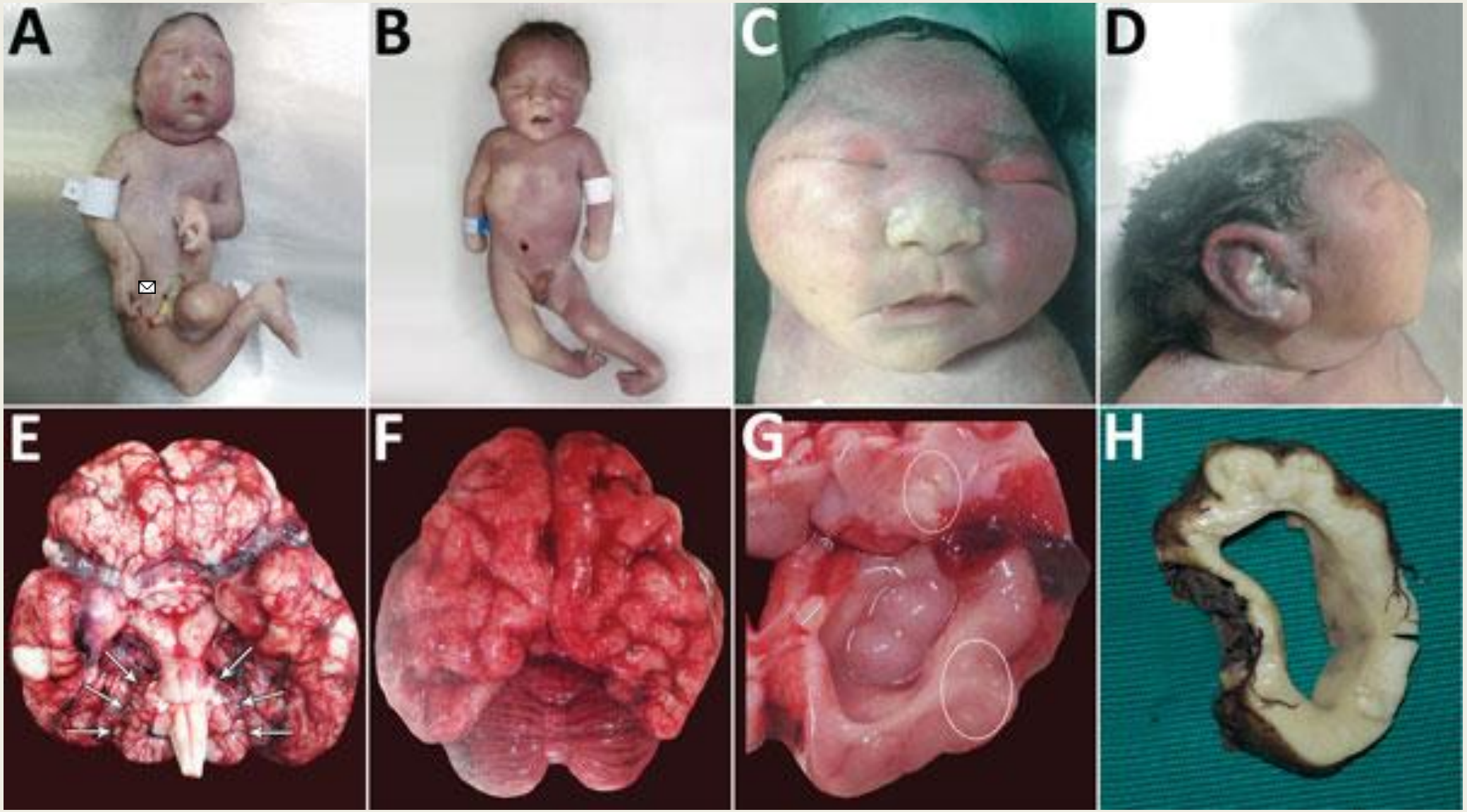
Table. Clinical Findings Comprising a Unique Pattern of Congenital Anomalies in Infants With Congenital ZIKV Infection: Congenital Zika Syndrome

Clinical Feature	Findings in Infants With Confirmed Congenital ZIKV Infection	Differential Diagnoses	Findings Potentially Unique to Infants With Congenital ZIKV Infection
Cranial morphology	FBDS: severe microcephaly, overlapping cranial sutures, prominent occipital bone, redundant scalp skin, and neurologic impairment	Congenital cytomegalovirus infection; possibly other congenital infections; and gene mutations in *JAM3*, *NDE1*, and *ANKLE2*	FBDS phenotype not unique to congenital ZIKV infection but rarely reported prior to 2015 when local transmission of ZIKV was confirmed in Brazil
Brain anomalies	Cerebral cortex thinning; abnormal gyral patterns; increased fluid spaces (ventriculomegaly or extra-axial); subcortical calcifications; corpus callosum anomalies; decreased white matter; and cerebellar (vermis) hypoplasia	Congenital cytomegalovirus infection; possibly other congenital infections; genetic syndromes, in particular Aicardi-Goutières syndrome and pseudo-TORCH syndrome; and gene mutations in *JAM3*, *NDE1*, and *ANKLE2*	Subcortical location of calcifications in congenital ZIKV infection unique among other congenital infections and genetic syndromes
Ocular anomalies	Structural anomalies (microphthalmia, coloboma); cataracts; and posterior anomalies: chorioretinal atrophy, focal pigmentary mottling, and optic nerve hypoplasia/atrophy	Congenital infections	Chorioretinal atrophy and focal pigmentary mottling, both affecting the macula, unique among other congenital infections
Congenital contractures	Unilateral or bilateral clubfoot and arthrogryposis multiplex congenita	Congenital infections (rubella, varicella, and coxsackie B only)	Contractures not previously reported with the FBDS phenotype
Neurologic sequelae	Motor disabilities; cognitive disabilities; hypertonia/spasticity; hypotonia; irritability/excessive crying; tremors and extrapyramidal symptoms; swallowing dysfunction; vision impairment; hearing impairment; and epilepsy	Congenital cytomegalovirus infections and other congenital infections	Early pyramidal and extrapyramidal symptoms unusual among other congenital infections

Abbreviations: FBDS, fetal brain disruption sequence; ZIKV, Zika virus.

Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians. Moore CA, Staples JE, Dobyns WB, et al. JAMA Pediatr. 2017:171:288-295

Postmortem findings in Neonates with CZS



Sousa AQ, Cavalcante DIM, Franco LM, et al. Postmortem Findings for 7 Neonates with Congenital Zika Virus Infection Emerging Infectious Diseases. Volume 23, Number 7—July 2017 Dispatch

Postmortem Findings in Infants with CZS:
Results of tests for Zika virus in CSF and organs and for dengue virus in brain and CSF for 7 neonates who died of congenital Zika virus infection, Brazil*

	Zika virus rRT-PCR								DENV			
										CSF		
Neonate no.	CSF	Brain	Lung	Heart	Liver	Spleen	Kidney		Brain rRT-PCR	rRT-PCR	IgM†	NS1‡
1	P	P	P	P	N	N	P		ND	N	N	N
2	P	P	N	P	P	P	P		ND	ND	N	N
3	P	P	P	P	P	P	P		ND	ND	N	N
4	P	P	N	N	N	N	N		N	DENV-1	P	P
5	P	P	P	P	P	P	P		N	N	N	N
6	P	ND	ND	ND	ND	ND	ND		N	N	N	N
7	P	ND	ND	ND	ND	ND	ND		ND	N	N	N

*CSF, cerebrospinal fluid; DENV, dengue virus; N, negative; ND, not done; NS1, nonstructural protein 1 (dengue virus antigen test); P, pos
†By antigen capture assay.
‡By ELISA.

CT Findings

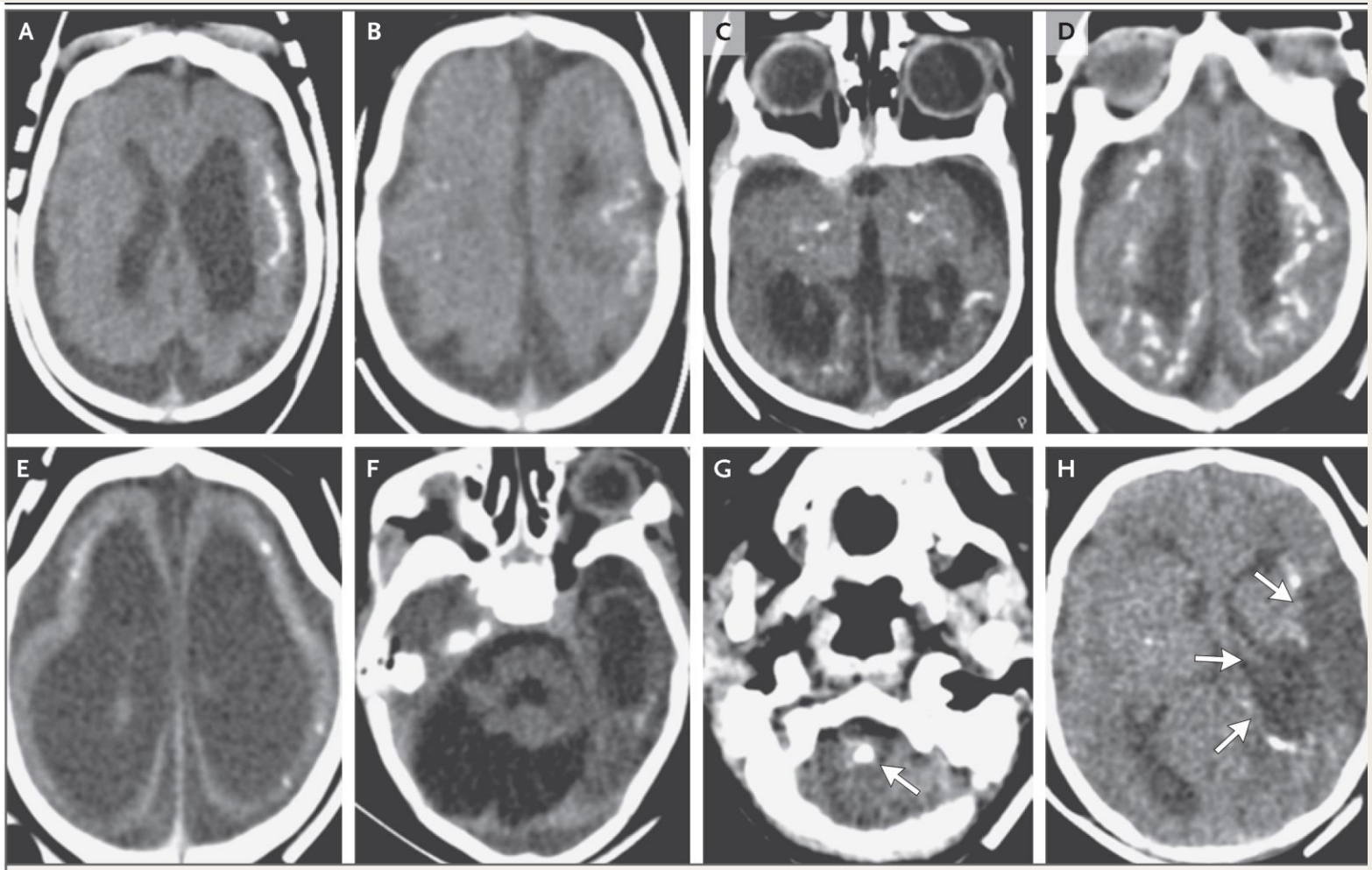
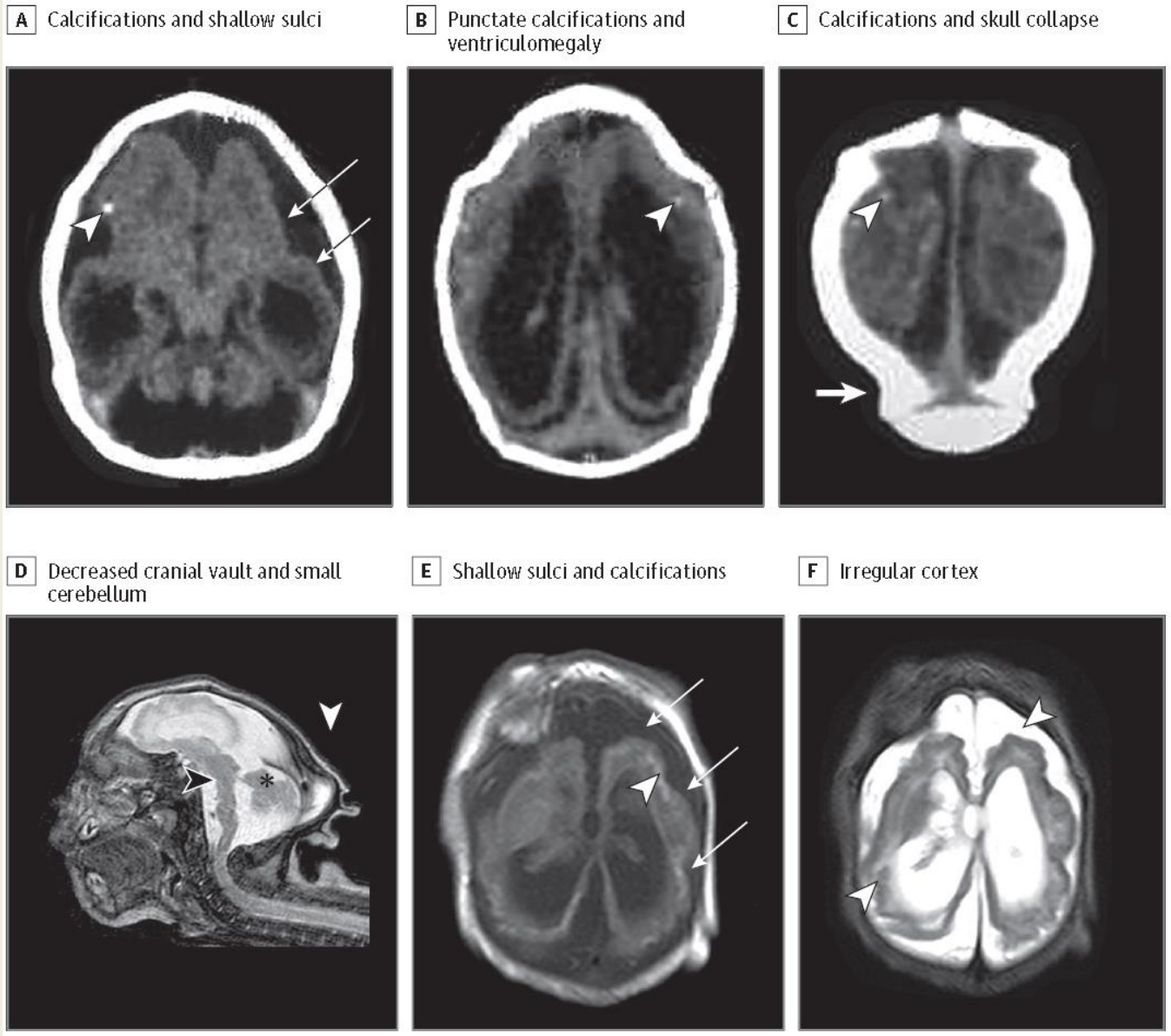


Figure 1. Computed Tomography in Eight Infants with Congenital Microcephaly.

Axial computed tomographic (CT) images of the heads of eight infants who were born with congenital microcephaly associated with intrauterine ZIKV infection show calcifications in bandlike distributions (Panels A, B, and D) with isolated configurations (Panels B, C, E, and G), punctate configurations (Panels B and E), and larger configurations (Panels A, C, D, and G) at the level of the corticomedullary junction (Panels A, B, and D) within the frontal, parietal, and temporal lobes, basal ganglia (Panel C), and upper cervical spinal cord (Panel G, arrow). In addition, there are visible signs of global cortical hypogyration (Panels A through F and H), moderate-to-severe ventriculomegaly (Panels A and C through F), severe global cerebellar hypoplasia (Panel F), abnormal hypodensity of the supratentorial white matter (Panels A, B, D, and H), and encephalomalacic changes after ischemic stroke in the vascular territory of the left middle cerebral artery (Panel H, arrows).

Hazen AN, Poretti A, Martelli, CMT, et al. Computed Tomographic Findings in Microcephaly Associated with Zika Virus. NEJM 2016:374;2193-95

Figure 2. Brain Findings in Infants With Presumed Congenital Zika Syndrome

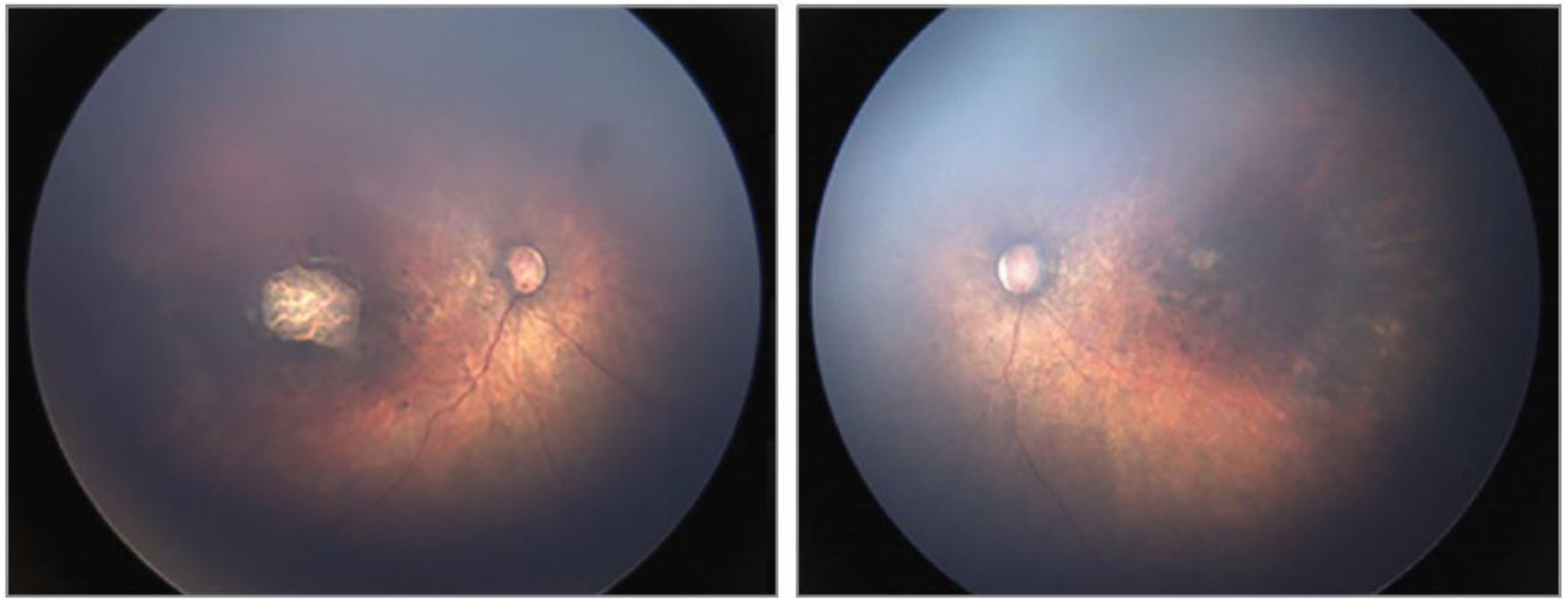


Computed tomographic scan in 1 infant and magnetic resonance imaging in another infant with prenatal Zika exposure show scattered punctate calcifications (A, B, C, and E; white arrowheads), very low forehead and small cranial vault (D), striking volume loss shown by enlarged extra-axial space and ventriculomegaly (all images), poor gyral development with few and shallow sulci (A and E; long white arrows), poor gyral development with irregular "beaded" cortex most consistent with polymicrogyria (F, white arrowheads), flattened pons and small cerebellum (D; black arrowhead and asterisk). The occipital "shelf" caused by skull collapse is seen in both infants (C, white arrow and D, white arrowhead).

Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians. Moore CA, Staples JE, Dobyns WB, et al. JAMA Pediatr. 2017;171:288-295.

CZS: Optic Nerve Hypoplasia

Figure 3. Wide-Angle Fundus Images (RetCam) of a Male Infant With Congenital Zika Infection



Optic nerve hypoplasia with the double-ring sign, increased cup-disc ratio, attenuated blood vessels, gross pigment mottling, and chorioretinal scar in the macular region.

Characterizing the Pattern of Anomalies in Congenital Zika Syndrom for Pediatric Clinicians. Moore CA, Staples JE, Dobyns WB, et al. JAMA Pediatr. 2017;171:288-295

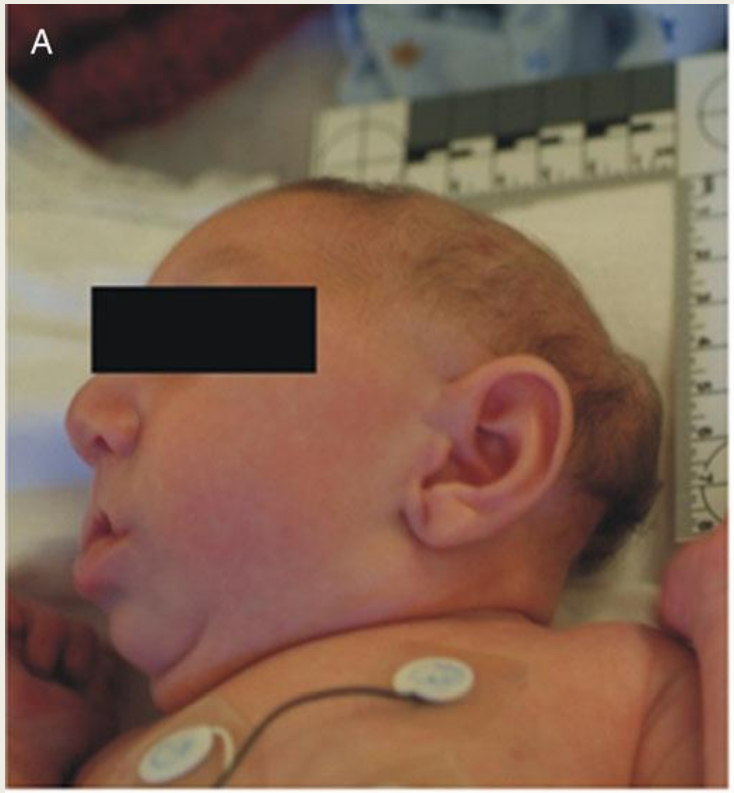
CZS: Microcephaly and arthrogryposis

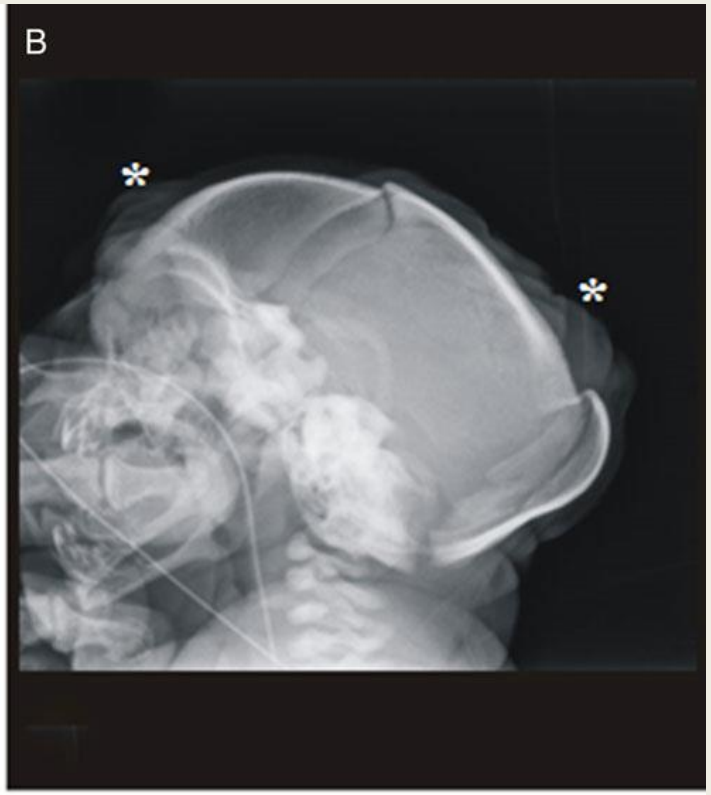
Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians. Moore CA, Staples JE, Dobyns WB, et al. JAMA Pediatr. 2017;171:288-295

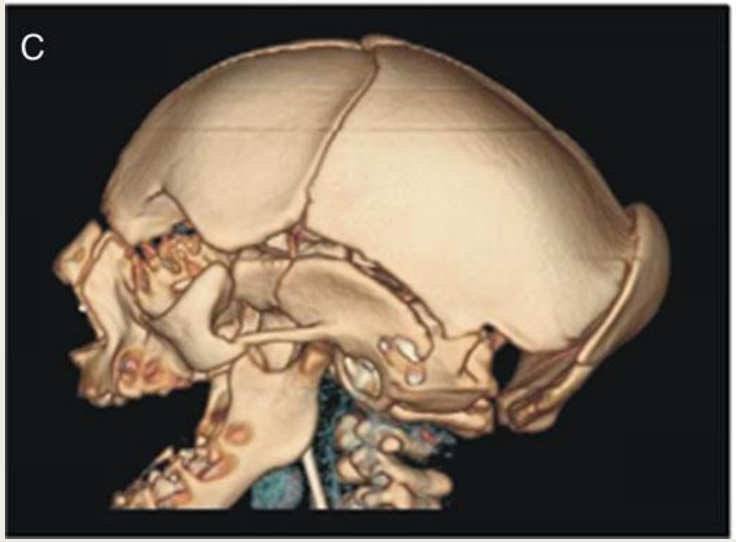
A Multiple contractures with knee dislocation

B Multiple contractures including right talipes equinovarus

A, Newborn infant with bilateral contractures of the hips and knees, bilateral talipes calcaneovalgus, and anterior dislocation of the knees. Hips are bilaterally dislocated. B, Newborn infant with bilateral contractures of the shoulders, elbows, wrists, hips, knees, and right talipes equinovarus. Hips are bilaterally dislocated.







Severe microcephaly, occipital prominence, collapse of calvarium and overlapping calvarial bones

Clinical and Imaging Findings in an Infant With Zika Embryopathy. CID 2016;63:805-11
Marko Culjat, Stephen E. Darling, Vivek R. Nerurkar, et al

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EXPEDITED AHEAD-OF-PRINT ARTICLES — June 12, 2017

Synopsis
Characteristics of Dysphagia in Infants with Microcephaly Caused by Congenital Zika Virus Infection, Brazil, 2015

Mariana C. Leal, Vanessa van der Linden, Thiago P. Bezerra, Luciana de Valois, Adriana C.G. Borges, Margarida M.C. Antunes, Kátia G. Brandt, et al.

Abstract
We summarize the characteristics of dysphagia in 9 infants in Brazil with microcephaly caused by congenital Zika virus infection. The Schedule for Oral Motor Assessment, fiberoptic endoscopic evaluation of swallowing, and the videofluoroscopic swallowing study were used as noninstrumental and instrumental assessments. All infants had a degree of neurologic damage and showed abnormalities in the oral phase. Of the 9 infants, 8 lacked oral and upper respiratory tract sensitivity, leading to delays in initiation of the pharyngeal phase of swallowing. Those delays, combined with marked oral dysfunction, increased the risk for aspiration of food, particularly liquid foods. Dysphagia resulting from congenital Zika virus syndrome microcephaly can develop in infants >3 months of age and is severe.

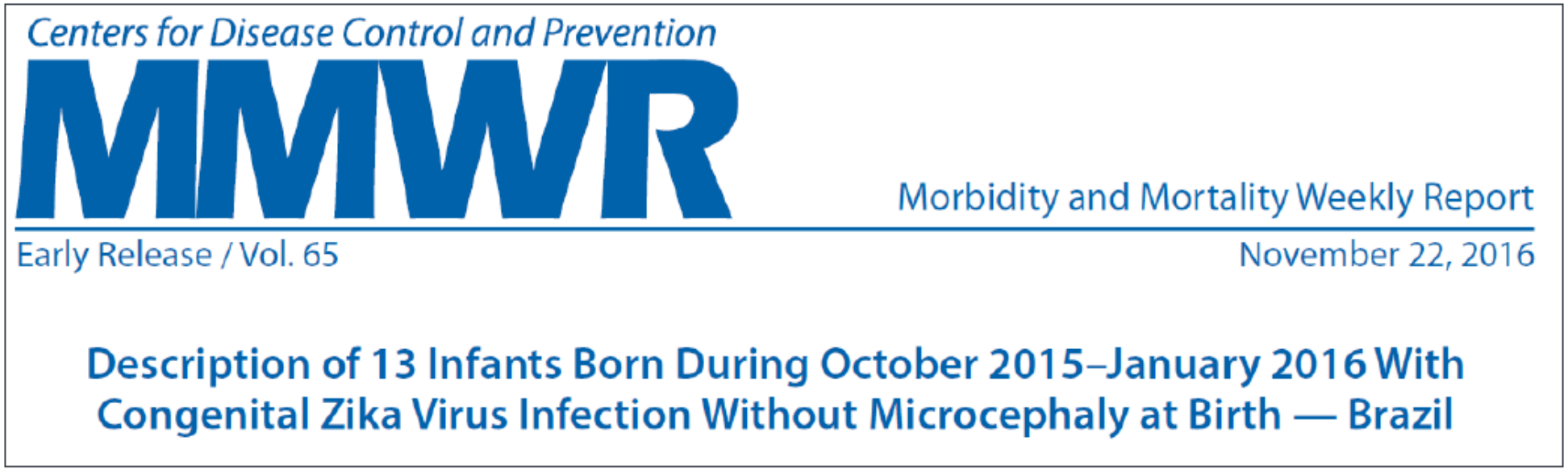
Volume 23, Number 8 - August 2017

Tip of Iceberg

- Likely much more to learn re: spectrum of disease
- Additional manifestations being reported after birth

Congenital Zika Syndrome without Microcephaly at Birth

- Microcephaly from congenital infection can occur after birth
- The full spectrum of poor outcomes caused by Zika virus infection during pregnancy remains unknown



Linden V, Pessoa A, Dobyns WB, et al. Description of 13 Infants Born During October 2015–January 2016 . . . MMWR. 22 Nov 2016.

CDC's Response to **Zika**

IMPLEMENTING CDC GUIDANCE FOR INFANT NEUROIMAGING AND INFANT AND PLACENTAL ZIKA VIRUS TESTING

Based on maternal Zika virus exposure and laboratory test results

Notes: (1) This tool summarizes general CDC guidance for the following scenarios. The tool only addresses live births. Please consult CDC* or your state or local health department for case-specific questions. Health departments should adapt CDC guidance depending on local capacity and circumstances.

(2) In all cases, infants with anomalies consistent with congenital Zika syndrome should also be evaluated for other etiologies of congenital anomalies.

(3) Infant serum and urine should be tested for Zika virus by Zika NAT, and infant serum for Zika virus IgM antibodies. If CSF is obtained, it can also be tested. Please refer to the published guidance for more information.

(4) Placental testing includes testing of formalin-fixed or formalin-fixed, paraffin-embedded placenta, umbilical cord, and fetal membranes by ZIKV RT-PCR. Microscopic evaluation of fixed tissues is conducted in selected cases. Please note that a positive RT-PCR result from placental testing cannot distinguish between maternal and fetal infection; therefore, a positive RT-PCR result from the placenta can confirm maternal Zika infection but cannot be used to confirm congenital Zika infection in the infant. Negative NAT results on placental tissue do not exclude maternal ZIKV since the duration of ZIKV persistence in the placenta is unknown and the samples evaluated may not reflect the placenta in its entirety. Please refer to the website for further guidance.

Timing of Zika virus exposure† relative to timing of maternal specimen collection		**EXPOSURE† WITHIN ANY TIME PERIOD**		**ALL EXPOSURE† WITHIN 12 WEEKS OF SPECIMEN COLLECTION (I.E., EXPOSURE† IS COMPLETELY WITHIN TESTING WINDOW§)**		
Test results and interpretation from maternal specimens (e.g.serum, urine, and whole blood) >>		**Recent ZIKV infection** NAT positive OR non-negative Zika IgM¶ **AND** Zika PRNT** ≥ 10, and dengue PRNT** < 10	**Recent flavivirus infection, specific virus cannot be identified**** non-negative Zika IgM¶ **AND** Zika PRNT** ≥ 10, and dengue PRNT** ≥ 10	**No evidence of ZIKV infection** Zika IgM negative OR non-negative Zika IgM¶ **AND** Zika PRNT** < 10	**Presumptive recent** ZIKV or flavivirus infection** non-negative Zika IgM¶ **AND** PRNT** pending	**Not tested**
Additional maternal testing on serum, urine, and whole blood >>		← **Additional maternal testing not indicated** →			**Additional Maternal Testing:** Follow up PRNT results, if indicated according to lab guidance. If maternal IgM is inconclusive, repeat IgM testing in accordance with EUA.	**Maternal Testing:** Recommended; specimens should be collected as soon as possible.
Infant outcome	**Anomalies consistent with congenital Zika syndrome††**	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. If technically difficult, consider MRI or CT.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. If technically difficult, consider MRI or CT.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. If technically difficult, consider MRI or CT.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. If technically difficult, consider MRI or CT.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. If technically difficult, consider MRI or CT.
		Infant Testing: Recommended; specimens should be collected within 2 days of birth. Consider testing CSF if serum and urine results are negative.	**Infant Testing:** Recommended; specimens should be collected within 2 days of birth. Consider testing CSF if serum and urine results are negative.	**Infant Testing:** Recommended; specimens should be collected within 2 days of birth. Consider testing CSF if serum and urine results are negative.	**Infant Testing:** Recommended; specimens should be collected within 2 days of birth. Do not wait for maternal test results. Consider testing CSF if serum and urine results are negative.	**Infant Testing:** Recommended; specimens should be collected within 2 days of birth. Consider testing CSF if serum and urine results are negative.
		Placental Testing: Not indicated; no added diagnostic value given known maternal ZIKV diagnosis.§§	**Placental Testing:** Should be considered to aid in maternal diagnosis.	**Placental Testing:** Fix and store placenta until infant results are available. Depending on infant test results, placental testing can be considered to aid in maternal diagnosis.¶¶	**Placental Testing:** Fix and store placenta until maternal PRNT results are available. Based on maternal PRNT result interpretation, refer to appropriate column.	**Placental Testing:** Fix and store placenta until maternal results are available. Based on maternal test result interpretation, refer to appropriate column.
	Phenotypically normal	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge.	**Neuroimaging:** Not indicated.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. Can be deferred until next outpatient visit if infant appears well and no concerns for loss to follow up.	**Neuroimaging:** Head ultrasound recommended; should be performed before hospital discharge. Can be deferred until next outpatient visit if infant appears well and no concerns for loss to follow up.
		Infant Testing: Recommended; specimens should be collected within 2 days of birth.	**Infant Testing:** Recommended; specimens should be collected within 2 days of birth.	**Infant Testing:** Not indicated.	**Infant Testing:** Specimens should be collected within 2 days of birth and stored. Decision to test the infant can be deferred until maternal test results are available. Based on maternal PRNT result interpretation, refer to appropriate column.	**Infant Testing:** Specimens should be collected within 2 days of birth and stored. Decision to test the infant can be deferred until maternal test results are available.
		Placental Testing: Not indicated; no added diagnostic value given known maternal ZIKV diagnosis.§§	**Placental Testing:** Should be considered to aid maternal diagnosis.	**Placental Testing:** Not indicated.	**Placental Testing:** Fix and store placenta until maternal PRNT results are available. Based on maternal PRNT result interpretation, refer to appropriate column.	**Placental Testing:** Fix and store placenta until maternal results are available. Based on maternal test result interpretation, refer to appropriate column.

Abbreviations: CT= Computed Tomography; EUA = Emergency Use Authorization; IgM = Immunoglobulin M; MRI= Magnetic Resonance Imaging; NAT = Nucleic Acid Test (includes rRT-PCR); PRNT = Plaque Reduction Neutralization Test; rRT-PCR = Real-time Reverse Transcription-Polymerase Chain Reaction; RT-PCR = Reverse Transcription-Polymerase Chain Reaction; ZIKV = Zika virus.

* Please contact CDC Zika Pregnancy Hotline at 770-488-7100 or zikamch@cdc.gov.

† Possible Zika virus exposure is defined as travel to or residence in an area with risk of Zika or sex without a condom with someone who traveled to or lived in an area with risk of Zika.

§ Start and end date of exposure are both are within the 12-week testing window.

¶ Non-negative serology terminology varies by assay and examples include positive, equivocal, presumptive positive, or possible positive results. For explanation of a specific interpretation and informaton on each assay, refer to https://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika, under the "Labeling" bullet for the specific assay. Inconclusive maternal IgM specimens should be retested in accordance with EUA. If the inconclusive maternal IgM cannot be reconciled, refer to the relevant exposure category "Not tested" column, and base decision to test placenta on maternal and/or infant test results.

** Currently, PRNT confirmation is not routinely recommended for individuals living in Puerto Rico. In Puerto Rico, for "presumptive recent ZIKV" guidance, refer to the column for "recent ZIKV infection;" and for "presumptive recent flavivirus infection" guidance, refer to the column for "Recent flavivirus, specific virus cannot be identified."

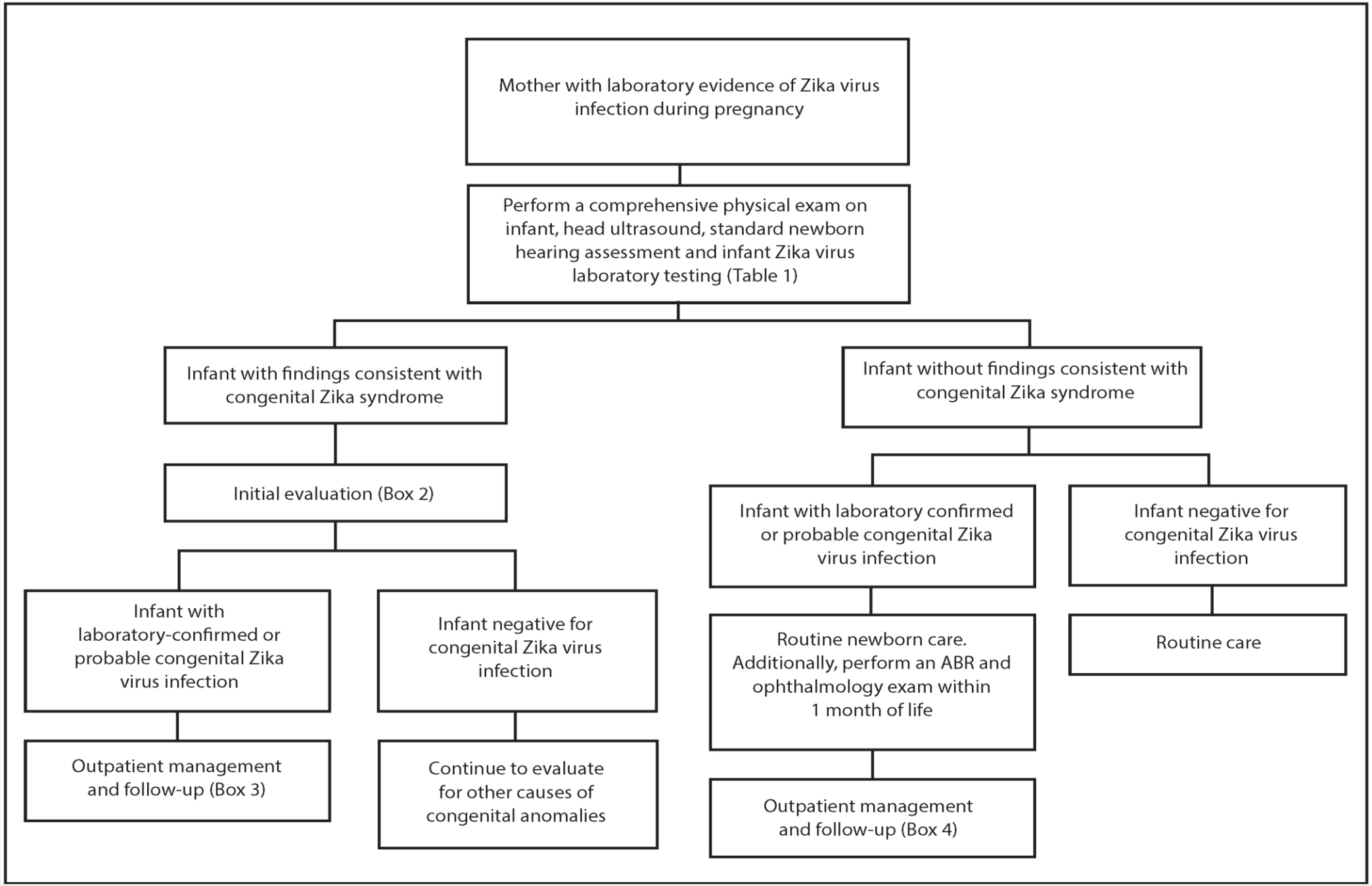
†† Including but not limited to: microcephaly; structural brain anomalies (e.g., decreased brain volume, calcifications); posterior eye anomalies (e.g., chorioretinal scarring, optic nerve hypoplasia); contracture of one or more joints; and functional neurologic abnormalities (e.g., spasticity/hypertonia, dystonia/dyskinesia). For complete list of anomalies please check the CDC Zika virus pregnancy outcomes website.

§§ In exceptional circumstances, placental testing may be considered in consultation with CDC at 770-488-7100 or zikamch@cdc.gov.

¶¶ If infant testing is done it should be performed before placental testing, if possible. If (1) infant NAT (rRT-PCR) is positive for Zika, or (2) infant IgM is Zika positive or equivocal AND infant or maternal PRNT is positive for Zika but negative for dengue, then there is limited utility of placental testing. If other infant test results are obtained, placental testing may provide another opportunity to identify maternal infection that would otherwise go unrecognized.

INTERIM GUIDANCE FOR ZV TESTING AND EVALUATION OF INFANTS BORN TO MOTHERS WITH LAB EVIDENCE OF ZIKA

FIGURE. Recommended Zika virus testing and evaluation of infants born to mothers with laboratory evidence of Zika virus infection during pregnancy *



Russell K, Oliver SE, Lewis L, et al. Update: Interim Guidance for the Evaluation and Management of Infants with Possible Congenital ZV Infection — US, August 2016. MMWR 2016;65:870–878

Interpretation of lab results of infant's blood, urine and or CSF for evidence of congen ZV infection

Russell K, Oliver SE, Lewis L, et al. Update: Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection — United States, August 2016. MMWR Morb Mortal Wkly Rep 2016;65:870–878

TABLE 1. Interpretation of results of laboratory testing of infant's blood, urine and/or cerebrospinal fluid for evidence of congenital Zika virus infection

Infant test results*		
rRT-PCR	**IgM**	**Interpretation**
Positive	Positive or Negative	Confirmed congenital Zika virus infection
Negative	Positive	Probable congenital Zika virus infection†
Negative	Negative	Negative for congenital Zika virus infection†

Abbreviations: rRT-PCR = real-time reverse transcription–polymerase chain reaction; IgM = immunoglobulin M.

* Infant serum, urine, or cerebrospinal fluid.

† Laboratory results should be interpreted in the context of timing of infection during pregnancy, maternal serology results, clinical findings consistent with congenital Zika syndrome, and any confirmatory testing with plaque reduction neutralization testing (PRNT).

Clinical evaluation of Infants with ZV infection

- Consultation with:
  - Neurologist for determination of appropriate neuroimaging and additional evaluation.
  - Infectious disease specialist for diagnostic evaluation of other congenital infections (e.g., syphilis, toxoplasmosis, rubella, cytomegalovirus infection, lymphocytic choriomeningitis virus infection, and herpes simplex virus infection).
  - Ophthalmologist for comprehensive eye exam and evaluation for possible cortical visual impairment prior to discharge from the hospital or within 1 month of birth.
  - Endocrinologist for evaluation for hypothalamic or pituitary dysfunction.
  - Clinical geneticist to evaluate for other causes of microcephaly or other anomalies if present.
- Consider consultation with:
  - Orthopedist, physiatrist, or physical therapist for the management of hypertonia, club foot or arthrogrypotic-like conditions.
  - Pulmonologist or otolaryngologist for concerns about aspiration.
  - Lactation specialist, nutritionist, gastroenterologist, or speech or occupational therapist for the management of feeding issues.
- Perform auditory brainstem response to assess hearing.
- Perform complete blood count and metabolic panel, including liver function tests.
- Provide family and supportive services.

Russell K, Oliver SE, Lewis L, et al. Update: Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection — United States, August 2016. MMWR 2016;65:870

Possible Congenital ZV infection: initial evaluation & management of infant in first 12 mos of life

TABLE 2. Initial evaluation and recommended outpatient management during the first 12 months of life for infants with possible congenital Zika virus infection, based on maternal and infant laboratory tests and infant clinical findings

Mother	Infant clinical exam	Before hospital discharge	Infant testing	2 wks.	1 mo.	2 mos.	3 mos.	4–6 mos.	9 mos.	12 mos.
Laboratory evidence of Zika virus infection*	No evidence of abnormalities	Routine newborn care: PE, HC, weight/length, and neurologic exam Hearing screen Head US Infant Zika virus testing (Table 1)	Negative for Zika virus infection	Routine care, including monitoring of OFC and development at every well child visit and age-appropriate developmental screening						
			Laboratory evidence of Zika virus infection*	Ophthalmology exam ABR				Consider repeat ABR	Behavioral audiology if ABR not done at 4–6 mos.	
				Monitoring of OFC and development at every visit and age-appropriate developmental screening (Box 4)						
	Abnormalities consistent with congenital Zika syndrome	As above plus: Consider transfer to hospital with subspecialty care CBC, metabolic panel, LFTs, ophthalmology exam ABR Consider advanced neuroimaging (Box 2)	Negative for Zika virus infection	Evaluate for other causes of congenital anomalies Further management as clinically indicated						
			Laboratory evidence of Zika virus infection*	Thyroid screen	Neurologic exam	Neurologic exam	Thyroid screen, ophthalmology exam		Repeat ABR	
				Routine preventive health care including monitoring of feeding and growth Routine and congenital infection-specific anticipatory guidance Referral to specialists, including evaluation of other causes of congenital anomalies as needed (Box 3)						
Not tested, or tested outside of appropriate window†	No evidence of abnormalities	Maternal Zika virus testing† Consider Zika virus placental testing Routine newborn care: PE, HC, weight/length and neurologic exam Hearing screen Head US	Perform infant Zika virus testing if evidence of Zika virus infection on maternal testing*,†	Outpatient management for appropriate infant clinical exam and test results						
	Abnormalities consistent with congenital Zika syndrome	As above, plus: Consider transfer to hospital with subspecialty care. CBC, metabolic panel, LFTs, ophthalmology exam ABR Consider advanced neuroimaging Infant Zika virus testing (Table 1)	Negative for Zika virus infection	Evaluate for other causes of congenital anomalies Further management as clinically indicated						
			Laboratory evidence of Zika virus infection*	Refer to outpatient management for infant with abnormalities consistent with congenital Zika syndrome						

Russell K, et al. Update: Interim Guidance MMWR 2016;65:870

USZPR Definition of Laboratory Confirmed Zika Infection

Zika virus infection can be confirmed by

- Zika virus RNA in any maternal or fetal/infant specimen detected by nucleic acid test (NAT) (e.g., rRT-PCR) OR
- Positive or equivocal Zika virus IgM with Zika virus plaque reduction neutralization test (PRNT) titer ≥10 and dengue virus PRNT <10

USZPR Definition of Possible Recent Zika Infection

Laboratory evidence of possible recent Zika virus infection

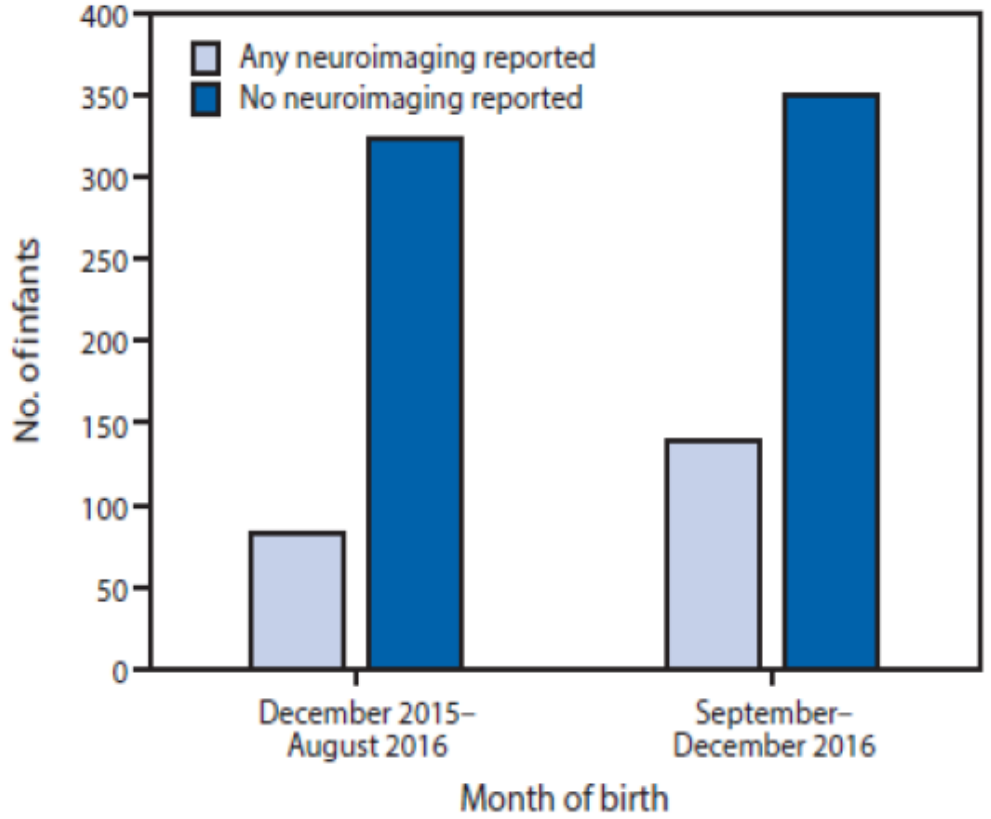
- Recent Zika virus infection detected by a Zika virus RNA nucleic acid test (NAT, e.g., [RT-PCR]) on any maternal, placental, or fetal/infant specimen or
- Detection of recent Zika virus infection or recent unspecified flavivirus infection by serologic tests on a maternal or infant specimen
  - Either positive or equivocal Zika virus IgM AND Zika virus PRNT titer ≥10, regardless of dengue virus PRNT value; or
  - Negative Zika virus IgM, AND positive or equivocal dengue virus IgM, AND Zika virus PRNT titer ≥10, regardless of dengue virus PRNT titer

Postnatal Neuroimaging and Testing

TABLE 2. Postnatal neuroimaging* and infant Zika virus testing results for 895 liveborn infants in the U.S. Zika Pregnancy Registry — 50 U.S. states and the District of Columbia, 2016

Testing	No (%) liveborn infants: With birth defects	Without birth defects	Total
Total	**45**	**850**	**895**
Neuroimaging			
Any neuroimaging reported to USZPR	29 (64)	192 (23)	**221 (25)**
Infant Zika virus testing			
Positive test result on an infant specimen†,§	25 (56)	69 (8)	**94 (11)**
Negative infant test results among infants with ≥1 infant specimen reported as tested	17 (38)	474 (56)	**491 (55)**
No infant specimen test results reported to USZPR	3 (7)	307 (36)	**310 (35)**

FIGURE 2. Postnatal neuroimaging for infants reported to the U.S. Zika Pregnancy Registry, by month of birth — United States, December 2015–December 2016



New Vital Signs Report

Zika Virus: Protecting Pregnant Women and Babies

44 States reported pregnant women with evidence of Zika in 2016

about **1 in 10** Pregnant women with confirmed Zika had a fetus or baby with birth defects

only **1 in 4** Babies with possible congenital Zika infection were reported to have received brain imaging after birth

CDC Vitalsigns™

www.cdc.gov/vitalsigns/zika-babies

Management of the Pregnant Woman with Possible Zika Virus Exposure

Ongoing Surveillance

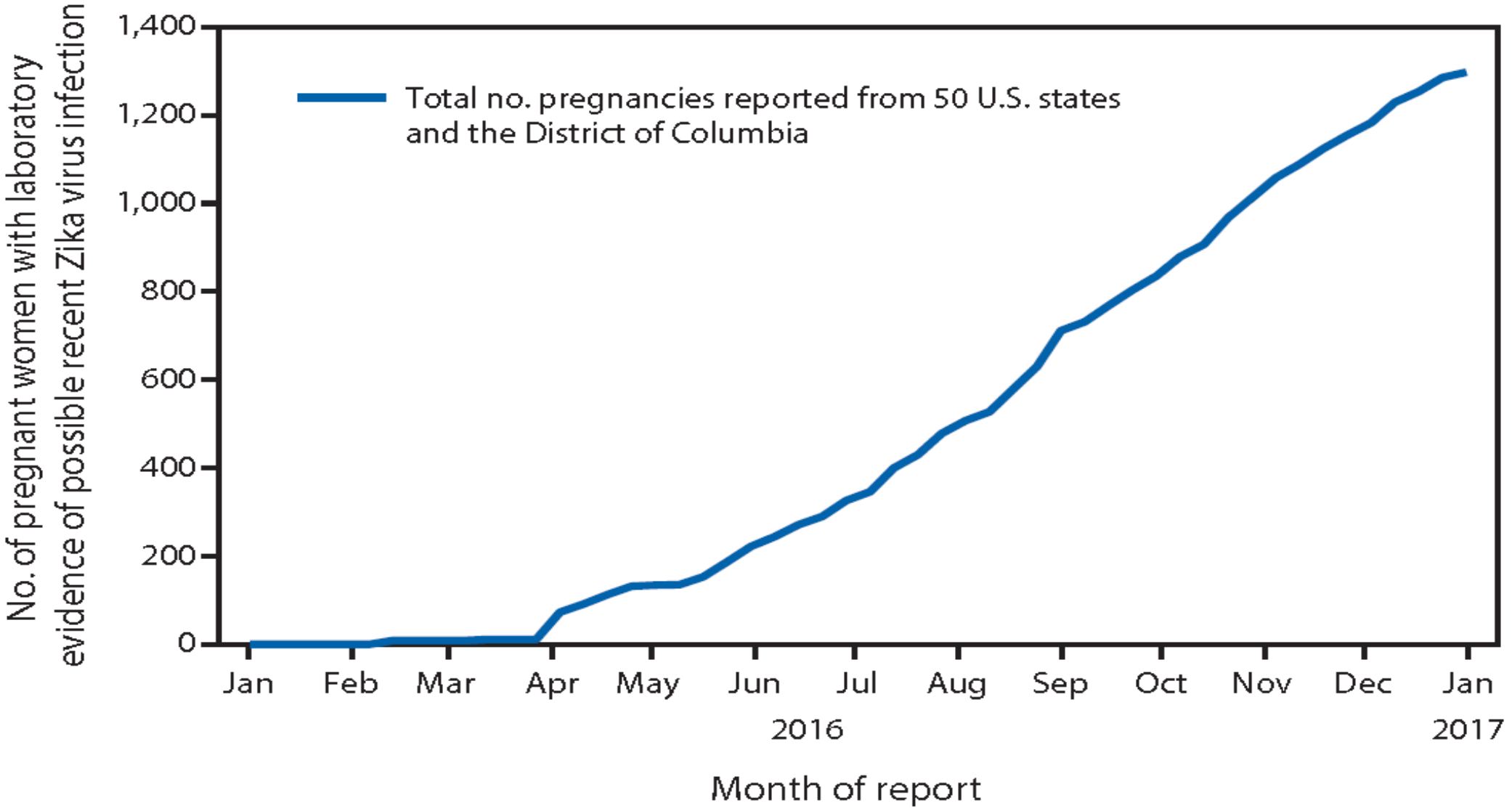
Zika Pregnancy Registries

US Zika Pregnancy Registry

Zika Active Pregnancy Surveillance System (Puerto Rico)

Proyecto Vigilancia de Embarazadas con Zika (Colombia)

FIGURE 1. Cumulative number of pregnant women with laboratory evidence of possible recent Zika virus infection reported to the U.S. Zika Pregnancy Registry, by month of report — United States, January–December 2016 (n = 1,297)



Reynolds MR, Jones AM, Petersen EE, et al. Vital Signs: Update on Zika Virus–Associated Birth Defects and Evaluation of All U.S. Infants with Congenital Zika Virus Exposure — U.S. Zika Pregnancy Registry, 2016. MMWR 2017;66:366-373

US Zika Pregnancy Registry: First Report


Research

JAMA | Original Investigation

Birth Defects Among Fetuses and Infants of US Women With Evidence of Possible Zika Virus Infection During Pregnancy

Among pregnancies in the United States with laboratory evidence of possible Zika virus infection

- **6%** of fetuses or infants had birth defects potentially related to Zika virus
- Similar proportion of pregnancies with birth defects **(≈6%)** among symptomatic and asymptomatic pregnant women
- Among women with infection in the 1st trimester of pregnancy, birth defects reported in **11%**

Honein MA, Dawson AL, Petersen EE et al. Birth Defects Among Fetuses and Infants of US Women With Evidence of Possible Zika Virus Infection During Pregnancy. *JAMA*. 2016 Dec 15 [Epub ahead of print]

Vital Signs MMWR: Update Previous Estimates

Morbidity and Mortality Weekly Report

Vital Signs: Update on Zika Virus–Associated Birth Defects and Evaluation of All U.S. Infants with Congenital Zika Virus Exposure — U.S. Zika Pregnancy Registry, 2016

Megan R. Reynolds, MPH[1]; Abbey M. Jones, MPH[1]; Emily E. Petersen, MD[2]; Ellen H. Lee, MD[3]; Marion E. Rice, MPH[1,4]; Andrea Bingham, PhD[5]; Sascha R. Ellington, MSPH[2]; Nicole Evert, MS[6]; Sarah Reagan-Steiner, MD[7]; Titilope Oduyebo, MD[2]; Catherine M. Brown, DVM[8]; Stacey Martin, MSc[9]; Nina Ahmad, MD[10]; Julu Bhatnagar, PhD[7]; Jennifer Macdonald, MPH[11]; Carolyn Gould, MD[9]; Anne D. Fine, MD[3]; Kara D. Polen, MPH[1]; Heather Lake-Burger, MPH[5]; Christina L. Hillard, MA[1]; Noemi Hall, PhD[6,12]; Mahsa M. Yazdy, PhD[8]; Karnesha Slaughter, MPH[1]; Jamie N. Sommer, MS[10]; Alys Adamski, PhD[1]; Meghan Raycraft, MPH[1]; Shannon Fleck-Derderian, MPH[4,13]; Jyoti Gupta, MPH[11]; Kimberly Newsome, MPH[1]; Madelyn Baez-Santiago, PhD[1]; Sally Slavinski, DVM[3]; Jennifer L. White, MPH[10]; Cynthia A. Moore, MD, PhD[1]; Carrie K. Shapiro-Mendoza, PhD[2]; Lyle Petersen, MD[9]; Coleen Boyle, PhD[14]; Denise J. Jamieson, MD[2]; Dana Meaney-Delman, MD[13]; Margaret A. Honein, PhD[1]; U.S. Zika Pregnancy Registry Collaboration

US ZV Pregnancy Registry – Updated information

- In 2016:
  - *972 completed pregnancies out of 1297 pregnancies with possible recent Zika infection*
  - *44 states with pregnant women who had possible Zika infection*
    - 6% women symptomatic; 5% asymptomatic
    - 9% with 1st trimester exposure
  - *15% infants with confirmed Zika infection had CZS*
  - *5% of women with possible Zika and 10% mothers with confirmed Zika had infant with birth defects*
    - 84% infants with Zika-associated birth defects had brain abnormalities and/or microcephaly

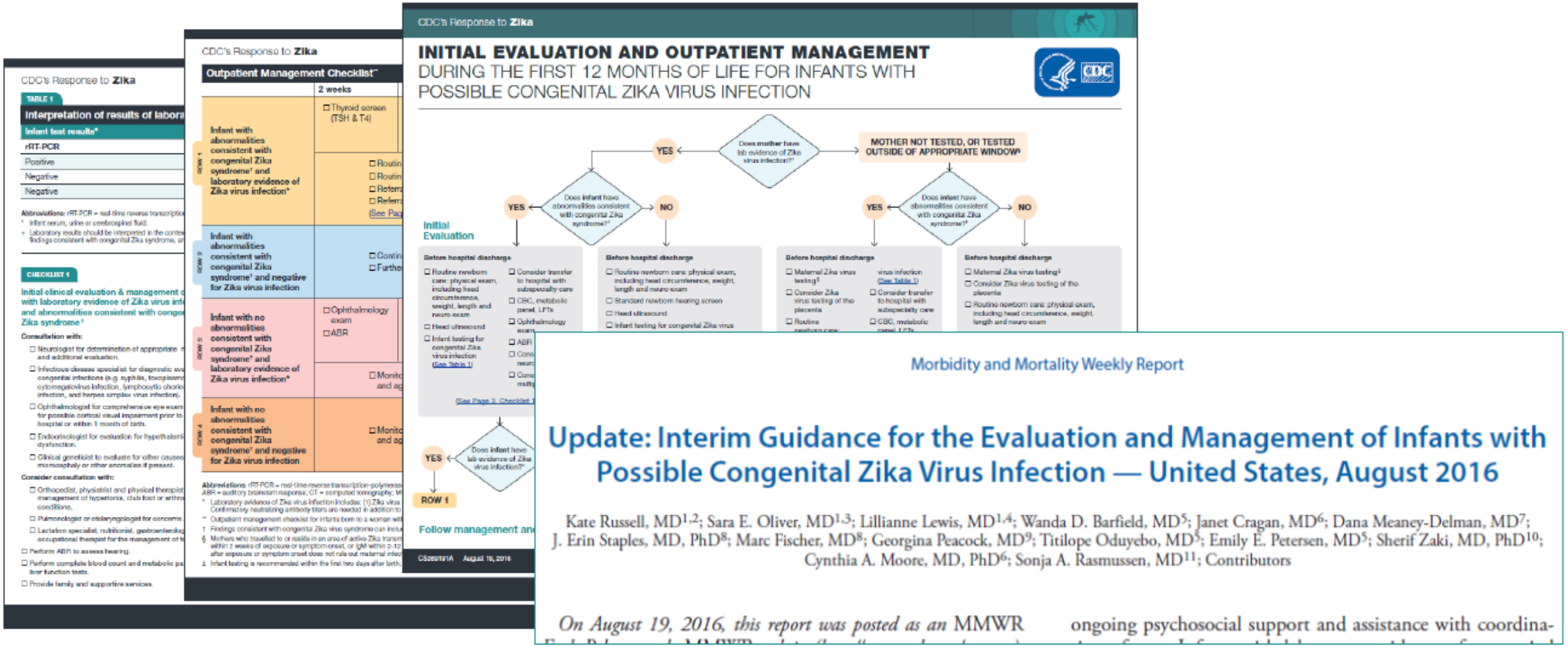
Outcomes in 972 pregnancies of women with possible or confirmed recent ZV

TABLE 1. Pregnancy outcomes* for 972 women with completed pregnancies† with laboratory evidence of possible recent Zika virus infection, by maternal symptom status and timing of symptom onset or exposure — U.S. Zika Pregnancy Registry, United States, December 2015–December 2016

Characteristic	Brain abnormalities and/or microcephaly (No.)	NTDs and early brain malformations, eye abnormalities, or consequences of CNS dysfunction without brain abnormalities or microcephaly (No.)	Total with ≥1 birth defect (No.)	Completed pregnancies (No.)	Proportion affected by Zika virus–associated birth defects, % (95% CI§)
Any laboratory evidence of possible recent Zika virus infection¶					
Total	**43**	**8**	**51**	**972**	**5 (4–7)**
Maternal symptom status					
Symptoms of Zika virus infection reported	18	3	21	348	6 (4–9)
No symptoms of Zika virus infection reported	24	4	28	599	5 (3–7)
Unknown	1	1	2	25	—
Timing of symptoms or exposure**					
First trimester††,§§	13	1	14	157	9 (5–14)
Multiple trimesters including first	22	6	28	396	7 (5–10)
Confirmed evidence of Zika virus infection¶¶					
Total	**18**	**6**	**24**	**250**	**10 (7–14)**
Maternal symptom status					
Symptoms of Zika virus infection reported	8	3	11	141	8 (4–13)
No symptoms of Zika virus infection reported	10	2	12	102	12 (7–19)
Unknown	0	1	1	7	—
Timing of symptoms or exposure**					
First trimester††,§§	8	1	9	60	15 (8–26)
Multiple trimesters including first	8	4	12	58	21 (12–33)

Reynolds MR, Jones AM, Petersen EE, et al. Vital Signs: Update on Zika Virus–Associated Birth Defects and Evaluation of All U.S. Infants with Congenital Zika Virus Exposure — U.S. Zika Pregnancy Registry, 2016. MMWR 2017;66:366

Pediatric Evaluation and Follow-Up: The First 12 Months



Link to updated infant guidance (April 2017): https://www.cdc.gov/zika/hc-providers/infants-children/evaluation-and-management.html?permalink=https://www.cdc.gov/zika/hc-providers/infants-children/evaluation-and-management.html

Evaluation and Management of Infants with Possible Congenital Zika Virus Infection

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report

Update: Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection — United States, August 2016

Kate Russell, MD[1,2]; Sara E. Oliver, MD[1,3]; Lillianne Lewis, MD[1,4]; Wanda D. Barfield, MD[5]; Janet Cragan, MD[6]; Dana Meaney-Delman, MD[7]; J. Erin Staples, MD, PhD[8]; Marc Fischer, MD[8]; Georgina Peacock, MD[9]; Titilope Oduyebo, MD[5]; Emily E. Petersen, MD[5]; Sherif Zaki, MD, PhD[10]; Cynthia A. Moore, MD, PhD[6]; Sonja A. Rasmussen, MD[11]; Contributors

http://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm?s_cid=mm6533e2_w

Update Posted April 2017: Additional Considerations

- Additional Considerations for Evaluation and Management of Infants with Possible Zika Virus Infection
  - Neuroimaging
  - Zika virus testing

https://www.cdc.gov/zika/hc-providers/infants-children/evaluation-and-management.html

Infants with Possible Congenital Zika Virus Infection

- Born to mothers with laboratory evidence of possible Zika virus infection
- With abnormal clinical or neuroimaging findings suggestive of congenital Zika syndrome and a maternal epidemiologic link*

*An epidemiologic link includes travel to or residence in an area with risk of Zika, or sex without a condom with a partner who traveled to or lived in such an area

Initial Evaluation of Infants with Possible Congenital Zika Virus Infection

- Comprehensive physical exam
  - Head circumference, weight, length measurements
  - Neurologic assessment
- Standard newborn hearing assessment
- Head ultrasound
- Zika virus laboratory testing

Infants with Possible Congenital Zika Virus Infection: Neuroimaging

Current Interim Guidance

- A head ultrasound is recommended before hospital discharge for infants with possible Zika virus infection

Additional Considerations

- For an infant with a small or absent anterior fontanelle and poor visualization of the intracranial anatomy on ultrasound, other imaging should be considered

- **Most Babies Born To Women With Zika Not Getting Recommended Brain Imaging Follow-Up.**
- NBC News (5/23/17) reports "only about one in four babies born to women with Zika virus infection during pregnancy are receiving the recommended brain imaging after birth," according to testimony given by Dr. Lyle Petersen, a Centers for Disease Control and Prevention expert on insect-borne diseases. Petersen, testifying before the House Energy and Commerce oversight subcommittee, added, "Some brain abnormalities are only identified with brain imaging, suggesting that the impact of Zika on babies born to mothers infected with the virus may be underestimated."

Timing of Laboratory Testing of Infants with Possible Congenital Zika Virus Infection

Current Interim Guidance

- CDC recommends testing specimens collected from infants within 2 days after birth.
  - If specimens are collected later, it may be difficult to distinguish congenital from postnatally acquired infection in areas with risk of Zika

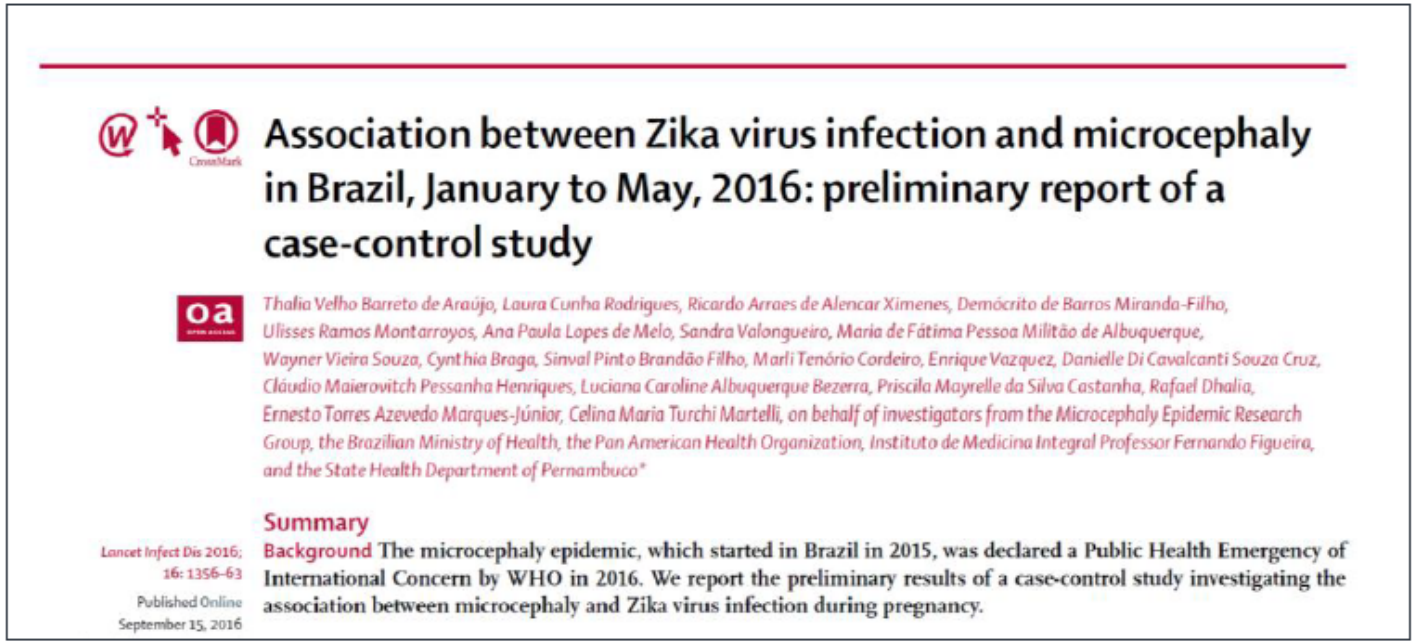
Additional Considerations

- Testing specimens collected within the first few weeks to months after birth may still be useful in the evaluation for infants with possible congenital Zika virus infection, particularly among infants born in areas without risk of Zika

Testing of Cerebrospinal Fluid (CSF)

Current Interim Guidance

- If cerebrospinal fluid (CSF) is obtained for other studies, Zika NAT (nucleic acid testing) for Zika virus RNA and Zika virus IgM should be performed on CSF



Association between Zika virus infection and microcephaly in Brazil, January to May, 2016: preliminary report of a case-control study

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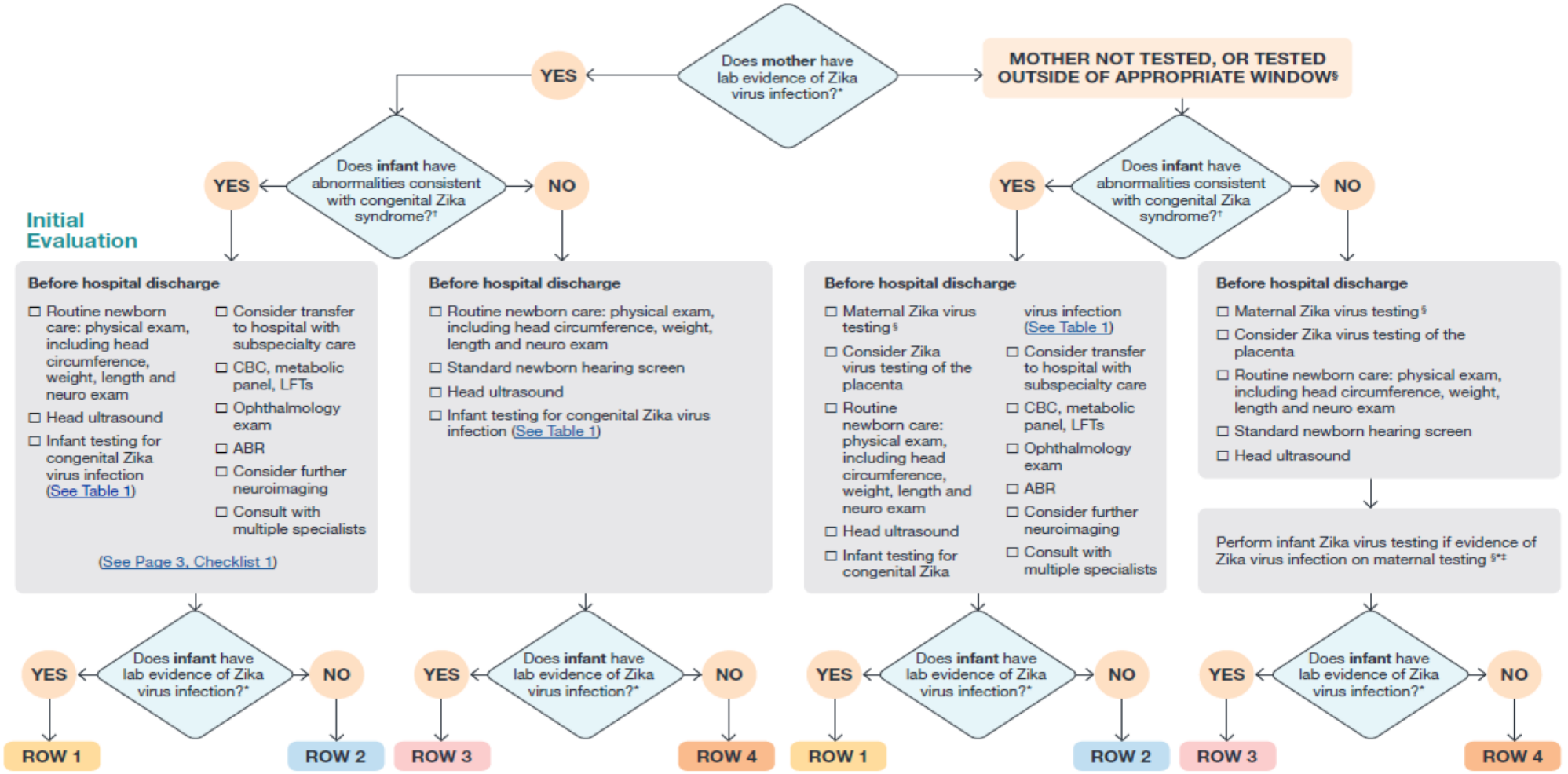
Thalia Velho Barreto de Araújo, Laura Cunha Rodrigues, Ricardo Arraes de Alencar Ximenes, Demócrito de Barros Miranda-Filho, Ulisses Ramos Montarroyos, Ana Paula Lopes de Melo, Sandra Valongueiro, Maria de Fátima Pessoa Militão de Albuquerque, Wayner Vieira Souza, Cynthia Braga, Sinval Pinto Brandão Filho, Marli Tenório Cordeiro, Enrique Vazquez, Danielle Di Cavalcanti Souza Cruz, Cláudio Maierovitch Pessanha Henriques, Luciana Caroline Albuquerque Bezerra, Priscila Mayrelle da Silva Castanha, Rafael Dhalia, Ernesto Torres Azevedo Marques-Júnior, Celina Maria Turchi Martelli, on behalf of investigators from the Microcephaly Epidemic Research Group, the Brazilian Ministry of Health, the Pan American Health Organization, Instituto de Medicina Integral Professor Fernando Figueira, and the State Health Department of Pernambuco*

Lancet Infect Dis 2016; 16: 1356–63
Published Online September 15, 2016

Summary

Background The microcephaly epidemic, which started in Brazil in 2015, was declared a Public Health Emergency of International Concern by WHO in 2016. We report the preliminary results of a case-control study investigating the association between microcephaly and Zika virus infection during pregnancy.

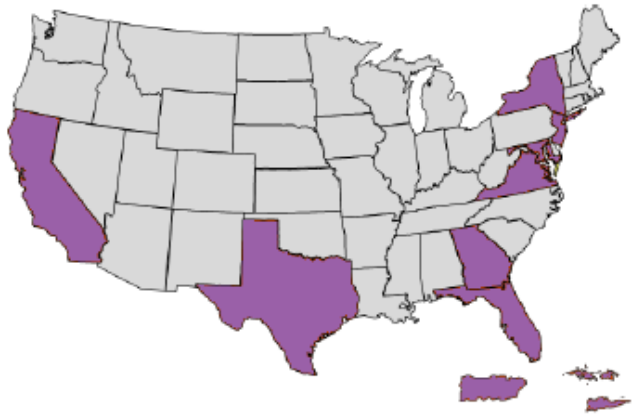
INITIAL EVALUATION AND OUTPATIENT MANAGEMENT
DURING THE FIRST 12 MONTHS OF LIFE FOR INFANTS WITH POSSIBLE CONGENITAL ZIKA VIRUS INFECTION



Follow management and follow-up recommendations indicated in Outpatient Management Checklist

Zika Care Connect: Improving Access to Clinical Services

- Provider Network for Families Affected by Zika
  - » Maternal-fetal medicine, mental health services, audiology, radiology, pediatric ophthalmology, pediatric neurology, developmental pediatrics, infectious disease, and endocrinology
- Laboratory Testing Web Portal for Healthcare Providers
  - » Identify laboratories offering Zika testing



HelpLine: 1-844-677-0447 (toll-free)

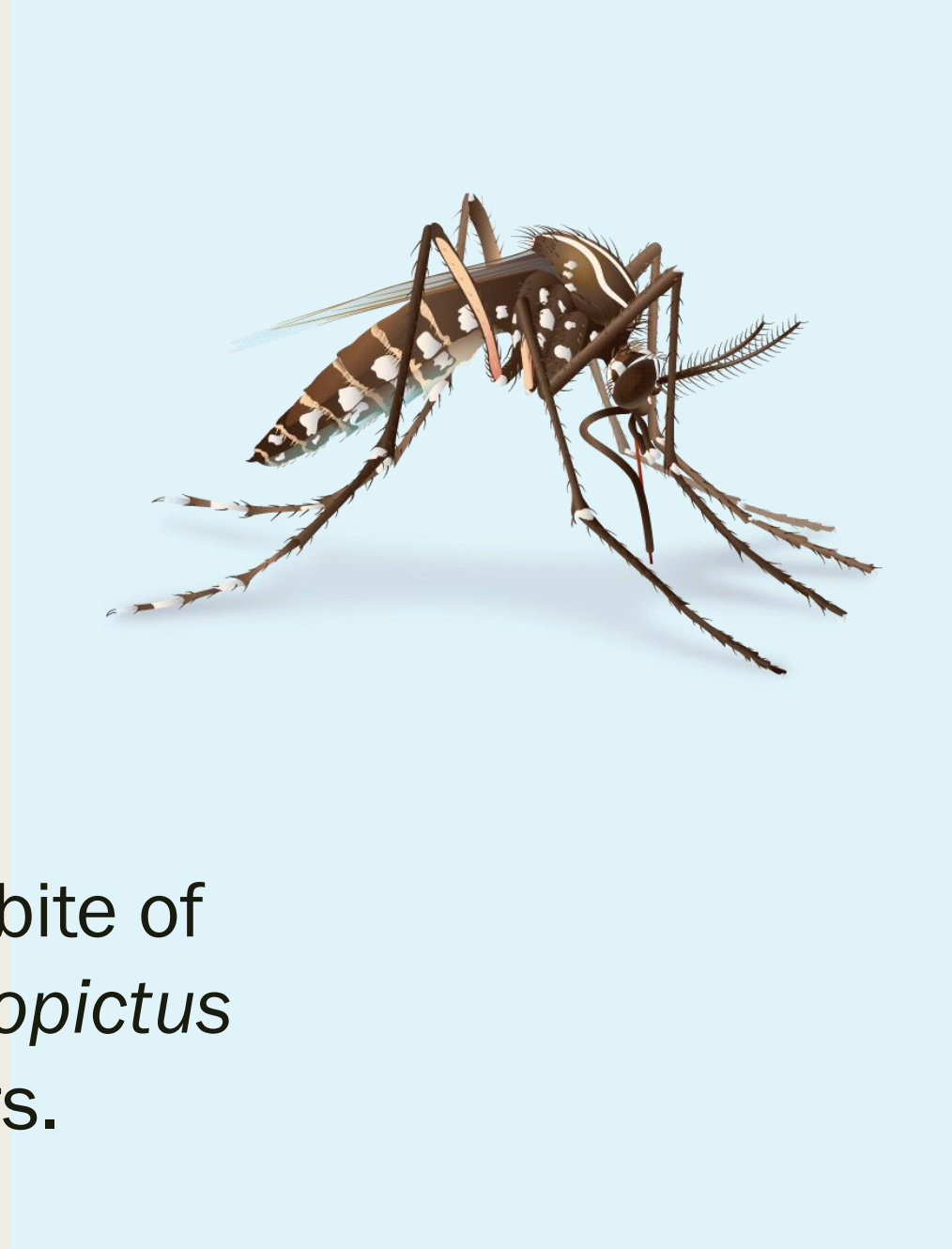
Website: www.zikacareconnect.org

ZIKAcareconnect

in collaboration with the March of Dimes

PREVENTION

Protect from mosquito bites



Zika is primarily spread through the bite of an infected *Aedes aegypti* or *Ae. albopictus* mosquito. Protect yourself and others.

Prevention

Prevention of Mosquito Bites

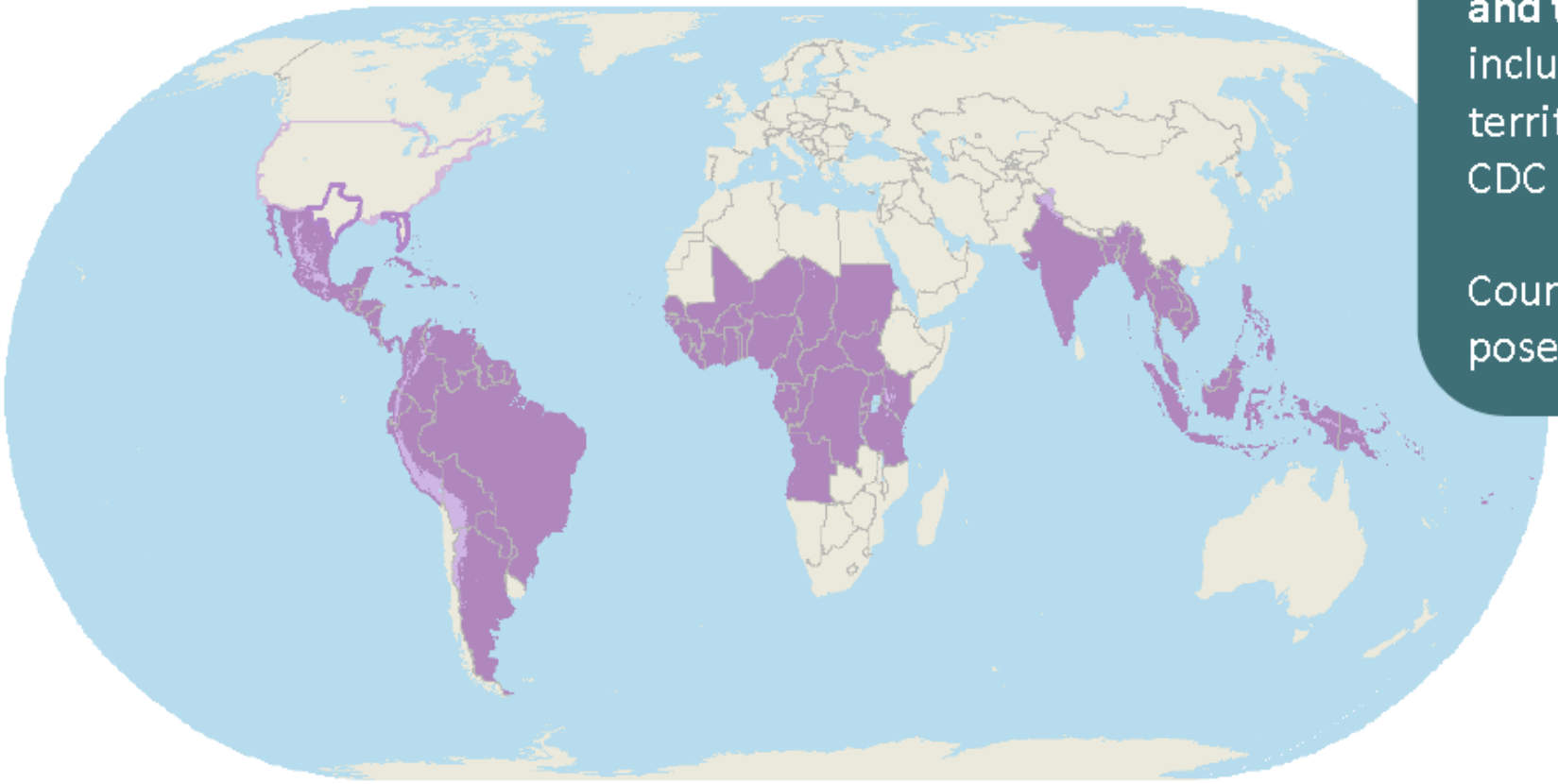
- Long-sleeved shirts
- AC with screened windows
- EPA-approved insect repellent
- Decrease standing water whenever possible

Do Not Travel to Areas with Risk of Zika

- Pregnant women should **not** travel to areas with risk of Zika

http://wwwnc.cdc.gov/travel/page/zika-information

World Map of Areas with Risk of Zika



There are currently **63 countries and territories worldwide,** including 49 countries and territories in the Americas, with a CDC Zika Travel Notice.

Countries with endemic Zika also pose a risk.

Domestic areas

State Reporting Zika:

No Known Zika:

International areas

Zika Travel Recommendation: Low elevation

High elevation

No Known Zika:

As of April 24, 2017

http://www.cdc.gov/zika/geo/active-countries.html

Do Not Travel to Areas with Risk of Zika

If a pregnant woman *must* travel, she should

- Talk with her healthcare provider before she goes
- Strictly follow steps to prevent mosquito bites during the trip
- Take steps to prevent sexual transmission
- Talk with her healthcare provider after she returns, even if she doesn't feel sick

http://wwwnc.cdc.gov/travel/page/zika-information

PREVENTION

Preventing sexual transmission

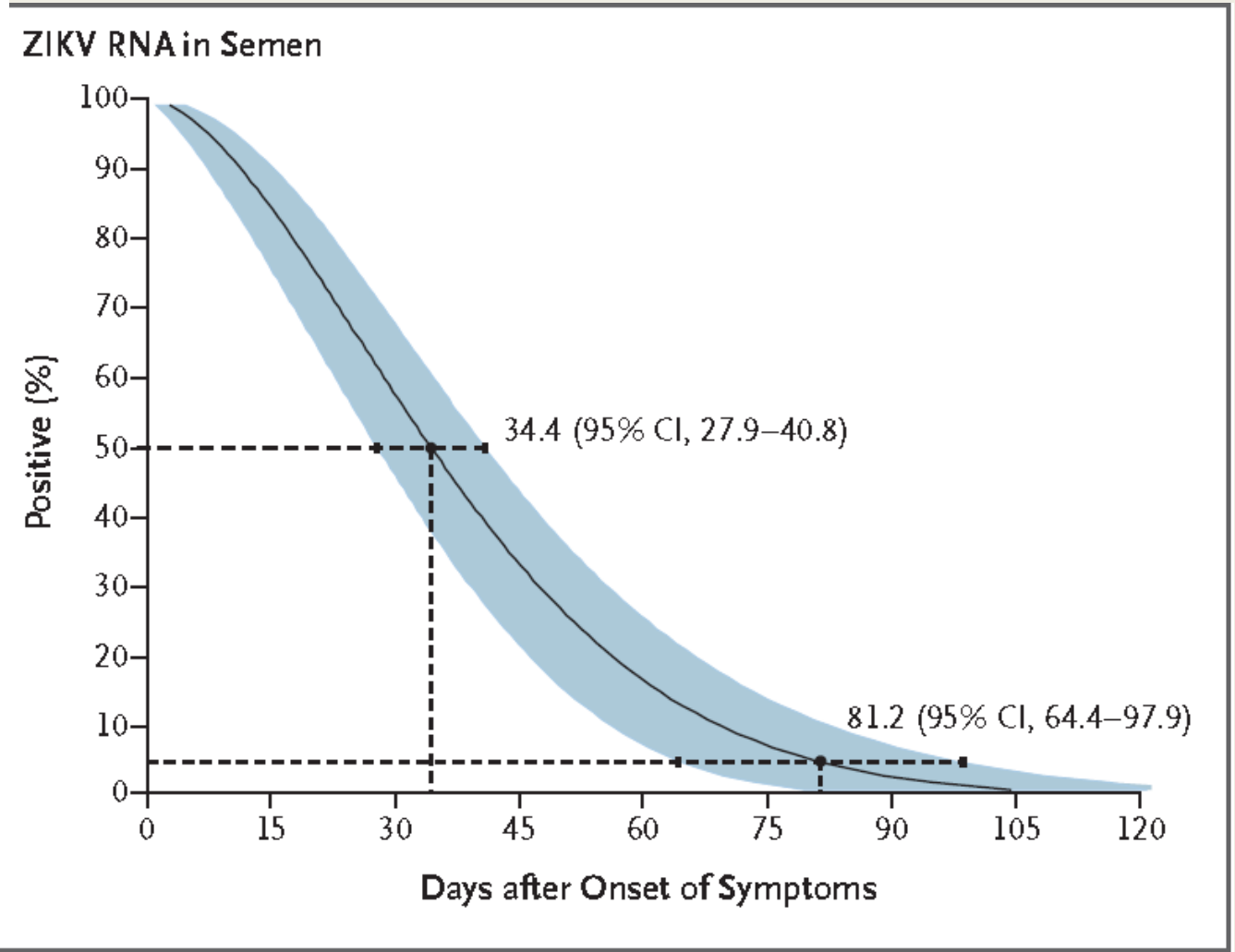
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Persistence of Zika Virus in Body Fluids — Preliminary Report

Gabriela Paz-Bailey, M.D., Ph.D., Eli S. Rosenberg, Ph.D., Kate Doyle, M.P.H., Jorge Munoz-Jordan, Ph.D., Gilberto A. Santiago, Ph.D., Liore Klein, M.S.P.H., Janice Perez-Padilla, M.P.H., Freddy A. Medina, Ph.D., Stephen H. Waterman, M.D., M.P.H., Carlos Garcia Gubern, M.D., Luisa I. Alvarado, M.D., and Tyler M. Sharp, Ph.D.

Semen ZV present
- -median 34 days
- -95th%ile was 81 dys
- -longest 188 days



Preconception Counselling

- Avoid travel to areas of active ZV transmission
- If have to travel, discuss prevention
  - *If develop Sx, test for ZV (NAT and IgM) – wait at least 8 wks if positive*
  - *If no Sx, consider baseline IgM testing in women*
- Couples planning to conceive who live or travel frequently to areas of active ZV
  - *Offer testing*
  - *Women – wait ≥ 8wks after travel to conceive*
  - *Men – wait ≥ 6 months after travel*

Pregnant women s/p possible exposure who are asymptomatic

- The CDC recommends that health care professionals evaluating asymptomatic pregnant women with potential Zika exposure should:
  - *screen for signs of infection and promptly test women using nucleic acid testing (NAT) if they develop symptoms during pregnancy or if their sexual partner develops Zika;*
  - *consider NAT testing at least once during each trimester, unless a previous test was positive*
  - *consider testing any specimens collected during amniocentesis for evidence of Zika virus*
  - *counsel all pregnant women during each trimester on Zika testing limitations*

Prevent Sexual Transmission of Zika Virus

A pregnant woman whose partner lives in or has traveled to an area with risk of Zika should

- Use condoms correctly every time they have sex, or
- Not have sex

For the duration of the pregnancy, even if the pregnant woman's partner does not have symptoms or feel sick.

Summary

- Assure reports submitted to the Zika Pregnancy Registry – normal and abnormal findings in infants of mothers with Hx ZV or possible ZV
- Latest travel notices and Zika updates at: wwwnc.cdc.gov/travel/page/zika-travel-information and cdc.gov
- CZS is a devastating disease
  - *Likely seeing tip of iceberg of Congenital Zika Syndrome with respect to the clinical, lab and radiographic findings – more to come, stay tuned*
  - *Even infants born to mothers with Zika who appear well, should have close developmental follow-up*

- Huge birth cohort affected in Brazil and other Latin American countries…and other areas.
  - *Potentially affecting a large # of a birth cohort*
    - major issue for longterm care and resources will be needed in future to care for these infants/children
    - Workforce losses

  - ***THANK-YOU for your questions and interest in Infectious Diseases in children!!!***