The Buzz on Zika: Should We Still Be Concerned?

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Aedes aegypti

Background

- Zika virus is transmitted to humans primarily through the bite of infected *Aedes* sp. mosquito
 - Nearly all Zika outbreaks due to *aegypti* & *albopictus*
 - These are the same mosquitoes that transmit dengue and chikungunya
 - Dengue and Zika are flaviviruses (YF) ; chikungunya: alphavirus
 - West Nile also arbovirus/flavivirus, but spread by Culex sp.
 - The mosquito vectors typically breed in domestic waterholding containers
 - Aegypti -- high "vectorial capacity": feeds primarily on humans, multiple humans in a single meal, lives close to humans, also daytime <u>and</u> nighttime feeders

PROTECT YOUR FAMILY AND COMMUNITY:

HOW ZIKA SPREADS

Other, less common ways, people get Zika:



Clinical Disease

- About 20% of people infected with Zika virus become symptomatic
- \odot Among those with clinical illness
 - Symptoms mild, typically develop within 1 week from exposure, lasting several days to a week
 - Characteristic clinical findings: acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis.
 - Severe disease requiring hospitalization is uncommon and fatalities are rare.
- Guillain-Barré syndrome also has been reported at increased rates in patients following Zika infection

Clinical Features of Zika Virus Infection in Pregnant Women.



Brazil Zika Outbreak

• May 2015: First infection in Brazil

October 2015: increase in microcephaly





Microcephaly: the tip of the iceberg?

- Microcephaly is a very specific diagnosis, and typically unusual as an isolated finding: initially seen in *newborns*
 - On ultrasound, defined as <u>HC < 3 SD</u> for GA (SMFM, 2016)*
 - <u>HC < 2 SD</u> for GA should trigger more detailed eval and f/u
- Microcephaly became an *early trigger* to search for Zika association, but spectrum of disease became apparent
 - Microcephaly can occur as a result of a **fetal brain disruption sequence**: this appears to be pathology of Zika infection

* ref: Chervenak FA, et al, AJOG 1984

Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?





CT Scans Reveal Extensive Abnormalities

23 infants with microcephaly in Pernambuco, Brazil

The NEW ENGLAND JOURNAL of MEDICINE



- Intracranial calcifications
- Global cortical hypogyration
- Ventriculomegaly
- Global cerebellar hypoplasia

Hazin et al, NEJM April 6, 2016

Fig 3 Severe microcephaly.



Maria de Fatima Vasco Aragao et al. BMJ 2016;353:bmj.i1901



Zika Associated Pregnancy Outcomes







Fetal loss/miscarriage, stillbirth

- Fetal growth abnormalities
- Fetal brain anomalies
 - Microcephaly
 - Ventriculomegaly
 - Intracranial calcifications
- Eye abnormalities
- Neurologic
 - Hypertonia
 - Arthrogryposis
 - Seizures



Miranda-Filho et al, AJPH April 2016, Vol 106 No. 4

Ophtho criteria for CZS

- First ophthalmological examination has to be performed within 30 days of birth.
 - Red Reflex Test does NOT work for diagnosis in cases of CZS
 - 72 patients with CZS -- normal RRT
- SIGNS: Focal pigment mottling of the retina and circular lesions of chorioretinal atrophy including the macula, along with optic nerve abnormalities
 - Identified in 30% of newborns with microcephaly (Frietas et al, JAMA Ophtho 2/16)

O UNIQUE CHORIORETINAL ATROPHY

Zika-Related Arthrogryposis



van der Linden at al, BMJ 8/16

Long Term Pregnancy Outcomes: Evolving

- Update on 13 infants born without microcephaly but ZKV-infected (Brazil)
 - 11 referred for small head size but > 2SD, 2 for devel. lag (5, 7 mos)
 - Neuroimaging abnormal in all: all w/ \downarrow brain volume, +/or \uparrow vents
 - 10 w/dysphagia, 3 w/chorioretinitis, all hypertonic (MMWR 11/16)

• Recent Brazil cohort Zin AA, et al. JAMA Pediatrics 7/17/17

- 112 mother-infant pairs w/confirmed maternal infx
- 10/24 with eye findings (42%) did not have microcephaly, while 8 (33%) had no CNS findings
- Anticipate a spectrum of outcomes?
 - Developmental and/or intellectual delay
 - Motor abnormalities

Pregnancy Risk Estimates

- Brasil et al: Rio cohort¹
 - Prospective study cohort of134 symptomatic pregnant women with <u>confirmed ZKV infection</u>
 - Overall, 49/117 (42%) liveborn ZKV-exposed infants had abnormal findings by 1st month of life [5% in ZKV(-): p< 0.001]
- Adverse outcomes seen regardless of trimester of infx
 - 55% risk if maternal infx in 1^{st} , 52% if in 2^{nd} , 29% if in 3^{rd}
- Updated report from US Zika Pregnancy Registry²
 - Birth defects related to Zika in 6%, 21 in live births
 - No risk difference regarding sx; 11% risk if exposure in $1^{st} \Delta$

1. Brasil et al, NEJM 12/16. 2. Honein M et al, JAMA 12/13/16

Health and Development at Age 19–24 Months of 19 Children Who Were Born with Microcephaly and Laboratory Evidence of Congenital Zika Virus Infection During the 2015 Zika Virus Outbreak — Brazil, 2017

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ZODIAC Study: compiled comprehensive description of children > 12 months of age born with microcephaly (< 3rd %ile at birth) and (+) Zika IgM from Oct 2015-Jan 2016

19 infants, mean age at followup 22 months (range 19-24 months)

15/19 infants had HC ranging from 3.7-8.4 SD below the mean (avg 6.3 SD) All of these infants were symptomatic and had developmental testing < 6 mos.

4/19 infants had HC within 1 SD of mean, all had testing results for > 6 mos.

December 15, 2017

TABLE 1. Growth measurements* of children aged 19–24 months with confirmed or probable congenital Zika virus infection^{†,§} and microcephaly classification at birth^{¶,**} — Paraíba, Brazil, August– October 2017

	No. (%)	
Growth	Male (n = 10)	Female (n = 9)
Head circumference ^{††}		
>3 SD below mean for age and sex ^{§§}	7 (70)	8 (89)
Length ^{¶¶}		
1-3 SD below mean for age and sex***	6 (60)	7 (78)
Weight ⁺⁺⁺		
1 to >3 SD below mean for age and sex ^{§§§}	6 (60)	7 (78)

TABLE 3. Health and developmental outcomes of 19 children aged 19–24 months with confirmed or probable congenital Zika virus infection,^{*,†} and microcephaly classification^{§,¶} at birth — Paraíba, Brazil, August–October 2017

Outcome	No. (%)
Medical findings	
Seizures**, ^{††}	11 (58)
Retinal abnormalities ^{§§}	4 (21)
Hospitalization**	8 (42)
Pneumonia/Bronchitis	6 (75)
Intestinal infection	1 (14)
High fever	1 (14)
Failure to thrive/feed	1 (14)
Functional outcomes	
Sleeping difficulties**	10 (53)
Feeding difficulties**	9 (47)
Impaired response to auditory stimuli (hearing asymmetric or no response) ^{¶¶}	13 (68)
Impaired response to visual stimuli ^{¶¶}	11 (58)
Neurologic outcomes ^{¶¶}	
Severe motor impairment ^{¶¶}	15 (79)
Cerebral palsy***	14 (74)

Summary

What is already known about this topic?

Congenital Zika virus infection has been linked to increased rates of microcephaly and a unique pattern of birth defects among infants. Although children with microcephaly and laboratory evidence of Zika virus infection have been described in early infancy, the subsequent health and development in young children have not been well characterized, constraining planning for the care of these children.

What is added by this report?

The growth and development of 19 children, aged 19–24 months, with laboratory evidence of Zika virus infection were

thoroughly assessed. All children had at least one adverse outcome including feeding challenges, sleeping difficulties, severe motor impairment, vision and hearing abnormalities, and seizures, and these outcomes tended to co-occur.

What are the implications for public health practice?

Children with microcephaly and laboratory evidence of Zika virus infection face medical and functional challenges that span many areas of development, some of which become more evident as children age. They will continue to require specialized care from clinicians and caregivers. These data allow for anticipation of medical and social services needs of affected children and families, such as early intervention services, and planning for resources to support these families in healthcare and community settings.

Zika – Where is it and where is it <u>not</u>?



Aedes aegypti and Aedes albopictus Mosquitoes in California Detection Sites by County/City



Counties with Aedes aegypti only: Fresno, Imperial, Kings, Madera, Riverside, Merced, Tulare

Both Aedes aegypti and Aedes albopictus:

Kern, Los Angeles, Orange, San Bernardino, San Diego

See pages 2 and 3 for *Aedes* detections by city or censusdesignated place in each county.



Health & Fitness

Mosquito Capable Of Carrying Zika Found In Pasadena

Eggs from the type of mosquito that can transmit Zika, dengue and chikungunya have been detected in Pasadena: BREAKING

By Paige Austin (Patch Staff) - Updated July 3, 2017 10:36 pm ET



Popular Video



As of Jan 2018: CDC.gov



Figure 2. Distribution of suspected and confirmed Zika cases by epidemiological week and sub-region. Region of the Americas, 2016 – 2017 (as of EW 18).¹⁶



Source: Data provided by countries and territories and reproduced by PAHO/WHO

Figure 3. Distribution of suspected and confirmed Zika cases by EW. Argentina, Brazil, Ecuador, and Peru, EW 25 of 2015 to EW 18 of 2017.



Zika as an Endemic Infection

 Zika virus is considered <u>endemic</u> in some countries, and a large number of local residents are likely to be immune. However, US travelers to endemic areas may not be immune to Zika virus and infections have occurred among travelers to Asia and Africa



 Zika evolving as an outbreak like other arboviruses : areas of endemicity but high potential (like West Nile and chikungunya) for ongoing sporadic cases and local outbreaks (Paules C, Fauci A: JAMA 1/12/17)



Confirmed Zika Cases in Mexico by State January 1, 2016 – January 8, 2018



Confirmed Zika Cases in Mexico by State January 1, 2017 – January 1, 2018







Entidad Federativa	Casos Confirmados 2015-2016	Casos Confirmados 2017	Total
Baja California Sur	6	0	6
Campeche	53	2	55
Coahuila	2	105	107
Colima	203	0	203
Chiapas	561	1	562
Guerrero	472	8	480
Hidalgo	134	13	147
Jalisco	36	31	67
México	0	1	1
Michoacán	20		21
Morelos	200	98	298
Nayarit	7	168	175
Nuevo León	594	63	657
Oaxaca	209	3221	210
Puebla	33	32	65
Querétaro	0	20.5	5
Quintana Roo	330	4	334
San Luis Potosi	20	295	315
Sinaloa	24	3	27
Sonora	2	1	3
Tabasco	278	8	286
Tamaulipas	95	464	559
Veracruz	870	14	884
Yucatán	915	9	924
Zacatecas	1	0	1
Total	5,065	1,327	6,392

Casos Confirmados Autóctonos de Enfermedad por Virus del Zika en Mujeres Embarazadas, por Entidad de Infección, México 2015-2017*

FUENTE: SINAVE/DGE/SS: Sistema de Vigilancia Epidemiológica de Enfermedad por virus del Zika. * Hasta el 23 de octubre de 2017.

Nota: Estos casos están considerados dentro del acumulado general de casos confirmados autóctonos.

L.A. County officials confirm first case of sexually transmitted Zika virus



Aedes aegypti mosquitoes, responsible for transmitting Zika, sit in a petri dish at the Fiocruz Institute in Recife, Brazil. (Felipe Dana / AP)



By Soumya Karlamangla · Contact Reporter

JANUARY 4, 2018, 12:10 PM



Zika in the US: as of Jan 10, 2018

<u>US States/DC (5635 cases): 407 in 2017</u>

- Travel-associated Zika virus disease cases reported:
 5355 (50 other routes)
- Locally acquired vector-borne cases reported: 228
 - In 2017: all travel cases, exc 4 local and 5 sexual

US Territories

- Travel-associated cases reported: 147 (0 in 2017)
- Locally acquired cases reported: 36,976 (631 in 2017)
 - 51 cases of Guillain-Barre syndrome

Current Zika Statistics (as of 10/17/17)

- 2364 pregnant travelers with laboratory evidence of Zika virus in US States and DC – vast majority imported/travel-related
 - \odot 2143 completed pregnancies
 - 102 reported liveborn infants and 9 fetal losses with Zika related birth defects (5.2% affected)
- 4690 pregnant cases in US territories (mostly Puerto Rico) --- 3738 completed, 150 affected liveborns or losses (4.0%)

Imported Zika Cases in California, 2015-17

(n = 609, through Nov 3, 2017,

with 101 total in 2017 so far)

Country Traveled To	Number of Imported Cases in California (%)
Mexico	195 (36%)
Nicaragua	61 (11%)
Guatemala	49 (9%)
El Salvador	37 (7%)
Dominican Republic	26 (5%)

These 5 countries account for 68% of travel cases in CA

Median age 35 66% in women



California Department of Public Health Division of Communicable Disease Control

CDPH Monthly Update on Number of Zika Virus Infections in California January 5, 2018

The following table provides the number of travel-associated infections with Zika virus in California residents during 2015 – 2017. CDPH is following CDC testing guidelines. This table is updated the first Friday of every month. As of January 5, 2018, there have been 634 travel-associated Zika virus infections in California.

- Total infections: 634
- New infections reported this month: 15
- Locally acquired infections: 0
- Cumulative number of infections due to sexual transmission: 9
- Cumulative number of infections in pregnant women: 168
- Cumulative number of completed pregnancies: 142^a
 - Liveborn infants with birth defects: 10^b
 - Pregnancy losses with birth defects: 0^c

Zika virus infections in California, 2015-2017 ^d (as of January 5, 2018)		
County	Travel-associated * 2015-2016	Travel-associated * 2017
Alameda	35'	10'
(City of Berkeley)	(3)	(3)
Butte	2	0
Contra Costa	26	4
Fresno	6	2
Humboldt	2	0
Imperial	0	1
Kern	5	1
Kings	1	0
Lake	1	0
Los Angeles (City of Long Beach) (Pasadena)	114 ⁹ (6) (1)	22 ⁹ (1) (0)
Marin	9	2
Mendocino	0	1
Merced	3	0
Monterey	5	1
Napa	3	0
Nevada	1	0
Orange	31	12
Placer	1	0
Riverside	14	3
Sacramento	7	0
San Benito	1	0

San Bernardino	18	7
San Diego	85 ^h	20
San Francisco	29	11
San Joaquin	7	1
San Luis Obispo	1	0
San Mateo	13	2
Santa Barbara	8	2
Santa Clara	36	14
Santa Cruz	3	0
Solano	3	2
Sonoma	11	5
Stanislaus	4	0
Tulare	5	2
Ventura	9	0
Yolo	6	1
Yuba	3	0
Total	508	126

Zika – Education and Testing

What do we tell our pregnant patients?

• How much fetal risk with confirmed maternal infection?

- Based on current data, range may be as high as 29%
- Rates are derived from methodologically diverse studies
- Despite earlier reports, recent data suggest later GA at infection does not exclude potential adverse impact
- Pregnant women should not travel to areas with active local Zika transmission

The role of prevention

- If in an area with transmission, protection and prevention strategies are important – <u>and repellent</u> <u>for 3 weeks after return from these areas</u>
- DEET, picaridin fine for use in pregnancy
 - Consumer Reports (Sept 2017): Deet at 25-30% concentrations works best, picardin 20% (spray, not lotion), oil of lemon eucalyptus 30% (Repel better than Coleman)



Early Release / Vol. 66

Morbidity and Mortality Weekly Report

July 24, 2017

Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure — United States (Including U.S. Territories), July 2017

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What informed the new testing guidelines?

- While consequences of Zika infection are better understood, accurate diagnosis continues to be challenging
 - Virus present in body fluids only transiently
 - Serologic testing (IgM) can't always reliably time infection
 - Serology prone to false-positive results and cross-reaction with other flaviviruses
- With declining prevalence of Zika infection, probability of false-positive tests increases
- Changing epidemiology further limits diagnostic capabilities of existing tests

Zika Immunity

- Presumption has been that Zika infection confers immunity after the IgM response
- Based on experience with other flaviviruses, previous Zika infection is likely to confer prolonged, likely lifelong immunity
 - If true, prior infection would prevent risks for a future pregnancy

 However, <u>no commercially-available IgG</u> <u>testing exists</u>, and IgM duration limited

New tests on the horizon .. NS1-based

New guidelines – what do the changes reflect?

- As many areas in the Americas move into a 2nd or 3rd mosquito season after introduction of Zika virus, testing becomes more complex
- Given the evolving epidemiology and the betterrealized limitations of testing, updated testing algorithms for symptomatic and asymptomatic pregnant women emphasize a <u>shared decision-</u> <u>making model</u>
- Need for pre-and post-test counseling, with results interpreted in context of limitations

New guidelines: what's the same (mostly)?

- Screen pregnant women for Zika exposure risk and/or symptoms at every prenatal and hospital visit
 - Knowledge of potential exposure before and during pregnancy is critical information for test interpretation
- Symptomatic pregnant women with recent possible Zika exposure: testing still recommended
 - Concurrent NAT (blood/urine) and IgM as soon as possible, through 12 weeks post-exposure (can consider if > 12 wks, but..)
- Pregnant women with exposure and u/s findings: <u>still test</u>
- Asymptomatic women with ongoing possible Zika exposure: testing still offered once/trimester
 - NAT testing of blood and urine, <u>not</u> IgM (diagnostic limits)

New guidelines: what's different (mostly)

- Asymptomatic women with recent possible Zika exposure <u>but not ongoing exposure</u>
 - Testing now *not routinely recommended* for this group
 - BUT: shared-decision making and <u>consideration of</u> <u>local/regional epidemiologic risks</u> involved for this group
 - CDC acknowledges that data indicate that while perinatal Zika risk doesn't differ by maternal symptoms, routine testing in a low-prevalence group increases risk of falsepositives in absence of any prevention or therapies
 - If testing done, default to algorithm for symptomatic/no ongoing exposure: PCR and IgM
- Until recently: CA, FL, TX, NY kept prior guidelines



State of California—Health and Human Services Agency California Department of Public Health



EDMUND G. BROWN JR. Governor

Date: January 10, 2018

To: California Health Care Providers

C. Asymptomatic Pregnant Women with recent but without ongoing exposure are not routinely tested but instead should be assessed carefully for factors that increase the likelihood of Zika infection. A patient's risk tolerance and decision-making regarding the pregnancy may be sufficient justification to test for Zika virus infection.

California has substantially declined. These factors together lead to a lower pre-test probability of infection when considering testing pregnant women and their newborns. As of November 24, 2017, 162 pregnant women with travel-associated Zika infection have been reported in California since 2015. Of these, 136 women have had completed pregnancies and 9 infants have been born with microcephaly and other Zika-associated anomalies. More than half of the infants born in California with Zika-associated birth defects were born to Zika-exposed mothers who were asymptomatic for Zika infection.



Pregnancy Management

- $\,\circ\,$ Microcephaly and intracranial calcifications typically detected during ultrasounds in the late 2nd/early 3rd Δ
 - These birth defects might be detected as early as 18-20 weeks gestation.
 - A recent study of 17 pregnancies with laboratory confirmed Zika virus infection and adverse fetal outcomes reported a *median of 18 weeks* from symptom onset to prenatal diagnosis of microcephaly. (*Paara-Saavedra et al, ObGyn 7/17*)
- If early testing negative and 2nd trimester or early 3rd trimester scan normal: usual care
- If confirmed/possible maternal Zika infection, consider serial u/s q 3-4 weeks

Zika "waiting periods" – not just pregnancy

- Timeframes to wait to get pregnant after travel to an area with a CDC travel notice (CDC 7/17)
 - Women -- 8 weeks Men -- 6 months
 - If both partners traveled, wait 6 months + condoms
- Egg and sperm donors (ASRM, 3/16)
 - Wait period 6 months after infx, travel, or contact
- Blood donors (FDA, 2/16)
 - 4 week waiting period

INTERIM GUIDANCE Neonatal coordination is Critical!

Evaluation and testing of infants with possible congenital Zika virus infection



*Laboratory evidence of maternal Zika virus infection includes: (1) Zika virus RNA detected by real-time reverse transcription-polymerase chain reaction (rRT-PCR) in any clinical specimen; or (2) positive Zika virus immunoglobulin M (IgM) with confirmatory neutralizing antibody titers. Mother's should be tested by rRT-PCR within 2 weeks of exposure or symptom onset, or IgM within 2-12 weeks of exposure or symptom onset. Due to the decline in IgM antibody and viral RNA levels over time, negative maternal testing 12 weeks after exposure does not rule out maternal infection. Abbreviation: ABR = auditory brainstem response.

More information on the evaluation, management, and follow-up of infants with possible congenital Zika virus infection is available at www.cdc.gov/zika/hc-providers/infants-children.html.



U.S. Department of Health and Human Services Centers for Disease Control and Prevention

Need for Neonatal Followup & Deficits

• Recent report on 2549 completed pregnancies (1/16-4/17)

- 5% of fetuses/newborns of women in Puerto Rico with confirmed Zika infection had likely Zika-associated birth defects ¹
- Of liveborns without birth defects, only 52% had postnatal neuroimaging and 78% had hearing screens

• Recent US Pregnancy Registry Data worse (MMWR, 4/7/17)²

- Among 895 liveborns with maternal infection: postnatal neuroimaging reported for 25%, Zika testing of at least 1 infant specimen 65%
- While 98% of pregnant women in P.R. in a recent survey took at least 1 measure to avoid Zika infection, use of repellents (45%) and condoms (40%) during pregnancy overall low ³

1. Shapiro-Mendoza CK, et al, MMWR 6/8/17. 2. Reynolds M et al, MMWR 4/7/17. 3. D'Angelo DV et al, MMWR 6/9/17

Which newborns need Zika surveillance?

- Zika testing for in 1st two days after birth for infants at risk: serum and urine for PCR, serum for IgM
 - Mothers with lab-confirmed infection
 - Abnormal clinical findings suggestive of congenital Zika and potential maternal epidemiologic link, regardless of maternal test results
- All infants born to women with lab-confirmed Zika infection should get:
 - Zika testing, comprehensive exam, head ultrasound, and standard hearing assessment
 - Based on newer data, they should also get formal eye exam (not just red reflex testing)

Zika Resources

- CDC Zika website: <u>www.cdc.gov/zika</u>
- ACOG's Zika webpage: <u>www.acog.org/zika</u>
- CDC Zika Pregnancy Hotline for Healthcare Providers: 770-488-7100 or email <u>ZikaPregnancy@cdc.gov</u> for concerns related to clinical mgmt or the Zika Pregnancy Registry
- CA Dept of Public Health webpage for health care professionals
 - www.cdph.ca.gov/zika