Update on Zika virus infection

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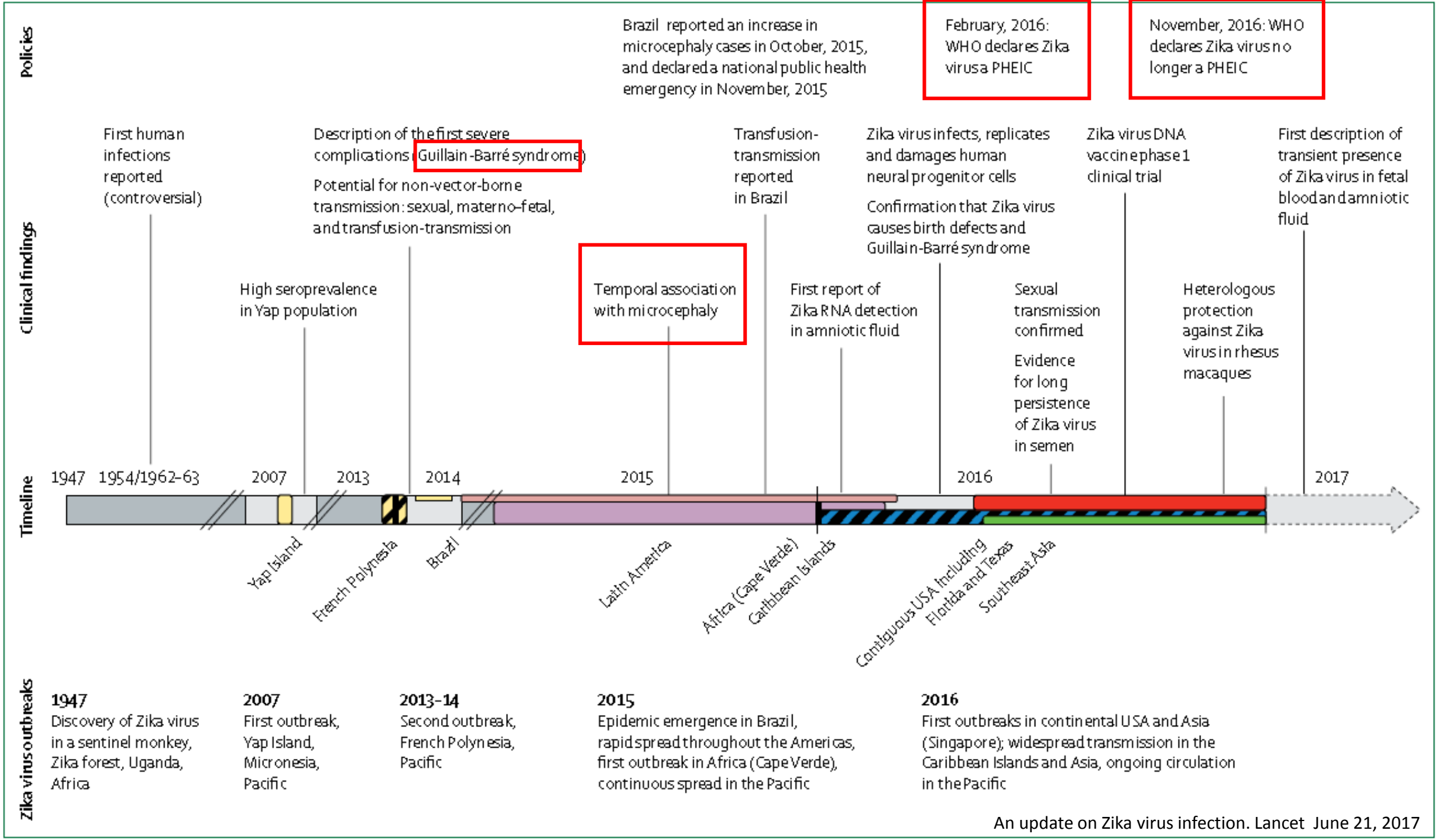
ID forum 13th July 2017

寨卡傳入香港

首宗外地感染 聯合醫院隔離

世衛：寨卡病毒如爆炸般擴散

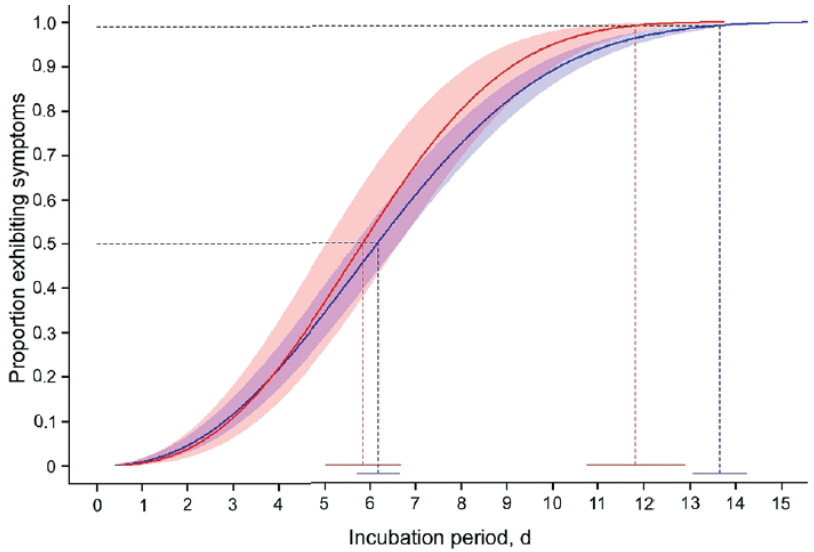
部分案例顯示病毒與初生兒小頭症有關



An update on Zika virus infection. Lancet June 21, 2017

Virology of Zika virus

- Incubation period 3-14 days



Data from 197 symptomatic travelers with samples tested at the CDC in 2015–2016

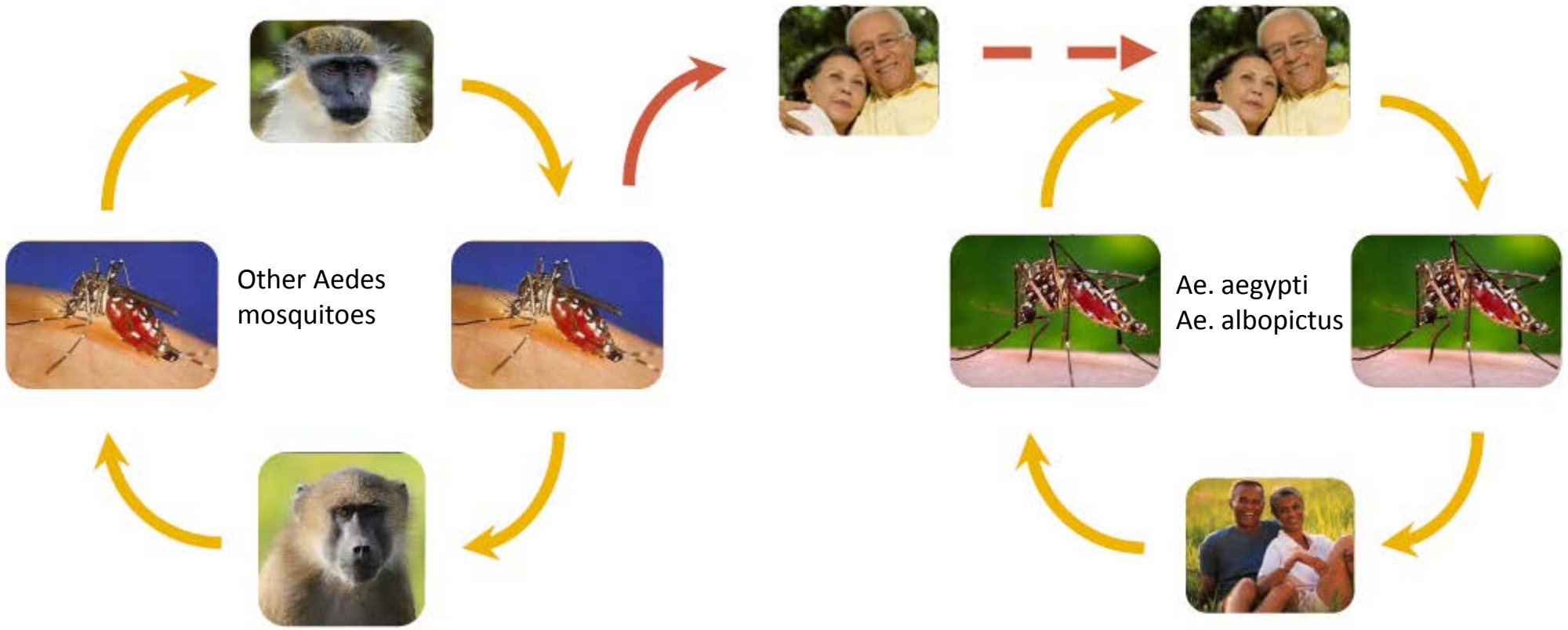
- Single stranded RNA enveloped virus
- Genus *Flavivirus*, Family *Flaviviridae*
- Closely related to dengue, yellow fever, Japanese encephalitis and West Nile viruses

Infection	Mosquito genus
Malaria (parasite)	Anopheles
Japanese Encephalitis	Culex
Dengue	Aedes
Chikungunya	Aedes
Zika	Aedes
West Nile virus	Culex
Yellow Fever	Aedes

Estimated Incubation Period for Zika Virus Disease. Emerging Infectious Diseases Vol. 23, No. 5, May 2017

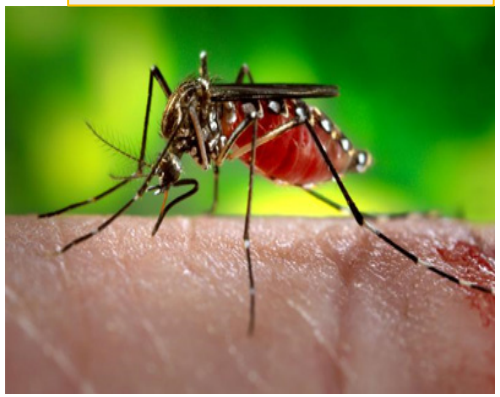
Mosquito-borne disease 蚊媒傳染病

Zika Virus Transmission Cycles



Zika Virus —What Clinicians Need to Know? CDC Clinician Outreach and Communication Activity January 26, 2016

埃及伊蚊
Aedes aegypti
(principal vector)



Flight range: 400 metres

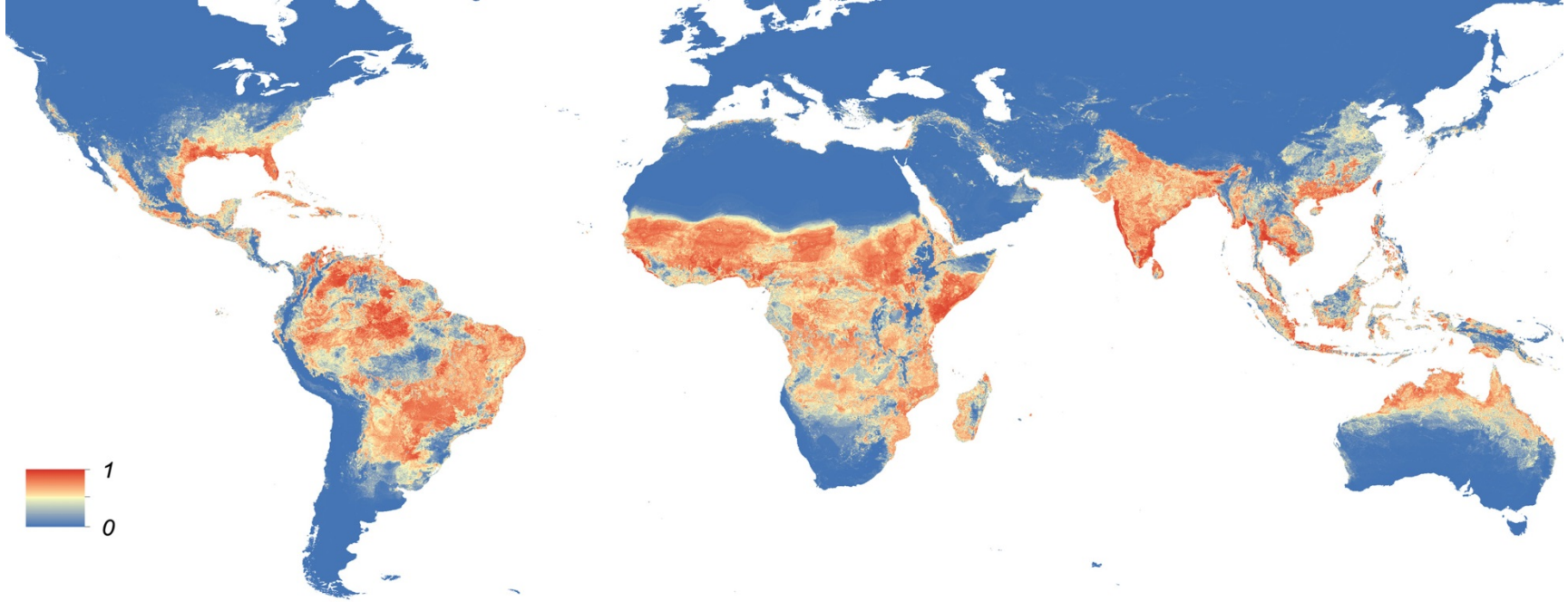
Yellow fever mosquito	Asian tiger mosquito
Has bright silvery lyre-shaped dorsal pattern and white banded legs	Has a single longitudinal silvery dorsal stripe and white banded legs
Occupies urban areas with or without vegetation	Associated with thickets and arboreal vegetation
Bites, rests, and lays eggs both indoors and outdoors	Mostly an outdoor (garden) mosquito
Sneaky biter	Aggressive biter
High preference for taking blood meals from humans and to lesser extent from domestic mammals, which makes it a very capable vector of dengue viruses	Bites humans but also a variety of available domestic and wild vertebrates that do not carry the dengue viruses, which lowers its capacity to transmit them
Main dengue vector worldwide	Main dengue vector in some areas but is mostly a secondary vector
The major production places are human-made containers, treeholes and bamboo internodes holding water	Shows preference for treeholes and bamboo internodes with water but can also utilize human-made containers for its immature development
Most containers with water used for immature development are within or in close proximity to households	Utilizes water-filled containers around or further away from households

白紋伊蚊
Aedes albopictus

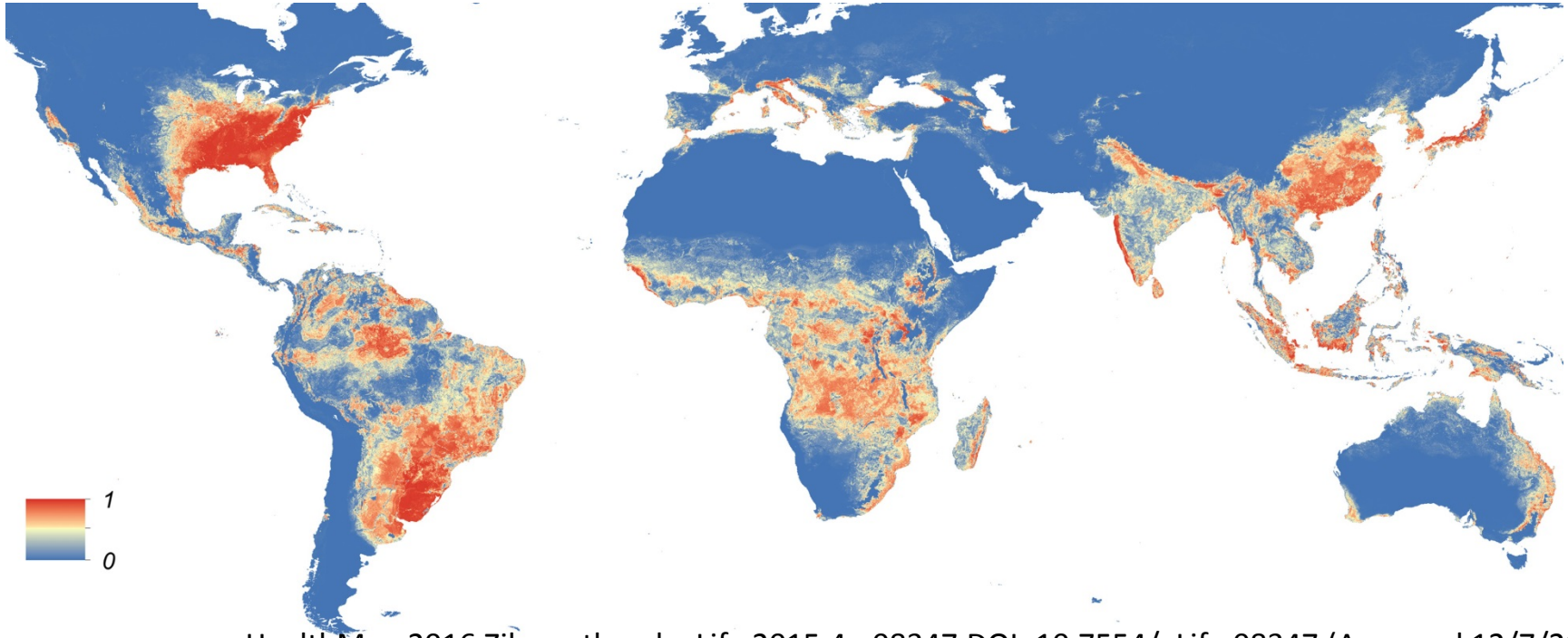
Flight range: 200 metres.
Can tolerate cooler temperatures

https://www.cdc.gov/dengue/resources/30jan2012/albopictusfactsheet.pdf
https://www.cdc.gov/dengue/resources/30jan2012/comparisondenguevectors.pdf
http://www.who.int/denguecontrol/mosquito/en/
https://www.cdc.gov/zika/vector/range.html

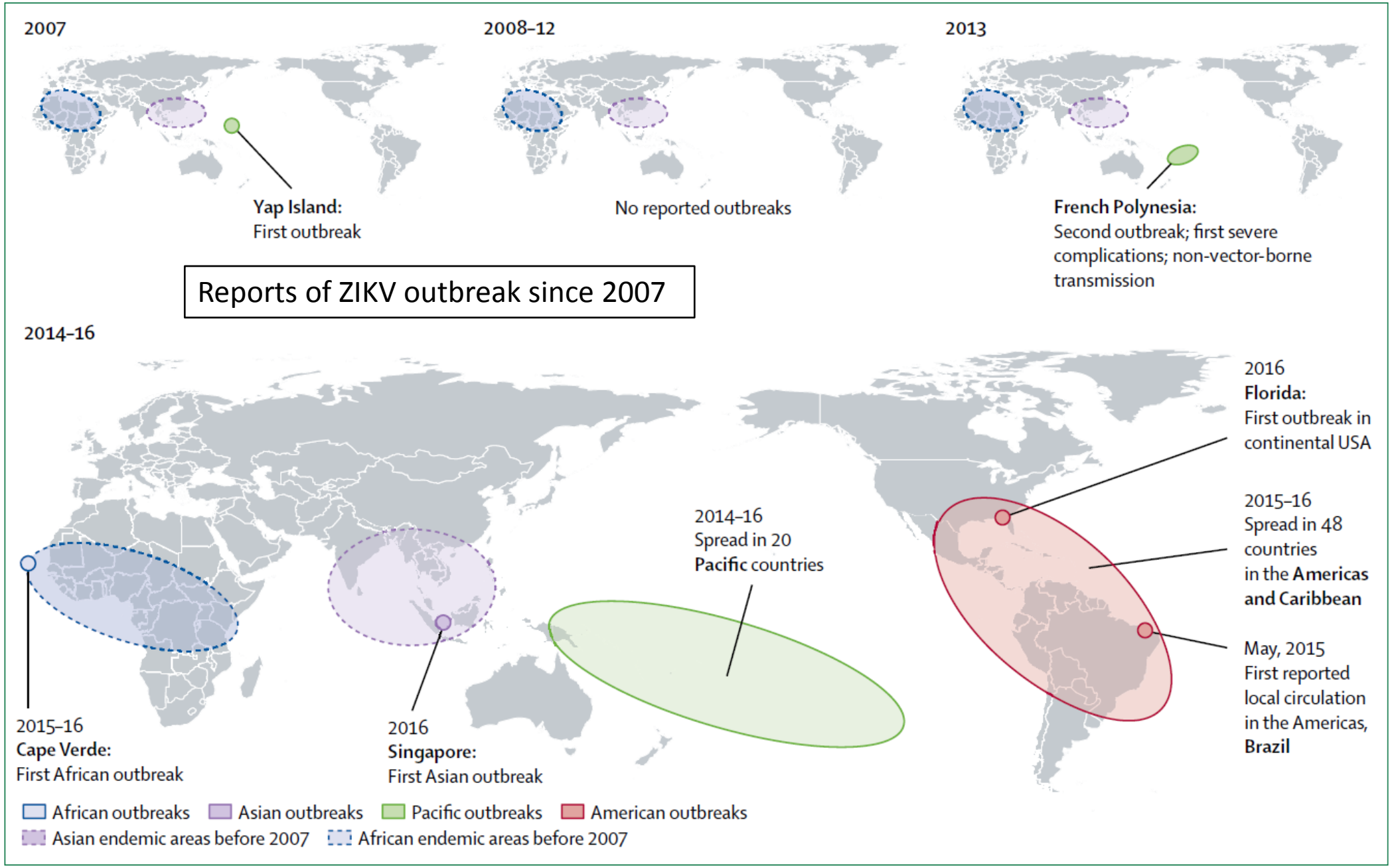
Aedes aegypti



Aedes albopictus



HealthMap 2016 Zika outbreak eLife 2015;4:e08347 DOI: 10.7554/eLife.08347 (Accessed 12/7/2017)



An update on Zika virus infection. Lancet June 21, 2017

Country classification by WHO

Category 1: Area with new introduction of Zika virus since 2015 or area where the virus has been re-introduced, with ongoing transmission.

Category 2: Area either with evidence of Zika virus circulation before 2015 OR with ongoing transmission but the area does not satisfy the criteria for category 1 or 3. Areas in category 2 may also experience an outbreak of Zika.

Category 3: Area with interrupted transmission but with potential for future transmission.

Category 4: Area with established Aedes aegypti mosquitoes but no known documented past or current transmission

Hong Kong – not in any of the four categories at the moment

http://www.who.int/csr/disease/zika/information-for-travelers/en/ (accessed 12/7/2017)
http://www.who.int/emergencies/zika-virus/classification-tables/en/ (accessed 12/7/2017)

Table 1. ZIKV classification[1,2]

	WHO Regional Office	Country / territory / subnational area	Total
Category 1: Area with new introduction or re-introduction with ongoing transmission	AFRO	Angola; Cabo Verde; Guinea-Bissau	3
	AMRO/PAHO	Anguilla; Antigua and Barbuda; Argentina; Aruba; Bahamas; Barbados; Belize; Bolivia (Plurinational State of); Bonaire, Sint Eustatius and Saba; British Virgin Islands; Cayman Islands; Colombia; Costa Rica; Cuba; Curaçao; Dominica; Dominican Republic; Ecuador; El Salvador; French Guiana; Grenada; Guatemala; Guyana; Honduras; Jamaica; Mexico; Montserrat; Nicaragua; Panama; Paraguay; Peru; Puerto Rico; Saint Kitts and Nevis; Saint Lucia; Saint Martin; Saint Vincent and the Grenadines; Sint Maarten; Suriname; Trinidad and Tobago; Turks and Caicos Islands; United States of America; United States Virgin Islands; Venezuela (Bolivarian Republic of)	43
	SEARO	Maldives	1
	WPRO	Fiji; Marshall Islands; Micronesia (Federated States of); Palau; Papua New Guinea; Samoa; Singapore; Solomon Islands; Tonga	9
Subtotal			56
Category 2: Area either with evidence of virus circulation before 2015 or area with ongoing transmission that is no longer in the new or re-introduction phase, but where there is no evidence of interruption	AFRO	Burkina Faso; Burundi; Cameroon; Central African Republic; Côte d'Ivoire; Gabon; Nigeria; Senegal; Uganda	9
	AMRO/PAHO	Brazil; Haiti	2
	SEARO	Bangladesh; India; Indonesia; Thailand	4
	WPRO	Cambodia; Lao People's Democratic Republic; Malaysia; Philippines; Viet Nam	5
Subtotal			20
Category 3: Area with interrupted transmission and with potential for future transmission	AMRO/PAHO	Guadeloupe; ISLA DE PASCUA – Chile; Martinique; Saint Barthélemy	4
	WPRO	American Samoa; Cook Islands; French Polynesia; New Caledonia; Vanuatu	5
Subtotal			9
Category 4: Area with established competent vector but no known documented past or current transmission	AFRO	Benin; Botswana; Chad; Comoros; Congo; Democratic Republic of the Congo; Equatorial Guinea; Eritrea; Ethiopia; Gambia; Ghana; Guinea; Kenya; Liberia; Madagascar; Malawi; Mali; Mauritius; Mayotte; Mozambique; Namibia; Niger; Réunion; Rwanda; Sao Tome and Principe; Seychelles; Sierra Leone; South Africa; South Sudan; Togo; United Republic of Tanzania; Zambia; Zimbabwe	33
	AMRO/PAHO	Uruguay	1
	EMRO	Djibouti; Egypt; Oman; Pakistan; Saudi Arabia; Somalia; Sudan; Yemen	8
	EURO	Georgia; Região Autónoma da Madeira – Portugal; Russian Federation; Turkey	4
	SEARO	Bhutan; Myanmar; Nepal; Sri Lanka; Timor-Leste	5
	WPRO	Australia; Brunei Darussalam; China; Christmas Island; Guam; Kiribati; Nauru; Niue; Northern Mariana Islands (Commonwealth of the); Tokelau; Tuvalu; Wallis and Futuna	12
Subtotal			63
Total			148

Category 1: Area with new introduction or re-introduction with ongoing transmission

Vector competence

Table. Competence of mosquitoes, by species, as Zika virus vectors, 14 days after peroral infection, United States*

	No. virus-positive/no. tested (%)								
	Biological replicate 1, mean 6.02 log_{10} PFU/mL ± SD 0.67			Biological replicate 2, mean 4.74 log_{10} PFU/mL ± SD 0.06			Biological replicate 3, mean 6.83 log_{10} PFU/mL ± SD 0.45		
Mosquito species	I	D	T	I	D	T	I	D	T
Culex pipiens†	0/20 (0)	0/20 (0)	0/20 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/30 (0)	0/30 (0)	0/30 (0)
Aedes triseriatus‡	ND	ND	ND	0/20 (0)	0/20 (0)	0/20 (0)	4/13 (31)	0/4 (0)	0/4 (0)
Ae. albopictus§	9/9 (100)	6/9 (67)	2/9 (22)	1/6 (17)	0/1 (0)	0/1 (0)	ND	ND	ND
Ae. aegypti¶	ND	ND	ND	ND	ND	ND	17/17 (100)	12/17 (71)	4/17 (24)

*Zika virus strain PRVABC59 (GenBank accession no.KU501215) was originally isolated from a traveler to Puerto Rico in December 2015. I, infected; D, disseminated; ND, no data; T, transmitted.
†Originated from egg rafts collected in Iowa in 2002 and colonized at the Iowa State University Medical Entomology Laboratory.
‡Originated from eggs collected in Iowa in 2002 and 2003 and colonized at the Iowa State University Medical Entomology Laboratory.
§Originated from eggs collected in Missouri in 2002 and colonized at the Illinois Natural History Survey.
¶Black-eyed Liverpool strain.

Aedes albopictus is more easily infected with ZIKV but less able to transmit virus to humans than Aedes aegypti

Experimentally infect Culex and Aedes triseriatus mosquitos by allowing them to feed on zika infected mice
Mosquitoes saliva collected, body homogenized and tested for presence of virus
All culex mosquitoes were negative for ZIKV
A. Triseriatus were susceptible when mice viremia was highest.

Table 2. Zika virus vector competence of *Aedes aegypti* and *Ae. albopictus* mosquitoes at 21 days after infection*

	Zika virus		Mosquitoes		
Mosquito species	Strain	Dose, log_{10} PFU/mL	Infected, % (no. tested)	Infected and disseminating, %	% Infected and transmitting
Ae. aegypti	HND	8.9	90.9 (22)	95.0	80.0†↑
		7.7	46.7 (30)†↓	85.7	78.0†↑
		6.6	16.7 (30)	40.0	40.0
		4.6	3.3 (30)	0	0
Ae. aegypti	CAM	8.7	80.0 (30)	100.0	75.0
		7.2	44.4 (26)	91.7†↑	75.0†↑
		5.6	10.0 (30)	66.7	33.3
		4.3	7.0 (30)	100	50.0
Ae. albopictus	HND	8.9	100.0 (30)	93.3	33.3S↓
		7.5	93.3 (30)†↑‡↑	75.0‡↑	21.4†↓
		5.9	33.3 (30)	40.0	10.0
		4.1	10.0 (30)	66.7	0
Ae. albopictus	CAM	8.6	95.2 (21)	95.0	55.0
		6.6	40.0 (30)‡↓	25.0†↓‡↓	25.0†↓
		5.3	23.3 (30)	85.7	14.3
		4.2	6.0 (16)	0	0

*Up and down arrows indicate value is significantly above or below the comparison value ($p<0.05$ by Fisher exact test).

Culex pipiens and Aedes triseriatus Mosquito Susceptibility to Zika Virus Emerging Infectious Diseases Vol. 22, No. 10, October 2016
Effects of Zika Virus Strain and Aedes Mosquito Species on Vector Competence Emerging Infectious Diseases Vol. 23, No. 7, July 2017
Amraoui F, Atyame-Nten C, Vega-Rúa A, Lourenço-de-Oliveira R, Vazeille M, Failloux AB. Culex mosquitoes are experimentally unable to transmit Zika virus. Euro Surveill. 2016;21(35):pii=30333

Table 2. Mosquitoes collected and Zika virus infection of potential vectors, Kédougou, 2011.

Species	Total collected	Proportion of the collection (%)	Females collected	Proportion of the collection (%)	Positive female pools	Minimum infection rate (‰)
Aedes aegypti	250	2.22	245	2.20	1	4.08
Aedes africanus	505	4.49	505	4.54	5	9.90*
Aedes dalzieli	1718	15.27	1718	15.44	2	1.16
Aedes furcifer	2966	26.37	2939	26.42	5**	1.36
Aedes hirsutus	34	0.30	34	0.30	2	58.82*
Aedes luteocephalus	1259	11.19	1259	11.32	5	3.97
Aedes metallicus	81	0.72	81	0.73	2	24.69*
Aedes taylori	422	3.75	395	3.55	2	5.06
Aedes unilineatus	38	0.34	38	0.34	1	26.31*
Aedes vittatus	1790	15.91	1728	15.53	3	1.74
Anopheles coustani	710	6.31	710	6.38	1	1.41
Culex perfuscus	22	0.19	22	0.20	1	45.45*
Mansonia uniformis	283	2.52	281	2.52	1	3.56
Others	1169	10.39	1169	10.51	0	
Total	11247		11124		30	

Although ZIKV has been detected in many other species of mosquito, none has been proven to acquire the virus and transmit it in a laboratory setting.

Diallo D, Sall AA, Diagne CT, Faye O, Faye O, et al. (2014) Zika Virus Emergence in Mosquitoes in Southeastern Senegal, 2011. PLoS ONE 9(10): e109442.doi:10.1371/journal.pone.0109442
Zika virus vectors and risk of spread in the WHO European Region March 2016

Other modes of transmission

- Blood product transfusion (1,2)
- Sexual (vaginal, anal, oral, others) (3)
  - Male to female (4)
  - Female to Male (4)
  - Male to Male (4)
- Vertical (mother to child)
- Laboratory exposure (5)

1. Evidence for Transmission of Zika Virus by Platelet Transfusion. NEJM September 15, 2016
2. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014 . Euro Surveill. 2014;19(14)
3. Update: Interim Guidance for Prevention of Sexual Transmission of Zika Virus — United States, July 2016 MMWR / July 29, 2016 / Vol. 65 / No. 29
4. Prevention of sexual transmission of Zika virus, Interim guidance update. 6 September 2016. WHO.
5. http://www.cidrap.umn.edu/news-perspective/2016/06/needle-stick-infects-lab-worker-zika-virus (accessed 12/7/2017)

Fatal Zika Virus Infection with Secondary Nonsexual Transmission

TO THE EDITOR: Epidemic transmission of Zika virus (ZIKV) has rapidly occurred in the Americas, with most cases limited to mild or asymptomatic disease.[1,2] To date, nine deaths from ZIKV infection that were unrelated to the Guillain–Barré syndrome have been confirmed in adults.[1] Here, we report a rapidly progressive, fatal ZIKV

cultures were negative. A presumptive diagnosis of dengue shock syndrome was made. The patient's clinical deterioration progressed, with progressive respiratory and renal failure, metabolic acidosis, and hepatitis. On day 4 of hospitalization, the patient died shortly after care was withdrawn.

patient 1 (73/M with radio and hormonal therapy to prostate cancer) admitted to Salt Lake City hospital in US for travel related ZIKV, died in 4 days
Patient 2 developed mild ZIKA infection 5 days after patient 1 died
Patient 2 reported taking care of patient 1 including assisting nurse of repositioning, wiped his eyes but no other body fluid contact.
No gloves were worn
Very high viral load in patient 1 may cause tears or sweat to be infectious
Aedes mosquito not detected in that area. Patient 2 had no travel history

NEJM November 10, 2016

Persistence in body fluids

- 150 participants (55 men) from Puerto Rico with Zika RNA detected in blood or urine
- Serum, urine, saliva, semen, vaginal secretions collected weekly x 4 and then 2, 4, 6 months
- 90% enrolled within first week of symptom onset
- All specimens were tested with PCR, serum tested for IgM
- Prolonged viremia (14 days) compared to dengue (10 days) → implication for testing strategy
- Urine shedding duration shorter than previous studies

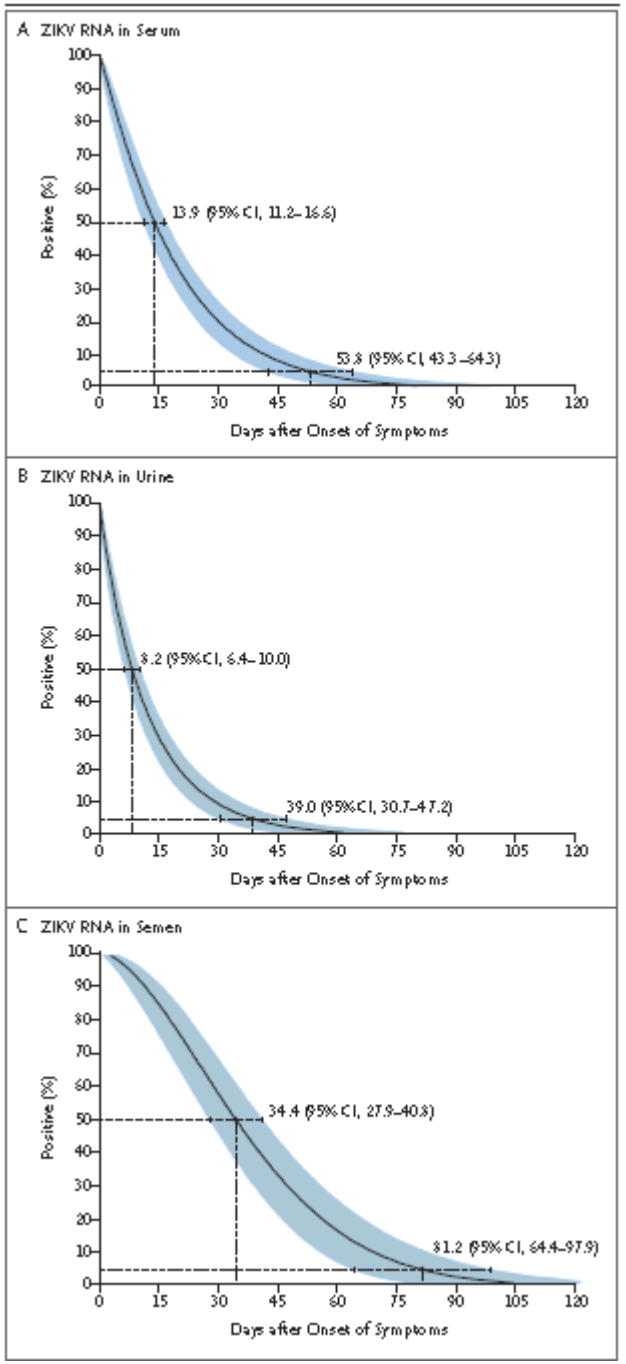
Gabriela Paz-Bailey, et al. Persistence of Zika Virus in Body Fluids — Preliminary Report. NEJM February 14, 2017

Specimen	Median	95th percentile
Serum	**14 days**	54 days
Urine	8 days	39 days
Semen	34 days	81 days

Saliva and vaginal secretions: few detected

Table 3. Detection of ZIKV RNA in Body Fluids and Anti–ZIKV IgM Antibody in Serum, According to the Number of Days after Symptom Onset.*

Positivity and Days after Symptom Onset	ZIKV RNA†					Anti–ZIKV IgM Antibody‡
	Serum	Urine	Saliva	Vaginal Secretions	Semen	Serum
	number/total number (percent)					
Participant analyses						
Any interval after symptom onset	128/146 (87.7)	90/145 (62.1)	13/143 (9.1)	1/49 (2.0)	31/55 (56.4)	137/139 (98.6)
0–7 days	118/134 (88.1)	77/129 (59.7)	3/6 (50.0)	1/1 (100)	0/1	17/50 (34.0)
8–15 days	10/28 (35.7)	12/29 (41.4)	1/25 (4.0)	0/6	5/8 (62.5)	28/28 (100)
16–30 days	27/129 (20.9)	21/125 (16.8)	5/127 (3.9)	0/39	20/40 (50.0)	120/121 (99.2)
31–45 days	14/126 (11.1)	6/119 (5.0)	4/125 (3.2)	0/42	20/46 (43.5)	108/111 (97.3)
46–60 days	6/67 (9.0)	1/65 (1.5)	1/64 (1.6)	0/21	6/25 (24.0)	58/60 (96.7)
>60 days	3/79 (3.8)	0/71	1/80 (1.3)	0/30	3/23 (13.0)	52/60 (86.7)
Specimen analyses						
Any interval after symptom onset	190/805 (23.6)	120/750 (16.0)	17/647 (2.6)	1/219 (0.5)	76/216 (35.2)	563/622 (90.5)
0–7 days	119/135 (88.2)	77/129 (59.7)	4/7 (57.1)	1/1 (100)	0/1	17/50 (34.0)
8–15 days	10/28 (35.7)	12/29 (41.4)	1/25 (4.0)	0/6	5/8 (62.5)	28/28 (100)
16–30 days	34/227 (15.0)	24/214 (11.2)	6/216 (2.8)	0/66	29/65 (44.6)	205/207 (99.0)
31–45 days	16/211 (7.6)	6/197 (3.0)	4/203 (2.0)	0/73	29/76 (38.2)	176/180 (97.8)
46–60 days	7/79 (8.9)	1/77 (1.3)	1/75 (1.3)	0/30	6/28 (21.4)	69/71 (97.2)
>60 days	4/125 (3.2)	0/104	1/121 (0.8)	0/43	7/38 (18.4)	68/86 (79.1)



Gabriela Paz-Bailey, et al. Persistence of Zika Virus in Body Fluids — Preliminary Report. NEJM February 14, 2017

ZIKV was found to persist in whole blood substantially longer than plasma. Findings may have implication for diagnosis and testing of blood donations

Zika Virus Infection and Prolonged Viremia in Whole-Blood Specimens

Jean Michel Mansuy, Catherine Mengelle, Christophe Pasquier, Sabine Chapuy-Regaud, Pierre Delobel, Guillaume Martin-Blondel, Jacques Izopet

Author affiliations: Centre Hospitalier Universitaire de Purpan, Toulouse, France (J.M. Mansuy, C. Mengelle, C. Pasquier, S. Chapuy-Regaud, P. Delobel, G. Martin-Blondel, J. Izopet); Institut National de la Santé et de la Recherche Médicale, Toulouse (C. Pasquier, S. Chapuy-Regaud, P. Delobel, G. Martin-Blondel, J. Izopet); Université Paul Sabatier, Toulouse (C. Pasquier, S. Chapuy-Regaud, P. Delobel, J. Izopet)

DOI: http://dx.doi.org/10.3201/eid2305.161631

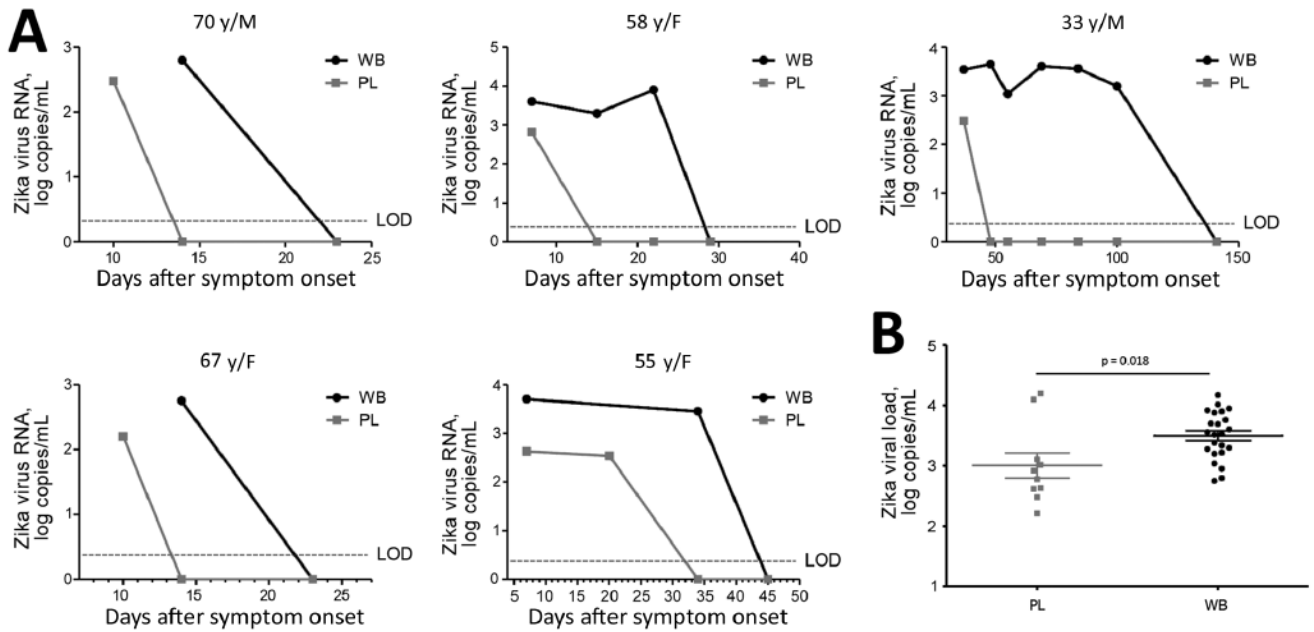
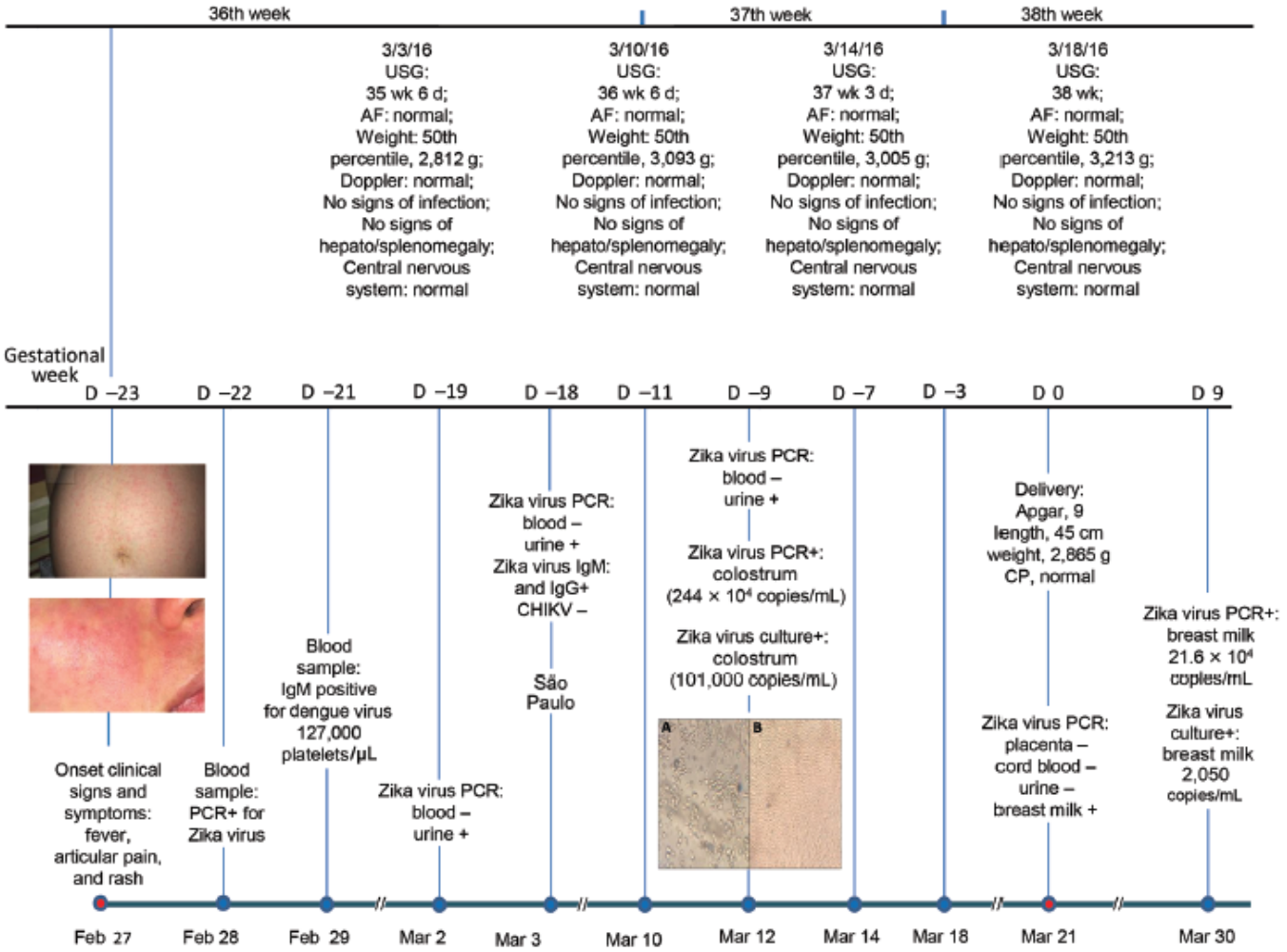


Figure. A) Zika virus viremia in whole blood and plasma from 5 immunocompetent patients in France (identified by sex and age, y) who had traveled to Central or South America or the Caribbean. B) Zika viral load in whole-blood (n = 23) and plasma (n = 10) samples from a point-to-point comparison of positive samples. Horizontal lines indicate mean ± SE. LOD, limit of detection; PL, plasma; WB, whole blood.

Emerging Infectious Diseases Vol. 23, No. 5, May 2017

Zika virus in breast milk

- No documented infection reported
- Cultured in colostrum (infective) and up to 9 days post delivery
- Breast feeding not carried out in this case
- WHO advises continue breast feeding in areas of zika transmission



Infant feeding in areas of Zika virus transmission Summary of rapid advice guideline 29 June 2016

José R. Sotelo, et al. Persistence of Zika Virus in Breast Milk after Infection in Late Stage of Pregnancy. EID Vol. 23, No. 5, May 2017

Prolonged Zika Virus Viremia during Pregnancy

- Colombian woman, symptom onset 9 week
- Serum sample remains positive for ZIKV 107 days after symptom onset (until 29th week gestation)
- Urine, vagina, endocervix were negative
- Fetal brain calcification and atrophy ++
- Evidence suggesting fetus and placenta as a reservoir of virus:
  - Viral load higher in amniotic fluid than maternal serum (CT value 28 vs 35)
  - Viral load in maternal serum remains stable instead of gradual decline
  - Neutralizing antibody present in maternal serum
  - PCR maternal urine negative

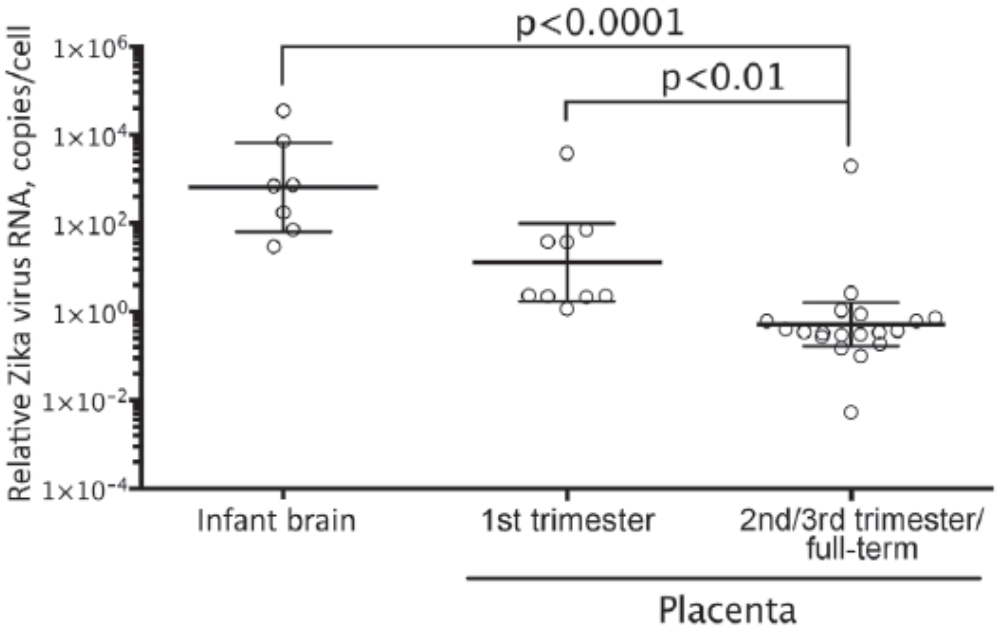
Prolonged Zika Virus Viremia during Pregnancy. NEJM 375; 26 Dec 29, 2016

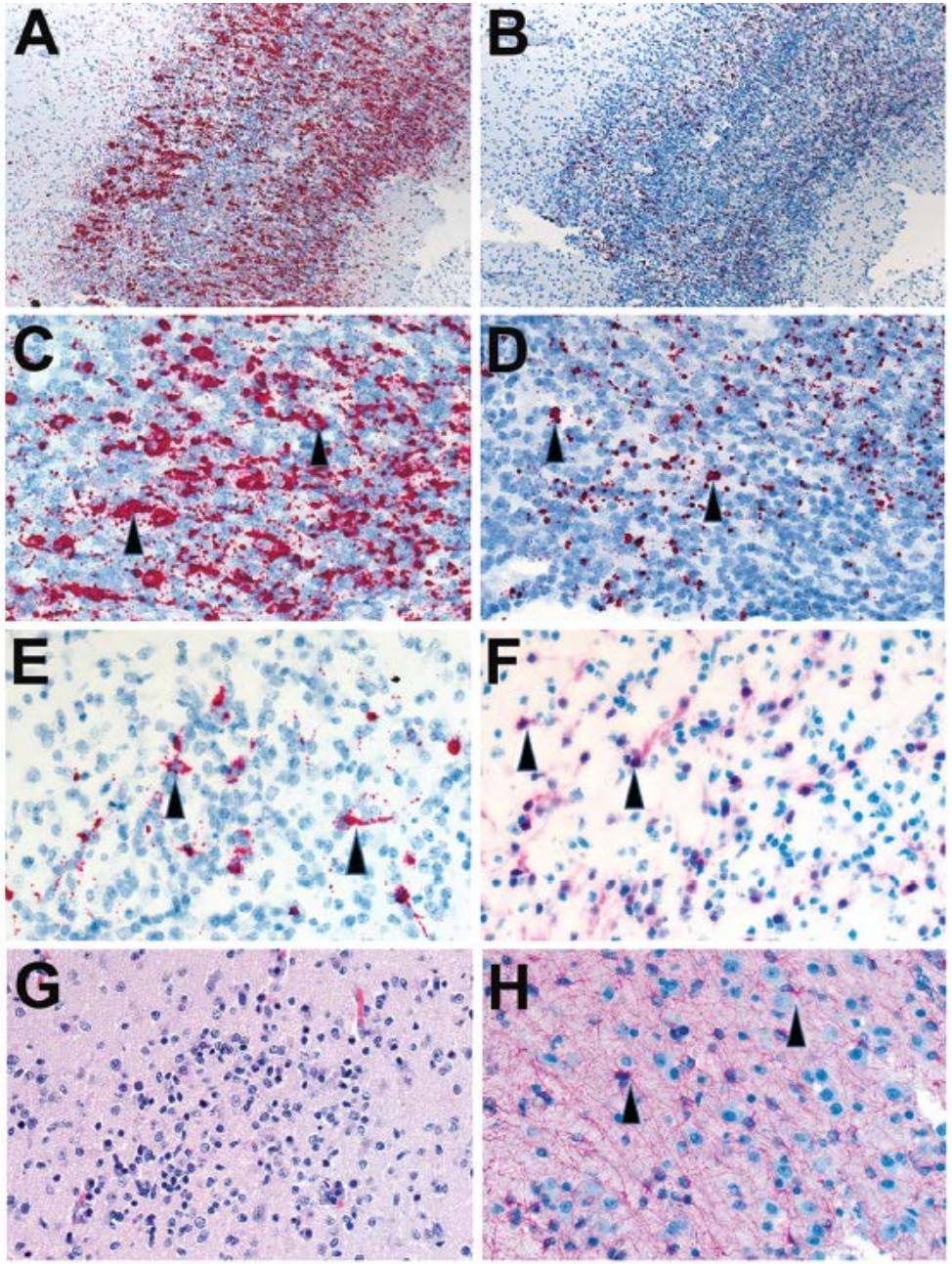
Zika Virus RNA Replication and Persistence in Brain and Placental Tissue

Julu Bhatnagar, Demi B. Rabeneck, Roosecelis B. Martines, Sarah Reagan-Steiner, Yokabed Ermias, Lindsey B.C. Estetter, Tadaki Suzuki, Jana Ritter, M. Kelly Keating, Gillian Hale, Joy Gary, Atis Muehlenbachs, Amy Lambert, Robert Lanciotti, Titilope Oduyebo, Dana Meaney-Delman, Fernando Bolaños, Edgar Alberto Parra Saad, Wun-Ju Shieh, Sherif R. Zaki

All 8 fetal brain tissue and 24/44 women suspected ZIKV infection Positive for ZIKA RNA

Provide direct evidence to causing microcephaly



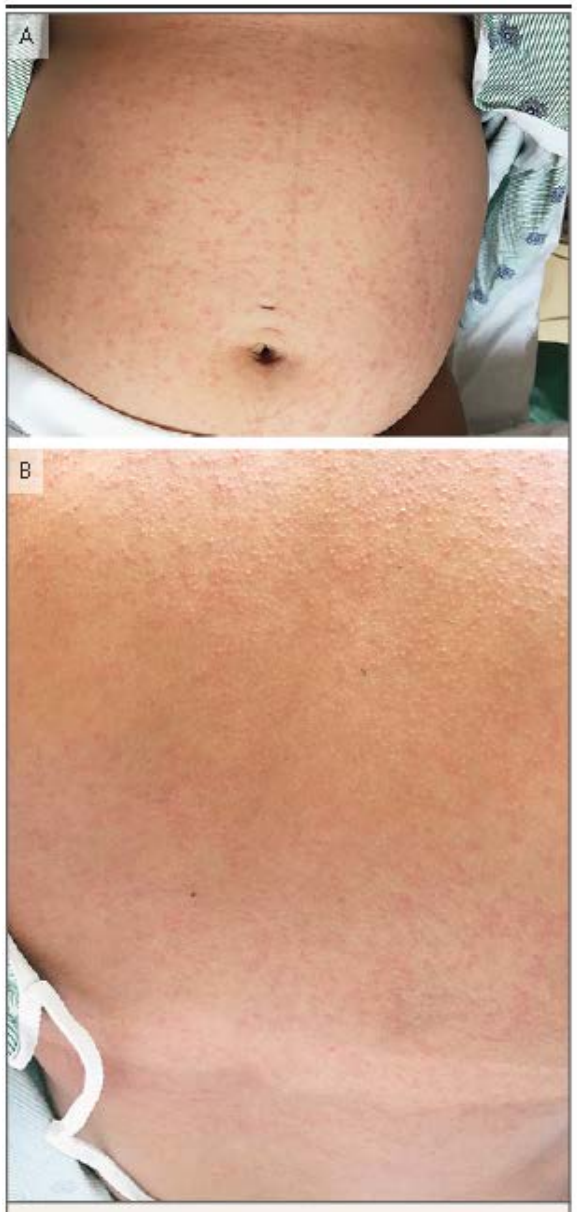


Localization of Zika virus RNA by in situ hybridization in brain tissues from infants with microcephaly

Clinical signs & complications

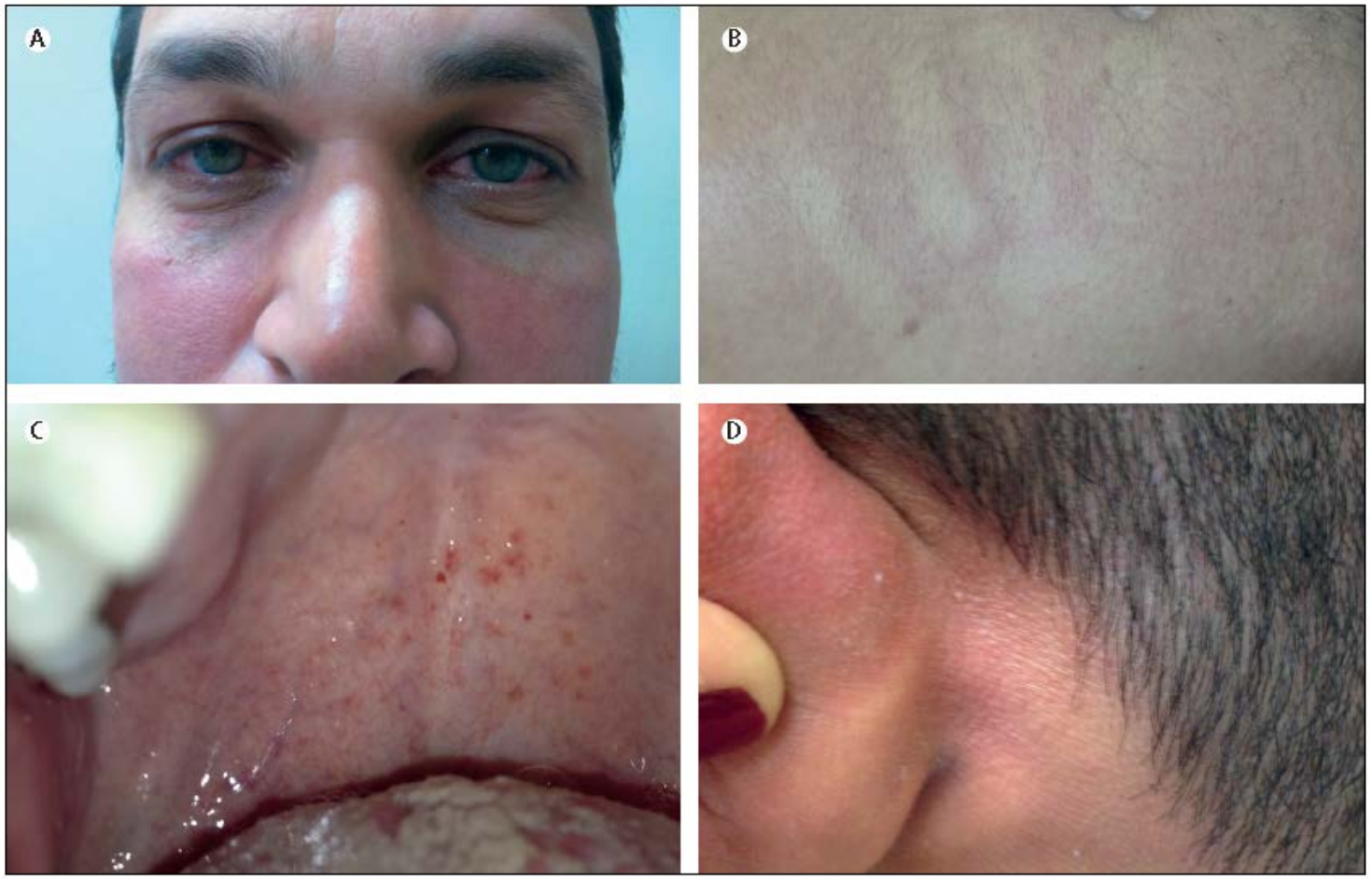
10 week Gestation

3 days history of fever, pruritic rash and sore throat



Cutaneous Eruption in a U.S. Woman with Locally Acquired Zika Virus Infection. NEJM January 26, 2017

39/M, 2 days headache, sore throat, myalgia
Acute onset macular rash, conjunctival injection, truncal erythema, petechiae on hard palate, tender head & neck LNs



Exanthema associated with Zika virus infection. Lancet Infect Dis 2016; 16: 866

Severe thrombocytopenia

Clinical Infectious Diseases

BRIEF REPORT

Zika Virus Infection Associated With Severe Thrombocytopenia

Tyler M. Sharp,[1] Jorge Muñoz-Jordán,[1] Janice Perez-Padilla,[1] Melissa I. Bello-Pagán,[5] Aidsa Rivera,[1] Daniel M. Pastula,[2,8] Jorge L. Salinas,[3] Jose H. Martínez Mendez,[6] Mónica Méndez,[7] Ann M. Powers,[4] Stephen Waterman,[1] and Brenda Rivera-García[5]

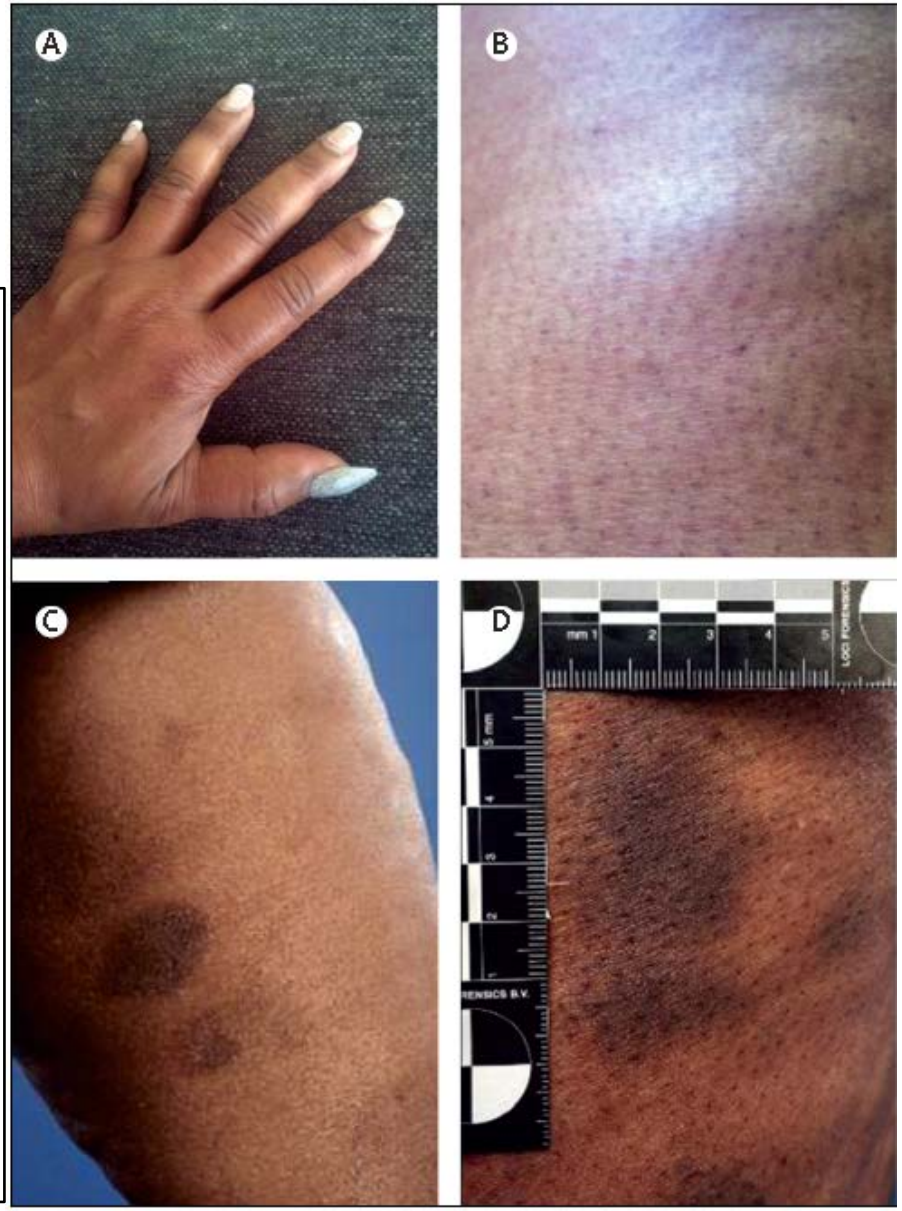
[1]Dengue Branch, [2]Division of Vector Borne Diseases, [3]Epidemic Intelligence Service, and [4]Arboviral Diseases Branch, Centers for Disease Control and Prevention, [5]Puerto Rico Department of Health, San Juan, [6]San Juan City Hospital, and [7]Hospital HIMA San Pablo, Bayamón, Puerto Rico; and [8]University of Colorado, Denver

We report two patients that developed severe thrombocytopenia after Zika virus (ZIKV) infection. The first patient had 1000 platelets/μL and died after multiple hemorrhages. The second patient had 2000 platelets/μL, had melena and ecchymoses, and recovered after receiving intravenous immunoglobulin. ZIKV may be associated with immune-mediated severe thrombocytopenia.

Keywords. Zika virus; thrombocytopenia; fatal; Puerto Rico.

Clinical Infectious Diseases 2016;63(9):1198–201

- 54/F visited Suriname Jan 2016
- Fever, fatigue, loss of appetite 11 days after arrival
- Generalised pruritus, MP rash
- Day 17 onset hematoma on arms and legs
- Platelet 80x10^9/L
- Dx: Post infectious ITP
- Urine Zika PCR+



Thrombocytopenia and subcutaneous bleedings in a patient with Zika virus infection. Lancet Vol 387 March 5, 2016

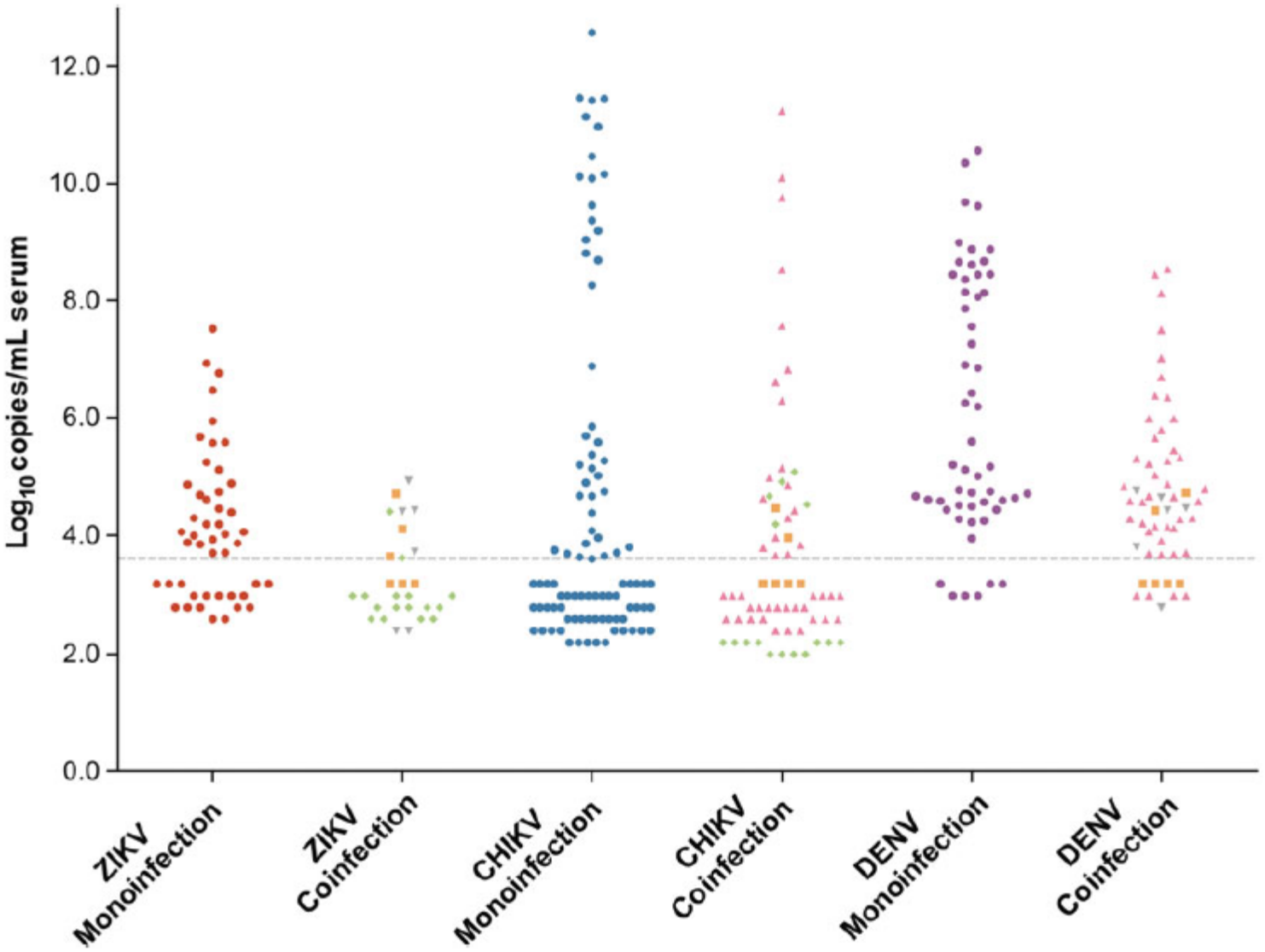
Clinical Features:
Zika Virus Compared to Dengue and Chikungunya

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

Zika Virus —What Clinicians Need to Know? CDC Clinician Outreach and Communication Activity January 26, 2016

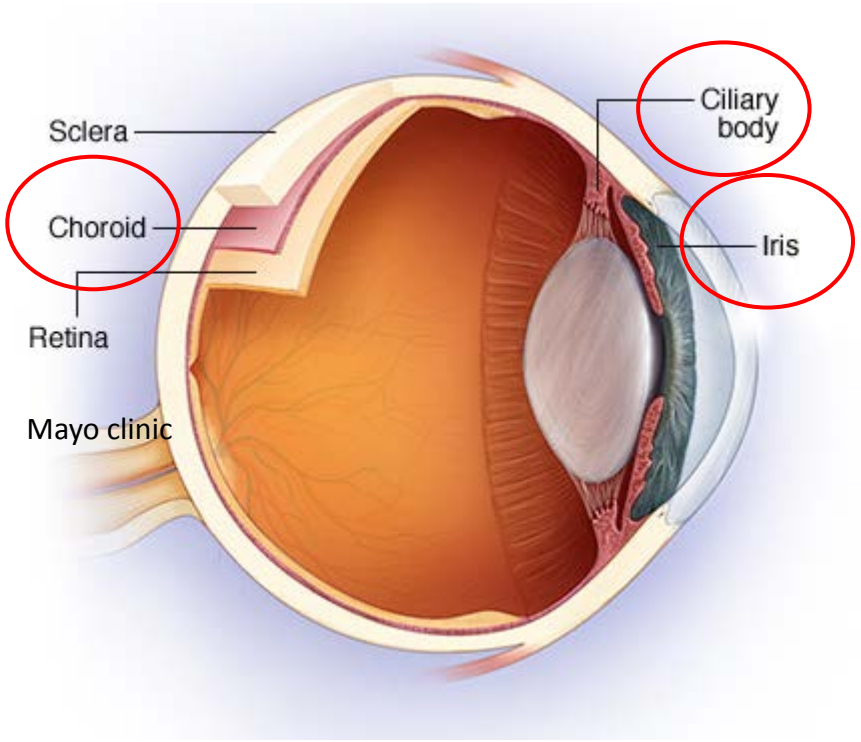
Co infection is common (71/263 patients in Nicaragua).

Compared to patients with CHIKV or DENV, ZIKV patients **more likely to have rash, less likely to be febrile or require hospitalization**

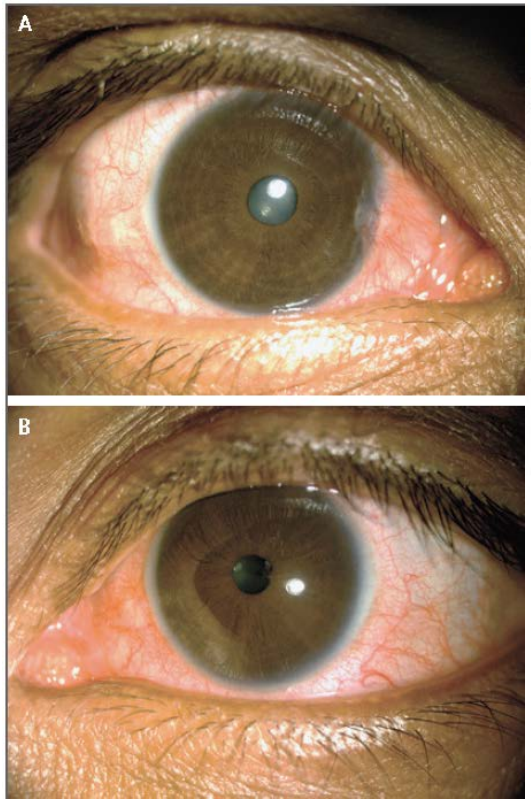


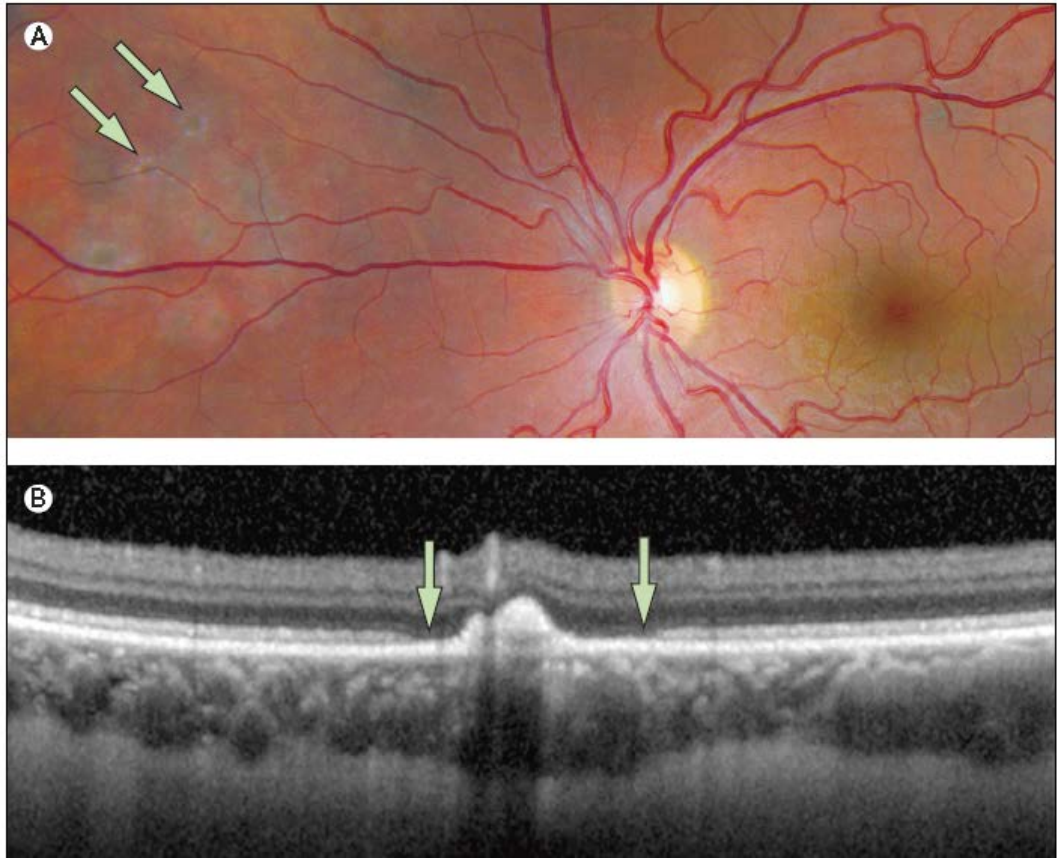
Jesse J. Waggoner, et al. Viremia and Clinical Presentation in Nicaraguan Patients InfectedWith Zika Virus, Chikungunya Virus, and Dengue Virus CID 2016;63(12):1584–90

Uveitis 葡萄膜炎



Conjunctival hyperemia 8 days after onset





Colour fundus photograph of the left eye showing nasal mid-peripheral chorioretinal lesions

Elevation of the outer retina with loss of the ellipsoid layer

Shilpa Kodati, et al. Bilateral posterior uveitis associated with Zika virus infection. Lancet 2017; 389: 125–26
Uveitis Associated with Zika Virus Infection. NEJM July 28, 2016

81/M cruise in pacific islands for 4 weeks

Admitted to ICU
Fever, GCS 6
Left hemiplegia
Babinski +
Transient rash
intubated

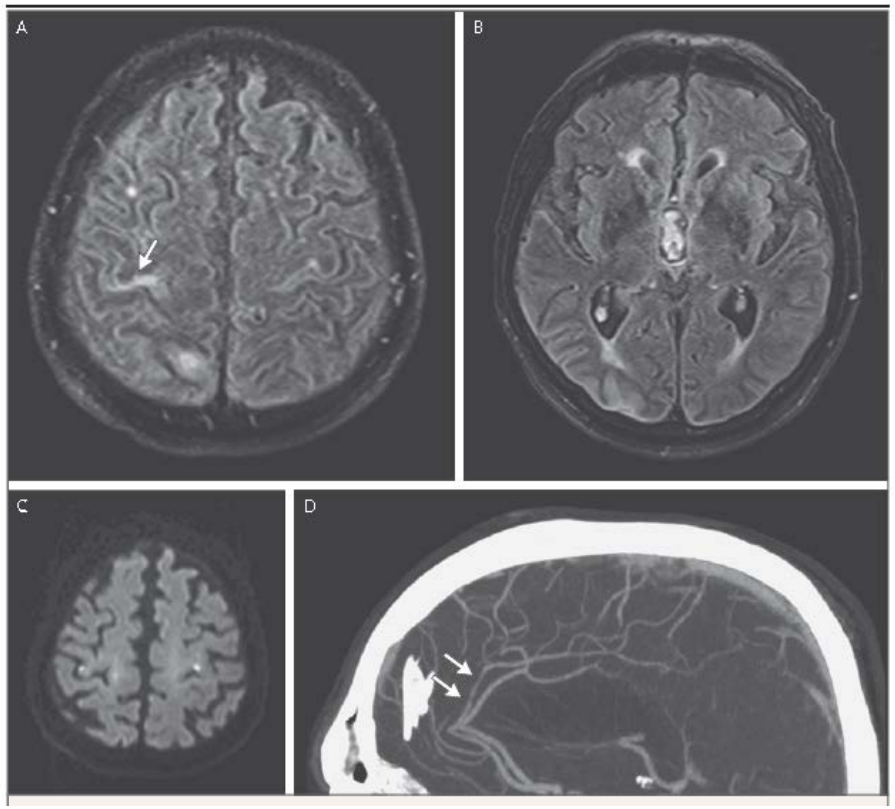
MRI flair imaging reveal hyperintensity in the subcortical white matter suggestive of meningitis with ischemic foci

LP (day1)
Wcc 41/mm3
98% Polymorph
Protein 76mg/dL
Glu CSF:Bld 0.75

RT-PCR ZIKV +
Vero cell C/ST+

Zika Virus Associated with Meningoencephalitis

TO THE EDITOR: Zika virus (ZIKV) is currently spreading widely, while its clinical spectrum remains a matter of investigation. Evidence of a relationship between ZIKV infection and cerebral birth abnormalities[1,2] is growing.[3] An increased incidence of some peripheral nervous syndromes



NEJM 374;16 April 21, 2016

Acute myelitis

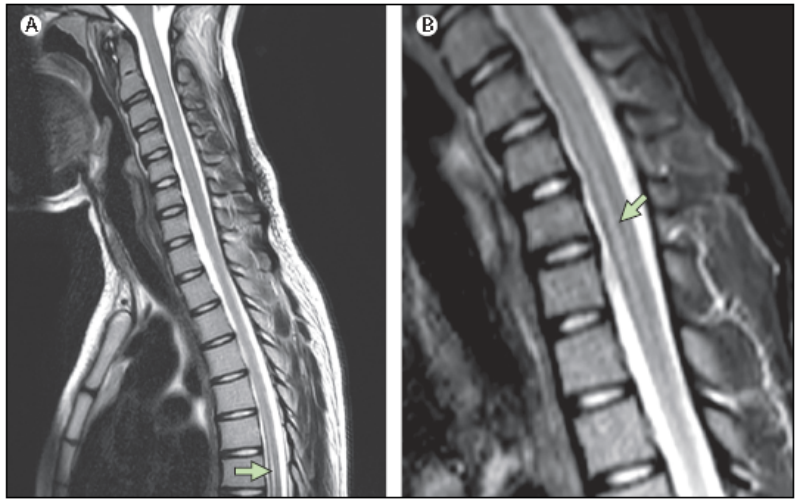


Figure: Magnetic resonance imaging (MRI) showing myelitis in Zika virus infection
(A) T2 sequences showing hypersignal in the thoracic cord T5–T8 (arrow) and enlargement of the cervical spinal cord.
(B) Sagittal short time inversion recovery (STIR) sequences showing hypersignal in the cervical spinal cord C4–C7 (arrow).

Sylvie Mécharles. Acute myelitis due to Zika virus infection. Lancet 2016; 387: 1481

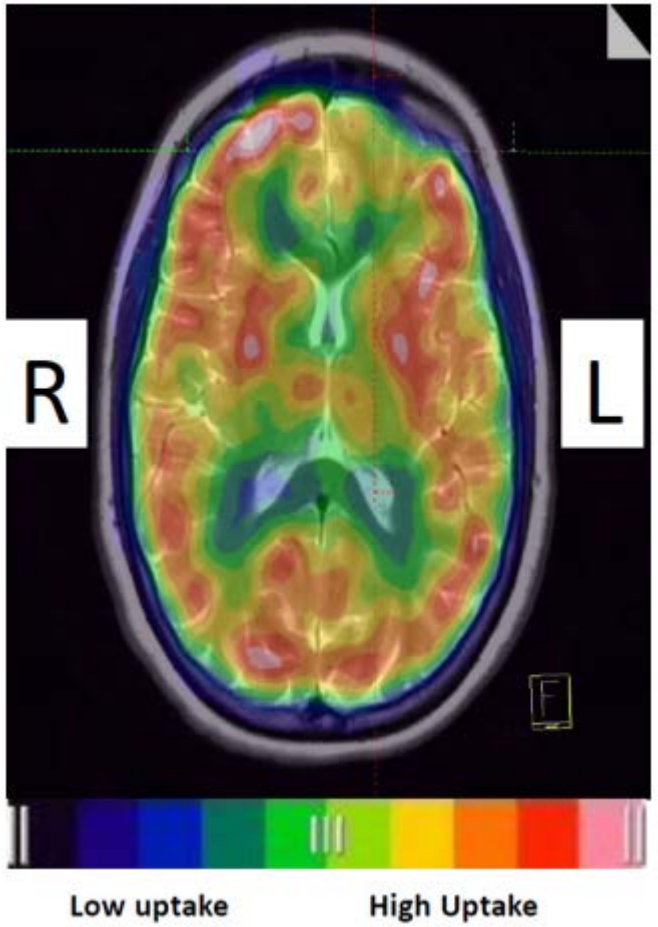
Myasthenia Gravis (重症肌無力)

- 2 cases : 45 year old and 62 year old man
- Onset of MG 8-10 weeks after ZIKV infection
- Presence of underlying thymoma for both
- Points to note:
  - Is ZIKV provoking factor or coincidental ?
  - Autoimmune complications is known to occur with ZIKV (GBS, ITP)
  - WNV, another Flavivirus, reported to be associated with MG
  - May need to consider MG as a ddx to GBS

Molko N, et al. Zika virus infection and myasthenia gravis: report of 2 cases. Neurology. 2017 Mar 14;88(11):1097-1098

Technical Appendix Table 3. Neuropsychological test findings

Intellectual Function	Score	Percentile
Wechsler Intelligence Scale for Children - 5	Standard Score	Percentile
Verbal Comprehension	118	88
Visual Spatial	117	87
Fluid Reasoning	118	88
Working Memory	115	84
Processing Speed	83	13
General Ability Index	121	92
Memory and Learning		
California Verbal Learning Test for Children	T/z-score	Percentile
Trials 1–5	45	34
Long Delay Free Recall	0	50
NEPSY - 2	Scaled Score	Percentile
Memory for Designs	12	75
Memory for Designs-Delayed		
Rey Complex Figure Test		
Immediate Recall		
Delayed Recall		
Recognition		
Wide Range Assessment of Memory and Learning 2	Sc	
Story Memory		
Story Memory Delay Recall		
Story Memory Recognition		
Executive Functions		
Delis-Kaplan Executive Function System	Sc	
Verbal Fluency		
Letter		
Category		
Switching		
Trail Making		
Visual Scanning		
Number Sequencing		
Letter Sequencing		
Number-Letter Switching		
Motor Speed		
Color Word Interference		
Color Naming		
Word Reading		
Inhibition		
Inhibition - Total Errors		
Inhibition/Switching		
Inhibition/Switching - Total Errors		



Cognitive impairment ?

PMH: mild depression on SSRI
1 week after return from Carribean rash, headache
Urine Zika PCR +ve

Excessive energy, grandiose thinking, impulsivity
Lower than expected memory score, worsened anxiety
Fatigue, etc

Lasting into 15th week after symptom onset

CSF IgM Zika+
MRI Brain normal
Trial of IVIG

SPECT focal hypoperfusion

Jason Zucker, et al. Zika Virus–Associated Cognitive Impairment in Adolescent, 2016. Emerging Infectious Diseases Vol. 23, No. 6, June 2017

Transient Hearing Loss in Adults Associated With Zika Virus Infection

Eriko S. Vinhaes, Luciane A. Santos, Lislane Dias, Nilvano A. Andrade, Victor H. Bezerra, Anderson T. de Carvalho, Laise de Moraes, Daniele F. Henriques, Sasha R. Azar, Nikos Vasilakis, ... Show more

Clin Infect Dis (2017) 64 (5): 675-677. **DOI:** https://doi.org/10.1093/cid/ciw770
Published: 01 December 2016 **Article history ▼**

Abstract

In 2015, during the outbreak of ZIKAV in Brazil, we identified three cases of acute hearing loss after exanthematous illness. Serology yielded finding compatible with ZIKAV as the cause of a confirmed (1patient) and a probable (2 patients) flavivirus infection, indicating an association between ZIKAV infection and transient hearing loss.

Transient Myocarditis Associated With Acute Zika Virus Infection

Marc Aletti,[1] Stephane Lecoules,[1] Vincent Kanczuga,[2] Charles Soler,[3] Marianne Maquart,[4] Fabrice Simon,[5] and Isabelle Leparc-Goffart[4]

[1]Department of Internal Medicine, [2]Department of Cardiology, and [3]Department of Microbiology, Percy Military Teaching Hospital, Clamart; and [4]Arbovirus Reference Center, French Armed Forces Biomedical Research Institute, and [5]Department of Infectious Diseases, Laveran Military Teaching Hospital, Marseille, France

Zika virus outbreak is spreading in the Americas. This emerging infection is associated with neurological complication. We report the first travel-acquired Zika acute infection complicated with myocarditis imported to mainland France. We recommend an electrocardiogram and troponin if any cardiac symptoms are present in a patient with acute Zika infection.

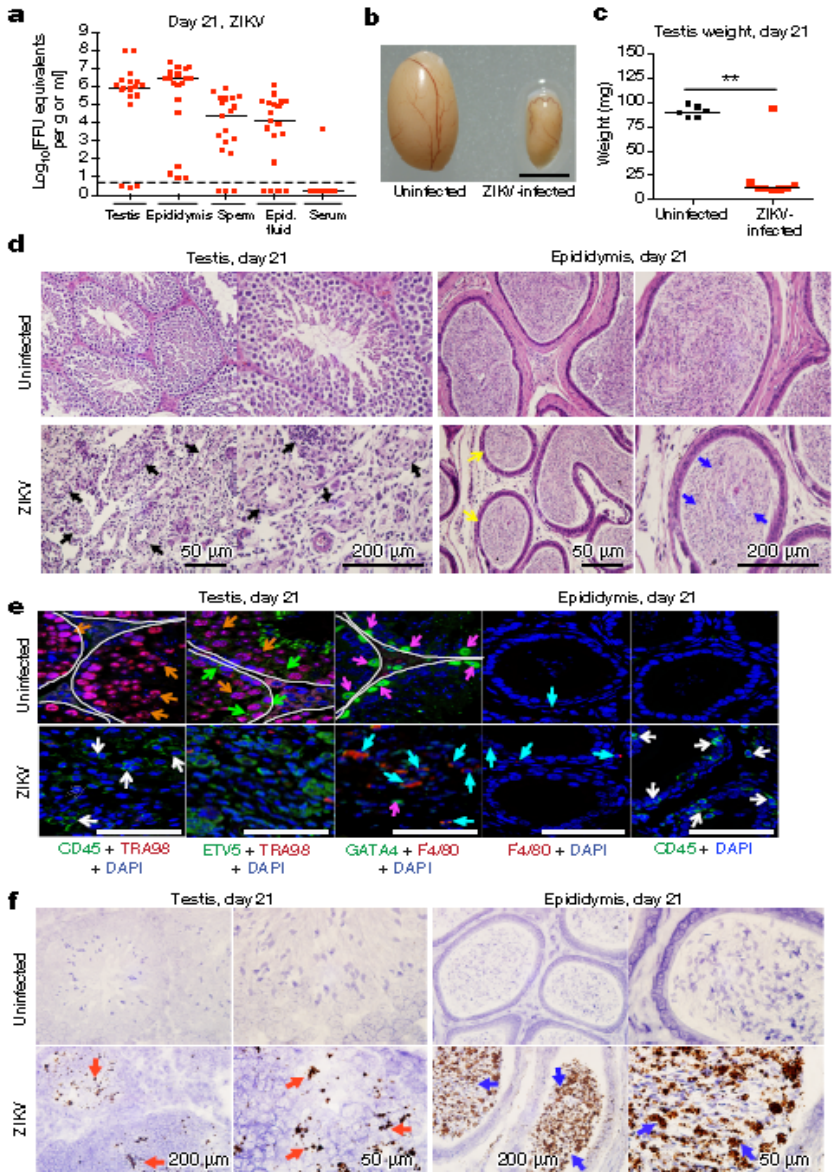
Keywords. Zika virus; myocarditis; imported viral disease; reemerging disease; sentinel surveillance.

CID 2017;64(5):678–9

ZIKV damages testes in mice

persistence of
ZIKV, but not the closely related dengue virus (DENV), in the testis
and epididymis of male mice, associated with tissue injury that caused diminished testosterone

ZIKV preferentially infected spermatogonia,
primary spermatocytes and Sertoli cells in the testis, resulting in
cell death and destruction of the seminiferous tubules.



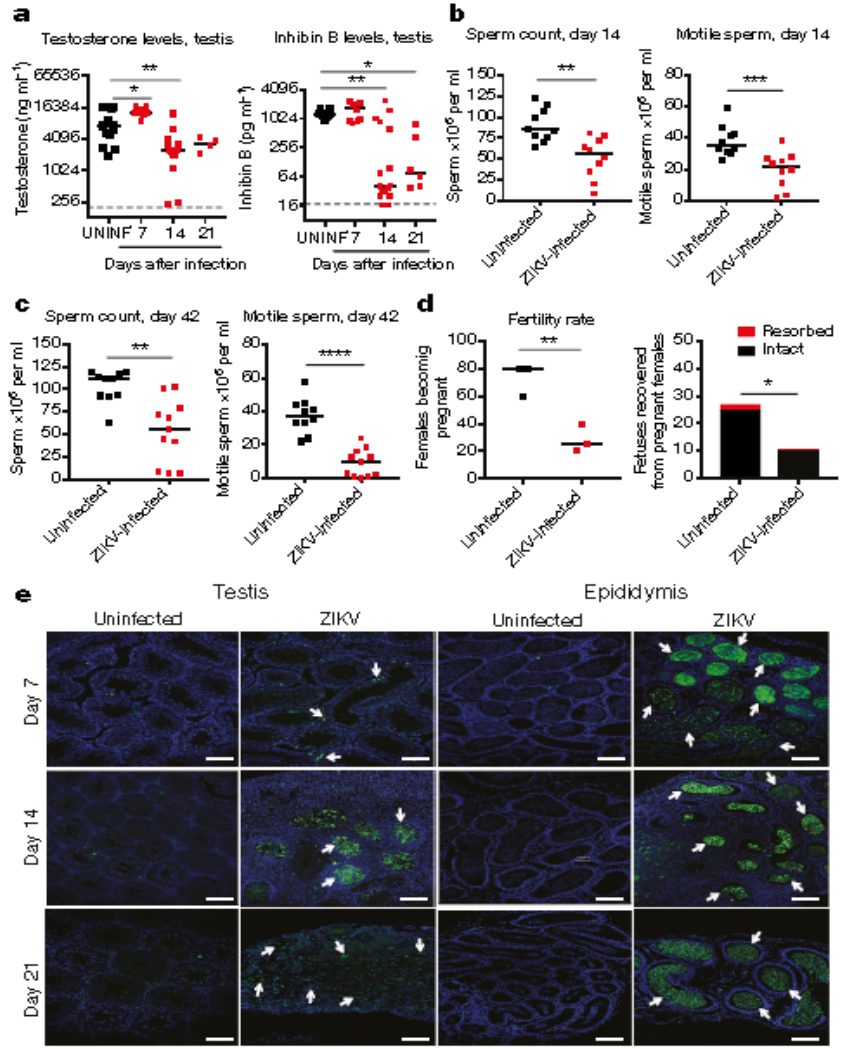


Figure 4 | Consequences of ZIKV infection of the testis and epididymis. a, Testosterone (left) and inhibin B (right) levels of testis homogenates from uninfected (UNINF) and ZIKV-infected (days 7, 14 or 21) mice. b, c, Computer-assisted sperm analysis (total (left) and motile (right))

Jennifer Govero, et al. Zika virus infection damages the testes in mice. Nature. Vol 540. 15 Dec 2016.

Microcephaly 小頭畸形症

- First detected in French Polynesia outbreak 2013-14
- Different cut off for head circumference (<2-3 SD, <3rd percentile).

https://www.youtube.com/watch?v=HjOxS0hkPBU

- Congenital ZIKV syndrome does not appear to be associated with maternal disease severity, ZIKV-RNA load at time of infection or existence of prior dengue antibodies.
- Potentially huge healthcare burden

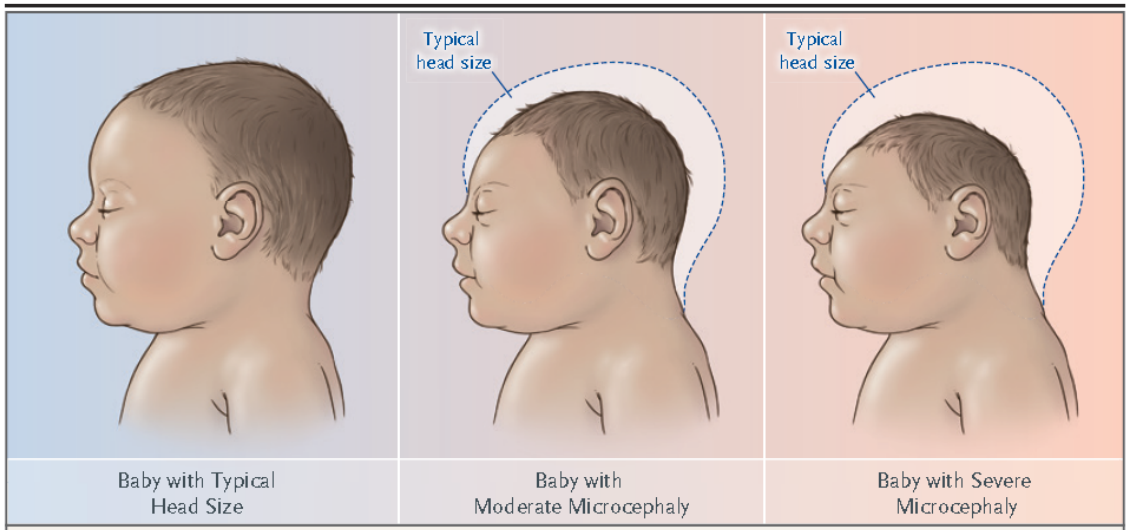


Figure 4. Infants with Moderate or Severe Microcephaly Associated with Maternal Zika Virus Infection, as Compared with a Typical Newborn.

	Yap Island (Pacific)[2]	French Polynesia (Pacific)[1]	Brazil (Americas) as of May, 2017[4,5]
Population	7500	270 000	206 000 000
Confirmed cases	49	340[10]	697
Estimated infections (% of population)	5005 (75%)	30 000 (11·5%)	220 213 (0·1%)
New epidemiological findings	First reported outbreak; first detection of Zika virus outside Asia and Africa	Non-vector-borne transmission possible (materno-fetal, sexual, transfusion)	First detection in the Americas; microcephaly association
Clinical findings	Rash, fever, arthralgia, and conjunctivitis	GBS; CNS malformation	GBS; CNS malformation
CNS malformation cases*	0	17[11]	2653
Main challenges	Identification of Zika virus	High incidence of GBS	Laboratory capacities to confirm cases; high incidence of microcephaly

GBS=Guillain-Barré syndrome. *Number of microcephaly or CNS malformation cases suggestive of congenital Zika virus infection or potentially associated with viral infection.

Table 1: Comparison of Zika virus outbreaks in Yap, French Polynesia, and Brazil

UA Halai et al. Maternal Zika Virus Disease Severity, Virus Load, Prior Dengue Antibodies and their Relationship to Birth Outcomes. Clin Infect Dis. 2017 May 23.
An update on Zika virus infection. Lancet June 21, 2017
Screening, assessment and management of neonates and infants with complications associated with Zika virus exposure in utero. 30 August 2016 WHO

Does ZIKV cause microcephaly ?

Table 2. Bradford Hill Criteria for Evidence of Causation as Applied to the Relationship between Zika Virus Infection and Microcephaly and Other Brain Anomalies*

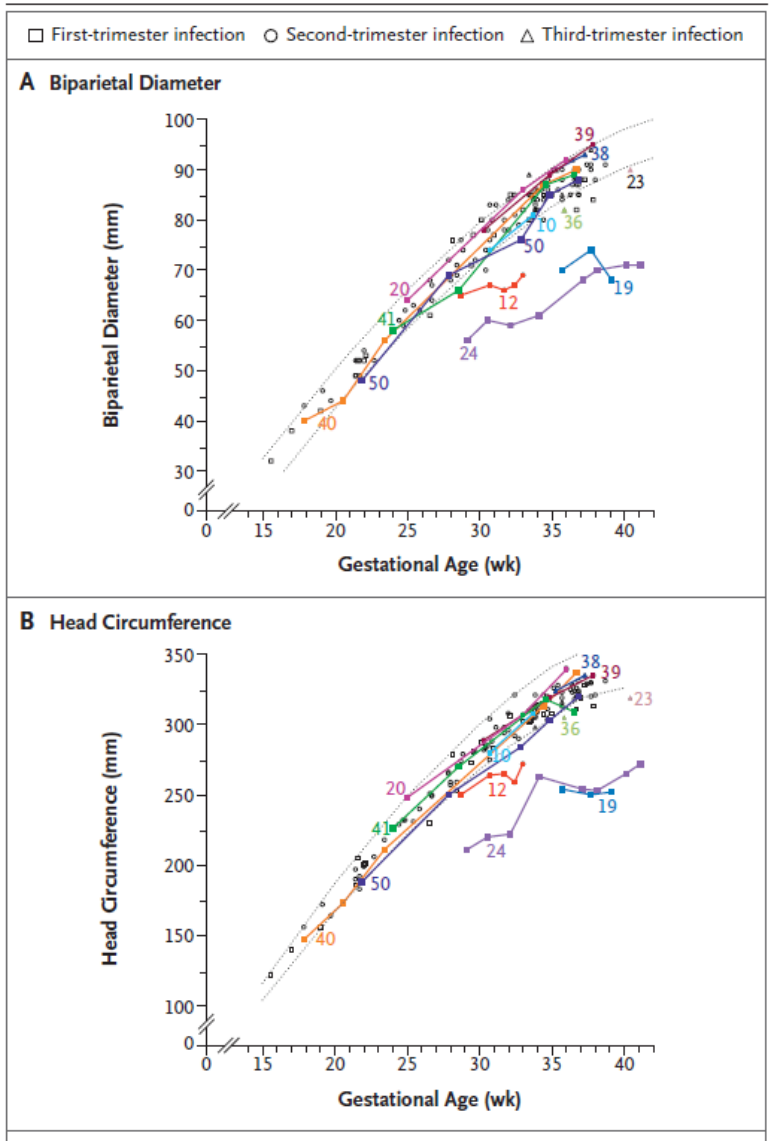
Criterion	Evidence	Criterion Met?
Strength of association	A recent epidemiologic study from French Polynesia suggests a strong association between prenatal Zika virus infection and microcephaly (estimated risk ratio, approximately 50).[2] The substantial increase in the number of cases of microcephaly and other brain anomalies that have been associated with the Zika virus outbreak in Brazil suggests a strong association.[1,2]	Yes
Consistency	Two epidemiologic studies, one from Brazil and one from French Polynesia,[2,14] support the association between prenatal Zika virus infection and microcephaly and other serious brain anomalies. The observed increase in the number of cases of microcephaly after outbreaks of Zika virus infection in Brazil and French Polynesia, as well as preliminary reports of cases in Colombia, support consistency.[1,2,42] Case reports of Zika virus infection in fetuses or infants with microcephaly or other brain anomalies who were born to mothers who traveled to areas of active Zika virus transmission support consistency.[16,18,19]	Yes
Specificity	Other causes of microcephaly exist; however, on the basis of clinical descriptions that are available for a small number of infants with presumed congenital Zika virus infection,[20] the clinical phenotype linked to the Zika virus appears to be an unusual form of microcephaly that is consistent with the fetal brain disruption sequence.	Yes
Temporality	Zika virus infection in mothers during pregnancy precedes the finding of microcephaly or other brain anomalies in fetuses or infants.[14-20] Zika virus outbreaks in Brazil and French Polynesia preceded the increase in the number of cases of microcephaly.[1,2]	Yes

Applying Hill's criteria to ZIKV infection & brain anomalies

Biologic gradient	Infection is a phenomenon that is either present or absent; there is no dose–response relationship. No data are available regarding whether women with an increased viral load have a higher risk of adverse pregnancy or birth outcomes.	NA
Plausibility	Findings are similar to those seen after prenatal infection with some other viral teratogens (e.g., cytomegalovirus and rubella virus).[26] Evidence that Zika virus infects neural progenitor cells and produces cell death and abnormal growth,[29] along with evidence of Zika virus in brains of fetuses and infants with microcephaly, on the basis of on immunohistochemical staining and identification of Zika virus RNA and live virus,[16,17,19] provides strong biologic plausibility.	Yes
Coherence	No results in an animal model of effects of Zika virus on pregnancy have yet been published, but animal models have shown that Zika virus is neurotropic,[27,28] a finding that is consistent with prenatal Zika virus infection causing microcephaly and other brain anomalies. Zika virus infects neural progenitor cells and produces cell death and abnormal growth,[29] a finding that is consistent with a causal relationship between Zika virus infection and microcephaly.	Yes
Experiment	No experimental animal model of Zika virus teratogenicity is available.	No
Analogy	No other flavivirus has been shown to definitively cause birth defects in humans,[4] but flaviviruses, Wesselsbron and Japanese encephalitis viruses, have been shown to cause stillbirth and brain anomalies in animals.[43] Findings are similar to those seen after prenatal infection with other viral teratogens (e.g., cytomegalovirus, rubella virus).[26]	Yes

Sonja A. Rasmussen, et al. Zika Virus and Birth Defects — Reviewing the Evidence for Causality NEJM May 19, 2016

Timing of infection – does it matter ?



345 women 2015-2016, 53% positive ZIKV
Infection from 6-39 weeks gestation
Rate of fetal death 7% both groups
Adverse outcome 46% vs 11.5%
Regardless of trimester of infection 55%/52%/29% (1st/2nd/3rd)

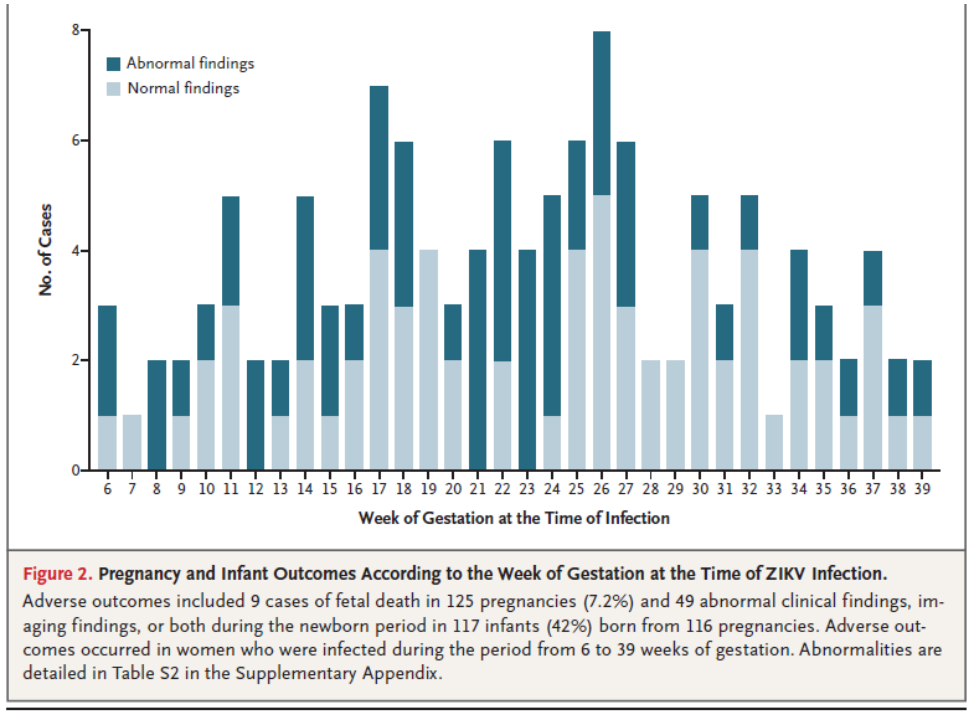


Figure 2. Pregnancy and Infant Outcomes According to the Week of Gestation at the Time of ZIKV Infection.
Adverse outcomes included 9 cases of fetal death in 125 pregnancies (7.2%) and 49 abnormal clinical findings, imaging findings, or both during the newborn period in 117 infants (42%) born from 116 pregnancies. Adverse outcomes occurred in women who were infected during the period from 6 to 39 weeks of gestation. Abnormalities are detailed in Table S2 in the Supplementary Appendix.

Zika Virus Infection in Pregnant Women in Rio de Janeiro. N Engl J Med 2016;375:2321-34

Microcephaly may not always be present at birth but may develop later

64.5% of infants were born with severe microcephaly, and 95.8% had a phenotype of fetal brain disruption sequence.

Screening should not only be based on HC but phenotype and imaging as well

Phenotype, n = 48
Craniofacial disproportion
Biparietal depression
Prominent occiput
Excess nuchal skin

Signs and symptoms:
Cerbral palsy
Motor disability
Epilepsy
Pyrimidal
Extrapyrimidal
Irritability
Dysphagia
Cognitive impairment

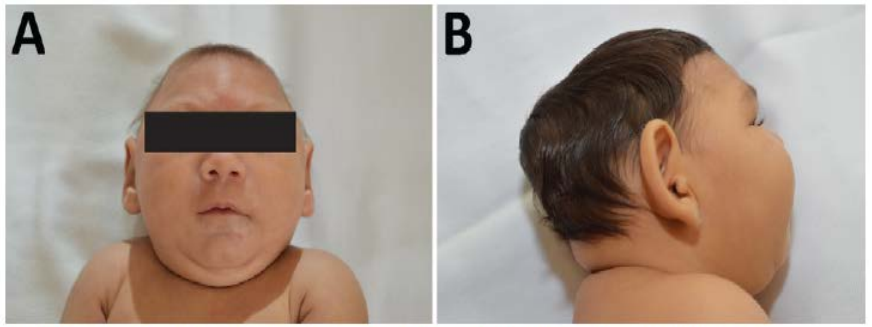
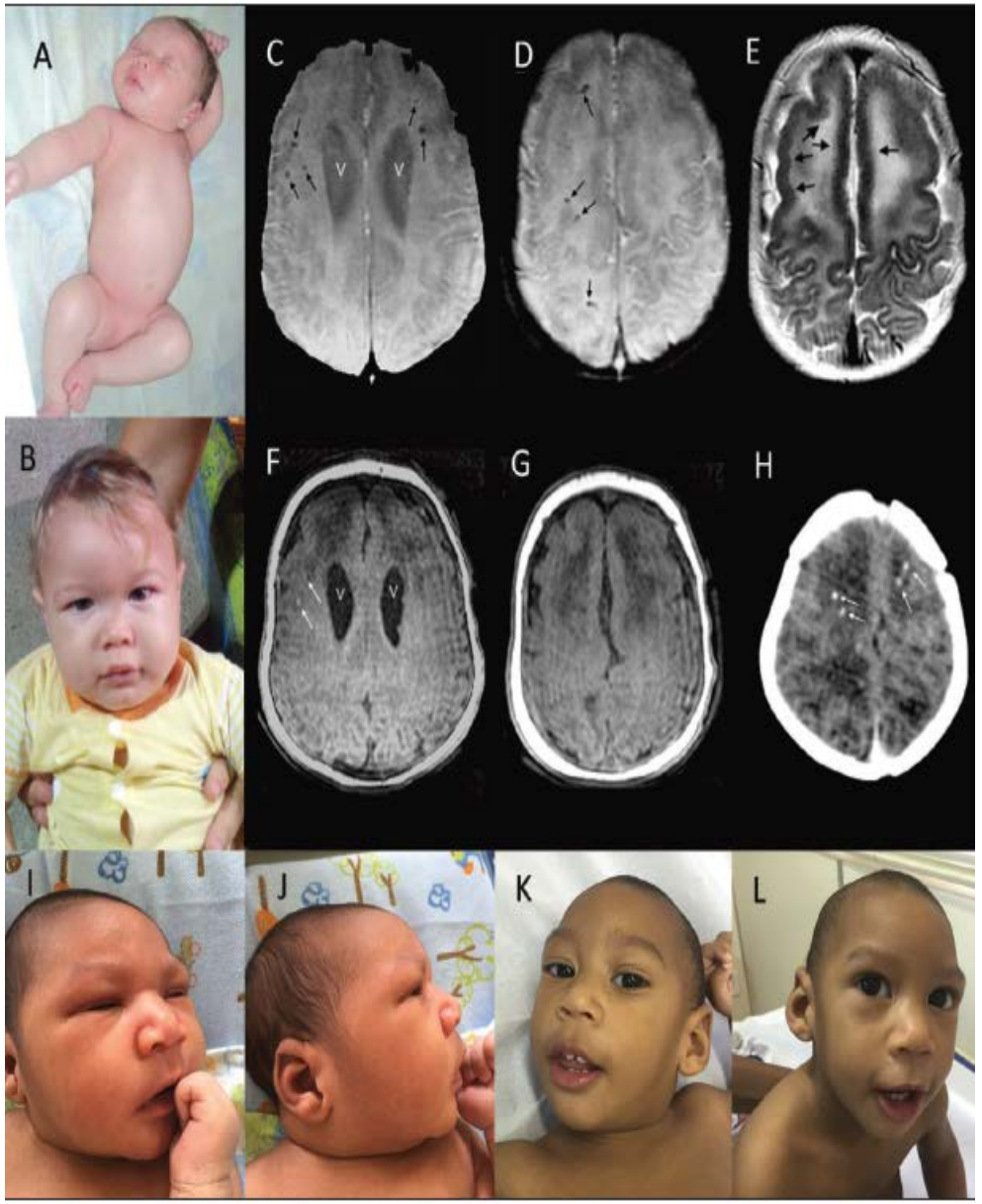
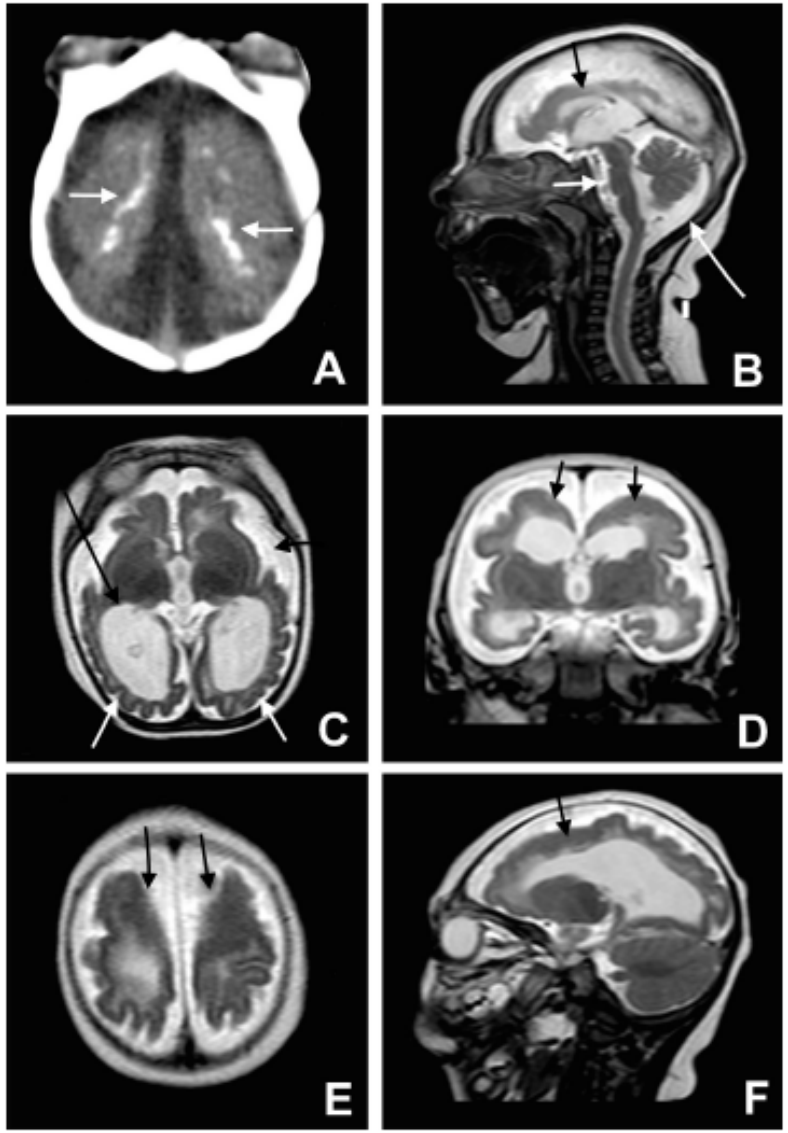


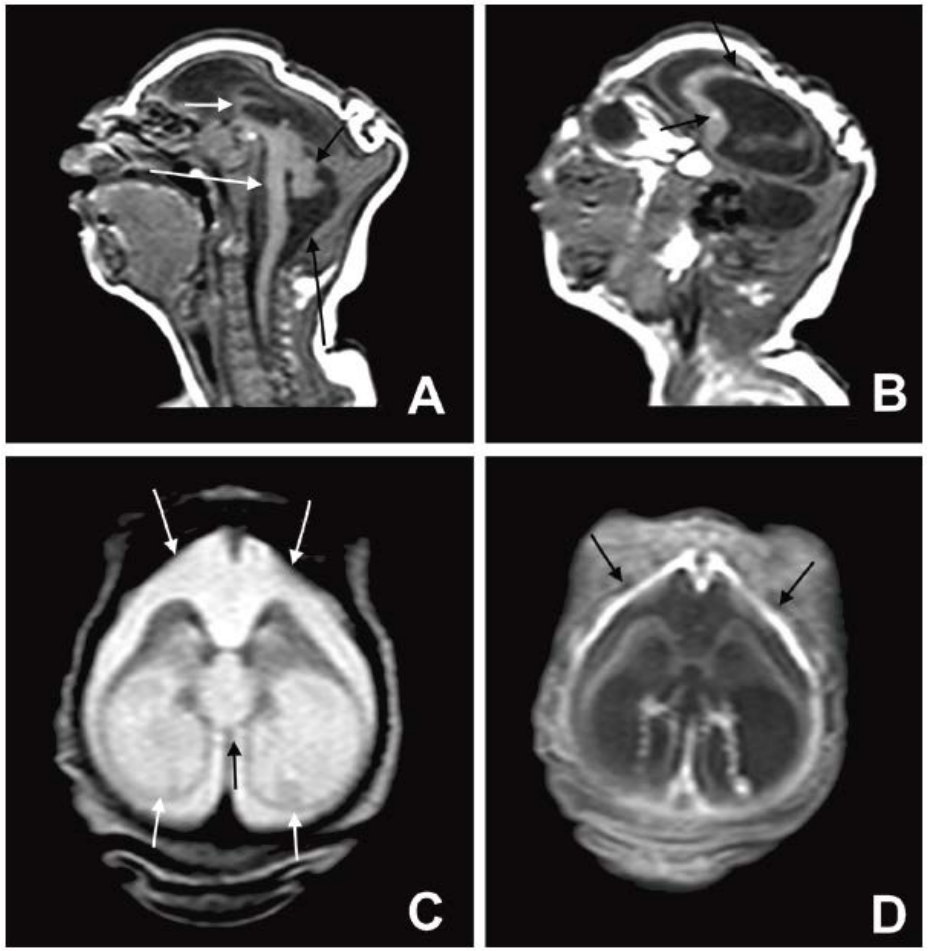
Figure 1. Characteristic phenotype of fetal brain disruption sequence in infants with probable congenital Zika virus syndrome, Sao Luís, Brazil, 2015–2016. A) Craniofacial disproportion and biparietal depression. B) Prominent occiput.



Calcification at cortical junction, reduced brain thickness



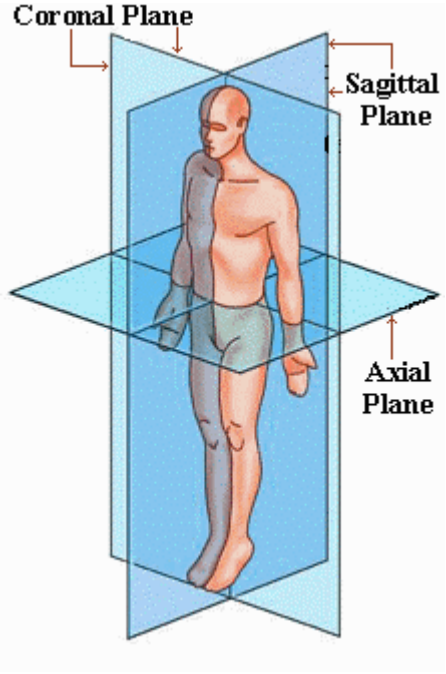
Severe microcephaly. Profound craniofacial disproportion



ventriculomegaly, enlarged SA space, enhanced meningies. Suggestive of blockage of CSF

Enlarged cistern magna. Brainstem and cerebellum hypoplasia

Extremely simplified gyral pattern



Maria de Fatima Vasco Aragao, et al. Clinical features and neuroimaging (CT and MRI) findings in presumed Zika virus related congenital infection and microcephaly: retrospective case series study. BMJ 2016;353:i1901

Arthrogryposis (congenital contractures of limbs)

A Multiple contractures with knee dislocation

B Multiple contractures including right talipes equinovarus

Club foot

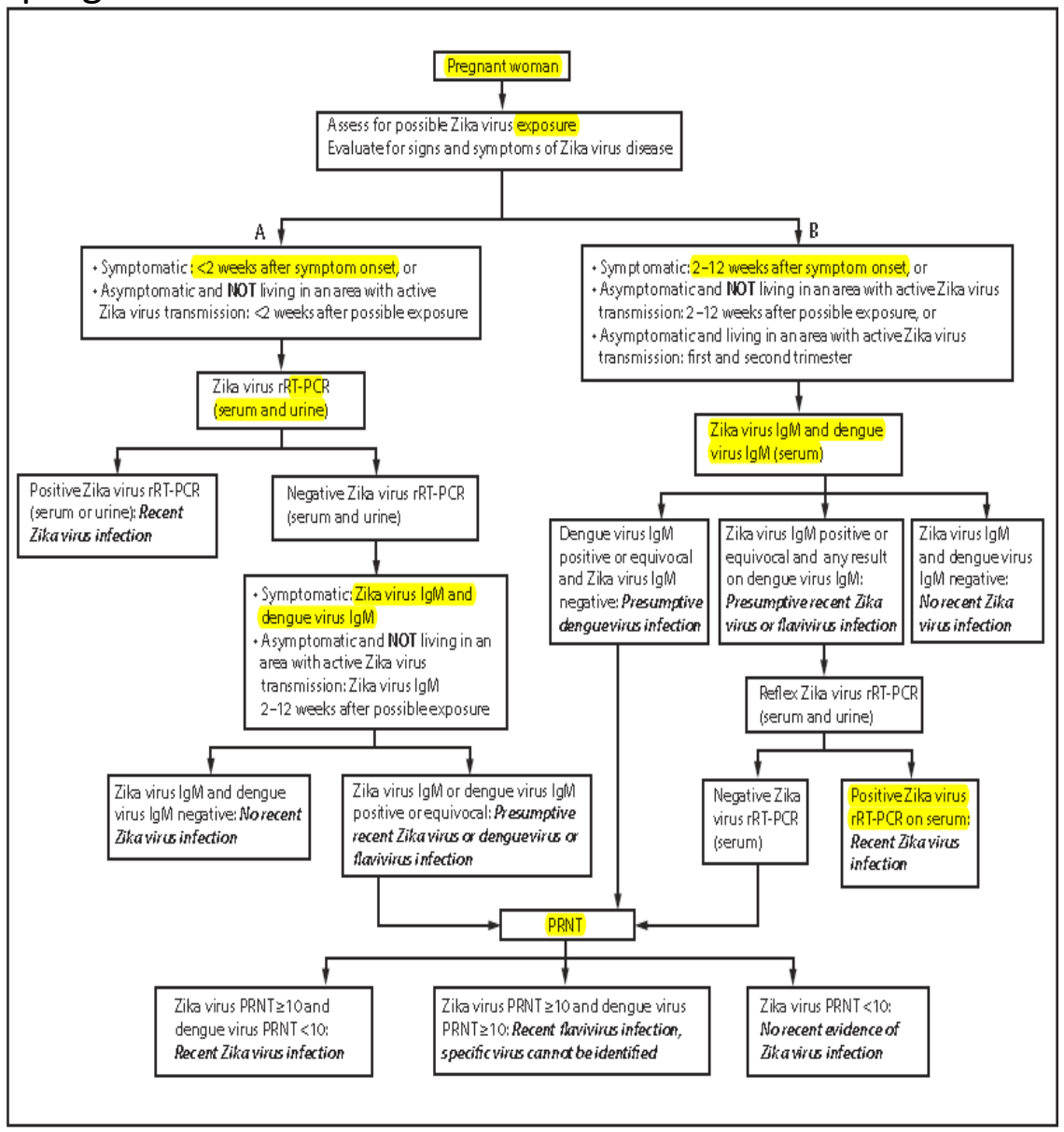
Table. Clinical Findings Comprising a Unique Pattern of Congenital Anomalies in Infants With Congenital ZIKV Infection: Congenital Zika Syndrome

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. JAMA Pediatrics March 2017 Volume 171, Number 3

US CDC testing algorithm for exposed pregnant women

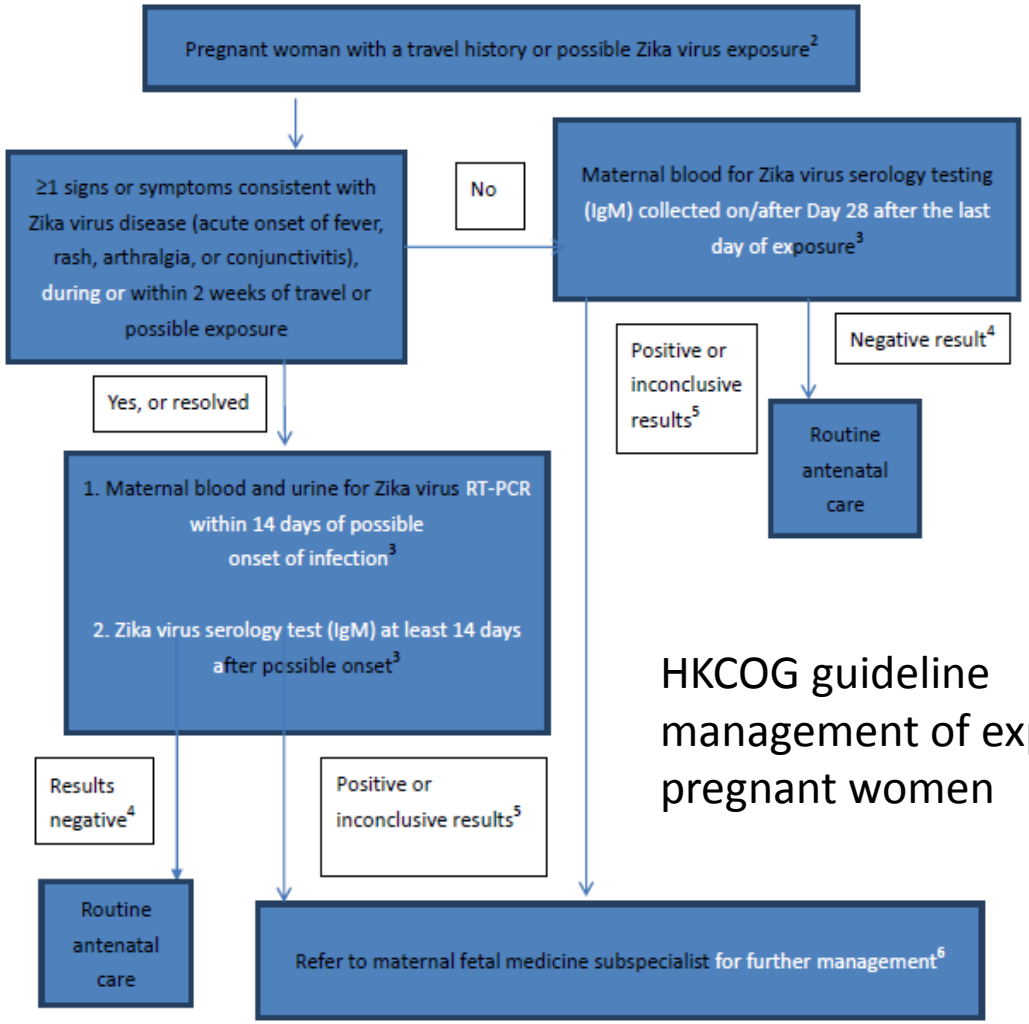


MMWR / July 29, 2016 / Vol. 65 / No. 29

Interim guidelines[1] on the management of a pregnant woman with possible Zika virus exposure[2]

Endorsed by the Hospital Authority Coordinating Committee in Obstetrics & Gynaecology and Hong Kong College of Obstetricians and Gynaecologists

with effect from 26 September 2016



HKCOG guideline management of exposed pregnant women

http://www.hkcog.org.hk/hkcog/Download/Interim_guidelines_on_Mx_of_a_pregnant_woman_with_a_travel_history_to_area_with_Zika_virus_transmission_(20160926).pdf

Association with GBS was first reported in French Polynesia outbreak 2013 吉巴氏綜合症

Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study

Van-Mai Cao-Lormeau*, Alexandre Blake*, Sandrine Mons, Stéphane Lastère, Claudine Roche, Jessica Vanhomwegen, Timothée Dub, Laure Baudouin, Anita Teissier, Philippe Larre, Anne-Laure Vial, Christophe Decam, Valérie Choumet, Susan K Halstead, Hugh J Willison, Lucile Musset, Jean-Claude Manuguerra, Philippe Despres, Emmanuel Fournier, Henri-Pierre Mallet, Didier Musso, Arnaud Fontanet*, Jean Neil*, Frédéric Ghawché*

Summary

Background Between October, 2013, and April, 2014, French Polynesia experienced the largest Zika virus outbreak ever described at that time. During the same period, an increase in Guillain-Barré syndrome was reported, suggesting a possible association between Zika virus and Guillain-Barré syndrome. We aimed to assess the role of Zika virus and dengue virus infection in developing Guillain-Barré syndrome.

Methods In this case-control study, cases were patients with Guillain-Barré syndrome diagnosed at the Centre Hospitalier de Polynésie Française (Papeete, Tahiti, French Polynesia) during the outbreak period. Controls were age-matched, sex-matched, and residence-matched patients who presented at the hospital with a non-febrile illness (control group 1; n=98) and age-matched patients with acute Zika virus disease and no neurological symptoms (control group 2; n=70). Virological investigations included RT-PCR for Zika virus, and both microsphere immunofluorescent and seroneutralisation assays for Zika virus and dengue virus. Anti-glycolipid reactivity was studied in patients with Guillain-Barré syndrome using both ELISA and combinatorial microarrays.

Findings 42 patients were diagnosed with Guillain-Barré syndrome during the study period. 41 (98%) patients with Guillain-Barré syndrome had anti-Zika virus IgM or IgG, and all (100%) had neutralising antibodies against Zika virus compared with 54 (56%) of 98 in control group 1 (p<0·0001). 39 (93%) patients with Guillain-Barré syndrome had Zika virus IgM and 37 (88%) had experienced a transient illness in a median of 6 days (IQR 4–10) before the onset of neurological symptoms, suggesting recent Zika virus infection. Patients with Guillain-Barré syndrome had electrophysiological findings compatible with acute motor axonal neuropathy (AMAN) type, and had rapid evolution of disease (median duration of the installation and plateau phases was 6 [IQR 4–9] and 4 days [3–10], respectively). 12 (29%) patients required respiratory assistance. No patients died. Anti-glycolipid antibody activity was found in 13 (31%) patients, and notably against GA1 in eight (19%) patients, by ELISA and 19 (46%) of 41 by glycoarray at admission. The typical AMAN-associated anti-ganglioside antibodies were rarely present. Past dengue virus history did not differ significantly between patients with Guillain-Barré syndrome and those in the two control groups (95%, 89%, and 83%, respectively).

Interpretation This is the first study providing evidence for Zika virus infection causing Guillain-Barré syndrome. Because Zika virus is spreading rapidly across the Americas, at risk countries need to prepare for adequate intensive care beds capacity to manage patients with Guillain-Barré syndrome.

Lancet 2016; 387: 1531–39
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http://dx.doi.org/10.1016/S0140-6736(16)00562-6
See Comment page 1486

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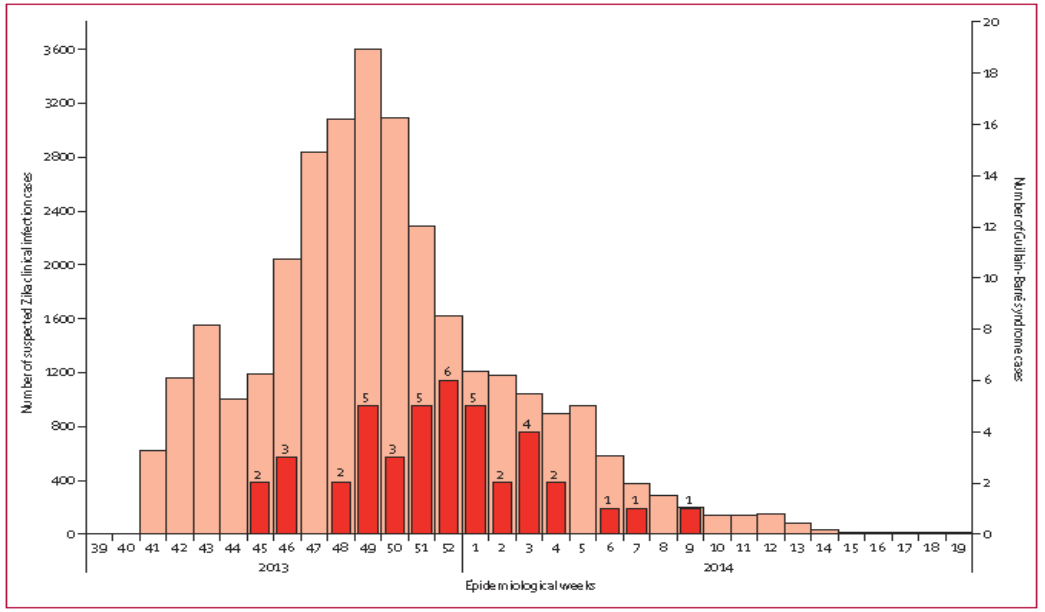
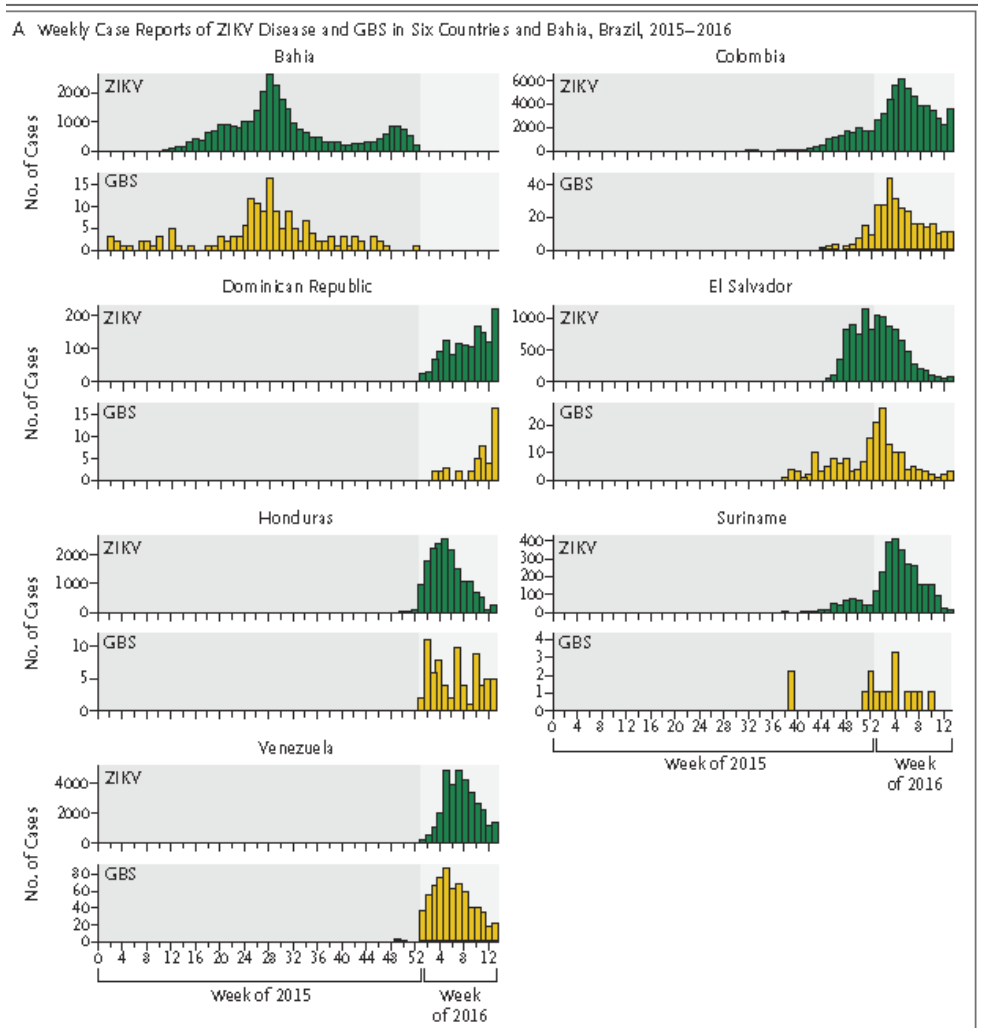


	n (%) or median (IQR)
Age (years)	42 (36–56)
Men	31 (74%)
Obese	11 (26%)
Smoking (n=40)	12 (30%)
High blood pressure	7 (17%)
Heart disease	3 (7%)
Previous viral syndrome	37 (88%)
Conjunctivitis (n=31)	15 (48%)
Rash (n=36)	29 (81%)
Fever (n=31)	18 (58%)
Arthralgia (n=31)	23 (74%)
Oedema of the limbs (n=29)	9 (31%)
Time between reported viral syndrome and onset of neurological symptoms (days) (n=37)	6 (4–10)

Lancet Vol 387 April 9, 2016

GBS Findings from Central and South America



- From April 1, 2015, to March 31, 2016, a total of 164,237 confirmed and suspected cases of ZIKV disease and 1474 cases of the Guillain–Barré syndrome were reported in Bahia, Brazil; Colombia; the Dominican Republic; El Salvador; Honduras; Suriname; and Venezuela
- The analysis suggests that changes in the reported incidence of ZIKV disease during 2015 and early 2016 were closely associated with changes in the incidence of the Guillain–Barré syndrome.
- Women 20-49 more common to have ZIKV infection, while GBS was 28% more common in males and consistently increased with age

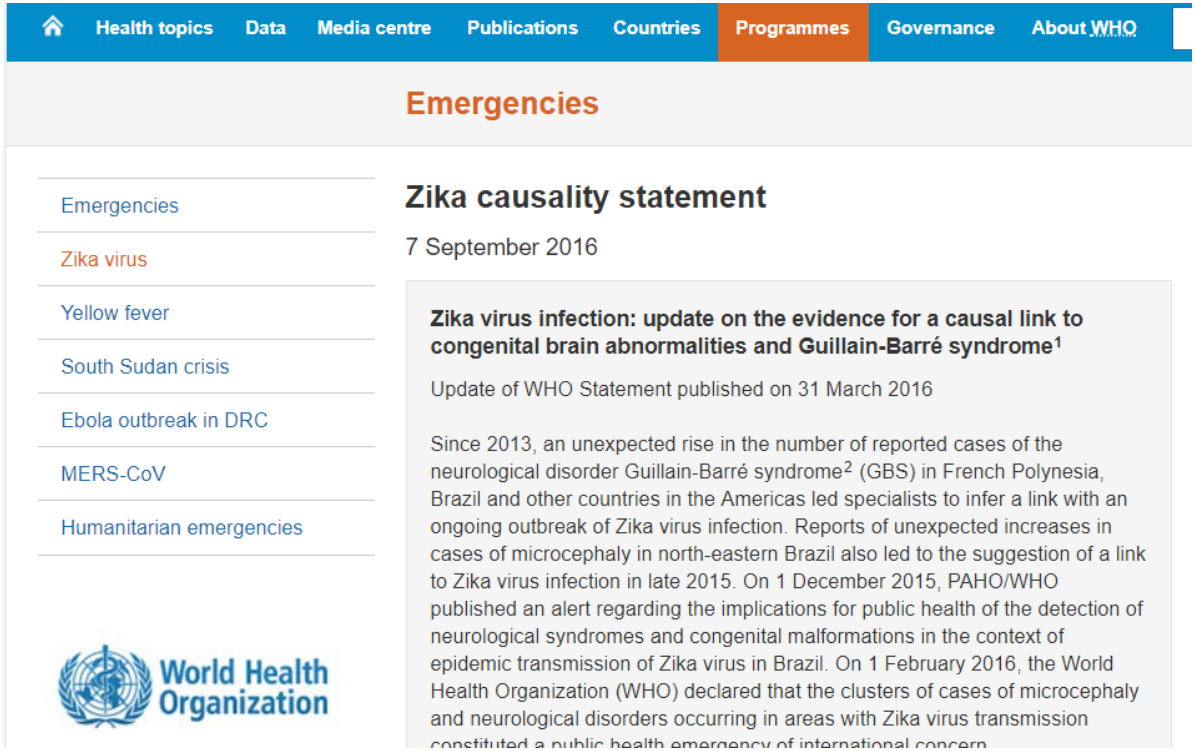
Zika Virus and the Guillain–Barré Syndrome — Case Series from Seven Countries. NEJM 375;16 Oct 20, 2016

WHO Causality Statement (Microcephaly & GBS)

The panel of experts concluded:

- The most likely explanation of available evidence from outbreaks of Zika virus infection and clusters of microcephaly is that Zika virus infection during pregnancy is a cause of congenital brain abnormalities including microcephaly;

- The most likely explanation of available evidence from outbreaks of Zika virus infection and Guillain-Barré syndrome is that Zika virus infection is a trigger of GBS.



RESEARCH ARTICLE

Zika Virus Infection as a Cause of Congenital Brain Abnormalities and Guillain–Barré Syndrome: Systematic Review

Fabienne Krauer[1], Maurane Riesen[1], Ludovic Reveiz[2], Olufemi T. Oladapo[3], Ruth Martínez-Vega[4], Teegwendé V. Porgo[3,5], Anina Haefliger[1], Nathalie J. Broutet[3], Nicola Low[1]*, WHO Zika Causality Working Group[¶]

1 Institute of Social and Preventive Medicine, University of Bern, Switzerland, **2** Pan American Health Organization, Washington DC, United States of America, **3** UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland, **4** Escuela de Microbiologia, Universidad Industrial de Santander, Santander, Colombia, **5** Department of Social and Preventative Medicine, Laval University, Québec, Canada

¶ Membership of the WHO Zika Causality Working Group is provided in the Acknowledgments.
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Krauer F, Riesen M, Reveiz L, Oladapo OT, MartõÂnez-Vega R, Porgo TV, et al. (2017) Zika Virus Infection as a Cause of Congenital Brain Abnormalities and Guillain±BarreÂ Syndrome: Systematic Review. PLoS Med 14(1): e1002203. doi:10.1371/journal.pmed.1002203

Management of ZIKV-associated GBS

- Same as other forms of GBS
  - Supportive care
    - Pain control
    - Nutritional support
    - Bowel and bladder care
    - Early rehabilitation
    - Psychosocial support
  - Close monitoring of cardiac and lung functions
  - Prevention of complications e.g. DVT, bedsores, corneal ulceration
- Immunotherapy (rapidly progressive, disability score > 2)
  - IVIG
  - Plasmapheresis
  - → most effective when given within 2 weeks of symptom onset
- Steroid is NOT useful

Fatal cases reported

Fatal Sickle Cell Disease and Zika Virus Infection in Girl from Colombia

Laura Arzuza-Ortega, Arnulfo Polo, Giamina Pérez-Tatis, Humberto López-García, Edgar Parra, Lissethe C. Pardo-Herrera, Angélica M. Rico-Turca, Wilmer Villamil-Gómez, Alfonso J. Rodríguez-Morales

15/F from north colombia in Oct 2015, sickle cell anemia for 5 years, no history of vaso-occlusive crises.
Present with dengue like syndrome for 4 days .
Severe jaundice, respiratory distress, required mech. ventilation
Died 37 hours later
Suspect vaso-occlusive crisis triggered by ZIKV (as reported for DENV)

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 22, No. 5, May 2016

www.thelancet.com/infection Vol 16 May 2016

Zika virus associated deaths in Colombia

Published Online
April 7, 2016
http://dx.doi.org/10.1016/S1473-3099(16)30006-8

Zika virus infection has emerged in Latin America as an important threat due to its association with Guillain-Barré syndrome, which can lead to deaths, and microcephaly in newborn babies.[1-3] Cases of fatal Zika virus infection are rare and misunderstood. The spectrum of clinical disease remains uncertain and considering the rapidly evolving epidemics of this new arbovirus in Latin America, it deserves further detailed assessment.[1-4] Here,

4 cases:
2/F & 30/F with severe thrombocytopenia, post mortem showed features of acute leukemia
61/M
72/F with Diabetes Mellitus

Morbidity and Mortality Weekly Report

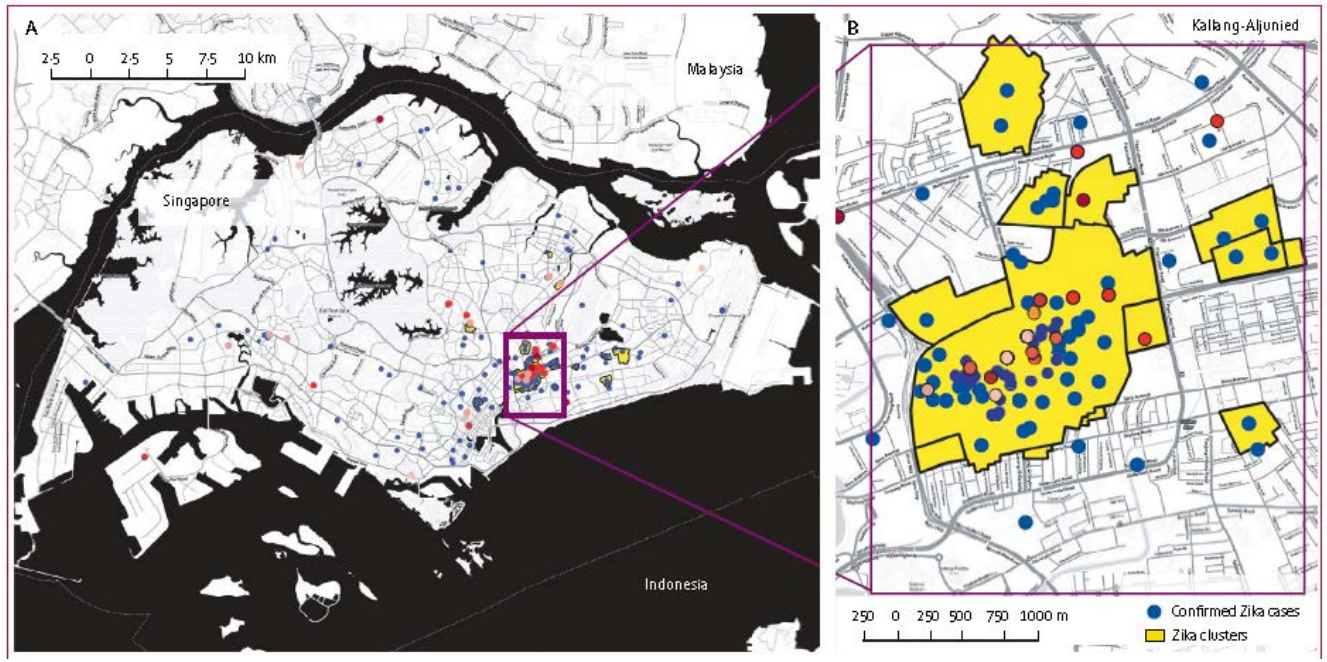
Update: Ongoing Zika Virus Transmission — Puerto Rico, November 1, 2015–April 14, 2016

Emilio Dirlikov, PhD[1,2]; Kyle R. Ryff, MPH[1]; Jomil Torres-Aponte, MS[1]; Dana L. Thomas, MD[1,3]; Janice Perez-Padilla, MPH[4]; Jorge Munoz-Jordan, PhD[4]; Elba V. Caraballo, PhD[4]; Myriam Garcia[5,6]; Marangely Olivero Segarra, MS[5,6]; Graciela Malave[5,6]; Regina M. Simeone, MPH[7]; Carrie K. Shapiro-Mendoza, PhD[8]; Lourdes Romero Reyes[9]; Francisco Alvarado-Ramy, MD[10]; Angela F. Harris, PhD[11]; Aidsa Rivera, MSN[4]; Chelsea G. Major, MPH[4,12]; Marrielle Mayshack[1,12]; Luisa I. Alvarado, MD[13]; Audrey Lenhart, PhD[14]; Miguel Valencia-Prado, MD[15]; Steve Waterman, MD[4]; Tyler M. Sharp, PhD[4]; Brenda Rivera-Garcia, DVM[1]

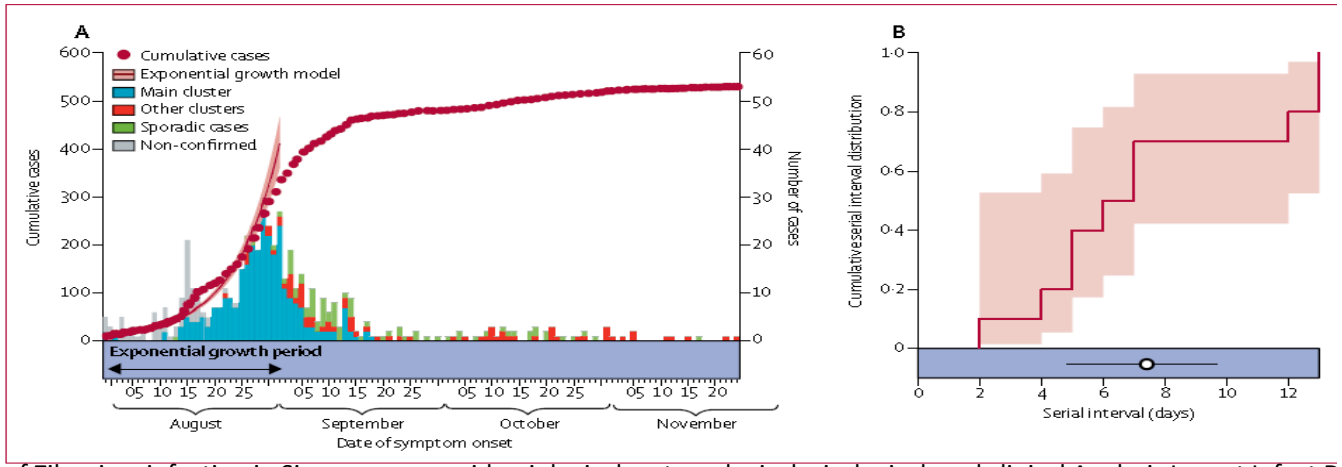
17 (2%) patients hospitalized
5(1%) patients with GBS
1 (<1%) patient died

MMWR / May 6, 2016 / Vol. 65 / No. 17

Outbreak in Singapore in August 2016



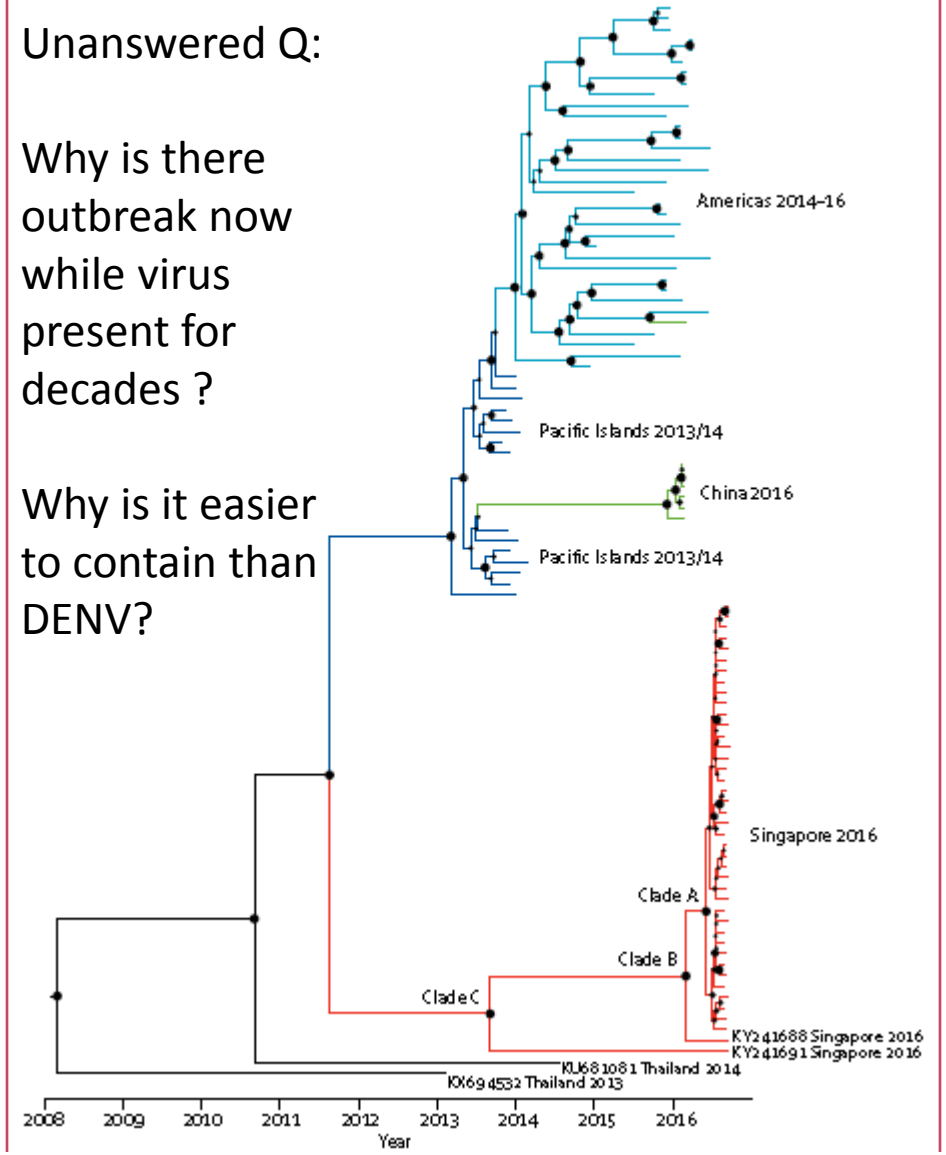
Kallang- Aljunied neighbourhood



Unanswered Q:

Why is there outbreak now while virus present for decades ?

Why is it easier to contain than DENV?



Outbreak of Zika virus infection in Singapore: an epidemiological, entomological, virological, and clinical Analysis Lancet Infect Dis May 17, 2017

Zika virus in Singapore: unanswered questions Lancet Infect Dis May 17, 2017

2 imported cases of Zika virus in Hong Kong

Caribbean
6-20 August

監測及流行病學處
衞生防護中心
Centre for Health Protection
保障市民健康
Protecting Hong Kong's health
Surveillance And Epidemiology Branch

本署檔號 Our Ref. : (17) in DH SEB CD/8/97/1 Pt.7

26 August 2016

Dear Doctor,

The first imported case of Zika Virus Infection

We would like to draw your attention to the first confirmed case of imported Zika Virus Infection (ZVI) reported in Hong Kong on 25 August 2016 and to remind doctors to remain vigilant against this disease.

The patient was a 38-year-old woman who lives in Lohas Park, Tseung Kwan O. She works in International Finance Centre, Central. She presented with joint pain since 20 August 2016. She attended the out-patient clinic of a private hospital on 23 August 2016 and was noted to have red eyes on examination. She did not require hospitalisation. Her blood and urine samples taken on 24 August were tested positive for Zika virus on 25 August 2016 by the Public Health Laboratory Services Branch (PHLSB) of the Centre for Health Protection (CHP). The patient was stable all along and was put under isolation in a vector free (mosquito-free) environment in United Christian Hospital for further management.

http://www.chp.gov.hk/files/pdf/letters_to_doctors_20160826.pdf

監測及流行病學處
衞生防護中心
Centre for Health Protection
保障市民健康
Protecting Hong Kong's health
Surveillance And Epidemiology Branch

本署檔號 Our Ref. : (153) in DH SEB CD/8/97/1 Pt.9

26 April 2017

Dear Doctor,

The first imported case of Zika Virus Infection in 2017

We would like to draw your attention to the first confirmed case of imported Zika Virus Infection (ZVI) reported this year in Hong Kong today and to remind doctors to remain vigilant against this disease.

The patient was a 31-year-old woman who lives in Fortune Plaza, Tai Po. She presented with headache, mild sore throat, nausea and vomiting since 21 April 2017 and developed generalised skin rash since 23 April 2017. She consulted a general practitioner at Tai Po on 22 April 2017; attended the Accident and

Ecuador and Peru 8-21 April

http://www.chp.gov.hk/files/pdf/letters_to_doctors_20170426.pdf

Treatment & Prevention

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

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Emergency Preparedness and Response

Home > Emergency Preparedness and Response > Counterterrorism and Emerging Threats > Medical Countermeasures Initiative > MCM Issues

MCM Issues

- Zika Virus Response Updates from FDA
- Ebola Response Updats from FDA

Zika Virus Response Updates from FDA

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Medical Products

There are no FDA-approved vaccines for Zika virus. Several investigational vaccines are under development, including early human clinical trials.

There are no FDA-approved treatments for Zika virus, nor is the FDA aware of treatments in advanced development for Zika at this time. *Also see Zika Virus Treatment Research, from NIAID, and BARDA's Medical Countermeasure Response to Zika*

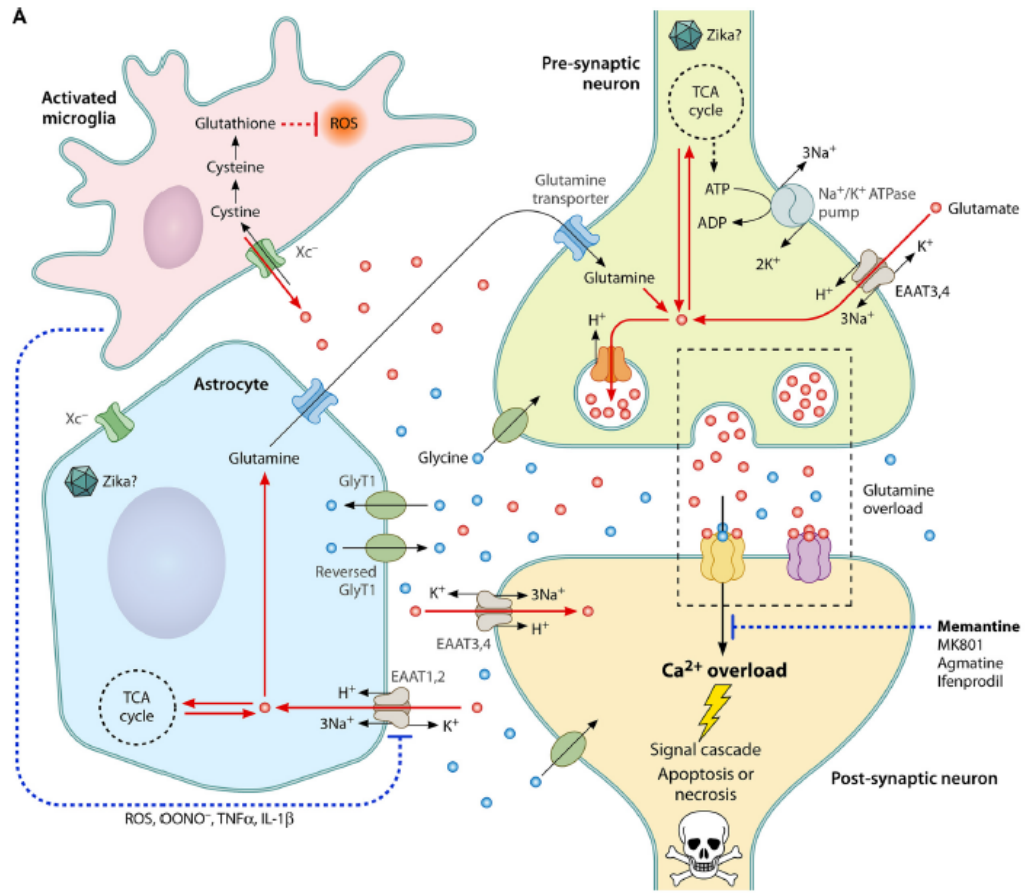
There are no commercially available diagnostic tests cleared by FDA for the detection of Zika virus. FDA encourages commercial diagnostic developers and researchers developing laboratory developed tests for Zika virus to submit an EUA request. FDA will work interactively with developers to support such requests. See **Zika Virus Diagnostic Development** for information on FDA support for Zika virus diagnostic development and **Emergency Use Authorization** for information about Zika virus diagnostics available under EUA.

Can an FDA-Approved Alzheimer's Drug Be Repurposed for Alleviating Neuronal Symptoms of Zika Virus?

Devika Sirohi, Richard J. Kuhn

Department of Biological Sciences, and Purdue Institute of Inflammation, Immunology and Infectious Disease, Purdue University, West Lafayette, Indiana, USA

ABSTRACT Zika virus caught the world by surprise by its rapid spread and frightening disease outcomes. This major epidemic motivated many scientists to focus their attention on controlling this emerging pathogen. As many as 45 vaccine candidates are being developed, but progress in the antiviral arena has been slower. In a recent article (mBio 8:e00350-17, 2017, https://doi.org/10.1128/mBio.00350-17), Costa and colleagues showed that an FDA-approved drug used to treat Alzheimer's disease may moderate Zika virus-induced neuronal damage. This work is based on the premise that overstimulation of *N*-methyl-D-aspartate receptors (NMDARs) may drive neurodegeneration and that this may be responsible for neuronal cell death associated with Zika virus infection of the central nervous system (CNS). Thus, blockage of the NMDAR channel activity with FDA-approved memantine or other antagonists may reduce neurological complications associated with Zika virus infection. Repurposing a preapproved drug and targeting the host represent intriguing strategies and yet require more analysis prior to moving into clinical trials.



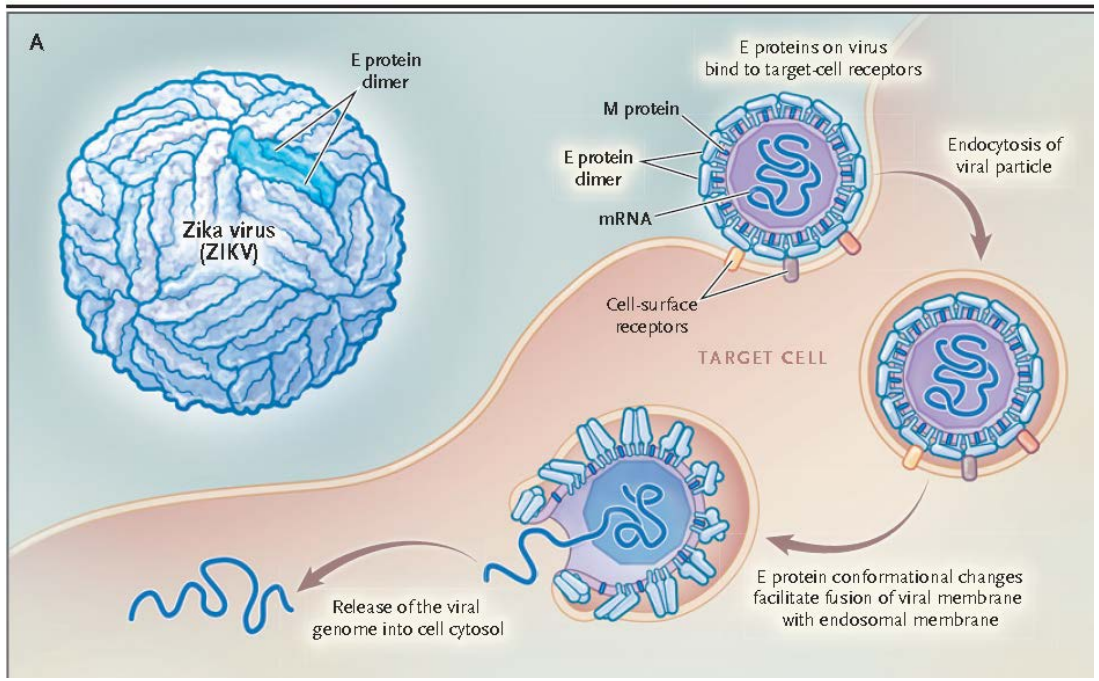
Vaccine development

- Being monitored by WHO, which convened workshop and perform scientific consultation on how best to conduct efficacy trials
- More than 10 vaccine candidates currently in different phases of development

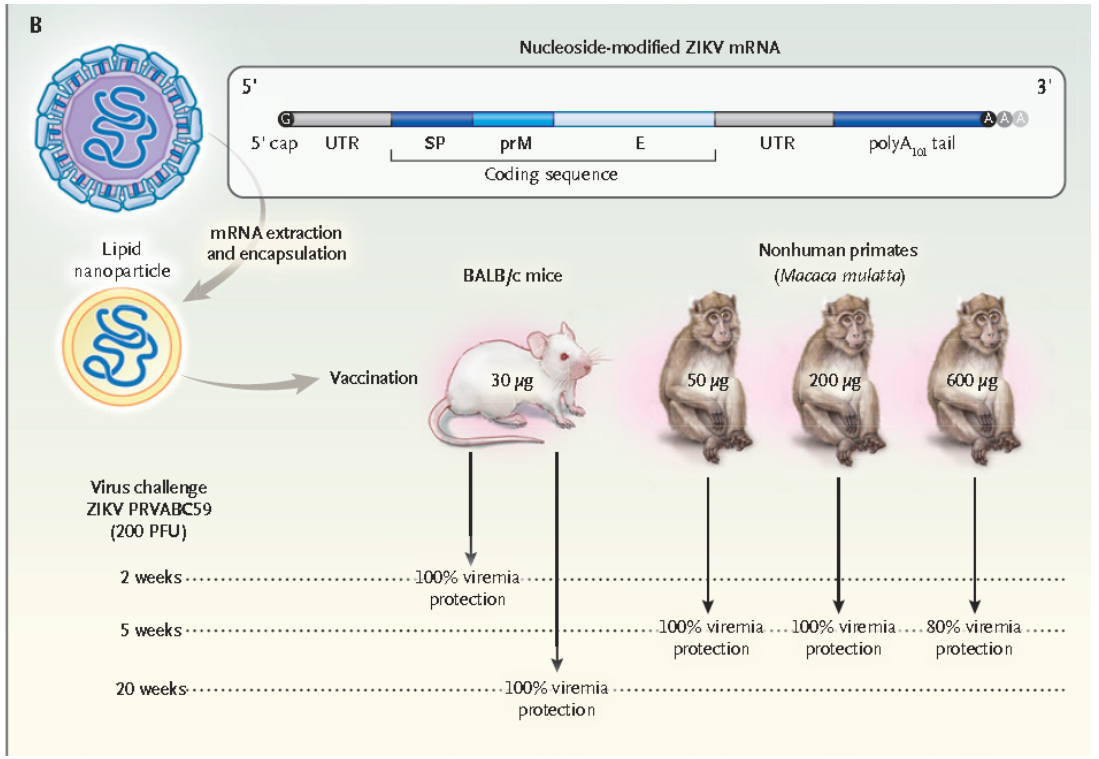
WHO vaccine pipeline tracker

& Pathogen	Vaccine Candidate							Clinical Trial Information						
Pathogen	Candidate Vaccine	Candidate Vaccine Status	Platform	Immunogen Type	Immunogen	Adjuvant Type	Adjuvant	Registry ID	Trial Status	Sponsor Name	Sponsor Type	Phase	Study Start date	Primary Compl (anticipated c (see not
ZIKV	GLS-5700	Active candidate /	DNA	Protein: specify	prME	None		NCT02809443	Open, not recruitir	GeneOne Life Scie	Industry	Phase 1	2016-07-01	2017-11-01
ZIKV	GLS-5700	Active candidate /	DNA	Protein: specify	prME	None		NCT02887482	Open, recruiting	GeneOne Life Scie	Industry	Phase 1	2016-08-01	2017-06-01
ZIKV and others	AGS-v	Active candidate /	Peptide	Protein: specify	Mosquito salivary	Novel other: speci	ISA-51	NCT03055000	Open, recruiting	NIH	Government	Phase 1	2017-02-09	2019-12-31
ZIKV	MV-Zika	Active candidate /	Recombinant viral	Protein: specify	prME	None		NCT02996890	Open, recruiting	Themis Bioscience	Industry	Phase 1	2017-04-04	2017-07-01
ZIKV	mRNA-1325	Active candidate /	mRNA	Protein: specify	prME	None		NCT03014089	Open, recruiting	Moderna Therape	Industry	Phase 2	2016-12-01	2017-11-01
ZIKV	VRC-ZKADNA085-00-VP	Active candidate /	DNA	Protein: specify	prME	None		NCT02840487	Open, not recruitir	NIAID	Government	Phase 1	2016-07-11	2017-12-29
ZIKV	VRC-ZKADNA090-00-VP	Active candidate /	DNA	Protein: specify	prME	None		NCT02996461	Open, recruiting	NIAID	Government	Phase 1	2016-12-08	2018-12-28
ZIKV	VRC-ZKADNA090-00-VP	Active candidate /	DNA	Protein: specify	prME	None		NCT03110770	Open, recruiting	NIAID	Government	Phase 2	2017-03-29	2020-01-01
ZIKV	ZIKV PIV	Active candidate /	Inactivated whole	Protein: specify	whole virus	Aluminum salts (a		NCT02963909	Open, recruiting	NIAID	Government	Phase 1	2016-11-01	2019-02-01
ZIKV	ZIKV PIV	Active candidate /	Inactivated whole	Protein: specify	whole virus	Aluminum salts (a		NCT02952833	Open, recruiting	NIAID	Government	Phase 1	2016-10-14	2018-01-15
ZIKV	ZIKV PIV	Active candidate /	Inactivated whole	Protein: specify	whole virus	Aluminum salts (a		NCT02937233	Open, recruiting	BIDMC	Academic	Phase 1	2016-10-01	2017-11-01
ZIKV	ZIKV PIV	Active candidate /	Inactivated whole	Protein: specify	whole virus	Aluminum salts (a		NCT03008122	Open, recruiting	NIAID	Government	Phase 1	2017-02-24	2019-07-18

http://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/ (accessed 12/7/2017)



ZIKV E protein vaccine candidate



Nucleoside-Modified mRNA Vaccine Candidate

Zika Virus Vaccines — A Full Field and Looking for the Closers. NEJM 376;19 May 11, 2017

Infection Control

- Standard precautions should be adopted when contacting confirmed and suspected cases
- No special cleaning or disinfection practices or reprocessing strategy are necessary. Please follow existing recommended protocols.
- Patient should be housed in a mosquito-free environment e.g. clinical areas of hospital until no longer transmissible i.e. viremia cleared

https://www.cdc.gov/zika/hc-providers/infection-control.html
Inactivation and Environmental Stability of Zika Virus Emerging Infectious DiseasesVol. 22, No. 9, September 2016
Hospital Authority Preparedness Plan for Zika Virus Infection March 2016

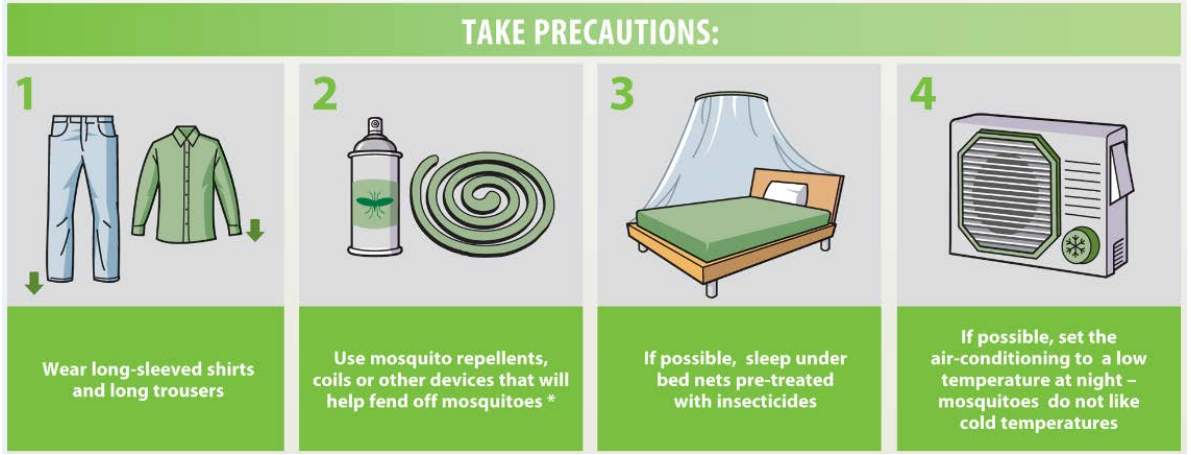
標 準 防 護 措 施
Standard Precautions

- Hand Hygiene
- Personal Protective Equipment (PPE)
  - Gloves
  - Mask, eye protection and faceshield
  - Gown/apron
- Environmental & equipment decontamination
- Prevention of sharps injury
- Respiratory hygiene and cough etiquette

Basic Infection Control Training for Non-Clinical Staff updated in March 2014
http://www.chp.gov.hk/files/pdf/isolation_precautions.pdf

Anti-mosquito measures

- Keep the environment clean
- Remove stagnant water
  - Unblock ditches
  - Careful of old tires and used cans
  - Even irregular ground surfaces
- Prevent breeding of mosquitoes
  - Cover water containers
  - Cover rubbish bins with lids
  - Use of fish to eat up larvae in cultivating ponds
- Prevent mosquito bites
  - Wear light coloured, long sleeved clothing outdoors
  - Apply insect repellent appropriately
  - Use mosquito net
  - Avoid fragrant cosmetics



ECDC

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http://www.fehd.gov.hk/english/safefood/risk-pest-mosquito.html#anchor4
http://www.chp.gov.hk/en/content/9/24/19.html

Choosing the right insect repellent

Active ingredient	有效成分	Usual concentration	Duration (hours)	remarks
DEET (most effetive)	避蚊胺	5-30%	1-6	<10% for children. Not for 0-6 months Can use up to 30% in pregnancy
Picaridin (Icaridin)	避卡蚋叮	5-25%	3-12	Good tolerability
IR 3535	伊默寧	7.5-20%	2-8	
2-undecanone (wild tomato extract)	甲基壬基酮	7.75-10%	2	EPA toxicity class IV (lowest)
PMD (from oil of lemon eucalyptus)	對-薄荷烷-3,8-二醇	10-40%	2-6	Not to be used in <3 years old
Citronella (found in lemongrass)	香茅油	4.2%	1	Minimal efficacy

http://www.chp.gov.hk/en/view_content/38927.html
http://www.fhs.gov.hk/english/health_info/woman/30064.pdf
https://wwwnc.cdc.gov/travel/yellowbook/2016/the-pre-travel-consultation/protection-against-mosquitoes-ticks-other-arthropods
https://www.consumer.org.hk/ws_chi/news/press/p46404.html

Advice to travellers to prevent sexual transmission

categories	WHO *	CDC	CHP
Returned travellers	Adopt safer sex practice or abstinence for at least 6 months upon return for both men and women	At least 6 months for men and 8 weeks for women after symptom onset or last exposure	Travellers returning from affected areas should consider abstinence from sex for at least 6 months upon return, or else condoms should be used.
Couples planning for pregnancy	should wait for at least 6 months before trying to conceive	Women should wait for at least 8 weeks from symptom onset or last possible exposure before trying to conceive. Men should wait for at least 6 months (8 weeks if asymptomatic no longer recommended)	
Sexual partner of pregnant woman	Sexual partner of pregnant woman should practise safer sex or abstinence for at least the whole duration of pregnancy	Use condom or abstain from sex for the duration of pregnancy	Pregnant woman should not have sex with her partner who had travelled to affected areas, or else condom should be used throughout the pregnancy.
Travel to areas with active transmission	advising pregnant women not to travel to Zika-affected areas in categories 1 and 2 in the country classification table	Pregnant women and partners should avoid nonessential travel to these areas	Pregnant women and women preparing for pregnancy should not travel to areas with ongoing Zika virus transmission.

*in regions with NO active Zika virus transmission

Sources: Prevention of sexual transmission of Zika virus, 6 September 2016 WHO/ZIKV/MOC/16.1 Rev.3

http://www.chp.gov.hk/en/content/9/24/43088.html

http://www.who.int/csr/disease/zika/information-for-travelers/en/

Cont'd

categories	WHO *	CDC	CHP
Advice for sex during travel			Should not have sex during travel or use condoms
Use of insect repellent	Travellers returning home should also continue to use insect repellent for at least three weeks to avoid being bitten and potentially spreading the infection to other people through mosquito bites.		Use of mosquito repellent containing DEET during travel and returning from these areas for a period of at least 21 days are advised for all travellers including pregnant women.
Additional advice for Pregnant women with possible exposure		Should be tested for zika virus infection in accordance with CDC's algorithm	attend antenatal follow up regularly and tell the attending doctor history of recent travel; observe for symptoms of Zika virus infection and seek medical advice as soon as possible if feeling unwell;

*in regions with NO active Zika virus transmission

Sources: Prevention of sexual transmission of Zika virus, 6 September 2016 WHO/ZIKV/MOC/16.1 Rev.3

http://www.chp.gov.hk/en/content/9/24/43088.html

http://www.who.int/csr/disease/zika/information-for-travelers/en/

News & Events

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Screening blood donors to prevent Zika Virus Disease (Updated on 22/6/2017)

In association with active Zika virus transmission, the Hong Kong Red Cross Blood Transfusion Service has put new screening guidelines in place. Anyone who has resided in or visited any of following countries which are affected by Zika Virus Disease will be deferred from blood donation at least 28 days from the date he/she departed from the affected areas.

	Continent	Countries with active Zika virus transmission
A. Area with new introduction or re-introduction with ongoing transmission (58)	Africa非洲 (3)	Angola安哥拉, Cape Verde佛得角共和國; Guinea-Bissau幾內亞比紹
	Americas美洲 (45)	Anguilla安圭拉; Antigua and Barbuda安提瓜和巴布達; Argentina阿根廷; Aruba阿魯巴; Bahamas巴哈馬; Barbados巴巴多斯; Belize伯利茲; Bolivia玻利維亞; Bonaire, St Eustatius and Saba博內爾, 聖尤斯特歇斯和薩巴; British Virgin Islands英屬維爾京群島; Cayman Islands開曼群島; Colombia哥倫比亞; Costa Rica哥斯達黎加; Cuba古巴; Curacao庫拉索; Dominica多米尼克; Dominican Republic多米尼加共和國; Ecuador厄瓜多爾; El Salvador薩爾瓦多; French Guiana法屬圭亞那; Grenada格林納達; Guadeloupe瓜德羅普島; Guatemala危地馬拉; Guyana圭亞那; Honduras洪都拉斯; Jamaica牙買加; Martinique馬提尼克島; Mexico墨西哥; Montserrat蒙特塞拉特島; Nicaragua尼加拉瓜; Panama巴拿馬; Paraguay巴拉圭; Peru秘魯; Puerto Rico波多黎各; Saint Kitts and Nevis聖基茨和尼維斯; Saint Lucia聖盧西亞; Saint-Martin聖馬丁島; St Maarten聖馬丁; St Vincent and the Grenadines聖文森特和格林納丁斯; Suriname蘇里南; Trinidad and Tobago特立尼達和多巴哥; Turks and Caicos Islands特克斯和凱科斯群島; the United States美國; the US Virgin Islands美屬維爾京群島; Venezuela委內瑞拉
	Southeast Asia 東南亞 (1)	Maldives馬爾代夫

http://www5.ha.org.hk/rcbts/enarticlelistview.asp?nid=214&bid=5&sid=0&MenuID=2#.WWYv4oh96M8

Unanswered research questions on Zika virus

- Can African lineage of virus cause severe complications ?
- What is the minimum infectious dose for transmission by transfusion ?
- What are the long term outcomes of neonates without abnormality at birth ?
- Does infection confer lifelong immunity ? Does prior dengue infection enhances antibody response ?
- Will ZIKV cause large outbreaks in Africa and Asia ?

An update on Zika virus infection. Lancet June 21, 2017

LETTER

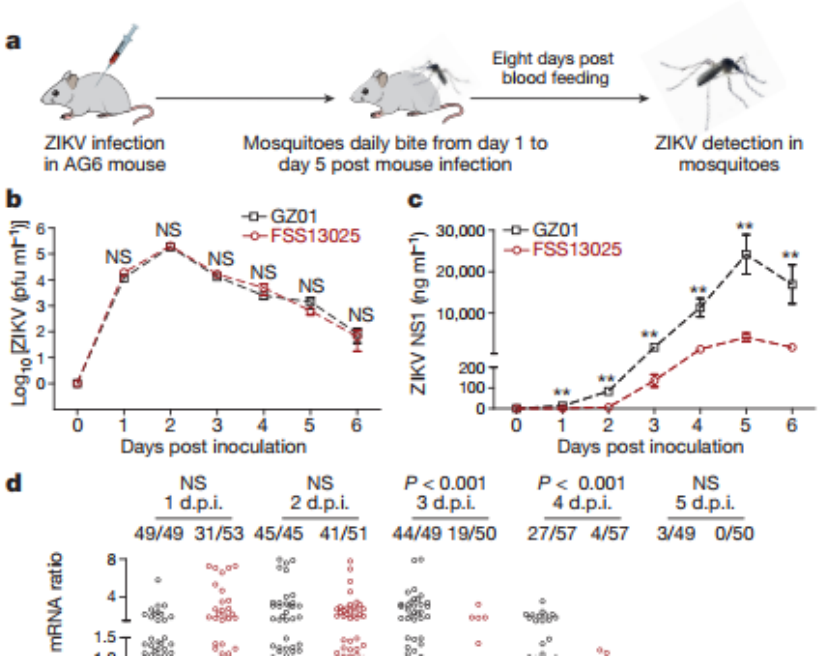
doi:10.1038/nature22365

Explanation for sudden appearance of outbreaks ?

Evolutionary enhancement of Zika virus infectivity in *Aedes aegypti* mosquitoes

Yang Liu[1,2,3*], Jianying Liu[1,3*], Senyan Du[1*], Chao Shan[4*], Kaixiao Nie[1], Rudian Zhang[1,2], Xiao-Feng Li[5], Renli Zhang[3], Tao Wang[3,6], Cheng-Feng Qin[5], Penghua Wang[7], Pei-Yong Shi[4] & Gong Cheng[1,3]

Zika virus (ZIKV) remained obscure until the recent explosive outbreaks in French Polynesia (2013–2014) and South America (2015–2016)[1–3]. Phylogenetic studies have shown that ZIKV has evolved into African and Asian lineages. The Asian lineage of ZIKV was responsible for the recent epidemics in the Americas[1,3]. However, the underlying mechanisms through which ZIKV rapidly and explosively spread from Asia to the Americas are unclear. Non-structural protein 1 (NS1) facilitates flavivirus acquisition by mosquitoes from an infected mammalian host and subsequently enhances viral prevalence in mosquitoes[4]. Here we show that NS1 antigenaemia determines ZIKV infectivity in its mosquito vector *Aedes aegypti*, which acquires ZIKV via a blood meal. Clinical isolates from the most recent outbreak in the Americas were much more infectious in mosquitoes than the FSS13025 strain, which was isolated in Cambodia in 2010. Further analyses showed that these epidemic strains have higher NS1 antigenaemia than the FSS13025 strain because of an alanine-to-valine amino acid substitution at residue 188 in NS1. ZIKV infectivity was enhanced by this amino acid substitution in the ZIKV FSS13025 strain in mosquitoes that



NATURE. VOL 545. 25 May 2017

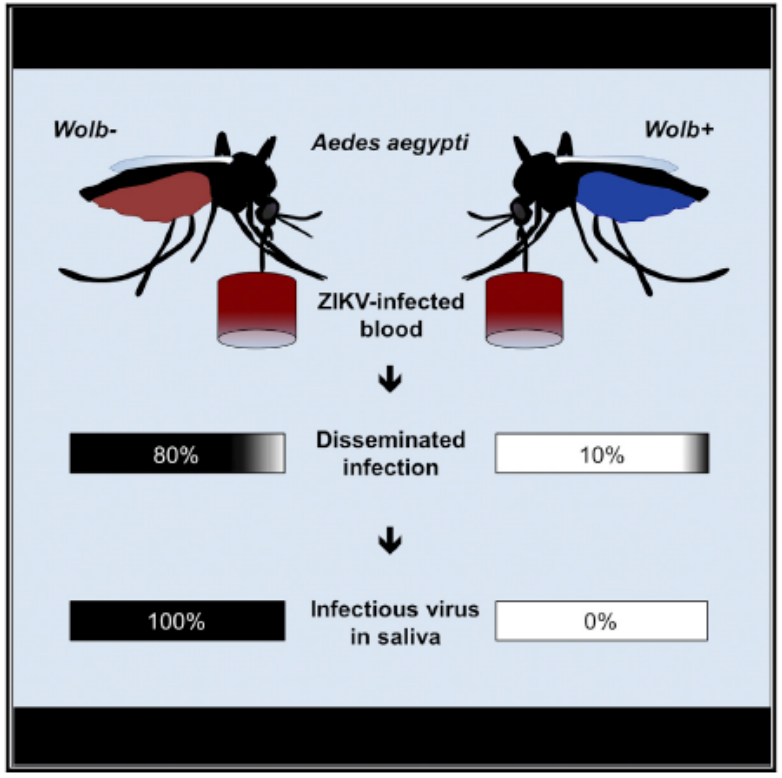
Infecting mosquitoes with *Wolbachia* bacteria

Brief Report

Cell Host & Microbe

Wolbachia Blocks Currently Circulating Zika Virus Isolates in Brazilian *Aedes aegypti* Mosquitoes

Graphical Abstract



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In Brief

Strategies to combat Zika virus (ZIKV) and its mosquito vector are urgently needed. Dutra et al. report that *Wolbachia*-carrying mosquitoes are highly resistant to ZIKV and display reduced virus prevalence and intensity. Saliva from *Wolbachia*-carrying mosquitoes did not contain infectious virus, suggesting the possibility to block ZIKV transmission.

Luciano Moreira (left) and Scott O'Neill in the Fiocruz laboratory with a vat for breeding *Wolbachia*-infected mosquitoes

Christophe Simon/AFP/Getty Images

Brazilian biologist Robert Costa Peres releases mosquitoes infected with the *Wolbachia* bacterium in Rio de Janeiro.

Nature news 26 Oct 2016
Dutra et al., 2016, Cell Host & Microbe 19, 771–774
Bull World Health Organ 2016;94:562–563

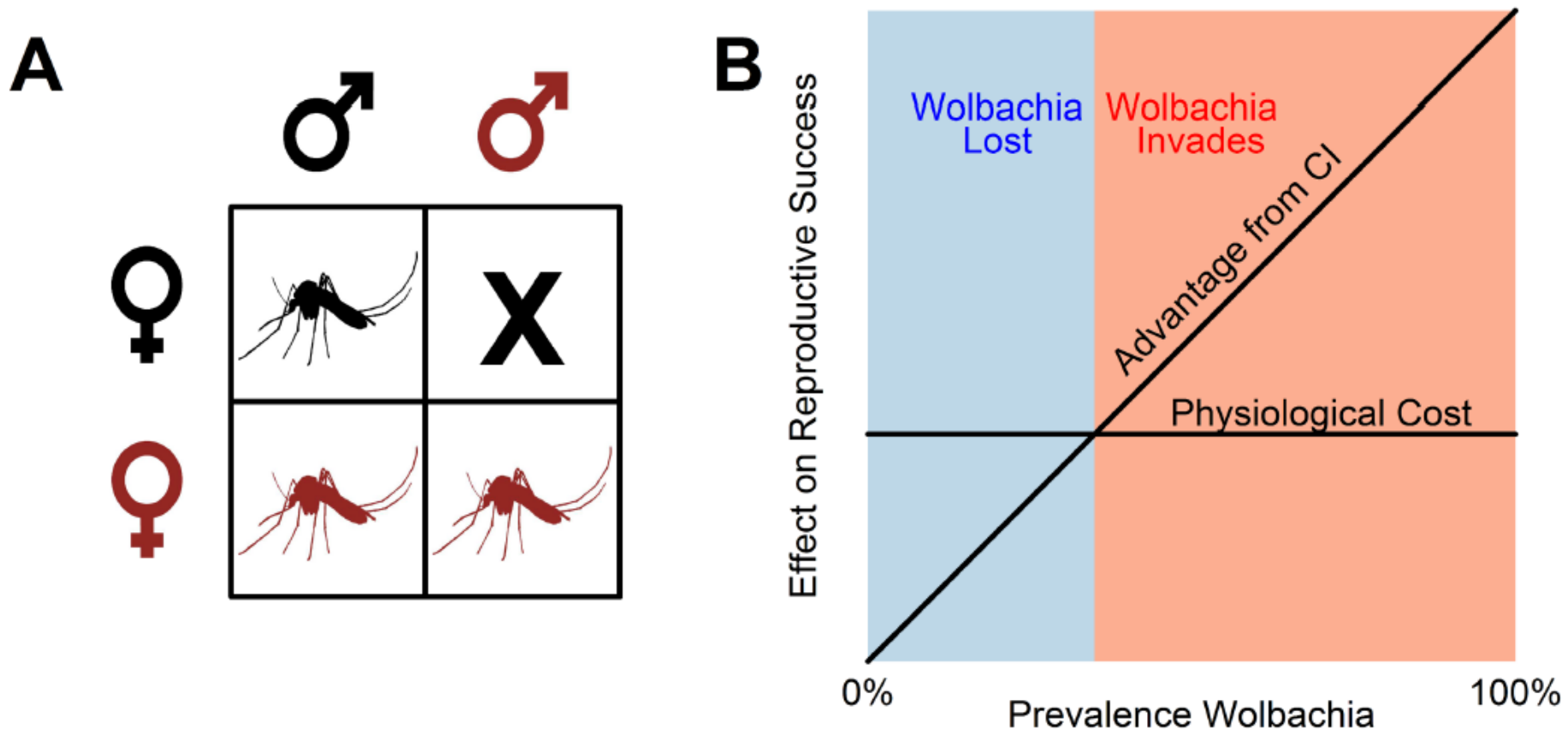

Fig 1. Cytoplasmic incompatibility. (A) When a *Wolbachia*-infected male (red) mates with an uninfected female (black), a sperm–egg incompatibility means that some or all of the embryos die. Therefore, infected females produce more offspring than uninfected females (red versus black mosquitoes). **(B)** This reproductive advantage depends on the prevalence of *Wolbachia* in the population, because when *Wolbachia* is rare, females are unlikely to mate with infected males. The *Wolbachia* strain in *Aedes aegypti* carries a physiological cost, reducing the fecundity of infected females. If this cost exceeds the advantage of cytoplasmic incompatibility, then the infection is lost from the population. This creates a threshold prevalence below which *Wolbachia* is lost and above which it invades the population. This cartoon assumes infected females transmit *Wolbachia* to all their offspring. *Image credit*: https://doi.org/10.1093/gbe/evw018.

Jiggins FM (2017) The spread of *Wolbachia* through mosquito populations. PLoS Biol 15(6): e2002780.

Genetically modified (sterile) mosquito

RESEARCH ARTICLE

Dispersal of Engineered Male *Aedes aegypti* Mosquitoes

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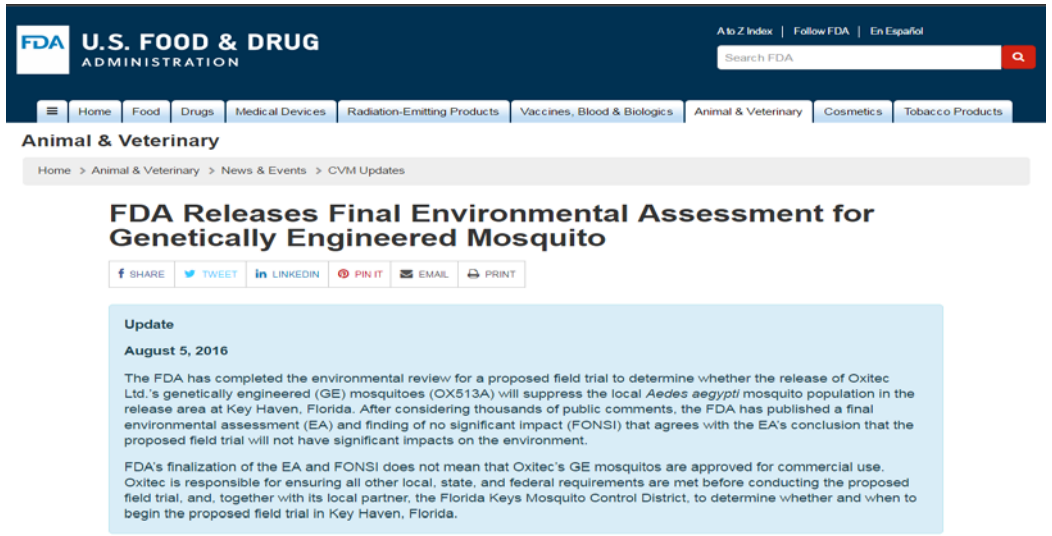
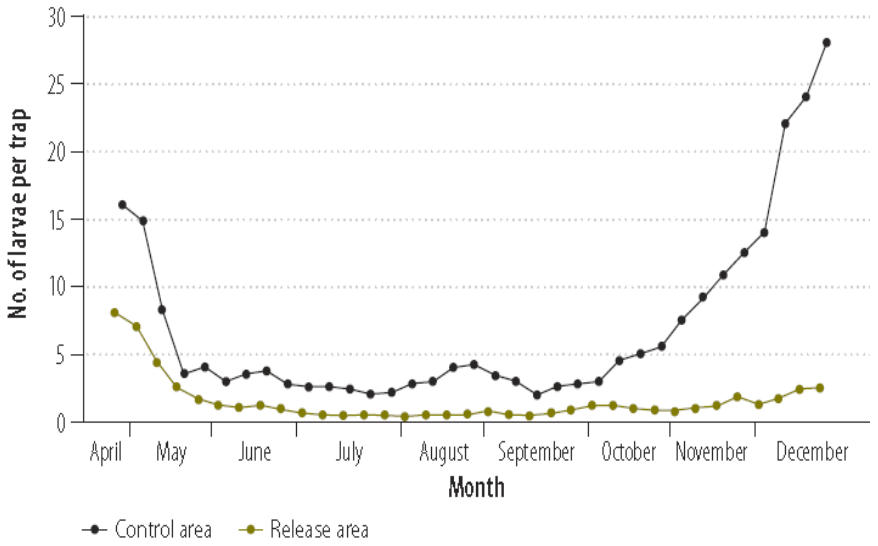
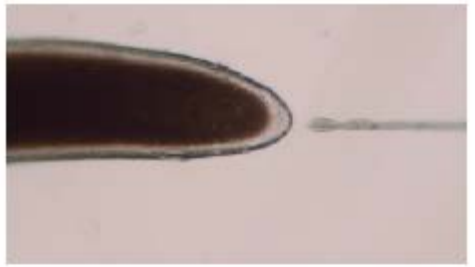


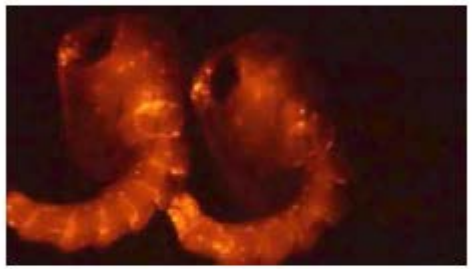
Expression of lethal gene is inhibited by tetracycline

Fig. 2. **Numbers of mosquito larvae in traps set up in a control area where males of the transgenic OX513A strain of *Aedes aegypti* were released, Piracicaba county, Brazil, 2015**

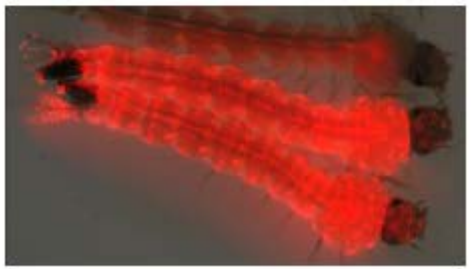




Synthetic DNA with a lethal gene is injected into a mosquito egg.



Larvae of OX513A grow in an antidote that keeps them alive.



The OX513A mosquito at bottom has a marker, unlike the wild mosquito at

Winskill P et al. (2015) Dispersal of Engineered Male Aedes aegypti Mosquitoes. PLoS Negl Trop Dis 9(11): e0004156.
Use of transgenic Aedes aegypti in Brazil: risk perception and assessment Bull World Health Organ 2016;94:766–771
http://edition.cnn.com/2016/03/07/health/zika-florida-gmo-mosquito/index.html (accessed 12/7/2017)
https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm490246.htm

Thank you