MOUNT AUBURN HOSPITAL

HARVARD MEDICAL SCHOOL

Zika: Recommendations to Travelers to Endemic Countries

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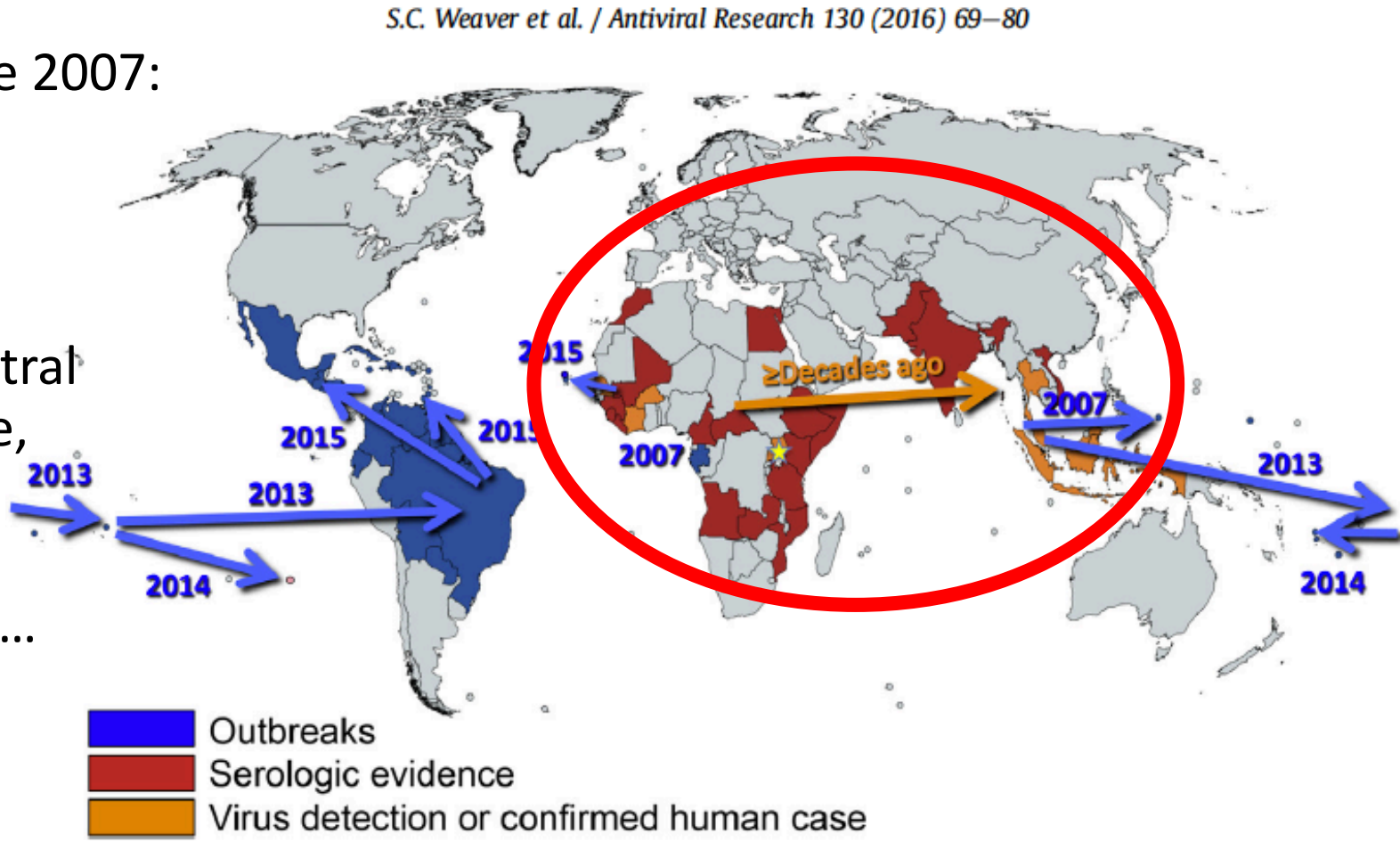
Outline

- Describe guidelines and illustrate how they evolved over time
- Discuss pre-conception recommendations for couples planning pregnancy after travel
- Summarize recommendation on travel and screening for pregnant travelers
- Review guidelines to address travelers to low-burden areas such as Thailand

Zika epidemiology

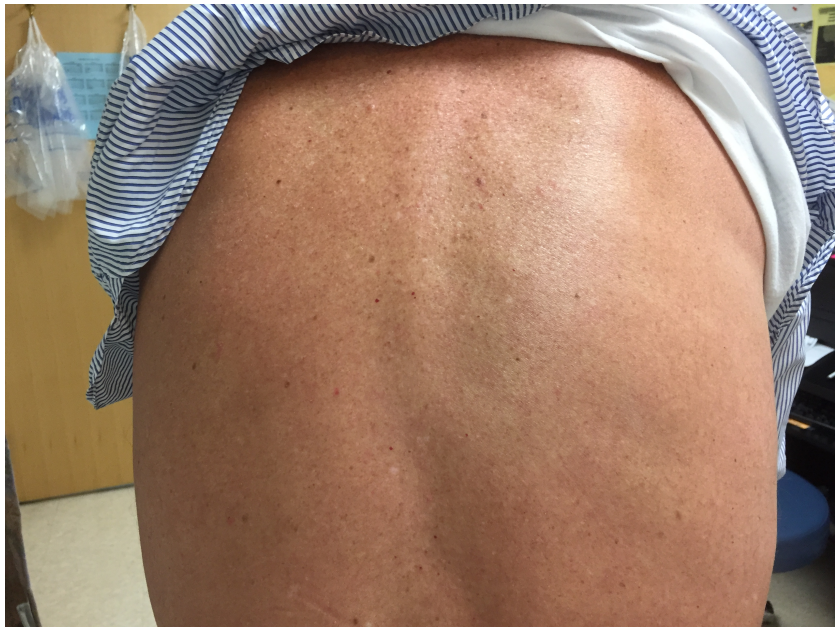
- Human infections sporadic before 2007:
  - Nigeria 1954, 1968, 1971-75
  - Indonesia 1977
  - 1951-99:
  - Uganda, Tanzania, Egypt, Central African Republic, Sierra Leone, Gabon, Senegal…
  - India, Malaysia, Philippines, Thailand, Vietnam, Indonesia…
- Mosquitoes Zika+:
  - Malaysia, Cote d'Ivoire



www.cdc.gov/zika/geo/active-countries.html (February 23, 2017)

Zika: clinical presentation

- Incubation: 2-7d (≈1-12d)
- Symptoms: 80% asymptomatic
  - Fever – usually 2 days
  - Rash, conjunctivitis
  - Arthralgia, myalgia - up to 1 week
- Severe: link to GBS, myelitis, encephalitis, sensory polyneuropathy, autoimmune disorder
- Congenital Zika syndrome



Chen LH. Ann Int Med 2016.

Initial travel recommendations

Prior to departure

Health authorities should advise travelers heading to any country with documented circulation of dengue, chikungunya, and/or Zika virus to take the necessary measures to protect themselves from mosquito bites, such as using repellents, appropriate clothing that minimize skin exposure, and using insecticides or nets. It is also important to inform travelers of the symptoms of dengue, chikungunya, or Zika virus, in order to assist them in identifying it promptly during their trip. This advice could be relayed through travel medicine services, clinics, travel health web pages of the Ministry of Health, or other relevant government web pages.

While visiting places with dengue, chikungunya and/or Zika virus transmission

Advise travelers to:

- Take appropriate measures to protect themselves from mosquito bites through use of repellents or use of appropriate clothes that minimize skin exposure.
- Avoid mosquito-infested areas.
- Use nets and/or insecticide.
- Recognize symptoms of dengue, chikungunya, and Zika virus and seek professional health care if any of these symptoms occur.

Upon returning

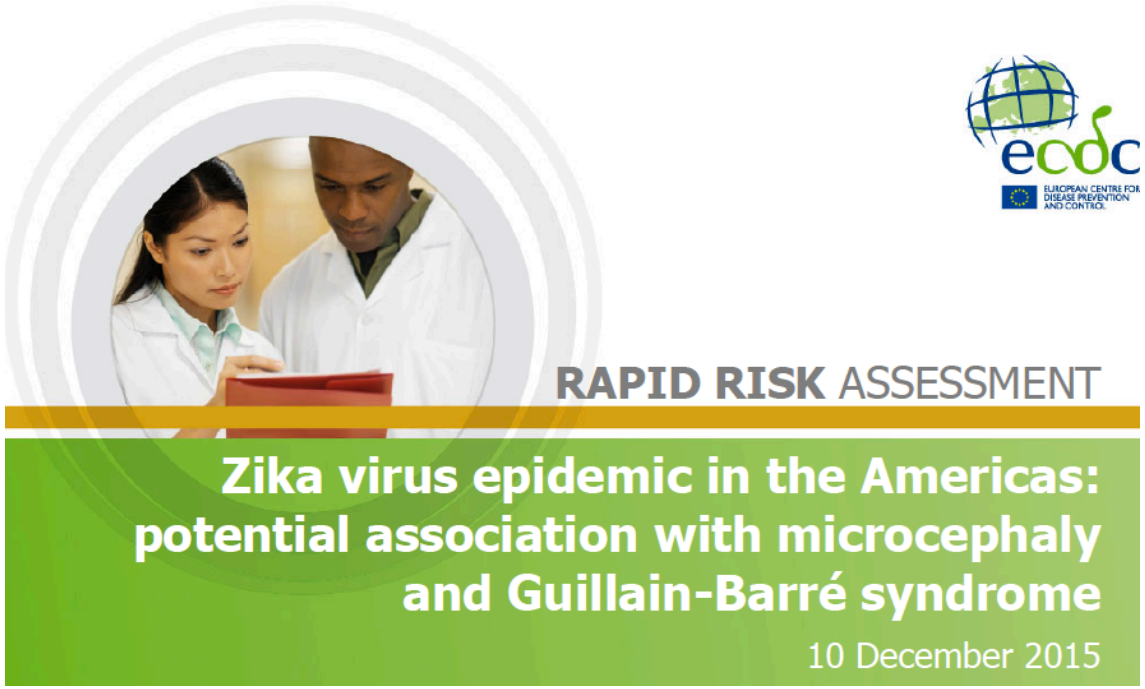
Advise travelers returning home, that if they suspect they have dengue, chikungunya, or Zika virus they should contact their health care provider.

Recommendations evolved with new information

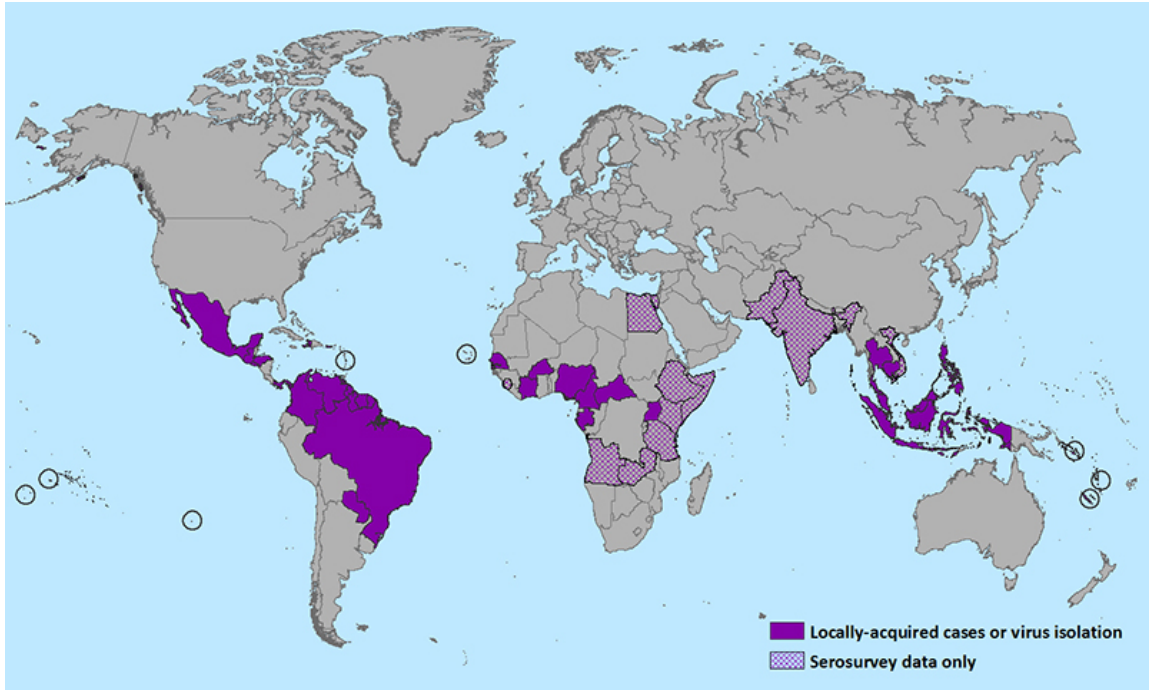
- October 2015: Brazil MOH reported unusual increase of microcephaly in Pernambuco, Paraiba and Rio Granded do Norte.
- November 11, 2015: Brazil declared national public health emergency due to increasing numbers of microcephaly.

Recommendations evolved: congenital Zika

December 2015: ECDC Rapid Risk Assessment

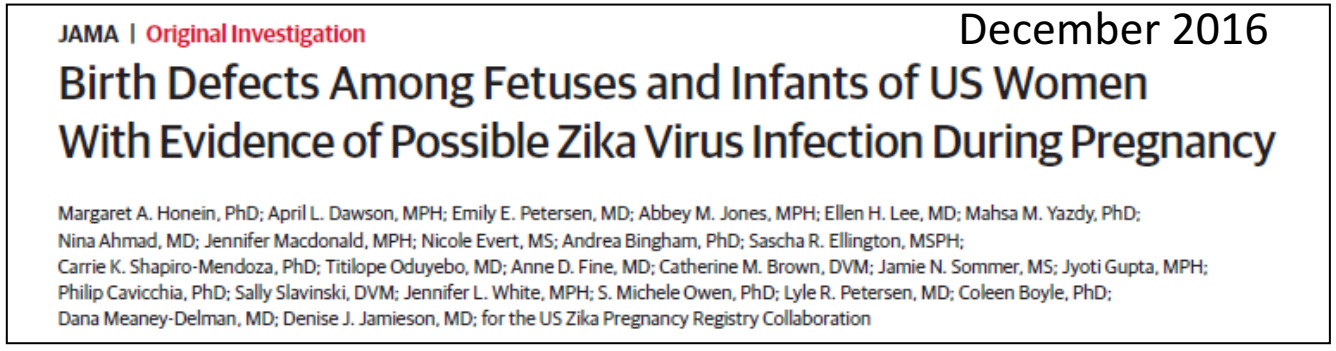


January 2016: CDC Alert Level 2 Enhanced Precautions: preventing mosquito bites



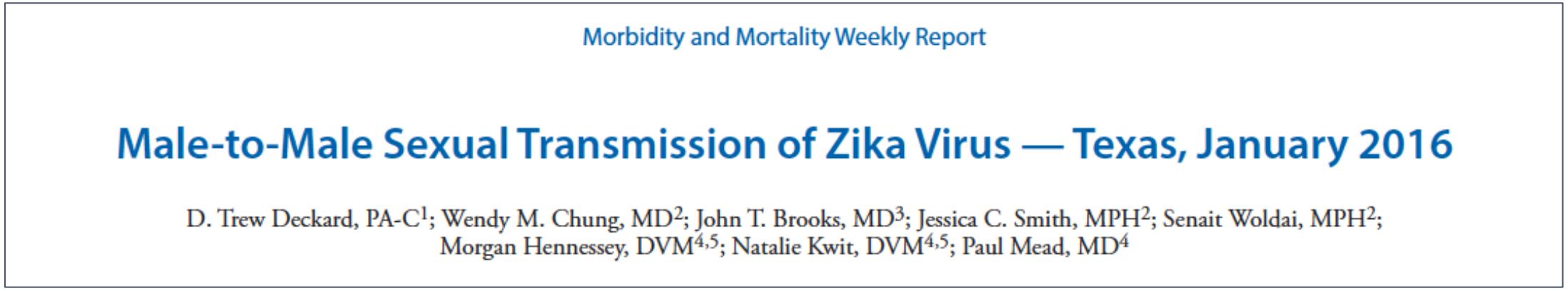
Microcephaly: causality

- Consensus: Zika virus infection can cause fetal congenital anomalies
- Other malformations: ocular abnormalities, hearing loss, hydrops fetalis, impaired growth, fetal loss, arthrogryposis
- CDC estimated risk for 1st trimester infection= 0.88% - 13.2%
- Pregnancy Registry with births: 6% fetuses/infants had birth defects
  - Infection in 1st trimester: 11% had defects



Sexual transmission: earlier reports

- November 2015: sexual transmission reported in German ex. Haiti



Morbidity and Mortality Weekly Report

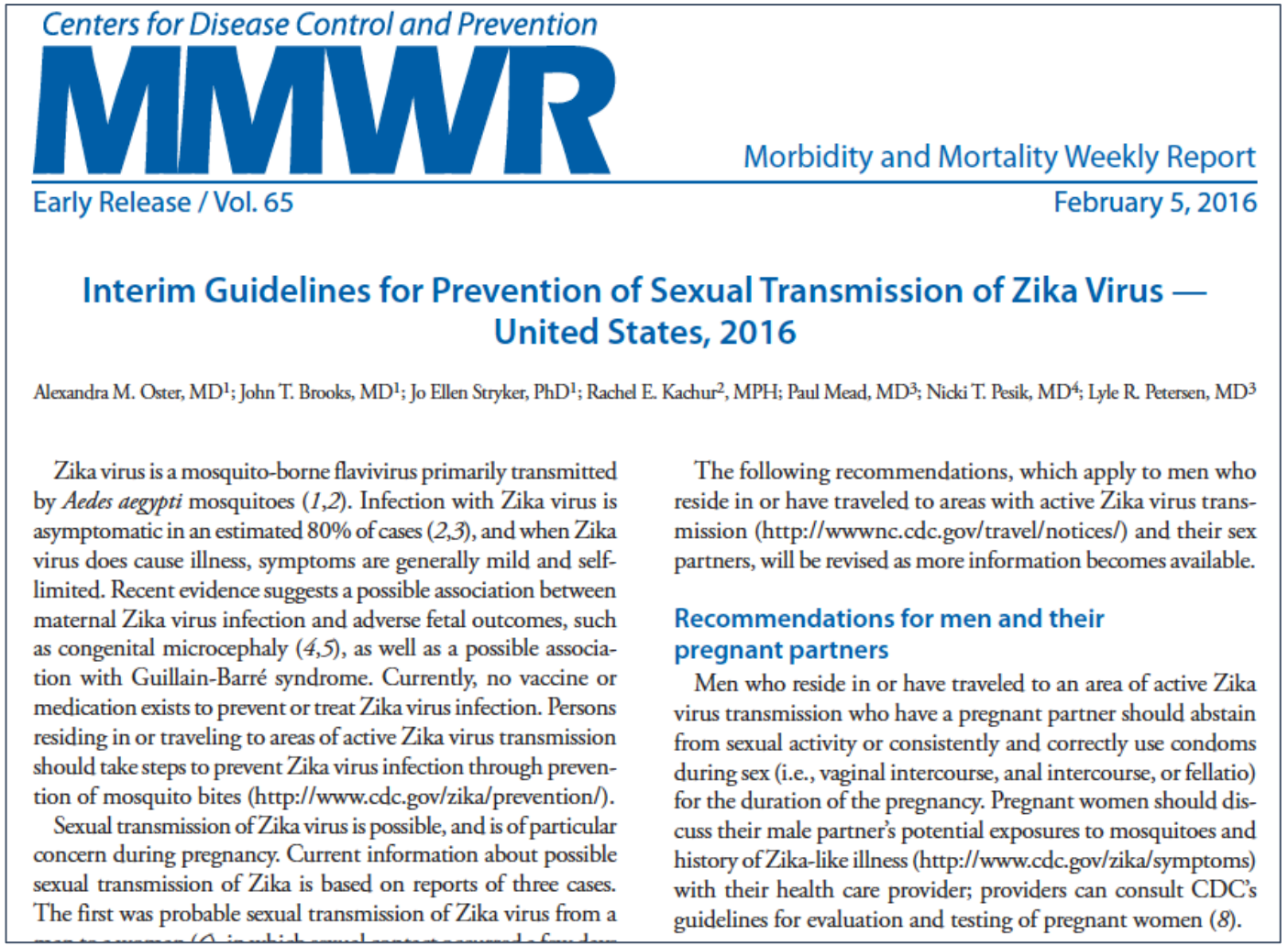
Male-to-Male Sexual Transmission of Zika Virus — Texas, January 2016

D. Trew Deckard, PA-C[1]; Wendy M. Chung, MD[2]; John T. Brooks, MD[3]; Jessica C. Smith, MPH[2]; Senait Woldai, MPH[2]; Morgan Hennessey, DVM[4,5]; Natalie Kwit, DVM[4,5]; Paul Mead, MD[4]

- Foy B, et al. Emerg Infect Dis 2011. (2008)
- Musso D, et al. Emerg Infect Dis 2015. (2013)
- Atkinson B, et al. Emerg Infect Dis 2016. (2014)

Recommendations evolved again: sexual transmission

- February 2016: health authorities published guidance to prevent sexual transmission –
- WHO, CDC, ECDC, Health Canada/CATMAT, Health Protection England/ NaTHNaC



Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 65
February 5, 2016

Interim Guidelines for Prevention of Sexual Transmission of Zika Virus — United States, 2016

Alexandra M. Oster, MD[1]; John T. Brooks, MD[1]; Jo Ellen Stryker, PhD[1]; Rachel E. Kachur[2], MPH; Paul Mead, MD[3]; Nicki T. Pesik, MD[4]; Lyle R. Petersen, MD[3]

Zika virus is a mosquito-borne flavivirus primarily transmitted by *Aedes aegypti* mosquitoes (*1*,*2*). Infection with Zika virus is asymptomatic in an estimated 80% of cases (*2*,*3*), and when Zika virus does cause illness, symptoms are generally mild and self-limited. Recent evidence suggests a possible association between maternal Zika virus infection and adverse fetal outcomes, such as congenital microcephaly (*4*,*5*), as well as a possible association with Guillain-Barré syndrome. Currently, no vaccine or medication exists to prevent or treat Zika virus infection. Persons residing in or traveling to areas of active Zika virus transmission should take steps to prevent Zika virus infection through prevention of mosquito bites (http://www.cdc.gov/zika/prevention/).

Sexual transmission of Zika virus is possible, and is of particular concern during pregnancy. Current information about possible sexual transmission of Zika is based on reports of three cases. The first was probable sexual transmission of Zika virus from a

The following recommendations, which apply to men who reside in or have traveled to areas with active Zika virus transmission (http://wwwnc.cdc.gov/travel/notices/) and their sex partners, will be revised as more information becomes available.

Recommendations for men and their pregnant partners

Men who reside in or have traveled to an area of active Zika virus transmission who have a pregnant partner should abstain from sexual activity or consistently and correctly use condoms during sex (i.e., vaginal intercourse, anal intercourse, or fellatio) for the duration of the pregnancy. Pregnant women should discuss their male partner's potential exposures to mosquitoes and history of Zika-like illness (http://www.cdc.gov/zika/symptoms) with their health care provider; providers can consult CDC's guidelines for evaluation and testing of pregnant women (*8*).

Prevention of sexual transmission of Zika virus

Interim guidance update

6 September 2016

WHO/ZIKV/MOC/16.1 Rev.3

World Health Organization

26 February 2016

The United States reports two sexually transmitted cases of Zika virus.

Image source: WHO/PAHO

This review comprises recent evidence on sexual transmission of Zika virus which includes sexual transmission from

- Asymptomatic males to their female partners,
- Symptomatic female to her male partner,
- Longer shedding of Zika virus in semen.

Based on this new evidence, the recommended length of time for safer sex practices for asymptomatic males

2. Sexual transmission of Zika virus

2.1 Current evidence

2.1.1 Summary of publications

As of 26 August 2016, a total of 17 studies or reports have been published on sexual transmission of Zika virus, including the following:

- Seven studies on symptomatic male to female transmission[2-8]
- One study on male to male transmission[9]
- One study on female to male transmission[10]
- Two studies on asymptomatic male to female transmission[11-12]
- Four case-reports reported by International Health Regulations National Focal Points[13-16]
- Two case-reports described through government/news media[17-18]

In addition, eight studies have been published on the presence of Zika virus in semen.[19-26]

Sexual transmission and other transmission

- Urine, saliva – live virus 6 days, RNA up to 91 days
  - RNA longer in urine (2-3 weeks), longest in whole blood (58 days)
- Semen – 24 days live virus; 46-69 days outliers; 188 days RT-PCR (RNA non-infective)
- Vaginal secretions – 3 days, cervical mucus 11 days, both by RT-PCR
- Breast milk + (infectious virus)
- Blood transfusion – platelet

Gourinat AC et al. EID 2015; Musso D et al. J Clin Virol 2015; Prisant N et al. Lancet ID 2016; Nicastri E et al. EID 2016; Dupont-Rouzeyrol M et al. Lancet 2016.

Pre-conception travel advice for travelers going to areas with active Zika virus transmission

Preconception planning	
Women	• Wait at least 8 weeks before attempting conception. *WHO: wait 6 months
Men	• Practice safe sex for 6 months.

Oduyebo T et al. MMWR 65(29); Petersen EE et al. MMWR 65(39);WHO/ZIKV/MOC/16.1 Rev.3.

Travel advice for pregnant women going to areas with risk for Zika virus transmission

Persons with risk for pregnancy and fetal complications	
Pregnant women	• Avoid travel. • If travel cannot be avoided, talk to a healthcare provider before travel, and optimize use of anti-vector measures.
Partners of pregnant women	• Practice safe sex or abstain from sexual activity for the duration of the pregnancy.

Oduyebo T et al. MMWR 65(29); Petersen EE et al. MMWR 65(39); WHO/ZIKV/MOC/16.1 Rev.3.

Advice for pregnant women residing in areas with ongoing risk for exposure to Zika: CDC

- Zika virus IgM antibody testing should be done as part of routine obstetric care during the 1st and 2nd trimesters
- Immediate rRT-PCR testing if IgM results are positive or equivocal

Oduyebo et al. MMWR 2016: 65(29)

Travel recommendations: additional messages

- Even if they do not feel sick, travelers returning from an area with Zika should take steps to prevent mosquito bites for 3 weeks so they do not spread Zika to uninfected mosquitoes.

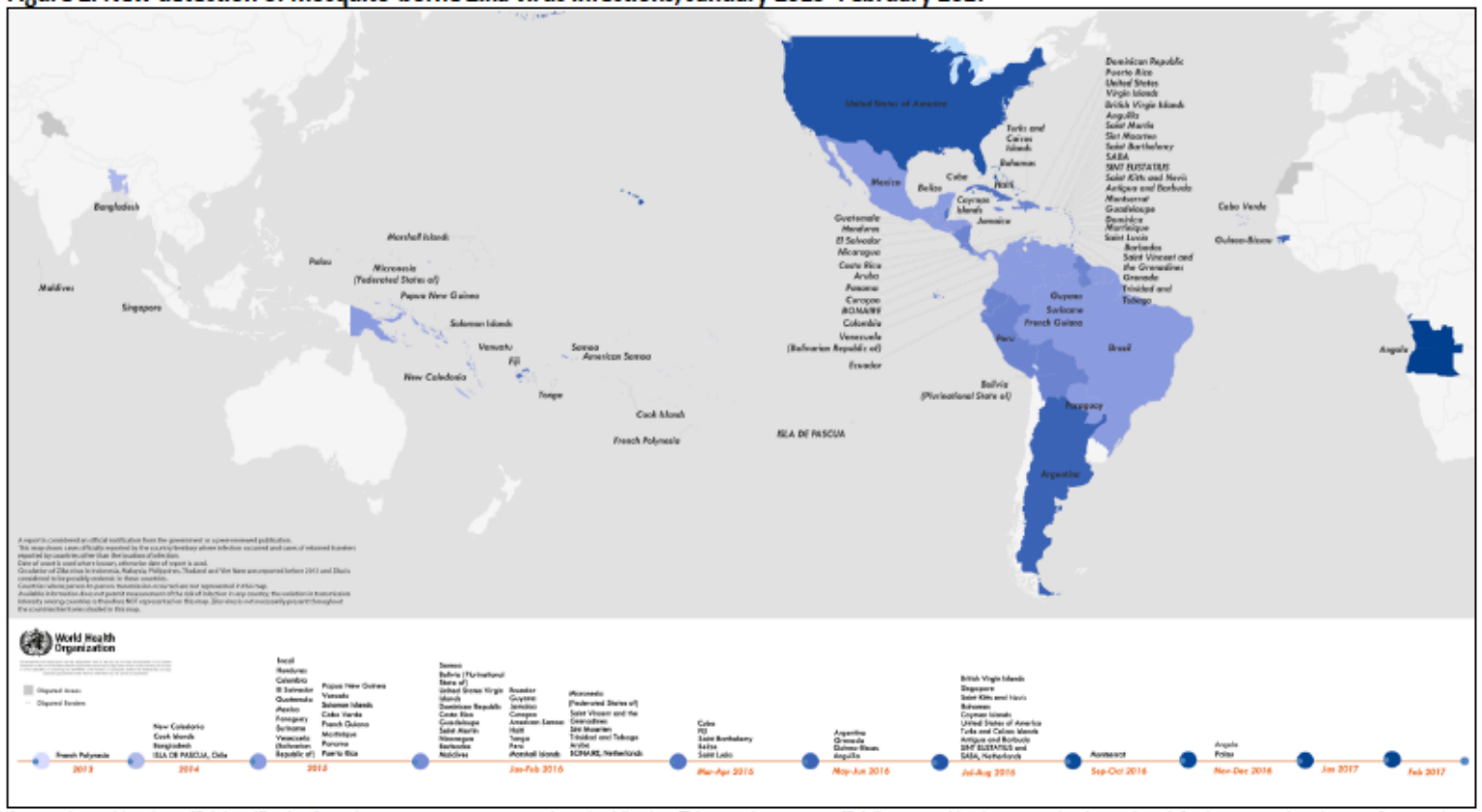
- The mosquito vectors do not live at elevations >6,500 feet (2,000 meters). Travelers who plan to be only in areas above this elevation are at a very low risk of getting Zika from a mosquito.

CDC. Key Messages – Zika Virus Disease. October 4, 2016

Current worldwide situation: WHO

- 76 countries/territories reported mosquito-borne Zika since 2007 (70 from 2015 on):
  - 59 reported outbreak from 2015
  - 7 possible endemic transmission or local mosquito-borne Zika
  - 10 with local mosquito-borne Zika pre-2015, no case 2016/2017, or outbreak over
- 13 countries: person-to-person
- 21 countries: increased GBS

Figure 2. New detection of mosquito-borne Zika virus infections, January 2013–February 2017



A report is considered an official notification from the government or a peer-reviewed publication. This map shows cases officially reported by the country/territory where infection occurred, and cases of returned travellers reported by countries other than the location of infection. Date of onset is used where known, otherwise date of report is used. Circulation of Zika virus in Indonesia, Malaysia, Philippines, Thailand and Viet Nam was reported before 2013, and Zika is considered to be possibly endemic in these countries. Countries where person-to-person transmission occurred are not represented in this map. Available information does not permit measurement of the risk of infection in any country; the variation in transmission intensity among countries is therefore NOT represented on this map. Zika virus is not necessarily present throughout the countries/territories shaded in this map.

Zika virus in low burden areas

http://apps.who.int/iris/bitstream/10665/254507/1/zikasitrep2Feb17-eng.pdf?ua=1

Table 1. Countries and territories that have reported mosquito-borne Zika virus transmission

Classification	WHO Regional Office	Country / territory	Total
Category 1: Countries with a reported outbreak from 2015 onwards[#]	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 – Netherlands; Brazil; British Virgin Islands; Cayman Islands; Colombia; Costa Rica; Cuba; Curaçao; Dominica; Dominican Republic; Ecuador; El Salvador; French Guiana; Grenada; Guadeloupe; Guatemala; Guyana; Haiti; Honduras; Jamaica; Martinique; Mexico; Montserrat; Nicaragua; Panama; Paraguay; Peru; Puerto Rico; Saint Barthélemy; Saint Kitts and Nevis; Saint Lucia; Saint Martin; Saint Vincent and the Grenadines; Sint Maarten; Suriname; Trinidad and Tobago; Turks and Caicos; United States of America; United States Virgin Islands; Venezuela (Bolivarian Republic of)	48
	WPRO	American Samoa; Fiji; Marshall Islands; Micronesia (Federated States of); Palau; Samoa; Singapore; Tonga	8
Subtotal			59
Category 2: Countries with possible endemic transmission or evidence of local mosquito-borne Zika infections in 2016 or 2017	SEARO	Indonesia; Maldives; Thailand	3
	WPRO	Malaysia; New Caledonia; Philippines; Viet Nam	4
Subtotal			7
Category 3: Countries with evidence of local mosquito-borne Zika infections in or before 2015, but without documentation of cases in 2016 or 2017, or outbreak terminated	AFRO	Gabon**	1
	PAHO/AMRO	ISLA DE PASCUA – Chile**	1
	SEARO	Bangladesh**	1
	WPRO	Cambodia**; Cook Islands**; French Polynesia**; Lao People's Democratic Republic; Papua New Guinea; Solomon Islands; Vanuatu	7
Subtotal			10
Total			76

[#]The wording has been revised in recognition of the fact that a country that has had a first outbreak since 2015 and in which that outbreak has since terminated, may again report a new outbreak or cases which would qualify the country to be re-included in category 1.

***These countries and territories have not reported Zika virus cases in 2015, 2016 or 2017.*

Widespread transmission in the past three months

Sporadic transmission in the past three months

Past transmission (2007 – three months ago)

EU/EEA Member States, including outermost regions

Other countries and territories

Maritime Exclusive Economic Zones for non-visible areas

ECDC. Map produced on 9 Feb 2017

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

- Zika Virus in Southeast Asia
- Guidelines for US Citizens and Residents Living in Areas with Ongoing Zika Virus Transmission
- Guidelines for Travelers Visiting Friends and Family in Areas with Chikungunya, Dengue, or Zika
- Visiting Friends or Family in an Area with Zika?
- Find a Clinic +
- Disease Directory
- Resources +
- Yellow Book +
- Partners +
- Mobile Apps
- RSS Feeds

Zika Travel Notices

- Zika Virus in Cape Verde
- Zika Virus in Mexico
- **Asia**
  Currently includes: Singapore
- **The Caribbean**
  Currently includes: Anguilla; Antigua and Barbuda; Aruba; The Bahamas; Barbados; Bonaire; British Virgin Islands; Cayman Islands; Cuba; Curaçao; Dominica; Dominican Republic; Grenada; Guadeloupe; Haiti; Jamaica; Martinique; Montserrat; the Commonwealth of Puerto Rico, a US territory; Saba; Saint Barthelemy; Saint Kitts and Nevis; Saint Lucia; Saint Martin; Saint Vincent and the Grenadines; Sint Eustatius; Sint Maarten; Trinidad and Tobago; Turks and Caicos Islands; US Virgin Islands
- **Central America**
  Currently includes: Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama
- **The Pacific Islands**
  Currently includes: American Samoa, Fiji, Marshall Islands, Micronesia, New Caledonia, Palau, Papua New Guinea, Samoa, Tonga
- **South America**
  Currently includes: Argentina, Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Peru, Suriname, Venezuela

- Zika Virus Health Advisory Infographics
- Questions and Answers: Zika risk at high elevations

Special Populations

- Going to Visit Friends or Family in an Area with Zika?
- Guidelines for Travelers Visiting Friends and Family in Areas with Chikungunya, Dengue, or Zika
- Guidelines for US Citizens and Residents Living in Areas with Ongoing Zika Virus Transmission

Special Travel Considerations for Endemic Countries in Southeast Asia

Zika Virus in Southeast Asia

Travelers have returned from certain areas of Southeast Asia with Zika virus infection. These countries have either reported local Zika virus transmission or are next to countries with known Zika virus transmission. Because of this, CDC recommends pregnant women should consult with their health care provider and consider postponing nonessential travel to countries listed below. Travel notices have not been issued for these destinations but would be considered if the number of cases rises to the level of an outbreak. Check this page for the most up-to-date information before you make travel plans.

Currently includes: Brunei, Burma (Myanmar), Cambodia, Indonesia, Laos, Malaysia, Maldives, Philippines, Thailand, Timor-Leste (East Timor), Vietnam

Other Countries with Endemic Zika

Some countries in Africa, the Pacific Islands, and Asia have reported Zika in the past and may report occasional new cases. The risk to travelers in these endemic countries is likely much lower than it is in countries with Zika outbreaks (see Q&A: Zika Risk in Countries with Endemic Zika). Because Zika infection in a pregnant woman can cause severe birth defects, pregnant women should consult with their health care provider and, if they decide to travel, should strictly follow steps to prevent mosquito bites during the trip. Travel notices have not been issued for these destinations but would be considered if the number of cases rises to the level of an outbreak. Check this page for the most up-to-date information before you make travel plans.

Africa: Angola, Benin, Burkina-Faso, Cameroon, Central African Republic, Côte d'Ivoire, Egypt, Ethiopia, Gabon, Guinea-Bissau, Kenya, Liberia, Mali, Mozambique, Niger, Nigeria, Senegal, Sierra Leone, Somalia, Tanzania, Togo, Uganda, Zambia

Asia: Bangladesh, India, Pakistan

The Pacific Islands: Easter Island, Vanuatu

Low burden areas?

	Country report of Zika	WHO	CDC	ECDC
Thailand	**October 2016**: 2 cases of babies with microcephaly	**5 Feb to 14 April 2016**: viral circulation, past transmission, with or without ongoing transmission	Endemic, risk to travelers is low	**21 Jan to 3 June 2016**: autochthonous or sporadic or past transmission
		7 July 2016 to present: Category 2	**30 Sep 2016:** Included in CDC's Southeast Asia Regional special considerations notice	**8 July 2016 to present:** changed to widespread transmission

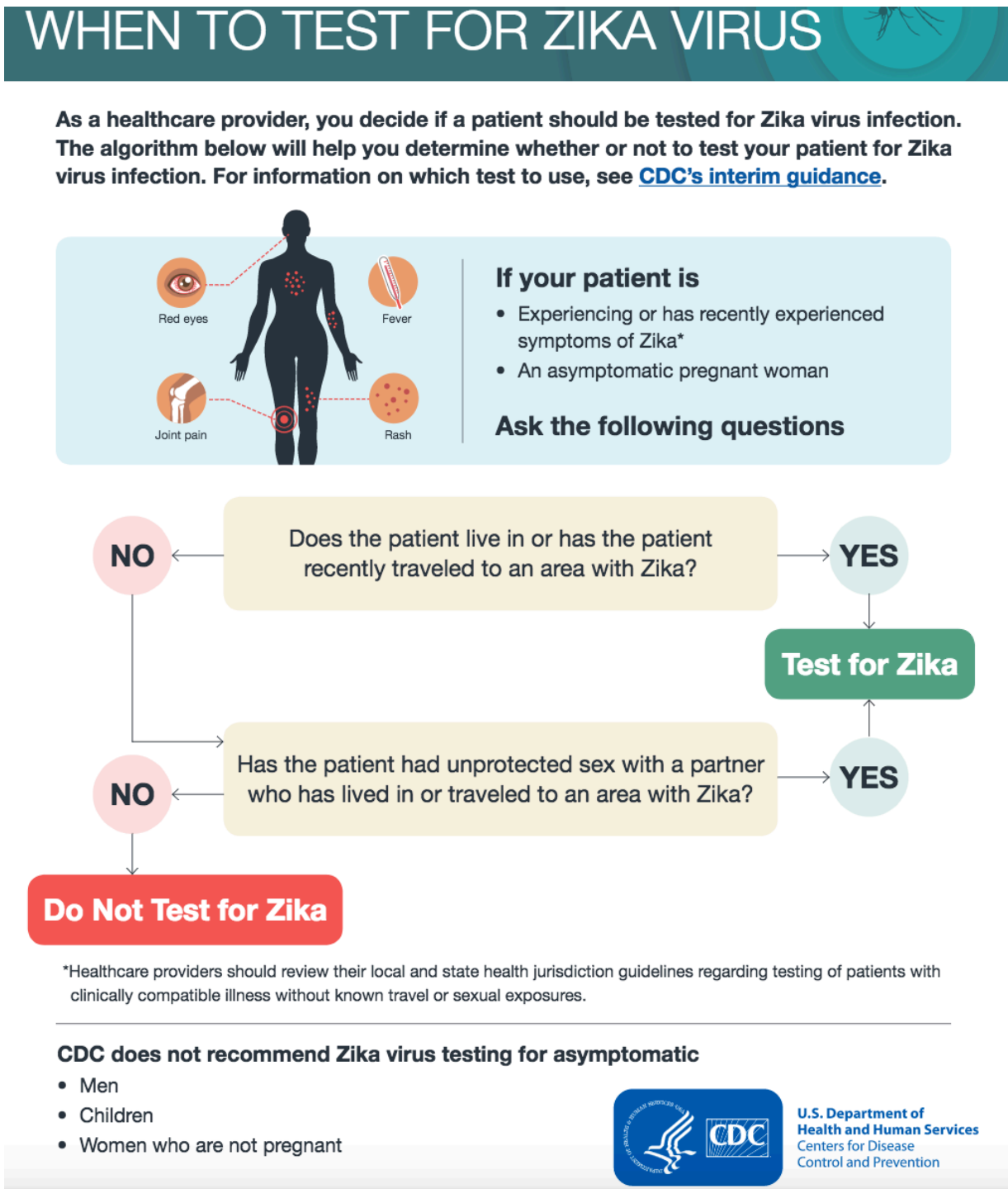
Data compilation: Karin Leder

Recommendations for low-burden areas

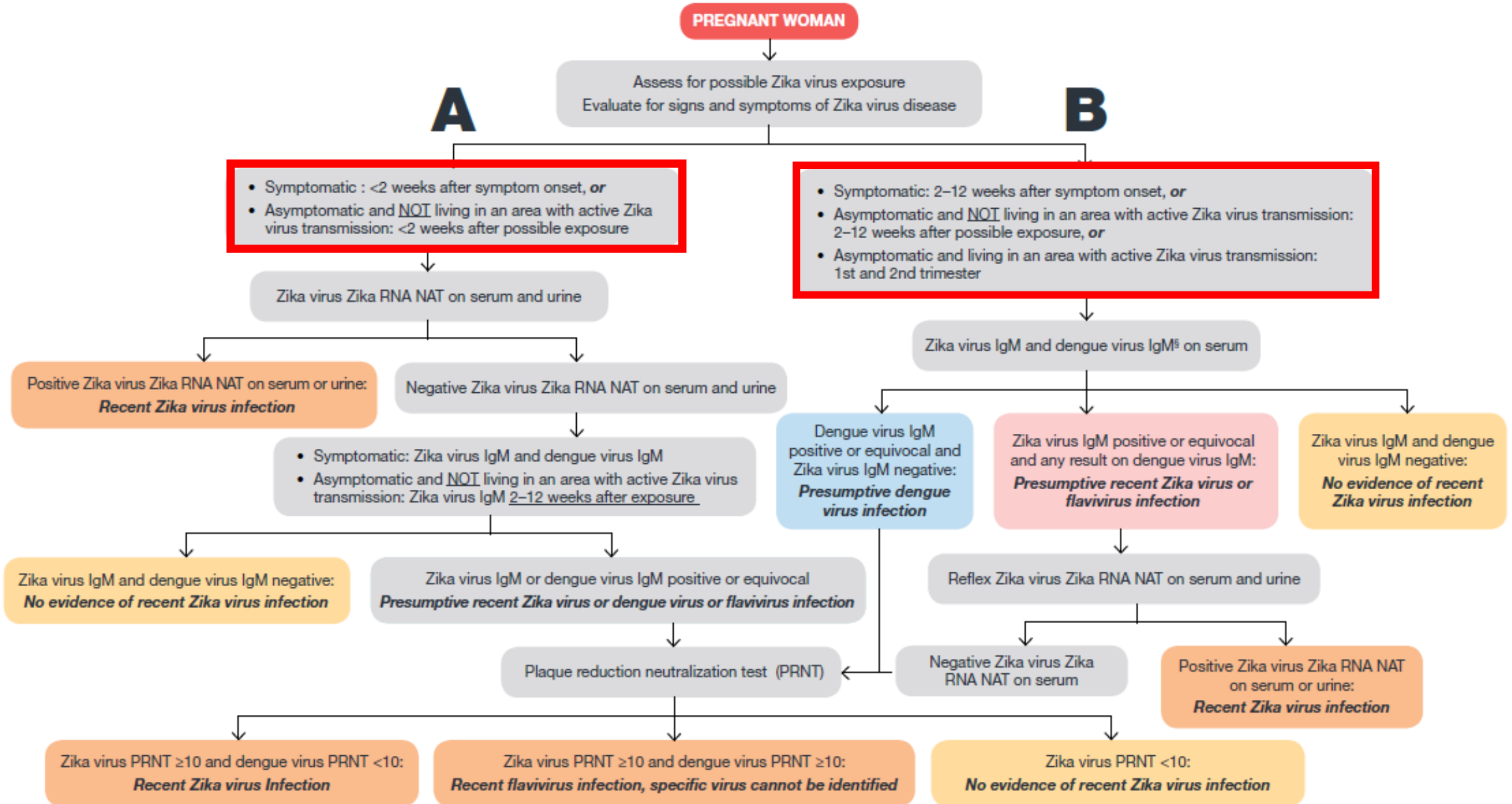
	Risk categories	"Low risk" areas
WHO	• Outbreaks from 2015 onwards • Possible endemic transmission 2007 to 2016-2017 • Evidence of transmission 2007-2015	• **Possible endemic transmission or evidence of local mosquito-borne Zika infections in 2016 or 2017 with the reporting period beginning in 2007**
CDC	• Epidemic • Endemic • "Special considerations" notice for Southeast Asia on September 30th 2016	• **Pregnant women should consult with their health care provider and consider postponing nonessential travel**
ECDC	• Increasing or widespread transmission >3 months • Sporadic transmission (<10 in 1 area within 3 months) • Past transmission (2007 up to 3 months ago)	• **Consider postponing non-essential travel**
Public Health England	• High (active transmission in last 3 months) • Moderate (sporadic transmission in last 3 months) • Low (no cases in last 3 months)	• **No Zika specific advisory… should seek advice from healthcare provider before travel for an individual risk assessment and to**

After travel: tests and criteria

- Molecular: **PCR (CDC Trioplex rRT-PCR)**
  - Serum, CSF, urine, amniotic fluid
  - Whole blood – more sensitive
- Serologic:
  - **Zika IgM MAC-ELISA**: serum, CSF
  - **Plaque reduction neutralization test (PRNT)**



Testing and interpretation recommendations[*,†,§,¶] for a pregnant woman with possible exposure to Zika virus[**] — United States (including U.S. territories)



https://www.cdc.gov/zika/pdfs/testing_algorithm.pdf

Clinical management of a pregnant woman with suspected Zika virus infection

Interpretation of Laboratory Results*	Prenatal Management	Postnatal Management
Recent Zika virus infection	• Consider serial ultrasounds every 3–4 weeks to assess fetal anatomy and growth† • Decisions regarding amniocentesis should be individualized for each clinical circumstance§	**LIVE BIRTHS:** • Infant serum and infant urine should be tested for Zika virus Zika RNA NAT. Infant serum should be tested for Zika IgM. If CSF is obtained for other reasons, it can also be tested.** • Zika virus Zika RNA NAT and IHC staining of umbilical cord and placenta is recommended.¶ **FETAL LOSSES:** • Zika virus Zika RNA NAT and IHC staining of fetal tissues is recommended.¶
Recent flavivirus infection; specific virus cannot be identified		
Presumptive recent Zika virus infection***	• Consider serial ultrasounds every 3–4 weeks to assess fetal anatomy and growth† • Amniocentesis might be considered; decision should be individualized for each clinical circumstance§	**LIVE BIRTHS:** • Infant serum and infant urine should be tested for Zika virus Zika RNA NAT. Infant serum should be tested for Zika IgM. If CSF is obtained for other reasons, it can also be tested. ** • Zika virus Zika RNA NAT and IHC staining of umbilical cord and placenta should be considered.¶ **FETAL LOSSES:** • Zika virus Zika RNA NAT and IHC staining of fetal tissues should be considered.¶
Presumptive recent flavivirus infection***		
Recent dengue virus infection	• Clinical management in accordance with existing guidelines (http://apps.who.int/iris/bitstream/10665/44188/1/9789241547871_eng.pdf).	
No evidence of Zika virus or dengue virus infection	• Prenatal ultrasound to evaluate for fetal abnormalities consistent with congenital Zika virus syndrome.† ◆ Fetal abnormalities present: repeat Zika virus Zika RNA NAT and IgM test; base clinical management on corresponding laboratory results. ◆ Fetal abnormalities absent: base obstetric care on the ongoing risk of Zika virus exposure to the pregnant woman.	

https://www.cdc.gov/zika/pdfs/testing_algorithm.pdf

Persistence of Zika virus in body fluids (NEJM)

	Median (d)	95% CI (d)	95th percentile(d)	95% CI (d)
Serum	14	11-17	54	43-64
Urine	8	6-10	39	31-47
Semen	34	31-47	81	64-98

Intermittently positive samples with intervals of:

- Serum – 14-62 days
- Urine – 14-35 days
- Semen – 21-36 days

Paz-Bailey G, et al. NEJM 2017.

Summary I: approach to travel and Zika virus

- Current recommendations:
  - Pregnant women from non-endemic areas: avoid travel
  - Pre-conception planning: wait 8 weeks (women) and 6 months (men) after possible exposure
  - Expatriate pregnant women living in areas with ongoing risk: routine testing with Zika IgM during 1st& 2nd trimesters; rRT-PCR if positive/equivocal

Summary II: approach to travel and Zika virus

- Health authorities differ in defining risk and designating risk areas
- Desirable to harmonize risk designations
- Low burden areas: “special considerations” risk category
- Recommendations continue to evolve
- Latest data may lead to modification
  - More than half of the participants had detectable viral RNA in urine for ≥1 week after symptom onset, in serum for 2 weeks, and in semen for >1 month.
  - Up to 5% had detectable viral RNA in urine for 6 weeks, in serum for 8 weeks, in semen for 3 months.
  - ZIKV RNA was infrequently detected in saliva and vaginal secretions.
- Sensitive, specific, and accessible diagnostic tests are needed

Resources

- www.cdc.gov/Zika
- www.who.int/emergencies/zika-virus/en/
- www.paho.org
- www.ecdc.europa.eu

TOP 5 THINGS EVERYONE NEEDS TO KNOW ABOUT ZIKA

1 Zika primarily spreads through infected mosquitoes. You can also get Zika through sex.

Many areas in the United States have the type of mosquitoes that can spread Zika virus. These mosquitoes are aggressive daytime biters and can also bite at night. Also, Zika can be passed through sex from a person who has Zika to his or her sex partners.

2 The best way to prevent Zika is to prevent mosquito bites.

- Use insect repellent. It works!
- Wear long-sleeved shirts and long pants.
- Stay in places with air conditioning or window and door screens.
- Remove standing water around your home.

3 Zika is linked to birth defects.

Zika infection during pregnancy can cause a serious birth defect called microcephaly that is a sign of incomplete brain development. If you have a partner who lives in or has traveled to an area with Zika, do not have sex, or use condoms every time you have sex during your pregnancy.

4 Pregnant women should not travel to areas with Zika.

If you must travel to one of these areas, talk to your healthcare provider first and strictly followsteps to prevent mosquito bites during your trip.

5 Returning travelers infected with Zika can spread the virus through mosquito bites.

If you get infected with Zika and a mosquito bites you, you can pass the virus to the mosquito. The infected mosquito bites other people, who get infected. Returning travelers should also use condoms or not have sex if they are concerned about passing it to their partners through sex.