



## More Than Just a Fly on the Wall: Mosquito-borne Infections

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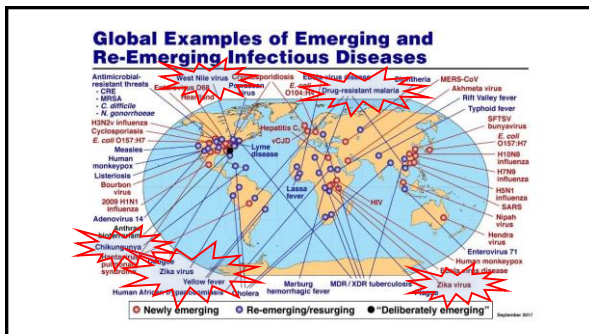
 

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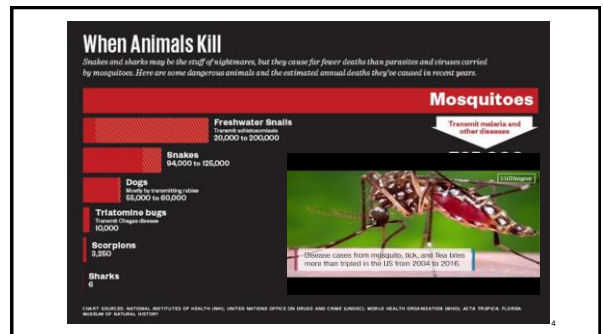


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**OUTBREAK**  
*Epidemic Risk Connected World*  
Open through 2021

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## Mosquito-Borne Diseases in Delaware

State: 73-year-old man is first death due to West Nile since 2012

By David Newman, Delaware News Journal | Published 10:11 p.m. ET Sept. 16, 2014

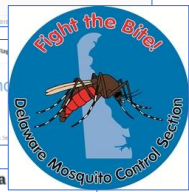
DELAWARE NEWS

DNREC's Mosquito Control Section announced expanded detection of Eastern Equine Encephalitis

Department of Natural Resources and Environmental Control | Division of Fish and Wildlife | Data Provided: Thursday, 9/16/2014

Second case of chikungunya in Delaware

By Shirley Hill | September 4, 2014



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## Learning Objectives:

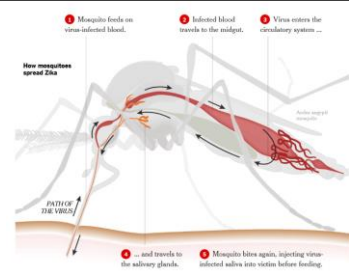
- Understand the enemy: Mosquitos as disease carriers and how mosquito-borne infections can emerge in new regions
- Be able to recognize the important mosquito-borne infections currently present in Delaware
  - West Nile Virus infections
  - Arboviral encephalitis
- Become familiar with emerging mosquito born diseases in the Western Hemisphere and potential of spread to the US
  - How to differentiate and diagnose emerging mosquito-borne infections in the returned traveler
- Learn what's new in the prevention of mosquito-borne infections in travelers: Malaria and Yellow Fever

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## Learning Objectives:

- Understand the enemy: Mosquitos as disease carriers and how mosquito-borne infections can emerge in new regions

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Source: The Hitchhikers Guide to the Galaxy Earth Edition



@Disney #malaria awareness video at <http://t.co/5Jiqy5lgIH> #TBT



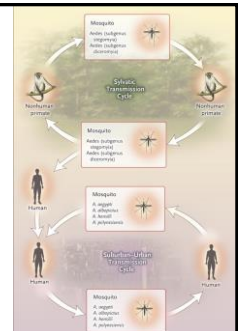
Source: US Army Environmental Command

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## Mosquito-borne Diseases in Humans: Requirements

- Competent Mosquito vector
- Reservoir of Infectious pathogens
- Human reservoirs
- AND/OR
- Non-human reservoirs
- Non-immune Human Hosts

Petersen LR et al. N Engl J Med 2016;374:1552-1563.



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## How Mosquito born infections spread: Another important vector



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## Learning Objectives:

- Be able to recognize the important mosquito-borne infections currently present in Delaware
- West Nile Virus infections
- Arboviral encephalitis

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### Case 1

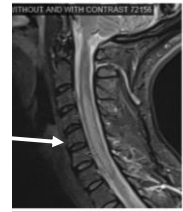
- 45 y.o. woman presents on 9/24/18 with neck pain, tremors, tingling, "numbness" in hands x 3 days; one day of fevers and "tremors" and progressive RUE weakness
- Living in Cape May for the summer, lots of "bug bites"
  - MRI brain negative
  - MRI spine: "elongated right cord lesion from C3-C6"
  - LP: WBC 300 (40% PMN, 34% L, 8% M) 17 RBC Protein 89, Glu 60
- Started on IV acyclovir and methylprednisolone; transferred to CUH
- Exam: non toxic, 100.8 F, mental status normal, supple neck, dysphonia
- Right UE strength 1/5 prox., 3/5 distal, Left UE 3/5 prox, 5/5 distal Reflexes mildly decreased in RUE and RLE, normal sensory exam

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➤ What does she have? How do we prove it? How do we treat her?

### Diagnosis: Neuroinvasive West Nile Virus Infection

Test Name	In Range	Out Of Range	Reference Range
WEST NILE VIRUS AB (IGG, IGM), CSF			
WEST NILE VIRUS ANTIBODY (IGG), CSF		1.63 M	<1.30 index
WEST NILE VIRUS ANTIBODY (IGM), CSF		>5.00 IM	<0.90 index
CRITICAL VALUE REPORT			



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### MMWR MORBIDITY AND MORTALITY WEEKLY REPORT

Outbreak of West Nile-Like Viral Encephalitis — New York, 1999

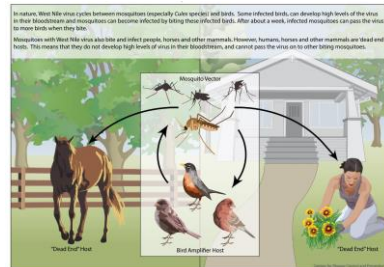
- First appearance in the US in NYC in 1999
- Rapid Spread across the US: 38 States by 2001
- Declared endemic in the US within 10 years
- Leading cause of mosquito-borne disease in the US



Progression of the West Nile Virus Through the Continental United States  
NASA Scientific Visualization Studio, 2002  
<https://svs.gsfc.nasa.gov/2564>

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### West Nile Virus: Transmission Cycle

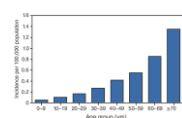
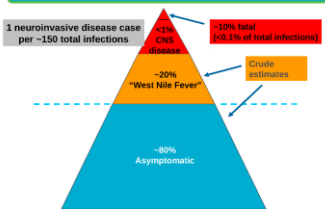


[https://www.cdc.gov/westnile/resources/pdfs/13\\_240124\\_west\\_nile\\_lifecycle\\_birds\\_plainlanguage\\_508.pdf](https://www.cdc.gov/westnile/resources/pdfs/13_240124_west_nile_lifecycle_birds_plainlanguage_508.pdf)

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### The West Nile Virus Infection "Iceberg"

#### West Nile Virus Human infection "Iceberg"



CDC, Average annual incidence\* of West Nile virus neuroinvasive disease by age group — United States, 1999–2008

Source: Quest Diagnostics

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### Clinical Manifestations

#### West Nile Fever: 15-20%

- Incubation 2-6 days (up to 14)
- Acute systemic febrile illness
- Headache
- Weakness
- Myalgia or arthralgia
- Gastrointestinal symptoms
- Transient maculopapular rash
- Generally complete recovery though Sx can linger

#### Neuroinvasive: < 1%

- Aseptic meningitis syndromes: fever, headache, nuchal rigidity
- Encephalitis: altered mental status, seizures, focal neurologic deficits, movement disorders such as tremor or parkinsonism
- Acute Flaccid paralysis (poliovirus like) with involvement of anterior horn cells
- Other: Radiculopathy, Guillain-Barré like illness

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## Neuroinvasive Disease

### Diagnosis

- CSF IgM Antibodies positive 3 to 8 days after Sx, persists 30 to 90 days
- CSF IgG Ab persists years
- Cross reactivity with other flaviviruses (Dengue, Zika...) → plaque reduction assays
- Can send blood/CSF PCR for virus but viremia transient, negative predictive value low

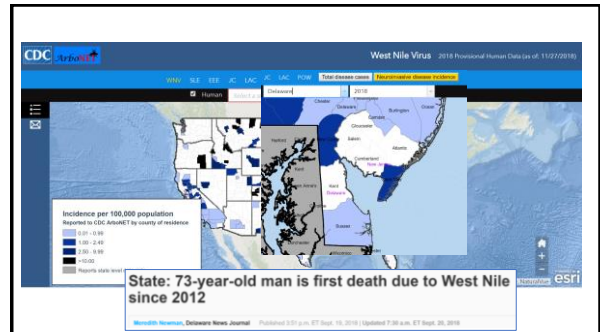
### Treatment

#### West Nile virus disease therapeutics

Review of the literature for healthcare providers

**Overview:** No antiviral or adjunctive therapies are approved or recommended for the treatment of West Nile virus (WNV) disease; clinical management is supportive. There are numerous case reports and case series regarding the use of various products (e.g., standard and hyperimmune polyclonal immune globulin, monoclonal immune globulin, interferon, ribavirin, and corticosteroids) in patients with WNV disease. ...None have shown clear benefit.  
<https://www.cdc.gov/westnile/resources/pdfs/WNV-therapeutics-summary-P.pdf>

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## West Nile Prevention

- Surveillance: Birds, Mosquito pools
- Mosquito control
- Personal Protective Measures
- Blood and organ donor screening
- Vaccination???



**It's Not Too Late This Year for West Nile Vaccination**  
**If you're a horse**

**Infectious Disease News**  
 Decades later, still no vaccine or treatment for West Nile virus

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TABLE 1. Number and percentage of reported cases of West Nile virus and other arboviral diseases, by virus type and selected patient characteristics — United States, 2017

Characteristic	Virus no. (%)				
	West Nile* (N=2,697)	Jamestown Canyon (N=75)	La Crosse (N=63)	Powassan (N=34)	St. Louis encephalitis* (N=11)
Age group (yrs)					
<18	50 (2)	4 (5)	54 (86)	5 (15)	0 (0)
18–59	1,020 (40)	36 (48)	6 (10)	10 (30)	5 (45)
≥60	1,027 (40)	35 (47)	3 (5)	19 (55)	6 (55)
Sex					
Male	1,201 (62)				
Female	796 (38)				
Period of illness onset					
January–March	7 (1)				
April–June	87 (4)				
July–September	1,814 (87)				
October–December	185 (8)				
Clinical syndrome					
Nonneuroinvasive	672 (32)				
Neuroinvasive					
Encephalitis	714 (34)				
Meningitis	530 (25)				
AFP	89 (4)				
Other	92 (4)				
Outcome					
Hospitalization	1,545 (74)	46 (61)	63 (100)	33 (97)	6 (55)
Deaths	146 (7)	2 (3)	0 (0)	2 (6)	0 (0)

- The “other” Arboviral Neuroinvasive infections
- All uncommon
- Predominantly summer but some into the fall
- Regional Distribution, but changes over time
- Age distributions vary by agent
- Most diagnosed in the hospital

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## Endemic Arbovirus Infections in Delaware 2016–2018

Virus	2016 Human	2016 Animal	2017 Human	2017 Animal	2018 Human	2018 Animal
Jamestown Canyon	0	0	0	0	0	0
Saint Louis Encephalitis	0	0	0	0	0	0
Eastern Equine Encephalitis	0	0	0	+	0	+
La Crosse	0	0	0	0	0	0
Powassan	0	0	0	0	0	0
West Nile Virus	0	+	1	+	10 (8 NI)	+

Source: <https://www.cdc.gov/arbovet> (accessed 1/1/19)

WNV 2018 NJ: 61, PA: 117

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## Learning Objectives:

- Become familiar with emerging mosquito born diseases in the Western Hemisphere and potential of spread to the US
  - Zika, Chikungunya, and a few words about Dengue
  - How to differentiate and diagnose emerging mosquito-borne infections in the returned traveler

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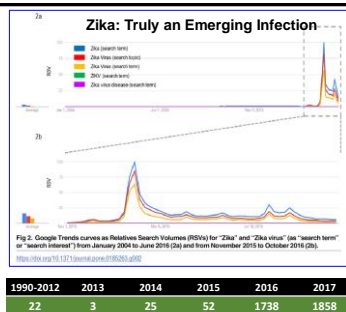
## Case 2

- A 24 year old from Middletown presents 1/12/19, one week after spending 5 days in the Dominican Republic with her fiancé.
  - She was well there, but now has fever to 102, chills, mild headache, and joint aches "all over". *A rapid flu test is Negative*
  - She is febrile and uncomfortable but non toxic, she has bilateral conjunctivitis without discharge and a faint, non petechial, erythematous maculopapular rash.
  - She does not think that she is pregnant, but she and her fiancé had unprotected intercourse while they were there.
  - She says that there weren't any mosquitos on the resort, but she did get "a few" mosquito bites on a day trip to a nature preserve
- What are you worried about? What to you do now?



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Google  
Search  
Trends: Zika

Pub Med  
Citations  
by year:  
Zika virus

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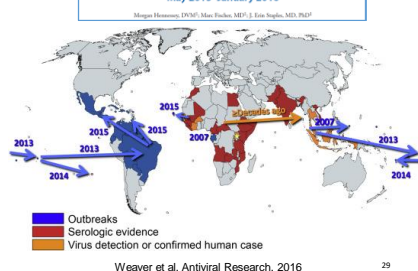
## Zika virus

- Mosquito born flavivirus (ss RNA) related to Dengue, Yellow Fever, WNV...
- Carried by *Aedes* mosquitos, mainly *Aedes aegypti*
- First identified in 1947 near the Zika River in Uganda
- Sporadic cases from Africa and Asia through 2007
- 2007-2014, outbreaks in SE Asia and W. Pacific, lasting 1-2 years
- Very high attack rates but mild illness-less severe than Dengue, complications not reported\*

HEALTH  
**Zika Virus a Global Health Emergency, W.H.O. Says**  
By SABRINA TAYEBNESE and DONALD G. MENSEL, Jr. FEB. 1, 2016

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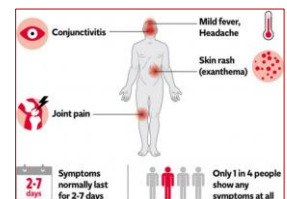
## Zika Virus Spreads to New Areas — Region of the Americas, May 2015–January 2016



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## Zika virus: Clinical Manifestations

- Onset of symptoms (if they occur) up to 14 days post exposure
- **BUT** ~80% of those infected are asymptomatic
- Symptom onset often abrupt onset, with any or all of these:



- Severe Disease rare:
  - CNS Disease, Including GBS
  - Thrombocytopenia
  - Other

Source: <http://www.independent.co.uk>

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## Zika virus: Pathogenesis

- Viremia during symptomatic periods
  - But most (up to 80%) are asymptomatic
  - Viremia (rRT PCR) for up to 7 days post Sx onset
  - Higher level of virus, prolonged shedding in urine
- Virus found in many other tissues/fluids:
  - CNS/CSF
  - Placental tissue and Fetal tissue including brain
  - Semen and vaginal secretions
  - Breast milk
  - Saliva, tears
- Zika-specific neutralizing IgM Ab day 4, but cross reactive with Ab against other flaviviruses (Dengue, West Nile...)



## Zika virus: A Couple of Questions

- What is the current status in the Western Hemisphere (and elsewhere)?
- What about transmission in the US?
- What are the severe complications of Zika virus infection?
- Zika virus and pregnancy: What do we know now?



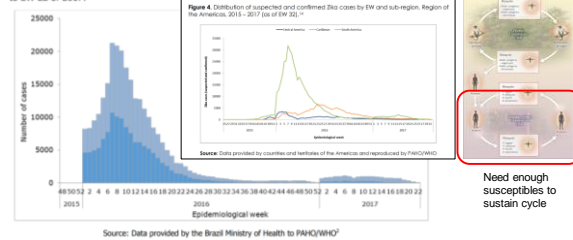
Source: Times of India

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## How long do Zika virus epidemics last? And why do they stop?

**Figure 1.** Suspected and confirmed cases of Zika by epidemiological week, Brazil, EW 48 of 2015 to EW 22 of 2017.<sup>1</sup>



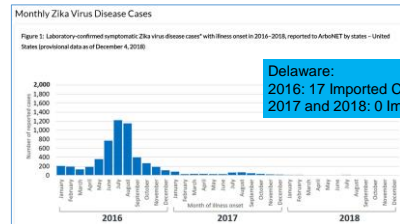
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Reported Zika Cases in US (excl. territories) as of 12/4/18

**Symptomatic Disease:** 5590

Returned travelers: 5454 **Presumed local mosquito-born:** 231

**Other:** 55



**Delaware:**  
2016: 17 Imported Cases  
2017 and 2018: 0 Imported Cases

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WASHINGTONIAN

HEALTH  
Zika Virus Mosquitoes Have Been Found...on Capitol Hill

By Georgetown Institute on February 26, 2016

**How far has (and could) Zika virus spread locally in the Continental U.S.? And what about Delaware?**

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## Where has Zika been locally transmitted in the US so far?

- Texas : 11 locally acquired cases, none in 2018  
<http://www.dshs.texas.gov>



- Florida: 220 locally acquired cases, but none in 2018  
<http://www.floridahealth.gov/>



Where could it go?

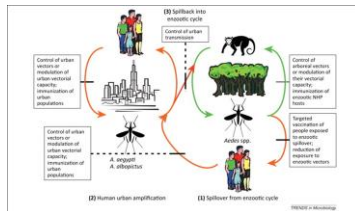
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### Chikungunya: "That Which Bends"

- Primary reservoirs
  - Humans (during epidemic periods)
- Other reservoirs (sylvan cycle)
  - Non-human primates, rodents, birds, small mammals
- Primary Vectors:
  - Ae. aegypti*
  - Ae. albopictus*



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### Chikungunya: Acute and Chronic Illness

- Acute: 1-12 days after bite: mean 3-7 days
- Most infected have symptoms: 72-97%
- Fever: Generally > 102 F (39 C)
- "Saddleback" fever, bradycardia**
- Polyarthralgias, polyarthritis**
  - Bilateral, symmetrical
  - Hands, feet, other prox. joints, back
  - Can be severe & debilitating**
- Headache, Myalgias, Nausea
- Conjunctivitis
- Maculopapular rash
- Acute Sx: usually 7-10 Days
- Subacute: up to ~ 3 months
  - Prevalence: up to 80%
  - Polyarthritides, Tenosynovitis, joint aches
  - Transient vasc. disease, Raynaud's
  - Fatigue, Weakness
- Chronic: Greater than 3 months
  - Up to 40-50% at 6 mo.
  - Recent study in Columbia: ¼ with joint Sx persisted at 20 mo. (Chang *Arth. and Rheum*, 2018)
  - Mechanism of chronic arthritis unknown- not direct infection
  - Optimal Rx not defined

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### Clinical Features: Zika Virus Compared to Dengue and Chikungunya

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

[https://emergency.cdc.gov/coca/ppt/2016/01\\_26\\_16\\_zika.pdf](https://emergency.cdc.gov/coca/ppt/2016/01_26_16_zika.pdf)

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### What You Need to Know About the Zika Virus



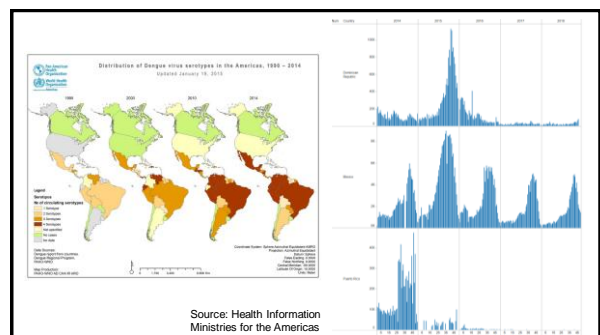
- <https://dhss.delaware.gov/dhss/dph/zika.html>
- <https://www.cdc.gov/zika/>
- Who and when to test? And how?
- What to advise if pregnant, planning pregnancy, or a male partner of a woman pregnant or planning pregnancy?
- What is the risk? Absolute vs relative risk?

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### Some comments about dengue

- WHO Guidelines (updated 2009)
  - <https://www.who.int/rpc/guidelines/9789241547871/en/>
- Primary vector: *Aedes aegypti*
- Multiple Serotypes so even though long lasting type specific immunity, epidemic curves can wax and wane as serotypes spread
- Diversity of serotypes has steadily increased many Western Hemisphere countries
- Risk of severe disease highest after re-infection "Heterotypic infection"
  - Implications for who is at risk for severe disease
  - Implications for vaccine development → the CYD-TDV Experience

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Source: Health Information Ministries for the Americas

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## Learning Objectives:

- Learn what's new in the prevention of mosquito-borne infections in travelers: **Malaria and Yellow Fever**

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## Case 3

- A 34 year old woman presents to your office for travel advice
- She works for an large international NGO, and will be leaving in 2 weeks to go to Ethiopia for 2 months to work in a refugee camp
- She is otherwise healthy, but is 18 weeks pregnant
- She has history of having received yellow fever vaccination at age 16

### WORLD Yellow fever kills 10 in Ethiopia, WHO ships 1.45m vaccines

WEDNESDAY, NOVEMBER 7, 2018 9:43

Source: Businessdailyafrica.com

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## Prevention in Travelers: Yellow Fever

- Where are the current Yellow Fever outbreaks?
- Where do you need Yellow Fever Vaccine?
- Is there Yellow Fever Vaccine available?
- Where can you get it? How often do you need it?



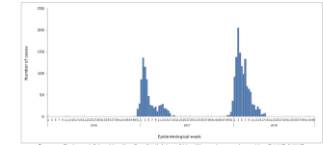
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## The Yellow Fever Outbreak in Brazil: 2015-2018

### End 2017 to Summer 2018

- 1,376 confirmed human cases
- 483 deaths
- Expanding areas of transmission in Brazil
- Ongoing Epizootic transmission in primates
- Shortages of vaccine and use of fractionated doses
- Higher numbers of cases in Bolivia and Peru also

Figure 2. Distribution of confirmed human yellow fever cases by epidemiological week, Brazil, 2016-2018.



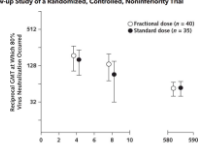
Source: Data published by the Brazil Ministry of Health and reproduced by PANIC/WHO

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## Yellow Fever Vaccine: Ongoing shortages here, but you can use less if you have to

- **US Yellow Fever Vaccine Shortage**
- Total Depletion of YF-Vax® Supply in 2017
- Limited availability of Stamaril® in selected travel clinics through an Expanded Access Program
  - Not an FDA approved in US vaccine but used in 70+ countries
- Return of YF-Vax® in mid 2019\*

Annals of Internal Medicine  
ORIGINAL RESEARCH  
Long-Term Protection After Fractional-Dose Yellow Fever Vaccination  
Follow-up Study of a Randomized, Controlled, Noninferiority Trial



New yellow fever vaccination requirements for travellers

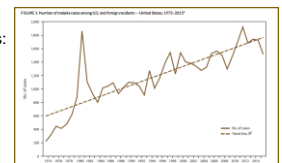
Amendment to the period of validity of the international certificate of vaccination against yellow fever, which is now extended to the life of person vaccinated  
27 July 2019



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## Whats new in Malaria prophylaxis and Treatment?

- Malaria, including drug-resistant disease, remains a global challenge
- Considerations for traveler prophylaxis: Includes a risk assessment
  - Exactly where going, and exactly when, activities while there
  - Who is the patient?
- A newly approved drug for both prophylaxis and as treatment for hepatic phase: tafenoquine
  - For treatment: Krintafe®™
  - For Prophylaxis: Arakota™



Source: CDC  
<https://www.cdc.gov/mmwr/volumes/67/ss/ss6707a1.htm>

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### Prevention of Mosquito-Borne Infections:

- Avoid Travel to known high risk areas if possible
- Pay attention to high risk season and times of day
- Avoid Mosquito bites; wear long sleeves, insect repellent, mosquito nets, permethrin treated clothing
- Mosquito proofing of homescreens, remove standing water
- New Vaccines in development



<https://www.cdc.gov/zika/prevention/prevent-mosquito-bites.html>

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### Prevention of Mosquito-borne Infections: Old and Emerging Mosquito Control Strategies

- Aerial Spraying and Indoor Spraying



- Genetically Modified (GM) Mosquitos



FDA says GMO mosquito likely OK to fight Zika in Florida  
<http://www.fda.gov>



- Wolbachia

From: Dutra et al, Cell Host and Microbe, 2016

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### Summary:

- Mosquito-borne diseases pose global and local health challenges; geographic range of these diseases are evolving
- West Nile Virus is the most common endemic mosquito borne infection in Delaware; 1/150 with West Nile infection develop neuroinvasive disease
- Important emerging/reemerging mosquito born diseases in Western Hemisphere include Zika, Chikungunya and Dengue
- There is an ongoing yellow fever outbreak in Brazil, and there is a national and international shortage of yellow fever vaccine
- There is a new drug for prevention of malaria that also can be used to treat the hepatic phase of malarial infection

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