An Overview of Vector-Borne Diseases: From A to Zika

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Disclosure

I have no actual or potential conflict of interest in relation to this program/presentation.
Vector-Borne Diseases

Definition

- Vectors = living organisms that can transmit infectious diseases:
  - Human → Human or Animals → Humans or Animal → Animal
  - Ingest disease-producing microorganisms during a blood meal from an infected host → pass to a new host during subsequent blood meal
# Vector-borne diseases

### Mosquitoes

- *Aedes*
  - Chikungunya
  - Dengue fever
  - Rift Valley fever
  - Yellow fever
  - Zika

- *Anopheles*
  - Malaria

- *Culex*
  - Japanese encephalitis
  - Lymphatic filariasis
  - West Nile fever

### Sandflies

- Leishmaniasis
- Sandfly fever (phlebotomus fever)

### Ticks

- Crimean-Congo haemorrhagic fever
- Lyme disease
- Relapsing fever (borreliosis)
- Rickettsial diseases (spotted fever and Q fever)
- Tick-borne encephalitis
- Tularaemia

### Triatomine bugs

- Chagas disease (American trypanosomiasis)

### Tsetse flies

- Sleeping sickness (African trypanosomiasis)

### Fleas

- Plague (transmitted by fleas from rats to humans)
- Rickettsiosis

### Black flies

- Onchocerciasis (river blindness)

### Aquatic snails

- Schistosomiasis (bilharziasis)
Outline

- Tick-borne Infections
  - Regional
  - Emerging

- Mosquito-borne Infections
  - Domestic
  - International
  - Emerging
Case 1

4 year old boy seen in clinic with 3 days of fever, headache and vague abdominal pain.

CBC: WBC 18, Hgb 12, Plt 80

Treated and fever resolved within 48h
Case 2

7 year old boy with 2 days of fever and maculopapular rash on arms, legs, trunk, palms and soles.

L sided abdominal pain, diffuse joint pain.

Seen in ED, diagnosed with viral illness (?Coxsackie virus)
1 week later, seen by PCP- fever continued, rash worse
Case 3

2 year old boy transferred to VCH for severe respiratory distress and altered mental status

- **9 days prior to Admission**: Seen at a local hospital for fever and rash in the setting of recent tick bite- given Amoxicillin and discharged home.
- **8 days prior to admission**: Still with rash and fever- given a dose of Ceftriaxone and discharged home.
- **1 day prior to admission**: Respiratory distress, altered mental status
- **Admission**: Transferred to Vanderbilt
Case 3

Labs

- WBC: 40,000;  Hgb: 10;  Plt: 87,000
- Na: 132, K: 4.9, Cl: 97, CO₂: 40, BUN: 27, Cr: 0.5
- Alb: 2.6, AST: 86, ALT: 29, Alk Phos: 222
- CKMB: 14.77  Troponin: 0.17  CPKTot: 415  BNP: 2026

- CXR: Diffuse interstitial opacities, cardiomegaly
- Echo: Severe LV dysfunction
Case 3

MRI Brain- Axial- DWI
What do they all have in common?

• 4 year old with fever, headache and mild abdominal pain x 2 days who recovered in 48h after treatment

• 7 year old with fever, rash, abdominal pain and myalgias who worsened over 1 week and is now admitted

• 2 year old with fever, rash x 10 days, now with respiratory distress, altered mental status and cardiac dysfunction
Small Vessel Vasculitis

Clinical Manifestations

- Fever
- Myalgia
- Severe headache (less common in young children)
- Photophobia
- Nausea/vomiting and anorexia
- Abdominal pain and diarrhea
- Rash (usually within the first 6 days) = erythematous macules or maculopapules
  - First on the wrists and ankles, spreading within hours proximally to the trunk and distally to the palms and soles
  - ***Can be atypical or absent in up to 20% of cases***
  - Petechial rash typically is a late finding and indicates severe disease
  - Lack of a typical rash is a risk factor for misdiagnosis and poor outcome
Rocky Mountain Spotted Fever

Other signs
- Hepatomegaly and splenomegaly (33%)
- Meningeal signs
- **Thrombocytopenia** (60%)
- **Hyponatremia** (serum sodium concentrations less than 130 mg/dL are observed in 20%)
- Elevated liver transaminase
- White blood cell count typically is normal, but leukopenia and anemia can occur

**If not treated, the illness can last as long as 3 weeks and can be severe**
- Central nervous system
- Cardiac
- Pulmonary
- Gastrointestinal tract and renal
- Disseminated intravascular coagulation (DIC)
- Shock leading to death
Rocky Mountain Spotted Fever

- ***Delay in appropriate antimicrobial treatment past the fifth day of symptoms is associated with severe disease and poor outcomes***

- Case-fatality rates of untreated RMSF range from 20% to 80%, with a median time to death of 8 days

- Long-term sequelae are common in patients with severe RMSF
  - Neurologic (paraparesis; hearing loss; peripheral neuropathy; bladder and bowel incontinence; and cerebellar, vestibular, and motor dysfunction)
Rocky Mountain Spotted Fever

Etiology
What organism causes RMSF?

*Rickettsia rickettsii*

- Obligate, intracellular, gram-negative bacillus

- The primary targets of infection = endothelial cells lining the small blood vessels of all major tissues and organs

- Increased permeability leads to a diffuse small vessel vasculitis

Red Book® 2015, 2015
Principal vector

- **Dermacentor variabilis** (American dog tick) in the eastern and central United States

- **Dermacentor andersoni** (Rocky Mountain wood tick) in the western United States

- **Rhipicephalus sanguineus** (brown dog tick) confirmed in Arizona and Mexico, may play a role in other regions

- RMSF also occurs in Canada, Mexico, Central America, and South America
Rocky Mountain Spotted Fever

Epidemiology

Rocky Mountain Spotted Fever

Epidemiology

Reported incidence and case fatality of RMSF in the United States, 1920–2010
Rocky Mountain Spotted Fever

- Majority of cases occur in April-September
- 12% still occur October-March
Rocky Mountain Spotted Fever

Diagnosis

- ***CLINICAL*** Never wait on confirmatory labs for treatment
- Serology
  - Indirect immunofluorescence assay (IFA) on acute and convalescent
  - Looking for four-fold rise in antibody titers
  - IgM rise near the end of the first week and remain elevated for months or even years
  - ~10% of healthy people in some areas may have elevated antibody titers due to past exposure
- PCR
  - Skin biopsy specimen (Sensitivity ~70%)
“Starry Sky”

Rocky Mountain spotted fever: ‘starry sky’ appearance with diffusion-weighted imaging in a child

Rocky Mountain Spotted Fever

- Doxycycline is the first line treatment for children of all ages and should be initiated immediately whenever RMSF is suspected.
  - Most effective if started in the first 5 days.
  - Fever generally subsides within 24-72 hours.
  - Treat until afebrile for 3 days (total 7 - 10 days).
  - Resistance or relapse after recommended course of treatment has not been documented.

Doxycycline saves lives!
A good reason to smile: New research shows NO evidence of tooth staining from short courses of doxycycline.
Doxycycline is the best treatment for suspected rickettsial infections in patients of all ages.

Click to learn more.
RMSF- 3 KEY POINTS

1. Rocky Mountain SPOTLESS Fever occurs Rocky Mountain Spotted AFEBRILE does not

2. Must have a high index of suspicion ALL YEAR round in Tennessee

3. Doxycycline (especially in short courses) is SAFE and LIFE-SAVING for children with RMSF
Case 4

14yo female with 3 days of fever, rash, myalgias, headache and arthralgias

Significant labs:

<table>
<thead>
<tr>
<th>3</th>
<th>12.4</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>77% poly</td>
<td>16% lymph</td>
<td></td>
</tr>
</tbody>
</table>

| 139 | 39 | 2.5 |
| AST: 140 | ALT: 134 |
Ehrlichiosis

- "Ehrlichiosis = broadly applied to several different infections
  - Ehrlichia chaffeensis (reported 1987, Southeast and central US)
  - Ehrlichia ewingii (reported 1999, Southeast and central US)
  - Ehrlichia muris-like (EML) (reported 2011 in MN and WI)
- Human Monocytic Ehrlichiosis (HME) majority of cases in our area
- Incidence increases with age- highest age-specific incidences 60–69yo
- Highest case-fatality rates:
  - Children aged <10 years
  - Adults aged ≥70 years
  - Immunosuppressed
Ehrlichiosis: Clinical

Usually present
• Fever 100%
• Rash 66% (less in adults)
• Headache 63%
• Myalgia 63%
• Nausea 57%
• ↑ liver, spleen 41%

Variably present
• Conjunctivitis
• Photophobia
• Meningitis
• Pharyngitis
• Arthralgias
• Peripheral edema
Ehrlichiosis: Laboratory

Common
• Thrombocytopenia
• Leukopenia
  – Lymphopenia
• ↑ AST, ALT
• Hyponatremia
• Anemia

Occasional
• ↑ BUN, creatinine
• ↓ Albumin
• CSF: lymphocytic pleocytosis
• CXR infiltrates
Vector

*Amblyomma americanum*

Lone Star tick
Seropositivity for *Ehrlichia* is common

Ehrlichia incidence increasing?

Number of Annual Ehrlichiosis Cases, 1994-2010

CDC reported cases 1994-2010

MMWR reported cases 2011-2013
Ehrlichiosis

Diagnosis

• PCR (whole blood) = very sensitive and specific

• Serologic = indirect immunofluorescence antibody (IFA) assay between paired serum specimens (first week of illness and 2–4 weeks later)

• Peripheral Blood Smear = Morula
Ehrlichia morula in WBC

IF SUSPECTED, DON’T WAIT ON LABS TO TREAT!

Red Book® 2015, 2015
Courtesy of Centers for Disease Control and Prevention/Emerging Infectious Diseases and Maria C. Martinez
Ehrlichiosis

**Treatment**
- IV/PO doxycycline until afebrile for 3 days (total 5 - 7 days)
- Inpatient monitoring or close follow up
  - May get worse before better despite antibiotic
Ehrlichiosis more severe with bactrim?


• Trimethoprim-sulfamethoxazole and fulminant ehrlichiosis. Brantley RK. *Pediatr Infect Dis J*. 2001

• Three 2009 severe cases (two fatal) were taking bactrim (two were immunocompromised)
Ehrlichia - 3 Key Points

• Similar clinical symptoms to RMSF but caused by the lone-star tick

• Treated same as RMSF = Doxycycline

• May be more severe in patients on bactrim or immunocompromised
Phone call

- Rash and fever that sounds exactly like Ehrlichia but...
- Lives in New England
- Tick he pulled off a week ago
Anaplasmosis

- The sickness formerly known as HGA
  - Which is the illness formerly known as HGE
- Caused by *Anaplasma phagocytophilum*
- Vector is black-legged ticks (*Ixodes spp*)
- Clinically similar to ehrlichiosis
- Treatment is the same
Ixodes vectors widely distributed…

Established and reported distribution of anaplasmosis vectors *Ixodes scapularis* and *Ixodes pacificus*, by county, United States, 1907-1996.
Though cases clustered differently
Southern Tick Associated Rash Illness

“STARI”

- “Lyme-like” illness reported in 1995

- Described in NC and Missouri

- PCR of lesions identified possible *Borrelia spp* (*B. lonestarii*) but not confirmed

- Lone star ticks have not been shown to transmit *Borrelia burgdorferi* → their saliva has been shown to kill Borrelia
  
  (Ledin et al., 2005, Zeidner et al., 2009)
STARI

Symptoms
• Red, expanding “bull's-eye” lesion that develops around the site of a lone star tick bite
• Appears within 7 days of tick bite and expands to a diameter of 8 centimeters (3 inches) or more
• Fatigue, headache, fever, and muscle pains

Diagnosis
• Clinical symptoms, geographic location, and h/o tick bite
• No diagnostic blood tests have been developed

Treatment
• It is not known whether antibiotic treatment is necessary or beneficial for patients with STARI.
• STARI resembles early Lyme disease, physicians will often treat patients with oral antibiotics.
Distinctions between STARI and Lyme disease symptoms

- Physical findings from STARI patients (MO) with Lyme patients (NY)

**STARI:**
- More likely to recall a tick bite
- Time from tick bite to skin lesion was shorter (6 days)
- Less likely to have other symptoms (other than EM)
- Less likely to have multiple skin lesions
- Lesions that were smaller in size (6-10 cm for STARI vs. 6-28 cm for Lyme disease)
- More circular in shape and with more central clearing
- After antibiotic treatment, STARI patients recovered more rapidly

Wormser et al, 2005
Lyme Disease

- **Borrelia burgdorferi**
- Transmitted by *Ixodes scapularis* (deer tick), predominantly nymph stage
- Animal reservoir *Peromysces leucopus* (white-footed mouse)
- >90% of cases within endemic region
One dot is placed randomly within the county of residence for each confirmed case. Though Lyme disease cases have been reported in nearly every state, cases are reported based on the county of residence, not necessarily the county of infection.
Case

- 9-year-old previously healthy male presents in status epilepticus
- One day prior to presentation = Subjective fever and diffuse headache
- Parents gave acetaminophen without improvement
- Morning of presentation - unresponsive at home with tonic–clonic seizure

- 4th grade
- Outdoors a lot
- Animal contacts: dogs, skunks, mice, chickens, frogs, pigs, & turtles
- Frequently swam in a nearby river, multiple mosquito bites
- No travel
- Vaccines UTD
Case

DAY 2 Physical Exam (pertinent):
• 38.1 °C, HR 136, BP 118/57, RR 26
• GEN: Ill-appearing, unable to follow most commands, breathing spontaneously
• Neuro: CN intact, PERRL, L>R LE weakness 2+ strength on R, 1+ on L, areflexia LE bilaterally, UE normal strength and tone; sensation intact throughout
Brain MRI with contrast
West Nile Virus

- 70% to 80% asymptomatic

- Acute systemic febrile illness
  - Headache
  - Myalgia/arthralgia
  - Gastrointestinal tract symptoms
  - Transient maculopapular rash

- Neuroinvasive disease (<1%)
  - Meningitis
  - Encephalitis
  - Acute flaccid paralysis

Infectious causes of acute flaccid paralysis.
Solomon, Tom; Willison, Hugh
West Nile Virus Transmission Cycle

In nature, West Nile virus cycles between mosquitoes (especially *Culex* species) and birds. Some infected birds can develop high levels of the virus in their bloodstream and mosquitoes can become infected by biting these infected birds. After about a week, infected mosquitoes can pass the virus to more birds when they bite.

Mosquitoes with West Nile virus also bite and infect people, horses and other mammals. However, humans, horses and other mammals are ‘dead end’ hosts. This means that they do not develop high levels of virus in their bloodstream, and cannot pass the virus on to other biting mosquitoes.
West Nile Virus Neuroinvasive Disease

Incidence by State – United States, 2016
(as of September 6, 2016)

<table>
<thead>
<tr>
<th>State</th>
<th>Non-Neuroinvasive</th>
<th>Total</th>
<th>Viremic</th>
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</thead>
<tbody>
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<table>
<thead>
<tr>
<th>Year</th>
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<th>Horses Positive</th>
<th>Birds Positive</th>
<th>Mosquito Pools Positive</th>
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<td>432</td>
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*As of 09/08/2016

<table>
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<tr>
<th>Year</th>
<th>Human Deaths</th>
<th>Viremic blood donors</th>
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<tr>
<td>2016*</td>
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Other Arboviruses (arthropodborne viruses)

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<tr>
<th>Virus</th>
<th>Systemic Febrile Illness</th>
<th>Neuroinvasive Disease</th>
<th>Hemorrhagic Fever</th>
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<tbody>
<tr>
<td>Domestic</td>
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<tr>
<td>Chikungunya</td>
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<td>Colorado tick fever</td>
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<tr>
<td>Dengue</td>
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<td>Rare</td>
<td>Yes</td>
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<td>No</td>
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<td>La Crosse</td>
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<td>St. Louis encephalitis</td>
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</tr>
<tr>
<td>Western equine encephalitis</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
<tr>
<td>West Nile</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Arboviruses

Testing

• TN Department of Health


• Reference Laboratories
  – ARUP laboratories
  – Quest Diagnostics
**Fever and the returning traveler**

**Vector-borne (common)**
- Malaria
- Dengue virus
- Chikungunya
- Yellow Fever

<table>
<thead>
<tr>
<th>GEOGRAPHIC AREA</th>
<th>COMMON TROPICAL DISEASE CAUSING FEVER</th>
<th>OTHER INFECTIONS CAUSING OUTBREAKS OR CLUSTERS IN TRAVELERS</th>
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<tbody>
<tr>
<td>Caribbean</td>
<td>Dengue, malaria (Haiti)</td>
<td>Acute histoplasmosis, leptospirosis, chikungunya</td>
</tr>
<tr>
<td>Central America</td>
<td>Dengue, malaria (primarily <em>Plasmodium vivax</em>)</td>
<td>Leptospirosis, histoplasmosis, coccidioidomycosis</td>
</tr>
<tr>
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</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>Malaria (primarily <em>P. falciparum</em>), tick-borne rickettsiae (main cause of fever in southern Africa), acute schistosomiasis, filariasis</td>
<td>African trypanosomiasis, chikungunya, enteric fever, filariasis</td>
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Dengue

- Most common arboviral disease globally
- 40% of the world’s population living in endemic areas
- ~100 million cases annually
- ~1 in 2,000 result in death
- Case-fatality rate of patients with severe dengue can be reduced from ~10% to <0.1% by the timing and quality of clinical care that patients receive.
Dengue

• Single-stranded RNA viruses of the genus Flavivirus, dengue viruses (DENV) 1, 2, 3, or 4

• Transmission = *Aedes aegypti & albopictus*
Dengue

- 75% asymptomatic
- Symptomatic = mild to moderate, nonspecific, acute, febrile illness
- 5% = severe, life-threatening disease
Dengue

- Three phases:
  1. Febrile
  2. Critical
  3. Recovery

- Risk factors for severe disease
  - Young children
  - Secondary infection
Antibody (Ab)-dependent enhancement

- Preexisting antibodies (primary infection) + different DENV serotype (secondary infection)
- Ab–virus complex attaches to receptors (FcyR)
- Antibodies help the virus infect monocytes more efficiently
- Increase in the overall replication of the virus and a higher risk of severe dengue

Dengue - 3 Keys

• Common cause of fever in the returning traveler

• Watch for warning signs of critical phase
  – Late fever
  – Bleeding
  – Decreasing platelets
  – Increasing hematocrit

• Support care is critical and life saving
Fever and the returning traveler

Vector-borne (common)

- Malaria
- Dengue virus
- Chikungunya
- Yellow Fever
- Zika Virus?

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They're here

Zika-carrying mosquitoes found for first time in US

These mosquitoes most likely to spread Zika | Congress' Zika battle to ramp up
April 1947: Zika virus first discovered in Uganda’s Zika forest (rhesus monkey).

1952: First human case recorded in Nigeria.

April 2007: Micronesia’s Yap Island experiences outbreak with 49 confirmed and 59 probable cases.

Oct 2013: Zika virus spreads through the French Polynesian islands.
2014

Jan
Chile confirms the first case of autochthonous transmission in Easter Island

Feb
North East of Brazil start reporting disease associated with a rash

May
Brazil identify the infection as ZIKV and confirm autochthonous transmission in the states of Bahia and Rio Grande do Norte

Sept
First autochthonous cases confirmed in Colombia

Oct
Brazilian states report 10x average incidence of microcephaly in new-borns

Nov
- Cape Verde Ministry of Health estimate 1,000 suspected cases
- 5 confirmed cases in Suriname
- 5 cases confirmed in the Caribbean

Jan
Imported cases of ZIKV in the US and several countries in Europe

Feb - June
- 121 cases of neurological manifestations and Guillain-Barré syndrome in Brazil
- >14,000 cases of rash-related illness in Salvador

Oct - Jan 2016
3,530 babies have been born with microcephaly in Brazil

WHO director-general Margaret Chan held an emergency meeting in Geneva to discuss the threat level of Zika virus.
Zika Virus

• *Flavivirus* similar to Dengue, Yellow Fever and West Nile viruses

• **Incidence** and attack rates, Yap 2007
  – Infection rate: 73% (95% CI 68–77)
  – Symptomatic attack rate among infected: 18% (95% CI 10–27)
  – No severe disease, hospitalizations, or deaths

• **Incubation period** is 3–14 days
• **Viremia** ranges from a 3 days to 1 week
  – Remains in semen and urine longer than in blood

Guillain-Barré syndrome in a small proportion of infected people

Zika Virus

Transmission

• Bite from an infected mosquito *Aedes spp.* (Ae. aegypti and Ae. Albopictus)
• Maternal-fetal
  – Intrauterine
  – Perinatal
• Sexual transmission from an infected person to his or her partners
• Probable: blood transfusion, organ and tissue transplant, fertility treatment, and breast feeding
Zika Virus

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Wynwood and Miami Beach- Miami-Dade County FL
Zika Virus

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Zika and pregnancy outcomes

• Can pass from a pregnant woman → fetus during pregnancy or around the time of birth
• Can cause:
  – Microcephaly
  – Eye defects
  – Hearing loss
  – Impaired growth
  – Fetal loss

• All pregnant women should be assessed for Zika at each prenatal care visit
  – Traveled to or live in an area with active Zika transmission
  – Had sex without a condom with a partner who lives in or traveled to an area with active Zika transmission
Zika Virus

Transmission

• Bite from an infected mosquito *Aedes spp.* (Ae. aegypti and Ae. Albopictus)

• Maternal-fetal
  – Intrauterine
  – Perinatal

• Sexual transmission from an infected person to his or her partners

• Probable: blood transfusion, organ and tissue transplant, fertility treatment, and breast feeding
### Suggested timeframe to wait before trying to get pregnant

**Possible exposure via recent travel or sex without a condom with a man infected with Zika**

<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zika symptoms</strong></td>
<td>Wait at least 8 weeks after symptoms start</td>
</tr>
<tr>
<td><strong>No Zika symptoms</strong></td>
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**People living in areas with Zika**

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<td><strong>Zika symptoms</strong></td>
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<td>Talk with doctor or healthcare provider</td>
</tr>
</tbody>
</table>
What should we be telling our patients?

- **Self-limited** febrile illness for most
- Associated with **Guillain-Barré syndrome** and in a small number of patients
- **Maternal-fetal transmission**
  - Associated with birth defects including **microcephaly**
- **Sexual transmission** has been reported
- We do not know many things including:
  - How long the virus stays in body fluids
- CDC has an great deal of information for patients and physicians
Thank you for your attention