Objectives

- There are a large group of infectious diseases that are not common in Utah.
- With rapid worldwide travel, you may have already seen or will see patients returning with tropical diseases.
- More familiar Tropical Diseases of recent importance:
  - Zika virus, Chikungunya, Dengue fever, Ebola
  - Learn the presentation, transmission, diagnoses, serious risk factors, prevention and/or treatment of above four diseases.
- No conflict of interest to disclose

CDC list of Neglected Tropical Diseases

- Buruli ulcer
- Chagas disease
- Cysticercosis
- Dengue Fever
- Dracunculiasis (Guinea Worm Disease)*
- Echinococcosis
- Fascioliasis
- Human African Trypanosomiasis (African Sleeping Sickness)
- Leishmaniasis
- Leprosy (Hansen’s disease)
- Lymphatic filariasis*
- Onchocerciasis*
- Rabies
- Schistosomiasis*
- Soil-transmitted Helminths (STH) (Ascaris, hookworm, and whipworm)*
- Chikungunya
- Zika virus
Tropical Diseases returning with fever or prolonged symptoms

- Top causes of acute fever in returning travelers:
  - Dengue, Malaria, African Tick Fever, Typhoid fever, Leptospirosis, Brucellosis, Tuberculosis

- Causes of more chronic diseases in returning travelers:
  - Persistent diarrhea, Tuberculosis, Brucellosis, Strongyloides, Leprosy,

- Recent outbreaks:
  - Dengue, Chikungunya, Zika Virus, Ebola

Quiz

- Which of the following viruses has the highest mortality rate?
- Which virus has resulted in the largest number of deaths?
  - A. Zika Virus
  - B. Dengue fever virus
  - C. Chikungunya virus
  - D. Ebola virus

Aedes Mosquitoes Factors Influencing Proximity

- Vector Migration
  - There are 3500 species of mosquitoes on earth
  - Estimated 75 Quadrillion mosquitoes at any given time
  - That's roughly 25kg of insects per person – 25 million mosquitoes for every human
  - Marked increase in mosquito borne diseases after 1976 when malaria eradication program was discontinued

- Mosquito Tourism: Asian Tiger Mosquito – Aedes albopictus
  - Prefers artificial water
  - Introduced into the Americas, Europe and Africa via cargo transports
  - Along with Aedes aegyptius is the vector for Chikungunya, Dengue, Zika
  - Has adapted to cooler temperatures
Zika Virus Vectors: Aedes Mosquitoes

- Aedes species mosquitoes
  - Ae aegypti more efficient vectors for humans
  - Ae albopictus
- Also transmit dengue and chikungunya viruses
- Lay eggs in domestic water-holding containers
- Live indoors and outdoors
- Aggressive daytime biters; can also bite at night
- Prefer to bite people

CDC slide set

Estimated range of Aedes aegypti and Aedes albopictus in the United States, 2016

Aedes aegypti mosquitoes are more likely to spread viruses like Zika, dengue, chikungunya than other types of mosquitoes such as Aedes albopictus mosquitoes.

*These maps show CDC-based estimates of the potential range of Aedes aegypti and Aedes albopictus in the United States. These maps include areas where mosquitoes are or have been previously found. Detailed data on the maps do not necessarily mean that there are infected mosquitoes in that area.

Maps have been updated from a variety of sources. These maps represent CDC-based estimates of the potential range of Aedes aegypti and Aedes albopictus in the United States. Maps are not meant to represent risk for spread of disease.


Aedes transmitted diseases increasing in the last 30 years

Dengue Fever – 50-100 million cases, 500,000 hospitalizations, 22,000 deaths

Chikungunya – was mainly Africa/Asia
  2004 – Kenya down the coast then Asia/SE Asia in next four years; 2013 Western hemisphere

Zika virus – Africa/Asia but since 2007 epidemics throughout the world. Brazil 2015

- WHO – 2016 -- Global Public Health Emergency regarding Zika virus
Fever, rash from Tahiti

61-year-old female
Tahiti from Feb 7th to 15th
Feb 16th developed dizziness
Feb 17th fever to 103.5° with severe headache, myalgia, vomiting. Went to ER for hydration
Feb 20th flushed appearance of skin, started on clarithromycin for possible pneumonia.
Feb 26th seen in travel clinic now with conjunctivitis and erythematous sunburn-like rash
Laboratory – normal, except for a low platelet count of 42,000

Fever and rash from Tahiti

- Dengue Fever
  - (Break bone fever)
    - Incubation 2-5 days
    - High risk area
    - Fever
    - Headache
    - Myalgia (feels like bone pain)
    - Erythematous skin rash and conjunctivitis
    - Low platelets
    - Supportive care
Epidemiology

- >100 countries
- 50 to 100 million infections per year
- Most often in epidemics
  - Guayaquil, Ecuador
- 4 antigenic types – 1, 2, 3, 4
- LDS missionaries – common cause of fever in the mission field

Severe Dengue Fever (Dengue Hemorrhagic Fever, Dengue Shock)

- Capillary leak syndrome
- Hemorrhage
- Hypotension/circulatory collapse
- Increased risk:
  - Small children
  - Elderly
  - With second episode of Dengue infection

Warning signs for Severe Dengue

- Severe abdominal pain or persistent vomiting
- Red spots (petechial) or patches (echymosis) on the skin
- Bleeding from nose or gums
- Vomiting blood
- Black, tarry stools (feces, excrement)
- Drowsiness or irritability
- Pale, cold, or clammy skin
- Difficulty breathing
Treatment of Dengue Fever

- Maintain hydration and rest
- Take antipyretics to control temperature but avoid aspirin and NSAIDS which can increase the chance of bleeding.
- If evidence of Severe Dengue – hospitalization improves survival
- Monitor hydration – dry mouth, dry skin, decreased urine
- Assess hemodynamic status -- heart rate, capillary refill, pulse pressure, blood pressure, and urine output.
- Baseline hematocrit testing, and platelet counts. *Prophylactic Platelet transfusion - not helpful unless active bleeding
- Continue to monitor --the critical phase of dengue begins with defervescence of fever

*Prophylactic Platelet Transfusion in Dengue Fever not Superior to Supportive Care Alone, Mary Wilson, Lancet March 2017

Chikungunya
Swahili for “that which bends over”

- Alpha virus, Tanzania, 1953
- Vector: Ae. aegypti and albopictus
- Incubation 3-7 days
- Fever, headache, fatigue, nausea, vomiting, muscle pain, rash, joint pain
- Duration: few days to several weeks
- Prolonged residual joint pain and/or arthritis.

Chikungunya epidemic began in 2005

- Kenya, Tanzania, Seychelles, Comoros, Mauritius, Reunion, Madagascar, Malaysia, India, Sri Lanka, Philippines, more recently in Americas.
- In Reunion in 2005-2006
  - 255,000 cases
  - 226 deaths
    - Worse in aged:
    - Cardiovascular disease
    - Meningo-encephalitis
Chikungunya in La Reunion -- 2006

- 56 yo female living in Reunion, Feb. 2006
- Mosquito bites
- Fever (>103°F) and shaking chills x 4 days
- Swollen feet, joint pain of hands and feet
- Total body rash with blisters of mouth and lip
- Lower grade temperature (102 F) x 4 weeks
- Difficulty walking, could not wear shoes x 9 weeks
Chikungunya Philippines

Fall 2013 – Acute febrile illness with skin rash and arthritis pains.

 Seen at St Luke’s Hospital in Manila – serology’s negative for Dengue and Chikungunya.

4-6 weeks, unable to walk because of joint pain

Seen in Travel Medicine Clinic – Serology for Chikungunya positive at CDC.

 January 2014 – improved but still difficulty walking

Treatment Chikungunya

- There is no medicine to treat Chikungunya virus.
- Symptomatic treatment – rest, maintain hydration, acetaminophen for fever and pain
- Do not take aspirin and other non-steroidal anti-inflammatory drugs (NSAIDS until dengue can be ruled out to reduce the risk of bleeding).
- Acute Chikungunya – prevent mosquito bites for the first week of illness.

During the first week of infection, Chikungunya virus can be found in the blood and passed from an infected person to a mosquito through mosquito bites. An infected mosquito can then spread the virus to other people.

Zika Virus

- Zika Virus
  - Single stranded RNA Virus
  - Genus Flavivirus, Family Flaviridae
  - Closely related to dengue, yellow fever, Japanese encephalitis, Chikungunya and West Nile viruses
  - RNA viruses more often mutate
Zika Case

Travel in good health
3 week visit to high risk areas –of the South Pacific
   Noted “lots of insect bites.”
Near end trip - temp 38C, vomiting, diarrhea malaise.
4 days later: fever, RASH, myalgias, Head ache, arthralgias, conjunctivitis
Labs: Dengue IgM pos, Chikungunya IgM neg
CDC vector-borne disease lab:
   Zika IgM Capture ELISA and PRNT: Positive
Diarrhea and rash – 2 weeks
Conjunctivitis -- 1 week.
Malaise -- 2 months.

What are the symptoms?

- For people with symptoms, the most common symptoms of Zika are
  - Fever
  - Rash
  - Headache
  - Joint pain
  - Conjunctivitis (red eyes)
  - Muscle pain

Copy from slide share
Zika Virus Epidemiology

- 1947 – Zika virus from a febrile monkey in the Zika forest of Uganda – Sylvatic cycle.
- 14 subsequent publications of humans
- Two variants
  - Africa: Uganda, Nigeria and Senegal
  - Asia: India in 1952 – 33/196 had serology evidence of Zika – thought to be a benign disease

Zika Migration

ZIKA clinical disease and outcomes in Yap epidemic

- Incubation time 2-7 days
- Very contagious – 73% on island of Yap
  - Clinical illness mild, only 18% symptomatic
  - Symptoms last several days to a week.
  - Severe disease requiring hospitalization uncommon – none in Yap outbreak
  - Fatalities are rare – none in Yap outbreak
2013 French Polynesia

- 8,300 confirmed cases
- 30,000 estimated cases (11% of population)
- S/S fever, rash, body aches, mouth ulcers
- Rapid decrease of virus in blood, longer shedding of virus in saliva
- 74 cases of neurological complications – encephalitis, myelitis, facial paralysis
- 42 cases of Guillain-Barre, Zika by PCR in only 1 but IGM positive in 41 and neutralizing antibody in all 42
- Increased incidence fetal malformations recognized after reports from Brazil

Besnard Euro Sur 2014; Coa-Lourmeau Emerg Infect Dis 2014

How did this reach South America

- Cases detected in Easter Island (Chile) in March 2014
- FIFA World Cup Summer 2014
- Va’a Sprint Canoe Championships in Rio De Janeiro August 2014
- December 2014 – 1st Cases in Brazil
- Autochthonous transmission - May 2015

Musso Clin Micro Infect 2014; Salvador Travel Med Infect 2015

Current Outbreak

- Since May 2015 South America: Brazil, Bolivia, Columbia, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Honduras, Mexico, Panama, Paraguay, and Venezuela.
- Caribbean: Barbados, Dominican Republic, Haiti, Martinique, Puerto Rico, Saint Martin and the Virgin Islands.
- Cape Verde, off the coast of Africa,
- Pacific Islands: Tonga, Samoa.
- Estimated incidence -- 500k-1.5 million cases in S. America
Zika Virus and Microcephaly in Brazil

Reports of a substantial increase microcephaly:
- 2014 150 cases (0.07%)
- Oct 2015 to Feb 2016: 3,893 (1-2%)
- Zika virus infection detected several infants with microcephaly and early fetal death
- Study of 88 pregnant women – 82% Zika Pos.
  - 42 had Ultra Sound –
    - 29% of 42 or 12 were abnormal
    - 18% of 88 or 16 had no abnormalities

What and Why Microcephaly

- Clinical finding of a small head
  - Measured by: head circumference (HC) or occipito-frontal circumference (OFC), ultrasound or brain scan
  - Mechanisms
    - primary – abn. development (often genetic)
    - secondary – arrest or destruction of normal forming brain tissue (infection, vascular disruption)
  - Zika virus
    - actively penetrates the placenta barrier*
    - Disrupts mitosis of Human Endothelial Stem cells
      - more likely to die, less likely to divide**
Zika Virus can be added to infectious agents resulting in birth defects

- TORCH plus syphilis and now Zika
  - TO for Toxoplasmosis
  - R for Rubella
  - C for Cytomegalovirus
  - H for Herpes simplex and HIV
  - S for Syphilis
  - Z for Zika virus

Zika Virus -- Continental United States and Territories April 12, 2017 CDC

<table>
<thead>
<tr>
<th>Territories</th>
<th>Symptomatic Blood donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puerto Rico</td>
<td>35,397 325</td>
</tr>
<tr>
<td>Am. Samoa</td>
<td>132 0</td>
</tr>
<tr>
<td>Virgin Is.</td>
<td>997 0</td>
</tr>
<tr>
<td>USA:</td>
<td>5,234 42</td>
</tr>
<tr>
<td>Utah</td>
<td>22 0</td>
</tr>
</tbody>
</table>

Zika Associated Birth Defects 2016

- Preg. - possible recent infection 1,297 tested
- 972/1297 with reported outcomes
  - Birth defects 52 (5%)
- Lab confirmed Zika 250
  - Birth defects 25 (10%)
- Confirmed/first trimester 60
  - Birth Defects 9 (15%)
- Brain abnormalities and/or microcephaly present in 43/51 (84%)

US Zika Registry. MMWR 4/7/17 66(3):366-373
Utah Department of Health as of April 17, 2017

- **tests approved for testing**: 987, **positive**: 30
- One death in patient with underlying diseases
- One local spread from infected patient – Respiratory secretions
- **pregnant women**: 539
- **Test results returned**: 487 (52 pending), **12 preg.**
- **Status of Pregnancy**
  - Delivered: 12
  - Normal delivery: 9
  - Abnormal delivery: 0
  - Miscarriage: 2
  - Unknown: 1

Other Modes of Transmission

- Maternal-fetal – Intrauterine
- Perinatal – at time of birth
- Sexual - prolonged shedding in genital secretions – women 2 mo. Men 6 mo
- Blood transfusion
- Laboratory exposure
- Theoretical
  - Organ or tissue transplantation – Breast milk

Zika Laboratory Testing -- Utah Department of Health

- Pregnant Women with travel to an active Zika area
  - < 7 days of symptoms – Reverse Trans PCR
  - > 4 days of Sx – Anti-Zika IGM
- Pregnant in Zika area:
  - Sx by M or F – Female tested immediately
  - No sx: Test 1st prenatal visit & mid 2nd trimester
  - If PCR or IGM positive then:
    - Dengue/Chikungunya testing
    - Ultrasound immediately and q month
    - Evaluation of newborn
Pregnancy recommendations

- Zika positive with symptoms
  - Females – avoid unprotected sex 2 months from illness/exposure
  - Males – avoid unprotected sex for 6 months
  - Highest risk – acute infection first trimester
    - Pregnant or considering pregnancy avoid travel to endemic areas

Prevention of Aedes borne diseases

- Avoid Mosquito bites:
  - Wear long sleeved shirts and long pants
  - Housing with window & door screens & air conditioning
  - Use mosquito nets – more effective for malaria
  - Use mosquito repellents: DEET, Picaridin
  - Use permethrin on clothes not skin
- If you are sick
  - Use abstinence or condoms
  - try to avoid infecting mosquitoes
- Destroy mosquito reproductive habitat – standing water, disposal of water and solid waste, cleaning and covering water storage containers.
- Don’t travel to areas where outbreaks are occurring

Vaccines

- Dengue – trials in progress
  - Approved for use in Mexico, Philippines, Brazil
    - Three dose vaccine over 6 months
    - 59.2% efficacy, 79.1% severe disease, 80% decrease in hospitalization
- Chikungunya – NIH testing in India
  - Phase 1 – good response, no safety problems
  - Phase 2 – in progress
- Zika – Five major vaccine producers
  - Phase I & II studies appear promising targeted approval 2018
Ebola Virus

- Prototype Viral Hemorrhagic Fever Pathogen
  - Filovirus: enveloped, non-segmented, negative-stranded RNA virus
  - Severe disease with high case fatality
  - Absence of specific treatment or vaccine

- >20 previous Ebola and Marburg virus outbreaks
- 2014 West Africa Ebola outbreak caused by Zaire ebolavirus species (five known Ebola virus species)

- Zoonotic virus – bats the most likely reservoir, although species unknown
- Spillover event from infected wild animals (e.g., fruit bats, monkey, duiker) to humans, followed by human-human transmission
This graph shows the total reported cases (suspected, probable, and confirmed) in Guinea, Liberia, and Sierra Leone provided in WHO situation reports beginning on March 25, 2014, through the most recent situation report on February 7, 2016.

2014 Ebola Outbreak
Reported Cases (Suspected, Probable, and Confirmed) in Guinea, Liberia, and Sierra Leone

Ebola Cases and Deaths

<table>
<thead>
<tr>
<th>Country</th>
<th>Reporting Date</th>
<th>Total Cases (Suspected, Probable, and Confirmed)</th>
<th>Confirmed Cases</th>
<th>Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea</td>
<td>26 Dec 15</td>
<td>4,485</td>
<td>3,351</td>
<td>2,218</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>7 Feb 15</td>
<td>14,124</td>
<td>8,706</td>
<td>3,956</td>
</tr>
<tr>
<td>Liberia</td>
<td>14 Mar 16</td>
<td>10675</td>
<td>5160</td>
<td>4009</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>28,639</td>
<td>15,251</td>
<td>11,316</td>
</tr>
</tbody>
</table>

Ebola Cases (United States)

Four health care workers diagnosed with Ebola in the USA

1 index case from Liberia to Texas who died
2 medical care providers of case 1
1 medical care provider from Guinea to New York

During this outbreak, 6 health workers and 1 journalist have been infected with Ebola virus while in West Africa and transported to hospitals in the United States.

- 1 of the health workers died on November 17, 2014, after being transported from Sierra Leone to Nebraska Medical Center
Human-to-Human Transmission

- Infected persons are not contagious until onset of symptoms
  - Possible that the virus can be transmitted through semen of a man who has survived Ebola
- Infectiousness of body fluids (e.g., viral load) increases as patient becomes more ill
  - Remains from deceased infected persons are highly infectious
- Human-to-human transmission of Ebola virus via inhalation (aerosols) has not been demonstrated

Early Clinical Presentation

- Acute onset, typically 8-10 days after exposure (range 2-21 days)
- Signs and symptoms
  - Initial: Fever, chills, myalgias, malaise, anorexia
  - After 5 days: GI symptoms, such as nausea, vomiting, watery diarrhea, abdominal pain
  - Other: Headache, conjunctivitis, hiccups, rash, chest pain, shortness of breath, confusion, seizures
  - Hemorrhagic symptoms in 18% of cases
- Other possible infectious causes of symptoms
  - Malaria, typhoid fever, meningococcemia, Lassa fever and other bacterial infections (e.g., pneumonia) – all very common in Africa

Clinical Features

- Nonspecific early symptoms progress to:
  - Hypovolemic shock and multi-organ failure
  - Hemorrhagic disease
  - Death
- Non-fatal cases typically improve 6-11 days after symptoms onset
- Fatal disease associated with more severe early symptoms
  - Fatality rates of 70% have been historically reported in rural Africa
  - Intensive care, especially early intravenous and electrolyte management, may increase the survival rate
Patient Recovery

- Patients who survive often have signs of clinical improvement by the second week of illness
  - Associated with the development of virus-specific antibodies
  - Antibody with neutralizing activity against Ebola persists greater than 12 years after infection

- Prolonged convalescence
  - Includes arthralgia, myalgia, abdominal pain, extreme fatigue, and anorexia; many symptoms resolve by 21 months
  - Significant arthralgia and myalgia may persist for >21 months
  - Skin sloughing and hair loss has also been reported


Practical Considerations for Evaluating Patients for Ebola in the United States

- CDC encourages all U.S. healthcare providers to assess patients for
  - International travel within the last 21 days, or
  - Contact with someone with confirmed Ebola, and
  - Fever or other symptoms of Ebola
- If a patient has both exposure and symptoms, know the initial steps to take
- CDC has developed documents to facilitate these evaluations
EVD Summary

- The 2014 Ebola outbreak in West Africa is the largest in history and has affected multiple countries

- Think Ebola: U.S. healthcare providers should be aware of clinical presentation and risk factors for Ebola

- Human-to-human transmission by direct contact
  - No human-to-human transmission via inhalation (aerosols)
  - No transmission before symptom onset

- Early case identification, isolation, treatment and effective infection control are essential to prevent Ebola transmission

Ask!

- In someone presenting with a contagious disease

  Ask about travel!!!!!