As a result of this presentation, participants will be able to:

- Identify the risk of malaria at destination & be able to select the appropriate regimen for chemoprophylaxis.
- State the WHO Strategic Advisory Group of Experts (SAGE) guidance on yellow fever vaccine & the current status of International Health Regulations.
- Use updated CDC ACIP guidelines for use of Japanese encephalitis vaccine in adults & children.
- Discuss insect precautions that might protect travelers at risk of dengue & chikungunya virus infections.

Malaria

Malaria is a blood borne parasitic infection spread from person to person through bites of infected female Anopheles mosquitoes.

Plasmodium species causing human infections:
- P. vivax
- P. falciparum
- P. malariae
- P. ovale
- P. knowlesi

Malaria Drug Resistance

- Drug-resistant P. falciparum
  - Chloroquine-resistant P. falciparum - widespread
  - Resistance to sulfadoxine/pyrimethamine, mefloquine, halofantrine, and quinine - less widespread geographically

- Drug-resistant P. vivax
  - Chloroquine-resistant P. vivax - Papua New Guinea, Southeast Asia, Indian subcontinent, South America
  - Emerging resistance to primaquine in P. vivax isolates from Oceania

Malaria Endemic Zones

Malaria in Africa, Middle East, Asia, Oceania

Malaria in the Americas

P. falciparum Malaria Chemoprophylaxis*

<table>
<thead>
<tr>
<th>Malaria risk sufficient to warrant prophylaxis</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine-sensitive area</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Chloroquine-resistant area</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Mefloquine-resistant area</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

* Agents are listed in temporal order of clinical use for malaria prophylaxis, newest to oldest.

Adapted from Connor BA. J Travel Med. 2001;8(suppl 3):S57–S64.
Malaria Chemoprophylaxis (United States)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pre-travel Dosing</th>
<th>Post-travel Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquone-proguanil1</td>
<td>1-2 days</td>
<td>7 days</td>
</tr>
<tr>
<td>Doxycycline2</td>
<td>1-2 days</td>
<td>4 wks</td>
</tr>
<tr>
<td>Mefloquine3</td>
<td>1-3 wks</td>
<td>4 wks</td>
</tr>
<tr>
<td>Chloroquine4</td>
<td>1-2 wks</td>
<td>4-8 wks</td>
</tr>
</tbody>
</table>

1. Atovaquone-proguanil (Malarone®) GlaxoSmithKline.

Mefloquine – FDA revises labeling

July 29, 2013, U.S. FDA revises mefloquine (Lariam) labeling.
- **Boxed warning:**
  - Rare reports of neurologic side effects (dizziness, loss of balance, and ringing in the ears) that were persistent or permanent.
  - Rare reports of psychiatric side effects (feeling anxious, mistrustful, depressed or having hallucinations) that were persistent or permanent.
  - Symptoms can occur at any time during use and can last for months to years after the drug is stopped, or can be permanent.
- FDA still approves of mefloquine for prevention and treatment of malaria.

Prevention of Malaria

- **Avoid mosquito bites**
  - Personal protection methods
  - Sleep under bed-nets
- **Malaria chemoprophylaxis**¹, ²
  - Chloroquine
  - Atovaquone + Proguanil (Malarone®)
  - Doxycycline
  - Mefloquine (Lariam®)
- **Standby treatment/ambulatory treatment**¹
  - Atovaquone + Proguanil (Malarone®)
  - Artemisinin + Lumefantrine (CoArtem®)


Stand-by Emergency Treatment (SBET)

- Traveler rejects advice to take prophylaxis
- Traveler must take a sub-optimal drug regimen for medical reasons
- Traveler going to remote area
- Recommended drugs may be scarce at destination

Tafenoquine plus Chloroquine

- December, 2013: Single-dose tafenoquine given with chloroquine was more efficacious than chloroquine alone in preventing vivax malaria relapse.
- Promotes improved treatment regimen compliance.
- FDA status: under review

Issues in Malaria Prevention

- Drugs available in U.S. may be costly for long-term traveler.
- Drugs available overseas at destination may be counterfeit.
- Adverse drug side effects may cause travelers to interrupt/discontinue chemoprophylaxis.
- Motivation to adhere to chemoprophylaxis in long-term travelers may wane.
- Personal insect precautions also require adherence.
- SBET for selected high-risk travelers
Yellow Fever

Yellow fever (YF) is a Flavivirus transmitted from non-human primates in jungle areas, and humans in transitional and urban areas, by Aedes aegypti and related species of mosquitoes in equatorial Africa, and in Central and South America.

- Infections are asymptomatic or non-specific influenza-like syndromes with fever, chills, headache
- 15% progress to more serious or toxic disease with jaundice & hemorrhagic symptoms
- 20-50% case-fatality ratio for severe cases with hepato-renal failure

Yellow Fever Endemic Zones

Yellow Fever Vaccine

- International Health Regulations (IHR) allow countries to require an International Certificate of Vaccination or Prophylaxis against YF for entry:
  - Vaccination may be required by selected countries outside the endemic zones for travelers arriving from an endemic-zone country—even if only in transit
  - Certificate valid from 10 days to 10 years after vaccination
  - Vaccination waiver must be obtained before departure
- WHO Strategic Advisory Group of Experts (SAGE) reports that 10-year YF vaccine booster is not necessary (May, 2013) BUT there is no change in the IHR.

Yellow Fever Vaccine: Adverse Events

- Yellow fever vaccine (YFV):
  - Contains live attenuated 17D strain YF virus
  - 2-5% vaccine recipients: fever, headache, muscle aches 5-14 days post vaccination
  - 1/1 million doses: immediate hypersensitivity reaction due to egg allergy
- Yellow fever vaccine-associated neurotropic disease (YEL-AND):
  - Young age < 6 months considered a significant risk factor
  - May occur 7-21 days post vaccination
  - Neurologic signs, CSF pleocytosis, increased CSF protein
  - Estimated rate 1/8 million doses

Yellow fever vaccine-associated viscerotropic disease (YEL-AVD)

- 13 cases reported / >100 million doses (1996-2002) = VERY RARE
  - Incidence rate inaccurate because of incomplete surveillance in some countries where YF vaccine is used
  - Fever, myalgia, arthralgia, increased liver enzymes & bilirubin, hypotension, thrombocytopenia, proteinuria, electrolyte disturbances, encephalopathy, jaundice, hypotension, oliguria
  - AKA "febrile multiple organ system failure"
  - Male: Female ratio approximately 2:1
- May occur 2-5 days after receiving YF vaccine
  - All cases reported to date occurred among persons receiving their first YF vaccine dose
  - Advanced age over 65 years old appear to be a risk factor
  - 8/1,000,000 recipients aged 65-74 years
  - 9.1/1,000,000 recipients aged >75 years

CDC and WHO have stated that no change in vaccine practices or indications is warranted based on these limited data.
Issues in Yellow Fever Prevention

- Global supply of Yellow Fever Vaccine (vaccine shortage)
- Egg allergy
- Live virus vaccine
- Pregnant travelers
- Infant travelers
- Senior travelers
- Travelers with altered immunity

Japanese encephalitis

Japanese encephalitis (JE) is a Flavivirus transmitted from animal reservoirs to humans by Culex tritaeniorhynchus & related mosquito species in Asia, including India, China and SE/SW Asia.

- 27,059 cases of JE reported to WHO during 2006-2009: 86% from China and India
- 1 in 300 to 1 in 1000 infections with JE lead to clinical disease
- Younger children and adults older 50 years old living in endemic areas are more at risk of developing clinical disease
- Immunologically-naïve adults of all ages (e.g. travelers) have a similar risk of infection as children living in endemic areas

Japanese encephalitis deaths

Risk Areas for Japanese Encephalitis

ACIP JE-VC Vaccine Recommendations

- JE vaccine is recommended for travelers who plan to
  - Spend > 1 month in endemic areas during JEV transmission season
  - Include long-term travelers, recurrent travelers, or expatriates who will be based in urban areas but likely to visit rural or agricultural areas
  - JE vaccine should be considered for the following persons
    - Short-term (<1 month) travelers if they plan to travel outside of urban areas especially if they will
      - Be outdoors in rural or agricultural areas during the evening or night
      - Participate in extensive outdoor activities (camping, hiking, trekking, biking, fishing, hunting, or farming)
      - Stay in accommodations without air conditioning, screens, or bed nets
    - Travelers to an area with an ongoing JE outbreak
    - Travelers in endemic areas with unpredictable itineraries
    - Special categories
      - Military, technical consultation, disaster relief, etc.)

Vero cell culture-derived Japanese Encephalitis Vaccine (JE-VC)

JE-VC was licensed in 2009 by FDA for use in persons aged >17 years.
- JE-VC primary series consists of 2 doses administered 28 days apart.
- Booster dose of JE-VC is recommended if the primary series of JE-VC was administered >1 year AND there is a new potential for JE virus exposure.
- A 2-dose primary series of JE-VC is recommended if a JE-MB primary series was administered >1 year AND there is a new potential for JE virus exposure.

CDC. Recommendations for use of a booster dose of inactivated Vero cell culture-derived Japanese encephalitis vaccine—Advisory Committee on Immunization Practices, 2011. MMWR 2011; 60 (20);661-663.

JE-VC Vaccine Use in Children

- In May, 2013, the FDA licensed inactivated vero cell culture-derived JE vaccine (manufactured as IXIARO) for use in children 2 months through 16 years of age.
- On June 19, 2013, the CDC ACIP extended recommendations for use of JE vaccine to include the use of IXIARO in children aged 2 months through 16 years.
- The primary series is 2 doses administered 28 days apart.
  - For adults and children aged >3 years, each dose is 0.5mL.
  - For children aged 2 months through 2 years, each dose is 0.25mL.
  - To administer a 0.25mL dose, HCP must expel and discard half of the volume from the 0.5mL prefilled syringe before injection. To enable this, the manufacturer has developed a prefilled syringe with a red line on the barrel to indicate the 0.25mL point.

www.cdc.gov/japaneseencephalitis/vaccine/vaccineChildren.html

Issues in J. encephalitis prevention

- WHO estimates that the disease is under-reported.
- Many countries in areas of risk have mass JE immunization public health programs for resident populations.
- JE vaccines available in destination countries may be different than JE vaccine licensed by FDA.
- Environmental control of animal reservoir hosts (mainly wading birds and pigs) and vector mosquitoes is unlikely.
- Regions of JE transmission may be changing and expanding due to multiple factors.

Dengue fever

- Tropical & subtropical distribution between 30º north and 30º south latitudes.
- A largely urban disease transmitted by Aedes aegypti and Aedes albopictus mosquitoes, which bite during the day.
- 50-100 million cases/year worldwide.

Dengue – Americas
Chikungunya virus

- Alphavirus transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes
- 2 million cases in Asia and Africa—attack rate up to 68% in some areas
- Infection associated with prolonged incapacitating joint pain (polyarthralgias)
- No specific cure
- Co-circulation of dengue fever in many areas

Photo source: CDC

Chikungunya - Caribbean

December 2013: WHO reports local transmission in Saint Martin
January 21, 2014: Local transmission of chikungunya in the Caribbean reported in
- Saint Martin (French)
- Sint Maarten (Dutch)
- Martinique
- Guadeloupe
- Saint Barthelemy
- British Virgin Islands

CDC Travel advisories*

- Watch -
  - Level 1, Practice Usual Precautions
- Alert -
  - Level 2, Practice Enhanced Precautions
- Warning -
  - Level 3, Avoid Nonessential Travel

*www.cdc.gov
### Signs & Symptoms

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>MAL</th>
<th>DEN</th>
<th>CHIKV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>97%</td>
<td>95%</td>
<td>+++</td>
</tr>
<tr>
<td>Chills</td>
<td>97%</td>
<td>77%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>94%</td>
<td>92%</td>
<td>+++</td>
</tr>
<tr>
<td>Severe eye pain</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Anorexia/N&amp;V</td>
<td>62%</td>
<td>69%</td>
<td>+</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>56%</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>50%</td>
<td>80%</td>
<td>+++</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>77%</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Rash</td>
<td>9%</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Backache</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dark urine</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Prevent Mosquito Bites

1. Use insect repellent on exposed skin
2. Wear insecticide-treated clothing (permethrin-impregnated)
3. Wear clothing with long sleeves & pants
4. Select time of day for outdoors activities
5. Sleep under a bed-net, sprayed or treated with permethrin
6. Stay in screened, air-conditioned rooms

### Effectiveness of Repellents

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration*</th>
<th>Min. before Bite</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEET</td>
<td>23.8%</td>
<td>301.5</td>
</tr>
<tr>
<td>Oil of Eucalyptus</td>
<td>30.0%</td>
<td>120.1</td>
</tr>
<tr>
<td>DEET</td>
<td>6.7%</td>
<td>112.4</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>2.0%</td>
<td>94.6</td>
</tr>
<tr>
<td>DEET</td>
<td>4.8%</td>
<td>88.4</td>
</tr>
<tr>
<td>IR3535</td>
<td>7.5%</td>
<td>22.9</td>
</tr>
<tr>
<td>Citronella</td>
<td>10.0%</td>
<td>19.7</td>
</tr>
</tbody>
</table>

*Do not apply to broken skin; also may absorb from 6% to 17% of the dose applied, usually eliminated through urine within 12-24 hours. Ref: New Engl J Med. July 2002; National Pesticide Info.Ctr. www.npic.orst.edu.

### Picaridin insect repellent vs. DEET

- Picaridin (KBR 3023) is a synthetic insect repellent commercially available in 7% and 19.2% formulations
- Registered in the U.S. since 2001
- Efficacy appears comparable to similar concentrations of DEET
  - Active against biting flies, mosquitoes, chiggers, ticks, fleas
  - EPA toxicity data base complete (safe skin repellent)

http://www.epa.gov/opprd001/factsheets/picaridin.pdf

### Issues in Personal Protection Measures

- All measures require awareness and self-motivation
- Repellants may require several re-applications during the day
- Repellants add to the travel supplies that must be acquired and packed
- Preferred products may not be available at destination (long-term travelers)
- Continuous use may not be acceptable for those at greatest risk (infants, elderly)

### Further Travel Medicine Resources*


*Consult www.cdc.gov and www.who.int for current advisories and updated information.