Dengue and Chikungunya: Diseases, Diagnosis, Vectors, and Threats

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Outline

- Describe dengue and chikungunya clinical diseases, including severe dengue
- List laboratory diagnostic tests for dengue and chikungunya
- Describe epidemiology including vectors
- Discuss current threats to California and preparedness and prevention measures
California Traveler #1

• In May 2015, a 55 y.o. male California resident presented to medical attention complaining of a week of fever, chills, night sweats, and joint pain. No headache, no eye pain, no muscle aches, no rash. Had some bleeding gums.

• He just returned from El Salvador where he had stayed for over 2 weeks. He recalled having had mosquito bites while there.

• Your guess on diagnosis?
In April 2015, a 44 y.o. male California resident was hospitalized for fever, headache, muscle aches, malaise, and rash. Blood tests show low WBC and low PLT.

A week before illness onset, he had returned from Honduras where he had stayed for a week. Did not recall mosquito bites.

Your guess on diagnosis?
Mosquito-Borne Infectious Disease Risks to Travelers

- Chikungunya
- Dengue
- Malaria
- Zika virus disease
- Japanese encephalitis
- Yellow fever
- West Nile virus disease
- Filariasis
Mosquito Vectors of Infectious Disease Risks to Travelers

- Chikungunya: *Aedes aegypti, Ae. albopictus*
- Dengue: *Aedes aegypti > Ae. albopictus*
- Malaria: *Anopheles* species
- Zika virus disease: *Aedes* species
- Japanese encephalitis: *Culex* species
- Yellow fever: *Ae. aegypti, other Aedes spp.*
- WNV disease: *Culex pipiens, Cx. tarsalis, Cx. quinquefasciatis, other mosquito species*
- Filariasis: *Anopheles, Culex, Mansonia* spp.
Invasive *Aedes* Detected Recently in California

**Aedes albopictus**  
(Asian tiger mosquito)  
2011-15: Los Angeles County

**Aedes aegypti**  
(Yellow fever mosquito)  
Aedes Mosquito Basics

- Only the female *Aedes* mosquitoes feed on blood, because they need protein to produce eggs. Male mosquitoes feed on plant nectar.

- On average, *Aedes* mosquitoes live 2 to 4 weeks.

- Average flight range is less than 500 meters (0.31 mile).
In dry conditions, eggs can survive up to a year.
Dengue

- **Pathogen**: Dengue virus (flavivirus) serotypes 1-4
- **Diseases**: Inapparent infection (up to 66-75%), Dengue Fever (DF), Severe Dengue (DHF, DSS)
- **Mosquito vectors**: Aedes aegypti, Aedes albopictus
Dengue Risk Areas and Burden

W.H.O. estimates 50-100 million infections including 22,000 deaths yearly in 100+ countries
Average number of dengue and severe dengue cases reported to WHO annually in 1955–2007 and number of cases reported in recent years, 2008–2010

WHO, 2012
Dengue Infections

All infections

Asymptomatic
66-75%

Symptomatic
25-34%

Dengue fever
95-99%

Severe dengue
1-5%

Survive
95-99.5%

Die
0.5 - 5%

Adapted from Vaccine 2004; 22: 1275-1280
Dengue Fever

- Incubation period: 3 – 10 days

- **Dengue Fever:**
  - High fever $\geq 102 \, \text{F}/39 \, \text{C}$ for 2 – 7 days, AND
  - two or more of: severe headache, pain behind eyes, muscle and bone pain, joint pain (without effusion), rash, easy bruising or mild bleeding (e.g., nose or gums bleed), low WBC

- Critical period 24 – 48 hours after defervescence
Severe Dengue

Dengue Hemorrhagic Fever (DHF):
- Warning signs during critical period 24-48 hrs after defervescence:
- Abdominal pain or persistent vomiting, red spots on skin, bleeding from nose or gums, tarry stools, drowsiness, clammy skin, difficulty breathing

Dengue Shock Syndrome (DSS):
- Increased vascular permeability / plasma leakage ➔ pleural effusions, ascites, hypotension, shock ➔ death (1-5%)
Meta-Analysis of Signs/Symptoms Predictive of Severe Dengue*

- Bleeding (OR: 13.6; 95% CI: 3.3-56.5)
  - Hematemesis (OR: 6.2; 95% CI: 2.7-14.3)
  - Melena (OR: 10.4; 95% CI: 3.1-35.0)
- Abdominal pain (OR: 2.3; 95% CI: 1.6-3.2)
- Skin rashes (OR: 2.0; 95% CI: 1.3-3.3)
- Hepatomegaly (OR: 4.8; 1.8-12.6)

Risk of Severe Dengue in Second Infection with Different Serotype

Documented in several studies in different countries, with most serotypes.

Postulated to be due to antibody-dependent enhancement (ADE) from heterotypic antibodies from first infection.

However, recent studies found antibodies from first infection protective up to 2 years; and risk of severe dengue increases if second dengue infection acquired >2-3 years after first infection.

Third and fourth infections milder clinically.
Dengue: Laboratory

Tests:

- RT-PCR
- Serology: IgM & IgG IFA, IgM antibody-capture ELISA (MAC-ELISA), IgG ELISA
- Neutralizing antibody for confirmation

Availability:

- CDPH Viral and Rickettsial Disease Laboratory (VRDL)
- CDC
Dengue Treatment & Prevention

Treatment:
- Supportive, fluid (oral rehydration solution or isotonic solutions), acetaminophen (avoid aspirin and NSAIDs which may increase risk of bleeding)

Prevention:
- Avoid mosquito bites in risk areas

Vaccine:
- No commercial vaccine yet
- Some in clinical trials
Selected Dengue Vaccine Candidates

- Live attenuated tetravalent chimeric YF-DEN (Sanofi Pasteur) _ Phase III
- Live attenuated tetravalent, licensed NIH (Butantan, Brazil) _ Phase II
- Live attenuated tetravalent chimeric (Takeda acquired Inviragen)(eng. at CDC) _ Phase II
- Recombinant E subunit protein (Merck) _ Phase I
- Tetravalent formulation (NIH) _ to begin Phase II
Efficacy and Safety of one Dengue Vaccine Candidate*

- Live attenuated tetravalent chimeric YF-DEN (Sanofi Pasteur) _ Pooled efficacy from phase III & IIb trials for symptomatic dengue during first 25 months:
  - 60.3% (95% CI, 55.7-64.5) for all participants
  - 65.6% (95% CI, 60.7-69.9) for ≥ 9 year olds
  - 44.6% (95% CI, 31.6-55.0) for < 9 year olds
  - Pooled serotype-specific efficacy ranged from 47.1% for DENV-2 to 83.2% for DENV-4.

*Hadinegoro SR, et al. NEJM 2015
Dengue in US

- Most U.S. cases were imported by infected travelers returning from Caribbean, Latin America, Asia, etc..
- Recent outbreaks with local transmission
  - **Florida**: (no locally acquired cases since 1934)
    - 2009-2010: 88 cases in Key West
    - 2013: 28 cases in Martin County outbreak
    - 2014: 7 cases
  - **Hawaii**: (no locally acquired cases since 1944)
    - 2001-2002: 122 cases
  - **Texas**: (no locally acquired cases since 1945)
    - 1980: 23 cases; 1980-1999: 64 cases
    - 2005: DEN-2 outbreak in Brownsville, Cameron Co
    - 2013: 33 cases in Cameron and Hidalgo counties:
      - 12 locally acquired, 16 traveled to MX
FIGURE 2. Number of cases of dengue fever, by week of report — City of Matamoros, Mexico,* and Cameron County, Texas,† 2005

- Cameron County, Texas
- Matamoros, Mexico

Autochthonous case of dengue hemorrhagic fever, Cameron County

Serosurveys conducted

Week and month

7 May 21 Jun 4 Jul 18 Aug 2 Sep 16 Oct 30 Nov 13 Dec

Number

Source: CDC MMWR 56(31); 785-789

* n = 1,596.
† n = 25.
**Chikungunya**

- **Pathogen**: chikungunya virus (alphavirus)
- **Diseases**: asymptomatic infection (5-25%), chikungunya fever (75-95%)
- **Mosquito vectors**: *Aedes aegypti, Aedes albopictus*
Approximate Global Distribution of Chikungunya Virus, by Country, 2008

Countries and territories where chikungunya cases have been reported* (CDC, as of March 10, 2015)
Chikungunya Virus in the Americas, 2013-2014*

- ~1,110,034 suspected cases; 24,375 lab-confirmed.

*Pan American Health Organization 2015
Chikungunya Fever

Incubation period:
- typically 3-7 days (range, 1-12 days)

Disease:
- High fever (>102 F/39 C), chills, headache, nausea, vomiting, multiple joint pain with or without swelling (finger joints, wrists, knees, ankles), lower back pain, rash.
- Mortality rare, mostly in older adults
DIFERENCIAS ENTRE EL DENGUE Y LA CHIKUNGUNYA

**Dengue**
- Dolor leve en articulaciones.
- Hemorragias, según el tipo de dengue.
- Alteraciones hematológicas.
- Dolor detrás de los globos oculares.
- Agrandamiento de ganglios linfáticos

**Síntomas**
- Duración de la fiebre: Entre 2 y 7 días

**Chikungunya**
- Dolor severo en las articulaciones que obliga a encorvarse
- Mayor picazón de manos y pies.
- No hay alteraciones importantes hematológicas.
- En algunos casos los dolores articulares pueden durar meses o incluso un año

**50%**
De los casos son indistinguibles
Chikungunya Treatment & Prevention

Treatment:
- Rest, fluids, acetaminophen for fever and joint pain (avoid aspirin and NSAIDs until dengue ruled out).
- usually recover in 7-10 days; in some, joint pain may persist months-over a year.

Prevention:
- Avoid mosquito bites in risk areas

Vaccine:
- None
Chikungunya: Laboratory

Tests:
- RT-PCR
- Serology: IgM & IgG IFA, IgM-capture ELISA, IgG ELISA
- Neutralizing antibody for confirmation

Availability:
- CDPH VRLD
- CDC
States reporting chikungunya cases – United States, 2014 *
N = 2,792 cases

*CDC
States reporting chikungunya cases – US, 2015 (as of August 11, 2015)*  _  N = 273 cases from 36 states

*CDC
Aedes aegypti and Aedes albopictus Mosquitoes Detection Sites in California, 2011-2015

Updated October 5, 2015

*Unincorporated Census-Designated Places
Critical Factors Needed for Local Transmission of Dengue or Chikungunya in California

- Presence of a competent vector *Aedes aegypti* or *Aedes albopictus*

- Presence of an infected person who is viremic (up to 7 days after illness onset) in an infested area during periods when vectors are active and abundant

- Mosquito vector biting infected person and then living long enough (approx. 10-11 days) to bite another person

➢ Risk of local transmission is currently low in California
2014 Human dengue and/or chikungunya cases in California, USA

- **Aedes aegypti**
  - San Diego
  - Los Angeles
  - Kern
- **Aedes albopictus**
  - Orange
  - San Mateo
  - Imperial

Reported cases:
- 1-10 reported cases
- 11-20 reported cases
- >21 reported cases
Chikungunya in California*

- Chikungunya is not yet reportable in CA, but LHDs are notified of laboratory-confirmed cases and can report to CDPH via CalREDIE.
- Between 2009 and 2013, CDPH was notified of 3 confirmed cases among returned travelers.
- In 2014, 137 cases were documented, all with travel history to chikungunya-affected areas in Latin America and Caribbean.
- Of 2014 case-patients, 67% likely viremic while in CA, 42% with illness onset after arrival and 26% with illness onset within 7 days before arrival.
- Of these likely viremic patients, 59% arrived in a county with a known invasive Aedes infestation.

*Porse CC et al. Emerg Infect Dis 2015
Dengue in California*

- To date, all CA cases were in travelers returning from dengue-affected areas.
- The annual number of dengue cases increased from 41 in 2011 to 132 in 2014.
- Of the 2014 dengue case-patients, 74% were likely viremic while in CA, 54% with illness onset after arrival and 20% with illness onset within 5 days before arrival.
- Of likely viremic patients, 43% arrived in a county with a known invasive Aedes infestation.

*Porse CC et al. Emerg Infect Dis 2015
Number of Dengue and Chikungunya Cases Reported in 2015

- Baja California: 532 Dengue, 58 Chikungunya
- Sonora: 358 Dengue, 11 Chikungunya
- Baja California Sur: 269 Dengue, 5 Chikungunya
- Coahuila: 245 Dengue, 358 Chikungunya
- Sinaloa: 235 Dengue, 191 Chikungunya
- Tamaulipas: 239 Dengue, 794 Chikungunya
- Nayarit: 176 Dengue, 415 Chikungunya
- Jalisco: 718 Dengue, 358 Chikungunya
- Guerrero: 1151 Dengue, 962 Chikungunya
- Chiapas: 394 Dengue, 225 Chikungunya
- Jalisco: 225 Dengue, 52 Chikungunya

Legend:
- Dengue cases
- Chikungunya cases
Mosquito Vectors of Infectious Disease Risks to Travelers

- Chikungunya: *Aedes aegypti, Ae. albopictus*
- Dengue: *Aedes aegypti > Ae. albopictus*
- Malaria: *Anopheles* species
- Zika virus disease: *Aedes* species
- Japanese encephalitis: *Culex* species
- Yellow fever: *Ae. aegypti, other Aedes spp.*
- WNV disease: *Culex pipiens, Cx. tarsalis, Cx. quinquefasciatis, other mosquito species*
- Filariasis: *Anopheles, Culex, Mansonia spp.*
Zika Virus

- Another Flavivirus transmitted by *Aedes* mosquitoes.
- About 80% asymptomatic, 20% symptomatic: fever, arthralgia, maculopapular rash, or conjunctivitis.
- Illness usually mild for several days; reports of Guillain-Barre syndrome (also seen with dengue).
- Test may cross-react with related flaviviruses (e.g., dengue and West Nile viruses).
- Treatment is supportive for symptoms; no specific antiviral available.
Countries with past/current Zika virus transmission (as of May 2015) *

* CDC
Mosquito Precautions for Travelers

- Protect yourself outside
  - Cover exposed skin (long pants, long-sleeved shirts, hats)
  - Use mosquito repellent (DEET, picaridin, oil of lemon eucalyptus, IR3535)
  - Use permethrin-treated clothing and gear

- Protect yourself inside
  - Stay in screened or air-conditioned rooms
  - Use bed nets
Guidance for Surveillance of and Response to Invasive Aedes Mosquitoes and Locally Acquired Exotic Infections Transmitted by These Mosquitoes in California - 2014

Recommended surveillance, coordination, and response actions for local vector control agencies and local health departments under four scenarios:

• Pre-detection of Aedes aegypti/albopictus
• Post-detection of Aedes aegypti/albopictus
• Detection of Aedes aegypti/albopictus positive for dengue, chikungunya, or another exotic mosquito-borne virus before local human infection documented
• Detection of locally acquired human infection with dengue, chikungunya, or another exotic mosquito-borne virus
Recommended Actions for Local Agencies

All actions emphasize coordination and collaboration between local vector control and public health agencies

Pre-detection of *Aedes* (Vector and/or LHD)

- Identify agencies and resources that can be consulted regarding identification, surveillance, and control of invasive *Aedes* and exotic arboviral infections in humans
- Develop and implement an early detection plan for invasive mosquitoes
  - Include mosquito identification, a public outreach program, and appropriate mosquito surveillance tools
- Develop a response plan that can be implemented at the first detection of invasive mosquitoes
- Continue to report any cases of dengue, chikungunya, and other exotic mosquito-borne viruses via CalREDIE
  - Ensure report includes travel history
Locally acquired human infection identified

• Issue joint media release and intensify all public outreach and education efforts
• Enhance mosquito surveillance and control in vicinity of case-patient’s residence, neighborhood, and other locations patient visited if *Aedes* present
• Enhance surveillance for additional locally acquired human cases by notifying the local medical community to look for and encourage testing of all suspected infections, regardless of travel history, and to report ASAP
• Follow-up promptly on all suspect cases and notify CDPH via CalREDIE or by phone
• Enhance mosquito surveillance and control in neighborhoods of suspect cases
Tests for dengue, chikungunya, WNV, other mosquito-borne viruses (e.g., WEE, SLE, Zika) in suspect patients

For dengue:
- RT-PCR
- Serology: IgM & IgG IFA, IgM-capture ELISA, IgG ELISA
- For confirmation, PRNT for neutralizing antibody

For chikungunya:
- RT-PCR
- Serology: IgM & IgG IFA
- For confirmation, PRNT for neutralizing antibody

For WNV:
- RT-PCR
- Serology: IgM & IgG IFA, IgM-capture ELISA, IgG ELISA
- For confirmation, PRNT for neutralizing antibody
Mosquito Breeding Sites for Dengue and Chikungunya

1. Keep gutters clean
2. Repair leaky faucets
3. Eliminate debris that holds water
4. Drain excess water from plant pots and saucers
5. Change bird baths twice a week
6. Maintain pools and spas; keep water from pooling on covers
7. Turn toys and equipment upside down to prevent water from collecting inside
8. Avoid overwatering

Help your community reduce mosquito-borne diseases like West Nile Virus by keeping your property free from mosquito breeding sites
In May 2015, a 55 y.o. male California resident presented to medical attention complaining of a week of fever, chills, night sweats, and joint pain. No headache, no eye pain, no muscle aches, no rash. Had some bleeding gums.

He just returned from El Salvador where he had stayed over 2 weeks. He recalled having had mosquito bites while there.

Diagnosis: acute and convalescent IgM for dengue positive; chikungunya negative.
California Traveler #2

- In April 2015, a 44 y.o. male California resident was hospitalized for fever, headache, muscle aches, malaise, and rash. Blood tests show low WBC and low PLT.
- A week before illness onset, he had returned from Honduras where he had stayed for a week. Did not recall mosquito bites.
- Diagnosis: Acute IgM dengue 0.74 negative, chikungunya 1:10 positive; Convalescent IgM dengue 4.33 positive, chikungunya 1:640 positive => coinfection!
Summary

• Dengue and chikungunya are mosquito-borne infections threatening California.
• Dengue and chikungunya human cases have recently increased, all among travelers returning from affected areas/countries.
• Recent transmissions documented in US states where *Ae. aegypti* and/or *albopictus* abundant.
• *Ae. aegypti* or *Ae. albopictus* are present and spreading in some counties in California.
• Local public health and vector control should have a plan for surveillance, coordination, and response, and continue monitoring of *Aedes* mosquitoes and human cases of dengue and chikungunya.
Resources

• Report suspect cases of dengue and chikungunya to the CDPH Vector-Borne Disease Section,
  Charsey Porse, PhD, MPH, (916) 552-9730
  Charsey.porse@cdph.ca.gov

• For information on testing for arboviruses:
  CDPH Viral and Rickettsial Disease Lab (VRDL), (510) 307-8585
  CDPH VRDL Guidelines for Laboratory Services:
  http://www.cdph.ca.gov/programs/vrdl/Pages/default.aspx

• CDPH website (type Aedes in search box)
• CDC website (Aedes, dengue, chikungunya)
Acknowledgments

- California local health departments
- California local vector control agencies
- CDPH: Vector-Borne Disease Section, Viral and Rickettsial Disease Laboratory.
- CDC and colleagues who posted useful slides on web
Questions?