10-6-2016

Emerging Trends in Infectious Disease

Jed Grant

University of the Pacific, jgrant@pacific.edu

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Objectives

- Describe emerging trends in infectious disease
- Recognize epidemiologic risk factors for emerging and resurgent infectious disease
- Develop a differential diagnosis that includes appropriate infectious disease

Unanticipated Epidemics since 1980

- Staphylococcus aureus toxic shock
- S. aureus USA 300
- AIDS
- West Nile virus
- Lyme disease
- Avian influenza
- Severe acute respiratory syndrome (SARS)
- Middle Eastern respiratory syndrome (MERS)
- Legionnaires' disease
- Measles
- Ebola
- Cryptosporidiosis
- H1N1 influenza ("swine flu")
- Iatrogenic fungal meningitis
- Clostridium difficile NAP1 strain
- Norovirus ("cruise-ship dysentery")
- Anthrax bioterrorism
Recent and Current Epidemics

**World Wide**
- Zika Virus
- Yellow Fever
- Ebola
- Dengue
- Chikungunya
- Enterovirus
- Influenza
- Middle Eastern Respiratory Syndrome

**In the US and California**
- Zika Virus
- West Nile Virus
- Meningitis
- Multi Drug Resistant Organisms
- Clostridium difficile Infections
- Community Acquired Pneumonia
- Influenza
- Vaccine Preventable Illness
  - Measles, others

Viral Hemorrhagic Fevers

- From one of 4 families
  - Flaviviridae (Dengue)
  - Bunyaviridae (Hanta)
  - Arenaviridae (Lassa)
  - Filoviridae (Ebola)

- All but Dengue may be spread by aerosol
- All cause increased vascular permeability and in severe cases systemic inflammatory response, shock, organ failure and death.
- Mortality ranges from 10% (Dengue) to 90% (Ebola)

Zika Virus

- An arbovirus (arthropod borne) in the genus Flaviviridae.
- Dengue, yellow fever, WNV, St. Louis encephalitis, Japanese encephalitis all in the same genus.
- ssRNA about 11k bases, 40 microns in size and is enveloped
- Enters host cell via membrane fusion, replicating in the cytoplasm and is shed via budding
- Humans are one of many hosts. Zika can reproduce in arthropods and vertebrates
- Vector is the Aedes mosquito, but is also sexually transmitted and crosses the placenta (in utero transmission)
Current Zika active transmission as of 8/2/16

US Zika cases as of 8/3/16

US range of *Aedes* mosquitoes
Zika vector: Aedes mosquitos

- **Aedes aegypti**
  - Tropical, sub-tropical and somewhat in temperate climates
  - Prefer to feed on humans, and will feed during the day
  - Aggressive: will follow you inside your house
  - Have developed localized resistance to several insecticides
- **Aedes albopictus**
  - Tropical and sub-tropical, but can live at a broader range of temperate climates than aegypti
  - Will feed on animals or humans
  - Aggressive, generally hang out around where humans live.
- Both like small sheltered containers to lay eggs
- Eggs are hearty and can withstand desiccation for one year, but perish at <10°C

Zika Signs and Symptoms

- Incubation period of 3-12 days, 80% of infections go unnoticed.
- Most are asymptomatic, but if symptomatic will be so for 2-7 days
  - Viremia is high in first week of illness and virus is shed for several days after resolution of symptoms.
- Rash, fever, and arthralgia are the main symptoms
  - Fine, diffuse maculopapular rash including palms and soles
  - Arthralgia predominates in small joints of hands and feet
  - Myalgias and HA may also occur
- Differential diagnosis is broad but should include other arboviruses common in area of travel
  - Dengue, chickungunya, etc

Zika Rash
Diagnostic Studies for Zika

- Lab
  - Reverse transcriptase polymerase chain reaction (RT-PCR) will become positive during the initial week.
  - After the 1st week anti-Zika IgM by ELISA will be positive but has cross-reactivity with other flaviviruses.
  - Individual flavivirus antibody can be tested by plaque reduction neutralization tests (PRNT).
  - CDC recommends urine or serum RT-PCR, if neg, then IgM with PRNT.
  - Urine samples remain positive for RT-PCR for at least two weeks longer than serum.

Complications and Treatment of Zika

- Really only a risk in pregnancy
  - Microcephaly incidence increased 20 fold in Brazil since outbreak
  - Also causes ophthalmologic abnormalities
- Guillain-Barre Syndrome (GBS) has been reported following Zika
- Current treatment consists of supportive therapy
  - Avid NSAIDS due to possible increased risk of bleeding (like Dengue)
  - IVig for severe GBS
- In those who are pregnant careful monitoring and evaluation of the fetus is indicated
  - Ultrasound for microcephaly or intracranial calcifications
  - Amniotic fluid testing for Zika

Prevention of Zika

- Control of vectors
  - DEET, mosquito nets, permethrin, long sleeves and pants
  - Reduce standing water, insecticide spraying.
  - Genetically modified mosquitoes: offspring are incapable of survival.
  - Chinese have infected mosquitoes with Wolbachia bacteria which causes infertility of female if from mating, or the offspring if female is infected from other means.
- Avoid intercourse or use condoms for 28 days after illness or travel
- Wait 8 weeks to attempt to conceive, men 6 months.
- Vaccine in development
  - One in Phase 1 trial, others developing

1. medscape.com/viewarticle/867009
2. medscape.com/viewarticle/866928
Chikungunya Virus (CV)

• Originally discovered in 1952 in Tanzania, Africa
• Name means “to be bent over” in Swahili. Known as “buka-buka” in the Congo, which means “broken-broken”, probably due to the debilitating arthralgias caused by the virus
• Arbovirus in the Togaviridae family, alpha virus genus (different family from Dengue and Zika)
  • Others in the same genus and family: WEE, EEE, Ross river virus
• ssRNA virus, about 11k bases, with envelope. Cell entry is under study

Chikungunya Virus (CV)

• Characterized by outbreaks and long periods of quiescence
• Outbreak in the Americas since June 2014
  • 2014 - 2811 cases in continental US and 4710 in territories
  • 12 locally transmitted cases in FL, almost all locally transmitted in territories
  • 2015 - 896 cases in continental US, and 237 in territories
  • 1 locally transmitted in TX, almost all locally transmitted in territories
  • 2016 - 59 cases in continental US, and 99 in territories
    • No locally transmitted cases in continental US, almost all locally transmitted in territories

Current or previous CV as of 4/22/2016

[Image source: CDC]
Chikungunya in the US as of 8/9/16

Image source: CDC

Range of Aedes mosquitoes US

Chikungunya Virus (CV)

- Major vector is *Aedes aegypti*, but CV mutated in 2006 to a form that could be transmitted by *Aedes albopictus*.
- Humans are the major reservoir during epidemics, but birds, primates, and rodents may also be in quiescent periods.
- Travel to endemic areas is the major risk factor, and likely cause for increased cases in US and Europe.
- Clinical illness occurs in 40-85% of infections.
- Clinical infection overlaps with Dengue and co-infection can occur.
- 3-7 day incubation period, not usually a prodrome.
Chikungunya Virus (CV) signs and symptoms

- Abrupt onset of high fevers (102-105°F) with shaking chills lasting 2-3 days
  - May defervesce for 4-10 days and then have a recurrence of fever for 1-2 days (saddle back fever)
- Pharyngitis, conjunctivitis and photophobia occur
- Severe arthralgias/myalgias and a rash are common
  - Arthralgias are more common in the small joints, and often involve more than 10 joint groups, incapacitating the patient
  - Patients typically lie still in a flexed posture, avoiding movement
  - Hips are usually spared, but the axial skeleton is usually involved
  - Most have a complete resolution in 1-2 weeks, but some 10% develop chronic debilitating joint pain lasting for years
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Chikungunya Virus (CV) Rash

- Flushed appearance of face and trunk
- Diffuse erythematous maculopapular rash involving trunk and extremities, sometimes including palms and soles
  - Occasionally with pustulae, xerosis, hypermelanosis or desquamation
- Mortality is about 10%
  - More common in elderly, young and those with co-morbidities
  - CV, respiratory and neurologic co-morbidities predispose to severe infection
  - Not as neuroinvasive as other alpha viruses
- Neurologic disease is more common in neonates.
- Vertical transmission does occur

Chikungunya Virus (CV) Diagnostic Criteria

- Fever and arthralgias with history of travel to endemic area
- Dengue, Malaria, other tropical diseases excluded
- Lab
  - CV specific IgM, IgG via ELISA labs take 5-7 days to become positive
  - At 2-3 days viremia is high, culture may be positive if test available
  - CDC offers a reverse transcriptase polymerase chain reaction (RT-PCR) test
- Treatment
  - Generally supportive, NSADS, Caution with ASA (bleeding risk)
  - Anti-virals and steroids are not effective
Dengue

- Originated in primates but moved to humans
- Most common arbovirus in humans
  - Earliest outbreak was 1635 in west indies but similar illness recorded in China CE 265-420, associated with flying insects near water
  - 1780 outbreak in North America
  - Became much more common after WWII vector spread with cargo
  - Vector control very effective at limiting until 1970s, resurgent since 1980s.
- 50-100 million cases/year worldwide
  - 500k cases of dengue hemorrhagic fever (DHF) annually, 22k deaths
  - About 250 cases/year in US; FL 2010, TX 2005

- ssRNA virus about 11k bases, enveloped
- Enters primarily Langerhans cells and WBC via membrane fusion
- Reproduces in the cytoplasm of dendritic cells, hepatocytes, and endothelial cells and is shed by budding
- Four distinct serotypes
  - Full immunity derived to serotype after infection, partial immunity to other
  - Serotypes co-wild, infection with more than one, and infection of one after another is associated with more severe disease (i.e. DHF)
- Humans are the reservoir, though some primates can serve as hosts without developing disease. The virus can also replicate in the vector.
- Aedes mosquitoes are the vector, and are not affected by the virus.

- Viremic host must coexist with sufficient number of vectors for outbreak to occur
- Follows two patterns: epidemic, and hyperendemic (ongoing)
  - Incubation period 3-14 days, average is 4-7 days
  - Initial infection is asymptomatic 50-90%, or may present as a non-specific viral illness
  - Usually self-limited
Dengue Signs and Symptoms

- May be asymptomatic, particularly if child <15 yrs old
- Recovery usually within 7-10 days
- Dengue Fever
  - Reddish mottling of skin and facial flushing
  - Aching pain all over, mostly neck and back ("breakbone fever")
  - Fever begins day 3 of illness and persists 5-7 days
  - Leukopenia, lymphopenia and thrombocytopenia are common
  - High fever (106°F), may be "saddleback fever": 1-2 days of fever, defervescence for a day, then recurrence of fever.
- 33% of patients may have mild hemorrhagic symptoms
  - Petechiae, gingival bleeding, positive tourniquet test (>20 petechiae after BP cuff)
  - Rarely fatal
  - Treatment is symptomatic and supportive

Dengue Hemorrhagic Fever (DHF)

- Almost always occurs in those with prior exposure to Dengue
- Primarily occurs in children but can affect anyone
- Biphasic fever, when recurs will have septic shock and hemorrhagic sx
- Increasing HCT (from plasma leakage into tissues) and low albumin, atypical lymphocytes, transaminases elevated, thrombocytopenia
- GI bleed or other sites due to profound capillary fragility
- Acute and/or pleural effusions due to increased capillary permeability
- DIC and severe metabolic acidosis may occur
- Mortality
  - Treated 2-5%, untreated 50%

Dengue diagnostic studies

- CBC
- LFT
- PT/INR, PTT, DIC panel if available
- UA
- Quilac
- Dengue virus IgM/IgG titer with x4 increase
- PCR for viral RNA is available at reference laboratories
- Serial US for pleural effusions shows DHF before labs are pos.
Dengue Treatment

• Usually self limited
• Supportive
• Avoid NSAIDS and ASA due to bleeding risk
• Steroids are not beneficial
• DHF should be treated in ICU
  • Careful attention to fluid balance and hemorrhage

Ebola Virus

• Outbreak June 2014 – December 2015 in West Africa
  • Largest Ebola outbreak in history
  • 28,652 infected; 11,325 deaths
  • 4 cases in US: two imported, two locally acquired
• Discovered in 1976 in Congo, near the Ebola river
• Natural reservoir is unknown, likely bats and primates
  • Bats can have high viremia and not get sick, live virus present in stool
  • Infected animals killed for consumption (bush meat) may contain virus
  • Body fluids of infected persons are highly contagious

Ebola

• Filamentous form, enveloped, negative stranded RNA
• 5 species
  • 4 cause disease in humans, 1 in animals only
  • Dogs can be infected
• Relative sparing of children
• Can reproduce in all tissues
  • Predilection for liver, endothelium, and mononuclear phagocytes
  • Necrosis is seen in liver, spleen, lymph nodes, kidney, lung and gonads
• May inhibit adequate immune response
**Ebola Clinical Course**

- Primary exposure
  - Travel to endemic area, incubation period 3-8 days
- Secondary exposure
  - Human to human contact with infected patient, incubation period up to 21 days
- Sudden onset of
  - Fever/chills, HA, myalgias/arthralgias followed quickly by GI symptoms
  - Abdominal pain, N/V/D, odynophagia and dysphagia
  - Half of patients will have conjunctivitis, mucus membrane/GI bleeding, and hemorrhage from puncture sites
  - May have a maculopapular rash which desquamates in survivors
- Tachypnea is a poor prognostic indicator

**Ebola Diagnostic Studies**

- Virus can be detected in sweat and urine with one hour turnaround but is not widely available. Most will have a 24-48 hour turnaround.
- Antigen detection test by ELISA
- IgM and IgG will be positive if patient survives long enough to mount an immune response.
- Thrombocytopenia and neutropenia are common.
- Various markers of organ function will decline as organ failure occurs.
- No useful imaging tests

**Ebola Treatment**

- STRICT BARRIER PRECAUTIONS/ISOLATION
  - All body fluids contain high numbers of infectious virions
- Supportive
  - Replacement of coagulation factors
  - Fluids and nutrition
  - Survivors will continue to shed virions for several weeks or months after clinical recovery, which is slow
  - Sexual transmission occurs. Unknown how long virus remains in semen after clinical recovery.
- Vaccines under development
West Nile Virus (WNV)

- Arbovirus in the Flavivirus genus like Japanese encephalitis
- ssRNA with 11k bases, enveloped, enters cell by membrane fusion, reproduces in the cytoplasm and is shed by budding
- First discovered in 1937 in Uganda, first cases in us in 1999
- Several large outbreaks in the US. About ½ are neuroinvasive
  - Since 1999 41762 cases, 18810 neuroinvasive
  - 2012: 5674 cases and 256 deaths.
  - 22 cases this year in CA, one death as of 8/14/16.

WNV in US and CA

- Birds are the host and reservoir
  - Non-bird animals and humans are dead end hosts
  - Dead birds can’t transmit the disease but are a marker of virus presence
  - Not transmitted animal to person, or person to person
  - Vertical transmission vector to offspring
- Culex mosquitos are the main vector
  - Ardea: VHF
  - Anopheles: malaria
Culex mosquito

- Worldwide distribution
- Most common mosquito in US cities
- Can extend to far north of temperate zone
- Smaller than Aedes
- No stripes
- Generally dawn/dusk or night feeder

WNV Signs and Symptoms

- Incubation 2-14 days but can be longer, especially if immune compromised
- Acute systemic febrile illness (20%)
  - Headache, weakness, myalgia, or arthralgia
  - Gastrointestinal symptoms
  - Maculopapular rash
  - Complete recovery is the rule, sometimes with lingering fatigue

WNV Signs and Symptoms

- Neuroinvasive disease (~1%)
  - Much more common in persons >50 years old and immunocompromised
  - 10% mortality, mostly for encephalitis and paralysis
  - Meningitis: fever, HA, nuchal rigidity
  - Encephalitis: fever, altered mental status (AMS), seizures, focal neurologic deficits, or movement disorders
  - Acute flaccid paralysis:
    - Clinically identical to poliovirus-associated poliomyelitis
    - Can occur without fever or apparent viral prodrome
WNV Diagnostic Studies

- Serum or CSF IgM for WNV by ELISA, with PRNT to confirm
- Some cross reactivity with other Flavaviridae
- CBC
- Hyponatremia may be seen in encephalitis from SIADH
- CSF shows viral picture
  - Elevated protein, lymphocytes, normal glucose
- Brain MRI usually normal but will show damage to basal ganglia, thalamus, and brainstem in encephalitis or damage to the anterior spinal cord in paralysis

WNV Treatment

- Supportive and symptomatic
- Many drugs have been tested, but none proven effective
- Monitor for development of neuroinvasive disease
- PREVENTION
  - Limit outdoor activity dusk to dawn
  - Use repellent, wear long sleeves
  - Vector control

Meningococcus

- Neisseria meningitidis
  - Encapsulated aerobic gram neg diplococci
  - 13 serogroups, but 5 cause 99% of disease
  - Current outbreak among MSM in southern CA.
  - Natural habitat is human nasopharynx
    - ~10% of population is asymptomatic carrier, up to 60% in closed populations
  - Transmitted via droplet or directly via close contact
  - Disease occurs when new subtype is introduced and there is a break in the mucosa - viral URI, smoking
Meningococcus

- Incubation is 3-4 days (range 1-10 days)
- Most infections have mild symptoms or subclinical infection
- 10-20% of infections will become meningococccemic
  - Organism reproduces rapidly and systemic symptoms occur before meningitis by 24-48 hours
  - Endothelial necrosis, thrombosis, hemorrhage, DIC occur
  - Suppurative complications occur
- Meningitis has 10% mortality even if properly treated early
  - 40% mortality if meningococcal sepsis occurs with meningitis

Meningococcus workup and treatment

- Septic workup
  - CBC, CMP, Lactate, blood cultures, UA, CSF studies
  - CT or MRI of brain (elevated ICP common)
  - LP shows elevated opening pressure, WBCs, low glucose, elevated protein
  - CSF gram stain positive 70-90%
  - Rapid PCR for meningococcus is positive even if abx have been started
- Treatment
  - Antibiotics (ceftriaxone very effective, higher dose), fluids, admission
- Prognosis
  - 10-20% of those that recover will have some form of sequelae

Meningococcus Prevention

- Prevention
  - Vaccines available for usual virulent strains
    - A, B, C, W, Y
  - High risk groups
  - Prophylaxis for close contacts in outbreak
    - ciprofloxacin for adults
    - ceftriaxone for children
Meningococcal Disease in the US

![Graph showing incidence of meningococcal disease in the US, 1970-2013](image)

Multi-Drug Resistant Organisms

<table>
<thead>
<tr>
<th>Antibiotics in use for 70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average time to use until resistance: 2-4 years</td>
</tr>
<tr>
<td>Inappropriate or incorrect use 50% of prescriptions</td>
</tr>
<tr>
<td>Viral, fungal organisms, partially treated.</td>
</tr>
<tr>
<td>Pressure to satisfy Rx</td>
</tr>
<tr>
<td>Use in animals has greatly contributed to resistance</td>
</tr>
<tr>
<td>CDC estimates 2.05 million illnesses and 23k deaths due to resistant organisms</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Urgent Category</th>
</tr>
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<tbody>
<tr>
<td>Clostridium difficile</td>
</tr>
<tr>
<td>Carbapenem-Resistant Enterobacteriaceae (CRE)</td>
</tr>
<tr>
<td>Includes Klebsiella and E. coli</td>
</tr>
<tr>
<td>Same resistant to ESBL/IMP/NDM</td>
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<tr>
<td>Neisseria gonorrhoeae</td>
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<table>
<thead>
<tr>
<th>Serious Category</th>
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<tbody>
<tr>
<td>Acinetobacter</td>
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<tr>
<td>Campylobacter</td>
</tr>
<tr>
<td>Candida</td>
</tr>
<tr>
<td>Enterobacteriaceae (ESBL)</td>
</tr>
<tr>
<td>Enterococcus (VRE)</td>
</tr>
<tr>
<td>Pseudomonas</td>
</tr>
<tr>
<td>Salmonella (typhus/non-typhus)</td>
</tr>
<tr>
<td>Shigella</td>
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<tr>
<td>Staphylococcus aureus (MRSA)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>M. tuberculosis</td>
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</tbody>
</table>
What can we do?

- **Inpatient**
  - Know what types of drug-resistant infections are present in your facility and patients.
  - Request immediate alerts from lab.
  - Alert receiving facility when you transfer a patient with a drug-resistant infection.
  - Follow relevant guidelines and precautions.
  - Prescribe antibiotics wisely.
  - Remove temporary medical devices such as catheters and ventilators as soon as possible.

- **Outpatient**
  - Prescribe wisely.
  - Narrow spectrum.
  - Appropriate antibiotics.
  - Use cultures and evidence-based decisions to prescribe antibiotics.
  - Stand your ground.

What is the CDC doing?

- **Four core actions**
  1. Prevent infections: Less illness, less antibiotic use.
  3. Improving Antibiotic Prescribing and Stewardship: Proper use in animals and humans.
  4. Developing New Drugs and Diagnostic Tests: Costs about $2 billion to bring new drug to market. Resistance in 2-4 years. No ROI.

Vaccine Related Disease

- Many parents are reluctant to immunize because of misinformation and ignorance of diseases prevented by vaccination.
- Resist the urge to become frustrated.
  - Most research says that parents are talking to you about it because they trust your opinion.
- CDC website has great parent-focused resources about vaccine safety.
- Finally, new law allows schools to refuse to admit unvaccinated children.
  - Sacramento county: 145 kids sent home 1st day of school 2016.
CA Vaccine Preventable Diseases Report 2014

- H. influenzae: 40 cases, none type b
- Hepatitis A: 142 cases
- Hepatitis B: 108 cases
- Measles: 75 cases
- Meningococcus: 56 cases
- Mumps: 37 cases
- Pertussis: 11,213 cases
- Rubella: 2 cases
- Tetanus: 4 cases
- Varicella: 41 DEATHS

Most cases in SF bay area and greater LA area.

Summary

- Zika
- Chikungunya
- Dengue
- Ebola
- West Nile
- Meningitis
- Drug Resistant Organisms
- Vaccine Preventable Disease

Sources