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# Emerging Trends in Infectious Disease

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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

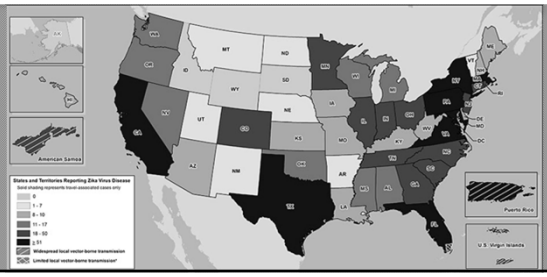
- From one of 4 families
  - Flaviviridae (Dengue)
  - Bunyaviridae (Hanta)
  - Arenaviridae (Lassa)
  - Filoviridae (Ebola)
- All but Dengue may be spread by aerosol
- All cause increased vascular permeability and in severe cases systemic inflammatory response, shock, organ failure and death.
- Mortality ranges from 10% (Dengue) to 90% (Ebola)

## Zika Virus

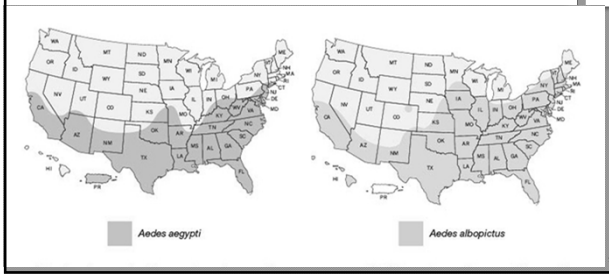
- Originally discovered in the Zika forest of Entebbe, Uganda in primates in 1947. Sporadic small outbreaks in 2007, 2013 and 2014 in equatorial region. Brazil January 2016, developing pandemic.
- An arbovirus (arthropod borne) in the genus *Flaviviridae*.
  - Dengue, yellow fever, WNV, St. Louis encephalitis, 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* mosquitos




Source: CDC

## 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

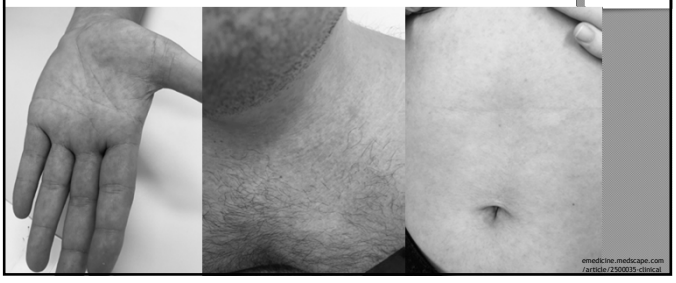
- *Aedes albopictus*
  - Tropical and sub-tropical, but can live at a broader range of temperate climates than *aegypti*
  - Will feed on animals or humans
  - Aggressive, generally hang out around where humans live.

- 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 sypmtoms
  - 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 flavivirus'
  - 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
- Guillian-Barre Syndrome (GBS) has been reported following Zika
- Current treatment consists of supportive therapy
  - Avoid NSAIDS due to possible increased risk of bleeding (like Dengue)
  - Ivlg for severe GBS
- In those who are pregnant careful monitoring and evaluation of the fetus is indicated
  - US 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 mosquitos: offspring are incapable of survival[1]
  - Chinese have infected mosquitos with *wolbachia* bacteria which causes infertility of female if from mating, or the offspring if female is infected from other means[2]
- 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

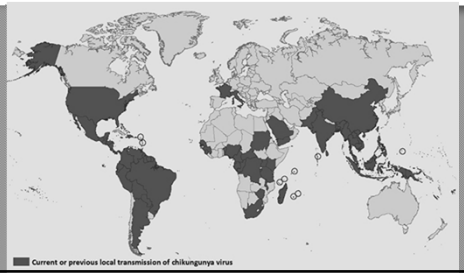



Image source: CDC

## Chikungunya in the US as of 8/9/16

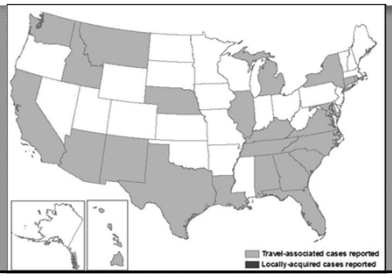
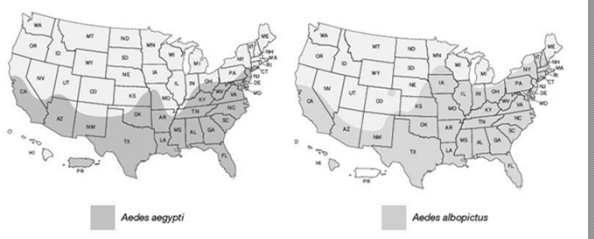



Image source: CDC

## Range of *Aedes* mosquitos 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 be also 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 30% develop chronic debilitating joint pain lasting for years

## Chikungunya Virus (CV)

- Rash
  - Flushed appearance of face and trunk
  - Diffuse erythematous maculopapular rash involving trunk and extremities, sometimes including palms and soles
  - Gradually fades, sometimes with petechia, 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, NSAIDS. 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

## Dengue

- 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-exist, 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* mosquitos are the vector, and are not affected by the virus.

## Dengue

- Viremic host must coexist with sufficient number of vectors for outbreak to occur
- Follows two patterns: epidemic, and hyperendemic (ongoing)
- Patient is viremic one day before symptoms and until symptoms resolve (5-7 days)
- 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 have "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 Signs and Symptoms

- 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
  - Ascites 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
- Guiac
- 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

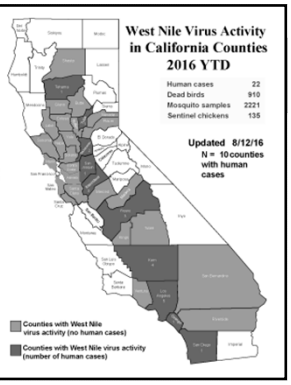
## Ebola Treatment

- 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


## WNV

- 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
  - *Aedes:* 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 immunosupressed
  - 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
    - isolated limb paresis or paralysis
    - 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 meningococcemic
  - 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

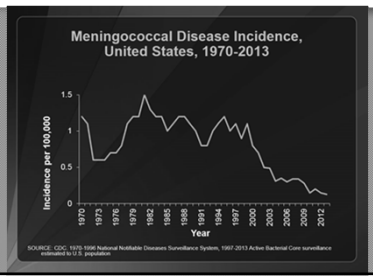
## Meningococcus workup and treatment

- 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




## Multi-Drug Resistant Organisms

- Antibiotics in use for 70 years
  - Average time in use until resistance: 2-4 years
- Inappropriate or incorrect use 50% of prescriptions
  - Viral, fungal organisms, partially treated.
  - Pressure to satisfy/Rx
- Use in animals has greatly contributed to resistance
- CDC estimates 2.05 million illnesses and 23k deaths due to resistant organisms

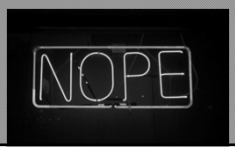
## Multi-Drug Resistant Organisms

- Urgent Category
  - *Clostridium difficile*
  - Carbapenem-Resistant *Enterobacteriaceae* (CRE)
    - Includes *Klebsiella* and *E. coli*
    - Some resistant to EVERYTHING
  - *Neisseria gonorrhoeae*

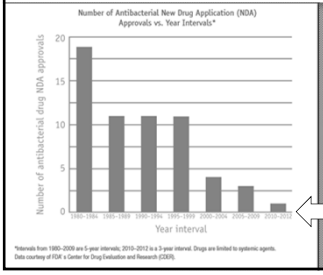

- Serious Category
  - *Acinetobacter*
  - *Campylobacter*
  - *Candida*
  - *Enterobacteriaceae (ESBL)*
  - *Enterococcus (VRE)*
  - *Pseudomonas*
  - *Salmonella* (typhus/non-typhus)
  - *Shigella*
  - *Staphylococcus aureus (MRSA)*
  - *Streptococcus pneumoniae*
  - *M. tuberculosis*

## 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 antibiotic
  - 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.
  2. Tracking resistance
     - Identification of risk factors, control spread
  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.
  - http://www.cdc.gov/vaccines/parents/index.html
- 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 (congenital rubella syndrome)
- Tetnus: 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

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