Emerging Infections

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Declaratives

- I have no conflicts of interest.
- I do not speak for any companies
- I have no grants other than Ryan White and AETC from the federal government

Objectives

- To identify the emerging infectious diseases facing us today
- To show how the landscape is changing in regards to new pathogens of concern
- To give insight into presentation and treatment of these emerging pathogens

Emerging Infectious Disease?

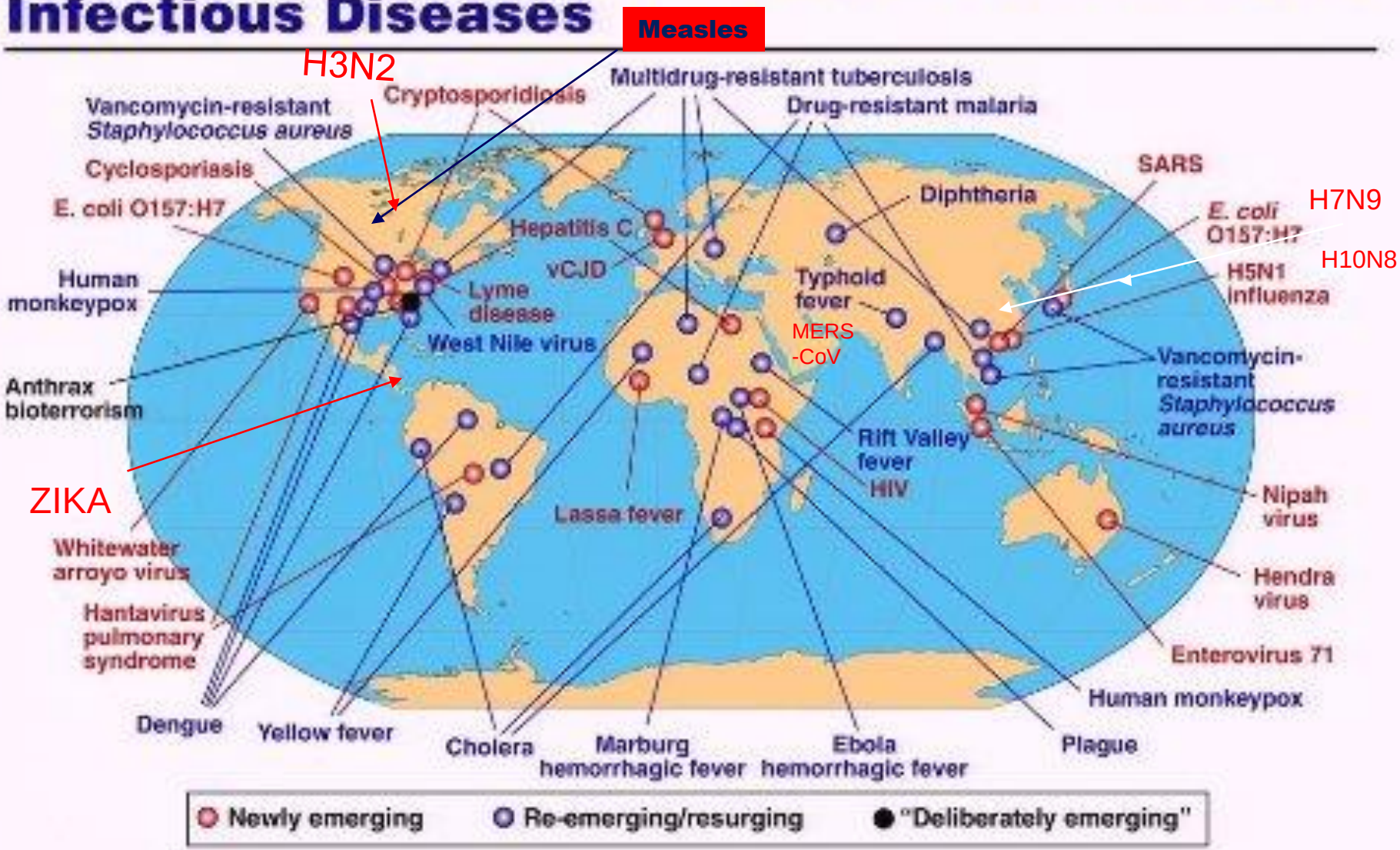
- “this time I will send the full force of my **plague**s against you and against your officials and your people”

Exodus 9:14

New Emerging Infectious Diseases

- Zika virus
- EBOLA
- Lassa Fever
- West Nile Virus
- Meningococcal strains
- Drug resistant microorganisms
- MERS-CoV
- Measles
- Influenza

Global Examples of Emerging and Re-Emerging Infectious Diseases



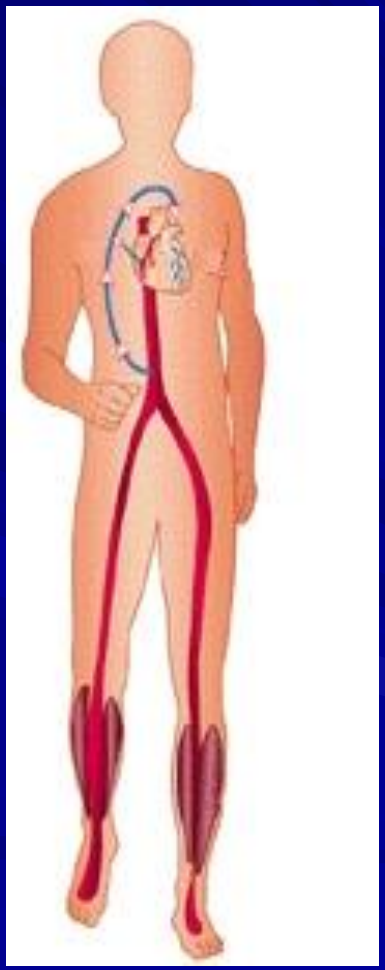
Viral Hemorrhagic Fever (VHF)

Syndromes
INFLUENZA
PULMONARY
HEPATIC
NEUROLOGICAL
DERMATOLOGICAL

Intracranial Hemorrhage
Conjunctival hemorrhage
Confusion
Facial flushing

Capillary Fragility
Disseminated Intravascular Coagulation
Shock
Pneumonia (Hanta)
Jaundice LFT (RVF, MHF, EHF, YF)

Hematemesis
Melena
Renal failure (HFRS)
Thrombocytopenia
Leukopenia



Headache
Deafness
Visual deficits (RVF)
Epistaxis
Sore throat

Black vomit (YF)
Nausea, Vomiting
Abdominal pain
Diarrhea

Myalgia
Petecchiae
Purpura
Ecchymosis
Macular rash (MHF, EHF)
Non-dependent swelling

Early Symptoms
Delayed Symptoms

Fever, Malaise, Prostration

Viral Hemorrhagic Fever (VHF)low incidence high--consequence

- Bunyaviridae
  - Hantavirus (HFRS)
  - Rift Valley Fever (RVF)
  - Congo-Crimean (CCHF)
- Arenaviridae
  - Lassa Fever (LF)
- Filoviridae Congo, Sudan Uganda
  - Marburg (MHF)
  - Ebola (EHF)
- Flaviviridae
  - Yellow Fever (YF)
  - Dengue (DHF)

EBOLA

Why Ebola is so dangerous

Health care workers are among those most at risk of catching Ebola

Classification of Ebola virus

- Order *Mononegavirales*
  - Enveloped, nonsegmented, negative strand RNA viruses
- Family *Filoviridae contains 3 genera:*
  - *Ebolavirus (1976)*
  - *Marburgvirus* – Lake Victoria marburgvirus (1967)
  - *Cuevavirus* – Lloviu virus (bats, Spain, 2002)

EBOLA OUTBREAK RESPONSE: REGIONAL CONFIRMED AND PROBABLE CASES

World Health Organization

MAP DATE: 03 October 2014

Recent Cases (21 Days Prior)

- 1 - 10
- 11 - 100
- 101 - 200
- 201 - 300
- 301 - 400

All cases

- 1 - 10
- 11 - 100
- 101 - 200
- 201 - 400
- 401 - 800

- NOT ACTIVE - No cases in previous 21 days
- ACTIVE - New cases in previous 21 days
- NEWLY INFECTED - New cases in previous 7 days (in previously uninfected areas)

Map Scale (A3): 1:3,700,000
1 cm = 37 km
0 40 80 160 km

Fig. 1: Air traffic connections from West African countries to the rest of the world

Air traffic connections from West African countries to the rest of the world. Guinea, Liberia, and Sierra Leone are not well connected outside the region. Nigeria, in contrast, being the most populous country in West Africa with more than 166 million people, is well connected to the rest of world. For historical reasons, all these countries have the strongest ties with European countries.

Reservoir and transmission to humans

- Fruit bats reservoir of virus - Drop partially eaten fruits
- Bats infect chimpanzees, gorillas, forest antelopes, porcupines
- Humans handle and eat bush meat (bats, chimpanzees, gorillas)
- Infected human passes from person to person

Centers for Disease Control and Prevention; Virus Ecology Graphic

http://www.cdc.gov/vhf/ebola/resources/virus-ecology.html

Pathogenesis - transmission

- Fastest incubation period has been reported associated with needle stick injury.
- Viral load may correlate with disease severity and survival
- This is NOT an airborne disease. Thus the pulmonary disease is hemorrhage and ARDS associated with severe sepsis.

Pathogenesis - how does Ebola cause disease?

- Virus enters the body via infected blood/body fluid in contact with a mucosal surface or a break in intact skin.
- Virus replicates preferentially in monocytes/macrophages and dendritic cells which facilitate dissemination of the virus throughout the body via lymphatic system.
- Other cells are secondarily infected and there is rapid viral growth in hepatocytes, endothelial and epithelial tissues.
- There is strong cytokine/inflammatory mediator release of TNF-a and inflammatory cascade.

Pathogenesis - inflammatory response

- Leads to endothelial damage, increased vascular permeability and shock.
- This results in the end organ damage and multi-organ dysfunction
- Diffuse intravascular coagulopathy(DIC) with platelet and coagulation factor consumption which leads to hemorrhage.
- IgM starts forming in 2 day and IgG in 5-8 days post infection . Immunologic response correlates with survival.
- Thus the observation that those who live >1 week are more likely to survive.

Clinical Manifestations

- Incubation period 8-10 days (range 2-21)
- Sudden onset of Fever >38.6^{0}C
- Flu-like symptoms: chills, myalgias, and malaise, sore throat
- Nausea, vomiting , abdominal pain, diarrhea
- Respiratory symptoms of chest pain, shortness of breath and cough
- CNS symptoms: Headache, confusion and coma

Clinical Manifestations

- Rash occurs around day 5
- Hypotension, peripheral edema
- Bleeding manifestations develop in >50% (internal/external)
- Can vary from petechiae& easy bruising, to mucosal hemorrhage, uncontrolled bleeding and massive GI blood loss
- Multi-organ dysfunction : kidneys and Liver
- Laboratory abnormalities
  - Thrombocytopenia and leukopenia
  - Elevated transaminases (AST > ALT), amylase, D-dimer
  - Reduced albumin

Immunity and Survival

- Treatment is supportive care
- IgG response appears to be protective
- Survivors may have persistent high antibody titres and associated sequelae of hepatitis, uveitis, muscle weakness etc.
- Previous observation was that serum from an Ebola survivor was therapeutic
- Anecdotal reports of Mab therapy being successful
- **Caution**, in a disease with 50% survival, any anecdotal observation can be a chance event
- It does support the potential role of vaccination

Key Ebola Virus Disease Facts

- Only spread by direct contact with blood and body fluids; not airborne
- Incubation 2-21 days; usually 8-10 days
- Only infectious when symptomatic
- Increasingly infectious as get sicker

IPAC Practices for EVD: Droplet + Contact Precautions

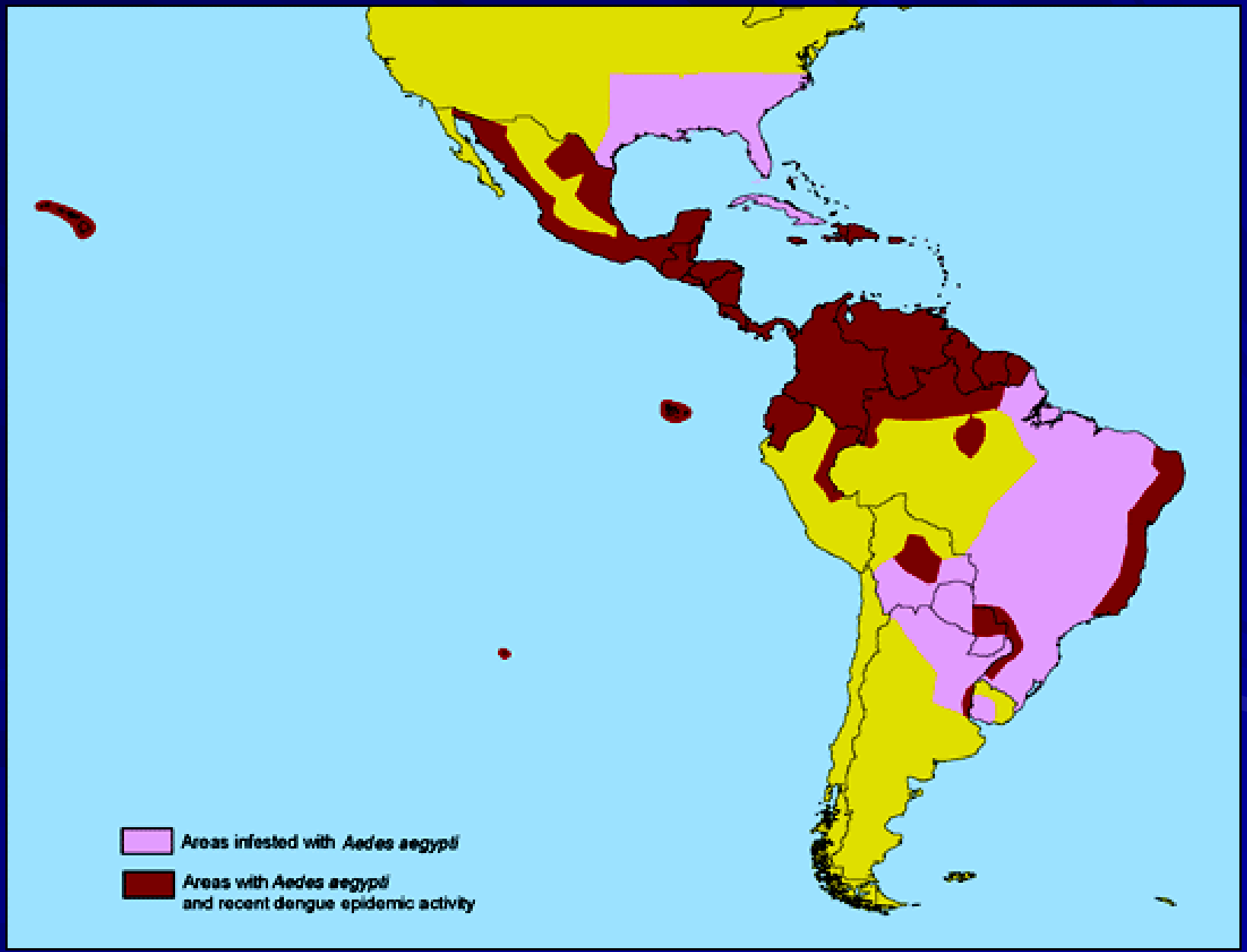
- Patient accommodation:
  - Single room with dedicated bathroom (minimum requirement); door closed
  - consider use of an isolation room that has an anteroom for donning or doffing PPE
- PPE for all staff entering the room:
  - fluid-resistant, long-sleeved, cuffed gown
  - gloves
  - full face protection (face shield)
  - surgical or procedure mask
- Maintain log of all individuals entering the room; only essential people should enter the room

Dengue Fever

Dengue

- Dengue is found mainly in tropical and subtropical areas of the world
- Present in more than 100 countries

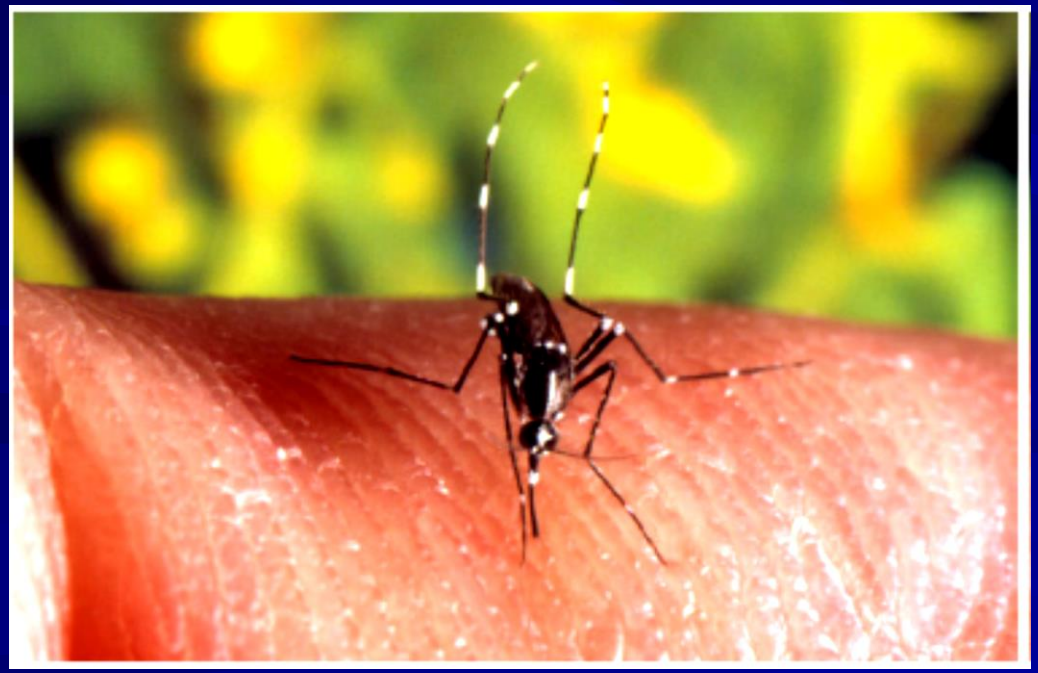
Distribution Western Hemisphere



Dengue

- Dengue fever and dengue haemorrhagic fever (DHF) are viral diseases transmitted by *Aedes* mosquitoes, usually *Aedes aegypti*.
- DHF can be fatal in 20% without supportive treatment
- There are four types of this virus (serotypes 1 to 4) and are closely related to one another.
- There is good evidence that sequential infection increases the risk of more serious disease resulting in DHF.

Aedes Aegypti



Aedes Albopictus

Dengue

- Classic Dengue
- DHF without shock
- DHF with shock

Dengue

- Incubation period of 3-10 days
- Sudden onset with chills and high fever
- Reddened eyes
- Intense muscle and joint pain
- Flushing or pale pink rash over face and then disappears
- Glands in neck and groin swollen
- Fever 2-4 D, recovery complete

DHF

- Due to double infection triggering immune response
- Headache and high fever
- Petechial rash
- Bleeding of gums and nose
- Black stools and bruising
- Can be life threatening

Dengue

- No specific treatment
- Supportive care
- Fluid resuscitation
- No immunization
- Good public health measures to prevent

Chikungunya virus disease

- Mosquito-borne viral disease characterized by acute onset of fever and severe polyarthralgia
- Often occurs in large outbreaks with high attack rates
- Outbreaks have occurred in countries in Africa, Asia, Europe, and the Indian and Pacific Oceans
- In 2013, first locally-acquired cases in the Americas reported on islands in the Caribbean

Chikungunya virus in the Americas*

- Seven Caribbean countries have reported locally-acquired cases
- >1,000 laboratory-confirmed cases have been reported
- Virus expected to spread to new areas

*As of February 10, 2014

Mosquito vectors

- Predominantly *Aedes aegypti* and *Aedes albopictus*
- Same mosquitoes that transmit dengue
- Widely distributed throughout Americas
- Aggressive daytime biters

Aedes aegypti

Aedes albopictus

Chikungunya virus infection

- Majority (72%–97%) of infected people develop clinical symptoms
- Incubation period usually 3–7 days (range 1–12 days)
- Primary clinical symptoms are fever and polyarthralgia

Fever and polyarthralgia

- Fever
  - Abrupt onset
  - Typically ≥39.0°C (≥102.2°F)
- Joint pain
  - Often severe and debilitating
  - Involves multiple joints
  - Usually bilateral and symmetric
  - Most common in hands and feet

Other clinical signs and symptoms

- Headache
- Myalgia
- Arthritis
- Conjunctivitis
- Nausea/vomiting
- Maculopapular rash

Clinical laboratory findings

- Lymphopenia
- Thrombocytopenia
- Elevated creatinine
- Elevated hepatic transaminases

Clinical outcomes

- Acute symptoms typically resolve in 7–10 days
- Mortality is rare; occurs mostly in older adults
- Some patients have relapse of rheumatologic symptoms* in the months following acute illness
- Studies report variable proportions of patients with persistent joint pains for months or years

*Polyarthralgia, polyarthritis, tenosynovitis, Raynaud's syndrome

Optimal timing for diagnostic assays

Diagnostic assay	Days post-illness onset
Viral culture	≤3 days
RT-PCR	≤8 days
IgM antibody tests	≥4 days

Treatment

- No specific antiviral therapy
- Supportive care with rest and fluids
- Non-steroidal anti-inflammatory drugs (NSAIDs) for acute fever and pain*
- Persistent joint pain may benefit from use of NSAIDs, corticosteroids, or physiotherapy

*Aspirin use is discouraged due to a theoretical risk of hemorrhage or Reye syndrome

ZIKA

Zika Virus

- Single stranded RNA Virus
- Genus *Flavivirus*, Family *Flaviviridae*
- Closely related to dengue, yellow fever, Japanese encephalitis and West Nile viruses
- Transmitted to humans primarily by *Aedes (Stegomyia)* species mosquitoes

Ingrid Rabe CDC

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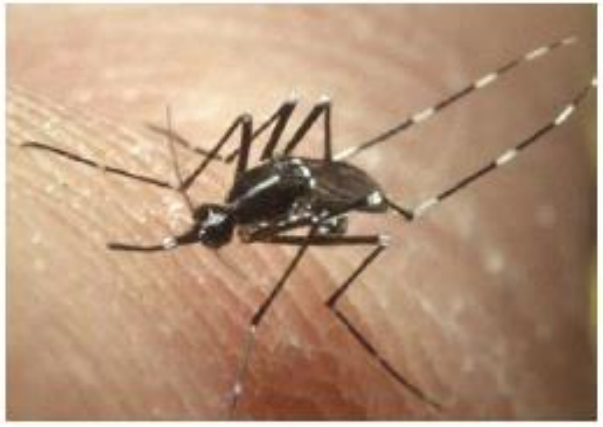
Zika Virus Vectors:
Aedes Mosquitoes

- *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 in and around households
- Aggressive daytime biters

Aedes aegypti



Aedes albopictus

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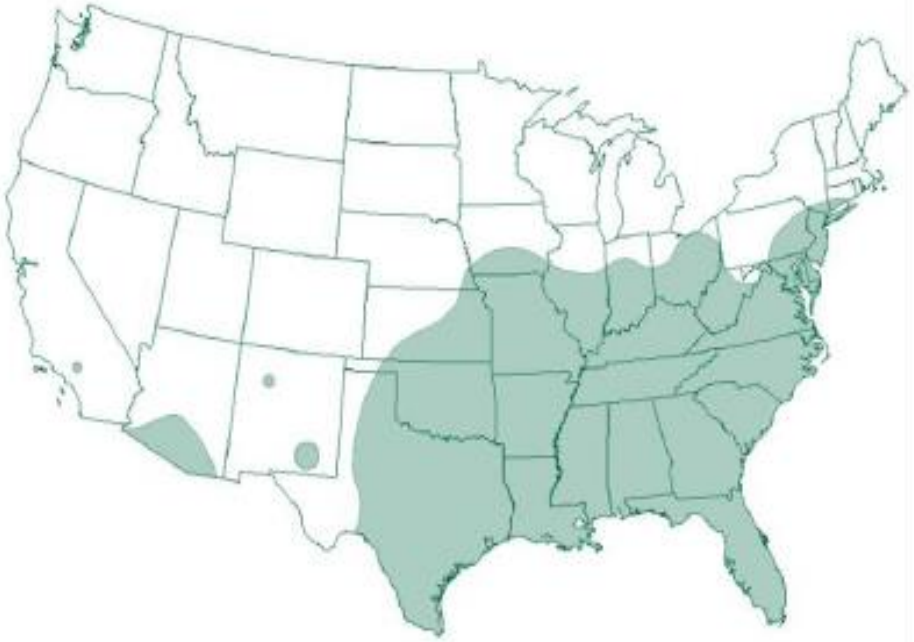
Aedes aegypti and *Aedes albopictus* Mosquitoes: Geographic Distribution in the United States

Aedes aegypti



Aedes albopictus

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Other Modes of Transmission

- Maternal-fetal
  - Intrauterine
  - Perinatal
- Other
  - Sexual
  - Blood transfusion
  - Laboratory exposure
- Theoretical
  - Organ or tissue transplantation
  - Breast milk

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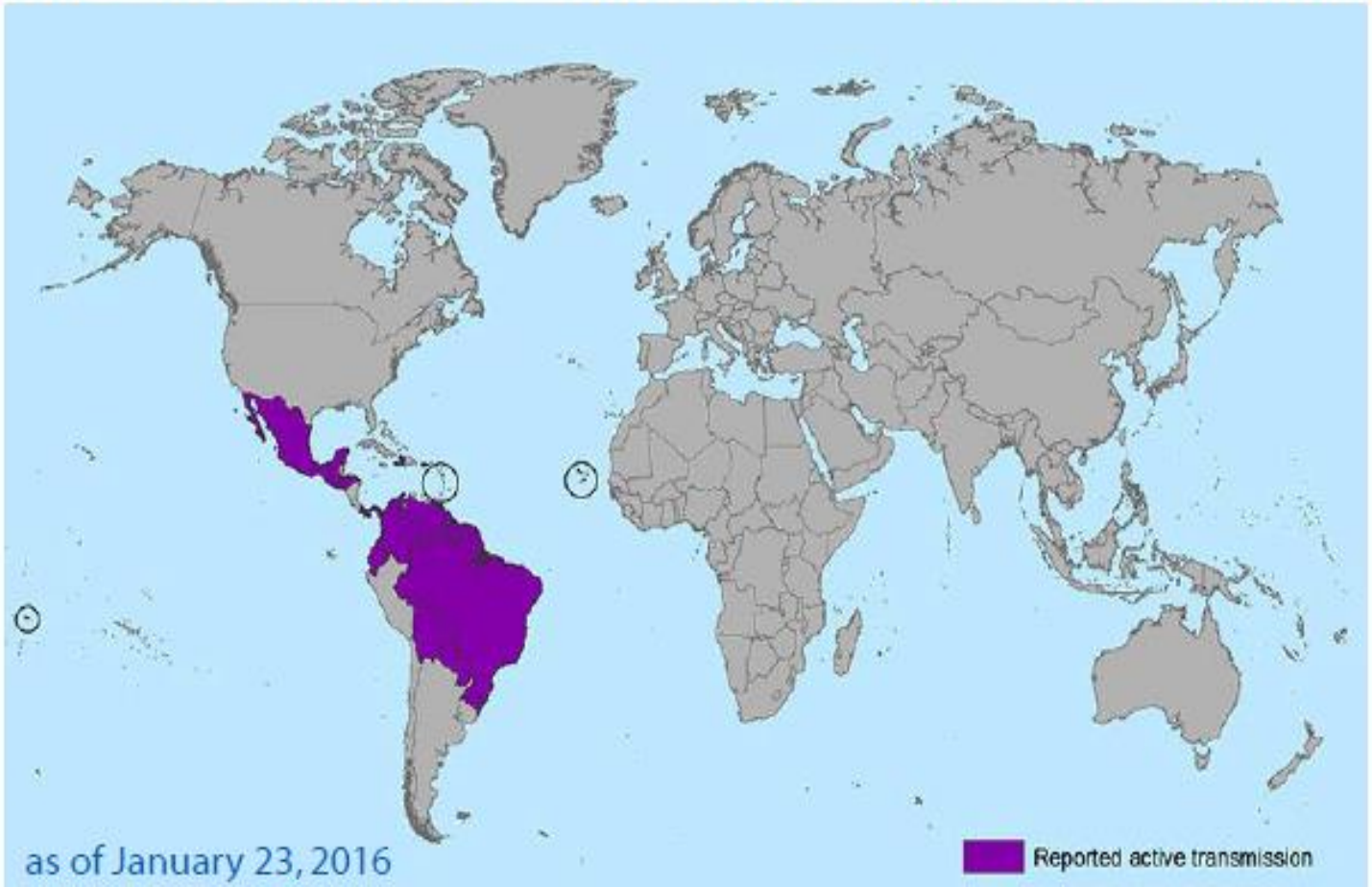
Zika Virus:

Countries and Territories with Active Zika Virus Transmission



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Zika Virus in the Americas

- In May 2015, the first locally-acquired cases in the Americas were reported in Brazil
- Currently, outbreaks are occurring in many countries or territories in the Americas, including the Commonwealth of Puerto Rico and the U.S. Virgin Islands
- Spread to other countries likely

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Zika Virus Incidence and Attack Rates

- Infection rate: 73% (95%CI 68–77)
- Symptomatic attack rate among infected: 18% (95%CI 10–27)
- All age groups affected
- Adults more likely to present for medical care
- No severe disease, hospitalizations, or deaths

Note: Rates based on serosurvey on Yap Island, 2007 (population 7,391)

Duffy M. N Engl J Med 2009

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Reported Clinical Symptoms
Among Confirmed Zika Virus Disease Cases

Symptoms	N (n=31)	%
Macular or papular rash	28	90%
Subjective fever	20	65%
Arthralgia	20	65%
Conjunctivitis	17	55%
Myalgia	15	48%
Headache	14	45%
Retro-orbital pain	12	39%
Edema	6	19%
Vomiting	3	10%

Yap Island, 2007

Duffy M. N Engl J Med 2009

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Zika Virus Clinical Disease Course and Outcomes

- Clinical illness usually mild
- Symptoms last several days to a week.
- Severe disease requiring hospitalization uncommon
- Fatalities are rare
- Guillain-Barré syndrome reported in patients following suspected Zika virus infection
  - Relationship to Zika virus infection is not known

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Zika Virus and Microcephaly in Brazil

- Reports of a substantial increase in number of babies born with microcephaly in 2015 in Brazil; true baseline unknown
  - Zika virus infection identified in several infants born with microcephaly (including deaths) and in early fetal losses
  - Some of the infants with microcephaly have tested negative for Zika virus
- Incidence of microcephaly among fetuses with congenital Zika infection is unknown

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Distinguishing Zika from Dengue and Chikungunya

- Dengue and chikungunya viruses transmitted by same mosquitoes with similar ecology
- Dengue and chikungunya can circulate in same area and rarely cause co-infections
- Diseases have similar clinical features
- Important to rule out dengue, as proper clinical management can improve outcome*

*WHO dengue clinical management guidelines:
http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf

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Clinical Features:
Zika Virus Compared to Dengue and Chikungunya

Features	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	-	-
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Hemorrhage	-	++	-
Shock	-	+	-

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Diagnostic Testing for Zika Virus

- Reverse transcriptase-polymerase chain reaction (RT-PCR) for viral RNA in serum collected ≤7 days after illness onset
- Serology for IgM and neutralizing antibodies in serum collected ≥4 days after illness onset
- Plaque reduction neutralization test (PRNT) for ≥4-fold rise in virus-specific neutralizing antibodies in paired sera
- Immunohistochemical (IHC) staining for viral antigens or RT-PCR on fixed tissues

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Serology Cross-Reactions with Other Flaviviruses

- Zika virus serology (IgM) can be positive due to antibodies against related flaviviruses (e.g., dengue and yellow fever viruses)
- Neutralizing antibody testing may discriminate between cross-reacting antibodies in primary flavivirus infections
- Difficult to distinguish infecting virus in people previously infected with or vaccinated against a related flavivirus
- Healthcare providers should work with state and local health departments to ensure test results are interpreted correctly

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Initial Assessment and Treatment

- No specific antiviral therapy
- Treatment is supportive (i.e., rest, fluids, analgesics, antipyretics)
- Suspected Zika virus infections should be evaluated and managed for possible dengue or chikungunya virus infections
- Aspirin and other NSAIDs should be avoided until dengue can be ruled out to reduce the risk of hemorrhage

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Zika Virus Disease Surveillance

- Consider in travelers with acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis within 2 weeks after return
- Inform and evaluate women who traveled to areas with Zika virus transmission while they were pregnant
- Evaluate fetuses/infants of women infected during pregnancy for possible congenital infection and microcephaly
- Be aware of possible local transmission in areas where *Aedes* species mosquitoes are active

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Zika Virus Preventive Measures

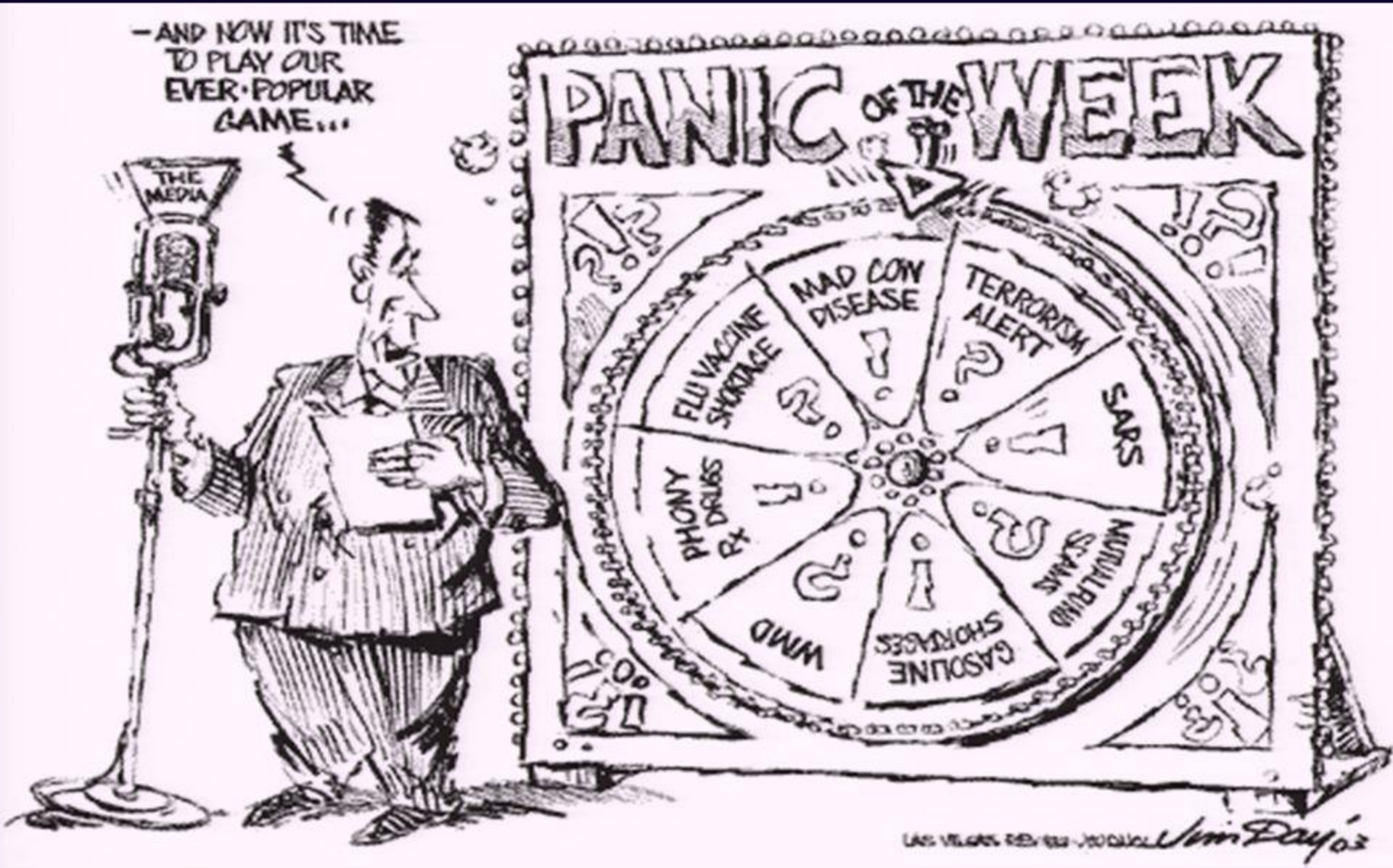
- No vaccine or medication to prevent infection or disease
- Primary prevention measure is to reduce mosquito exposure
- Pregnant women should consider postponing travel to areas with ongoing Zika virus outbreaks
- Protect infected people from mosquito exposure during first week of illness to prevent further transmission

Lassa Fever

- West Africa
- Infected rodent
- 1-3 week incubation period
- Fever malaise, deafness, n/v, bleeding gums
- Ribavirin and supportive
- Most recover

Conclusions

- Emerging infectious diseases are omnipotent and will continue to command attention.
  - EID's are most deleterious in 1) developing nations and 2) among children, the elderly, females, and those with weakened immune systems
- EID's are controllable!
- It is the responsibility of the global community to continue to develop / refine public health infrastructures to deal with burgeoning crises.
- Initiatives must be developed in order to overcome social, religions, and regional barriers to prevention and control.


– AND NOW IT'S TIME TO PLAY OUR EVER-POPULAR GAME...
THE MEDIA
PANIC OF THE WEEK
MAD COW DISEASE
TERRORISM ALERT
SARS
MUTILATING SPAM
GASOLINE SHORTAGES
WMD
PHONY Rx DRUGS
FLU VACCINE SHORTAGE
Jim Day '03