Emerging Infectious Diseases: A - Zika

2017 SIDP Programing at Microbe
New Orleans, June 1, 2017

Scott K. Fridkin, MD
Professor of Medicine
Division of Infectious Diseases, Department of Medicine and Department of Epidemiology, Rollins School of Public Health, Emory University

Director of Antimicrobial Stewardship Research, Emory Healthcare

Disclosures

• Centers for Disease Control and Prevention
  • Emerging Infections Program Cooperative Agreement
  • Co-investigator
• Sponsored Research - Pfizer Inc. and Emory University
  • S. aureus surveillance in Fulton County, GA.

• Vaccines and Related Biological Products Advisory Committee (VRBPAC) Strategic Advisory Board Meeting (Pfizer)

Opinions expressed not those of Emory University or Emory Healthcare
Historical Epidemiologic Transitions – 1st Transition

• Paleolithic Age
  • 2.5 million years ago
  • Hunters and gatherers
  • Nomadic, Small groups
  • Parasitic infections
  • 10,000 years ago
  • New social order due to agriculture
  • Zoonoses through animal domestication
  • Increases in infectious diseases
  • Epidemics in non-immune populations
**Historical Epidemiologic Transitions – 2nd Transition**

- Coincided with mid-19th century Industrial Revolution
- Decreases in infectious disease mortality
- Increasing life expectancy
- Improved nutrition
- Antibiotics
- “Diseases of Civilization” – cancer, diabetes, cardiovascular diseases
- Environmental problems
- Chronic diseases

**Cholera – ecosystems and behavior (urbanization)**

- London, 1800s – first major vertical urbanization
- The Ghost Map
  - describes the most intense outbreak of cholera in Victorian London
  - “1854 Broad Street cholera outbreak – Broad Street Pump”
  - Dr. John Snow, who created a map of the cholera cases and Reverend Henry Whitehead, whose extensive knowledge of the local community helped determine the initial cause of the outbreak
  - Water – not “Miasma”
  - The cholera outbreak from 1848-49 killed approximately 54,000-62,000 in London, and the outbreak from 1853-54 killed an estimated 31,000 in London
- Extensive rapid spread from point source, crossed social lines
Historical Epidemiologic Transitions – 3rd Transition

- Last 25 years
- Emerging infectious diseases globally
- New diseases and increases in mortality; first since 19th century
- Antimicrobial resistance
- 75 percent of diseases are zoonotic
- Anthropogenic factors of emergence; the microbial “perfect storm”

Examples of Emerging and Re-emerging Infectious Diseases
Speed of Global Travel in Relation to World Population Growth

From: Murphy and Nathanson Semss. Virol. 5, 87, 1994

Convergence Model

Genetic and Biological Factors
Physical and Environmental Factors
Social, Political, and Economic Factors
Ecological Factors

Pathogen
Environment/Animals
Humans
EID
No. 1

CLUE:
The monstrous Swamp Thing can control every iota of plant life on this planet, from the fungus on stale bread to forests of towering oaks.
Candida auris

The monstrous Swamp Thing can control every iota of plant life on this planet, from the fungus on stale bread to forests of towering oaks.

Candidemia is one of the most common HAIs in the U.S.

- Bloodstream infection caused by Candida spp.
- #1 organism in hospital-associated bloodstream infections in recent study
- Incidence is approximately 10-14 per 100,000; varies by geographic location and patient population
- Mortality 30-50%

Very modest emergence of resistance

A new Candida species: First report of C. auris from Japan in 2009

ORIGINAL ARTICLE

Candida auris sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital

Kazuo Satoh1,2, Koichi Matsumura1,2, Hayou Hasumi1, Hayari Hishiyama1, Katsumi Uchida1 and Hideyo Yamaguchi1

1Tokyo University Hospital of Medical Science, Tokyo, Japan; 2Tokyo Metropolitan Hospital, Tokyo, Japan

• Discovered during the course of a study to analyze antifungal yeast diversity in humans

Satoh K et al. Microbiol Immunol, 2009
**C. auris** is concerning

- Multi-drug resistant
  - Exhibits almost always resistance to fluconazole
  - Variable susceptibility to other azoles, amphotericin B, and echinocandins
- Causing outbreaks/spread within healthcare facilities in India, UK
- Challenging to identify
  - Can be misidentified as *C. haemulonii*, other *Candida* spp, or *Saccharomyces*
  - Need MALDI-TOF or sequencing to identify *C. auris*

### Some hospitals reported 40% of candidemia was from *C. auris*

<table>
<thead>
<tr>
<th>Year</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Japan</td>
</tr>
<tr>
<td>2010</td>
<td>Korea</td>
</tr>
<tr>
<td>2011</td>
<td>India</td>
</tr>
<tr>
<td>2012</td>
<td>Kenya</td>
</tr>
<tr>
<td>2013</td>
<td>Kuwait</td>
</tr>
<tr>
<td>2014</td>
<td>South Africa</td>
</tr>
<tr>
<td>2015</td>
<td>Pakistan</td>
</tr>
<tr>
<td>2016</td>
<td>Venezuela</td>
</tr>
</tbody>
</table>

**C. auris** WGS of 47 isolates from 4 world regions

Strains were:

- Very different across regions
- Highly related within regions
- 93% resistant to fluconazole
- 54% resistant to voriconazole
- 35% resistant to amphotericin B
- 7% resistant to echinocandins
- 41% MDR isolates
- 4% resistant to all three major antifungal classes

- **India/Pakistan**<60 SNPs
- **South Africa**<70 SNPs
- **Japan**<70 SNPs
- **Venezuela**<16 SNPs

**40,000-140,000 SNPs across regions**
CDC issued a clinical alert to healthcare facilities – June 2016 – “be on the lookout”

- First description in U.S. - As of August 31, CDC aware of 7 cases
- All retrospectively found except for 1
  - Most from New York, includes positive surveillance cultures, likely more to come
  - In the US, most isolates resistant to fluconazole, some resistant to amphotericin B, no echinocandin resistance
- Continued need for reference testing of all
  - *C. haemulonii, Saccharomyces, or C. auris* – with pre-emptive infection control

No. 2

Clue

The Hulk has explosive strength, creating chaos and havoc when loose, destroying most of that he comes in contact with…”
Ebola (VIRAL HEMORRHAGIC FEVERS)

- Acute infection: fever, myalgia, malaise; often progression to prostration
- Small vessel involvement: increased permeability, cellular damage
- Multisystem compromise (varies with pathogen)
- Hemorrhage often small in volume (indicates small vessel involvement, thrombocytopenia)
- Poor prognosis associated with shock, dehydration, encephalopathy, extensive hemorrhage

VHF: POPULATION AT RISK

Ebola Virus Ecology and Transmission

- Animal-to-animal Transmission: Transmission suggests that bats are the natural reservoir, with other primates (gorillas, chimpanzees, and others) as well.
- Splatterer Event: "Splatterer event" occurs when an infected human comes into contact with the reservoir host and is most commonly transmitted through contact with the respiratory tract or skin of the host animal.

Human-to-Human Transmission

- Once inside the human body, the virus spreads from one host to another, often through contact with the blood and bodily fluids of sick people or with the blood of those who have died of Ebola.

Survivor

Ebola survivors face new challenges after recovery, including potential transmission to others and psychological challenges as they re-enter their communities.

Not everybody is equal

- Africa includes several countries
- Urban vs. rural
- All zoonosis
- Travelers vs visitors
- Healthcare workers, humanitarians
- Ecologists, field workers

Unprotected contact with blood and body fluids

Traditional transmission pathways

- Urban vs rural
- All zoonosis
- Travelers vs visitors
- Healthcare workers, humanitarians
- Ecologists, field workers

Unprotected contact with blood and body fluids
Most burn out quickly
Occasionally peripheral to cities
Most < or = 300 cases

**2016 Ebola outbreaks in Africa**

**SIERRA LEONE**
- Cases: 14,123
- Deaths: 4,800
- HCWs: 221/301

**GUINEA**
- Cases: 3,814
- Deaths: 1,000
- HCWs: 100/196

**MALI**
- Cases: 8
- Deaths: 6
- HCWs: 2/2

**LIBERIA**
- Cases: 10,678
- Deaths: 4,810
- HCWs: 193/378

**NIGERIA**
- Cases: 20
- Deaths: 6
- HCWs: 5/11

WHO May 19, 2016
26 Ebola cases outside West Africa

26 via air travel: From Guinea: 1; from Sierra Leone: 16; from Liberia: 9 (+1 Nigeria)

Was there anything different?

• Virus - no
• Clinical manifestations - no
• Transmission mechanisms - no
• New countries involvement - yes
• People and behavior – yes
  • Difficult to break the transmission chain
    • Locally dense population/cultural obstacles
    • Little experience in U.S.
Ebola therapeutics 2014

- Nothing for approved for human use before 2014
- Convalescent plasma
  - Valuable option for resource poor settings if overcome blood bank obstacles, experience since 1995
  - Phase 2/3 100 person in Guinea – inconclusive
  - Phase 2/3 Liberia and Sierra Leone interrupted (low enrollment)
- ZMAPP (humanized monoclonal antibody cocktail)
  - Reversed symptoms in non human primates
  - Compassionate use now –
    - Phase 2 study in West Africa, Phase 1 study in UK/Italy planned
- Favipiravir – influenza
  - Non-random open label phase 2 in Guinea – some effect if low viral load to start
- Vaccine – two trials concluding – 100% effective, just approved for use for small outbreak now

No. 3

CLUE:
What keeps coming back, more times than you want....

1996

2018
No. 3 Emerging Novel Influenza A Viruses:

- H9N2 (1998-2014)
- H7N7 (2003)
- H3N2v (2009)
- pH1N1 (2009)
- H10N8 (2017)

Influenza A Reservoirs and Interspecies Transmission:

Novel Influenza

People getting infected with non-human influenza viruses
Clue

...[King of the sevens seas]...thrive in water and withstands its perils and puts himself in the ensuing conflicts between water and the breathable environment..."

No. 4 Legionella

- Gram-negative bacillus
- Intracellular parasite of free-living protozoa primarily found in freshwater environments
- ≥60 species and 70 serogroups
- Not all strains equally pathogenic
  - 22 species associated with human disease
  - *Legionella pneumophila* serogroup 1 accounts for 80-90%
  - Monoclonal antibody type 2 responsible for most outbreaks
What is Pneumonia?

- Pneumonia
  - Abnormal inflammation of lung parenchyma (alveoli)
  - Diagnosis confirmed by chest X-ray
  - Other terms: lower respiratory tract infections, severe acute respiratory infections

- Many causes
  - Bacterial, viral, fungal, non-infectious
  - Top causes: *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae*, Respiratory syncytial virus, influenza

- Leading killer – in top 10 in U.S. and globally

History of Legionellosis

- First described following 1976 outbreak at American Legion convention in Philadelphia
- 221 cases of Legionnaires’ disease with 34 deaths
- Hotel cooling tower suspected to be the source
U.S. Legionellosis 2000–2014*

Between 2000 and 2014, 286% increase in legionellosis (based on NNDSS*)

Events Leading to Legionnaires’ Disease

Supply Water → Amplification → Aerosolization → Transmission

Amplification:
- Temperature 25–42°C
- Stagnation
- Scale and sediment
- Protozoa
- Biofilm
- Absence of disinfectant

Aerosolization:
- Showerheads
- Cooling towers
- Decorative fountains
- Hot tubs

Transmission:
- Susceptible Host

*National Notifiable Diseases Surveillance System
Probable and Definite Healthcare-associated Cases of Legionnaires’ Disease by Month
Pittsburgh VA Medical Center, 2011–2012

- 22 infections, 6 deaths
- Environmental investigation
  - 23 of 25 locations sampled grew *Legionella* (most < 10 cfu/ml *Legionella*)
  - Low residual chlorine (0.0 – 0.1 ppm)
- Microbiology - matched clinical samples (ST1395) to multiple locations

Acute Response and Remediation Efforts

- Hospital shut down potable water system
- Used bottled water and point-of-use filters
- Superheating, hyperchlorination
  - Disruptive
  - Concerns about plumbing infrastructure, scalding, reduced water quality
- Installation of chlorine drip
- Repeat sampling 2 weeks later → no growth
- Water restrictions lifted
- No additional healthcare-associated LD cases detected
COMING! June 6, 2017

• 1 in 3 outbreaks CDC investigates is Health care-associated Legionnaires’ disease: increased risk for transmission and severe outcome
  • Size and complexity of their water systems
  • Vulnerability of populations served
• Legionnaires’ disease is deadly for about 1 in 10 people diagnosed with it
• Prevention through water management programs and rapid response to cases important to reducing number of cases and outbreak size
  • Requires coordination among health care facility leaders, health care providers, and public health professionals

http://www.cdc.gov/vitalsigns/

CDC Legionella Toolkit

• Translates ASHRAE 188 into plain language for wider audiences
• Step-by-step guide to creating a water management program

www.cdc.gov/legionella/WMPtoolkit
Conclusions

- Legionnaires’ disease increasing cause of pneumonia and pneumonia outbreaks
- Number of factors contributing to disease ‘emergence’
- Physicians/healthcare key to identifying cases
- Identifying and reporting cases prevents more cases
- Water management programs needed to reduce risk of *Legionella* growth and transmission—new standards can help

No. 5

Well, he is a doctor....

Technology always seems like a good idea....until its not
Healthcare-associated emergence, the microbiome, and Clostridium difficile infection

- Certain epidemiologic factors in common
  - Direct and indirect contact transmission between patients
  - Colonized patients far exceed those infected
  - Colonization precedes infection by days to weeks and may last weeks to months and even years after
- Colonization occurs at:
  - Pathologic biofilms
  - Body sites normally inhabited by a complex and diverse human microbiota
Factors in Emergence (Healthcare AR)

- Biology - Resistance determinants come/go quickly

Molecular Evolution of a *Klebsiella pneumoniae* ST278 Isolate Harboring *bla*<sub>NDM-7</sub> and Involved in Nosocomial Transmission

Tara Lynch,1,2,3 Liang Chen,1,4 Giselle Peinano,1,2 Dax B. Gregory,1,4,5 Deirdre L. Church,1,4,5 John Conly,1,4,5 Barry P. Keim1,6,7 and Johann D. Pitout1,2,8,9

1Division of Microbiology, Calgary Laboratory Services, Department of Pathology and Laboratory Medicine, Department of Microbiology, Immunology, and Infectious Diseases, Department of Medicine, and Tidwell Institute for Chronic Diseases, Cumming School of Medicine, University of Calgary, Canada. Department of Medical Microbiology, University of Pretoria, South Africa, and Public Health Research Institute, Tisch Science Center, Rutgers University, Newark, New Jersey.

During 2013, *Klebsiella pneumoniae* with *bla*<sub>NDM-7</sub> was isolated from the urine (KpN01) and rectum (KpN02) of a patient in Calgary, Canada. The same strain (KpN04) was subsequently isolated from another patient in the same unit. Interestingly, a carbapenem-susceptible *K. pneumoniae* ST278 (KpN06) was obtained 3 months later from the blood of the second patient. Next-generation sequencing (NGS) revealed that the loss of carbapenem resistance in KpN04 was due to a 5.8-kb deletion on the *bla*<sub>NDM-7</sub>-harboring IncF plasmid. In addition, an IncF plasmid in KpN06 had a 27-kb deletion that removed genes encoding for heavy metal resistance. Phylogenetic analysis showed that the *K. pneumoniae* ST278 from patient 2 was likely a descendant of KpN02 and that KpN06 was a close progenitor of an environmental ST278. It is unclear whether KpN06 lost the *NDM-1* gene in vivo. This study detailed the remarkable plasticity and speed of evolutionary changes in multidrug-resistant *K. pneumoniae*, demonstrating the highly recombinant nature of this species. It also highlights the ability of NDM to clarify molecular macroevolutionary events within antibiotic-resistant organisms.

J Infect Dis 2016 (Sept 1); 214: 798-806

Factors in Emergence (Healthcare AR)

- Social/Political/Economic: International Travel

Fig. 2. Distribution of countries (shown by an explosive star) in which New Delhi metallo-beta-lactamase 1 (NDM-1)–producing Enterobacteriaceae have been identified up to September 2010.

Key Epidemiologic Factors that Drive Antibiotic Resistance

• Genetic and biological factors
  • Microbial adaptation and change
  • Human susceptibility to Infection

• A physical or environmental factor
  • Antibiotic use

• An ecologic factor
  • Transmission

New evidence these are linked - microbiota

Roles of the Microbiome in AR

Antibiotic pressure on the microbiome

Spread of MDR determinant

Traditional way to interrupt transmission, i.e., contact precautions
The more dense (dominate) MDRO in Gut Microbiome, The more Environmental Contamination; *C. difficile* example


---

Role of the Microbiome in AR

- Long interactive microbiomes of humans, environment, animals, and commensal bacteria
- Genetic mutation, rearrangement, and recombination events within and between microbial species
- Antibiotic selection pressure

Antibiotic pressure on the microbiome

- Spread of MDRO dissemination

Maintain Microbiota/Diversity

NEW Traditional way to interrupt transmission
Therapeutic means to maintain GI Microbiome (Diversity)

- Fecal Microbiota Transplants (recurrent CDI, other) - FMT
  - No FDA approval
  - Effective (limited data) to treat recurrent CDI. 75-90% effective
  - Delivered via colonoscopy, some frozen capsule,
  - Openbiome (stool source) http://www.openbiome.org/

- CDI specific: nontoxigenic C. difficile spores
- Monoclonal antibodies to prevent recurrence
- Vaccine for active antibody

No. 5
Zika virus epidemiology

- First isolated from a monkey in Uganda in 1947
- Before 2007, only sporadic human disease cases reported from Africa and Southeast Asia
- In 2007, first outbreak reported on Yap Island, Federated States of Micronesia
- From 2013–2015, >30,000 suspected cases reported from French Polynesia and other Pacific islands

Reported presentation of confirmed Zika virus disease cases, Yap, 2007

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular or papular rash</td>
<td>28</td>
<td>90%</td>
</tr>
<tr>
<td>Subjective fever</td>
<td>20</td>
<td>65%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>20</td>
<td>65%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>17</td>
<td>55%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>15</td>
<td>48%</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>45%</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>12</td>
<td>39%</td>
</tr>
<tr>
<td>Edema</td>
<td>6</td>
<td>19%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>10%</td>
</tr>
</tbody>
</table>

Why is Zika virus spreading now?

World’s Urban and Rural Populations

International Arrivals

Source: UN Dept. of Economic and Social Affairs

Source: World Tourism Organization
Aedes aegypti: A particularly efficient vector

- “Urban” mosquito; lives in close proximity to humans and prefers to bite humans
- Peak feeding during daytime
- Often bites indoors
- May feed on multiple humans in a single blood meal
- Difficult to control
  - Breeds in small pools of water
  - Cryptic breeding sites
  - Outdoor control may not kill mosquitoes indoors
- Vector of Zika, dengue, chikungunya, yellow fever

Approximate distribution of Aedes aegypti and Aedes albopictus mosquitoes

Maps have been updated from a variety of sources. These maps represent CDC’s best estimate of the potential range of Aedes aegypti and Ae. albopictus in the United States. Maps are not meant to represent risk for spread of disease.
Locally transmitted Zika virus disease cases reported by country/territory in the Americas, 2015–2017 (as of Jan. 5, 2017)

<table>
<thead>
<tr>
<th>Country (N=48)</th>
<th>(N=714,636)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>321,366     (45%)</td>
</tr>
<tr>
<td>Colombia</td>
<td>106,552     (15%)</td>
</tr>
<tr>
<td>Venezuela</td>
<td>61,615      (9%)</td>
</tr>
<tr>
<td>Martinique</td>
<td>36,692      (5%)</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>36,326      (5%)</td>
</tr>
<tr>
<td>Honduras</td>
<td>32,234      (5%)</td>
</tr>
<tr>
<td>Guadeloupe</td>
<td>31,224      (4%)</td>
</tr>
</tbody>
</table>

*25% of cases are lab-confirmed


Mosquito-borne Zika virus transmission in Florida

- Beginning in July 2016, sporadic, locally acquired cases identified in multiple counties in South Florida
- Active transmission later identified in three areas of Miami-Dade County
  - Recommendations for pregnant women to avoid travel to those areas and for testing of pregnant women and postponing conception for couples exposed to those areas
  - Intensive public health response, including aerial adulticide and larvicide applications, helped control the outbreaks
- No further evidence of ongoing Zika virus transmission in these areas

Likos et al. MMWR 2016:
Mosquito-borne Zika virus transmission in Texas

- In November 2016, Texas Department of State Health Services reported state's first case of local mosquito-borne Zika virus infection in Brownsville
- Additional cases identified in Brownsville
- Cameron County borders Mexico – frequent border crossings for work, school, family, and medical care
  - Active Zika virus transmission reported in Mexico near the US-Mexico border
- On December 14, CDC designated Brownsville a Zika cautionary (yellow) area
  - Pregnant women should consider postponing travel to Brownsville
  - Guidance for testing of pregnant women and postponing conception for couples who live in or traveled to Brownsville

Zika cautionary area in Brownsville, TX

Zika cautionary area in Miami-Dade County, FL

Age group for reported Zika virus disease cases — US states and territories, 2015–2016 (as of Dec. 7, 2016)

Other modes of Zika virus transmission

- Documented
  - Intrauterine resulting in congenital infection
  - Intrapartum from viremic mother to newborn
  - Sexual
  - Laboratory exposure
  - Platelet transfusion

- Possible
  - Organ or tissue transplantation
  - Breast milk
  - Other body fluids
Zika virus in semen and vaginal fluid

- Zika viral RNA detected in semen up to 6 months after illness onset and in vaginal fluid up to 2 weeks after illness onset
  - Detection of Zika RNA might not indicate presence of infectious virus
- Zika virus cultured from semen up to 70 days after illness onset
- Sexual transmission reported up to 40 days after illness onset in the transmitting partner
- Data from case reports and may not reflect true incidence or risk of transmission


Risk of adverse outcomes of pregnancy

- Incidence and clinical spectrum of congenital Zika virus infection unknown
- Risk of congenital anomalies appear to be greater with infections early in pregnancy
  - Risk with both symptomatic and asymptomatic infections
- Estimated 1–13% risk of congenital microcephaly following Zika virus infection during the first trimester of pregnancy

Zika virus public health impact and response

- Rapidly spreading disease with multiple modes of transmission and potentially devastating outcome
- Required large and complex public health response
  - Many organizations at local, national, and international levels
  - Broad and varied expertise (e.g., reproductive health, birth defects, neurology, epidemiology, laboratory, vector control, vaccinology, and communications)
  - Continual adjustments in response and guidance with new information
- Outbreaks waning in most parts of the Americas
  - May become endemic with periodic outbreaks like dengue and chikungunya

Zika virus vaccine development and clinical trials

- US government interagency working group objectives
  - Evaluate promising candidate vaccines for safety, immunogenicity, and efficacy
  - Have one or more candidate vaccines available in 2018 for emergency use in US populations at high risk of exposure or disease
  - Work with partners to commercialize vaccines for broad distribution by 2020
- Current status
  - Many vaccine candidates in preclinical development
  - Four vaccines in phase 1 clinical trials by end of 2016
  - Phase 2 studies scheduled to begin in 2017
Finding the Source
Linking Cooling Towers and Patients by DNA

- Affected Area
- Outbreak Pattern Found
  - Opera House Hotel Cooling Tower
  - Patients (with Legionella DNA results?)
- Outbreak Pattern Not Found
  - Cooling Towers
  - Patients (without Legionella DNA results)

*As of last update, all patients tested inside the outbreak pattern.
*Includes cooling towers in which the outbreak pattern could not be determined and those with pending results.
Map updated on August 26, 2019.