Emerging Infectious Diseases

Robert T. Schooley, MD
Chief, Division of Infectious Diseases
Academic Vice Chair, Department of Medicine
University of California, San Diego

Emerging Infections:
What is On the Horizon?

Robert T. Schooley, M.D.
Head, Division of Infectious Diseases
University of California, San Diego
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rschooley@ucsd.edu
Disclosures

- Scientific Advisory Board - Gilead Sciences (Honoraria are paid to UCSD)
- CytoDyn – Consultant
- Farmak - Consultant

Emerging Infectious Diseases: Ancient History

- Human settlement patterns following the development of agriculture
  – Critical population densities
  – Animal domestication
Nipah Virus

• Perak, Malaysia in September 1998
• Presentation:
  – segmental myoclonus, areflexia, hypertension, and tachycardia
  – High mortality rate
• Initial evaluation: Japanese encephalitis
  – Wrong epidemiology: Pig farmers rather than young children

Lam and Chua, Clin Infect Dis, 1999

Axial MRI Findings in Patients with Acute (Panel A) and Relapsed (Panel B) Nipah Virus Encephalitis with Use of Fluid-Attenuated Inversion Recovery.

Nipah Virus

• Spread to other areas of Malaysia with trading in pigs
• March 1999: Emerged in 11 abattoir workers in Singapore
  – No more pigs imported from Malaysia – no more encephalitis in Singapore
  – 1,000,000 pigs culled: epidemic halted after 200 cases had been diagnosed
• Agent isolated turned out to be a paramyxovirus related to Hendra virus

Lam and Chua, Clin Infect Dis, 1999

Nipah Virus

• Reservoir found to be “flying fox” – a large fruit bat that lived in orchards
• Solution: active surveillance of pigs; no pig farms in close proximity to orchards
• Example: “Edge effect” in which humans or food production are placed into new relationships with previously uncultivated areas

Lam and Chua, Clin Infect Dis, 1999
Domestication of Animals

• Smuggling of exotic pets
  – 70 cases of Monkeypox in the US Midwest
  – Infection of prairie dogs who were cross-infected by imported rodents in an animal distribution facility
• Proximity of domestic animals to emerging infection reservoirs
  – *Y. pestis* from prairie dogs to dogs and cats

Emerging Infectious Diseases: Ancient History

• Human settlement patterns following the development of agriculture
  – Critical population densities
  – Animal domestication
• Emerging Infections Changed Early History
  – Peloponnesian war: typhus
  – Devastation of Constantinople: *Y. pestis*
Emerging Infectious Diseases: Exploration and Industrialization

• Age of Exploration
  – Measles and smallpox introduced to the Americas by Cortes and Pizarro
    • Syphilis to Europe “in return”

• Industrial Revolution and the development of cities
  – Crowding, poverty, food situation
    • Smallpox, typhus, tuberculosis, cholera
  – Childhood diseases spread by concentrations of children
    • Measles, mumps, pertussis

Emerging Infectious Diseases: More Recent Developments

• Travel
  – Air travel, in particular
  – Shipment of cargo by boat

• Pursuit of natural resources
  – Opening of previously isolated areas with the creation of local and global supply chains

• Wars and Natural Disasters
Travel: An Important Contributor to Spread of Emerging Infections

• Transportation of infected patients
  — Recent examples
    • SARS: Hong Kong to Canada
    • MERS: Middle East to Europe, US and Korea
    • Ebola to the US and to Nigeria
    • Dengue and Chikungunya fever returning with travelers from the Caribbean, India and Africa
  — Inter-passenger transmission of infection

• Transportation of vectors
  • Mosquitos carrying malaria to non-indigenous locations
  • Introduction of vectors to new ecological niches
Emerging Infectious Diseases: More Recent Developments

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• Wars and Natural Disasters

Connectivity with Population Centers

Emerging Infectious Diseases: More Recent Developments

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  – Air travel, in particular

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• Wars and Natural Disasters

Wars and Natural Disasters

• Wars
  – Refugee camps
  – Disruption of vaccination campaigns
  – Interruption of public health efforts
  – Driving populations into undeveloped areas

• Natural disasters
  – Cholera to Haiti after the 2010 earthquake

• Economic setbacks
  – Increased childhood illnesses in Thailand with 30% reduction in GDP
Changing Human Behavior Patterns

• Twigs and leaves
  – Vaccine apathy: autism and measles, mumps and pertussis
  – “Natural” foods: unpasteurized food products
• Casual sex through social media
  – Upsurge of syphilis and gonorrhea in association with increase in the “hookup” culture

Changing Medical Practices

• Misuse of antibiotics
  – Drug resistant gram negative infections
  – C. difficile
• More immunosuppression
  – More zygomycetes infection with use of voriconazole to prevent aspergillosis
• More tissue sharing
  – Transplant associated CJD, HIV, HCV, tuberculosis
Climate Change

- Vector spread into less “tropical” regions
  - Mosquitos
  - Ticks
- Changing ocean temperatures
  - Cholera in estuaries
- Flooding in coastal regions
  - Sanitation
  - Vector spread
- Drought

West Nile Encephalitis and Drought: Mississippi

Wang, BMC Infectious Diseases, 2010
Emerging Infections: Challenges for Hospital Systems

<table>
<thead>
<tr>
<th>Category</th>
<th>Patient</th>
<th>Travel History</th>
<th>Health System</th>
<th>Examples</th>
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<tbody>
<tr>
<td>1a</td>
<td>Yes</td>
<td>Yes</td>
<td>+</td>
<td>Chikungunya, Dengue</td>
</tr>
<tr>
<td>1b</td>
<td>Yes</td>
<td>Perhaps</td>
<td>+</td>
<td>Plague, Hantavirus, Cocciidymycosis</td>
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<tr>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>+</td>
<td>Ebola, SARS, MERS, Anthrax</td>
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Category 1 Diseases

- Important for patient management; less of an issue for the hospital or the community in terms of a public health response
  - Category 1a: Usually travel associated
    - Chikungunya
    - Dengue
  - Category 1b: Travel not required
    - Plague, tularemia, hantavirus, Cocci
Chikungunya Fever: Fact Sheet

- Etiologic agent: *Alphavirus*
  - Positive Sense Single stranded RNA virus
  - Chickungunya: Makonde for “that which bends”
- Insect vector
  - *Aedes aegypti* and (more recently) *Aedes albopictus*
- Animal reservoirs
  - monkeys, birds, cattle, and rodents
- Initially a disease primarily of East Africa
  - 2004 Indian Ocean Islands
  - 2006 India proper->1.4 million cases
- High penetrance in epidemic situations
- Mortality rate: 0.1%
Aedes albopictus.


World Distribution of the Aedes albopictus Mosquito.

Chikungunya in the Americas

- Previously primarily a disease of returning travelers
  - 1995 – 2003: 3 cases
  - 2006 – 2010: 106 cases
  - 2013 first locally transmitted cases
  - 2014 first locally transmitted cases
- Now endemic in the Caribbean and South America
Chikungunya in the US: 2014

Chikungunya: Clinical Manifestations

- **Acute disease**
  - 3 – 10 days
    - Sudden onset of fever
    - Severe joint pain
    - Headache
    - Myalgias
    - Nausea and vomiting

- **Chronic phase**
  - Longer term symptoms of arthritis in up to 50% of patients – especially in those over 50
Chikungunya: Diagnosis and Treatment

- Diagnosis
  - PCR
  - Viral isolation
  - Serology (may be delayed)

- Treatment
  - Supportive
  - NSAIDS – avoid aspirin because of Reyes syndrome risk

Dengue: Fact Sheet

- Etiologic agent: *Flavivirus*
  - Positive Sense Single stranded RNA virus with 4 serotypes
- Insect vector
  - *Aedes aegypti, Aedes albopictus and Aedes polynesiensis*
- Animal reservoirs
  - Mainly man but may also be found in forest monkeys
- Worldwide distribution but still mainly a disease of travelers among US patients
- High penetrance in epidemic situations especially a disease of children
- Mortality rate: low except in young or elderly
Dengue: Clinical Manifestations

• Incubation period 4 – 7 days
• Headache, musculoskeletal pain, fever and rash
• Followed by anorexia, nausea and vomiting
• Most cases see fever lyse in 3 – 4 days at which time a scarlatinaform rash that misses hands and soles of the feet may appear
• Most cases are uncomplicated
• Laboratory findings
  – Thrombocytopenia
  – Hepatocellular enzyme elevations
Dengue Hemorrhagic Fever

Mandell 2011

Dengue: Clinical Manifestations

• Dengue Shock Syndrome
  – Extravasation of fluids into extravascular space
  – Hemoconcentration
  – Hypotension
  – ARDS
  – Death in up to 50% in poorly resourced settings
    but should be <1% with fluid management
Dengue: Treatment

- Supportive in most patients
- In DSS
  - Maintenance of intravascular volume during hemoconcentration
  - Monitoring for fluid overload with restoration of vascular integrity

Category 1b: “Indigenous” Emerging Infectious Diseases

- *Y. pestis* (plague)
  - Bubonic
  - Pneumonic
- Tularemia
- Coccidiodomycosis
- Hantavirus
## Emerging Infections: Challenges for Hospital Systems

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<td>Yes</td>
<td>Perhaps</td>
<td>+</td>
<td>Plague, Hantavirus, Coccidiomycosis</td>
</tr>
<tr>
<td>Category 2</td>
<td>Yes</td>
<td>Yes</td>
<td>+</td>
<td>Ebola, SARS, MERS, Lassa Fever, HPAI</td>
</tr>
</tbody>
</table>

### Middle East Respiratory Syndrome (MERS): An Early Case

- 60 year old previously healthy Saudi man admitted on June 13, 2012 to a hospital in Jeddah, Saudi Arabia with 7 days of fever, productive cough, sob
- PE: Obese, Pulse Rate 120, T 38.3°C, Resp 20
- CXR: Low lung volumes; increased vascular markings; patchy middle and lower lung field opacities

Clinical Course

- Transferred to ICU and intubated the next day
- Treated empirically for pneumonia
  - Piperacillin/Tazobactam
  - Levofloxacin
  - Oseltamavir
  - Micafungin
- Progressive respiratory failure
- Renal failure
- Died 11 days after admission

Microbiological Evaluation

- Mixed bacterial pathogens of various types during his course of illness
- Negative cultures and PCR for influenza, parainfluenza, RSV
- Cytopathic effect seen in tissue culture
  - PCR for usual respiratory viruses all negative
  - “Family wide” PCR for coronavirus ultimately positive


Coronavirus: Electron Microscopy

“Crowns”

Mandell PPID 7th edition
Coronaviruses

- Single stranded, positive sense, enveloped RNA viruses with large genomes (30 kilobases)
- Genetically and phenotypically diverse
- Worldwide in distribution and found in multiple animal species
  - Bats, birds, cats, dogs, pigs, mice, horses, whales, and humans
- High levels of replicative infidelity
- Capable of recombination


Coronaviruses: History

- 1965: Tyrell and Bynoe cultured a cytopathic agent from the respiratory tract of a boy with a common cold in a human embryonic tracheal organ culture
- Simultaneously two other investigators isolated a similar agent from medical students with colds
Coronaviruses: Clinical Manifestations in Humans

• Respiratory Infection
  – Mild to mortal depending on the coronavirus and the host
  – Worldwide in distribution
  – Episodic (q 2-3 years) epidemics
  – Cause 15 – 35% of adult colds

• Gastrointestinal
  – Usually mild disease or asymptomatic shedding for prolonged periods in infants <1 year old

SARS 2002: Initial Recognition of Coronavirus as a Major Pathogen
SARS Epidemic

- First cases in Guangdong Province, PRC in mid-November 2002
- Came to world’s attention when cases were exported to Hong Kong and Singapore in March 2003
- Rapid spread in hospitals among health care workers, patients, visitors with secondary cases in residential settings

SARS 2003: Worldwide Spread

Mandell PPID 7th edition
SARS: Morbidity and Mortality

- >8000 Cases by the end of 2003
- 774 deaths
  - Fatality rates: 7 – 17%
  - Fatality rate in those with underlying medical conditions and > 65: ~50%
  - No mortality in children <12 years of age

SARS: Containment by Epidemiologic Intervention

- Initially mishandled within China because of concerns that candor would be detrimental to commerce
- Isolation of patients
- Careful attention to contact, droplet and airborne precautions in health care settings
- Quarantine of exposed persons
- Limitation of travel
- Global transmission ended by July 2003
  - Only cases since then: laboratory accidents
  - Contact with civet cats
SARS: Where did it “Come From”? 

Palm Civet

Like Donald Trump, Palm Civets are Cute and Cuddly
The “Real” Reservoir

The Horseshoe Bat

Coronavirus: Typical Course

• Similar to rhinovirus infection
• Incubation period ~ 3 days
• More rhinorrhea than with rhinoviruses but less coughing and sore throat
• Median duration of symptoms ~ a week

• NB: In healthy adult challenge studies, asymptomatic shedding is not at all uncommon
Coronavirus: Complications

- Infants: Pneumonia and bronchiolitis
- Children and young adults: otitis; exacerbation of asthma
- Healthy Adults
  - OCCASIONAL pneumonia
  - exacerbation of asthma and chronic bronchitis
- Elderly
  - Serious bronchitis and pneumonia
- Immunocompromised: Pneumonia

SARS: Clinical Course

- Fever->headache, malaise, myalgia
- Very little URI symptomatology (rhinorrhea)
- Several days to a week later: Nonproductive cough and sometimes dyspnea
- Diarrhea in 25% of cases
- CXR: Scattered air space disease (often in periphery and lower lobes)
- ~25% severe respiratory disease -> ARDS
- Worse in those >50 or with underlying disease
  - Diabetes, hepatitis, cardiac disease
- Often worsens clinically as viral titers are falling suggesting inflammatory pathogenesis
And...back to MERS

• Second case discovered almost simultaneously in September 2012 in a patient from Qatar in a UK ICU
• Retrospectively, first cases were noted in 2 fatal and 9 probable non-fatal cases in Jordan in March – May
  – As with SARS, the Jordan outbreak featured human to human spread between the apparent index case and health care workers (and their families) from several hospitals

MERS CoV: Epidemic Curve

-European Center for Disease Prevention and Control, April 2013-
MERS CoV: The Initial Outbreak

Distribution of Initial MERS CoV Cases by Gender and Age
The Animal Host: “I’d Walk a Mile from a Camel”
14 camel nasal swabs obtained

3 camels had MERS CoV Sequences Consistent with human Cases on the same farm

8 others had fragments Of MERS CoV RNA

All camels were MERS-CoV Seropositive

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### Review

**Bats as reservoirs of severe emerging infectious diseases**

Hui-Ju Han, Hong-ling Wen, Chuan-Min Zhou, Fang-Fang Chen, Li-Mei Luo, Jian-wei Liu, Xue-Jie Yu, Xu-Mei Yang

<table>
<thead>
<tr>
<th>Virus</th>
<th>Primary host</th>
<th>Intermediate host</th>
<th>Modes of transmission</th>
<th>Drivers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nipah virus</td>
<td>Flying foxes</td>
<td>Pigs</td>
<td>Close contact with the sick ones, drinking date palm juice</td>
<td>Climate changes, changes of farming practices, transportation of pigs as merchandise, social/cultural practices, animal-human interaction</td>
</tr>
<tr>
<td>Hendra virus</td>
<td>Flying foxes</td>
<td>Horses</td>
<td>Close contact with horses</td>
<td>Climate changes, urbanization, social/cultural practices</td>
</tr>
<tr>
<td>SARS-CoV</td>
<td>Horseshoe bats</td>
<td>Palm civets</td>
<td>Slaughtering, farming of wildlife</td>
<td>Economic growth, animal-human interaction, international travel</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Rats</td>
<td>Domesticated camels</td>
<td>Direct contact with camels, consumption of camel milk/nutrition</td>
<td>Preference for bush meat, handling practices, poor healthcare practice</td>
</tr>
<tr>
<td>Ebola virus</td>
<td>Egyptian fruit bats</td>
<td>Non-human primates</td>
<td>Slaughtering, hunting for bush meat</td>
<td></td>
</tr>
</tbody>
</table>

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*Specific bat species not identified.*
Camel Transmission to Humans

• Widespread in camels
  – MERS Co-V antibodies found in camels from Saudi Arabia, Jordan, Oman, Egypt, Sudan, Ethiopia, and the Canary Islands
  – One camel serum sample positive from as far back as 1992
• Transmission routes
  – Living in close proximity
  – Consumption of un-Pasteurized camel’s milk
  – Exposure to camel urine or dung

MERS: Clinical Presentation and Clinical Course

• Very similar to SARS: fever
  – Chills, rigor, headaches, myalgia, malaise, diarrhea
• ~600 cases worldwide by 2014
• Case fatality rate: 30 – 40% overall
  – >60% in those who develop severe respiratory disease and ARDS.
**MERS CoV Through May 14, 2014**

- **Cases Total**: 433
- **Deaths**: 181
- **Alive**: 252

**USA Cases: 2014**

- April and May, 2014
- Orlando and Indianapolis
- Both involved travelers returning from Saudi Arabia
- Both had respiratory symptoms when leaving Middle East
- No secondary cases
USA Case 1

May 1: Jeddah -> London -> Boston -> Atlanta -> Orlando

May 1: Fever, Chills, slight cough

May 9: Presentation to Orlando ER

USA Case 2

April 24: Riyadh -> London -> Chicago -> Indiana

April 14: Ill  April 27: cough, sob, fever  April 28: Hospitalized for Pneumonia
MERS in the US

- US health care worker working in a Saudi Hospital in April of 2014
- No recollection of caring for a patient with known MERS but he did care for patients with respiratory illness including several intubated patients in the ICU
- Performed several non-invasive pulmonary procedures; used appropriate PPE each time.

Breakwell, Emerging Infect Dis 2015

MERS in the US

- No colleagues, friends or household members with respiratory illness
- April 18: low grade fever, fatigue and myalgias
- Departed for US on April 23
- April 27 developed mild, non-productive cough and SOB
- Admitted to the hospital the next day with RLL pneumonia and hypoxia

Breakwell, Emerging Infect Dis 2015
Inpatient Course

• Hospital day 2: MERS Co-V suspected
  – Isolation: respiratory precautions with N-95 masks instituted
• Hospital day 3: MERS Co-V confirmed
  – Isolation: airborne isolation room; contact precautions added
  – MERS-CoV detected in sputum through hospital day 6
• Discharged after 11 days in the hospital

Breakwell, Emerg Infect Dis, 2015

Lack of Secondary Transmission in the US

Breakwell, Emerg Infect Dis, 2015
MERS in Korea

UAE early May
May 11: Fever and cough
May 12, 14, 15: Local Clinic

Admitted to St. Mary’s Hospital
In Pyeongtaek

May 17: No improvement:
Patient left St. Mary’s for
a small hospital in Seoul

By May 20: Samsung General
Where diagnosis was made
When a travel history was obtained

37 Secondary Cases
35 Secondary Cases
Epidemic Course

By June 12, 2015
126 Cases
13 Deaths (all with underlying diseases)
3000 in Quarantine

MERS Co-V In Korea
Korean Epidemic: The Course

• Vigorous quarantine of >3000 people
• Travel restrictions
• Epidemic declared over by the end of July

• Lessons learned
  – Identification of index cases is critical
  – Hospital infection control precautions are critical
  – Once identified, transparency is critical

Khan, J Infect Developing Countries, 2015

Chicken Market in Xining, China

[Wikipedia]
Highly Pathogenic Avian Influenza

- Young healthy Canadian citizen who flew to China on December 6, 2013
- No contact with live poultry, wet markets, or handling of fresh poultry
- Return flight December 27: malaise, chasm pain, fever
- ER: Leukocytosis, right apical infiltrate
  - CAP diagnosed: levofloxacin and sent home

Highly Pathogenic Avian Influenza

- January 1, 2014: Back to ER with more pleuritic chest pain and SOB, headache and multi-lobar pneumonia on CXR with a pleural effusion
- Thoracentesis: dark fluid with no bacterial growth
- Admitted to general medicine ward and placed on pip/tazo
- January 2: Disease progression -> ICU for intubation
- January 3: tachycardia; hypertension->hypotension and brain death
- Post mortem: PCR from nasal washing H5N1 influenza

Pabbaraju. Emerg Infect Dis 2014
Influenza: Human Respiratory Epithelial Tropism Determines Pathogenicity

• Determined by amino acids at the tip of the hemagglutinin protein
• Typical influenza has a hemagglutinin sequence that binds to receptors in the human nasal mucosa
• Highly pathogenic influenza has a hemagglutinin sequence that binds to receptors in the lung
• So far, it has been difficult for the virus to evolve a hemagglutinin that is able to bind both and be highly transmissible and highly pathogenic
• Not clear that this is an impossible problem to overcome.

Lassa Fever: Fact Sheet

• Etiologic agent: *Arenaviridae*
  – single-stranded segmented ambisense RNA virus
• Animal vector
  – Multimammate rat (*Mastomys natalensis*)
• Incubation period: 3 days to 3 weeks
• Cases: 100,000 to 300,000/year in West Africa
• Deaths: 5,000 deaths/year
• Mortality rate: 1 – 2%
Lassa Fever in the US: May 2015

- Patient traveled from Liberia to Morocco to JFK May 17th.
- Afebrile on departure from Liberia and without symptoms including diarrhea, vomiting, or bleeding during the flight
- Afebrile on arrival in the U.S.
- May 18th: presented to a NJ hospital with a sore throat, fever and tiredness; did not indicate travel to West Africa.
- Discharged but returned on May 21st with worse symptoms.
- Transferred to another hospital prepared to treat viral hemorrhagic fevers
- Blood tested positive for Lassa fever on May 25. Tests for Ebola and other viral hemorrhagic fevers were negative.
- The patient died on May 25
What’s Next?

- Hard to know for certain – but there will definitely be more to come
  - If I were a betting man, I would be most worried about highly pathogenic influenza or a coronavirus (MERS/SARS)
  - Lassa fever and Ebola viruses lower on the list
  - Nonetheless new pathogens will continue to emerge

What Should Hospitals Do?

- Maintain vigilance – especially on the front lines in the ER and inpatient units
  - Travel history is important
  - Be wary of empiric diagnosis and treatment
  - Streamline communications with public health authorities
  - Decrease turnaround time for laboratory testing
  - Utilize multiplex diagnostics
- Open access to health care is critical
- Public health responses cannot be effective without transparency
- Politically driven decision making is counterproductive
The World is a Much Smaller Place

Public Health in the Absence of Functioning Health Care Systems is only an Exercise in Accounting.

rschooley@ucsd.edu

The End
Questions?

Thank you

Robert Schooley, MD
rschooley@ucsd.edu