Demystifying Medicine 2016

Ebola, MERS, and the Likelihood of More Epidemics

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Examples of Notable Epidemics

<table>
<thead>
<tr>
<th>Year</th>
<th>Disease (cause)</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1340s</td>
<td>“Black Death” (Yersinia pestis)</td>
<td>~50 million</td>
</tr>
<tr>
<td>1494</td>
<td>French Pox (Syphilis - Treponema pallidum)</td>
<td>&gt;50,000</td>
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<tr>
<td>1520</td>
<td>Hueyehuatuil (Smallpox - Variola minor)</td>
<td>3.5 million</td>
</tr>
<tr>
<td>1790s</td>
<td>“The American plague” (Yellow Fever)</td>
<td>~25,000</td>
</tr>
<tr>
<td>1832</td>
<td>2nd cholera pandemic (Paris)</td>
<td>&gt;18,000</td>
</tr>
<tr>
<td>1918</td>
<td>“Spanish” influenza</td>
<td>~50 million</td>
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</tbody>
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Progress in the Control of Infectious Diseases

- Recognition that microbes cause many serious diseases
- Improvements in sanitation, hygiene, vector control
- Discovery and development of antimicrobials
- Development of vaccines and implementation of vaccination programs
- Advances in detecting and monitoring infectious diseases

Crude Infectious Disease Mortality Rate, United States, 1900 to 1996

A Premature Declaration of Victory Over Infectious Diseases

"We can look forward with confidence to a considerable degree of freedom from infectious diseases at a time not too far in the future. Indeed...it seems reasonable to anticipate that within some measurable time...all the major infections will have disappeared."

– T. Aidan Cockburn
The Evolution and Eradication of Infectious Diseases, 1963
**Infectious Diseases Cause ~16% of All Deaths Worldwide**

- Non-Communicable Diseases: 38.3 Million
- Infectious Diseases: 8.9 Million
- Maternal, Neonatal, and Nutritional Disorders: 3.0 Million
- Injuries: 4.8 Million

*Total Deaths (2013): ~55 Million*

**Broad Categories of Infectious Diseases**

- Established Infectious Diseases
- Newly Emerging Diseases
- Re-Emerging Diseases

**Selected Established Infectious Diseases of Global Public Health Importance**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estimated Annual Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory infections</td>
<td>&gt;2,000,000</td>
</tr>
<tr>
<td>Diarrheal Infections</td>
<td>1,800,000</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1,600,000</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1,300,000</td>
</tr>
<tr>
<td>Hepatitis (A, B, C, E)</td>
<td>900,000-1,200,000</td>
</tr>
<tr>
<td>Malaria</td>
<td>600,000</td>
</tr>
<tr>
<td>Vaccine Preventable Childhood Diseases (measles, pertussis, tetanus, etc.)</td>
<td>400,000</td>
</tr>
<tr>
<td>Neglected Tropical Diseases*</td>
<td>320,000-700,000</td>
</tr>
</tbody>
</table>

*Source: www.who.int, January 2016; Thrus et al., Lancet 2010*
Global Examples of Emerging and Re-Emerging Infectious Diseases

Selected Infectious Disease Outbreaks, 2015-2016
- Measles
- Drug-resistant TB and malaria
- H7N9, H5N1 and H5N6 avian influenza
- MERS
- Antibiotic-resistant bacterial infections
- Chikungunya
- Ebola
- Cholera
- Dengue
- Zika virus

Factors Contributing to Disease Re-emergence
- Human demographics and behavior
- Technology and industry
- Economic development and land use
- International travel and commerce
- Breakdown of public health measures
- Ecologic and environmental
- Microbial adaptation and change

~75 Percent of Emerging Pathogens are Zoonotic
Common Zoonotic Diseases
- Chikungunya
- Ebola virus disease
- HIV/AIDS
- Influenza
- Lyme disease
- MERS-CoV

Global Air Travel Promotes the Spread of Infectious Diseases
**Broad Categories of Infectious Diseases**

- Established Infectious Diseases
- Newly Emerging Diseases
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**Global Examples of Emerging and Re-Emerging Infectious Diseases**

- **HIV**

**Current Status of the Global HIV/AIDS Pandemic**

- **36.9 million people living with HIV (end-2014)**
  - 46% unaware they are infected
- **1.2 million AIDS deaths in 2014**
  - Decline of 42% since peak in 2004
- **2.0 million new HIV infections in 2014**
  - Decline of 35% since peak in 2000

**Rounds at NIH Clinical Center, Early 1980s – AIDS Patient**

- Median survival of AIDS patients: ~6-8 months

**FDA-Approved Antiretroviral Drugs**

- NRTI: Zidovudine, Didanosine, Stavudine, Abacavir, Tenofovir (TDF, TAF), Emtricitabine, 4 multi-drug combinations
- NNRTI: Nevirapine, Etravirine, Delavirdine, Etavirenz
- Integrase Inhibitors: Raltegravir, Elvitegravir, Dolasetravir
- PI: Saquinavir, Indinavir, Nelfinavir, Amprenavir, Lopinavir, Atazanavir, Kaletra, Fosamprenavir, Tipranavir, Darunavir
- Pharmacokinetic Enhancers: ritonavir, cobicistat
- Multi-Class Combinations: Atripla, Complera, Stribild, Triumeq
- Fusion Inhibitor: Enfuvirtide
- Entry Inhibitor: Maraviroc

Antiretroviral Therapy Helps People with HIV Live Longer

A person with HIV diagnosed at age 20 and taking current HIV medications: ~32 years
A person with HIV diagnosed at age 20 and not taking current HIV medications: ~71 years
A person without HIV: ~79 years


The Washington Post
January 10, 2016
Opinions
No More Excuses. We Have the Tools to End the HIV/AIDS Pandemic.
Anthony S. Fauci

Ebola Outbreak in Zaire, 1976: Evacuation of Medical Worker from Yambuku, Zaire, to Johannesburg, S. Africa

Ebola virus disease

Courtesy of Joel Shreve

Early Cases of Severe Acute Respiratory Syndrome (SARS): Guangdong Province, China

Nov 16, 2002: first known cases of atypical pneumonia in Foshan
Feb 15-17, 2003: China reports 306 cases of acute respiratory syndrome in Guangdong Province

Global Examples of Emerging and Re-Emerging Infectious Diseases

SARS

Global Examples of Emerging and Re-Emerging Infectious Diseases

Newly emerging
Re-emerging/resurging
Deliberately emerging
Evaluation of Candidate Vaccine Approaches for MERS-CoV
L Wang, MG Joyce, SS Rao, BS Graham, et al.

- DNA prime, protein boost elicits neutralizing antibodies in mice and rhesus macaques
- Reduces radiographic evidence of pneumonia in rhesus macaques

Global Examples of Emerging and Re-Emerging Infectious Diseases

- Antimicrobial-resistant threats
  - CRE
  - MRSA
  - *C. difficile*
  - *N. gonorrhoeae*

- Drug-resistant malaria
- West Nile virus

Broad Categories of Infectious Diseases

- Established Infectious Diseases
- Newly Emerging Diseases
- Re-Emerging Diseases

First Dengue Fever Vaccine Gets Green Light in Three Countries

- Sanofi’s Dengvaxia® approved for use in Mexico, Brazil, and the Philippines
- Vaccine based on a yellow fever vaccine strain genomic backbone with substitutions of genes encoding dengue proteins

Global Examples of Emerging and Re-Emerging Infectious Diseases

Chikungunya Virus Distribution, 2010

- Newly emerging
- Re-emerging/resurging
- “Deliberately emerging”

Chikungunya Virus Distribution, 2016

- First locally acquired cases 12/2013

Chikungunya Virus Emerges in the Caribbean in Late 2013

- 2016 Global Distribution >70 Countries
- Global Distribution ~40 Countries

Source: CDC, WHO
Safety and Tolerability of Chikungunya Virus-Like Particle Vaccine in Healthy Adults: A Phase 1 Dose-Escalation Trial

Immunogenicity, Safety, and Tolerability of a Recombinant Measles-Virus-Based Chikungunya Vaccine: A Randomised, Double-Blind, Placebo-Controlled, Active-Comparator, First-In-Man Trial

Global Examples of Emerging and Re-Emerging Infectious Diseases

Ebola virus disease

Reported Ebola Virus Disease Cases in Guinea, Liberia, and Sierra Leone, 2014-2016

Guinea
3004 cases / 2200 deaths

Sierra Leone
14,122 cases / 3955 deaths

Liberia
10,675 cases / 4809 deaths

Total: 28,601 cases 11,300 deaths

Source: WHO, data through 31/08/2016.

Ebola Virology

- Filovirus family
- Species and average fatality in the genus *Ebolavirus*
  - Bundibugyo – ~30%
  - Zaire – 50-90%
  - Reston – animal disease
  - Sudan – ~60%
  - Tai Forest – 1 non-fatal human case

Ebola Transmission Cycle

Enzootic cycle
Epizootic cycle
Fruit bats putative reservoir; evidence inconclusive

Ebola Transmission Routes

- Bodily fluids
- Objects (fomites)
- Transmission occurs once symptomatic (viral load rises at symptom onset)
- Infected animals
Typical Ebola Virus Disease Clinical Course

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Incubation period</th>
<th>Symptoms begin</th>
<th>Recovery or death</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Average 6-10 days, range 2-21</td>
<td>Days 1-3: Weakness, fever, influenza-like illness</td>
<td>Days 7-10: Confusion, possible bleeding (typically minor), shock</td>
</tr>
</tbody>
</table>

Source: Adapted from E. Blakemore as shown in the New England Journal of Medicine

Ebola Cases First Reported in March 2014

“On March 21, 2014, the Ministry of Health reported the outbreak of an illness characterized by fever, severe diarrhea, vomiting, and a high case-fatality rate (59%) among 49 persons”

Tracing Origins of the Outbreak in Guinea

Dec. 6, 2013

Patient zero: 3-year-old child

Figures are positioned at their date and location of death

Sources: Adapted from the Wall Street Journal September 3, 2014

State of the Outbreak: March 2014

State of the Outbreak: May 2014

State of the Outbreak: July 2014

Sources: E. Erwin, CDC, WHO
**Factors Facilitating Spread**

- Poor nations with limited health infrastructure
- No prior experience with Ebola
- Few health professionals; multiple health threats
- Frequent travel across porous borders
- Limited cooperation between neighboring governments
- History of regional conflicts
- Local customs, e.g., burial practices
September 2, 2014: Phase I Trial of NIAID/GSK Ebola Vaccine Candidate Launches

- Twenty healthy adult volunteers enrolled

Associated Press
February 2, 2015

Ebola Vaccines Testing Starts in Liberia
- Liberia-U.S. Partnership leads Phase 2/3 trial
- cAd3-EBOZ vs. rVSV-EBOV vs. placebo

The New York Times
July 31, 2015

Experimental Ebola Vaccine Tested in Guinea Shows Promise, Report Says
Sheri Fink

Efficacy and Effectiveness of an rVSV-Vectored Vaccine Expressing Ebola Surface Glycoprotein: Interim Results from the Guinea Ring Vaccination Cluster-Randomised Trial
AM Hensel-Restrepo, MP Kieny, J-A Rolfsing et al.
Liberia-U.S. Clinical Research Partnership Opens Trial to Test Ebola Treatments

Initial Study Will Evaluate Experimental Drug Cocktail ZMap

Adults testing positive for Ebola Virus Disease

Optimized Standard of Care: e.g., careful electrolyte and fluid management, antibiotics prn

Optimized Standard of Care + ZMap

Vaccines
Therapeutics
Diagnostics
Resources for Researchers/Industry to Advance Product Development

NIH Research and Development

Clinical Research

NIH Special Clinical Studies Unit: Designated Ebola Treatment Facility

As of Oct. 2014, three Designated Ebola Treatment Facilities existed in the U.S.

The Washington Post
October 25, 2014
Nina Pham, Nurse Who Contracted Ebola, is Now Free of Virus and Leaves NIH

CNN
March 12, 2015
U.S. Ebola Patient Headed to NIH
Zika Virus

**Virology:**
- Flaviviridae family
- Enveloped, icosahedral RNA virus
- First isolated from a monkey in 1947 in the Zika forest, Uganda
- First known human case Nigeria 1952
- Spread by *Aedes aegypti* and other *Aedes* mosquitoes
- Additional case reports of perinatal, possible sexual and transfusion-related transmission

Source: European Centre for Disease Prevention and Control, ViruZone

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Zika Virus Clinical Manifestations

- **Incubation period:** 3 to 12 days after mosquito bite
- **4 in 5 individuals** asymptomatic
- **Symptoms** include fever, conjunctivitis, polyarthralgia, myalgias and headache
  - Maculopapular rash (pictured) is also common
- **Diagnosis:**
  - Viral RNA detectable on RT-PCR for 3-5 days
  - IgM detected by day 5, though significant cross-reactivity with Dengue and West Nile

Source: CDC, European Centre for Disease Prevention and Control
Zika Virus Infection Complicated by Guillain-Barré Syndrome – Case Report, French Polynesia, December 2013

- A total of 42 cases of Guillain-Barré Syndrome reported in French Polynesia

Microcephaly

- An occipitofrontal circumference at least 2 standard deviations below the mean (definitions differ)
- Associated with reduced life expectancy and abnormal neurocognitive development
- Major etiologies include:
  - Genetic anomalies
  - Fetal alcohol syndrome
  - Other maternal factors (malnutrition, endocrine disorders)
  - Maternal infections (including cytomegalovirus, toxoplasmosis, rubella)
  - Zika?

Zika as a Potential Cause of Microcephaly

- Nine states with Zika infections see surge in babies born with small heads

A Delicate Balance

- The Extraordinary Capability of Microbial Pathogens to Persist, Emerge, and Re-Emerge
- Public Health Measures, Biomedical Research, and Technological Advances

Emerging Infections: A Perpetual Challenge

- DM Morens, GK Folkers & AS Fauci