Emerging and Re-emerging Infectious Diseases: The Perpetual Challenge to Global Health

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January 10, 2012

Examples of Epidemic Emerging Infections

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Causal Agent</th>
<th>Deaths (est.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>430-426 BC</td>
<td>Plague of Athens</td>
<td>Unknown</td>
<td>40,000</td>
</tr>
<tr>
<td>1340s</td>
<td>Black death (plague)</td>
<td>Yersinia pestis</td>
<td>~50 million</td>
</tr>
<tr>
<td>1520-21</td>
<td>Smallpox in Aztec Empire</td>
<td>Variola major</td>
<td>3.5 million</td>
</tr>
<tr>
<td>1793-98</td>
<td>The American plague</td>
<td>Yellow fever virus</td>
<td>~25,000</td>
</tr>
<tr>
<td>1918-19</td>
<td>Spanish influenza</td>
<td>H1N1 influenza virus</td>
<td>~50 million</td>
</tr>
<tr>
<td>1981</td>
<td>AIDS pandemic</td>
<td>HIV</td>
<td>~30 million</td>
</tr>
</tbody>
</table>

Source: Moreno, Folkers, Fauci. (Lancet Infect Dis, 2006); UNAIDS, 2011
Progress in the Control of Infectious Diseases

- Recognition that microbes causes 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

Source: DL Armstrong et al., JAMA 281:01, 1999

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.”

A Failure to Look Beyond our Borders

Infectious Diseases Cause ~24% of All Deaths Worldwide

- Cardiovascular Diseases: 17.1 Million
- All Other Causes of Death: 16.6 Million
- Injuries: 5.6 Million
- Nontuberculous Disease: 7.5 Million
- Infectious Diseases: 14.2 Million

Total Deaths: ~58.8 Million

Source: WHO, 2020

Proportion of Deaths Due to Infectious Diseases

High-Income Countries: ~6%
Sub-Saharan Africa: ~63%

Source: Disease Control Priorities Project, 2006
Global Health and Infectious Diseases

Established Infectious Diseases

Emerging and Re-Emerging Infectious 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>4.0 million</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1.8 million</td>
</tr>
<tr>
<td>Diarrheal Infections</td>
<td>1.8 million</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.7 million</td>
</tr>
<tr>
<td>Vaccine Preventable Childhood Diseases (measles, pertussis, tetanus, etc.)</td>
<td>1.1 million</td>
</tr>
<tr>
<td>Hepatitis (B and C)</td>
<td>950,000</td>
</tr>
<tr>
<td>Malaria</td>
<td>655,000</td>
</tr>
<tr>
<td>Neglected Tropical Diseases</td>
<td>547,000</td>
</tr>
</tbody>
</table>

Sources: WHO; Hotez et al., Lancet Infect Dis, 2009
Global Health and Infectious Diseases

Established Infectious Diseases

+ Emerging and Re-Emerging Infectious Diseases

Global Trends in Emerging Infectious Diseases
KE Jones, Peter Daszak, et al.

“In the global human population, we report the emergence of 335 infectious diseases between 1940 and 2004.”

Global Examples of Emerging and Re-Emerging Infectious Diseases
Factors Contributing To Infectious Disease Emergence

- International travel, trade and commerce
- Human demographics and behaviour
- Human susceptibility to infection
- Poverty, social inequality, war, lack of political will
- Breakdown of public-health measures
- Technology and industry
- Ecological and environmental factors
- Microbial adaptation and change
- Economic development and land use

~75 Percent of Emerging Pathogens are Zoonotic

Examples:

- HIV
- Influenza
- Human monkeypox
- Nipah virus
- BSE/vCJD
- SARS
- Ebola

Emerging Infectious Diseases

- Newly Emerging
- Re-emerging or Resurging
Global Examples of Emerging and Re-Emerging Infectious Diseases

30 Years of AIDS

June 5, 1981
Pneumocystis Pneumonia – Los Angeles

July 4, 1981
Kaposi’s Sarcoma and Pneumocystis Pneumonia Among Homosexual Men – New York City and California

Origin of HIV-1 in the chimpanzee
Pan troglodytes troglodytes

The Scope of the Global HIV/AIDS Pandemic

- Cumulative HIV infections: 65 million
- People living with HIV/AIDS: 34 million
- New HIV infections in 2010: 2.7 million
- Deaths due to AIDS in 2010: 1.8 million
- Cumulative AIDS deaths: ~30 million

UNAIDS estimates, 11/2011

HIV/AIDS in the United States – Latest Estimates

- 594,496 cumulative deaths
- ~1.2 million living with HIV, 20% unaware of their infection
- ~50,000 new infections/yr.
  - 61% male-to-male sexual contact, 27% heterosexual contact
  - Incidence rates among blacks >7 times higher than whites

Source: CDC, 2011. Includes 50 States and District of Columbia.

NIH HIV/AIDS Research Funding

~$45 Billion in Cumulative Funding (through FY 2010)

Grants in Millions

Fiscal Year

Chart: Estimates AFHA funds in FY 2010
Advances in HIV Science
- Etiology
- Diagnosis
- Molecular Virology and Epidemiology
- Natural History
- Pathogenesis
- Treatment
- Prevention
- Vaccine Development

Treatment of the HIV-Infected Individual

Rounding on AIDS Ward, NIH Clinical Center, Early 1980s
- Median survival of AIDS patients: ~6-8 months
**HIV Replication Cycle: Targets for Antiretroviral Therapy**

- gp120
- gp41
- Protease Inhibitors
- Reverse Transcriptase Inhibitors
- Integrate Inhibitors
- Fusion/Entry Inhibitors
- Protein Synthesis, Processing and Assembly
- Reverse Transcripse
- Integrate Protease DNA
- Integrate DNA
- Unintegrated Linear DNA
- Co-receptor
- Cellular DNA
- Envelope
- Reverse Transcriptase
- Integrate DNA
- Integrate DNA
- Integrate DNA
- Reverse Transcripse
- Reverse Transcripse
- Cellular DNA
- Envelope
- gp120
- gp41

**FDA-Approved Antiretroviral Drugs**

- **NRTI**
  - Zidovudine
  - Didanosine
  - Zalcitabine
  - Stavudine
  - Lamivudine
  - Abacavir
  - Tenofovir
  - Emtricitabine
- **NNRTI**
  - Nevirapine
  - Delavirdine
  - Efavirenz
  - Etravirine
  - Rilpivirine
- **PI**
  - Saquinavir
  - Ritonavir
  - Indinavir
  - Nelfinavir
  - Amprenavir
  - Lopinavir
  - Atazanavir
  - Fosamprenavir
  - Tipranavir
  - Darunavir
  - Fusion Inhibitor
    - Enfuvirtide (T-20)
- **Entry Inhibitor**
  - Maraviroc
- **Integrate Inhibitor**
  - Raltegravir
- **Combinations**
  - 6 available, combining 2 or 3 drugs

**Life Expectancy of Recently Diagnosed Asymptomatic HIV-infected Patients Approaches that of Uninfected Individuals**

A. van Sighem et al. on behalf of the ATHENA National Observational Cohort Study

- **Life expectancy** for HIV-infected patients (without AIDS) aged 25 yrs at six months postinfection
  - Men: an additional 52.7 yrs (versus 53.1 yrs in general population)
  - Women: an additional 57.8 yrs (versus 58.1 yrs in general population)
**Examples of Programs Providing HIV/AIDS Prevention, Treatment and Care to Developing Nations**

- President's Emergency Plan for AIDS Relief (PEPFAR)
- Global Fund to Fight AIDS, Tuberculosis and Malaria
- Philanthropies and NGOs (e.g. Gates Fdn., Clinton Fdn., MSF)

**Number of People Receiving Antiretrovirals in Low- and Middle-Income Countries**

![Bar chart showing the increase in the number of people receiving antiretrovirals from 2002 to 2010](image)

Source: UNAIDS, 2011

**Major Challenges Globally in the Treatment of HIV Disease**

- 47% of people in need of ARV therapy in low- and middle-income countries are receiving it
- For every person put on ARV therapy in 2010, about 2 others were newly infected with HIV

UNAIDS estimates, 11/2011
Advances in HIV Science

- Etiology
- Diagnosis
- Molecular Virology and Epidemiology
- Natural History
- Pathogenesis
- Treatment
- Prevention
- Vaccine Development

Combination HIV Prevention

- Education
- Condoms
- PrEP
- Microbicides
- Male circumcision
- Drug/alcohol treatment
- PMTCT
- STI treatment
- Testing/counseling
- Treatment as prevention
AIDS: Let Science Inform Policy

Anthony S. Fauci

“We now have an unprecedented opportunity, based on solid scientific data, to control and ultimately end the AIDS pandemic. . . . Major investments in implementation now will save even greater expenditures in the future; and in the meantime, countless lives can be saved.”
SARS: A New Challenge to Global Health

Early Cases of SARS: Guangdong Province, China

Nov 16, 2002: first known cases of atypical pneumonia in Foshan

Feb 11-12, 2003: China reports 359 cases of acute respiratory syndrome in Guangdong Province

Spread of SARS from Hotel Metropole

Source: MMWR, March 20, 2003
**Death Rate for Tuberculosis, United States, 1900-2000 (per 100,000 population)**

![Graph showing the death rate for tuberculosis from 1900 to 2000](image)

**The Global Burden of Tuberculosis**

- One-third of the world’s population is infected with *Mycobacterium tuberculosis* (MtB)

- In 2010
  - 8.8 million new cases, incl. 1.1 million among HIV+
  - 1.45 million deaths, incl. 350,000 among HIV+
  - 650,000 prevalent cases of MDR-TB
  - XDR-TB reported in ~70 countries

Source: WHO, 2011

**Major Challenges in the Control of Tuberculosis**

- Standard diagnostics are antiquated, insensitive and slow
- Current drug regimens are complex and lengthy
- Available vaccine not effective in preventing adult pulmonary TB
- Our understanding of TB pathogenesis is limited
**The Global Burden of Malaria, 2010**

- ~655,000 malaria deaths, 91% in Africa
- ~216 million malaria cases
- Malaria present in 106 countries and territories
  - Half the world’s population is at risk
- Every 60 seconds a child dies from malaria

Source: WHO, World malaria report 2011

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“The final challenge is to ensure the vigor and sustainability of the substantial biomedical research efforts that will be required to eliminate and ultimately eradicate malaria.”

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**First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children**

- Initial report on efficacy, safety, and immunogenicity in the first 6,000 children, age 5 to 17 months
- Vaccine prevented about half of malaria infections
#2. A First-Ever Malaria Vaccine

Global Examples of Emerging and Re-Emerging Infectious Diseases

Global Distribution of West Nile Virus, 1999
Reported Human Cases of West Nile Virus Infection, USA, 1999-2011

Source: CDC

Dengue: 2.5 Billion People at Risk

- ~50 million annual infections, incl. 500,000 hospitalizations
- ~700,000 DALYs/yr.
- Prompt, skilled medical care can reduce death rates to <1%

Source: WHO; Hailes et al., 2009

Average Annual Number of Cases and Countries Reporting Dengue Fever and Dengue Hemorrhagic Fever

Source: WHO, 2006
Dengue and Hemorrhagic Fever
A Potential Threat to Public Health in the United States
DM Morens and AS Fauci

Global Examples of Emerging and Re-Emerging Infectious Diseases

28 Cases of Locally Acquired Dengue in Key West, 2009-2010

"Clinicians should include dengue in the differential diagnosis of acute febrile illnesses in patients who live in or have recently traveled to subtropical areas of the United States or to the tropics."
**Second Case of Locally Acquired Dengue Fever Found in Miami-Dade**

Miami-Dade health officials announced a second case of locally acquired dengue fever this year, and urged residents to drain standing water and wear protective clothing and mosquito repellent.

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

![Map of emerging and re-emerging infectious diseases]

- Cholera
- Dengue
- Human African trypanosomiasis
- Ebola
- West Nile virus
- Lyme disease
- SARS
- MERS
- Chikungunya
- Human metapneumovirus

Legend:
- Newly emerging
- Re-emerging/resurging
- "Deliberately emerging"

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**Amid Cholera Outbreak in Haiti, Fear and Misery**

- First large cholera outbreak in Haiti in >100 years
- 473,649 cases and 6,631 deaths (PAHO, November 7, 2011)
Influenza

- Re-emerging disease (seasonal influenza)
- Newly emerging disease (pandemic influenza)

Seasonal vs. Pandemic Influenza

- **Seasonal Influenza**
  - Predictable annual occurrence
  - Residual immunity in population
- **Pandemic Influenza**
  - Unpredictable rare occurrence
  - "Naive" population

The Influenza Pandemic of 1918-1919

- 25-30% of world's population (~500 million people) fell ill
- >50 million deaths worldwide; ~60 percent in people ages 20-45
- >500,000 deaths in United States; 196,000 in October, 1918 alone

Source: WHO, 1998
Induction of Unnatural Immunity: Prospects for a Broadly Protective Universal Influenza Vaccine

GJ Nabel and AS Fauci

Selected Targets for “Universal” Influenza Vaccines

- M2
- Conserved epitopes of HA
- NP

Source: Subbarao/Murphy

Binding of Antibodies to Influenza Hemagglutinin (HA)

- Most abs bind to epitopes of highly variable head region
- Abs that neutralize multiple strains (both within a virus subtype and from different subtypes) bind to a highly conserved region (red) in the stem region

Source: Drake, Science 328:1081, 2010
Emerging and Re-emerging Infectious Diseases – A Delicate Balance

The Extraordinary Capability of Microbial Pathogens to Change, Adapt, Emerge, Re-Emerge, and Persist

Public Health Measures, Biomedical Research, and Countermeasure Development

Microorganisms versus Man

Homo sapiens
~6 million years
2% genome change

Human virus
<one day
2% genome change

“The future of humanity and microbes likely will unfold as episodes of a suspense thriller that could be titled Our Wits Versus Their Genes.”

~Joshua Lederberg, Science, April 14, 2000