Pandemic Influenza and Other Emerging Infectious Diseases: Public Health Threat and the Research Agenda

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May 10, 2006

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."


Infectious Diseases Cause ~26% of All Deaths Worldwide

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious Diseases</td>
<td>14.9 Million</td>
</tr>
<tr>
<td>Neoplastic Diseases</td>
<td>7.1 Million</td>
</tr>
<tr>
<td>Injuries</td>
<td>5.2 Million</td>
</tr>
<tr>
<td>Asthma and COPD</td>
<td>3.6 Million</td>
</tr>
<tr>
<td>All Other Causes of Death</td>
<td>16.7 Million</td>
</tr>
<tr>
<td>Total Deaths</td>
<td>~57 Million</td>
</tr>
</tbody>
</table>

Background "Matrix" of Infectious Diseases of Global Public Health Importance

<table>
<thead>
<tr>
<th>Disease Category</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>3.1 million</td>
</tr>
<tr>
<td>Diarrheal Diseases</td>
<td>1.8 million</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.6 million</td>
</tr>
<tr>
<td>Malaria</td>
<td>1.3 million</td>
</tr>
<tr>
<td>Vaccine Preventable Childhood Diseases (measles, pertussis, tetanus, etc.)</td>
<td>600,000</td>
</tr>
<tr>
<td>Meningitis</td>
<td>170,000</td>
</tr>
<tr>
<td>Tropical Parasitic Diseases (trypanosomiasis, leishmaniasis, etc.)</td>
<td>130,000</td>
</tr>
</tbody>
</table>

Global Examples of Emerging and Re-Emerging Infectious Diseases

- Pneumocystis Pneumonia - Los Angeles, June 5, 1981
- Kaposi's Sarcoma and Pneumocystis Pneumonia Among Homosexual Men - New York City and California, July 4, 1981
Advances in AIDS Research, 1981-2006

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

FDA-Approved Antiretroviral Drugs

<table>
<thead>
<tr>
<th>NRTI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Amprenavir</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Atazanavir</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Fosamprenavir</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Indinavir</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Lopinavir</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Saquinavir</td>
</tr>
</tbody>
</table>

NNRTI

- Delavirdine
- Efavirenz
- Nevirapine

Fusion Inhibitor

- Enfuvirtide (T-20)

Combinations

- 4 available, combining 2 or 3 drugs

AIDS Cases, Deaths, and People Living with AIDS, United States, 1981-2004

The President's Emergency Plan for AIDS Relief – $15B Over 5 Years

<table>
<thead>
<tr>
<th>Goals:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent 7 million new infections</td>
</tr>
<tr>
<td>Treat 2 million HIV-infected people</td>
</tr>
<tr>
<td>Care for 10 million HIV-infected people, orphans and other vulnerable children</td>
</tr>
</tbody>
</table>
Three Major Mechanisms for Providing HIV Prevention, Treatment and Care to Developing Nations

- Global Fund to Fight AIDS, Tuberculosis and Malaria
- President's Emergency Plan for AIDS Relief (PEPFAR)
- Individual Bilateral Agreements

Global Access to Antiretroviral Drugs in Low and Middle Income Countries is Improving

12/2002: 300,000 people on ARVs
12/2005: ~1.3 million people on ARVs

- In 2005, 250,000-350,000 deaths were averted because of recent treatment scale up.
- However, only 1 in 5 people in need of ARVs in low- and middle-income countries are receiving them.

Source: WHO, 3/2008

The AIDS Research Model

Robust Financial Commitment

Human Capital “Best and the Brightest”

Research Capacity/Infrastructure

Understanding etiology, pathogenesis, etc.

Countermeasures

Global Distribution of West Nile Virus, 1999

Source: CDC

West Nile Virus Cases Reported in USA, 2005*

*As of 27 August

Source: CDC
A Live, Attenuated Recombinant West Nile Virus Vaccine

Thomas P. Monath, et al.

- Acambis "chimeric" WNV vaccine research began in 2000 with NIAID funding.
- ChimeriVax-WN02 is based on yellow fever 17D vaccine, used worldwide for 70+ years in >400 million people.
- Well-tolerated, induces strong immune response after single dose.

22 Anthrax Cases Associated with Bioterrorism: United States, 2001

Source: CDC

The Anthrax Attacks of 2001

Biological Impact

Fear and Disruption
Expansion of Research Capacity for Emerging Infectious Diseases

- National Biocontainment Laboratories (BSL4) - 2
- Regional Biocontainment Laboratories (BSL3) - 13
- Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research - 10
- New NIH Facilities - 4

Biodefense Countermeasures: Key Achievements

- Smallpox
  - Dryvax; MVA; antiviral drugs
- Anthrax
  - rPA; antitoxins
- Botulinum
  - Vaccine; antitoxins
- Ebola
  - First human vaccine trials

SARS: A New Challenge to Global Health

NIH Dedicates the C.W. Bill Young Center for Biodefense and Emerging Infectious Diseases

A new building focused on research on infectious diseases of global importance — those that occur naturally or that may be caused by agents intentionally released through an act of bioterrorism — was dedicated yesterday on the Bethesda, Maryland campus of the National Institutes of Health (NIH).
Early Cases of SARS: Guangdong Province, China

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

Feb 11-12, 2003: China reports 306 cases of acute respiratory syndrome in Guangdong Province

Cumulative Reported Cases of Severe Acute Respiratory Syndrome (SARS), Sept. 26, 2003

8,096 Cases (774 deaths)

Influenza

- Re-emerging disease (interpandemic flu)
- Newly emerging disease (potential pandemic flu)

Influenza A Virus

- Hemagglutinin (H) - 16 subtypes
  (attachment, penetration)
- Neuraminidase (N) - 9 subtypes
  (release)
- 8 viral genes
  (assembly, replication, etc.)
- M2 Protein
  (penetration)

SARS Characterization and Vaccine Development

SARS CoV Discovered

SARS CoV Sequenced

SARS Vaccine Developed

A DNA Vaccine Induces SARS Protective Immunity in Mice

SARS Phase I Clinical Trial Initiated at NIAID YRC
### Influenza: Antigenic Drift and Shift

- Neuraminidase (N)
- Hemagglutinin (H)

### Seasonal Influenza

### Pandemic Influenza

#### The Burden of Seasonal Influenza
- 250,000 to 500,000 deaths globally/yr
- 36,000 deaths and >200,000 hospitalizations/yr in U.S.
- $37.5 billion in economic costs/yr in U.S. related to influenza and pneumonia
- Ever-present threat of pandemic influenza

Sources: CDC, WHO, Am. Lung. Assoc.

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#### Percent of Visits for Influenza-Like Illness (ILI) Reported by Sentinel Providers, National Summary 2005-06 and Previous 2 Seasons

![Graph showing ILI visits over weeks]

#### U.S. Seasonal Influenza Vaccine: Production and Use

<table>
<thead>
<tr>
<th>Year</th>
<th>Doses Produced (millions)</th>
<th>Doses Distributed (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>15.7</td>
<td>12.4</td>
</tr>
<tr>
<td>1985</td>
<td>23.1</td>
<td>20.1</td>
</tr>
<tr>
<td>1990</td>
<td>32.3</td>
<td>29.4</td>
</tr>
<tr>
<td>1995</td>
<td>71.5</td>
<td>54.8</td>
</tr>
<tr>
<td>1999</td>
<td>77.2</td>
<td>76.8</td>
</tr>
<tr>
<td>2000</td>
<td>77.9</td>
<td>70.4</td>
</tr>
<tr>
<td>2001</td>
<td>87.7</td>
<td>77.7</td>
</tr>
<tr>
<td>2002</td>
<td>95.0</td>
<td>83.0</td>
</tr>
<tr>
<td>2003</td>
<td>86.9</td>
<td>83.1</td>
</tr>
<tr>
<td>2004</td>
<td>61.0</td>
<td>56.5</td>
</tr>
<tr>
<td>2005</td>
<td>86.0</td>
<td>&gt;80 so far</td>
</tr>
</tbody>
</table>

Source: WHO

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#### Seasonal Influenza Preparedness

#### Pandemic Influenza Preparedness

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#### The New York Times

November 24, 2005

**Drug Makers Plan Big Increase in Flu Vaccine for Next Fall**

Pharmaceutical companies say they are preparing to produce as many as 120 million doses of flu vaccine for the next flu season, by far the most ever.
Antiviral Therapies for Influenza

- Hemagglutinin (H)
- Neuraminidase (N)
- Oseltamivir (PO)
- Zanamivir (Inhaled)
- Peramivir* (PO/IV)
- Amantadine (PO)
- Rimantadine (PO)

*Investigational

Influenza: Antigenic Drift and Shift

- Neuraminidase (N)
- Hemagglutinin (H)
- Drift
- Shift
- Influenza Virus
- Seasonal Influenza
- Pandemic Influenza

Past Antigenic Shifts: Pandemics in the 20th Century

<table>
<thead>
<tr>
<th>Year</th>
<th>Type</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918</td>
<td>H1N1</td>
<td>&gt;50 million</td>
</tr>
<tr>
<td>1957</td>
<td>H2N2</td>
<td>1-2 million</td>
</tr>
<tr>
<td>1968</td>
<td>H3N2</td>
<td>700,000</td>
</tr>
</tbody>
</table>

Influenza Viruses Infecting Humans

- Influenza A
  - H1N1
  - H2N2
  - H3N2
  - H5N1
- Influenza B

H5N1 Influenza Cases, 2003-2006

- Map showing H5N1 cases across various countries from 2003 to 2006.
Potential Impact of an Influenza Pandemic in the U.S.: Two Scenarios*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Moderate (1958/68-like)</th>
<th>Severe (1918-like)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness</td>
<td>90 million (30%)</td>
<td>90 million (30%)</td>
</tr>
<tr>
<td>Outpatient medical</td>
<td>45 million (50%)</td>
<td>45 million (50%)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>866,000</td>
<td>0,000,000</td>
</tr>
<tr>
<td>ICU care</td>
<td>128,750</td>
<td>1,485,000</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>64,875</td>
<td>742,500</td>
</tr>
<tr>
<td>Deaths</td>
<td>209,000</td>
<td>1,903,000</td>
</tr>
</tbody>
</table>

* Estimates based on extrapolation from past pandemics in the United States. Note that these estimates do not include the potential impact of interventions not available during the 20th century pandemics.

Source: HHS Pandemic Influenza Plan

Seasonal Influenza Preparedness

Pandemic Influenza Preparedness

Pandemic Influenza Preparedness Strategy and Implementation

- International Surveillance
- Domestic Surveillance
- Vaccines
- Antivirals
- Communications
- State and Local Preparedness

Production of a Human Vaccine Against H5N1 Avian Influenza Using Reverse Genetics
NIAID Influenza Genome Project

**Avian and Human Influenza Viral Strains**

- NIAID
- IVSDDH
- NCBINLM
- CDC
- St. Jude's Children's Hospital
- Others

**Flu Sequence Data Publicly Accessible:**
- GenBank/NIAID Bioinformatics Research Center

**NIAID Microbial Genome Sequencing Center**

- Strain Selection
- Sample Preparation
- Flu Sequence Data

As of May 5, 2006, full genomic sequences of 1867 human isolates released

- Basic Research
  - How flu virus evolves/spreads/causes disease

- Applied Research
  - Drugs/Vaccines/Diagnostics

Antiviral Therapies for Influenza

- Hemagglutinin (H)
- Neuraminidase (N)
- Oseltamivir (PO)
- Zanamivir (Inhaled)
- Peramivir* (PO/IV)
- M2 Protein
- Amantadine (PO)
- Rimantadine (PO)

*Investigational

Influenza Antivirals: Examples of Current and Planned Projects

- Evaluation of novel drug targets (e.g., viral entry, replication, HA maturation)
- Development/testing of next-generation neuraminidase inhibitors (e.g., peramivir)
- Antiviral screening program
- Combination therapy studies
- Clinical trials of oseltamivir in SE Asia
- Assessment of oseltamivir in young infants

Pandemic Influenza Vaccine

- Pre-pandemic
- Intra-pandemic

Pre-Pandemic H5N1 Vaccine Evaluation: Preliminary Results

- Sanofi Inactivated H5N1 Subunit Vaccine
  - Evaluated in 451 healthy young adults
    - Well-tolerated overall
    - Two 90 μg doses induced immune response predictive of protection
    - Results published in New England Journal of Medicine March 30, 2006
  - Trial in elderly initiated in October 2005
  - Pediatric study initiated in January 2006

Pandemic Influenza Vaccine

- Pre-pandemic
- Intra-pandemic
Major Challenges to Pandemic Vaccine Development and Availability are Production and Surge Capacity

- Accelerate development of cell culture based vaccine technology
- Develop novel vaccine approaches
- Evaluate dose-sparing technology (adjuvants, intramuscular vs. intradermal)

Selected Strategies for Influenza Vaccines

- Inactivated or “Killed” Vaccines
- Live, Attenuated Vaccines
- DNA Vaccines
- Recombinant Subunit Vaccines
- Recombinant Vector Vaccines
- Synthetic Peptide Vaccines

Development of Effective Vaccines against Pandemic Influenza

Kanta Subbarao, Brian R. Murphy, and Anthony S. Fauci

“... the development of effective pandemic vaccines poses both practical and immunological challenges.”
A Perpetual Struggle

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

Public Health Measures, Biomedical Research, and Technological Advances