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

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National Institute of Allergy and Infectious Diseases
National Institutes of Health
August 8, 2006
"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

Total Deaths: ~57 Million

Source: WHO, World Health Report, 2004
# Background "Matrix" of 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>3.1 million</td>
</tr>
<tr>
<td>Diarrheal Diseases</td>
<td>1.8 million</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.7 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

- Vancomycin-resistant Staphylococcus aureus
- Cryptosporidiosis
- Multidrug-resistant tuberculosis
- Drug-resistant malaria
- Cyclosporiasis
- E. coli O157:H7
- Hepatitis C
- vCJD
- Lyme disease
- West Nile virus
- Diphtheria
- SARS
- E. coli O157:H7
- H5N1 influenza
- Lyssavirus
- Rift Valley fever
- HIV
- Anthrax bioterrorism
- Whitewater arroyo virus
- Hantavirus pulmonary syndrome
- Dengue
- Yellow fever
- Human African trypanosomiasis
- Cholera
- Marburg hemorrhagic fever
- Ebola hemorrhagic fever
- Plague
- Human monkeypox
- Nipah virus
- Hendra virus
- Enterovirus 71

Legend:
- Red circle: Newly emerging
- Blue circle: Re-emerging/resurging
- Black dot: “Deliberately emerging”
June 5, 1981

Pneumocystis Pneumonia - Los Angeles

July 4, 1981

Kaposi’s Sarcoma and Pneumocystis Pneumonia Among Homosexual Men – New York City and California
Adults and Children Estimated to be Living with HIV, 2005

Global Total: ~38.6 million

Source: UNAIDS, 6/2006
NIH HIV/AIDS Research Funding

$30 Billion in Cumulative Funding (through FY 2005)
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>
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<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>
<tr>
<td></td>
<td>Tipranavir</td>
</tr>
<tr>
<td></td>
<td>Darunavir (TMC114)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine</td>
<td>5 available, combining 2 or 3 drugs</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>– e.g. Atripla: efavirenz + emtricitabine + tenofovir</td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fusion Inhibitor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfuvirtide (T-20)</td>
<td></td>
</tr>
</tbody>
</table>
AIDS Cases, Deaths, and People Living with AIDS, United States, 1981-2004

- Newly diagnosed AIDS cases
- Deaths
- Persons living with AIDS

Estimates adjusted for reporting delays

Source: CDC
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.

The AIDS Research Model
Implications for Other Infectious Diseases of Global Health Importance

Gregory K. Folkers, MS, MPH and Anthony S. Fauci, MD
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
Reported Human Cases of West Nile Virus Infection, USA, 1999-2006

Source: CDC

Reported as of 8/1/2006
NIH West Nile Virus Research Agenda

- Basic Research on the Virus
- Animal Models
- Vector Biology
- Vaccine Development
- Antiviral Therapies
- Rapid Diagnostics
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.
Development of a Humanized Monoclonal Antibody with Therapeutic Potential Against West Nile Virus

T. Oliphant et al.

- Single dose of humanized monoclonal antibody protected mice (>90%) when given up to 5 days following lethal WNV challenge

- Partial support from NIAID Midwest Regional Center of Excellence for Biodefense and Emerging Infectious Diseases
22 Anthrax Cases Associated with Bioterrorism: United States, 2001

Source: CDC
The Anthrax Attacks of 2001

Biological Impact

Fear and Disruption
Bush Proposes Record $27.3 Billion Budget for NIH

$1.5 Billion Aimed At Bioterrorism

President Bush will propose spending a record $27.3 billion to fund the National Institutes of Health in 2003, enough to complete a five-year doubling of the agency's budget that began in 1998 and to jumpstart a major new NIH emphasis on bioterrorism. . .
Biodefense Research Priorities

Therapeutics

Vaccines

Diagnostics

Basic Research (including Genomics)

Expansion of Research Capacity
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
Early Cases of SARS: Guangdong Province, China

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

Feb 11-12, 2003: China reports 305 cases of acute respiratory syndrome in Guangdong Province
Spread of SARS from Hotel Metropole

Source: MMWR, March 28, 2003
Cumulative Reported Cases of Severe Acute Respiratory Syndrome (SARS), Sept. 26, 2003

Source: WHO
SARS Characterization and Vaccine Development

- March 24, 2003: SARS CoV Discovered
- April 14, 2003: SARS CoV Sequenced
- March 31, 2004: SARS Vaccine Developed
- December 13, 2004: SARS Phase I Clinical Trial Initiated at NIAID VRC

A DNA Vaccine Induces SARS Coronavirus Neutralization and Protective Immunity in Mice
Zhi-yong Yang, Wing-pui Kong, Yue Huang, Anjeanette Roberts, Brian R. Murphy, Kanta Subbarao and Gary J. Nabel
Influenza

- Re-emerging disease (interpandemic flu)
- Newly emerging disease (potential pandemic flu)
Seasonal Influenza Preparedness

Pandemic Influenza Preparedness
Influenza: Antigenic Drift and Shift

Neuraminidase (N)

Hemagglutinin (H)

Influenza Virus

Seasonal Influenza

Pandemic Influenza

Drift

Shift
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.
Antiviral Therapies for Influenza

Hemagglutinin (H)

Neuraminidase (N)

M2 Protein

Oseltamivir (PO)
Zanamivir (Inhaled)
Peramivir* (PO/IV)

Amantadine (PO)
Rimantadine (PO)

*Investigational
## 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>28.3</td>
</tr>
<tr>
<td>1995</td>
<td>71.5</td>
<td>54.9</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: NVPO
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.
Influenza: Antigenic Drift and Shift

Neuraminidase (N)
Hemagglutinin (H)

Influenza Virus

Seasonal Influenza

Drift
Shift

Pandemic Influenza
### Past Antigenic Shifts: Pandemics in the 20th Century

<table>
<thead>
<tr>
<th>Year</th>
<th>Subtype</th>
<th>Pandemic</th>
<th>Global Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918</td>
<td>H1N1</td>
<td>Spanish Flu</td>
<td>&gt;50 million</td>
</tr>
<tr>
<td>1957</td>
<td>H2N2</td>
<td>Asian Flu</td>
<td>1-2 million</td>
</tr>
<tr>
<td>1968</td>
<td>H3N2</td>
<td>Hong Kong Flu</td>
<td>700,000</td>
</tr>
</tbody>
</table>
The Next Killer Flu: Can we stop it?

AVIAN FLU: Ready for a pandemic?

The Next Big One

DEATH THREAT

The Next Pandemic?

Bird Flu: Is Asia hatching the next human pandemic?
H5N1 Influenza Cases, 2003-2006

Total: 233 WHO laboratory-confirmed cases including 135 deaths

Avian Cases (53 countries)
Human and Avian Cases (10 countries)

Source: WHO and OIE (World Organization for Animal Health), 8/7/2006
Lack of Transmission of H5N1 Avian-Human Reassortant Influenza Viruses in a Ferret Model

TR Maines, LM Chen, Y Matsuoka, H Chen, T Rowe, J Ortin, A Falcón, NT Hien, LQ Mai, ER Sedyaningsih, S Harun, TM Tumpey, RO Donis, NJ Cox, K Subbarao, and JM Katz
Pandemic Influenza Preparedness
Strategy and Plan

- International Surveillance
- Domestic Surveillance
- Vaccine
- Antivirals
- Communications
- State and Local Preparedness
Antiviral Therapies for Influenza

Hemagglutinin (H)
Neuraminidase (N)
M2 Protein

Oseltamivir (PO)
Zanamivir (Inhaled)
Peramivir* (PO/IV)

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

- Trial in elderly initiated in October 2005

- Pediatric study initiated in January 2006
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)
Low-Dose Glaxo Bird Flu Vaccine Works in Trial

GSK Announces H5N1 Vaccine Trial Results

- Evaluated in 400 healthy adults, aged 18-60 years
- Safe and well-tolerated overall
- Achieved high immune response at a low dose of antigen
- 3.8µg antigen + proprietary adjuvant induced immune response predictive of protection in > 80% of subjects
The Future: A "Universal" Influenza Vaccine?

PRECLINICAL STUDY OF INFLUENZA VIRUS A M2 PEPTIDE CONJUGATE VACCINES IN MICE, FERRETS, AND RHESUS MONKEYS


PROTECTION AGAINST MULTIPLE INFLUENZA A SUBTYPES BY VACCINATION WITH HIGHLY CONSERVED NUCLEOPROTEIN

Epstein SL, Kong WP, Misplon JA, Lo CY, Tumpey TM, Xu L, Nabel GJ

THE UNIVERSAL INFLUENZA VACCINE M2E-HBC ADMINISTERED INTRANASALLY IN COMBINATION WITH THE ADJUVANT CTA1-DD PROVIDES COMPLETE PROTECTION

De Filette M, Ramne A, Birkett A, Lycke N, Lowenadler B, Min Jou W, Saelens X, Fiers W
A Perpetual Struggle

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

Public Health Measures, Biomedical Research, and Technological Advances