Biodefense and Pandemic Influenza: The Research and Public Health Interface

Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
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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

Global Examples of Emerging and Re-Emerging Infectious Diseases

NIAID Infectious Disease Research: A Dual Mandate

Maintain and “grow” a robust basic and applied research portfolio in microbiology, immunology and clinical research

Respond rapidly to new infectious disease threats

New/Improved Countermeasures

Biodefense Research Priorities

Therapeutics
Vaccines
Diagnostics

Basic Research (Including Genomics)
Expansion of Research Capacity
**Biodefense Countermeasures: Key Achievements**

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

**Expansion of Research Capacity for Emerging Infectious Diseases**

- National Biocontainment Laboratories (BSL-4) - 2
- Regional Biocontainment Laboratories (BSL-3) - 13
- Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research - 10
- New NIH Facilities - 4

**Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCEs)**

- RCE Network established in 2003
- 10 centers (8 funded in 2003, 2 in 2005)
- >150 research projects; ~100 pilot projects; >60 career development projects
- $350M total funding over 5 years
- >170 publications on Category A, B and C pathogens, host immunity, countermeasure development

**Selected NIAID Category B and C Pathogens**

- Influenza
- Antibiotic resistant microbes (except STDs)
- Dengue
- Diarrheagenic E.coli
- Entamoeba histolytica
- Giardia lamblia
- Hepatitis A
- Multi-drug resistant TB
- Rift Valley Fever
- Tickborne encephalitis viruses
- Toxoplasma
- Typhus fever (Rickettsia prowazekii)
- Vibrio cholera and other pathogenic Vibrios
- West Nile Virus
- Yellow fever

**Small-Molecule Inhibitor of Vibrio cholerae Virulence and Intestinal Colonization**

DT Hung et al.

**Bats Are Natural Reservoirs of SARS-Like Coronaviruses**

W. Li, et al.

**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
Scientists Discover How Nipah Virus and Hendra Virus Enter Cells

**Ephrin-B2 is the Entry Receptor for Nipah Virus, an Emergent Deadly Paramyxovirus**

O.A. Negrete et al.

**Ephrin-B2 Ligand is a Functional Receptor for Hendra Virus and Nipah Virus**

M.I. Bonaparte et al.

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**Influenza**

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

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**Influenza A Virus**

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

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**Influenza: Antigenic Drift and Shift**

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

Past Antigenic Shifts

<table>
<thead>
<tr>
<th>Year</th>
<th>Type</th>
<th>Deaths</th>
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</thead>
<tbody>
<tr>
<td>1918</td>
<td>H1N1</td>
<td>&gt;40 million</td>
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<tr>
<td>1957</td>
<td>H2N2</td>
<td>1-2 million</td>
</tr>
<tr>
<td>1968</td>
<td>H3N2</td>
<td>700,000 deaths</td>
</tr>
<tr>
<td>1976</td>
<td>H1N1</td>
<td>No pandemic</td>
</tr>
</tbody>
</table>

The Influenza Pandemic of 1918-1919

- 25-30% of world’s population (~500 million people) fell ill
- >40 million deaths worldwide; ~60% percent in people ages 20-45
- >500,000 deaths in United States; 196,000 in October, 1918 alone

Seasonal Influenza Preparedness

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Doses Produced (millions)</th>
<th>Doses Distributed (millions)</th>
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</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>
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<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: WPO*

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### H5N1 Influenza Cases, 2003-2006

![H5N1 Influenza map](image)

*Total: 169 human laboratory-confirmed cases including 51 deaths*

*Source: WHO and OIE, World Organization for Animal Health.*

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### Chest Radiographs of Patient with Severe H5N1 Influenza Pneumonia: Vietnam, 2004

![Day 5, Day 7, Day 10 X-rays](image)


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### Migratory Bird Flyways

![Migratory Bird Flyways](image)


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### Seasonal Influenza Preparedness

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### Pandemic Influenza Preparedness

- [ ]
Pandemic Influenza Preparedness
Strategy and Plan

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

The New York Times
November 1, 2005

Bush Calls for $7.1 Billion to Prepare for Bird Flu Threat

President Bush today unveiled a strategy to combat the threat of an avian flu pandemic, calling for $7.1 billion in emergency spending to stockpile reserves of medicines and to press ahead with the development of a new vaccine.

Congress Approved $3.8 Billion for Pandemic Influenza Preparedness

$3.3 billion: HHS, includes:
- $2.6 B – Office of Public Health Emergency Preparedness “core preparedness activities” including vaccine production capacity expansion, development and purchase of vaccines and antivirals
- $246 M – International activities
  - $18 M to NIAID CCR and DMID for international research in SE Asia
- $350 M – Upgrade state & local response capacities
- $50 M – Increase CDC laboratory capacity

$0.5 billion: Other agencies, including DoD and USAID

$3.8 billion total

NIAID Influenza Research Funding

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

NIAID Influenza Research

Vaccines
Therapeutics
Diagnostics
Surveillance and Epidemiology
Basic Research
Expansion of Research Capacity

H5N1 avian flu virus
Time-tested flu strain
New flu strain (vaccine)

Chicken eggs
**NIAID Influenza Genome Project**

- **Avian and Human Influenza Viral Strains:**
  - NIAID
  - NVSDOH
  - H3N2
  - Others

- **Strain Selection**
- **Sample Preparation**

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

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

**Applied Research**
- Drugs/Vaccines/Diagnostics

**NIAID Influenza Genome Sequencing Project: Publications**

- *PLoS Biology*
  - Whole-Genome Analysis of Human Influenza A Virus Reveals Multiple Persistent Lineages and Reassortment among Recent H3N2 Viruses
  - E. Holmes et al.

- *Nature*
  - Large-Scale Sequencing of Human Influenza Reveals the Dynamic Nature of Viral Genome Evolution
  - E. Ghedin et al.

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**Science**

Published Online January 26, 2005

**Large-Scale Sequence Analysis of Avian Influenza Isolates**

JC Obenauer et al.

- St. Jude Repository contains ~11,000 influenza viruses incl. ~7,000 avian influenza viruses (AIVs).
- This analysis is first large-scale sequencing of AIVs.
- 2,186 genes and 169 complete genomes deposited to GenBank, doubling the amount of genetic information available on AIVs.

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**Science**

October 7, 2005

**1918 Flu and Responsible Science**

Phillip A. Sharp

"...it is reassuring that the NSABB was asked to consider these papers before publication and concluded that the scientific benefit of the future use of this information far outweighs the potential risk of misuse. People may be reassured that the system is working, because agencies representing the public, the scientific community, and the publishing journals were involved in the decision."

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**Antiviral Therapies for Influenza**

- Hemagglutinin (H)
- Neuraminidase (N)
- Oseltamivir
- Zanamivir
- M2 Protein
- Amantadine
- Rimantadine
**Influenza Antivirals: Examples of Current and Planned Projects**

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

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**Pandemic Influenza Vaccine**

- Pre-pandemic
- Intra-pandemic

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**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
  - Publication submitted January 2006
- Trial in elderly initiated in October 2005
- Pediatric study initiated in January 2006

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**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)

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**Influenza Vaccine Production: Cell Culture as an Alternative to Chicken Eggs**

Provide target viruses to vaccine manufacturers

- Identify target influenza strains
- Egg-based
- Cell culture-based
**Selected Strategies for Influenza Vaccines**

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

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**The Future: A "Universal" Influenza Vaccine?**

**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.”

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**A Perpetual Struggle**

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

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Public Health Measures, Biomedical Research, and Technological Advances