The Role of NIH Research in Pandemic Influenza Preparedness

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1943-2004
John R. La Montagne, Ph.D.
Selected Career Highlights

- Vaccinology
  - Vaccines for acellular pertussis, malaria, pneumococcus, rotavirus, influenza, tuberculosis
  - Advising WHO and others on immunization and vaccines
  - Children's Vaccine Initiative

- Fostering International Collaboration
  - e.g. US-Japan Program, Multilateral Initiative on Malaria

- Influenza
  - Long-standing vision of importance of preparedness

- Emerging Diseases, including Bioterrorism
  - Recognized importance long before it became "fashionable"
"Dr. John La Montagne was a true public health hero whose leadership, especially in the realm of infectious diseases, left the world a healthier place."

– HHS Secretary Tommy G. Thompson, Nov. 3, 2004
Pandemic Influenza Preparedness
Pandemic Influenza Preparedness: Complementary Roles within DHHS

**CDC**
- Surveillance and detection
- Train local response teams
- Maintain vaccine/antiviral stockpiles
- Disease control/prevention

**NIH**
- Conduct basic research
- Develop medical interventions (vaccines, antivirals)
- Conduct clinical evaluation of vaccines and antivirals

**FDA**
- Regulatory approval – vaccines, therapeutics, diagnostics

**OPHEP**
- Office of Public Health Emergency Preparedness coordinates HHS-wide emergency preparedness activities
NIAID FY 2005 Budget (est)

FY 2005 NIAID Budget
$4.40 B

Vaccine Research
$1.17 B

27%
NIH Influenza Research Funding

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Dollars in Millions</th>
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<tbody>
<tr>
<td>2001</td>
<td>$20.6M</td>
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<tr>
<td>2002</td>
<td>$22.8M</td>
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<tr>
<td>2003</td>
<td>$57.4M</td>
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<tr>
<td>2004</td>
<td>$113.1M</td>
</tr>
<tr>
<td>2005 (est.)</td>
<td>$119.1M</td>
</tr>
<tr>
<td>2006 (P.B.)</td>
<td>$119.4M</td>
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Influenza Surveillance
NIAID Pandemic Preparedness in Asia Contract

- PI: Robert Webster, St. Jude's Children's Research Hospital

- Activities include:
  - animal influenza surveillance in Asia
  - generating vaccine candidates against pandemic influenza strains
  - studying newly emerging influenza strains infecting swine in the U.S.

- Generated a 2004 H5N1 vaccine reference virus using the 8-plasmid system; NIAID has provided this reference virus to both Sanofi Pasteur and Chiron.
October 29, 2004: WHO announced a new study by St. Jude’s Children’s Research Hospital that showed “... that domestic ducks might now be acting as a ‘silent’ reservoir for the H5N1 virus...”

Source: WHO
Basic Research
NIAID-Supported Influenza Research Activities

Basic Research

- Pathogenicity of pandemic influenza viruses: virulence factors
- Transmission of H5N1 influenza viruses among different animal species
- Mechanisms of animal to human transmission
- Animal models to study pandemic influenza viruses
NIAID-Supported Research on 1918 Pandemic H1N1 Influenza Virus: Current Studies

- Complete sequence of 1918 influenza virus genes
- Identify signature sequences responsible for virulence
- Determine molecular mechanisms leading to emergence
- Understand contribution of 1918 HA and NA genes to unprecedented virulence
Pathogenicity and Immunogenicity of Influenza Viruses with Genes from the 1918 Pandemic Virus
Terrence M. Tumpey et al.

Enhanced Virulence of Influenza A Viruses with the Haemagglutinin of the 1918 Pandemic Virus
D. Kobasa et al.

The Structure and Receptor Binding Properties of the 1918 Influenza Hemagglutinin
S.J. Gamblin et al.

Transmissibility of 1918 Pandemic Influenza
Christina E. Mills et al.
Influenza Seed Virus for Inactivated Virus Vaccine Production Using a Reverse Genetics System

Highly pathogenic H5 or H7

A/Puerto Rico/8/34 (H1N1)

Removal of additional basic amino acids

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

1. Identify target influenza strains
2. Provide target viruses to vaccine manufacturers
3. Egg-based production
4. Cell culture-based production

[Diagram with images of vaccine production process]
Potential Advantages of Cell Culture-Based Influenza Vaccines

- Allows greater flexibility for surge capacity.
- Provides opportunity for year-round vaccine production.
- Requires less manufacturing space.
- Circumvents possible problems presented by highly virulent influenza strains (i.e., lethality to chicken embryos).
- Tolerated by people with egg allergies.
NIAID Influenza Genome Project

Avian and Human Influenza Viral Strains

- NIAID
- NYSDOH
- NCBI/NLM
- CDC
- St. Jude’s Children’s Hospital
- Others

Strain Selection → Sample Preparation

NIAID Microbial Genome Sequencing Center
TIGR

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

As of Mar. 31, 2005, full genomic sequences of 93 human isolates released

Basic Research
How flu virus evolves/spreads/causes disease

Applied Research
Drugs/Vaccines/Diagnostics
Antiviral Therapies
Antiviral Therapies for Influenza

- Hemagglutinin (H)
- Neuraminidase (N)
- M2 Protein

Drugs:
- Oseltamivir
- Zanamivir
- Amantadine
- Rimantadine
Antiviral Drugs in Strategic National Stockpile

<table>
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<tr>
<th>Drug</th>
<th>Number of Treatment Courses</th>
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<tr>
<td>Tamiflu (capsules and suspension)</td>
<td>2,269,624</td>
</tr>
<tr>
<td>Rimantadine (tabs and syrup)</td>
<td>5,054,720</td>
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- Roche is the single supplier of Tamiflu (oseltamivir)
- Currently single production facility in Switzerland

Source: US Dept. Health & Human Services
Antivirals: NIAID-funded Projects

- Development/testing of long-acting next-generation neuraminidase inhibitor
- Animal studies to assess effectiveness of combination antiviral therapy
- Development of inhaled polyclonal IgG as immunoprophylactic
- Evaluation of novel drug targets (viral entry, replication, HA maturation)
**Antivirals**

**Use Profile of Oseltamivir in Infants**

- Currently licensed for treatment of individuals \( \geq 1 \) year old (chemoprophylaxis \( \geq 13 \) years old)

- Animal study to further characterize safety profile of oseltamivir in infants

- Safety protocol to administer oseltamivir to children \(< 2\) years with confirmed influenza A infection in the setting of an H5N1 outbreak

- Goal: Identify the optimal use of oseltamivir
Pandemic Influenza Vaccine
NIH Role in Influenza Vaccine Development

Academia
- Basic Research (e.g. Reverse Genetics)
- Seed Virus
- Pilot Lots

Industry
- Clinical Evaluation (e.g. in VTEUs)

Influenza Virus

New Vaccine
NIH NEWS RELEASE

National Institutes of Health

FOR IMMEDIATE RELEASE
Thursday, May 27, 2004

NIAID Announces Contracts to Develop Vaccine Against H5N1 Avian Influenza

NIH NEWS RELEASE

National Institutes of Health

FOR IMMEDIATE RELEASE
Tuesday, August 17, 2004

NIAID Taps Chiron to Develop Vaccine Against H9N2 Avian Influenza
Award Part of NIAID Pandemic Influenza Preparedness Program
H5N1 Vaccine Contracts

- NIAID awarded contracts to Sanofi Pasteur and Chiron to produce H5N1 pilot lots of inactivated vaccine for Phase I/II clinical trials

- >8,000 doses delivered from Sanofi Pasteur: trial has begun

- 10,000 doses to be received from Chiron: trials to begin late fall 2005

- Initial Trial: Safety/Immunogenicity in healthy adults with possible expansion to elderly and pediatric populations
HHS Orders Avian Flu Vaccine Doses as Preventive Measure

HHS Secretary Tommy G. Thompson announced today the awarding of a contract to Aventis Pasteur Inc. to manufacture and store 2 million doses of avian influenza H5N1 vaccine, an important initial acquisition to better prepare the nation for an influenza pandemic.
H9N2 Vaccine Contracts

- NIAID task order to Chiron for production of an investigational inactivated vaccine based on an H9N2 strain

- Chiron produced a total of 40,000 doses of vaccine formulated with and without MF59 adjuvant

- Initial Trial: Safety/Immunogenicity in healthy adults

- Trial has begun; results expected late summer/early fall
Live Attenuated Cold-Adapted Pandemic Influenza Vaccine

**H5N1:**
- 3 vaccine candidates made and compared
- Clinical lots to be generated from best candidate
- Clinical trials planned for 2005/2006

**H9N2:**
- Clinical lot produced
- Clinical trials (70 subjects) planned for summer 2005
Potential Advantages of a Live Attenuated Influenza Virus Vaccine

- Induces both serum and local mucosal antibodies
- Induces both antibodies and cellular immune protective mechanisms
- Induces immunity rapidly, usually following one dose
- Has wider breadth of cross-reactivity with related influenza virus strains
- Does not require a needle injection
- More effective in infants and children than inactivated virus vaccines
NIAID’s Network of Vaccine and Treatment Evaluation Units (VTEUs)

- Rochester
- Baltimore
- Cincinnati
- Los Angeles
- Houston
- St Louis
- Nashville
Fragility of the Influenza Vaccine Enterprise
U.S. Flu Vaccine Supply Halved

Health Officials Face Record Shortage as Britain Shuts Down Supplier

Americans' supply of flu vaccine was cut in half Tuesday as Britain abruptly shut down a major supplier just as flu season is about to begin. Facing a record shortage, U.S. health officials scrambled to reserve remaining shots for the elderly and others at highest risk from influenza.
Money Plans
March 6, 2005

Delays in Australian Flu Vaccine Likely This Year

Australia’s chief medical officer today warned there could be delays in obtaining the flu vaccine this year...because one of the influenza strains in the vaccine was not present in as great a concentration as required... Sanofi pasteur was contracted to supply 35 per cent of the government’s vaccine supplies...
Addressing the Fragile Vaccine Enterprise

- Research resources: developing and sharing new technologies, e.g.
  - reverse genetics
  - cell culture-based vaccines
  - recombinant DNA technologies
  - “perennial” vaccines based on conserved epitopes
  - dose-sparing strategies
Vaccine Dose-Sparing Strategies

- Intramuscular (IM) vs. Intradermal (ID): Clinical protocol to compare IM vs. ID H5N1 vaccine is in preparation.

- NIAID is in discussions with manufacturers concerning production of an alum-adjuvanted H5N1 vaccine.
Invited Commentary:

Intradermal Influenza Vaccination: Can Less Be More?

John R. La Montagne and Anthony S. Fauci

"These studies raise the possibility of using alternative routes of immunization (e.g., intradermal as opposed to intramuscular administration) with smaller doses of vaccine as a means of "stretching" available doses of influenza vaccine in times of shortages."
Addressing the Fragile Vaccine Enterprise (continued)

- Incentives to industry, e.g.
  - regulatory relief
  - guaranteed purchases and fair pricing
  - liability protection
  - research resources and clinical trials capacity
  - tax incentives
  - ensure demand through public education on health benefits of vaccination
GSK Clinical Trial

NIAID rapidly initiated a Phase III trial to evaluate safety and immunogenicity of GSK’s inter-pandemic Fluarix® vaccine in healthy adults:

– Trial began in Dec. 2004
– 952 subjects enrolled in 5 days
– Trial conducted through VTEUs
– Results expected Q2 2005
A Delicate Balance

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

Public Health Measures, Biomedical Research, and Technological Advances
"We believe that success in controlling a new pandemic will benefit from new advances made by the scientific community, which provides the pool of scientific solutions to combat the new emerging threats."