

2006 Joseph Leiter Lecture

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

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 National Institutes of Health
 May 10, 2006

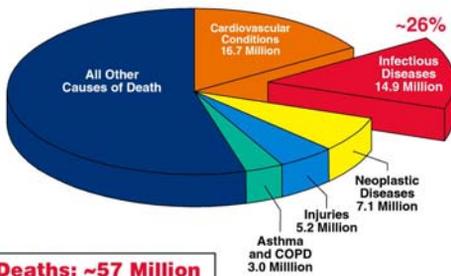


A Premature Declaration of Victory Over Infectious Diseases

"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."

- Aidan Cockburn, *The Evolution and Eradication of Infectious Diseases*, 1963.

Infectious Diseases Cause ~26% of All Deaths Worldwide



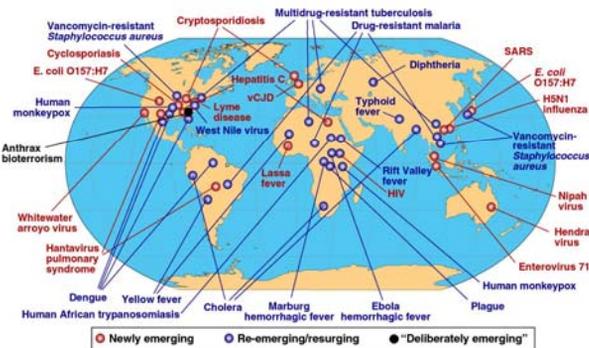
Total Deaths: ~57 Million

Source: WHO, World Health Report, 2004

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

	Estimated Annual Deaths
Respiratory Infections	4.0 million
HIV/AIDS	3.1 million
Diarrheal Diseases	1.8 million
Tuberculosis	1.6 million
Malaria	1.3 million
Vaccine Preventable Childhood Diseases (measles, pertussis, tetanus, etc.)	600,000
Meningitis	170,000
Tropical Parasitic Diseases (trypanosomiasis, leishmaniasis, etc.)	130,000

Global Examples of Emerging and Re-Emerging Infectious Diseases

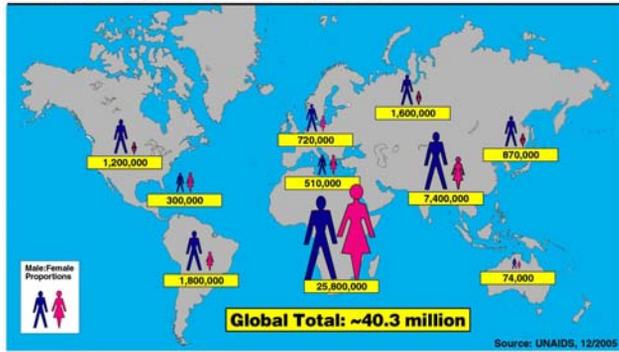


CENTERS FOR DISEASE CONTROL
MNWR
 MORBIDITY AND MORTALITY WEEKLY REPORT

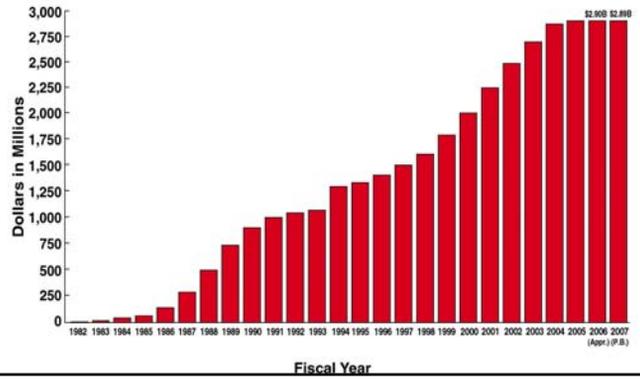
June 5, 1981
***Pneumocystis Pneumonia* - Los Angeles**

July 4, 1981
***Kaposi's Sarcoma and Pneumocystis Pneumonia* Among Homosexual Men - New York City and California**

Estimated Number of Persons Living with HIV/AIDS, December, 2005



NIH HIV/AIDS Research Funding



Advances in AIDS Research, 1981-2006

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

FDA-Approved Antiretroviral Drugs

NRTI

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Zidovudine
- Zalcitabine
- Tenofovir

NNRTI

- Delavirdine
- Efavirenz
- Nevirapine

PI

- Amprenavir
- Atazanavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

Fusion Inhibitor

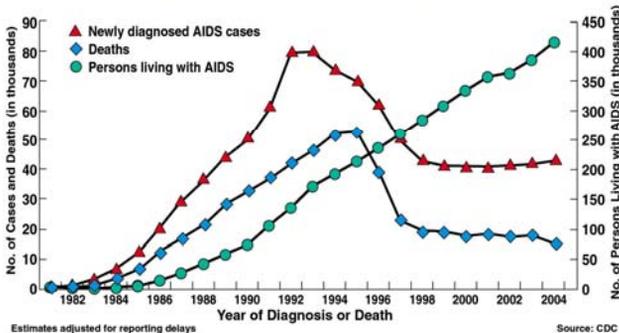
- Enfuvirtide (T-20)

Combinations

- 4 available, combining 2 or 3 drugs

Source: FDA, Oct. 2005

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



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



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.

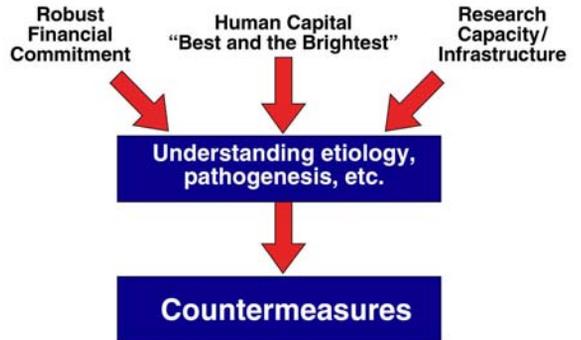
Source: WHO, 3/2006



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

Gregory K. Folkers, MS, MPH and Anthony S. Fauci, MD

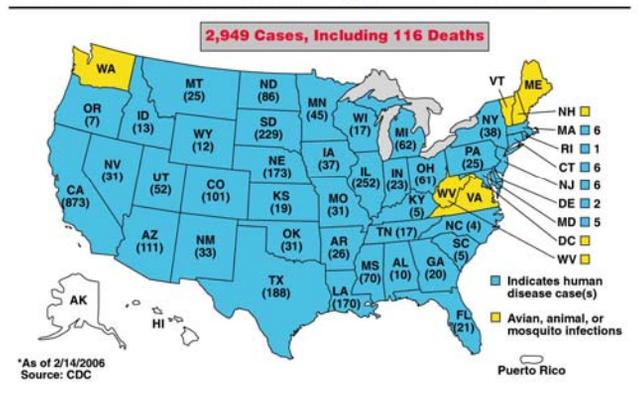
The AIDS Research Model

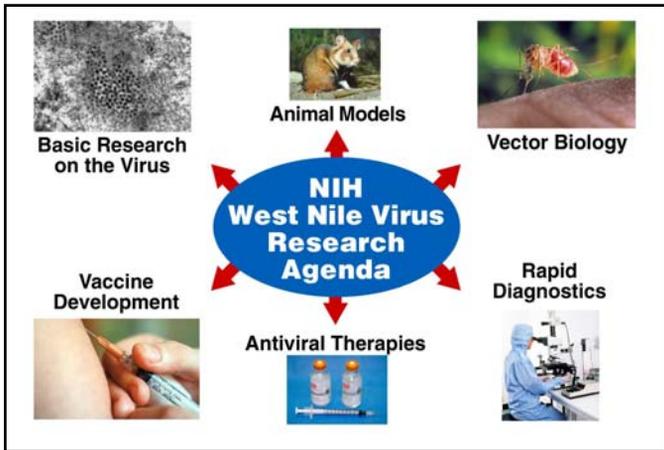


Global Distribution of West Nile Virus, 1999



West Nile Virus Cases Reported in USA, 2005*





PNAS
Proceedings of the National Academy of Sciences of the United States of America
 Published online April 16, 2006

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.

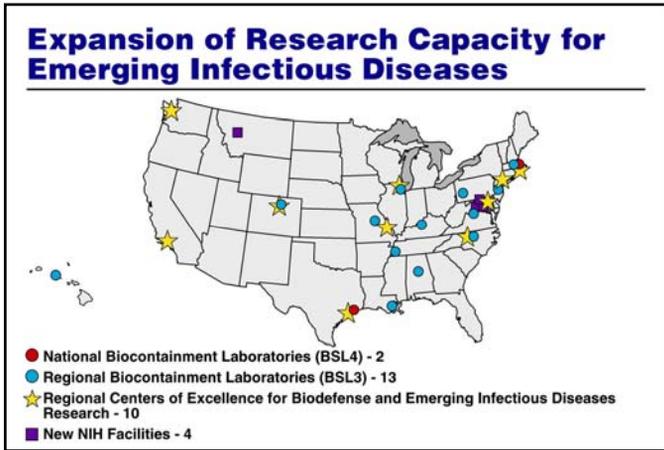
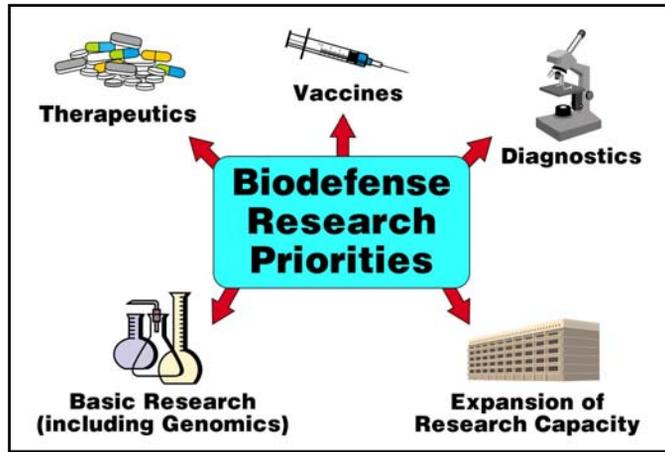


The Anthrax Attacks of 2001

Biological Impact

Fear and Disruption





U.S. Department of Health and Human Services
NIH News
 National Institutes of Health

National Institute of Allergy and Infectious Diseases (NIAID)
<http://www.niaid.nih.gov/>

FOR IMMEDIATE RELEASE
 Wednesday, May 3, 2006

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).

Biodefense Countermeasures: Key Achievements

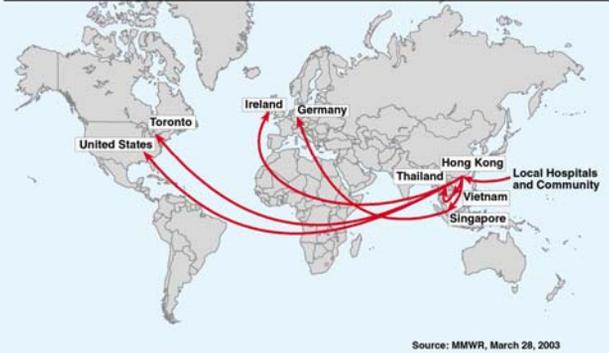
- **Smallpox**
 – Dryvax; MVA; antiviral drugs
- **Anthrax**
 – rPA; antitoxins
- **Botulinum**
 – Vaccine; antitoxins
- **Ebola**
 – First human vaccine trials

SARS: A New Challenge to Global Health

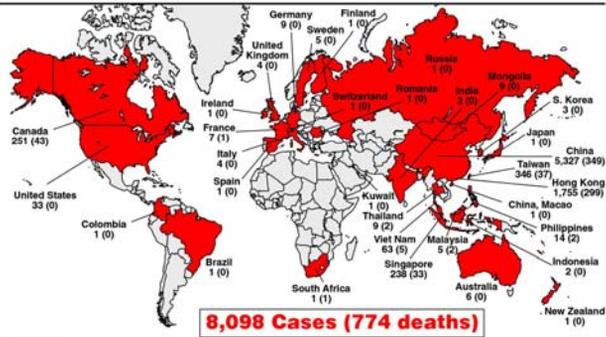
Early Cases of SARS: Guangdong Province, China



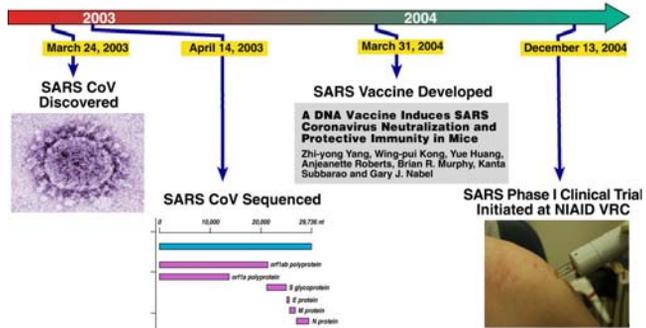
Spread of SARS from Hotel Metropole



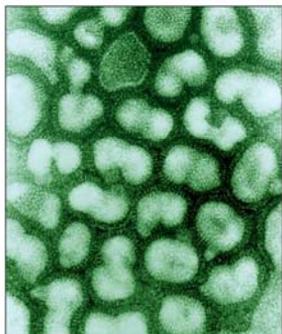
Cumulative Reported Cases of Severe Acute Respiratory Syndrome (SARS), Sept. 26, 2003



SARS Characterization and Vaccine Development

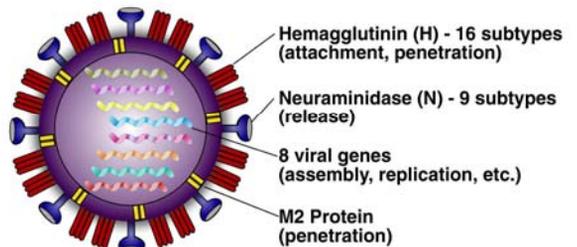


Influenza

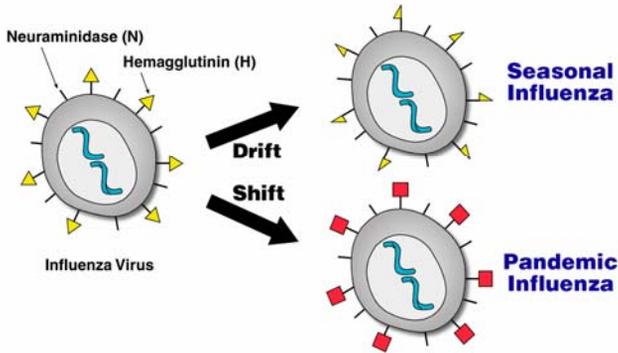


- Re-emerging disease (interpandemic flu)
- Newly emerging disease (potential pandemic flu)

Influenza A Virus



Influenza: Antigenic Drift and Shift

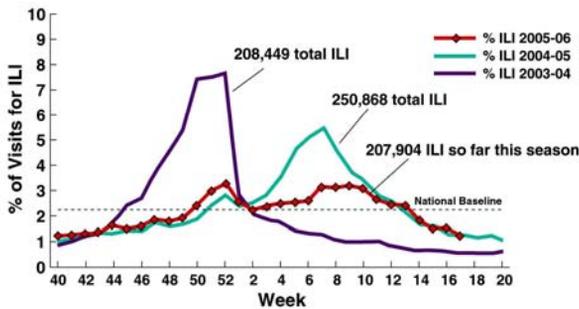


The Burden of Seasonal Influenza

- 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.

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



Source: CDC

Seasonal Influenza Preparedness

Pandemic Influenza Preparedness

U.S. Seasonal Influenza Vaccine: Production and Use

Year	Doses Produced (millions)	Doses Distributed (millions)
1980	15.7	12.4
1985	23.1	20.1
1990	32.3	28.3
1995	71.5	54.9
1999	77.2	76.8
2000	77.9	70.4
2001	87.7	77.7
2002	95.0	83.0
2003	86.9	83.1
2004	61.0	56.5
2005	86.0	>80 so far

Source: NVPO

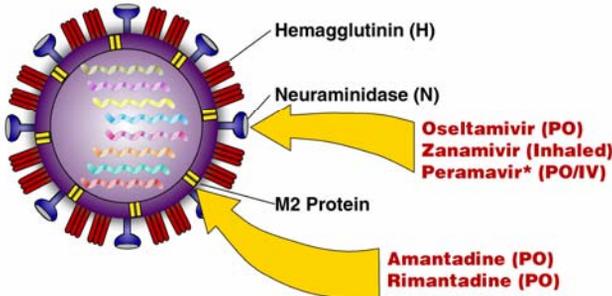
The New York Times

November 24, 2005

Drug Makers Plan Big Increase in Flu Vaccine for Next Fall

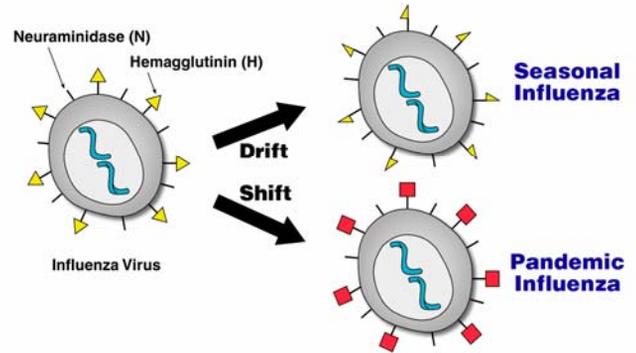
Pharmaceutical companies say they are preparing to produce as many as 120 million doses of flu vaccine for the next flu season, by far the most ever.

Antiviral Therapies for Influenza



*Investigational

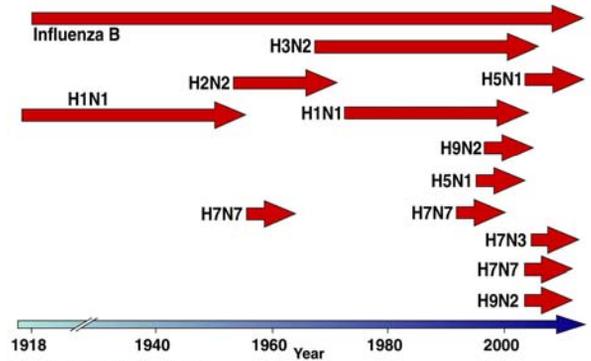
Influenza: Antigenic Drift and Shift



Past Antigenic Shifts: Pandemics in the 20th Century

Year	Strain	Event	Global Deaths
1918	H1N1	Spanish Flu	>50 million
1957	H2N2	Asian Flu	1-2 million
1968	H3N2	Hong Kong Flu	700,000

Influenza Viruses Infecting Humans



Adapted from Nature Medicine 10, 582-587 (2004)

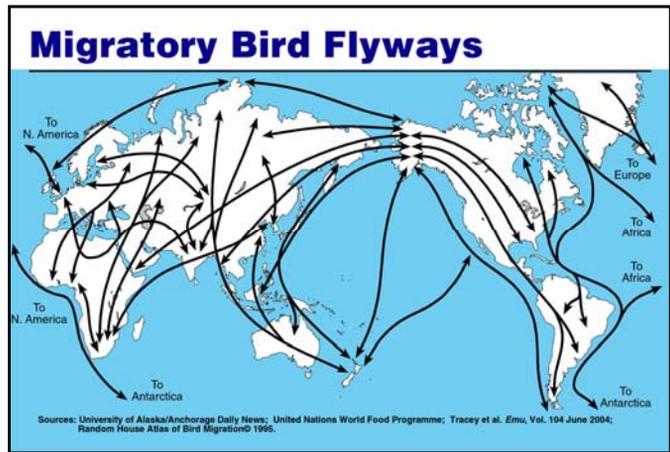
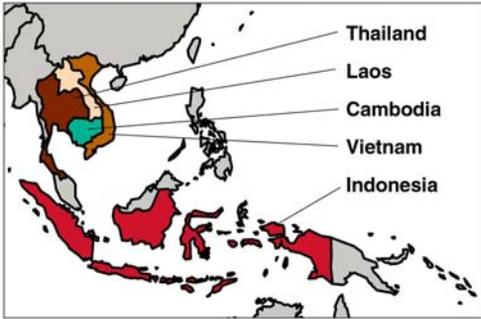
H5N1 Influenza Cases, 2003-2006



Source: WHO and OIE (World Organization for Animal Health), 5/8/2006



HHS Delegation to Southeast Asia October 8-18, 2005



Potential Impact of an Influenza Pandemic in the U.S.: Two Scenarios*

Characteristic	Moderate (1958/68-like)	Severe (1918-like)
Illness	90 million (30%)	90 million (30%)
Outpatient medical care	45 million (50%)	45 million (50%)
Hospitalization	865,000	9,900,000
ICU care	128,750	1,485,000
Mechanical ventilation	64,875	742,500
Deaths	209,000	1,903,000

* 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



ABC ORIGINAL MOVIE



Fatal Contact: Bird Flu in America

Tuesday, May 9 at 8/7c

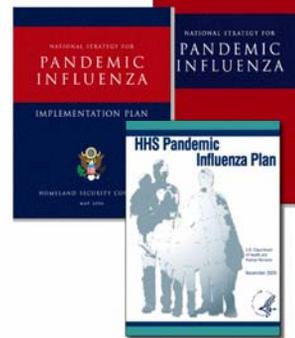
Starring Josly Richardson, Stacy Kesch, Ann Cusack, Justina Machado, Scott Cohen and David Ramsey

"Despite the early warning, the H5N1 virus has mutated into a version that can spread from human to human -- shown in eye-opening detail whenever the microbes start to permeate the atmosphere - across races, nationalities, genders and ages."

■ Seasonal Influenza Preparedness

■ Pandemic Influenza Preparedness

Pandemic Influenza Preparedness Strategy and Implementation



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



Vaccines

Therapeutics



Diagnostics

**NIAID
Influenza
Research**



Surveillance
and
Epidemiology

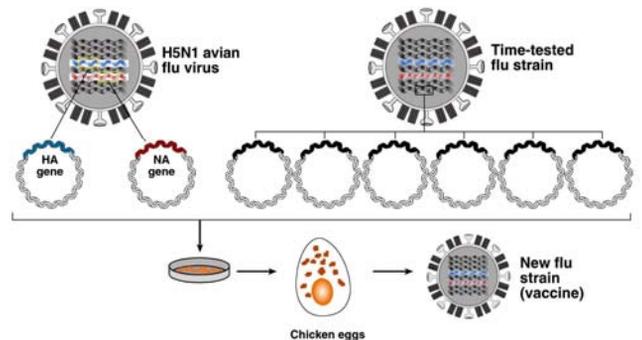


Basic Research

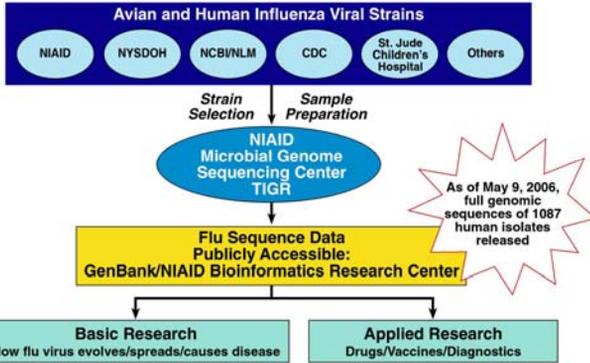


Expansion of
Research
Capacity

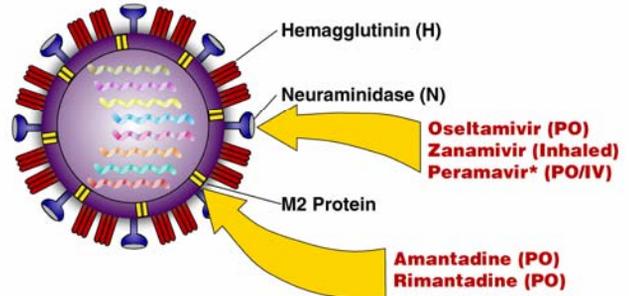
Production of a Human Vaccine Against H5N1 Avian Influenza Using Reverse Genetics



NIAID Influenza Genome Project



Antiviral Therapies for Influenza



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

AS Fauci/NIAID

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)

HHS News
U.S. Department of Health and Human Services
www.hhs.gov/news

FOR IMMEDIATE RELEASE
Thursday, May 4, 2006

HHS Awards Contracts Totaling More Than \$1 Billion to Develop Cell-Based Influenza Vaccine

Selected Strategies for Influenza Vaccines

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

The Future: A "Universal" Influenza Vaccine?

<p>August 13, 2004</p> <p>Vaccine</p> <p>PRECLINICAL STUDY OF INFLUENZA VIRUS A M2 PEPTIDE CONJUGATE VACCINES IN MICE, FERRETS, AND RHESUS MONKEYS</p> <p>Fan J, Liang X, Horton MS, Perry HC, Citron MP, Heldecker GJ, Fu TM, Joyce J, Przysiecki CT, Keller PM, Garsky VM, Ionescu R, Rippeon Y, Shi L, Chastain MA, Condra JH, Davies ME, Liao J, Emini EA, Shiver JW</p>	<p>November 15, 2004</p> <p>Vaccine</p> <p>PROTECTION AGAINST MULTIPLE INFLUENZA A SUBTYPES BY VACCINATION WITH HIGHLY CONSERVED NUCLEOPROTEIN</p> <p>Epstein SL, Kong WP, Mispion JA, Lo CY, Tumpey TM, Xu L, Nabel GJ</p>	<p>January 20, 2006</p> <p>Vaccine</p> <p>THE UNIVERSAL INFLUENZA VACCINE M2E-H3C ADMINISTERED INTRANASALLY IN COMBINATION WITH THE ADJUVANT CTA1-DD PROVIDES COMPLETE PROTECTION</p> <p>De Filette M, Ramme A, Birkett A, Lycke N, Lovenadler B, Min Jou W, Saelens X, Fiers W</p>
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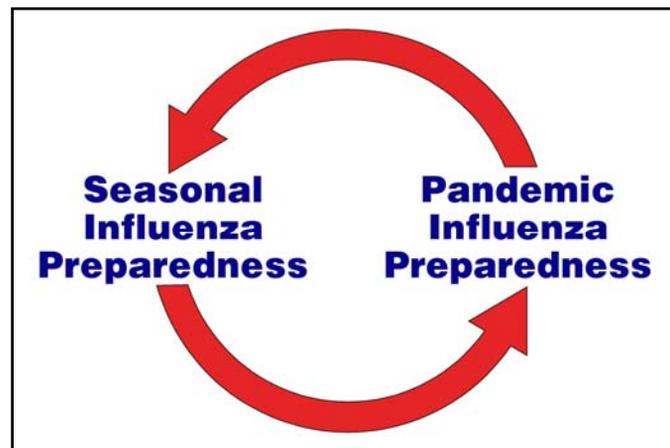
Immunity

January 2006

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**