Biodefense and Pandemic Influenza: The Research and Public Health Interface

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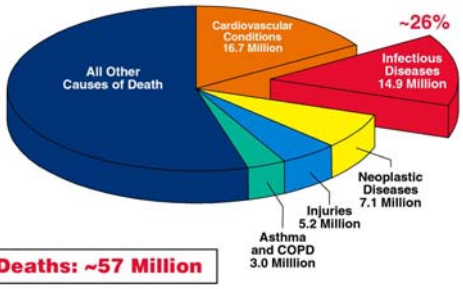
February 16, 2006

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.

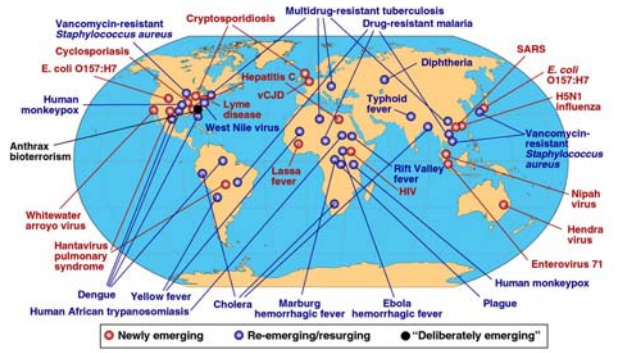
Infectious Diseases Cause ~26% of All Deaths Worldwide



Total Deaths: ~57 Million

Source: WHO, *World Health Report, 2004*

Global Examples of Emerging and Re-Emerging Infectious Diseases

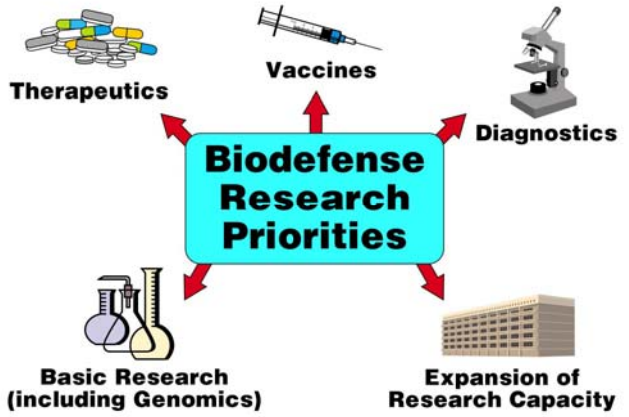


NIAID Infectious Disease Research: A Dual Mandate

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

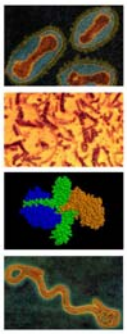
Respond rapidly to new infectious disease threats

New/Improved Countermeasures

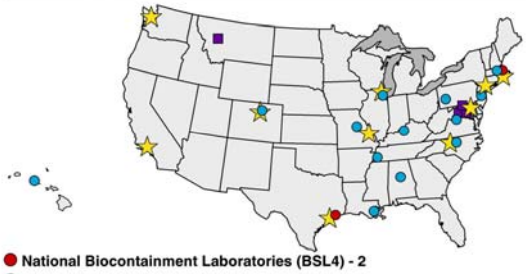


Biodefense Countermeasures: Key Achievements

- 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 (BSL4) - 2
- Regional Biocontainment Laboratories (BSL3) - 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

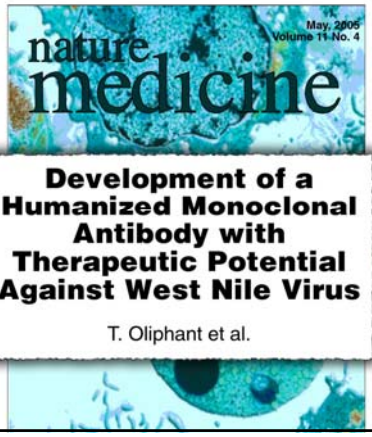
- Influenza
- Antibiotic resistant microbes (except STDs)
- Dengue
- Diarrheagenic E.coli
- Entamoeba histolytica
- Giardia lamblia
- Hepatitis A
- Multi-drug resistant TB
- Rift Valley Fever
- Tickborne encephalitis viruses
- Toxoplasma
- Typhus fever (Rickettsia prowazekii)
- Vibrio cholera and other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

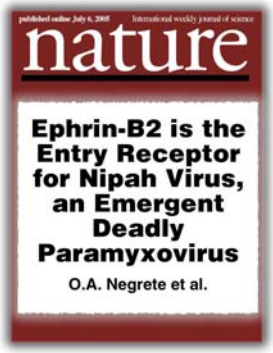


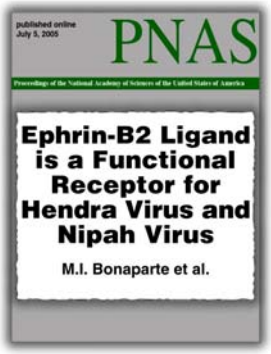
Development of a Humanized Monoclonal Antibody with Therapeutic Potential Against West Nile Virus

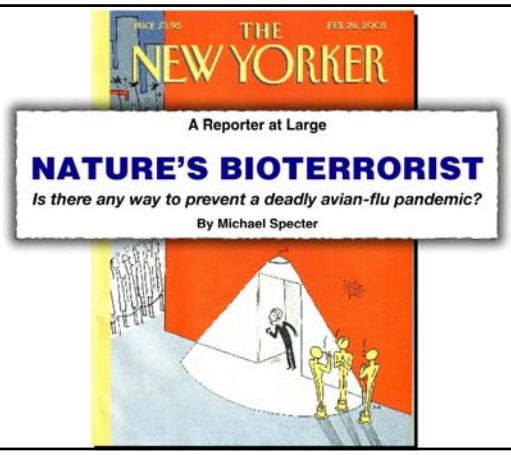
T. Oliphant et al.

- 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

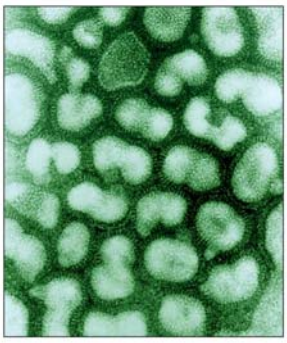
Scientists Discover How Nipah Virus and Hendra Virus Enter Cells





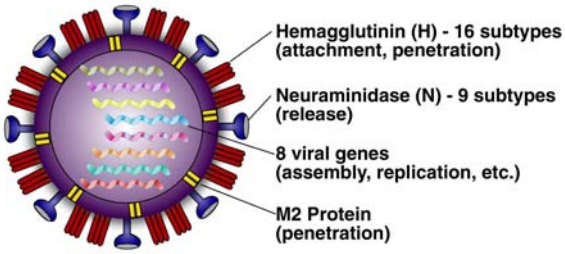


Influenza

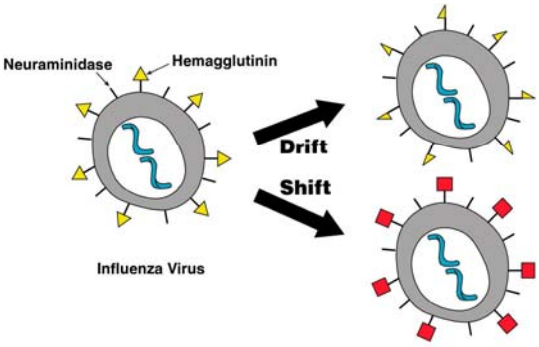


- Re-emerging disease (interpandemic flu)
- Newly emerging disease (potential pandemic flu)

Influenza A Virus



Influenza: Antigenic Drift and Shift

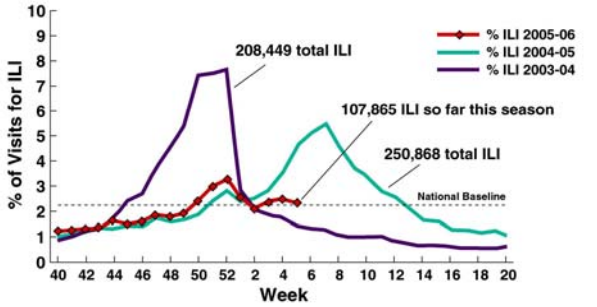


The Burden of Seasonal Influenza

- 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

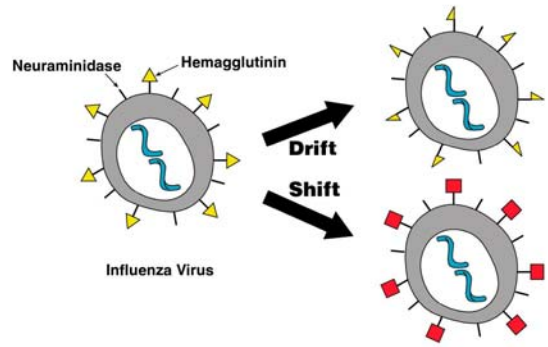
Sources: CDC, WHO, Am. Lung. Assoc.

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



Source: CDC

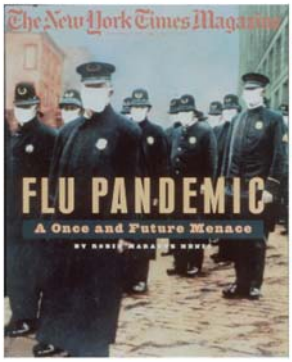
Influenza: Antigenic Drift and Shift



Past Antigenic Shifts

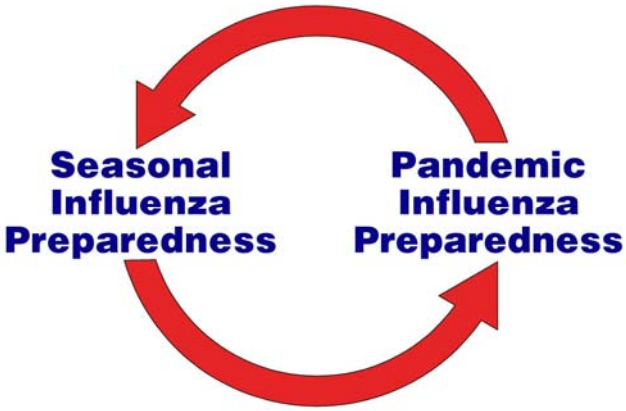
1918	H1N1	Spanish Flu	>40 million deaths
1957	H2N2	Asian Flu	1-2 million deaths
1968	H3N2	Hong Kong Flu	700,000 deaths
1976	H1N1	Swine Flu	No pandemic

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

Source: WHO, 1/2005



- **Seasonal Influenza Preparedness**
- Pandemic Influenza Preparedness

U.S. Seasonal Influenza Vaccine: Production and Use

	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

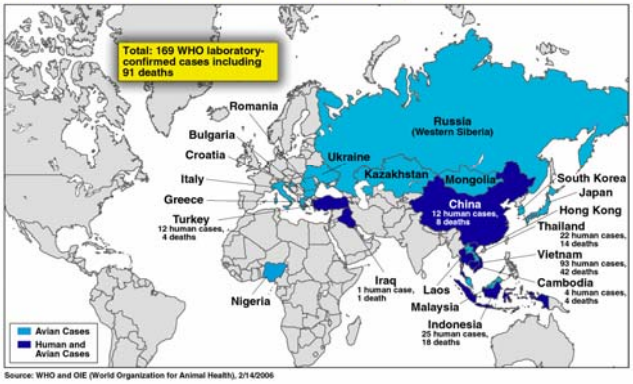
The New York Times

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.

H5N1 Influenza Cases, 2003-2006

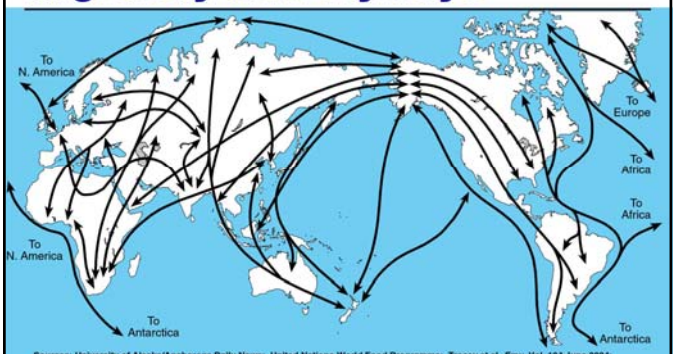


Source: WHO and OIE (World Organization for Animal Health), 2/14/2006

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

Source: Tran et al. N Engl J Med 350:1171, 2004.

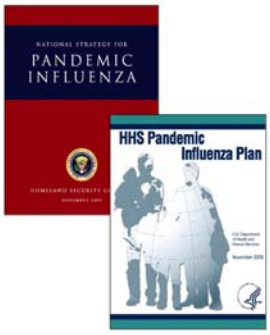
Migratory Bird Flyways



Sources: University of Alaska/Anchorage Daily News; United Nations World Food Programme; Tracey et al. *Emu*, Vol. 104 June 2004; Random House Atlas of Bird Migration© 1995.

- Seasonal Influenza Preparedness
- **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 OCR and DMID for international research in SE Asia

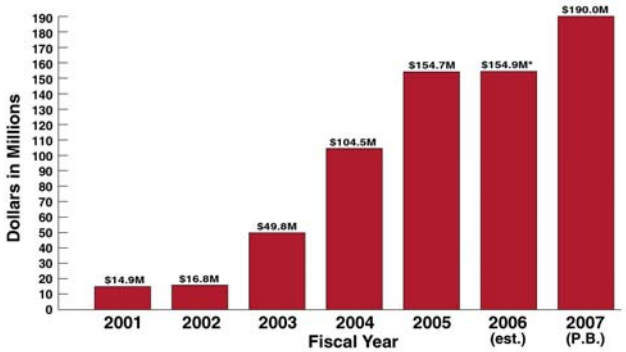
$350 M – Upgrade state & local response capacities

$50 M – Increase CDC laboratory capacity

$0.5 billion: Other agencies, including DoD and USAID

$3.8 billion total

NIAID Influenza Research Funding



*Does not include $18M from President's emergency supplemental funding for pandemic influenza

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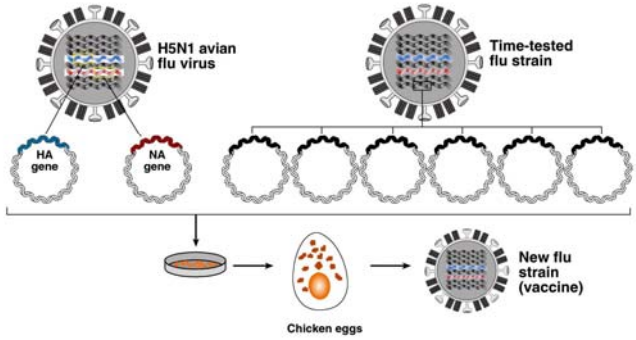
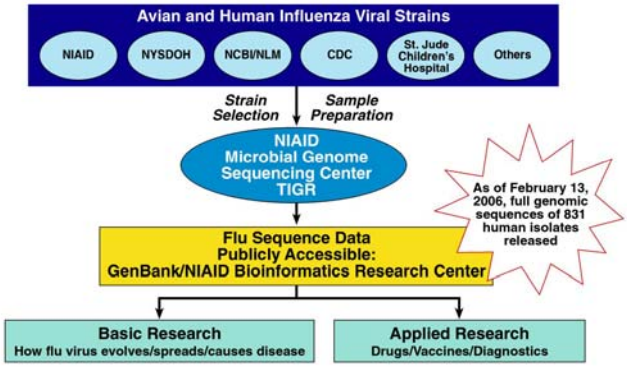
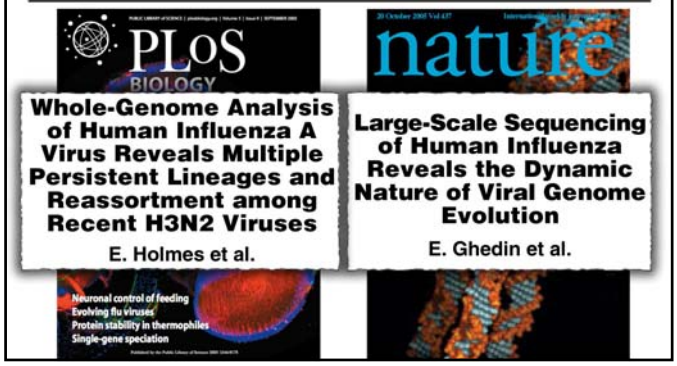
Production of a Human Vaccine Against H5N1 Avian Influenza Using Reverse Genetics



NIAID Influenza Genome Project



NIAID Influenza Genome Sequencing Project: Publications



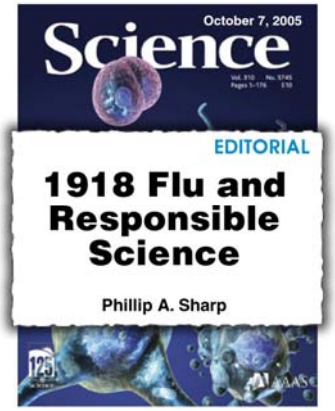
Published Online January 26, 2006

SCIENCE

Large-Scale Sequence Analysis of Avian Influenza Isolates

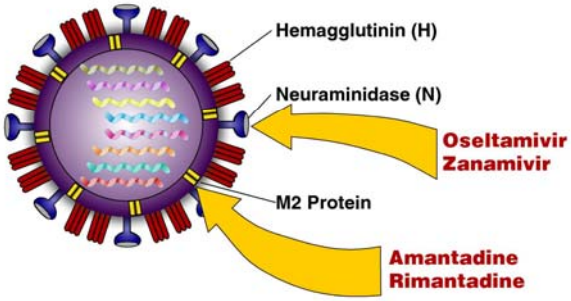
JC Obenauer et al.

- St. Jude Repository contains ~11,000 influenza viruses incl. ~7,000 avian influenza viruses (AIVs).
- This analysis is first large-scale sequencing of AIVs.
- 2,196 genes and 169 complete genomes deposited to GenBank, doubling the amount of genetic information available on AIVs.



"....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."

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

Pandemic Influenza Vaccine

- Pre-pandemic
- Intra-pandemic

NIH NEWS RELEASE

National Institutes of Health

National Institute of Allergy and Infectious Diseases

FOR IMMEDIATE RELEASE
Thursday, May 27, 2004

NIAID Announces Contracts to Develop Vaccine Against H5N1 Avian Influenza

NIH NEWS RELEASE

National Institutes of Health

National Institute of Allergy and Infectious Diseases

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

Pre-Pandemic H5N1 Vaccine Evaluation: Preliminary Results

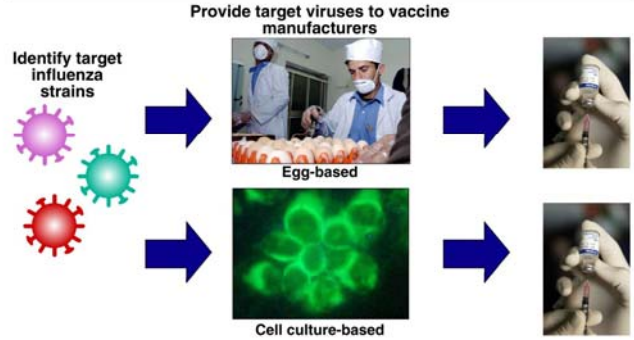
Sanofi Inactivated H5N1 Subunit Vaccine

- 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

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)

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



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?

August 13, 2004

Vaccine

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

Fan J, Liang X, Horton MS, Perry HC, Citron MP, Heidecker 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

November 15, 2005

Vaccine

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

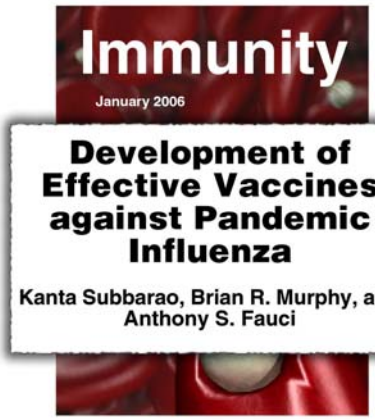
Epstein SL, Kong WP, Misplon JA, Lo CY, Tumpey TM, Xu L, Nabel GJ

January 30, 2006

Vaccine

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

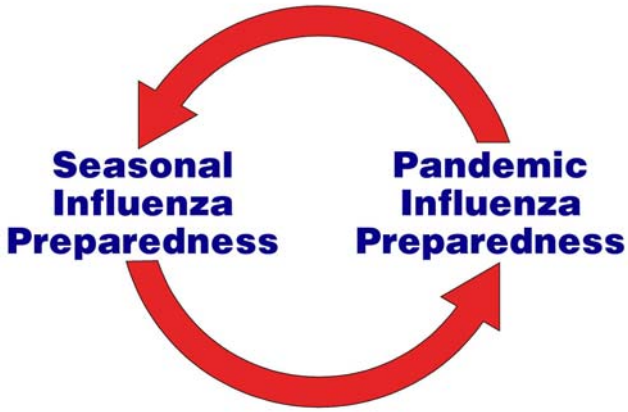
De Filette M, Ramne A, Birkett A, Lycke N, Lowenadler B, Min Jou W, Saelens X, Fiers W



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