International Health and Tropical Infectious Diseases Research: An NIAID Perspective

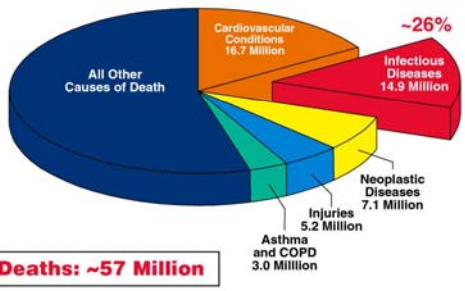
Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
December 11, 2005

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



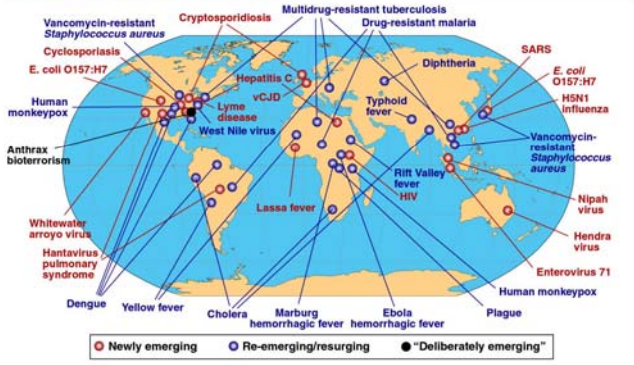
Total Deaths: ~57 Million

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



Emerging and Re-Emerging Diseases

- Newly Emerging Diseases
  - e.g. HIV/AIDS, SARS, Nipah virus, vCJD
- Re-Emerging or Resurging Diseases
  - e.g. West Nile virus, monkeypox, dengue, MDR-TB, malaria
- "Deliberately Emerging" Diseases
  - agents of bioterrorism, e.g. anthrax attacks of 2001

A Perpetual Struggle

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

Public Health Measures, Biomedical Research, and Technological Advances

NIH 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

Biomedical Research in the 21st Century: Striking a Balance

Basic Research

Product Development

CENTERS FOR DISEASE CONTROL

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

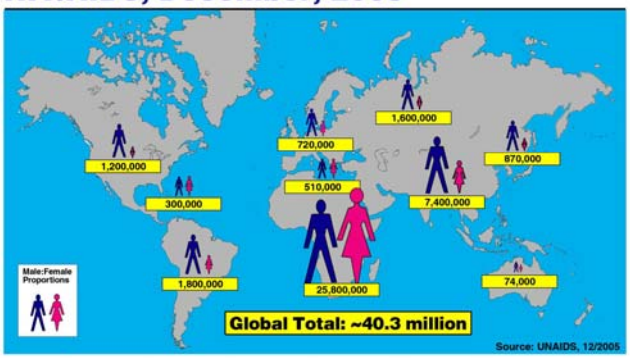
June 5, 1981

***Pneumocystis* Pneumonia – Los Angeles**

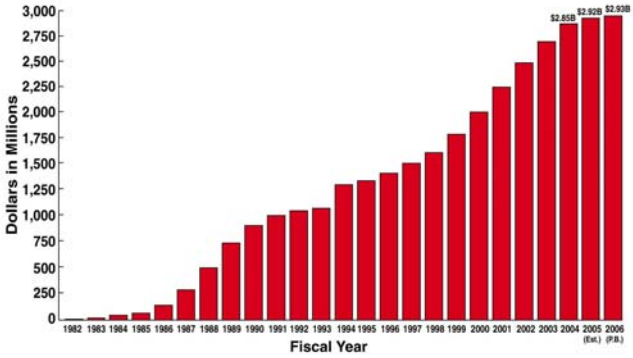
July 4, 1981

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, 1981-2005

- 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

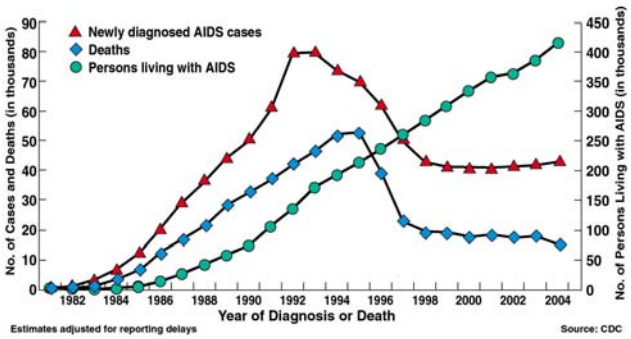
PI
- Amprenavir
- Atazanavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

Fusion Inhibitor
- Enfuvirtide (T-20)

Combinations
- 4 available, combining 2 or 3 drugs

Source: FDA, Oct. 2005

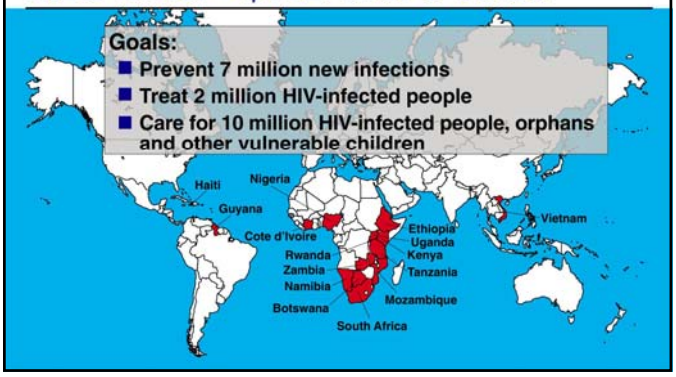
AIDS Cases, Deaths, and People Living with AIDS, United States, 1981-2004



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

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



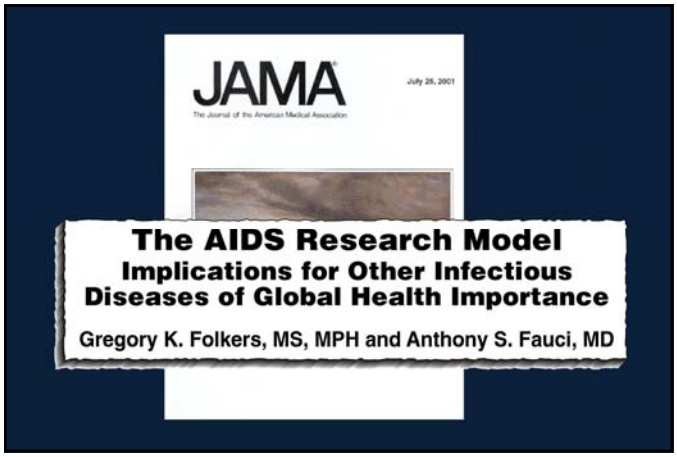
Global Access to Antiretroviral Drugs in Low and Middle Income Countries is Improving

2003: 400,000 people on ARVs

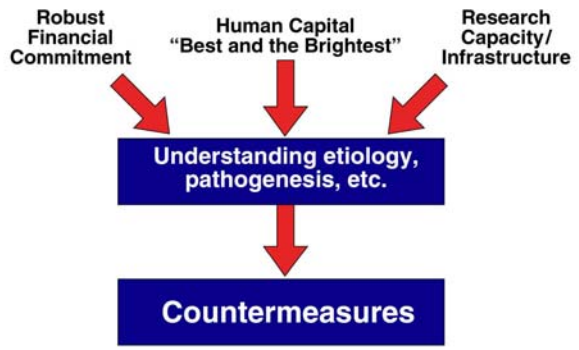
2005: ~1 million people on ARVs

- In 2005, 250,000-350,000 deaths were averted because of recent treatment scale up.
- However, only 1 in 10 Africans and 1 in 7 Asians in need of ARVs are receiving them.

Source: UNAIDS, 11/2005



The AIDS Research Model



The Burden of Tuberculosis

- One-third of the world's population is infected with *Mycobacterium tuberculosis* (TB).
- 8.8 million active TB cases in 2003.
- 1.7 million TB deaths in 2003; TB accounts for ~13% of AIDS deaths worldwide.
- 300,000 new cases per year of multi-drug resistant (MDR)-TB worldwide.

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
Monday, January 26, 2004

First U.S. Tuberculosis Vaccine Trial in 60 Years Begins

- Mtb72f, an adjuvanted fusion subunit protein vaccine
- Developed through NIAID challenge grants and Millennium Vaccine Initiative
- Protected animal models against aerosol challenge

Press Release

gsk GlaxoSmithKline

AERAS

GlaxoSmithKline Biologicals and Aeras Global TB Vaccine Foundation Partner to Develop New TB Vaccine

- Additional phase I testing in Europe
- Safety and efficacy testing in populations in Africa and elsewhere highly affected by TB

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

June 14, 2005

First Tuberculosis Drug Developed by a Non-profit Begins Clinical Trials

- PA-824, a nitroimidizole originally studied for cancer treatment
- Anti-TB activity studied under NIAID CRADA, published in Nature in 2000
- TB Alliance acquired world rights to distribution from Chiron in 2002
- Now in phase I trial

The Global Burden of Malaria

- 1.1 million annual deaths, most under age 5
- 350 - 500 million clinical episodes/yr.
- Every 30 seconds, a child dies of malaria

Source: WHO, World Malaria Report, 2005

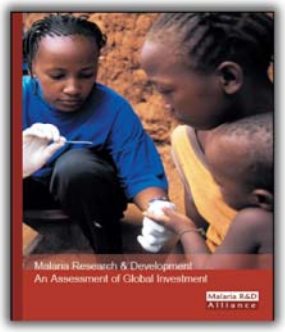
NIAID Priorities in Malaria Research

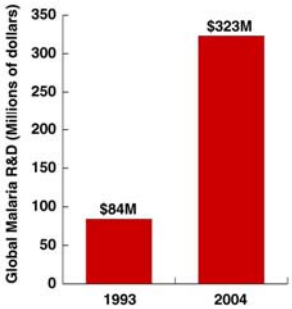
- Basic Research
  - Genomics and Proteomics: data mining and functional analysis
- Prevention
  - Vaccines: continued implementation of NIAID Malaria Vaccine Plan
  - Vector Biology and Control
- Treatments
  - Novel Artemisinin synthesis
  - Collaborations with industry and PPPs
- Diagnostics
- Capacity Enhancement in Developing Countries
  - Training
  - Multilateral Initiative on Malaria
  - In-country sites

Highlights of NIAID's Research Plan for Malaria Vaccine Development

- Improved access to well-characterized research materials
- Discovery and preclinical testing of new vaccine candidates
- Production and evaluation of candidate malaria vaccines
- Clinical research and trial preparation sites in endemic areas

Malaria Research & Development: An Assessment of Global Investment





The Washington Post

July 1, 2005

Bush Pledges $1.2 Billion for Africa to Fight Malaria

The Human Toll of Three Trypanosomatids

Disease	Regions affected	Estimated number of cases	Estimated number of annual deaths
African sleeping sickness	Sub-Saharan Africa	300,000-500,000	50,000
Leishmaniasis	Tropics and subtropics	12 million	59,000
Chagas' disease	Latin America	16-18 million	13,000

Source: WHO

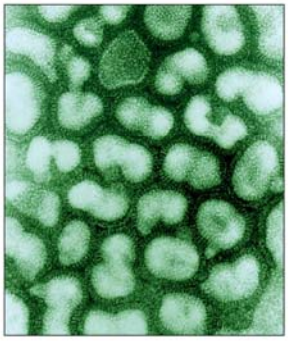
Three Deadly Parasite Genomes Sequenced

- *Trypanosoma brucei* (African sleeping sickness)
- *Trypanosoma cruzi* (Chagas' disease)
- *Leishmania major* (Leishmaniasis)

Trypanosomatid Genome Sequencing: Partners

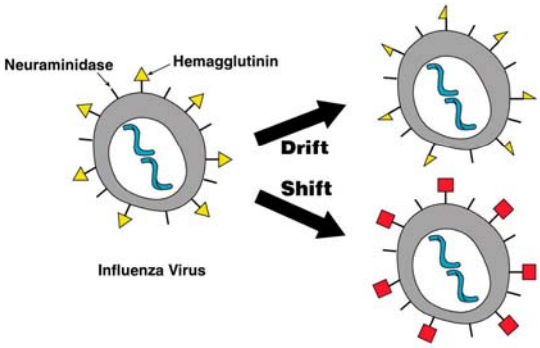
- **Research funding agencies**
  - NIAID
  - Burroughs Wellcome Fund
  - M.J. Murdoch Charitable Trust
  - WHO Special Programme for Research & Training in Tropical Diseases
  - Wellcome Trust
  - European Union
- **Sequencing centers**
  - Seattle Biomedical Research Institute, Seattle WA
  - The Institute for Genomic Research, Rockville MD
  - Sanger Center, Hinxton, UK
  - Karolinska Institute, Stockholm, Sweden

Influenza



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

Influenza: Antigenic Drift and Shift



Seasonal Influenza vs Pandemic Influenza

The Burden of Influenza

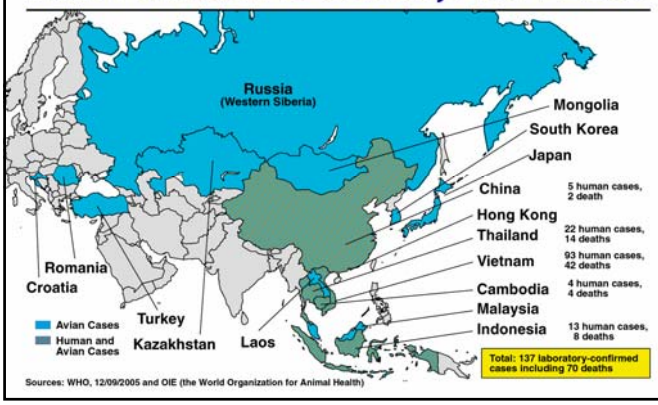
- 250,000 to 500,000 deaths globally/yr
- 36,000 deaths and >200,000 hospitalizations/yr in U.S.
- $37.5 billion in economic costs/yr in U.S. related to influenza and pneumonia
- Ever-present threat of pandemic influenza

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

Past Antigenic Shifts

1918	H1N1	Spanish Influenza	20-40 million deaths
1957	H2N2	Asian Flu	1-2 million deaths
1968	H3N2	Hong Kong Flu	700,000 deaths
1976	H1N1	Swine Flu	No pandemic

H5N1 Influenza Cases, 2004-2005



Sources: WHO, 12/09/2005 and OIE (the World Organization for Animal Health)

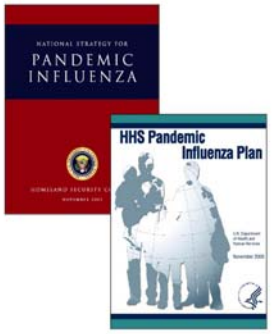
Number of Episodes of Illness, Healthcare Utilization, and Death Associated with Moderate and Severe Pandemic Influenza Scenarios*

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

Pandemic Influenza Preparedness Strategy and Plan



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

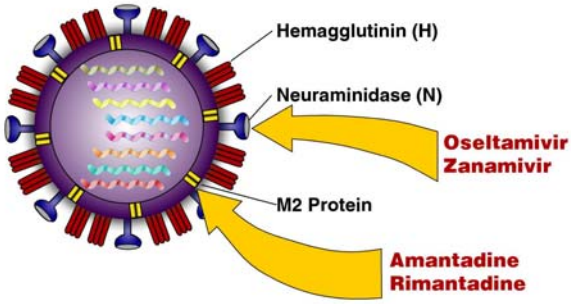
The New York Times

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.

Antiviral Therapies for Influenza

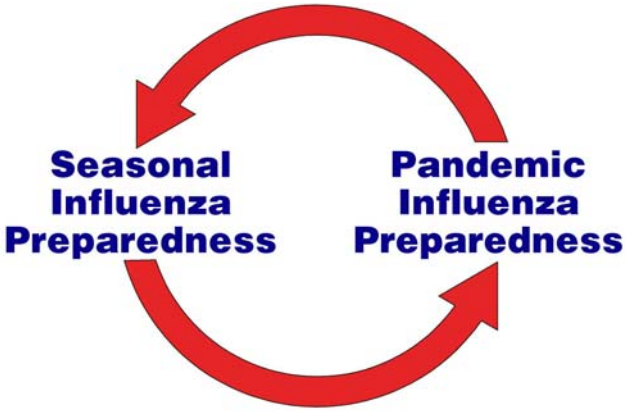


Pandemic Influenza Vaccine

- Pre-pandemic
- Intra-pandemic

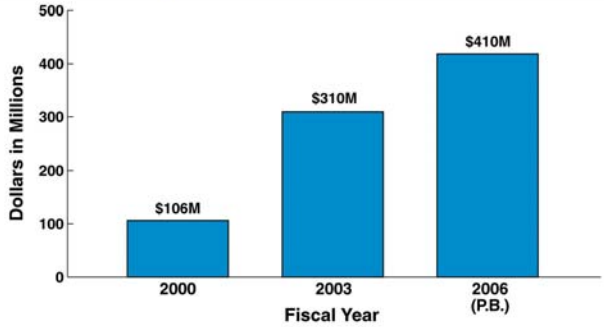
Major Challenges to Pandemic Vaccine Development and Availability are Production and Surge Capacity

- Accelerate development of cell culture based vaccine technology
- Develop novel vaccine approaches
- Evaluate dose-sparing technology (adjuvants, intramuscular vs. intradermal)

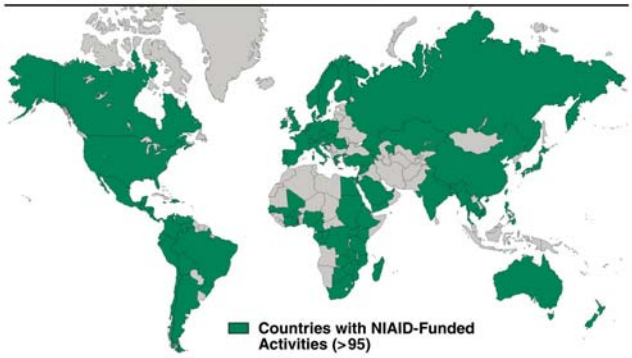


Outlook for the Future

NIAID Funding for International Research, 2000-2006



NIAID Projects Worldwide



Key NIAID Global Health Strategies

- Adapt disease prevention and treatment methods to developing countries
- Develop research capacity within developing countries
- Form partnerships among scientists, governments, companies and non-governmental organizations