

# **Emerging and Re-Emerging Infectious Diseases: The Perpetual Challenge to Global Health**

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**Director**

**National Institute of Allergy and Infectious  
Diseases**

**National Institutes of Health**

**August 8, 2006**



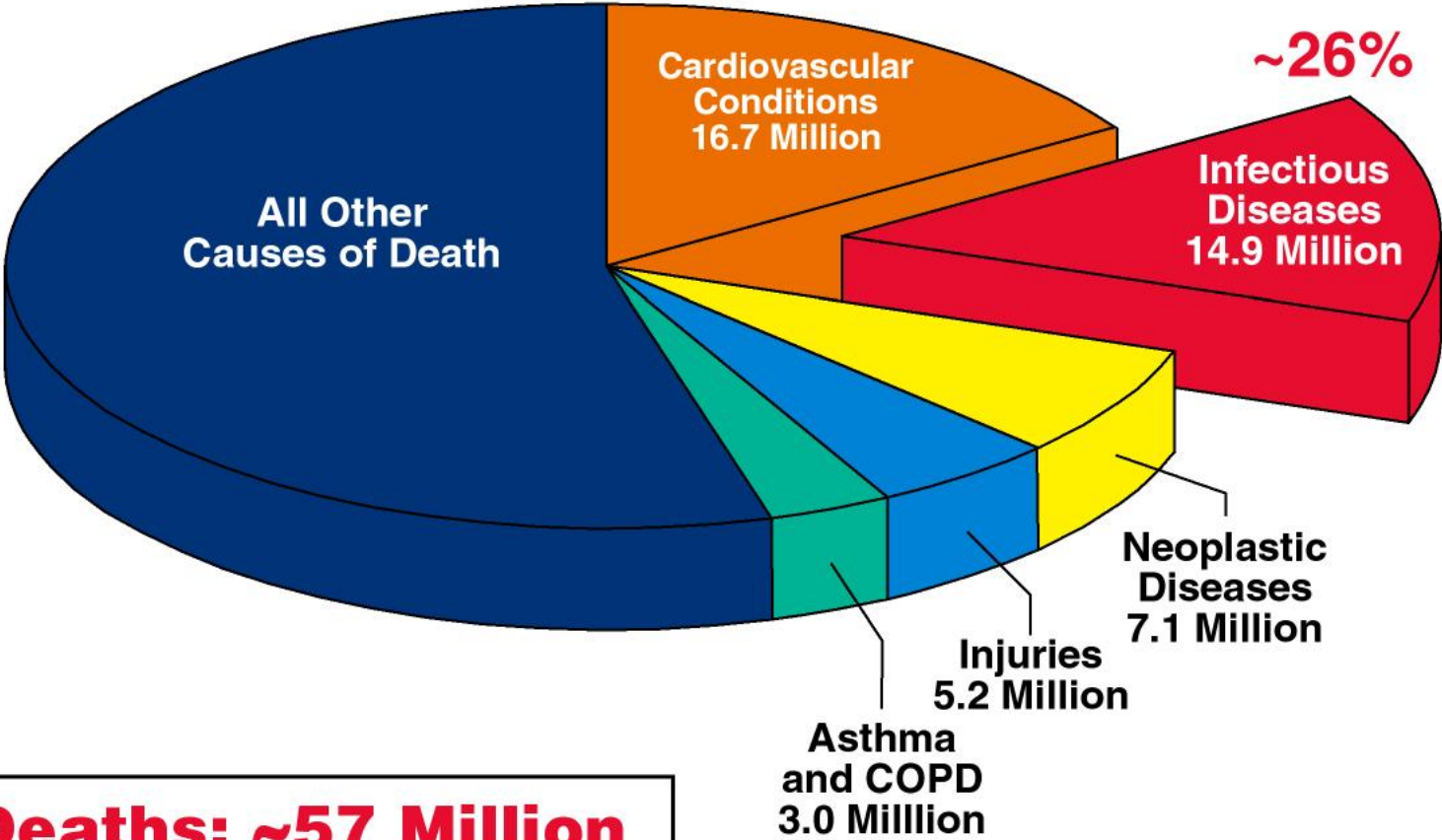
# **A Premature Declaration of Victory Over Infectious Diseases**

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***"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**

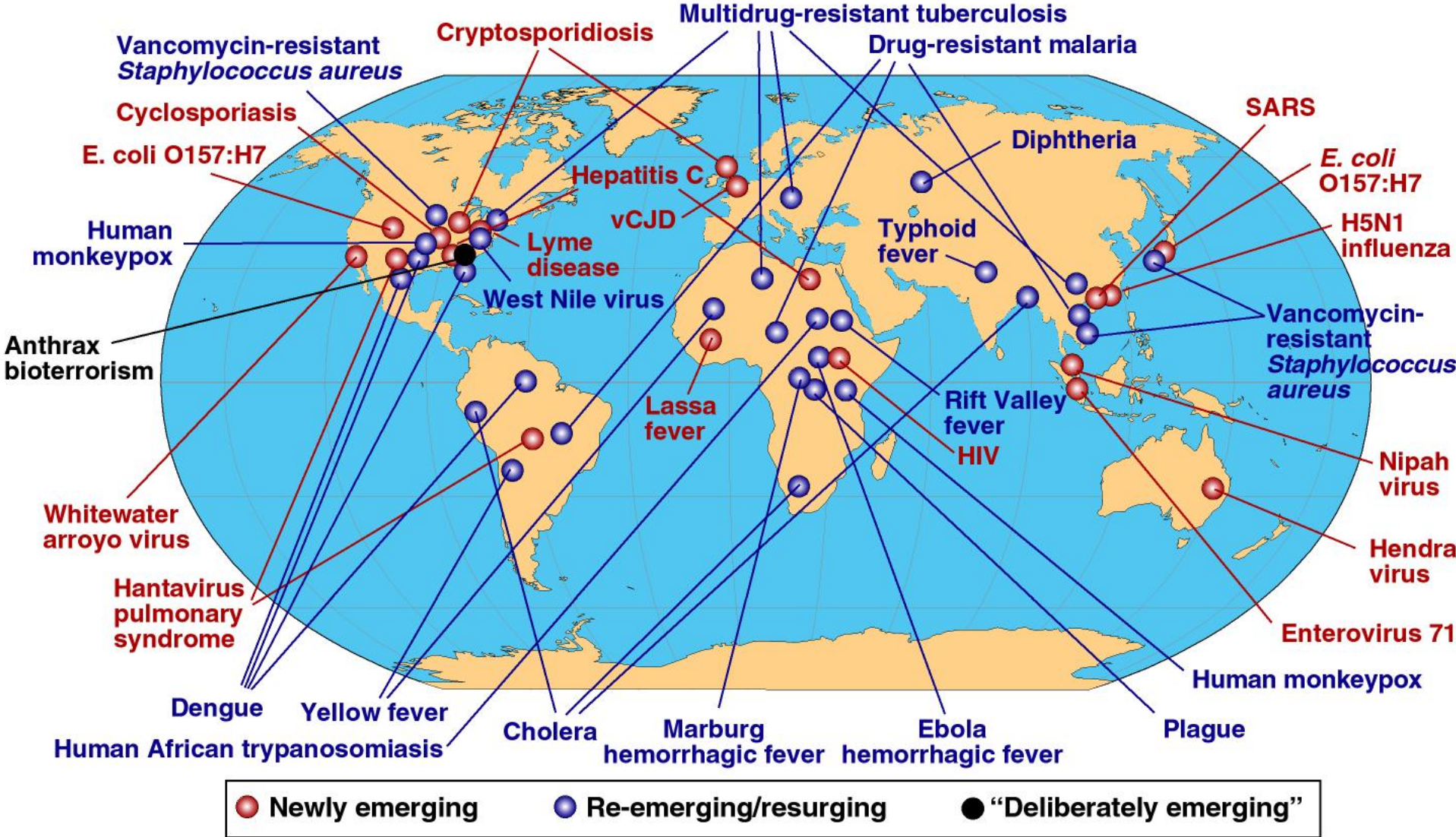
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	<b><u>Estimated Annual Deaths</u></b>
<b>Respiratory Infections</b>	<b>4.0 million</b>
<b>HIV/AIDS</b>	<b>3.1 million</b>
<b>Diarrheal Diseases</b>	<b>1.8 million</b>
<b>Tuberculosis</b>	<b>1.7 million</b>
<b>Malaria</b>	<b>1.3 million</b>
<b>Vaccine Preventable Childhood Diseases (measles, pertussis, tetanus, etc.)</b>	<b>600,000</b>
<b>Meningitis</b>	<b>170,000</b>
<b>Tropical Parasitic Diseases (trypanosomiasis, leishmaniasis, etc.)</b>	<b>130,000</b>

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# Global Examples of Emerging and Re-Emerging Infectious Diseases



CENTERS FOR DISEASE CONTROL

**MNWR**<sup>TM</sup>

MORBIDITY AND MORTALITY WEEKLY REPORT

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June 5, 1981

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***Pneumocystis Pneumonia -  
Los Angeles***

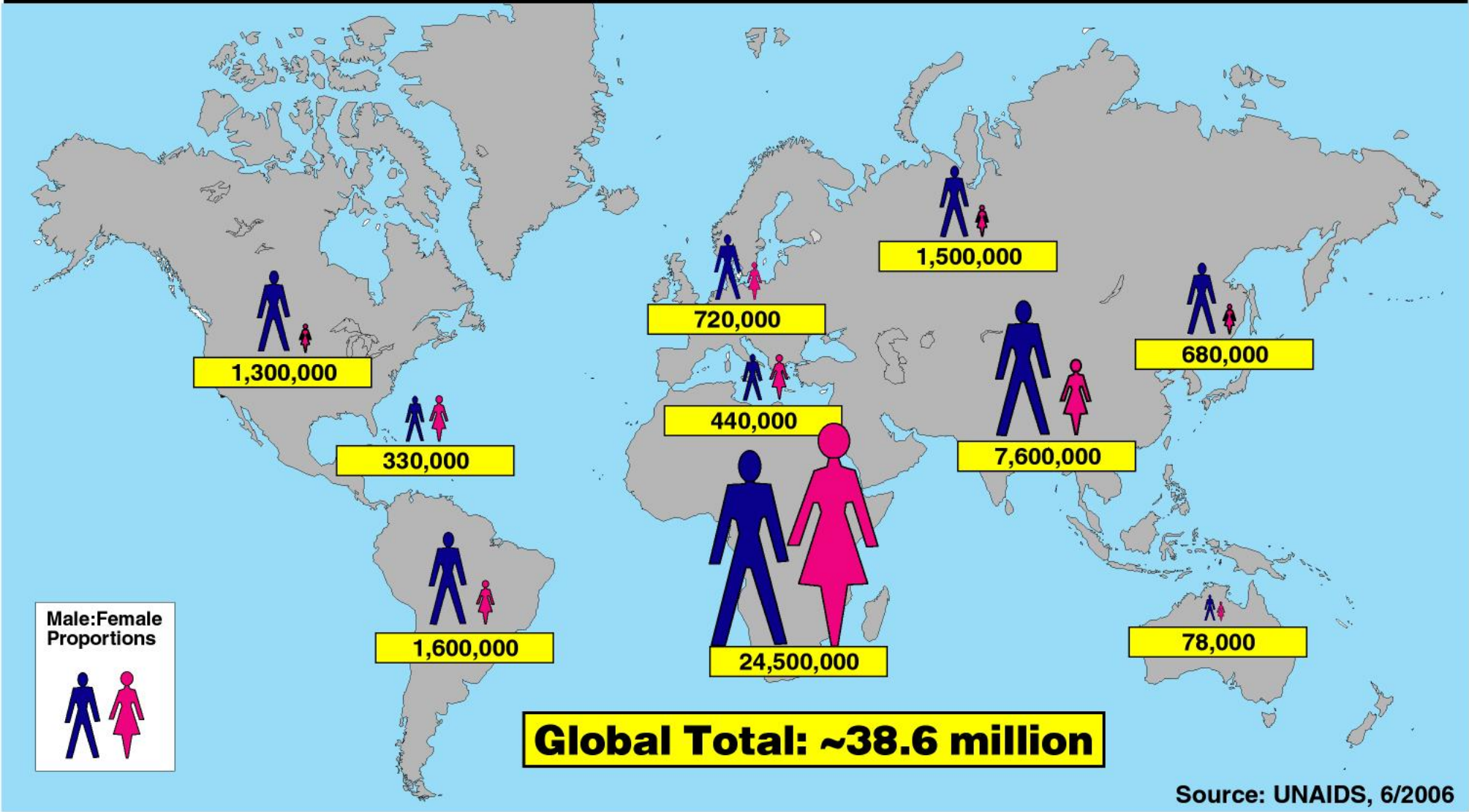
July 4, 1981

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



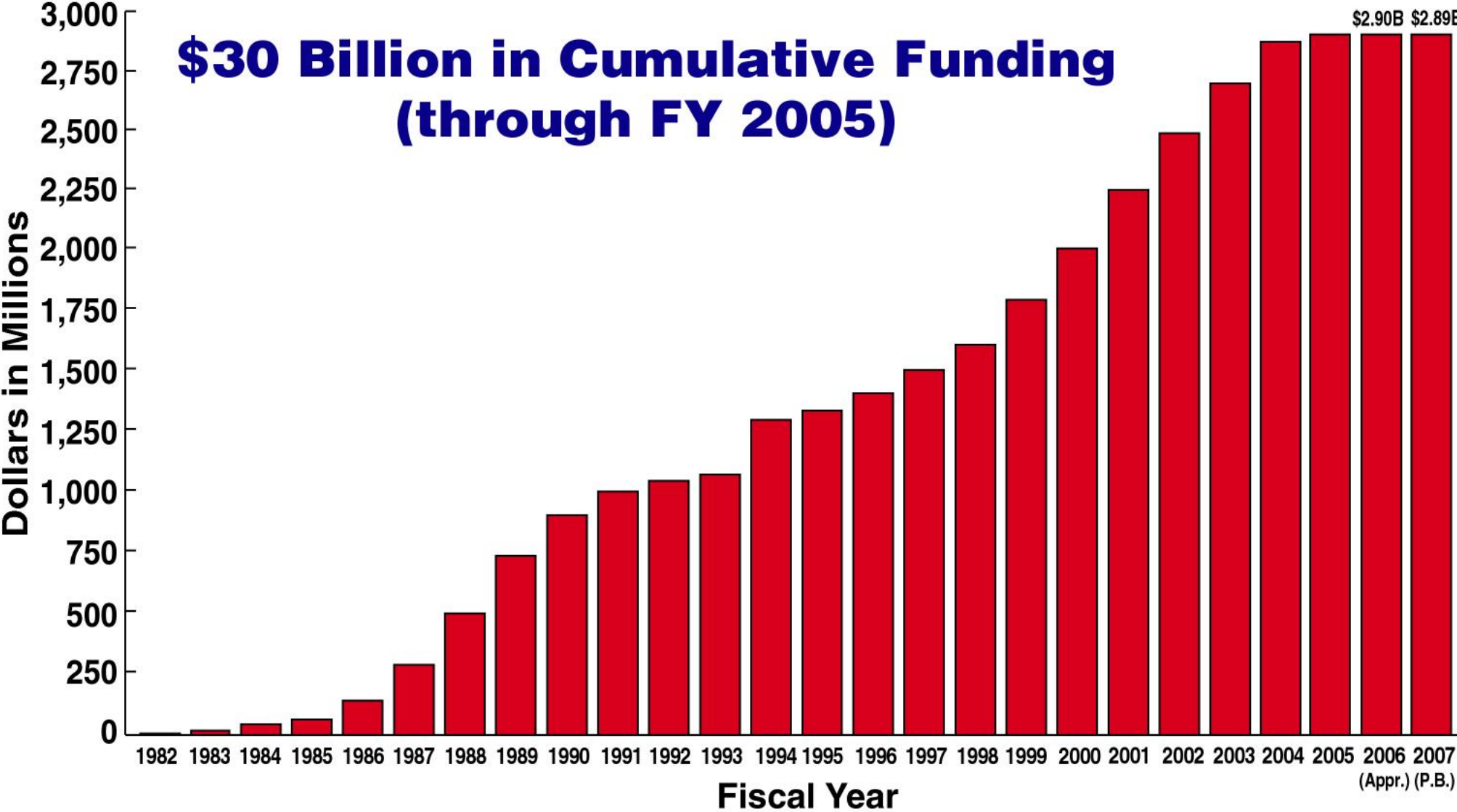
# Adults and Children Estimated to be Living with HIV, 2005



Source: UNAIDS, 6/2006



# NIH HIV/AIDS Research Funding



# **Advances in AIDS Research, 1981-2006**

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

# FDA-Approved Antiretroviral Drugs

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## NRTI

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

## NNRTI

- Delavirdine
- Efavirenz
- Nevirapine

## Fusion Inhibitor

- Enfuvirtide (T-20)

## PI

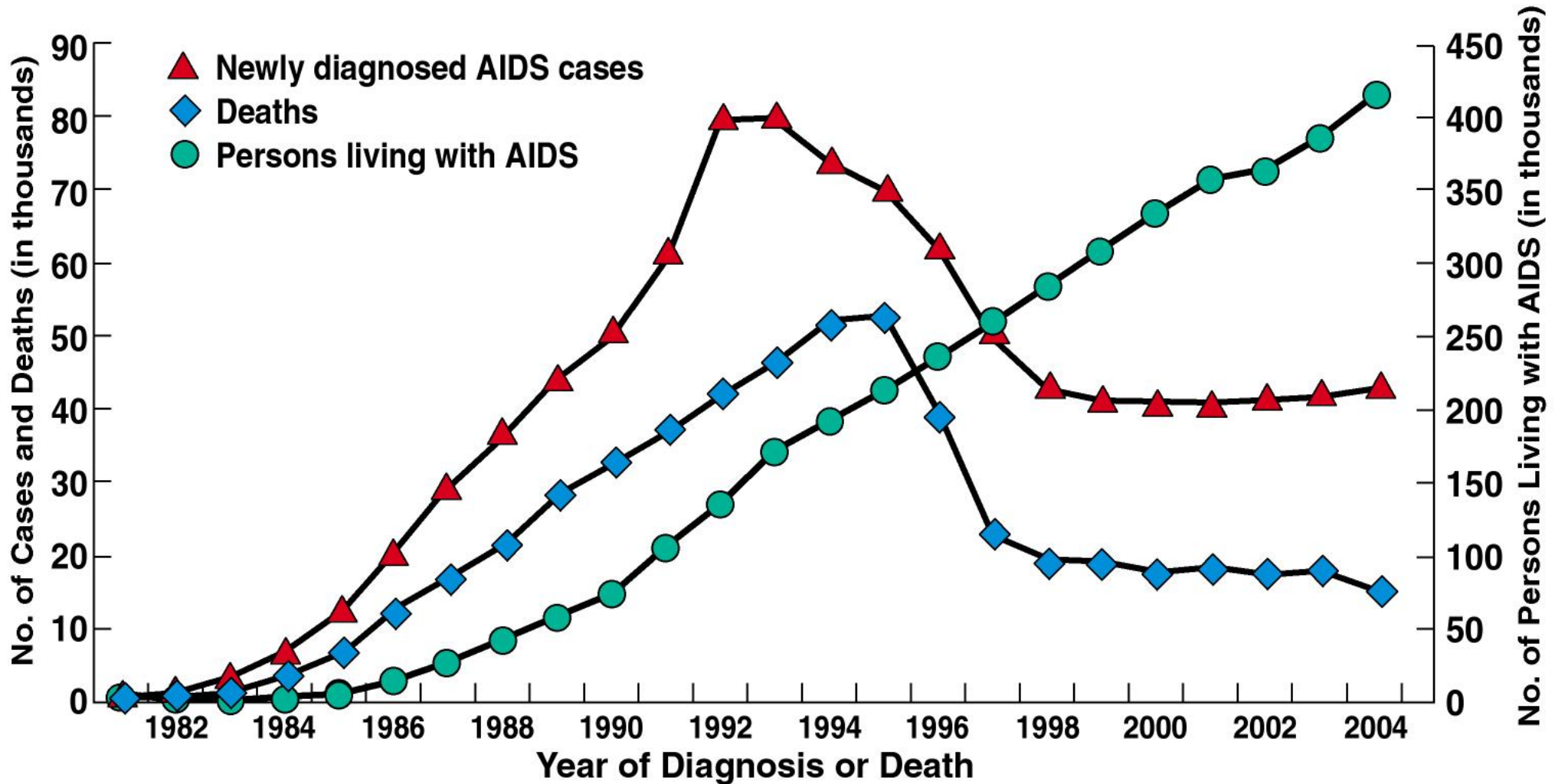
- Amprenavir
- Atazanavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir
- Darunavir (TMC114)

## Combinations

- 5 available, combining 2 or 3 drugs
  - e.g. Atripla: efavirenz + emtricitabine + tenofovir



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



Estimates adjusted for reporting delays

Source: CDC

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

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**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.**

**JAMA**<sup>®</sup>

The Journal of the American Medical Association

July 25, 2001



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

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



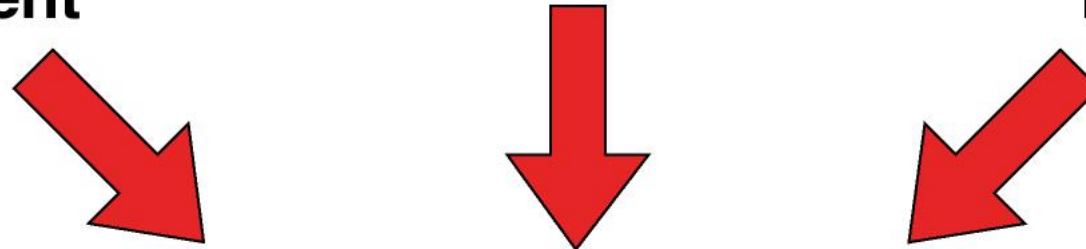
# The AIDS Research Model

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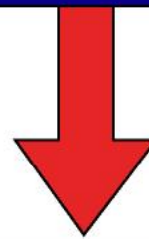
**Robust  
Financial  
Commitment**

**Human Capital  
“Best and the Brightest”**

**Research  
Capacity/  
Infrastructure**

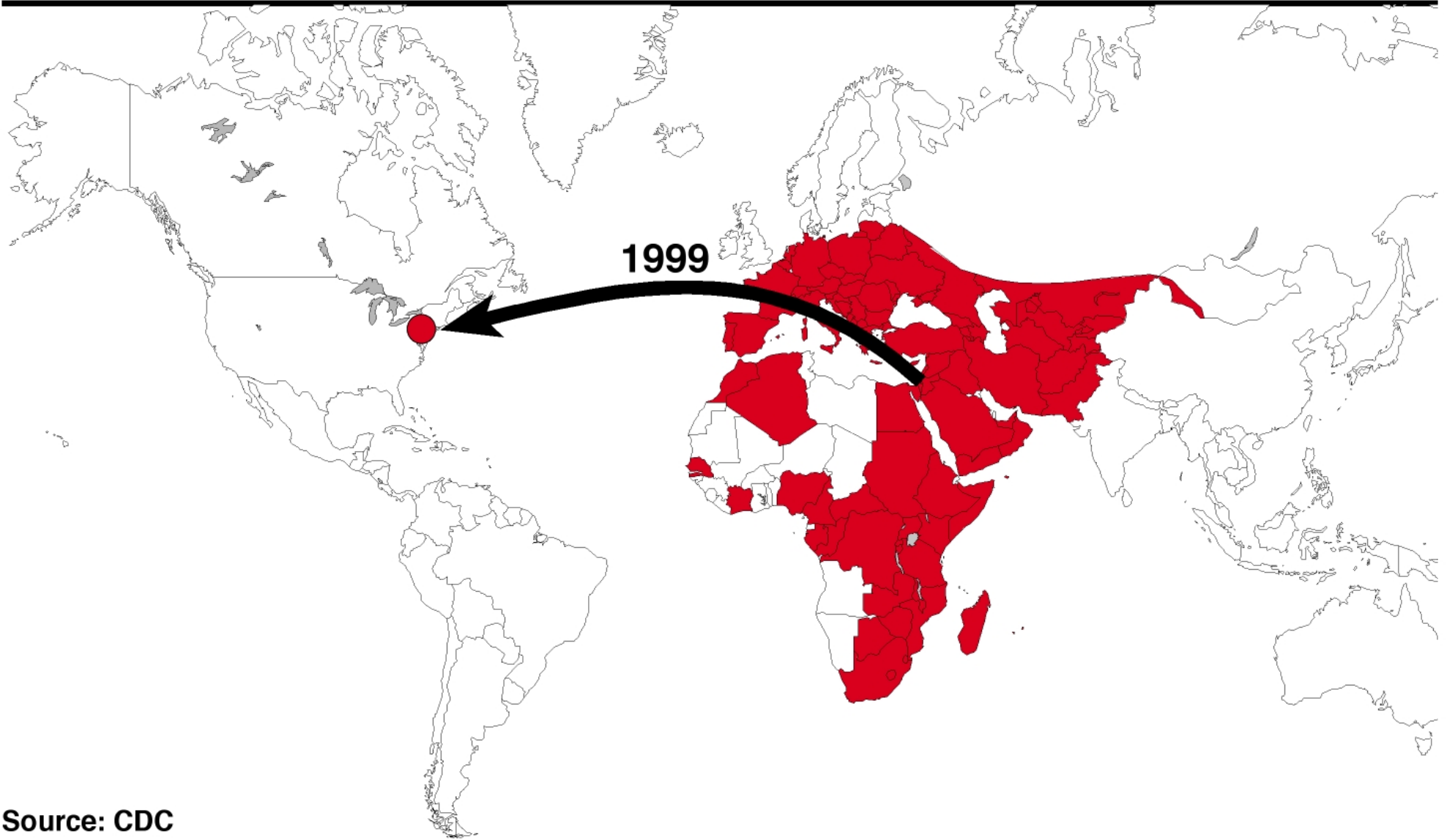


**Understanding etiology,  
pathogenesis, etc.**



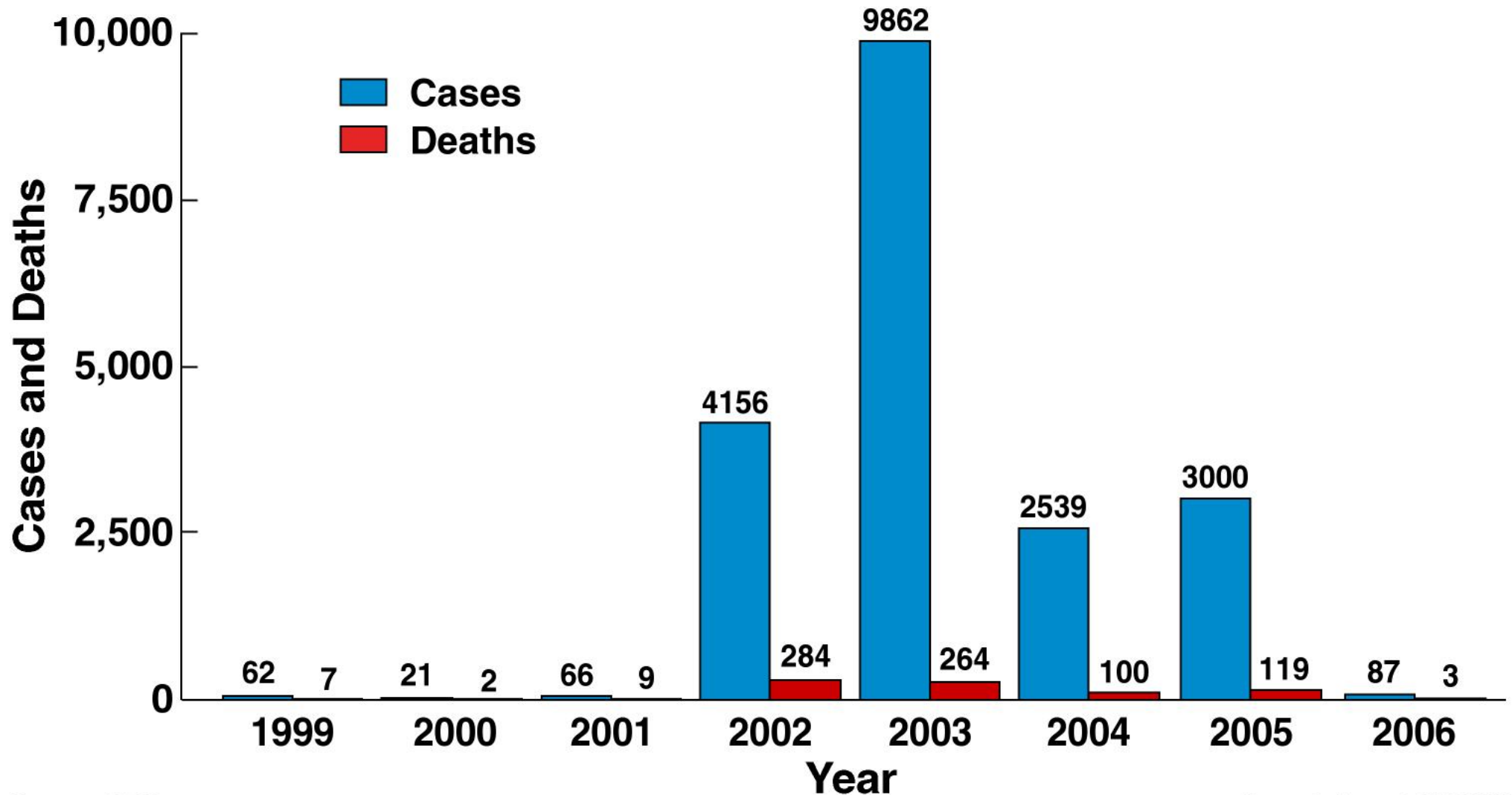
**Countermeasures**

# Global Distribution of West Nile Virus, 1999



Source: CDC

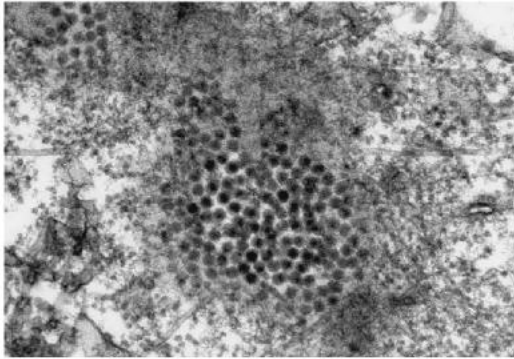
# Reported Human Cases of West Nile Virus Infection, USA, 1999-2006



Source: CDC

Reported as of 8/1/2006





**Basic Research  
on the Virus**



**Animal Models**



**Vector Biology**



**Vaccine  
Development**



**Antiviral Therapies**



**Rapid  
Diagnostics**



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.**



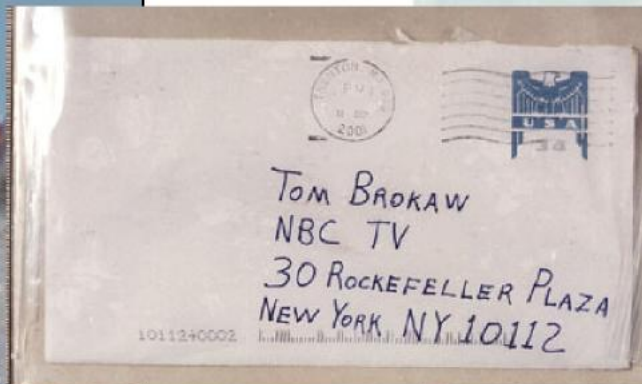
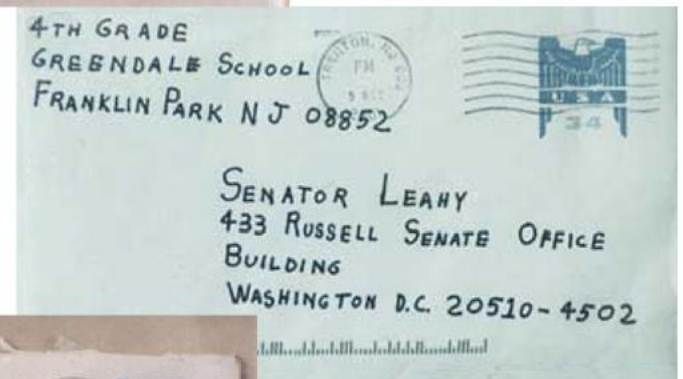


**Development of a  
Humanized Monoclonal  
Antibody with  
Therapeutic Potential  
Against West Nile Virus**

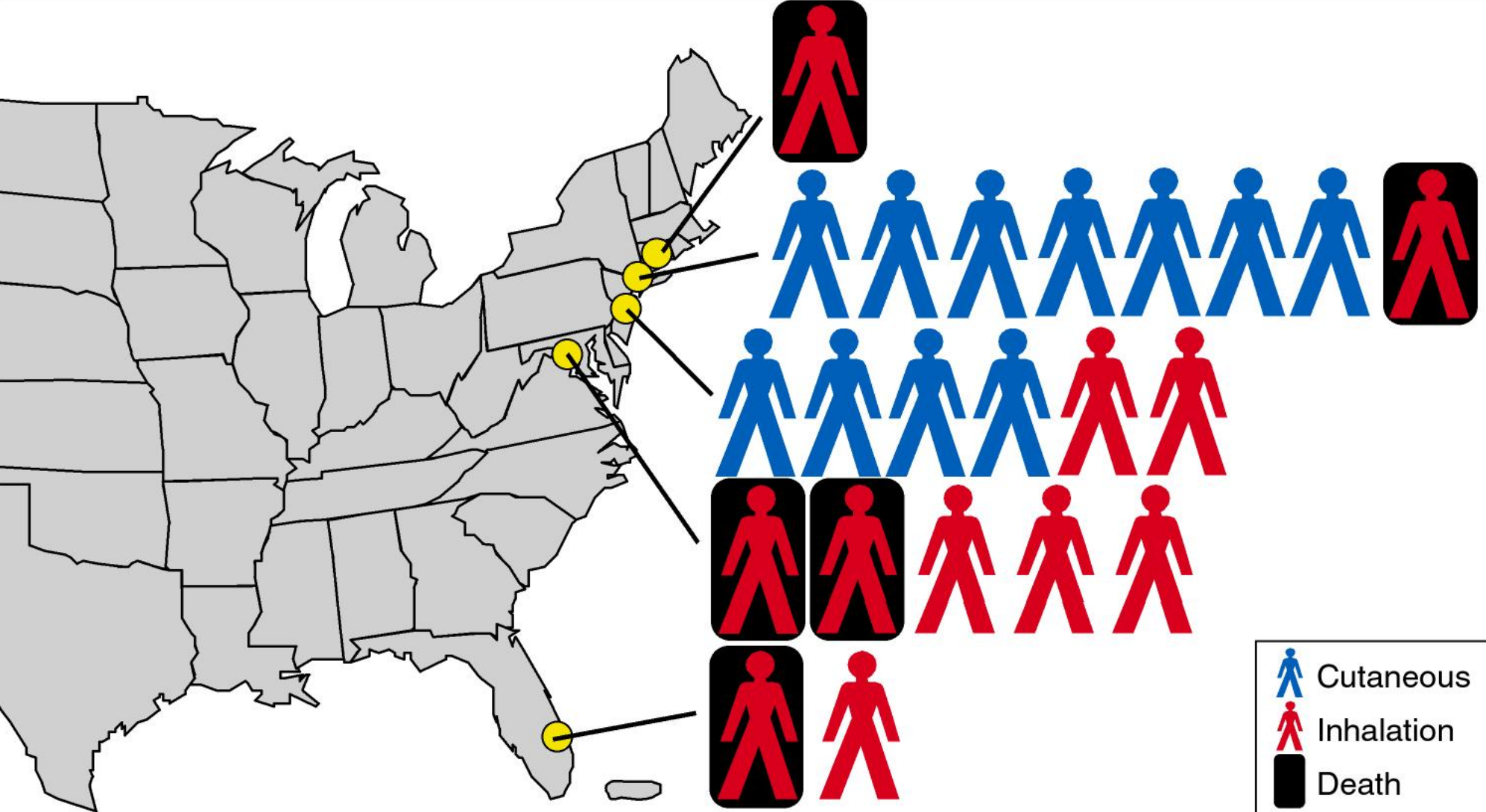
T. Oliphant et al.

- **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**





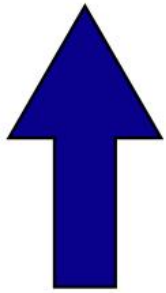
# 22 Anthrax Cases Associated with Bioterrorism: United States, 2001



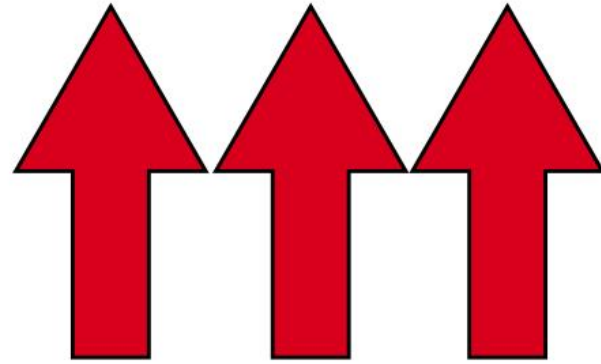
Source: CDC

# **The Anthrax Attacks of 2001**

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**Biological  
Impact**



**Fear and  
Disruption**





# The Washington Post

January 26, 2002

## Bush Proposes Record \$27.3 Billion Budget for NIH

*\$1.5 Billion Aimed At Bioterrorism*



President Bush will propose spending a record \$27.3 billion to fund the National Institutes of Health in 2003, enough to complete a five-year doubling of the agency's budget that began in 1998 and to jumpstart a major new NIH emphasis on bioterrorism. . .



## NIAID Strategic Plan for Biodefense Research



## NIAID Biodefense Research Agenda for CDC Category A Agents



## NIAID Biodefense Research Agenda for CDC Category A Agents

### Progress Report



August 2003



## NIAID Biodefense Research Agenda for Category B and C Priority Pathogens



## NIAID Biodefense Research Agenda for Category B and C Priority Pathogens

### Progress Report



June 2004



January 2003





**Therapeutics**



**Vaccines**



**Diagnostics**

**Biodefense  
Research  
Priorities**



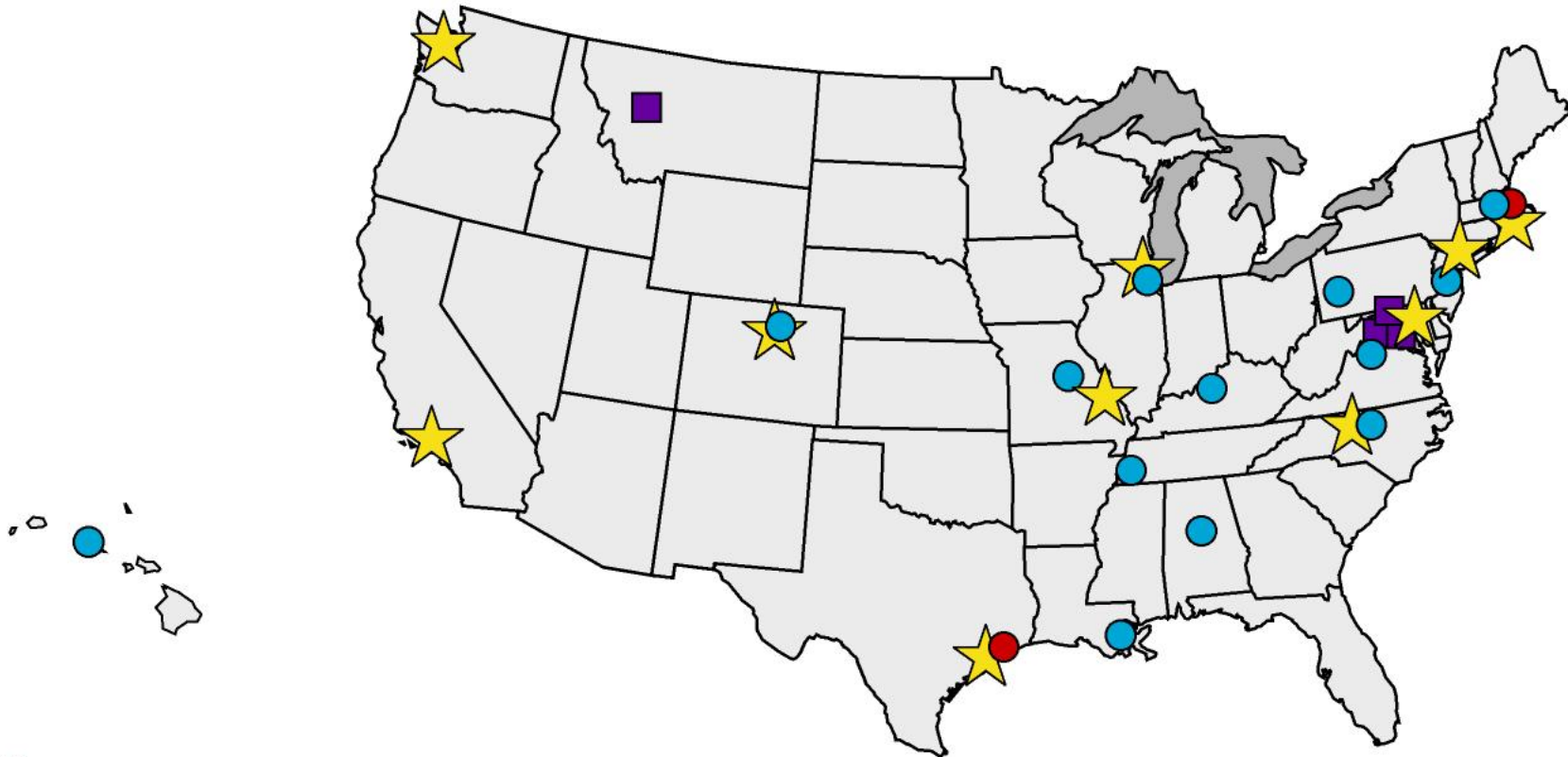
**Basic Research  
(including Genomics)**



**Expansion of  
Research Capacity**

# Expansion of Research Capacity for Emerging Infectious Diseases

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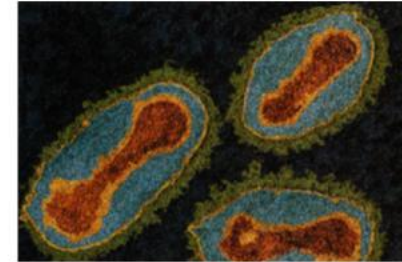
- National Biocontainment Laboratories (BSL4) - 2
- Regional Biocontainment Laboratories (BSL3) - 13
- ★ Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research - 10
- New NIH Facilities - 4

# Biodefense Countermeasures: Key Achievements

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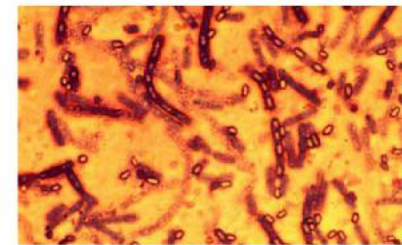
## ■ Smallpox

- Dryvax; MVA; antiviral drugs



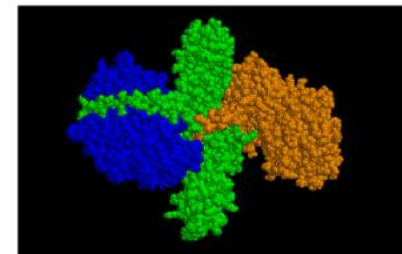
## ■ Anthrax

- rPA; antitoxins



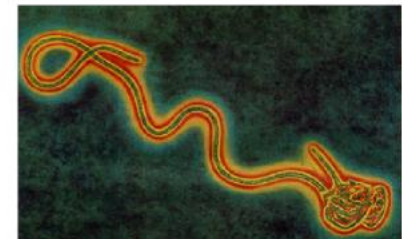
## ■ Botulinum

- Vaccine; antitoxins



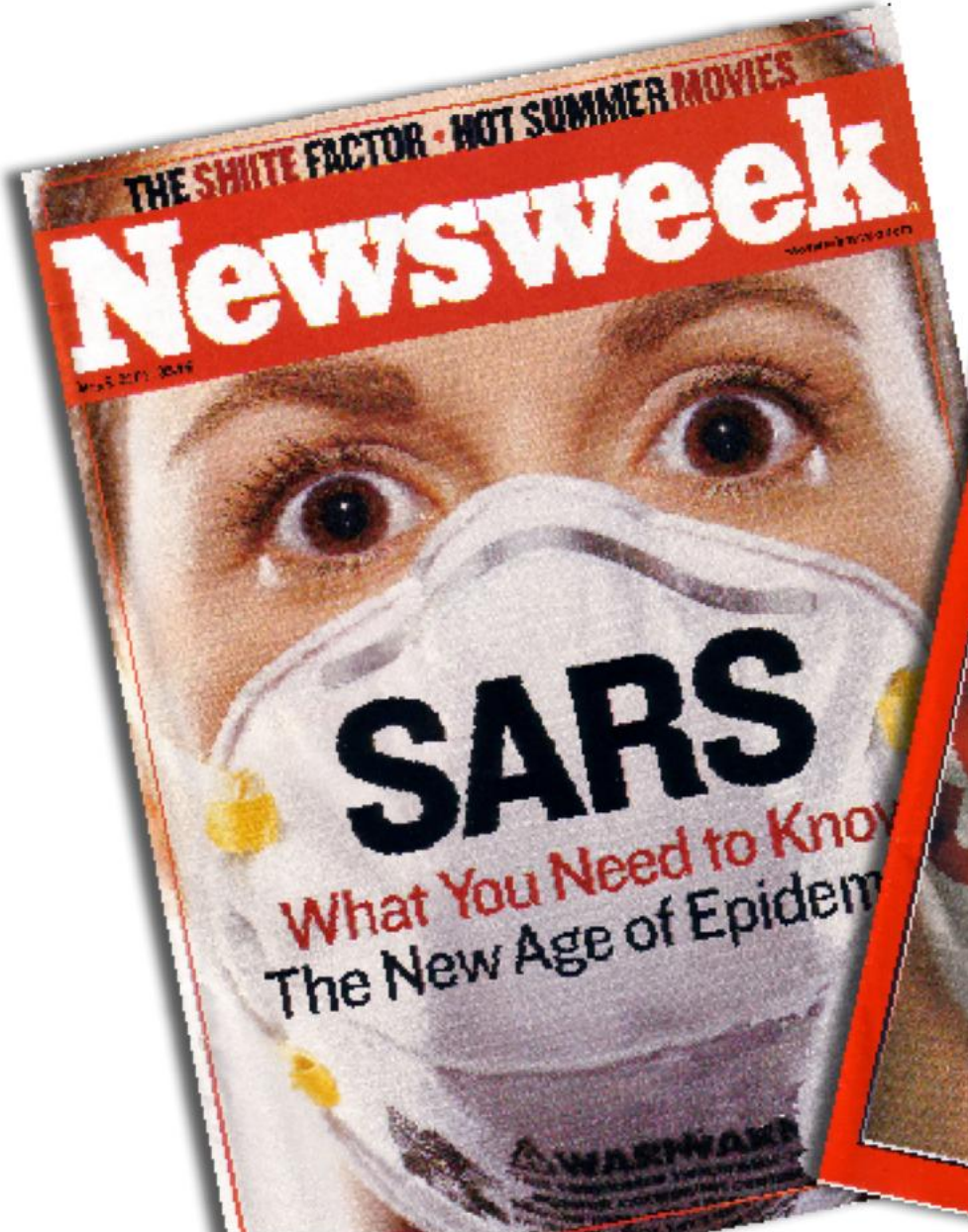
## ■ Ebola

- First human vaccine trials





# SARS: A New Challenge to Global Health





# Early Cases of SARS: Guangdong Province, China



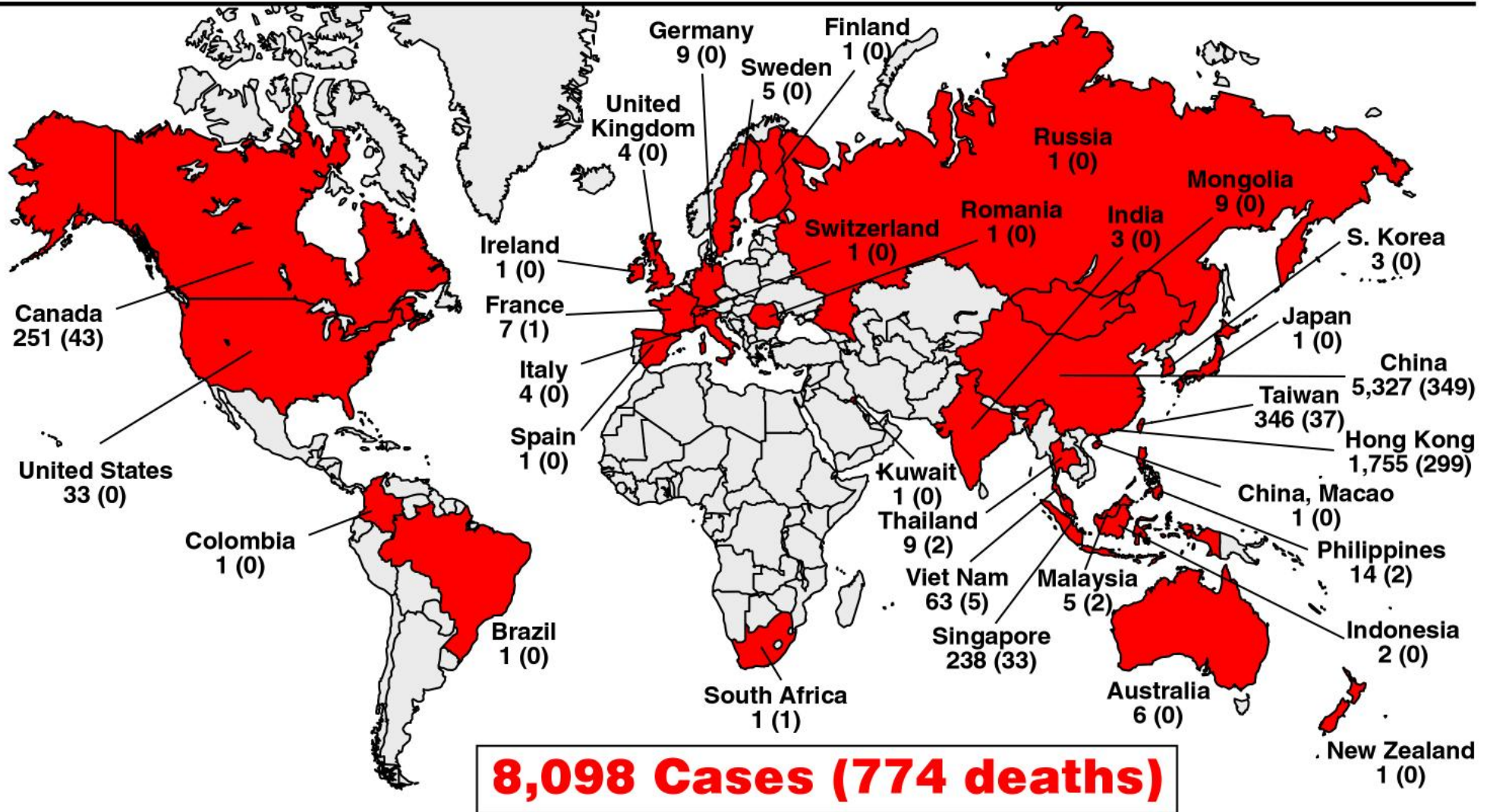
# Spread of SARS from Hotel Metropole



Source: MMWR, March 28, 2003



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



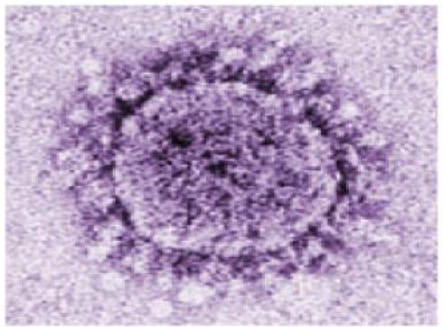
Source: WHO

# SARS Characterization and Vaccine Development



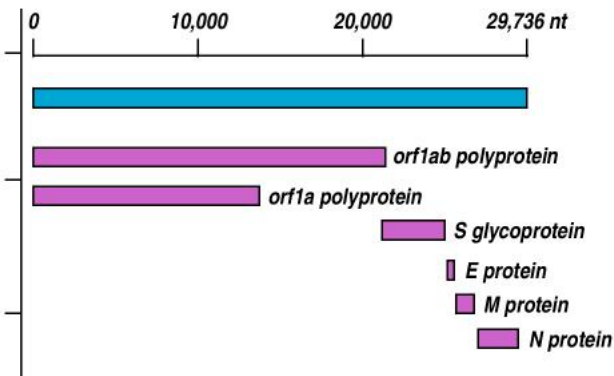
March 24, 2003

SARS CoV Discovered



April 14, 2003

SARS CoV Sequenced



March 31, 2004

SARS Vaccine Developed

**A DNA Vaccine Induces SARS Coronavirus Neutralization and Protective Immunity in Mice**  
 Zhi-yong Yang, Wing-pui Kong, Yue Huang, Anjeanette Roberts, Brian R. Murphy, Kanta Subbarao and Gary J. Nabel

December 13, 2004

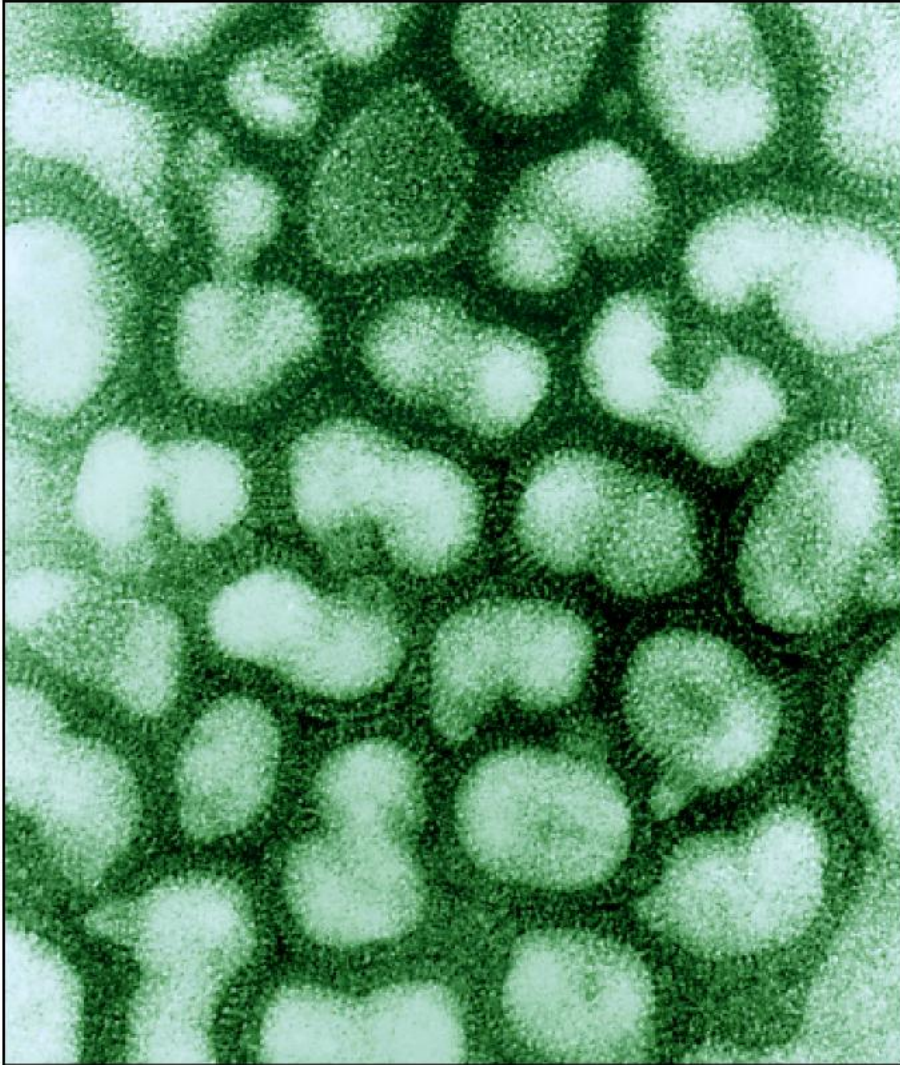
SARS Phase I Clinical Trial Initiated at NIAID VRC





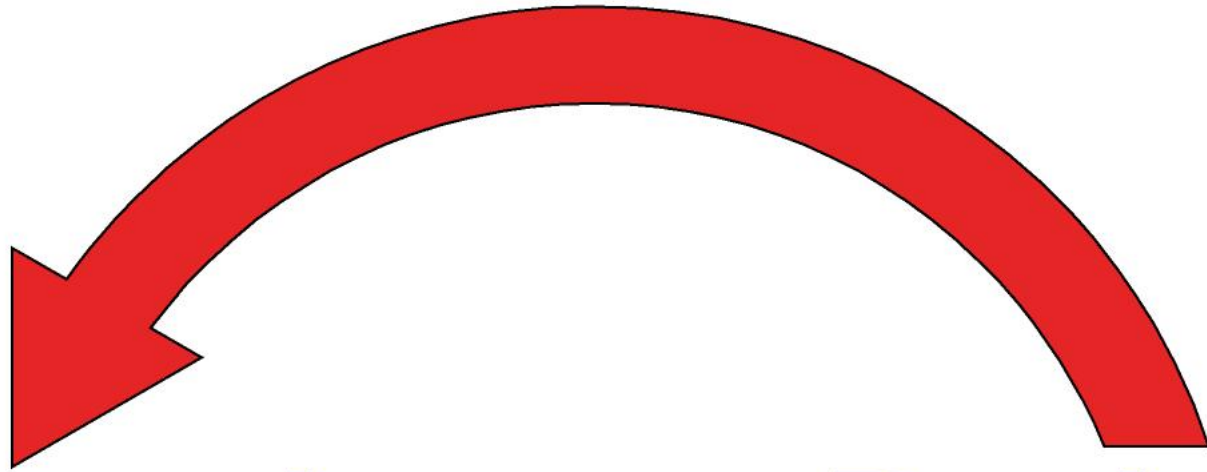
# Influenza

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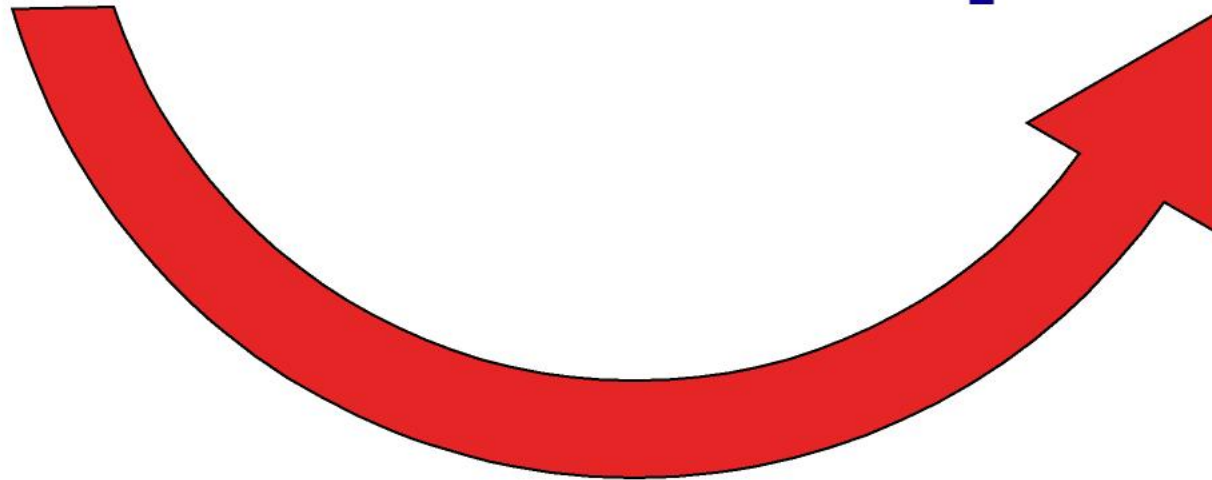
- **Re-emerging disease (interpandemic flu)**
- **Newly emerging disease (potential pandemic flu)**





**Seasonal  
Influenza  
Preparedness**

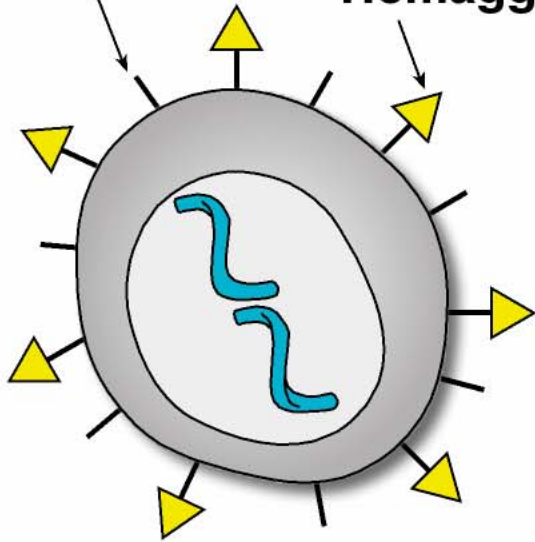
**Pandemic  
Influenza  
Preparedness**



# Influenza: Antigenic Drift and Shift

Neuraminidase (N)

Hemagglutinin (H)



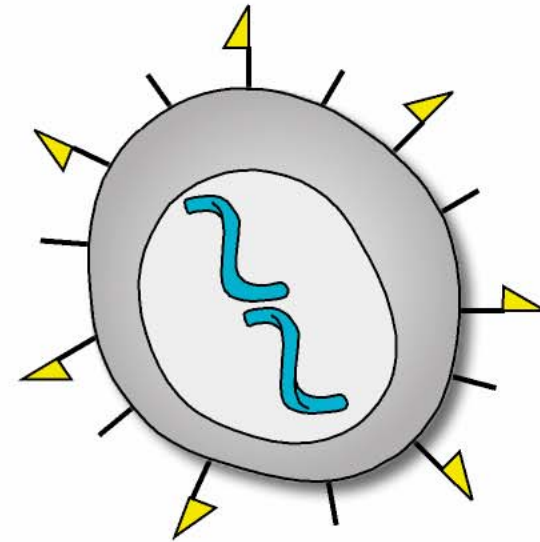
Influenza Virus



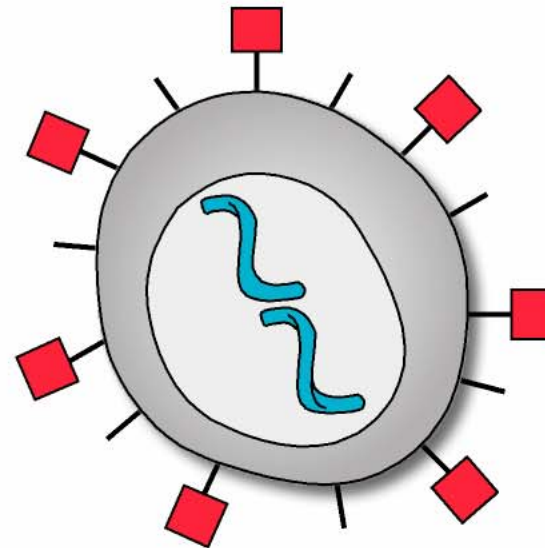
**Drift**



**Shift**



**Seasonal  
Influenza**



**Pandemic  
Influenza**

# **The Burden of Seasonal Influenza**

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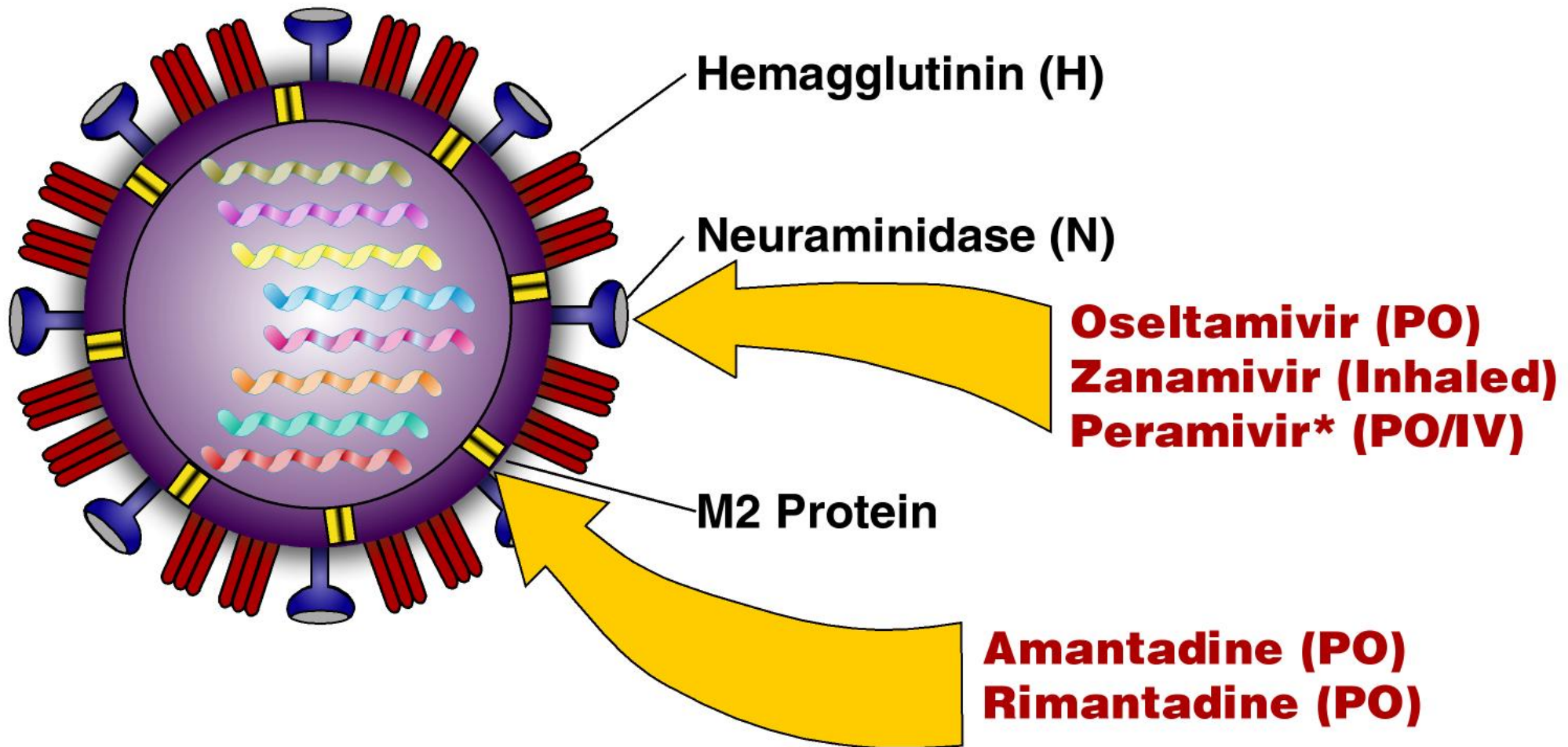
- **250,000 to 500,000 deaths globally/yr**
- **36,000 deaths and >200,000 hospitalizations/yr in U.S.**
- **\$37.5 billion in economic costs/yr in U.S. related to influenza and pneumonia**
- **Ever-present threat of pandemic influenza**

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



# Antiviral Therapies for Influenza

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\*Investigational

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

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	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

# The New York Times

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November 24, 2005

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## ***Drug Makers Plan Big Increase in Flu Vaccine for Next Fall***

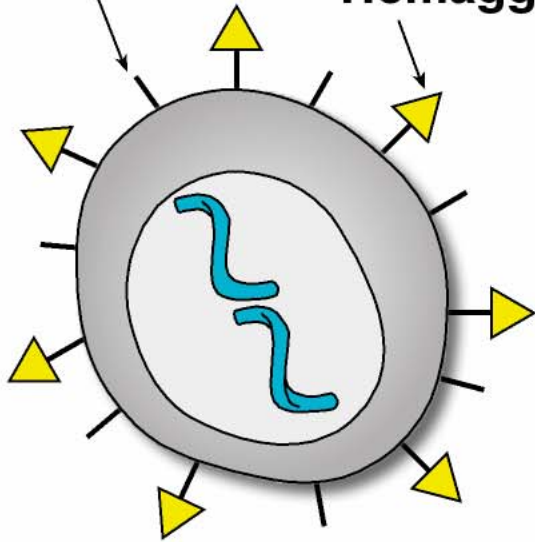
Pharmaceutical companies say they are preparing to produce as many as 120 million doses of flu vaccine for the next flu season, by far the most ever.



# Influenza: Antigenic Drift and Shift

Neuraminidase (N)

Hemagglutinin (H)



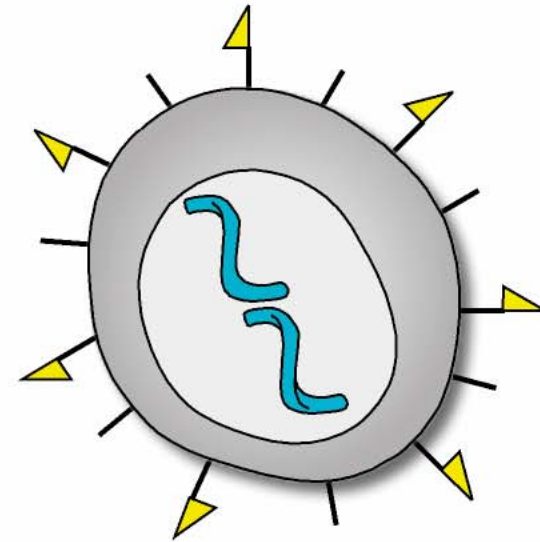
Influenza Virus



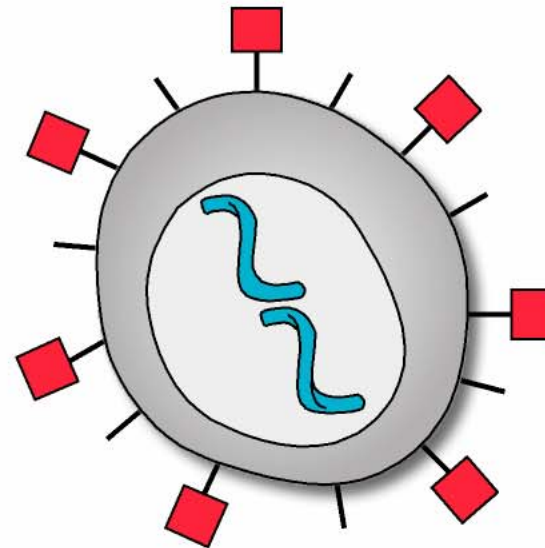
**Drift**



**Shift**



**Seasonal  
Influenza**

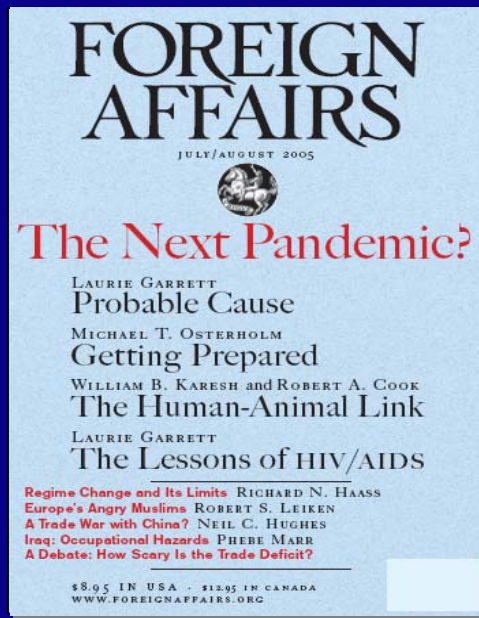
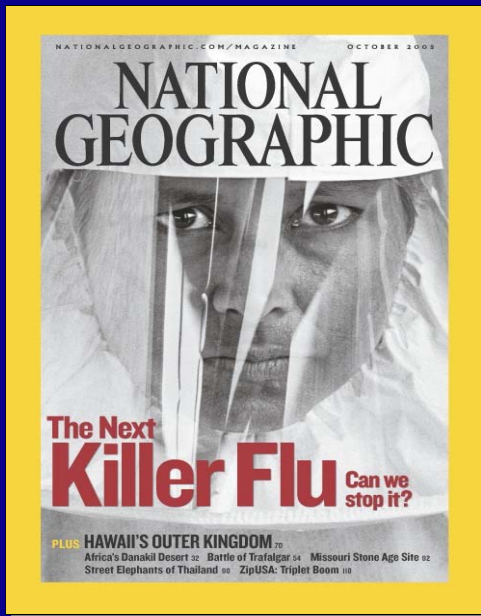


**Pandemic  
Influenza**

# Past Antigenic Shifts: Pandemics in the 20th Century

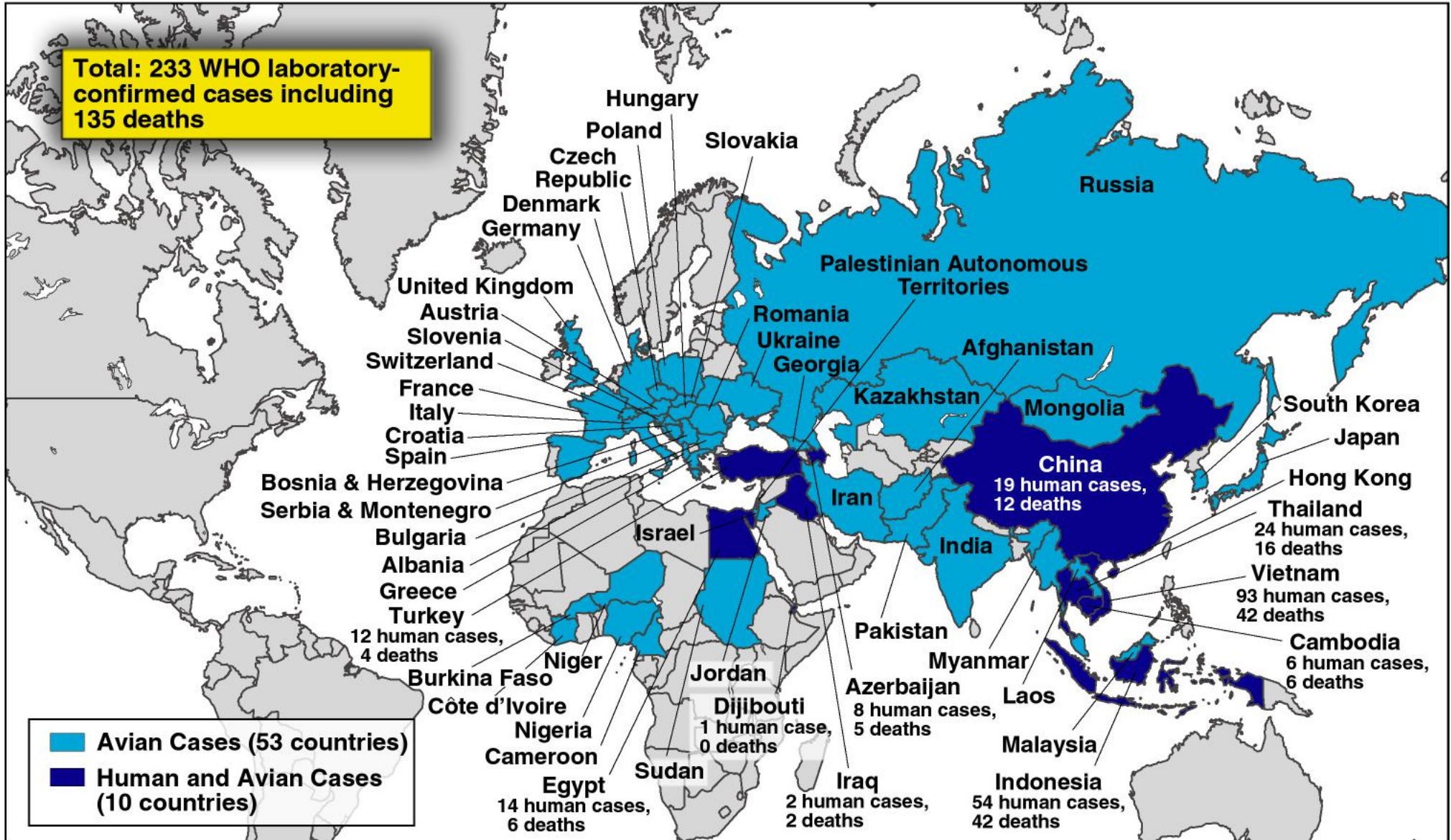
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			<b>Global Deaths</b>
<b>1918</b>	<b>H1N1</b>	<b>Spanish Flu</b>	<b>&gt;50 million</b>
<b>1957</b>	<b>H2N2</b>	<b>Asian Flu</b>	<b>1-2 million</b>
<b>1968</b>	<b>H3N2</b>	<b>Hong Kong Flu</b>	<b>700,000</b>





# H5N1 Influenza Cases, 2003-2006



Source: WHO and OIE (World Organization for Animal Health), 8/7/2006

# PNAS

Proceedings of the National Academy of Sciences of the United States of America

Published online before print July 31, 2006

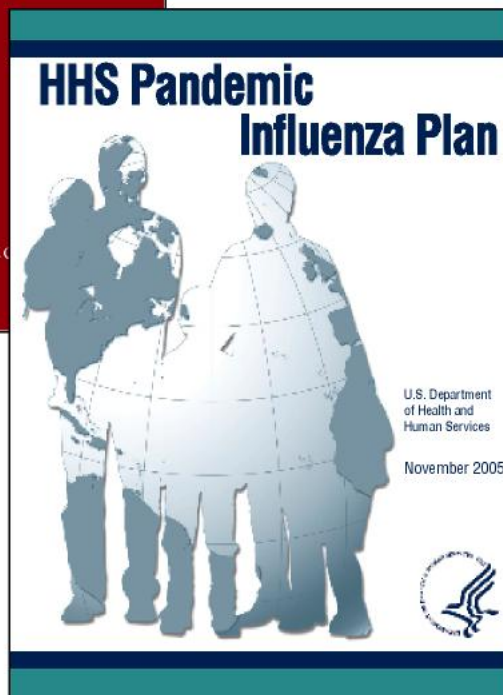
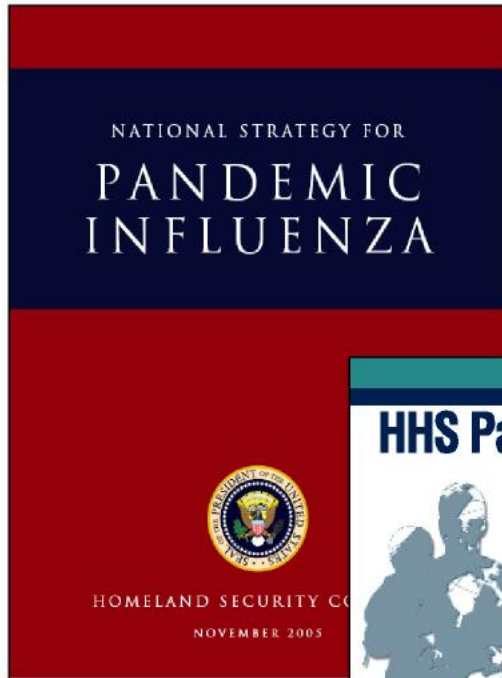
## **Lack of Transmission of H5N1 Avian-Human Reassortant Influenza Viruses in a Ferret Model**

TR Maines, LM Chen, Y Matsuoka, H Chen, T Rowe, J Ortin, A Falcón, NT Hien, LQ Mai, ER Sedyaningsih, S Harun, TM Tumpey, RO Donis, NJ Cox, K Subbarao, and JM Katz



# Pandemic Influenza Preparedness Strategy and Plan

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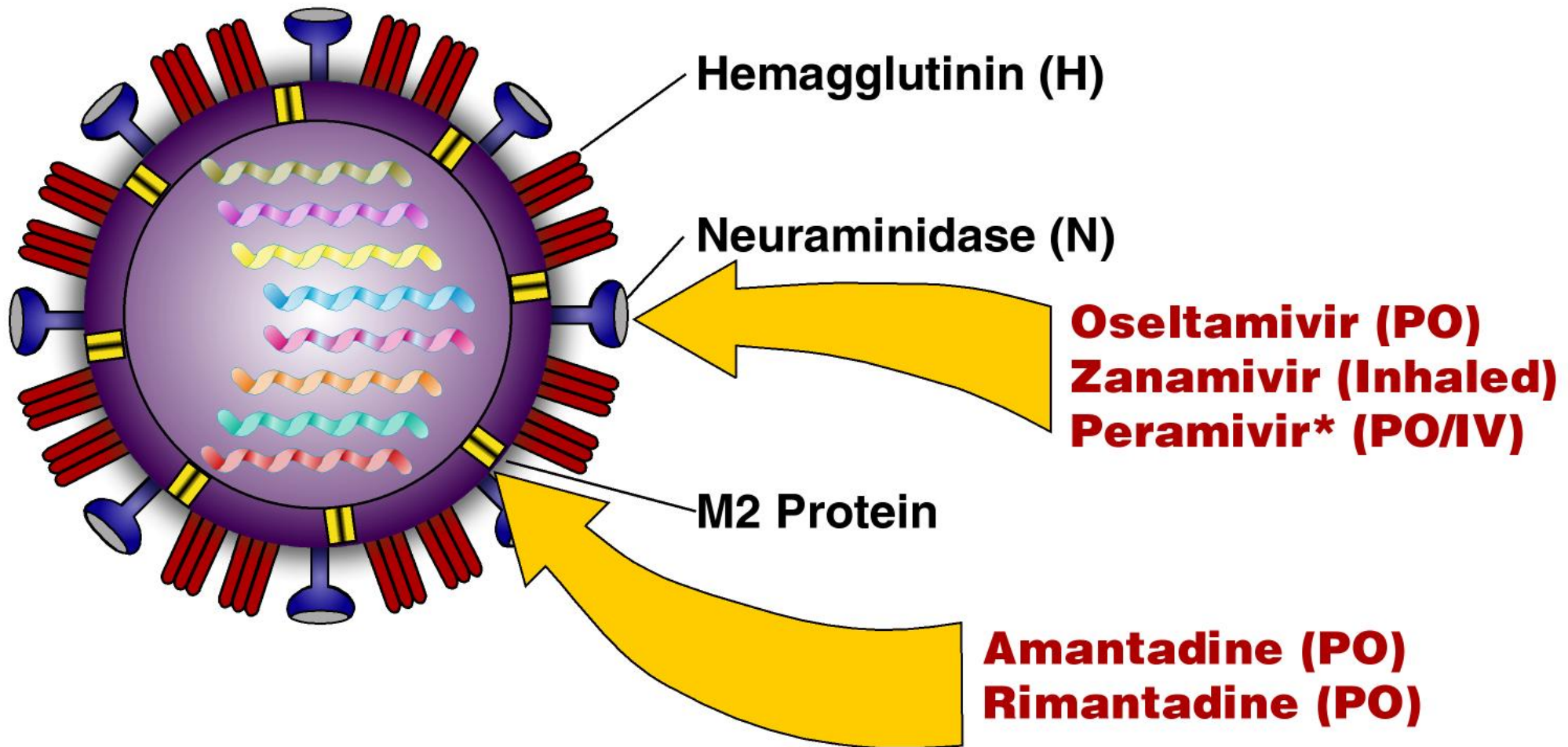


- **International Surveillance**
- **Domestic Surveillance**
- **Vaccine**
- **Antivirals**
- **Communications**
- **State and Local Preparedness**



# Antiviral Therapies for Influenza

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\*Investigational

# **Influenza Antivirals: Examples of Current and Planned Projects**

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- **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**

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- **Pre-pandemic**
- **Intra-pandemic**



# **Pre-Pandemic H5N1 Vaccine Evaluation: Preliminary Results**

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## **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**

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

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

**Reuters**

July 26, 2006

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*Low-Dose Glaxo Bird Flu Vaccine  
Works in Trial*

**GSK Announces H5N1 Vaccine Trial Results**

- Evaluated in 400 healthy adults, aged 18-60 years
- Safe and well-tolerated overall
- Achieved high immune response at a low dose of antigen
- 3.8 $\mu$ g antigen + proprietary adjuvant induced immune response predictive of protection in > 80% of subjects



# 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 16, 2005

## Vaccine

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

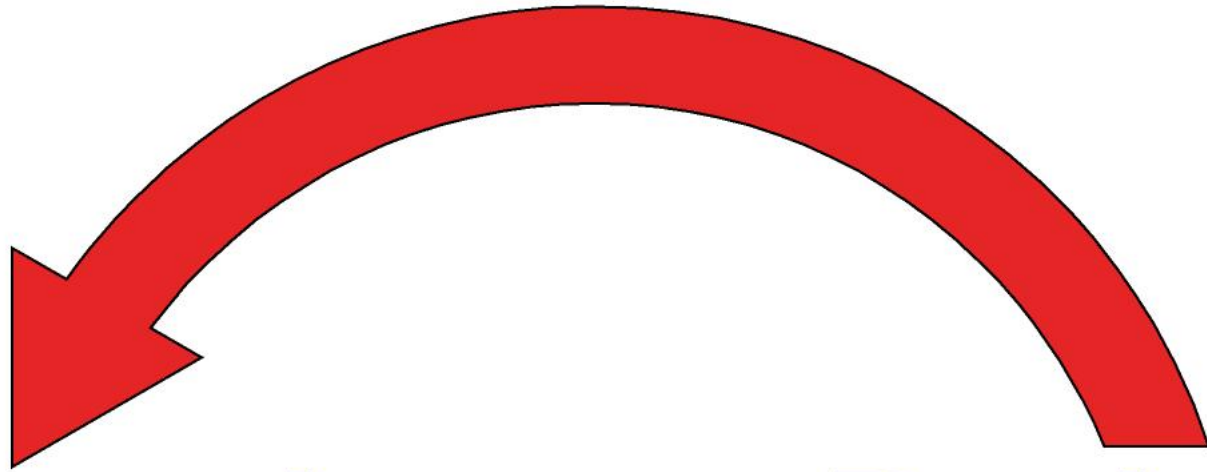
Epstein SL, Kong WP, Misplon JA, Lo CY, Tumpey TM, Xu L, Nabel GJ

January 30, 2006

## Vaccine

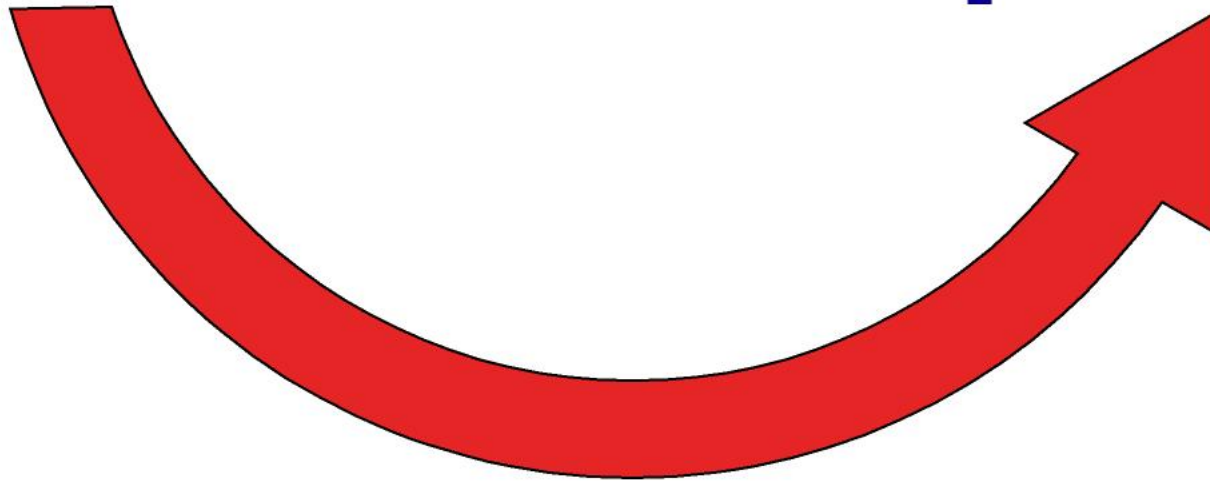
### **THE UNIVERSAL INFLUENZA VACCINE M2E-HBC ADMINISTERED INTRANASALLY IN COMBINATION WITH THE ADJUVANT CTA1-DD PROVIDES COMPLETE PROTECTION**

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



**Seasonal  
Influenza  
Preparedness**

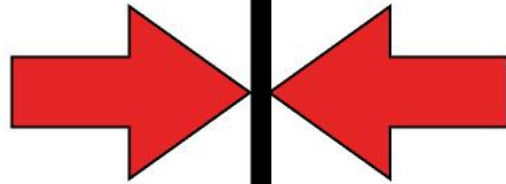
**Pandemic  
Influenza  
Preparedness**



# A Perpetual Struggle

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



**Public Health  
Measures,  
Biomedical  
Research, and  
Technological  
Advances**