AIDS Vaccine Research: A Perspective from the U.S. National Institutes of Health

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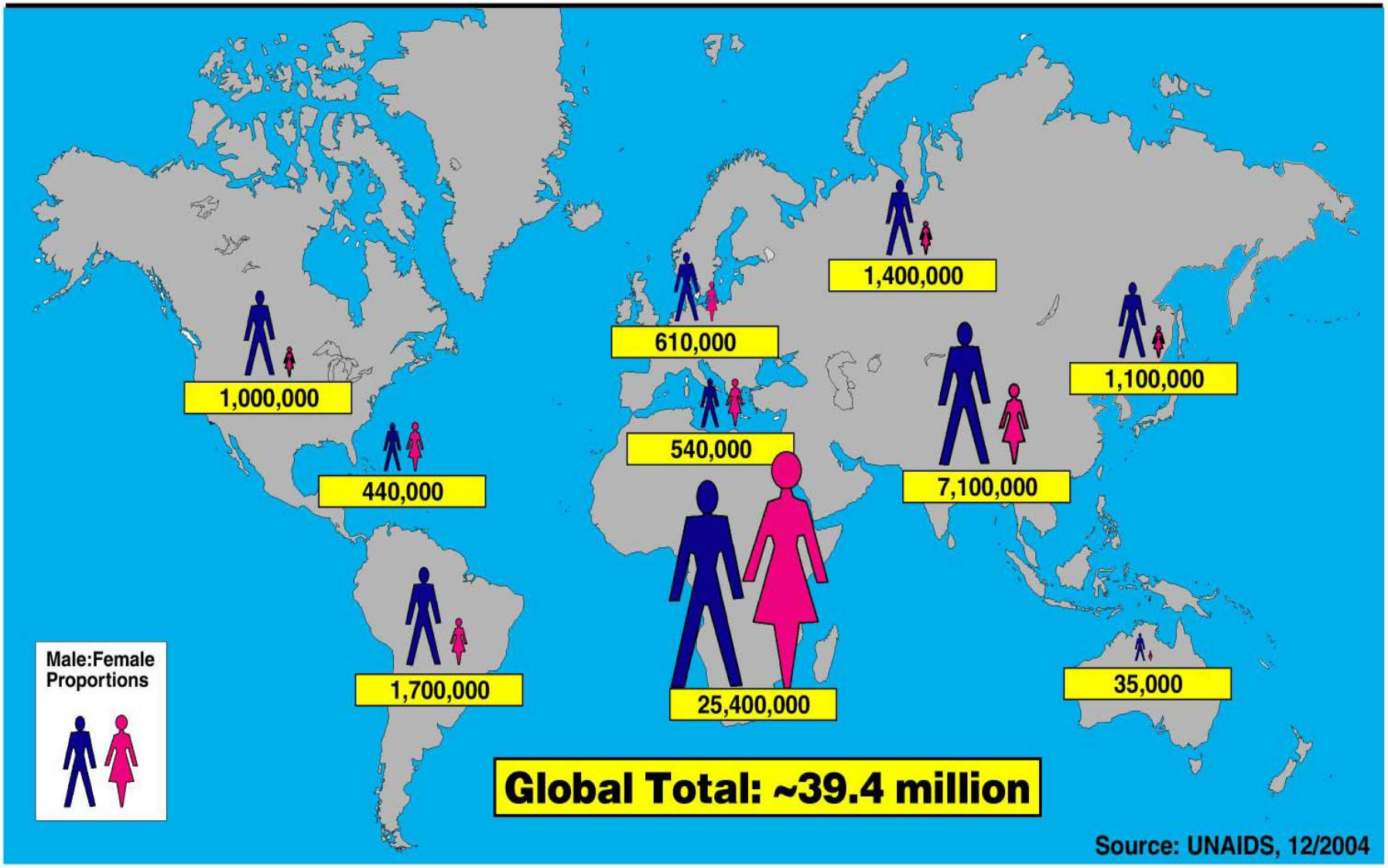
National Institute of Allergy and Infectious Diseases

National Institutes of Health

September 6, 2005

Estimated Number of Persons Living with HIV/AIDS, December, 2004



Estimated Number of Adults and Children Newly Infected with HIV During 2004

Source: UNAIDS, 12/2004

Approaches to HIV Prevention

- Interruption of transmission from mother to child
- Education and behavior modification
- Drug abuse treatment (e.g. methadone)
- Condoms, clean syringes
- Topical microbicides
- Treatment of other sexually transmitted diseases
- Antiretroviral therapy
- **Vaccination**

A Safe and Effective HIV Vaccine

- Critical to the effective control of HIV globally.
- The most important and difficult scientific challenge in AIDS research.

Duration Between Discovery of Microbiologic Cause of Selected Infectious Diseases and Development of a Vaccine

Disease	Years to Develop Vaccine
Typhoid	105
Haemophilus influenzae	92
Pertussis	89
Polio	47
Measles	42
Hepatitis B	16
HIV	22.....

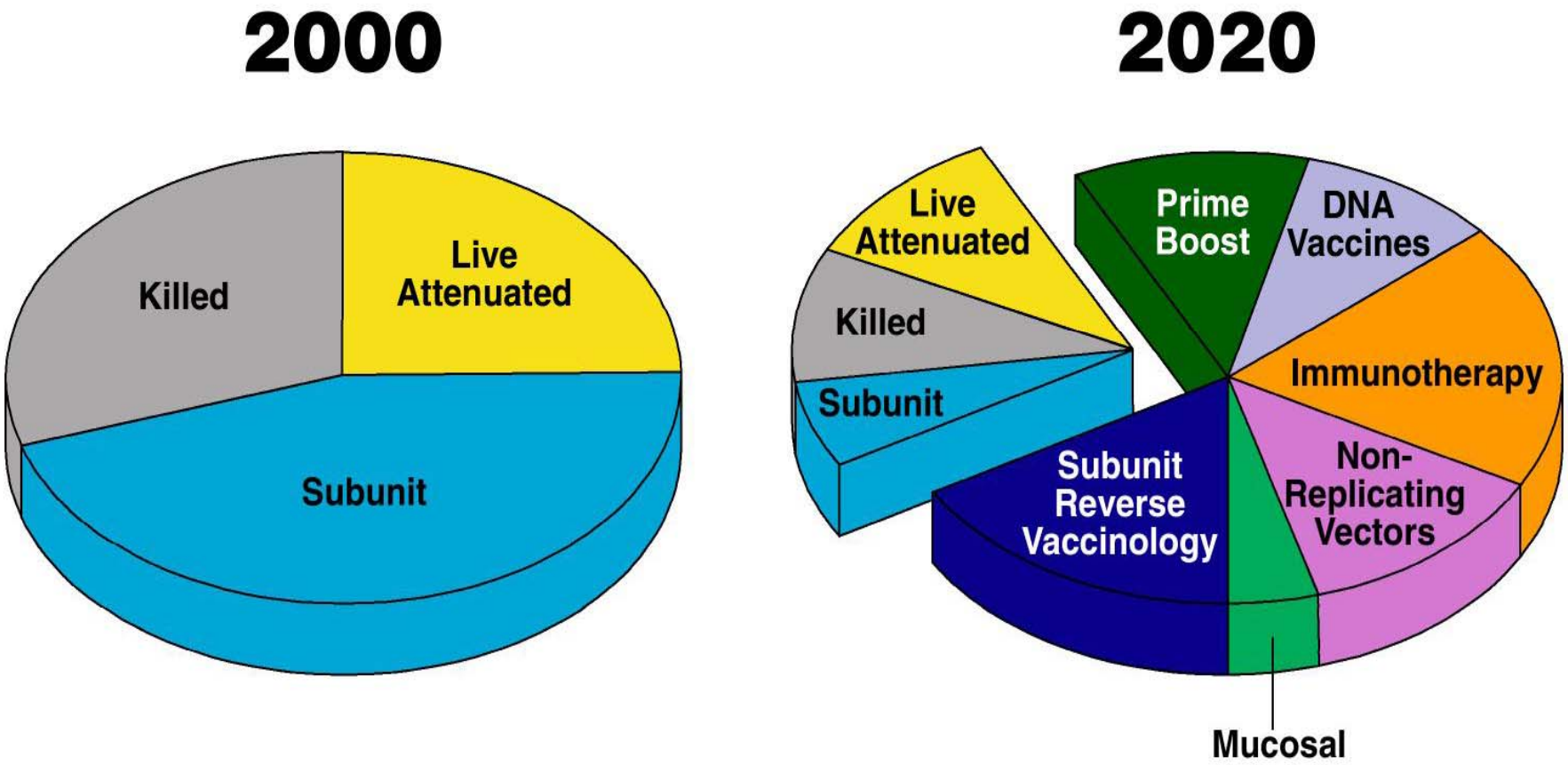
Source: H. Markel, NEJM, Aug. 25, 2005

The Impact of Vaccines in the United States

Disease	Baseline 20th Century Annual Cases	2003 Cases	Percent Decrease
Measles	503,282	56	99.9%
Diphtheria	175,885	1	99.9%
Mumps	152,209	231	99.9%
Pertussis	147,271	11,647	92.1%
Smallpox	48,164	0	100%
Rubella	47,745	8	99.9%
Haemophilus influenzae type b, invasive	20,000	32	99.9%
Polio, paralytic	16,316	0	100%
Tetanus	1,314	20	98.5%

Source: *MMWR* 4/2/99, 4/22/05

Type of Vaccines Licensed in 2000 and Those Predicted to be Available in 2020



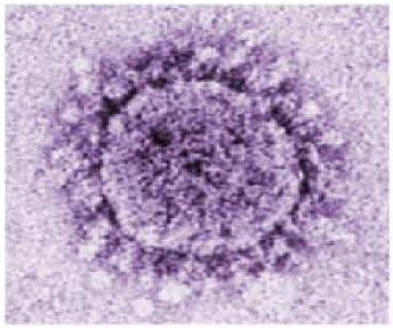
Source: Rappuoli, R. *Nature Med* 10:1177, 2004

SARS Characterization and Vaccine Development

2003 — 2004

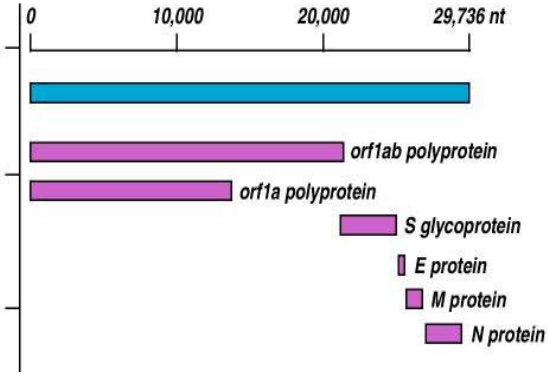
March 24, 2003

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

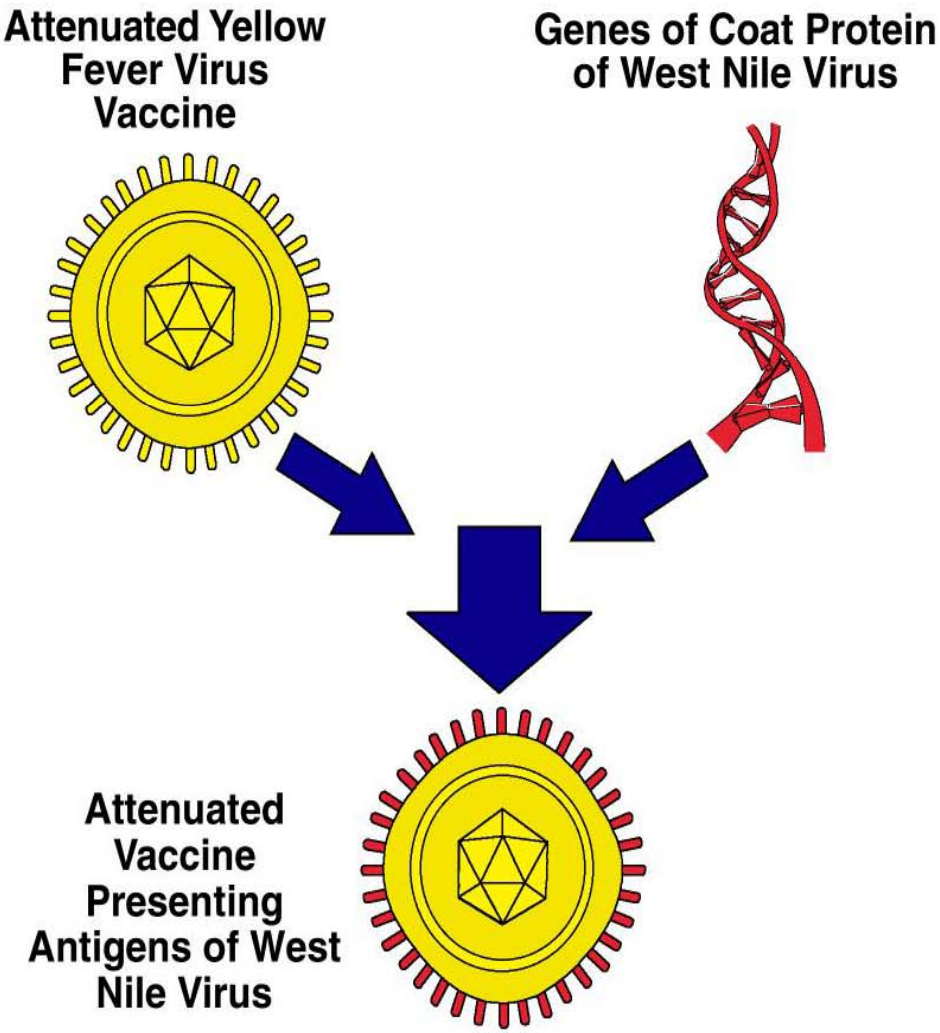
Zhi-yong Yang, Wing-pui Kong, Yue Huang, Anjeanette Roberts, Brian R. Murphy, Kanta Subbarao and Gary J. Nabel

December 13, 2004

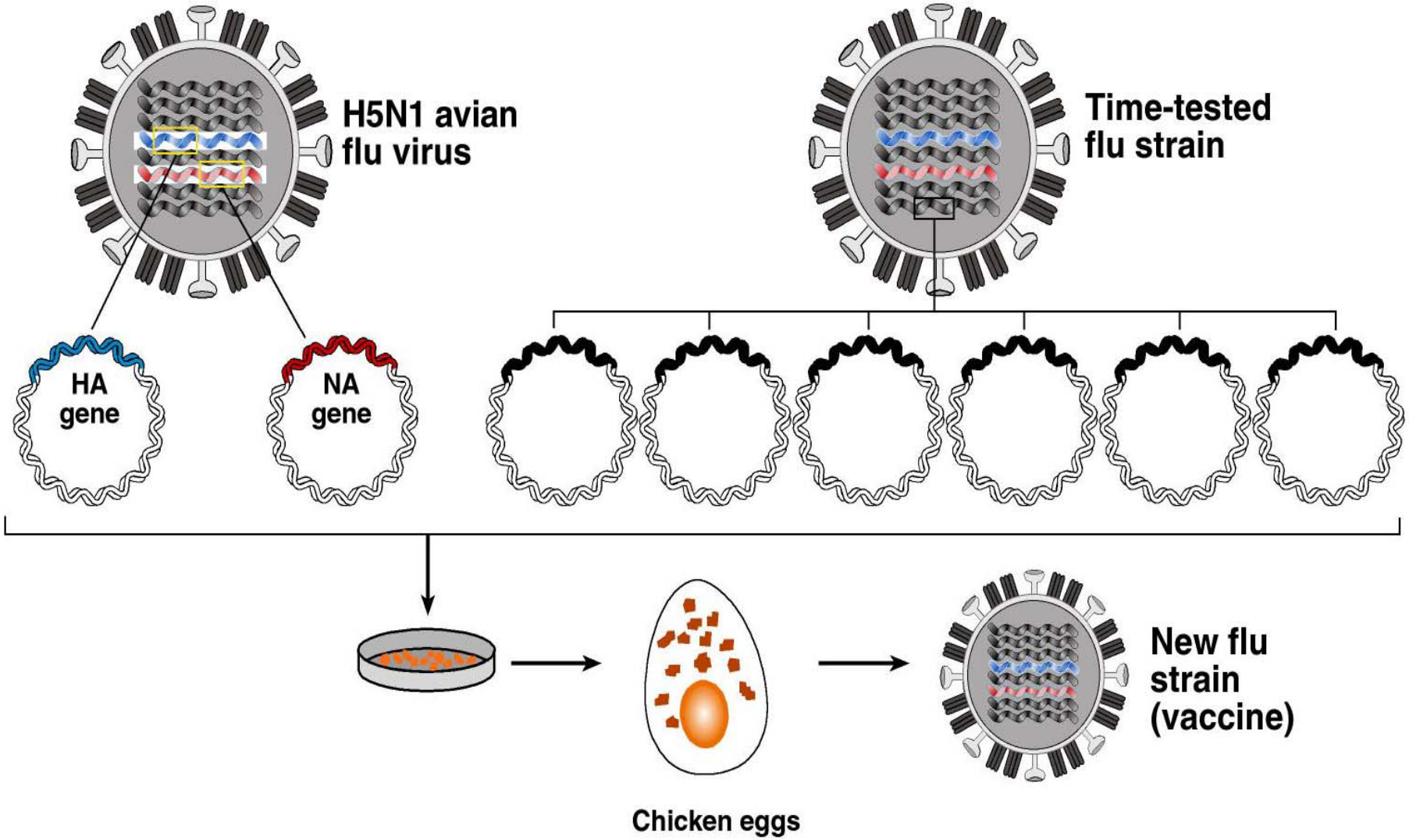
SARS Phase I Clinical Trial Initiated at NIAID VRC

Development of a "Chimeric" West Nile Virus Vaccine

Chimera of Arezzo, 6th century BC
(lion/goat/serpent)



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



Reuters

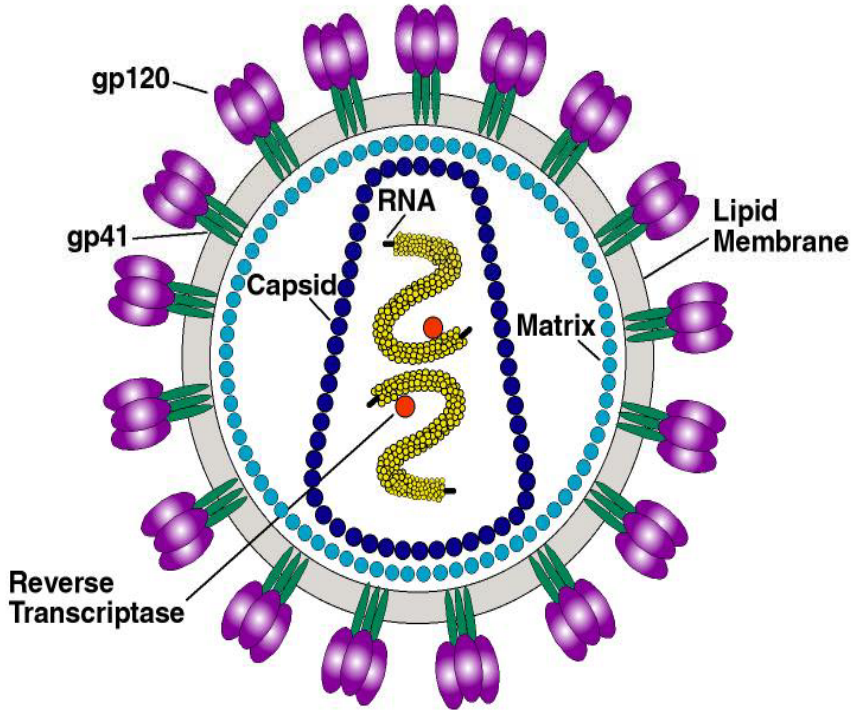
March 24, 2005

U.S. Starts Human Tests of Bird Flu Vaccine

Phase 1 trial on 450 adults will determine safety of shots

U.S. health officials said on Wednesday they have started human tests of a vaccine against avian flu, which experts believe could kill tens of millions of people if it becomes easily passed from person to person.

HIV is Different



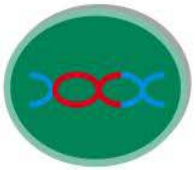
- The natural immune response to HIV is inadequate
- HIV hides from the immune system
- HIV targets and destroys the immune system
- HIV mutates rapidly

HIV Vaccines: A Timeline

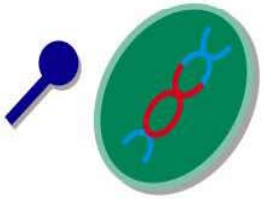
- AIDS recognized in 1981
- HIV identified as the cause of AIDS in 1983/1984
- First Phase I HIV vaccine trial in 1987
- From 1987-2004:
  - >80 Phase I/II trials of >30 candidate vaccines
  - 2 Phase III trials concluded, and one ongoing

The Spectrum of HIV Vaccine Strategies

Viral surface proteins



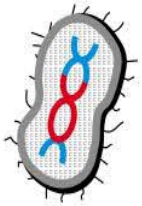
Live vector viruses



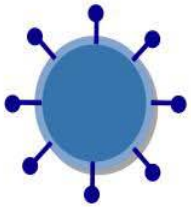
Combination of elements

Naked DNA

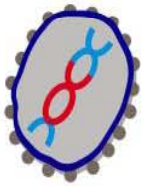
HIV peptides



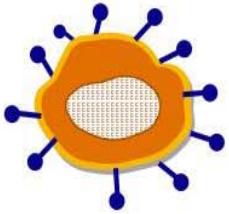
Live bacterial vectors



Pseudovirions



Replicons



Whole, killed HIV

Live, attenuated HIV

Progress in HIV Vaccinology

- Production of multiple candidate vaccines that stimulate anti-HIV immune responses
- Protection (partial) in animal models
- Safety and immunogenicity in human trials

Although We Face Many Operational, Social and Financial Obstacles in the Quest for an HIV Vaccine,

SCIENTIFIC CHALLENGES

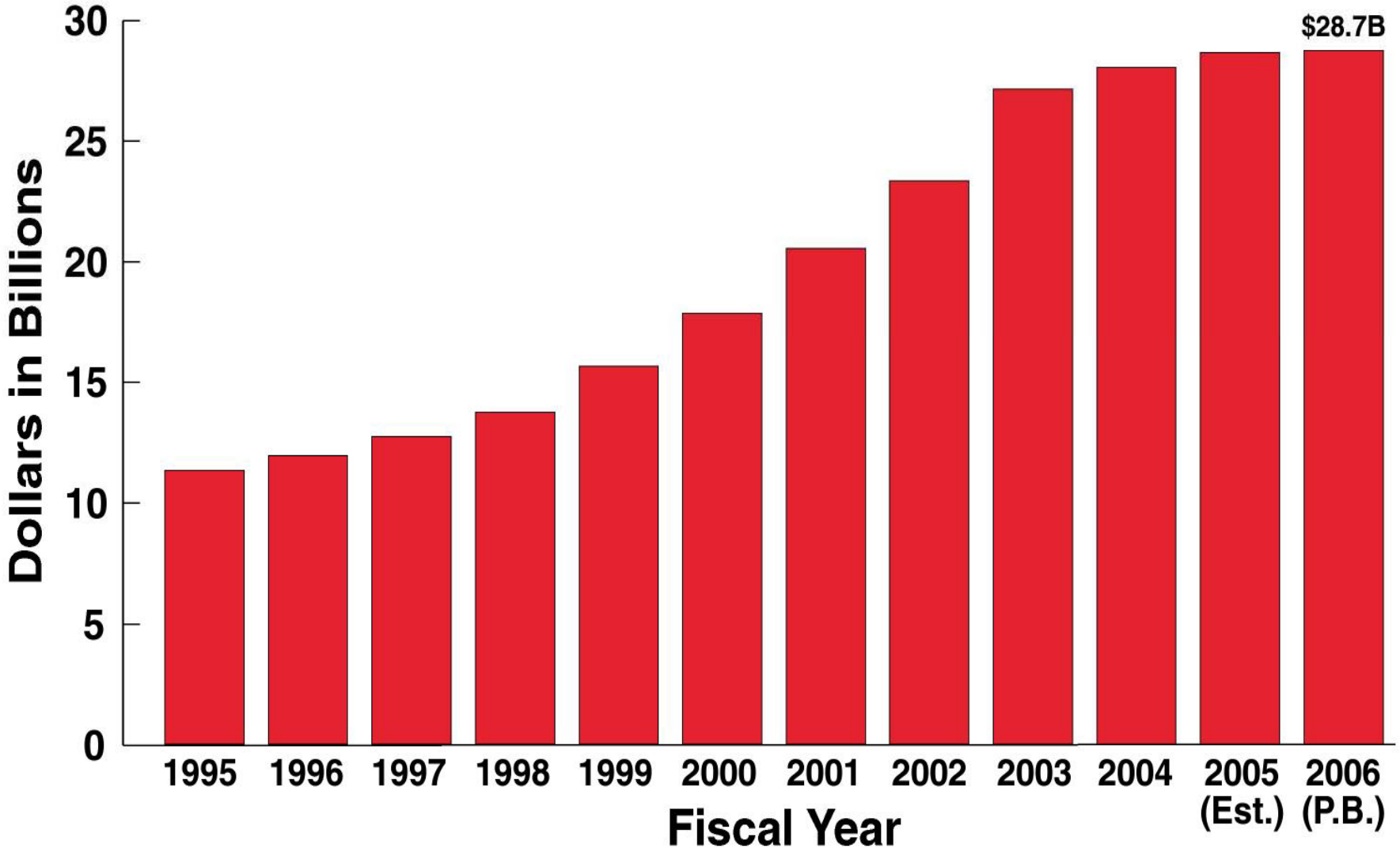
are the Most Significant Rate-Limiting Factors in HIV Vaccine Development Today.

NIH Scientific Priorities in HIV Vaccinology

- Continue fundamental research to inform vaccine design
  - Characterizing transmitted virus
  - Relationship of envelope structure and immunogenicity
  - Correlates of immune protection
  - Role of host factors in immune response
- Identify 'improved' vaccine designs
  - Broadly neutralizing, high titer Ab
  - Broad, high level cellular responses
  - Mucosal responses ?
- Identify and advance the most promising candidates
  - Evaluate potential immune correlates in efficacy trials

A Commitment to HIV Vaccine Research in an Era of Fiscal Constraint

NIH Funding History



National Institutes of Health
Budget Comparison by Institute/Center
(Dollars in Thousands)

IC	FY 2005 Enacted Conference	FY 2006 President's Budget	Percent Change
NIAID	$4,402,841	$4,459,395	1.3%
NCI	4,825,258	4,841,774	0.3%
NHLBI	2,941,201	2,951,270	0.3%
NHGRI	488,608	490,959	0.5%
NIDA	1,006,419	1,010,130	0.4%
Other IC's	14,146,550	14,201,359	0.4%
Subtotal	$27,810,877	$27,954,887	0.5%
NLM	315,146	318,091	0.9%
OD	358,046	385,195	7.6%
B&F	110,288	81,900	-25.7%
Total	$28,594,357	$28,740,073	0.5%

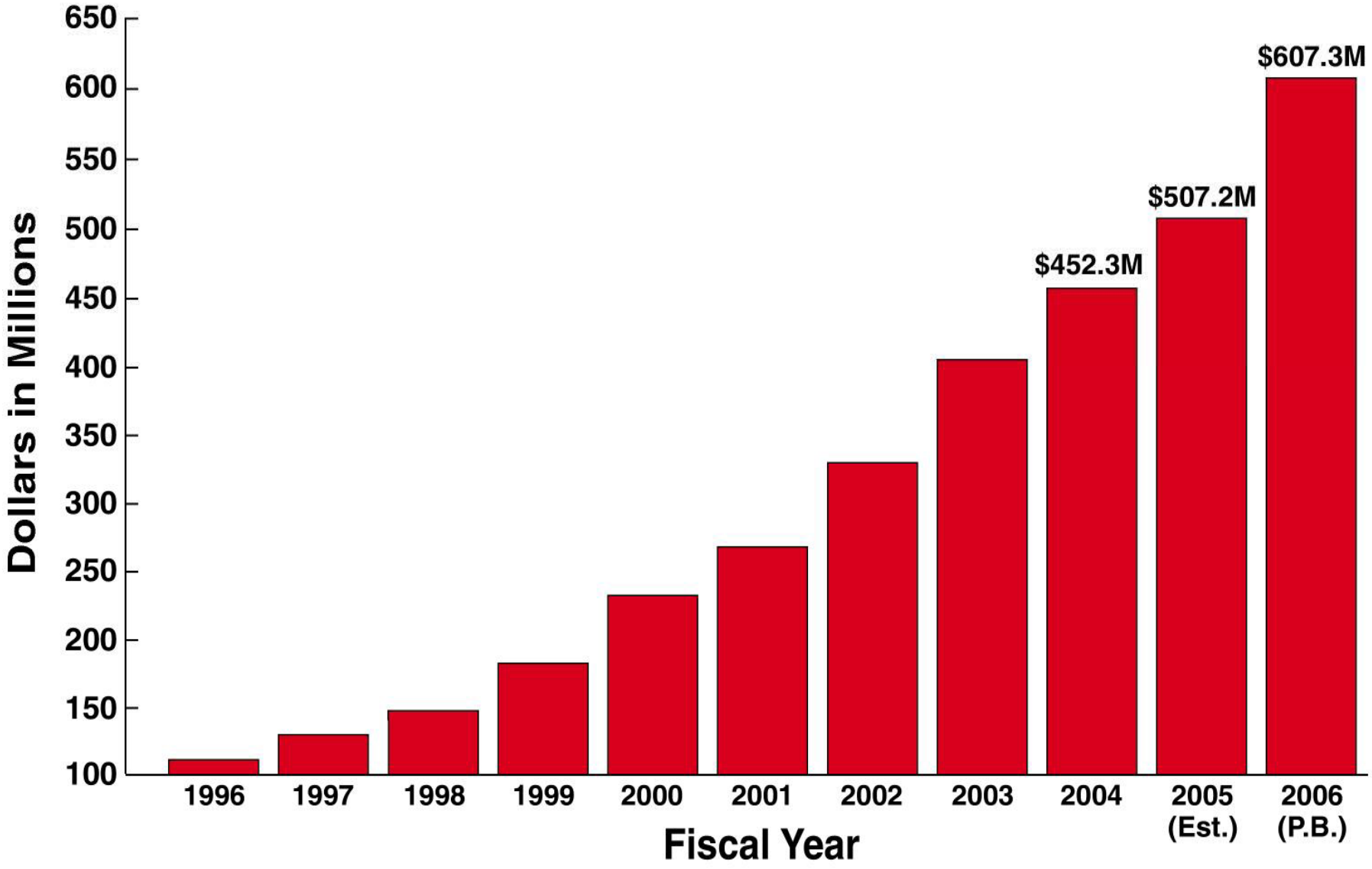
FY 2005 includes $99.2M for the Global Fund and $14.4M for the virtual VRC.
FY 2006 includes $100.0M for the Global Fund and $34.0M for the virtual VRC.

Five High Priorities of NIH FY 2006 Budget

- HIV Vaccine Development
- Research Project Grants - preserve to the greatest extent possible the ability of scientists to obtain individual support
- The Roadmap for Medical Research
- Biodefense Research
- Neuroscience Blueprint

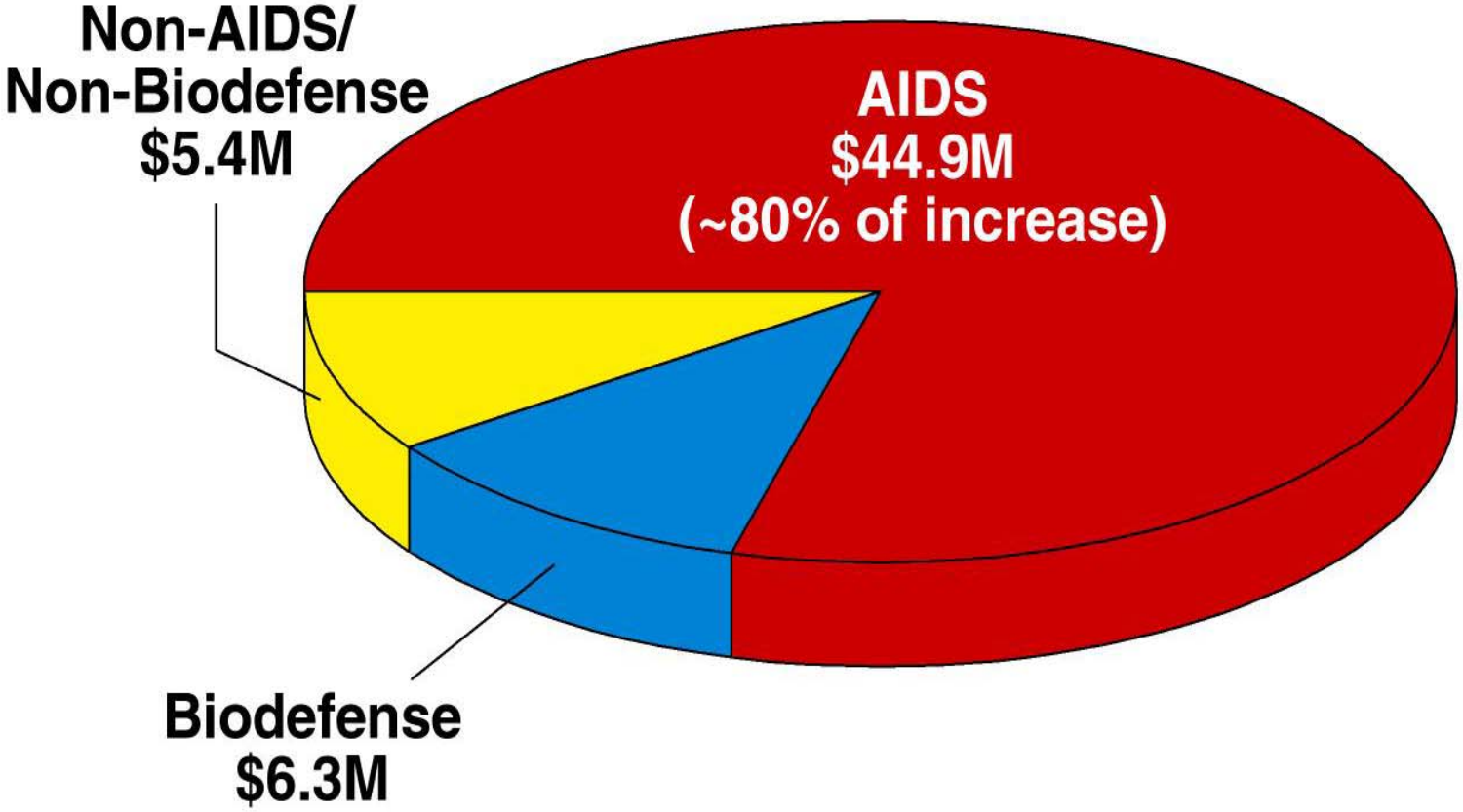
Testimony of NIH Director Elias A. Zerhouni, M.D, to the Senate Subcommittee on Labor-HHS-Education Appropriations, April 6, 2005.

NIH HIV Vaccine Research Funding



Increase in NIAID Budget, FY 2005 (est.) to FY 2006 (P.B.)

Total Increase: $56.6M



THE LANCET

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Volume 348 October 12, 1996

Biomedical Research in an Era of Unlimited Aspirations and Limited Resources

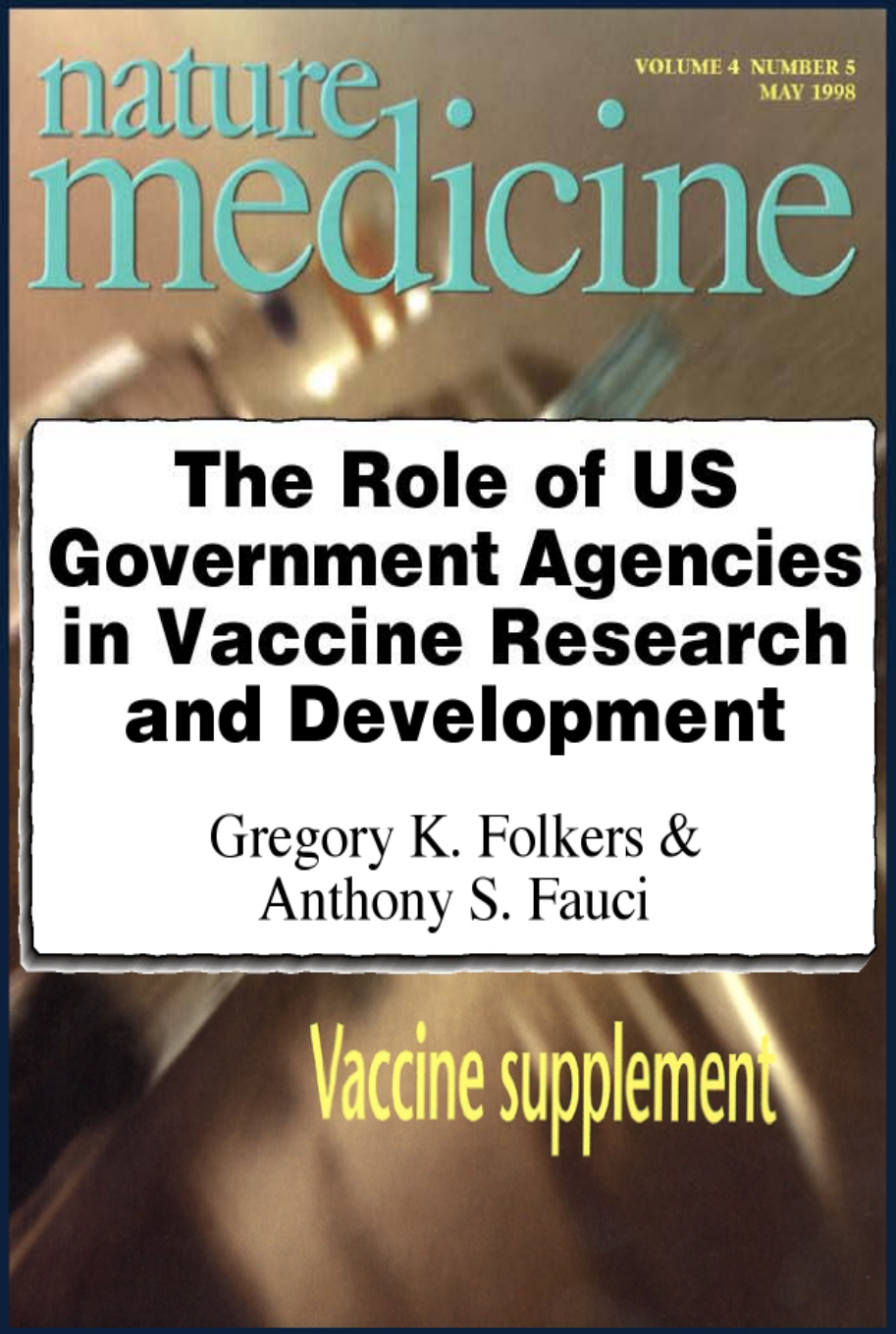
Anthony S. Fauci

"Resources for biomedical research in general are unlikely to increase substantially in the foreseeable future, and in some areas will be constrained. Yet the opportunities for advances in knowledge and the practical application of these advances will surely increase. Hence, the dichotomy between aspirations and resources will probably widen."

Need for Portfolio Analysis and Re-Examination of Priorities

The Necessity for Collaboration

- No one sector can single-handedly address the complex challenges -- scientific, technical, social, economic and political -- involved in product development.

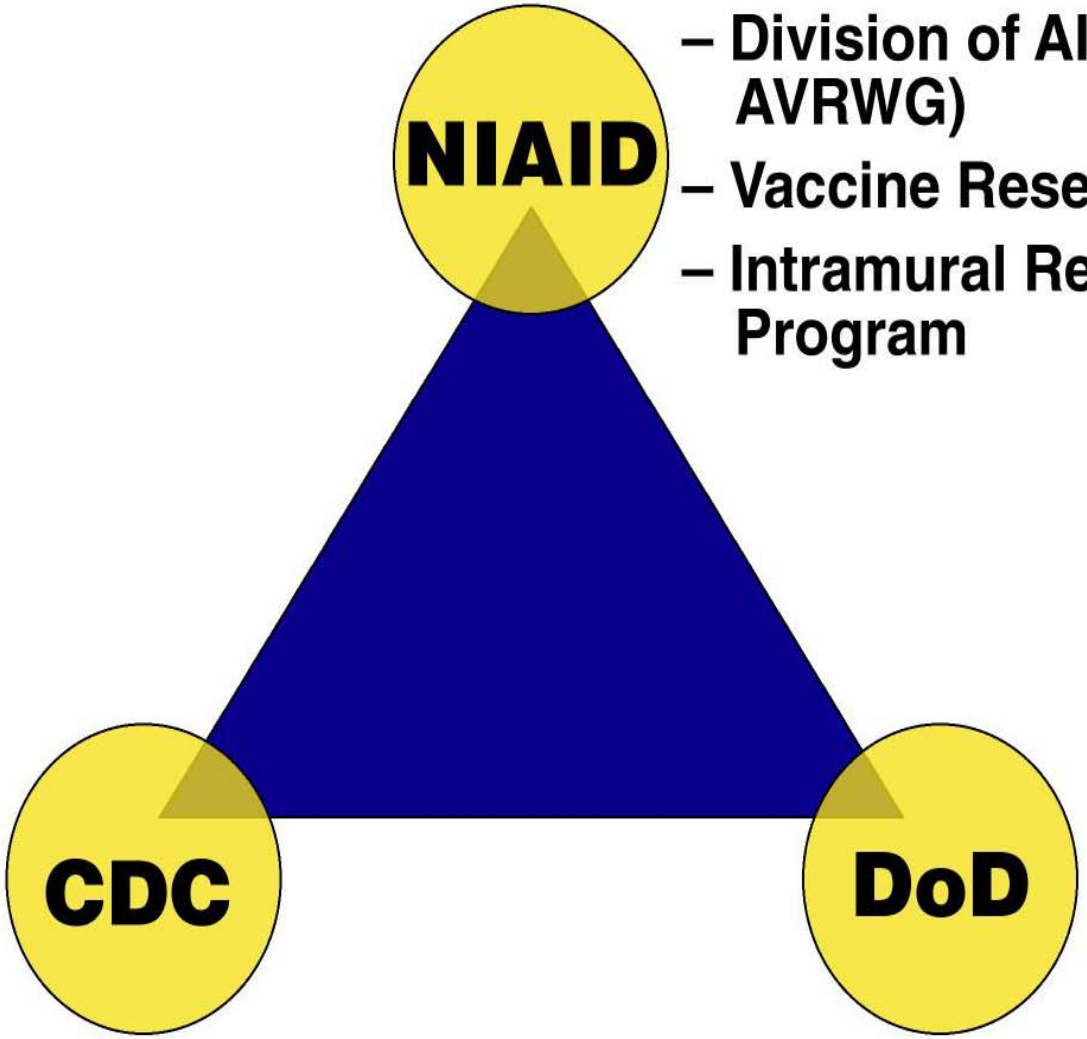


"The various partners in vaccine development bring perspectives, resources and skills that are sometimes unique, but more often overlapping and complementary."

Necessary Steps

- Collaborate/Cooperate
- Harmonize
- Achieve Economies of Scale
- Eliminate Duplication
- Standardize
- Consolidate Clinical Trials Networks
- Push for Tangible Results, i.e. Products

Partnership for AIDS Vaccine Evaluation (PAVE)



- Division of AIDS (HVTN, AVRWG)
- Vaccine Research Center
- Intramural Research Program

Science
27 June 2003
Vol. 300 No. 5628
Pages 1989–2124 $10

The Need for a Global HIV Vaccine Enterprise

R.D. Klausner, A.S. Fauci, L. Corey, G.J. Nabel, H. Gayle, S. Berkley, B.F. Haynes, D. Baltimore, C. Collins, R.G. Douglas, J. Esparza, D.P. Francis, N.K. Ganguly, J.L. Gerberding, M.I. Johnston, M.D. Kazatchkine, A.J. McMichael, M.W. Makgoba, G. Pantaleo, P. Piot, Y. Shao, E. Tramont, H. Varmus, J.N. Wasserheit

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Published online January 18, 2005

Policy Forum

The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan

Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise

www.plosmedicine.org

What is the Global HIV Vaccine Enterprise?

- A **virtual consortium** of independent organizations committed to accelerating the development of a preventive vaccine for HIV/AIDS.
- Enterprise partners will advance HIV vaccine research and development through:
  - the implementation of a shared strategic scientific plan
  - mobilization of additional resources
  - greater collaboration among HIV vaccine researchers worldwide.

"A plan to coordinate global HIV vaccine research got a moral boost last week when the leaders of the world's richest countries endorsed the Global HIV Vaccine Enterprise at the G8 summit in Sea Island, Georgia."

AIDS VACCINES

G8 Leaders Endorse Global Effort

The White House
PRESIDENT GEORGE W. BUSH

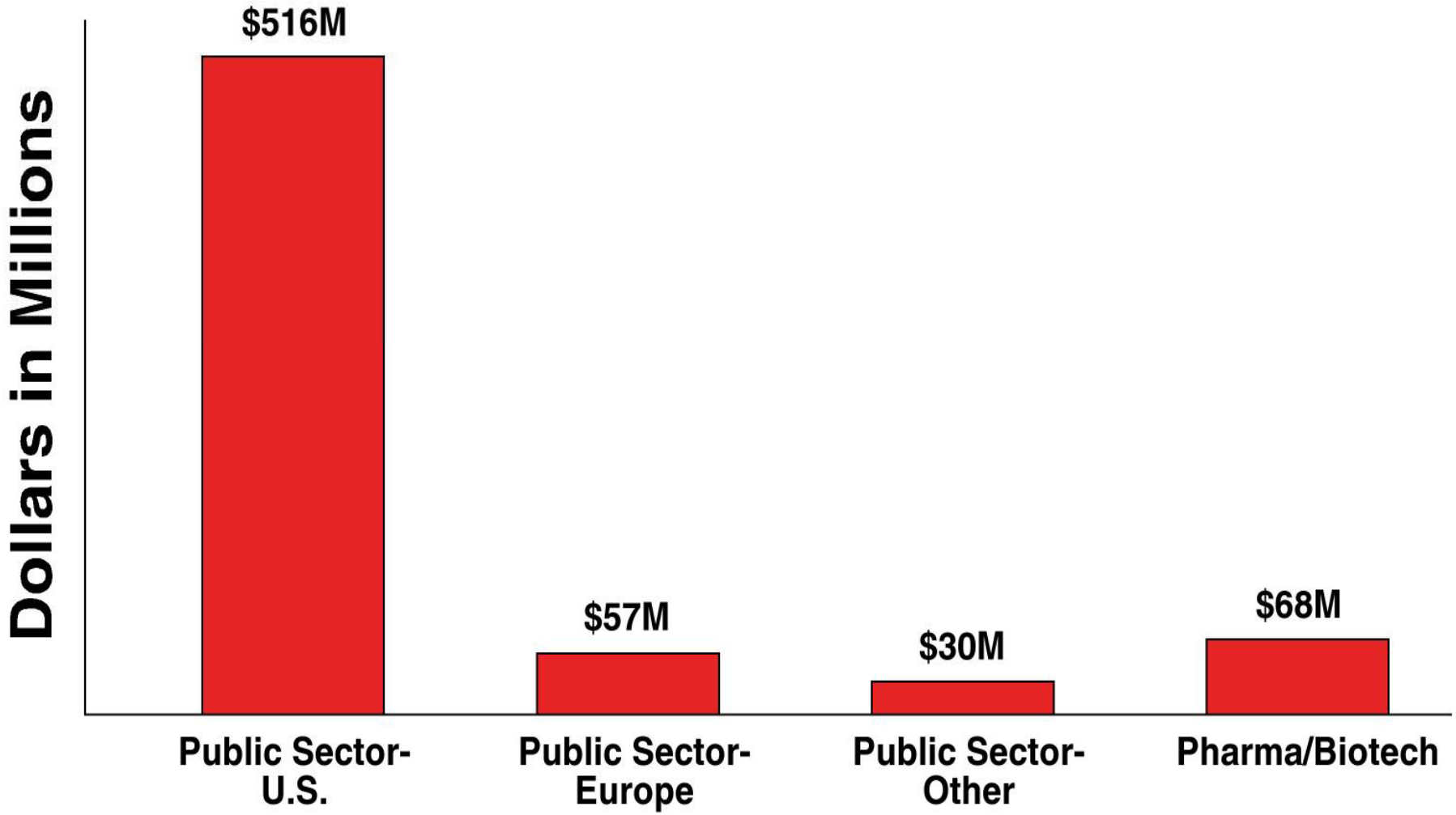
For Immediate Release
Office of the Press Secretary
June 10, 2004

Global HIV Vaccine Enterprise

Presidential Action

President Bush led the G-8 today in endorsing the establishment of a Global HIV Vaccine Enterprise, a virtual consortium to accelerate HIV vaccine development. The President also announced plans to establish a second HIV Vaccine Research and Development Center in the U.S., and urged his G-8 counterparts to increase their commitment to vaccine development.

Investment in Preventive HIV Vaccine R&D, 2004: Appx. $682M



Source: AVAC, 6/2005

Science
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The Need for a Global HIV Vaccine Enterprise

R.D. Klausner, A.S. Fauci, L. Corey, et al.

"Increasing the diversity of approaches and coordinating the types of vaccines entering clinical trials are fundamental to speeding global HIV vaccine development. **We believe that this requires the creation of a series of coordinated global HIV vaccine centers...."**

NIAID Vaccine Research Center

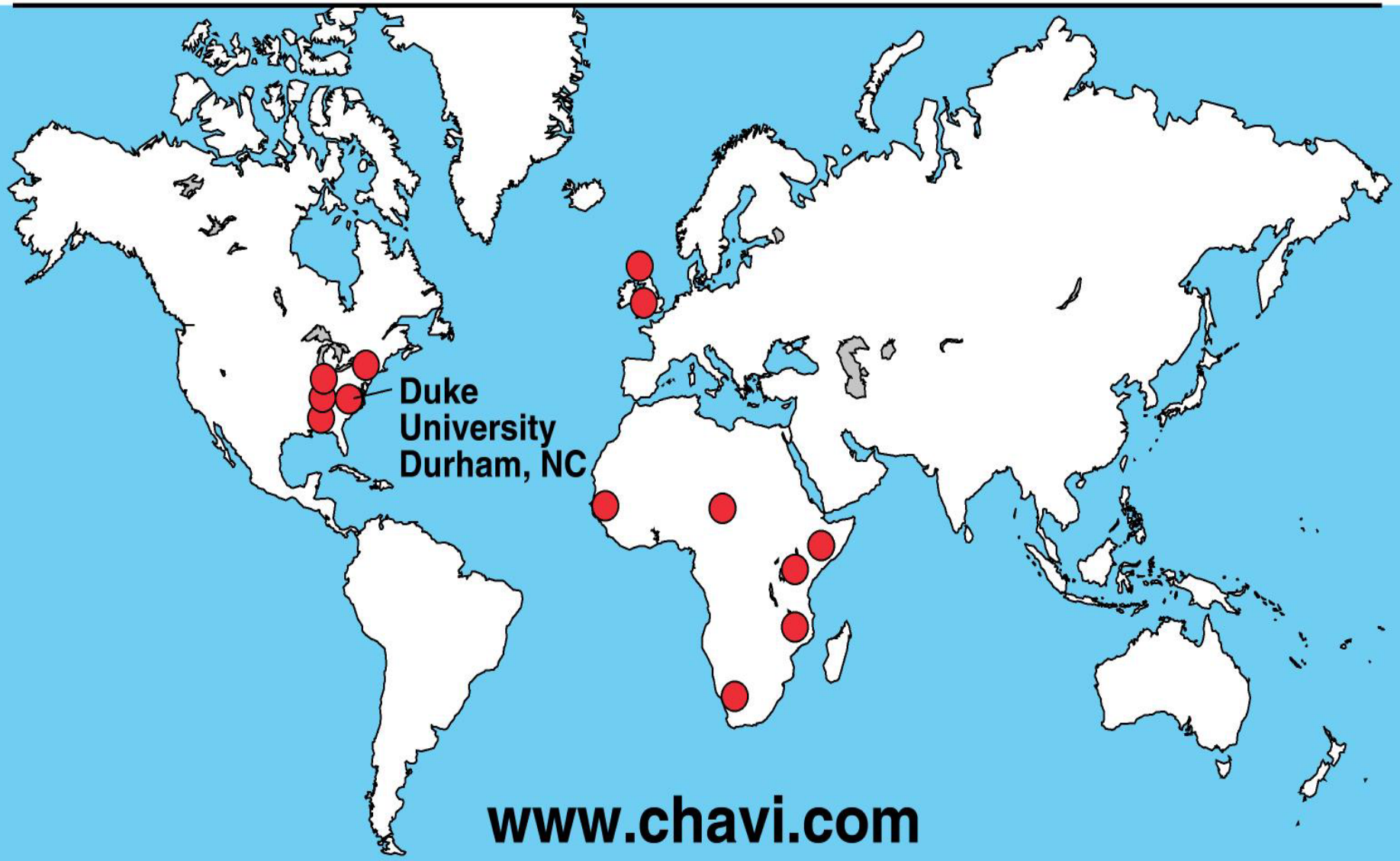
Basic Research → Clinical Trials

- 5-story state-of-the-art facility, opened fall 2000
- 170 employees
- HIV, smallpox, ebola and other HFVs, SARS, WNV
- Close collaborations with clinical trials groups - HVTN, WRAIR, CDC

The Center for HIV/AIDS Vaccine Immunology (CHAVI)

- Intensive, multi-resourced, coordinated, consortium approach to address key scientific roadblocks in HIV vaccine R&D.
- Goals are linked to Enterprise priorities.
- One 7-year award made in August, 2005
- Budget: 1st year: ~ $14.9M
  2nd year: up to $50.0M; expansion plan must be peer reviewed by external advisory board and approved by NIAID

CHAVI Members and Affiliates



www.chavi.com

CHAVI Goals

- Elucidate early viral and immunological events and host genetic factors associated with HIV-1 transmission, establishment of productive infection, and (partial) containment of virus replication.
- Determine correlates of SIV immune protection in primates.
- Design, develop, and test novel immunogens and adjuvants that elicit persistent mucosal and/or systemic immune responses in humans and primates.
- Evaluate HIV-1 vaccine candidates in early phase clinical trials.

Source: B Haynes

Two Examples of Promising HIV Vaccine Candidates

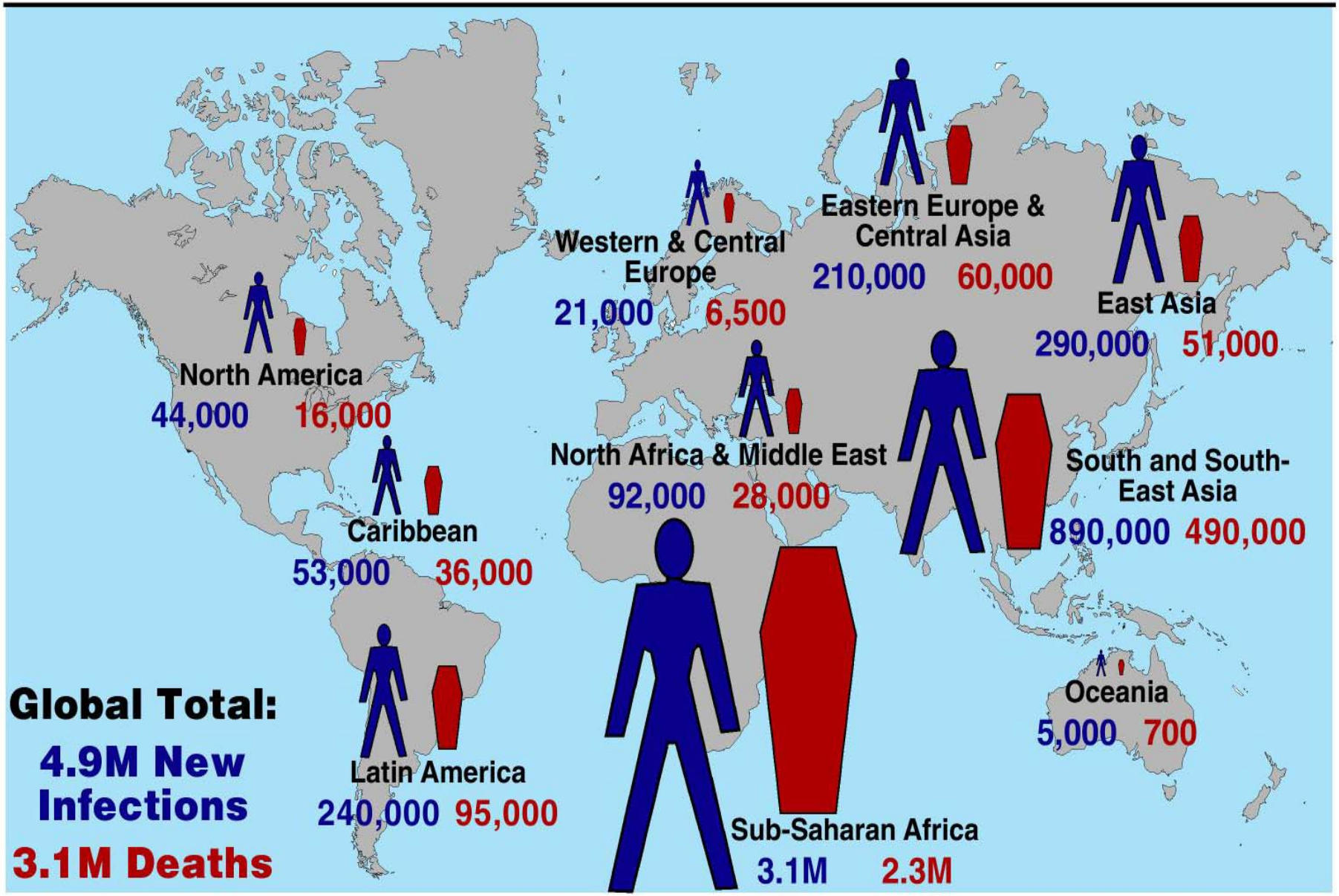
HVTN 502/Merck 023

- Adenovirus vectors expressing gag, pol or nef
- Phase 2b trial underway in US, Puerto Rico and 5 other countries

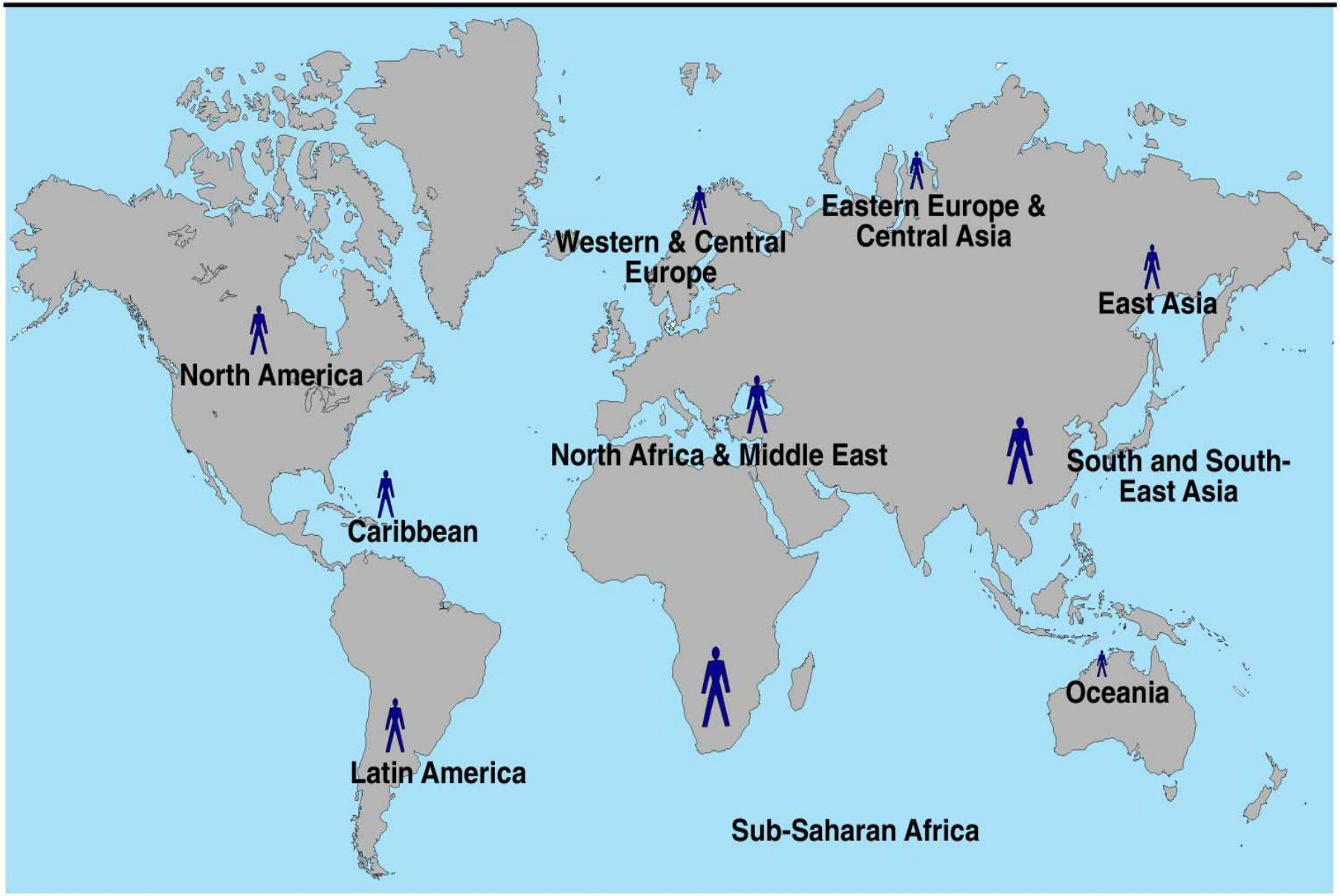
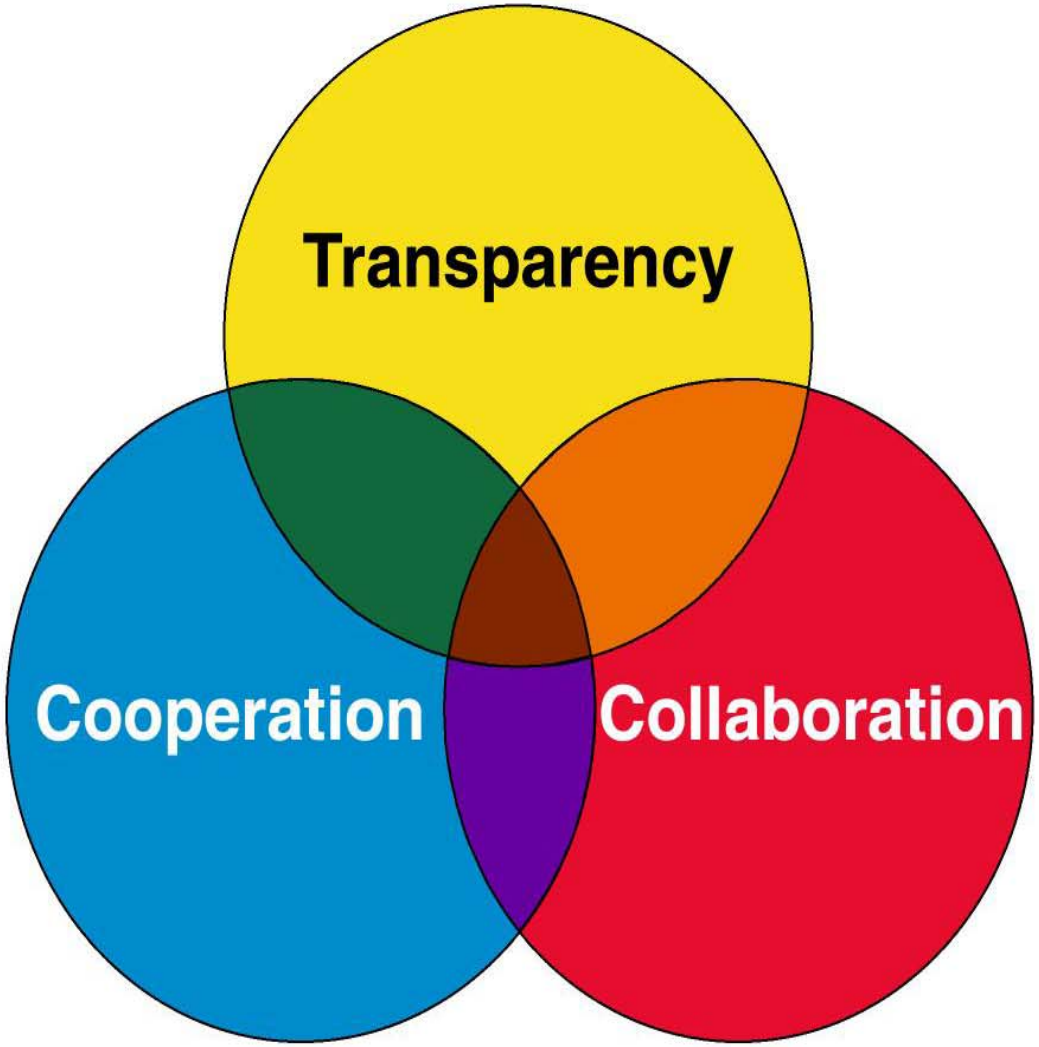
NIAID/VRC DNA/rAd5 Candidate Vaccine

- Prime-boost strategy using multi-clade (A,B,C), multi-gene (including env) constructs -- DNA plasmid vector prime, followed by adenoviral vector
- Phase 2 human trials with NIAID clinical network partners (HVTN, DoD, IAVI) will commence in late 2005

New HIV Infections and AIDS Deaths, 2004



The End of AIDS, 20??



HIV Vaccine Research and Development: The Way Forward