

9
8
7

6
5
4
3
2
1

**YEARS
AND
COUNTING...**

**How Can We Overcome Obstacles
to an AIDS Vaccine?**

**AIDS VACCINE ADVOCACY COALITION
MAY 2000**

This report is dedicated to Neal Nathanson, Director, Office of AIDS Research, in appreciation for his masterful attention to all AIDS issues and his commitment to developing an HIV/AIDS vaccine.

AVAC gratefully acknowledges many friends and colleagues in government, industry, and community advocacy for their expertise and advice as we researched and prepared this report. We especially thank Deborah Birx, Ann Cacho, Jose Esparza, Pat Fast, Gregg Gonsalves, Peggy Johnston, Wayne Koff, Bonnie Mathieson, and Gary Nabel for their helpful comments.

AVAC does not accept funding from government or industry. This publication and AVAC's other policy and advocacy work is made possible by the dedicated work of AVAC advocates and contributions from the Royal S. Marks Foundation Fund, Until There's a Cure Foundation, Broadway Cares/Equity Fights AIDS, the John M. Lloyd Foundation, the Gill Foundation, amfAR, and many individual donors' contributions and in-kind support.



TABLE OF CONTENTS

EXECUTIVE SUMMARY 2

INTRODUCTION: WHERE WE STAND TODAY 4

RECOMMENDATIONS 5

U.S. GOVERNMENT 9

THE GLOBAL RESPONSE 22

INDUSTRY 31

THE PUBLIC: BLUEPRINT FOR ACTION 40

ABOUT AVAC 45

PROFILES

The Dollar Value of Prevention 7

Announcement of Interim Goals and Milestones 18

Moving Toward US Government-Sponsored Efficacy Trials 19

The Long March of Science, What’s New 26

The Push to “Pull” 29

Vaxgen 36

Tax Incentives for Vaccine Research and Development 37



EXECUTIVE SUMMARY

The idea of finding a vaccine to prevent HIV has finally captured the attention of government leaders and affected communities. Increasing sums of public money are available for the effort. Research is percolating in industry. Willing trial volunteers have signed up for injections. Politicians and the public have opened their eyes to the devastation of AIDS in Africa, and decided they should do something.

So why are we still writing reports?

Because scientists do not yet understand the basics, including how to build protective immunity to HIV in humans, or how to use animal models most effectively in research. Because, for all the hype, governments have not passed legislation to help the private sector work on HIV vaccines. Because no one knows how we would get a vaccine to the people of Africa, India and other countries in Asia if we had one. Because Merck recently announced that their current HIV candidate is likely only a first step. Because we have not come close to demonstrating an efficacious vaccine.

The last year was one of great activity across US agencies and throughout the world. We should all be proud. But neither the rhetoric nor more dollars got us a major breakthrough. HIV remains one of the most puzzling and challenging foes to face humanity.

And behind all the activity, we see real signs of trouble: private industry driven increasingly by the

thirst for huge profits and blockbuster products, government programs resisting coordination and losing leadership, mounting controversy over a proposed government vaccine trial, and a tendency in Congress to spend money without making structural policy changes.

This year's AVAC report documents the steadily increasing activity in the quest for a vaccine against HIV:

- Leadership by President Clinton to find vaccines for the major infectious-disease killers, including HIV/AIDS.
- Needed increases in funding at the National Institutes of Health.
- Modest research programs at the major pharmaceutical companies and among some biotech mavericks.
- Five thousand individuals, predominantly in the US, volunteering to participate in the first HIV vaccine efficacy trial.
- Progress toward a government-sponsored, large-scale human trial.
- Establishment of milestones for public sector research.
- Growing public awareness of the international AIDS crisis.
- Activity by governments, researchers, and advocates in scores of countries.

- Funding of product-oriented research outside of government institutions.
- New guidelines on the ethics of vaccine trials and expectations of improved international coordination.

We also voice our impatience:

- The US Department of Defense has a directed HIV vaccine research program. So why is it consistently underfunded?
- The President and Congress proposed important incentives. So why are these bills facing opposition or disinterest?
- Industry says it faces difficulties in dedicating resources to HIV vaccine research. So why do they seem tongue-tied when asked what incentives they need?
- NIH funding has skyrocketed. So why are there still not enough non-human primates available for needed research?
- We are almost 20 years into the epidemic and 30 million people live with HIV. So why has there been only one Phase 3 trial of a vaccine that might prevent this disease?

Several actions are necessary to accelerate development of HIV vaccines, including 1) expanding government programs and providing additional targeted funding for specific research priorities, 2) passing legislation that provides incentives for private sector involvement in HIV vaccine research, and, 3) funding public outreach, education and communication programs.

Business as usual and territorial mentalities are the enemy of rapid progress towards an HIV vaccine. No one agency or company can find a vaccine and make it readily available. Public and private sectors must find new ways to partner. The Centers for Disease Control has been criticized for the way in which it funded ancillary studies in the VaxGen trial, but it is just these kinds of partnerships that are critical to moving research forward and securing the benefits of science for everyone.

In 1997, the President said he wanted a vaccine within a decade. We have seven years to go. There's funding, public support, and renewed hope in the scientific community. With new partnerships, a new sense of urgency, and broad based cooperation, the dream of a vaccine that saves tens of millions of lives is within reach.



INTRODUCTION: WHERE WE STAND TODAY

In less than four months, the 10-year challenge to create an AIDS vaccine will be one-third over, and the daring challenger, President Bill Clinton, will leave office. This year, dramatic changes in the rhetoric and actions surrounding development of an HIV vaccine appear everywhere we look.

You will see a difference in this year's AVAC report. We believe the world has turned an important corner. The political will to make an AIDS vaccine finally shows signs of life. The National Institutes of Health are not our primary focus this year. The foresight and continuing effort of NIH is beginning to be repaid and replicated around the world.

On the other hand, in some ways, Clinton's challenge seems like wishful thinking. Not only have we been unable to agree on what a promising AIDS vaccine candidate would look like, objections are raised when a publicly-funded large scale trial of a modestly promising vaccine is proposed.

The vaccine issue belongs not to Clinton or the Democrats—rather it touches on the security of our country and stability in the world, particularly in Africa, Asia, and Eastern Europe. A change in the political landscape with Presidential and Congressional elections this fall may very well

change the balance of power in both branches, which raises concerns for continuing and expanding the effort. Each candidate for President and Congress must realize that the ultimate goal—preventing AIDS—has staggering, far-reaching consequences. We do and will call on each active politician, regardless of the rest of his or her political agenda, to endorse accelerated development of HIV vaccines. If there ever were a bipartisan issue, this is it.

Six years have passed since the decision not to go ahead with monomeric gp120 in the US in 1994. Something like \$781 million has been spent during those years, and there's so much we still don't know. As Mark Schoofs points out in, "The Agony of Africa" in *The Village Voice*, (November, 1999) "Even when pushed, science crawls."

The moment has come to step up the effort, put on some pressure and prepare to run a series of efficacy trials around the world. All the old, AIDS-activist slogans could be dusted off and still apply: *People Are Dying* and people need experimental vaccines. It is 1982–83 again in other parts of the world and in communities across America. Nobody's storming the NIH, disrupting the stock market, or staging die-ins in the streets. It might help if we did.



RECOMMENDATIONS

AVAC started criticizing NIH and industry for the inadequacy of their HIV vaccine programs in 1995 and telling everyone else to get on the ball. There was too little going on anywhere else to criticize. Today, we are happy to report interest and activity have grown to a point where advocates can compliment and critique multiple efforts on many fronts. Today it is possible to see how to actually get to an AIDS vaccine.

Not that the way will be quick or easy. It has taken 18 years to get here. We only have managed that—and with limited resources—because a small band of dedicated people recognize the importance of their work and are working as hard as they can.

We must prepare for the difficult road ahead by putting sufficient resources into what are known to be the key contributing components of a comprehensive vaccine research effort. This year, we have three overarching recommendations, with a few specific recommendations for each.

1. Expand government programs as rapidly as they can effectively handle expansion.

- Expand translational work at NIH: the research that facilitates moving products from the lab to development.
- Permanently and adequately fund Department of Defense vaccine research.
- As industry becomes more involved, negotiate for trade-offs, such as reasonable pricing, before public funds are handed out.
- Conduct clinical trials more smoothly and expeditiously.
- Supplement funding beyond current and proposed increases for NIH in seven specific areas identified by AVAC. AVAC estimates that an additional \$70 million could be effectively used to:
 - Prepare research sites in the US and other countries (including epidemiological studies, immunologic studies, training investigators, preparing countries, building infrastructure, and other site preparation work).
 - Provide more and higher quality non-human primates. (Implement plans to increase the stock of primates, including pathogen-free and immunologically characterized and related animals.)
 - Develop new assays rapidly and place advance orders for new cell-sorting and other technology that would be used to analyze results from efficacy trials.
 - Target additional resources to biotech companies through the Vaccine Design and Development Teams initiative.

- Prepare key communities and the public for the ongoing vaccine effort.
- Provide adequate funds to expeditiously conduct efficacy trials in the US and abroad as soon as candidates become available.
- Create private-public partnerships to champion and develop orphan-vaccine concepts and support vaccine trials.

2. Pass legislation that provides incentives for private sector involvement in HIV vaccine research—both “pushes” and “pulls” are needed, because purposeful company activity is crucial.

- Pass the *Vaccines for the New Millennium Act* introduced by US Senator John Kerry and Representative Nancy Pelosi.
- Establish purchase funds and other access assurances now.

3. Fund public outreach, education and communication programs.

- Focus education and communication efforts in key communities.
- Develop and implement a strategic communications plan.

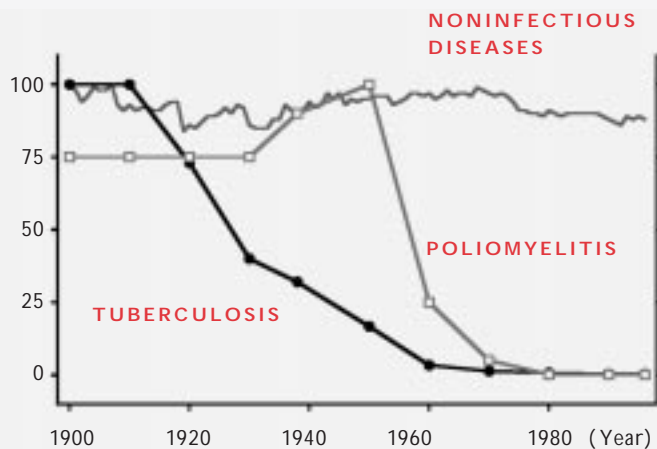
In two more years, we come to the halfway mark of 10 years to develop a vaccine. By then we could have a real, substantial and significant international drive underway. This is a fantastic, almost incredible challenge, but mankind has done monumental things before. Let's get together, stop quibbling, cheer the workers on, and go!

To get involved or to read past AVAC reports, visit our Web site: <http://www.avac.org>

<http://www.avac.org>

THE DOLLAR VALUE OF PREVENTION

Annual Disease Rates for Selected Infectious and Noninfectious Diseases United States, 1900–1996



Source: Armstrong et al, JAMA, 1999, 281: 61; and CDC

This chart shows that a new treatment or vaccine can slash the incidence of a deadly infectious disease. Because infectious diseases are transmissible, the health of others is your health. Yet, private and public health-care plans often don't pay for check-ups or immunization.

Vaccines, even administered to millions, are worth hundreds or thousands of times more per person and per dose than the pennies we expect them to cost. For people who have not caught and do not expect to catch an infectious disease, this is a difficult argument to sell, particularly when vaccination and hygiene has made occurrence of a disease rare.

A vaccine is insurance against rare catastrophic events and the insurance itself is a form of protection. That's why vaccine advocacy is hard to generate especially when the disease burden has been reduced as dramatically as it has in the developed world. In the US, we live in a relatively healthy bubble of a relatively unhealthy globe. Given emerging infections, clearly, the best way to keep the diseases out—is not to build barriers—but to improve health “out there.”

Like clean air and water, an infection-free environment is a common good. Sanitation and vaccination are the only two proven routes to that end. If we, as individuals, can happily spend a hundred billion dollars a year treating sometimes minor ailments, why can't we find adequate resources for full-scale efforts on the vaccines needed most desperately in the world?

According to the US Department of Health we will spend an estimated \$110–120 billion on prescription drugs this year, which has almost doubled since 1995 and quadrupled since 1990. The entire budget for vaccines around the world is estimated to be no more than \$3 billion. Where's the sense in that?

“Today marks the first time, after more than 4,000 meetings stretching back more than half a century, that the Security Council will discuss a health issue as a security threat. We tend to think of a threat to security in terms of war and peace. Yet no one can doubt that the havoc wreaked and the toll exacted by HIV/AIDS do threaten our security. The heart of the security agenda is protecting lives—and we now know that the number of people who will die of AIDS in the first decade of the 21st Century will rival the number that died in all the wars in all the decades of the 20th Century.”

Vice President Al Gore

United Nations Security Council Opening Session
January 10, 2000

U.S. GOVERNMENT

► **STATUS** Presidential and Congressional proposals • Growing budgets ► **RECOMMENDATIONS** Sustain increased NIH funding • Ensure leadership at all agencies involved • Increase funding for Department of Defense research • Identify possibilities for acceleration of FDA review • Provide enough non-human primates for research • Coordinate work of agencies • Set milestones for cooperative agreements and contractors • Move forward with planning a Phase 3 trial of Canarypox

NATIONAL POLICY

President Clinton Calls for a Vaccine

President Clinton advocated development of an AIDS vaccine at least six times during his two terms in office. He promised to make NIH the “engine of discovery” for HIV vaccines in his 1997 State of the Union address to Congress. He proposed that our country develop an AIDS vaccine in the next decade in May that year. He pledged at the UN’s General Assembly to work with industry on vaccines for AIDS, tuberculosis and malaria in fall 1999, perhaps in response to the Lifesaving Vaccine Technology Act that Congress introduced in the 105th session.

“...today I commit the United States to a concerted effort to accelerate the development and delivery of vaccines for malaria, TB, AIDS, and other diseases disproportionately affecting the developing world.”

President Bill Clinton
The United Nations, September 1999

This year we got more: State of the Union promises about vaccines, announcement of existing programs and a purchase-tax-credit proposal, which costs the government nothing until a vaccine is licensed and sold. The proposal will take years to implement.

The words are good. The danger is that they will not be enacted with new incentives and funding. The President’s advisors in the Office of Management and Budget, Treasury, and National Security support action. The President’s Advisory Council on HIV/AIDS urged concrete steps and passed seven resolutions relevant to AIDS vaccine development—dormant proposals still on the table.

Congress Keeps Pace with Funds, Proposed Legislation

Congress continues to increase funding to record levels for medical research at the National Institutes of Health. NIH has, in turn, continued to increase the share for AIDS vaccine research, which rose from \$111 million in 1996, when we published our first report, to \$239 million in fiscal year 2000—not a pace comparable to a hot stock market but enough to allow broader basic research grants and applied research programs.

On the legislative front, the *Lifesaving Vaccine Technology Act*, introduced a year ago in March would create incentives for industry to invest more heavily in areas with the greatest global public-health need.

This year, Senator John Kerry and Representative Nancy Pelosi added a vaccine-purchase fund to the legislation proposed last year in order to make the proposed incentives both “push” on research and “pull” to create a market for these vaccines. The *Vaccines for the New Millennium* bill is this year’s gold standard for legislation to spur HIV vaccine research and development. (see page 37).

Show Political Will

The executive and legislative branches of our government seem to lack the political will to make the more difficult policy changes that must follow the funding. Money for research is the easiest element in the equation. The other elements are partnerships with industry, incentives for private sector investment, shared objectives, and consistent, concerted action. We must raise this issue to the level of an intensive program with ambitious goals. Everyone involved should be encouraged to be on a faster track.

Only the US government is in a position to “Marshall” that plan and “Manhattan” this project with commitment and leadership. As President Clinton said: “...a new national goal for science in the age of biology. If America commits to find an AIDS vaccine and we enlist others in our cause, we will do it. I am prepared to make it happen.”

US AGENCIES

Congress Narrowly Tops Past Funding

Congress appropriated \$5,962.7 million for AIDS

programs this year, which the Clinton administration touts as the most ever. This appropriation barely tops past figures and getting those funds becomes more and more difficult. Two of the greatest supporters of aggressive funding for NIH will or have moved on: Representative John Porter (R-IL) who chairs the House Appropriations Subcommittee on Labor-Health and Human Services-Education and NIH Director Harold Varmus, who charmed that Subcommittee for years. That leaves the question of maintaining the funding for AIDS to us. We must redouble our efforts on the legislative front.

NATIONAL INSTITUTES OF HEALTH

This year NIH got a healthy 15% increase. The annual increase has traditionally been the discretionary part of NIH’s budget, since NIH is reluctant to cut from previous institute budgets. A smaller share than in previous years will go to AIDS research. The Office of AIDS Research (OAR) manages that share, which allots a larger portion of its increase to vaccine programs.

Vaccines have gone from 9% of the NIH AIDS budget when Neal Nathanson took over the Office of AIDS Research to 12% proposed for this year. This adds up to \$239 million, enough to support the proposed new programs minimally. Nathanson announced recently that he will be leaving his position in September 2000. The NIH operating budget (for staff, supplies, travel, etc.) has not increased nearly as much as the budget for grants and contracts. For vaccines, which have expanded disproportionately to the total NIH budget, this means more work per staff person and insufficient travel funds.

OAR may use a discretionary fund for peer-reviewed projects, in addition to the budgets of individual institutes. In past years, this fund has often supported vaccine or other prevention projects. OAR is

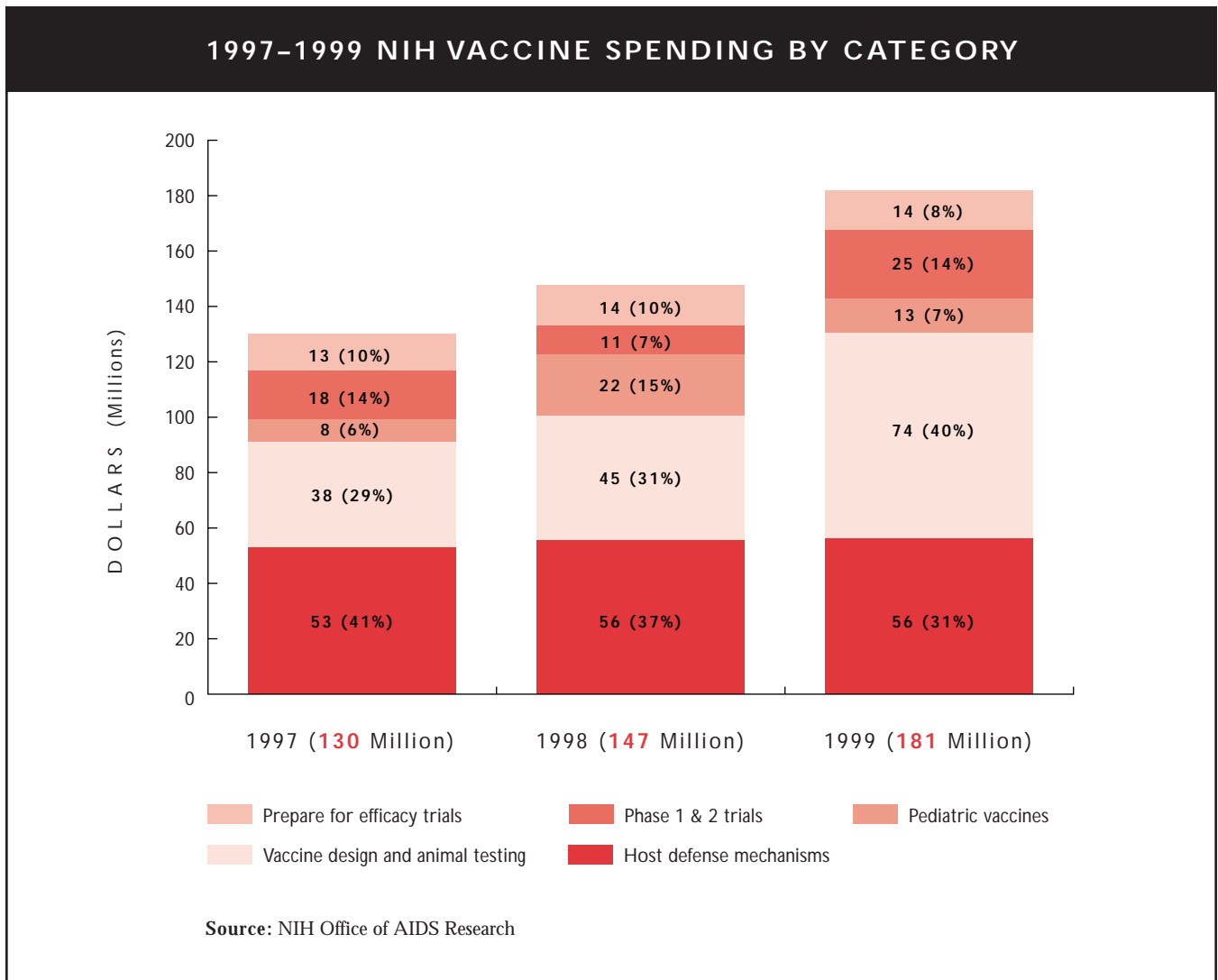
required by law to update its *Plan for HIV-Related Research* each year before submission of budget requests for the coming year. To identify priorities in the plan in the past has been difficult because the plan must include all current and probable areas of research. OAR identifies priorities for future research up front for each topic, which helps with an analysis of the plan.

The 2001 plan proposes to:

- Conduct domestic and international vaccine trials.

- Develop and test new vaccine strategies.
- Improve animal models and trials.
- Identify and develop functional antibodies to use against maternal-infant transmission in order to inform vaccine design.
- Move vaccine concepts rapidly to clinical tests.

These priorities are very close to the Treatment Action Group’s recommendations made in its recent report on NIH-funded research. OAR has tracked NIH vaccine spending in five categories. Trends for the last three years are shown below.



CENTERS FOR DISEASE CONTROL AND PREVENTION

The CDC created an AIDS vaccine unit, headed by Dr. Bill Heyward, last year, after years without one. That program primarily supports VaxGen in its efficacy trials by providing domestic and international logistical support and funds to perform additional epidemiological, social, and behavioral research—a total of \$8 million over a period of four years. Dr. Heyward's move to VaxGen was followed by negative articles in the media, which increased scrutiny from Congressional appropriators.

Dr. Timothy Mastro recently accepted the position of chief of the HIV Vaccine Unit in the Epidemiology Branch of CDC's Division of HIV/AIDS Prevention. Dr. Mastro served as Director of The HIV/AIDS Collaboration-Thailand, a joint research project between CDC and the Thai Ministry of Public Health, for the past seven years. The vaccine unit currently has a staff of four, a small staff by CDC standards. One or two people may be hired in the near future.

Another CDC activity was an NIH-funded, qualitative study of community attitudes toward vaccine testing. This study is out of money and in the doldrums, with large amounts of potentially important data unanalyzed and unpublished.

DEPARTMENT OF DEFENSE: WALTER REED ARMY INSTITUTE OF RESEARCH

Since the beginning of this epidemic, the US Army has played an important research role, extraordinary for its funding level. The Army must protect our troops and has a long history of vaccine research and development of vaccines not developed aggressively by industry.

WRAIR complements NIH research programs, and is an essential component of the HIV vaccine research enterprise. Aside from the fact that it consistently produces important scientific work, the military, by design, runs highly structured, directed programs unlike NIH's broader, peer-reviewed grant programs. Each approach has its strengths, and we believe government should pursue both.

Annual Dance for Dollars Must Stop

WRAIR has five sets of products in clinical trials and four new products in production or development. Their clinical testing sites are in the US and Thailand. They are building infrastructure in Uganda, with cohorts for Phase 2 trials in development in Uganda, Kenya, and Thailand. They have surveillance activities throughout South America, Africa (East, West, and North) and Southeast Asia.

Funding for this program is an annual skirmish. Pentagon officials have consistently cut the program's budget requests, which Congress then restores because of public support. In past years, the National Organization Responding to AIDS (NORA) and AVAC have succeeded in restoring the budget, but DoD uses this dance to get budget increases for areas other than vaccines.

President Clinton's proposed annual AIDS-vaccine budget for WRAIR is \$24 million, with \$17 million available for scientific work. With annual expenditures for scientific projects of approximately \$32 million, WRAIR has relied on Congress for supplemental funding each year. WRAIR needs an annual appropriation of close to \$50 million to have \$32 million available for vital vaccine research and development projects.

We strongly believe that DoD should recognize the important public contribution that is being made and will be made by its HIV vaccine program.

The defense department should give WRAIR reasonable funding in its budget requests, in light of the fact that the UN Security Council and others clearly identify AIDS as a serious security risk. An annual DoD appropriation of approximately \$280 billion, with a pittance of \$50 million for vaccine research, will allow meaningful progress against this disease, which our troops could now contract anywhere in the world.

WRAIR plans to conduct a Phase 3 trial in Thailand in 2002 that will compare several prime boost strategies, which will probably include combinations of DNA or Canarypox and gp120 or gp140.

FOOD AND DRUG ADMINISTRATION

Because HIV vaccines have progressed so slowly, the ultimate role of the FDA has been under-appreciated. This agency must approve the initiation of human trials of any candidate vaccine, any efficacy trials, and license any product. FDA must secure public safety for drugs, foods, and biological products—an increasingly overwhelming responsibility.

We have heard few complaints to date about FDA's willingness to work with vaccine developers and move their products forward. FDA encourages companies and others to work with them before application to accelerate the process.

Last year, FDA gave two candidate vaccines Investigational New Drug status, allowing them to move forward with clinical trials. The average for the last five years has been three per year. These applications must come from researchers, developers, or government sponsors, but the FDA review process, coupled with rapidly escalating agency requirements for data needed to complete an application, can add many years of research after

completion of the first successful efficacy trial.

FDA must be encouraged to expedite the vaccine development process as much as possible. In response to activists' demands for expedited approvals, the agency developed streamlined processes and special programs to get drugs for AIDS and other life-threatening illnesses to the people who need them. Drug companies welcomed this change. The Biologics group at FDA, which oversees vaccines, could take a lesson from the Therapeutics division.

AVAC knows that trial participants' safety must be foremost, but we commit to work with FDA and investigators to improve existing regulations and processes.

COORDINATION

AVAC and the President's Advisory Council have criticized the mechanisms by which federal agencies work together. Dr. Nathanson was charged with coordinating the work of these agencies at a President's meeting on AIDS in 1998. He convenes a biennial meeting of NIH, Walter Reed, CDC, and FDA to share information. Dr. Margaret "Peggy" Johnston, Assistant Director for HIV/AIDS Vaccines at the Institute of Allergy and Infectious Diseases, reports directly to Dr. Fauci for this responsibility. Individual managers in the agencies maintain close relationships with counterparts in other agencies.

Still, as in years past, we see little evidence that these agencies coordinate efforts effectively. With increased awareness of the economic and security impact of AIDS and the need for international research and trials, the State Department, USAID, and others should be brought into the process.

AIDS VACCINE PROGRAMS AT NIH

NIAID DIVISION OF AIDS

The NIAID Division of AIDS funds and manages the lion's share of AIDS research at NIH and the world. Its Director, Dr. Jack Killen, has announced that he will leave this year. The Division states that "basic science and applied research, fueled by NIAID investments, are creating unprecedented opportunities to expand vaccine discovery and development within the next five years." A good faith effort is being made to do so for basic research, translational and applied research, and clinical research.

But the Office of AIDS Research (OAR) has identified 85 separate strategies to pursue in fiscal year 2000, so it is a juggling act to apportion ever rising resources between investigator-initiated and directed research. By plan, the bulk of the research is investigator-initiated, that is, investigators compete for grants through a peer-review process. A separate study section for evaluating vaccine grant proposals was piloted in 1998. In fiscal year 1998, 38% went for basic research, 34% was used for targeted research involving preclinical product development, and 28% funded adult and perinatal research and development of clinical trial infrastructure. (Based on research by TAG and AVAC.)

Dr. Peggy Johnston came to her position as Assistant Director for HIV/AIDS Vaccines in 1997 after program management had planned several newly conceptualized initiatives which were not yet in place. With a number of vacancies in her group, she is valiantly dealing with the fallout, but is a long way from a fully-staffed, smooth-running program.

The challenge—to take the peer-review system and put in place a well-coordinated, overall program—will be achieved by managing grant portfolios and developing targeted programs such as those outlined

"Every NIAID research program aims to improve health. Even the most esoteric investigation is undertaken with the hope that it, in combination with many other studies, will provide insight to improve diagnostics, treatment, and/or prevention."

NIAID Strategic Plan, October 1999

below to fill the gaps. The schema for these programs, conceived in 1996–98, and developed over the last few years, has taken many years to put in place (See page 16). Unfortunately, more years will pass before we can evaluate whether they worked and fit together well.

A description and status report for each program and other useful information can be found at the NIAID Division of AIDS (DAIDS) Web site: <http://www.niaid.nih.gov/aidsvaccine>

DAIDS PROGRAMMATIC GOALS AND MILESTONES FOR FISCAL YEARS 2000 AND 2001

FY 2000 Funding

- Continue active oversight of unsolicited awards.
- Fund Innovation Grants (ongoing).
- Fund new HIVRAD and IPCAVD applications.
- Fund Vaccine Design and Development Teams.
- Establish Vaccine Trials Network.

FY 2001 New and Continuing Initiatives

- Innovation Grant program announcements (ongoing).
- Second IPCAVD program announcement.
- SIV Evaluation Units Requests for Proposals.
- HIV Database Request for Proposals.
- HIV Production Contracts, a 3-part Request for Proposals.

Planning is underway for fiscal year 2002.

Soon it will be possible to examine the ability of this system to generate a pipeline of product research and development. We encourage DAIDS to do so carefully in order to make sure its initiatives are performing as planned.

DALE AND BETTY BUMPERS VACCINE RESEARCH CENTER

Last spring, near the second anniversary of President Clinton's ten year challenge, he attended the ground-breaking ceremony for the Dale and Betty Bumpers Vaccine Research Center. The Center will be a beautiful new laboratory dedicated to vaccine research and development, with an initial focus on an HIV vaccine. Since the ground breaking, the Center's new director, Dr. Gary Nabel, has been putting together an organization and waiting to move in.

Meanwhile, Nabel's former laboratory at University of Michigan has been making a wide range of construct antigens to test in animals and humans. Their first protocol will be a small Phase 1 safety trial of one DNA construct at the NIH clinical center. Nabel has conducted a number of planning meetings and recruited at least two top scientists to lead two of the four areas of the lab: Dr. Gordon Douglas, formerly of Merck, to manage product development efforts, and Dr. Norm Letvin to lead its animal testing program. Douglas and Letvin are not full time employees, so the program may have the best people but not their full effort. Remaining to be filled are leaders for the human immunology labs and human testing groups.

This team will be under tall orders. At last year's ceremony, President Clinton said, "I am confident that this is a place where miracles will happen.

AIDS VACCINE RESEARCH COMMITTEE

One of the major recommendations of the 1996 Levine panel was to "restructure the entire NIH/AIDS vaccine research effort and that a trans-NIH vaccine program should be established with leadership and oversight provided by distinguished, non-government scientists." The restructuring, such as it is, is described above. The distinguished panel is the AIDS Vaccine Research Committee (AVRC), chosen and led by Dr. David Baltimore. This high-profile group of ten scientists and one AVAC member has been meeting three times a year since 1997.

What it has done and how well it has worked is open to discussion. *IAVI Report* quoted one unnamed researcher as referring to the Committee as "a science club." The group has reviewed a large number of scientific issues and made recommendations about them. It gave its imprimatur to the innovation grant program and organized with NIAID the only national AIDS vaccine meeting last year. The Committee has relied on management at NIH to help guide its efforts, and focused on particular issues that have been brought to or come to its attention. To date, it has not attempted to provide leadership and oversight for the entire NIH/AIDS vaccine research program. In its tenure, AVRC has focused on a number of critical scientific issues, including animal models and primate resources, neutralizing antibody, CTL measurement, mechanisms of live attenuated vaccines, the role of clades, vectors, and, of course, innovation.

We agree with the original Levine Committee recommendation that the Committee should provide advice and consent for the program overall, not just the scientific agenda. This will require more resources, direction from the Committee, and cooperation from NIH.

NIH VACCINE FUNDING PROGRAMS: WILL THEY DELIVER A PREVENTIVE HIV VACCINE?

INITIATIVES	PURPOSE	DATE OF 1ST APPLICATIONS	FREQUENCY OF APPLICATIONS	# OF AWARDS TO DATE (4/00)
Extramural R01 Grants; Intramural Contracts	Unsolicited investigator-initiated research.	—	On-going	80 new R01 grants, 55 full and partial intramural awards in FY1999
Reagent Support; HIV Molecular Immunology Database	Researcher support.	—	On-going	2 contracts (1 each)
Innovation Grants	To draw researchers into the HIV vaccine field and increase the number of promising concepts entering the research pipeline.	1997	3x/year	191 grants
HIV Vaccine Research and Design (HIVRAD)	To support development of HIV vaccine concepts into products.	1998	1x/year	3 complete awards, 1 partial award
HIV Vaccine Design and Development Teams	To promote a development-oriented approach to vaccines by funding teams of researchers for long-term coordinated projects.	1999	5 year awards	Pending
Integrated Preclinical / Clinical AIDS Vaccine Development (IPCAVD)	To encourage academic-industry collaborations that will move vaccines through the final preclinical stages and into early clinical trials.	1997	1x/year	8 active awards, 12 total awards
Primate Testing Contracts	To create a standardized challenge system that would allow investigators around the world to generate comparable results with vaccines in primates.	—	On-going	Supplements to 2 existing contracts
Simian Evaluation Units	To evaluate promising SIV and HIV vaccines in non-human primates.	1998	5 year awards	Renewal competition pending
HIV Vaccine Development Resources Contracts	Resources to facilitate development of promising vaccine candidates into testable products.	1998	7 year awards	14 contracts
Vaccine Trials Network (VTN)	Domestic and international human testing of HIV vaccine candidates, all phases.	1998	5 year awards	3 core functions awarded, site awards pending

Source: NIAID Division of AIDS and Office of AIDS Research

SCIENTIFIC REVIEW

In the second half of 1999 there was a spirited debate in the scientific community about proposed changes in the NIH system for scientific review. OAR Director Neal Nathanson, with support from many AIDS scientists and activists, led successful opposition to a proposed reorganization that would have redefined the system of Integrated Review Groups and eliminated the dedicated AIDS review group. AIDS study sections will continue to be organized together into an AIDS specific review group.

Another Levine panel recommendation was to create a separate vaccine study section dedicated to applications that focus on vaccine development for AIDS and non-AIDS vaccine research. The goal was to have a panel of vaccinologists and applied scientists review vaccine grant applications that are perceived to be less appealing to basic science review groups. After studying this proposal, the Center for Scientific Review, which manages the majority of peer review at NIH, created a Special Emphasis Panel, which should eventually become a Chartered Review Committee. This pilot study section has met five times since November 1998. To date, it has considered more than 450 grant applications, including the AIDS vaccine innovation grant applications. One-third to one-half of the applications have been AIDS vaccine

applications. We consider this a success and recommend that the study section be allowed to mature and be made permanent.

The Fogarty Center has a thriving program in the US to train researchers and clinicians from the developing world in the US, and also provides direct funding of developing country research institutes. Fogarty, with the Institutes, should consider broadening its focus to increase the capacity of affected countries to establish their own research and development efforts, which several countries have expressed interest in doing.

In addition to NIAID, other NIH institutes do important AIDS vaccine research. The National Cancer Institute (NCI) received \$21.4 million in fiscal year 1999 that goes almost exclusively for pre-clinical work. About half of this funding stayed within NCI for intramural researchers. The National Center for Research Resources (NCRR) received \$8.9 million in fiscal year 1999, mostly for primate centers and General Clinical Research Centers at universities and hospitals. NCRR provides important core support for primate researchers. Neither of these efforts, NCI intramural research nor NCRR AIDS programs, has received proper scrutiny. We call for careful evaluation of their effectiveness and relation to the larger programs by the AVRC in the near future.

ANNOUNCEMENT OF INTERIM GOALS AND MILESTONES

In last year's report, we printed an open letter to NIAID Director Fauci and OAR Director Nathanson asking that NIH establish clear, publicly identified interim milestones, and a system to monitor NIH programs to determine how well they work at broadening the product pipeline. We want the program leaders to have ambitious, realistic targets to measure themselves against, because we believe that without interim goals that can be tracked, the ultimate goal of an HIV vaccine is less likely to be realized in a timely way.

In their two-page reply, which cited recent leadership positions filled, scientific advances, and efforts they have made to move things forward, Fauci and Nathanson made this response, "*progress cannot be measured simply by the number of products passing specific milestones, because the quality of the product is much more important than the number tested*, as documented by the failure to identify many highly promising vaccine candidates in spite of the large number of NIH-funded Phase 1 and 2 trials conducted over the last 10 years." They close by suggesting that the question of vaccine monitoring be discussed by the AVRC.

When this answer was quoted in

IAVI Report, Bill Snow of AVAC made the following reply, "of course the quality of products is most important, but key questions can be answered by testing and improving on every reasonable approach. We still hope that NIH can identify appropriate annual objectives that keep things moving as quickly as possible."

So, Dr. Nathanson put this on the AVRC agenda and it was discussed at two of the last three meetings. In January, Dr. Peggy Johnston, who heads the NIAID Division of AIDS vaccine program, presented the programmatic goals on page 14. She also presented the following current scientific milestones for her programs and team:

- Pseudovirion into Phase 1 trial: Q2-2000
- P55 particle into Phase 1 trial: Q3-2000
- Viral vector into newborns: Q2/3-2000
- MVA into Phase 1 trial: Q1-2001
- VEE replicon into Phase 1 trial: Q1-2001
- Vaccine Design & Development Teams milestones: TBD Q2-2000

- Canarypox Phase 2 US/Caribbean, Q1-2000 (*will not occur until the second quarter*)
- Canarypox into Phase 2b trial: Q1-2001 (*already an unrealistic goal*)

Making these objectives public is a big step forward in helping the AVRC, AVAC, the interested public, and the DAIDS team itself all become aware of the reasonable expectations for progress. Circumstances may change, but if we all know precisely what we're working toward in the short term, we stand a much better chance of meeting those interim objectives and reducing delays between activities. We encourage Dr. Johnston's group to set goals for all of their cooperative agreements and contractors, particularly for the big, high-priority projects like the comparative animal studies and Vaccine Trials Network.

We also think it still would make sense to set some goals for the less tangible but equally important needs, such as the number of industry partners involved in developing HIV vaccines and the number of countries ready to participate in vaccine research.

MOVING TOWARD U.S. GOVERNMENT-SPONSORED EFFICACY TRIALS

Agonizingly slow progress is being made toward a US government-sponsored efficacy trial of the Canarypox vector with some HIV antigens inserted and an envelope boost. Aventis Pasteur (formerly Pasteur Merieux Connaught) has improved its antigen and vectors at least four times since 1994, requiring new Phase 1 trials to be conducted by AVEG. In the same period, confidence that the envelope boost would provide functional antibody has eroded to the point where only VaxGen is pursuing that approach, while others search frantically for an envelope construct that will elicit broadly neutralizing antibodies. As time has ticked away, several other viral vectors, designed to induce cell-mediated immunity have been advanced. Only two of those have even begun in human trials despite the involvement of IAVI and many others.

The HIVNET network was set up to run vaccine efficacy trials that never materialized, but did run behavioral and microbicide efficacy trials. This network is now being dismantled, and the newer Vaccine Trials Network (VTN) is only now about to fund a limited number of core sites. Site expansion will follow only when a particular large trial moves forward.

The VTN proposes that its first venture into efficacy studies with the Canarypox-gp120 approach be not a full-scale definitive licensing trial, but what is variously called a “Phase 2b,” “intermediate,” or “proof-of-concept trial.” Such a trial could give a rough estimation of any efficacy (<30% vs. 30–70% vs. >70%) and provide the opportunity to do some informative sub-analyses.

Two techniques are being developed that would allow a reasonable analysis for cellular correlates of immunity in larger numbers than any human or animal trials to date: 1) ELISPOT assays that identify individual cells by the antibody or cytokine they secrete, and 2) flow cytometry that would sort cells by the surface markers and cytokines they contain. The ability to do such assays in bulk on frozen samples has not yet been achieved, but will almost surely be available in time.

Any decision about whether or not to move into an efficacy trial of the Canarypox vector must take into account how long it will be before other products will realistically be ready for efficacy trials. Waiting for other antigens may not be the optimal way to move

quickly, since experience has taught us that no approach has ever gone directly from the lab through human trials without iteration and improvement. As we have learned with this approach and others, those processes take years.

Acknowledging that reality, there is every reason to move ahead as quickly as possible with the Phase 2b Canarypox trial. To delay testing of one product simply because something better is believed to lie down the road, could be a scientific and human tragedy. We call your attention to the Salk and Sabin polio vaccine story in which the less scientifically appealing and sophisticated approach carried the day and ended an epidemic. Whether Canarypox is a useful vector for HIV vaccines is an empirical question that can only be answered with experimentation.

When Neal Nathanson took office at the Office of AIDS research in 1998, he said, “The crucial thing is to explore all promising ideas as quickly as possible. The way this epidemic is going, any other approach would be intellectually absurd and ethically unconscionable.” We agree, and support NIH in moving forward with preparations for a Phase 3 trial.

Maybe all we'll find out is that this approach to an HIV vaccine is not efficacious, but even that would be progress. Certainly we'll have a better idea of how the animal experiments relate to the human. And government will have done a Phase 3 HIV vaccine trial for the first time, which will make the subsequent trials of related or different vaccines smoother and faster.

Two years ago in our *Agenda for Action*, AVAC stated that a far greater number of clinical trials must be initiated if there is to be any chance of reaching a ten-year goal for an HIV vaccine. Then and now, we support the evaluation of vaccine products in clinical trials when the products and trial designs are likely to help researchers learn more about vaccines and protection from HIV.

If candidate HIV vaccines were drugs that could totally eradicate an infection, they would be tested on even the slimmest evidence of potential. For both drugs and vaccines, uncertainty is involved and lives potentially saved. Where there is real potential for progress on HIV vaccine research, it is incumbent upon us to act.

“Last year, AIDS killed about ten times more people in Africa than did armed conflict... The breakdown of health and education services, the obstruction of humanitarian assistance, the displacement of whole populations and a high infection rate among soldiers—as in other groups which move back and forth across the continent—all these ensure that the epidemic spreads ever further and faster.”

Secretary-General Kofi Annan

United Nations Security Council Opening Session
January 10, 2000

THE GLOBAL RESPONSE

► **STATUS** UNAIDS Ethics Guidelines issued • IAVI receives funding and signs contracts • Public awareness of global nature of epidemic • Multiple human trials beginning • Increasing government interest • Increasing number of partnerships • Growing advocacy ► **RECOMMENDATIONS** Ensure ethical trials through advocacy • Fund IAVI and other efforts to advance international research • Support new mechanisms to deliver existing vaccines • US government agencies should facilitate partnerships

Governments and citizenry in countries rich and poor have finally woken up to the magnitude of the international epidemic and its catastrophic impact on Africa, Asia, and other regions. Hopefully, we will not return to pleasant slumber.

Leaders in the West have recognized the importance of making vaccines primarily for use in developing world populations. Yet development of these targeted products has a long lead-time and somewhat uncertain outcomes. Deciding to make a product, or multiple products, to test in a certain population allows infecting viruses from that location to be used in the vaccine design. But the time between that decision and large scale testing could easily be five or more years.

In the mean time, these approaches may look less appealing, and new approaches may be conceptualized and developed. Simultaneously, almost every desirable population for testing is changing—its virus, its seroincidence (especially with quality prevention efforts) and its politics. The countries with demonstrated interest in vaccine trials, Thailand, Uganda, South Africa, and China are working with research partners. Other countries may not be

politically stable enough to live up to commitments to launch trials.

Partnerships for clinical trials

Other players have adopted the Department of Defense and IAVI mode of developing vaccines by brokering between developers and affected countries. Each research group wants a trial site to have:

- Cooperative, enthusiastic government and agencies.
- Scientific experience.
- Some health infrastructure.
- A sizable cohort of at-risk individuals.
- A high seroincidence.

Every site wants:

- Whatever vaccine approach currently looks most promising.
- An antigen developed from local virus strains.
- Access to a successful vaccine.
- Improvement of their infrastructure.

The prime, targeted countries have an embarrassment of suitors. Most also have a serious enough epidemic to work with many researchers. These relationships require a long-term commitment from developed countries to work with developing-country scientists and provide training and infrastructure over many years. These important negotiations should probably not be left entirely to the agencies and scientists involved. Other US government agencies, including the State Department and USAID, and European Union agencies should help facilitate these matches. Since 1992, WHO and UNAIDS have been assisting developing countries in the development and implementation of national AIDS vaccine plans.

Several developing countries have made the long-term commitment of educating their populations and are already conducting preventive vaccine trials: Thailand, China, Cuba, Brazil, and Uganda. A VTN trial is set to begin in Haiti, Trinidad/Tobago, and Brazil. Planning for trials is in various stages of discussion or development in several more countries, including Russia, India, and a number of African countries, including Kenya, Zambia, Zimbabwe, Botswana, Malawi, and Ethiopia.

Several countries in the developed world are also beginning to create programs and invest in vaccine research and development. These include the UK, European Union, Japan, Australia, and Canada. Canada and the Netherlands are also participating in the Vaxgen efficacy trial.

Most encouraging to us has been the awakening of developing countries to the possibility of developing or contributing to the pre-clinical development of vaccine candidates themselves. Their resources are dwarfed by the companies, governments, and foundations of the Northern hemisphere, but these moves toward empowerment in the face of an overwhelming disaster bode well for cooperative activity and concerted action. Nothing, perhaps, would

move the vaccine development effort forward more quickly than invigorated governmental and scientific partnerships, and a sense of ownership by populations where vaccines must be tested and where they are most needed.

INTERNATIONAL ORGANIZATIONS AND AGENCIES

The important international agencies, WHO-UNAIDS and World Bank are each making different contributions to globalize the AIDS vaccine development effort. A few charities and foundations, notably amfAR and Elizabeth Glaser Pediatric AIDS Foundation, are funding pre-clinical research. The International AIDS Vaccine Initiative, however, stands out for its activities and accomplishments. These include assembling a staff of fundraisers, scientists, and communicators that are attracting substantial charitable and public contributions, financing product development, and keeping the field informed of activity and progress. They have also been instrumental in the development of similar initiatives in other countries.

UNAIDS/WHO

The multi-agency UNAIDS has represented the United Nations since 1996 in calling the world's attention to the severity of this epidemic. In February, 2000, the UNAIDS AIDS vaccine program was reorganized as a joint program of UNAIDS and the World Health Organization's Expanded Program for Immunization called the WHO-UNAIDS HIV Vaccine Initiative. The Initiative "will focus on strengthening the [research] capacity in developing countries to ensure that vaccine trials are conducted with the highest ethical and scientific standards." Leaders of the Initiative

hope it will be able to “broker partnerships between public and private sectors,” in order to accelerate research.

Since 1989, WHO and UNAIDS have been establishing international co-ordination and collaboration on HIV vaccines, and assisting selected developing countries in establishing infrastructures where HIV vaccine trials could be conducted with the highest ethical and scientific standards. In 1992–3 they assisted Brazil, Thailand, and Uganda in the development of their National AIDS Vaccine Plans. National plans provide, 1) policy frameworks for vaccine activities, 2) procedures and mechanisms for review, approval and monitoring of vaccine proposals, and, 3) preparatory research (virology, epidemiology, clinical trials, social behavioral studies).

These plans were instrumental in the conduct of trials in the countries noted above. Of the twelve HIV vaccine trials conducted in developing countries since 1983, eight have been, or are being conducted in Thailand. The others were conducted in China (1993), Cuba (with technical support from UNAIDS), Brazil, and Uganda. WHO-UNAIDS is currently assisting China, Ethiopia, Zambia, South Africa, Russia, and India in the development of national AIDS vaccine plans, strategies, and missions, and focusing on regional approaches, with development of an African AIDS vaccine strategy.

In February, 2000, UNAIDS released its *Guidance Document on Ethical Considerations in HIV Preventive Vaccine Research*. The document contains eighteen “guidance points” on HIV-vaccine-trial ethics. Among its conclusions: if a vaccine proves to be efficacious, all trial participants “as well as...other populations at high risk of HIV infection” should receive the vaccine as soon as possible; and, community representatives should be involved “early and in a sustained manner” in research-design and planning.

The most controversial issue addressed by UNAIDS was the extent to which researchers in all countries are obligated to provide HIV-related health care to vaccine trial participants who become infected with HIV during the trial. After extensive debate, the UNAIDS Guidance document took a middle ground, calling for care and treatment for HIV for participants, “with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country.”

Advocates, researchers, and community members must press for the best possible care in every trial. At the same time, the West should not insist on provision of Highly Active Anti-Retroviral Therapy (HAART) to every vaccine-trial participant in countries where HAART is unavailable to persons not involved in the trials. Local governments, researchers and health authorities have a responsibility to strive for the highest quality care possible, as do researchers not from these countries. We believe local communities and authorities should decide when to participate in trials.

This important work is done with less than \$2 million per year, to serve all UN member nations.

INTERNATIONAL AIDS VACCINE INITIATIVE

The Bill and Melinda Gates Foundation provided the International AIDS Vaccine Initiative (IAVI) a large grant to fund its HIV vaccine research. IAVI has raised about \$75 million to fund five to six vaccine development projects. If any one proceeds to wide testing, IAVI will need hundreds of millions more. IAVI continues to make an invaluable contribution by keeping the issue of HIV vaccines before the public, scientific community, and governments around the world. It has helped similar efforts in the UK and South Africa, and will continue in other countries.

WORLD BANK

The World Bank has established an AIDS Vaccine Task Force co-chaired by Amie Batson and Martha Ainsworth. They have been exploring ways that this international lending agency could accelerate development of an AIDS vaccine for developing countries. Their work has helped clarify alternative approaches and shown governments and foundations how their contributions can influence the effort. One part of their recommended program is establishment of a purchase fund or low-interest loan replenishing fund to spur investment and to buy a vaccine when available.

GLOBAL ALLIANCE FOR VACCINES AND IMMUNIZATION

Every year, 6.7 million children under the age of five die of infectious diseases, almost entirely (99%) in the developing world. Approximately 4.1 million (70%) die from diseases preventable through immunization: Pneumococcus, Measles, Types of Haemophilus, Pertussis, Tetanus, and Hepatitis B. This current deficit is raised when planning for future

vaccines, such as HIV. In the past, it has typically taken many years and massive international efforts with intensive worldwide support to achieve broad access to critically needed vaccines.

Global Alliance for Vaccines and Immunization (GAVI) has received funding from the Bill and Melinda Gates Foundation, the International Federation of Pharmaceutical Manufacturers Associations, UNICEF, WHO, and the World Bank. GAVI is intended as a demonstration project to deliver existing vaccines and to pave the way for delivery of new vaccines worldwide when they become available. (The Bill and Melinda Gates Foundation also pledged \$750 million to a global fund for children's vaccines and has made a commitment of \$100 million for the Bill and Melinda Gates Children's Vaccine Program, both of which will promote delivery of existing vaccines to children in low and middle-income countries.)

Somehow or other, most countries in the industrialized world allowed fifteen years to pass, before the discovery that AIDS is a monumental problem in Africa. Asia, Eastern Europe, and South America face the same unbearable catastrophe.

THE LONG MARCH OF

“Usually, we take a small amount of the tiny little monsters from people who are sick. We do lots of very complicated things to make them weak. But none of the complicated things worked very well with the little monsters that caused mumps.”

Jean-Louis, Y. with Simon, D., *The Story of Jeryl Lynn* Based on a true story about the discovery of the Jeryl Lynn mumps strain and the creation of the combined vaccine against measles, mumps, and rubella. Merck Vaccine Division, 1997.

Many dedicated researchers are devoting time and resources to improving our knowledge about HIV and immune responses in a concerted effort to help design and develop HIV vaccines. This work ranges from basic immunology in small animals and HIV pathogenesis and epidemiological research, to experimentation with various vaccine techniques and concepts in the test tube, in animals, and in vaccinated or infected individuals. In this arena, every new bit of scientific evidence adds to our ability to conceptualize and develop better vaccines. Without passing judgment on the importance of any individual work and with the awareness of being unable to mention many lines of research that will certainly be important, here is a very limited snapshot of what's going on in several research areas.

Basic immunology

Investigators are plumbing the complexities of the immune system, often in mouse models. This is leading, step-by-step: to improved understanding of the role of antigen presentation, immune help, development of memory cells with their initial expansion and subsequent reduction, maintenance of memory, and killing of infected cells by cytotoxic T lymphocytes and other mechanisms.

Dynamics of infection

Of great interest for designing vaccines are the dynamics of early infection. HIV can replicate in resting and activated CD4 cells at the portal of entry, rapidly producing chronically infected cells (Haas and others.) It would be useful to know how much of infection is from cells vs. free virus; where infection begins; and how, where,

and how fast it spreads and establishes itself in the lymph system.

HIV presentation

Investigators focusing on mechanisms of cellular immunity and its absence in early and late HIV infection are probing the function of professional antigen-presenting cells. Recent work has identified that dendritic cells can pick up HIV from mucosal linings and shuttle it to T cells in lymph nodes without becoming infected themselves (Geijtenbeek and others.)

Neutralizing antibody

The intractability of making broadly neutralizing antibodies to HIV with vaccines has captured the attention of another group of investigators who are trying to understand how the few monoclonal antibodies identified in infected individuals work. These researchers may be beginning to understand why HIV is so difficult to neutralize. Scientists are also trying to understand and confirm experiments that captured “fusion competent” molecules on cell surfaces that induced broadly cross-reactive antibodies in mice (Nunberg.) Some investigators believe that gp140 (gp120 with part of gp41) looks to be a more

SCIENCE, WHAT'S NEW

promising antigen and it is being developed by at least two groups (Progenics and Chiron.) Other investigators are deleting variable loops from the virus which appears to enhance immunogenicity (Desrosiers and others.)

Viral entry

Structural biologists have recently made strides in understanding the crystal structure of gp41 and identifying sites to block viral entry for drugs and vaccines (Kim and others.)

Immune signaling

Other distinguished investigators, particularly Fauci, Levy, Paul, and Gallo, are studying the complex and very important interaction of immune signals by cellular cytokines and chemokines.

Immune failure

Epidemiologists and field researchers are meanwhile trying to piece together the mysteries of long-term non-progressors and highly-exposed-but-uninfected individuals. Clinical researchers are re-examining the role of therapeutic vaccination, which might be combined with highly effective antiviral drugs. Not only might this approach assist with immune

reconstitution and defense in infected individuals, it also may help answer some key questions about their value as preventive vaccines to control subsequent infection.

VACCINE DESIGN DERBY

The use of viral and bacterial vectors is currently a very active area of research, and a wide range of vectors is being studied. These vectors have different safety profiles, licensing statuses, and abilities to accept HIV genes or sequences. Now that safer, non-replicating Canarypox vectors are far along in human testing, replicating vectors, such as attenuated vaccinia, are getting much attention. Other interesting vectors that may hold promise include: attenuated herpes viruses, adenovirus, and adeno-associated viruses (AAV.) The alphaviruses, Venezuelan equine encephalitis (VEE), Semliki forest virus (SFV), and Sindbis also hold promise because of their apparent ability to target antigen presenting cells. DNA vaccines are being refined and explored on many fronts, in an attempt to optimize their genetic composition and delivery.

Adjuvants that can boost or direct the activity of an antigen are an

under-appreciated area for improvement. Dozens of potential adjuvants could be tested with a variety of antigens in animals and humans. Some of these may promote antibody formation, others may be more likely to promote cell-mediated immunity. Cytokines might also be used as adjuvants for vaccines.

ANIMAL TRIALS, AND TRIBULATIONS

From animal researchers, the two main lines of inquiry are attempting to understand protection from attenuated SIV, and comparative challenge studies with intensive immunological analysis. Monkeys can be challenged with virus strains that display various levels of virulence, selected for their genetic type allowing sophisticated immunological analysis, and biopsied or sacrificed to analyze effects in tissue and other compartments. Parallel testing in human trials and animal challenge experiments may allow a better understanding of the type of immune response induced. Such findings may also help us to be more selective in the regimes we choose to move forward into future efficacy trials.

The development of twin or cloned monkeys with identical histocompatibility (tissue) types would allow the kind of experimentation that is occurring in smaller animals to be validated and extended to non-human primates. Such experiments might help focus the vaccine-development process by providing firm evidence of the relative roles of different immune responses in protection against retrovirus infection or disease.

Shortages of Indian macaques for vaccine experiments and insufficient planning for future needs may jeopardize or delay this essential and informative research, making it almost prohibitively expensive to conduct experiments with large enough numbers to obtain statistically significant results. The provision of adequate numbers of non-human primates from pathogen-free colonies would improve the ability to conduct more meaningful experiments.

ASSAYS NEEDED

It will probably be just as important to have good assays as good

immunogens. Hard work is finally being done, especially by Becton Dickinson Biosciences, Merck Research Laboratory, Oregon Health Sciences University Vaccine and Gene Therapy Institute, Harvard Medical School/Massachusetts General Hospital, the Vaccine Trials Network, and NIAID Division of AIDS to develop measurements that can efficiently and reliably be used to measure immunogenicity more sensitively and more practically in field situations.

As great as all this activity sounds, and is, there are reasons for reservations. There are avenues for future vaccine development that appear to be stuck in research labs without sponsors or champions who have product development experience. IAVI and the government are assisting to some degree, but much more could be done. Aside from the risk and lack of scientific certainty, companies want to have patentable techniques or approaches to protect their work, and seldom will move forward without “intellectual property.” The lack of any validated surro-

gate measurements for efficacy or proven animal models hampers progress. Unfortunately, because there is no alternative, some human efficacy trials will be required to establish the relationship between vaccine responses and efficacy. It is possible that this relationship will never be conclusively determined even after an efficacious vaccine has been discovered, licensed, and distributed.

That said, every year incremental progress is made toward understanding the mechanisms of HIV infection and varying degrees of protection. We've discovered that one of the most important attributes of a good scientist is knowing which important questions are amenable to getting an answer with current techniques. The attribute of a brilliant scientist is to develop novel techniques to answer an important, previously-untestable question. While we can't afford to wait until the complete picture is clear to us, these remarkable and varied contributions advance our ability to make decisions and move forward.

THE PUSH TO "PULL"

Starting with the groundbreaking work of IAVI and the World Bank, intense interest has been kindled in the desirability of creating a market for AIDS vaccines in advance. The reasons are twofold. First, it is generally agreed that lack of a guaranteed profitable market slows the pace of research and development. Second, the history of vaccines has been that their introduction into the developing world has been unacceptably delayed while developers recoup their investments with sales in rich-country markets. There can be no argument that a widely distributed HIV vaccine for the developing world is a top international public health priority.

These facts have spawned a number of global initiatives: for a purchase fund; guaranteed low-cost loans; a tax credit that purchasers could pass on to sellers; "roaming market exclusivity," which would allow extension of one patent in exchange for giving up the vaccine patent for the developing world; and a liability fund similar to the one for childhood vaccines. The promise of widespread access at the end of the road is the chief benefit of these plans.

On the other hand, the market for global vaccines will never be as big as for computers or the Internet. It will probably never be as big as for

the blockbuster lifestyle drugs. And it will be a managed market. A case can be made that we are undervaluing immediate incentives in our rush to fill a pot of gold at the end of the rainbow. Money for research and development, and incentives that make research and development less expensive, also can have a substantial impact on the pace of research and development. At least one vaccine maker believes that an HIV vaccine could more profitably be sold and cost-justified, country by country.

We continue to push for "push" interventions, especially direct funding for research and development and tax credits that are more generous and targeted than those available for general research and development. These efforts to entice more companies and investigators into the effort give immediate incentives to those brave enough to try—not just to a single winner at rainbow's end. For this reason, The Gates Foundation is investing in push initiatives for all three big killers, through IAVI, their newly formed Malaria Vaccine Initiative, and the Tuberculosis International Vaccine Collaborative.

As described in *BioCentury*, the Bernstein Report on BioBusiness, the cost of developing a vaccine can be justified only by

a market of \$500 million to \$1 billion a year at maturity, and it will be difficult, if not impossible, for a purchase fund to maintain such expenditures. More promising would be to create a bona fide global market by reducing cost with global distribution. The original cost of the Hepatitis B vaccine was \$40 per shot, but the price has decreased substantially for developing-world markets. As *BioCentury* recognizes, the size of this market is potentially immense, but pharmaceutical companies "do not normally venture" there.

The immense investment to get all the way to a vaccine can probably only be borne by a large pharmaceutical company, even with substantial government assistance. This means that "pull" mechanisms are largely of value to the few biggest companies that can afford to run that course. Smaller companies must count on acquisition by a large pharmaceutical company or by making investment and marketing deals with them.

Do we really only want only a handful of companies working on an AIDS vaccine, considering they will have other, more lucrative fish to fry? Even the sixth biggest company, Chiron, looks like it's having a hard time keeping pace.

“Problems with liability and profitability have sharply reduced the number of private firms in the vaccine industry. Recognizing that monopolies inevitably place the public interest at risk, I believe that interest is best served by multiple manufacturers and competition, not by monopolistic or universal government purchase, which will limit development of new and improved vaccines.”

Barry Bloom

Dean of the Harvard School of Public Health, in *Science*
September 4, 1994

INDUSTRY

► **STATUS** Industry consolidation • Thirst for blockbusters • Seven research programs (mostly limited) at big pharma • Scraping for resources at biotechs ► **RECOMMENDATIONS** Pass the Vaccines for the New Millennium Act • Establish both “push” and “pull” incentives • Recruit internal company “champions” for vaccines • Urge wealthy companies to step up efforts • Develop technology that facilitates vaccine design

“We will challenge America’s pharmaceutical industry, which leads the world in innovative research and development, to work to make the successful development of an AIDS vaccine part of its basic mission.”

President Bill Clinton
May 18, 1997

LARGE PHARMACEUTICAL COMPANIES

Industry consolidation into goliath companies is not an encouraging trend. Private sector drug companies are under growing pressure to maintain the sizeable profits of the last few years. This pressure drives consolidation, a search for efficiencies in research and production, and an emphasis on blockbuster drugs. These mergers and acquisitions do not bode well for HIV vaccine research. Several important industry vaccine research efforts are already in jeopardy.

Glaxo Wellcome is merging with SmithKline

Beecham, to temporarily become the world’s largest pharmaceutical company with a stock market value of \$186 billion, annual sales of over \$25 billion and an annual R&D budget of more than \$3.6 billion. Pfizer is merging with Warner Lambert after outbidding American Home Products to create an even larger company. Monsanto is proposing to merge with Pharmacia & Upjohn, having already digested G.D. Searle. Aventis is a conglomeration of Hoechst, Rhone-Poulenc and DuPont. In the last decade, Novartis/Syngenta, American Home Products, and AstraZeneca were created to be massive “life sciences” companies.

The US giants, Merck, Pfizer, Bristol Myers Squibb, and Johnson & Johnson have surpassed the large European drug companies—Swiss Roche and Novartis, British Glaxo Wellcome, SmithKline, and AstraZeneca—each with over \$135 billion market capitalization. This is largely because the US is the world’s largest, most lucrative, and fastest expanding pharmaceutical drug market. The only large, industrial country without government health insurance, the US accounts for almost 40% of global drug sales, growing at 12–14% per year—greater than double the rate in Europe where cash-conscious governments rein in windfall profits. High domestic

growth has provided US pharmaceuticals with “a torrential income stream to reinvest in the ever more costly business of finding new drugs,” according to *Financial Times*.

In this monster market, vaccines are a relatively small, niche industry, which may be lost in the shuffle of merger mania. The global market for vaccines was estimated at only \$1.7 billion 10 years ago and it has not risen much above \$3 billion today. Drugs give larger profit margins, less liability risk, and patent protection that is easier to maintain.

After a round of consolidations a decade ago, when there were three times as many vaccine companies, there are now only five big vaccine makers:

- Merck & Company
- Aventis Pasteur
- Wyeth-Lederle/American Home Products
- SmithKline Beecham
- Glaxo Wellcome.

Because of its parent, Novartis, and its history and activity with HIV vaccines, we consider Chiron a sixth. Because of its recently financed capital base, we consider VaxGen a seventh major vaccine company in the AIDS vaccine arena.

This year, we are able to say that, *at this moment*, all seven major companies appear to be working on HIV vaccines. Though several of these programs are modest for them, the increased activity is an achievement. SmithKline and Glaxo Wellcome have only begun their efforts, Wyeth’s remains very small, and the scope and depth of Chiron’s commitment is in question. In the last year, we have noted the following activity and changes, among them:

MERCK

After some years testing DNA constructs, Merck & Company began its first clinical trial of an HIV vaccine, an optimized *gag* vaccine. The company funds all of its own research and the Phase 1 trial is at several sites. The company plans for results of this trial to lead to a multi-gene DNA vaccine, which may be used ultimately with a vector boost. Merck has a history of developing important vaccines over the long haul and the resources to maintain this program, probably as long as they believe they can capitalize on their rights to the DNA immunization technology, licensed from Vical.

Unfortunately, in March, 2000, Merck warned that their current candidate HIV vaccine represents only a first step and is not likely to represent a final vaccine candidate. A company spokesman also predicted that development of an AIDS vaccine will take a number of years, but indicated Merck’s long-term, ongoing commitment to produce such a vaccine.

AVENTIS PASTEUR

The French government, through the Agence Nationale de Recherches sur le Sida (ANRS) and the European Community, heavily support Aventis Pasteur’s HIV vaccine program which has also relied heavily on the US government’s clinical trials networks. Aventis controls the rights to several poxvirus vectors and have focused on their Canarypox vector, called ALVAC. It has taken the company almost a decade to improve this approach by adding to their constructs. They are now poised to test their ALVAC in a Phase 2 trial in the US, Caribbean, and Brazilian sites through the US HIV Vaccine Trials Network, which is in preparation for an efficacy trial planned for next year. Aventis Pasteur is also moving forward with WRAIR in Thailand. (See Trials: page 19). The company has rights to most poxvirus vectors, including

the attenuated vaccinia strain NYVAC, and to the Semliki Forest virus, but they have not been developing them aggressively, choosing instead to focus on Canarypox and expand the large database accumulated on its safety and immunogenicity.

VAXGEN

VaxGen made remarkable accomplishments in the last year. First and foremost, they received approval and completely enrolled the first Phase 3 efficacy trial of a candidate HIV vaccine, their bivalent B-clade gp120, AIDSVAX. Its sister trial is being conducted in intravenous drug users in Bangkok with a combined B- and E-clade product. VaxGen completed an initial public offering with net proceeds of \$42 million and raised an additional \$24 million in a private placement of stock to the investment organization of Paul G. Allen, co-founder of Microsoft. VaxGen has reported clinical expenses, largely for the Phase 3 trials in North American and Thailand, of more than \$9.1 million for two no-frills trials with 7,900 participants at more than sixty sites. The CDC supports ancillary studies for their trials by conducting behavioral research at selected US sites. While awaiting the interim review (2001) and final results of these trials in 2003, Vaxgen hopes to make a trivalent clade A, C, and D version of their envelope vaccine for Africa.

CHIRON

The Chiron Corporation has taken the alternative approach to Vaxgen by stepping back from their original focus on stand-alone vaccines employing gp120 envelope proteins, instead, re-focusing their research on alternative mixed (“prime-boost”) approaches that use novel gene-delivery technologies in combination with next-generation

recombinant proteins. Under the leadership of Margaret Liu (who has recently departed), the Chiron team has developed several new and innovative vaccine approaches in the last few years. These include potent new gene-based vaccines that utilize plasmid DNA adsorbed to microparticles and alphavirus replicon particles to target human dendritic cells—the professional antigen presenting cells of the immune system. These approaches show dramatic improvements in cellular response over conventional DNA vaccines. A prime-boost vaccine strategy using these new gene deliveries, in combination with modified HIV envelope proteins that appear to induce primary isolate neutralizing activity, should provide a strong candidate HIV vaccine for clinical trials in the near future.

Nonetheless, in November, 1999, Chiron announced plans to cut spending for early-stage research in gene therapy and vaccines. Chiron made a substantial investment and contribution to the field of HIV vaccines and should not lose heart now, but redouble its efforts. A great deal of important background work is about to come to fruition. If this newly acquired technology base proves itself, Chiron may be able to join the top ranks of vaccine developers, extend its new technologies to other intractable diseases, and make an immeasurable contribution to science and world health. We call on Chiron and their partner, Novartis, to make that commitment.

Whatever Chiron and other dedicated vaccine companies have been spending, it is, from the point of view of public good, money well-spent. The potential societal cost of reduced activity clearly illustrates the deficiencies of market dynamics. Of the relatively few papers presented at the Retrovirus meeting about vaccines, Chiron had twelve, all of which related to finding better HIV candidate vaccines. We hope that this important work can continue to move forward.

AMERICAN HOME PRODUCTS, SMITHKLINE BEECHAM, AND GLAXO WELLCOME

Of our big seven, that leaves American Home Products (AHP), SmithKline, and Glaxo Wellcome. None of these vaccine/drug giants come close to having the commitment of the other four, and each needs to reassess and expand its commitment to HIV vaccines. Though American Home Products houses several pertinent subsidiaries, only its DNA vaccine effort from Wyeth-Lederle Vaccines has moved into human trials that will hopefully lead to improved constructs and more rounds of Phase 1 trials. The company also has relationships with several academic and NIH researchers, which they state demonstrate a strong interest in developing an HIV vaccine. The subject of takeover speculation, AHP must consolidate its conglomerate parts and commit to a more aggressive approach. SmithKline has stayed on the sidelines, but they have been developing exciting adjuvants in their candidate malaria vaccine that can be used to deliver HIV antigens—which we have heard they are beginning to explore.

Glaxo Wellcome stands alone as the single company that has made the largest contribution and investment in AIDS therapeutics. The company has profited accordingly. While not a vaccine giant, they currently make a rubella vaccine not distributed in the US. Glaxo may enter the HIV vaccine arena with the Powderject technology, that was acquired a few years ago, to deliver DNA vaccines.

As vaccine or AIDS giants, these three companies owe the world a more serious, scaled-up effort on HIV vaccines. AVAC, Congress and the current Administration are working to discover what combination of public opinion, incentives, and persistence can get them to step up to this challenge.

Pharmaceuticals have larger profit margins, less liability risk, and easier-to-maintain patent

protection than do vaccine makers. This situation led Merck, the most successful private vaccine developer, to establish a separate business unit headed by a “champion” for vaccines. For years, this was Maurice Hilleman, followed by Gordon Douglas. Douglas has now retired from Merck Vaccines and joined Gary Nabel at the NIH Bumpers Vaccines Center. Emilio Emini has taken that role at Merck for HIV vaccines. The other companies should follow suit by creating their own vaccine champions.

SCIENTIFIC EQUIPMENT

Industry support is needed in another significant area. Manufacturers of scientific equipment and testing devices must make a commitment to develop products that will aid HIV vaccine research. HIV vaccine science needs to develop new means for assaying how the candidate immunogens work, particularly in the human immune system during and after clinical trials. A promising technology for quantitatively assaying CTL activity, which is the mechanism of most of the current vaccine approaches, is ELISPOT visual imaging. This technology needs to be improved, standardized, and made available.

Scientists are working on sophisticated reagents and technology to measure CTL and T cell immunity. Technology to permit large-scale evaluation by flow cytometry could be the key that will bring us out of the thumbs-up/thumbs-down dark ages. These, and reliable mucosal testing techniques, will be needed to support and contribute to the worldwide scientific effort. We call on industry and government to support development of this critical technology. NIH could place an order for CTL cell sorters for large clinical trials in advance, as the defense department does with its contractors.

BIOTECH COMPANIES

Vaccine development life is even more difficult for the small biotechs and startups that are trying to develop new approaches more or less independently. Given the innovative potential of this sector in other scientific arenas, this is a tragedy. Vaxgen's ability to raise venture capital and then public investment seems to have been based solely on being in efficacy trials, due to early Genentech and government support and the charismatic character and business savvy of its founder, Don Francis, and CEO, Robert Nowinski.

The notables who are surviving in this arena are: Alphavax with its alphavirus VEE; Targeted Genetics Corp. with AAV supported by IAVI; Progenics Pharmaceuticals Inc. with monoclonal antibodies and gp140; CelSci with its HGP30; UBI with its peptides (though it may be dropping this approach); Immune Response with its killed virus (that remains untested in HIV negatives); and Therion, which supports its HIV work in vaccinia and attenuated HIV vaccines solely with government support. This is a sad situation, given our current financial wealth, biotechnological expertise, and innovation capabilities.

Unique among the small biotechs is Therion, which is primarily working on cancer vaccines, with venture capital not available for HIV work. Dennis Panicali, Therion's president, has a commitment to make HIV vaccines and is doing so with a variety of scientific and public partners. The company has a vaccine production contract and an Integrated Pre-Clinical/Clinical AIDS Vaccine Development (IPCAVD) grant from NIAID, to develop three MVA products for clinical testing, a vaccinia-based particle vaccine TCB-IIIB in government Phase 1 trials, and agreements to work with developers in fowlpox and live attenuated HIV.

In a recent interview in *IAVI Report*, Panicali said

he believes a combination of poxviruses may give the best results, but that "Therion is too small to carry many programs simultaneously." When asked what the US government could do to speed things along, he says, "It's just a matter of getting a couple of strong leaders to say, 'This looks good, I've seen the data, let's do the trials. And I'll put my ass on the line and do whatever has to be done to get this trial ready in a year.'"

Government and industry must develop some good, new way to create a thriving competitive market for biomedical prevention R&D. Otherwise, we won't have bright new ideas to bring into the development pipeline quickly enough, if the current predilection for DNA and vectors comes up short. These, and more high-risk exploratory approaches need stimulation with government and foundation support until they can be viewed as credible by "big pharma" and the public. Senator Kerry's and Representative Pelosi's proposed R&D tax incentive has a passthrough credit for investors in biotechs that don't pay tax, so it could very well spur this segment of activity.

In *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895–1995*, authors Louis Galambos and Jane Sewell conclude that there are distinct advantages, over the long term, of a mixed system that combines public, non-profit, professional, and profit-seeking institutions in a manner that achieves specialization of function and employs market constraints to ensure efficiency. They conclude that public institutions and those in the private sector experience cycles of innovation, and that adequate returns for innovation would accelerate new vaccine development by the private sector. By way of example, the Merck varicella vaccine, Varivax, was approved in 1995 after more than a quarter-century of company support of research and development and five chief executive officers.

VAXGEN

VaxGen is not your traditional biotech company. They have broken the mold several times, commencing from their unorthodox beginnings in the halls of Genentech, to the way CEO Robert Nowinski raised their huge first-round of financing from hundreds of people with both investment and philanthropic interests. Even tackling a high risk/high payoff project, such as making an effective AIDS vaccine from a single recombinant protein, gp120, without a major back-up program, challenges the unwritten rules for start-ups.

And yet, they seem to achieve results year after year that would make the largest pharmaceutical company envious. VaxGen is currently carrying out two large-scale Phase 3 clinical trials of its AIDSVAX vaccines, one princi-

pally in North America and one in Thailand. VaxGen has completed the initial inoculation and enrollment of more than 5,000 volunteers in their North American Phase 3 clinical trial of their bivalent gp120-based AIDSVAX vaccine formulated with alum. There is still significant uncertainty about whether the antibodies induced by AIDSVAX will be protective.

VaxGen has recently teamed up with the CDC to conduct epidemiological, social and behavioral research at approximately one-tenth of their trial centers. Although work with the CDC has not yet started at these sites, it broadens the useful information that will be gleaned from the first Phase 3 HIV vaccine trial.

Founder Don Francis has always been tenacious in dealing with the

many issues surrounding clinical trial design and implementation, and has overcome many hurdles. Breakthroughs (becoming infected with HIV some time after receiving the vaccine when one would hope for protection) are expected in any vaccine trial, and analysis of HIV serotypes and time course of infection may lead to a better understanding of the vaccine's efficacy, or partial efficacy, or lack thereof.

One way or another, VaxGen will have an answer regarding the effectiveness of the first recombinant HIV vaccine, as well as precedent for testing other AIDS vaccines as they move forward into the clinic. This answer will be a triumph for AIDS vaccine development and will provide a rudder of sorts for the next generation of AIDS vaccine researchers.

TAX INCENTIVES FOR VACCINE RESEARCH AND DEVELOPMENT

Representative Nancy Pelosi made history in March, 1999 by introducing the *Lifesaving Vaccine Technology Act of 1999* (HR 1274.) This was the first legislative attempt to build a bridge between the vaccine industry and government, to address the most urgent global public health needs. Last fall, Senator Kerry, the bill's Senate sponsor, attempted to add the bill to expiring tax provisions.

This year, Kerry and Pelosi have introduced *Vaccines for the New Millennium Act* (S. 2132 and H.R. 3812), an expanded version of last year's bill that would provide a range of important incentives for vaccine research and development. *This legislation now becomes the focal point for HIV vaccine advocacy in the US legislative arena.*

VACCINES FOR THE NEW MILLENNIUM ACT

S. 2132 and H.R. 3812 would provide a comprehensive package of incentives to deliver and develop vaccines against malaria, TB, HIV, and other diseases that kill over one million people each year. The bills would:

- Declare universal vaccination and immunization of all children within ten years a major goal of US foreign policy.
- Authorize \$50 million in fiscal year 2001 and \$100 million in fiscal year 2002 for GAVI.
- Authorize \$10 million in fiscal year 2001 and \$20 million in 2002 for the International AIDS Vaccine Initiative.
- Provide a tax credit on R&D costs for priority vaccines to reduce the cost of research and development. (Senate bill would provide a 50% credit on increased R&D on these vaccines; House bill would provide 30% credit on all qualified R&D on these vaccines.)
- Allow smaller firms to pass through a 25% tax credit to their shareholders for investments towards R&D on priority vaccines in order to help biotech companies raise capital for needed research.
- Establish a tax credit for sales of priority vaccines, with the credit equaling 100% of the amount paid by a qualifying organization for purchase of a priority vaccine to be distributed in lower income countries —to a total value of \$1 billion.
- Establish a purchase fund administered by the Treasury Secretary, and authorize appropriations of up to \$100 million per year, for ten years, to facilitate the purchase and distribution of priority vaccines. (Appropriations would begin in a year in which a priority vaccine is determined to meet technical requirements set in advance.)
- Direct the President to initiate negotiations with officials of foreign governments for the establishment of an international vaccine purchase fund for the priority vaccines.
- Establish a *Lifesaving Vaccine Advisory Commission* to review progress of efforts to develop priority vaccines, examine the merits of innovative financing mechanisms, and develop consensus among industry and public health advocates on policy recommendations to advance public-private partnerships toward the development of priority vaccines (House bill only.)

In January, President Clinton announced a set of initiatives in his 2000 State of the Union and budget for 2001, including a tax credit on vaccine sales and a contribution to GAVI. These and other recommendations were modified and included in the new Kerry/Pelosi legislation outlined above.

AVAC still thinks that a tax credit on R&D for neglected vaccines, like that in both Kerry/Pelosi bills, could have an enormous impact:

- An R&D tax credit highlights the importance of work on vaccines for HIV, malaria, and TB and costs a fraction of the amount invested by companies themselves.
- It requires participants to justify their work in business terms, but makes it easier for them to do so.
- It rewards companies that have already made this commitment and believe in it, encouraging them to persevere. It should capture the attention of companies that have not committed to research on priority vaccines for a variety of reasons.

- Unlike other push mechanisms, such as direct funding of private R&D, a tax credit is available to all and is not dependent on annual Congressional appropriations.

The R&D tax credit wouldn't interfere with a company's rights to their discoveries or product pricing, but it would require submission of a plan for global access and distribution within one year of product licensing.

We know an R&D tax credit isn't the complete answer, but it does use the taxing power of government to send a clear message to industry. This incentive holds the pharmaceutical companies to their oft-stated humanitarian rhetoric while supporting their proven business methods for getting things done efficiently and well.

“So why has doubt arisen about such a fundamental good? A lack of confidence in public health policy is certainly part of the reason. But so, ironically, is the remarkable success of vaccines which has left parents who have never seen a case of polio or measles to focus their attention solely on the failures.”

Michael Specter

The New Yorker
October 11, 1999

THE PUBLIC: BLUEPRINT FOR ACTION

► **STATUS** Increased visibility of international epidemic • Ongoing advocacy by affected communities • Successful trial recruitment by VaxGen ► **RECOMMENDATIONS** • AIDS service-organizations should have staff dedicated to vaccine issues • Social harm studies and alleviation efforts must continue • CDC should integrate vaccines as a key part of the prevention agenda • NIH must continue to invest in communications • Interested people should: demand action from elected officials: join a Community Advisory Board: consider the pros and cons of participating in a trial: help build a social movement for vaccines

Vaccine Activism Wanted

A high level of community activity has graced the battle against AIDS almost from the beginning. Community activists critiqued and encouraged AIDS research and policy, which created a new model to combat disease. Activists played key roles in decision-making about how to treat people with AIDS, medically and socially, since the mid-eighties.

The NIAID Division of AIDS pioneered inclusion of community representatives in research, through Community Constituency Groups and Community Advisory Boards, with varying degrees of success. AVAC's existence speaks to community involvement in AIDS vaccine research.

Yet, in general, the sense of urgency about therapeutic research fails to animate vaccine work, for some obvious and subtle reasons:

- People with AIDS do not clamor for a vaccine.
- The science involved is difficult.
- Industry faces economic disincentives to develop a vaccine.

- Americans have a predilection to solve problems rather than prevent them.

All these factors contribute to inertia in the quest for an effective HIV vaccine.

Activism Promotes Success

Public engagement is critically important, especially now that vaccine research and delivery issues are receiving increasing attention among the general public and in the halls of Congress.

POSITIVE FACTORS

The President Boosts Vaccines

President Clinton used his bully pulpit to effect an unprecedented awareness about HIV vaccine research in the United States. He called for an increased focus on and resources for vaccine research—using AIDS as a focal point—most notably in his last State of the Union address and a variety of domestic and international venues.

The US media followed suit with news articles and features on the effort to develop an AIDS vaccine in outlets such as major daily newspapers, television's *60 Minutes*, and National Public Radio's *Marketplace*.

Other factors in the mix include several foundations, which led in supporting the efforts of IAVI, PAF, and amfAR to provide direct funds for HIV vaccine research and development. *Until There's a Cure Foundation* provided start-up money for both IAVI and AVAC. Many more foundations, especially large foundations, are needed. Led by the Gates Foundation, large, private foundations garnered publicity for increased attention and funding for vaccine work. The size of some awards made news before a single dime was spent. VaxGen's marketing campaign for sixty American test sites increased awareness in the gay and bisexual male community, although it took one and a half years to fill 5,400 slots in VaxGen's US efficacy trial. VaxGen's record pales when compared to the Salk polio trials in the fifties, which took only six months to fill with hundreds of thousands of children.

Polls show Americans support vaccine development strongly. In a Harris Poll conducted for amfAR in late 1998–early 1999, an overwhelming majority (96%) of American adults of all ages and educational levels think it is important to develop an AIDS vaccine. Seventy-two percent stated they would be very or somewhat willing to take a vaccine themselves or have their children vaccinated, and more than one-third (36%) said they would consider being a participant in an HIV vaccine clinical trial. The Global Health Council (GHC) released stunning results from a June, 1999 poll. Conducted by Lake Snell Perry and Associates, a Washington, DC firm, the poll revealed that 80% of Americans fear the global spread of infectious diseases, and the same number of people know that AIDS is a greater problem today than 10 years ago. Some 90% said they

support fighting such diseases at their source—in poor communities and the developing world. Eighty-five percent recognize that vaccines are crucial to the effort. GHC commissioned the poll in the hope that these issues resonate with citizens, in order to increase politicians' receptivity about a vaccine. GHC found that 40% of respondents were self-identified as conservative, compared to only 33% as liberal, and 23% as moderate.

One private poll showed large majorities of African Americans would participate in vaccine studies. This is significant, given that African Americans have been the subject of unethical research studies in the past, and, as a group, continue to suffer disparities in health care access.

NEGATIVE FACTORS

Anti-vaccine and Animal-rights Protests Increase

Despite the underlying foundation for positive public engagement, growing elements are decidedly negative about vaccines. A nascent anti-vaccine movement challenges the use of childhood vaccines.

Led by parents who probably have never known a death from polio or measles, this movement has made a real splash. At their behest, the US House Government Reform Committee, led by chair Daniel Burton (R-IN), held hearings in 1999 on whether childhood vaccinations should be required. Representative Burton, himself, made a heartfelt but specious connection between vaccinations and autism in a member of his family.

In addition, some US military personnel resist taking required vaccinations against anthrax, a biological warfare agent. Without doubt, widespread media coverage of this issue encourages a negative climate for vaccines.

Animal-rights activists in the US and UK have stepped up campaigns against animal research without offering the public alternative strategies for effective medical research. Activists have made terrorist threats against animal researchers.

Both government and the private sector need leaders to build public support for an HIV vaccine. For the first time, AIDS was diagnosed in more African American and Hispanic gay men than in white gay men, in 1999. To his credit, US Surgeon General David Satcher called for African-American organizations to fight AIDS with the same zeal they brought to the civil-rights struggle. Yet a recent *St. Louis Post-Dispatch* editorial excoriated African-American leaders, who were so instrumental in the civil-rights movement, for their aching silence with regards to AIDS—particularly in communities of faith.

Data show that younger, white, gay men account for the majority of new cases of AIDS in San Francisco—a city that may have the most educated, organized population in the world with regard to AIDS. Still there is no outcry for a vaccine.

The void in government leadership is no less astounding. It isn't that messages about prevention can't reach a public. Countries with far less wealth and behavioral-research ability have shown it can be done. Thailand, Uganda, and Senegal have safer-sex promotion programs, which are orders of magnitude better than the US.

In Thailand, the success of prevention programs has caused seroconversion rates to decline so much that researchers are scrambling to adjust their strategies for trials. Thailand, Uganda, and Brazil have had much more thorough press coverage, which has energized activists and nurtured a climate for political action. In the United States—at least when it comes to AIDS—it seems that the “prevention” in Centers for Disease Control and Prevention has gone AWOL, despite the millions spent.

The Division of AIDS at the National Institutes of Health has begun to make a stab at the task, with the hiring of a consulting firm to advise on developing public support for AIDS vaccine research. The Daystar Group returned a fine report and credit is deserved for commissioning it. The Division has another firm implementing the blueprint provided in the Daystar report, and, at this writing, the key staff position for this work remains unfilled at that firm.

Shamefully, the “Big 6” AIDS agencies in the United States—AIDS Action Boston, AIDS Project Los Angeles (APLA), Gay Men's Health Crisis (GMHC) in New York, Northwest AIDS Foundation in Seattle, San Francisco AIDS Foundation, and Whitman-Walker Clinic in Washington, DC—do not adequately acknowledge the issue. None has a vaccine department or even a contact person working specifically on vaccines.

THE IMPERATIVE TO ACTION

Consensus and Clarity Work

Clearly, there is fertile ground for public support of the AIDS vaccine research effort. But absent a concerted effort by researchers and advocates, the ground will yield a bitter crop.

This will be particularly true if the first real knowledge of HIV vaccine research reaches the public in some unpredictable and potentially sensational or damaging way. Vaccine researchers and advocates must reach the public in the broadest manner with realistic and responsible information or risk continuing negative definition of the issues and work by their detractors. The pieces are all in place—from government agencies to established private organizations—they are simply not being used.

What must be communicated is, at its core, remarkably uncomplicated. Infectious diseases are a clear and present danger, with AIDS leading the way; they can be prevented and there is real, tangible value in doing so; and vaccines are by far the very best and most effective way to do so. The work is substantial and subtle in its detailed implementation, but conceptually, is quite simple. The most important thing all involved can accomplish right now is to reach consensus for action, clarity in the message, and begin the work.

GOVERNMENT

NIH Must Lead

This and past AVAC reports point out that the US government, through its programs at the National Institutes of Health, has the most extensive vaccine research program in the world. Accordingly, it must be the touchstone for public education and awareness on research issues.

One can question why the work was not done sooner, but the consultants hired by the Division of AIDS have done their job well. The Daystar report recommends a focused message similar to that above and urges a thoroughly integrated strategic public awareness campaign, which includes training for key personnel, written materials for internal and external dissemination, identification of lines of authority to respond quickly to public communications needs, and, perhaps most importantly, the use of a clear, consistent message.

However, the first target of the campaign must be the researchers themselves. At the few sites that have been conducting vaccine trials for many years, intense local efforts have enhanced visibility of vaccine issues. Community awareness and education can no longer be thought of as an extra, an

“add-on.” It must be integral to all research. A general public campaign will succeed only in this context.

The CDC must adopt HIV vaccines as a key part of its prevention work. It has an extensive network of prevention planning councils throughout the country, yet vaccine is not found on their agendas. Given that most people involved in research believe that the first vaccine released for use will be moderately efficacious at best, prevention educators must begin the work now, to plan how to integrate that vaccine into communities.

The omission is especially glaring in light of the fact that large efficacy trials have begun in some fifty US cities, yet no prevention organizations have focused on the impact of trials on overall prevention efforts. Fortunately, at least in initial data from Thailand, the presence of trials seems to have increased awareness of prevention in general and had a desirable impact on seroincidence.

Different communities and cultures behave differently, however. We don't know what impact vaccine trials will have on behavior in other affected communities. It is entirely plausible, for instance, that in some communities safer behavior might actually decrease with awareness of vaccine trials because people come to believe that a vaccine is on the way to solve the problem—making responsible decisions about behavior unnecessary.

NON-GOVERNMENTAL ORGANIZATIONS

AIDS organizations are struggling to maintain adequate funding. Meanwhile philanthropic foundations have clearly signaled their interest in vaccines, so this would seem a rich area for organizational investment from a financial position alone,

in addition to the moral position of ending a pandemic. The AIDS service organizations with a history of effective community involvement must revise their strategic planning to respond to the impact of HIV vaccine research on their constituents.

Just as government must have a holistic approach embracing community involvement and public education, so must non-governmental organizations. Research must be undertaken about how best to reach affected populations. Policy must be developed about how to make vaccines accessible to those in need. The public and political leaders must be educated about how vaccines work and their immense promise to defeat AIDS. Researchers and advocates must work with those leaders to ascertain cultural and community needs and concerns. This work is not happening.

The need for an HIV vaccine is most pressing in the developing world. Work must be done now to assess how vaccine research will confront the reality of the international setting. There is more to site infrastructure than equipment. Issues of cultural dissonance, government support, and social acceptance of trials—contentious in the United States—will only be magnified in the international context.

Models for community involvement in research are new enough in the United States. They are non-existent in many other nations. Yet all the issues, problems, and tensions present in the US are present in those countries, undoubtedly along with new ones we have yet to encounter.

A Compelling Argument

The logic of vaccines is compelling. It is almost inconceivable that anyone familiar with vaccines as a public-health tool with the potential to stop an epidemic in its tracks, would be deaf to a call for support. But one need not be deaf to ignore a call that is not made.

Responsible, accurate information about HIV vaccines and the research needed to develop them will engender the support needed for success only if those with the ability are wise enough to provide the information. Without the compelling argument, success is far from guaranteed. Mistrust will continue, fear will grow, and more people will die.

Support from core constituencies and their involvement in the process is key to building and maintaining broader community and public support. Advocates, investigators and governments each have responsibilities and opportunities to build support separately and collectively.

In the introduction to this report, we lamented that no one stages die-in's in the streets, as they did in the past. People are still dying and experimental agents are still not getting into people. Frederick Douglass wrote, "Power concedes nothing without the demand. It never did and it never will. People might not get all they work for in this world, but they certainly must work for all they get."

ABOUT AVAC

AVAC has had a productive year. We led the way to support Congressional efforts to provide incentives for vaccine research and development, and we brought increased attention to the cause. We distributed over 5,000 copies of our book on HIV development and trials, the *HIV Vaccine Handbook*, which the CDC Clearinghouse is stocking and shipping free of charge.

Last year's update, *8 Years and Counting*, was distributed to over 4,500 individuals in the field, organizations, and press, and was mentioned in many publications including *USA Today* and the *Los Angeles Times*. We are very proud of our effort to hold NIH to established interim goals and milestones.

All this activity only increases our obligation to do thorough research and analysis and maintain our reputation for unbiased, insightful public opinion.

To that end, we have increased our staff 50%, from two to three, by adding a Policy Director, with plans to add a fourth person to work on community outreach and education planning. All this has been done without taking away from current AIDS prevention efforts or care, and without support from the companies or governmental organizations that we monitor.

We believe that developing a vaccine is only the first third of AVAC's challenge. The second will be making the vaccine available through pricing and purchasing, which is in large part why we support current proposed legislation. The third will be to get the vaccine to those who need it. There is much more work to do and you can help. Please contact Rose McCullough, our Executive Director, to offer ideas, support, and/or your time (rose@avac.org).

AVAC contributors to this report:

Bill Snow

Sam Avrett

Chris Collins

Adrian Marinovich

Mike Powell

Steve Wakefield

Jim Thomas

Dana Cappiello

David Gold

Rose McCullough

Luis G. Santiago

Allison Bauer

AIDS VACCINE ADVOCACY COALITION
WWW.AVAC.ORG