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6 Years and Counting:

CAN A SHIFTING LANDSCAPE ACCELERATE AN AIDS VACCINE?

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AIDS VACCINE ADVOCACY COALITION — MAY 2001

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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: Regina Aragón, Col. Deborah Birx, Dr. Donald Burke, Jon Cohen, Dr. Jose Esparza, Dr. Patricia Fast, Dr. Bruce Gellin, Ian Grubb, Dr. Wayne Koff, Tom LaSalvia, Dr. Margaret Liu, Donna Lomangino, Dr. Bonnie Mathieson, Craig McClure, Ann McDonald-Cacho, and Rona Siskind.

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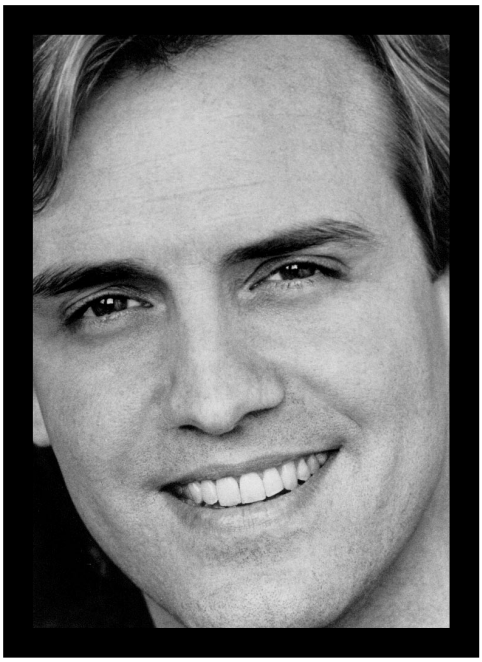
A New Vision

FOR VACCINE DEVELOPMENT

IMAGINE that one could scrap the patchwork system of vaccine development and delivery and put in its place something more efficient and equitable. Put aside for a moment the eternal cautiousness of government agencies, the fickleness of elected officials, the short-sightedness engendered by the profit motive, the perversity of market forces and the simple drudgery of trying to sell prevention to a world captivated by the quick fix. The AVAC vision for how vaccines *should* be made and distributed has seven guiding principles:

- Gaps in research are filled.
- The public is engaged.
- Enlightened self-interest reigns.
- Every avenue is pursued.
- Leadership is ongoing.
- Lives in the developing world matter.
- Risk taking is rewarded.



We dedicate this report to Gary Bonasorte, who died unexpectedly of AIDS-related lymphoma in November 2000. A long-time member of ACT UP/New York's Treatment & Data Committee, Gary was a person of unusual kindness, decency and generosity of spirit. In the early 1990s, Gary recognized the importance of AIDS vaccines and advocated for them at high levels and in his community. While working on community-based treatment trials at New York's Community Research Initiative on AIDS, he helped organize a milestone event, the first-ever community Vaccine Forum, with Gay Men's Health Crisis (GMHC). A decade later, this work continues with support from a burgeoning new generation of activists working together locally, and around the world.

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EXECUTIVE SUMMARY

This was the year it really began to seem possible. A stream of tantalizing headlines signaled new optimism about the prospects for creating an HIV vaccine. The world's richest foundation pledged $100 million to the effort. Global health captured and seemed to hold the world's interest.

This moment of confidence must not be squandered, but used to confront the considerable challenges ahead: answering scientific unknowns, fostering research on products that can be used in developing countries, ending exasperating delays in clinical trials, and preparing to manufacture and deliver an HIV vaccine that can benefit the world.

For all the optimism, significant scientific and political roadblocks remain. And brutal facts bear repeating: half the 15 year old boys in South Africa alive today will perish from AIDS, and still only one vaccine is being tested to determine whether or not it works.

Yet even with these stubborn facts and admonitions, it's clear HIV vaccine research has advanced significantly. For over a decade, we had heard the steady refrain "the science just isn't there" as justification for mediocre industry efforts on HIV vaccine research. This year, Merck's CEO spoke of "recent scientific advances in understanding the biology and immunology of HIV infection," as reason for expanding their HIV vaccine program.

Where once industry steered away from the field, now every major vaccine maker in the world has an HIV vaccine program — and a press release to go with it. Merck confirmed that one of its candidate HIV vaccines has been able to prevent monkeys from becoming sick. GlaxoSmithKline promised Phase 1 trials by the end of 2001. The HIV Vaccine Trials Network (HVTN) proceeded with a Phase 2 study of Aventis Pasteur's newest canarypox product, combined with a gp120 boost. VaxGen awaits interim review of its Phase 3 efficacy trial in November. The International AIDS Vaccine Initiative (IAVI) announced plans to expand well beyond its five research partnerships.

Where once there was a profound failure of will, government leaders are now full of plans and proposals. The European Union pledged additional funding for HIV vaccines, while US funding for research through the National Institutes of Health (NIH) continued to grow. The United Kingdom and the US Congress proposed tax credits for vaccine research and development. The World Bank set aside $1 billion for fighting infectious disease as governments and international institutions began discussions about how to purchase HIV vaccines when they are available. The inability to get HIV medications to most of the developing world captured intensive attention.

REALITY CHECK

To be sure, there is an abundance of activity on HIV vaccines. But letting a thousand flowers bloom doesn't work, even in the flower industry. What is needed now are expanded pre-clinical and clinical research, coordination, and thinking ahead. Numerous obstacles and unknowns are before us.

The Shifting Landscape

Today there are more players in HIV vaccine development than ever before, and this diversity of effort can accelerate research. But absent leadership and coordination, there is no guarantee the expanding research effort will be as efficient or speedy as it should be.

Over the last two years the National Institute of Allergy and Infectious Diseases (NIAID) has created funding programs to help industry and academics develop HIV vaccines. A large new commitment of funds from the Bill & Melinda Gates Foundation to

the International AIDS Vaccine Initiative guarantees that IAVI will engage in more vaccine development partnerships. There is an increased acknowledgment that vaccine development and trials must occur in the developing world. AIDS has finally been recognized as the real social, economic, and security threat that it has always been.

Community

Though AIDS activists have changed the way that the community and researchers interact, vaccine advocacy has a long way to go. A genuine partnership between research and community is essential for successful vaccine trials, but no organization has stepped up to the plate in a serious way to help communities develop meaningful HIV vaccine advocacy or education.

Industry

Every big pharma vaccine company boasts an HIV vaccine program, but most of these programs are relatively narrow and some rely on funding from NIH. Biotechs remain a potential hotbed of research on new products and technologies, but they can't raise investor interest in HIV vaccines.

Protection of intellectual property rights and low levels of liability risk drive industry — but these may get in the way of testing and combining the best approaches. Public/private liability and mechanisms to share rights must be explored.

We applaud Chiron, VaxGen, IAVI, and several others who are developing products designed to be useful in Africa and Asia. This is a welcome change over past years when the overall HIV vaccine research enterprise put development of profitable markets before the needs of developing country populations.

The *Vaccines for the New Millennium Act*, proposed in the US Congress, would provide incentives for private sector research and development on vaccines for HIV, TB, and malaria, but Congress has so far failed to enact this important legislation.

Major New Players

The work of IAVI, the HIV Vaccine Trials Network (HVTN), and the Vaccine Research Center (VRC) — all begun within the past few years — have contributed to the changing landscape of HIV vaccine development. They hold real promise of exercising leadership and filling gaps that plague the organization of HIV vaccine development.

Several major universities have started programs to better coordinate HIV vaccine research at their institutions and have expanded private fundraising to supplement government grants.

US Government

Restructured US government funding and new grant initiatives are doing more than ever before to support product development, but questions remain about how well these limited, publicly funded programs will truly harness the best expertise in industry.

The Centers for Disease Control and Prevention (CDC) must begin HIV vaccine outreach and education efforts to communities of color in the US. VaxGen successfully recruited thousands of volunteers for its Phase 3 trial in the US, but representation among communities of color is limited.

The Department of Defense continues to undervalue its own HIV vaccine effort, and additional government avenues for progress aren't supported at levels needed.

Policy makers acknowledge that public education campaigns will be needed to promote vaccines and explain their limitations, but NIH has stumbled in its efforts to move forward on education efforts — leaving few other major players to focus on this difficult challenge and important need.

Global Issues

Conducting Phase 3 vaccine trials in the US and the developing world will present some of the biggest challenges of HIV vaccine development. We need to resolve if and how to provide treatment for individuals who become infected during trials in countries where treatment is not currently available.

AVAC believes the urgency of the epidemic demands that we initiate HIV vaccine trials as soon as possible, without throwing more roadblocks in the already difficult path to get these trials going. This could mean that, in some instances, HIV vaccine trials begin without the issue of therapy for trial participants completely resolved. But HIV vaccine trials do not take place in a social or public health vacuum. It is neither practical nor morally tenable to promote HIV vaccine research without looking for opportunities to expand access to HIV therapies.

Clinical trials in several developing countries have proceeded, but major delays in launching every one of them have become a disturbing precedent.

There is talk, but little concrete action, on the principle issues that will determine the accessibility of HIV vaccines. The US government has not endorsed tiered pricing. No credible purchase mechanism exists. Health care infrastructure remains negligible or non-existent in countries across the world. When a vaccine is developed, funding to purchase HIV vaccines for poor countries must be in place or we will repeat the sad history of decade or longer delays in delivering new vaccines to the developing world.

VaxGen's AIDSVAX is heading into it's last year and a half of an efficacy trial with the issue of building a manufacturing plant adequate to make the vaccine, if it works, unresolved. Without new public/private cooperation, other HIV vaccine companies will face this same dilemma.

In 1996, the AIDS Vaccine Advocacy Coalition was the first organization to demand that development of an AIDS vaccine become a national goal. President Clinton set that goal in May 1997, calling for a successful vaccine by 2007.

We are now six years away from the goal and counting. None of the challenges are insurmountable. The optimism that characterizes HIV vaccine research today should drive policy makers and researchers to grapple effectively with the issues that remain. An HIV vaccine is possible. The question is how soon we find it, and who gets it when we do.

RECOMMENDATIONS

FOR COMMUNITY INVOLVEMENT:

- The US government and foundations should make funding available to national and community-based organizations to engage in vaccine education and public awareness efforts. They must also support research to identify the best methods to improve community involvement in HIV vaccine research.
- The Centers for Disease Control and Prevention must give real support to HIV vaccine awareness and preparedness objectives included in its new HIV Prevention Strategic Plan.
- The Walter Reed Army Institute of Research (WRAIR), the International AIDS Vaccine Initiative and pharmaceutical companies must specifically include community involvement in their vaccine development efforts.
- Public and private sponsors of vaccine trials must agree to a comprehensive "Participant's Bill of Rights" for vaccine trials.
- All organizations doing any kind of AIDS work should include the development of vaccines in their messages and work.

FOR INDUSTRY:

- The vaccine and biotech industries must demonstrate a civic responsibility to give higher priority to and put more resources into developing HIV vaccines. Cooperative ways to share intellectual property, liability risk, costs and rewards need to be explored.
- VaxGen and its partners must prepare for its release of the first-ever efficacy trial results. Careful media and public education messaging must be crafted to cover all contingencies.

FOR NEW PLAYERS:

- The International AIDS Vaccine Initiative, the Vaccine Research Center (VRC), and the HIV Vaccine Trials Network (HVTN) must exert leadership to work together and coordinate their efforts toward multiple efficacy trials, licensing, purchasing and access for products. They must also share methods, assays, and other vaccine preparedness activities.
- HIV vaccine researchers must give more attention to the need for mucosal protection as a vaccine strategy.
- The National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, the Food and Drug Administration and others must begin the work now that will allow and encourage adolescents to enroll in all vaccine trials so they can benefit immediately from the first efficacious HIV vaccine.
- HVTN and VRC must complete their scientific agendas and set milestones for accomplishing them.

FOR GOVERNMENTS:

- The Bush administration must take ownership of the HIV vaccine challenge, and provide global public leadership toward developing and delivering an HIV vaccine.
- Government agencies must take particular care to work together effectively as they move toward efficacy trials globally.
- Congress must pass the *Vaccines for the New Millennium Act.*
- The directorships of the Office of AIDS Research (OAR), the Division of AIDS (DAIDS), and the National Institutes of Health (NIH) must be filled by vaccine advocates.

- NIH must implement a plan to provide sufficient non-human primates for all HIV vaccine research needs.
- Congress must establish stable funding for The Walter Reed Army Institute of Research at $50 million or more in 2002 and thereafter.
- CDC, NIH and industry must make additional commitments to getting representative participation in vaccine trials by communities of color and other disproportionately affected groups.
- The Food and Drug Administration (FDA) must streamline the investigational new drugs (IND) process for HIV vaccine candidates.
- The US government and other wealthy nations must support expanded efforts to provide Highly Active Anti-Retroviral Treatment (HAART) in developing countries, which will facilitate conducting vaccine trials in those countries.
- The US Patent and Trademark Office should advocate harmonization of international patent laws in ways that encourage vaccine development and affordability.
- The US government, other G8 nations and relevant international agencies must explore all methods for making an effective HIV vaccine available to those who need it, including commitments to tiered pricing, purchasing mechanisms, sufficient production capacity, and intellectual property agreements.
- The US Government must lead the way in creating a credible and sustainable multi-billion dollar purchase mechanism for vaccines against HIV, malaria, and TB. A purchase guarantee should not tie up funds before these vaccines are ready. Instead, governments and foundations should pledge to fund purchase of priority vaccines for developing countries and increase their contributions to multi-lateral organizations for delivery of current and future vaccines.

PRINCIPLE

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Gaps in research are filled.

A credible authority closely tracks public and private research efforts, sets goals and tracks milestones for scientists, provides funding to fill gaps, runs head-to-head trials of differing approaches, and develops technology to facilitate research.

AIDS VACCINES IN A SHIFTING LANDSCAPE

The search for an HIV vaccine has been slow, overly cautious and bureaucratized. HIV vaccine research got off to a quick start once the virus was identified and the SIV/monkey model needed for animal research was developed. But it was a small field. Only a few pharmaceutical companies dominated private research and development efforts. Basic research was conducted by a relatively small group of investigators at universities or in government laboratories. Now the landscape appears to be shifting. *6 Years and Counting: Can a Shifting Landscape Accelerate an AIDS Vaccine?* explores each of these shifts in greater detail. Here is an overview.

THE SHIFTING ROLE OF GOVERNMENTS

Internationally, several European governments and Canada have scaled back or abandoned their directed programs completely — including those in the United Kingdom and The Netherlands. In contrast, the French government, despite frequent changes in its program at the Agence Nationale de Recherches sur le SIDA, has been steadfast in support of vaccine research and development.

In the US, the primary government agency responsible for research and development of an HIV vaccine remains the National Institutes of Health (NIH). In the past, the lead institute on AIDS, the National Institute of Allergy and Infectious Diseases (NIAID), made a concerted effort to become more adventurous in funding basic research. Their Innovation Grants were designed to nurture investigators who are new to the field or have new ideas. NIAID staff had a greater role than usual in the initial phases of this program, but more recently it seems to have slipped back toward business as usual.

In applied research, particularly clinical trials, NIAID reorganized the two consortia of academically affiliated field sites — the AIDS Vaccine Evaluation Group (AVEG), which conducted trials of vaccines, and the HIV Network for Prevention Trials (HIVNET). The newly reorganized entity, named the HIV Vaccine Trials Network (HVTN), operates with a cooperative agreement that charges the HVTN Leadership Group with the dominant role and prime responsibility for the planned activities. HVTN leadership is supposedly held accountable for the level of progress (or lack thereof) in clinical trials. In fact, however, NIAID continues to exert important influence over HVTN, leaving open the question of who is actually and, more importantly, appropriately accountable.

SORTING OUT THE ROLES OF INDUSTRY AND GOVERNMENT

Private industry has the best expertise and infrastructure to bring a product to market, and must participate in the development, licensure and commercialization of an AIDS vaccine. The commitment of the big pharmaceutical companies to HIV vaccines is hard to track. Smaller biotechnology companies cannot manage the development and commercialization of a new product alone, and so must ally themselves with large pharmaceutical partners. A few biotech companies have devoted their limited resources to HIV vaccines, but these efforts are virtually stalled by lack of funds. The one exception is the privately financed Phase 3 trials by VaxGen, which notably is using a vaccine developed by a much bigger firm that had extensive clinical-trial support from NIAID.

Now several biotechs, and even one large pharmaceutical firm, are receiving substantial financial support from government contracts. It remains to be seen whether these NIAID-funded teams will be as motivated, goal-oriented and performance-based

AN INTERVIEW WITH JON COHEN: AUTHOR *SHOTS IN THE DARK: THE WAYWARD SEARCH FOR AN HIV VACCINE.*

AVAC: What if anything has changed on the HIV Vaccine development landscape since you completed "Shots?"

JC: Several important changes have occurred since my book went to the printer. Merck, a major pharmaceutical, is about to announce exciting new results in monkey experiments, which is important both for practical and symbolic reasons. The NIH seems healthier than ever to me, with many products about to emerge from its retooled program at the National Institute of Allergy and Infectious Diseases. With a new $100 million shot in the arm from the Bill & Melinda Gates Foundation, the International AIDS Vaccine Initiative also continues to expand. EuroVac, the European AIDS vaccine consortium, has a little more money and a lot more momentum. Then there's a new AIDS vaccine consortium, the Waterford Project, that links Robert Gallo's Institute for Human Virology, with Harvard University, and the University of California, San Francisco. I think all of this activity is for the good — and long overdue.

That said, I'm still concerned about the central thesis of my book: that there's an absence of overall leadership or direction for the field. Just look at how monkey experiments remain so uncoordinated that you cannot compare one lab's results to another.

AVAC: You make some suggestions regarding "what it will take" to develop and distribute a vaccine. Which were the ones you hoped people would focus on?

JC: I think an important lesson from history is that a mediocre vaccine with less than optimal use by the public can still achieve great things. Look at the first polio vaccine. It had an efficacy of about 60% and only 70% of Americans took it between 1955 and 1961. Despite those limitations, polio in the US dropped 96.6% during those years. The take-home message, I think, is that it's worth testing vaccines that may not appear that promising.

Then again, one of the most difficult challenges facing the field is to decide which vaccines deserve efficacy trials. As a ballpark figure, I know of about 100 different vaccine strategies out there. They obviously all cannot move forward into full-scale, real-world trials. How does the world decide which ones to advance? It will come down to money. Look at VaxGen. The company moved its gp120 vaccine into efficacy trials, even though the NIH decided not to fund the trials, because of a consensus opinion that the preparation likely will fail. Now the world can of course just test everything that has financial backing and appears safe and at least scientifically rational, but that approach I suspect will hit the wall somewhere. Choices will have to be made. Right now, researchers primarily are relying on human immune responses in early phases of testing to decide which vaccines to move forward. I think the monkey model isn't plugged into this equation half as much as it should be.

Distribution issues are enormous, and I have no simple solutions to offer. Jonathan Mann once floated the intriguing idea of having the US government offer a company that develops an AIDS vaccine an incentive to donate the vaccine to the government, which could then distribute it at cost. Mann proposed a patent commodity, which said to the company you can extend any other patent you hold for 20 years or sell the right to do that to another company. I thought it was a terrifically inventive idea, but it went nowhere.

AVAC: You suggested a "March of Dollars." Can you remind us of why you suggested this strategy?

JC: I propose a "March of Dollars," modeled after the March of Dimes, for two main reasons. One is to stage a large, comparative monkey trial that would arrive at, say, the six most effective and safe vaccines in that model. This is a radically different approach than relying on human immune responses to decide which vaccines to advance through the three phases of testing. I'm saying, no one knows which immune responses correlate with

protection, so gamble on the empirical evidence that some vaccines worked better than others in monkeys, for whatever reasons.

The second purpose for a "March of Dollars" would be to have a "gap-filling" committee that met regularly, and quickly gave out money to stimulate basic research. This committee, made of pre-eminent AIDS researchers, would not evaluate grant proposals. Rather, it would discuss the latest insights, contact the groups that made them, and ask them how much money they needed to speed their efforts (no group I know of would turn this down). Then the gap-filling committee would contact a few other groups that worked in the same area and give them money to start competing with the first group. At subsequent meetings, the gap-filling committee would evaluate progress and make sure that these good ideas did not languish or disappear simply because of funding problems.

AVAC: Many readers of the "6 Years and Counting" report are involved in HIV vaccine development or research. Do you have any advice or admonitions for them?

JC: The basic question that I think scientists need to ask themselves more aggressively is this: What do you need to know to solve the problem? The scientific culture in the US — which spends more on AIDS vaccine research than the rest of the world combined — has a profound impact on the scientific culture everywhere. Right now, this culture favors basic research projects that explain mechanisms and often shuns the more applied, trial-and-error type of science that has led to the discovery of many vaccines. I am not advocating that governments cut back on the funding of basic research: understanding mechanisms is critically important. I am simply arguing that we could have a working AIDS vaccine long before we discover why the vaccine works.

as they would be if industry were paying the whole bill. It is also unclear whether such programs will be supported as well by company infrastructure, as those funded solely by the companies.

Meanwhile, the US Congress almost moved into action. Initiated by grassroots activists, tax incentives for research and development of HIV, TB and malaria vaccines were nearly enacted in 2000, with support from such economic heavyweights as former Treasury Secretary Lawrence Summers and Harvard's Jeffrey Sachs. Unfortunately, the measure got lost in an end-of-year legislative train wreck. Congressional action would make a strong statement, but legislation will require broader political support to move forward.

PRIVATE FOUNDATIONS

To date, the US Government and pharmaceutical companies have funded most HIV vaccine research. Foundations have funded some advocacy and social research, but have been much less prominent in funding basic and applied vaccine research. For a number of years the Elizabeth Glaser Pediatric AIDS Foundation and amfAR have given grants for basic research on vaccines.

A dramatic change occurred, however, when the Rockefeller Foundation initially funded the International AIDS Vaccine Initiative (IAVI), which has since raised nearly $140 million for vaccine research — primarily from the Bill & Melinda Gates Foundation and from government sources in the US and Europe. In January 2001, the Gates Foundation announced a $100 million for IAVI over the next five years. Gates Foundation funding for IAVI has made private philanthropy a significant force in AIDS vaccine development and testing efforts. In theory, as an independent organization, IAVI can work rapidly without bureaucratic hindrance. Whether they are actually able to carry a vaccine

TANGLED WEBS OF INTEREST

Government employees and members of official federal government committees, such as FDA advisory committees, must conform to strict regulations regarding real and apparent financial conflicts of interest. In the new landscape, significant power is wielded by less official groups, such as the AIDS Vaccine Research Committee (AVRC), the HVTN steering committee, the IAVI boards of advisors, or kitchen-cabinet groups that are not formally advisory.

AVAC believes that conflicts — not only financial but also more subtle conflicts relating to intellectual or professional interests — should be disclosed and dealt with openly in these settings so they don't inadvertently become a hindrance to vaccine development. AVAC recognizes that individuals often play pivotal roles in one or more organizations, as principals or advisors. This can serve to promote open communication and cooperation, provided all recognize the tangled motivational webs that might influence their decisions. Organizations and individuals have a responsibility to create plans for managing any identified or potential conflict.

AVAC has done some self-examination in this regard. We will be posting information on our web site about our board members' affiliations. We urge other vaccine advisory and decision making groups to develop their own disclosure policies and procedures.

through to efficacy testing and large-scale manufacturing and licensure, or how quickly they are able to do so, of course, remains to be seen.

THE GROWING IMPORTANCE OF INTERNATIONAL RESEARCH

A major concern in HIV vaccine research has been that insufficient testing is conducted in developing countries on HIV strains prevalent in those areas. Progress in testing vaccines in less developed countries is critical. If approval for clinical trials is less certain, if timelines are longer, and costs are higher than in industrialized countries, these countries will lose their place at the table. Clear procedures for timely and sound scientific and ethical review in developing countries are critical. IAVI and the Joint UN Programme on HIV/AIDS (UNAIDS), in particular, have begun to focus on these needs.

Investigators in countries where vaccine trials are planned and carried out must avoid the agonizing delays that characterized trials in Thailand, Brazil, Trinidad, Haiti and Uganda. Lessons learned from these pioneers must be shared so that other countries may move more quickly. Partners from abroad have a responsibility to make a long-term commitment to enhance local scientific capacity, and produce vaccine candidates designed for the regional epidemic.

AIDS IS FINALLY UNDERSTOOD AS A SOCIAL, ECONOMIC AND SECURITY THREAT

Economists are becoming more involved in the AIDS vaccine story, and that is very good news. The global financial community is becoming aware that a disease that halves life expectancy in a country and robs it of its educators, engineers, business leaders and public health professionals, is going to result in dramatic economic dislocation and increased poverty. Political and other world leaders have also recognized that the AIDS pandemic threatens to undermine political stability in many countries. The US and other industrialized countries finally understand that AIDS is a national security problem for them, as well as for the developing countries that will be hardest hit.

With substantial funding by the Bill & Melinda Gates Foundation, the World Bank has joined with several United Nations organizations to form the Global Alliance for Vaccines and Immunization (GAVI), devoted to increasing utilization of existing vaccines worldwide. If this is successful, it will provide a paradigm for delivering new vaccines (for HIV, malaria, TB) to the world's poorer countries.

BEGINNING TO ADDRESS A FRACTURED AND UNCERTAIN REGULATORY ENVIRONMENT

The US, the European Community and Japan are in the process of implementing guidelines developed by the International Commission on Harmonization (ICH) that should allow sponsors of clinical trials to work more efficiently in an international setting. These guidelines may prove helpful to developing countries by providing consistent standards they can follow. Methods for registering new drugs and biological products across the entire European Union are evolving. Once an effective HIV vaccine is identified, regulatory developments designed to speed the transition from research to a licensed product can be utilized widely.

Unfortunately, the US Food and Drug Administration may be moving in the opposite direction. Responding to pressure from anti-vaccine advocates, and the identification of a rare but serious side effect during the first months of marketing of a new vaccine, FDA is considering increasing the size of required safety trials five-fold or more prior to licensing any new vaccine. If implemented, this change would so increase the cost and time involved in HIV vaccine development that it could have a chilling effect on pharmaceutical company investment in HIV vaccines, reducing the chances of success even further.

Recently, several groups have held consultations on the ethics of HIV vaccine trials. *The Helsinki Declaration*, which sets forth international standards for medically and ethically sound scientific research, has also been revised. While no one argues that ethical principles should be overlooked in developing countries, the methods devised to assess the risks and benefits of efficacy trials are very controversial. The unintended result of applying a single "risk/benefit ratio" calculation upon radically different environments may be to restrict vaccine trials to industrialized countries. If HIV vaccines are tested in industrialized countries alone, there will be two unfortunate outcomes: the trials will proceed more slowly, and the vaccines will not be designed for the practical requirements of less developed countries. The difficulty of such issues demands that each of the countries involved play a leading role in decisions concerning ethics of trials.

PRINCIPLE

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The public is engaged.

The public demands an HIV vaccine and is unsatisfied with what is perceived as the slow pace of research. It continually pressures politicians and the scientific community to broaden the vaccine pipeline and initiate more trials, recognizing that failure to act is more culpable than action even when success is not guaranteed.

LAYING FOUNDATIONS IN COMMUNITIES

■ STATUS NIH Starts Communications Steering Group • Non-Governmental Organizations Begin To Get Involved • Media Coverage Remains Uneven • Most Foundations Remain Uninvolved • Study Participants Rights Still In Question ■ RECOMMENDATIONS Governments And Foundations Must Fund Education And Awareness • Research On Community Best Practices Needed • Research Institutions Must Include Community Involvement • Trial Sponsors Must Protect Participant Rights.

What has perhaps set AIDS apart from most other diseases is the extent to which an active community constituency follows research, lobbies for changes in the way business is done, and actively participates in the research effort itself. If there has been one guiding ethical principle that has emerged, it is that those affected by research deserve a role in decisions that impact their lives.

Enlightened self-interest also dictates the need for direct community involvement in HIV vaccine development. For example, VaxGen Phase 3 trials involve thousands of volunteers in several countries. The release of results from that study in 2002 raises a number of issues. What consequences would misunderstandings and misconstructions of the results have on future trials by VaxGen and others? Making productive plans for every contingency requires that community members be actively engaged.

In addition to the benefit of avoiding or managing potential problems, community involvement also yields many other positive results. Good relationships between the scientists and governments of nations involved in research; the building of trust between researchers and trial participants; the ongoing successful enrollment of trials — all flow more easily if the communities affected and the public-at-large are educated and meaningfully involved in the effort.

BUILDING SUCCESSFUL COMMUNITY INVOLVEMENT

In a world of science illiteracy and mistrust of authority, successfully engaging the general public and getting affected communities involved in vaccine development is not a simple challenge. It will require action on a number of fronts:

- **Consistent and understandable messages about HIV vaccines and vaccines in general must be developed and used by those working on an HIV vaccine.**
- **Researchers, policy makers and public health leaders must be forthcoming in communicating their work and goals to the public.**
- **Affected community members must become more involved in the substantive work of research through public education and mechanisms such as Community Advisory Boards.**
- **Opinion leaders and institutions from affected communities, AIDS service organizations (ASO), and public health organizations must be involved locally, nationally and globally in such areas as funding, education and planning.**
- **The rights of trial participants must be safeguarded through negotiated and enforceable agreements.**
- **Coordination must occur between vaccine researchers, other HIV prevention and health promotion efforts, and community vaccine advocates.**
- **Contingency plans for communication with the public must be developed in advance for the inevitable but unpredictable problems that will occur in the course of research. The public must be reminded that failed strategies teach us how to plan future and better strategies.**

- **Finally, there must be funded support for research on successful models of community involvement and for effective public education on AIDS vaccine issues.**

All these efforts must take into account various aspects of public opinion that may act as barriers to community involvement. These include a small but vocal anti-vaccine movement and historical fears of medical research in resource-poor and ethnically diverse communities in the US and other countries. Also, there is a perception in the industrialized world that, with the advent of Highly Active Anti-Retroviral Treatment (HAART), the epidemic is "over" in industrialized countries and is therefore no longer of deep concern.

SUPPORT BUT LITTLE ACTION

One can see the beginnings of a successful engagement of the public and affected communities in HIV vaccine research.

Whether or not one agrees with all the details of former President Clinton's policies, he did use some of his time in office to raise awareness of AIDS issues — including the need to develop an effective vaccine. VaxGen's campaign to enroll volunteers in its study raised awareness of vaccine research in gay and bisexual communities throughout the US. The media has also shown some willingness to cover the vaccine story. These and other factors have laid the groundwork for real progress on the public front.

That there is little information on public attitudes about an HIV vaccine is indicative of how little attention has been paid to the issues of community involvement and education. However, polls conducted by the Harris organization, the Global Health Council and others, indicate that a majority of the US public understands the importance of finding an HIV vaccine; would be willing to use such a vaccine; and comprehends the global threat of infectious diseases, including AIDS.

Sadly, this opportunity for public education has not been seized.

U.S. GOVERNMENT ATTEMPTS AT ACTION

Two years ago, the National Institutes of Health, through the National Institute of Allergy and Infectious Diseases, commissioned an independent report by the Daystar Group that supports many of the concerns outlined above. To their credit, officials at NIAID recognize that they bear some responsibility for communicating information about HIV vaccine issues to the public. In June 2000, NIAID established the National HIV Vaccine Communications Steering Group to implement the report's findings. However, the lack of meaningful progress over many months, is reason to simultaneously pursue additional avenues to accomplish this vital work.

At the insistence of community activists, NIAID has historically required HIV research programs it funds to create Community Advisory Boards, with the intention that these boards be fully engaged in the programs. The new network, HIV Vaccine Trials Network (HVTN), hired staff for its community education program but it is still not a fully functional community program as it deals with reinvigorating efforts at existing sites and helps new sites engage their communities.

The Centers for Disease Control and Prevention continues to squander important opportunities for community education on HIV vaccine issues. Although CDC-sponsored Prevention Planning Councils exist in communities throughout the US, vaccine issues have never emerged as part of their agenda, despite the fact that human vaccine trials

are active in scores of cities. In its January 2001 *HIV Prevention Strategic Plan*, the CDC has at long last begun to acknowledge the important issues it must address for vaccine research. But the acknowledgment will only have meaning if actions follow the plan.

AVAC is very concerned with protecting the rights of vaccine trial participants. The old HIVNET Community Advisory Board proposed a "Participant's Bill of Rights," most of which was accepted by HIVNET without controversy. To date, however, there is still no agreement with the new network on two major issues: 1) medical coverage for participants who suffer trial-related injury, and 2) access to treatment for those who become HIV infected during a trial. These protections have sometimes been negotiated for individual trials, but there is no overall policy. HVTN leadership says it is committed to resolving these issues, but this has not yet occurred. Obtaining those rights for all trials would be an important step.

The AIDS epidemic is spreading fastest among young people, yet adolescents, who are just entering the age of sexual activity, are not included in vaccine studies. It is important that NIAID, the National Institute of Child Health and Human Development and the Food and Drug Administration, along with those organizing and sponsoring trials, begin to review regulations, policies and guidelines now, to allow adolescents to be included in trials so they too can benefit from the first successful vaccine.

Finally, no comprehensive research is being done to study effective models for community involvement in the vaccine effort. As vaccine research expands and progresses, we need to understand what does and does not work. This research must pay particular attention to communities of color because they have historical reasons for being distrustful about involvement in research.

ANTICIPATING MISUNDERSTANDINGS OF AN HIV VACCINE: THE COMMUNICATIONS CHALLENGE

By Bruce Gellin, MD, MPH
Executive Director, National Network for Immunization Information

The HIV vaccine effort can benefit from our experience with other vaccines that have come before it. Few doubt that these vaccines have greatly improved health and well-being. In fact, immunizations are responsible for most of the 30 years that have been added to the average American's life expectancy between 1900 and 1999.

The paradox of this success is that these serious infectious diseases and their consequences — once common in every community — are now largely unknown. This lack of familiarity is leading an increasing number of well-meaning parents to question the continued need for these vaccines for their children. With the diseases gone, the focus has turned to the vaccines themselves, and many wonder and worry whether they are safe enough.

Some of the growing concern can be attributed to individuals and groups who are convinced that their children have been harmed by recommended vaccines. They question the science and safety of current vaccines, convinced that vaccines cause more harm than good. Others question the morals of those who acquire the disease that a vaccine is intended to prevent. "We already have a vaccine for diseases like hepatitis B and AIDS—this vaccine is called 'values'!" they say.

The "vaccine controversy" has become a popular story. It isn't hard to find magazine articles, books, web sites, Internet chat rooms and talk radio programs that emphasize a tragic anecdote and depict the "mass vaccination" program as a conspiracy between the government and the pharmaceutical companies, who are believed to have co-opted the entire health care system. Some even question the role that vaccines have

played in the control and elimination of infectious diseases. They argue that the observed decline in vaccine-preventable diseases resulted from improved nutrition and sanitation, rather than the development and widespread use of modern vaccines. Others protest the state-based school and day care requirements for immunization on principles of individual freedom and civil liberty. Still others see immunization as "unnatural" and prefer to take their chances with natural diseases to build up "natural immunity." A few even question the germ theory of infectious diseases that underlies the immunization concept in the first place.

Many of these themes have been part of the history of immunizations since the creation of the smallpox vaccine over 200 years ago. Then, as now, the voices of protest were relatively few. Yet their volume — regularly included in media coverage of the vaccine controversy to provide "balance" to the stories and create the tension that lures readers and sells advertising — is out of proportion to their number. This preoccupation with controversy and anecdote has worldwide impact in our current era of communication. Therefore, we need to recognize that this dynamic is now part of the landscape of vaccine research and is likely to become more prominent as promising HIV vaccine candidates are tested and eventually available for general use.

Some of the messages are striking a chord with thoughtful individuals who are trying their best to be informed consumers. Most who question their health care providers about immunizations don't consider themselves to be "anti-vaccine, they are just trying to navigate confusing seas. To help such individuals make informed decisions, it is therefore critical that they know where to find credible and understandable information about vaccines and US immunization policies and practices. Otherwise, those who question will find answers from sources with a different agenda. In the "information age" it is easy to be informed, but it is another thing to be well informed.

There are many reasons for differing views about immunization that may influence one's perception of a vaccine. These include religion, philosophy and alternative health beliefs. But it is important that the necessary public debates reflect the best available science. If education is our objective, then in order to provide answers to the questions that are posed, we need to better understand what people think they understand about vaccines. We recently conducted a national survey of parents of young children, which found that 25% of parents were concerned that too many vaccines could actually weaken their child's immune system, and nearly one parent in five had little understanding of the arduous regulatory process that a vaccine candidate must navigate even before it is administered to the first volunteer, let alone approved for use.

Misunderstandings about vaccines, coupled with perceptions of HIV and the real and perceived medical and social implications of receiving an AIDS vaccine, will only multiply the challenges ahead. If 20% of an inner-city adult population refuses the influenza vaccine because of concerns of harmful "undeclared ingredients" and nearly the same numbers of adults think that you can get the flu from the inactivated influenza vaccine, it isn't hard to imagine how an AIDS vaccine is likely to be perceived.

If we expect to reproduce the long lines of "Polio Pioneers" who volunteered for the large clinical trials that resulted in the licensure of the first vaccine against polio, then we need to undertake a serious education effort. An informed public will need to understand immunizations and know where they can get reliable answers to their questions. "If you build it, they will come" is a grand fantasy for a baseball park, but not likely to be enough to convince the public that the AIDS vaccine is good medicine.

NON-GOVERNMENTAL ORGANIZATIONS (NGO)

The International AIDS Vaccine Initiative (IAVI) has partnerships with non-governmental organizations in eight countries and has jointly funded work plans with four of those. IAVI needs to consider forming additional partnerships with others, both in the US and internationally, in order to broaden its outreach and education efforts. As IAVI moves further into its studies, it too must ensure community participation in its research by establishing mechanisms for involvement.

A few of the US' larger AIDS Service Organizations (ASO) that could play a leadership role in vaccine issues have begun to do so. These groups could contribute much more to the vaccine effort. A number of organizations representing minorities that have active programs around AIDS, such as the NAACP and National Council of La Raza, have begun to pay attention to vaccine issues — although none has truly entered the fray in a significant way. The Latino Commission on AIDS (New York) includes information about prophylactic vaccines in its HIV treatment education curriculum. The National Minority AIDS Council has also begun including vaccine issues in their annual conference programs.

Foundations could become instrumental in the area of community education, by providing funding incentives for such work to community-based organizations. In tandem with government funding, foundation support could help such groups develop models for community action and education in anticipation of multiple efficacy trials and a much larger vaccine development effort. Just as science research needs money, so do community organizing, policy advocacy and education.

Community-based AIDS Service Organizations are on the front line in the battle against AIDS. Ultimately, they will have to deal with the consequences of research and eventual release of a vaccine in their communities. They, and their national counterparts, must assume a greater leadership role in vaccine advocacy before these eventualities occur.

OTHER COMMUNITY OPPORTUNITIES

Community involvement facilitates and improves vaccine research. This is as true for industry-sponsored research as for government and NGO-sponsored research. It is important for companies developing HIV vaccines to create and implement community involvement plans. VaxGen has made a start by establishing a Community Advisory Board for its American/European AIDSVAX study. Vaccine advocates must hold other industry sponsors to the same standard of meaningful community engagement to which we hold public and NGO-funded entities. If Community Advisory Boards prove too cumbersome for some industry cultures, then other effective community-involvement mechanisms must be found.

Although it would be easy to blame the research community for the quality and quantity of media coverage of HIV vaccine research, that would be unfair and inaccurate. The media itself is also responsible for the quality of its coverage, or lack thereof. Although some major media outlets are doing a good job, mainstream media coverage of public health and medical research issues is often scanty and of poor quality. This is true not just for AIDS, but also for coverage of other serious health issues. The media must accept responsibility for this state of affairs and act to redress it.

Last year, Pallotta Teamworks held the first-ever AIDS Vaccine Ride, modeled after bicycle rides in support of AIDS treatment. The 150 riders were required to raise at least $3,200 each to participate in a grueling trek across Alaska. Organizers hoped to donate $1,000,000 to three basic research centers. This event was so successful that each recipient got $1.2 million and three additional rides are scheduled for 2001. To attract donations of that size, the education and appeal must have been powerful indeed.

ACCEPTING RESPONSIBILITY

With AIDS, for the first time ever, those affected by a disease not only called for research to solve its mysteries, but also demanded that they be included as legitimate partners in the effort. Vaccine researchers and advocates must pursue this dynamic model. Community leaders must take charge to ensure appropriate education for trial participation. The unique problems raised by the AIDS epidemic — from social stigma, to the layers of historic mistrust in affected communities — demand this. With it, vaccine research will be stronger and more powerful.

PRINCIPLE

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Enlightened self-interest reigns.

Private sector vaccine giants and upstart biotechs realize that real revenues await the maker of an AIDS vaccine. These companies also take seriously the moral imperative of finding a vaccine. They use some of their own profits and also take advantage of flexible public funding and tax incentives to expand their research programs. Each of the five major vaccine companies has at least one HIV vaccine approach under development to which it commits full resources.

INDUSTRY ISSUES

■ STATUS Intellectual Property Rights Concerns • Research Programs Grow • Spotlight On Public-Private Collaboration ■ RECOMMENDATIONS Companies Must Give Higher Priority To AIDS Vaccine Research

AVAC has said it before, but it bears repeating: the wherewithal and expertise to develop an effective HIV vaccine most clearly resides in industry. Yet industry has been a fitful contributor to the search. The turbulence of company consolidations, the complex challenges of the science and the worries about liability are all difficulties that AVAC has discussed before.

Now another issue — intellectual property (IP) rights — is coming to the fore, as evidenced by the human genome project and on-going battles over licensing and pricing of AIDS drugs. Pharmaceutical companies are, after all, profit-making ventures. The HIV vaccine enterprise demands collaboration, but intellectual property concerns loom over corporate calculations because they cut to the reason these companies exist — to make money from products they develop.

A FORK IN THE ROAD

The very manner in which the completion of the genome project was announced — simultaneously by both private and public research entities — underscored the two conflicting options presented by each new advance in biomedical technology: 1) either protect IP rights to the technology, in order to ensure adequate private investment in research and development; or 2) make discoveries available for use by anyone, in order to reap the benefits of truly collaborative and cooperative science. AVAC believes that vaccine and biotech companies have a civic responsibility to give higher priority to and put more resources into developing HIV vaccines. For this to happen, ways must be found for them to profit from this work without hindering progress in any way. Public/private partnerships and mechanisms to share risks and rights might be explored.

Often industry bases its products on work done by government and academic scientists, and rights are shared. But inconsistencies and inequities in this system have been highlighted in the wrenching machinations of making AIDS drugs available in poor countries. Today there is no coherent mechanism whereby researchers from different sectors can appropriately share relevant discoveries in the best interests of those who will need them.

POSITIVE DEVELOPMENTS

The past year saw more investment in biotechnology than any other year. This spring, both Merck and GlaxoSmithKline got positive publicity in the financial press for their HIV vaccine efforts. These vaccine programs are welcome.

An additional positive development has been the HIV Vaccine Design and Development Teams, which the National Institute of Allergy and Infectious Diseases instituted in the last year to provide "push" incentives to industry to prod their products into clinical testing. The recipients are: Advanced Bio-Science Laboratories; Chiron Corporation; Virax and the University of New South Wales; and Wyeth-Lederle Vaccines. Similarly encouraging public/private partnerships are also underway through the International AIDS Vaccine Initiative (IAVI) — with Targeted Genetics, Alphavax, Virax, Therion, and Maxygen.

Former President Clinton and industry also brought attention to the need for public/private collaboration during a White House summit on vaccine development in March 2000. Pharmaceutical and biotech industry leaders, alongside a cadre of foundation and international health officials, pledged to support increased development of, and access to, vaccines for Hepatitis B, influenza, polio and elephantiasis. A year later, it is still not clear whether efforts begun in this meeting will lead to further public/private collaboration specific to HIV vaccine development.

UNDERSTANDING EFFICACY

EFFICACY in vaccine research is the ability of a vaccine to produce a desired benefit. It is determined through testing in humans called Phase 3, or efficacy, trials. A Phase 3 trial is conducted after earlier phases of testing that measure safety and immune response in increasing numbers of individuals who ultimately reflect the target population for the vaccine. A Phase 3 trial is conducted in a large enough number of individuals who are at risk to measure the effect of the vaccine with statistical validity. The efficacy trial can be designed to see if the candidate vaccine lessens the number of infections, lessens the severity of infections when they occur, reduces infectiousness (transmission), or a combination of these outcomes. It may be possible from a successful efficacy trial to also determine the characteristics of the benefit (only for certain individuals, only for a certain period of time, only under certain risk situations, etc.), and if there is a correlate or connection between the benefit and a measurable immune response.

VACCINES FOR TREATMENT

For companies, the prospect of a therapeutic vaccine — one that prevents or slows progression of HIV disease in someone already infected — is very attractive. The ratio of benefit to risk is likely to be considered favorable in a person with a life-threatening disease: repeated use is likely; insurance will pay handsomely; and HIV-infected individuals would be highly motivated to participate in trials and to request the treatment. The potential market for a therapeutic vaccine is estimated to be much greater than for a preventive vaccine.

REVIEW OF THE MAIN PLAYERS

Of the industry giants who now dominate the vaccine field, Merck and Aventis-Pasteur have active HIV vaccine programs; Wyeth has potential to emerge as a stronger player; and GlaxoSmithKline has promised Phase 1 trials by the end of 2001. If a Merck vaccine candidate is successful in initial clinical trials, and the company continues to aggressively develop it, the landscape will change significantly. Among biotechs, VaxGen faces some critical moments in the next couple years with the scheduled release of results from its AIDSVAX trials. For now, they may be credited with getting a large and complicated trials successfully underway. Once again, Chiron's commitment to its program continues, their science remains sound, and an HIV Vaccine Design and Development Team (HVDDT) grant has helped them stay active.

Merck & Co: Merck's overall research and development (R&D) budget was $2.4 billion in 2000. While the company releases no figures on individual programs, Merck reports that HIV gets the lion's share of its vaccine R&D budget. Merck's CEO, Raymond Gilmartin, said the company would expand its HIV vaccine effort, "given recent scientific advances in understanding the biology and

immunology of HIV infection." Merck currently licenses rights to develop HIV DNA vaccines from Vical, but has other products as well. Ed Scolnick, president of Merck Research Labs, hired Peter Kim as his successor. Kim was formerly at the Whitehead Institute at MIT and was a member of NIAID's AIDS Vaccine Research Committee. Merck is currently conducting a Phase 1 trial of a DNA gag construct, developing a multivalent DNA vaccine and testing an Adenovirus vector in humans.

Aventis-Pasteur: Pasteur-Merieux Connaught, one of the most active vaccine companies, was absorbed first by Rhone-Poulenc and then by the mega-corporation, Aventis. Aventis Pasteur, the vaccine arm of this agri-pharma-chemical giant, continues to work with the French and US governments on development of ALVAC canarypox vaccines, but progress is very slow and the company's commitment to this product at times seems lukewarm. Canarypox vectors have been in the most human trials and elicit a cellular immune response in some vaccinees. If sufficient response is demonstrated in their ALVAC 1452 product in Phase 2 trials this year, it would be possible for the Walter Reed Army Institutes of Research (WRAIR) or the HIV Vaccine Trials Network (HVTN) to mount an efficacy trial, with and without the VaxGen AIDSVAX or Chiron's boost, having cellular immune responses as a correlate endpoint. This would be the fastest way to see what, if any, effect cell mediated immunity has on human infection or disease, advancing our scientific knowledge accordingly. In addition, Aventis has other vaccine candidates in trials or under development.

American Home Products/Wyeth-Lederle: With assistance from one of NIAID's new HVDDT partnerships, Wyeth is working with the University of Pennsylvania and Duke University on a DNA vaccine approach that will be enhanced by immunomodulatory proteins. The group at Wyeth has the expertise and credibility to make any vaccine, should they get the mandate from upper management. The HVDDT partnership may allow Wyeth to establish itself as one of the important HIV vaccine research and development companies. This external funding has recently transformed its back-burner work into a full-fledged HIV vaccine program.

GlaxoSmithKline: Finally, on the day after word of Merck's HIV vaccine program's progress appeared in the Wall Street Journal, GlaxoSmithKline announced their own HIV vaccine program, promising Phase 1 trials by the end of 2001 with HVTN. As the largest maker of AIDS drugs in the world, this commitment is long overdue. The company says they have good results in primates a year after challenge with HIV.

VaxGen: The first efficacy trials of an HIV vaccine, using VaxGen's AIDSVAX gp120, are now fully underway with almost 8000 volunteers enrolled in Canada, Puerto Rico, the US, the Netherlands, and Thailand. VaxGen's current estimate of the trials' final cost is about $80 million. Preliminary analysis of self-reported risk behaviors among trial participants show: declines in injection drug use and needle sharing; increases in condom use among Thai trial participants; and in the American/European trial, a decline in the number of male partners among men who have sex with men. Retention in both trials is over 95%. If the interim review in November 2001 is inconclusive, the trial in North American and Europe will conclude at the end of 2002. A second trial in Thailand is running about nine months behind the North American/European trial. In January 2001, VaxGen was awarded a Small Business Innovation Research grant from NIH for development of a clade C version of AIDSVAX for Africa and India. (See VaxGen: A Case Study, *page 27*)

Chiron: In 1999, Chiron's overall R&D budget was $303 million. Chiron continues to refine its strategy with support from an HVDDT award. Chiron's HIV vaccine approach involves "priming" with DNA vaccines delivered on microparticles, and "boosting" with recombinant viral envelope proteins and alphavirus particles. Chiron also deserves kudos for branching out and developing a vaccine based on the clade C virus, found predominantly in sub-Saharan Africa and India.

REVIEW OF BIOTECHNOLOGY PLAYERS

The field of biotech companies also continues to change and evolve. In the course of time, Appollon has been absorbed by Wyeth-Lederle Vaccines, Virogenetics by Aventis, and Viagene by Chiron. Progenics has emerged as a relatively new player. Two biotechs — Advanced Bioscience Laboratories and Virax — have received HVDDT awards. Therion's focus on cancer had relegated its HIV vaccine program to the backburner, but it has just joined with IAVI and the Indian government on a new initiative. Cel-Sci completely dropped its HIV vaccine program in favor of its cancer program last year.

Advanced Bioscience Laboratories: An affiliate of Organon Teknika, ABL is working with the University of Massachusetts on a DNA vaccine to be boosted by recombinant HIV proteins. Their work is supported by an HVDDT contract from NIAID. The DNA prime and protein boost vaccine will use HIV env, gag and pol genes taken from multiple HIV strains, which may make the approach better suited for use around the world.

AlphaVax: In partnership with IAVI, NIAID, WRAIR, and the South African Medicines Research Council, Alphavax will develop a Venezuelan equine encephalitis (VEE) vector approach. Human trials are planned to begin in 2001, with testing expected in South Africa and the US, though product development is taking longer than the original timeline projected.

Progenics Pharmaceuticals: Although industry interest has shifted to T-cell immunity, Progenics is developing a neutralizing-antibody-oriented approach, using a construct meant to mimic HIV envelope glycoproteins, a more sophisticated gp120/gp41 approach. The company, whose product is still in the pre-clinical phase, collaborates with John Moore, formerly of the Aaron Diamond AIDS Research Center; now of Cornell University. They recently won a two-year, $4 million NIAID grant.

Targeted Genetics: Working with IAVI, the Children's Research Institute of Columbus, and the University of Ohio, Targeted Genetics will focus on an Adeno-associated virus (AAV) vector for testing in eastern and southern Africa. As with other IAVI partnerships, IAVI maintains certain rights to distribute a successful vaccine in developing countries, at a reasonable price.

Therion Biologics: Therion's major focus has been cancer, but it has worked through government and scientific partners on MVA products, a vaccinia based particle approach, fowlpox and live attenuated HIV. It and the government of India have just joined with IAVI as that organization's fifth Vaccine Development Partnership. It will be working on an MVA product specifically designed for India with the hope of human trials in two years.

Virax: This Australian company, in collaboration with the University of New South Wales (Sydney), will conduct trials of a DNA vaccine prime, followed by a boost using a fowlpox vector containing HIV and immunomodulatory genes, which is meant to generate mucosal immunity. Initial testing will be as a therapeutic vaccine in HIV infected individuals, but with support from an HVDDT grant and collaboration with IAVI, testing as a preventive vaccine will follow in Australia and perhaps Thailand.

VAXGEN: A CASE STUDY OF THE BIOTECH CHALLENGE

The hurdles for developing an HIV vaccine change over time, and are very company-specific. While some companies struggle with clinical trials, others face the daunting prospect of manufacturing a product. One company that may soon find itself at the interface between trials and manufacturing is VaxGen. Its current situation provides a glimpse of the issues that other HIV vaccine developers will likely face in the future.

VaxGen is well along in Phase 3 clinical trials with AIDSVAX. While Genentech has the rights to manufacture for VaxGen, it currently has neither the personnel nor the available manufacturing capacity scheduled to provide a realistic long-term solution for manufacturing this product. The situation is not made easier by the fact that manufacturing a recombinant protein product such as gp120 in CHO (Chinese hamster ovary) cells is probably one of the most regulated and complicated of all pharmaceutical processes. In addition, gp120 is not a trivial molecule to make, even compared to other recombinant proteins made in CHO cells. Thus the FDA may scrutinize the manufacturing of gp120 even more tightly than other biopharmaceuticals such as antibodies or growth factors.

The cost of a single CHO manufacturing run can be millions of dollars, and that estimate does not include amortizing the cost of the manufacturing plant. Genentech recently built a plant in Vacaville, California, at a cost close to $300 million. Shortly after completion, it was fully booked with current products and those in Phase 3 clinical trials, with little consideration given to additional proteins such as gp120.

One solution might be to make gp120 at a commercial plant under contract, but the waiting list is long and the price is high. Most contract manufacturing plants are fully booked for months and sometimes years to come. There are also the added risks that a company takes when putting its product's manufacture into the hands of others.

Alternatively, Genentech might waive its right to manufacture and take an added royalty to compensate for loss of manufacturing revenue. Then VaxGen would need to explore raising additional funds on a few different levels: raise capital to book capacity where they can; raise more money to start the manufacturing validation process, in one or two facilities; raise lots of capital to build their own plant.

The likelihood of a slow entry to market would make it virtually impossible for VaxGen to have a pricing and market strategy that maintains consumer satisfaction and avoids shortages of vaccine. A formidable challenge to face without knowing how its trials will go.

"We have stated publicly for some time that we will not be able to meet worldwide demand from day one," Lance Ignon, of VaxGen, recently wrote to AVAC. "Consider, however, the pressure that VaxGen, Genentech and other CHO cell facilities will be under to make this vaccine. This is not going to be like the introduction of any other medical product."

PRINCIPLE

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Every avenue is pursued.

The best scientific minds are put to work researching the dozens of possible approaches to HIV vaccine design, using candidate products that combine various vaccine strategies, searching for vaccines effective against the multiple sub-types of the virus.

MAJOR NEW PLAYERS

■ STATUS IAVI Continues Growth, VRC And HVTN Organizing • Agendas And Collaboration Still Too Limited • Academic Centers Emerging • Gates Foundation Shows Leadership ■ RECOMMENDATIONS IAVI, VRC And HVTN Should Coordinate And Share • Include Adolescents In Trials • VRC And HVTN Should Develop Agenda And Milestones • Gates Should Build On Leadership

As further evidence of the shifting landscape in HIV vaccine development, the last few years have seen the creation of several new organizations expressly for such purpose. New government initiatives, more varied sources of public support, and new major funding from the Bill & Melinda Gates Foundation have led to the establishment of the International AIDS Vaccine Initiative (IAVI) in 1996, NIH's Vaccine Research Center (VRC) in 1997, and the HIV Vaccine Trials Network (HVTN) in 1999. At the same time, a handful of academic and research institutions have also made efforts to better coordinate and focus their vaccine research. Together, these changes mark a new level of specialization and a welcome multiplicity of efforts.

Unfortunately, none of these new players — or anyone else in the field for that matter — has yet to demonstrate the ability or willingness to transcend its own limited agenda to address the need for a comprehensive and coordinated approach to vaccine development. In this regard, each and together, the three organizations still fall short. There has been some initial interaction around product and assay development, as well as trial preparation, and the HVTN will conduct a Phase 1 trial of an IAVI sponsored vaccine. These efforts are laudable and should grow. Even better would be coordination that included the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Walter Reed Army Institute of Research (WRAIR), as well as European researchers, when appropriate.

INTERNATIONAL AIDS VACCINE INITIATIVE (IAVI)

The goal of IAVI is to put HIV vaccines on the global agenda by: creating global demand for vaccines; developing vaccine candidates and products for developing countries; increasing the number of vaccine candidates in the pipeline; increasing industry incentives for participation in vaccine development; and ensuring speedy, global access to any vaccine ultimately licensed.

In the past year, IAVI's budget has grown exponentially, to $25 million, and it has just received a five-year pledge of $100 million from the Bill & Melinda Gates Foundation. Of the $25 million for 2001, approximately three-quarters will be used for scientific work, including funding for five development partnerships. More partnerships are planned for 2001, with the ultimate goal of having eight to twelve in place. IAVI began its first Phase 1 trial in 2000.

IAVI goals for the coming year are many:

- **Begin two additional Phase 1 trials (including an oral HIV vaccine candidate).**
- **Conduct an audit of international sites and cohorts for vaccine trials.**
- **Expand primate studies and efforts to develop standardized assays.**
- **Hold policy meetings on demand for an HIV/AIDS vaccine globally, and ways to streamline regulatory procedures.**

- **Explore new work with the European Community, G-8 and Japan to expand support for vaccine funding and research.**
- **Begin programs with China and India to explore transfer of vaccine technology (a memorandum of understanding was signed with the Indian government in March 2001).**

Clearly, IAVI has been a hive of activity and members of other groups do participate in their activities. Nevertheless, the benefits do not consistently seem to be shared well with the rest of the HIV vaccine community.

IAVI philosophy regarding future clinical trials seems to be to gather data on products in Phase 1 and 2 trials, and then hope to get a large vaccine company to take on the product for Phase 3 trials and licensing. Within the next four to six years, IAVI plans to conduct or catalyze three Phase 3 trials, each in at least two different regions of the globe (matched and unmatched), though they need to communicate how they plan to get there from where we are today.

IAVI's work — including its ability to communicate to governments and business leaders the urgent need to recognize the AIDS pandemic as the public health crisis it is — are clear assets to the speedy development of an HIV/AIDS vaccine. Although IAVI's rapid growth is a good sign for vaccine development, it could become a major challenge for the organization in the years ahead. Emphasis on speed is welcome and necessary. While wishing IAVI success, some question if IAVI will be able to move products as quickly as they say. We applaud their work and urge them to continue to be a strong, global force for HIV vaccine development. As they move forward with trials, IAVI must also provide clear opportunities for genuine community involvement.

NIH VACCINE RESEARCH CENTER (VRC)

NIH first announced the creation of the Dale and Betty Bumpers Vaccine Research Center four years ago. Dr. Gary Nabel was selected as director of the center two years later, and a new, dedicated building will open in Spring 2001. Under Nabel's leadership, VRC hopes to create a niche for itself at the front end of vaccine development, making the process more rational by deliberately designing vaccine constructs and comparing them early. The hope is that by doing so, VRC could usher the most promising concepts through the pre-clinical process and to the start of clinical trials. VRC sees its particular role as combining concepts, coordinating scientists, and housing the many aspects of design and development "under one roof."

The VRC is planning to conduct Phase 1 trials on its own, with the NIH clinical center, and with the HVTN. Like IAVI and HVTN, VRC is working to develop new assays. While the Center is focused primarily on HIV vaccines, they claim that other vaccine work, such as that on Ebola, has contributed to HIV vaccine work, by helping provide information to choose prime and boost strategies. Nabel has secured support from the Office of AIDS Research for funding to develop a Good Manufacturing Practices (GMP) production facility at Frederick, MD and expects that this would take three years; Good Laboratory Practices (GLP) production will be done at VRC labs.

Operating under a new administration, it is not yet clear how new appointees will help or harm the work at VRC. At this critical point in VRC development and vaccine efforts, both growth and retrenchment are possible. The truth is that, despite its wealth of facilities and brainpower, VRC may actually be under funded to do its proposed work. AVAC's opinion is that VRC has not really embraced

its unique position to "shepherd" the overall HIV vaccine research and development effort, but is focusing more on doing the job itself. Perhaps a different mix of these two important tasks is needed and will be considered seriously during VRC's 2001 strategic planning.

Four years after President Clinton announced the VRC, and two years after a director was selected, there is a new lab building, four labs fully set-up as of March, and some additional scientists hired but not yet on site. In the year ahead, we will look for more rapid and substantial progress in moving products into Phase 1 trials, fully operational labs, and increased leadership on HIV vaccine issues across the Federal government.

HIV VACCINE TRIALS NETWORK (HVTN)

The HIV Vaccine Trials Network is the new US government-funded trials network, composed of the former AVEG sites (6), a few of the former HIVNET sites, and one new international site in South Africa. These core sites also sponsor additional domestic and international satellite sites. Dr. Larry Corey, at the University of Washington and Fred Hutchinson Cancer Research Center, heads this network. He describes the network as a tool to speed development of an HIV/AIDS vaccine, by helping vaccine developers along the pathway to and through trials. The sites that compose HVTN have one clear advantage for this task, as they — either through HVTN or its predecessors — have conducted by far the largest percentage of all human HIV vaccine trials.

Compared with previous trials networks, HVTN leadership believes it is: more directly connected with companies; more decentralized; better able to use the expertise of network researchers and to include researchers from other institutions; and more supportive of individual investigator ideas and initiatives. HVTN believes it will fill a gap between the level of clinical trials the private sector will conduct and what will actually be needed. In particular, it may be necessary to conduct multiple Phase 3 trials to find a preventive HIV vaccine. This prospect may prove too risky for companies.

The goal for HVTN in 2001 is to determine if its canarypox plus gp120 vaccine strategy qualifies to move into Phase 3 trials. It lists its first year accomplishments as:

- **Starting a large Phase 2 trial of canarypox (ALVAC 1452) plus a gp120 boost.**
- **Developing a high volume cell mediated immunity (CMI) assay.**
- **Beginning public comment on a Phase 3 trial.**
- **Establishment of guidance criteria to inform the decision of whether to move from a Phase 2 to a Phase 3 canarypox plus gp120 trial.**

The scientific leadership of HVTN intends to establish milestones annually and the sites (HVTUs) will be expected to meet performance standards. In addition, the entire network will be examined for speed and efficiency after the third year.

In its first year, HVTN did not spend the full $29 million available, but Corey says that in 2001 the network will exceed these figures as it expands clinical trials and initiates network expansion in Africa, South America, and Asia. Also by 2002, additional resources will be needed if a Phase 3 trial is ready to start. The scientific agenda for 2001 includes:

- **Evaluation of current constructs of poxvirus vectors to determine if they merit Phase 3 trials.**
- **Evaluation of a new qualitative method to measure CMI, and its usefulness to define a correlate of immunity.**

- **Initiation of a truly multi-national trial in South Africa and the US.**

Corey views the role of community as helpful and necessary and is proud that the network has HVTN staff dedicated to community development.

HVTN is still establishing itself, and the first year has been one of necessary organizational activity. It is disappointing that only one new clinical trial was initiated, in December 2000. In the next year, AVAC will look for the following progress:

- **A scientific agenda with milestones.**
- **Progress toward a Phase 3 trial, including preparation of domestic and international cohorts.**
- **More outreach to and close collaboration with industry, investigators, and other groups, including IAVI.**
- **Affirmative community organizing and training programs at all HVTUs.**
- **Leadership in development, validation, and broad acceptance of new assays.**
- **Leadership in trial protocol design and execution.**

ACADEMIC VACCINE CENTERS

Several major universities have also been establishing HIV vaccine centers to provide a focus for the work of their investigators. They include the Emory University Vaccine Center, UCLA AIDS Institute, Aaron Diamond AIDS Research Center, and the University of Maryland's Institute of Human Virology. Although located in independent research institutions, the organizational model they've chosen is not very different from the VRC.

Emory Vaccine Center: In 1999, the six year old Emory Vaccine Center dedicated its own building on the Emory University campus in Atlanta, with funding ranging from the Georgia state lottery to NIH grants. Dr. Rafi Ahmed, an eminent immunologist, was recruited to head the Center and he hired others already doing HIV work — including Harriett Robinson, a pioneer on DNA vaccines who had already been working on AIDS vaccines, John Altman, and Mark Feinberg. Center scientists collaborate with others at Emory and the CDC. The Center's goal is to make promising vaccine candidates through basic immunology research and translate them to Phase 1 human trials. The Center is also a clinical trial site for Merck's HIV vaccine program, and has several grants to move its DNA plus MVA (modified vaccinia Ankara) combination into trials with the HVTN. This combination gave impressive results in animal studies published earlier this year. Emory has established a community advisory board for the Center and is conducting local research on perceptions among high-risk populations about participating in vaccine research. The Vaccine Center is exploring the establishment of a non-profit organization modeled on industry's product development process, which would be dedicated to providing expertise on GMP production, product development and the regulatory process to university researchers and others.

UCLA AIDS Institute Vaccine Initiative: UCLA established the UCLA AIDS Institute Vaccine Initiative in July 2000 to organize and encourage partnerships with investigators at UCLA, other universities, and the Los Angeles community. In its first year, the Institute established partnerships with Emory, Aaron Diamond AIDS Research Center, and UC San Francisco. Scientifically, Kathie Grovit-Ferbas and Irvin Chen demonstrated success in maintaining envelope integrity while inactivating HIV viral particles. Publicity on their pre-clinical work caused some renewed interest in work on a whole killed HIV vaccine.

Aaron Diamond AIDS Research Center: Under the Directorship of Dr. David Ho, the Aaron Diamond AIDS Research Center (ADARC) continues work on DNA vaccines with focus on a CCR5-tropic subtype C strain, and is planning work in China. This will be the first foray by ADARC into product development and a sign that they are continuing their interest in HIV vaccines despite the loss of several senior researchers to other programs.

The Institute of Human Virology: Dr. Robert Gallo founded IHV in 1996, at University of Maryland, upon leaving NIH. Three of its five divisions do work related to HIV vaccines. It is developing Salmonella and Shigella bacterial vectors and DNA vaccines, and new envelope complexes and adjuvants, with funding from NIH, IAVI, and other collaborators. Its Clinical Division is part of HVTN and Merck sponsored trials, and it is preparing to test a tat toxoid therapeutic vaccine from Aventis. They are actively working with sites in the Caribbean and Nigeria. IHV is thus a participant in just about every collaborative effort described in this section. IHV is also joining with the Harvard AIDS Institute and the University of California, San Francisco to form a new AIDS vaccine consortium called the Waterford Project.

OBSERVATIONS

In interviews with the leaders of each of the vaccine institutions and academic centers, there were common themes and messages sounded, but surprisingly few unique approaches identified.

Each describes its niche, at least in part, as bridging the gap between basic research and Phase 3 trials. By helping fill the pipeline with potential products, the hope is that the development process will be both shorter and more rational. Each of these entities would like to be the first group to develop an HIV vaccine, and all say they operate more like industry than government. However, there is at least one critical distinction. Unlike private industry, these groups have the freedom to say they do not care whether they, or someone else, develop the first HIV vaccine. And while each may have the best leader possible for its own mission, it does not seem that, as a group, they are working together towards the shared goal of speeding development of an HIV vaccine.

In the course of our interviews, almost everyone mentioned the need to dedicate more resources and attention to product development. Leaders at VRC, Emory, HVTN, and IAVI all raised this issue in particular, and several have plans to take action in this area in 2001. Almost everyone agrees that large vaccine companies could do this best — if they were fully committed. AVAC concurs that this step in the process requires immediate attention, given the state of vaccine research and development. It is vital that this effort is real and sustained. However, it must not detract from needed focus on the other critical steps that are only slightly further along.

Most leaders interviewed also raised concerns about the need for new assay development and hope that this will occur in the near future. Based upon concerns about the quality of assays currently available, all the groups we talked with are doing some work in this area. Open and early sharing of information about new assays and the validation and standardization of assays will be key to speeding vaccine development. This would complement other areas where coordination is needed, including efforts toward multiple efficacy trials; licensing, purchasing and access for products; standardized protocols; and other vaccine preparedness activities.

The institutions and organizations discussed here have a varying level of community engagement. It is important that all of them ensure meaningful community

input to their research agenda and develop mechanisms to collaborate with other efforts for community education, both in the US and internationally.

AVAC welcomes the increased activity on the part of these entities, even if, at times, such efforts may overlap. In responding to this global public health crisis, some redundancy is necessary to ensure that we are moving ahead with all possible speed. Looking ahead, we would like to see more broad scientific leadership that transcends any one organization or group. We would also like to see greater focus on long-term challenges and issues, rather than issues that may be trendy now. Perhaps leaders of HVTN, IAVI, and VRC, collectively, could help fill this leadership gap by integrated strategic planning. Perhaps one of the academic vaccine centers or another group, infused with major resources, will rise to the leadership challenge in the year ahead. That would be a welcome and significant development.

BILL & MELINDA GATES FOUNDATION

While not itself a research or development organization, the Bill & Melinda Gates Foundation has certainly helped shape the landscape of HIV vaccine research and development. Their contributions and pledges to support IAVI alone give the foundation a place of honor in HIV vaccine history. The foundation is the lead donor to the Global Fund for Children's Vaccines with a $750 million contribution; funds research and development of malaria, TB and other vaccines; and supports reduction of mother-to-child transmission of HIV. The Bill & Melinda Gates Foundation has an annual budget of $550 million for global health and directs 50% into vaccine-related work. It has given approximately $26.5 million dollars to support HIV vaccine research and has pledged an additional $100 million to IAVI over the next five years. Vaccine scientist Margaret Liu, who was Chiron's Vice President for Vaccine Research and Gene Therapy, recently joined the Foundation to provide in-house expertise and to work with vaccine development organizations that it funds, including IAVI. AVAC would like to see this extraordinary foundation continue to expand its strategic involvement consistent with its overall global health mission, and strongly urges other foundations to follow its lead.

PRINCIPLE

7 6 5 4 3 2 1

Leadership is ongoing.

Elected officials around the world consistently make HIV vaccine development and delivery a top priority and back it with funding, incentives and planning. One-time proclamations of concern are relics of the past.

BUILDING MOMENTUM IN A NEW U.S. ADMINISTRATION

■ **STATUS** Bush Transition • Legislation Languishes • Sustained Leadership Remains A Challenge • Budgets Continue Growth

■ **RECOMMENDATIONS** Bush Administration Must Lead • Agencies Must Work Together • Congress Must Pass *Vaccines for the New Millennium Act* • Key Positions Must Be Filled By Advocates • Primate Shortage Must Be Solved • Army Program Needs Stable Funding • Trials Need Better Diversity • FDA Must Streamline Regulations

NATIONAL POLICY AND LEADERSHIP: THE PASSING OF THE BATON?

The *Millennium Vaccine Initiative*, announced by President Clinton in his January 2000 *State of the Union* address, outlined crucial incentives for the development and distribution of vaccines against HIV, TB and malaria. As the year progressed, key members of the Administration continued to visibly focus on vaccine issues. In addition to hosting a Vaccine Summit in March 2000, the White House supported a special meeting of the United Nations Security Council to highlight the threat posed by HIV to international economic, social and political security. By the end of summer, in the wake of intense media scrutiny generated at the International AIDS Conference in South Africa, Clinton signed into law a small portion of the legislative agenda championed by Representative Nancy Pelosi and Senator John Kerry.

In the months leading up to the November 2000 election, it became clear that major initiatives proposed in the *Vaccines for the New Millennium Act*, as well as FY2001 Federal appropriations, would get caught in Congressional gridlock. Although a welcome increase in Federal appropriations for HIV research finally passed the Congress in January 2001, the ultimate fate of other initiatives proposed during the past year now rest with a new Congress and Administration.

AN UNFINISHED AGENDA

The Clinton Administration legacy on AIDS issues, including vaccines, is considerable. Highlights include support for a doubling of all Federal AIDS spending since 1993; a 100% increase in NIH funding for vaccine research between FY1997 and FY2000; and establishment of the Dale and Betty Bumpers Vaccine Research Center at NIH.

Despite this praiseworthy legacy, the Presidential Advisory Council on HIV/AIDS (PACHA) noted in its final report to President Clinton — aptly titled *No Time to Spare* — that much more remains to be done if the goal of an HIV vaccine within the next six years is to be realized. Foremost among PACHA's future priorities are:

- **Tax credits for vaccine research and sales.**
- **Creation of an international purchase fund.**
- **Meaningful debt relief for developing countries.**
- **Expansion of private/public partnerships.**
- **Greater coordination and collaboration between government agencies.**

PACHA also recommended immediate international action to address the "myriad of societal, ethical, economic and regulatory issues that must be solved prior to the wide-scale distribution of any effective vaccine," pointedly noting, "the time to address these issues is now, before an actual vaccine has been developed."

TAX INCENTIVES FOR VACCINE RESEARCH, DEVELOPMENT, AND DELIVERY

Last year we reported that Representative Nancy Pelosi and Senator John Kerry had introduced the *Vaccines for the New Millennium Act* as companion bills (H.R. 3812 and S. 2132, reintroduced as H.R. 5219) to provide a range of economic incentives for vaccine research, development, and delivery.

Congress passed and President Clinton signed into law a small portion of this legislation as part of the *Global AIDS and Tuberculosis Relief Act of 2000*. But key economic incentives that would address practical concerns of large and small vaccine developers and of vaccine purchasers are still lacking and should be enacted this year in new legislation.

Fortunately, there is growing international interest in providing incentives for vaccine R&D and delivery of therapeutic drugs and vaccines. The government of the United Kingdom has announced plans to develop a targeted R&D tax credit for several vaccines, including HIV. Last year, the UK enacted a new law providing financial incentives for biotech companies. Italy has proposed the development of purchase mechanisms for drugs. The World Bank created a $1 billion revolving fund for infectious disease and is considering expanded programming to facilitate vaccine purchase.

The new US administration under President Bush has not yet announced publicly its position on tax incentives for developing vaccines against HIV. Although President Bush did not make HIV or AIDS treatments an issue in his presidential campaign, he has expressed support for existing tax incentives that benefit the pharmaceutical industry, such as the Research and Experimentation tax credit. This credit and a similar credit for development of orphan drugs have not been successful in providing companies with targeted incentives sufficient to significantly advance HIV vaccine research. Senator Kerry has been appointed to the Senate Finance Committee where, it is hoped, he will pursue passage of targeted vaccine tax legislation.

AVAC is hopeful the new Congress will enact legislation to provide workable tax credits for R&D and delivery of priority vaccines. To maximize incentives to engage in neglected vaccine R&D, a new bill should:

- Provide full and immediate tax credits for pre-clinical vaccine R&D, as well as for clinical R&D.
- Provide a tax incentive designed specifically for use by smaller biotech companies that do not yet pay taxes.
- Provide 100% tax credit for sales of priority vaccines purchased for distribution in lower income countries.
- Create a purchase guarantee or fund mechanism that can credibly promise to buy an HIV vaccine, when one becomes available.
- Include a Sense of Congress statement in favor of tiered pricing to facilitate delivery of vaccines to developing countries.

AVAC intends to continue working with elected officials and staff from the Treasury Department and the Internal Revenue Service on devising manageable and enforceable tax credit mechanisms to accomplish the legislation's objectives. AVAC has developed a position paper that identifies simplified enforcement options to ensure an R&D credit is used appropriately.

Tax incentives must be viewed as mechanisms working in tandem with other economic incentives such as creation of appropriate financing instruments to purchase vaccines.

MAINTAINING MOMENTUM IN THE GEORGE W. BUSH ADMINISTRATION

The stakes involved in the global search for a vaccine demand that the transition to a new presidency does not itself become an obstacle to vaccine development. The moral imperative to develop an effective HIV vaccine has no party affiliation; neither should the US government's financial and political commitment to this goal. Under former President Clinton, the US government reached an understanding that AIDS represents a national and international security threat. It now looks as if President Bush will continue to act on that understanding. President Bush must also reaffirm the US goal of developing an AIDS vaccine as soon as possible.

The beginnings of the Administration's plans are emerging. President Bush has appointed Scott Evertz, a gay man from Wisconsin, as director of the White House Office of National AIDS Policy (ONAP), whose mandate will expand to include international policy. Evertz is politically close to Tommy Thompson, the Secretary of Health and Human Services. The Administration is also establishing an AIDS task force chaired by Thompson and Secretary of State Colin Powell, which will include Evertz, National Security Advisor Condoleezza Rice, and domestic policy advisor Margaret LaMontagne. Vice President Richard Cheney has said that the Bush Administration is planning a comprehensive proposal which includes education, prevention and provision of drugs, but as yet there has been no mention of vaccines.

The fate of the PACHA, which will dissolve on July 27, 2001 in the absence of executive action, remains undecided. The first Bush budget sends mixed messages. While spending for NIH — and thus presumably money for AIDS research — would rise, money for treatment remains unchanged, a loss when one accounts for inflation. AVAC remains strongly committed to the principle that money for research should never come at the expense of money for treatment.

At the Department of Health and Human Services, which oversees both the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC), AVAC hopes that newly appointed Secretary Tommy Thompson's stated support for international health will also include a commitment to strong leadership on HIV vaccine development.

Secretary of State Colin Powell can also play a pivotal role. The State Department oversees the US Agency for International Development (USAID), which distributes billions of dollars in the developing world for economic, political and health programs. USAID has the largest international HIV program in the world, funded at $340 million in 2001. With its long reach and established in-country relationships, USAID could offer significant help in organizing AIDS vaccine trials.

The US Patent and Trademark Office should advocate harmonization of international patent laws in ways that encourage vaccine development and affordability.

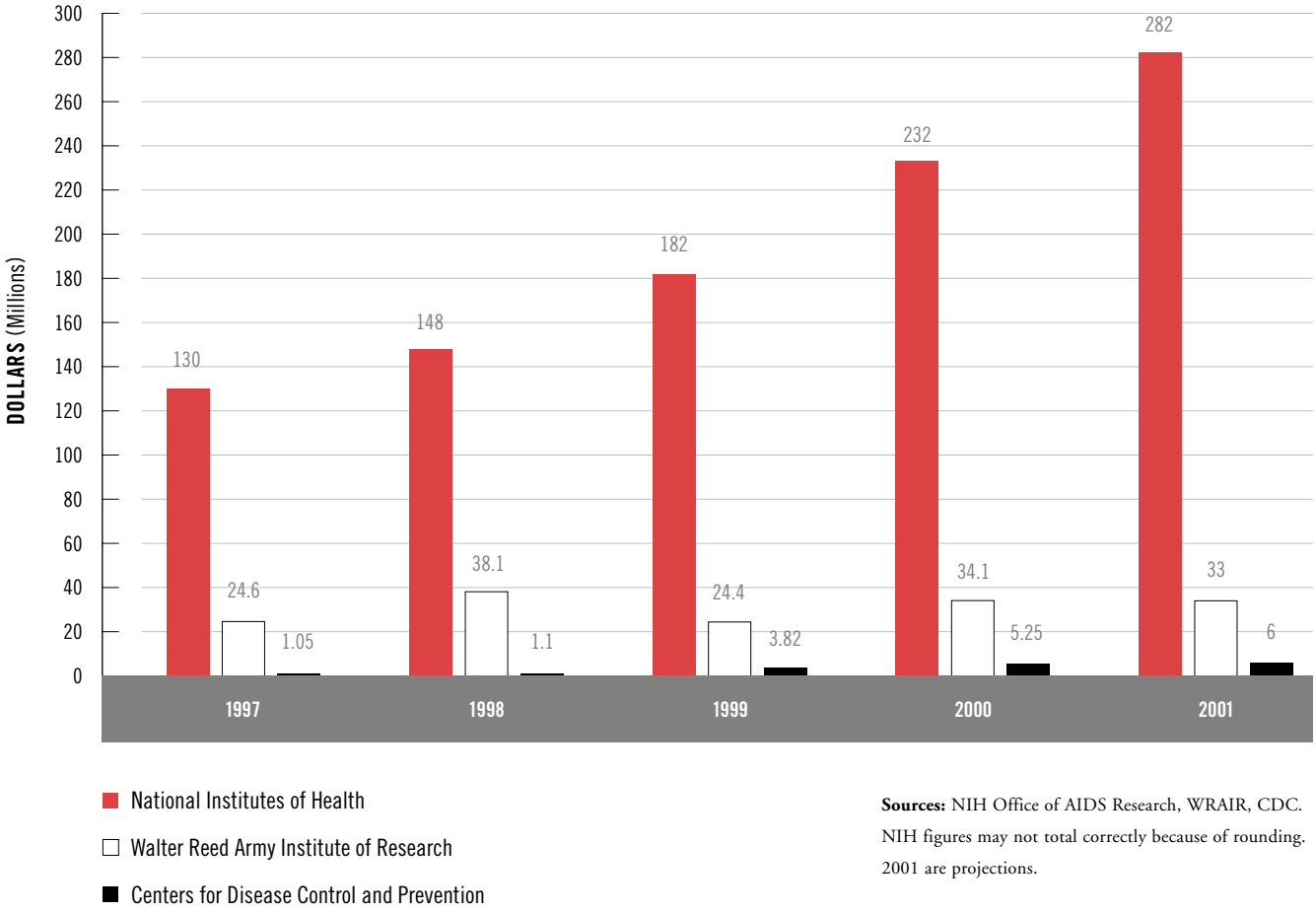
Today, given the relatively well funded, but fragmented state of US efforts towards finding an HIV vaccine, the need for government activities to be led by a "uniter, not a divider" has never been greater. AVAC is committed to working with the President and his Administration to speed the development of an HIV vaccine.

NATIONAL INSTITUTES OF HEALTH (NIH)

Office of AIDS Research (OAR)

The Office of AIDS Research continues to oversee AIDS research funding at NIH. Between FY1994 and FY2001, funding for AIDS research overall and vaccine research in particular, increased dramatically. Vaccine research now constitutes 12.6% of the overall

AIDS VACCINE BUDGETS FOR MAJOR U.S. RESEARCH AGENCIES



Sources: NIH Office of AIDS Research, WRAIR, CDC. NIH figures may not total correctly because of rounding. 2001 are projections.

AIDS research budget ($282 million of $2,243 million in FY2001, up from $232 million of $2,004 million in FY2000).

The departures of Dr. Neal Nathanson as Director of OAR and Dr. Harold Varmus as NIH Director last year represented a significant setback in leadership on HIV vaccine research at NIH. In the interim, Acting OAR Director Dr. Jack Whitescarver has enabled the Office to continue its work. Our hope is that, in the future, OAR will demonstrate more bold and visible leadership.

Each year OAR prepares a plan for HIV-related research for the upcoming Fiscal Year. For FY2001, the plan identifies five scientific objectives, each accompanied by a set of strategies for achievement. It also proposes five priorities for future research: 1) conduct domestic and international vaccine trials; 2) develop and test new vaccine strategies; 3) improve animal models and trials; 4) identify and develop functional antibodies to use against maternal-infant transmission; and 5) move vaccine concepts rapidly to clinical tests.

NIAID DIVISION OF AIDS (DAIDS) MILESTONES – PROGRAM

2000	2001	2002
Active oversight of unsolicited awards (ongoing)	Active oversight of unsolicited awards (ongoing)	Active oversight of unsolicited awards (ongoing)
Innovation Grant Program Announcements (ongoing)	Innovation Grant Program Announcements (ongoing)	Innovation Grant Program Announcements (ongoing)
Fund new IPCAVD Program applications	Second IPCAVD Program Announcement	IPCAVD Program announcements (ongoing)
Fund Vaccine Design and Development Teams	—	HIV Vaccine Design and Devt. Teams Expansion
Fund new HIVRAD applications (ongoing)	—	HIVRAD Program Announcements
Establish Vaccine Trials Network	HIV Database Renewal	Comprehensive International Program for Research on AIDS Announcement
—	HIV Production Contracts 3-Part Request For Proposals	New Technologies for HIV and HIV Vaccine Related Research Renewal/Expansion
—	SIV Evaluation Units Renewal/Expansion	HIV Vaccine Development Resources Announcement (ongoing)

NIAID DIVISION OF AIDS (DAIDS) MILESTONES – SCIENTIFIC

2000	2001	2002
P55 particle into Phase 1 trial (Q3-2000)	P55 particle into Phase 1 trial (Q4)	DNA + env protein into Phase 1 (Q3/4)
Viral vector (MVA#1) into newborns (Q2/3-2000)	MVA#1 into HIV+ children on HAART (Q4)	DNA + env and tat protein into Phase 1 (Q3/4)
MVA#2 into Phase 1 trial (Q1-2001)	—	MVA#2 into Phase 1 trial (Q3)
VEE replicon into Phase 1 trial (Q1-2001)	VEE replicon into Phase 1 trial (uncertain)	DNA + fowlpox into Phase 1 (Q2)
Canarypox into Phase 2b trial (Q1-2001)	Canarypox into Phase 2b trial (uncertain-probably now 2002)	DNA + peptide into Phase 1 (Q1)
Cararypox into Phase 2-US/Caribbean (Q1-2000)	Canarypox into Phase 1 in Caribbean (Q2) *(in US, started in Q4-2000)*	—
Pseudovirion into Phase 1 trial (Q2-2000)	DNA into Phase 1 trial (Q4)	—

DAIDS scientific milestones are evaluated on an ongoing basis and updated for presentation prior to each AIDS Vaccine Research Committee meeting, three times a year. The milestones represent an evolutionary process and changes occur regularly. For instance, Pseudovirion into Phase 1 Trial from 2000 disappeared because the product is no longer being pursued. AVAC notes that 2001 and 2002 collectively show a rich stream of products in preparation for Phase 1 trials. The chart above reflects milestones as of 03/15/2001.

Global Aids Research Initiative (GARI): A New US Government Effort

On World AIDS Day 2000, OAR announced a new strategic plan for global research on AIDS — the Global AIDS Research Initiative. GARI was developed by a group of experts from academia, industry and community representatives. In FY2001, NIH will spend more than $100 million on AIDS research conducted with international partners, including vaccine research. The GARI working group will be co-chaired by the new Director of OAR and Dr. Tony Fauci, Director of NIAID. GARI aims to foster collaboration between NIH and other federal agencies, including the Department of Defense, the CDC, the Food and Drug Administration, and the USAID. In addition, OAR will establish a new Global Strategy Group to link federal research efforts with international partners. Announced with fanfare, only time will tell whether this is a meaningful initiative that will have the support of the Bush Administration.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

Within NIH, the National Institute of Allergy and Infectious Diseases has primary responsibility for HIV vaccine research and development. Of the total $282 million in NIH funding for HIV vaccine research, NIAID received $232 million.

AIDS Vaccine Research Committee (AVRC)

The AIDS Vaccine Research Committee was established in 1997 to provide leadership and oversee the establishment of a trans-NIH vaccine program. The Committee makes recommendations to NIAID, OAR and NIH on key scientific questions in vaccine development. Known widely as the "Baltimore Committee," it has never lived up to original expectations. This is due in part to the limitations of advisory committees, the primarily scientific focus of its membership, and the intractable organizational apparatus of NIH. Nevertheless, AVRC is an independently minded, reality-checkpoint for the overall NIH AIDS vaccine development program, which is in turn still a substantial portion of all AIDS vaccine investment worldwide.

DIVISION OF AIDS (DAIDS)

The Division of AIDS manages the NIAID AIDS research program. As of this writing, Dr. Jack Killen has accepted a position at the NIH Clinical Center Bioethics program, but remains in place as a caretaker director. His departure will leave another gap in leadership that must be filled by a vaccine champion. Dr. Peggy Johnston, Assistant Director for HIV/AIDS Vaccines at NIAID, has long been a dynamic force in the vaccine cause and continues to provide instrumental leadership towards collaborative, milestone-driven research and development. Also, to Dr. Johnston's credit, her program is now fully staffed; a welcome change.

RESEARCH AND DEVELOPMENT PROGRAMS

In June 2000, NIAID announced funding of $70 million over five years, for four public/private partnerships to accelerate development of promising vaccine candidates. These HIV Vaccine Design and Development Teams (HVDDT) are incentive-based contracts aimed at vaccine candidates in the middle of the development pipeline — those not yet in human trials. Funding is provided in increments as preset milestones are reached.

The new HVDDT awards complement these other NIAID-supported HIV vaccine research and development programs:

- **The Innovation Grant Program (IGP)** supports novel, high-risk, and exploratory studies in AIDS vaccine-related research.

NIH VACCINE FUNDING PROGRAMS

INITIATIVES	PURPOSE (DATE OF 1ST APPLICATIONS)	APPLICATION FREQUENCY	TOTAL GRANTS OVER LIFE OF PROGRAMS	TOTAL ACTIVE GRANTS FY2000 (INCLUDING NEW)	NEW OR RECOMPETE IN FY2000
Extramural Grants / Intramural Contracts	Unsolicited investigator-initiated research	On-going	__* / __*	76 / __*	17 / __*
Reagent Support / HIV Database and Analysis	Researcher support	On-going	1 / 1	1 / 1	0 / 0
Innovation Grants	Draw researchers into the HIV vaccine field and increase the number of promising concepts entering the research pipeline (1997)	3X / year	218	71	32
HIV Vaccine Research and Design (HIVRAD)	Support development of HIV vaccine concepts into products (1998)	1X / year	19	17	9
HIV Vaccine Design and Development Teams	Promote a development-oriented approach to vaccines by funding teams of researchers for long-term coordinated projects (1999)	5 year awards	4	4	4
Integrated Pre-clinical / Clinical AIDS Vaccine Development (IPCAVD)	Encourage academic-industry collaboration that will move vaccines through the final pre-clinical stages and into early clinical trials (1997)	1X / year	14	10	2
Primate Testing Contracts / Simian Vaccine Evaluation Units and Lab Support	Create a standardized challenge system that would allow investigators around the world to generate comparable results with vaccines in primates / Evaluate promising SIV and HIV vaccines in non-human primates (1998)	On-going; 5 year awards	2 / 3	2 / 3	0 / 0
HIV Vaccine Development Resources Contracts	Resources to facilitate development of promising vaccine candidates into testable products (1998)	7 year awards	14	8	0
HIV Vaccine Trials Network (HVTN)	Domestic and international human testing of HIV vaccine candidates, all phases (1998)	5 year awards	3 Core Function Contracts / 10 HIV Vaccine Trial Units	3 Core Function Contracts / 10 HIV Vaccine Trial Units	2 Core Function Contracts / 10 HIV Vaccine Trial Units

* Number not available

Source: NIAID Division of AIDS

- **The HIV Vaccine Research and Design Program (HIVRAD)** supports studies emphasizing targeted AIDS vaccine research and development, and is designed for vaccine concepts that have already generated significant preliminary data.
- **The Integrated Pre-clinical/Clinical AIDS Vaccine Development Program (IPCAVD**) supports grants designed to move promising HIV vaccine candidates into preliminary human studies.
- **The Vaccine Development Resources Program** assists AIDS researchers by manufacturing pilot lots of vaccine for testing, conducting preliminary safety and efficacy evaluations, and preparing submissions to FDA for trials in humans.

NIAID INTRAMURAL RESEARCH

In addition to the extramural (external) vaccine research funded by the Division of AIDS, a few of NIAID's intramural (internal) labs are doing HIV vaccine work. Among these are those of Bernie Moss who has developed recombinant poxvirus vaccines, including MVA used in experiments by Harriet Robinson at Emory, Malcolm Martin and Vanessa Hirsch who's labs study pathogenesis with vaccine implications, passive antibody protection, and DNA vaccines.

NATIONAL CANCER INSTITUTE (NCI)

The National Cancer Institute conducts important research investigating AIDS-related malignancies. It has also received funding for intramural pre-clinical HIV vaccine research. NCI has received $8.5 million in FY2001 for HIV vaccine research.

AVAC reported last year that the several unrelated parts of the NCI intramural vaccine research program had not received scrutiny as parts of the overall NIH AIDS vaccine effort. This is still the case, leading us to recommend that the AIDS Vaccine Research Committee examine more closely this significant part of NIH AIDS vaccine investment.

One noteworthy NCI lab program is headed by Larry Arthur, at its Frederick Center in Maryland. Almost all of its work is focused on the development of preventive HIV vaccines. It is conducting basic research on both DNA and whole inactivated virion vaccines tested in the SIV-macaque model; as well as p6 gag and cellular proteins; and the effects of vaccine-induced immune responses in animals, with Jeff Lifson. Also of note are the labs of Jay Berzofsky who has recently become interested in mucosal immunization, Geneveffa Franchini which has been systematically studying vaccine protection in primates, and Marjorie Robert-Guroff who has helped develop Adenovirus vectors for HIV vaccines.

NATIONAL CENTER FOR RESEARCH RESOURCES (NCRR)

Monkey Shortage Threatens Progress

The National Center for Research Resources is responsible for overseeing the Regional Primate Research Centers (RPRC) that provide non-human primates for animal studies. NCRR has been criticized as unresponsive, even negligent in its management of the Primate Centers, as well as other programs for primate breeding. So far, it has failed to resolve the increasingly critical shortage of Indian rhesus macaques for vaccine research. The time for patience is over. AVAC believes it is now time for the acting NIH Director to take this issue in hand.

WALTER REED ARMY INSTITUTE OF RESEARCH (WRAIR)

AVAC has reported previously on the key role the Walter Reed Army Institute of Research has played

in vaccine development. The Army has a long history of vaccine research and development — particularly for infectious diseases that pose a serious threat to military personnel, but have not been pursued aggressively by industry. In 2001, overall HIV program funding to WRAIR is $35 million, about 55% of which goes to vaccines. It receives a base of $25 million from the Administration and must go to Congress every year for "plus-up" additions, which have usually been $10-15 million.

WRAIR supports pre-clinical discovery and research, pilot lot production, non-human primate studies and clinical trials, with a focus on non-clade B candidate vaccines. Its research programs are highly structured and directed at evaluation of a limited number of candidate vaccines, both pre-clinically and clinically. This differs from the majority of NIH programs, which have a large investigator-initiated component that includes a broad array of basic, as well as targeted programs.

WRAIR's plans for FY2001 and 2002 are ambitious:

- **Ongoing Phase 2 trials in Thailand comparing three boosting strategies with Aventis Pasteur's ALVAC-E 1521, with a Phase 3 trial using one of the boosts planned for 2002.**
- **Development of new products, including modified vaccinia Ankara (MVA) vector encoding env, gag and pol genes for HIV-1 clade E, (they will fund GMP production) and the same vector designed to be used in regions where clade D HIV is prevalent.**
- **Ongoing discussions with Ugandan officials regarding a trial to test ALVAC encoding env, gag and pol from a clade A isolate.**
- **Phase 1 trial of a p24 vaccine product that has recently completed GMP production.**
- **Ongoing work with three biotech companies for the development of gp120/gp140 (envelope) boosts to provide a stronger humoral response.**
- **New collaboration with an Israeli group for the development of an HIV-1 clade C vaccine.**
- **Ongoing preliminary work with the South African AIDS Vaccine Initiative (SAAVI) and IAVI to support a trial of the HIV clade C VEE replicon vaccine, when available.**

The Military HIV Research Program at WRAIR has been actively pursuing collaborations with industry, academia, NIH and foreign governments. WRAIR and NIAID agreed in 2000 to more fully integrate their planning processes to ensure that their programs — particularly their collaborations with the private sector and their activities within specific countries — proceed according to a cohesive and rational plan. AVAC applauds this commitment.

Future Funding for WRAIR

Unlike NIH, WRAIR has struggled over the past eight years to maintain funding for HIV vaccine research in an era of deep cuts to defense spending. For long-term, complex work of this nature, particularly clinical trials, it is unacceptable that the military leadership does not have the foresight to allocate adequate funding on a stable basis. WRAIR's base funding for AIDS vaccines should be increased from $25 million to $50 million. Conversely, AVAC believes that the program should be cautious in undertaking new projects; limiting them in order to maintain the high standard of commitment and continuity that it established in Thailand. In particular, it should not duplicate the efforts of other groups.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

The Centers for Disease Control and Prevention is the leading federal agency in the US for HIV prevention. The agency has had a long history of vaccine development and evaluation for other diseases (measles, hepatitis B and polio). The CDC FY2001 budget for HIV vaccine related activities is $6 million ($4 million for the HIV Vaccine Section and $2 million for CDC international field sites). In 1998, CDC created a small HIV Vaccine Unit. Dr. Tim Mastro became Chief in June 2000.

CDC activities are modest in scope compared with NIH and Department of Defense programs and focus on three areas:

- **Epidemiological and socio-behavioral sub-studies in the ongoing Phase 3 efficacy trial of AIDSVAX B/B in North America and the Netherlands.**
- **Epidemiological and socio-behavioral sub-studies in the ongoing Phase 3 efficacy trial of AIDSVAX B/E in Bangkok, Thailand.**
- **Preparation for eventual Phase 1, 2 and 3 trials in West Africa.**

Resolving the Potential for False Positives from HIV Vaccines

CDC has conducted a study of the serologic reactivity (on several different assays) of specimens from a variety of HIV vaccine trials to determine if current assays can distinguish a false positive result, caused by the vaccine, from a true positive for HIV infection. CDC is currently developing and evaluating simpler, less-expensive assays that would be sensitive and specific for HIV infection. AVAC expects CDC to address this issue expeditiously.

Project LinCS Revived

Project LinCS: Linking Communities and Scientists was a qualitative research study funded jointly with NIAID, which was designed to learn about community attitudes towards research, especially preventive HIV vaccine trials. Researchers conducted in-depth interviews with individuals in three, albeit overlapping, communities: African Americans, gay men and injection drug users.

AVAC reported last year that this study appeared to be dead-in-the-water, having collected enormous amounts of data before it ran out of funding. We are happy to report that the study was since revived, and that data analysis is occurring. CDC expects to complete a summary report of major findings and recommendations from LinCS by June 2001.

Involving US Communities of Color in Future Vaccine Trials

It has become increasingly clear that further education and consultation with communities of color in the US is necessary to address vaccine trial participation, and ultimately vaccine access and usage. Participation by communities of color in the domestic VaxGen trial is minimal, indicating a reluctance to participate in vaccine research. This is an important issue that requires greater effort on the part of CDC.

External Review of CDC Vaccine Activities Completed

In the wake of adverse publicity about its relationship with VaxGen, an external review of the CDC HIV Vaccine Unit was conducted in November 2000. The review concluded that all three of the current major program areas are scientifically sound and cost-effective. In addition to endorsing continued collaboration with VaxGen in its ongoing efficacy trials, the review recommended an expansion and acceleration of vaccine trial preparatory activities in West Africa, and the development of a formal

long-term strategy for AIDS vaccine research. CDC must seek to collaborate more effectively with other US government agencies, international institutions, the pharmaceutical industry and affected communities in future trials. The report concludes: "The CDC strategy should be structured so as to make maximal use of CDC excellence in epidemiology, socio-behavioral research, and international capacity building." Unfortunately, the report did not urge the HIV Vaccine Unit to work with other CDC programs such as the Assistance, Planning and National Partnerships Branch of the Division of HIV/AIDS Prevention, which funds local Community Planning Groups. These groups could play an important role in HIV vaccine community education.

FOOD AND DRUG ADMINISTRATION (FDA)

The Food and Drug Administration is responsible for reviewing applications for investigational new drugs (INDs). INDs must be secured before a vaccine product can move from animal studies to human studies. In 2000, FDA issued only one new IND for a prophylactic HIV vaccine, lower even than the disappointing past average of three per year.

AVAC is working to promote the development of an accelerated application and approval process for HIV vaccines similar to what is now in place for HIV treatments. There are a variety of proactive ways in which FDA could ease the way for IND applicants that would not sacrifice stringent safety testing. These include procedural changes and addressing common scientific challenges in advance for all applicants rather than only responding to individual applicants' specific issues as they arise and in confidence. In addition, FDA should continue its work with other countries, on harmonization of regulations and guidelines pertaining to vaccine approval and use.

US GOVERNMENT OVERSIGHT AND ADVICE

WHITE HOUSE

Office of National AIDS Policy (ONAP): White House Office to provide broad policy and leadership guidelines on the federal response to AIDS. Its director is often called the "AIDS Czar".

Presidential Advisory Council on HIV/AIDS (PACHA): Advisory council to the President composed of members outside of government. Scheduled to expire in late July 2001.

NATIONAL INSTITUTES OF HEALTH (NIH)

AIDS Vaccine Research Committee (AVRC): Also known as the "Baltimore Committee" for its founding chair, Dr. David Baltimore. Independent advisory committee to AIDS Subcommittee of the National Institute of Allergy and Infectious Diseases Council. It advises the NIH on key scientific questions of vaccine development. Administered by NIAID.

Interagency HIV Vaccine Collaborative Group: Interagency information exchange forum that meets twice a year. Chaired by Office of AIDS Research (OAR), includes any agencies working on vaccines, including those outside NIH such as the CDC and WRAIR.

Global AIDS Research Initiative (GARI): Initiative of OAR, which is charged to foster collaboration between the NIH and other US agencies funding AIDS research. Co-chaired by the Directors of OAR and NIAID.

Global Strategy Group: Initiative of OAR to link US government research efforts with international partners. Co-chaired by the Directors of OAR and NIAID.

FOOD AND DRUG ADMINISTRATION (FDA)

Center for Biologics Evaluation and Research (CBER): Component of the FDA with regulatory authority over research, development and approval of biological products, including vaccines.

PRINCIPLE

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Lives in the developing world matter.

For every promising vaccine approach under development, scientists are working to ensure it will be appropriate for use in the developing world. Contracting agreements between public and private entities reserve some intellectual property rights to the public sector, in order to facilitate vaccine access in poorer countries. Solutions to pricing and purchase barriers are found that encourage industry action today and facilitate rapid delivery of a vaccine to the entire world, not just wealthy nations, when one is ready.

ETHICS, ACCESS AND THE GLOBAL CONTEXT

■ STATUS Vaccine Trial Ethics Debated • Treatment Issues Impact Vaccine Research • Access Issues Remain Problematic ■ RECOMMENDATIONS Move Ahead With Vaccine Trials • Expand Access To Effective Treatments In Developing Countries • Governments Must Address Pricing, Purchase, Production and Intellectual Property Issues

Twenty years into the AIDS pandemic, with an estimated 36 million infected — mostly in developing countries — the vaccine research world seems finally and truly to be coming to grips with the global role it must assume. Effective research in a meaningful international context, however, raises a large patch of thorny issues. In order to get to the science, serious ethical issues must be addressed — issues on which people of good conscience can disagree and for which correct answers may vary due to local conditions. In order for the science to do any good, the very high hurdles of getting that science to the people most in need must be resolved.

ETHICAL CONSIDERATIONS FOR ETHICAL SCIENCE

In October 2000, the World Medical Association revised the *Declaration of Helsinki*. This is the fourth time the Declaration has been amended since its original adoption in 1964, when it became one of the pillars of clinical research ethics.

The most fundamental revision to the Declaration is related to the use of placebos as control arms in clinical research. The previous version stated that "In any medical study, every patient — including those of a control group, if any — should be assured of the best proven diagnostic and therapeutic method." Since clinical studies are designed precisely to test a new method that differs from the "best proven method," this statement was not logical. The revised Declaration clarifies what the Association believes a clinical trial should require: "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists."

Several alternate positions were debated and rejected during three years of discussions. One proposed allowing placebos in trials where risks were minimal and there was no possibility of death or disability. It also supported the use of "the highest attainable and sustainable therapy," which amounts to the "best" possible care available in the site country, as controls. Others suggested that "proven, effective treatment," but not necessarily the best, was sufficient. This last position appears to coincide with the US National Bioethics Advisory Commission (NBAC), which recently released its own report entitled, "Ethical and Policy Issues in International Research." The NBAC report recommends the use of "established, effective treatment," incorporating the notion of widespread acceptance of the therapy.

POTENTIAL IMPACT ON HIV VACCINE TRIALS

The main impact of this revision on current and future preventive HIV vaccine trials may be added pressure to provide the "best current therapy" to trial participants who get infected with HIV. Although these are prophylactic and not therapeutic studies, participants who get infected will still be followed in the original or a subsequent study because the vaccine

may have an impact later, in the course of the disease, even if it doesn't stop the initial HIV infection itself.

Unfortunately, there is a possibility that more pressure to provide the "best current treatment" might not result in more ethical trials, but in a delay in the start of new preventive HIV vaccine trials. This potential risk is particularly true for trials in the least developed nations. Providing this level of treatment, even for the few hundred participants who potentially would get infected in studies that can include thousands, will be difficult to achieve.

FINDING A WORKABLE PATH

Perhaps the strongest argument against providing anti-retroviral therapy in a country where it is otherwise practically unavailable has been that it would provide an undue inducement to join a vaccine study. Some believe that this argument is seriously flawed since trials, as currently designed, already include "inducements," such as routine health check-ups and other benefits that are not currently available to the general population. More troubling is the fact that trials with subsequent treatment may not be as relevant where subsequent treatment will not be available outside the trial, since trial conditions no longer match those of the general population.

In recent years, access to anti-retroviral treatment has been expanding in many developing countries, especially in Latin America and Asia. Effective, although perhaps not optimal, therapies are being achieved with fewer drugs and without some of the very expensive protease inhibitors. Companies in Brazil, India and Thailand are making generic versions of these drugs, and these are available at substantially lower prices. While Brazil and Thailand make enough product to satisfy their local demand, Indian companies such as Cipla and Ranbaxy Laboratories intend to make enough product to export to Africa and other less developed nations.

Recognizing the changing situation, the major pharmaceutical companies have begun lowering the prices to developing countries and participated in private meetings with the World Trade Organization and World Health Organization in April 2001 to begin discussion of drug access issues.

It is true that questions remain about the sustainability of and access to the drug programs, but anti-retroviral drugs have become, in some developing nations, part of their highest attainable standard of care. While this is far less true in the poorest countries, particularly in hardest hit Africa, it is increasingly difficult to justify no provision of at least a minimum of anti-HIV medications to the infected population.

As community vaccine advocates in a country that generally provides Highly Active Anti-Retroviral Therapy (HAART), considered the "best current treatment," for HIV disease and AIDS, AVAC supports all efforts to expand access to HAART in developing countries. Of equal importance, AVAC supports HIV vaccine clinical trials with sound ethical standards starting as soon as possible. How can we reconcile these two issues, which are seemingly at odds?

It is clear that in developing countries where either HAART, or (at a minimum) proven effective anti-retroviral treatment therapies are available, the same treatments should be available for vaccine trial participants who become infected during the trial. But what about the poorest countries that currently lack any significant provision of treatment for the infected and, in general, are the ones most desperate for an HIV vaccine?

First, we think the urgency of the epidemic demands that we initiate HIV vaccine trials as soon as possible, without throwing more roadblocks in the already difficult path these trials face. This may mean that, in some instances, HIV vaccine trials begin without the issue of therapy for trial participants completely resolved.

Second, we believe that communities participating in HIV vaccine trials — community members, researchers, health care practitioners, and public officials, working together — must decide for themselves the ethical questions posed by HIV vaccine research.

Third, the public health community must promote both HIV vaccine research and the real opportunities to expand access to life-prolonging care. HIV vaccine trials do not take place in a social or public health vacuum. These trials will be conducted in communities in which a significant share of the population is desperate for AIDS drugs that are beginning to be delivered in other developing countries.

HIV vaccine trials in the poorest countries should be used as opportunities to expand access to AIDS treatments. Communities hosting HIV vaccine trials are making enormous contributions to international public health, and they have the right to negotiate how these trials can be coupled with efforts to expand health care delivery infrastructure, access to basic or advanced HIV treatments and access to a vaccine, when one is available. Efforts to expand access to treatment should also be used as opportunities to make it possible to expeditiously conduct ethical vaccine trials.

A more serious effort must be undertaken by national governments of both rich and poor countries, in conjunction with international organizations and drug manufacturers, to increase access to anti-retroviral treatment for their HIV infected population, including those in HIV vaccine trials. We are in a fast-changing environment. Companies are making cheaper generics and willing to export them. A new US president declares he will stick to a policy of not penalizing hard-hit countries for legalizing the manufacture or importation of generic AIDS drugs. There are simpler anti-retroviral regimes, and multiple philanthropic organizations are willing to contribute at least some of the cost of these therapies. There is real opportunity to move forward on broader provision of HIV treatments in developing countries.

The richer countries of the West, which have acknowledged this disease is a threat to international stability, must put more money where their mouths are. The pandemic will not end until we have both an effective, affordable vaccine, and widespread access to effective treatment. In the best of worlds, the two will go hand in hand.

ACCESS TO A SAFE, EFFECTIVE AND AFFORDABLE HIV VACCINE

An effective vaccine that is not available to those who need it is not truly an effective vaccine. Two cases in point: the Hepatitis B vaccine licensed in the early 1980s and the Haemophilus influenza b (Hib) vaccine licensed in the late 80s, are still not available in many countries — at the cost of hundreds of thousands of lives.

How to deliver a vaccine to where it is needed, thankfully, has emerged as an urgent international issue. In May 2000, the Joint United Nations Programme on HIV/AIDS (UNAIDS) issued *Ethical Considerations in HIV Preventive Vaccine Research*, stating: "Any HIV preventive vaccine demonstrated to be safe and effective, as well as other knowledge and benefits resulting from HIV vaccine research, should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at high risk for HIV infection."

In its July 2000 Blueprint, *Preparing Now to Assure Access*, the International AIDS Vaccine Initiative (IAVI) outlined five steps to assure simultaneous, global access. They are: 1) pricing and global financing mechanisms, 2) reliable estimates of demand to guide production capacity, 3) delivery systems and procedures for at-risk populations, 4) harmonizing national and international regulations and guidelines

for vaccine approval and use, and 5) efforts to achieve maximum use in developing countries of one or more under-utilized non-AIDS vaccines.

Political attention has also risen. Harvard economists Jeffrey Sachs and Michael Kremer have proposed a system of purchase pre-commitments for HIV, TB and malaria vaccines. Countries would pledge to fund purchase of these vaccines when they become available and an international body would negotiate on purchase and pricing. Each country would have its own account, allowing it a role in deciding whether to purchase vaccines for their populations.

In June 2000, the World Bank's International Development Association established a $1 billion revolving fund to fight communicable disease. These funds can be used to purchase needed drugs and vaccines, including HIV vaccines, when available.

Pricing

Tiered or differential pricing means charging different prices for the same product in different countries, usually based on the purchasing capacity of the local market and/or local regulations. Lower prices would make the product affordable in poor countries, while allowing companies to obtain a satisfactory return on investment and profit from higher prices in countries with greater resources. Tiered pricing has been common practice with preventive vaccines. In general, however, preventive vaccines have been distributed in poor countries many years after they are developed — after the demand in rich countries has been satisfied and companies have recouped their investments and made substantial profits.

In its Access Blueprint, IAVI makes a call for key political leaders, governments, international organizations, as well individual companies and industry associations to support a tiered pricing structure for HIV vaccines. For its part, World Bank health specialists have declared that "One price for the world would be disastrous."

AVAC fully endorses the IAVI call for support of a tiered pricing structure for HIV vaccines. We believe that it is possible to achieve a balance, which will allow companies that develop an HIV vaccine to recoup their investment in R&D and make a profit, while making the vaccine available in poorer countries. Furthermore, tiered pricing should be available from day one, and enough manufacturing capacity should be created from the start to satisfy the demand in both rich and poor countries. Due to the enormous political and economic clout of the United States, domestic political leaders and consumer groups must be convinced of the need for tiered pricing of HIV vaccines. This will require intensive lobbying efforts, especially by international health agencies, in concert with national AIDS organizations in the US.

Purchasing Mechanisms

New purchasing mechanisms must also be explored. Even with an agreement on differential pricing for HIV vaccines, there will still be many countries that cannot afford to buy the amount of vaccine they will need to successfully vaccinate their at-risk populations. In addition to the cost of the vaccine itself, the infrastructure for delivering the vaccine either doesn't exist or is insufficient to accomplish this enormous task without substantial investments.

Some of the proposals outlined above are important and will contribute to solving the problem. Nonetheless, a more concerted commitment is needed from national and regional governmental institutions, as well as philanthropic organizations, to estimate the cost of delivering one or several HIV vaccines in the neediest countries and to provide the resources to do so.

Those with the power and resources to provide sufficient funding for HIV vaccine purchase and delivery would be more inclined to do so if they understand the costs and benefits of providing such support. This is not a simple calculation. The answers will

vary depending on the efficacy level of a given vaccine, its price, and the cost of delivering it, relative to the cost of current prevention measures. Nevertheless, the study must be done.

Public and private sectors must work together to create a credible and sustainable multi-billion dollar purchase mechanism for vaccines against HIV, malaria, and TB. Such a mechanism has the potential to spur additional research on these desperately needed products and ensures that they will be delivered to developing world populations soon after they are licensed for use. A purchase guarantee should not tie up funds before these vaccines are ready. Instead, governments and foundations should pledge to fund purchase of priority vaccines for developing countries and increase their contributions to multi-lateral organizations for delivery of current and future vaccines.

Intellectual Property Agreements

In 1999, IAVI broke new ground with its novel Intellectual Property Agreements included in its vaccine development partnerships. By subsidizing initial product development, IAVI, a non-profit, obtains the commitment of the vaccine developers to make the product available for a reasonable price in lower income countries. Failure to do so would allow IAVI to contract with a third party to produce the vaccine for lower cost.

Unfortunately, not everything has worked smoothly since then. In the first IAVI partnership to include such an agreement, a conflict emerged over the failure of British researchers to include their Kenyan collaborators in a patent application. Initially claimed as an oversight, debate ensued over where the "crucial" research had occurred. Although resolved satisfactorily, with the trial timetable relatively unaffected, this provides a case study of the some of the difficult issues that arise in meaningful research collaborations with less developed countries — something essential to appropriate product development. The rights and responsibilities of all partners must be agreed upon and documented clearly at the very beginning of the collaborative process.

Production Capacity

Production capacity concerns will shortly appear as another issue for access. As an example, if VaxGen's AIDSVAX vaccine shows moderate levels of efficacy when results are released, it may be approved for use in some countries. In order to use it, however, a process known as scale-up — gearing up to be able to manufacture the large number of doses needed to satisfy demand — must take place. Building manufacturing plants can take up to five years to complete. Even if started today, and assuming approval occurs in two years, it would take an additional three years to be able to supply the product, depending on the size of the demand.

The problem gets more complicated because the market for a vaccine remains unknown. Who is going to use it — and of course who is going to pay for it? Depending on the efficacy level of the vaccine, the product may only be used in countries with a rampant HIV epidemic. These are mostly the poorest countries in Africa, Asia and the Caribbean.

The issues of demand and production capacity were considered by IAVI in its Access Blueprint, and by the World Bank AIDS Vaccine Task Force in its position paper. IAVI has called for experts to compare demand estimates using a number of different approaches. With these estimates on hand, "appropriate multinational and national financial institutions should collaborate with private industry…to ensure that sufficient production capacity exists to ensure worldwide distribution of new vaccines." The World Bank AIDS Vaccine Task Force, based on its 1999 calculations, suggests that an initial global market for an AIDS vaccine would be approximately $8 billion. This figure could certainly vary substantially, depending on the vaccine efficacy level.

There is general agreement on the need to determine market demand for an HIV vaccine, in both industrialized and developing countries, and several proposals have been made to address that. Particularly relevant to the international community, is how to ensure that production capacity will be there for a vaccine with only a limited market in the industrialized world, where most profits will be generated. One possibility is to start the process of building manufacturing capacity in some developing countries now. Granted it will be difficult to decide what type of facility to build before knowing the specific product to be produced, but there is some basic start-up work that is common to this process no matter what product one intends to make. Fortunately there are several developing countries that have enough scientific and industrial expertise to assume a leading role in this, with proper support.

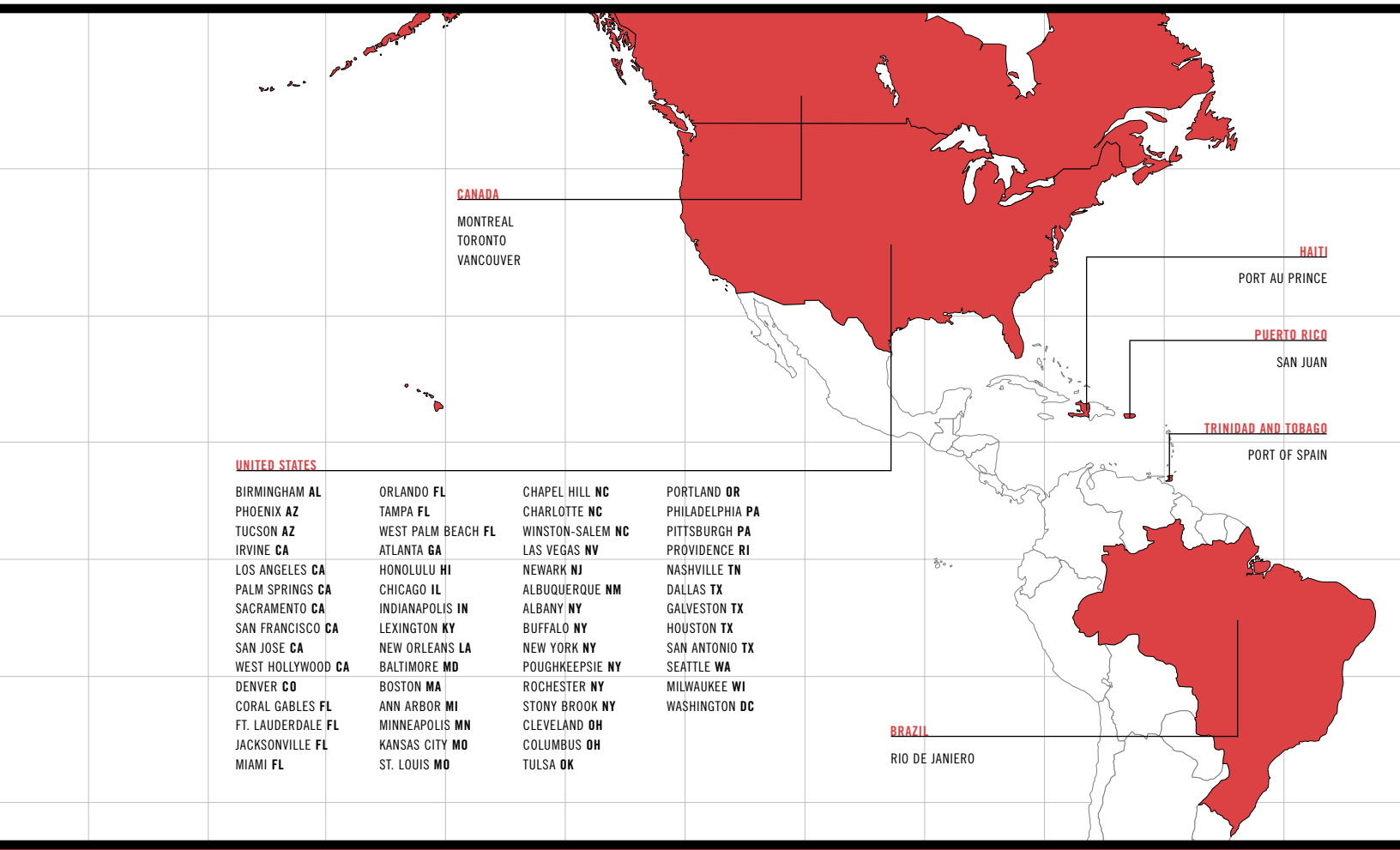
THE JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS (UNAIDS)

While the leadership for research on AIDS vaccines remains largely centered in wealthy industrialized countries, the pandemic is global. An important player on the global stage is the Joint United Nations Programme on HIV/AIDS. UNAIDS is co-sponsored by five other programs at the United Nations that saw a need for efforts beyond their individual scopes, along with the World Bank and the World Health Organization. UNAIDS does no direct funding of research. Instead it provides a facilitating role, addressing a broad array of issues and acting as a catalyst for action, usually with a special emphasis on including and empowering developing countries.

UNAIDS sponsored a series of workshops around the world on the ethics of AIDS vaccine research in the international context. This culminated in the May 2000 release of its guidance document, *Ethical Considerations in HIV Preventive Vaccine Research.*

UNAIDS has also issued a report on access issues, is spearheading a meeting in collaboration with IAVI to estimate demand for an HIV vaccine, and has sponsored forums in Africa and elsewhere on including AIDS vaccines in the plans of local AIDS organizations.

It has also worked on the practical issues of international research, helping local officials and researchers in developing countries build capacity for trials. It held a meeting in March 2001, focused on harmonizing regulatory procedures between countries. Another focus has been to assist researchers, government agencies and companies in identifying and developing trial sites.



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WASHINGTON **DC**

ACTIVE CLINICAL TRIALS AND TRIALS PLANNED TO START IN 2001

(as of March 2001, prospective trials may be delayed for a variety of reasons)

AGENCE NATIONALE DE RECHERCHES SUR LE SIDA (ANRS)/AVENTIS

ACTIVE TRIALS: ALVAC/lipopeptide
ACTIVE SITES: Paris, France

HIV VACCINE TRIALS NETWORK (HVTN)

ACTIVE TRIALS: ALVAC, ALVAC/DNA gag-pol, ALVAC/p24/gp120, ALVAC gp120
PROSPECTIVE TRIALS: VEE, NYVAC
ACTIVE SITES: Birmingham AL • San Francisco CA • Baltimore MD • Boston MA • St. Louis MO • New York NY • Rochester NY • Nashville TN • Seattle WA, United States • Rio de Janiero, Brazil • Port au Prince, Haiti • Port of Spain, Trinidad and Tobago
PROSPECTIVE SITES: Durban, South Africa

INTERNATIONAL AIDS VACCINE INITIATIVE (IAVI)

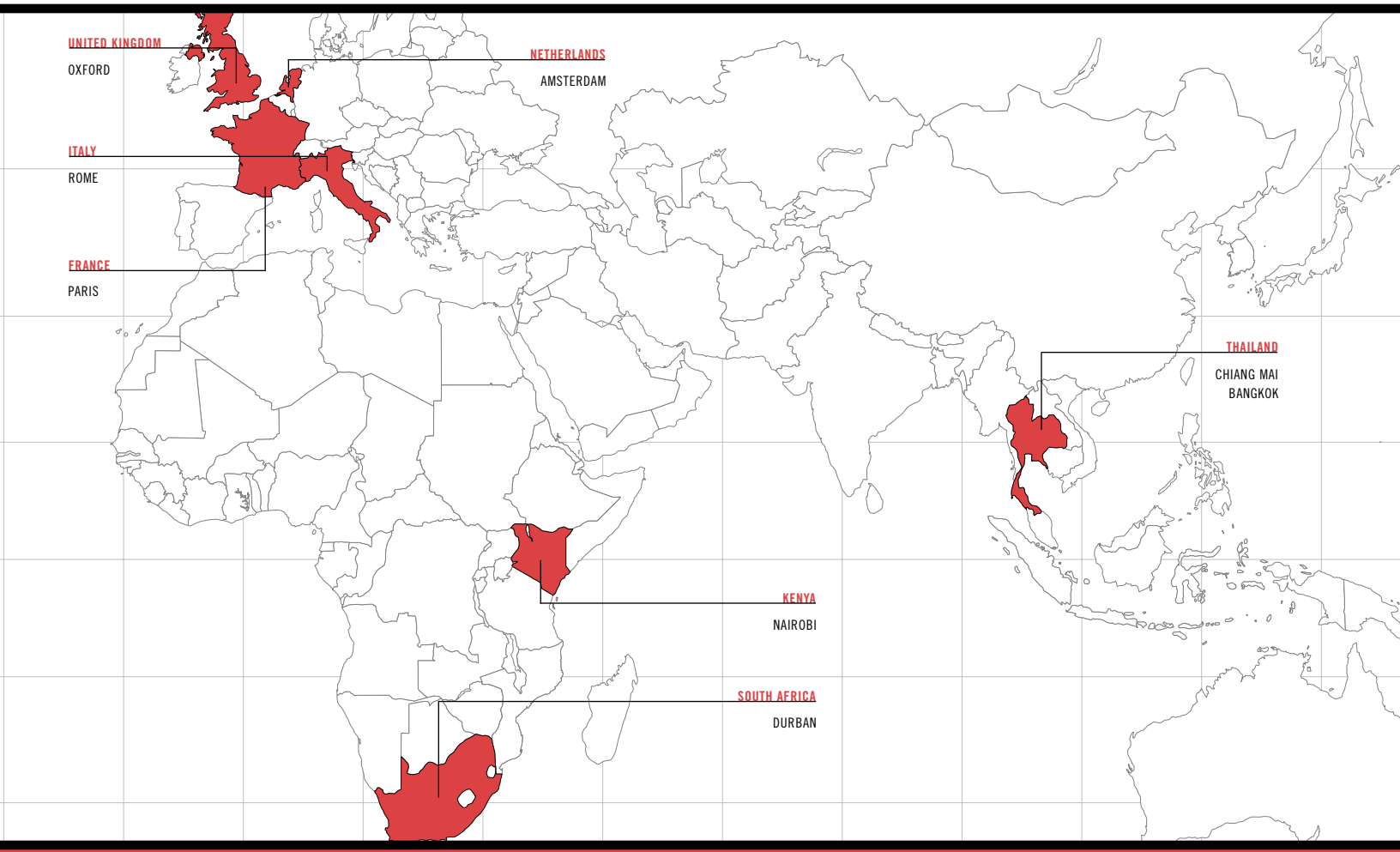
ACTIVE TRIALS: MVA
PROSPECTIVE TRIALS: VEE
ACTIVE SITES: Oxford, United Kingdom • Nairobi, Kenya
PROSPECTIVE SITES: Durban, South Africa

ITALIAN MINISTRY OF HEALTH/GERMAN RESEARCH CENTER FOR BIOTECHNOLOGY

PROSPECTIVE TRIALS: DNA/tat
PROSPECTIVE SITES: Milan • Rome, Italy

MERCK & CO

ACTIVE TRIALS: DNA, Adenovirus
ACTIVE SITES: Birmingham AL • Los Angeles CA • Sacramento CA • Atlanta GA • Baltimore MD • Boston MA • Minneapolis MN • St. Louis MO • New York NY • Rochester NY • Stony Brook NY • Providence RI • Nashville TN • San Antonio TX • Washington DC, United States
PROSPECTIVE SITES: San Francisco CA • Denver CO • Ft. Lauderdale FL • Miami FL • Lexington KY • Ann Arbor MI • Albany NY • Chapel Hill NC • Seattle WA, United States



VAXGEN

ACTIVE TRIALS: gp120

ACTIVE SITES: Birmingham AL • Phoenix AZ • Tucson AZ • Irvine CA • Sacramento CA • Palm Springs CA • San Francisco CA • San Jose CA • West Hollywood CA • Denver CO • Coral Gables/Ft. Lauderdale FL • Jacksonville FL • Orlando FL • Tampa FL • West Palm Beach FL • Atlanta GA • Honolulu HI • Chicago IL • Indianapolis IN • New Orleans LA • Boston MA • Minneapolis MN • Kansas City MO • St. Louis MO • Las Vegas NV • Newark NJ • Albuquerque NM • Albany NY • Buffalo NY • New York NY • Poughkeepsie NY • Rochester NY • Charlotte NC • Winston-Salem NC • Cleveland OH • Columbus OH • Tulsa OK • Portland OR • Philadelphia PA • Pittsburgh PA • Providence RI • Dallas TX • Houston/Galveston TX • Seattle WA • Milwaukee WI • Washington DC, United States • Vancouver BC • Toronto ON • Montreal QU, Canada • Amsterdam, Netherlands • San Juan, Puerto Rico • Bangkok, Thailand • Chiang Mai, Thailand

WALTER REED ARMY INSTITUTE OF RESEARCH (WRAIR)

ACTIVE TRIALS: ALVAC, ALVAC/gp140, ALVAC/gp120/gp140

PROSPECTIVE TRIALS: VEE

ACTIVE SITES: Washington DC • Durban, South Africa • Bangkok, Thailand • Chiang Mai, Thailand

Sources: Aventis, HIV Vaccine Trials Network, International AIDS Vaccine Initiative, Merck & Co., VaxGen, Walter Reed Army Institute of Research

PRINCIPLE

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Risk taking is rewarded.

The public, media and government leaders demand an explanation every time an HIV vaccine that meets safety tests and shows a promising immune response is not immediately put into an efficacy trial. Scientists worry about the costs of *not* moving forward with trials across the globe.

Is AVAC's vision merely a dream? We don't think so. In fact, we believe it is more rational than revolutionary. It is a plausible improvement over what exists today. The ingredients for an accelerated HIV vaccine research and delivery effort are all present today. This report, *6 Years and Counting: Can a Shifting Landscape Accelerate an AIDS Vaccine?* attempts to move us one step closer towards this vision.

ABOUT AVAC

The AIDS Vaccine Advocacy Coalition (AVAC) was founded in December 1995 with the mission to speed the development of an AIDS vaccine, identify obstacles to HIV vaccine development and advance solutions to those obstacles. AVAC seeks to provide independent analysis, public advocacy and innovative policy to enhance the search for a successful AIDS vaccine.

In 2000, AVAC continued its push for tax legislation to provide more incentive for needed research, began a pilot community advocacy program targeting key cities, worked with other organizations to explore issues of access and delivery to an AIDS vaccine when it is available, and distributed 4500 copies of "7 Years and Counting: How Can We Overcome Obstacles to an AIDS Vaccine?"

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