

# HOW DO YOU FIGHT A DISEASE OF MASS DESTRUCTION ?

...

AND OTHER QUESTIONS ON THE ROAD TO AN AIDS VACCINE.



Y E A R S   &   C O U N T I N G



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Last year the AIDS Vaccine Advocacy Coalition (AVAC) lauded the suddenly robust AIDS vaccine pipeline. *Why did so few of those products make it into clinical trials?* AVAC begged for accelerated, coordinated efforts and a sense of urgency. *Why did our society come through for bioterror vaccines and not AIDS?* For several years, leaders in the field have cited the need for multiple, parallel efficacy trials internationally. *Why aren't we prepared to run those trials?*

Today there are many ideas for AIDS vaccine design but product development and testing still move at a leisurely pace — as the pandemic rages. This can be changed. The comprehensive incentives for bioterror vaccines — expanded direct funding, shortcuts around bureaucratic hold-ups, regulatory acceleration, guaranteed purchase capacity — are a blueprint for what is needed in AIDS vaccine policy.

We still insist that more efficacy trials must be run. This year VaxGen completed a Phase 3 trial and showed that you can get a result without putting trial participants at increased risk of infection (see sidebar, page 9). AVAC applauds the company's tenacity (though not unproductive exaggerations that occurred during the announcement of the results). That kind of determination is needed from more players in AIDS vaccine development. But the vaccines of the future must benefit from a better synthesis of the lessons being learned as research advances.

Isolated policy changes and unilateral efforts will not cure what is wrong with AIDS vaccine research fast enough. Growing acknowledgement of this is bred from an ongoing sense of frustration with the lack of progress to date. A more systematic, integrated AIDS vaccine effort is needed to:

- 1 Ensure products are not unnecessarily delayed en route to human trials. Just about every vaccine maker could use help with the multiple steps that go into process development and manufacturing.*
- 2 Fully utilize advances in standardization, including assays and validation procedures, while retaining flexibility for development and use of new assays.*
- 3 Serve the multiple needs common among vaccine producers — from access to non-human primates, isolates and reagents, to better-prepared clinical sites globally.*
- 4 Deliver the new resources and coordination required to meet the international standards being established — in the areas of multi-site trial designs, provision of treatment in vaccine trials, and community involvement.*

A more rational, well-funded system would stimulate better and faster synthesis and application of knowledge gained across the field. It would better harness the expertise and energy in private industry that has been driving the vast majority of product development. And it would encourage more collaborative efforts overall.

The scientific news this year offered fresh hope, confusion and the first actual efficacy data. There was a glimmer of forward movement on efforts to induce neutralizing antibodies, and studies demonstrated protection of macaques with antibody vaccines. In another study, protection from infection was observed in infant macaques challenged with “low dose” virus that more closely resembles the dose of viral exposure humans encounter. The new dosing approach, and the fact that these animals did not exhibit robust responses to standard immune measures, raises tantalizing prospects for future research.

The National Institutes of Health (NIH), the International AIDS Vaccine Initiative (IAVI), CANVAC, the US Army and others collaborated on important assay standardization studies, with recommendations that should finally enable better comparison of research. ViroLogic, Inc. and others unveiled rapid assays that should advance understanding of HIV escape mutations and facilitate vaccine development. Two vaccine giants, Merck and Aventis, announced plans to collaborate on a trial combining two of their AIDS vaccine candidates. Trimeris, the spin-off of an AIDS vaccine research lab, got US Food and Drug Administration (FDA) approval for the first new class of antiviral drugs that block virus entry into cells, an advance that holds promise for use in salvage therapy for people living with HIV and presents new targets for vaccine research. EuroVac is becoming an important collaborative effort and its plans for a clinical trials platform will be an addition to the field. The CANVAC network of academic, industry, government and consumer interests promises to be a valuable partnership to advance overall vaccine research.

Other news raised concerns and questions. In particular, several studies reemphasized the serious challenge posed by viral escape from AIDS vaccines and the need to design vaccines aimed at multiple targets.

*The take-away from all this, once again and predictably, is the ever more urgent need to press forward on basic science, product development and clinical research simultaneously.*

This year both the NIH-sponsored HIV Vaccine Trials Network (HVTN) and IAVI formulated plans to make antiretroviral treatment available to vaccine trial participants who become infected with HIV during a trial. As we have said for years, AIDS vaccine trials must be used as opportunities to expand access to treatment and prevention to whole communities where trials take place.

*How do you fight a disease of mass destruction?* Multilaterally, for sure. You do it by delivering the treatments and prevention technology you have while driving research on better technology with generous funding, appropriate incentives, global coordination and a sense of urgency. This is all eminently doable. But war, deficits and limited budget increases at NIH could easily undermine each of these priorities. All of us need to demand continued increases in resources for AIDS care, prevention and research, as well as a comprehensive AIDS prevention policy based on research — rather than political and social agendas.

AVAC has redesigned our report this year. Rather than attempt to review the work at multiple agencies yet again, we offer a series of articles on particular subjects that raise important questions.

The opening chapter compares our government's response to the bioterror threat with the federal effort on AIDS vaccines. We also recount what we heard from industry leaders during our recently completed survey of pharmaceutical and biotech companies.

The AVAC Report then examines two crucial questions about the AIDS vaccine pipeline. Why have the NIH milestones (which set goals for getting products into clinical trials) consistently slipped over the years? And is the current pipeline as diverse as it needs to be, or is it showing signs of faddishness and duplication?

These two chapters provide no simple answers, but they point to one disturbing observation: in the push to advance products, most product developers are failing to work collaboratively and systematically to design improved products and investigate fundamental mechanisms. Systematic collaboration may be happening in one or two companies and research centers, but not nearly enough across the diverse expertise and efforts in the field.

The AVAC report closes with case studies that highlight the spirit (and challenges) of collaborative efforts. The first reviews the impressive work at the NIH Vaccine Research Center (VRC). We close with an examination of the VEE candidate vaccine and delays in getting this novel product into humans.

**The world is allowing AIDS vaccine research to crawl forward — with blinders on. What is needed to improve the effort?**

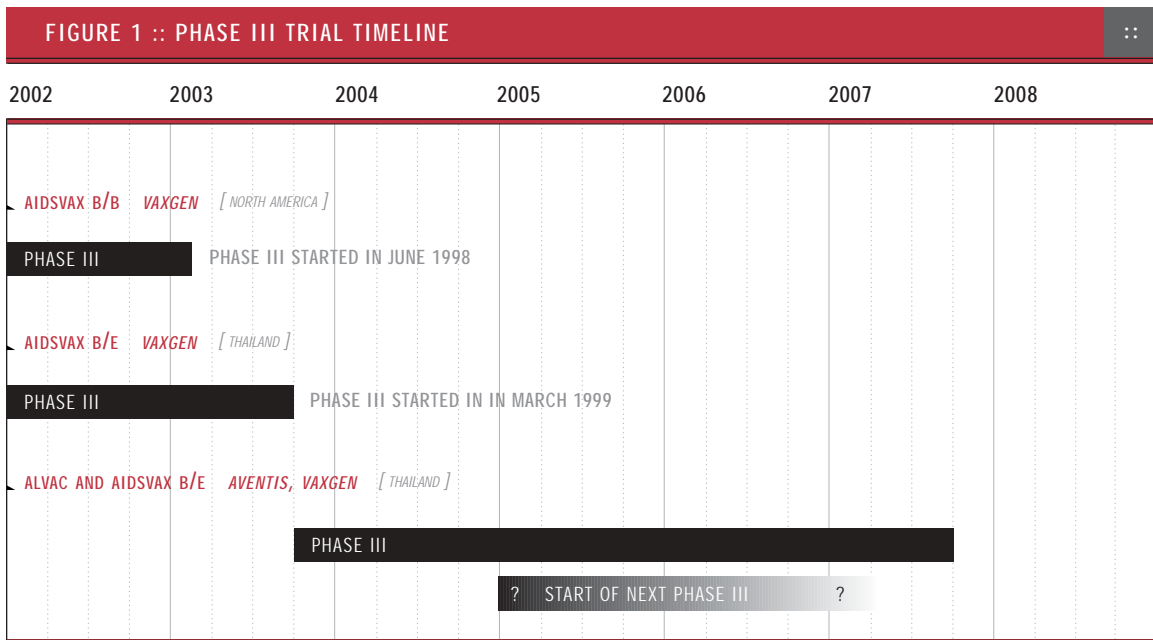
- ***More trials must be run.*** Advocates and researchers need to create an environment in which the world expects and demands more efficacy trials; understanding that these expensive, difficult trials involving thousands of people are vital to advancing the field.
- For that to happen, ***a significantly expanded clinical research infrastructure is essential*** in many resource-limited countries as well as in some communities in the United States. Continued and expanded investment is necessary to bolster vaccine trial preparedness internationally. Trial participants need guaranteed compensation for physical harm and companies require protection from liability not due to negligence. Some entity must provide this coverage in order to foster multiple large-scale clinical trials.
- ***Delays in moving products forward must be addressed systematically.*** Each cause of delay in advancing candidate vaccines to trial must be addressed expeditiously. NIH should assemble teams to help researchers with promising ideas speed up translation of those ideas into products. Product developers in industry and the public sector must have ongoing assistance with process development and manufacturing challenges.
- The ***comprehensive policy incentives*** and sense of urgency set in place for bioterror by the US Congress and the Administration must be adapted to accelerate AIDS vaccine development in both industry and the public sector. These incentives include creating a credible purchase pre-commitment to make AIDS vaccines globally accessible. AIDS vaccine candidates are not developed in a year or two. Longer-term small business funding mechanisms must be created for biotech companies.
- The US Congress must continue to ***increase NIH funding*** to enable the Institutes to press forward on basic science, product development and clinical research that addresses the greatest infectious disease challenge of our time.
- The US Congress must ***increase FDA funding*** to enable the agency to step up its work on AIDS vaccines and other infectious disease products. Researchers and product developers need early and continual input from FDA. Several other organizations have a role to play in supporting vaccine developers with regulatory issues, including the National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS), trial sponsors and site developers. This regulatory gestalt needs to work more efficiently. FDA should also be encouraged to work with the World Health Organization and others to help build regulatory capacity around the world.

- The field as a whole must become more *integrated, fostering iterative product development and testing*. It is essential to strike a balance between healthy competition (where each developer works with speed and focus) and cooperation (where data are shared and product comparisons are run). Products must be spirited forward while fundamental mechanisms are explored and results are fed back into the product development system. Collaborations, like the new partnership between Merck and Aventis, need to be encouraged.

The ten-year timeline to find an AIDS vaccine that was set in motion by a US President is about to become a pipe dream. Thailand's forthcoming prime-boost trial is the last chance to find an AIDS vaccine within a decade of the Clinton challenge. The field is only one efficacy trial into this enterprise and initial data make it clear we are in this for the long haul. Now we must lay the groundwork for a sustainable, better-coordinated and intensified global effort that begins to look like a real horse race — rather than a promenade around the paddock.

**AVAC hopes this report is a tool for discussion, advocacy and change.**

**Chris Collins**  
*Executive Director*





The results of the AIDSVAX trial in the overall study population were a disappointment, though not a great surprise to many. VaxGen, the vaccine's maker, presented some provocative data on subgroups in the trial cohort and these data need to be thoroughly investigated by leading scientists in and outside the company.

VaxGen has also accumulated the world's largest collection of gp120 genetic sequences from newly infected people. This database provides the best estimate of the true genetic variation of HIV in North America and it could be extremely valuable to the field. We encourage the company to make it available to other researchers. Future partnerships between government and industry should include agreements regarding access to this kind of groundbreaking data that can inform the whole field.

The VaxGen trial also offered important lessons for everyone involved in AIDS vaccine research. It demonstrated that you can successfully recruit and retain thousands of volunteers in AIDS vaccine trials and that, given proper counseling, volunteers will not increase their risk behavior. *This is extremely important because it shows that future (and multiple) efficacy trials are feasible and can be run without being hazardous to study populations.*

There were other lessons too. It has become abundantly clear that expanded trial recruitment and involvement among women and communities of color are essential. More attention needs to be paid to potential gender and racial differences in immunological responses. The controversy that surrounded the VaxGen announcement should make trial sponsors cautious about announcing claims for data that are inconclusive. Overly enthusiastic interpretation of uncertain results ultimately helps no one.

After the AIDSVAX results were made public, AVAC and several other groups (including Balm in Gilead, Black AIDS Institute, Gay Men's Health Crisis, National Minority AIDS Council, Project Inform, and Treatment Action Group) wrote Dr. Anthony Fauci, Director of NIAID. We raised concern about the many questions associated with the AIDSVAX results and asked Dr. Fauci to convene a broadly-representative external review group to fully analyze the data and make a recommendation for further study, if warranted. At this writing, NIAID has announced plans to convene meetings to involve company representatives, scientists, community representatives and others to discuss next steps on the AIDSVAX data.

AVAC also developed a brochure that explains what is known and what is yet to be determined as the AIDSVAX results are analyzed. The brochure is available on our web site:

< <http://www.avac.org/pdf/UnderstandingAIDSVAX.pdf> >



# 1

WHAT CAN THE FEDERAL RESPONSE TO BIOTERROR  
TEACH US ABOUT FINDING AN AIDS VACCINE?



Bioterror has rapidly become a lush federal funding stream. The government response to the bioterror threat is comprehensive and has a sense of urgency. *What have the politicians done for bioterror that they could do for AIDS vaccines?* Before we consider the details, it's useful to remember how this massive government effort all started back in October 2001.

On the first Tuesday of October, 63-year-old Florida resident Robert Stevens became disoriented, ran a high fever and started vomiting. By the time his family got him to the hospital, Mr. Stevens was unable to speak. It had been only a few weeks since the terrorist attacks of September and the nation was bracing for more untold calamities. When officials at JFK Memorial Hospital announced that Mr. Stevens had pulmonary anthrax, the diagnosis instantly became national news. "It's an isolated case and it is not contagious," Secretary of Health and Human Services Tommy Thompson said. "There is no terrorism."

Over the coming days and weeks it became clear that the Stevens case was in no way isolated. A coworker of Stevens was hospitalized. Anthrax-laden letters started arriving in the halls of Congress. Postal workers fell ill. Mr. Stevens died. The FBI took over the investigation and the Centers for Disease Control (CDC) mobilized.

The day before this string of events began, National Guard soldiers arrived at a little known biotech company in Michigan called BioPort. The soldiers brought barbed wire fencing and concrete barriers and began to secure the company's facility. In the wake of September 11, and as the only supplier of anthrax vaccine to the US military, BioPort was suddenly an important national asset.

The only problem was that the company had twice failed FDA inspections and had not produced a dose of vaccine for three years.

What went wrong at BioPort? Many pointed fingers at the company itself. One Senator called BioPort's record "an unmitigated disaster." Others said there was another side to the story. "The Defense Department (BioPort's client) significantly underfunded the whole effort and didn't give it the priority it deserved," Tara O'Toole of the Center for Civilian Biodefense Studies at Johns Hopkins University was quoted as saying. The debate capped off growing awareness in industry and public health circles about the sorry state of the vaccine industry in general.

Then anthrax became political. Secretary Thompson wanted to buy millions of doses of Cipro, an antibiotic made by Bayer and used to prevent and treat anthrax. But given the size of the purchase, the Secretary wanted to pay less than the usual \$1.77 per pill price. Bayer objected. Thompson threatened to ignore the company's patent and buy generics. In late October, Bayer reconsidered.

Wait a minute...a Republican administration threatening to break a pharmaceutical company's patent? It was a stunning example of how the rulebook gets thrown out when people get scared, and the potential for action when an emergency is perceived.

Over the years of writing reports, AVAC has often called for more "leadership" in the AIDS vaccine effort but we were always hard pressed to say exactly what that would mean. We'd know it when we saw it. Now we see it. And it's not for AIDS vaccines.

Leadership in health research means identifying priorities, breaking through procedural impediments and dedicating substantial new resources. It means identifying barriers and fixing them and pushing through policies that address the challenges at hand.

In February 2003, CIA Director George Tenet reminded the nation that AIDS is a national security threat to the United States that could "undermine the stability and economies" of many nations. For the year 2001, at the height of the anthrax scare, there were eighteen cases of domestic bioterror-related anthrax — and 40,000 new HIV infections in the US. That means 2,200 new HIV infections in the country for every one case of anthrax.

It's fair to ask, if we can do it for smallpox and anthrax vaccines, why wouldn't we do it for vaccines against the biggest infectious disease killer of our time? AVAC acknowledges from the outset that the problems are different in important ways. Researchers have already established protective mechanisms against smallpox and anthrax, so the scientific hurdles are far less daunting than with AIDS vaccines. It is one thing to cut through the red tape and get products approved when you are adapting the use of an existing drug or making improvements to a current product. It is an altogether different challenge to do this with wholly new technology and new products in the absence of a correlate of immunity.

What is similar about bioterror and AIDS vaccines are several policy challenges: the need to streamline governmental efforts, fully engage industry, and ensure a paying market to embolden industry and enable access to these products by all who need them. What follows is a checklist of federal policies and proposals designed to create and purchase bioterror-related products — annotated with the status of these ideas in the AIDS vaccine effort.

“Very simple. Money.” That was Phil Russell’s answer to *IAVI Reports* last fall when asked what financial incentives could encourage industry to research and mass-produce new bioterror vaccines. Russell, who has a long history in vaccine research, is currently serving as Assistant Secretary for Public Health Emergency Preparedness at the US Department of Health and Human Services (HHS).

And the money began to flow — first to produce products based on existing technology, next to create better products. Within months of 9-11, contracts were awarded for production of anthrax and smallpox vaccines and NIH was slated for substantial increases, with most of the new money going to the bioterror effort. By December 2001, two months after Robert Stevens fell ill, NIAID issued a Request for Proposals (RFP) for anthrax vaccine. By August 2002, new RFPs were issued for production of a national stockpile of anthrax vaccine and development and testing of a Modified Vaccinia Ankara (MVA) vaccine against smallpox.

Public sector research expanded dramatically. In the fiscal year 2003 budget, Congress appropriated \$1.5 billion for biodefense at NIH, up from \$270 million in 2002. (The only thing standing in the way was Congress’ seeming inability to pass FY03 appropriations bills.) For FY 2004, the President’s request was up to \$1.63 billion.

It wasn’t just money for more academic research. NIAID efforts were calibrated to produce products as rapidly as possible. A NIAID strategic plan for biodefense research issued in February 2002 pledged to ensure “...manufacturing capacity for all delivery vehicles, vectors and types of vaccines” and provide “...the required standardization and validation for development of vaccines against other select organisms.”

Eleven months after the first anthrax cases, NIAID had a long list of accomplishments including completion of a human study of the ability to dilute existing smallpox vaccine so as to use it more widely, and expanded genomic sequencing of potential agents of bioterror.

By January 2003, President Bush had proposed the bio-equivalent of the race to the Moon. Project BioShield would create an array of policy changes and incentives to spur public and private research. This included new flexibility for Dr. Fauci of NIAID to award contracts and grants, hire technical experts and buy items needed for research. The grueling peer review process would be expedited as well. It remains to be seen how well these streamlining proposals will work. At the least, though, government leaders at the highest levels have recognized the need for policies and procedures to change.

The federal incentives have their limits. So far they have been more successful at enticing cash-strapped biotechs than the more experienced pharmaceuticals. Big companies still worry that profit margins for bioterror vaccines won't come close to those for the next cardiovascular drug. The initial industry response to the need for products targeting Severe Acute Respiratory Syndrome (SARS) has been cautious for similar reasons: the size of the market is uncertain. With bioterror, SARS, AIDS vaccines, and other neglected health technology research, the policy lesson is clear: a variety of incentives are needed to engage industry, including firm commitment to purchase products in the future.

Even with all these challenges, about 100 biotech companies are now engaged in bioterror defense research today. In March, Human Genome Sciences, a major biotech player, announced that it had developed a new drug for anthrax and the government bioterror initiatives were credited.

#### COMPARING THE AIDS VACCINE EFFORT:

The money is flowing for AIDS vaccine research too, with NIH AIDS vaccine research funding growing by 127% over the last five years (from \$182 million in FY 1999 to \$413.6 million in FY 2003). It's made a huge difference, allowing NIH to create innovative funding mechanisms, support product development in industry, launch an international trials network and create support labs for several functions.

Deficits, war and the preoccupation with bioterror however, now threaten the needed funding increases. Biotechs (and some pharmaceutical companies) need help with vaccine manufacturing. Grants and contracts still take too long to be approved and are time limited. Many biotechs with good ideas still struggle to maintain and accelerate their AIDS vaccine programs. None of the new administrative flexibility envisioned for bioterror is available for AIDS vaccines. Limited accessibility of non-human primates for research — long a problem in AIDS vaccine development — will only be exacerbated by pressure for bioterror product testing.

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## 2 :: ACCELERATING THE REGULATORY PROCESS

Regulatory delays for approval of human trials or licensure of new products are legendary. But so too are examples where FDA-approved products wound up causing harm and had to be pulled. FDA has a tough job handling a massive workload on limited resources — coupled with demands to speed up its work but never compromise on safety. What exactly does that mean, when new vaccines or treatments use novel approaches?

Congress and the Administration plan several important policy reforms to hasten consideration of bioterror products at FDA. But the message from the top that bioterror products get first consideration will perhaps mean the utmost. As Phil Russell has pointed out, “bioterrorism issues jump the queue.” In March 2003, FDA hired 100 new staff to review drug applications related to bioterrorism and provide guidance to companies working on these products.

As for legal changes, the *Public Health Security and Bioterrorism Preparedness and Response Act*, signed into law June 2002, authorizes the Secretary of HHS to designate a bioterrorism-related vaccine or treatment as a “fast track” product for accelerated FDA approval. The President’s Project BioShield proposes to take this authority a step further, creating an “emergency use authorization” that would permit public use of treatments and vaccines still under FDA review when an attack occurs.

#### COMPARING THE AIDS VACCINE EFFORT:

AVAC has been hearing encouraging things about researchers’ experiences with the FDA. Many in industry consider the agency’s staff highly professional and generally available to discuss safety and regulatory issues with companies. Of course, vaccine makers would like more advance warning of what the testing requirements and approval thresholds are for advancing to human trials. Outside of our Industry Survey AVAC has heard concerns voiced by some researchers about FDA requirements and we will pursue these issues in more depth over the coming year.

The major problems are priorities and money. FDA says that it gives AIDS vaccine candidates “fast track” consideration but no one can deny the agency is underfunded and the staff overburdened. That’s a major concern. When bioterror jumps the queue, it jumps past a lot of other priorities — including AIDS vaccines. AIDS vaccines often employ new technology and these products need the same top priority designation as bioterror. And FDA desperately needs additional funding, particularly for consideration of products to address the most deadly infectious diseases.

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### 3 :: ADDRESSING LIABILITY CONCERNS

Vaccines have long been a convenient target. They get blamed for everything from earaches to autism. Sometimes, of course, they do harm even as they are saving thousands of lives. President Gerald Ford learned that industry wouldn’t touch swine flu vaccine research until the government promised to pay for damage suits. Over a decade later, the Childhood Vaccine Compensation System was created to speed



consideration of individual claims and limit the liability of manufacturers who were not negligent — but only for childhood vaccines. The system is credited with saving the vaccine industry, though it periodically becomes a political football, as it has in the current session of Congress.

When it came to bioterror, the Administration wasted little time with political machinations. Six weeks after September 11, 2001 an Executive Order granted the Secretary of HHS authority to indemnify contractors against lawsuits, with the intention this be used to speed development of bioterror-related products. But that authority only really addresses manufacturer and federal government concerns and not the demands of consumers for a rational injury compensation system.

In March 2003 health care workers across the country were refusing to line up for smallpox vaccines. Faced with widespread challenge to its policy, the Administration responded swiftly with a proposed compensation plan, a version of which was passed by Congress in April. The plan fails to indemnify the institutions and health care workers who give these vaccinations.

#### COMPARING THE AIDS VACCINE EFFORT:

There is no system in place to provide protection from liability in exchange for reasonable compensation for injury in the case of AIDS vaccines. Adding AIDS vaccines (all vaccines in development, actually) to the childhood program, extending HHS indemnification to apply to AIDS vaccines, or creating a new system would demonstrate government commitment and encourage work in this area. Government assurance that companies will be able to buy adequate insurance coverage for clinical trials, or government stepping up to the plate to buy or guarantee such insurance itself, is also needed.

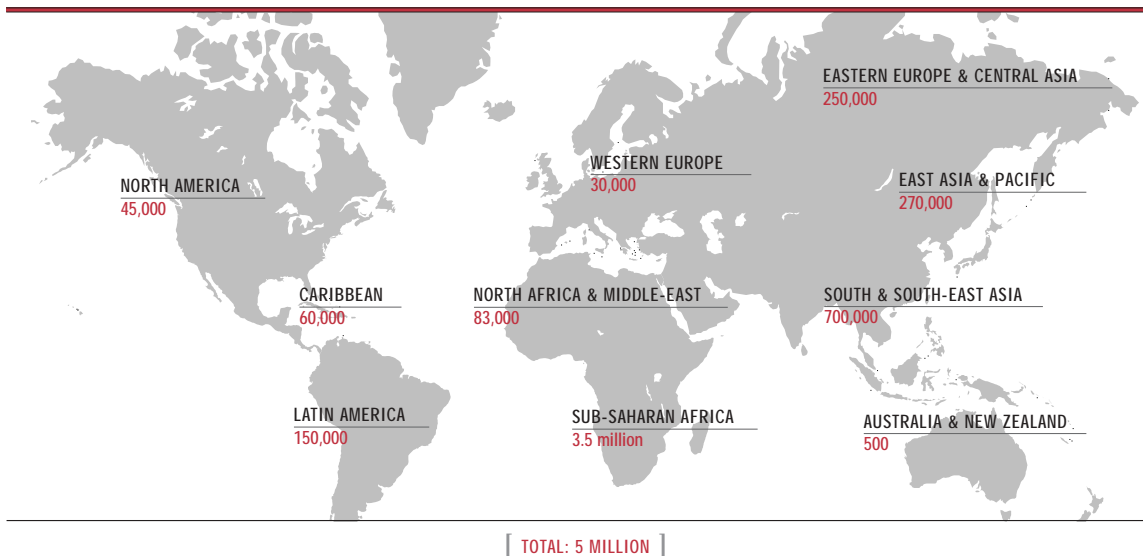
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#### 4 :: CREATING ADEQUATE PURCHASE CAPACITY

Faced with a significant bioterror threat, the federal government created and proposed whole new systems to enable it to guarantee a paying market for urgently needed products. The *Public Health Security and Bioterrorism Preparedness and Response Act* authorized \$640 million for a Strategic National Stockpile of drugs, vaccines and other supplies, and the government has announced its intention to buy tens of millions of doses of anthrax and smallpox vaccines.

With Project BioShield, things got more creative. The President has proposed creation of a “permanent indefinite funding authority” to buy “next generation” medical countermeasures. According to the Administration, the proposal amounts to \$6 billion over ten years in purchase capacity for bioterror





Sources: Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO).

products and would, by providing a paying market, ensure “that the private sector devotes efforts to developing the countermeasures.”

Perhaps most interesting, the BioShield purchase authority would be a “mandatory” program — like Medicare or Medicaid — that is not subject to the annual whims of the Congressional appropriations process. It’s a worthy approach because it makes the new purchase capacity fully credible while not requiring large expenditures until there is actually a product to buy.

Vaccine advocates have been looking for such a mechanism for years. AVAC has heard that in its original version, the BioShield purchase capacity was to include vaccines and other products to fight global infectious diseases. That inspired idea made it all the way up through NIH, up to the head of HHS and over to the Office of Management and Budget (OMB) where it died a quick and quiet death.

#### COMPARING THE AIDS VACCINE EFFORT:

There is no provision to purchase AIDS vaccines. Together, the US Government, other rich governments, the World Bank, the Global Fund to Fight AIDS, Malaria and TB, the Vaccine Fund and private funders must forge a credible guarantee to buy AIDS vaccines for the world. As it considers Project BioShield, Congress should add back global disease products to the purchase capacity program.

Global AIDS vaccine research is fueled in large part by NIH funding. With the approaching end of the five-year effort to double NIH funding and mounting federal deficits, pushing for continued increases at NIH remains at the top of the policy advocacy agenda. But a broad-based research effort that marshals expertise from all quarters requires more than NIH dollars. More must be done to engage industry and lay the groundwork for global vaccine delivery.

Since last fall, a coalition of advocates working on microbicides and vaccines against malaria, tuberculosis and HIV/AIDS have been meeting to map out key, shared legislative priorities. We were impressed by the comprehensive government effort to make and procure anti-bioterror products. Based on that response, we are designing model legislation that would provide many of the same incentives for development of products to prevent the three infectious diseases that collectively kill seven million people annually around the world.

For years, AVAC backed the idea of using targeted tax credits to inspire more private sector involvement in AIDS vaccine research. We thought that using the tax code would avoid a fight for more appropriations and temporarily sidestep controversial policy issues, while utilizing a tried and true incentive for the private sector. Bioterror changed all that. We now know that if government perceives a serious and immediate threat it can relatively quickly implement a range of initiatives with no apologies.

Our new coalition proposal <<http://www.avac.org/actionMemo.htm>> calls for a series of legislative changes designed to spur more research in industry and the public sector, and address global access issues down the road. At this writing, our coalition is talking with legislators about these proposals and we seek support from other health advocates and industry leaders. We are also working closely with BIO and others representing private sector concerns. We propose that the US Government:

1. **Adapt incentives for bioterror vaccine and treatment research** to encourage development of vaccines against AIDS, malaria and TB, and microbicides. *These measures include:*

- *Expanded direct contracting for research and product development in the private sector*
- *Public assistance with vaccine manufacturing*
- *Non-negligent liability protection for manufacturers of licensed products (in combination with a system to provide reasonable injury compensation)*
- *Priority regulatory consideration of products*

2. **Ensure maintenance of effort** by directing that federal research agencies sustain their research efforts on priority prevention technologies in the face of growing demands for bioterror-related research, development and testing.

3. **Create credible purchase pre-commitments to buy vaccines and microbicides for the world** by mandating that the Administration engage in collaborative efforts with other nations, international organizations and private funders to establish capacity to buy future prevention products. This must be accomplished without taking current funding away from purchase and delivery of existing treatments and vaccines. Build on the “permanent, indefinite funding authority” proposed in Project BioShield for the purchase of bioterror vaccines and treatments by adding global disease products to this purchase plan.
4. **Significantly increase the number and grant amounts of Small Business Innovation Research (SBIR) grants for priority vaccines and microbicides.** Improve the quality of the grant reviews so that people who understand product development are involved.
5. **Expand the current tax credit on contract arrangements** so that pharmaceuticals have a greater incentive to develop contracts with other research companies (e.g. biotechs) for research and development on priority vaccines and microbicides.
6. **Expand delivery of existing vaccines through increased authorization and appropriations to The Vaccine Fund.**
7. **Voice support for tiered pricing of vaccines and microbicides globally through a Sense of the Congress resolution.**
8. **Promote public sector support for R&D** by increasing funding and creating or expanding programs in priority disease areas at NIH, the Centers for Disease Control and Prevention, the United States Agency for International Development (USAID) and the Department of Defense (DOD).
9. **Accelerate regulatory consideration** of priority vaccines and microbicides by exploring legislative proposals to achieve speedier, more flexible FDA review and approval of products addressing the biggest infectious disease killers. Expand the FDA mandate to review priority products not for US use. Encourage FDA collaboration with the World Health Organization (WHO), EMEA (Europe’s regulatory agency for pharmaceutical products) and resource-limited countries to provide systematic regulatory dialogue and technical assistance.

*Organizations collaborating on the legislative effort include:* AIDS Vaccine Advocacy Coalition, Alan Gutmacher Institute, Alliance for Microbicide Development, Global Campaign for Microbicides, Gay Men’s Health Crisis, International AIDS Vaccine Initiative, International Partnership for Microbicides, Malaria Vaccine Initiative, and the Sequella Global Tuberculosis Foundation.

# 2

THE NEW AVAC INDUSTRY SURVEY



Seven years ago, AVAC got its start by doing interviews with high-level professionals at seventeen biotech and pharmaceutical companies. We asked them about their AIDS vaccine research programs (or lack thereof) and recorded their thoughts on the major barriers and policy needs in the field.

The AVAC *Industry Involvement in HIV Vaccine Research* report, issued in December 1996 chronicled an AIDS vaccine enterprise in disrepair. Industry leaders talked about how numerous scientific unknowns and economic disincentives were standing in the way of full-scale efforts. Not surprisingly, they called for government support in the form of grants and other incentives. And they said leadership was key.

The field is somewhat healthier today, with more products in development, more clinical research and government support, and a growing international effort. But we all know public and private activity still falls far short when compared with the enormity of the AIDS pandemic. What's in the way? And what should we do?

AVAC thought we should retrace our steps and do interviews with the major companies involved in AIDS vaccine research today. We contacted eleven leading pharmaceutical and biotech companies and asked for confidential interviews. We asked a series of questions about each company's research programs, plans for manufacturing, relations with regulators, perspectives on intellectual property, comparative immunological studies, barriers to increased research, and policy priorities to hasten discovery and delivery of AIDS vaccines.

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## :: WHAT WE HEARD

***New business models.*** The AIDS vaccine research enterprise is to a large degree already a public-private partnership and companies see many ways in which it needs to become even more so. Programs at numerous biotechs and some big vaccine companies survive only because of NIH contracts. Big pharmaceuticals will rely on public clinical trials networks. Pharmaceutical leaders worry about being able to manufacture for the world and about who will buy their product unless the public sector gets more involved. Honest brokers are needed to advance assay standardization and help companies with process development. Liability protection will be necessary when a product is licensed and in this post 9-11 world, some companies need help today getting insurance for clinical trials. FDA guards the entrance gates and relationships between companies and this government agency are of primary importance.

Looking forward, it's obvious that more public sector involvement is absolutely essential to move products from the bench, get them tested and manufactured, and buy them for the world. *We have to repeat the*

*question we asked seven years ago: if the public sector gives companies more help (as it should), what does the public get back in the way of tiered pricing, cost-plus pricing, voluntary licensing or other guarantees to assure that global access is possible?*

***Where you sit is where you stand.*** What is the key barrier to expanded AIDS vaccine research? Big pharmaceuticals say “science.” Biotechs say “money.” To state the obvious, the true answer is “both.” The financial underpinnings of companies correlate directly with their answers to questions about what is challenging and what is needed in the field. Pharmaceuticals need government to support a clinical trials infrastructure, to help with manufacturing and, in one case, to work on accelerating regulatory consideration of products. Biotechs call for more outright public support for companies. This is said in a number of ways, like: “investing in broadening the range of products,” “minimizing liability and financial risk,” “supporting novel technology,” “supporting the D in R&D” and “expanding accessibility to animal models.”

Everyone, pharmaceuticals and biotechs, seems to agree on one thing: **the public sector must guarantee purchase of AIDS vaccines for global delivery.** That means building a credible purchase capacity, making legally binding purchase pre-commitments, investing in delivery infrastructure internationally and delivering currently available vaccines and treatments. Action on each of these fronts would improve the investment climate for companies and hasten vaccine access down the road. Companies also call for more work now on estimating global need and demand.

***Regulators at the center.*** We are happy to report largely positive comments by industry about their working relations with FDA (Would they dare tell us anything negative?). “The agency is tough,” said one respondent. “But they are supposed to be.” Another said, “Their standards are very high...but they’ve been quite supportive.” What appears to be working is increased willingness on the part of FDA to do consultations with companies in advance of Investigational New Drug (IND) applications and other hurdles. Several companies said they had benefited from these contacts, though a couple wanted more help. In a field where the science is always changing and companies need to be encouraged to take risks and be innovative, this kind of cooperation is critical. The problem isn’t FDA staff — it’s agency resources. Recent agency reorganization, staff turnover and chronic underfunding undermine the good work of knowledgeable FDA staff. And the new federal fixation on bioterror products doesn’t help move other infectious disease vaccines and treatments either.

***An acceptable mess.*** We asked companies whether they had concerns about intellectual property (IP) disputes standing in the way of their development efforts. There was wide acknowledgement of the messy overlay of patent claims in AIDS research generally and AIDS vaccines in particular, but the general consensus is that this mess will get cleaned up through negotiations when a product gets close

to market. “The industry is pretty facile with IP,” one biotech leader said. *AVAC has heard elsewhere that, in fact, IP can and has inhibited product development and we are not prepared to fully accept industry statements to AVAC on this issue.*

***A noble idea, but...*** We also asked whether companies would be willing to participate in comparative human immunological studies of various vaccines. The idea would be to test a number of AIDS vaccine candidates using an agreed set of standards and measures. The goal would be to advance everyone’s work by generating knowledge about immune responses. Almost every respondent had two things to say. First, we heard phrases like: “it’s a noble idea,” or “as a scientist, I think it’s a good idea.” Then our respondents put their business hats on. Many seemed to think the risks for companies were substantial and the payoffs murky. (Industry reservations with comparative studies are discussed further in Chapter 4.) To address business concerns, they tell us one priority would be to find a trustworthy body — to run the trials, assure confidentiality and forge workable intellectual property and legal protections. A major question is how to decide on which immunological measures to use — which assays, which processes? Some promising products are not as far along in development — would they risk being discarded over more refined vaccines? And for all the cautious interest, one pharmaceutical representative had these final words: “We don’t have a correlate of protection. Only efficacy trials will tell you what works.”

#### THE AVAC FUND MAKES ITS FIRST AWARDS

One year ago, we inaugurated the AVAC Fund. The idea was to create a small-scale “emergency fund” to assist needy clinical trial sites that require immediate help with purchases such as additional medical or lab supplies not covered by grants or contracts for vaccine research.

In February, the Fund made its first two awards: to the Kenya AIDS Vaccine Initiative for rapid HIV test kits and medicines for common ailments, and to the United States Army Medical Research Unit in Kenya for furniture, linen and medical instruments.

**The AVAC Fund now seeks new applications for grants to support the work of clinical trial sites.**

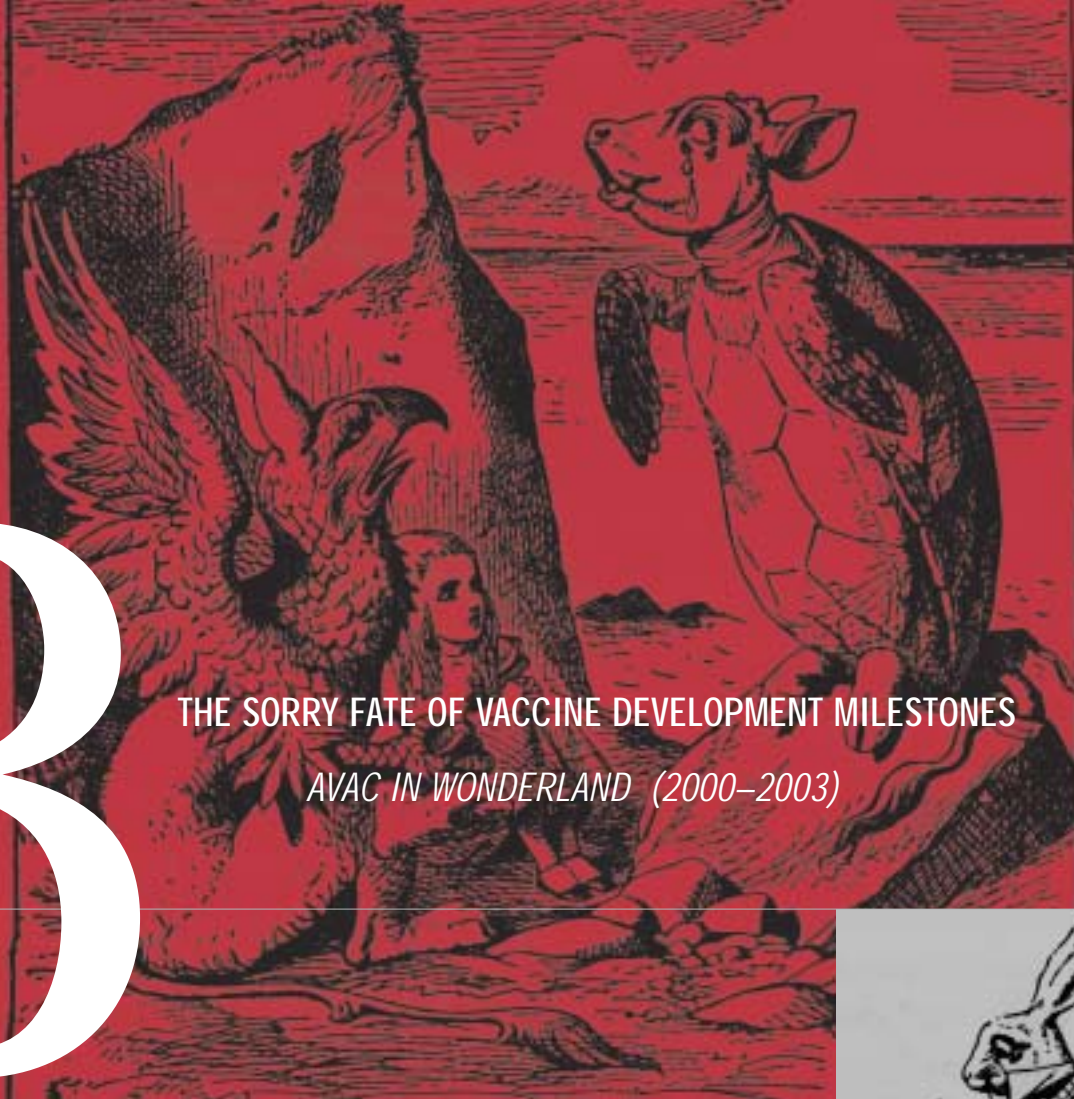
Resources for the AVAC Fund come from generous individual donations. Fund monies are administered separately from general AVAC resources. Donations are tax deductible and are always welcome.

***For more information please contact us at <Fund@avac.org>***



# 3

THE SORRY FATE OF VACCINE DEVELOPMENT MILESTONES  
*AVAC IN WONDERLAND (2000–2003)*





**THE LOBSTER QUADRILLE.** The Mock Turtle sighed deeply, and drew the back of one flapper across his eyes. He looked at Alice and tried to speak, but for a minute or two sobs choked his voice. "Same as if he had a bone in his throat," said the Gryphon, and it set to work shaking him and punching him in the back. At last the Mock Turtle recovered his voice, and, with tears running down his cheeks, he went on again: "...when you've cleared all the jelly-fish out of the way—"

...

*"That generally takes some time," interrupted the Gryphon.*

*"You advance twice—"*

*"Each with a lobster as a partner!" cried the Gryphon.*

*"Of course," the Mock Turtle said: "advance twice, set to partners—"*

*"Change lobsters, and retire in the same order," continued the Gryphon.*

*"Then, you know," the Mock Turtle went on, "you throw the—"*

*"The lobsters!" shouted the Gryphon, with a bound into the air:*

*"As far out to sea as you can—"*

*"Swim after them?" screamed the Gryphon.*

...

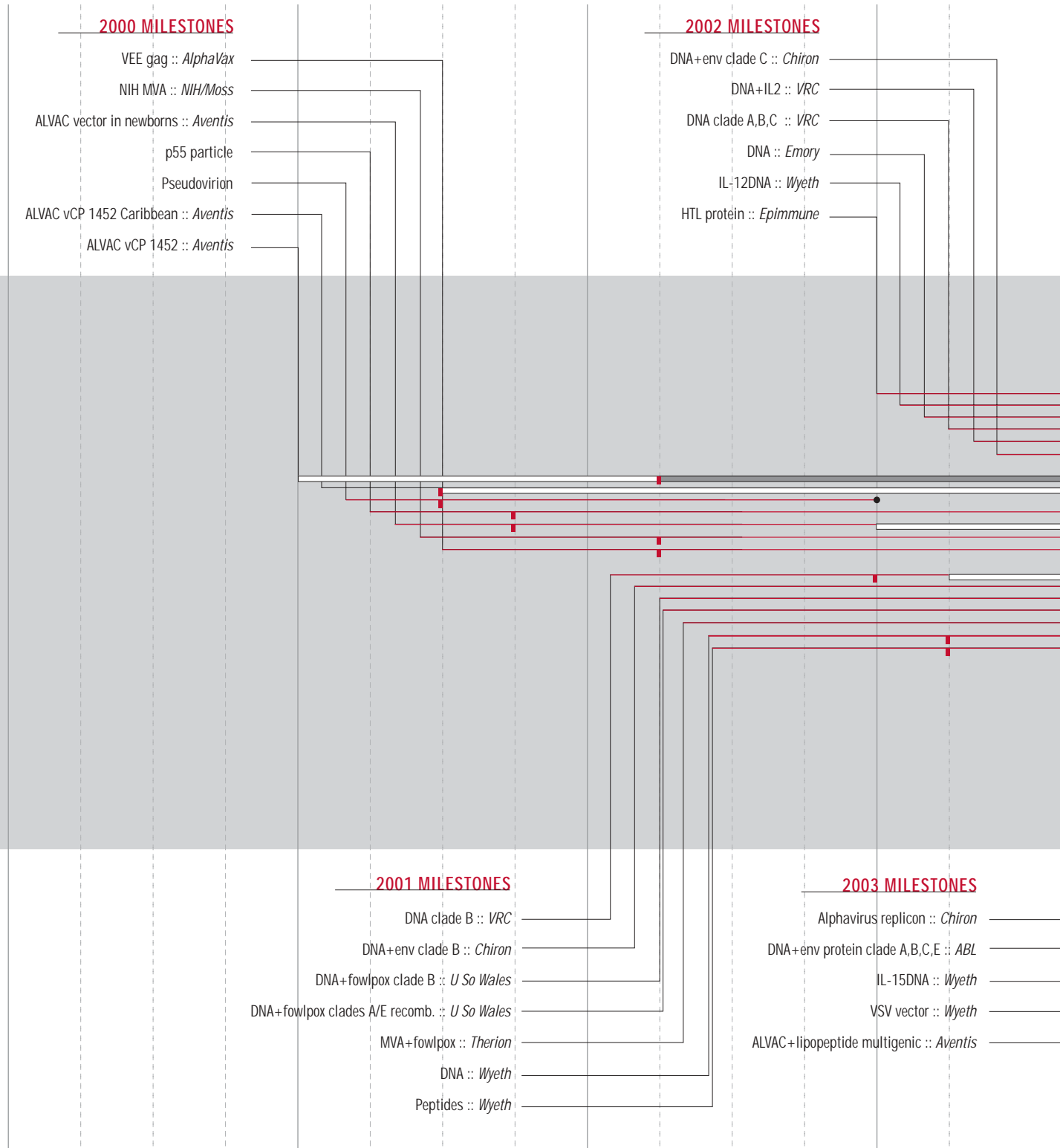
FIGURE 2 :: NIH SCIENTIFIC MILESTONES

1999

2000

2001

2002



<sup>3</sup> Milestones are labeled "Delayed" if they have not reached the next stage of development more than a year (4 Quarters) after the 1st milestone date.

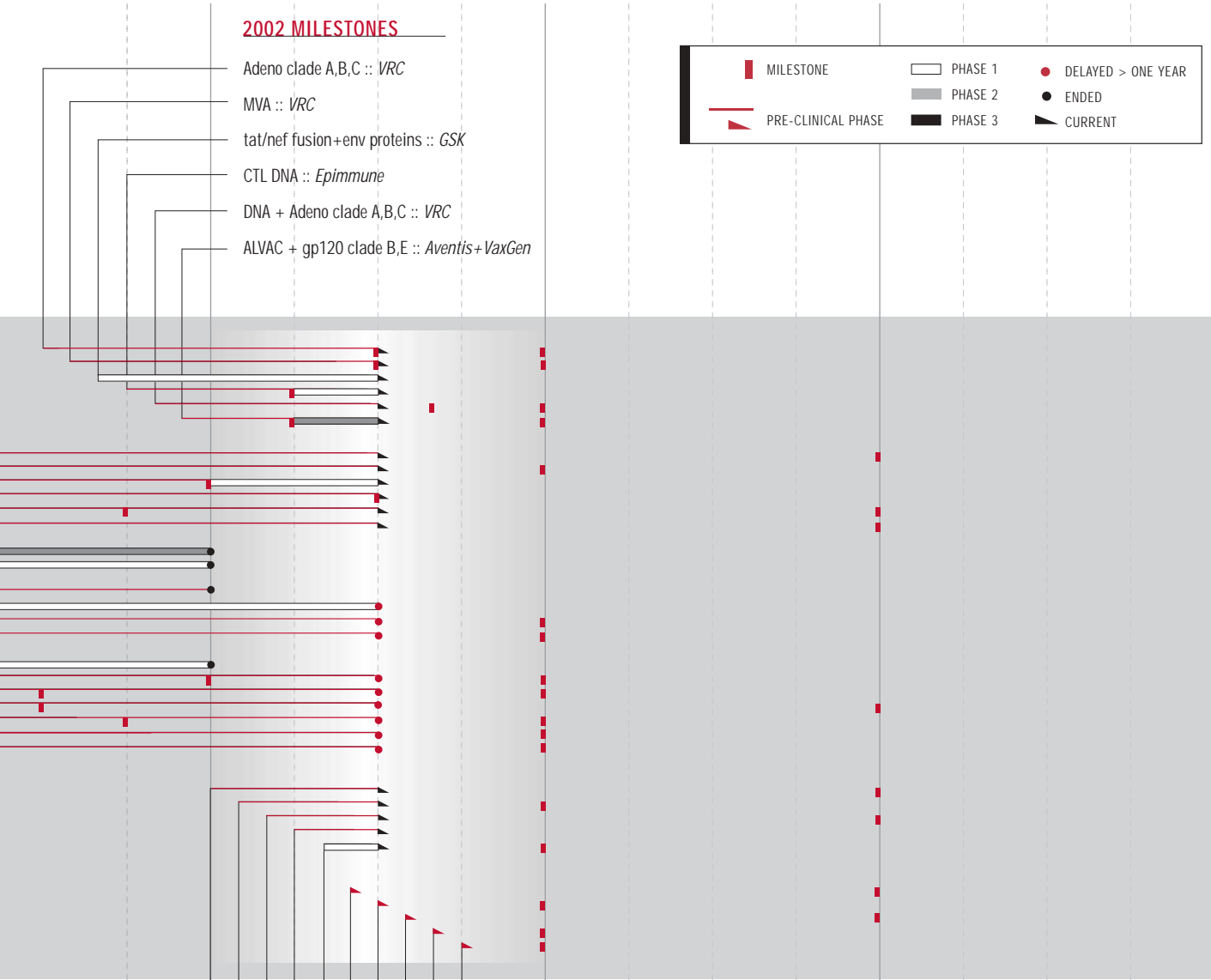
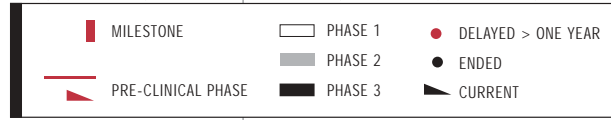
2003

2004

2005

**2002 MILESTONES**

- Adeno clade A,B,C :: *VRC*
- MVA :: *VRC*
- tat/nef fusion+env proteins :: *GSK*
- CTL DNA :: *Epimmune*
- DNA + Adeno clade A,B,C :: *VRC*
- ALVAC + gp120 clade B,E :: *Aventis+VaxGen*



**2003 MILESTONES**

- Adeno multigenic :: *Merck*
- DNA gag :: *Merck*
- DNA+MVA clade C :: *SAIVI*
- Yeast vector gag :: *GlobelImmune*
- Adeno gag :: *Merck*

NIH Division of AIDS (DAIDS) data is based on Scientific Milestones presented at the AVRWG meetings (three times per year) since January 2000 and on the updates provided to us for the AVAC Annual Report: X Years and Counting each March/April. Discrepancies in numbers are due to changes in the way each program has been described over time. At initial funding, a single approach has very often been given one milestone. As pre-clinical work has proceeded, an approach becomes subdivided into a number of pieces, each with its own Phase 1 trial/milestone. In general, developers have begun with a single gene product in a single clade with plans to expand the number of genes and add other clades over time, based on initial responses. This elaboration can multiply one candidate/approach into a handful of milestones. This is seen most clearly with the IAVI/Oxford program (Figure 4), though it is also true of several NIH programs (Figure 2). Milestone multiplication highlights the fact that progress through phases generally requires a number of Phase 1 trials in order to complete development and optimize the product, even though the “pipeline” is often shown as a simple 1-2-3 process. It can be difficult to track each effort when the terms can change up to four times a year.

As the best funded AIDS vaccine research program in the world, NIH has special opportunities and responsibilities in the field. And to a large degree, these responsibilities cut against the grain of the agency’s history. NIH has been challenged to foster product development in the public and private sectors, and ensure these products get tested in a speedy manner — all while continuing in its traditional role as the major funder of basic research.

To meet new and ambitious targets, everyone needs checkpoints. In our May 1999 annual report, *9 Years and Counting: What Will Speed Development of an AIDS Vaccine?*, AVAC proposed to NIH that without setting interim goals, “the ultimate goal of an HIV vaccine cannot be met in a timely way.” We identified six indicators (or milestones) of progress that could be evaluated annually:

- 1 The number of targeted research projects that are applicable to new and improved vaccine concepts.***
- 2 The number of industry partners involved in developing HIV vaccines.***
- 3 The number of vaccine concepts evaluated in primate models.***
- 4 The number of vaccine products evaluated in Phase 1 trials.***
- 5 The number of domestic and international trial sites with capacity to participate in efficacy testing of HIV vaccines.***
- 6 The number of products that move from Phase 1 into Phase 2, proof-of-concept, or Phase 3 efficacy trials.***

FIGURE 3 :: FUNDING LEVELS BY GROUP AND YEAR <sup>1</sup>			
*YEAR	NIH	IAVI	WRAIR
1998	\$148M	~\$2M	\$38M
1999	\$182M	\$6M	\$24M
2000	\$232M	\$12M	\$34M
2001	\$269M	\$18M	\$33M
2002	\$329M	\$40M	\$30M
2003 <sup>2</sup>	\$413M	\$59M	\$34.7M

<sup>1</sup> Funding levels cannot be compared between programs, since each program funds different additional work.

<sup>2</sup> Budget (v Actual).

By January the next year (2000), AVAC had received a long reply of after-the-fact administrative and programmatic accomplishments — leadership positions filled, scientific advances and new funding initiatives — that concluded by saying, “progress cannot be measured simply by the number of products passing specific milestones, because the quality of the product is much more important than the number tested, as documented by the failure to identify many highly promising vaccine candidates in spite of the large number of NIH-funded Phase 1 and 2 trials over the last ten years.” One could take issue with the “large number of trials” hypothesis since virtually all these trials tested two concepts, envelope proteins and canarypox constructs.

The issue of interim goals was raised with the AIDS Vaccine Research Working Group (AVRWG) at the suggestion of Drs. Nathanson, Fauci and Baltimore. Since January 2000, a set of scientific and programmatic milestones for the Division of AIDS has been presented at each AVRWG meeting. These markers allow us to review what has happened with NIH milestones over three years (2000–2003). We can also make less formal comparisons with the scientific plans of the other HIV vaccine development networks, namely the International AIDS Vaccine Initiative (IAVI) and Walter Reed Army Institute of Research (WRAIR) over a similar or longer period.

As discouraging to us as the overall crawling pace of vaccine development is, this analysis points out some areas of activity that may be more productive in the future. The fact that researchers and program managers are setting ambitious goals is a good thing, and we appreciate the hard work at each organization discussed here. But the fact that these goals have consistently not been met tells us something important: that a variety of barriers to rapid advancement of products exists and need to be addressed. So, let’s take a

look at some data, based on publicly presented goals in the seven years from 1996–2003. As we will show, these “milestones” are actually overly optimistic goals — best-case scenarios that have never been met.

The initial DAIDS scientific milestones (January 2000) identified seven trials to be initiated by the first quarter (Q1) of 2001, at the latest. For a variety of reasons, only two of these (ALVAC Phase 2 and ALVAC in newborns) have been conducted. Two products (pseudovirion and p55 particle) were dropped prior to the clinic and one large trial (ALVAC Phase 2B) was cancelled for not meeting immune response benchmarks. The remaining two products (NIH MVA/Moss and VEE gag) are still delayed<sup>3</sup> by manufacturing difficulties, two long years past the benchmark.

By May 2001, eight new scientific milestones had been added. Among these, only two have had clinical trials (ALVAC in Caribbean sites and DNA clade B at the NIH Vaccine Research Center). All of the remainder, which were given milestones between Q1 and Q4 2002 have been delayed for a variety of reasons that are regulatory in nature (safety requirements imposed, for better or worse, by FDA) or have to do with manufacturing problems. By May 2001, however, NIH was funding more product development in outside companies or academic labs. And with the advent of the AIDS Vaccine Design and Development Team projects<sup>4</sup> the buck had begun to be passed. New — but equally optimistic — milestones were set.

By this time last year (April 2002), twelve new milestones had been added, largely through the awarding and clarification of the Design and Development Team awards and through the elaboration of development plans at the VRC. With the exception of the Phase 3 prime-boost in Thailand, these projects were reported to have milestones ranging from Q3 2002–Q4 2003 for initiation of Phase 1 trials. Four have commenced to date (three in the most recent quarter). This places four of them behind their original schedule.

These delays or overly optimistic original estimates were reflected in the update presented to the AVRWG in January 2003. Ten more milestones were added with projected dates in the next seven quarters, between Q2 2003 and 2004 . This is now a familiar pattern of adding a large number of new milestones, each with the projection of being able to begin human trials some less-than-definite time in the next year — or so. In all, DAIDS now reports a total of 31 pending projects, as of March 2003, including two non-NIH supported vaccine candidates from Merck and GlaxoSmithKline, which already have reached the clinic in NIH supported trials.

<sup>3</sup> Milestones are labeled “Delayed” if they have not reached the next stage of development more than a year (4 Quarters) after the 1st milestone date.

<sup>4</sup> Four HIV Vaccine Design and Development Teams were funded in 2001. Two of these--University of So. Wales and Chiron--appear on that year's milestones list; the others, Wyeth Lederle Vaccines (Wyeth) and Advanced Bioscience Laboratory (ABL) make their appearance with milestones in 2002 and 2003

## What conclusions can be drawn from this three-year history?

- *DAIDS scientific milestones have been poor at predicting progress to the clinic. Generally, no milestone is ever set much more than a year away, while experience shows much longer pre-clinical periods. This raises expectations, and — oddly enough — in the end defeats them, like the boy who cried wolf.*
- *The number of active projects has multiplied several-fold.*
- *The number of new clinical trials, particularly of new products, has been extremely small.*

Since so many of the NIH milestones are now driven through the Vaccine Design and Development Teams (five by our count, but working on at least 10 distinct products), a word is in order about how that mechanism works. Essentially, NIH has contracted with private companies or academic groups to design, develop and manufacture vaccine for Phase 1 clinical trials. These arrangements are structured as five-year renewable contracts with milestones, in the form of progress payments. This is typical private business practice, common in government defense contracting but unusual for NIH. It must be said that structuring the contracts around progress payments has not ensured speedy movement to trials.

**In September 2000, Dr. Peggy Johnston, Assistant Director for AIDS Vaccines at NIAID, reported to the AVRWG on the reasons for the nine delays in meeting the DAIDS milestones at that time:**

### 1. Product dropped by NIAID

- *Final product contaminated*
- *Lack of interest in re-manufacturing due to poor immunogenicity*

### 2. Products referred back to research

- *Solubility problems (2)*
- *Poor immunogenicity*

### 3. Candidate preparation

- *Complex construction took longer than expected*

### 4. Intellectual property negotiations

### 5. Manufacturing

- *Inexperienced manufacturer misjudged timelines*
- *Tech transfer: yields too low in initial GMP (Good Manufacturing Practices) pilot lot*

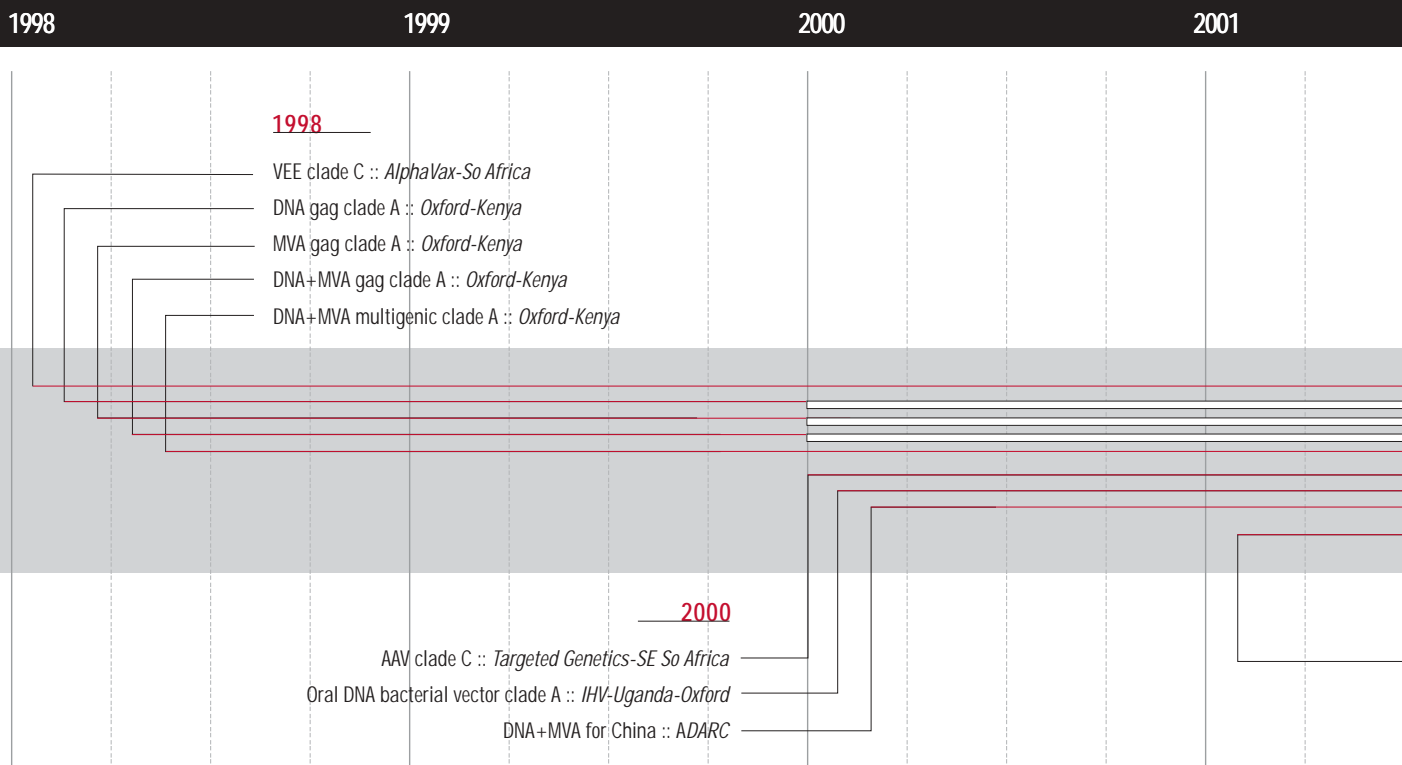
### 6. Safety Study Design

- *Decision to do safety study of two components together delayed one component*
- *Uncertain requirements of non-US regulatory agency*

### 7. Safety Issues

- *Initial integration study positive requiring repeat and revised testing*
- *Contaminant in final material (2)*

FIGURE 4 :: IAVI SCIENTIFIC PARTNERSHIPS AND PLANS<sup>5</sup>

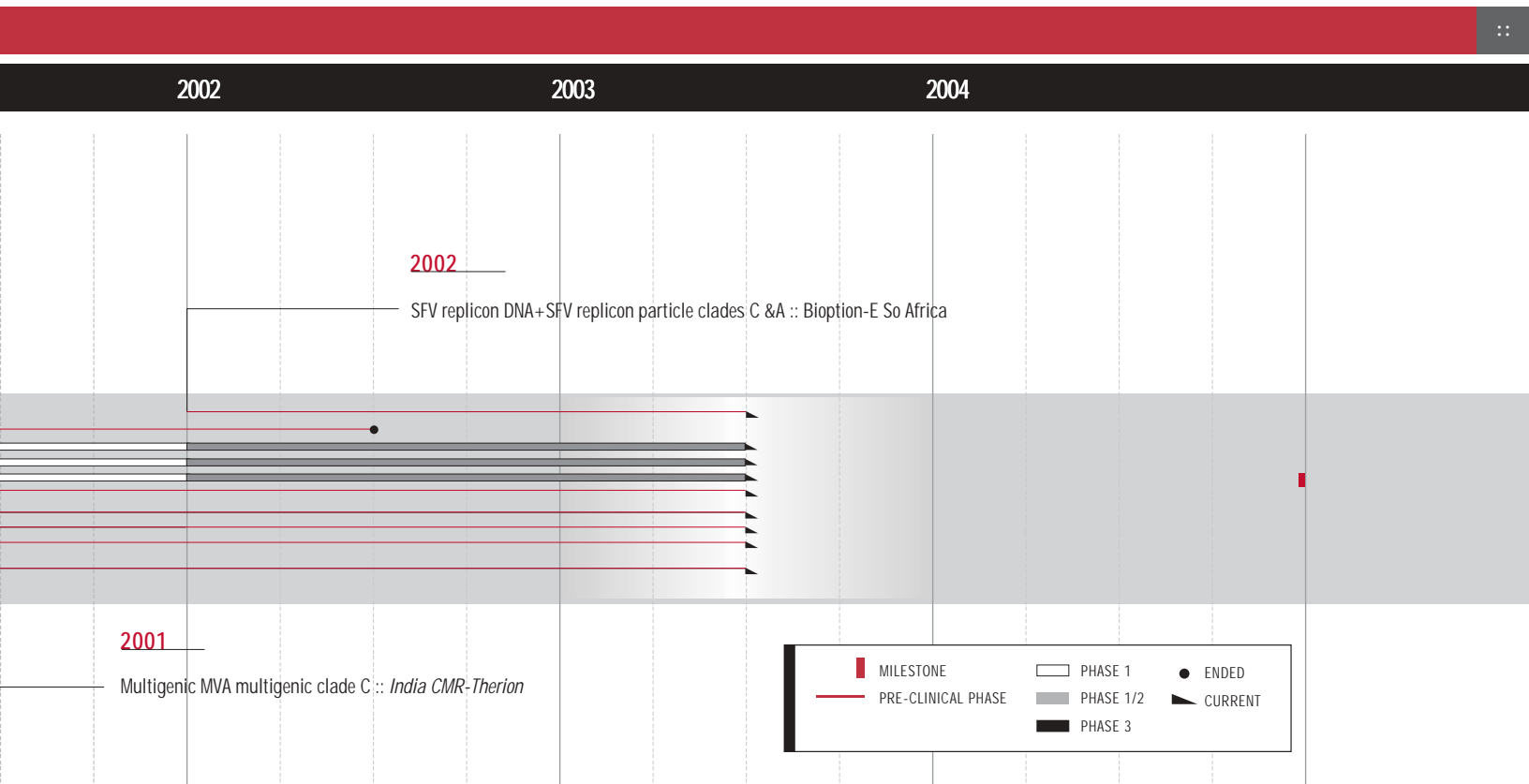


<sup>5</sup> Based on IAVI *Scientific Blueprints* published in 1998 and 2000, and *Improving and Accelerating the Clinical Pipeline of AIDS Vaccines for Worldwide Use: The IAVI Research and Development Agenda 2002-4* published in 2002, plus personal communication in March and April 2003.

This list does catalog the variety of things that can arise to delay or even stop products in their tracks. The conclusion drawn at the September 2000 meeting, however, was that the reasons were too varied to be subject to being fixed. As David Baltimore, ex-Chair of the AVRWG pointed out at the time, “in industry, *each and every reason would be addressed since these same problems are likely to occur again.*” Doing this requires more than just “learning by experience.” It requires a concerted effort to take action to educate and help new developers avoid or work around predictable challenges.

Recently, Dr. Lawrence Corey, Principal Investigator of the HVTN made the related point that most of the delays noted above can be boiled down to manufacturing or process issues — problems which should be subject to improvement with the right expertise and resources.





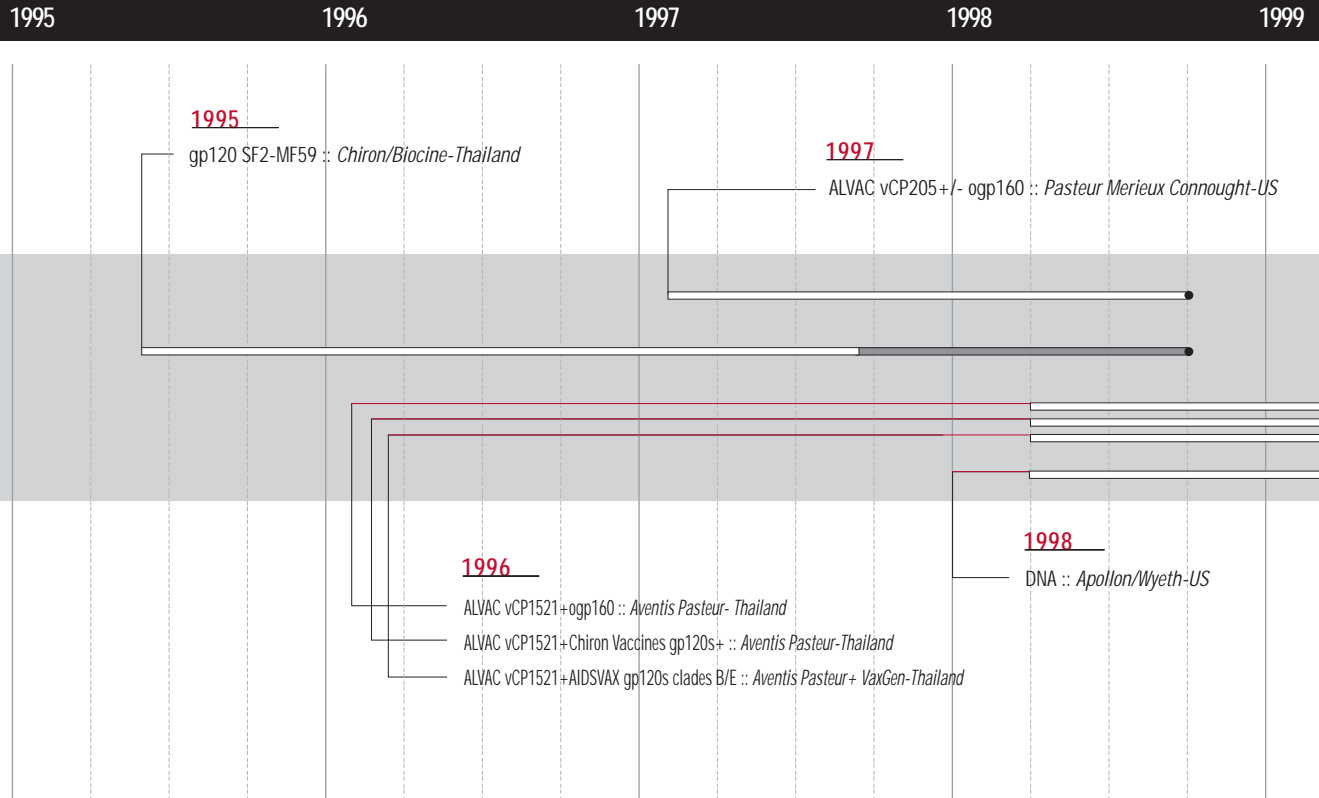
**:: PLUMBING PROBLEMS**

Paradoxically, the preventive vaccine development pipeline is simultaneously losing candidates, sluggish, and in some cases clogged. Adding new projects has indeed made the current pipeline more “robust,” in that it has more candidates, but the ability to push or pull existing candidates through manufacturing and regulatory hurdles has been dismal and slow.

In addition, the field is just beginning to iron out the complicated business of planning and coordinating international multi-site trials just in time to begin them. Only VaxGen and WRAIR have managed this successfully so far, and only in Thailand, which presented different challenges than those faced in Africa and other parts of Asia.

Two other groups have also been attempting to push (by funding development) and pull (by funding trials) vaccine concepts into and through clinical testing: IAVI and WRAIR. Comparison shows that neither of their models, non-governmental organization (IAVI) or military (WRAIR), has made the process demonstrably faster, easier or more predictable.

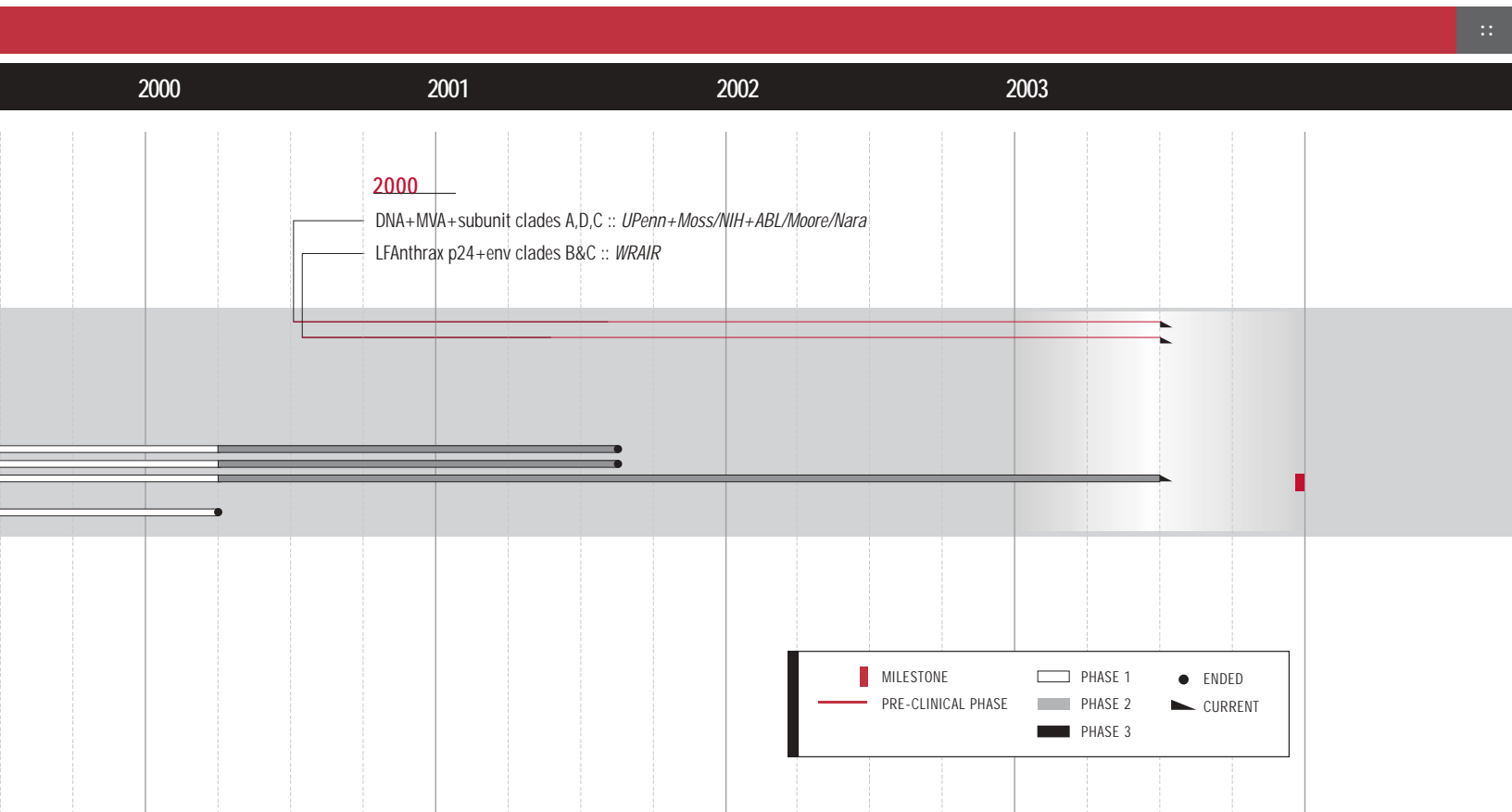
FIGURE 5 :: WRAIR STRATEGIC PLANS<sup>6</sup>



<sup>6</sup> Based on information provided by WRAIR each March/April for AVAC *X* Years and Counting Reports, and their NIH Review documents and presentations, supplied in March 2003. Background information came from an old WRAIR Development Program document describing the program in 1995.

Since its inception in 1996, IAVI has been forthcoming about its strategic objectives, if not always interim milestones. In 1997, IAVI committed itself to fund two scientific areas that it decided had not received adequate attention: 1) development of HIV DNA vaccines, and 2) safety studies of live attenuated SIV and HIV vaccines. For the years 1998 and 2000 IAVI published *Scientific Blueprints* and in 2002, a Research Agenda (2002–4) titled *Improving and Accelerating the Clinical Pipeline of AIDS Vaccines for Worldwide Use*. The Initiative has established seven Vaccine Development Partnerships. All but one (VEE/AlphaVax, see Chapter 6) are still active, with plans for efficacy testing of lead candidates by 2004 in east Africa. At least four of the five remaining were set to enter the clinic in 2002–5, though none have done so as yet (see Figure 4).

IAVI claims to have brought its DNA+MVA into the clinic in a record two years and if it meets its plans, into efficacy trials by the sixth year. This would indeed be accelerated development compared to the envelope and canarypox vaccines. Its other partnerships, perhaps with the exception of replicon DNA for eastern and southern Africa, have been somewhat less rapid with none yet having reached the clinic.



From the Initiative's seminal documents about accelerated vaccine development, we assume that, like NIH milestones, the march to the clinic has been more difficult and slower than originally anticipated. IAVI also now clarifies its plans by stating that they will advance to efficacy trials in 2004 with either their DNA+MVA candidate if it meets safety and immunogenicity criteria or with a better candidate — whether or not IAVI has sponsored its development.

The AVAC idea to request milestones originally came from the example set by WRAIR. As early as 1995, they were regularly presenting long-range plans with proposed dates for moving from one stage of development to another — in military fashion. Unfortunately, those plans too have gone awry because of changes in the field. Dating back to the days when Don Burke was directing the program, 60% of the WRAIR effort was allocated to develop and evaluate preventive vaccines (particularly Chiron's gp120) and to develop new immunogen and immunogen/adjuvant combinations. Even as early as 1995, an additional 10% went to prepare for efficacy evaluations in Thailand. The balance went for therapeutic vaccines (20%) and trying to identify correlates of protection (10%).

The WRAIR US Military HIV Research Program Vaccine Initiative has always had somewhat more of a site orientation than other government initiatives — first in Thailand, then in east and west Africa. This is because of its primary mission to protect American troops. It has also been a top-down organization befitting the military as compared to the Scientific Committee approach of IAVI and the grant, contract and cooperative agreement approaches of NIH. As such, it has always had very specific long-term plans and projections that have impressed AVAC since 1996, when we began covering the government groups. Unfortunately, best-laid plans do change. In Thailand, the very welcome prevention successes of the government have made it more difficult to conduct efficacy trials. And an inordinate number of other problems with funding and partners have hampered WRAIR's plans of attack.

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## :: CONCLUSIONS

Four years ago, AVAC proposed interim goals to NIH, which has become an accepted practice, with marginal benefit at best. Thanks to recent data from the Office of AIDS Research, we can report on some of our original parameters by all NIH and non-NIH players after the fact from August 2001 to March 2003:

- *The number of targeted research projects that have reached IND submission: from 20 up to 28<sup>7</sup>*
- *The number of vaccine products that had reached Phase 1 trials: from 5 up to 14*
- *The number of vaccine products that have reached Phase 2 trials: from 2 up to 3*
- *The number of Phase 3 trials: 1 completed, 1 to be completed and 1 slated to begin later this year*

This is indeed improvement. Nevertheless, it is our belief that when an AIDS vaccine is ultimately validated we will be asking ourselves why it took so long to test and evaluate known candidates — rather than slapping one another on the back and popping magnums of champagne.

An experienced industry vaccine developer made the following comment to AVAC about slipping milestones: “While that’s never good, when one is pioneering, it is sometimes unavoidable. What is of more concern is whether there is enough attention being paid to fundamental mechanisms and issues — rather than just racing to get somewhere. Slippage can occur because there isn’t enough basic understanding (for example, how does prime-boost work, so how can it be made better?).”

<sup>7</sup> Including those that reached the clinic during the subject period.

We believe that more conscientious use of detailed, industry-like planning practices and tracking could provide more accurate time estimates and a better sense of when human trials of products in development could commence. A better sense of each product's critical path would greatly benefit developers.

We conclude that as implemented the whole notion of milestones has not been taken seriously or served to expedite or track progress very well. Even the metaphor of a "pipeline" may have hampered the ability of the scientific community to explore the scientific parameters that could lead us deductively, or for that matter inductively, toward a workable solution to the design of an effective HIV vaccine.

Walt Disney notwithstanding, the accomplished mathematician Charles Dodgson (Lewis Carroll)'s *Wonderland* is not a benign place.<sup>8</sup> It is a place where the absurdities of adulthood are seen through innocent eyes, for the ongoing delight of children and adults at the same time. The book's timeless success comes from having been the first children's book without a moral, just by taking the adult world down a few notches, and making something as serious as a formal Victorian quadrille into a genuinely crazy dance.

<sup>8</sup> At a school for fish, for example, the Mock Turtle learns "ambition, distraction, uglification, and derision."

...

*“What matters it how far we go?” his scaly friend replied.*

*“There is another shore, you know, upon the other side.*

*The further off from England the nearer is to France.*

*Then turn not pale, beloved snail, but come and join the dance*

...

# 4

ARE THERE TOO MANY "ME TOO" PRODUCTS IN THE PIPELINE?



This year AIDS vaccine advocates are asking whether there is too much duplication in the pipeline. It's a question that lends itself to pithy formulations like: Are all our eggs in one basket? Is there too much "me-too" research going on?<sup>9</sup>

There's good reason for raising these questions. At the moment, the pipeline is dominated by a handful of concepts. More than half of today's trials are testing one or both components of a DNA prime-viral vector boost strategy, with a handful of viruses — MVA, canarypox and adenovirus (Ad) — taking up most of the research resources.

This holds true across the pipeline and within individual research entities. The HIV Vaccine Trials Network has two separate but similar Ad-containing combinations (produced by Merck and the US Vaccine Research Center) queued up to enter human trials. IAVI is co-sponsoring ongoing trials in the UK and Kenya of a DNA+MVA combination developed by Tomas Hanke (Oxford University). A trial of the same regimen, delivered on different dosing schedules, is underway in Uganda. At the same time, IAVI has initiated partnerships with several other groups also developing DNA vaccines. The same DNA+MVA combination is also poised to enter a Phase 1 trial in South Africa, co-sponsored by IAVI and the South African AIDS Vaccine Initiative (SAAVI). To follow up, SAAVI is considering yet another DNA vaccine trial, again using the Hanke backbone, with local clade C South African genetic inserts.

Based on this simple arithmetic, the labels of "me-too" and "all our eggs-in-one-basket" definitely stick. But while the phrases are catchy and the numbers are stark, assessments are not that simple. Several factors complicate the diagnosis. First: the "me-too" epithet is, in a way, a sign of progress — it cannot crop up in the context of an empty pipeline. Indeed, there are more products in Phase 1 and Phase 2/3 trials than ever before. That's very good news. Some of what looks like unnecessary duplication is actually a planned outcome of research agendas which start with Phase 1 trials of vaccine prototype, and move to additional Phase 1 trials, which add genes to the prototype and make changes to the immunization schedule (see Chapter 3).

Second: duplication is not, by definition, a bad thing. Competition can accelerate research. Pursuing a wide variety of similar products can be useful, since a slight adjustment in how a vaccine is formulated could make the difference between a blockbuster and a total disappointment. Testing different genes in similar constructs is an important strategy for learning more about the importance of each gene, especially across clade.

<sup>9</sup> A note on terminology: the phrase "me too" can mean different things to different people. From an FDA perspective, "me-too" can refer to compounds that are structurally and chemically similar to the point that a compelling rationale may be available for issuing separate marketing approvals without duplicating test data. In this article, "me-too" is used in a looser sense, to refer to AIDS vaccine strategies based on similar, or identical concepts.



Does this mean that the pipeline is the picture of health? Not at all. But the most obvious conclusion — that the current spate of DNA prime-viral vector boost trials is an example of needless duplication — is too simple. In conversations with a range of researchers and advocates, AVAC found a consensus that concentration of clinical trials on one or two concepts is a natural consequence of scientific research.

These same individuals also voiced warnings about several problems, including lack of coordination among the researchers conducting similar trials; lack of mechanism-driven research that could inform and improve future vaccine designs; and a failure to plan ahead for failure. The remedies: a willingness to subject similar products to head-to-head comparisons and a truly collaborative approach to tackling tough scientific questions. If this sounds simple, think again. It means getting vaccine developers to move fluidly between capitalist and collective mindsets — which is a bit like asking marathon runners to participate in quilting bees during their water breaks.

Without these remedies, duplication becomes a problem. Here is a closer look at the symptoms — and some possible solutions — for a syndrome that’s more than a simple case of the “me-too’s.”

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#### SYMPTOM #1 :: UNDERUTILIZED DIVERSITY

To understand how we got here, it helps to look back to 1993, when the concept of DNA vaccines hit the scene. Suddenly, the AIDS vaccine field had a new technology on its hands — one that was heat stable and easy to modify, as well as being, at least theoretically, cheap and easy to manufacture. DNA vaccines enabled vaccine developers to add and subtract different pieces of HIV genetic material and to learn about the different immune responses induced by different regions of the virus.

Given these promising attributes, it is not surprising that there are so many DNA vaccines in the pipeline today. What is surprising, however, is that ten years later there have been a scant handful of systemic optimization studies — which directly compare multiple forms of the same vaccine — in monkeys or humans. These efforts happened early on in small animals but these data may or may not point the way to strategies that work in humans.

In the early days of DNA, the “Gee Whiz” factor of a scientific advance may have taken precedence over time-consuming, labor intensive studies of how slight variations in a candidate affect its overall performance. Today, however, concerns about low yields, high costs and the need for high doses of current formulations are adding a dose of reality. These developments have heightened the need for

optimization studies that ask, for example, whether a given adjuvant makes a difference, by inserting same the genes into several different formulations and testing them. A similar approach could be taken with genes — either to identify the optimal genes to include in a vaccine or to determine the best way to package desired genetic material.

Today, the field may be paying the price for having bypassed some of this work. Many people are now admitting that they are at a bit of a loss when it comes to determining whether one DNA vaccine is better than another. This is coming at a time when some areas of the field of adjuvants are rapidly expanding — for example, there are now a number of promising adjuvant candidates, including cytokines, co-stimulatory molecules and molecules that target dendritic cells — key players in the immune system.

Without organized comparisons, these innovations could go to waste — or linger on the shelf. That's why, when Peggy Johnston, Assistant Director for AIDS Vaccines at NIAID, surveys the pipeline, she says she doesn't see enough of what might look like repetition. "If resources were not limiting, we would like to have more duplication. There are so many variables to consider. Ideally, we'd like the answers to all those questions in Phase 1 trials," she says.

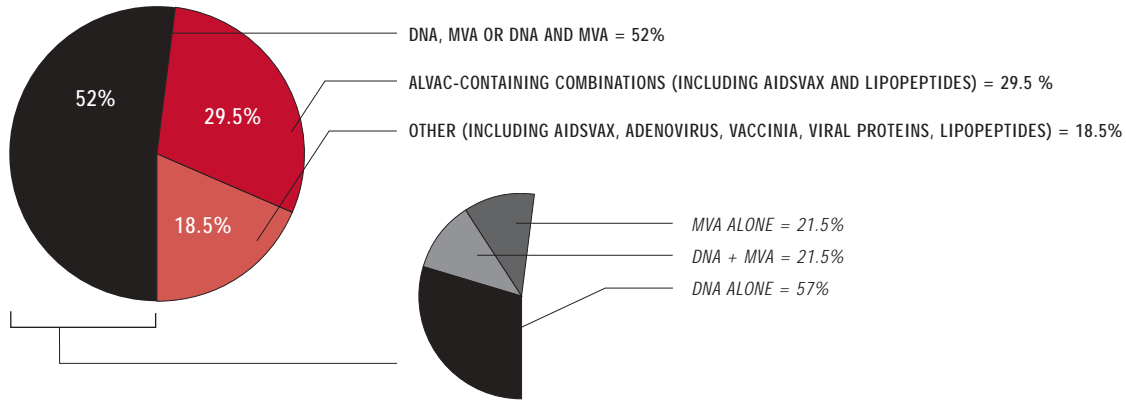
Johnston and others envision a suite of Phase 1 trials that are variations on a theme. That is not what they see when they look at the present field. "Diversity for the sake of diversity is not going to work," Johnston said. "There's got to be coordination to make sure that we all address different questions."

Today, this is not happening. In an ideal world, many candidates would advance into Phase 1 trials and the results from these studies could be used to determine whether a given candidate is a me-too or a breakthrough.

"As a field, this optimizing and comparison of approaches hasn't been done except in a couple of instances, such as IAVI and Merck," says IAVI scientific director Wayne Koff. "If we could go back, I think we would do things a little differently — asking how do you optimize a DNA vaccine, how do you optimize an MVA vaccine, and so on."

Two years ago, IAVI sponsored a DNA vaccine meeting that laid out many of these variables. The meeting generated a conceptual overview and a preliminary plan for gathering more comparative data to optimize DNA vaccines, but this plan was never fully implemented. As AVAC found in its new industry survey (see Chapter 2) many vaccine developers balk at making their products available for these kinds of comparative studies. Another obstacle to optimization studies is the costly and time consuming FDA approval process.

:: ACCORDING TO IAVI CLINICAL TRIALS DATABASE AS OF APRIL 2003 ::



Funding constraints being what they are, this approach is not realistic. One partial remedy is to do a better job at linking monkey and human trials. “There might be ways to refine our assays so that we learn more about the relationship between results from tests of the same products in monkeys and humans,” says AVAC co-founder Bill Snow. “Right now, we do the monkey trials separate from human trials, so we don’t know much about the correlation between the two.” Could these comparisons be futile? Perhaps. Without an efficacy trial that at least sets the bar for vaccine efficacy, it would be unwise to waste too much time on aligning monkey and human trials. On the other hand, isn’t it also unwise to use limited resources, whether human, animal or financial, in a way that fails to gather the maximum amount of data?

Another more acceptable and realistic approach is to get all the trial sponsors to use the same assays and reagents so that results from different Phase 1 trials can be compared. There are important signs of progress in this arena. Last year saw the launch of three efforts aimed at standardizing results of three of the most common measures of immune responses in human trials: EliSpot, intracellular cytokine staining and neutralization assays. Many of the major laboratories involved in vaccine research are participating in these exercises, which AVAC hopes to see supported and expanded in the coming year.

There are also signs of an optimization-oriented approach in the pre-clinical pipeline. For example, IAVI and its partners in the Neutralizing Antibody Consortium (NAC) are designing a study that will test several envelope antigens in small animals and move the most promising candidates into parallel monkey studies.

Such efforts are valuable, but it remains to be seen whether these first steps will translate into true cooperation, particularly in areas where there is more room for individual products to advance to market. It's not surprising that the most sportsman-like collaboration in the field today centers around one of the toughest problems. Would the NAC, or any other similar entity, exist if there were plausible data to move neutralizing antibody-inducing products into human trials? Maybe. The AIDS vaccine field is not mercenary and collaboration has helped the field arrive at where it is today.

But breakthroughs on the development front can also breed secrecy. The harsh reality is that direct comparisons like these might lead to the swift selection of stand-outs products — and the rejection of others. No developer wants to see their candidate fall by the wayside. Here, competition may serve as a negative force, by causing developers to drag their heels in comparing products directly. AIDS vaccine advocates must work to ensure that this does not happen, and that, where useful, head to head comparisons are made even if it means that some candidates are discarded.

One reason to act now is that there are signs of disillusionment creeping into the DNA vaccine field. For example, Merck has, for now, dropped its DNA vaccine from the DNA-Ad combination which is advancing into Phase I trials. If this disaffection spreads and DNA ceases to be a hot ticket item, it will have been set aside without an organized consideration of the variables which might contribute to its success or failure. Conversely, if a DNA vaccine-containing combination does turn out to show some efficacy — and there is still hope one will — then we will have a vaccine on our hands and very little information on how to make it better.

Neutralizing antibodies are not the only scientific challenge that could benefit from a consortium approach. As IAVI's Koff suggests, there could be collective efforts to learn more about the durability of vaccine-induced protection, the variability of HIV and its impact on vaccine design, and correlates of protection. These would advance in alongside trials, which move the best products towards efficacy trials. Establishment of task forces or consortia of scientists to solve these scientific challenges would be one mechanism to address these issues.

Overall, the field must find structures that allow it to pool resources, data, and intellectual property rights while simultaneously promoting head to head competition. It's a tall order. But without some form of organization along these lines, AIDS vaccine research could well veer across the fine line that separates diversity from duplication; and iterative progress from repetition.

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## SYMPTOM #2 :: COMPLACENCY WITH OUR CURRENT ORGANIZING PRINCIPLES

Another point of concern is that what looks like diversity today might look like duplication tomorrow. If field assumptions about what makes one vaccine different from another turn out to be wrong, then we could see a flourishing field go flat as a pancake. Here, the primary example is clade, as it is currently defined.

Clades (also called subtypes) are defined on the basis of genetic sequences. Within a clade, there are multiple strains, all of which are related like members of a family. It's not yet known whether a vaccine based on one clade will protect someone who is exposed to a virus from a different clade.

Clade became a political and a scientific rallying cry in 2000, at the 13th International AIDS Conference in Durban. It's been effective: by raising the issue of the global diversity of HIV, AIDS vaccine stakeholders have put developing countries in the spotlight, and accelerated development of clinical trials capacity in these countries. Clade has also been a powerful force in shaping the current pipeline.

One of the VRC rationales for pursuing a DNA-Ad combination, which is similar to the Merck strategy, is that the VRC combination contains genes from clades A, B and C. The Merck combination is only clade B. "This is a global epidemic and that diverse nature hasn't been addressed in vaccine research," says VRC Senior Investigator and Director of Clinical Studies Barney Graham. Similarly, the current SAAVI plan will test clade-matched and unmatched versions of the same vaccine.

Here again, there are good reasons for a "me-too" approach. The clade of the immunogens in a vaccine could affect vaccine efficacy and these trials are a way to find out. But what if clade doesn't matter? Will the field have endorsed a needless carbon-copy approach? And will there be new, potentially relevant parameters waiting in the wings, ready to be tested? At present, the answer is probably not.

"My biggest concern is that it has been too facile for people to say that we're using a clade from Africa or Asia," says Margaret Liu, Vice-Chairman, Transgene, Visiting Professor, Karolinska Institute, and Chairman of the Scientific Advisory Group of the International Vaccine Institute. Pontiano Kaleebu, Principal Investigator of the IAVI-Uganda Virus Research Institute HIV Vaccine Programme agrees, "Diversity is important, but whether this is related to subtype is another question. You may find viruses in the same subtype that behave differently."

Liu and Kaleebu are among those who suggest that other forms of classification could prove to be equally, if not more important than clade in predicting whether or not a vaccine works in one population or another. Liu points to today's licensed influenza vaccine, which must be updated every year to keep pace with intra-clade variability in the virus.

There are several ways to identify some of these other variables. Kaleebu suggests a study that groups viruses based upon the immune responses they elicit. For example, all of the viruses neutralized by the same type of antibody could be grouped together, then studied to determine the common features between these viruses. In this case, the genetic sequence of the virus (which is currently used to differentiate between strains) might not turn out to be the critical determining factor. Right now, one is more likely to hear about these other organizing principles at a cocktail party than an AIDS vaccine conference. “People are just talking about them,” says Kaleebu.

Another approach is to evaluate the vaccine-induced immune responses against the virus strains (not just clades) present in a given country. This would help determine whether clade governs a vaccine’s ability to protect. It would also shed light on whether intra-clade protection is possible. Following the flu example, Liu points out that it’s not yet known whether a subtype C vaccine will protect all individuals exposed to subtype C virus or whether variations within clades will impact on vaccine efficacy, too.

These are important questions. If the field waits for answers from clinical trials, it may find itself in a situation where a governing principle makes its exit and there is nothing waiting in the wings to take its place.

A similar argument can be made for markers like CTL and neutralizing antibodies that are currently being used to make decisions about which candidates to advance through the pipeline. The field needs some common criteria on which to base its decisions. But AIDS vaccine advocates must ensure that the field does not become complacent with these criteria, since not one of them has yet to prove itself in human trials as a true correlate of protection.

So if we’re seeing too much repetition in the pipeline, we must ask whether it’s because of the paces that candidates are being put through — the assays and immunogenicity analyses — in order to advance. Putting all the candidates through the same course may seem like the fastest way forward. It isn’t. But by applying the same standards, we could erroneously narrow the pipeline and discard the best candidate.

To be truly successful, it's important to use what we do know, while searching for what we have not yet discovered. How can the field do this? One strategy is to investigate the mechanisms underlying the results that are seen in pre-clinical and clinical trials, and to develop and invest in an agenda which has objectives other than identifying potential candidates. "Why exactly does a prime-boost produce the observed immune responses? And why does this strategy provide protection in some animal models?" asks Margaret Liu. "If we understood that, could we do better than we are currently doing in clinical work?"

It's an approach that runs counter to the history of vaccine research. Almost nothing is known about the mechanism of protection of today's licensed vaccines. There are correlates of protection — generally antibody titers — but this does not mean that these antibodies alone account for the protection. More insights could come from the Vaccine Research Center, which is starting to look at this question.

Don Burke, Director of the Center for Immunization Research at Johns Hopkins, calls this a "deconstruction/reconstruction" approach, or more technically, "clinical research vaccinology." In it, clinical trials are used to evaluate and understand concepts in addition to — or instead of — candidates. For example, if each arm of the potential immune response to a vaccine — antibodies, CD8 T cells and CD4s — is seen as a different conceptual challenge, then a trial could be designed to understand how the immune system can be manipulated to optimize each of these responses.

If the field takes this approach, it will have to take a deep breath and accept that what looks like a detour may actually be a shortcut. Yes, an effective vaccine will probably activate all of the arms of the immune responses. But that does not mean that we will find a vaccine that does this by trying to induce all of the arms of the immune system with a single strategy. It might be more beneficial to look at each immune response in isolation — then combine the best of these approaches.

There are already many examples of this type of research but they have yet to be consolidated into a coherent agenda that is embraced and endorsed by the vaccine field as a whole. One reason is that it is a costly, time-consuming endeavor, particularly if the studies are done in humans. "No company is going to do it. Most investigators aren't going to do it either, because you need to make GMP lots of different products and that is expensive," says Burke.

But it is not an insurmountable problem. For example, the National Cancer Institute has invested heavily in GMP facilities at universities, so that small lots of experimental reagents can be made for human trials of cancer drugs.

Concept-testing trials and comparative studies are part of the antidote to a repetitive, narrow pipeline. But there is no escaping the need for more genuine innovation, as well. A broad pipeline depends on an open pocketbook and open minds. And funding and faddishness remain obstacles for AIDS vaccine developers.

Rather than worrying about the similarity of products in Phase 1 trials, we should be asking whether there is a similar suite of approaches on deck, should these fail. Put another way, the question isn't whether or not we have all of our eggs in the same basket, but how difficult it will be to refill the basket if our current cargo ends up looking like Humpty-Dumpty.

Is the henhouse full? Not really. One warning sign is that the non-human primate field — the locale where more innovation could be happening than will ever occur in humans — is showing similar distribution of research efforts to the human clinical trials pipeline. Some of this is to be expected, since non-human primate studies have preceded most of the human trials being conducted today. But in addition to laying the groundwork for human trials, the non-human primate model can also be used to identify novel concepts. This type of innovation is not apparent. One rough measure of this can be gleaned by looking at the SIV vaccine studies database compiled by Bette Korber and her team at the Los Alamos National Laboratory. From 2000 to the present DNA and recombinant vector strategies comprised nearly half of the strategies published in peer-reviewed publications.

It is vital that funds be allocated for truly innovative research, even if it means funding approaches which depart from today's current paradigms. "Pre-clinical research is constrained by what is perceived as useful and needed with respect to humans. When these perceptions narrow, it impacts pre-clinical research," says Marta Marthas, a primate researcher at UC Davis.

Looking beyond the current crop of candidates in trials, there are some new kids on the block, including viral vector prime-boost combinations, new adjuvanting strategies and novel delivery methods. But many more approaches must be moved forward rapidly if the field is to have a true fall back plan for failure. Other than the ALVAC-AIDSVAX prime-boost study starting this fall, the next Phase 3 trial of an AIDS vaccine will not come until 2004, at the earliest. That's a year after the release of the AIDSVAX North America trial data and six years after the trial began. The world cannot afford to follow this time line again.



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## AGAINST COMPLACENCY

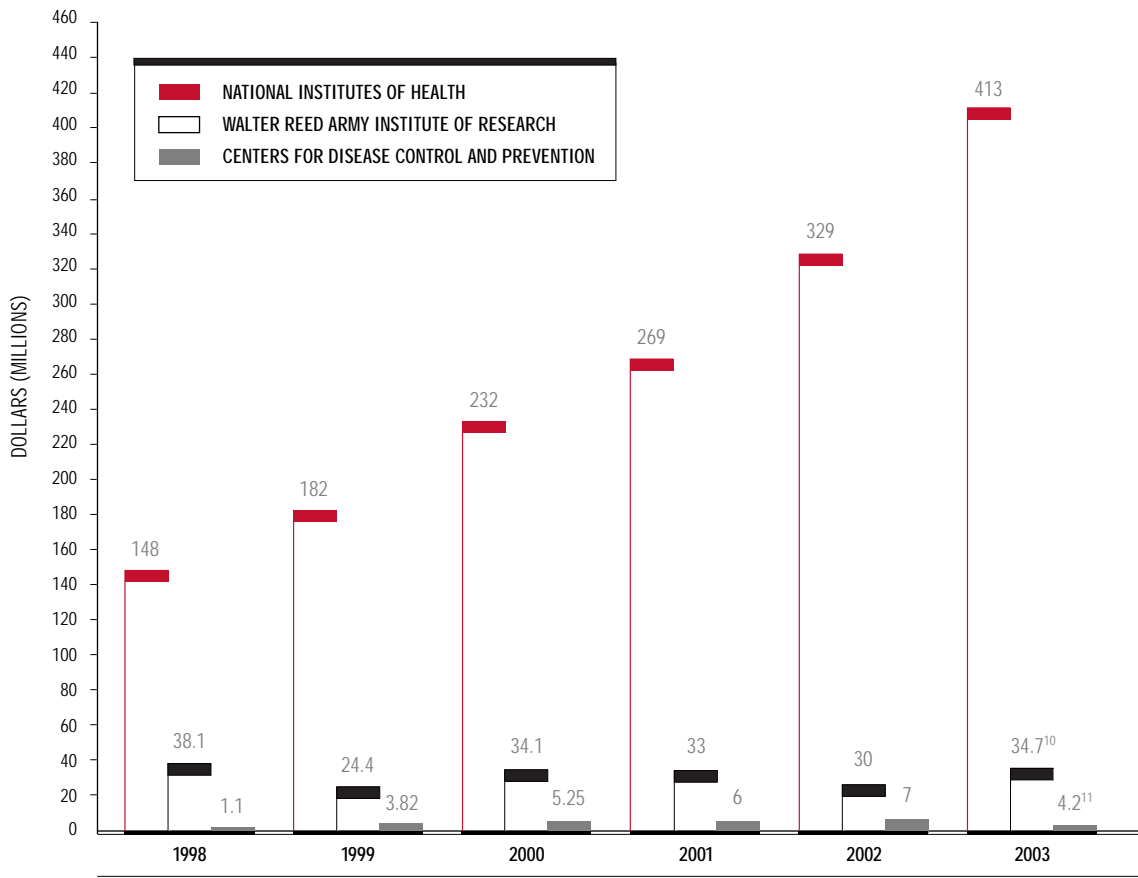
Where the AIDS vaccine field ends up depends, to a large degree, on our complacency — or lack thereof. It is not enough to move a number of candidates into trials. We must also ensure that we gather adequate information about how these candidates compare to one another. We must not celebrate the competition that got us to this point, if this same spirit is preventing teams from comparing their results. And it is not enough to say that we have a diverse pipeline by today's criteria. We must question these criteria and always look for better ones.

It is helpful to remember that, in the AIDS context, “me-too” became a catch phrase in the late 1990s, after protease drugs hit the market. At that time, every company was racing to develop its own moneymaker in at least one of the three approved classes of drugs.

This experience holds some important lessons for AIDS vaccines. One is that, when a single idea predominates, novel strategies are slow to emerge. This year brought the FDA approval of the entry inhibitor Fuzeon — the first truly novel compound to become available in the eight years since the licensure of protease drugs.

But there are also critical differences. When drug companies raced to bring their versions of potent antiretrovirals to market, there was a proven mechanism and a known market. The situation is different for AIDS vaccines. There are no vaccines that work — even a little bit. The bar has yet to be set. Until it is, the field should commit to constant, collaborative efforts to make the pipeline more diverse, more efficient, and more likely to yield useful information about current and future candidates. Steps taken in this direction are a safeguard against complacency. They are also the best, if not the only option, for finding an effective vaccine.

FIGURE 7 :: AIDS VACCINE BUDGETS FOR MAJOR U.S. RESEARCH AGENCIES



<sup>10</sup> All but \$6.2 million of WRAIR funds in this year come from NIH funding

<sup>11</sup> The shift in CDC funding from FY2002 to FY2003 is due to the end of supplemental research supporting the VaxGen trial of AIDSVAX B/B in the U.S. and reduced activities in the Ivory Coast related to civil unrest.

5

ARE THEY GETTING IT RIGHT AT VRC?



One of the key components of the US Government's overall effort to develop a safe and effective HIV vaccine is the NIH Vaccine Research Center (VRC). Creation of a new center at NIH devoted exclusively to vaccine research was first announced in 1997 as part of then-US President Bill Clinton's call for development of an AIDS vaccine within a decade. But the real push for the VRC came from the leadership of NIH, including NIAID Director Anthony Fauci and a number of officials no longer with the agency — NIH Director Harold Varmus, NCI Director Rick Klausner, OAR Director Neal Nathanson and Nobel Laureate David Baltimore, who headed the NIH advisory committee on AIDS vaccine research.

In September 1999, Gary Nabel was appointed by Varmus to be the first VRC Director. Nabel had been Director of the Center for Gene Therapy and a Howard Hughes Medical Institute investigator at the University of Michigan. He was well regarded in the scientific community for his work on HIV, cancer and Ebola virus, and for his gene therapy clinical studies.

It is now almost three years since the VRC opened its gleaming 85,000 square foot central building on the NIH Bethesda, Maryland campus (complete with conference rooms and a cyber café). We felt it was time to take a look at what progress was being made and what lessons could be learned that could impact the overall vaccine effort, and the work of the VRC itself. AVAC spoke with a broad range of researchers in the AIDS vaccine field from government, industry, academia and the philanthropic sector. We also visited the VRC to meet with Nabel and some of his key staff.

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## :: OVERVIEW

The Center, formally known as the Dale and Betty Bumpers Vaccine Research Center (following the practice of naming NIH buildings for the agency's advocates in the US Congress), now includes ten major laboratories and a staff of about 150 people, of whom approximately 80% are researchers. The VRC 2002 Annual Budget totaled about \$50 million, of which 80-90% goes to HIV vaccines. The budget is expected to grow to approximately \$80 million in 2003. There is a concerted pilot-production lab in the VRC building and a new, larger production center is being built in Frederick, MD.

Nabel has hired what appears to be an impressive roster of researchers. These include: Deputy Director John Mascola, Rick Koup (who leads the Immunobiology Lab), Peter Kwong (Structural Biology section), Rich Wyatt (Structural Virology), Barney Graham (Viral Pathogenesis and Clinical Trials) and Phil Gomez (Vaccine Production). Harvard's Norm Letvin is working in a part-time capacity on the Center's primate studies.

The VRC is developing a number of different products, including HIV DNA vaccines (some of which have already entered clinical trials), adenovirus vectors (using the adenovirus 5 strain–Ad5) and MVA (modified vaccinia Ankara) vectors. The Center also has a substantial program designed to develop candidate vaccines that can generate potent and broad neutralizing antibodies.

Nabel clearly believes that the VRC must develop vaccine candidates through a rational and systematic design process. “We have made hundreds, if not thousands of prototypes using higher throughput and evaluated multiple genes and clades in the process,” he notes. The VRC Director describes “a Darwinian process which candidate vaccines have been through to identify the most promising products.”

The VRC strategy is to identify the optimal HIV antigens to include in a vaccine and then to engineer them into the different molecular carriers (DNA, adenovirus and MVA). The HIV inserts currently being prepared include: clade B Gag-Pol- Nef, and modified Env sequences of clades A, B and C. Although the impact of clade-specific antigens is unknown, this “multi-clade” approach is a novel way of trying to deal with global diversity and to address scientific questions and potential political concerns where the vaccines may be tested.

Nabel notes that the VRC is also providing these HIV inserts to a broad range of outside vaccine researchers and developers. “We have sent these inserts to hundreds of academic researchers and companies free of charge.”

In addition, the VRC has attempted to play a central role as a “convener of the field.” A series of meetings on key research questions have been organized. The Center collaborated in an effort led by NIAID and the Jackson Foundation to compare methods of measuring ELISPOT assays between different laboratories.

Virtually every person with whom AVAC spoke was generally pleased with the progress that has been made at the VRC. “Gary has done an outstanding job bringing it all together,” says Rick Klausner, now the Executive Director of Global Health for the Bill & Melinda Gates Foundation. “He has succeeded in recruiting top people and has initiated a number of impressive collaborations.”

“Gary Nabel has been successful in putting together a very capable team,” says John Moore, an AIDS researcher at Cornell University and member of the NIH AIDS Vaccine Advisory Committee. “The mixture is impressive.”

Not surprisingly, NIH leaders are satisfied with the progress so far. NIAID Director Anthony Fauci reports that the VRC is, "...working great. It has demonstrated an ability to combine quality research, product development and clinical studies." But Moore and others correctly note that it is difficult to measure real success in AIDS vaccine R&D without having an effective vaccine.

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## :: WHAT CAN BE LEARNED FROM THE EARLY DEVELOPMENT OF THE VRC?

While a definitive evaluation of VRC progress may be difficult at this point, there are some lessons that can be learned from the Center's development so far. These lessons may help us in developing new R&D models and considering whether to invest significant resources in specific R&D efforts. They may also help the US Government continue to provide the VRC with opportunities to advance its programs.

### ***1. Attracting top-quality researchers is essential***

Every person with whom we spoke mentioned the fact that the VRC has attracted top-quality researchers. "Gary has attracted an impressive core staff," says John Shiver, one of the leaders of Merck's AIDS vaccine program. Early on, Nabel spent a lot of time and energy in seeking out good researchers. "We invested a great deal in trying to hire the very best people," he says. "And we looked for three criteria: 1) excellence, 2) expertise in key areas, and 3) collaborative people." ("nice people" as Nabel notes.) He did not rush into setting up new programs until he had key members of this team in place. This appears to have paid off so far.

### ***2. A culture of collaboration is important***

The VRC actively seeks out collaboration with credible R&D partners. It is working with such companies and groups as Merck, Vical, Therion, GenVac, Crucell, and IAVI and is in active discussions with others. Internally, there appears to be a real focus on collaboration between researchers. As Mascola notes, "It is a whole mindset that has been created. We also have the ability to share products. We are all part of the process of deciding whether to put something into clinical trials, like a biotech company." The VRC has been actively working to provide other companies and academic researchers with assistance.

### ***3. The ability to design, produce and test products in one center has significant advantages***

Unlike many biomedical research projects, the VRC is vertically integrated — it has the ability to design, manufacture and test candidate AIDS vaccines. This gives it a big advantage in being able to move products forward. VRC researchers can produce their own constructs, study them in animal and human trials, and prioritize the approaches as appropriate. The Center also has the ability to invest in process

development to ensure, early on, that vaccines being studied can be manufactured in sufficiently large quantities. Until now, only the large vaccine companies had the ability to combine all these capabilities.

***4. A more rational, systematic approach to designing and prioritizing candidates is likely to lead to getting better vaccines into the pipeline sooner.***

A number of researchers noted that the candidate vaccines that have moved into larger trials thus far are not necessarily the most promising ones. Factors such as access to funding by the sponsor (private, philanthropic capital, etc.), individual drive of the sponsor, and available clinical trial sites have greatly influenced which products moved forward. One researcher we spoke with described current development efforts as, “scattershot and lacking in systematic evaluation and prioritization.”

The VRC is attempting to use a more systematic and rational process to develop and evaluate vaccine approaches. The Center is investing significant resources in pre-clinical research designed to produce immunogens capable of generating potent neutralizing antibodies. While these efforts do not usually garner headlines, they are critically important in ensuring that when products do move into clinical trials, the trials will help generate useful data. In addition to its own efforts in the area of antibodies, the VRC has partnered with IAVI and a number of academic laboratories in the Neutralizing Antibody Consortium. “They are doing some very interesting work on antibodies,” notes Wayne Koff, who heads the IAVI R&D effort.

***5. Despite its early success, even VRC faces concerns about investing in “me-too” products.***

One concern about the VRC did emerge. Some researchers questioned whether the Center should be investing significant resources on DNA and adenovirus — the same approaches being pursued by the well-regarded team at Merck. But the concern about pursuing “me-too” approaches is certainly not unique to the VRC (see Chapter 4). And to be fair, most of the individuals we spoke with, including Nabel, noted that there are some significant differences between adenovirus vectors at Merck and those at the VRC. Merck is unlikely to include pieces of the HIV envelope while the VRC vectors include env sequences from three clades. In addition, Merck researchers appear more interested in combining their adenovirus vectors with another viral vector (most likely canarypox) rather than a DNA construct. Finally, given the apparent ability of adenovirus to generate unusually potent immune responses in animals, a number of researchers told AVAC that “a little friendly competition between Merck and the VRC on adenovirus is a good thing.”

### ***6. Protection from bureaucratic obstacles***

Being situated within a \$26 billion government agency that has a well-established bureaucracy will undoubtedly create challenges for the VRC. However, the Center is nested within NIAID and Nabel reports directly to Anthony Fauci, the Institute's politically savvy Director. "There is a crisp chain of command and we are working hard to avoid bureaucratic hurdles at NIH," says Fauci. In the past, the VRC could also count on the support of such NIH heavyweights as Varmus, Klausner and Baltimore. It is important that this type of influential support continue.

### ***7. Significant future funding will be needed***

The VRC appears to be getting the financial support that it needs to operate at maximum efficiency. Yet there could be some funding challenges ahead. With a sluggish US economy, an overall NIH budget that is not likely to increase significantly in the short term, and costly Phase 3 vaccine trials on the horizon, funding challenges are likely. As long as the VRC continues to progress, it is hoped that NIH will continue to provide it with the funds that it needs.

Overall, the VRC appears to have made significant progress in building a very credible R&D program and attracting top-rate researchers in a relatively short time period. What impact it will have over the long-term remains to be seen. Even at this point, we can already learn some lessons from the VRC's early development. And with a promising start, it is vitally important the Center continue to receive sufficient funding and political support in pursuing its mission.



# 6

THE VEE DELAY: WHAT ARE THE LESSONS  
FOR FUTURE COLLABORATION?



It is the first experimental AIDS vaccine developed for South Africa, which has five million people living with HIV — more than any country in the world. By all accounts, it represents one of the more promising scientific approaches to ameliorating HIV infection. But AlphaVax, Inc., the Durham, NC biotech company making the vaccine, has encountered a manufacturing setback that has put the product's entry into human trials more than a year behind schedule. Similar set backs have befallen other AIDS vaccine candidates, and these are the perils to be expected of high-risk research. (For a more general discussion of these issues, see Chapter 3.)

The AlphaVax vaccine, known as a VEE-vectored vaccine, is made with genetically engineered particles from a South American horse virus, which are used to carry HIV genes into human cells (VEE stands for Venezuelan Equine Encephalitis). In experiments with rhesus macaques, the vaccine kept the animals from developing the monkey version of AIDS, though it did not prevent infection. Even so, it could prove to be a powerful tool in combating HIV.

For more than a year, however, AlphaVax has been working to resolve a problem in manufacturing its vaccine. In February 2002, the FDA put a “clinical hold” on a planned Phase 1 trial after the company found that a small amount of bovine herpes virus had contaminated one of the vaccine production lots. However this sounds, it is not uncommon for initial batches of an experimental product to pick up some kind of contamination as the production process is developed. A likely source was one of the animal-derived raw materials used in the production process. AlphaVax officials say they have now implemented corrective measures have submitted a revised application to the FDA.

Until recently, the company also anticipated trouble making enough of the product for larger clinical trials using the original version of its technology. That's because the manufacturing process is more complex than most. But company officials say they have now dramatically improved their yields of the virus-like particles used to make the vaccine and they foresee no problem in having enough vaccine to carry out all planned trials.

Though AlphaVax officials say they have moved as quickly as possible to address the problems, the pace has frustrated the firm's original benefactor, IAVI, whose *raison d'être* is to accelerate AIDS vaccine research and development. By mutual agreement, the parties decided last summer not to renew their contract because of differences that each has declined to discuss publicly.

Peter Young, CEO of AlphaVax, said he is hopeful that additional funds will be awarded by the federal government, which has already contributed more than \$2 million to the VEE project, in addition to its support for testing the vaccine in clinical trials. The company also has a federal contract to develop a vaccine against Marburg virus, one of the world's most lethal pathogens, using its VEE vector technology. But to stay afloat, AlphaVax will have to attract more private investment as well. And to do that, it has to get into the clinic with its lead product—the VEE-vectored vaccine against HIV—as soon as possible, to demonstrate the vector's benefits in humans and dispel concerns about its theoretical risks.

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:: LEARNING ALONG THE WAY

The delay in testing the AlphaVax vaccine provides important lessons for the field. It illustrates the manufacturing challenges posed by a new generation of experimental HIV vaccines using novel viral vectors. It reveals the tensions that can arise between small biotech companies and their larger partners over how to control the pace of research. And it provides a cautionary tale about the pitfalls of promising to HIV-ravaged communities, a vaccine trial too far in advance of regulatory approval—seriously testing the patience of communities where vaccines are to be tested.

As early as the spring of 2000, for instance, major efforts were underway in the hard-hit community of Hlabisa in South Africa's KwaZulu Natal Province to prepare villagers for testing of an HIV vaccine. Billboards went up announcing the place as a site for HIV vaccine trials. Educators went hut to hut, explaining what it would mean to be a trial volunteer. The tribal council held special meetings to give its blessings to the potentially life-saving human experiment that was about to begin. With more than 30% of pregnant women in the area infected with HIV, an effective vaccine couldn't arrive too soon.

Although no specific HIV vaccine had yet been approved for human trials by the South African Medicines Control Council (MCC), everyone assumed that the first vaccine out of the starting gate would be the AlphaVax product. At the time, it was the only vaccine being made for South Africa. Its development was being bankrolled by IAVI. And South African leaders regarded it as the quintessential “African vaccine” because not only was it made with genes from clade C virus circulating in South Africa, but also because South African researchers had played a vital role in creating the vaccine.

Today, nearly four years later, two other competing vaccine candidates have now moved into the South African regulatory pipeline. While the VEE-vectored vaccine was originally expected to be the first out of the starting gate in South Africa, it now looks as if a competing vaccine, made by Merck & Co., will be the first to be tested in the country. Not far behind is a third vaccine candidate, developed by IAVI-sponsored scientists in Great Britain and Kenya, which is also to enter a Phase I trial in South Africa. The MCC has spent nearly a year evaluating the applications for Phase 1 trials while wrangling over a thicket of common issues including safety, informed consent and the provision of antiretroviral drugs for breakthrough infections.

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## :: RELATIONSHIP BUILDING

Originally, Phase 1 safety trials of VEE were to begin simultaneously in South Africa and the United States in June 2002. It will now be at least June 2003 before they begin in the US — and at least September 2003 before they start in South Africa. Of the three vaccines now awaiting MCC approval, the AlphaVax vaccine is the only one made with genes from the clade C subtype of the virus, which predominates not only in South Africa but also in Botswana, Zambia, Malawi, Zimbabwe, Mozambique and the southern part of Tanzania. (The Merck vaccine is made with genes from clade B virus, which circulates in North America, while the IAVI MVA-DNA vaccine is made with genes from clade A virus, found in east Africa.)

The AlphaVax product is also the only vaccine that has been developed through a close collaboration between US and South African scientists—the kind of North-South partnership pioneered by IAVI as one requirement for companies to receive IAVI funding. Virologist Robert E. Johnston and his colleagues at the University of North Carolina designed the vaccine strategy. Two leading South African scientists, Lynn Morris at the National Institute of Communicable Diseases and Carolyn Williamson at the University of Cape Town, isolated, grew and sequenced the C viruses, which were also being studied by South African virologist Salim Karim.

Johnston, who resigned as chairman of the AlphaVax board in October 2001, worked hard to keep AlphaVax and IAVI together. “There were problems on both sides of the relationship. But there is no reason it had to break up. They were all fixable things,” he said. As a co-inventor of the VEE replicon technology, Johnston is convinced that the science behind the vaccine is sound. He predicts that one day, in the not too distant future, a trial volunteer at the sparkling new HIV vaccine trials clinic at Chris

Hani Baragwanath Hospital in the Black township of Soweto, will roll up a sleeve and get the first injection. “I’m going to be there,” Johnston vows. “Even if I’m just standing in the back of the room.”

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## :: HITTING A BUMP AND MOVING FORWARD

Vaccines go through numerous steps in the production process; it is not uncommon for new products to pick up some contamination in the course of this process, as noted earlier. It might be bacteria from a test tube or traces of chemical reagents that shouldn’t be there. The problem has occurred at small biotech companies such as AlphaVax and also at large pharmaceutical firms. To protect their products from such potentially damaging and costly problems, companies establish systems to identify contaminants early on and eliminate them.

That’s what happened at AlphaVax, explained CEO Young, only the problem cropped up late in the game. He said the company didn’t discover the low levels of an unidentified contaminant until just before it submitted its IND application to the FDA in December 2001. Because the contaminant was not originally found in the batch of vaccine to be used in the clinical trial, the company decided to submit the IND application to the FDA while it pursued its investigation. Two months later, when the FDA imposed the clinical hold until the contaminant issue was resolved, AlphaVax was not surprised. “We fully expected that,” Young said.

AlphaVax subsequently identified the contaminant as a bovine herpes virus, which company scientists believe may have come from the medium used to grow the cells in which the virus-like replicon particles (VRPs) are harvested. The VRPs are harvested from what’s known as Vero cells, a commonly used laboratory strain of kidney cells originally taken from African green monkeys. These cells, in turn, are grown in culture medium containing bovine serum. AlphaVax scientists speculate that, either in their own lab or elsewhere, the monkey cells picked up a stray bovine herpes virus from the serum or other raw materials and the virus ultimately got swept into a batch of the vaccine.

According to a number of scientists inside and outside AlphaVax, this bovine herpes virus would likely be harmless to humans. But it is unacceptable to knowingly use a vaccine containing any contaminating virus.

To address the problem, AlphaVax has systematically tried to identify every possible source of the contamination, according to Young. It has also switched to “a more pristine” source of live Vero cells obtained from the World Health Organization. In addition, the company now irradiates virtually everything used to make the vaccine. “Anything we can irradiate, we do,” Young said.

While it was re-manufacturing the vaccine, AlphaVax hit upon new techniques that have allowed it to increase by 1000-fold the number of VRPs produced from the Vero cells. Instead of yielding hundreds or even thousands of potential vaccine doses from each cell harvest, the company may now be able to produce millions, Young said.

The company has recently submitted the results of its year-long corrective action plan to the FDA. Young said the release tests on the vaccine, now made with the new Vero cells and irradiated raw materials, have turned up no contaminants. If the regulatory review concludes without additional questions, the company expects the FDA to approve the Phase 1 trial, allowing the first trial volunteer to be injected in the United States sometime in June. To move forward in South Africa, the trial must also be approved by the MCC. The company is planning a staggered start-up, with volunteers injected in the US before they are injected in South Africa.

Some of the lessons of the VEE experience are obvious. Clearly, the North-South partnership that has informed the vaccine’s development demonstrates that scientific collaboration of the first order is possible between researchers in affluent countries and researchers in resource-limited countries — but it may take extra time and effort.

Secondly, it’s clear from the experience in making the VEE vaccine that bringing a new vector into the clinic presents new and difficult manufacturing and regulatory problems. With a string of other new vectors on the horizon, the field needs to be prepared to put extra time and effort into manufacturing and regulatory challenges. All this is worth doing. But all cannot be expected to run smoothly, all of the time.

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## ABOUT AVAC

The AIDS Vaccine Advocacy Coalition (AVAC) was founded in December 1995 to accelerate the ethical development and global delivery of vaccines against HIV/AIDS. We provide independent analysis, policy advocacy, public education and mobilization to enhance AIDS vaccine research and development.

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