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The Need to Understand Demand

Why Plans to Deliver AIDS Vaccines Are on Agendas Today

BY EMILY BASS

Given the scale of the AIDS epidemic and the limits of existing prevention technologies, demand for an AIDS vaccine can seem like a given. After all, who *wouldn't* want an AIDS vaccine? Similarly, with immediate scientific challenges to overcome, plans for manufacturing an AIDS vaccine may seem like a distant concern.

But a chorus of voices, including veterans of other vaccine campaigns as well as AIDS vaccine advocates, warns that neither the science nor the supply-and-demand research can be shifted to the back burner. "I tell basic scientists that finding an AIDS vaccine is easy, compared with delivery," says José Esparza, head of the WHO-UNAIDS Joint Vaccine Programme.

"There's a belief that 'if you build it, they will come,'" says Mark Miller, who directs international epidemiology and population studies at the National Institutes of Health Fogarty International Center (Bethesda). "We know that this is just not the case." Miller has tracked the slow uptake of hepatitis B (HB) and *Haemophilis influenzae* type B (HiB) vaccines, both approved in the last twenty-five years.

Instead, say Miller and others, vaccine stakeholders must plan ahead and gather information on a wide range of topics that fall under the broad rubric of need and demand. These familiar terms have specific meanings in the public health lexicon: Demand refers to the number of doses that a country can deliver using existing infrastructure, and the number of people who are willing to be immunized. Need refers to the maximum number of people who could benefit from the vaccine, based on disease burden and the size of at-risk populations.

Experts seeking to understand need and demand ask deceptively simple questions, like how much vaccine the world actually needs: How much can be made, and how many people are likely to come forward for immunization.

While these queries are common to all vaccines, others will be faced for the first time by the AIDS vaccine field: What will the demand be for a vaccine that offers only partial protection (a likely scenario for a first-generation AIDS vaccine)? How can vaccines for a highly-stigmatized disease be delivered safely and swiftly to adults, who are not the primary target of existing immunization programs? If the world is to avoid delays in delivery, these questions must be addressed long before a vaccine is licensed. "We've only started to scratch the surface" of these issues, says Jane Rowley, a health economist and IAVI advisor.

A glimpse of what's at stake could come soon. In early 2003, VaxGen is expected to release results from the first of its two Phase III AIDS vaccine trials. If the results are favorable, the world could have the first partially-effective AIDS vaccine—and a host of decisions about licensing and distribution—on its hands. Should demand outstrip supply, the world will need fast, reliable directives on where the vaccine will have the most impact and how it can be delivered rapidly to different populations.

Vaccine properties such as route and immunization schedule are known for the VaxGen candidate, making it easier to query countries, communities and individuals about anticipated demand. But most of today's assessments concern products that don't yet exist, and where it's unclear what properties they will have.

A survey of vaccine delivery in the last century underscores the urgent need for advance planning. Yellow fever vaccine, available since 1937, is used in less than one-third of the countries where the disease is endemic. Hepatitis B vaccine was licensed in 1981 but reaches less than half of the world's children in routine schedules. Several factors account for this delay. A study by Mark Miller and colleagues found that vaccine cost, delivery infrastructure and burden of disease were the strongest predictors of whether or not HB and HiB were added to childhood immunization programs. Such studies—and the difficulties faced by global vaccine procurers from UNICEF to the

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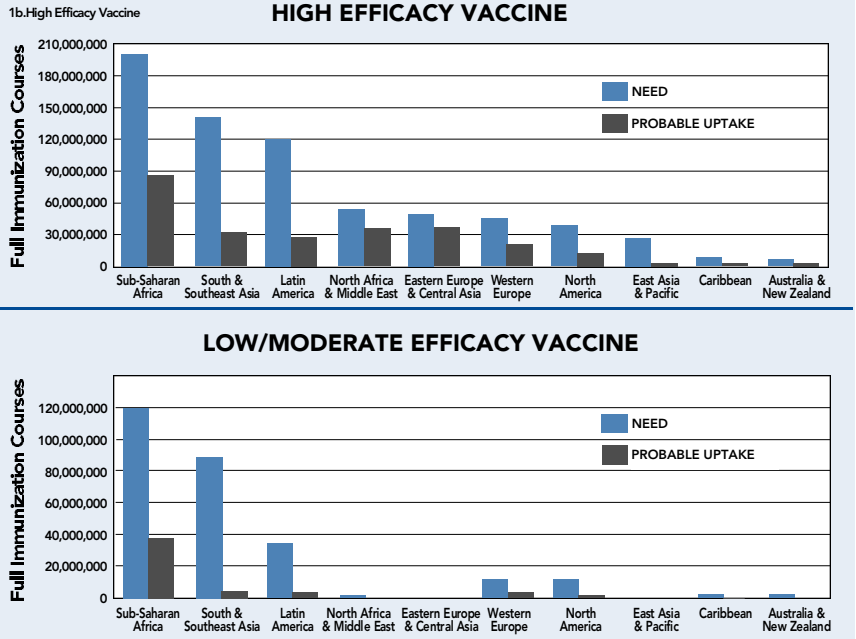
Global Alliance for Vaccines and Immunization (GAVI)—reveal the problem in stark relief: Without planning and action, vaccine need will far exceed vaccine demand.

Opening Acts

There are many ways to approach demand assessments. Surveying this wide and varied field, José Esparza reaches for the parable of the blind man and the elephant, in which each man describes a wholly different beast depending on where he stands in relation to it. "Immunology people will say that the most important determinant of AIDS vaccine use is efficacy," he says. "Policy people will say that it is cost."

Studies to date (see references, p. 14) offer a variety of perspectives on the elephant. In 2000, Esparza's group, along with IAVI, co-sponsored four regional consultations (in Africa, Latin America, Eastern Europe and Asia) that gathered representatives from government, NGOs, and research institutions to discuss public sector demand for AIDS vaccines of different efficacy levels. After being briefed on the nature of partially-effective vaccines (see *IAVI Report*, July-September 2002, p. 5), participants used epidemiological and public health data from one country as the basis for assessing regional need and demand for two vaccines: one of low to moderate efficacy (30-50%), the other with high efficacy (80-90%).

UNAIDS-WHO-IAVI REGIONAL CONSULTATIONS:
Need and Demand Estimates for High and Low Efficacy Vaccines



Source: WHO-UNAIDS, Global Need and Current Delivery Capacity for Future HIV Vaccines, *2002 (XIVth International AIDS Conference, Abs. #WeOrD1297)*

Need and demand are estimated using different types of data. Models of need draw on epidemic conditions, incidence and prevalence data, along with assumptions about how long vaccine protection will last. Demand estimates draw on actual vaccine usage, as well as data on accessibility (the number of people who could reasonably be vaccinated by existing services), and acceptability (the willingness of individuals, health ministries, and other entities to purchase and use vaccines with a given set of properties).

Ultimately, the consultations found striking gaps between need and demand (see figure, below). The groups came up with an estimated global need of 260 million immunization courses for a low-to-moderate efficacy vaccine, but a demand for only 49 million. For a high-efficacy vaccine, need was estimated at 690 million courses and demand at 260 million.

While these figures throw the gap between need and demand into stark relief, veterans of the field say that these discussions, which did not draw on recent modeling work, probably underestimated the actual numbers. Esparza agrees, emphasizing that these discussions were "more qualitative than quantitative." One striking example came from Russia and Eastern Europe, where AIDS incidence has increased by 1300% between 1996 and 2001—yet participants from the region said that a low-efficacy vaccine might not be used at all. The concern voiced by health authorities was that a low-efficacy vaccine could do more harm than good by creating a false sense of security in vaccinees.

So far, a handful of studies have looked at whether or not behavior change could negate (or improve) the positive effect of a vaccine. One recent paper came from the Harvard School of Public Health. Using data from a Thai cohort of intravenous drug users, they modeled the long-term (40-year) impact of vaccines with 30%, 75% or 90% efficacy, delivered to 50% of the cohort. Their findings: In the absence of behavior change, both vaccines reduced prevalence. For the higher-efficacy vaccine, a 50% increase in risky behavior had only a minimal effect on long-term prevalence. Looking further, they found that even if 50% of vaccinees given the low-efficacy vaccine increased risk behavior, prevalence did not increase over forty years.

Of course, the world is unlikely to launch huge vaccination campaigns that may have only marginal effects on long-term prevalence. To maximize the effect of low-efficacy vaccines, Esparza says that countries should prepare to couple immunization campaigns with robust prevention and care services. This means that, at least in the short term, vaccines should not be seen as potential cost-saving measures.

Countries and vaccine stakeholders will also need to consider immunization strategies that seem

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SETTLING INTO THE NEW GROOVE: AIDS VACCINE RESEARCH 2002

1994 was a watershed year for AIDS vaccine research. That year, without hard proof, envelope-based vaccines were determined inadequate to prevent HIV infection. The long-term fallout was substantial. Genen-tech left the business while Vaxgen picked it up. Chiron began a long re-tooling. Can-arypox-based (ALVAC) vaccines became ascendant for clinical trials. IAVI came into being. NIH moved into financing product development. So the field settled into a second groove—testing various permutations of ALVAC, making other clinical material with government support, running the first efficacy trials…And eight years flew by.

As others have pointed out, 2002 looks a lot like 1994. Again, without hard proof, one efficacy trial of the last decade's approach was cancelled (ALVAC with or without a gp120 boost) and one will begin in Thailand (ALVAC + gp120). DNA and adenovirus have captured the spotlight while preparation still continues for a wider variety of Phase I trials to see where we stand with vaccine design. It seems prudent to ask now where we will be when this song winds down, many years from now. Already, some big unanswered questions—how to induce neutralizing antibody and deal with viral escape and diversity—are making people uncomfortable.

At this rate the epidemic will be devouring new regions by the time we get a vaccine, costing the human race significant productivity and self-respect. The whole AIDS experience is beginning to look like proof of the 200-year-old Malthusian theory that population outruns resources. Or like the start of a painful demonstration of how viruses and humans, through long and destructive evolutionary processes may ultimately learn to coexist: by killing the weak, poor and unlucky—for more generations than mankind will care to count.

So, what else can be done? Everyone in AIDS vaccines is working flat-out hard and every little step is excruciatingly slow and difficult. We need some answers. We could use a breakthrough. We need a bigger, better plan.

Probably the biggest questions have to do with tethering free-floating research to the real world:

- What do the assays we have actually mean clinically, if anything?
- How do animal studies relate to human studies, if at all?
- How do we prioritize our activities, or can we?
- Is there any way we can jump some cycles or speed things up?

These are difficult, humbling questions to ask, let alone try to answer. So everyone is doing his own thing, head down, nose to grindstone. With all energies focused on designing each idea of the best antigen, or developing an existing approach, or solving the riddles the virus presents us with, we very well may never get anywhere in any of our lifetimes. And half a billion dollars a year could be spent, ad nauseam, as Rome continues to burn. As Maurice Hilleman once illustrated it, the same mice are eating an ever-bigger piece of cheese.

Breakthroughs are, by definition, unpredictable and serendipitous. Fertilizing that field is the specialty of NIH and others—funding grants that are deemed worthy by peer review, not keeping too-close tabs on the work, and facilitating cross-communication. Like democracy, it's the best bad system we've got.

VIEWPOINT

BY BILL SNOW

Bill Snow has been one of the most vocal AIDS vaccine advocates in the US for over a decade. During this time he has served on the CAB at San Francisco's vaccine trial site (now part of the HVTN), as a member of NIH's AIDS Vaccine Research Committee (the "Baltimore" committee) and on various national AIDS vaccine policy groups. He was also a co-founder of AVAC in 1995 and is an Emeritus Member of its Board of Directors. As an openly HIV-positive man, Snow has also played a pivotal role in engaging the broader AIDS community in the search for a vaccine.

This article is reprinted, in slightly revised form, from the first issue of AVAC's new newsletter. The full* AVAC Update *can be viewed at www.avac.org

In the meantime, that leaves us with virtually no collective, systematic strategy—discussing what could happen across programs, planning ahead for all contingencies, setting priorities and taking risky action with the best knowledge available. Such coordinated effort doesn't suit independent-minded scientists or multiple-research networks. Like any battle plan, it will go awry. It's a great deal of work and difficulty making decisions—but at least it's not 100% dependent upon individuals and chance. When you're at sea, looking out to the horizon is a scary but essential business. So, here's a modest proposal:

- **Set broader goals for government-funded research.** Think about designing research programs to try to tentatively answer those big, real-world questions above.
- **Design immunogens and trials to explore vaccine design questions.** Do this, rather than vetting isolated products as each exits the Phase I/II obstacle course.
- **Encourage industry to cooperate (a bit).** Explore

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◀ **AIDS VACCINE RESEARCH 2002** *continued from 3*

information-sharing, patent-pooling and intellectual property agreements that reduce the risk to most and share some benefit with all from shared intellectual property and know-how.

- **Engage the world.** Make some public commitments that are congruent with the seriousness of the epidemic. Take that risk.

The vaccine programs are led by some of the most talented and dedicated scientists in the world: Anthony Fauci (NIAID), Seth Berkley (IAVI), Larry Corey (HVTN), Debbie Birx (US Army), Peggy Johnston (NIAID), Gary Nabel (Vaccine Research Center). You have to admire every one of them and the dedicated public and private teams developing each vaccine candidate. But the outlook is not good because we've settled into a familiar, easy and well-worn groove. If the people working on AIDS vaccines don't shake this up, there's no otherconstituency to do so. ◆

Progress in the Search for a Vaccine Against Human Papilloma Virus

By Emily Bass

Merck presented two sets of encouraging data from Phase I and II studies of a vaccine against human papilloma virus (HPV) at the HPV Clinical Workshop and 20th International Papillomavirus Conference (4-9 October, 2002).* HPV is the virus that causes genital warts and is linked to both anal cancer and cervical cancer, which is the leading cause of cancer deaths among women in the developing world. Merck's candidates, among the most advanced in the HPV vaccine pipeline, use HPV's L1 capsid protein. The capsid assembles itself into non-infectious "virus-like particles" (VLPs) that elicit both antibodies and, in some cases, cell-mediated immunity against HPV. Pre-clinical models show that protection is "exclusively dependent on neutralizing antibody responses," says Kathrin Jansen, director of Merck's HPV vaccine program.

Other firms are also developing HPV vaccines, which are likely to have markets in the developed world—where 75% of adults have HPV, by some estimates—as well as in developing countries. GlaxoSmithKline (in collaboration with biotech firm MedImmune) is developing a vaccine based on VLP technology, that has completed Phase I proof-of-principle studies. Other strategies in early development stages are looking at vectors based on Salmonella bacteria and yeast, which can be given orally.

There are over 100 different types of HPV. Of these, a few are associated with the majority of cases of genital warts (HPV 6 and 11) or cancer (HPV 16 and 18). L1 proteins are well-conserved within types, but have considerable inter-type variation, meaning that separate vaccines are needed for each type. HPV is more difficult to diagnose in men than women. While anal pap smears can detect HPV infection in the rectum, this is not the site of exposure for all men. Consequently, nearly all HPV vaccine trials to date have involved exclusively women volunteers.

Designed to determine safety and immunogenicity, Phase I trials of the Merck vaccine have also provided early signs of promising efficacy. At the October meeting, Laura Koutsky (University of Washington), a principal investigator in the Merck HPV vaccine program, presented an analysis of combined data from Phase I trials of HPV-16 and HPV-11 vaccines (Abs. #P450). She looked for cases of HPV-16 in participants who received the HPV-16 vaccine, compared to those receiving the placebo or the HPV-11 vaccine. There were no cases of HPV-16 among the 66 women who received the HPV-16; in contrast, 14/129 of the women in the combined control group were infected with HPV-16 (including 10 who received the HPV-11 vaccine).

Koutsky also presented encouraging data from a Phase II proof-of-principle study of HPV-16 vaccine (Abs. #O98), in which 1,533 HPV-16 -negative women between 16 and 23 years of age completed the full course of immunization (given at 0, 2 and 6 months) with either vaccine or placebo, and were followed for average of a year and a half following the final immunization. Out of more than 750 women who received the HPV-16 vaccine, none developed persistent HPV-16 infection, compared with 41 women in the control group, which was roughly the same size.

Merck has also completed a multicenter Phase IIb dose-ranging study of an HPV vaccine that includes capsid proteins from four HPV types (6, 11, 16 and 18) (Abs.# O99). This "quadrivalent" vaccine would address the type specificity of vaccine-induced immunity and protection. GlaxoSmithKline has also completed early phase trials of a combined HPV-16/HPV-18 vaccine. A Phase III trial of Merck's quadrivalent vaccine is ongoing. ◆

** Abstracts available at www.hpv2002.com*

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  - **GAVI partners meeting**
  - **Immunoprophylaxis Workshop for HIV-1 in Pediatrics**
- **Clinical Trials Watch: Snapshot views of upcoming and ongoing trials**

Malaria Vaccine Trials Underway in Africa

BY PATRICIA KAHN

While AIDS researchers often say that HIV is one of the most formidable pathogens ever targeted for a vaccine, the same holds true for the parasites that cause malaria—a disease that claimed 1 to 2 million lives every year, 75% of them children under five.

One of the biggest obstacles for malaria vaccine developers is that they express between 5,000 and 6,000 proteins, compared to only 9 for HIV—vastly complicating the task of determining which antigens to include in a vaccine. The parasites also show a high degree of genetic diversity, which—given their huge genome size—has defied classification into groups analogous to HIV subtypes. And its complex life cycle encompasses three very different forms (see figure) and a highly sophisticated strategy for evading the immune system through frequent switching of surface antigens.

Yet despite these immense challenges, two lines of evidence indicate that it is indeed possible to generate protective immunity against malaria parasites, which fall into four separate species of Plasmodium (of which two are responsible for most disease). One is that highly-exposed people who survive multiple bouts of malaria in childhood gradually develop partial ("semi"-) immunity that reduces the severity of disease during later infections. Another is that infection can be blocked by immunization with irradiated sporozoites—the parasite form that invades liver cells immediately after infection, where it replicates intracellularly for 1-2 weeks without inducing symptoms. While this latter protection requires cellular immunity (and can be transferred in mice via CD8 cells), natural semi-immunity appears to depend mainly on antibodies to the merozoite, the form that enters the bloodstream and invades erythrocytes after infected liver cells finally burst.

Attempting to exploit these findings, malaria researchers have developed vaccines based on both sporozoite and merozoite antigens, using some of the same new technologies used for HIV vaccines. And, thanks largely to support from Malaria Vaccine Initiative (Washington, DC), and the Wellcome Trust (UK) three of these candidates are now in clinical trials in Africa: two protein-based vaccines, including one that already showed significant but short-lived protection in an efficacy trial in The Gambia, and another based on a DNA/MVA prime-boost approach, a widely-used strategy in the HIV field.

Some developers expect that these candidates may not be instant "home runs" conferring highly effective, long-lasting immunity. Rather, they could be contributors to a multi-component vaccine, seen by many as the more likely formula for success. "Most people in the field expect that an effective malaria vaccine will require targeting multiple stages and antigens," says Dan Carucci, director of the Malaria Program at the US Naval Medical Research Center. While immune responses directed at sporozoite-infected liver cells could reduce the number of parasites entering the bloodstream, he adds, others aimed at the merozoite stage would blunt the severity of disease. In babies, the overall effect could be "to catapult their malaria immune status into that of adolescents," says malaria researcher Hermann Bujard of the University of Heidelberg.

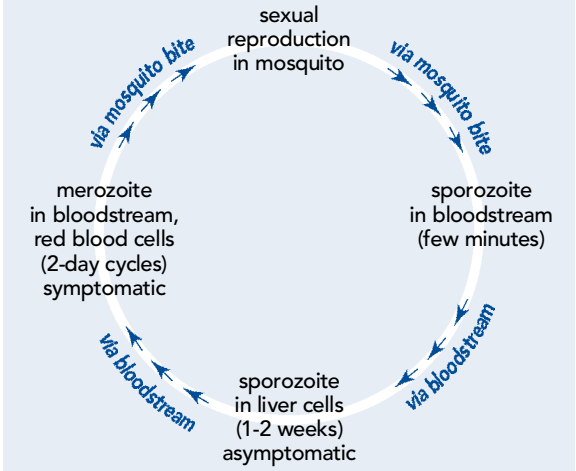
Testing Malaria Vaccines

Determining vaccine efficacy is simpler for malaria than for HIV. Once a candidate's safety is established, first indications of effectiveness may be gathered by challenging small numbers of vaccinated volunteers (at experienced research centers) under carefully controlled conditions where they are bitten by infected mosquitoes; volunteers who become infected are treated immediately with anti-malarial drugs.

Gray Heppner, who heads the Malaria Vaccine Program at the Walter Reed Army Institute of Research (WRAIR, Rockville) where many of these challenge studies have been done, points out that it's a somewhat artificial model. The challenge uses a single strain of parasite at up to 10-fold the natural dose, to ensure that all volunteers are exposed to an infectious dose. What's more, volunteers at these US or European centers have no prior exposure to malaria, unlike people in endemic regions where a vaccine is most urgently needed. But prevention or delay of infection is nonetheless a useful, albeit highly stringent, hint of efficacy, says Heppner.

Then comes the real test in endemic regions among semi-immune populations normally exposed to a wide diversity of circulating strains. In high-incidence regions, vaccine efficacy can be measured in small, short trials (compared to those needed for testing HIV vaccines). For example, in The Gambia, where malaria occurs only in the July-to-November rainy season, about 60% of adults become infected during a single season, and efficacy trials require only a few hundred volunteers and about six months time.

LIFE CYCLE OF MALARIA PARASITE
(Plasmodium falciparum)



GSK's Protein Subunit Vaccine

As the most advanced candidate now in African trials, GlaxoSmithKline's so-called RTS,S vaccine contains about half of the major sporozoite coat protein fused to the Hepatitis B surface antigen. When formulated with GSK's AS02 adjuvant, challenge studies done collaboratively with the WRAIR found RTS,S to be about 50% effective in blocking infection with homologous sporo-

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◀ **MALARIA VACCINE TRIALS** *continued from 5*

zoites (i.e., of the same strain as the vaccine protein), and to protect one in five volunteers upon re-challenge 6 months later. Immune analysis detected strong antibody responses and some cellular responses, including "modest" CD8 levels, according to Joe Cohen, who directs GSK's program on vaccines against emerging diseases.

Moving to the field, safety studies in The Gambia were followed by a collaborative efficacy trial in 306 highly exposed male volunteers (*Lancet* 358:1927;2001). The results: significant delay in time to infection, with about 70% protection in the first two months, but waning to zero by week 15. Re-vaccination of 158 volunteers the next year showed about 47% protection over 9 weeks. Protection extended beyond the vaccine strain to other, "unmatched" circulating strains.

The vaccine was also tested in Gambian children, looking first at safety and dosage in 6-11-year olds, then in 1-4 year olds. Based on these results, Phase I studies are now underway in children in Mozambique, where malaria is transmitted year-round rather than seasonally; by the end of 2002, a Phase IIb pediatric study will begin to gather preliminary efficacy data. That trial will also introduce a new element, says Cohen: Rather than measuring only sterilizing immunity, it will also look at endpoints reflecting severity of disease at the time children become ill and are brought to the clinic for treatment.

In the meantime, further work aims at improving the levels of CD8 T-cell responses, for example through the use of other adjuvants and immunization schedules. And, in keeping with the goal of developing multi-component vaccines, small clinical studies are looking at prime-boost combinations with different candidates, including one in Oxford with the MVA-based vaccine described below.

Sporozoite Antigens in DNA/MVA Vaccines

Another strategy now in efficacy studies is a prime-boost combination developed by Adrian Hill's group at Oxford University. The two vaccines encode a complete TRAP protein (Thrombospondin-Related Adhesion Protein), one of the main sporozoite antigens, downstream from 20 individual peptides containing mostly CD8 T-cell epitopes from six sporozoite or liver-stage antigens.

Multiple clinical studies resulted in an immunization regimen generating a 10-fold boost in T-cell Elispot numbers with DNA/MVA compared DNA or MVA alone, to levels in the 1,000 spots per million PBMC range; the better regimes (using DNA/MVA or fowlpox plus DNA) yielded broad strain cross-reactive results. About 100 volunteers in Oxford have now been challenged-in this case with a heterologous strain, resulting in delay of average time to infection that corresponds to "substantial" reduction in the estimated numbers of parasites emerging from the liver. In addition, about 50-60 volunteers have been safely immunized in Phase I studies at the Medical Research Council Laboratories in Banjul, including 20 children who were given MVA alone. Results will be known in Spring 2003.

Also in development: the same vaccine antigens (TRAP and sporozoite coat protein) in fowlpox, which Hill says so far looks "as good, and maybe much better."

Merozoite Protein-Based Vaccines

Will people vaccinated with one of two main strains of merozoite coat protein (MSP-1) also recognize the other one? That's the question being studied in WRAIR's ongoing 60-person trial, launched in Kenya in April 2002 in collaboration with the Kenya Medical Research Institute, MVI and USAID. The vaccine contains a portion of the MSP-1 protein formulated with GSK's AS02 adjuvant. Also in the pipeline: the first full-length MSP-1-based vaccines, made by Hermann Bujard's group at the University of Heidelberg, which synthesized the two main strains of this notoriously unclonable protein from scratch. The first clinical tests will be conducted in Tübingen, Germany and WRAIR before moving into trials in Burkina Faso. In addition to the protein-based MSP-1 vaccines, Bujard's group is developing MVA-based versions.

Finding the Right Antigens: Future Directions

Since 1993, the US Navy's malaria program has been developing DNA-based candidates, working towards the strategy of using cocktails containing plasmids with different antigens. With three Phase I trials under their belts, their current vaccine contains 5 different antigens (3 from sporozoites, 2 from merozoite); in parallel they are developing MVA- and adenovirus-based vectors as possible boosts, following encouraging protection results in monkeys. Other groups, including WRAIR and the malaria program at NIAID (the US National Institute of Allergy and Infectious Diseases) are studying additional antigens for clinical evaluation.

But as they work to improve immunogenicity of DNA-based vaccines, the Navy program is also seeking better ways to identify which antigens from the huge number of potential candidates might really matter, says Carucci. So far, studies of protected versus unprotected volunteers (from vaccination with irradiated sporozoites) have proved frustratingly inconclusive: the researchers find only low, although detectable, cellular responses to peptide pools from the few antigens they've looked at. "Maybe we're missing something big," says Carucci.

But the completion of the Plasmodium falciparum genome sequence offers a way to approach the problem on a large scale rather than antigen-by-antigen, he adds. Looking at the total pool of encoded proteins, the researchers have identified over 1,000 new proteins, and are developing assays to screen the blood of protected volunteers for responses to any of them—so they can determine whether there is a dominant response that correlates with protection and also identify potential new antigenic targets. So far, they've found six new parasite proteins on the surfaces of infected erythrocytes.

Still, says Heppner, "we need more antigens, more adjuvants, to increase the magnitude and duration of protection. And we need more money. So many good concepts are still restricted by lack of funds." ◆

MAJOR CONTRACTS AWARDED FOR ANTHRAX, MALARIA VACCINES

On 3 October, the US National Institute of Allergy and Infectious Diseases (NIAID) announced that it had awarded two contracts, totaling US$22.5 million, to spur the development of an improved anthrax vaccine. Contract recipients VaxGen (US) and Avecia (UK), will be charged with developing candidates from an experimental vaccine, called rPA102, made by the US Army Medical Research Institute of Infectious Diseases (MD). This recombinant vaccine contains the anthrax "protective antigen" (which facilitates the entry of anthrax toxins into cells) and is based on the same technology as VaxGen's gp120 AIDS vaccine. The contract calls for a product that protects against inhalation anthrax with no more than three immunizations; the current vaccine requires six vaccinations spread over 18 months. Both VaxGen and Avecia will submit a feasibility plan to manufacture, secure FDA approval and deliver up to 25 million doses of vaccine to the US government. VaxGen may base its manufacturing plan on use of the South San Francisco manufacturing plant now under construction as one production site for AIDSVAX.

NIAID also announced an award of up to $3.5 million over five years to Epimmune, Inc., for development of a malaria vaccine based on conserved cytotoxic and T helper cell epitopes. Epimmune is using a similar strategy to design an HIV vaccine that could provide cross-clade protection against disease.

BAVARIAN NORDIC ANNOUNCES PRELIMINARY DATA FROM HIV-MVA THERAPEUTIC VACCINE TRIAL

A therapeutic vaccine containing HIV-*nef* in the MVA-BN vector (Modified Vaccinia Ankara-Bavarian Nordic strain) appears to be safe and immunogenic in HIV-infected people, according to Danish biotechnology company Bavarian Nordic, which released preliminary data in September 2002. Conducted at the University of Erlangen by Thomas Harrer, the Phase I/II trial enrolled 14 HIV-positive individuals (13/14 in chronic infection phase) who were on antiretroviral therapy for at least three months prior to the study and had undetectable viral loads and CD4 counts >400. Participants received three immunizations (weeks 0, 4 and 16) of 5 x 10^8 TCID50 of the vaccine.

Following the vaccinations, 11 of 14 volunteers showed increased numbers of Nef-specific T-cells. All participants maintained undetectable viral loads and showed an overall improvement in CD4 and CD8 T-cell counts. In an ongoing second phase of the study, HAART treatment was interrupted and volunteers are being followed, according to Barbara Petzold, Bavarian Nordic's Manager of Clinical Development. Treatment will be reinstated if viral load exceeds 5,000 at two consecutive timepoints (four weeks apart) or CD4 counts drop below 400. Plans call for testing the vaccine in HIV-negative volunteers next year.

Bavarian Nordic is also working with Epimmune (San Diego) on HIV vaccines containing epitopes (rather than whole genes), in a project comparing antigen delivery via DNA vaccines to MVA vectors. The epitopes were selected for their conservation across multiple HIV clades and the ability of several common HLA alleles (genes which play a key role in cellular immunity) to respond to them. Epimmune is currently testing a DNA vaccine prototype with 21 CTL epitopes in HIV-infected people and will soon begin Phase I studies in HIV-negative people, according to Mark Newman, Epimmune's Vice President for Infectious Diseases. Later in 2003, Bavarian Nordic will test a "next-generation" candidate that also contains helper T-cell epitopes.

Bavarian Nordic is a leading player in MVA-based vectors, building on their MVA-BN platform technology derived from Anton Mayr's MVA, which was extensively used in Germany as a smallpox "pre-vaccine" in the early 1970s The company is also developing MVA-BN as a potentially safer smallpox vaccine than the current one, which is dangerous for people with immune deficiencies (see interview, p. 8). Evidence that MVA-BN is safe even for HIV-infected people therefore has important implications beyond HIV therapeutics.

ORAL VACCINE TECHNOLOGY LICENSED TO UK-COMPANY FOR NON-HIV VACCINES

University of Maryland Biotechnology Institute (UMBI) licensed Bactofaction, a DNA delivery technology, to Microscience, a UK-based biotechnology company that recently launched an oral typhoid vaccine trial in the US. UMBI will retain the rights to develop HIV vaccines using the technology, which uses an attenuated Salmonella bacterial vector and allows for oral administration of DNA vaccines. The Institute of Human Virology at UMBI is collaborating with IAVI to move a vaccine based on this technology into clinical trials in Uganda and the US. Microscience will now be able to use Bactofaction in the development of orally-delivered vaccines for cancer and infectious diseases.

REMUNE IN THE NEWS

On 26 September, the Thai subcommittee on HIV/AIDS Vaccine Development rejected an application from The Trinity Medical Group to extend a Phase II study of Remune, the whole-killed HIV immunogen developed by the California-based Immune Response Corporation. The request for a two-year extension to gather more information on the clinical effects of Remune used without anti-retroviral drugs, was denied on the grounds that the objectives had already been met by the previous study, said Dr. Prasert Thongcharoen, head of the AIDS vaccine subcommittee. Earlier this year, Trinity applied to the Thai FDA to have Remune licensed as a drug rather than a vaccine, but withdrew the application when approval appeared unlikely.

In Europe, Remune is moving towards a large-scale trial as a therapeutic vaccine used in conjunction with highly active antiretroviral therapy. In September, the Spanish Medication Agency (Agencia de Medicamento) submitted a written recommendation for a Phase III HAART-Remune trial to the European Agency for the Evaluation of Medicinal Products (EMEA). The recommendation drew on data from Eduardo Fernandez-Cruz (Gregario Maranon Hospital, Spain), some of which was presented at Barcelona (Abs. #ThOrA1482), showing that HIV-infected individuals treated with vaccine and HAART were 37% less likely to show viral loads exceeding 5,000 over a 30-month observation period than individuals receiving HAART alone.

Accelerating Development of Bioterrorism Vaccines

AN INTERVIEW WITH

Philip Russell

Since October 2001, Dr. Philip Russell has been a senior advisor in the US government's scaled-up program to stockpile vaccines against the most threatening bioterror agents, and to develop a new generation of safer, faster-working products. The program sits within a newly created Office of the Assistant Secretary for Public Health Emergency Preparedness in the Department of Health and Human Services (HHS).

Russell's career in vaccine development and infectious disease research spans over 40 years. An MD certified in internal medicine, he held leading positions at the Walter Reed Army Institute of Research in Rockville, Maryland and conducted medical research in Pakistan, Thailand and Vietnam. After retiring from the military in 1990 , Russell joined the faculty of the Johns Hopkins School of Hygiene and Public Health, and was named Professor Emeritus in 1997. He also served as special advisor to the Children's Vaccine Initiative from 1990-1994, was a founding member of the Albert B. Sabin Vaccine Foundation, and is now on IAVI's Board of Directors.

Here Russell speaks with IAVI Report editor Patricia Kahn about new vaccines in the pipeline, how the R&D is being fast-tracked—and what lessons this might offer the AIDS vaccine field.

What does your role as special advisor on vaccines entail?

My basic responsibility is to coordinate efforts of the public health service agencies in bringing the new vaccine products we need into the inventory, starting with smallpox and moving onto others.

One of the reasons for creating this office was that HHS did not have what in government parlance is called an 'acquisition mechanism.' HHS has never had a continuing program for research, development, stockpiling and use of vaccines. It's done all of the pieces, but one at a time. So there wasn't any process in place for defining requirements, contracting for research and development of a state-of-the art vaccine, purchasing the product, seeing to licensure and so forth. Those are the issues we're coordinating from this office, starting with the new smallpox vaccine.

What strategies are being used to make improved smallpox vaccines?

The first thing is that we're re-manufacturing the old vaccine in cell culture, under a contract with Acambis, a US-British company. [*Editor's note: Traditional smallpox vaccines contain live vaccinia virus harvested from the skin pustules of infected calves.*] That's not scientifically very novel, but it's a major step forward in terms of developing the production, purification and testing techniques for this vaccine. Over time, we will replace all old vaccine with this new product. It's the same virus in the vaccine, just a more efficient production and a much purer product.

But the big problem with the current vaccine is that it's dangerous for certain people [due to replication of the vaccine virus]. It's very dangerous for those with eczema, especially kids. It's dangerous, or even lethal, for seriously immuno-suppressed individuals—people with HIV, transplant recipients, those undergoing cancer chemotherapy. That's a substantial population.

So the next big task is to find a safer way to immunize than with the current vaccinia strain. The preferred short-term option is to use MVA [*modified vaccinia Ankara, a highly attenuated vaccinia strain*]. NIH is now soliciting proposals for potential contractors to develop and manufacture an MVA-based smallpox vaccine.

Why MVA?

There is 1970's data from Germany showing that intramuscular injection of MVA at high titer was a very good way of modifying subsequent immunization with standard vaccinia vaccine. So the idea is to rapidly develop an MVA strain as a first vaccination for people where vaccinia is contraindicated. If MVA works well, maybe it could even replace a follow-up vaccinia immunization. Both options—MVA and then vaccinia, or two doses of MVA—will be tested.

How can the efficacy of smallpox vaccines be tested, and what proof of efficacy will be required for licensure?

For this first Acambis vaccine, we don't a problem proving efficacy. All we have to do is prove that it gives the same types of clinical and serological responses as the current vaccine. The large-scale trials are merely safety trials.

But licensing the next generation of smallpox vaccines will test the FDA's new animal rule. According to this rule, if there's no ethical way to test a new vaccine in humans—for example when it's against an eradicated disease—we have to show that the vaccine produces similar immune responses in humans and an animal model, and then demonstrate that it induces protective immunity in this model.

Smallpox doesn't infect monkeys except in very high intravenous doses, so there isn't a good monkey model of variola [*the virus that causes smallpox*] But there is a closely related monkeypox virus, which produces a serious pox disease in monkeys.

There's also rabbitpox, camelpox—almost a pox virus for every animal. They are all orthopox viruses, a family of viruses closely related to smallpox.

The immune response to vaccinia is focused on structural proteins that are highly conserved between variola and the orthopox viruses, which is why Jennerian vaccination works. *[Jenner's original smallpox vaccine used cowpox.]* We also know that vaccinia protects against monkeypox, mousepox, rabbitpox and so on. So for licensing, we will test whether MVA can protect in these animal surrogates. And we'll need to show that the vaccine generates anti-variola neutralizing antibody. It's going to be difficult because we are breaking a lot of new ground here.

Will you also look for cellular immune responses, and with what assays?

We'll look for everything we can measure, but focus on the antibody response. Not because it's necessarily more important, but we know that if you don't get an antibody response, you're unlikely to have protective immunity. In terms of assays for measuring cellular immunity, we're going to lean on the HIV and cancer vaccine communities for guidance.

What's known about immune correlates of protection for smallpox?

Despite the huge amount of experience we've had using vaccinia-based vaccines to protect against variola, the exact correlates of immunity aren't well-understood. We know that both cellular and humoral components are important, and that immunization with vaccinia produces neutralizing antibody against both vaccinia and variola.

MVA is also being used as a vector for candidate vaccines against HIV and malaria. What would it mean for these efforts if there's a new MVA-based smallpox vaccine?

That's a very good question and I can't answer it. Widespread use of MVA, or any smallpox vaccination program, would seriously interfere with the use of these vectors for other vaccines. That's a significant worry. The whole issue of widespread vaccination against variola has to be factored into decision-making.

But the probability of widespread global vaccination with vaccinia or MVA is very low, especially in the developing world. So there's no justification at this point for changing course and not pursuing MVA-based vaccines for HIV and other diseases.

What about the US?

How widely we're going to vaccinate is still an open question.

Is it far-fetched to ask whether MVA could be used to make a vaccine against multiple diseases?

No. I think the work of NIH and its contractors on MVA will enhance knowledge of how this virus functions, both as an immunogen and as a vaccine platform. It may well be that a national strategy downstream is to include other antigens.

It usually takes some time after vaccination until protective immunity is established. Why is smallpox vaccine effective even when it's given shortly after exposure?

The data are pretty clear that vaccination within a few days of exposure to smallpox has a dramatic impact. It is a unique situation; maybe the only vaccine that works this way.

The pathogenesis of smallpox involves a long incubation period. Infection occurs by inhalation, which gives primary replication in the oral pharynx. Then there's a viremic spread that seeds the skin. During this period, the patient is asymptomatic. Finally there's viral replication in the skin, which produces the serious illness.

But the vaccine grows a lot faster—when vaccinia is injected into the skin, it immediately starts an infection. The cellular response begins very quickly, although antibody doesn't come up very fast.

There's also a lot of attention now on anthrax vaccines. What is being done?

NIH recently gave two contracts for the rapid development of a second-generation anthrax vaccine, which will be a recombinant vaccine against the so-called protective antigen of anthrax [*a protein that helps anthrax toxins enter cells*]. Antibody against this protein has been shown to be the dominant—perhaps the only—important factor in the current anthrax vaccine and the contracts went to VaxGen and to Avecia in the UK [see Industry Insider, p. 7].

A recombinant vaccine would be an important step forward, since it could be produced and highly purified on a large scale. And it would be a very safe vaccine, and easy to control quality.

How will it be tested for efficacy?

Again, through the animal rule. In this case, the animal models, especially the monkey, are very good.

What other new vaccines against potential bioterror agents are being developed?

There's been a very rapid surge in the bioterrorism business at NIAID.

For smallpox, MVA is a first attempt at a safer vaccine. I think it will probably succeed. But I don't know if it will be the final answer. There's obviously going to be more work on how to better protect against smallpox.

Then there's a whole set of vaccines that are less urgent for civilians, but are needed to protect laboratory workers and the military. We need a plague vaccine, a Rift Valley Fever vaccine, encephalitis virus vaccines. And I would assume that there'll be some serious efforts soon on what we used to call orphan vaccines.

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◀**INTERVIEW** *continued from 9*

Let's talk about vaccine supply and manufacture. We often hear that the vaccine market is much smaller than that for drugs. What are the financial incentives for industry to develop and mass-produce these new vaccines, especially with pressures to keep prices low?
Very simple. Money.

But isn't the profit for vaccines relatively low?
I can't answer that. I have no insight into what the profit margin is for Acambis, for example. But obviously they're business people. They made a bid, came in with a price, and it was acceptable to the government.

What got Acambis involved initially was a long-term contract that called for research and development first, then for an initial production and finally annual production of a certain amount for 20 years.

I suspect that a major incentive was that this is a virtually guaranteed market for a long time. In the second Acambis contract, I think the size of the order was enough of an incentive: 154 million doses.

So you're talking hundreds of millions of dollars. Somewhere in there is some profit—enough that companies bid on it. They were probably also betting on the fact that this would give them an entree into the international market.

"It all comes down to money...If you have enough to guarantee a large first buy, then you can provide the incentive for a company to move fast."

Do you think that advance purchase commitments like these would also be an incentive for AIDS vaccine developers?
Yes. For anthrax, and for all the accelerated development programs, we're including promises of a substantial initial purchase. So even if there's more than one company involved, the companies are assured of at least a certain size market. To the extent that they see it as big enough to justify their opportunity costs, they've bitten.

Is there enough existing capacity to produce the new vaccines we need, or will more need to be built?
Some of both. We're taking maximum advantage of existing capacity but also building new capability, especially where there's new technology. The smallpox vaccine from Acambis and its partner, Baxter International, is a mixture. The bulk manufacturing took advantage of an existing plant that makes flu vaccine, but had a down period. So it was available to produce the bulk of the Acambis smallpox vaccine.

On the other hand, for later manufacture using a new process, Acambis has to either build or renovate a plant.

There are now serious shortages of certain basic childhood vaccines for the developing world. Will the new production demands for smallpox and anthrax vaccines make this worse?
I don't think so. The short supplies of existing childhood vaccines has a mixture of causes. Some of it is capacity. Some is regulatory, and the economic requirements to meet more stringent regulatory standards.

As far as we can tell, we've avoided any impact on basic vaccines. The only one that came close was that we had to work around Wyeth's influenza manufacturing capacity to process the stored material for the Wyeth DryVax**.** But we were able to work around this.

How does Acambis have enough capacity to produce hundreds of millions of doses of a new smallpox vaccine?
Partly by teaming up with Baxter, and partly because they were a startup vaccine company. They've been working on several vaccines, so they had internal capability and purchased manufacturing capacity. Some of the work, for example bottling, lyophylizing and labeling, is being subcontracted.

How is liability being handled in these large contracts?
With great difficulty. It's a complex issue and frankly, one I've left to the lawyers.

Acambis was able to get insurance to cover liability for the first parts of its contract. But the issue shifts when you get into large-scale vaccination, and that's where the government will have to provide some liability protection.

Are there any plans for speeding up FDA review?
For these high priority projects, the FDA has made special efforts to manage the review and regulatory aspects very rapidly. They are having frequent meetings with the companies and scheduling the submissions. So when the submissions come in, the FDA is immediately poised to respond.

They have also been incredibly responsive on manufacturing issues. There are none of the usual delays—bioterrorism issues jump the queue. The process is just as complete, but it's a lot faster.

What else is being done to move things more quickly?
A lot of things we're doing to compress the timeline involve enormous risk-taking. Acambis and Baxter manufactured maybe 200 million doses of bulk vaccine before submitting the initial file, and before there was any clinical data. No company in the world would take that risk under ordinary circumstances. Normally they don't do large-scale manufacturing until they've had lots more experience, and more feedback from the FDA.

But we've had to start doing things based on what we predict will happen. We now have between 25 and 30 million doses, bottled and lyophilized, of Acambis smallpox vaccine, even though the first clinical trial doesn't start until about mid-October.

Ugandan Parliamentarians Gather for Vaccine Summit

BY EMILY BASS

On 12-13 August, 2002, a Policymakers Conference on HIV/AIDS and AIDS Vaccine Initiatives was held in Kampala, Uganda. Attended by 180 Ugandan MPs, 3 Kenyan MPs, along with religious leaders, scientists and NGO representatives, the meeting was organized by a working group led by the Ugandan AIDS Commission (UAC) and funded by IAVI. The two-day meeting featured talks from Professor Edward Rugomayo, Minister of Trade and Industry (on behalf of President Yoweri Museveni), Minister for Ethics and Integrity Miriam Matembe, (on behalf of the Minister of the Presidency), Gilbert Bukenya, Minister of Health Brigadier Jim Muhwezi, and John Rwomushana, Director of Research and Policy Development at the Ugandan AIDS Commission. IAVI speakers included CEO Seth Berkley and Vaccine Preparedness Vice President Balla Silla.

The meeting was designed to raise MPs' awareness of the status of HIV/AIDS and HIV vaccine development; to mobilize MPs to join in advocacy and outreach efforts aimed at enhancing regional collaboration around vaccine trials; and to advocate for AIDS vaccines on the global stage.

At present, an estimated 1.1 million Ugandans are living with HIV, a prevalence of roughly 5%, according to the most recent UN estimates. Often singled out for its successes in addressing AIDS, Uganda needs continued, innovative action, said Minister of Health Brigadier Jim Muhwezi, who estimated that 120,000 of HIV-infected Ugandans were in symptomatic stages of disease, requiring additional care and support. He placed particular emphasis on the provision of antiretroviral therapies, which will be purchased using a US$9 million grant from the Global Fund to Fight AIDS Tuberculosis and Malaria.

The speech read on behalf of President Museveni also emphasized the need for new efforts."Whereas Uganda has made commendable progress in combating the epidemic," Museveni wrote, "the remaining challenges for the country are still grave and urgent." These include the rising rate of new infections among some populations over the past year and a recognition that, without treatment, it is difficult if not impossible to control the epidemic. "ARV treatment is an achievement that we must consolidate as we search for lasting solutions. There is no doubt at all that the ultimate weapon against AIDS is a preventive vaccine.,"

Professor Roy Mugerwa (Makerere University) provided a brief history of the ALVAC trial (Africa's first AIDS vaccine trial, a Phase I study of a subtype B-based canarypox candidate), noting that, "From the start, we knew that this trial was only the beginning." Pontiano Kaleebu of the Uganda Virus Research Institute (UVRI) spoke about the trial and revisited Uganda's decision to test a non-clade matched vaccine—a choice made in 1999, at a time when it was "unclear" when clade A and D based vaccine candidates would be available for testing on Africa. The decision-makers also saw the trial—which was primarily focused on determining vaccine safety—as a step towards understanding the importance of clade in vaccine design.

There are now several candidates entering early phase trials the East African region, as summarized by Kaleebu. The Walter Reed Army Institute of Research has a collaborative project with Makerere University and the Rakai Project; the Joint Clinical Research Center, site of the ALVAC trial, is working with the Italian National Institute of Health to plan for Phase I and II trials of a *tat*-based vaccine. Also in the preclinical pipeline: A clade A vaccine based on virus-like particles produced in a baculovirus expression system, under development by the Naples Viral Oncology Institute and UVRI. In September, an IAVI-sponsored trial of a clade A DNA-MVA vaccine strategy received final approval. Immunizations are set to begin at UVRI before the end of 2002.

Balla Silla's speech emphasized the need for policymakers to facilitate vaccine testing and delivery through financial and political support, and public education. These goals were reflected in the meeting's outcomes, which included accelerated plans for the creation of a Permanent Standing Committee on HIV/AIDS in the Ugandan Parliament, and the creation of a Parliamentarian Declaration similar to that signed at IAVI's Parliamentarian Meeting in Delhi, India in May. Participants suggested other potential action steps, such as launching a pilot project to deliver an already-licensed vaccine to adults; developing linkages with other parliaments in East Africa and around the world; and supporting creation of simplified educational materials on vaccines and vaccine trials. ◆

In this case it wasn't an inordinate risk. From the preclinical data, this looks just like the old vaccines. And the seed viruses were derived from the Wyeth vaccine, so there's a high level of virologic confidence that allows us to take that risk. Nonetheless, from a regulatory and manufacturing point of view, it's a very high-risk business.

It's striking how many ways there are to accelerate vaccine development when there's enough push. Do you think some of this will spill over onto AIDS vaccines?

I hope we've learned things that are generalizable in terms of driving programs faster. It all comes down to money in the end. If you have enough to guarantee a large first buy, then you can provide the incentive for a company to move fast. And if the developer is willing to accept risk, there are ways of short-cutting the usual process—for example, manufacturing at risk, as we've done, and doing things in parallel rather than serially.

The huge question with an HIV vaccine is how much risk to take before you have solid information on efficacy. When do you invest in scaling up and manufacture?

Actually there are two risks. One is if you do a Phase III trial, prove efficacy and then it takes two years to scale up and manufacture. That's a terrible scenario. The other risk is that you manufacture the vaccine but the Phase III trial bombs, so you've blown a lot of money. ◆

IMMUNOGENICITY ASSAY STANDARDIZATION EFFORTS UNDERWAY

By Emily Bass

This year saw the launch of three separate projects designed to ease comparison of results from vaccine trials by standardizing aspects of assays that measure cellular immune responses (Elispot and intracellular cytokine, or ICC) and neutralizing antibodies. It's a step that many feel is critical for the vaccine field to move forward. "As soon as possible, we need to get a handle on comparing the types of assays used so that the different groups doing clinical trials can get a sense of how vaccines compare with one another," said John Shiver of Merck Research Labs at the IAVI-organized vaccine satellite meeting in Barcelona.

Elispot

Elispot assays are currently the most widely used measure of vaccine-induced cellular immune responses. The assay measures the number of T-cells activated by a specific antigen. Following antigen exposure, responding cells are detected by staining for secreted (extracellular) cytokines —signaling molecules that are markers of activation. These cells are tallied by computerized "spot-counting" machines.

Patricia D'Souza (National Institute of Allergy and Infectious Diseases; NIAID), coordinator of the Elispot standardization exercise, says that she was spurred to action during analysis of data from HVTN 203, a Phase II canarypox vaccine trial. "Data using the same samples and the same assays from the Duke and Seattle labs were different," she recalls. "If two dominant labs in the first world can't get the same data, then what's happening in the rest of the world?"

To address this problem, D'Souza and colleagues Jo Cox (NIAID), Guido Ferrari (Duke University, Durham) and Spyros Kalams (Partners AIDS Research Center, Boston) set up a study involving 11 labs (see table below) to identify and eventually reduce sources of variation in Elispot data. Each lab received a standardized panel of peptides and other reagents, and carried out the assays on 11 different cell samples according to their own lab protocol.

Along with their own counts, labs returned their Elispot plates, which were sent to contractors for independent counting. Results will be discussed at a meeting in Washington, DC in late November (see www.niaid.nih.gov/daids/vaccine/news.htm), where predictable sources of variation (i.e., those between spot-counting machines) will be identified, along with less predictable sources of fluctuation. "It's too early to tell whether we need to focus on the assay itself, on [training for] a particular technician, or suggesting optimum parameters for Elispot readers," says D'Souza, stressing that this exercise is a first step towards standardization.

Intracelluar Cytokine Assays

In a related effort, Pierre-Rafick Sekaly, Program Leader and Scientific Director at CANVAC (Montreal), together with Jill Gilmour (IAVI) is coordinating a multi-lab comparison of ICC assays. ICC is a newer assay than Elispot and also measures cytokine production in response to a specific antigen. In this case, cytokines are detected inside (rather than outside) cells using fluorescently-labelled, cytokine-binding antibodies. Fluorescing cells are then counted using flow cytometry. The technique can be used to stain multiple markers, and therefore to define more precisely the population of activated cells (e.g., CD4 or CD8). All labs participating in this exercise will assay the same samples using the same peptides, antibodies and data-analysis software from Becton-Dickenson, the company which invented the flow cytometer.

The exercise, scheduled to begin before the end of 2002,

ELISPOT

Participants

CANVAC
HIV Vaccine Trials Network (3 sites)
Walter Reed Army Institute for Research
AIDS Clinical Trials Group
EuroVac
National Institute of Communicable Diseases (South Africa)
IAVI
Vaccine Research Center
US Centers for Disease Control

ICC

Participants

HVTN
CANVAC
EuroVac
IAVI
National Institute of Communicable Diseases (South Africa)

NEUTRALIZATION

Participants

John Mascola, Vaccine Research Center, Bethesda
David Montefiori, Duke University, Durham
Christianne Moog, Institute of Virology, Strasbourg, France
Christos Petropoulos, Virologic, San Francisco
George Shaw, University of Alabama, Birmingham

Viral Isolates

Clade	Strain	Related Co./Research Group
B	Bal-Ab1	VRC
B	SF-162	Chiron
B	Bx08	EuroVac
B	W61D	GlaxoSmithKline
B	ADA	Harriet Robinson (Emory University) & Bernie Moss (NIH)
C	Du151	AlphaVax
C	TV1	Chiron
E	CM244	VaxGen

Other

Monoclonal Antibodies: 2g12, IgG1B12, 2F5, 4E10

will compare data from fresh, fixed and frozen samples at different time intervals following stimulation. These results and their implications for assay standardization will be discussed at the May 2003 HVTN meeting.

Neutralization Assays

Coordinated by David Montefiori (Duke University, Durham), the neutralizing antibody assay comparison involves five laboratories and an extensive panel of reagents, including eight primary isolates of HIV that have all been used as the basis for vaccines now in development (see table).

Neutralizing antibody assays provide a measure of whether an antibody or serum sample blocks HIV entry into human T-cells. This is done by incubating virus with antibody for a set time, adding cells, incubating the mixture to allow for several rounds of viral replication and then measuring the amount of virus present, usually as a function of viral antigen expression. The traditional assay does this in peripheral blood mononuclear cells (PBMC) by collecting the cell culture supernatant and testing for p24 (viral core protein) secreted from the infected PBMCs.

The collaboration will test this technique against three newer assays. One, developed by John Mascola (Vaccine Research Center, Bethesda), is a straightforward variation of the traditional PBMC assay, using antiretroviral agents to stop viral replication after a single round. These cells are then enumerated by staining intracellular p24 and analyzed by using flow cytometry. In a paper comparing this assay with the traditional PBMC assay (*J. Virol* 76:4810;2000), Mascola found these two assays offered highly similar results.

The two other approaches to be analyzed make use of "reporter" genes that luminesce when expressed, allowing quantification by a luminometer. One version of this assay, developed by Chris Petropoulos and colleagues (Virologic, San Francisco), builds luciferase (a firefly enzyme) into an *env*-deleted HIV DNA construct. Target cells are co-transfected with this and an *env*-containing DNA construct, producing infectious virus particles that cannot produce new, functioning virus. Instead, replication stops after a single cycle, and infected cells, which luminesce, are counted. George Shaw (University of Alabama) uses a similar approach, in which the luciferase gene is incorporated into a target cell line.

Assays such as these may produce different results than traditional methods, says Montefiori, because engineered viral particles and/or cell lines change the type of cell-surface proteins contained in the coating of new virions—which, in turn, may influence the type and magnitude of neutralization detected. The standardization exercise will provide important information on how to compare the results of assays that use virus grown and assayed in PBMCs, with those done with cloned viruses made and assayed in cell lines.

But the luciferase assays offer several technical advantages, says Montefiori. They are faster and [at least for those using luciferase-expressing cells] easier to perform than PBMC assays. They offer a five-fold reduction in cost compared to traditional PBMC assays. Montefiori says that understanding how luciferase and PBMC assays compare will help increase capacity for neutralization assays around the world. "It's hard to get PBMC assays up and running at resource-poor international sites. Luciferase in cell lines will be much more portable." Results from the exercise will be presented in mid-2003. ◆

◀ **UNDERSTANDING VACCINE DEMAND** *continued from 2*

counter-intuitive at first glance. Roy Anderson and colleagues at Imperial College (London) have created models which suggest that targeting high-risk individuals is not always the best use of low-efficacy vaccines. In an early epidemic, a targeted strategy may contain HIV spread. However, in a mature epidemic, many people from high-risk groups will already be infected by the time a vaccine program reached them. In this case, a universal immunization strategy would be more effective.

What Industry Needs

Need and demand estimates are also crucial to private sector decision-making about advancing products from the laboratory to clinical trials and then to the marketplace. At early stages, trial planners rely on models that help set the minimum efficacy threshold a trial should be powered to detect. Then, as products move into trials, questions about demand come to the fore. How many of the countries that need vaccine will be able to deliver it, and how many doses will they need? Perhaps the most important question: Is there sufficient manufacturing capacity and technology to meet global demand?

Building industrial capacity for vaccine production typically requires four to five years lead-time, hundreds of millions of dollars and extensive regulatory oversight. Making matters worse, decisions about building production plants must be made before the results of Phase III trials are known (as VaxGen has done) if major delays between licensing and wide-scale availability are to be avoided. To help hedge its bets, VaxGen has designed its new manufacturing facilities (in Seoul, South Korea, and San Francisco, USA) to be multi-

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◀ **UNDERSTANDING VACCINE DEMAND** *continued from 13*

purpose, suitable for producing a range of human therapeutic proteins.

None of this is new terrain for pharmaceutical giants like Merck and GlaxoSmithKline. "Industry always does a lot of marketing projection and demand work for its own purposes, but this information is usually regarded as commercially sensitive and not publicly available," says Saul Walker, IAVI's European Policy Coordinator. But since vaccines, including AIDS vaccines, are needed most in countries with little ability to pay, public sector groups also need information on demand, both to encourage investment in vaccine development and to inform plans for delivery infrastructure and financing mechanisms.

Increasing Infrastructure

While making, purchasing and bringing vaccines to developing countries is a daunting task, many experts say that the real challenges start at the airport, after the vials have been unloaded for distribution throughout the country. It's here that the issue of uptake—demand with a reality check—comes into play. Are there sufficient refrigerators, trucks, syringes and syringe disposal facilities for the vaccine dispensaries? Are there trained

Existing AIDS Vaccine Demand and Related Studies in the Public Domain*

(published 2000 or later)

PUBLIC SECTOR DEMAND

Bishai, D. *et al.* **Algorithms for the Purchase of an AIDS Vaccine** *Working Paper #2321* (2000) from the World Bank Health and Population, Fertility and HIV/AIDS Working Group available at: http://econ.worldbank.org/docs/1072.pdf

Two mathematical models of decision-making on purchase of hypothetical vaccine: one employing health sector priorities (minimizing government health spending on HIV/AIDS); and one based on societal priorities (minimizing impact of HIV/AIDS on health spending and GDP

Bishai, D. *et al.* **Modeling the Economic Benefits of an AIDS Vaccine** *Vaccine* 20:526;2001

Global demand estimates based on cost-benefit analyses

Esparza J. *et al.* **Global and Regional Estimates of Need and Probable Uptake for HIV/AIDS Preventive Vaccines**. *Vaccine* 2002 (in press)

Regional experts indicate likely policies for use, which are translated into aggregated public health needs for vaccine. Estimates made for vaccines of low and high efficacy

Tangcharoensathien, V. *et al.* **The Potential Demand for an AIDS Vaccine in Thailand**, *Health Policy* 57:111;2001

Demand estimates based on targeted delivery to 8 risk groups, calculating cost/savings per HIV infection averted

INDIVIDUAL WILLINGNESS TO PAY

Suraratdecha, C. *et al.* **The Demand for an HIV/AIDS Vaccine: Does Risk Matter?** PowerPoint Presentation from 14th International AIDS Conference, Barcelona 2002 available at: http://www.iaen.org/ files.cgi/7420_chutima.pdf.

Estimates of individual (high risk groups and general population) willingness to pay for vaccines with 50 or 95 percent efficacy

Whittington, *et al.* **Private Demand for an HIV/AIDS Vaccine: Evidence from Guadelejara, Mexico** *Vaccine* 20:2585;2002

Private demand estimates based on willingness of individuals to pay for AIDS vaccines

IMPACT STUDIES

Bogard, E. *et al.* **The Impact of a Partially Effective HIV Vaccine on a Population of Intravenous Drug Users in Bangkok, Thailand: A Dynamic Model** *JAIDS* 29:132;2002

Models impact (on 40 year prevalence rates) of 30, 75, and 90 percent efficacious vaccines in a cohort of Thai IV drug-users

Longini, I., *et al.* **Model-based Estimation of Vaccine Effect from Community Vaccine Trials** *Stat Med* 21:481;2002

Estimates of epidemiological and economic impact of intervention based on a "Thailand-like" situation

Stover, J., *et al.* **The Epidemiological Impact of an HIV/AIDS Vaccine in Developing Countries** (2002) *Working Paper #281* from the World Bank Development Research Group available at: http://www.policyproject.com/pubs/countryreports/Vaccine_World_Bank_article.pdf

Three models for impact of partially-effective vaccines based on epidemiological data from rural Zimbabwe, Kampala, Uganda, and Bangkok, Thailand

OTHER

Miller, M. *et al.* **A Model to Estimate the Probability of hepatitis B- and Haemophilis influenzae Type b-Vaccine Uptake into National Vaccination Programs** *Vaccine* 18 2223;2000

Analysis of determining factors in countries' decision to include two new vaccines in existing childhood immunization programs

Watts, C. *et al.* **The Public Health Impact of Microbicides: Model Projections** Powerpoint presentation (and other documents and tools related to prevention, treatment and microbicide impact) available at http://www.hivtools.lshtm.ac.uk/

Model of impact of partially effective microbicides

**Compiled by Tom Nassim (IAVI consultant), Yvette Madrid (IAVI consultant) and Saul Walker (European Policy Coordinator, IAVI).*

personnel at these dispensaries? Is there capacity for community outreach and for follow-up to individuals who do not complete their immunization course? In short, is the necessary infrastructure in place? If the answer is no, then it will not matter whether a country has an explosive epidemic or an early one that could be stopped with a relatively small-scale immunization campaign. Without infrastructure, there is an unbridgeable chasm between need and demand.

Given the singular level of global advocacy around AIDS, stakeholders may be able to mobilize for improved infrastructure and the funds to build it. But to succeed, they must figure out what delivery infrastructure is needed for vaccines with different properties so that steps to build it can begin early; just as with manufacturing capacity, delivery capacity cannot be built overnight once a vaccine is licensed.

Even countries that seem prepared for delivery may need extra support. This is one lesson GAVI learned in 2000 when it adopted DTP coverage (defined as a full, three-dose cycle of diptheria, tetanus and pertussis vaccine given to children under age one) as its indicator of whether a country has adequate infrastructure to qualify for funding. Two years later, preliminary results reveal a patchy infrastructure in many countries, with cold chains, safe syringe disposal, and trained personnel lacking. GAVI has since opened a new funding "window" to improve delivery infrastructure.

The GAVI experience gives some sense of the road ahead—but it could be an even bumpier ride for AIDS vaccines, which cannot rely on DTP coverage (which reflects the ability to deliver vaccines to infants) as the sole "proxy" for estimating capacity. Instead, new infrastructure surrogates for AIDS vaccines will have to be developed under different sets of assumptions about vaccine properties and use, such as whether they need refrigeration, the number and route of immunizations, and the population the vaccine is approved for—which is likely to be an adult population, at least initially. Proxies will also depend on who among the adult population is being targeted for vaccination.

Miller says that voluntary counseling and testing sites may be a reasonable proxy for AIDS vaccines, and that, by expanding these services, countries can lay the groundwork for eventual delivery.

But even with a healthy infrastructure and stacks of impact studies, the best laid plans will still go awry if people refuse immunizations, or do not come forward. This could happen for many reasons, including rumors and misinformation, mistrust of the medical establishment or the vaccine itself. Stigma could also play a role—especially in immunization campaigns targeting high-risk groups.

The world learned this lesson with hepatitis B vaccine. When it was licensed, experts recommended universal infant immunization in some areas, and targeted immunization of high-risk groups in others. However, stigmatization of the disease (and, by extension, its vaccine) led to low numbers of high-risk people coming forward to be vaccinated, so the targeted strategy was abandoned in favor of universal infant immunization. Similarly, uptake of treatments that reduce mother-to-child transmission of HIV has been lower than expected in some areas of the developing world, in part because many women are reluctant to learn their HIV status or discuss it with their partners.

Future Actions

The good news is that the demand "elephant" is beginning to get more attention from a variety of perspectives. With the imminent announcement of VaxGen's trial results, the WHO-UNAIDS Vaccine Programme is holding a meeting (20-21 November) on the potential uses of partially-effective vaccines and the specific questions that could be raised by the VaxGen data. José Esparza and Mark Miller have also mapped out a comprehensive set of actions addressing facts of demand that will be pursued in the coming years.

At IAVI, a new Demand Project will help fill in some of the gaps by collecting background data to inform detailed projections of need and demand. This includes infrastructure needs for delivering health commodities to adults, and in-country approval processes for new products licensed by global agencies. The project will also support further modeling work and analyses of factors influencing decisions on vaccine use.

But estimating demand is an evolving task that won't end when the field has completed this (or any other) set of studies, or derived a particular set of numbers; rather, it will continue to shift along with the epidemic and the world's response to it. Forward-looking studies are also needed to track the impact of more widely available antiretroviral treatment on the capacity to deliver AIDS vaccines.

One such analysis is an ongoing project at Johns Hopkins and the Rakai Project (Uganda) that uses epidemiological data from Rakai to explore the potential impact of vaccine and treatment strategies on HIV prevalence. Increases in access to antiretrovirals (ARVs) should not be seen as reducing the need for an AIDS vaccine, says Mark Miller. Instead, the two may work in tandem, with ARVs increasing countries' interest in vaccines by setting a precedent for spending on more complex, costly interventions. "If major treatment options are implemented, this will only make prevention with an effective vaccine more valuable," he says. ◆

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IAVI Report

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IAVI is a scientific organization founded in 1996 whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI focuses on four key areas: accelerating scientific progress; education and advocacy; ensuring vaccine access and creating a more supportive environment for industrial involvement in HIV vaccine development.

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vaccine BRIEFS

NEW REPORT ON AIDS AS SECURITY THREAT

Unchecked spread of the AIDS epidemic in five countries could have grave destabilizing effects with global consequences, said a September report produced by the National Intelligence Council (NIC), a panel of experts that advises the Central Intelligence Agency and other US government agencies. The report focused on China, India, Nigeria, Ethiopia, and Russia, which are in relatively early stages of the epidemic, and projected that they could cumulatively have 50-75 million HIV-infected people by 2010, at which time the NIC predicts 100 million infections worldwide.

The paper has received particular attention because its projections exceed other published estimates. UNAIDS does not provide projections for individual countries, but has released a global estimate of 60 million by 2010. One reason for the discrepancy is the difficulty of predicting the course of early epidemics, when infections are still concentrated in high-risk populations. The NIC projections are based on "worst-case scenarios" in which the epidemic spreads into the general population. UNAIDS is currently providing countries with training in projection methodology, and these forecasts may be included in future UNAIDS reports.

GLOBAL FUND BOARD MEETS AS DIFFICULTIES MOUNT

The third board meeting of the Global Fund to fight AIDS Tuberculosis and Malaria (10-11 October) began with Fund Director Richard Feachem warning that, without new resources, the Fund will be bankrupt by 2003. The Fund currently has approximately US$2 billion in pledges, with $500 million in hand; the first round of grants (made in April 2002) exceeds $600 million. According to Feachem, the Fund has received grants "worthy of funding" in excess of $8 billion.

The Fund drew criticism from some quarters for its announcement that it will scale back to two grant cycles per year instead of three, with the next round scheduled for early 2003. However, the Board's decision to support the use of high-quality generic drugs was cheered by AIDS activists and advocates as a significant step towards increasing access to affordable antiretrovirals in resource-poor settings.

US FDA ISSUES FIRST OFFICIAL GUIDANCE ON PREGNANCY REGISTRIES

In September, the US Food and Drug Administration (FDA) issued its first official guidance document on pregnancy exposure registries that would gather information on women who become pregnant during clinical trials. Most pharmaceuticals, including vaccines, are licensed with little information about effects on pregnant women or fetuses, since pregnant women are generally excluded from trials or dropped if pregnancy occurs. The guidance recommends registries in several situations, including when "inadvertent exposures to the medical product in pregnancy are or are expected to be common, such as when products have a high likelihood of use by women of childbearing age"—a likely scenario for AIDS vaccines. The guidance states that the FDA (whose decisions influence those in many developing countries) may ask for pregnancy exposure registry as part of Phase IV post-marketing studies. The complete guidelines are available online at www.fda.gov/cber/gdlns/pregexp.htm

UNITED NATIONS UPDATES GUIDELINES ON HIV/AIDS AND HUMAN RIGHTS

In September, 2002, the United Nations issued revisions which ensconce the right to treatment for HIV/AIDS in the International Guidelines on HIV/AIDS and Human Rights. Created in 1998 by the Office of the High Commissioner for Human Rights and UNAIDS, the guidelines are not legally binding, but can be used as a "cudgel" by groups and individuals seeking to spur governments into stronger action, says Chris Beyrer of the Johns Hopkins School of Public Health.

The new Guideline 6 makes an unprecedented call for specific actions from governments, including the creation of concrete national plans with timelines for progressing to universal, equitable access to HIV/AIDS-related treatment, care and support. Commentary accompanying the guidelines lists antiretrovirals, medications for opportunistic infections, condoms, clean syringes, vaccines and microbicides (when approved) among those commodities that governments must commit to providing. Beyrer says that the new guidance puts the needle exchange policies of many governments—including that of the US—in a new light. "What this means is that a federal ban on needle exchange is in violation of human rights principles," he says. The International Guidelines can be found at www.unaids.org/ publications/documents/human/HIVAIDS HumanRights_Guideline6.pdf

PHASE I DNA VACCINE TRIAL TO LAUNCH IN LATE 2002

By the end of 2002, a Phase I trial (HVTN 045) will begin the process of clinically evaluating a DNA/MVA prime-boost strategy developed by Harriet Robinson (Emory University, Atlanta). HVTN 045 will test the DNA vaccine (which contains the *gag*, *pol*, *env*, *vpu*, *tat* and *rev* genes from HIV-1 subtype B) in 30 volunteers at three domestic sites of the US HIV Vaccine Trials Network. Volunteers will receive two injections (days 0,56) with either 0.3 or 3 mg DNA. The MVA vaccine will be tested separately in HVTN 046. Depending on the timing of the second trial, says Robinson, the prime-boost combination will be tested either by boosting consenting participants of HVTN 045 with MVA or through a new DNA/MVA trial.

Robinson's vaccine has been shown to protect monkeys against challenge with SHIV89.6P (see *IAVI Report* Oct-Dec 2001, p.13), with 23 protected monkeys still healthy and maintaining low or undetectable viremia for over two years. Future plans include development of clade C and A versions of this vaccine, as well as an ABC "multiclade" version.

DNA-MVA TRIALS APPROVED IN KENYA

Kenyan regulatory authorities approved two Phase I trials that will advance the DNA-MVA prime-boost strategy developed by a collaboration among Oxford University, the University of Nairobi and IAVI. The two trials—one with MVA alone, the other using a DNA-MVA prime-boost protocol, will gather information about optimal dosing, immunization route and schedule. The trials will enroll 70 people and are expected to begin before the end of 2002.