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VAX is a monthly bulletin featuring shorter versions of articles from the IAVI Report, a newsletter on vaccine research published by the International AIDS Vaccine Initiative. VAX is available as an e-newsletter, and a downloadable PDF. A VAX template is also available for groups that would like to produce their own editions, combining VAX articles with local content. For more information, email vax@iavi.org

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RESEARCH & TRIALS

◆ VaxGen: Are There Hints of Race-Based Effects?

In February 2003, AIDS vaccines hit the headlines when VaxGen, a California-based company, announced the final results from the world's first Phase III trial of an AIDS vaccine. The study tested a candidate called AIDS-VAX® B/B, which contains part of the outer coat (envelope) protein of HIV. The vaccine was tested in the United States, Canada and Europe in roughly 5,500 volunteers. 95% of the volunteers were men who have sex with men, and the remainder were high-risk women.

The trial was designed to find out whether AIDS-VAX® could either prevent HIV infection or reduce the severity of disease in people who were vaccinated and went on to acquire HIV through sexual exposure. VaxGen scientists reported that, overall, AIDS-VAX® did not provide either type of protection: Volunteers who received the vaccine were just as likely to become infected as those who received a placebo (see Glossary, below). And vaccinated participants who later became infected had similar CD4 cell counts and viral load levels as infected volunteers in the placebo group.

But VaxGen also made the startling and highly controversial claim that, when they subdivided the volunteers by race, the vaccine protected 2/3 of the African-American, Asian and mixed-race volunteers.

This finding was instantly challenged when statisticians pointed out a key flaw in the data analysis. The flaw hinged on the fact that, like most clinical studies, the AIDS-VAX® trial was designed to answer a scientific question based on data from all the volunteers. (A certain number of volunteers is needed to be sure that an observed effect is real and not just a coincidence.) When statisticians single out specific subgroups, they adjust their analyses to make it more likely that they will be able to identify a real finding.

VaxGen apparently did not make this adjustment. The small number of minority volunteers (less than 500 total) also made it difficult to draw firm conclusions, since there were only a handful of infections in the entire group.

Scientists and advocacy groups have also questioned the company's justification for the pooling of data from different non-white racial groups, since these groups are not known to share common genetic features or immune markers. VaxGen did not look for this type of data initially. However, the company does have a repository of stored blood samples from volunteers which could be studied further.

Since the initial announcement there has been a great deal of debate and discussion about these results. At the same time, VaxGen has attempted to find biological data that support or explain its claim of race-based differences in protection. Simply put, at this point there is no good evidence for the claim, nor is there enough data to be absolutely sure that it can be dismissed.

This dilemma prompted the US National Institutes of Health to give VaxGen technical and financial support for further data analysis. VaxGen had said that it did not have enough money to fund extensive analyses of the data.

At press time, the follow-up analysis was focused on two areas: the levels of antibodies induced by the vaccine in volunteers of different races, and the precise strains of HIV seen in infected volunteers of different races. Another open question is whether there were gender-based trends in protection. The data suggested a possible increase in rates of protection among women, compared to men. However, with only 309 women enrolled, there were not enough data to yield answers by traditional statistical analysis.

More data on AIDS-VAX® will come from a second Phase III trial in 2,500 intravenous drug users in Thailand that will be completed in late 2003.

In the meantime, vaccine developers are emphasizing the need for future Phase III trials of other vaccines to enroll sufficient numbers of different



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ethnic groups, and both genders, so that if trends towards race- or gender-based effects appear for other candidates, they will be easier to detect. When Phase III trials of other candidates take place in Africa and Asia, they will provide important information about whether there are differences in vaccine-induced responses within broad racial categories.

Antibodies: Immune defense proteins which block virus, bacteria and microorganisms that are “free” in the blood, and have not infected any of the body’s cells.

Placebo: an inactive substance given to some study participants, while others receive the test substance (e.g., a vaccine or a drug). Placebos provide a more accurate basis for evaluating the activity of the test substance.

■ **For more information:**

International AIDS Vaccine Initiative
www.iavi.org
AIDS Vaccine Advocacy Coalition
www.avac.org

◆ **VaxGen Trial Social and Behavioral Data**

When a scientific trial ends with the experimental product proving to be ineffective, it is easy to say that the trial was a failure. This was one of the responses to the news that the world’s first Phase III vaccine trial, which tested AIDS VAX®, showed no protection overall (for more on scientific data, see above). But this is not the whole story: at least some success can be measured in how a trial was conducted; how many volunteers remained through the end of the study; and how volunteers’ behaviors and beliefs were affected by the trial. Here, the AIDS VAX® trial provided some good news, and some interesting lessons.

Before the trial began, many scientists doubted whether enough high-risk volunteers could be recruited at North American and European clinical study sites to establish a trial population, also called a **cohort**, with sufficiently high infection rates (**incidence**) and stability to meet the trial requirements. The trial followed volunteers for three years, and called for 7 immunizations.

But both the incidence and retention rates for the trial proved these fears unfounded. The trial enrolled over 5,100

men and 309 women. At the end of the 3 year study, VaxGen reported an incidence of 2.7% in men and 0.8% in women. The company also reported a retention rate of over 80%, a figure which is considered a success for a trial occurring over such an extended time period. These retention rates are particularly striking in the trial’s high-risk women, most of whom live marginalized lives: the majority are poor, use drugs, exchange sex for shelter or money, and have unstable housing situations. During the study, many were also arrested and spent time in prisons and jails. Against this stark backdrop, the women and the trial site staff established durable, trusting relationships, reflected in the over 80% retention rates.

Another early concern was that trial participation would dramatically change volunteers’ frequency of risk behavior. On the one hand, participants might assume that the vaccine is protective and therefore increase their risk behaviors. On the other hand, the risk reduction counseling that volunteers receive at each study visit might lead to greatly reduced rates of risk behaviors, which could lower HIV incidence to the point where it becomes impossible to get a scientifically reliable answer on the vaccine’s ability to protect.

In the end, neither of these scenarios came to pass. Three years after enrolling in the trial, men and women reported rates of high-risk behavior that were at or just below those reported at the beginning of the trial.

These were overall data. There were other studies asking more specific questions, such as whether volunteers’ beliefs about whether they received the vaccine or placebo affected risk behavior. The trial was blinded, meaning that neither volunteers nor staff actually knew who received the vaccine or the placebo. In spite of this, volunteers made assumptions about what they had received. Researchers at the U.S. Centers for Disease Control and Prevention (CDC) found that these assumptions changed rates of risk behavior.

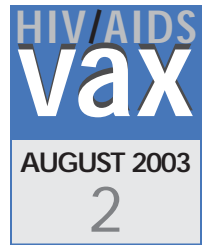
The CDC team grouped volunteers by whether they believed they had received the vaccine, the placebo or had no fixed idea about what they received. For the men who have sex with men, volunteers who thought they

had received the vaccine reported consistently higher rates of unprotected anal intercourse than men who believed they had received the placebo or did not know. In contrast, at the 12 and 24 month visits, women who thought they had received the placebo had higher rates of risk behavior than those who thought they were given vaccine.

So despite the trial’s overall successes with recruitment and retention, there are areas for improvement in future studies. Even when trial staff repeatedly explained that the vaccine was experimental and might not provide any protection at all, some people still leapt to conclusions about being protected—without knowing whether they had received the vaccine or not. Data from the women volunteers (a group with less education than the men) suggests that there may have been some confusion around the terms “vaccine” and “placebo.” Both findings highlight the need for clear, ongoing, audience-appropriate education and information for vaccine trial volunteers.

Cohort: A group of people who are followed over the course of a scientific study.

Incidence: The rate of new infections per year, measured by determining the number of new infections in a specific population over a given period of time. HIV incidence rates are often expressed as percentages (the percentage of people in the population who acquired HIV over a specified period of time).



GLOBAL NEWS

◆ **New Proposal for a Global AIDS Vaccine Enterprise**

In an article titled, “The Need for a Global Vaccine Enterprise” (*Science*: 300:2039;2003), 24 of the world’s leading vaccine researchers and advocates called for a major effort to expand and restructure the search for an AIDS vaccine. Richard Klausner, Executive Director of the Bill and Melinda Gates Foundation global health program, was lead author on the paper.

The proposal calls for a coordinated effort similar to the Human Genome Project, in which an international group of scientists agreed on a scientific road map and voluntarily divided tasks. Similarly, this new vaccine enterprise would systematically identify critical tasks, allocate funds and ensure that participating teams of researchers collectively covered the entire range of potential vaccine approaches. To accomplish this, the enterprise would establish new Vaccine Development Centers (VDCs). These could be actual institutes, collaborations or consortia between existing groups, and could also include efforts sponsored by existing funders, such as the National

Institutes of Health, IAVI and the European Union—all of whom were signatories to the article.

The VDCs would be part of an interconnected network that also includes manufacturing facilities, central laboratories, and clinical trial sites capable of enrolling a projected figure of 35,000 volunteers into clinical studies each year. The paper did not specify funding requirements or sources for this massive endeavor, and many details still need to be filled in. At press time, major vaccine stakeholders were planning an August meeting, hosted by the Bill & Melinda Gates Foundation, to discuss the next steps.

◆ European Union Launches African Clinical Trials Program

In March, the European Union officially launched a new collaboration called the European and Developing Countries Clinical Trials Partnership (EDCTP), to help prepare for large-scale clinical studies of strategies to treat and prevent the major infectious disease killers in the developing world: HIV, tuberculosis and malaria. The money will be used to fund these studies, which may require thousands of volunteers, hundreds of medical personnel and countless data collection forms, as well as physical facilities and equipment.

The EDCTP will link many of Europe's major research institutions, and will build on already existing links between these groups and African sites. Like other efforts underway in this arena, the EDCTP will focus on strengthening capacity for AIDS vaccines and other therapeutic and preventive measures—including drugs, vaccines and microbicides.

The program comes with a funding commitment of €200 million for 2003-2008, but its planners hope for the equivalent of another €400 million in institutional support from research partners, and additional donations from government and private sector sources. Priorities and agendas for the EDCTP will be set by a partnership board of 12 researchers from Africa and Europe. The EDCTP will have a secretariat in the Hague and another at an African location, yet to be determined.

SPOTLIGHT

◆ Does Gender Matter for AIDS Vaccines?

VaxGen's Phase III results

brought attention to the question of whether a vaccine might work differently in different populations. Although inconclusive, the study's data raised questions about different levels of protection in various racial groups and in men and women. Discussions of potential differences between the sexes have led some scientists to re-examine a few previous studies which showed some evidence that vaccines might work differently in men and women.

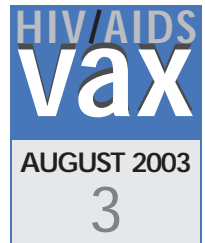
The first indication of a possible gender gap in vaccine protection came in 2000 from two Phase III trials of a candidate vaccine against a strain of herpes virus (called HSV-2), which causes genital lesions. Among women who did not carry any other herpes viruses, the vaccine was 75% effective in preventing symptomatic disease. But among men, no protection was seen.

However, as with the VaxGen trial, the number of women in the HSV-2 studies was too small for firm conclusions to be drawn. So in November 2002 the vaccine's developer, Glaxo-SmithKline, launched a second larger trial in 6,000 women, to find out whether the observation holds up.

If this trial confirms the initial trend, then the world could have its first sex-specific vaccine on its hands.

Historically, there's been no indication of gender or racial differences in how well vaccines work. Globally, millions of men, women, boys and girls of all races have been immunized against diseases, like measles, mumps, polio and tetanus. Yet there has been very little evidence of subgroup-specific effects for any of them.

So why are apparent differences emerging? Perhaps because the vaccines in question are targeting sexually-transmitted diseases (STDs). STDs start in the genital tract, which is the site of the most dramatic differences in men's and women's bodies, including distinct tissue types and immune defenses. These differences have long



EDITORS Patricia Kahn, Emily Bass

PRODUCTION Michael Hariton

DESIGNER DESIGNdeFrancesco.com

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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.

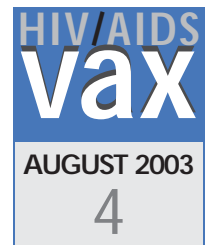
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been linked to men's and women's varying symptoms from and susceptibility to STDs. Vaccines against STDs must protect in these varied environments. This is different from other viruses (for example, polio) that enter the body through the nasal and oral cavities, where men and women are very similar. There is no evidence that polio vaccine offers different types of protection to men and women.

Another example of a sex-specific vaccine for an STD comes from Merck & Co., which in November 2002 launched a large, women-only Phase III trial of a vaccine against human papillomavirus (HPV), a disease causing genital warts and cervical cancer. The company has conducted its trials almost entirely in women because cervical cancer, the most serious outcome of HPV infection, occurs only in women. (Merck also plans a later test

of its vaccine in men, in whom HPV causes warts and anal cancer.)

Will gender prove important for AIDS vaccines? Right now, no one knows. The only way to get an answer is through large-scale trials that enroll enough men and women for gender-specific effects to become apparent.



HOW ARE AIDS VACCINES TESTED?

Contrary to some people's fears, AIDS vaccines are not tested by vaccinating people and then deliberately exposing them to HIV. This strategy is rarely used for tests of any experimental vaccine, and never for a vaccine against a disease as serious as HIV. Rather, vaccines are evaluated through a series of trials, called Phase I, Phase II and Phase III. While these trials serve different purposes, all of them involve volunteers who have been counseled about the vaccine being studied and the risks and benefits of trial participation. This is called the informed consent process, and it is designed to ensure that trial volunteers are well-informed of their rights and responsibilities.

Phase I trials enroll small numbers of people who are at low risk for HIV. The primary goal of these first trials is to determine the safety of these products for human use. Vaccines in Phase I trials have already been through extensive testing in animals, which give a good indication of the products' overall safety and possible toxicities. Once vaccinated, the volunteers are monitored to determine whether or not the vaccine causes any side effects. They also periodically have their blood drawn, and scientists analyze these blood samples to see whether the vaccine has induced immune responses to HIV. It's important to remember that these responses may or may not protect against HIV—only later, larger trials can determine this.

Phase II trials enroll larger numbers of people and may include some individuals who are at higher risk for HIV. They yield further data on safety and side effects, and on immune responses to the vaccine in this larger population. Phase I and Phase II trials also gather information on vaccine doses and the best schedule for a series of immunizations (most AIDS vaccines in development will require a sequence of immunizations delivered over several months or longer).

Phase III trials are the true test of whether a vaccine provides any protection against infection or disease. These trials generally evaluate an experimental vaccine by comparing the rate of infection in individuals given the experimental vaccine with the rate of infection in a group given an inactive substance, called a placebo. Neither the trial staff nor the volunteers know who has been assigned to receive the vaccine or the placebo until the study is over. This is called a blinded study.

The trials make the assumption that some of them will be exposed to HIV, i.e., through unprotected sex, over the course of the study period. Prior to starting a Phase III trial, vaccine developers gather information on rates of infection, or incidence, in different regions and communities, since this is what determines how many volunteers will be needed and for how long they will have to be followed. The higher the incidence, the fewer volunteers and/or shorter the follow-up period required.

For HIV vaccine trials, these volunteers are usually followed for a period of 2-3 years. Throughout the entire trial, volunteers receive regular HIV/AIDS tests and risk reduction counseling, which reinforces the message that they should not consider themselves to be protected. Those who nevertheless become infected will be monitored to see whether the vaccine has an impact on viral load or CD4 cell counts, which are markers of the stage of HIV disease. Once completed, the study is "unblinded" and scientists look for differences in infection rates between the vaccine and placebo groups and, in infected participants, in viral load and CD4 counts. If differences are detected, statistical tests are performed to determine whether they are due to the vaccine, or whether they are coincidental. A "statistically significant" result is one which is very unlikely to arise by coincidence, and—if the trial was well designed and carried out—gives a solid scientific answer on whether, and how well, the vaccine works.

In an ideal scenario, a Phase III trial will yield clear answers. But in the real world, there may still be open questions—as with VaxGen's Phase III study, or the Phase III herpes vaccine trial, both described above. So in practice, there are sometimes multiple Phase III trials of the same product.

Once efficacy is proven, vaccines must then go through an approvals process before they are licensed for use. Even then, countries may need time to develop sites and strategies for delivering the vaccine. These steps can take as long as the trial itself! This is one reason why it is important to design and build these systems in advance in the countries where they are not already in place.

PRIMER UNDERSTANDING vaccine TRIALS

■ For more information:

IAVI clinical trials database: www.iavi.org/trialsdb

HIV Vaccines Pipeline project: <http://chi.ucsf.edu/vaccines/>

HIV Vaccine Trials Network: www.hvtn.org

The AIDS Vaccine Primer (published by the International Council of AIDS Service Organizations/ICASO): www.icaso.org