



Spotlight

Cervical cancer vaccines

Introduction of vaccines for HPV may offer lessons for a future AIDS vaccine.

Two vaccine candidates designed to protect against a common pathogen known as human papillomavirus (HPV) have proven highly effective in large clinical trials and should be approved and licensed in the US and Europe later this year. This is considered a major medical advancement since HPV is a sexually-transmitted infection that is now widely accepted among scientists as a necessary, but not itself sufficient, step in the development of cervical cancer. This is the leading cause of cancer-related mortality among women in developing countries and accounts for more than 290,000 deaths worldwide each year.

Even with these promising vaccines nearly in hand, researchers still face a difficult challenge: making them available where they are needed the most. The question of who will gain access to these vaccines looms large in developing countries where the disease burden is the greatest. The pricing of the vaccine and the ease of administering an adolescent immunization program are complications that might affect the global use of HPV vaccines. "It's very exciting to have this vaccine that works so well, but there is still much work to be done," says Mark Feinberg of Merck, a US-based company that is developing one of the promising vaccine candidates.

Many of these same issues may arise

when an effective AIDS vaccine is developed and this has many closely watching how the debut of this important vaccine plays out. "This is a sort of test case for HIV vaccines and there will be a lot of lessons on acceptability and delivery," says Jessica Kahn, a pediatrician at Cincinnati Children's Hospital in Ohio.

Behind the virus

HPV is one of the most common sexually-transmitted infections (STIs) in the world and most studies suggest it infects at least 25% of sexually active adults—with one study reporting prevalence close to 80% in a cohort of adolescent women in the US. Exact prevalence is difficult to pinpoint in many parts of the world because of the varying sensitivity of the assays used to detect the virus.

There are nearly 120 types of the virus that infect humans and a third of these primarily cause genital infection. These HPV types are further classified as high and low risk based on their ability to cause cancer. HPV types 6 and 11 are responsible for 90% of cases of genital warts. Two of the high-risk HPV types, 16 and 18, are responsible for 70% of the cervical cancer cases worldwide, according to Kahn, but the predominant HPV types can vary geographically and these types are not as common in sub-Saharan Africa or Asia as they are in North America and Europe.

There is limited research on the epidemiology of HPV infection in developing countries but a study published in the *New England Journal of Medicine* in 2003 pooled data from 11 case-controlled studies in 2506 women with cervical cancer in

Morocco, Mali, Colombia, Brazil, Paraguay, Peru, Thailand, the Philippines, and Spain. HPV type 16 was the most common with an overall prevalence of 59%, reaching 70% in some countries. The second most common HPV type was 18, with an overall prevalence of 15%, followed by types 45, 31, and 35. The authors suggest that the predominant HPV type should be considered if vaccines are to be created for a specific geographic region. Philippe Monteyne, vice president of worldwide operations for GlaxoSmithKline's cervical cancer vaccine program, acknowledges limited regional differences in HPV types but says his company's vaccine "is really useful on a worldwide basis."

The candidates

Not every woman that is HPV infected will develop cervical cancer. Many infections with either the high- or low-risk HPV types can be temporary and cleared easily by the immune system. But HPV becomes dangerous when infection with a high-risk type isn't cleared. A persistent and active HPV infection can cause pre-cancerous lesions on the cervix known as cervical intraepithelial neoplasia (CIN) that

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may eventually lead to non-invasive and then advanced cervical cancer, which can be a life-threatening condition. An unresolved HPV infection is also associated with both anal and oral cancer in men and women.

Precisely how cervical cancer develops isn't fully understood. Routine screening protocols like Pap smears can be used to detect early-stage abnormalities in the cells of the cervix that could be the first signs of cervical lesions. Catching cervical cancer in its earliest stages has substantially reduced the rate of mortality due to this disease in the US. But regular gynecologic care is not always available to women in developing countries. "The vaccine is the solution for countries where mandating good screening programs is difficult," says Monteyne.

Preventive HPV vaccines that are in development—Merck's and GSK's could be licensed soon—may help reduce the reliance on screening methods in the future. Both candidates consist of a single HPV protein that can self assemble into a virus-like particle (VLP), a non-replicating shell that resembles an actual virus particle closely enough to fool the immune system into thinking it is encountering a natural HPV infection.

Merck's vaccine candidate, known as Gardasil, is now in Phase III testing in over 25,000 women and men and an application was recently submitted to the US Food and Drug Administration (FDA) for approval and licensure. Gardasil contains HPV proteins from four viral types, HPV 6, 11, 16, and 18. In one of their Phase III trials involving 12,167 women aged 16-26, 3 doses of the vaccine were able to prevent all cases of high-grade CIN or non-invasive cervical cancer associated with the virus types included in the vaccine. "It's really hard to do better than that," says Feinberg.

The vaccine was also able to prevent cases of persistent HPV infection that caused high-grade CIN and non-invasive cancer associated with strains 16 and 18 by 97% in women who received at least one injection, a more "real world" example of the vaccine's efficacy since people may

not return for all 3 inoculations.

The HPV vaccine in development at GSK in Rixensart, Belgium, in collaboration with MedImmune is expected to reach the European Medicines Agency (EMA) later this year for approval and licensure. The vaccine, known as Cervarix, is also a VLP vaccine but only includes HPV proteins from types 16 and 18.

GSK now has 5 ongoing Phase III efficacy trials with Cervarix in 28,000 female volunteers. Last year they reported that 3 doses of the vaccine were 100% effective at preventing persistent HPV infection with the two types

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Mark Feinberg

of virus in the vaccine. The vaccine was 95% effective at preventing persistent HPV infection and 93% effective at preventing CIN in women who received at least one injection.

GSK is only testing its vaccine in women but Merck has chosen to evaluate the efficacy of Gardasil in both male and female adolescents, as well as in trials with men who have sex with men (MSM). Not only does HPV cause significant disease burden in males, says Feinberg, it is also likely that vaccinating both men and women will increase immunity levels on a population basis and therefore decrease overall the number of life-threatening infections in women. Merck has yet to report results on the efficacy of Gardasil in male volunteers and their application to the FDA is based on safety and immunogenicity data in women only.

Implications for HIV

Since both HPV and HIV can be sexually-transmitted and enter the

body through the same tissues, researchers have been studying the link between these two infections. The cervical lesions caused by persistent HPV infection can enhance women's risk of acquiring HIV because of increased bleeding and the recruitment of CD4⁺ T and dendritic cells to the mucosal tissues of the cervix, believed to be a target site for establishment of HIV infection in women.

And a study presented at last summer's International AIDS Society Conference in Brazil found that anal HPV infection was independently associated with HIV acquisition in a cohort of 1409 MSM (Abstract no. TuOa0403).

Several studies have also found that HIV-infected individuals are at greater risk for acquiring HPV and the two prove to be perilous partners. Co-infected individuals are more likely to develop severe cervical lesions than those only infected with HPV. It is estimated that HIV-infected women are three to five times more likely to develop cervical lesions due to HPV infection. HIV's ability to hinder the immune system may be at the root of this problem, either directly or indirectly, because it allows HPV to persist longer, making cancer development more likely. Even people on highly active antiretroviral therapy (HAART) for HIV infection are more likely to develop serious anal and cervical lesions.

Rollout plans

Ideally a preventive HPV vaccine would be administered prior to infection, which for such a common virus means vaccinating girls and boys before they become sexually active. There is some controversy brewing within the US over the eventual introduction of a vaccine to protect against an STI with some groups arguing, as they do for HIV, that promoting abstinence is a better message. Researchers are also discussing whether parents will be willing to have their children vaccinated against HPV in other countries where discussion of sexual activity is particularly difficult.

Vaccinating early adolescents (age 9-12) in developing countries might also require a new structure for vaccine delivery. "There really isn't any infrastructure in developing countries for administering vaccines to adolescents," says Feinberg, who attributes much of the progress made with vaccination programs in developing countries to infant immunizations.

All of these are significant challenges that some international organizations are now addressing. The Program for Appropriate Technology in Health (PATH), an advocacy group

in Seattle, received a planning grant from the Bill & Melinda Gates Foundation to explore ways to make HPV vaccines available in developing countries. Their initial focus is on countries that already have active vaccination programs and high levels of HPV disease burden, which currently includes India, Peru, Vietnam, and Uganda.

PATH will also work on a proposal to the Global Alliance for Vaccines and Immunization (GAVI) to explain why funding should be allocated for the purchase of HPV vaccines. The price

for the Merck or GSK vaccines won't be set until after they receive approval but they could be prohibitively expensive for use in developing countries. "We expect to look at a range of strategies to encourage an affordable supply," says Sherris.

New research into the epidemiology of HPV infection by region may also be an important consideration in the implementation of these vaccine programs, but without a doubt introducing these vaccines in developing countries "could have a tremendous impact on mortality," says Kahn.

Global News

Pharmexa-Epimmune initiates Phase I AIDS vaccine trial

Pharmexa-Epimmune, a US subsidiary of a Danish vaccine and immunotherapy company, recently initiated a Phase I AIDS vaccine trial to evaluate the safety and immunogenicity of two candidate vaccines that will be tested either alone or in combination. This trial will enroll 124 volunteers at 3 sites in the US and in Lima and Iquitos, Peru, in partnership with the HIV Vaccine Trials Network (HVTN).

The first candidate, known as EP HIV-1090, is a DNA plasmid vaccine that has already undergone testing in human volunteers while the second, EP-1043, is a protein vaccine designed to induce cellular immunity. Neither candidate can cause HIV infection. In the first part of this trial volunteers will be randomly selected to receive either a low or high dose of EP-1043 to determine which is optimal. In the second part of the trial researchers will be comparing the safety and immune responses generated by EP-1043 and EP HIV-1090 alone or in combination. Volunteers will be randomized to receive four inoculations of either vaccine candidate or four injections of both.

This trial is sponsored by the US National Institutes of Allergy and Infectious Diseases within the National

Institutes of Health and the vaccines are being manufactured by Pharmexa-Epimmune.

AIDS vaccine trial opens in India

India started the country's second Phase I AIDS vaccine trial recently in Chennai to determine the safety and immunogenicity of a modified vaccinia Ankara (MVA) vaccine candidate at varying doses. This trial will enroll and follow 32 volunteers at the Tuberculosis Research Centre over 2 years.

The vaccine candidate, TBC-M4, uses a weakened and non-infectious MVA virus as a vector to deliver HIV fragments to the immune system, but importantly the candidate can not cause HIV infection because only part of the virus is used. The fragments included in the candidate are from clade C HIV, which is the predominant virus circulating in India and China, as well as parts of Africa. Researchers and an independent advisory board will evaluate the safety of the candidate at the low dose before administering a higher dose to volunteers in this trial.

IAVI is sponsoring the trial in partnership with the Indian Council of Medical Research and the National AIDS Control Organization of India. Therion Biologics, a US-based biotechnology company, is manufacturing the vaccine.

India is also conducting another Phase I AIDS vaccine trial with a different vaccine candidate that began last year and is ongoing at the National AIDS Research Institute in Pune.



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IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 23 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it.

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What are the major considerations influencing the decision to volunteer for an AIDS vaccine trial?

Making the decision to participate in an AIDS vaccine clinical trial is a complex and personal process and it is important that all potential volunteers fully understand what is involved in the trial when making this choice. Researchers and staff conducting AIDS vaccine trials take several measures to ensure that, to the best of their ability, any possible benefits and risks of trial participation are identified. These are then reviewed before the trial begins by local and independent groups known as ethical review committees (ERC) or institutional review boards (IRB) and sponsors to ensure the list is complete. The ERC is committed to ensuring that the trials are run to the highest safety and ethical standards. All of the possible benefits and risks are also explained carefully to each interested volunteer during the informed consent process (see June 2005 *Primer on Understanding Informed Consent*).

Benefits

There are several ways that clinical research, including AIDS vaccine trials, can benefit the countries and communities in which the trials take place even if the vaccine candidate being tested is eventually found to be not effective. Before AIDS vaccine trials are conducted, educational campaigns take place to raise awareness within the community about HIV transmission and prevention and these can benefit all community members, not just those who choose to volunteer for the trial. Many of these outreach programs also promote voluntary counseling and testing (VCT) for community members to find out if they are HIV infected, which can influence future decisions about their health and help reduce the stigma associated with HIV testing.

There are also several possible benefits for those who decide to participate in an AIDS vaccine clinical trial. They include the VCT services and risk-reduction counseling that the volun-

teers will receive regularly throughout the course of the trial (see August 2005 *Primer on Understanding Risk-Reduction Counseling*). Volunteers will also have continuous access to the best available prevention measures in their community, including male and female condoms. Participants in AIDS vaccine trials also benefit from the rewarding feeling of being involved in medical research that may benefit others. Altruism, or concern for the welfare of others, is one of the most common reasons trial volunteers give for their participation.

Other possible benefits include the basic medical care that volunteers receive during the trial. People interested in volunteering for AIDS vaccine trials who are found to have malaria or tuberculosis can receive referrals to treatment programs in their community, therefore improving their overall health. This is also true for people who are found to be HIV infected or who become HIV infected during the course of the trial through exposure in their community. These individuals can be referred to treatment programs, as well as to support groups.

Volunteers in AIDS vaccine trials might also receive reimbursement for transportation to and from the trial site or for food if they are expected to be at the site during a mealtime. A reasonable amount is determined, with input from the community advisory board, before the trial begins and is reviewed and approved by the ERC.

Researchers and the ethics committees take these considerations seriously because they don't want the compensation or the health care provided at the trial sites to be the reason that people join the study. All trial organizers and approval bodies work carefully to avoid undue inducement. To prevent this, some trial sites may strive to provide a level of care that is consistent with what is available in the broader community. Other sites try to extend some basic healthcare services as much as possible to the wider community, which can be difficult at urban sites.

Volunteers should not feel pressured by the trial staff into enrolling in a trial but should make a decision only after

weighing all of the potential benefits and risks. Ethicists are also studying how to ensure that adolescents fully understand the risks and benefits of participation in medical research before agreeing to enroll. This may be an important issue in the future as researchers consider the possibility of testing AIDS vaccine candidates in this age group.

Risks

It is equally important that all volunteers understand the potential risks of participating in AIDS vaccine clinical trials. All vaccine candidates are tested extensively before they enter human clinical trials, but there is still the possibility that there will be side effects or adverse reactions caused by the vaccine candidate. Often these are mild and can include headaches, fever, and inflammation at the injection site, but these effects should be explained to all volunteers clearly during the informed consent process. However, researchers can't predict each individual's response to the vaccine.

It is also critical for volunteers to understand that there is a possibility that the vaccine candidate will not be effective or that they will be randomly selected at the start of the trial to receive an inactive substance known as a placebo. Either way, the volunteers won't be protected against HIV infection by participating in the trial, emphasizing the need to practice risk-reduction behaviors.

Other potential risks include the possibility of receiving a false-positive HIV test result in the future (see November 2005 *Primer on Understanding HIV Testing*), being unable to donate blood after participation in the trial, and social risks such as facing possible stigma or discrimination.

Despite these inherent risks, researchers and trial staff are dedicated to making sure that AIDS vaccine trials are run safely and ethically and that these trials contribute to the overall health and welfare of the communities that participate in AIDS vaccine research, especially in developing countries.