Filling the Gaps To Fight Cervical Cancer

By Samantha Beres

Pap screening programs have substantially reduced the incidence of cervical cancer, yet it is hard to deny the promise of human papillomavirus (HPV) vaccines for further reducing the burden of this preventable disease. The two available vaccines—Merck’s Gardasil and GlaxoSmithKline’s Cervarix—target the most common HPV types that are responsible for 70% of cervical cancers. In girls not previously exposed to HPV, both vaccines have shown nearly 100% efficacy against these HPV strains.

But not all women at risk for cervical cancer are benefiting from these preventive measures. Millions of women and girls do not receive Pap screening, nor are they able to get the vaccine, particularly in resource-poor countries where education, access, and money are lacking. Also, the vaccines don’t protect against all HPV strains that cause the disease, and they do not treat existing HPV infections. At greatest risk are those who have been exposed to the virus and don’t get screened regularly. With these gaps in mind, academic and industry scientists are testing new technologies that may be more effective at detecting and preventing the disease: fast, simple HPV screening tools and second-generation vaccines that target more HPV strains and are cheaper to produce and distribute.

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Adel Mahmoud, M.D., Ph.D., former president of Merck Vaccines, now at Princeton University. The current vaccines target HPV types 16 and 18, leaving out approximately 13 additional cancer-causing strains. (Gardasil also targets HPV-6 and -11, which cause most cases of genital warts.) “Seventy percent is a fantastic achievement, but I think to make the vaccine a major player in the prevention of cervical cancer, it would be advantageous to increase the range of viruses” it protects against.

GlaxoSmithKline’s director of U.S. product communications, Liad Diamond, confirmed that the company is investigating “vaccines that provide broader coverage for the longest duration of time.” Merck would not comment on their next generation of vaccines, but South County Consultants in Clinical Trials, a medical company in Rhode Island, posted an online call to recruit women for a trial in which participants will receive either Gardasil or Gardasil plus a new vaccine that covers an additional four HPV strains.

Building on the current vaccines by covering more strains is straightforward, researchers point out, but it does not address the cost issue. At $360 for three shots (in the U.S.), Gardasil ranks as one of the most expensive vaccines ever made. But Merck and GlaxoSmithKline have both announced that they will offer their HPV vaccines for lower prices to developing countries—this is pending the World Health Organization’s “prequalification” of the vaccines for purchase by United Nations agencies. Only with widespread use in public vaccination programs will there be sufficient volume to justify lower prices.

Cheaper Vaccine Delivery

Another way to reduce vaccine costs is through cheaper production. Current vaccines use the L1 protein, which is derived from the two most important oncogenic strains of the papillomavirus. L1s self-assemble into virus-like particles (VLPs), which look enough like the real virus to trick the body’s immune cells and provoke antibodies to attack the HPV strains. “The L1s of the current vaccines are produced in yeast or insect cells and are difficult to manufacture,” said Denise Nardelli-Haefliger, Ph.D., of the University of Lausanne in Switzerland.

Nardelli-Haefliger is leading the development of a new HPV vaccine that will produce L1s in a lower-cost system. The vaccine supplements an established commercial typhoid vaccine, which is taken in three oral doses within 5 days. The active ingredient is an attenuated Salmonella bacterium that expresses the gene responsible for making L1. In the body, the bacteria produce L1 proteins to trigger the appropriate immune response.

“It is going to be quite ideal for delivery. Three closely spaced doses that people can take themselves eliminate the need for medical assistance,” Nardelli-Haefliger said. It may also reduce the number of dropouts, people who don’t return for the second and third dose. Preclinical studies are ongoing, and phase I clinical trials to test for safety and immune response will start before the end of the year. The typhoid-HPV vaccines will be produced by Indian Immunological in India, where facilities are less expensive and labor costs are considerably lower.

Another approach is that of Robert Garcea, M.D., of the University of Colorado in Aurora, who is also developing an inexpensive vaccine that is more amenable for use in resource-poor areas. In the currently available vaccines, 360 L1s...
assemble into a VLP, but first there is a "preassembly" where L1s link together in groups of five, called capsomeres. In established animal models, equal doses of capsomeres and VLPs elicited equal immune responses.

"You can grow capsomeres in bacteria really easily. It’s inexpensive to make and purify," Garcea said. Another advantage of capsomeres, he added, is stability. VLPs fall apart if not refrigerated, whereas capsomeres can withstand temperature variations. Preclinical evidence indicates that capsomeres can be formulated as a powder and then reconstituted for immunization (although this approach will need to be tested in humans). Garcea points out that a powder can be more easily transported to remote areas, stored, reconstituted, and administered in shots.

The vaccines that Garcea and Nardelli-Haeflinger are developing target the L1 protein of HPV-16 and -18, as do the Merck and GlaxoSmithKline vaccines. A third candidate aims not only for cheap production but also to target more HPV types by using the L2 protein. “While L2s elicit a lower immune response than L1 VLPs, the advantage of using L2 is that it can trigger a cross-type protective immune response,” said Richard Roden, Ph.D., of Johns Hopkins University in Baltimore, who is developing the L2 vaccine. That is, vaccination with an L2 derived from one HPV strain might protect against many other strains. The current vaccines based on the L1s, on the other hand, provide type-restricted immunity—they provide excellent protection against the types used to make the VLP vaccine but offer limited or no protection against other HPV types. The L2s are unstructured, and therefore proteins of several HPV strains can be "stitched" together and delivered as a single-molecule vaccine. Roden’s group has linked L2 peptides derived from many HPV strains with the hope that this method will result in a vaccine that is simple to manufacture and broadly protective against all oncogenic types.

“If it is possible to get very broad and long-term protection against the known and unknown cancer-associated HPV types with an L2 vaccine, it may lessen the need, eventually, for intensive screening of vaccinated women,” Roden said.

Cervical Cancer Interventions: Not One Size Fits All

Cervical cancer rates in the U.S. have dropped 70% in the past 60 years, due mainly to screening with the Pap test. But even with new vaccines and screening tools, there are still groups of U.S. women with disproportionately high cervical cancer rates. For example, from 2004 to 2007, incidence rates among women in Little Haiti, Miami— the largest enclave of Haitians in the U.S.— were estimated to be 38 per 100,000 women, compared with 9 per 100,000 in the general U.S. female population. Other hotspots include Appalachia, the border with Mexico, and the Deep South.

Researchers are studying these areas to validate approaches that might work in other less developed parts of the world. A project in the Mississippi Delta is investigating whether women will self-collect clinical specimens for HPV testing. Women in this area tend to stop going to the health clinic or doctor’s office after their childbearing years—usually between 30 and 40 years of age—which is the prime time for cervical cancer to be detected, said Philip Castle, Ph.D., an NCI scientist and head of the project. If a woman is willing to collect specimens at home, she won’t have to visit the doctor if the test is negative. This approach allows clinics with limited resources to focus on women with positive results.

“We’re not going to affect cervical cancer rates dramatically by introducing a vaccine to those who can afford the vaccine. We’re going to affect cervical cancer rates by reaching the pockets of underserved populations,” Castle said. “There’s got to be a menu of options that are validated, that are designed to be culturally appropriate and age appropriate.”

Another intervention, known as the Community Awareness Resources and Education project, is trying to determine whether Appalachian women have unique risk factors for abnormal Pap smears that might contribute to their increased rate of cervical cancer. The project works with rural clinics in 16 counties in Ohio and is expected to include more than 10,000 women.

The first set of studies from the project show extremely high rates of abnormal Pap tests in Ohio—Appalachia, almost four times the national average of 3%. Of those women with abnormal Paps, 68% smoke cigarettes. About a quarter of all the women in the study report depression.

“This is very similar to what we find when we look at the depression in cancer patients,” said Electa Paskett, Ph.D., of Ohio State University in Columbus, who heads the project. "These women are depressed because they’re in socially isolated situations. That leads to risky behaviors, which can lead to poor health outcomes.”

Paskett’s group is also validating a scale that weights sexual behaviors, such as age at first intercourse and number of sexual partners, to predict whether a woman would have had a history of abnormal Pap smears. “We’ll be able to quantify not only the health disparities but the disparities in the risk factors or healthy behaviors that contribute to these health disparities,” Paskett said.

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years, the risk is 1% or less for precancer. So you can bet that the negatives are safe and devote your limited resources only to the positives.”

In resource-poor areas, Castle and other public health experts advocate for “Screen and Treat” programs where both steps happen in one day. FastHPV is one screening option. Another is visual inspection of the cervix with acetic acid (VIA), which requires only a flashlight, a speculum, vinegar, and a cotton swab. The two tests can also be combined: screen with an HPV test and use VIA among the HPV-positive women to determine what kind of treatment is needed.

“We hope to be moving toward the FastHPV test, but there will always be places that will not have the laboratory facility or won’t be able to afford the $2 test if it gets to that price,” said Vivien Tsu, Ph.D., a senior advisor at PATH, an international organization that sponsors demonstration projects for HPV vaccines and screening around the world. In these cases, Tsu said, VIA would be a feasible option. Once swabbed on the cervix, the acetic acid (vinegar) will indicate any abnormal areas or lesions after just 1 minute. A 7-year study in India that used VIA to screen and treated abnormal cells and precancerous lesions with cryotherapy (the freezing off of abnormal cells) showed a 25% reduction in cervical cancer incidence and a 35% reduction in cervical cancer mortality in the intervention group.

Scott Wittet, also a PATH advisor, said, “We’re urging countries to do VIA now, and when we have the new technology, such as FastHPV, the health worker will know what the screening is all about. If we can start building up that infrastructure by educating people, it will be ready to absorb new and better technologies as they come along.”

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