

HPV Vaccine: An Evolving Promise?

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Introduction

The discovery that human papillomavirus (HPV) causes the vast majority of cervical cancers opens exciting new possibilities for controlling this disease, which is the second most common cancer among women worldwide¹. Biotechnology firms, pharmaceutical companies, and academic researchers are working to develop vaccines against the types of HPV that cause most, if not all, cases of cervical cancer. Some are designing prophylactic vaccines to prevent initial infections with HPV; if successful, these vaccines ultimately could eliminate the public health problem of cervical cancer. Others are focusing on therapeutic vaccines to control the progress of established disease or prevent its recurrence in women who already have cervical dysplasia or cancer.

Vaccine developers face many technical challenges, in part because the HPV virus itself has evolved various strategies for evading the immune response. A safe, effective, and affordable vaccine to prevent cervical cancer must meet several programmatic challenges. First, it must be multivalent; that is, it must be effective against several of the most common types of HPV associated with cervical cancer. Second, the vaccine must offer long-lasting protection against HPV infection, preferably without booster shots. Third, a vaccine suitable for developing countries must minimize financial and logistical demands on health care systems^{1, 2}. The fact that the type of HPV prevalent in each region of the world is variable makes it mandatory to individualize the type of vaccine accordingly³.

Vaccines that protect against HPV infection, if administered prior to initiation of sexual activity, theoretically would prevent women from developing cervical cancer later in life. Compared with the current strategy of regularly screening women for precancerous lesions and treating them as necessary, immunization should offer a cheaper, logistically simpler, and more effective intervention that places fewer demands on the health care system as well as on women^{1, 2}.

Challenges in HPV Vaccine Development

The promise of HPV vaccines does not come without challenges. Some of these reflect characteristics of the virus itself and its interaction with cervical cancer. Others reflect the challenges of stimulating an effective immune response to a mucosal infection. Because HPV does not cause disease in animals, it is difficult to conduct the animal research needed for vaccine development³.

Scientists do not know precisely which elements of the human immune system are important in preventing or resolving HPV infections. Although there is evidence that immune response does play a role in controlling HPV infections, it is not known why HPV infections persist in some individuals and regress naturally in others^{4, 5}.

HPV enters the body through the mucosal membranes and does not spread systemically. Therefore, a vaccine against HPV will be most effective if it induces a strong immune response at the mucosal surface^{6, 7}; although some researchers argue that a systemic immune response might be sufficient⁸.

Approximately 90 types of HPV that infect the genital tract have been identified⁴. Two types (HPV-6 and HPV-11) account for 90 percent of genital wart cases, while as many as 15 to 20 types may be associated with cervical cancer⁹. Because HPV types differ significantly at the genetic and protein level, antibodies raised against one kind of HPV generally do not protect against other types¹⁰. Preventing a majority of cervical cancer cases therefore will require a multivalent vaccine, that is, a combination vaccine effective against the common carcinogenic types of HPV (including types 16, 18, 31, and 45)³.

Three phases of clinical trials must be fulfilled before a commercially available vaccine against HPV evolves. Phase I trials include small numbers of volunteers and determine the safety of the vaccine; Phase II trials are open to hundreds of volunteers to test the vaccine for safety, the ability to evoke an immune response, and the ability to prevent disease; Phase III trials are large-scale studies in thousands of people to confirm that a vaccine safely prevents disease with minimal side effects.

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HPV Antigens Targeted by Vaccines

Regardless of the approach they take, researchers must first choose which HPV antigens to include in their candidate vaccines. Three categories of HPV proteins are potential targets for vaccines; each is expressed during different stages of infection and disease.

- *The capsid proteins L₁ and L₂* makes up the outside coat or shell of HPV particles. Because they are present during the initial infection, they are ideal targets for a prophylactic vaccine. Once HPV is integrated into tumor cells, however, the capsid proteins are not always present. This means L₁ and L₂ are not reliable targets for a therapeutic vaccine⁴.
- *The oncoproteins E₆ and E₇* continues to be expressed during later stages of disease. They bind p53 and pRB, which are human tumor suppressor genes. These oncoproteins are involved in the malignant transformation of HPV-infected cells and are thought to be required for continued tumor growth¹¹. They are the primary targets of therapeutic vaccines, most of which have been designed to treat later stages of disease.
- *The replication proteins E₁ and E₂* is necessary for HPV to replicate within cells before the virus is integrated into the host DNA. Because E₁ and E₂ are expressed in higher levels than E₆ and E₇ early in the progress of an HPV infection, several researchers have suggested that they may be the best targets for a therapeutic vaccine designed to treat early stages of disease, such as low-grade dysplasias^{3, 12}.

Vaccine Types

Since few types of HPV can be propagated in tissue culture, it is not possible to develop inactivated or attenuated live virus vaccines as with some other viral diseases^{8, 13}. Therefore, HPV vaccines currently under development are part of a new generation of vaccines that employ genetic engineering. Recombinant genetic engineering also allows the production of subunit vaccines that include only a portion of a disease causing organism; since they do not contain the cancer-inducing viral genes, these may be safer and create fewer side effects than vaccines made of whole organisms⁷.

Types of HPV vaccines Researchers are investigating the following five approaches to producing HPV antigens and delivering them to vaccine recipients:

- *Recombinant live vector vaccines*: A harmless host virus or bacteria is genetically engineered to produce an HPV antigen. The immune system responds both to the host organism and the HPV antigen¹⁴.
- *Protein and peptide vaccines*: An organism, such as yeast, is genetically engineered to produce an HPV protein or peptide. After this antigen is purified, it is combined with an adjuvant that helps trigger the immune system¹⁵.
- *Virus-like particles (VLPs)*: Cultured cells are genetically engineered to produce HPV capsid proteins which self-assemble into empty shells resembling virus particles¹⁶.
- *“Naked” DNA vaccines*: HPV genetic material is inserted into bacterial plasmids. When these circular DNA structures are used in a vaccine, the DNA is expressed in human cells that then produce an HPV antigen¹⁷.
- *Edible vaccines*: Plants are genetically engineered to express HPV antigens in fruits and vegetables. Eating the foods leads to immunization in the gastrointestinal tract¹⁸.

Vaccination Trials

One multicenter pilot study has enrolled 2392 women from 16 to 23 years in age¹⁹. Participants were randomly assigned to receive three shots of either an HPV-16 vaccine or a placebo. Participants were followed for an average of 17 months after getting the third shot. Of the placebo group, 41 developed HPV-16 infection; nine of them went on to develop precancerous lesions. Twenty-two other women from the placebo group also developed precancerous lesions on their cervixes, but these were not associated with HPV-16. By comparison, no one who got all three vaccine shots developed an HPV-16 infection. Twenty-two women receiving the vaccine did develop cervical abnormalities that can lead to cancer but these precancerous lesions were not associated with HPV-16¹⁹.

Another randomized, double-blind, placebo-controlled, phase II trial has included more than 500 non-pregnant women from Brazil, Europe, and

the US with a mean age of approximately 20 years²⁰. One group of women received three active vaccines via intramuscular injection at Day 1, Month 2, and Month 6, while another group received one of two placebo preparations at the same time intervals. Follow-up continued for 3 years. The vaccine was effective and generally well tolerated. Most (94%) adverse events were mild or moderate in intensity; only one patient discontinued treatment. Pain was the most common injection site event; headache was the most common systemic event. Since women are at risk for HPV infection for as long as they are sexually active, it is unclear at this point whether booster doses will be necessary to provide protection beyond a 3-year period²⁰.

The latest data release concerns a trial of a quadrivalent recombinant vaccine that included HPV types 6, 11, 16, and 18²¹. In all, 12167 women at 90 centers in 13 countries participated in the trial, the FUTURE II study. In this prospective double blind study, women aged 16 to 26 were randomized to receive three doses of either vaccine or placebo over six months. The reported efficacy of the vaccine after an average follow-up of 17 months was 100%. In the 5301 vaccinated women there were no observed cases of high grade precancer or non-invasive cancer (CIN 2 or 3) related to HPV 16 or 18, but there were 21 cases in the 5258 women given placebo.

These data from FUTURE II are the most recent in a series of highly promising trial results of monovalent (HPV 16), bivalent (HPV 16, 18) and quadrivalent (HPV 6, 11, 16, 18) vaccines^{23, 23, 20}. Reported side effects in all the vaccinated groups were mostly limited to mild symptoms at the injection site, which did not affect overall compliance. No serious adverse events attributable to the vaccines have occurred.

Questions before Strating an HPV Vaccination Programme

- What fraction of cervical cancer overall will be prevented by a vaccine against HPV 16 and 18?
- Will immunity induced by vaccines alter the distribution of other, non-vaccine HPV types?
- Will a vaccination program against a sexually transmitted infection prove acceptable to adolescents who are not yet sexually active and their parents?
- Should teenage boys be vaccinated as well as teenage girls?
- Will booster vaccinations be necessary, and if so, when?

- How will a vaccination program affect current programs for cervical cancer screening, and how and when should screening change in response?
- What benefits might vaccination confer on adults who are already infected with HPV?
- Should older sexually active adults be included as part of a catch-up campaign at the outset of a vaccination program?
- What will be the cost effectiveness of various strategies for vaccination programs?

Conclusion

Assuming that one day most women will be routinely vaccinated with a prophylactic vaccine that prevents HPV 16 and 18 infections, Pap screening will still continue for many decades. Thousands of women will remain at risk for cervical cancer either because they were infected with HPV 16 or 18 before the vaccine became available or because they're infected with a cancer-associated HPV type that the vaccine cannot prevent. Although Pap screening won't disappear, a smaller percentage of women will develop abnormal Pap smears and fewer women will require colposcopies, biopsies, and treatments for intraepithelial lesions and cancers. Ideally, researchers will develop a screening test that is more accurate than the Pap smear and, over a lifetime, a woman will require fewer screening tests.

The need for a program of HPV vaccination can only intensify, and every country should be planning actively to implement and budget for early vaccination. The vaccines under evaluation already have the potential to prevent a substantial proportion of cervical cancer cases, and a second generation of HPV vaccines containing additional high risk types and combined with other vaccines is being developed. Large scale, multi-country, multi-site trials of several HPV vaccines are currently under way. The end points comprise incident and persistent HPV infection (during 2-3 years' follow-up) and associated precancerous cytological and histological lesions (cervical intraepithelial (CIN) neoplasia during 2-3 and 4-5 years' follow-up). The World Health Organization is expecting at least one of these vaccines to be licensed for use in 2006²⁴.

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