Chapter 16: Prophylactic Human Papillomavirus Vaccines

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Candidate prophylactic vaccines based on papillomavirus L1 virus-like particles (VLPs) are currently in human clinical trials. The main long-term goal of the vaccine is to reduce the incidence of cervical cancer and its precursors. In animal papillomavirus models, systemic immunization with L1 VLPs can induce high titers of neutralizing antibodies that confer protection against high-dose experimental papillomavirus challenge. In humans, systemic vaccination with L1 VLPs has been well tolerated and induced high serum antibody titers (at least 40 times higher than titers seen following natural infection). A recent proof of principle HPV16 L1 VLP efficacy trial has shown excellent protection against persistent HPV16 infection and associated cytological abnormalities. Large scale efficacy trials of L1 VLPs from HPV16 and 18 (the HPV types found most frequently in cervical cancer), with or without HPV6 and 11 (the HPV types responsible for most genital warts), are planned. If the results of these large trials support the encouraging results of the early trials, they should lead to a commercial prophylactic HPV vaccine. Implementation issues may include how to make the vaccine available in the developing world, where the majority of cervical cancer cases occur, the appropriate age of vaccination, and the role of male vaccination. Because a VLP vaccine is likely to provide type-specific protection, increasing the number of cancer-associated HPV types in the vaccine is a likely approach to broadening the protection to additional types. There will probably also be efforts to develop alternative vaccine formulations better suited to implementation in developing countries as well as attempts to develop vaccines with a therapeutic activity against established HPV infection because a combined prophylactic/therapeutic vaccine may be expected to have an even greater impact than a purely prophylactic vaccine on HPV induced disease. [J Natl Cancer Inst Monogr 2003;31:111–6]

As discussed in other chapters, a wealth of epidemiologic and molecular evidence has led to the conclusion that virtually all cases of cervical cancer, as well as its precursor lesions, are attributable to infection with a subset of mucosatropic human papillomavirus (HPV) types (1). HPV infection also appears to contribute to the development of a variable proportion of other cancers, as well as causing benign condylomata and warts (2).

Rationale for an HPV Vaccine and Desirable Vaccine Attributes

Identification of an infectious agent as a necessary cause of disease implies that interfering with the infection should prevent development of the disease. Historically, vaccines have represented a cost-effective means to prevent disease induced by microbial agents (3,4). The main public health goals of an HPV vaccine should be to reduce the incidence of cervical cancer and its precursor lesions. Secondary goals would include efforts to reduce the incidence of other cancers and the benign conditions caused by HPV.

Compared with a purely prophylactic vaccine, a combined prophylactic–therapeutic vaccine would be able to reduce the incidence of cervical cancer in a shorter time (5,6). A vaccine that could both prevent new infections and successfully treat established infections would be preferred because cervical cancer arises many years after the initial infection, eradicating the infection during this interval would be expected to prevent cancer development, and the greatest public health problem for cervical cancer is found in settings that lack the resources for effective population-wide cervical cancer screening programs. However, it has proven much easier to develop effective prophylactic vaccines than those with therapeutic efficacy, and all approved vaccines in widespread use are prophylactic (3,4). Therefore, public health-oriented vaccine efforts have emphasized development of a prophylactic vaccine against HPV.

An ideal prophylactic vaccine would need to possess several attributes. First, it should be safe because it would be given to young, normal individuals, the vast majority of whom, even without a vaccine, would not be expected to develop cancer from HPV infection. Second, it should be able to be administered in settings with poor resources. It would be desirable for the vaccine to be inexpensive to produce and purchase, not to require a cold chain, to be administered without injection, and to be fully effective after a single dose. Third, protection should last many years because it is neither practical nor desirable to revaccinate frequently. Fourth, the vaccine should confer a substantial reduction in the incidence of cervical cancer. To accomplish this goal, the vaccine would need to be effective against the HPV types most frequently identified in cervical cancer. Although multiple HPV types are implicated in cervical cancer (7), HPV16 accounts for more than one-half of cervical cancer cases worldwide, and the worldwide frequency of other specific HPV types can also be estimated (1).

It is difficult to define precisely what degree of reduction in cervical cancer would justify the widespread use of an HPV vaccine. Mammography is recommended for breast cancer screening, although it is believed that mammography reduces breast cancer deaths by no more than one-third (8,9). By comparison, an HPV vaccine that successfully targeted all cervical...
cancer cases attributable to HPV16 alone would be expected to reduce the worldwide incidence of cervical cancer by more than one-half (Fig. 1). In countries with effective population-wide cervical cancer screening programs, other considerations are whether introduction of a vaccine might be able to reduce the physical, psychological, and financial costs associated with screening and follow-up, through a reduction in the frequency of detection of cervical abnormalities and/or the frequency of screening.

**Current Trials of Candidate Vaccines**

The difficulty of propagating large amounts of HPV together with the presence of viral oncogenes in HPVs have contributed to efforts to develop a sub-unit vaccine, rather than an attenuated live-virus vaccine or an inactivated virion-based vaccine. The leading current candidate vaccines are based on purified virus-like particles (VLPs) composed of the viral L1 protein. The L1 protein has the intrinsic capacity to self-assemble into VLPs that contain the neutralization epitopes present on authentic virions. In cutaneous and oral mucosal animal papillomavirus models, systemic vaccination with L1 VLPs can induce high titer neutralizing antibodies and can protect against high dose experimental challenge with the homologous virus (10–12). Passive transfer of immune immunoglobulin G can confer protection against experimental challenge, which strongly suggests that the effectiveness of L1 VLPs derives primarily from their capacity to induce high levels of neutralizing antibodies.

Early phase human trials of L1 VLP vaccines have indicated that, as was true in animals, L1 VLPs are highly immunogenic in humans (titers at least 40 times higher than those following natural infection) (13–15). The candidate vaccines appear to be well tolerated, with side effects similar to those seen in approved vaccines. In addition, a recent proof of principle double blind placebo controlled trial of an HPV16 L1 VLP vaccine, with alum as adjuvant, has reported highly encouraging efficacy results in young female volunteers who had been fully vaccinated (three doses of vaccine or placebo), had been negative for genital HPV16 DNA both before immunization and 1 month after the last dose of placebo or vaccine, and had then been tested every 6 months for the presence of genital HPV-DNA (16). During a mean follow-up period of 17 months after completing vaccination, there was substantial protection against incident HPV16 infection that was transient (only a single positive case of HPV-DNA; 27 cases in the placebo group versus six cases in the vaccinees), and complete protection of incident persistent HPV16 infection (defined as two or more samples positive for HPV-DNA; all 41 cases occurred in the placebo group) and of related cytological abnormalities (nine cases: five low-grade dysplasias, four moderate dysplasia, and zero high-grade dysplasia, all in the placebo group). Protection against cytological abnormalities appeared to be type-specific because the placebo group and vaccinatum group each had 22 instances of cytological abnormalities not attributable to HPV16.

These compelling results notwithstanding, current VLP vaccines do have some shortcomings, when viewed against the ideal attributes noted above. They are expensive to produce, still require a cold chain, and achieve peak immune responses only after multiple injections. Administering a purified protein vaccine may have theoretical regulatory advantages over a DNA-containing vaccine, but it has the disadvantages of production complexity and administration. Also, because papillomavirus neutralizing antibodies induced by L1 VLPs are type-specific (17,18), protection by L1 VLPs is predicted to be type-specific, and the cytology results of the above HPV16 efficacy trial are consistent with this prediction.

**Large Scale Vaccine Efficacy Trials: Scope and Endpoints**

Encouraging results from animal and human vaccine trials are leading to planned large scale efficacy trials of L1 VLP vaccines. Each trial will involve more than 10,000 female volunteers. All of the trials will use multiple systemic injections (three doses) with purified L1 VLPs. Each trial will test a vaccine composed of HPV16 and 18 VLPs alone or in combination with HPV6 and 11 VLPs, which are responsible for most cases of genital warts.

The appropriate endpoints to use for these trials have recently been discussed by a panel that is advisory to the U.S. Food and Drug Administration (FDA) (19). The panel recommended a combination of clinical and laboratory endpoints. The recommended clinical endpoints were moderate- to high-grade cervical dysplasia. In monitoring volunteers, current standards of clinical care should be followed. These standards make it unethical to wait for the development of cervical cancer in the vaccinees, who will be receiving frequent Pap smear screening during the trials. It may not even be considered ethically or medically appropriate to continue passive follow-up to high-grade dysplasia in some instances, especially for women with persistent infection with a high-risk HPV type (20).

The laboratory endpoint recommended by the panel was persistent infection by the same HPV type, with persistence being defined as at least two consecutive positive HPV-DNA tests separated by at least 6–12 months. Although it was important to know the effect of vaccine on incident infection, this parameter was felt to be less critical than persistent infection because pro-
progression to high-grade dysplasia and cervical cancer is more closely associated with persistent infection. It was argued that because most cervical HPV infections are transient, it was theoretically possible for a vaccine to provide a high degree of protection against those infections destined to be transient, but not to protect against those that were destined to be persistent. Although it was not clear biologically how a prophylactic vaccine might have such distinct effects against transient versus persistent infection, a vaccine that did possess these properties would not accomplish the goal of reducing the incidence of cervical cancer.

There may be some scientific arguments for giving particular weight to HPV-DNA test results. The reproducibility of HPV-DNA testing is much greater than that of Pap smear results (21). Also, persistent infection is predictive of progression to moderate- and high-grade dysplasia, with the predictive value increasing with the duration of infection (22). On the other hand, the Pap smear endpoint can be justified medically because therapeutic intervention is recommended for women whose Pap smears show moderate or severe dysplasia (20), and a reduction in the incidence of these interventions would represent a medical benefit of the vaccine. In addition, moderate- and high-grade dysplasias have been the traditionally recognized precursors to cervical cancer.

The planned large scale efficacy trials should provide answers to many important questions. They should develop much more information on the safety profile of the candidate vaccines. The trials should also determine the degree of efficacy of the vaccines; whether protection is truly type-specific; the degree to which protection is against incident infection, persistent infection, and dysplasias; and the durability of the immune response. They should also establish whether variants within an HPV type are protected to the same degree, provided that the analysis of the HPV types is sufficiently detailed to permit such classification. In vitro analysis of sera from HPV16 L1 VLP vaccinees indicates that the neutralization activity against the HPV16 strain that was used to make the L1 VLPs and against a spectrum of HPV16 variants was similar (23).

The duration of protection against new infection and the laboratory correlates of protection are two important related issues. Analysis of women who represent vaccine failures should provide useful information about the immunologic parameters that correlate with protection, and lead to an estimate of the frequency of revaccination that might be needed to maintain high levels of protection. The measurement of specific serum antibodies, by ELISA and neutralization assays, will be the main parameter used in the trials to monitor the immune response to the vaccine. Although serum antibody levels seem likely to correlate with protection, it may be worthwhile to analyze other aspects of the immune response to determine if they might provide additional correlated information. For example, validated assays of specific cellular reactivity and of antibodies in genital secretions might prove useful in this regard.

The current trials are not likely to determine definitively if the vaccine actually reduces the incidence of cervical cancer. The long interval between infection and cervical cancer, combined with the ethical issues related to waiting passively for an immunized population to develop cancer, mean that it may be difficult to establish this point. However, it may be possible to design community-based trials that could determine if vaccination has an overall impact on cervical cancer (24).

**POSSIBLE VACCINE MODIFICATIONS**

Determining whether any significant protection is provided between genotypes will be a prerequisite to increasing the breadth of genotype coverage for prophylactic vaccines. If VLP vaccines are found to confer a high rate of type-specific protection, there may be efforts to develop second-generation vaccines to broaden their efficacy against additional HPV types, which might be accomplished by adding VLPs from these HPV types. The potential impact of these additions can be predicted (Fig. 1). This polyvalent vaccine should be technically feasible to produce, although it might increase production costs. It should be relatively straightforward to determine whether the immune response to the new HPV types is similar when each is given as a univalent vaccine or when they are combined with the types in the first-generation vaccine, whether the presence of the new HPV types influences the immune response to the types in the first-generation vaccine, and whether the safety profile of the vaccine is altered. Although the determination of immunological equivalence has been deemed sufficient to permit incorporation of new types into a commercial vaccine (25).

Another approach to broaden vaccine efficacy might take advantage of a recent observation that the minor capsid protein L2 contains cross-reacting neutralization epitope(s) (18,26,27). This epitope from the L2 of a single HPV type may therefore have the potential to confer protection against multiple HPV types. A serious disadvantage of the L2 epitope is that it is not as immunogenic as the L1 neutralization epitopes. It is unclear whether the levels of neutralizing antibodies achievable with standard immunization protocols would actually be protective, and what the duration of such protection might be. These disadvantages might be overcome if an approach were discovered that could increase the immunogenicity of the L2 cross-neutralization epitope.

There may also be efforts with an L1 based vaccine to reduce production costs and/or simplify the mode of vaccine administration. Such modifications could have a particular impact on vaccine implementation in low resource settings. A variety of vaccine approaches might lead to an immunogen that possesses a good safety profile and the ability to induce the high titer neutralizing antibodies. These include mucosal or transdermal delivery of purified VLPs, oral delivery of crude VLP preparations in yeast or plants, L1 capsomers that retain the neutralization epitopes, or vectors that encode L1, such as polynucleotides, a viral vector, or a mucosal bacterial vector (28–30). For promising vaccine candidates, it should be possible to carry out focused efficacy trials that compare the ability of the new immunogen to protect against incident HPV infection with vaccinees who receive the standard series of systemic immunization with purified VLPs.

While the prophylactic trials are in progress, there are likely to be ongoing trials of other candidate vaccines designed to have
therapeutic efficacy against established HPV infection (5,6,31,32). Most of these trials involve the use of nonstructural viral proteins, based on the current understanding of interaction between the virus and the immune system (33). Several immunogens have shown some efficacy in animal papillomavirus models. If a vaccine in these human trials demonstrated evidence of efficacy, it might be possible to consider producing a combined vaccine that would be both therapeutic and prophylactic. Chimeric VLPs, composed of L1 VLPs plus polypeptides from one or more nonstructural viral proteins either incorporated into L1 or fused to L2, are a VLP-based approach that might combine the prophylactic properties of L1 VLPs with the therapeutic potential of immunity directed against nonstructural viral determinants. Analogous chimeric capsomers may also be feasible (34).

**QUESTIONS FOR THE FUTURE**

If the VLP vaccine proves successful, a number of important issues will need to be addressed. Anticipating these issues may help to resolve them sooner.

**Duration of Protection**

Because the VLP vaccines appear to work by inducing neutralizing antibodies, the level of protection is likely to be modeled by serum vaccine specific antibody titers. If this is the case, protection may be expected to be relatively long lived, given the high titer of antibody induced by vaccination in phase I/II clinical trials and its slow decay. However, because protection must be provided at virus entry points, persistence of antibody at mucosal surfaces may be the determinant of the level of protection, and the rate of decay of transudated mucosal antibody is unknown.

For many vaccines, if immunity has waned, exposure to infectious virus results in subclinical infection with natural reboostering of immunity. However, the relevance of this scenario to HPV-specific immunity is undetermined. It may not be strong, given the late and weak immune response to primary natural infection.

**Promoting Vaccine Use**

Although the utility of a successful papillomavirus vaccine for the prevention of cervical cancer may seem self-evident to those developing the vaccines, current consumer awareness of the link between papillomavirus infection and cancer is variable. Further, there are strong lobbying groups that take issue with the virtues of public health vaccine programs generally, and other groups that may raise concerns about the social consequences of vaccines for sexually transmitted infections. Thus, an extensive and well-considered education program may be required for vaccine use to be sufficiently widespread to have an impact on cervical cancer epidemiology. Further, because infection with HPV is not in itself a disease, and most infected individuals are not aware that they are infected, there is a risk that education will result in a group of “worried well” individuals who do not require treatment and develop significant anxiety. The education strategies adopted will therefore also need to aim to prevent this undesirable result.

**Vaccine for Males, and Herd Immunity**

Because the main mode of transmission of genital HPV infection is between men and women, it would seem appropriate to vaccinate males as well as females, especially in regions with sufficient financial resources. Vaccinating males would seem an important part of efforts to develop herd immunity against the targeted HPV types, particularly because vaccine coverage of women is likely to remain less than 100% (35).

There is less information about genital HPV infection in males, and there is as yet no evidence that the vaccine can protect men against infection or reduce exposure to women. It would be very useful to undertake clinical vaccine trials to develop evidence for such protection. To the extent that male vaccination would be aimed at reducing the risk of cervical cancer (in women), it may be noted that altruism is already a feature of some commonly used vaccines (e.g., rubella, where males are vaccinated primarily to reduce the likelihood of pregnant women being exposed to the virus). However, there could be social and clinical benefits for male vaccinees because both genders are at risk of developing cancers attributable to HPV infection at sites other than the cervix (2), and the vaccine might be able to reduce the risk for these tumors (see below). In addition, if the HPV6 and 11 component in one of the vaccines protects males against genital warts, this would be a direct benefit, although against a benign condition.

Parenthetically it may be noted that although the VLP vaccine is not likely to be therapeutic, there is some possibility that the prophylactic vaccine, if it were given to individuals already infected with an HPV targeted by the vaccine, might reduce the likelihood of its transmission to new partners, because the neutralizing antibodies might reduce or eliminate the infectious inoculum. If this possibility were verified in a clinical trial, it might provide an argument for vaccinating a target population of already infected individuals (e.g., commercial sex workers?).

**Vaccine for Children**

The average age of onset of sexual intercourse is falling in most westernized communities, and is generally below the age where consent for medical procedures can be given without parental agreement. Therefore, young adolescents who are not yet sexually active are likely to be the primary target group for the vaccine. Given the need for parental consent, education programs about HPV infection and the vaccine will probably need to be directed at the young potential vaccinees and at their guardians. Although ethical considerations may make it difficult to test the vaccine extensively in young adolescents prior to commercialization, tests for equivalence in small groups using a surrogate marker assay will probably overcome this difficulty.

**High Risk Groups**

Immunocompromised individuals are at higher risk of persistent HPV infection and of progression to malignancy at several sites, including the cervix (2). Such individuals are less likely to respond to immunization with a conventional prophylactic vaccine. Patients who have acquired human immunodeficiency virus (HIV) infection via sexual transmission are also likely to have been exposed to genital HPV infection, which reduces the likelihood they would benefit from a prophylactic HPV vaccine. However, an HPV vaccine might benefit individuals who have acquired HIV via non-sexual routes, if they could mount an immune-effective response to the vaccine. Studies will be needed to examine the extent and persistence of HPV protection in (particularly) persons with HIV infection, depending on whether they were immunized before or after the development
Management of Cervical Cancer Screening Programs in the Developed World

In countries with effective cervical cancer screening programs, one aim of a vaccine program would be to reduce the number of abnormal Pap smears requiring further management because this procedure and its follow-up represent a major cost each year (4 million abnormal Pap smears in the United States, of which only 0.3 million require management) (20). If this aim is achieved, the percentage of positive Pap smears will fall. However, screening programs will continue to be important because the current vaccines are not likely to be completely protective, nor are they expected to cover all HPV types associated with cervical cancer. It will be relevant to counsel women who receive the vaccine that they will need to participate in regular cervical cancer screening to counteract possible misconceptions that vaccination might protect them completely against this disease. Because the age at vaccination is likely to be much younger than the age at which screening begins, continual educational efforts will be needed.

Deploying Vaccines in the Developing World

The primary public health need for vaccines to prevent cervical cancer is in the developing world, where approximately 80% of the 250,000 annual deaths due to cervical cancer occur. As noted earlier, however, the logistics of delivering a new vaccine to the developing world are formidable, particularly considering that the vaccine requires multiple injected doses and is likely to be targeted to adolescents, which is a population not currently reached by any global health care program. To facilitate implementation, it would be useful to carry out trials in all areas of the world where cervical cancer is common. At the moment, for example, there are no trials planned in India, although approximately 30% of cervical cancer deaths worldwide occur there. It would also be important to determine whether malnutrition, which may be a serious problem in some areas, may have an impact on vaccine response. Given the limited resources available for dealing with all health problems, it will be useful to determine the cost effectiveness of the vaccine if it is given only to females, versus also giving it to males (35,36).

At the time that a commercial prophylactic vaccine is offered, there will be many cases of established cervical HPV infection, with perhaps as many as 5 million women globally who already have an HPV infection that will eventually lead to cervical cancer. Because this group of infected women would not be expected to derive benefit from the vaccine, it would be highly desirable to combine delivery of a prophylactic vaccine with the development of effective public health-oriented cervical cancer screening and treatment suitable for use in developing countries.

It is uncertain whether current efforts to develop an effective combined prophylactic/therapeutic vaccine will prove successful, but such a vaccine would have several potential benefits. It could target at least some of the women who are already infected, and vaccinating an older age group would lead to the vaccine having an impact on cervical cancer incidence in a shorter time than would vaccinating young adolescents.

REFERENCES


NOTES

Editor’s note: I. H. Frazer is the beneficial owner of intellectual property in the papillomavirus vaccine field that is currently assigned to the University of Queensland and licensed to CSL and to Merck.