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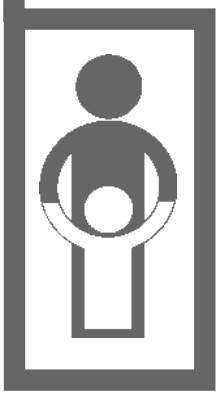
The current status of development of prophylactic vaccines against human papillomavirus infection

Report of a technical meeting, Geneva, 16-18 February 1999



DEPARTMENT OF VACCINES AND OTHER BIOLOGICALS

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INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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Contents

Glossary

ACUS/LSIL	atypical squamous celles of uncertain significance/ low-grade squamous intraepithelial lesion
CIN	cervical intraepithelial neoplasia
COPV	canine oral papillomavirus
CRPV	cottontail rabbit papillomavirus
DNA	deoxyribonucleic acid
DTH	dalayed type hypersensitivity
HAI	hemagglutination inhibition
HPV	human papillomavirus
HSIL	high-grade squamous intrpithelial lesion
IARC	International Agency for Research on Cancer
PV	papillomavirus
SIL	squamous intraepithelial lesion
STD	sexually transmitted disease
VLP	virus-like particles

1. Introduction

Papillomaviruses cause epithelial lesions in humans and animals. Research carried out over the past twenty years has indicated that there are many human papillomavirus genotypes (HPV types), and that HPVs are associated with a remarkable number of benign and malignant proliferative conditions. These diseases include cervical cancer, which is second most common cancer of women worldwide and the most common cancer of women in less developed countries. Such findings have stimulated considerable interest in developing vaccines against HPVs. Since infection by papillomaviruses is species-specific, papillomavirus vaccine testing has relied primarily on animal papillomavirus (PV) models. Preclinical trials with systemically administered recombinant sub-unit vaccines, in several animal PV models, have produced excellent protection against experimental viral challenge. Protection in these models correlates with the development of neutralizing antibodies and can be passively transferred by immune globulin. Analogous preparations of candidate sub-unit HPV vaccines can induce high levels of neutralizing antibodies in animals and, very recently, in normal human volunteers.

These promising results prompted the World Health Organization (WHO) to organize a technical meeting to review the current status of development of prophylactic vaccines against HPV infection. The meeting was held at the WHO headquarters in Geneva, 16-18 February, 1999. It was coordinated by Dr. Yuri Pervikov from WHO and chaired by Professor Harald zur Hausen, the Scientific Director of the Deutsches Krebsforschungszentrum in Heidelberg. An important outcome of the meeting is that the WHO will encourage the testing of subunit HPV vaccines in clinical efficacy trials, with the goal of identifying an effective vaccine that could be used globally to reduce the disease burden from HPV infection.

2. Disease burden

There are more than 80 HPV types whose DNA genomes have been completely sequenced, and there exist more than 100 additional HPV types that have been less well characterized. A sub-set of these HPV types has been closely associated with a variety of malignant diseases. The relationship between HPV infection and cervical cancer has been studied in great detail because it is such an important cancer worldwide and because many developed countries have established cervical cytologic screening programmes to detect pre-malignant lesions. At least 95% of these cancers contain HPV DNA. Many different HPV types are found in cervical cancer. However, a single type, HPV16, is present in more than 50% of them, and an additional three types (HPV18, 31, and 45) are present in approximately an additional 30%. Thus approximately 80% of cervical cancers contain one of these four HPV types. Although there are some regional differences in the relative proportion of cases associated with a given HPV type, the similarities are striking. For example, HPV16 is the type found most frequently in cervical cancer in every region of the world. Longitudinal studies demonstrate that HPV infection precedes the development of virtually all high grade cervical dysplasias and that the distribution of HPV types in high grade dysplasias is similar to that found in cervical cancer. Cervical infection with these so-called high risk HPV types is a very important biomarker associated with the development of high grade dysplasia, with odds ratios of 50-200 reported for several large studies. In addition, the genomes of high risk HPVs contain oncogenes that are preferentially retained and expressed in the tumors. These considerations have led the International Agency for Research on Cancer (IARC) to conclude that cervical HPV infection is required for the development of virtually all cases of cervical cancer and high-grade dysplasia.

The disease burden from cervical HPV infection can be considered at several levels. IARC has estimated that in the year 2000 there will be approximately 450 000 cases of cervical cancer worldwide. In addition, screening for pre-malignant lesions and their follow-up and treatment represents another facet of morbidity associated with these infections. In the United States, there are about 300 000 new cases each year of high grade dysplasia, one million of low grade dysplasia, and 10 million of cervical HPV infection not associated with detectable cervical abnormalities. Comparable worldwide figures are approximately 10 million cases of high grade dysplasia, 30 million cases of low grade dysplasia, and 300 million cases of cervical infection without cytologic abnormalities. While many cases of cervical HPV infection without cytologic changes are self-limited, an important subset will subsequently become associated with cytologic abnormalities, and it is widely recognized that virtually all cases of cervical cancer come from high grade dysplasias. In developed countries where many women undergo regular cytologic screening, such screening entails

substantial cost. For example, it has been estimated that in the United States of America the cost of cervical cancer screening, follow-up, and treatment is approximately US $5 billion per year.

Papillomavirus infection has also been closely linked to a variable proportion of other tumors. It has been estimated that approximately 85% of the 44 000 cases of anal cancer worldwide are attributable to HPV infection, with HPV16 accounting for the vast majority of the HPV positive cancers. In addition, close to 50% of cancers of the vulva, vagina, and penis may be attributable to HPV infection, as well as approximately 20% of oropharyngeal cancers, and 10% of cancers of the larynx and aerodigestive tract. Sensitive techniques have also identified DNA of cutaneous HPV types in a considerable proportion of non-melanoma skin cancers; additional research is being carried out to arrive at clear estimates of the proportion of such cancers that may be attributable to HPV.

Excluding non-melanoma skin cancers, approximately 6% of the estimated nine million cases of cancer worldwide per year may be attributable to HPV infection. Women from less developed countries carry a particularly high burden from HPV-associated cancers. For example, 20-24% of all cancers in women from Latin America, Southwest Asia, and Sub-Saharan Africa are attributable to HPV.

HPV infection without premalignant potential can also cause substantial morbidity, have socially devastating consequences, and be costly to treat. Laryngeal papillomatosis, a potentially life-threatening HPV infection, usually occurs in very young children. Non-genital warts, which occur most frequently in children below 10 years of age, can be very extensive and disfiguring, especially in individuals with impaired cellular immune function. Genital warts develop most commonly in sexually active adults less than 25 years of age, but they also occur in children, often as a consequence of sexual abuse. In the United States and the United Kingdom approximately 1-3% of sexually active people have genital warts.

3. Vaccine prospects

The large disease burden from HPV infection has stimulated interest in developing an effective HPV vaccine. It could reduce a large cancer burden in less developed countries and in more developed countries could reduce the incidence of precancers and other frequent genital HPV lesions. A prophylactic vaccine would have a major impact on HPV disease burden. However, since progression from benign infection to cancer usually takes decades, it would be some time before an effect of a prophylactic vaccine programme on cervical cancer rates would be seen. A therapeutic vaccine could also have considerable utility, and its impact might be more immediate. The greatest versatility and applicability would be obtained from a vaccine that possessed prophylactic and therapeutic properties.

The presence of viral oncogenes in HPVs poses theoretical obstacles to the development of a prophylactic vaccine that carries the viral genome. Therefore, efforts have been aimed at developing sub-unit vaccines. It was discovered that the L1 major structural viral protein, when expressed in eukaryotic or prokaryotic cells, can self-assemble into virus-like particles (VLPs), thus allowing the production of preparative amounts of VLPs. L1 contains the immunodominant neutralizing epitopes, which are conformation-dependent. Since L1 VLPs closely resemble the conformation of authentic virions, they can induce high levels of neutralizing antibodies. The neutralizing antibodies tend to be type-specific, although some cross-reactivity may occur between the most closely related types. There is a second structural viral protein, L2, which when co-expressed with L1 can co-assemble with L1 with a stoichiometry that is similar to what is seen in authentic virus (approximately 30 molecules of L1 for each molecule of L2).

Preclinical models: Papillomaviruses are species-specific. Therefore preclinical vaccine trials have emphasized animal models, particularly a cutaneous rabbit model (caused by the cottontail rabbit papillomavirus, CRPV), a bovine oral mucosal model (caused by bovine papillomavirus type 4, BPV4), and a canine oral mucosal model (canine oral papillomavirus, COPV). Systemic vaccination with VLPs in all three systems has resulted in 90-100% protection against experimental challenge. In those animal models where it has been examined, protection is no greater for L1/L2 VLPs compared with L1 VLPs, can be passively transferred with IgG, depends on the induction of neutralizing antibodies, can last at least one year, can be induced without adjuvant, and is not induced by heterologous VLPs. In the rabbit system, similar protection has been achieved by injection of an L1 containing plasmid that expresses L1 that induces neutralizing antibodies against conformational epitopes. Non-human primates immunized systemically with HPV11 L1 VLPs can induce neutralizing IgG in the serum and vaginal tract.

Despite the vaccine studies, our understanding of the immunology of papillomavirus infection remains incomplete. Animal PV models can be extremely valuable in elucidating the parameters that determine whether papillomavirus infection persists, progresses, or regresses, in addition to their utility for probing the mechanisms by which HPV infection can be prevented. The immune response to genital HPV infection in humans also deserves further study.

Serologic assays: A number of *in vitro* neutralization assays have been developed for HPVs, and they can be used to assess the response to vaccination. Some neutralization assays use authentic virus, while others rely on pseudovirions in which L1 alone or L1 combined with L2 have pseudotyped a DNA whose expression can be detected in cultured indicator cells. Since immunoprophylaxis seems to correlate with virus neutralization, these assays represent the "gold standard" in measuring the response to vaccination. Although each assay seems to be reproducible, it should be noted that their relative sensitivity may vary, depending upon the particle to infectivity ratio. In addition, neutralization assays are cumbersome, time consuming, technically difficult, and expensive. It is therefore important to have simpler surrogate assays that can be used more routinely.

The availability of preparative amounts of VLPs has led to the development of surrogate assays to monitor the humoral response to VLPs or other preparations of structural viral proteins. The most widely used is a VLP-based ELISA, which is sensitive, rapid, inexpensive, and relatively type-restricted. It has the potential disadvantage that the ELISA antigen includes, in addition to properly assembled VLPs, some at least partially denatured L1, which means the assay can detect antibodies to linear epitopes (which are non-neutralizing) in addition to neutralizing antibodies to conformational epitopes. This limitation is not a problem for measuring the serologic response to natural infection, since the immunodominant epitopes are conformational. However, it could represent a disadvantage in monitoring the response to VLP vaccination, since reactivity to denatured VLPs might yield ELISA titres that would not correlate directly with neutralizing activity. A second type of assay is hemagglutination inhibition (HAI), which takes advantage of the ability of HPVs to induce hemagglutination of mouse red blood cells. In contrast to the ELISA, HAI only measures antibodies to conformational epitopes, and is as type-restricted as neutralizing antibodies. However, there are two classes of PV neutralizing antibodies: those that can inhibit VLP binding to cells and those that do not prevent VLP binding. The HAI has the disadvantage of detecting only that subset of neutralizing antibodies that can inhibit VLP binding to cells. In addition, the HAI is less sensitive than the ELISA. A third type of surrogate assay measures the ability of the antibodies to interfere with the binding of a neutralizing monoclonal antibody. Such assays can be specific and sensitive, but will measure only that subset of neutralizing antibodies that interfere with the binding a given monoclonal antibody.

Early phase human clinical trials: Results from three early phase human clinical trials with L1 VLPs are just becoming available. One was a dose-escalation trial, in which 65 normal volunteers were given placebo or three systemic doses of HPV11 L1 VLPs in alum. The vaccine was well tolerated, with only mild side effects, such as headache and local pain at the injection site. The volunteers who received 9, 30, or 100 µg of VLPs per dose had similar serum responses. These included endpoint HPV11 ELISA titres of 1259 to 5012, cross-reactivity in an HPV6 ELISA, and

HPV11 neutralizing titres of 1000 or greater in 33/34 subjects. Those individuals who received 3 µg per dose did not respond as well. In a second trial, subjects with genital warts were vaccinated with 1, 5, or 10 µg of HPV6 L1 VLPs without adjuvant. None of the vaccinees developed serious local or systemic reactions. Of 33 tested subjects, 29 developed antibodies to the VLPs and 32 of 34 developed DTH responses. A lower antibody response was seen in subjects vaccinated with 1 µg VLPs. Only interim results are available for a third trial, involving 48 normal volunteers, which tested three systemic doses of HPV16 L1 VLPs given with no adjuvant or with alum, or placebo. The vaccine was well tolerated, with side effects similar to those in the HPV11 trial. One month after the first boost, geometric mean serum HPV16 ELISA titres were one order of magnitude higher for those receiving 50 µg doses, compared with 10 µg doses (4450 versus 400, respectively). At this time point, the presence of alum did not increase the immune response.

Alternative vaccine approaches: Although it is hoped that systemic administration of L1 VLPs will prove to be effective, other vaccine approaches are also being considered. It is possible that the induction of specific mucosal immunity might be required for an L1 vaccine to be effective, or that its effectiveness might be greater if the vaccine induced such immunity in addition to systemic immunity. Therefore, some efforts are being made to study mucosal immunity in preclinical models, and in planned early phase human trials.

In addition, other viral polypeptides are being added to L1 or L2, with the hope of improving the ability of the vaccine to prevent HPV infection and to confer a therapeutic potential to the vaccine. Such “chimeric” VLPs that fuse peptides from non-structural viral proteins have been constructed. When injected in mice, they induced an immune response to the fusion peptide, including protection against tumor formation induced by a syngeneic cell line that expresses the non-structural viral protein (E7) from which the fusion peptide was derived. Fusing the peptide to L1 carries the advantage of having as many molecules of the fusion peptide as of L1. However, only a limited number of amino acids (perhaps not more than 60) can be added to L1 while maintaining its ability to self-assemble. Fusing the peptide to L2 has the disadvantage that VLPs contain many fewer molecules of L2 than of L1. However, since L2 is not required for VLP formation, very large polypeptides can be added to L2 (at least 500 amino acids), without interfering with the ability of such chimeric VLPs to induce high levels of neutralizing antibodies. Early phase clinical trials of both types of chimeric VLPs are planned, including efforts to assess their possible efficacy against established HPV infection. Preclinical and clinical trials are also being carried out with non-structural viral proteins alone. Vaccination with these viral proteins would be used primarily in therapeutic settings.

Clinical efficacy trials: It is anticipated that prospective prophylactic efficacy trials may be initiated in the next few years. To determine efficacy, such trials will probably require large numbers of individuals, studied over several years. Young women who are initiating sexual activity will probably represent the cohort for such trials. However, vaccination of both men and women might ultimately be considered, since this strategy is the one most likely to be effective in breaking the cycle of sexual transmission and thereby preventing disease. Selection of appropriate efficacy endpoints in the trials will require careful consideration. To have a major impact on disease burden, it will be necessary for a vaccine to protect against several different HPV types. This might include both high risk types, to prevent cancers and their

precursors, and low risk types, to prevent genital warts and laryngeal papillomatosis. However, demonstrating efficacy against even one HPV type would stimulate further efforts to develop a multivalent vaccine. In contrast to prophylactic trials, therapeutic trials could examine fewer individuals, studied over a shorter period.

4. An agenda to accelerate development, evaluation and introduction of prophylactic vaccine against human papillomavirus

4.1 Burden of HPV-related lesions

Perceptible disease related to HPV: Cervical cancer represents the most common severe clinical consequence of HPV infection. It is now clear that virtually all cervical cancer cases show HPV markers against a background point prevalence of HPV DNA in their reference populations of 10 –15%. A limited number of HPV types account for the majority of the cases, with HPV 16 accounting for about half of the cervical cancer cases. The other lower anogenital tract cancers (vaginal, vulvar, penile, anal) are also closely related to HPV, albeit with a lower percentage of cases attributable to the known HPV types. Research is now focusing on the etiologic role of HPV in aerodigestive, and non-melanoma skin cancers.

Current IARC estimates of HPV-related cancers are at least 11% and 2% of all cancers in females and males, respectively, with a disproportional burden in the developing world. These proportions represent over 450 000 cases in women and 100 000 cases in men. Cervical cancer alone will cause almost 200 000 deaths worldwide in 1999 and is particularly damaging because it often strikes women of childbearing age.

Other types of HPV (namely HPV 6 and 11) are responsible for genital warts, a common sexually transmitted disease (STD), and for a rarer condition, laryngeal papillomatosis, which can be acquired at birth from HPV carrier mothers. Persistent venereal warts and laryngeal papillomatosis may require extensive and repeated treatment and laryngeal papillomatosis may be life threatening in children.

In addition to cancer and warts, HPV is closely related to pre-invasive cervical neoplasia (CIN or SIL). CIN is largely identified in screening programmes, and the diagnosis generates a considerable burden of medical interventions in countries with established organized programmes or sporadic screening activity.

It is estimated that close to 300 million women in the world are carriers of HPV DNA without clinical implications. Males are also carriers of HPV DNA, probably at rates roughly similar to those of women.

Recommendations: WHO should launch activities to increase awareness of the role of HPV in human disease, notably in cervical cancer. Information should include the potential promise of the new HPV vaccines.

It is recognised that lack of epidemiologic information on HPV and related outcomes is still a major problem in extensive areas of the world. This makes it difficult to make final estimates of disease burden attributable to HPV. Identified areas in which more information is needed are:

1) The fractions of cervical and other cancers caused by various HPV types in different regions. These estimations require a) cancer surveys with type-specific HPV DNA and or b) serologic testing in selected developing areas (e.g. Africa, China and India) and matched surveys to estimate the prevalence of type specific HPV infections in the general populations.
2) The incidence/prevalence of genital warts.
3) The incidence/prevalence of laryngeal papillomatosis.
4) Complete epidemiological studies implicating HPV in other cancer sites, particularly the aerodigestive tract and skin.

The World Health Organization should support the groups conducting or planning the epidemiological studies required to implement vaccination trials (e.g knowledge of their cancer incidence, the prevalence of specific viral types).

Introduction of the HPV vaccines would require cost-benefit analyses. To this end it would be useful to collect economic data on the current costs of screening and treatment of cervical neoplasia and cervical cancer.

4.2 Clinical evaluation of HPV vaccines

Selection of optimal vaccines

Background: Several approaches to vaccination are possible. Vaccines being proposed include primary prevention vaccines that prevent initial infection, secondary prevention vaccines that prevent established infections and early cervical lesions from progressing, and therapeutic vaccines. The panel discussion focused mainly on primary prevention vaccines. The consensus was that these vaccines are likely to include structural antigens. However, it could be beneficial to include additional antigens which might provide a secondary prevention or therapeutic effect, in addition to the primary prevention of infection. Various vaccines are currently being tested in early safety and immunogenicity trials, including most notably VLP-based vaccines. The VLP vaccines being considered include L1-VLPs, L1/2-VLPs, and chimeric VLPs. Other vaccines are also undergoing early trials.

Recommendations: Given that results from safety and immunogenicity trials are not all available, it is too early at this point to settle on a single vaccine formulation. The WHO should encourage and assis trials to evaluate several approaches.

Clinical trials

Background: Various phase I/II clinical trials are currently underway to evaluate the safety and immunogenicity of an HPV vaccine. In addition, planning for at least one efficacy trial has begun. Additional efficacy trials are likely. Initial trials are likely to be conducted among women of various ages, although vaccination of males and vaccination during adolescence (i.e. before the onset of sexual activity) may ultimately be required to allow for effective interruption of HPV transmission.

Recommendations: The panel recommends that efforts be made to assure that efficacy trials be initiated without delay, following the completion of safety and immunogenicity trials. Safety and immunogenecity data should be available on the population where efficacy trials are planned, prior to the initiation of such larger trials. The panel further recommends that more than one efficacy trial be conducted, since this would allow for the evaluation of HPV vaccines in different populations (including both developed and developing countries) and also because the conduct of multiple trials would allow for the evaluation of efficacy of more than a single vaccine formulation.

Expected impact of vaccination

Background: The motivation for the use of an HPV vaccine might vary between countries, particularly between developed and developing countries. In developing countries, the major focus is likely to be on the prevention of invasive cervical cancer while in more developed countries, where screening programmes are currently available, the emphasis might include prevention of cancer precursors and benign HPV-related lesions (i.e. warts).

Conclusions: The panel felt that an HPV vaccine has the potential to interfere with the establishment of HPV infection and thereby to prevent cervical cancer precursors, cervical cancer, and benign HPV-related lesions.

Clinical trial endpoints

Background: Our current understanding of the natural history of cervical cancer provides clues for the selection of endpoints for vaccine efficacy trials. These include viral infection, its early cytological manifestations (ASCUS/LSIL), and more severe precursor lesions (HSIL). All initial efficacy trials will undoubtedly measure persistent HPV DNA as one endpoint. Clinical endpoints are also important but will need to be evaluated in the context of HPV DNA genotyping, since the vaccine will probably protect against those cervical lesions caused by the specific HPV types included in the vaccine. It is unlikely that HPV DNA alone would be used as the trial enpoint in initial efficacy trials. Natural history studies are currently underway and should provide information on the pathways through which HSIL can arise and therefore provide additional clues to the most desirable clinical endpoints in vaccine efficacy trials.

Recommendations: Data from ongoing natural history studies will become available shortly and should be evaluated closely with the objective of selecting ideal trial endpoints. In addition to persistent HPV DNA, clinical enpoints might include all cytological abnormalities (ASCUS/LSIL/HSIL), or HSIL alone. Clinical outcomes will need to be evaluated in the context of HPV DNA genotypes. When trials are designed, consideration should be given for long-term follow-up to allow for a determination of the duration of protection provided by the HPV vaccine.

Standardization and monitoring of laboratory assays and trial endpoints

Background: Multiple groups are planning HPV vaccine trials in the near future. These prophylactic trials will need to evaluate the immunogenicity of the vaccine (including the neutralizing ability of the antibodies generated by the vaccine) and also to have reliable measurements of HPV infection and clinical outcomes. It is important that results obtained be comparable across trials.

Recommendations: The panel recommends that the WHO establish one or two working groups. These groups would assure the standardization of assays used to evaluate the persistence of HPV DNA and the immune response to a vaccine, with the objective of making it possible to compare results obtained in different trials. They would also establish standard criteria for the evaluation of clinical outcomes in efficacy trials.

4.3 Development of second generation of HPV vaccines

Background: The first generation vaccines will likely contain L1 VLP plus alum adjuvant. This is an attractive approach because it uses established technology, has been demonstrated to be effective in animal models, and is immunogenic in man. Nevertheless there are reasons to develop second generation vaccines. A second generation vaccine might increase efficacy, duration of protection, coverage of target populations, and decrease transmission. Desirable properties of a second generation vaccine include increased number of viral antigen targets (both early and late gene products), generation of cell mediated responses to early antigens, generation of secretory IgA, increased suitability for world wide use (e.g. decreased cost, elimination of a cold chain, a simpler dosing schedule), increased protection against more types, and targeting of other infectious diseases.

Possible approaches for a second generation vaccine include polynucleotide vaccines, live bacterial and viral vectors, bacterial produced proteins, mucosal delivery systems, chimeric VLPs, and alternative adjuvants. These approaches have given promising results in preclinical papillomavirus and other studies.

Recommendations: Preclinical and clinical studies of alternative vaccine strategies should proceed. At the present time there is a window of opportunity to test these strategies in phase I and II prior to the completion of phase 3 trials of the first generation vaccine. There is a need to develop surrogate assays for efficacy and to standardize such assays. This could involve development of a bank of standard reagents. This is an area in which the WHO could materially contribute to HPV vaccine development. The WHO should also play a continuing role in facilitating progress through organizing meetings and exchange of information.

4.4 Regulatory, safety, ethical, and licensing issues

WHO and IARC recognize the imperative for an HPV vaccine. The primary aim of an HPV vaccine would be prophylactic, although an effective therapeutic vaccine could also have considerable utility. Compared with other vaccines, the contemplated HPV vaccines do not pose unusual ethical, regulatory, safety, and licensing issues, although we recognize that such issues are very important. Therefore, WHO and IARC recommend that HPV vaccines follow accepted guidelines as well as standards of good manufacturing practice and good clinical trial practice and be responsive to national and international guidelines. For global implementation of a vaccine, it would be important for vaccine manufacturers to interact at an early stage with national and international regulatory agencies. Also, there may be a vaccine that is both therapeutic and prophylactic. The process for licensing such a vaccine should be handled similarly.

A prophylactic vaccine would ideally be targeted to a young population that has not yet become sexually active, although older individuals may also benefit from such a vaccine. Therefore, the main target population for a prophylactic vaccine will be adolescents and/or children. Furthermore, to have the greatest utility, it would be important to target males and females in the cohort target population.

However, it is recognized that the majority of clinical efficacy trials for a prophylactic vaccine may be carried out primarily in women, and these trials may also involve an age cohort that is somewhat older than the ultimate main target population for the prophylactic vaccine. Given the diversity of the population at risk for HPV infection, it is essential for vaccine trials to include representative populations, to ensure global relevance. Ultimately, it will also be important to test the vaccine, at least in bridging studies, in the younger target populations, both in males and females.

It would be highly desirable to have host-response assays and laboratory endpoints that correlate with clinical efficacy. If such correlates can be developed, it will greatly facilitate the addition of other HPV genotypes/serotypes to a vaccine.

Annex
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