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Douglas R. Lowy

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Harrington Prize Essay

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HPV vaccination to prevent cervical cancer and other HPV-associated disease: from basic science to effective interventions

Douglas R. Lowy

Laboratory of Cellular Oncology, National Cancer Institute, NIH, Bethesda, Maryland, USA.

Identification of HPV infection as the etiologic agent of virtually all cases of cervical cancer, as well as a proportion of other epithelial cancers, has led to development of three FDA-approved multivalent prophylactic HPV vaccines composed of virus-like particles (VLPs). This essay describes the research and development that led to the VLP vaccines; discusses their safety, efficacy, and short-term effect on HPV-associated disease; and speculates that even a single dose of these vaccines, when given to adolescents, might be able to confer long-term protection. The HPV field exemplifies how long-term funding for basic research has lead to clinical interventions with the long-term potential to eradicate most cancers attributable to HPV infection. Although this essay is the result of my receiving the 2015 Harrington Prize for Innovation in Medicine from the Harrington Discovery Institute and the American Society for Clinical Investigation, this clinical advance has depended on the research of many investigators, development of commercial vaccines by the pharmaceutical companies, and participation of many patient volunteers in the clinical trials.

Introduction

Compared with diseases attributable to noninfectious causes, it is often easier to prevent or treat diseases caused by infectious agents. This truism was an important reason that the identification of HPV as the infectious agent responsible for cervical cancer in the early 1980s, by Harald zur Hausen and his colleagues at the German Cancer Research Center (DKFZ), was hailed as a major advance (1). This fundamental discovery was followed up by additional research that has resulted in the development of effective vaccines for preventing infection and disease caused by HPV and new approaches, based on HPV detection, for cervical cancer screening (2). In this article, I highlight the development of prophylactic HPV vaccines, their ability to reduce HPV-induced disease, and their potential to influence vaccinology. The initial HPV vaccine research was conducted in academic and government laboratories and led to the technology that underlies the vaccines. Pharmaceutical industry involvement has been critical for downstream aspects of vaccine development and testing, with important contributions by academic investigators validating the utility of the vaccines.

My role in HPV vaccine development has been enabled by many factors. The most important is that I have conducted my papillomavirus (PV) research together with John Schiller for more than 30 years. This remarkably fruitful and collegial collaboration has enabled me to accomplish much more than would otherwise have been possible. We have been fortunate to work in the intramural program of the National Cancer Institute (NCI) at the NIH, where principal investigators have considerable freedom in choosing the projects for which they use their laboratory resources, although these choices need to be rigorously defended, retrospectively, at quadrennial laboratory site visits conducted by extramural colleagues. This wide latitude was especially important for John and me, because prior to the early 1990s, when we started our vaccine research, we did not have a background in immunology, vaccinology, or translational research and had not studied the genes that give rise to the viral capsid, L1 and L2, whose evaluation was critical to development of the vaccine. Instead, our prior research had focused on the molecular biology of other PV genes, such as the viral oncogenes (E5, E6, and E7) and the main viral gene (E2) that regulates the expression of other viral genes (3–5).

The freedom of the intramural program made it straightforward for us to use some of our resources to initiate the vaccine research. In addition, we benefited from advice provided by many intramural colleagues from other NIH institutes, who freely shared their expertise in vaccinology and related areas. In addition, we have been fortunate that the intramural population science program at NCI has an extraordinarily strong group of molecular epidemiologists with expertise in the natural history of HPV infection and a commitment to studying interventions with potential to reduce HPV-associated disease. These colleagues have conducted a long-term HPV vaccine trial that has provided unexpected insights into the char-

Conflict of interest: As part of D.R. Lowy's US government–supported research at the NCI/NIH, he is an inventor of technology that underlies the L1-based prophylactic VLP HPV vaccine and technology that underlies an L2-based candidate prophylactic HPV vaccine. The NIH has licensed the technology for the L1 VLP vaccine to Merck, the manufacturer of Gardasil; to GSK, the manufacturer of Cervarix; and to Indian Immunologicals Ltd. The L2-based vaccine technology is the subject of a cooperative research and development agreement among the NCI, Johns Hopkins University, and Shantha Biotechnics and has been licensed to Shantha Biotechnics, PaxVax, Acambis Inc., and GSK. US Federal law entitles D.R. Lowy to a limited share of the royalties the NIH receives for these technologies.

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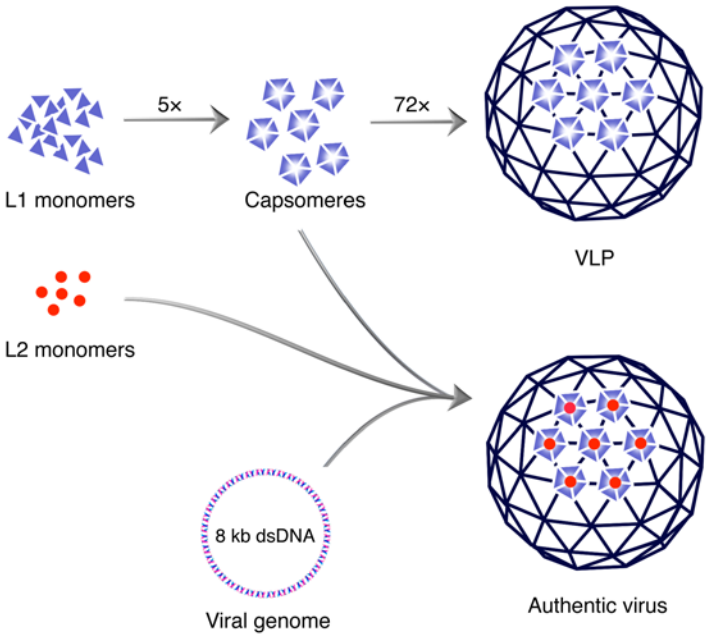

Figure 1. Assembly of L1 VLP vs. assembly of authentic virus. Inside cells, five L1 monomers (5×) self-assemble to form a capsomere, and 72 capsomeres (72×) then self-assemble to form a VLP. In authentic virus, the capsid is composed of both L1 and L2, and it surrounds the 8-kb double-stranded (ds) viral DNA genome. L1, the PV major capsid protein; L2, the PV minor capsid protein. Reproduced with permission from *The Lancet Oncology* (50).

acteristics of the vaccine, with important conceptual and practical implications for future clinical research in this area (6, 7).

HPV types and HPV-associated cancers

HPV infection causes several different cancers (8). Cervical cancer, which is the third most common cancer in women worldwide, accounts for the most cases. Virtually all cases of cervical cancer are attributable to HPV infection. There are more than 500,000 cases each year and more than 250,000 deaths. HPV infection is also responsible for other malignant anogenital tumors, including the vast majority of anal carcinomas and a high proportion of vulvar, vaginal, and penile cancers. HPV also causes a subset of oropharyngeal cancer; about three-quarters of these cases arise in men. In the US, the incidence of HPV-positive oropharyngeal cancer increased more than three-fold during a recent 25-year period, with analogous increases arising in other industrialized countries (9).

Approximately 200 HPV genotypes (types) have been described (10). Infection by a subset of these types accounts for the HPV-associated cancers described above (11). HPV16 is the most oncogenic, followed by HPV18. Together, these two types (HPV16/18) account for about 70% of cervical cancer, with infection by approximately 10 other types accounting for the vast majority of the remaining 30%. More than 80% of the noncervical HPV-associated cancers are attributable to HPV16/18 (12). In addition, HPV6 and HPV11 cause about 90% of genital warts, while other HPV types cause nongenital warts or asymptomatic infections.

Although most HPV infections clear spontaneously, some persist. If the persistent infection is with an oncogenic HPV type, it places the patient at risk of developing precancerous lesions and invasive cancer (13). The interval between the acquisition of infection and cancer is usually 15 to 25 years or more.

HPV vaccine development: bovine PV type 1 virus-like particles induce high-titer neutralizing antibodies against conformational epitopes

The public health importance of cervical cancer provided the initial impetus for vaccine development. Most licensed vaccines against infectious agents are preventive, as it has proven easier to use the immune system to prevent new infection or the disease that follows it than it is to treat established infection or disease. The induction of pathogen-neutralizing antibodies is the principal protective immune response induced by most preventive vaccines.

PVs have two capsid proteins, each of which contains neutralization epitopes: the L1 major capsid protein and the L2 minor capsid protein (Figure 1). When we started our vaccine research, bovine PV type 1 (BPV-1) was widely used for in vitro analysis of PV function, because authentic infectious virus was readily available (from BPV-1–induced cow warts) and because we had previously developed a quantitative in vitro cell transformation bioassay for BPV-1 infection (14). That assay could also measure anti–BPV-1–neutralizing antibodies. The only described HPV neutralization assay at that time was a cumbersome in vivo assay for HPV11 (15).

Reinhard Kirnbauer, the talented postdoctoral fellow in the lab who conducted the experiments, used BPV-1 to initiate the vaccine research because the induction of neutralizing antibodies was the key test we would use to evaluate whether we had a vaccine candidate. At the time, it was known that immunization with BPV-1 virions could induce high titers of neutralizing antibodies, but it was unclear whether these antibodies were attributable to L1, L2, or a combination of the two proteins. Reinhard expressed L1, L2, or both proteins in insect cells via recombinant baculoviruses. He quickly developed encouraging results with extracts from the L1 preparation: they contained self-assembled virus-like particles (VLPs) that morphologically resembled authentic BPV-1 virions and were able to raise high-titer serum antibodies when injected in rabbits (Figure 1 and ref. 16). This was the first time

that such results had been observed for any PV. The neutralizing antibodies were conformationally dependent, as denaturing the L1 in the VLPs by boiling them in detergent abolished the ability to induce neutralizing antibodies. L1/L2 particles were qualitatively similar and self-assembled somewhat more efficiently.

HPV16 VLPs: inefficient VLP assembly and its solution

Despite the positive BPV-1 VLP results, recombinant HPV16 L1 was found to self-assemble about three orders of magnitude less efficiently than BPV-1. Given that HPV16 was the most oncogenic HPV type, it was critical to determine whether the inefficient self-assembly with HPV16 was intrinsic to HPV16 or whether it was an aberrant result. The HPV16 genome that was used by our laboratory, and by almost all researchers during this period, was the reference strain that had been isolated from a cervical cancer by zur Hausen and his colleagues. At that time, it could not be unequivocally determined whether our HPV16 preparation could induce neutralizing antibodies, as an HPV16 neutralization assay had not yet been developed. We speculated that the inefficient self-assembly might imply that the HPV16 preparation would be much less efficient than the BPV-1 preparation in displaying the conformation-dependent neutralization epitopes.

As it was known that the E5 open reading frame in the HPV16 reference strain was a mutant, we speculated that an analogous change in L1 might account for its inefficient self-assembly. To assess this possibility, we asked colleagues for their HPV16 genomes that had been isolated from infections that had not progressed to cancer. The L1 protein of these HPV16 isolates were found to self-assemble with an efficiency similar to that of BPV-1. When the sequence of the L1 open reading frame in these isolates was compared with L1 from the reference strain, the latter L1 was found to have a single-point mutation, at codon 202, which encoded His instead of Asp (17).

Examination of the alignment of the L1 of all known PVs indicated that each L1 encoded either Asp or the closely related Glu at that codon. We therefore concluded that L1 from the HPV16 reference strain was a mutant, that the wild-type HPV16 L1 self-assembled efficiently into VLPs, and that efficient self-assembly of L1 into VLPs was a characteristic shared by animal PVs and HPVs. When we did develop an HPV16 neutralization assay, it turned out that the HPV16 wild type induced high levels of neutralizing antibodies, while the mutant L1 preparation from the reference strain did not induce detectable levels of neutralizing antibodies (and, therefore, presumably would not have been useful in an HPV vaccine) (18).

Animal model testing: VLP vaccines prevent disease but don't treat it

Authentic HPVs are not infectious for experimental animals, which precluded the testing of HPV VLPs in an experimental HPV challenge model. (We subsequently developed a mouse genital tract HPV challenge model (19) — see below — but it was not available in the mid-1990s.) Therefore, animal PV models were used to test the potential of the VLP approach. Most studies were conducted in the cottontail (Shope) rabbit PV model, which causes cutaneous lesions, but some used the canine oral PV or BPV-4, both of which cause (nongenital) mucosal lesions. The results indicated that VLP vaccines induce strong protection when given prior to experimental challenge but not when given to treat established infection (reviewed in ref. 20). Passive transfer of immune sera could protect naive animals against experimental challenge, implying that protection can be mediated by the induced neutralizing antibodies. Furthermore, protection was induced by the intact homologous VLP, but not if it was denatured by boiling in 1% SDS or was from a different PV, providing additional evidence that induction of the conformationally dependent neutralizing antibodies was needed for protection.

VLPs induce type-restricted neutralization

In the mid-1990s, we developed an in vitro neutralization assay for HPV16 and a hemagglutination-inhibition assay (HIA) for several HPV types. The latter served as a stringent surrogate assay for neutralization. The HIA results indicated that L1 VLPs from HPV16 and HPV18 did not cross-react with each other, although some cross-reactivity was seen between HPV types that were more closely related phylogenetically (21). The HPV16 neutralization results indicated all HPV16 isolates behave as a single serotype, as antibodies induced by any HPV16 VLP strongly neutralized even the most divergent HPV16 isolates (22). These data implied that VLPs from a single HPV16 isolate should induce a similar degree of protection against all HPV16 isolates, a prediction that has been validated in the human clinical trials described below.

Human clinical trials

The initial controlled clinical trials determined that VLPs were highly immunogenic, even without adjuvant, and well tolerated (23). The most striking early results were observed in a phase II efficacy trial, in sexually active women, of a monovalent HPV16 VLP vaccine conducted by Merck (24). In that trial, whose results were reported in 2002, all 41 cases of new persistent cervical infection with HPV16 occurred in the placebo control group. Even when single time point infections were measured, there were about five times more HPV16 infections in the control group compared with the HPV16 group, which suggested that the vaccine was inducing sterilizing immunity in most patients. This observation implied that the vaccine was quite potent, as the effectiveness of many approved vaccines is attributable to their ability to prevent disease, rather than to prevent initial infection. In addition, the trial reported that an equal number of cervical dysplasias caused by types other than HPV16 had occurred in each experimental arm. The lack of protection against lesions caused by HPV types other than HPV16 made it likely that, if there were cross-protection against heterologous HPV types, it would be limited. A phase IIb trial of a bivalent HPV16/18 VLP vaccine manufactured by GlaxoSmithKline (GSK) produced analogous results against HPV16/18 infection (25).

The phase III trials, conducted in sexually active young women, confirmed and extended the above results (26). GSK tested its bivalent HPV16/18 VLP vaccine, while Merck increased the valency of its vaccine to 4 HPV types by including VLPs from HPV6 and HPV11 in addition to HPV16/18 (Figure 2). Thus, both vaccines targeted oncogenic infection and

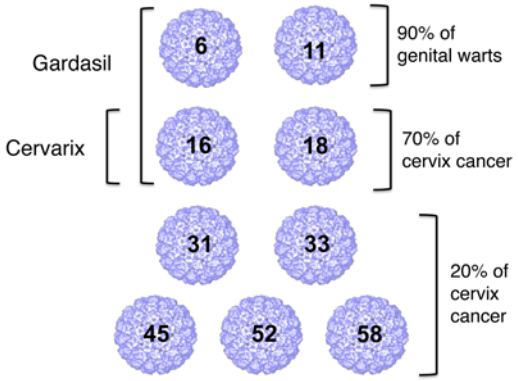

Figure 2. HPV VLP types in the various HPV vaccines. HPV VLP types (HPV6, HPV11, etc.) in the bivalent (Cervarix), quadrivalent (Gardasil), and 9-valent (Gardasil 9) vaccines are shown, with the approximate percentage of genital warts or cervical cancer attributable to the grouped HPV types. Reproduced with permission from *The Lancet Oncology* (50).

disease, while the quadrivalent vaccine also targeted genital warts. The primary endpoint for the trials was moderate cervical intraepithelial neoplasia or worse (CIN2+) attributable to the HPV types in the vaccine, rather than persistent infection by those types. The main rationale for that endpoint was that, in cervical cancer screening, a diagnosis of CIN2+ triggers treatment of the lesion because of the risk of malignant progression. Therefore, if the vaccine led to a reduction in the incidence of CIN2+, it would represent a clinical benefit, as fewer therapeutic procedures would be needed. It is unethical to use cervical cancer as an endpoint in such a trial because the women who develop CIN2+ lesions need to be treated.

Both vaccines, given as three parenteral doses over a six-month period, induced close to 100% protection against CIN2+ that was attributable to new HPV16/18 infections but had no effect on preexisting infections. In addition, the quadrivalent vaccine induced strong protection against vulvar and vaginal dysplasia and against genital warts caused by the HPV types in the vaccine. The efficacy of the quadrivalent vaccine was subsequently tested in males, and it was shown to protect them against warts and anal dysplasia.

Although the quadrivalent vaccine had limited cross-protection against cervical infection and disease associated with nonvaccine types, the bivalent vaccine displayed partial cross-protection against several HPV types that were phylogenetically related to HPV16 or HPV18 (26). The greater cross-protection of the bivalent vaccine may be attributable to differences in the adjuvants and/or in the manufacturing process of the two vaccines. The quadrivalent vaccine uses a standard alum adjuvant, while the bivalent vaccine uses a proprietary adjuvant, AS04, which is composed of monophosphoryl lipid A — a TLR4 agonist — and alum. It is presumably the AS04 that accounts for the higher titers induced by the bivalent vaccine compared with the quadrivalent vaccine (27). Other potentially relevant differences are that the VLPs for the bivalent vaccine are produced in insect cells with recombinant baculoviruses, while those for the quadrivalent vaccine are produced in yeast. Furthermore, the VLPs from both vaccines are subjected to distinct disassembly-reassembly steps, which might result in subtle, but important, differences.

Regulatory approvals

Both vaccines have been approved by the European Medicines Agency (EMA) and the US FDA (and the regulatory bodies of many other countries; reviewed in refs. 28, 29). The FDA approved the bivalent vaccine for 9- to 25-year-old women for prevention of cervical precancer and cervical cancer in 2009. The quadrivalent vaccine was approved in 9- to 26-year-old women in 2006 for this indication as well as for the prevention of genital warts and vulvar and vaginal precancer and cancer and for prevention of anal dysplasia and anal cancer in 2011. It was approved in males for preventing genital warts in 2009 and for preventing anal dysplasia and anal cancer in 2011. While the clinical efficacy trials were conducted in males and females who were at least 16 years old, the approvals for individuals below that age were based on immunobridging studies, which showed that the immune responses of the younger individuals to the three doses were not inferior to those induced in the individuals in the efficacy trials.

Short-term impact

Although the greatest public health potential of the vaccines lies in their ability to reduce the risk of the cancers attributable to HPV infection, the long interval between infection and the development of invasive cancer means that it will take until at least 2030 before there may be a measurable vaccine-induced reduction in cervical cancer and other HPV-associated cancers. However, it has been possible to evaluate earlier parameters for the population-wide impact of vaccination. Australia was the earliest country to adopt widespread uptake of the HPV vaccine, predominantly the quadrivalent vaccine. Approximately 75% of the female population under 18 was vaccinated, which has led to a dramatic reduction in the incidence of genital warts in women under 30, including evidence of herd immunity, because the incidence of genital warts in young heterosexual men — who were not vaccinated during this period — has also been reduced (30). There has also been a reduction in high-grade cervical dysplasia among young Australian women, together with a substantial and specific decrease in the prevalence of the vaccine types in young women (31). Analogous reductions are being seen in other countries with national HPV vaccine programs (32). Although vaccine uptake in the US has been less widespread — as of the end of 2014, 60% of 13- to 17-year-old girls had received at least one vaccine dose, and 40% had received at least 3 doses, with the vast majority of the doses having been with the quadrivalent vaccine — there has been a selective reduction in the prevalence of vaccine HPV types and genital warts in young women (33).

Safety and duration of protection

The safety profile of the vaccines has been studied in several countries. In the US, a rigorous assessment of the frequency of

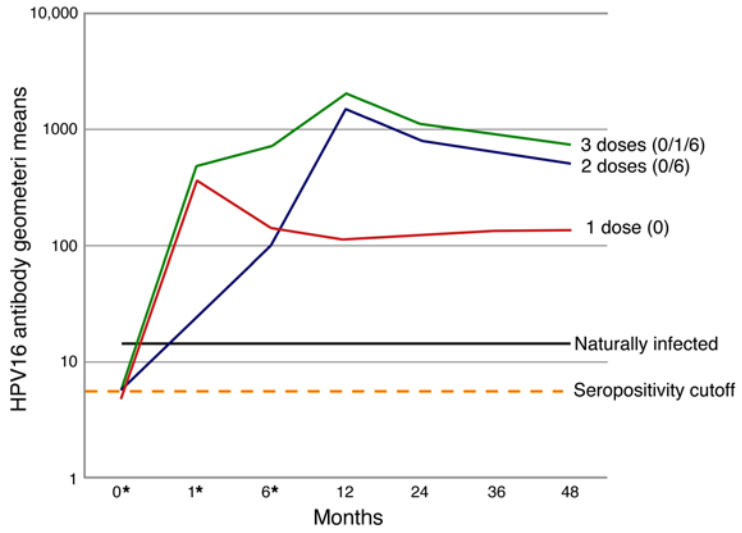

Figure 3. Relationship between the number of HPV vaccine doses received and the HPV16 VLP antibody geometric mean titers during a 48-month trial of the bivalent vaccine in women in Costa Rica. Women who received only one dose had stable antibody titers between months 12 and 48. In post-hoc analyses, vaccine efficacy was similar regardless of the number of doses given (6). Three doses of the bivalent vaccine were given at months zero, one, and six; two doses were given at months zero and six; and one dose was given at month zero. Asterisks indicate the months the vaccine was given. Reproduced with permission from *The Lancet Oncology* (50). For more information, see ref. 7 and above.

possible side effects — the list was based on reports from a passive reporting system, which is anecdotal — concluded that the frequency of the serious adverse events was not higher among girls who received approximately 600,000 doses of the HPV vaccine compared with those who did not receive the vaccine (34, 35). Similar conclusions have been drawn in Scandinavia (36).

Post-licensure surveillance of both vaccines is in place to monitor whether protection remains durable or wanes over time. Thus far, the bivalent vaccine has been shown to confer high protection for at least 9 years (37) and the quadrivalent vaccine for at least 8 years (38). If waning of protection is found to occur, it could be overcome by a booster dose. However, an additional dose would increase the overall cost of the vaccine and might be logistically challenging, as it tends to be difficult, in nonepidemic situations, to vaccinate a high proportion of people beyond school age.

Understanding the basis of the high efficacy of VLPs

Prior to the efficacy trials, there was understandable skepticism on whether a systemically administered vaccine could induce protection against local mucosal sexually transmitted infections, given the lack of prior success of vaccines that targeted other local mucosal infections that are sexually transmitted. The effectiveness of the HPV vaccines may be attributable to several factors (39–41). First, the induction of neutralizing antibodies seems to be sufficient to prevent clinical HPV infection and disease. Second, HPVs have DNA genomes, which do not evolve rapidly to escape neutralizing antibodies. Third, the immune system has been selected to make a strong response to the repetitive structure of viral capsids, which probably accounts for the high immunogenicity of the VLPs. Fourth, HPVs are quite sensitive to low concentrations of neutralizing antibodies, perhaps because the binding of a few antibodies is able to prevent infection. Fifth, based on a mouse genital tract HPV challenge model that we developed after the initial preclinical vaccine studies, HPV infection requires local microtrauma and the binding of virions to the basement membrane that separates the dermis and epidermis. The microtrauma leads to exudation of antibodies from the underlying tissue, which means that sites of potential HPV infection have antibody levels that resemble the higher levels in serum, rather than the low levels in mucosal fluid or the skin. Sixth, neutralizing antibodies inhibit at least two early steps in the virus life cycle: they can bind to virions in fluids, which prevents virion binding to the basement membrane, and they can bind to virions attached to the basement membrane, which prevents the transfer of the virion from the basement membrane to the target epithelial cell. The HPV virion apparently remains on the basement membrane for several hours before its transfer to the epithelial cell, which may provide ample time for even low antibody levels to bind the virion and prevent the transfer.

Fewer vaccine doses

Although the current vaccines are highly effective in preventing persistent infection and disease attributable to the HPV vaccine types, numerous issues have contributed to their underutilization in many countries, including the US. The need for three doses is a logistical and economic barrier in the developing world.

The high immunogenicity and efficacy of the vaccines, combined with the apparent sensitivity of the virus to the induced neutralizing antibodies, suggested that the vaccines might retain their long-term efficacy even if vaccinees are administered fewer than three doses. Clinical trials to evaluate this possibility have focused on adolescents. They are the main target group because the vaccine is most cost-effective when given before the initiation of sexual activity, and adolescents mount a stronger immune response than the 16- to 23-year-old participants in the efficacy trials. Immunogenicity trials in adolescents showed that their antibody titers after two doses given at least six months apart are not inferior to those induced after three doses given over six months in 16- to 23-year-old individuals (42, 43). In addition, post-hoc analyses of results from the NCI efficacy trial of the bivalent vaccine in 18- to 25-year-old women in Costa Rica have found that the women who received either one or two doses were as protected against HPV16/18 infection during the four years of the trial (6), with similar results from the international GSK phase III efficacy trials (44). Follow up of the women in the trial is underway to see whether this protection is maintained longer term. These findings led the EMA to approve a two-dose regimen for 9- to 14-year-old girls for the bivalent vaccine and 9- to 13-year-old boys and girls for the quadrivalent vaccine (45). The safe

reduction in the number of doses should make it logistically easier and less expensive to fully vaccinate individuals. These changes may have their greatest impact in the developing world, where the vaccine has its greatest public health potential but where resources for the control of disease are very limited.

Unexpected data from the NCI Costa Rica vaccine trial have shown that, in addition to the high protection against HPV16/18 infection in women who received only one dose, their HPV16/18 serum antibodies remained stable during years 1 to 4 of the trial (Figure 3 and ref. 7). There is no precedent for one dose of a protein-based subunit vaccine inducing a sustained immune response in people, which is usually limited to recipients of live-attenuated vaccines. The repetitive structure of the VLPs, perhaps in conjunction with the TLR agonist adjuvant present in the bivalent vaccine, may contribute to this sustained immunogenicity (46). The surprising nature of this finding, together with the post-hoc nature of the analysis, makes it important to conduct a randomized controlled efficacy study before a one-dose recommendation might be widely accepted for either vaccine. If such a trial were to validate this aspect of the Costa Rica trial, the results might have implications for the design of immunogens in future non-HPV vaccines, in addition to their implications for logistics and cost for HPV vaccination.

Protection against more HPV types

The first-generation vaccines specifically target about 70% of infections that may lead to cervical cancer, thus omitting almost one-third of potentially oncogenic infections. To address this issue, Merck developed a second-generation nonavalent (9-valent) vaccine, which was approved by the FDA in 2014 (47). In addition to the 4 VLP types in their quadrivalent vaccine, the 9-valent vaccine contains VLPs of the 5 HPV types (HPV31, HPV33, HPV45, HPV52, HPV58) found most commonly in cervical cancer after HPV16 and HPV18 (Figure 2). When the quadrivalent vaccine was used for the control group, the 9-valent vaccine had more than 95% efficacy against new persistent infections and CIN2+ by these 5 HPV types. Infection by the 7 oncogenic HPV types in the vaccine accounts for approximately 90% of cervical cancer worldwide. The vaccine should prevent the vast majority of HPV infections that rapidly progress to CIN2+, which might facilitate increasing the age at which cervical cancer screening is initiated in vaccinees.

Going beyond HPV vaccines with VLPs

The VLP platform has several possible applications beyond the prevention of HPV-induced disease. If one dose of an HPV vaccine is found to confer long-term protection, it could suggest that VLP technology should be seriously considered for reducing the number of doses for future vaccines (46). This platform may also be relevant for noninfectious diseases. For example, incorporating multiple copies of cell-encoded antigens into a VLP can markedly increase the humoral immune response to these antigens, as the immune system has been selected to make strong responses to the repetitive VLP structure (48). This observation implies that the induction of autoantibodies by a VLP-based vaccine that contains a cell-encoded antigen might be an alternate approach to interventions that use therapeutic monoclonal antibodies directed against such antigens, providing that the induced autoantibodies do not have serious side effects (49). This vaccine approach might be especially cost-effective in the developing world, where regular administration of therapeutic monoclonal antibodies might be logistically complicated and expensive.

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Address correspondence to: Douglas R. Lowy, Laboratory of Cellular Oncology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA. Phone: 301.496.9513; E-mail: lowyd@mail.nih.gov.

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