

# Human Papillomavirus Vaccines Six Years After Approval

Alan R. Shaw

Vedantra Pharmaceuticals, Cambridge, Massachusetts 02139;  
email: alan.shaw@vedantra.com

Annu. Rev. Med. 2013. 64:91–100

First published online as a Review in Advance on  
November 19, 2012

The *Annual Review of Medicine* is online at  
med.annualreviews.org

This article's doi:  
10.1146/annurev-med-061511-125226

Copyright © 2013 by Annual Reviews.  
All rights reserved

## Keywords

cervical cancer, genital warts, Pap smears

## Abstract

Human papillomavirus vaccines were developed beginning in the early 1990s. Two similar vaccines were approved in 2006 and 2009 following extensive clinical testing. Both vaccines prevent HPV infection. Implementation of these vaccines is the next challenge.

**CIN:** cervical  
intraepithelial  
neoplasia

## INTRODUCTION

Vaccines for human papillomavirus (HPV) were approved in the United States in 2006 and 2009, following a long development process that began in the early 1990s. The key piece of information that drove development was the demonstration of self-assembly of the HPV surface protein, L1, into virus-like particles (VLPs). Prior experience with VLP-based hepatitis B vaccines suggested that VLPs would be immunogenic and that antibody against VLPs should be protective. Two similar vaccines based on this VLP strategy are now widely available. Although these two vaccines share the same antigen design, based on a VLP, there are several differences that may prove significant in the long run. For a more detailed history of the laboratory aspects of the development of these vaccines, please refer to Reference 1.

The first vaccine, developed by Merck and approved by the US Food and Drug Administration (FDA) in 2006, was Gardasil®. Gardasil contains four VLPs representing HVP types 6 (20 µg protein), 11 (40 µg protein), 16 (40 µg protein), and 18 (20 µg protein). The different antigen doses reflect the slightly different immunogenicity of each component. Each component is produced separately in yeast by standard rDNA methods, similar to the hepatitis B vaccine. The vaccine is adsorbed to aluminum hydroxyphosphate and is delivered by intramuscular injection as a three-dose regimen (at zero, two, and six months).

The second vaccine, Cervarix®, was developed by GlaxoSmithKline (GSK) and approved in 2009. Cervarix contains 20 µg of HPV type 16 and 20 µg of HPV type 18 VLPs. The VLPs in Cervarix are produced in insect cells, now a common system for new vaccine production. The VLPs are formulated with a proprietary GSK adjuvant, AS04, containing aluminum hydroxide and monophosphoryl lipid A (MPL-A), a potent toll-like receptor agonist. The vaccine is delivered as a three-dose regimen at zero, one, and six months.

The two vaccines perform very similarly in the clinic. The differences in manufacturing

are trivial; VLPs made in insect cells or yeast are essentially indistinguishable, once purified. The adjuvants and the serotype content are the bigger differences and reflect the development philosophies of the two companies and their collaborators. The Merck group took a conservative brute-force approach, using a well-known yeast manufacturing system and a traditional aluminum hydroxyphosphate adjuvant. The GSK group used a relatively novel insect cell system for manufacturing in conjunction with a novel adjuvant, AS04. Merck chose to include two HPV types covering ~70% of cervical cancer (16 and 18) plus two types (6 and 11) causing ~90% of genital warts. Genital warts are not often life-threatening, but the added protection was thought to be an extra incentive for vaccination. The GSK group chose a more streamlined program, licensed from Med-Immune, focused on the two HPV types that cause the majority of cervical cancer.

The other big difference is the timing of approval. Gardasil was approved in the United States in June 2006, and Cervarix was approved in October 2009. Much of the difference in timing is attributed to the FDA review of the novel aspects of Cervarix and its adjuvant.

Both vaccines were approved on the basis of very large clinical trials with long follow-up periods required to show protection against a relatively slowly developing infection.

The initial clinical studies were designed to assess the impact of the VLP vaccines on the incidence of persistent infections and cervical intraepithelial neoplasia (CIN) (1, 3). These clinical endpoints were accepted by the regulatory authorities as surrogates for protection against frank cervical cancer. These early monovalent and bivalent vaccines against types 16 and 18 produced encouraging clinical results, essentially complete protection from persistent infection and CIN. These data drove the design and execution of multiple clinical efficacy studies in multiple geographic and social settings. The Merck program comprised four major studies in ~30,000 women followed for an average of three to five years; GSK's studies were of a similar magnitude. A

combined analysis of the main studies (4, 5) yielded 99% efficacy against the primary endpoint of persistent infection in the per-protocol group over a three-year follow-up period. One perhaps surprising finding was the apparent lack of therapeutic effect of the vaccines in women who were already infected at the time of vaccination (6). There were numerous debates about the likelihood of a prophylactic vaccine of this type providing a benefit for women already infected. Because the trial enrollment criteria did not exclude volunteers who were currently infected, a large number of subjects were available to answer this question definitively.

Another important issue for any new vaccine is safety. At the time they are vaccinated, vaccinees have nothing wrong with them and are seeking protection from some future infection. In the case of cervical cancer, the consequences of infection may not appear for several decades. Therefore, the safety profile of a new vaccine is under intense scrutiny. Most of the studies supporting licensure included an analysis of safety, including local injection-site reactions and systemic reactions. Overall, both vaccines were well tolerated, with injection-site pain, mostly transient, being the most common complaint. This pattern continues in postlicensure trials. In a study in young males, injection-site complaints were noted by 60% of vaccine recipients and by 53.7% of placebo recipients. Systemic complaints were similar, 31.7% and 31.4% in the respective groups (7). A pediatric study of female and male vaccinees showed a similar positive safety profile and an increased rate of injection-site complaints in vaccinees (77% in vaccinees versus 50% in placebo recipients) (8). In a comparative study (9) of the two vaccines, both were generally well tolerated, with injection-site pain being the most common solicited complaint. Overall, solicited systemic symptoms were higher with Cervarix. Rates of completion of the three-dose regimen were similar (9).

A number of other important issues were covered in the context of these trials. The original trials were based on the endpoints of persistent infection and low-grade CIN and adeno-

carcinoma in situ (AIS). Further analysis of the data showed that CIN and AIS graded as stage 2 or 3, the most advanced stages, were also prevented in women who were not infected at the time of vaccination (10). This reinforced the hypothesis that vaccination would prevent persistent infection that leads to CIN and AIS of increasing severity, which ultimately develops into cervical cancer. Vaccination also prevents anogenital disease in women caused by vaccine serotypes (11).

Although the main objective of the vaccine program was to assess the impact of vaccination on cervical disease, the size of the volunteer population afforded the opportunity to look at other, less common events. Among women not infected at the time of vaccination, vaginal intraepithelial neoplasia (VaIN) stage 2–3 and vulval intraepithelial neoplasia stage 2–3 were completely prevented in the per-protocol subjects (12). Efficacy was somewhat lower but still significant in the intent-to-treat population, again underlining the importance of completing the vaccine regimen before sexual activity begins.

One of the key questions that will be answered over the coming years is, “How long will protection last?” The trial designs and follow-up methodologies will ultimately give us an answer, but some information is now emerging. The Merck pilot monovalent type 16 vaccine was tested in the clinic beginning in 1998. Eight years later, a follow-up study of Seattle subjects showed that the per-protocol vaccinees remained HPV16 DNA negative through 2006–2008. Several cases of HPV disease were noted in the placebo group. This suggests that the type 16 vaccine remains efficacious for at least eight years. A detailed follow-up of >17,000 women who received the quadrivalent vaccine, first administered in December 2001, showed essentially 100% efficacy in the per-protocol, HPV-naïve-before-vaccination group. In the intent-to-treat group that included women of any HPV status and regimen completeness, there was still a reduction of ~19% in high-grade CIN, a 23% reduction in cervical therapy, and a 62% reduction in genital warts (13). This

---

**AIS:** adenocarcinoma in situ

**VaIN:** vaginal intraepithelial neoplasia

---

is encouraging, and once again we see the difference between the HPV-naïve vaccinees and those who are HPV positive when vaccinated.

A key feature of the efficacy studies for both vaccines was the enrollment of a substantial fraction of volunteers in the Scandinavian countries, where gynecological data are included in routine medical records and are readily retrieved. The women in this Scandinavian cohort serve as a sentinel group. The appearance of cervical disease in them will signal the need for a booster dose. In order to model the dynamics of the immune response, a subset of volunteers from the quadrivalent study was followed for 60 months post vaccination with periodic serological analysis. Antibody levels declined slowly and reached a plateau above the cut-off at ~24 months. A booster dose at month 60 elicited antibody titers greater than those attained post dose 3 in the primary series (14). Vaccine-induced immunity would appear to be robust. Similar studies of the bivalent vaccine showed excellent durability of the antibody response, with antibody levels approximately three- to ninefold higher in a pseudovirion-based assay than those attained with the quadrivalent vaccine. ELISA antibody results were similar for both vaccine types (15). The significance of the difference in durability between the bivalent and quadrivalent vaccine will be determined during the time of surveillance for breakthrough.

The other potential immunological difference is protection against HPV types not included in the vaccines (16–19). Up to 40 HPV types have been implicated in cervical and anal disease, and making a 40-valent VLP vaccine is not practical. Fortunately, there is enough similarity among types (e.g., 16 and 31, 18 and 45) to afford some cross protection with both vaccines. Clinical serology has been developed to support an eventual nonavalent vaccine comprising types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (20).

One major element of any vaccine program is the establishment of a correlate of protection. What level of immune response is associated with protection from disease? This informa-

tion is of enormous value for long-term maintenance of a vaccine program over the decades of the life of the project. New techniques for manufacturing and for clinical diagnosis will evolve over time and may be implemented. Because most vaccines are defined by the processes and materials used in production, any updates may require a clinical study to ensure performance equivalent to the original product made by the original methods. Having an immunological correlate of protection makes it possible to keep up with improvements in technology. In the case of HPV vaccines, this is a problem. We noted early in development that the serological response to HPV infection was quite weak, almost undetectable. T cell response to natural infection was also difficult to detect with the techniques available at the time. In contrast, the antibody response following vaccination was significantly stronger than that raised by natural infection. For most current vaccines, the immune response following infection is much stronger than the vaccine response. Unfortunately, this makes it difficult to create a correlate to support future improvements, since the only way to prove the new product/process is an improvement would be to run an efficacy study. If breakthrough occurs and if the sentinel cohort immune response tracks with it, then we may be able to extract a correlate.

## VACCINE ACCEPTANCE AND UPTAKE

Prior to the discovery of HPV as the cause, cervical cancer was something that just happened, and there was nothing anyone could do about it. The notion of a virus that causes cervical cancer, and the existence of a vaccine to prevent it, initially excite the imagination of many people. Then, the realization that this is the most common sexually transmitted infection comes into play, along with the need to vaccinate our daughters before they become sexually active. When we add the data showing sexual debut commonly occurring in the very early teens, and the university studies showing that over half of college women are infected with HPV during

the course of the usual four years, offering an HPV vaccine brings home a message that many parents would rather not hear. There is also a notion, so far unsupported, that vaccinating teens will encourage sexual activity. Now we have a choice: to act and vaccinate or to continue in denial, claiming that *our* kids are different and will not be sexually active until some ideal advanced age. Six years into the availability of HPV vaccines, how are we doing on this issue? How widespread is the uptake of the vaccines?

The advice of a physician remains the major component in the decision to vaccinate. A survey of physicians who favor HPV vaccination in general showed that their recommendation was influenced by the “relationship status” of the patient. The primary recommendation by the Advisory Committee on Immunization Practices was to vaccinate females 9–26 years of age, an age span that includes women old enough to be parents themselves. Patients who were married or in a committed relationship were less likely to be vaccinated than those who were single and dating (21). In a separate study by the same group, when women were asked about the likelihood of their seeking vaccination, a substantial fraction said they were unlikely to do so if they were in a committed or monogamous relationship, or lacked information about the vaccine (22). In the case of children, the advice of a physician is even more important, especially when parents hold misconceptions about adolescent sexuality. In a population of 34,000 girls 9–17 years of age in a California managed care setting, completion of the three-dose regimen was 41%. In a parallel population of young women aged 18–26, 47% completed the regimen. Coverage by the Medi-Cal program was a positive factor for completion of the regimen. Negative factors were black race and low socioeconomic neighborhood (23).

Vaccine uptake in the United States to date has been good, but not as brisk as predicted. The Centers for Disease Control and Prevention (CDC) carried out a survey of adolescent females in 2010 (<http://www.cdc.gov/vaccines/stats-surv/nisteen/data/tables>

[\\_2010.htm](#)) asking whether they had received an HPV vaccine, and if so, how many doses. The US national average showed 48.7% had received at least one dose, and 32% had completed the three-dose series. As expected, there is considerable variability from state to state and between urban and rural areas. The states with the highest proportion of women having at least one dose were Rhode Island, Delaware, South Dakota, and Washington. This survey included a subanalysis of cities versus rest of state for large metropolitan areas such as New York, Chicago, and Philadelphia. As one might expect, the urban uptake was about 10%–12% greater than the overall state uptake. Texas received particular attention, with Austin, Dallas, Houston, and El Paso analyzed versus the state. Dallas had a 34% one-dose uptake, but El Paso had 67%. These numbers will certainly evolve over time. This same survey included questions about receipt of at least one dose of Td or Tdap (tetanus, diphtheria, and pertussis vaccine) and meningococcal conjugate vaccine after age 10. The national average uptake figures were 81% and 63%, respectively, reflecting perhaps a higher comfort level with these older vaccines.

The immunization schedule in the United States now includes an adolescent visit for Tdap, meningococcal conjugate vaccine, and HPV vaccine. Because these are all administered at the same time, the developer of the new vaccine component (HPV in this case) is obligated to demonstrate lack of impact on the safety and immunogenicity of the older components. Several studies showed a lack of negative impact (24, 25), an important point for the efficiency of the adolescent visit.

## NEW DEVELOPMENTS

The HPV vaccines were initially recommended for females aged 9–26 years. This age range includes the prime time for adolescent vaccination in general and for the years of highest sexual activity. Vaccination of males in this age group was discussed in multiple settings. One side argued that females suffer most from

AIN: anal  
intraepithelial  
neoplasia

HPV infection and it is most cost-effective to just vaccinate females. Vaccination of males, the vectors of transmission, is costly for the incremental benefit achieved. Gardasil was initially priced at \$120 per dose, so cost-effectiveness calculations come into play. The counterargument was that single-sex vaccination is not effective. In the 1960s the rubella vaccine was introduced for females of reproductive age in middle of an epidemic of rubella, rubella birth defects, and abortions. Within a few years, it became apparent that single-sex vaccination was not sufficient, and the rubella vaccine was implemented in the pediatric regimen for both sexes. Rubella has all but disappeared from the United States.

The initial HVP vaccine studies included some younger male subjects. Immunogenicity in males was at least as good as in females, and in two studies it was demonstrably better (8, 26), so the immune response is not gender specific. The anus has an epithelial transition zone similar to the cervix. This transition zone is the most common site of anal intraepithelial neoplasia (AIN). In a study of 602 men who have sex with men, the quadrivalent vaccine showed a significant impact on the development of persistent HPV infection and, more importantly, high-grade AIN (27). In the intent-to-treat cohort, efficacy against AIN caused by the vaccine types (7, 12, 17, 19) was 50%. In the per-protocol cohort, efficacy was 77%. Efficacy against persistent infection was 95%. On the basis of this study and other supporting data (28, 29), the Advisory Committee on Immunization Practices recommended the use of the quadrivalent vaccine in males aged 11–26 years (<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6050a3.htm>).

Although the peak years of sexual activity are typically in the late teens to mid twenties, activity continues to be high for quite some time. Changing social dynamics trend toward marriage at later age or no marriage at all. This favors the extension of vaccination to women beyond age 26 years (30). Clinical studies have shown that both vaccines are immunogenic and efficacious in this age range (31, 32), so at some

point in the not too distant future, this cohort should be covered as well.

A separate question is the expansion of vaccination to children and young adults living outside the United States and Europe. In most places, cervical screening and treatment are not commonly available, and rates of cervical cancer are high. Vaccination would seem to be an expedient solution. Several studies in Latin America and Asia confirm the general picture of safety and immunogenicity of the vaccines (33, 34). However, implementing an adolescent immunization campaign in areas where even the standard pediatric vaccine program stretches the limits of resources is logistically daunting and will require a dedicated effort and significant financial support.

As a consequence of the HPV vaccine development programs, a number of HPV diagnostic tools were developed within and outside of the clinical trials. We now have several sensitive and convenient tools for detecting and typing papillomavirus DNAs in various tissues. These tools have been used to document virus distribution and antibody raised by natural infection as a baseline for epidemiological studies to gauge the impact of vaccination over time (35–38).

Recent work showed that HPV, especially type 16, is associated with a higher risk of head and neck squamous cell carcinomas (39, 40). Seropositivity for type 16 is related to oral sex and number of lifetime sex partners, similar to the risk of cervical cancer. This raises the obvious question of whether the HPV vaccines can impact directly or indirectly the incidence of head and neck carcinomas. We know that HPV types 6 and 11, particularly type 11, cause wart-like growths on the larynx. This is a relatively rare occurrence, but targeted surveillance might reveal a protective effect over time.

## FOLLOW-ON ACTIVITIES

Support for approval of the HPV vaccines included a variety of cost-effectiveness calculations. The input assumptions vary, but overall the general conclusion of these models is that



vaccinating against HPV will be cost-effective in the long term, although in the near term there will be a period of relative increased cost due to the cost of the vaccines and the long incubation period of HPV disease. Overall, the modeling studies predict a cost saving (41–43). The history of Pap test screening may be instructive here. The prevailing view at the time of approval was that we should continue Pap testing at the then current intervals and revisit the question as more data accumulated. As this is written, the American Cancer Society recommendations have been updated to reflect current data. The annual Pap screening is discontinued and discouraged in favor of a three-year interval for women up to age 29 years, and an interval of 3–5 years plus an HPV DNA test for older women.

The introduction of a new vaccine carries with it an obligation for a significant effort to follow its performance in terms of safety, persistence of immunity and protective efficacy, pregnancy outcomes in women inadvertently vaccinated during pregnancy, and diseases of particular interest, such as autoimmune diseases. Merck's postlicensure surveillance initiatives have been reviewed in detail (44) and include extensions to the Nordic studies mentioned above, as well as monitoring of changes of circulating HPV types covered by the vaccine and not covered. This summary conveys the magnitude of effort that is required to monitor and maintain a new vaccine.

The CDC also assumes a huge burden of monitoring vaccine implementation and coverage, monitoring vaccine safety via the Vaccine Adverse Experience Reporting System (VAERS), the Vaccine Safety Data Link, and

the Clinical Immunization Safety Assessment network. These programs are described in detail by Markowitz and colleagues (45), who provide a window into the detailed effort necessary to execute a large-scale vaccine program.

## SUMMARY AND FUTURE DIRECTIONS

HPV vaccines have been demonstrated to be safe, efficacious, and well tolerated both in prelicensure studies and in field use. In the context of controlled clinical trials, a benefit in terms of reduction of CIN, AIS and AIN, and VaIN was shown in a relatively short time, 2–5 years in populations under intense follow-up. In current practice, the frequency of screening is triannual at best, so demonstration of benefit may take longer. The full effect of the vaccines will become apparent when we achieve close to the ~90% coverage that we have for the current pediatric vaccines, and vaccination has to begin at an age when children are still HPV naïve.

There is still work to do on this topic. In the laboratory, there are efforts to expand the number of HPV types covered by the vaccines, and several attempts are under way to make a therapeutic vaccine. This will keep us busy for quite some time! In the public health arena, there are multiple programs to introduce these vaccines into less developed countries where screening is not available and cervical cancer is number one or two among cancers that kill women. Conceptually, a vaccination program could be simpler than setting up and maintaining a screening program, but the results of both activities should be synergistic.

## DISCLOSURE STATEMENT

The author was an employee of Merck & Co. and was involved in the development and testing of Gardasil.

## LITERATURE CITED

1. Shaw A. 2004. Human papillomavirus vaccines and prevention of cervical cancer. *Annu. Rev. Med.* 55:319–31

2. Koutsky LA, Ault KA, Wheeler CM, et al. 2002. A controlled trial of a human papillomavirus type 16 vaccine. *N. Engl. J. Med.* 347:1645–51
3. Billich A. 2003. HPV vaccine MedImmune/GlaxoSmithKline. *Curr. Opin. Invest. Drugs* 4:210–13
4. Ault KA. 2007. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. *Lancet* 369:1861–68
5. Paavonen J, Naud P, Salmeron J, et al. 2009. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 374:301–14
6. Haupt RM, Wheeler CM, Brown DR, et al. 2011. Impact of an HPV6/11/16/18 L1 virus-like particle vaccine on progression to cervical intraepithelial neoplasia in seropositive women with HPV16/18 infection. *Int. J. Cancer* 129:2632–42
7. Moreira ED Jr, Palefsky JM, Giuliano AR, et al. 2011. Safety and reactogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 viral-like-particle vaccine in older adolescents and young adults. *Hum. Vaccines* 7:768–75
8. Reisinger KS, Block SL, Lazcano-Ponce E, et al. 2007. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. *Pediatr. Infect. Dis. J.* 26:201–9
9. Einstein MH, Baron M, Levin MJ, et al. 2009. Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18–45 years. *Hum. Vaccines* 5:705–19
10. Future II Study Group. 2007. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N. Engl. J. Med.* 356:1915–27
11. Garland SM, Hernandez-Avila M, Wheeler CM, et al. 2007. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N. Engl. J. Med.* 356:1928–43
12. Joura EA, Leodolter S, Hernandez-Avila M, et al. 2007. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *Lancet* 369:1693–702
13. Munoz N, Kjaer SK, Sigurdsson K, et al. 2010. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. *J. Natl. Cancer Inst.* 102:325–39
14. Olsson SE, Villa LL, Costa RL, et al. 2007. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine. *Vaccine* 25:4931–39
15. Einstein MH, Baron M, Levin MJ, et al. 2011. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 vaccine and HPV-6/11/16/18 vaccine: follow-up from months 12–24 in a Phase III randomized study of healthy women aged 18–45 years. *Hum. Vaccines* 7:1343–58
16. Wheeler CM, Castellsague X, Garland SM, et al. 2012. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol.* 13:100–10
17. Smith JF, Brownlow M, Brown M, et al. 2007. Antibodies from women immunized with Gardasil cross-neutralize HPV 45 pseudovirions. *Hum. Vaccines* 3:109–15
18. Brown DR, Kjaer SK, Sigurdsson K, et al. 2009. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naïve women aged 16–26 years. *J. Infect. Dis.* 199:926–35
19. Wheeler CM, Kjaer SK, Sigurdsson K, et al. 2009. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16–26 years. *J. Infect. Dis.* 199:936–44
20. Opalka D, Matys K, Bojczuk P, et al. 2010. Multiplexed serologic assay for nine anogenital human papillomavirus types. *Clin. Vaccine Immunol.* 17:818–27
21. Zimet GD, Stupiansky NW, Weiss TW, et al. 2011. Influence of patient's relationship status and HPV history on physicians' decisions to recommend HPV vaccination. *Vaccine* 29:378–81
22. Zimet GD, Weiss TW, Rosenthal SL, et al. 2010. Reasons for non-vaccination against HPV and future vaccination intentions among 19–26 year-old women. *BMC Women's Health* 10:27



23. Chao C, Velicer C, Slezak JM, et al. 2009. Correlates for completion of 3-dose regimen of HPV vaccine in female members of a managed care organization. *Mayo Clin. Proc.* 84:864–70
24. Reisinger KS, Block SL, Collins-Ogle M, et al. 2010. Safety, tolerability, and immunogenicity of Gardasil given concomitantly with Menactra and Adacel. *Pediatrics* 125:1142–51
25. Vesikari T, Van Damme P, Lindblad N, et al. 2010. An open-label, randomized, multicenter study of the safety, tolerability, and immunogenicity of quadrivalent human papillomavirus (types 6/11/16/18) vaccine given concomitantly with diphtheria, tetanus, pertussis, and poliomyelitis vaccine in healthy adolescents 11 to 17 years of age. *Pediatr. Infect. Dis. J.* 29:314–18
26. Petaja T, Keranen H, Karppa T, et al. 2009. Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuncted vaccine in healthy boys aged 10–18 years. *J. Adolesc. Health: Off. Publ. Soc. Adolesc. Med.* 44:33–40
27. Palefsky JM, Giuliano AR, Goldstone S, et al. 2011. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N. Engl. J. Med.* 365:1576–85
28. Guimaraes MD, Grinsztejn B, Melo VH, et al. 2011. Anal HPV prevalence and associated factors among HIV-seropositive men under antiretroviral treatment in Brazil. *J. Acquir. Immune Defic. Syndr.* 57(Suppl. 3):S217–24
29. Elbasha EH, Dasbach EJ. 2010. Impact of vaccinating boys and men against HPV in the United States. *Vaccine* 28:6858–67
30. Grant LA, Dunne EF, Chesson H, et al. 2011. Considerations for human papillomavirus (HPV) vaccination of mid-adult women in the United States. *Vaccine* 29:2365–70
31. Munoz N, Manalastas R Jr, Pitisuttithum P, et al. 2009. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomised, double-blind trial. *Lancet* 373:1949–57
32. Schwarz TF, Spaczynski M, Schneider A, et al. 2009. Immunogenicity and tolerability of an HPV-16/18 AS04-adjuncted prophylactic cervical cancer vaccine in women aged 15–55 years. *Vaccine* 27:581–87
33. Perez G, Lazcano-Ponce E, Hernandez-Avila M, et al. 2008. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 virus-like-particle vaccine in Latin American women. *Int. J. Cancer* 122:1311–18
34. Kang S, Kim KH, Kim YT, et al. 2008. Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: a randomized, placebo-controlled trial in 176 Korean subjects. *Int. J. Gynecol. Cancer* 18:1013–19
35. Newall AT, Brotherton JM, Quinn HE, et al. 2008. Population seroprevalence of human papillomavirus types 6, 11, 16, and 18 in men, women, and children in Australia. *Clin. Infect. Dis.* 46:1647–55
36. Paavonen J. 2008. Baseline demographic characteristics of subjects enrolled in international quadrivalent HPV (types 6/11/16/18) vaccine clinical trials. *Curr. Med. Res. Opin.* 24:1623–34
37. Six L, Leodolter S, Sings HL, et al. 2008. Prevalence of human papillomavirus types 6, 11, 16 and 18 in young Austrian women—baseline data of a phase III vaccine trial. *Wiener Klin. Wochenschr.* 120:666–71
38. Skjeldestad FE, Mehta V, Sings HL, et al. 2008. Seroprevalence and genital DNA prevalence of HPV types 6, 11, 16 and 18 in a cohort of young Norwegian women: study design and cohort characteristics. *Acta Obstet. Gynecol. Scand.* 87:81–88
39. Furniss CS, McClean MD, Smith JF, et al. 2007. Human papillomavirus 16 and head and neck squamous cell carcinoma. *Int. J. Cancer* 120:2386–92
40. Settle K, Posner MR, Schumaker LM, et al. 2009. Racial survival disparity in head and neck cancer results from low prevalence of human papillomavirus infection in black oropharyngeal cancer patients. *Cancer Prev. Res.* 2:776–81
41. Dasbach EJ, Insinga RP, Yang YC, et al. 2008. The cost-effectiveness of a quadrivalent human papillomavirus vaccine in Taiwan. *Asian Pac. J. Cancer Prev.* 9:459–66
42. Insinga RP, Dasbach EJ, Elbasha EH. 2008. Structural differences among cost-effectiveness models of human papillomavirus vaccines. *Expert Rev. Vaccines* 7:895–913

43. Insinga RP, Dasbach EJ, Allen SE, et al. 2008. Reductions in human papillomavirus-disease resource use and costs with quadrivalent human papillomavirus (types 6, 11, 16, and 18) recombinant vaccination: the FUTURE Study Economic Evaluation. *Value Health* 11:1022–32
44. Bonanni P, Cohet C, Kjaer SK, et al. 2010. A summary of the post-licensure surveillance initiatives for GARDASIL/SILGARD. *Vaccine* 28:4719–30
45. Markowitz LE, Hariri S, Unger ER, et al. 2010. Post-licensure monitoring of HPV vaccine in the United States. *Vaccine* 28:4731–37



# Contents

Abiraterone and Novel Antiandrogens: Overcoming Castration Resistance in Prostate Cancer <i>R. Ferraldeschi, C. Pezaro, V. Karavasilis, and J. de Bono</i> .....	1
Antibody-Drug Conjugates in Cancer Therapy <i>Eric L. Sievers and Peter D. Senter</i> .....	15
Circulating Tumor Cells: From Bench to Bedside <i>Marija Balic, Anthony Williams, Henry Lin, Ram Datar, and Richard J. Cote</i> .....	31
Cytokines, Obesity, and Cancer: New Insights on Mechanisms Linking Obesity to Cancer Risk and Progression <i>Candace A. Gilbert and Joyce M. Slingerland</i> .....	45
Glioblastoma: Molecular Analysis and Clinical Implications <i>Jason T. Huse, Eric Holland, and Lisa M. DeAngelis</i> .....	59
Harnessing the Power of the Immune System to Target Cancer <i>Gregory Lizée, Willem W. Overwijk, Laszlo Radvanyi, Jianjun Gao, Padmanee Sharma, and Patrick Hwu</i> .....	71
Human Papillomavirus Vaccines Six Years After Approval <i>Alan R. Shaw</i> .....	91
Reduced-Intensity Hematopoietic Stem Cell Transplants for Malignancies: Harnessing the Graft-Versus-Tumor Effect <i>Saar Gill and David L. Porter</i> .....	101
The Need for Lymph Node Dissection in Nonmetastatic Breast Cancer <i>Catherine Pesce and Monica Morrow</i> .....	119
The Role of Anti-Inflammatory Drugs in Colorectal Cancer <i>Dingzhi Wang and Raymond N. DuBois</i> .....	131
The Human Microbiome: From Symbiosis to Pathogenesis <i>Emiley A. Elloe-Fadrosh and David A. Rasko</i> .....	145
The Rotavirus Saga Revisited <i>Alan R. Shaw</i> .....	165

Staphylococcal Infections: Mechanisms of Biofilm Maturation and Detachment as Critical Determinants of Pathogenicity <i>Michael Otto</i>	175
Toward a Universal Influenza Virus Vaccine: Prospects and Challenges <i>Natalie Pica and Peter Palese</i>	189
Host Genetics of HIV Acquisition and Viral Control <i>Patrick R. Shea, Kevin V. Shianna, Mary Carrington, and David B. Goldstein</i>	203
Systemic and Topical Drugs for the Prevention of HIV Infection: Antiretroviral Pre-exposure Prophylaxis <i>Jared Baeten and Connie Celum</i>	219
Hyperaldosteronism as a Common Cause of Resistant Hypertension <i>David A. Calhoun</i>	233
Mechanisms of Premature Atherosclerosis in Rheumatoid Arthritis and Lupus <i>J. Michelle Kahlenberg and Mariana J. Kaplan</i>	249
Molecular Mechanisms in Progressive Idiopathic Pulmonary Fibrosis <i>Mark P. Steele and David A. Schwartz</i>	265
Reprogrammed Cells for Disease Modeling and Regenerative Medicine <i>Anne B.C. Cherry and George Q. Daley</i>	277
Application of Metabolomics to Diagnosis of Insulin Resistance <i>Michael V. Milburn and Kay A. Lawton</i>	291
Defective Complement Inhibitory Function Predisposes to Renal Disease <i>Anuja Java, John Atkinson, and Jane Salmon</i>	307
New Therapies for Gout <i>Daria B. Crittenden and Michael H. Pillinger</i>	325
Pathogenesis of Immunoglobulin A Nephropathy: Recent Insight from Genetic Studies <i>Krzysztof Kiryluk, Jan Novak, and Ali G. Gharavi</i>	339
Podocyte Biology and Pathogenesis of Kidney Disease <i>Jochen Reiser and Sanja Sever</i>	357
Toward the Treatment and Prevention of Alzheimer's Disease: Rational Strategies and Recent Progress <i>Sam Gandy and Steven T. DeKosky</i>	367
Psychiatry's Integration with Medicine: The Role of DSM-5 <i>David J. Kupfer, Emily A. Kuhl, Lawson Wulsin</i>	385

Update on Typical and Atypical Antipsychotic Drugs <i>Herbert Y. Meltzer</i> .....	393
Ataluren as an Agent for Therapeutic Nonsense Suppression <i>Stuart W. Peltz, Manal Morsy, Ellen M. Welch, and Allan Jacobson</i> .....	407
Treating the Developing Brain: Implications from Human Imaging and Mouse Genetics <i>B. J. Casey, Siobhan S. Pattwell, Charles E. Glatt, and Francis S. Lee</i> .....	427
Genetic Basis of Intellectual Disability <i>Jay W. Ellison, Jill A. Rosenfeld, and Lisa G. Shaffer</i> .....	441
Sickle Cell Disease, Vasculopathy, and Therapeutics <i>Adetola A. Kassim and Michael R. DeBaun</i> .....	451
Duty-Hour Limits and Patient Care and Resident Outcomes: Can High-Quality Studies Offer Insight into Complex Relationships? <i>Ingrid Philibert, Thomas Nasca, Timothy Brigham, and Jane Shapiro</i> .....	467
Quality Measurement in Healthcare <i>Eliot J. Lazar, Peter Fleischut, and Brian K. Regan</i> .....	485

## Indexes

Cumulative Index of Contributing Authors, Volumes 60–64 .....	497
Article Titles, Volumes 60–64 .....	501

## Errata

An online log of corrections to *Annual Review of Medicine* articles may be found at  
<http://med.annualreviews.org/errata.shtml>