EXPERT REVIEWS

The next generation of HPV vaccines: nonavalent vaccine V503 on the horizon

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HPV infection with 'high-risk' genotypes is associated with ano-genital and oropharyngeal cancers. Two currently licensed prophylactic HPV vaccines designed to prevent disease associated with HPV 16 and 18 are in use around the world. Both vaccines have very high efficacy for prevention of vaccine type–associated cervical precancers, preventing approximately 70% of these lesions. Quadrivalent HPV vaccine has also been shown to prevent HPV16/18-associated vaginal, vulvar and anal precancers, and HPV6/11-associated ano-genital warts. To broaden protection against HPV genotypes not in the current vaccines, 'second-generation' vaccines with additional genotypes are under development. Merck, Sharp and Dohme has submitted a Biologics License Application for its investigational nonavalent HPV vaccine V503 to the US FDA, with standard review being granted. The nonavalent HPV vaccine appears to be safe and effective in preventing persistent infection and precancerous lesions associated with HPV types 16/18/31/33/45/52/58, as well as genital warts related to HPV types 6 and 11.

Keywords: efficacy • HPV • nonavalent • safety • vaccine

The concept that infection with HPVs can lead to precancerous lesions and cancer was first introduced in the 1970s by Harald zur Hausen and colleagues [1]. Since then, HPV infection has been associated with malignancies including cervical, vulvar, vaginal, penile, anal and oropharyngeal cancer [2]. Among cancers associated with HPVs, cervical cancer is the third most common cancer and the fourth most common cause of cancer-related deaths in women worldwide [2–4]. Of all HPV-related cancers, approximately 94% occur in women and 88% affect the cervix [3]. HPV is present in 99.7% of cases of cervical cancer, and persistent infection with an oncogenic type of HPV is a recognized precursor of cervical cancer [5,6].

With an estimated 528,000 new cases in 2012, a large majority (around 85%) of the global burden of cervical cancer occurs in the less-developed regions of the world, where it accounts for almost 12% of all female cancers [4]. High-risk regions, with estimated age-standardized rates over 30 per 100,000, include Eastern Africa (42.7), Melanesia (a subregion of Oceania extending from the western end of the Pacific Ocean to the Arafura Sea, and eastward to Fiji; the region comprises the countries of Vanuatu, Solomon Islands, Fiji and Papua New Guinea; besides these independent countries, Melanesia also includes New Caledonia, a special collectivity of France, and the region of West Papua, which includes two provinces of Indonesia, Papua and West Papua) (33.3), Southern (31.5) and Middle (30.6) Africa. Rates are lowest in Australia/New Zealand (5.5) and Western Asia (4.4). Cervical cancer remains the most common cancer in women in Eastern and Middle Africa. There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths [4]. Almost 9 out of 10 (87%) cervical cancer deaths occur in the less-developed regions. Mortality varies 18-fold between the different regions of the world, with rates ranging from less than 2 per 100,000 in Western Asia, Western Europe and Australia/New Zealand to more than 20 per 100,000 in Melanesia (20.6), Middle (22.2) and Eastern (27.6) Africa. Insufficient resources and a lack of infrastructure devoted to widespread, effective cervical cancer screening and HPV testing programs in less wealthy countries lead to the high cervical cancer incidence in the developing world [7–9]. By contrast, screening programs for

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Table 1. Components of 9vHPV, 4vHPV and 2vHPV (HPV L1 proteins in micrograms).

	9vHPV	4vHPV	2vHPV
HPV6	30	20	–
HPV11	40	40	–
HPV16	60	40	20
HPV18	40	20	20
HPV31	20	–	–
HPV33	20	–	–
HPV45	20	–	–
HPV52	20	–	–
HPV58	20	–	–
Adjuvant	500 µg Amorphous aluminum hydroxyphosphate sulfate	225 µg Amorphous aluminum hydroxyphosphate sulfate	500 µg Aluminum hydroxide and 50 µg 3-*O*-desacyl-4′-monophosphoryl lipid A

cervical intraepithelial neoplasia (CIN), a precursor to cervical cancer, have substantially reduced the incidence and mortality from this disease in industrialized countries [10]. For example, in the USA, the incidence of cervical cancer is 7.5 per 100,000 and the mortality rate is 2.3 per 100,000 [11]. However, many thousands of women in countries with lower disease incidence continue to suffer anxiety and possibly unnecessary treatment as a result of abnormal or even inadequate cytology [12,13]. Vaccination against HPV, which first became available in 2006, is a major advancement, as it offers primary prevention against the infectious agent that is the main cause of the disease, irrespective of the availability or utilization of secondary prevention through cervical cancer screening and HPV testing programs [14,15].

Belonging to a large family of small dsDNA viruses, HPVs are classified into 'high-risk' genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68), which are recognized as being necessary for the development of cervical cancer, and 'low-risk' genotypes (6 and 11) which are associated with 90% of ano-genital warts and recurrent respiratory papillomatosis (RRP) [16,17]. Of the 'high-risk' category, types 16, 18 and 45 together account for approximately 75% of squamous cell carcinoma, 94% of adenocarcinoma, 50% of high-grade CIN, 25% of low-grade CIN, approximately 80% of anal cancers and approximately half of all vulval and vaginal cancers [16,18,19]. HPV infection is very common among young people, but is transient in most (70–80%) [20]. Malignant transformation following persistent HPV infection with 'high-risk' types may take a decade or more, and is more likely to occur in women older than 30 years [21].

While they do not carry the same mortality risk, the psychosocial and economic burden from infection with 'low-risk' HPV genotypes is also substantial [22]. Whereas ano-genital warts represent an extremely prevalent sexually transmitted disease, RRP is a rare disease that can be life threatening and requires multiple surgical procedures. Stressors from these diseases include the shame and embarrassment related to diagnosis, dyspareunia, as well as the inconvenience and discomfort of treatment and the fear of recurrence and transmission. Costs relate to treatment of genital warts and multiple procedures necessary for patients with RRP [23]. While worldwide epidemiological data are lacking, the prevalence of genital warts has been examined using nationally representative surveys and health care claims data in the USA [24,25]. An estimated 1% of sexually active adolescents and adults in the USA have clinically apparent genital warts at any given time [20]. In one national survey in the USA, 5.6% of males and females aged 14–59 reported having been diagnosed with genital warts in their lifetime [25]. Genital warts are the most common viral sexually transmitted disease in the UK, with 81,000 new diagnoses in 2005 and a 30% increase in the last 10 years [7,17]. The estimated costs of genital wart treatment in genitourinary medicine clinics in 2004 in the UK were approximately £31 million [17]. Estimated disease burden due to HPV6/11 in Finland, calculated as number of annual new cases by anatomic region and tumor type, indicates that a minimum of 12,666–13,066 new cases of HPV6- or HPV11-associated clinical lesions would be detected each year in Finland, if all were registered [26]. RRP occurs in juvenile-onset and adult-onset forms. Estimates of the incidence of juvenile-onset RRP are relatively imprecise, but range from 0.12 to 2.1 cases per 100,000 children aged <18 years in the USA [27]. Even less is known about the incidence of the adult form of RRP [28].

Currently licensed HPV vaccines

There are currently two licensed prophylactic HPV vaccines, Gardasil® (Merck, Sharp and Dohme) (referred to as quadrivalent vaccine or 4vHPV henceforth) and Cervarix® (GlaxoSmithKline [GSK]) (referred to as bivalent vaccine or 2vHPV hereafter), both of which consist of virus-like particles (VLPs) of recombinant L1 capsid proteins, designed to prevent disease associated with HPV 16 and 18. They contain adjuvants that are thought to contribute to the production of antibody titers that are 60–100 times higher (up to 18 months after vaccination) than those produced by natural infection [29–35]. Both vaccines are directed against HPV 16 and 18, the types that cause cervical and other HPV-associated cancers. The quadrivalent vaccine is also directed against HPV6 and HPV11, the types that cause ano-genital warts and RRP. 4vHPV was licensed by the US FDA in 2006 for use in females aged 9–26 years and in 2009 for use in males aged 9–26 years [36]. 2vHPV was licensed by the FDA in 2009 for use in females aged 10–25 years [37]. Components of both vaccines are presented in Table 1 [38,39].

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Data from clinical trials show that both vaccines, when given in a three-dose series, have very high efficacy for prevention of vaccine type–associated cervical precancers (Table 2) [30,31,40]. Quadrivalent HPV vaccine has also been shown to prevent HPV16- and HPV18-associated vaginal, vulvar and anal precancers [34,41], and HPV6- and HPV11-associated ano-genital warts [32]. It is important to note that both vaccines are prophylactic and do not prevent progression of existing infection to disease or treat existing disease [42]. No clinical trial data are currently available to demonstrate their efficacy for prevention of oropharyngeal or penile cancers. However, HPV16 is found in a proportion of these cancers, and thus, they are presumed attributable to HPV infection. HPV16-containing vaccines have the potential to offer protection against these cancers as well [43]. The Advisory Committee on Immunization Practices of the US CDC recommends that girls and boys be routinely vaccinated at age 11 or 12 years; vaccine may be given starting at age 9 years [44–46]. In addition, for those who were not vaccinated when they were younger, all girls/young women through age 26 years [45] and all boys/young men through age 21 years should be vaccinated [46]. The Advisory Committee on Immunization Practices recommends that gay, bisexual and other men who have sex with men be vaccinated through age 26 years [46].

Table 2 lists the results of selected clinical trials on bivalent and quadrivalent HPV vaccine efficacy against HPV vaccine-type precancers and ano-genital warts.

Table 2. Results of selected clinical trials on HPV vaccine efficacy against HPV vaccine-type precancers and ano-genital warts.

Outcome	Vaccine	Sex	Vaccine efficacy
Cervical precancer	Bivalent and quadrivalent	Females	>93%
Vaginal/vulvar precancer	Quadrivalent	Females	100%
Anal precancer	Quadrivalent	Males	75%
Ano-genital warts	Quadrivalent	Females Males	99% 89%

Data taken from [30–35].

Impact of currently approved HPV vaccines

For the developed world, cervical cancer prevention prior to vaccine development was largely achievable through effective implementation of screening programs based on cervical cytology assessment and treatment of premalignancy by surgical means [47]. Vaccines are an additional measure, with the rationale for introduction based on analysis of cost–effectiveness, public demand and acceptability. Some countries, including Australia and the UK, were early adopters of universal, publicly funded immunization of young women before the onset of sexual activity and, as of 2013, the Australian program has been extended to young men. The Australian program's success can be measured by a 73% uptake rate of vaccination among 12- to 13-year-old girls, and also by the virtual disappearance of genital warts during the past 5 years, not only among immunized younger women, but also among unimmunized younger men [48,49], presumably as a result of the protective effects of herd immunity. Australia is also the first to report a significant decline in the rate of high-grade precancerous lesions [49]. In addition, significant reductions in the prevalence of HPV 16 and 18 DNA have been observed in cervical smear samples from 18- to 24-year-old women [50]. In England, 86% of the target age group (12- to 13-year-old girls) is reported to have received the full course of HPV vaccine [51]. The prevalence of HPV 16/18 infection in a post-immunization survey in 2013 was 6.5% among 16–18 year olds, compared to 19.1% in the baseline survey prior to the introduction of HPV immunization in 2008 in the UK [52].

Recently, a decline in the rate of high-grade cervical lesions was also observed in the state of Connecticut [53], which represents the first report of a reduction in cervical neoplasia in North America since HPV vaccines were introduced. Connecticut is among the leaders in vaccine coverage in the USA, with reports estimating that 61% of adolescent girls (13–17 years) received at least one dose of the vaccine in 2011 [54]. Although uptake among young women more than 17 years of age is still very low across North America [55], in 2013, British Columbia became the first province to offer free vaccination to women up to age 26, which is expected to have a more rapid potential impact on cervical precancerous abnormalities (based on the Australian experience). Whereas herd immunity may help protect men from HPV-associated ano-genital and oropharyngeal cancers, the low level of coverage of the female population in many countries (38% in the USA in 2013, 55% in Ontario Province in Canada in 2012, 60% in the UK in 2012, unknown in other countries) [56–58] is likely currently insufficient to provide good herd immunity, a justification for immunization of young men as a public health measure where cost–benefit analyses permit. While modeling studies have assumed that a rate of 75% vaccine coverage will provide herd immunity, it should be noted that the actual rate of vaccination that would do so in unknown [59]. Studies to date suggest that vaccination of preadolescent males may be cost–effective if vaccination coverage in females cannot be increased above approximately 50%; but if it is possible, increasing coverage in females appears to be a better return on investment [60].

Introduction of HPV vaccines on a global scale has encountered some significant issues [61], including an anti-vaccine lobby that has tried to use misinterpreted adverse events in vaccine recipients unrelated to vaccination, as well as adverse events in placebo recipients to suggest that the vaccines are not safe. This has had significant consequences in some countries such as India, where vaccine programs were halted [62], and in the USA, where uptake has been slow (~33% for all three doses in girls in 2012) [56]. Vaccine costs have also had an impact on uptake. The initial programs sponsored by GSK and Merck for the developing world and the recent announcement

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Table 3. Merck V503 (nonavalent HPV vaccine V503) study list.

Rank	Status	Study	Conditions	Interventions	Ref.
1	Active, not recruiting	V503-006	Cervical cancers, vulvar cancers, vaginal cancers, genital warts	Biological: V503; biological: placebo to V503	[95]
2	Completed	V503-005	HPV infection	Biological: V503; biological: comparator: Menactra™ (concomitant); biological: comparator: Adacel™ (concomitant); biological: comparator: Menactra (non-concomitant); biological: comparator: Adacel (non-concomitant)	[96]
3	Completed	V503-007 AM1	Papillomavirus infections	Biological: V503 vaccine; biological: REPEVAX™ (concomitant); biological: REPEVAX (non-concomitant)	[97]
4	Active, not recruiting	V503-002	Cervical cancer, vulvar cancer, vaginal cancer, genital lesions, Pap test abnormalities, HPV infections	Biological: V503	[98]
5	Active, not recruiting	V503-003	Genital warts, anal cancer, anal intraepithelial neoplasia	Biological: V503 vaccine	[99]
6	Active, not recruiting	V503-010	HPV infection	Biological: V503 (nonavalent HPV L1 virus-like particle vaccine)	[100]
7	Completed	V503-008	Papillomavirus infections	Biological: V503	[101]
8	Active, not recruiting	V503-001	Cervical cancer, vulvar cancer, vaginal cancer, genital warts, HPV infection	Biological: comparator: 4vHPV; biological: experimental: V503	[102]
9	Recruiting	A study to compare immune response of V503 to Gardasil®in 16- to 26-year-old men	Papilloma viral infection	Biological: V503; biological: 4vHPV	[103]
10	Completed	Immunogenicity and tolerability of V503 versus 4vHPV	HPV	Biological: one dose at day 1, one dose at month 2 and one dose at month 6	[104]

Data taken from [94].

that the vaccines will be made available to the Global Alliance for Vaccines Initiative eligible countries at US$ 5 per dose and that the Gates Foundation will meet this cost for a period for approved programs [63] should enhance more rapid deployment in countries where routine cervical cancer screening has not been implemented and most of the deaths from cervical cancer occur. One clear lesson learned from the introduction of the first generation of HPV vaccines is that education about the vaccines is key to their successful deployment, and that education needs to be directed at health care professionals, governments, recipients, parents and schools to ensure effective delivery programs [64]. A recent program in the developing Pacific island nation of Vanuatu established the high prevalence of high-risk HPV infection [65] and of cervical dysplasia [66] in that country. This has enabled a joint program with GSK to deliver vaccines through schools, which achieved a 93% uptake rate of the full vaccine program across eligible children on Efate Island. Thus, effective partnerships between health care professionals, public health authorities, vaccine manufacturers, recipients, parents, schools and other organizations are necessary for the successful deployment of HPV vaccines.

Introduction to vaccine/review of pharmacology

While the licensed preventive HPV vaccines only contain two high-risk types of HPV (HPV 16 and 18), which can protect against approximately 70% of all cervical cancers, second-generation preventative vaccine candidates may broaden protection through the use of more multivalent L1-VLPs, vaccine formulations, or alternative antigens such as L1 capsomeres, L2 capsid proteins and chimeric VLPs [67]. Merck, Sharp and Dohme is currently evaluating a nonavalent HPV VLP vaccine in Phase III clinical trials (Table 3). The company has announced that the FDA has accepted its Biologics License Application for its investigational nonavalent HPV vaccine V503 (9vHPV),

with standard review being granted [68,69]. In addition to the non-oncogenic HPVs 6 and 11, this vaccine includes VLPs of HPV types 16, 18, 31, 33, 45, 52 and 58. Approximately 20% of cervical cancers and 25–35% of high-grade cervical dysplasia are caused by HPV 31/33/45/52/58 [70]. 9vHPV has the potential to expand the prophylactic cervical cancer coverage offered by 4vHPV from approximately 70 to 90% and the prevention of high-grade dysplasia from approximately 50 to 75–85% [70]. Figure 1 shows the composition of 9vHPV compared to 4vHPV [71]. It should be noted that 9vHPV contains higher amounts of adjuvant and HPV 6, 16 and 18 L1 proteins (Table 1), and could as a result be potentially more reactogenic than 4vHPV. It is also important to clarify that there are no identified serologic correlates of protection against HPV, and that comparative serologic data from clinical trials must be interpreted carefully, keeping this in mind.

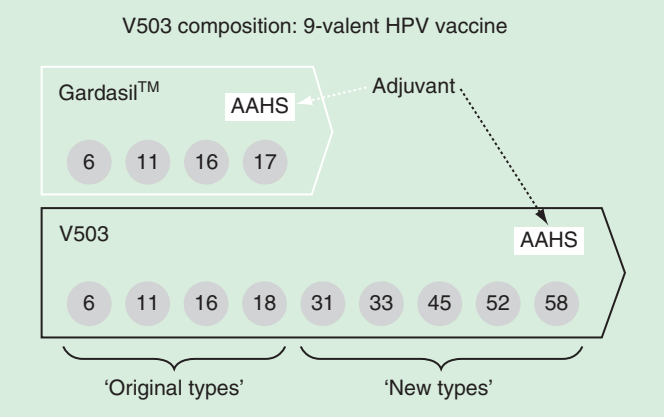

Figure 1. Composition of nonavalent HPV vaccine V503 compared to 4vHPV.
AAHS: Amorphous aluminum hydroxyphosphate sulfate.
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Phase II/III clinical trials

A summary of all Phase III clinical trials for V503 (9vHPV) is presented in Table 3.

The Phase III studies collectively were conducted in female subjects of age 9–26 years and in male subjects of age 9–15 years [70]. Over 13,000 study participants were administered 9vHPV. The pivotal efficacy and immunogenicity study (Protocol V503-001) was designed to evaluate vaccine efficacy against persistent HPV infection and disease in females of age 16–26 years. The study used 4vHPV (one of the two established standards of care for prevention of HPV infection and disease) as an active comparator. Vaccine efficacy was assessed separately for the original types and the new types. Since 4vHPV is a highly efficacious vaccine, very few cases of HPV 6/11/16/18 persistent infection and disease were expected. Therefore, a direct comparison of 9vHPV and 4vHPV prophylactic efficacy with respect to HPV 6/11/16/18 was not feasible. For this reason, the efficacy findings with 4vHPV were bridged to 9vHPV based on the demonstration of non-inferior anti-HPV 6/11/16/18 responses. HPV 6/11/16/18-related persistent infection and disease endpoints were also collected; a supportive analysis was conducted to demonstrate that efficacy of 9vHPV against HPV 16/18-related persistent infection and disease (normalized to historic placebo) was non-inferior to that of 4vHPV. Efficacy with respect to types 31/33/45/52/58 was established by demonstrating that 9vHPV reduces the combined incidence of HPV 31/33/45/52/58-related high-grade cervical/vulvar/vaginal disease.

Due to cultural, social and legal constraints around performing gynecological and genital examinations in preadolescents and younger adolescents, these study participants could not be included in an evaluation involving HPV genital infection and disease endpoints [70]. Also, these subjects are infrequently exposed to HPV, making an efficacy study in this population impossible. Therefore, an immunobridging strategy was undertaken in Protocol V503-002 to bridge the efficacy findings in young women of age 16–26 years to girls and boys of age 9–15 years, based on the demonstration of non-inferiority of anti-HPV 6/11/16/18/31/33/45/52/58 responses in boys and girls compared to women. An additional study (Protocol V503-009/GDS01C) was conducted to demonstrate that anti-HPV 16/18 responses were non-inferior in girls of age 9–15 years administered 9vHPV, compared with girls of same age administered 4vHPV. Three other studies were conducted to assess the following: concomitant administration of V503 with Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine and Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Protocol V503-005); concomitant administration of 9vHPVwith Diphtheria, Tetanus, Pertussis (acellular component) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen[s] content) (Protocol V503-007); and administration of 9vHPV in prior 4vHPV recipients (Protocol V503-006). The co-administration of the vaccines in two of the studies listed was to evaluate any potential interference among vaccines that may be administered at the same time, for example, at adolescent vaccination visits. Results from these studies have not yet been published.

Efficacy & immunogenicity

The Protocol V503-001 study is a randomized, international, double-blind, Phase IIb/III efficacy and immunogenicity study of the nonavalent HPV vaccine, abbreviated as 9vHPV in the rest of this paper (controlled with 4vHPV), conducted in 14,204 healthy women of age 16–26 years, to demonstrate that the immunogenicity of 9vHPV vaccine with respect to 4vHPV is non-inferior and that 9vHPV vaccine is highly efficacious compared with 4vHPV in preventing HPV 31/33/45/52/58-related persistent infection and disease [72]. The study design is summarized in Table 4. Subjects received 9vHPV vaccine or 4vHPV as a series of three 0.5-ml intramuscular injections at day 1, month 2 and month 6. Serum was collected from all subjects 4 weeks post-dose 3 for analysis of vaccine HPV-type responses by competitive Luminex® immunoassay (cLIA). Primary immunogenicity analyses included subjects who did not

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Table 4. V503-001 study design.

Enrollment	Part A • 1240 women (16–26 yo); three dose formulations of V503 or 4vHPV Part B • 13,380 women (16–26 yo); V503 (mid-dose) or 4vHPV; multicenter international study
Vaccine administration	Three vaccination visits: D1, Mo2, Mo6
Study visits	Efficacy → D1, Mo7, then every 6 months from Mo12 to the end of study Study visits • Pap test • Cervical and external genital swabs (HPV PCR testing) → As needed per protocol triage algorithm • Biopsy and DT samples (pathology and PCR) Immunogenicity • D1, Mo3, Mo7, Mo12, Mo24, Mo36, Mo42 • Serum samples for anti-HPV titers Safety • Injection-site and systemic AEs (days 1–15 post-vaccination) • SAE (day 1–180 days post-vaccination 3) • VR-SAE and deaths (day 1 to the end of study) • New medical history (post-day 1 to the end of study)
Key study endpoints	Efficacy • High-grade cervical, vulvar, vaginal disease due to vaccine HPV types • All cervical, vulvar, vaginal disease due to vaccine HPV types • Persistent infection due to vaccine HPV types • Abnormal Pap tests irrespective of HPV • Cervical, vulvar, vaginal disease irrespective of HPV • Cervical and external genital procedures irrespective of HPV Immunogenicity • Anti-HPV titers at Mo7 (post-vaccination visit 3) • Anti-HPV titers Mo12 through 42 (antibody persistence) Safety • Fever and injection-site AEs (days 1–5 post-vaccination) • Systemic AEs (days 1–15 post-vaccination) • Severe injection-site AEs (days 1–5 post-vaccination) • SAEs and VR-SAEs
Study objectives	• Superior efficacy of V503 vs GARDASIL for new types • Non-inferior immunogenicity of V503 vs GARDASIL for original types • Acceptable safety profile for V503

AEs: Adverse experiences; D: day; DT: Definitive therapy; Mo: month; SAEs: Serious AEs; VR-SAE: Vaccine-related SAEs.
Reproduced with permission from [105].

violate the protocol and who were also seronegative at day 1 and PCR negative from day 1 to month 7 only for the HPV type being analyzed. Gynecological examinations were performed at day 1 and months 7, 18, 30, 42 and 54. Labial/vulvar/perineal/perianal and endo/ectocervical swabs for HPV DNA testing, as well as a ThinPrep Pap test for liquid-based cytology testing were collected at day 1 and months 7, 12, 18, 24, 30, 36, 42, 48 and 54. Subjects with abnormal Pap tests were referred to colposcopy using a protocol-mandated triage algorithm. Tissue obtained by biopsy/definitive therapy was tested for HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. Endpoints were adjudicated by a pathology panel. Primary efficacy analyses took place in a per-protocol efficacy (PPE) population including subjects seronegative to the appropriate HPV type(s) at day 1 and PCR negative to the appropriate HPV type(s) on all cervicovaginal swabs and biopsies from day 1 to month 7 and who were not protocol violators.

Anti-HPV 6/11/16/18 responses were non-inferior to those generated by 4vHPV [72]. These results support the bridging of the efficacy findings with 4vHPV to 9vHPV vaccine. Efficacy of 9vHPV vaccine against a composite endpoint of HPV 31/33/45/52/58-related high-grade cervical/vulvar/vaginal disease in the PPE was 96.7% ([95% CI: 80.9, 99.8] 1 case in the 9vHPV vaccine group vs 30 cases in the 4vHPVgroup) [72]. Efficacy against HPV 31/33/45/52/58-related cervical/vulvar/vaginal disease (any grade) in the PPE was 97.1% ([95% CI: 91.8, 99.2] 3 cases in the 9vHPV vaccine group vs 103 cases in the 4vHPV group) [72]. Efficacy against HPV 31/33/45/52/58-related 6-month persistent infection in the PPE was 96.0% ([95% CI: 94.4, 97.2] 35 cases in the 9vHPV vaccine group vs 810 cases in the 4vHPV group) [72]. The 9vHPV vaccine was thus shown to be highly efficacious in preventing HPV 31/33/45/52/58-related persistent infection and disease. A supportive analysis showed that the efficacy of 9vHPV vaccine against HPV 16/18-related persistent infection and disease (normalized to historic placebo) was non-inferior to that of 4vHPV, thereby demonstrating that 9vHPV vaccine was highly efficacious with respect to types 16 and 18 and that its efficacy was similar to that of 4vHPV [72].

Since an efficacy study of the 9vHPV vaccine was not possible in sexually naive adolescents who are not frequently exposed to HPV, the Protocol V503-002 study (international, multicenter) was conducted to provide immunological bridging from women of age 16–26 years (the population used to establish 9vHPV vaccine efficacy) to adolescent girls and boys of age 9–15 years, to investigate whether the 9vHPV vaccine induced non-inferior serum geometric mean titers (GMTs) in boys and girls of age 9–15 years compared to women of age 16–26 years [73]. In this study, 3066 subjects received 9vHPV vaccine as a series of 0.5-ml intramuscular

injections administered at day 1, month 2 and month 6. Blood samples for anti-HPV 6/11/16/18/31/33/45/52/58 cLIA serologic assays were obtained at day 1 and month 7. Primary immunogenicity analyses included subjects who were seronegative at day 1 and (for 16- to 26-year-old women) PCR negative from day 1 to month 7 only for the HPV type being analyzed [73]. The primary non-inferiority hypothesis with respect to anti-HPV 6/11/16/18/31/33/45/52/58 GMTs at 4 weeks post-dose 3 in 9- to 15-year-old boys or girls compared to 16- to 26-year-old young women was tested by constructing a two-sided 95% CI for the ratio of GMTs [73]. The statistical criterion for non-inferiority required that the lower bound of two-sided 95% CI of GMT ratio (boys/young women or girls/young women) be greater than 0.67 for each HPV type.

At 4 weeks post-dose 3, over 99% of girls, boys and young women in the primary analysis population seroconverted for HPV types 6/11/16/18/31/33/45/52/58 [73]. Marked elevations in cLIA GMTs to HPV types 6/11/16/18/31/33/45/52/58 were elicited in all vaccine groups at 4 weeks post-dose 3 [73]. Non-inferiority of the GMT responses for each of the HPV types in both girls and boys, 9–15 years of age, relative to GMT responses in young women was established, thereby supporting bridging the 9vHPV vaccine efficacy findings in women of age 16–26 years to adolescent girls and boys of age 9–15 years [73].

Another double-blind study was conducted to evaluate the immunogenicity and safety of 9vHPV vaccine compared with 4vHPVvaccine in girls of age 9–15 years. Six hundred subjects were randomized 1:1 to receive a three-dose regimen (day 1, month 2 and month 6) of either 9vHPV vaccine or 4vHPV vaccine, in two age-strata (9–12 and 13–15 years of age) [74]. Immune response to the nine HPV types was evaluated 1 month after dose 3 by cLIA. The primary objective was to demonstrate the non-inferiority of 9vHPV vaccine compared to 4vHPV vaccine for both HPV 16 and 18, based on the lower bound of the 95% CI for post-dose 3 GMT ratios (9vHPV/4vHPV) being >0.67 (non-inferiority margin) in the per-protocol subjects seronegative at day 1 [74]. Non-inferiority was demonstrated at month 7 – GMT ratios (9vHPV/4vHPV) were 0.97 (95% CI: 0.85–1.11) for HPV16 and 1.08 (95% CI: 0.91–1.29) for HPV18 [74]. In addition, the GMT ratios were 1.07 (95% CI: 0.93–1.23) for HPV6 and 0.93 (95% CI: 0.80–1.08) for HPV11 [74]. The 9vHPV vaccine was highly immunogenic to the five new types. After 4vHPVvaccine, all subjects seroconverted to the four vaccine types (HPV 6, 11, 16 and 18) and a number of subjects seroconverted to non-vaccine HPV types (HPV 31, 33, 45, 52 and 58), mainly HPV31 (73.5%) and HPV58 (54.8%) [74]. However, the GMTs elicited by 4vHPV vaccine for these types were at least 80-fold lower than GMTs in subjects receiving 9vHPV vaccine [74]. It should be noted that the GMTs have not been shown to correlate with vaccine protection.

Safety & tolerability

Since the 9vHPV vaccine contains higher amounts of antigen and adjuvant than 4vHPV, the safety of the 9vHPV vaccine was evaluated across two large clinical trials (V503-001 and V503-002) in different study populations. Each subject in these studies received a vaccination report card at the day 1, month 2 and 6 study visits [75]. The vaccination report card was used to record oral temperatures, injection-site and systemic adverse experiences (AEs), concomitant medications and concomitant vaccinations for 15 days after vaccination. Serious AEs were collected regardless of causality from day 1 through 6 months following the last vaccination [75]. Pregnancy and lactation information were also collected.

The 9vHPV vaccine was generally well tolerated among women aged 16–26 years and boys/girls aged 9–15 years [73–75]. Vaccine-related AEs were largely attributable to injection-site AEs, most of which were of mild or moderate intensity [73,75]. Few subjects discontinued from these studies because of an AE. Vaccine-related serious AEs (SAEs) were rare [73,75]. The 9vHPV vaccine displayed an adverse event profile generally comparable to that of 4vHPV [74,75], except in Protocol V503-001, where a higher incidence of injection-site AEs was noted from day 1 to 15 following administration of the 9vHPV vaccine (90.8%) compared with 4vHPV administration (85.1%) [71,75]. Systemic vaccine-related AEs were reported in 29.5% of subjects who received 9vHPV versus 27.3% of subjects who received 4vHPV in the V503-001 study [71]. Vaccine-related SAEs were reported in 2 of 7071 subjects who received 9vHPV versus 1 of 7078 subjects who received 4vHPV in the V503-001 study [71]. Five subjects in the 9vHPV arm and three in the 4vHPV arm discontinued participation due to vaccine-related AEs, while only one subject who received 9vHPV discontinued from the V503-001 study due to a vaccine-related SAE. The proportion of subjects from Protocol V503-002 reporting at least one vaccine-related AE within 15 days of vaccination with 9vHPV vaccine was generally comparable among females aged 9–15 years (83.9%), males aged 9–15 years (75.5%) and females aged 16–26 years (87.1%) [75]. Only two vaccine-related SAEs were reported among 3051 subjects in Protocol V503-002, and only one subject discontinued from the study due to a vaccine-related SAE [71,73].

Conclusion

The 9vHPV vaccine appears to be safe and effective in preventing persistent infection and precancerous lesions as well as genital warts related to HPV types 6/11/16/18/31/33/45/52/58. Anti-HPV 6/11/16/18 responses in subjects vaccinated with 9vHPV were non-inferior to those induced by 4vHPV. Additional immunogenicity and efficacy were noted for infection and disease related to HPV types 31/33/45/52/58. The overall safety profile of the 9vHPV vaccine was comparable across multiple studies and populations to 4vHPV. The nonavalent vaccine has been submitted to and accepted by the FDA for standard review prior to licensure.

Expert commentary

With the introduction of the first generation of HPV vaccines, primary prevention of HPV-related diseases became feasible.

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Uptake of these vaccines has been variable, reaching only 38% among girls in the USA and 72% in the UK (for all three doses) [76,77], and resulting in reported HPV-related disease reduction in only a fraction of the world's population. The initial results from the clinical trials for the 9vHPV vaccine are promising, indicating non-inferior immunogenicity and high levels of efficacy when compared with 4vHPV in preventing HPV 31/33/45/52/58-related persistent infection and disease, and a safety profile comparable to 4vHPV. Once licensed and marketed, rekindled interest in HPV vaccines and improved vaccination coverage with them will be crucial to their success [76].

Changing from a bivalent (quadrivalent) to a nonavalent vaccine is predicted to reduce the cumulative number of ano-genital wart episodes by an additional 66.7% (0.0%), CIN2 and CIN3 episodes by an additional 9.3% (12.5%) and squamous cell carcinoma cases by an additional 4.8% (6.6%) over 70 years [78]. In another recent study comparing the potential impact of the bivalent with the nonavalent HPV vaccines in Galicia, Spain, it was found that when cross-protection with the bivalent vaccine is considered, it is expected to reduce the cumulative incidence of CIN2 by 48.2% and CIN3+ by 70.2% [79]. An additional reduction of 12.4% of CIN2 and 4.9% of CIN3+ would be achieved if the nonavalent vaccine were to be used instead of the bivalent vaccine [79]. It should be noted that the duration of cross-protection has not been demonstrated yet, and therefore, the estimations presented here may not hold true in long-term observations.

High levels of vaccination with 9vHPV could eventually replace screening for cervical cancer as the primary means of cancer prevention. However, before any change in current practices, detailed and careful evaluation of such change potentially by both clinical trials and models will be necessary. Continued safety monitoring after licensure and evaluation of duration of protection is essential. Questions with regard to revaccinating women and men previously vaccinated with HPV vaccines remain unanswered, and will likely need additional studies as well as regulatory and public health policy responses. The subject of cost–benefit, particularly in developing countries where the need is greatest, must also be addressed. Thus, there are a range of issues around HPV vaccination that are beyond the scope of this paper, but will need future study.

Five-year view

Since the introduction of the first clinical HPV tests nearly 20 years ago and the availability of the first generation of HPV vaccines in the past decade, the field of HPV research has experienced tremendous growth, with a 400% increase in the annual number of articles on papillomavirus listed in Medline's PubMed database over the past 20 years [80]. Despite this, the evidence base in the area of cervical cancer prevention remains limited, making it difficult to predict what lies ahead. It is expected that widespread HPV vaccination will lead to decline in cervical cancer incidence and mortality. However, the licensure and deployment of these vaccines has not been without controversy [81,82]. Concerns regarding cost, the need for HPV vaccination in settings with low cervical cancer mortality, duration of HPV protection, the possibility of type replacement and the safety of the vaccines in general have been expressed [82,83].

Collaborative efforts between vaccine manufacturers and the governments of resource-restrained countries to help make HPV vaccination affordable in these countries are encouraging [84]. It should be noted that even in developed countries, precursor lesions requiring surgical intervention exceed the incidence of cervical cancer frequently by a factor of 20 [84]. In addition to associated costs, the risk for adverse effects of these procedures (in particular for subsequent pregnancies) amounts to 2–7%. Therefore, vaccination is also an important issue for affluent and well-screened societies [84]. The potential cost–effectiveness of the nonavalent and quadrivalent HPV vaccines was compared in a recent Canadian study which showed that the nonavalent vaccine can be a cost–effective alternative to the quadrivalent vaccine, even in scenarios where the efficacy of nonavalent vaccine is 85% [85]. The rates of reported adverse events among vaccinated individuals have been comparable to the rates among placebo recipients and within the expected background rates in the general population [86]. Clinical trial results show that protection against HPV-related diseases has endured unabated for nearly a decade (for licensed HPV vaccines) and longer (approximately 13 years for the prototype HPV16 vaccine) without any indication of waning antibodies [32,35,87]. Finally, epidemiological studies investigating the potential for HPV type replacement (i.e., non-vaccine HPV types taking over the niches vacated by the eradication of vaccine target types) have so far provided no strong evidence of natural type competition, considered to be a prerequisite for type replacement to occur in vaccinated populations [88].

The currently licensed HPV vaccines and the nonavalent vaccine in development are type restricted, expensive, and also require refrigeration, multiple doses and intramuscular injection [89]. Second-generation vaccines are currently being developed to address these shortcomings [89]. New expression systems, viral and bacterial vectors for HPV L1 capsid protein delivery, and use of the L2 capsid protein will hopefully aid in decreasing the cost and increasing the ease of use and breadth of protection [89]. Even with a nonavalent vaccine, total protection against HPV will not be achieved. Cervical cancer rates should decrease, but will take 20–30 years to do so [89]. In the interim, cervical cancer screening will still be necessary, but needs to be modified.

The next 5 years will likely continue to be an important period of discovery in the field of HPV-related disease prevention, but perhaps with more effort placed on evaluation of novel technologies (including the introduction of the second generation of HPV vaccines) and policy decisions surrounding their implementation. Policymakers will need to readjust screening guidelines [90] that will need to be flexible in order to adapt to the growth of these new technologies. While preventative vaccines are crucial to controlling the transmission of HPV, the hundreds of millions of infected individuals who already have HPV-associated lesions that are silently progressing

toward malignancy remain a major concern. Therapeutic HPV vaccines that can trigger T cell killing of established HPV lesions, including HPV-transformed tumor cells, are needed for these individuals. In order to stimulate antitumor immune responses, therapeutic vaccine candidates that can deliver HPV antigens *in vivo* by employing various bacterial, viral, protein, peptide, dendritic cell and DNA-based vectors are in development [67]. The deployment of improved vaccines offers the hope that vaccination will eventually replace screening for cervical cancer as the primary means of cancer prevention. Recent exciting discoveries in the field of HPV microbicides and therapeutic vaccines research may transform the landscape of cervical cancer prevention and control strategies to include novel treatment options for HPV and associated malignancies [90–92].

Information resources

- WHO website provides contemporary estimates of the incidence of, mortality and prevalence of major types of cancer, at a national level, for 184 countries of the world. It may be used by both the public and health professionals [4].
- CDC website for health care professionals: HPV vaccine resources for health care professionals [93].
- National Institutes of Health Clinical Trials website provides the list of nonavalent HPV clinical trials. It may be used by both the public and health professionals [94].

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Key issues

- Primary prevention of cervical cancer by vaccination against high-risk HPV types has been a significant public health development.
- HPV vaccination also has the potential to protect against other ano-genital tract cancers and cancers of the oropharynx in both men and women.
- Currently licensed HPV vaccines protect against HPV types that cause approximately 70% of cervical cancers. The nonavalent HPV vaccine has the potential to prevent an additional 20% of cervical cancers.
- If the nonavalent vaccine is licensed, protocols for vaccinating individuals who have previously received bivalent or quadrivalent HPV vaccines will need to be developed.
- The focus of HPV vaccination efforts thus far has primarily been on young women. Improving the vaccination rates not only in this population, but also among older and previously exposed women, boys and men would provide herd immunity and also protect men who have sex with men.
- Cervical cancer screening programs will likely need to adapt and may move to HPV testing by self-sampling in the future. Alternative strategies for screening are likely to be required for vaccinated and unvaccinated women.
- Cheaper vaccine options are crucial for developing countries, where the need for HPV vaccination is greatest.

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