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HPV Vaccines: state of the art and novel approaches

Edited by the SIAIP Vaccine Committee
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SUMMARY

High-risk genotypes of Human Papillomavirus (HPV) are responsible for cervical cancer and have been shown to be related to the occurrence of other less frequent malignancies (vulva, penis, anus, head and neck). Although in the majority of cases the infection resolves spontaneously, some people fail to clear the virus with an increased risk of neoplastic development. In Italy, HPV vaccination is recommended and offered free of charge to girls and boys from 11 years of age. It is also recommended for immunocompromised patients, individuals with high risk sexual behavior, and women with cervical lesions. The efficacy of HPV vaccination in preventing cervical cancer, especially in uninfected women, has been widely demonstrated. Further advances in technology to improve the efficacy of existing vaccines and the development of novel vaccines are necessary to prevent HPV-associated cancers. The aim of this non-systematic review is to provide an update on the available vaccines and future perspectives for HPV vaccination.

KEYWORDS: alphaHPV, vaccines , VLP-L1, VLP-L2

INTRODUCTION

HPV infection is prevalent among individuals of reproductive age. The two primary high-risk genotypes (16 and 18) are responsible for cervical carcinoma, often facilitated by cofactors such as sexually transmitted infections (e.g., Chlamydia and HIV), long-term use of estrogen-progestin contraceptives, tobacco consumption, sexual promiscuity, and immunosuppression [1]. In 2020, approximately 600,000 women were diagnosed with cervical cancer and 342,000 died, 90% of them in developing countries [2,3]. In 2012, in Italy, there were 1515 cases of cervical neoplasia with an incidence rate of 5.3/100,000 (age-standardized 4/100,000) and 697 deaths with a mortality rate of 2.4/100,000 (age-

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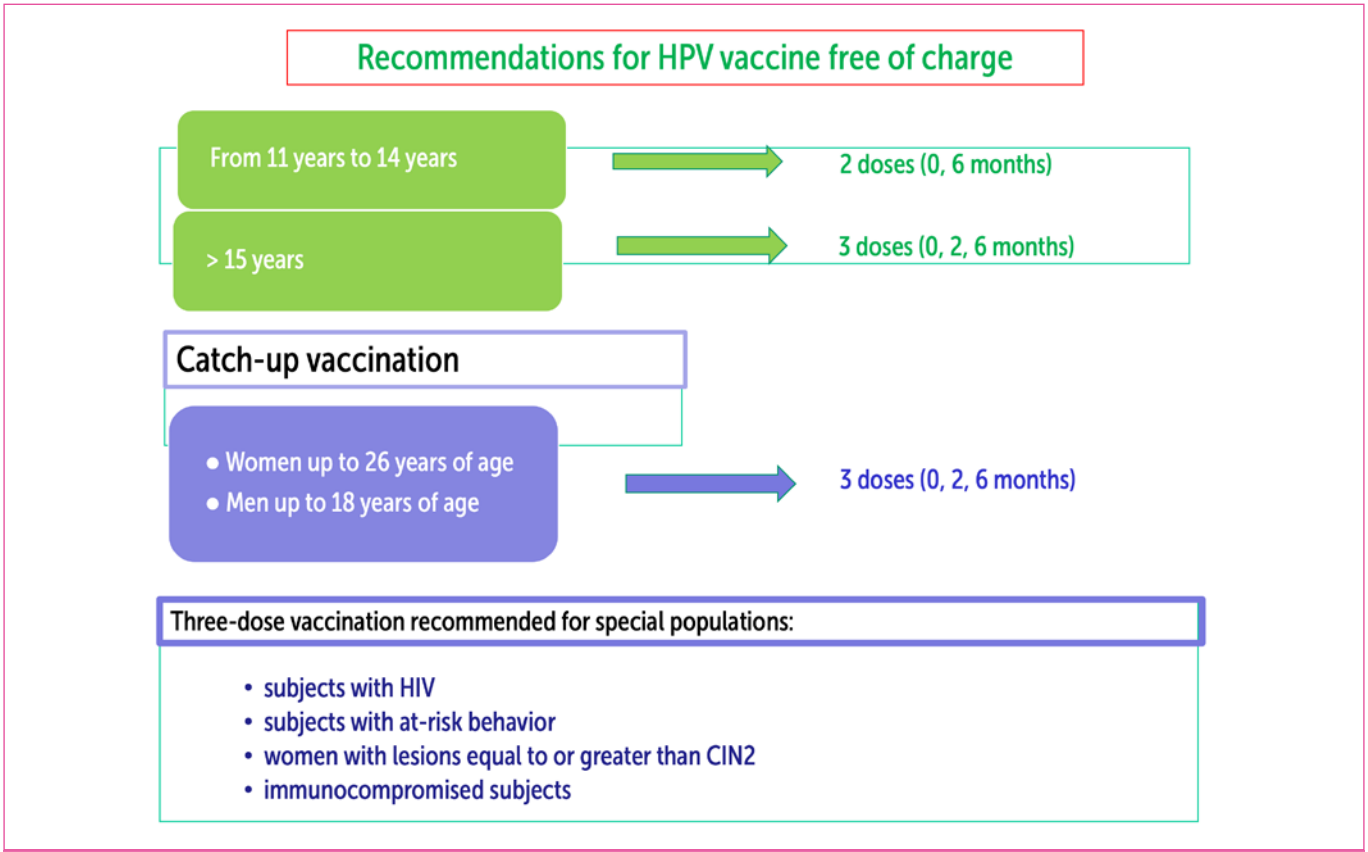

FIGURE 1. HPV vaccine schedule according to Italian Ministry of Health recommendations.

standardized 1.5/100,000), showing a significant reduction in the incidence and mortality rate of cervical cancer, in line with other European countries. These reductions are attributed to screening programs and the implementation of HPV vaccination. Although up-to-date data are not yet available, there is significant concern regarding the impact of the COVID-19 pandemic on HPV vaccine adherence [4]. The World Health Organization (WHO) considers vaccination as one of the three pillars, alongside screening and treatment, to eliminate cervical cancer by 2030. As there has been a gradual decline in vaccine coverage worldwide since 2022 (from 25% to 15% as to the first dose), WHO has rescheduled the vaccination offer with one or two doses up to the age of 20 and two doses after the age of 20, in order to reach more girls to be vaccinated before the onset of sexual activity and to reduce health costs for developing countries [5-7]. In addition to girls, WHO recommends vaccination for boys and adult women, prioritizing immunocompromised individuals (including those with HIV) to receive at least two doses [8]. Long-term studies primarily conducted in Costa Rica and India have demonstrated the stability of antibody levels following the administration of a single dose of HPV vaccine [9]. Based on this scientific evidence, the governments of Australia (https://www.health.gov.au/sites/default/files/2023-02/hpv-vaccine-fact-sheet-outlining-changes-under-the-national-immunisation-program-in-2023.pdf) and the United Kingdom (https://www.gov.uk/government/publications/hpv-vaccination-programme-changes-from-september-2023-letter/hpv-vaccination-programme-changes-from-september-2023) have modified their national HPV immunization programs. Indeed, since 2023, nonavalent HPV vaccination is offered as a single dose to adolescents (aged 12-13) and to MSM (aged under 25), with the exception of immunocompromised individuals, for whom the vaccination schedule remains unchanged. Some primary immunodeficiencies, mainly characterized by impaired function of cellular immunity and NK defects, may be associated with increased susceptibility and persistence of HPV infection. For instance, patients with mutations in GATA2, EVER1/2, DOCK8, CXCR4 and SASH3 have a higher susceptibility to HPV lesions, which can range from warts to genital condyloma to cervical and squamous cell cancer. HPV vaccination with three doses is strongly recommended in these patients [10,11]. The new Italian National Preventive Vaccination Plan (PNPV) 2023-2025 includes among its objectives the reinforcement of prevention of cervical cancer

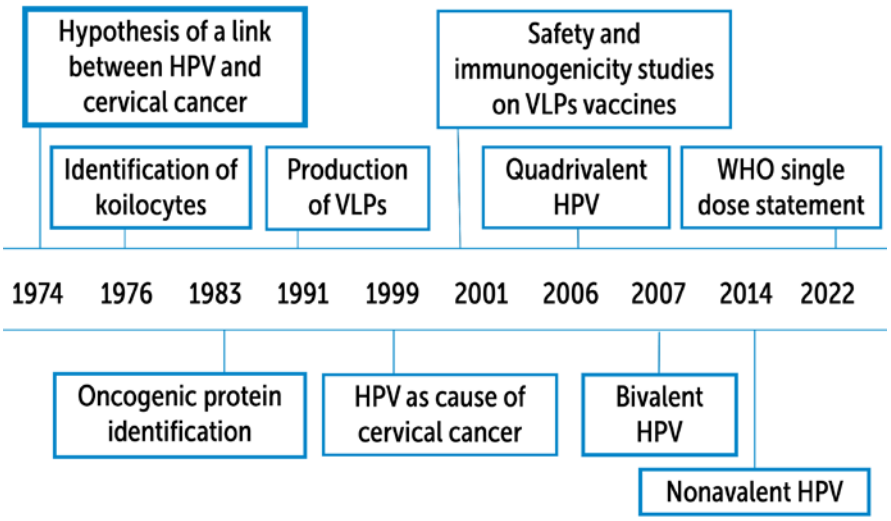

FIGURE 2. Chronology of HPV vaccine development (from Wang et al., 2020, mod.) [35].

and other HPV-related diseases [12]. HPV vaccination, although not mandatory, has been included in the Essential Levels of Care since 2017 and is offered free of charge according to the two-dose schedule (0-6 months) for girls and boys aged 11-14 years and according to the three-dose schedule (0-2-6 months) after the age of 15 years. (Fig. 1) The catch-up HPV vaccine program for boys up to 18 years of age and girls up to 26 years of age is also offered free of charge. HPV vaccination is further recommended for immunocompromised individuals, individuals with at-risk behavior, and women treated for cervical intraephitelial neoplasia (CIN) grade 2 or higher [13]. In 2022, as part of its annual monitoring of vaccination coverage, the Italian Ministry of Health has identified regional differences in vaccination coverage and called for specific measures to close the gaps that still exist in some geographical areas [14].

STATE OF THE ART

Approximately 200 human HPV genotypes are known, classified in five major phylogenetic genera referred to as Alpha (α)-, Beta(β)-, Gamma(γ)-, Mu(μ)-, and Nu(ν), of which Alpha predominantly infects mucosal epithelial cells and Beta predominantly infects skin cells. High-risk (HR) alpha-HPVs are responsible for neoplastic evolution, while low-risk (LR) ones are responsible for flat warts, genital condylomas, and respiratory papillomatosis. During interaction with the host, HPV does not show cytolytic activity, cell death, or viremia and does not induce a local inflammatory process, thus resulting in a weak host immune response [15]. HPV vaccines administered before the onset of sexual activity have been shown to reduce both the risk of infection and the development of HPV-related diseases. The question of their full efficacy when administered to already exposed individuals remains open, although recent data suggest an important adjuvant role for HPV vaccines in reducing CIN recurrence [16,17]. HPV-associated head and neck cancers are more prone to aggressive forms with no pre-neoplastic lesions that would allow early detection by appropriate screening. Even in such cases, vaccination remains an option to prevent infection [18,19]. Vaccines available since 2006 (Fig. 2) are based on recombinant DNA technology and differ in terms of number of genotypes (2 or 4 or 9) to which they induce an immune response, expression system (baculovirus for two-valent and Saccharomyces cerevisiae for four-valent) and type of adjuvant used (AS04 for two-valent and AAHS for four-valent). The bivalent (HPV 16, 18) and quadrivalent (HPV 6, 11, 16, 18) vaccines have been gradually replaced by the nonavalent HPV vaccine, which consists of nine genotypes, seven of which are HR (16, 18, 31, 33, 45, 52, 58) and the two LR (6, 11). Other HPV vaccines are in advanced stages of development worldwide. The quadrivalent Cervavac (SIIPL, Pune, India) (6,11,16 and 18) has been shown to be comparable to Gardasil4 in terms of efficacy and safety, with the advantage of being less expensive [20]. Two bivalent vaccines (HPV 16, 18) are currently marketed in Asia, Cecolin (Xiamen Innovax, China) and Walrinvax (Walvax, China) (Tab. I), which have different expression systems. The first uses Escherichia coli, the second Pichia pastoris. Both offer time and cost savings in the production of recombinant proteins [21]. Reports of severe allergic reactions associated with HPV vaccination are rare. These are likely to be related to prior sensitinization to HPV vaccine components. Individuals who are allergic to yeast are at increased risk of severe adverse reactions since yeast is used as an expression system in the three most widely used HPV vaccines worldwide. The presence of

TABLE I. Currently available HPV vaccines (from Williamson et al., 2023, mod.) [28].

Trade name	Genotypes	Pharma company	Expression system	VLP
Cervarix	16,18	Glaxo Smith Kline	*Baculovirus*	L1
Gardasil 4	16,18,6,11	Merck Sharp & Dohme	*Saccharomyces cerevisiae*	L1
Gardasil 9	16,18,6,11,31,33,45,52,58	Merck Sharp & Dohme	*Saccharomyces cerevisiae*	L1
Cecolin	16,18	Innovax Biotechnology	*Escherichia coli*	L1
WalrivaxV	16,18	Walvax Biotechnology	Pichia pastoris	L1
Cervavac	16,18,6,11	Serum Institute of India	*Hansenula polymorpha*	L1

polysorbate 80, a vaccine stabilizer, may also be responsible for hypersensitivity reactions. In 2017, WHO published its latest report on HPV vaccine safety where the risk of anaphylaxis was found to be 1.7 cases per million doses administered, confirming a good safety profile [22].

IMMUNOGENICITY OF HPV VACCINES

HPV vaccines induce the production of antibodies against the genotypes contained in the vaccine at higher levels than natural infection does. Studies on the efficacy of HPV vaccines (immunobridging) refer to the production of antibodies, which are considered markers of protection, especially neutralizing antibodies (predominantly IgA, IgG1 and IgG3 types) [23,24]. However, the use of different methods for their titration (PBNA, cLIA, ELISA) does not allow the definition of a cut-off that is suitable to standardize the results obtained from monitoring studies [24,25]. The antibody titer against HPV18 seems to decline earlier, especially in women receiving the quadrivalent vaccine than those receiving the bivalent one. Similarly, anti-HPV16 antibody levels halve at 2-4 years after quadrivalent vaccination and at 5-7 years after bivalent vaccination [26-28]. There is still no evidence to explain why the bivalent vaccine is more protective than the quadrivalent vaccine in the long term. It is thought that the expression system based on baculovirus allows for a conformation of the neutralizing epitopes that are more similar to native virions and that the adjuvant system used (AS04) allows for a higher and persistent production of protective antibodies over time [26,27]. However, quadrivalent and bivalent vaccines are equally effective in protecting against genotypes not included in the vaccine (cross-protection) and seropositivity is maintained longer in adolescents receiving the vaccine than in individuals older than 25 years [28,29]. The nonavalent vaccine is immunogenic, effective, and safe as well and demonstrates a prevention potential of 90% for cervical neoplasms caused by other high-risk HPV genotypes [30,31] with persistence of neutralizing antibody titer over the time. This is due to the conformational structure of VLPs and to the exposure of repetitive epitopes that promote better activation of B-cell receptors [30,32]. There are few studies on the role of T lymphocytes in the course of vaccination and their results are inconclusive. No significant changes were observed in the number of CD4+ T cells after administration of the bivalent and nonavalent vaccines, although a slight increase was recorded after the third dose of nonavalent vaccine [30]. However, a correlation was observed between the development of humoral immunity and the age of vaccinated subjects and between the development of T cell immunity and the number of doses administered [27,29].

NOVEL APPROACHES

The continuous advancement of technologies has improved the efficacy of existing vaccines and allowed the production of new ones with the aim of preventing the integration of viral DNA into the host cell. Because HPV does not grow in culture, vaccines are based on the construction of L1 Virus-like Particles (VLPs) derived from some common *alpha*-type genotypes, but not from *beta*-type HPV which are frequently associated with cutaneous squamous cell carcinoma especially in immunocompromised patients. The difficulty in producing VLP-L1s against all oncogenic HPV genotypes is due to their high cost and to partial efficacy in counteracting pre-existing cervical and cutaneous lesions. Therefore, the approach for the near future is to develop new platforms and to search for other viral proteins that are better suited to induce a sustained and potent immunologic response. The L2 protein, for example, is highly conserved among HPV genotypes and has been shown to promote protection from infection and regression of preexisting lesions, even if it induces a lower neutralizing antibody titer than L1 [33-35]. In recent years, some preclinical data on the production of cross-neutralizing antibodies induced by modification of L1 and L2 epitopes have been published and the list of technologies used for the development of VLP L2 vaccines has been growing over time [34]. New platforms under study involve two new HPV vaccine "candidates": HPV16 RG1-VLP and CUT-PANHPVAX. In the former, VLPs expose the HPV16 epitope on their surface; in the latter, L2 sequences of 12

skin genotypes are present and have been shown to induce cross-protection and cross-neutralization [36]. It should also be mentioned the attempt to develop HPV vaccines with plant-based platforms in order to allow oral rather than parenteral administration, but it has been unsuccessful so far. Preclinical studies on oral immunization of mice with alga-expressed HPV VLPs have not yielded the hoped-for results due to low antigen expression and lack of adequate glycosylation [37].

In another preclinical trial, the immunomodulatory effects of the vaccine based on HPV-16 recombinant E6 protein expression were tested in *Lactococcus lactis*. At 6 months after oral administration, preliminary results showed an E6-specific cytotoxic T lymphocyte (CTL) response although the antibody response was lower than the placebo group [38]. Preclinical and clinical phase I studies for a new HPV vaccine (2AP01) are more encouraging. It is formulated on adeno-associated VLPs and free of adjuvant [39] and seems to be able to protect against L2 protein of cutaneous and mucosal HPV genotypes, including beta HPV [40]. New bioinformatics and immunoinformatics approaches are enabling the construction of experimental vaccines that rely on the ability to stimulate both B cells to produce specific antibodies and T cells to develop vaccine-specific memory subsets through interaction with different major histocompatibility complex (MHC) alleles. In this regard, a multi-epitope chimeric HPV vaccine capable of sustaining a long-term anti-viral response is ongoing [41].

THERAPEUTIC HPV VACCINES

Unlike preventive HPV vaccines, therapeutic ones stimulate cytotoxic T cell immunity mainly against the E7 protein, which is better immunologically characterized than E6 and is present on both HPV16+ and/or HPV18+ cutaneous and mucosal neoplastic lesions [42,42]. Some vaccines based on live vectors, both bacterial and viral, are being studied. They are highly immunogenic, but progressively lose efficacy after repeated immunization with the same vector [42]. Other types of vaccines are based on antigens derived from cancer-associated proteins; even if they are easy to produce, they are poorly immunogenic and not very stable in vivo. For these reasons, new production systems and adjuvants suitable for the production of nanovaccines are being tested [44]. Regarding vaccines based on nucleic acid, including mRNA vaccines, these have shown efficacy in regression of some HPV+ lesions, although the results from a mouse model are variable [45,46]. In contrast, whole-cell vaccines, e.g., dendritic cell vaccines, have limitations referable to the technology employed and the quantity and quality of the cells selected [47]. Undoubtedly, progress in the development of therapeutic vaccines is promising. However, the satisfactory results obtained in the preclinical phase have not yet been confirmed in phase III clinical trials for the treatment of human HPV-related cancers [47].

CONCLUSIONS

Vaccination is currently the most effective strategy to counter HPV infection. New approaches will have to take into account the different geographic distribution of HPV genotypes, the choice of more cross-immunogenic viral proteins, and the more favorable cost-effectiveness ratio. Novel vaccines should be able to prevent HPV infection as well as counteract the progression of malignancy if present.

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Conflicts of interest statement

All authors declare that they have no conflict of interest with respect to the topics discussed in the article.

Ethical considerations

None.

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Authors' contribution

VM: conceptualization. GMFM, VS, AB: data curation and writing. EDD, MS, GC, MFM, DM, GO, CR: draft critical revision. GMFM, VM, BM: writing review. All authors gave final approval of the manuscript to be published.

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