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Human Papillomavirus Vaccination: A Review

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ABSTRACT

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide, affecting the majority of people at some point in their lives. The persistence of high-risk HPV is not only critical for the development of cervical cancer, but also contributes to the development of cancers in other anogenital areas, including the penis, vulva, vagina, anus and oropharynx. Prophylactic HPV vaccines have the potential to prevent HPV infection and thereby reduce the burden of HPV-related disease. The primary target population for HPV vaccination is individuals aged 9-14 years with no history of HPV infection. Vaccination is also recommended for those who are already infected, although efficacy may not be as robust as in the HPV-naive group. Many countries are implementing gender-neutral vaccination programmes, encouraging both males and females to receive the vaccine. This approach aims to reduce the risk of HPV-related cancers, prevent anogenital warts, and promote herd immunity. While routine single-dose vaccination is not the norm, it may be considered in resource-limited settings where access to multiple doses is difficult. Long-term data confirm that HPV vaccines significantly reduce the incidence of cancer and HPV-related diseases, and underscore their safety and efficacy.

Keyword: HPV vaccine, Human papillomavirus, Cancer prevention

Overview of HPV: Human papillomavirus (HPV), the most prevalent sexually transmitted infection globally, infects the majority of individuals at some stage in their lives (1). Infections commonly target epithelial tissues and are typically transmitted through sexual contact. Around 90% of HPV infections are either clear or become inactive within 12 to 24 months of exposure to the virus (2). However, infections caused by high-risk HPV types persist, increasing the likelihood that they will progress to cervical cancer. The development of cervical cancer requires the prolonged presence or persistence of the HPV virus. Age-specific progression is shown in Figure 1. It also contributes to the development of other anogenital cancers such as those affecting the vulva, vagina, and anus, as well as oropharynx cancers (3). The initial HPV infection typically occurs at the onset of sexual activity, and the detection of cervical precancers depends on the age at which cervical cancer screening takes place. Cervical cancer is commonly diagnosed many years after the initial infection (4).

There are over 200 identified human papillomavirus genotypes, categorized into different families (*alpha*, *beta*, *gamma*, *mu*, and *nu*) based on their viral genome structure and tropism for human epithelial tissues. Alpha family, notably comprising twelve types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), is commonly linked to high-risk infections. From those, Approximately 70% of invasive cervical cancers worldwide are attributed to HPV types 16 and 18. (5). Conversely, low-risk types such as HPV 6 or HPV 11, which are commonly associated with genital warts, and others are generally associated with beta and gamma papillomavirus infections (6).

On a global scale, approximately 600,000 women and 70,000 men are diagnosed with an HPV-related cancer annually. Cervical cancer, with approximately 604,000 new cases and 341,000 deaths globally in 2020, stood as the fourth most common cancer and cause of cancer-related deaths in women. Cervical cancers constitute 93% of HPV-related cancers in women. Almost all HPV-related cancers in women are comprised of cervical cancers (7, 8). Although HPV infection is notably correlated with cervical cancer, it also holds a substantial role in the development of anal, oropharyngeal, penile, vaginal, and vulvar cancers. HPV infection potentially contributes to around 90-93% of anal cancers, 12-63% of oropharyngeal cancers, 36-40% of penile cancers, 40-64% of vaginal cancers, and 51% of vulvar cancers. (9).

Most cases and deaths from cervical cancer are concentrated in low- and middle-income countries, where comprehensive cervical cancer screening is limited. Furthermore, roughly 90% of

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anogenital warts are attributed to HPV types 6 and 11. Prophylactic HPV vaccines have the potential to prevent HPV infection and reduce the burden of HPV-related disease.

HPV and Cervical Cancer Prevention: HPV infections typically do not show symptoms. The diagnosis of most genital HPV infections is made through HPV testing, often conducted as part of cervical cancer screening. HPV infections typically do not show symptoms. The diagnosis of most genital HPV infections is made through HPV testing, often conducted as part of cervical cancer screening. There is agreement that screening should commence no earlier than 21 years of age, with some advocacy for considering the initiation of screening at 25 years of age (10).

In addition to screening, strategies are being developed to more effectively combat cervical cancer associated with HPV by employing a combination of various approaches. The World Health Organization (WHO) has put forth recommendations to eliminate cervical cancer through screening, vaccination, and treatment. In 2020, the WHO introduced the 90-70-90 targets with the objective of eradicating cervical cancer by 2030. This entails vaccinating 90% of girls, screening 70% of women, and treating 90% with cervical disease. In theory, WHO supposed has to eliminate cervical cancer as less than 4 new cases per 100 000 women-years (11). When we look at real world data, it seems that the most promising applications for the prevention of cervical cancer to date are HPV vaccination applications.

HPV Vaccines: The circular, double-stranded papillomavirus DNA genome encompasses a regulatory region, structural proteins such as L1 and L2 (late proteins), and six early proteins responsible for replication. Late proteins are structrual proteins; L1 functions as the major capsid protein, while L2 is a minor protein composing capsomere. The formation of virus-like particles (VLP) through the self-assembly of L1 constitutes the base of modern HPV vaccines (12).

Currently, there are 6 licensed prophylactic HPV vaccines available in the market: 3 bivalent, 2 quadrivalent, and 1 nonavalent vaccine (Table 1). Bivalent HPV vaccines specifically address HPV types 16 and 18, while quadrivalent vaccines target HPV types 6, 11, 16, and 18. The 9-valent HPV vaccine covers the same HPV types as the quadrivalent vaccine) and introduces additional types as 31, 33, 45, 52, and 58.

HPV vaccination induces a durable immune response that lasts for at least 8-14 years in the general population(13, 14). Following the licensure of Gardasil in 2006, HPV vaccination programs have been introduced in more than 100 countries. It has shown a decrease in the prevalence of high-grade cervical intraepithelial neoplasia (CIN) and diagnoses of anogenital warts in young women in the period between 5 and 9 years after the introduction of national vaccination campaigns. The reduction in anogenital wart diagnoses was also observed in men after vaccination (15).

Clinical Trials in young females: In international, randomized, controlled trials encompassing women aged 15 to 26 who exhibited no signs of infection or exposure to HPV types and had received the full three-dose vaccination, the efficacy of the vaccine in preventing CIN degree 2 or worse (CIN2+) caused by targeted HPV types according to the protocol has been demonstrated to range between 89.5% and 100% (16, 17). Quadrivalent vaccine trials revealed a 100% efficacy in preventing anogenital warts. Nearly all vaccine recipients developed HPV type-specific antibodies, and their antibody titers were significantly higher compared to those following natural infection(18). Furthermore, The robust immunogenic responses to all four types of HPV in the quadrivalent vaccine allow efficacy data established in young women to be extended to much younger girls. These studies have shown that, as a lower limit, the vaccine can be safely used in adolescents as young as 9 years old. The long-term high efficacy of the HPV vaccine supports the use of a two-dose series in children and adolescents aged 9 to 14. Furthermore, in the study of the Nonavalent HPV vaccine, antibody titers in children aged 9 to 14, regardless of gender, receiving two doses 6 or 12 months apart were noninferior to antibody levels after three doses in adolescent girls and women aged 16 to 26 (19, 20). Additionally, data obtained from vaccine applications in male children support the implementation of a gender-neutral HPV vaccination program (21).

HPV Vaccination in Males: Gender-neutral vaccination has dual benefits: firstly, it aids in establishing herd immunity, and secondly, it plays a role in averting HPV-associated ailments in males. Immunizing males against HPV holds the potential to reduce both HPV infection and associated lesions. A randomized controlled trial demonstrated approximately 90% efficacy of the quadrivalent vaccine in preventing vaccine-type

Table 1: Characteristics of HPV Vaccines Available In Market

Vaccine and Manufacturer Name; Licensure Date	Vaccive Type	Adjuvant	Expression System	Dose Schedules
GARDASIL®, Merck & Co., 2006	Quadrivalent	Amorphous aluminium hydroxy phosphate sulphate	Yeast, Saccharomyces cerevisiae expressing L1	For girls and boys aged 9–13 years as a 2-dose schedule (6 months apart). From age 14, a 3-dose schedule should be given (at 0, 1–2 and 4–6 months).
Cervarix®, GlaxoSmithKline, 2007	Bivalent	Aluminium hydroxide and 3-0-desacyl-4 monophosphoryl lipid A	Insect cell line, recombinant baculovirus encoding L1	For girls and boys aged 9–14 years as a 2-dose schedule (5–13 months apart). If recipient's age at first dose is ≥15 years, three doses proposed (at 0, 1–2.5 months and 5–12 months)
GARDASIL9®, Merck & Co., 2014	Nonavalent	Amorphous aluminium hydroxy phosphate sulphate	Yeast, Saccharomyces cerevisiae expressing L1	For girls and boys aged 9–14 years as a 2-dose schedule (5–13 months apart). From age 15, a 3-dose schedule is proposed (at 0, 1–2 and 4–6 months).
Cecolin®, Xiamen, Innovax Biotechnology, 2020	Bivalent	Aluminium hydroxide	Bacteria, Escherichia coli expressing L1	For girls aged 9–14 years as a 2-dose schedule (6 months apart). From age 15, a 3-dose schedule is proposed (at 0, 1–2 months and 5–8 months).
Walrinvax® Zerun Biotechnology, 2022	Bivalent	Aluminium phosphate	Yeast, Pichia pastoris expressing L1	For girls aged 9–14 years as a 2-dose schedule (6 months apart, with a minimum interval of 5 months). From age 15, a 3-dose schedule is proposed (at 0, 2–3 and 6–7 months).
Cervavac®, Serum Institute of India, 2022	Quadrivalent	Aluminium based		For girls and boys aged 9–14 years, as a 2-dose schedule (6 months apart). From age 15, a 3-dose is proposed (at 0, 2 and 6 months)

genital warts and external genital lesions in the HPV-naive population. Moreover, the vaccine exhibited nearly 85% effectiveness against persistent vaccine-type HPV infections (22). All vaccines, except for Cecolin and Walrinwax, have been approved for use in males (Table 1).

Clinical Trials in Older Females: Previous exposure to HPV may reduce the effectiveness of the vaccine, and there is no evidence that the vaccine prevents the progression of existing infections to disease or facilitates the clearance of infections or disease already present at the time of

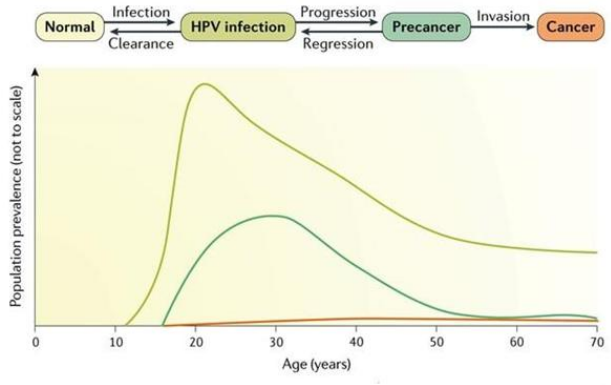

Fig. 1. Model of HPV infection progression towards cervical cancer (4)

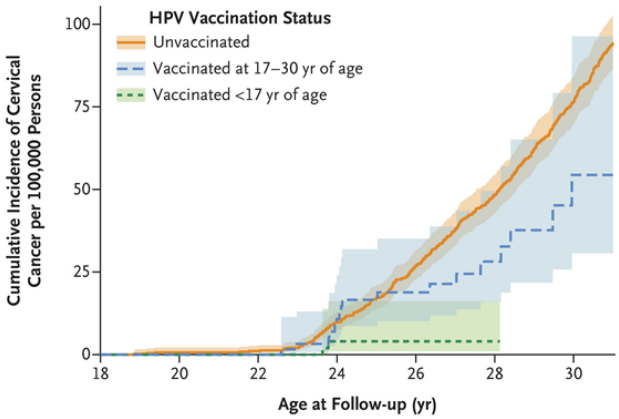

Fig. 2. The incidence of cervical cancer according to HPV vaccination status (27)

vaccination(18). When evaluating the efficacy of the quadrivalent vaccine in women aged 24 to 45, the vaccine demonstrated an 88.7% effectiveness in preventing CIN1+ in HPV-naive women and a 30.9% efficacy in all women. In similar age groups, double-blind studies with other quadrivalent vaccines have observed this rate reaching up to 94% (12). In 2018, using the findings from studies on the quadrivalent vaccine in women aged 24 to 45 and incorporating bridging immunogenicity and safety data in both genders, the FDA extended the authorized age range for the utilization of the nonavalent vaccine in women from 9 to 45 years old (23).

Catch-up HPV vaccination is a strategy aimed at enhancing vaccine coverage beyond adolescence. In individuals who are HPV positive, the positivity may be due to types not covered by the vaccine. Therefore, catch-up vaccination may provide protection against other HPV types that the individual has not encountered. As natural HPV infection does not confer immunity against reinfection or reactivation of latent infection, there is a potential for reinfection with different HPV types. Studies have shown a reduction in HPV and cervical dysplasia rates with catch-up HPV vaccination, accompanied by an increase in herd immunity (12).

Single dose HPV vaccine: Data on single-dose vaccination were obtained from analyses of trials in which not all women completed the full three-dose series. Despite lower antibody titres in women who received a single dose, antibodies against the targeted HPV types were found to be present and protection was sustained for a longer period of time.

Long-term follow-up studies of 11 years in the Costa Rica vaccine trial and 10 years in the India trial, which included data on single-dose HPV vaccination, reported stable antibody levels. High vaccine efficacy against HPV 16/18 infection was observed in India at ten years post-vaccination, averaging 95.4%, while in Kenya the average was 97.5% at eighteen months post-vaccination. The potential impact of HPV vaccination using a single-dose programme in India was modelled, showing that implementing a single-dose programme could help achieve WHO's goal of eliminating cervical cancer. Based on these data, WHO recommends that a single dose of the vaccine be administered to females aged 9-20 years in less developed countries where there is no opportunity to complete the full series (24).

WHO Recommendations for HPV Vaccination: Most countries endorsing HPV vaccination primarily target young adolescent girls aged 9-14. The vaccination schedule for all vaccines is determined based on the age of the vaccine recipient. In 2022, the WHO recommends the following schedule:

- 1 or 2 schedule for girls aged 9-14
- 1 or 2 schedule for girls and women aged 15-20
- 2 doses with a 6-month interval for women older than 21

In HIV-infected individuals and those with a compromised immune system for various reasons, at least 2 doses of HPV vaccine should be given, preferably 3 doses if possible (25).

Vaccination and the Risk of Cervical Cancer / HPV Infection: Many countries worldwide have implemented HPV vaccination programs, and observational data have been obtained from countries that initiated the vaccine early, demonstrating the population-level impact of the vaccine. As a result, published data indicate a significant decrease in HPV-related infections and diseases. A meta-analysis revealed a significant reduction of 68% in HPV types 16 and 18

infections between the pre-vaccination and post-vaccination periods in situations where female vaccination coverage encompassed at least half of the population. Anogenital warts also markedly decreased by 61% in girls aged 13-19. Furthermore, substantial reductions in anogenital warts were reported in adolescent boys and women aged 20 and above, indicating a potential herd effect (26).

The broad implementation of the HPV vaccine in Sweden is backed by a comprehensive study revealing a substantial decrease in cervical cancer incidence. Girls vaccinated before the age of 17 experienced an almost 90% reduction in cervical cancer cases. The proven efficacy and effectiveness of the quadrivalent HPV vaccine in preventing CIN2+ lesions reinforce its significance in averting invasive cervical cancer (27, 28). Figure 2 shows the incidence of cervical cancer according to HPV vaccination status.

Vaccine Safety: Adverse reactions at the injection site are frequently reported following vaccine administration, with local injection site reactions being the most common. Systemic adverse events rates in clinical trials have been found to be comparable between vaccine and control groups. Commonly reported systemic adverse events include fever, nausea, headache, and dizziness. There was no discernible difference in the occurrence of serious adverse events between the groups in these trials. HPV vaccination is currently not recommended during pregnancy. Furthermore, the vaccine's safety has been investigated in relation to autoimmune diseases, venous thromboembolism, and neurological disorders, with no observed association between the HPV vaccine and these conditions (28).

According to WHO recommendations, the primary target group for HPV vaccines is the group of individuals aged 9-14 years who are not infected with HPV. Vaccination is also recommended for those already infected with HPV, but the effectiveness of the vaccine is not as robust as in the HPV-naive group. Many countries are implementing gender-neutral vaccination programmes, advocating vaccination of both males and females to reduce the risk of HPV-related cancers, prevent anogenital warts, and promote herd immunity. Routine single-dose vaccination is not recommended, but may be administered in resource-limited areas where vaccination is not available. Long-term data show that HPV vaccines significantly reduce the incidence of cancer and HPV-related diseases, suggesting that they are safe and effective.

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