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HUMAN PAPILLOMAVIRUS VACCINE, BENEFITS AND RECOMMENDATIONS - REVIEW

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Abstract:
Vaccination to prevent HPV-related infection that leads to cancer, particularly cervical cancer, is a significant public health breakthrough. Narrative review conducted through literature, targeting relevant articles published up to the end of 2021, using the electronic databases such as PubMed and Embase. There are now two licensed HPV vaccinations available, both of which include recombinant virus-like particles of HPV types 16 and 18 (which cause over 70% of cervical cancer). In addition, one vaccine protects against HPV strains 6 and 11, which cause genital warts. The safety profile of both vaccines was extensively evaluated before to licensure in randomized controlled clinical trials, and it has been further elucidated following licensure by surveillance and particular research in large populations.

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INTRODUCTION:

Human papillomavirus (HPV) vaccinations are among the most effective preventive vaccines on the market, and they have set several major milestones in human vaccinology. They are the first vaccinations to prevent infection by a mucosatropic sexually transmitted infectious pathogen without the need for particular mucosal immunity induction [1].They are also the first subunit vaccines that consistently generate durable serum antibody responses over a lengthy period of time (more than a decade). Without repeated booster immunization, HPV vaccines appear to provide sterilizing immunity from initial infection for at least a decade [1]. The high efficacy discovered in prelicensure clinical studies has been validated by the dramatic impact and effectiveness shown in national immunization programs over the last decade [2]. There are now aggressive goals in place to reduce HPV-related illness [3].

The human papillomavirus (HPV) is a DNA virus that replicates in stratified squamous epithelia [4]. Mucosal forms are spread sexually, primarily through skin-to-skin contact. The most frequent sexually transmitted infection is HPV [5]. Although most HPV infections are undetectable after two years and do not cause clinical illness, persistent infections with oncogenic or high-risk strains can cause precancerous lesions and cancer [6]. Cervical, vulvar, vaginal, penis, anus, and oropharyngeal cancers are all caused by HPV. Cervical cancer is the most common HPV-associated disease worldwide, with the majority of cases and deaths happening in low-income countries with insufficient screening and treatment for cervical precancer. HPV is responsible for an estimated 630 000 malignancies worldwide each year, including 570 000 cancers in women [6]. Oropharyngeal cancer caused by HPV is on the rise in high-income nations, particularly among men [7].

HPV infection is required for the progression of cervical, other anogenital, and some non-genital malignancies [8]. Primary prevention of oncogenic HPV infection has the potential to reduce morbidity and mortality worldwide. Cervical cancer is the fourth leading cause of cancer-related death globally [9,10]. In addition to cancer, HPV infection causes genital warts, which are the most common sexually transmitted disease in many affluent countries [11]. There are two HPV vaccines available: Cervarix (2vHPV, GlaxoSmithKline Biologicals, Belgium), which protects against the two oncogenic HPV types 16 and 18, which account for *70% of cervical cancer, and Gardasil (4vHPV, Merck and Co., USA), which protects against both types 16 and 18, as well as the non-oncogenic types 6 and 11 [10]. Adjuvants are also included in the vaccines, which help to boost the humoral immune response. The adjuvant for 4vHPV is a patented aluminium hydroxyphosphate sulphate system, while the adjuvant for 2vHPV is named AS04 and contains both an aluminum salt and monophosphoryl lipid A. [12]. Pre- and post-licensure studies have shown that these vaccinations are effective in preventing persistent HPV infection and intraepithelial neoplasia (possibly pre-cancerous lesions) at the cervix in women [10-12].

DISCUSSION:

Following the discovery of HPV as the principal cause of cervical cancer in the 1980s, efforts were made to create a vaccine [13, 14]. In the 1980s and 1990s, animal studies demonstrated that using purified virions, animals could be protected against papillomavirus lesions, that neutralizing antibody was both necessary and sufficient for protection against viral challenge, and that protection was likely specific to HPV type [15]. Because of the difficulties in proliferating papillomaviruses and the presence of oncogenes in the viral genome, vaccine development has concentrated on subunit methods [16].

GlaxoSmithKline Biologicals (GSK) and Merck & Co [22] were the first companies to commercialize HPV vaccinations. GSK created Cervarix, a bivalent vaccine made up of HPV-16 and HPV-18 VLPs. Merck created a quadrivalent vaccination (Gardasil) that included HPV-16 and HPV-18 VLPs, as well as HPV-6 and HPV-11 VLPs. The adjuvants and the production cells for the viral L1 proteins are also different between the two vaccinations. Cervarix proteins are produced in L1-recombinant baculovirus-infected insect cells, while Gardasil proteins are synthesized in yeast (Saccharomyces cerevisiae). Cervarix contains a proprietary adjuvant AS04, which is made up of aluminum hydroxide and 3-deacylated mono-phosphoryl lipid A, a detoxified form of lipopolysaccharide, and a Toll-like receptor 4 agonist, whereas Gardasil contains an aluminum salt adjuvant (aluminum hydroxyphosphate sulfate). Merck then produced Gardasil 9, a nonavalent vaccination similar to Gardasil but contains L1 VLPs of five additional carcinogenic types HPV 31, 33, 45, 52, and 58, with the potential to provide type-specific protection against nearly 90% of cervical malignancies worldwide [16].

A recent report from a nationwide cohort study in Denmark found an 86% reduction in cervical cancer among 16-year-olds and younger people, and a 68% reduction among older teens [17], as well as a non-

statistically significant increase in cervical cancer among women vaccinated between the ages of 20 and 30 years compared to unvaccinated women. The Swedish study, on the other hand, discovered a 62% reduction in cervical cancer among women vaccinated between the ages of 20 and 30 [18]. The World Health Organization (WHO) has established a target of global cervical cancer eradication, defined as an annual incidence of less than 4 per 100,000 women. A 90-70-90 aim has been established: 90% of girls should be fully vaccinated with human papillomavirus (HPV) vaccine by the age of 15, 70% of women should be screened with a high-performance test by the age of 35 and again by the age of 45, and 90% of women with cervical illness should be treated [19]. The aim is necessary due to the sluggish rollout of HPV vaccine, poor levels of cervical cancer screening and early detection, and restricted access to comprehensive cancer treatment. Unfortunately, low- and middle-income nations bear the majority of the burden of cervical cancer (86%), but 30% of these countries have implemented the vaccination. The main barrier is the expense of the vaccine as well as the distribution to teenagers in countries with poor infrastructure for adolescent immunization. The problem is aggravated by vaccine supply limits, which are expected to last until 2022/25. Alternative schedule and/or dose reductions are being considered. The original three-dose schedule, with priming doses at 0 and 1/2 months followed by a boost at 6 months, was revised in 2014 by WHO SAGE for adolescents aged 15 to two doses, at 0 and 6 or 12 months [20]. National immunization programs, post-hoc RCT analysis, and a large observational cohort research are all gathering evidence that one dose may be enough to protect against persistent HPV infection and high-grade cervical illness for at least 7-10 years [21].

Efficacy and Effectiveness of the Human Papillomavirus Vaccine:

The impact of HPV vaccination in real-world settings has become clear, especially among women who are immunized prior to HPV exposure in countries with high vaccine uptake. There have been reports of maximum reductions of roughly 90% for HPV 6/11/16/18 infections, 90% for genital warts, 45% for low-grade cytological cervical abnormalities, and 85% for high-grade histologically verified cervical abnormalities. The immunization efficacy with one or more doses of the HPV vaccine was predicted to be 83-96.1% [22].

The bivalent HPV vaccine (at least one dose) demonstrated vaccine efficacy (VE) of 91-100% (95% CI = 64.6% to 86% and 94.2% to 100%, respectively) against HPV 16/18 incident and significant cross protection against HPV types 31, 33, 35, 45, 53, and possibly 58 in young women who were previously uninfected. However, with increased follow-up, the efficacy against persistent infections with types 31 and 45 appeared to decline, indicating a waning of cross protection [23,24]. Furthermore, regardless of baseline HPV infection, effectiveness against HPV 16/18 infection reduced to 76% (95% CI = 67% to 83%). The vaccine efficacy against the incidence of cervical intraepithelial neoplasia grade 2+ associated with HPV 16/18 was 92.9-97.4% (95% CI = 79.9% to 88.0% and 98.3% to 99.6%, respectively) and against cervical intraepithelial neoplasia grade 3+ was 87.0-94.9% (95% CI = 54.9% to 73.7% and 97.7% to 99.4%). Regardless of the baseline HPV infection, the effectiveness was lower. Furthermore, regardless of HPV DNA in lesions, vaccination effectiveness against CIN2+ was 70.2% (95% CI = 54.7% to 80.9%) [24,25].

The nonavalent HPV vaccination, which targets the same kinds as the quadrivalent vaccine plus five more carcinogenic types, became released in 2015 [26,27]. In naive HPV infection, the vaccination efficacy in preventing persistent infections of HPV 31/33/45/52/58 6 months after injection was 95.2% (95% CI = 81.4% to 98.4%) and 95.8% (95% CI = 87.8% to 98.9%) regardless of baseline HPV infection. In the per-protocol group, vaccine efficacy was 97.6% (95% CI = 91.7% to 99.6%) and 96.7% (95% CI = 80.9% to 99.8%), respectively, for low- and high-grade disease associated with HPV 31/33/45/52/58, while in the intention-to-treat group, vaccine efficacy was 84.0% (95% CI = 67.2% to 92.2%) in low-grade disease and 80. A recent study found that nonavalent vaccine-induced antibodies could be transmitted across the placenta, potentially protecting the infant from HPV 6 and 11 infections [28].

In males, HPV types 16 and 18 are responsible for 92% of anal cancer cases, 63% of penile cancer cases, and 89% of oral or oropharyngeal cancer cases [29].

Block et al.'s (prelicensure) noninferiority immunobridging research established the efficacy of the quadrivalent HPV vaccine in 10- to 15-year-old males. The randomized, placebo-controlled, double-blind trial found that the quadrivalent HPV vaccine reduced the incidence of external genital lesions caused by HPV types 6, 11, 16, and 18 by 90% in 16- to 26-year-old males from 18 countries when compared to the placebo, with efficacy of 65% (95% CI = 45% to 78%) in the intention-to-treat population [30].

The vaccine was effective against the detection of HPV 16 and HPV 18 DNA in 28.0-45.1% and 33.9-49.5% of cases, respectively. Estimates of vaccine efficacy for preventing persistent (defined as 6 months) anogenital and anal infections were greater than estimates for incident infections (46.9-73.6%) [31]. The efficacy and effectiveness of the vaccine against anal condyloma was reported to be 57.2-67.2% [32]. Vaccine efficacy against AIN grade 1 was reported to be 49.6% and against AIN grade 2 to be 61.9% [33], but vaccine effectiveness in a non-randomized study was somewhat lower (50%). The claimed efficacy against AIN grade 3 was a non-significant 46.8% [33]. Furthermore, PIN grade 2 or 3 was reported in one RCT, but the number of cases in both the vaccinated (n = 3) and placebo (n = 2) groups was too small to give a meaningful assessment of vaccine efficacy [33].

HPV vaccinations elicit substantial antibody responses, with peak titers significantly higher than the normally modest titers seen following spontaneous infection [34]. In clinical trials, seroconversion was close to 100% for all kinds following a three-dose series, and GMTs were high and comparable across racial/ethnic groupings and regions of residency [34]. Titers rise after each dose, fall over time after the final treatment, and level off after around two years [35]. Antibodies appear to be persistent over time, with studies showing antibody levels persisting for 11 or 12 years following immunization. HPV vaccination produces antibody titers that are negatively related to age. The greater titers among adolescent girls and boys (ages 9 to 14 or 15 years) compared to women of the same age engaged in efficacy studies permitted the vaccines to be licensed in the younger age group via immunobridging. Immunogencity data has also aided in the approval of additional applications. As previously stated, antibody response to the four forms of Gardasil vaccine was noninferior among Gardasil 9 vaccine recipients, which was an important finding in the prelicensure experiment [36].

Gardasil, Cervarix, Gardasil 9, and Cecolin studies all indicated noninferiority with two doses given at 6- or 12-month intervals [82-85]. The Gardasil 9 study, for example, compared a two-dose schedule (0 and 6 or 0 and 12 months) in girls and boys aged 9 to 14 years to a three-dose schedule (0, 2, and 6 months) in women aged 16 to 26 years [37]. 97.9% of about 1500 subjects seroconverted to all 9 types, and GMT noninferiority criteria were met (value >0.67 for the lower bound of the 95% CI of the GMT ratio for 3 doses in women versus 2 doses in girls and boys). Not only were noninferiority criteria met, but GMTs were considerably higher in children aged 9 to 14 years who received two doses compared to women aged 16 to 26 years who received three doses. GMTs were usually higher for two doses given at a 12-month interval than with two doses given at a 6-month interval [37].

CONCLUSION:

HPV vaccinations have shown extraordinary performance in clinical studies as well as impact in real-world situations across a wide range of HPV-related diseases. Robust evidence suggest that HPV vaccinations are safe, even though safety concerns have stymied vaccine introductions or coverage goals in several countries. As new data became available and aggressive disease reduction targets were considered, HPV vaccination policy developed. Although demand for HPV vaccinations now exceeds supply, increased manufacturing capacity from current producers as well as new manufacturers in late phases of vaccine development should alleviate the current shortage and enable for the achievement of additional global disease prevention goals.

HPV vaccination was found to be highly effective against oral HPV type 16/18 infection, with a considerable proportion of subjects developing IgG antibodies in their oral fluid following vaccination. However, due to the low prevalence of HPV infection in the asymptomatic population, low vaccine uptake rate, and long duration between infection and cancer development, vaccine effectiveness in reducing the incidence of and mortality related to HPV-related head and neck cancer should be observed over time.

REFERENCES:

1. Drolet M, Bénard É, Pérez N, Brisson M; HPV Vaccination Impact Study Group . Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet* 2019; 394:497–509.
2. Brisson M, Kim JJ, Canfell K, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. *Lancet* 2020; 395:575–90.
3. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer* 2017; 141:664–70.
4. Schiller JT, Castellsagué X, Garland SM. A review of clinical trials of human papillomavirus

prophylactic vaccines. *Vaccine* 2012; 30(suppl 5):F123–38.
5. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007; 356:1915–27.
6. Paavonen J, Jenkins D, Bosch FX, et al.; HPV PATRICIA study group . Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet* 2007; 369:2161–70.
7. Schiffman M, Castle PE, Jeronimo J, et al. Human papilloma- virus and cervical cancer. Lancet. 2007;370:890–907.
8. Chaturvedi AK. Beyond cervical cancer: burden of other HPV- related cancers among men and women. J Adolesc Health. 2010;46:S20–6.
9. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
10. Ferlay J, Shin H, Bray F, et al. GLOBOCAN 2008 v1. 2, cancer incidence and mortality worldwide: IARC CancerBase No. 10. Lyon: International Agency for Research on Cancer, 2010; 2012.
11. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. Vaccine. 2006;24:S4–15.
12. Weinstock H, Berman S, Cates W Jr. Sexually transmitted dis- eases among American youth: incidence and prevalence esti- mates, 2000. Perspect Sexual Reprod health. 2004;36:6–10.
13. Da Ros CT, da Silva Schmitt C. Global epidemiology of sexu- ally transmitted diseases. Asian J Androl. 2008;10:110–4.
14. Harper DM. Currently approved prophylactic HPV vaccines. Expert Rev Vaccines. 2009;8:1663–79.
15. Cutts F.T., Franceschi S., Goldie S., Castellsague X., de Sanjose S., Garnett G., Edmunds W.J., Claeys P., Goldenthal K.L., Harper D.M., et al. Human papillomavirus and HPV vaccines: A review. *Bull. World Health Organ.* 2007;85:719–726.
16. Zhang Q., Zheng R., Fu Y., Mu Q., Li J. Mental health consequences during alerting situations and recovering to a new normal of coronavirus epidemic in 2019: A cross-sectional study based on the affected population. *BMC Public Health.* 2021;21:1499.
17. Basu P., Malvi S.G., Joshi S., Bhatla N., Muwonge R., Lucas E., Verma Y., Esmy P.O., Poli U.R.R., Shah A., et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: A multicentre, prospective, cohort study. *Lancet Oncol.* 2021;22:1518–1529.
18. Kjaer S.K., Dehlendorff C., Belmonte F., Baandrup L. Real-World Effectiveness of Human Papillomavirus Vaccination Against Cervical Cancer. J. Natl. Cancer Inst. 2021;113:1329–1335.
19. Gee J., Naleway A., Shui I., Baggs J., Yin R., Li R., Kulldorff M., Lewis E., Fireman B., Daley M.F., et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink. *Vaccine*. 2011;29:8279–8284.
20. Bonde U., Joergensen J.S., Lamont R.F., Mogensen O. Is HPV vaccination in pregnancy safe? *Hum. Vaccines Immunother*. 2016;12:1960–1964.
21. Angelo M.-G., Zima J., Tavares Da Silva F., Baril L., Arellano F. Post-licensure safety surveillance for human papillomavirus-16/18-AS04-adjuvanted vaccine: More than 4 years of experience. *Pharmacoepidemiol. Drug Saf*. 2014;23:456–465.
22. Villa A., Patton L.L., Giuliano A.R., Estrich C.G., Pahlke S.C., O'Brien K.K., Lipman R.D., Araujo M.W.B. Summary of the evidence on the safety, efficacy, and effectiveness of human papillomavirus vaccines: Umbrella review of systematic reviews. *J. Am. Dent. Assoc*. 2020;151:245–254.
23. Malagón T., Drolet M., Boily M.C., Franco E.L., Jit M., Brisson J., Brisson M. Cross-protective efficacy of two human papillomavirus vaccines: A systematic review and meta-analysis. *Lancet Infect. Dis.* 2012;12:781–789.
24. Lukács A., Máté Z., Farkas N., Mikó A., Tenk J., Hegyi P., Németh B., Czumbel L.M., Wuttapon S., Kiss I., et al. The quadrivalent HPV vaccine is protective against genital warts: A meta-analysis. *BMC Public Health.* 2020;20:691.
25. Zhang X., Zeng Q., Cai W., Ruan W. Trends of cervical cancer at global, regional, and national level: Data from the Global Burden of Disease study 2019. *BMC Public Health.* 2021;21:894.
26. Rosenblum H.G., Lewis R.M., Gargano J.W., Querec T.D., Unger E.R., Markowitz L.E. Declines in Prevalence of Human Papillomavirus Vaccine-Type Infection Among Females after Introduction of Vaccine United States, 2003–2018. *MMWR Morb. Mortal. Wkly. Rep.* 2021;70:415–420.
27. Safaeian M., Sampson J.N., Pan Y., Porras C., Kemp T.J., Herrero R., Quint W., van Doorn L.J.,

Schussler J., Lowy D.R., et al. Durability of Protection Afforded by Fewer Doses of the HPV16/18 Vaccine: The CVT Trial. *J. Natl. Cancer Inst.* 2018;110:205–212.
28. Zizza A., Banchelli F., Guido M., Marotta C., Di Gennaro F., Mazzucco W., Pistotti V., D'Amico R. Efficacy and safety of human papillomavirus vaccination in HIV-infected patients: A systematic review and meta-analysis. *Sci. Rep.* 2021;11:4954.
29. Quadrivalent Vaccine against Human Papillomavirus to Prevent High-Grade Cervical Lesions. *N. Engl. J. Med.* 2007;356:1915–1927.
30. Muñoz N., Manalastas R., Jr., Pitisuttithum P., Tresukosol D., Monsonego J., Ault K., Clavel C., Luna J., Myers E., Hood S., et al. 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.* 2009;373:1949–1957.
31. Dobson S.R., McNeil S., Dionne M., Dawar M., Ogilvie G., Krajden M., Sauvageau C., Scheifele D.W., Kollmann T.R., Halperin S.A., et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: A randomized clinical trial. *JAMA.* 2013;309:1793–1802.
32. McCormack P.L., Joura E.A. Spotlight on quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine(Gardasil®) in the prevention of premalignant genital lesions, genital cancer, and genital warts in women. *BioDrugs.* 2011;25:339–343.
33. Steinau M., Unger E.R., Hernandez B.Y., Goodman M.T., Copeland G., Hopenhayn C., Cozen W., Saber M.S., Huang Y., Peters E.S., et al. Human papillomavirus prevalence in invasive anal cancers in the United States before vaccine introduction. *J. Low. Genit. Tract Dis.* 2013;17:397–403.
34. Canadian Immunization C. Summary of Canadian Immunization Committee (CIC) Recommendations for Human Papillomavirus Immunization Programs. *Can. Commun. Dis. Rep.* 2014;40:152–153.
35. Giuliano A.R., Palefsky J.M., Goldstone S., Moreira E.D., Jr., Penny M.E., Aranda C., Vardas E., Moi H., Jessen H., Hillman R., et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. *N. Engl. J. Med.* 2011;364:401–411.
36. Palefsky J.M., Giuliano A.R., Goldstone S., Moreira E.D., Jr., Aranda C., Jessen H., Hillman R., Ferris D., Coutlee F., Stoler M.H., et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N. Engl. J. Med.* 2011;365:1576–1585.
37. Spinner C., Ding L., Bernstein D.I., Brown D.R., Franco E.L., Covert C., Kahn J.A. Human Papillomavirus Vaccine Effectiveness and Herd Protection in Young Women. *Pediatrics.* 2019;143:e20181902.