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Literature Review: HPV Vaccine Development Over Time

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Abstract
Cervical cancer is the fourth most common cancer case in the world. The mortality rate caused by this disease also high especially in the low and middle income countries including Indonesia. In an attempt to decrease the mortality rate, WHO and the government work on strategies, one of which is HPV vaccination by adding HPV vaccine into routine immunization program given to girls on primary school. This study aims to review and analyze literatures about HPV vaccine. The result shows that HPV vaccine has a significant efficacy on preventing cervical cancer, even more effective once given as early as possible towards adolescents. The vaccine's dose required in order to form a long term protection is still being studied but some researchs find that a single dose is on par with 2 or even 3 doses in terms of giving protection. Further and longer duration of research needed in order to support this theory. That way, the limited amount of vaccine could be directed to a larger population and in the end formed the long awaited herd immunity.

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Introduction

Cervical cancer remains one of the major unresolved global health issues. According to the World Health Organization (WHO), there were 660,000 new cases of cervical cancer in 2022, resulting in 350,000 deaths. These figures rank cervical cancer as the fourth most common type of cancer worldwide (WHO, 2024a).

The highest incidence and mortality rates of cervical cancer are found in low-income countries. In Indonesia, data from the International Agency for Research on Cancer (IARC) in 2022 reported that out of 408,661 new cancer cases, 36,964 (9%) were cervical cancer, making it the third most prevalent cancer in the country and responsible for 20,708 deaths in the same year. (WHO, 2024b).

Compared to Singapore, a developed country in Southeast Asia, Indonesia still lags significantly behind. This is evidenced by the cervical cancer prevalence in the same year, where Indonesia recorded a high rate of 87.2 per 100,000 population, while Singapore reported only 47.4 per 100,000. Limited resources, inadequate public awareness, and delays in diagnosis have exacerbated the complications and hindered mitigation efforts of cervical cancer in developing countries, in stark contrast to the situation in developed nations (Reza et al., 2024).

In an effort to achieve Sustainable Development Goal (SDG) 3: Good Health and Well-being, all United Nations (UN) member states have agreed to eliminate cervical cancer as a public health problem (UN SDGs; WHO, 2020). The Ministry of Health of the Republic of Indonesia (Kemenkes RI) has formulated a National Action Plan (NAP) for the Elimination of Cervical Cancer, based on the WHO's Global Strategy to Accelerate the Elimination of Cervical Cancer. This strategy includes the following key targets by 2030, 90% HPV vaccination coverage among girls by age 15, 70% screening coverage using HPV DNA testing for women at ages 35 and 45, and 90% treatment coverage for women diagnosed with pre-cancerous lesions and invasive cervical cancer (WHO, 2020).

Cervical cancer is classified as a sexually transmitted infection, with persistent HPV infection detected in 99.7% of cervical cancer cases. While most HPV infections are self-limiting, persistent infection with oncogenic HPV types may lead to cancers of the oropharyngeal and anogenital regions (Okunade, 2020). There are more than 130 types of HPV, but only around 20 have been associated with cancer. Among these, types 16 and 18 are the most common causes of cervical cancer, while types 6 and 11 are considered low-risk (Fowler *et al.*, 2023; Luria and Cardoza-Favarato, 2023). According to Luria and Cardoza-Favarato (Luria & Cardoza-Favarato, (2023), HPV infection often requires co-factors to trigger carcinogenesis, such as smoking, folate deficiency, UV radiation exposure, immunosuppression, or pregnancy.

To date, reports show that HPV can be found in the majority of sexually active individuals at some point in their lives. Although HPV affects all genders, screening is primarily conducted in women, while for men it is generally limited to research or specific clinical studies. HPV transmission occurs through skin-to-skin contact, including intercourse, genital-hand contact, and oral sex (Fowler *et al.*, 2023). As a sexually transmitted infection, HPV is largely preventable through targeted health education, routine screening, and preventive interventions.

HPV vaccines have been available since 2006 to prevent cervical cancer. According to Fowler et al. (Fowler et al., (2023) vaccination is a key strategy for reducing mortality, particularly in populations with high death rates and in low- and middle-income countries where resources for regular screening may be limited.

In Indonesia, HPV vaccination has been included in the national immunization program for fifth- and sixth-grade girls following the issuance of Minister of Health Decree No. HK.01.07/MENKES/679/2021 concerning the Introduction of the Human Papillomavirus Vaccine Immunization Program for 2022–2024. Since then, HPV immunization has become a part of the routine school-based vaccination program. Nevertheless, questions and misconceptions about HPV remain prevalent, which motivates the author to further explore and discuss various aspects of the HPV vaccine.

Method

This article was written using a literature review method, drawing from both international and national sources via databases such as EBSCO, ScienceDirect, and ProQuest. The author navigated websites including SearchProquest.com and GoogleScholar.com, applying keywords based on Medical Subject Headings (MeSH) to guide the search process.

Result and Discussion

History and Development of the HPV Vaccine

In 1951, Henrietta Lacks, a wife and mother, was diagnosed with cervical cancer at the age of 30. She sought treatment at Johns Hopkins University Hospital, where Dr. George Gey collected her cell samples without her knowledge or consent for research purposes. Although the origin of these cells remained largely unknown until the 1970s, Lacks' legacy profoundly influenced scientific discoveries, such as the development of the polio vaccine and the identification of the link between HPV and cervical cancer (Askandar, 2020).

Statistical studies on breast and cervical cancer show a striking contrast in frequency distribution between two populations: married women and nuns. These findings have served as early evidence of a potential relationship between cervical cancer and sexual activity. In the early 19th century, Rigoni-Stern discovered that cervical cancer was significantly more prevalent among sexually active women compared to nuns or virgins. After centuries of misconceptions surrounding cervical cancer's causes, progress was made in 1983 following Dr. Richard Shope's foundational hypothesis regarding the transmission and symptoms of the virus. Further advancements in DNA technology led German virologist Harald zur Hausen to identify HPV as a papillomavirus, with HPV types 16 and 18 being the primary causes of cervical cancer. This marked the beginning of significant innovations to combat HPV, prompting doctors to research treatments and vaccines once the underlying cause was confirmed (Frazer, 2019; Askandar, 2020).

Initially, Dr. Jian Zhou and Dr. Ian Frazer developed virus-like particles (VLPs) that mimic HPV. These VLPs, which are devoid of DNA, cannot cause HPV infection or cancer. Upon exposure, the body begins to produce antibodies against these particles, leading to the development of immunity. Consequently, should future exposure to the actual virus occur, the body is equipped to prevent the infection (Frazer, 2019).

Using similar technology, Dr. Douglas Lowy and Dr. John Schiller developed the HPV vaccine after discovering that certain HPV proteins could self-assemble into non-infectious virus-like particles (VLPs). These VLPs can trigger the human immune system to produce antibodies and mount protection against future HPV infections. In 2002, Laura Koutsky provided compelling evidence of the efficacy of a monovalent HPV16 vaccine, demonstrating its protective effect against cervical cancer and paving the way for the development of broader-spectrum HPV vaccines (Askandar, 2020).

In 2006, Gardasil 4 (developed by Merck) was introduced, offering protection against four HPV types (6, 11, 16, and 18), which are responsible for over 70% of cervical cancer cases. This followed a 7-year clinical trial showing 100% protection against HPV types 16 and 18. Initially, Gardasil was administered only to females aged 9–26 years in the United States. In 2009, its use was extended to males aged 9–26 years to prevent genital warts (condyloma acuminata). During the same period, Cervarix, which targets HPV types 16 and 18, was approved by the U.S. FDA for preventing HPV-related precancerous lesions and cervical cancer in females. However, Cervarix was withdrawn from the U.S. market in 2016, although it remains in use in other countries for cancer prevention (Okunade, 2020).

The withdrawal of Cervarix was attributed to the successful adoption of Gardasil, which received updated FDA approval in 2014 (Kanan *et al.*, 2024a). The next generation, Gardasil 9, expanded protection to nine HPV types and was initially approved for females aged 9–26 years. Two years later, its indication was broadened to include both females and males aged 27–45 years, following further review and approval by the FDA (Soca Gallego, Alvio and Parmar, 2024). By 2020, Gardasil 9 was no longer limited to preventing cervical cancer but was also approved for the prevention of vaginal, vulvar, anal, and oropharyngeal cancers, as well as other head and neck cancers (Kim *et al.*, 2024).

Types of HPV Vaccines

1. Bivalent Vaccine

The bivalent HPV vaccine, also known as HPV2 or 2v-HPV, is designed to prevent cervical cancer by providing protection against oncogenic human papillomavirus (HPV) types 16 and 18. The bivalent vaccine is composed of virus-like particles (VLPs) derived from recombinant L1 capsid proteins of HPV (Kanan *et al.*, 2024b). One of the widely distributed HPV2 vaccines is Cervarix, which was licensed by the U.S. Food and Drug Administration (FDA) on October 16, 2009. Cervarix became the second HPV vaccine approved for use in females in the United States and is recommended for adolescent girls aged 10 to 25 years (Okunade, 2020).

In addition to Cervarix, another bivalent HPV vaccine called Cecolin is available on the market. Cecolin was licensed by the National Medical Products Administration (NMPA) of China on December 30, 2019. Similar to Cervarix, Cecolin contains aluminum hydroxide adjuvants that absorb recombinant L1 capsid proteins of HPV types 16 and 18 to form virus-like particles (Yu *et al.*, 2020). However, Cecolin differs in its production method; it utilizes recombinant DNA technology using Escherichia coli as the expression system. This vaccine has been distributed in China, Bangladesh, Morocco, Nepal, Thailand, the Democratic Republic of Congo, and Cambodia.

2. Quadrivalent Vaccine

The quadrivalent HPV vaccine, also known as HPV4 or 4v-HPV, provides protection against four HPV types: the oncogenic types 16 and 18, as well as the non-oncogenic types 6 and 11. HPV types 6 and 11 are known to cause condyloma acuminata (genital warts). Similar to the bivalent vaccine, the quadrivalent vaccine is formulated using recombinant L1 capsid proteins of HPV, which self-assemble into virus-like particles (VLPs) (Kanan *et al.*, 2024b). Gardasil-4, developed by Merck & Co., is the most widely recognized quadrivalent HPV vaccine. It was licensed by the U.S. Food and

Drug Administration (FDA) in 2006 for use in females aged 9 to 26 years. This vaccine is the one currently used in Indonesia's national immunization program.

3. Nonavalent Vaccine

Furthermore, the nonavalent HPV vaccine, approved by the FDA for females aged 9–45 years, protects against nine HPV types: 6, 11, 16, 18, 31, 33, 45, 52, and 58. These types are responsible for the majority of precancerous lesions and cancers of the cervix, vagina, vulva, anus, and head and neck, including the oropharyngeal region. While HPV-related penile cancer may also be prevented by the nonavalent vaccine, current research in this area remains limited (Kim *et al.*, 2024). The most well-known nonavalent HPV vaccine is Gardasil 9, which is currently administered in routine immunization programs for both females and males in the United States (Soca Gallego, Alvio and Parmar, 2024).

How the HPV Vaccine Works

Virus-like particles (VLPs) in HPV vaccines induce both T-cell and B-cell immune responses. However, their primary mechanism of protection involves the production of antibodies that bind to virions, thereby preventing initial infection (Soca Gallego, Alvio and Parmar, 2024). Upon exposure to HPV, the vaccine-generated antibodies attach to the virus and block it from infecting epithelial tissues, thereby averting more severe infection (Luria, Cardoza-Favarato and Doerr, 2023). While naturally acquired antibodies during infection are often insufficient to halt the progression of disease, vaccine-induced antibodies can reach titers 10 to 100 times higher. The lack of secondary lymphoid tissue in the infected cervical area means there is limited local antibody production capable of neutralizing the virus prior to absorption—unless a strong pool of memory B cells is present (Markowitz and Schiller, 2021).

Systemic antibodies, particularly immunoglobulin G (IgG) induced by intramuscular (IM) injection, can access the cervicovaginal infection site via two pathways. First, transudation of IgG across epithelial barriers into the mucosal secretions occurs through the neonatal Fc receptor (FcRn) expressed in the cervical tissue. Second, exudation of serum and interstitial antibodies at sites of microtrauma allows virions to bind at the basal membrane—an essential event in HPV infection initiation (Ashique *et al.*, 2023). The second mechanism is considered more critical in preventing infection, explaining the high efficacy of Gardasil 4 and Gardasil 9 in preventing anogenital warts, which often occur on keratinized, non-mucosal skin. Secretory IgA plays a limited role in this process, as intramuscular injection does not efficiently induce mucosal IgA responses (Markowitz and Schiller, 2021; Ashique *et al.*, 2023).

For the 9-valent HPV vaccine (9vHPV), researchers agree that its protective effect is primarily mediated through the activation of the humoral immune response. The L1 protein is expressed using recombinant Saccharomyces cerevisiae and forms virus-like particles. Each 0.5 mL dose contains aluminum, sodium chloride, L-histidine, polysorbate, sodium borate, >7 mcg of yeast protein, and water. The vaccine formulation contains no antibiotics or preservatives (Ashique *et al.*, 2023)

A 2016 immunological study reported that the L1 VLPs in HPV vaccines elicit a strong humoral response that provides protection against HPV-related dysplastic lesions. The same study emphasized that early-age immunization results in higher antibody titers compared to vaccinations administered later in life (Castle and Maza, 2016; Ashique *et al.*, 2023).

HPV Vaccine Dosing Schedule

According to CDC recommendations, HPV vaccination can begin as early as age 9. For individuals who initiate the vaccination series between the ages of 9 and 14, two intramuscular (IM) doses of 0.5 mL are administered. The recommended and optimal interval between doses is 6 to 12 months, with a minimum interval of 5 months. If the second dose is given less than 5 months after the first, a third dose must be administered 4 months after the second dose (Luria and Cardoza-Favarato, 2023; Soca Gallego, Alvio and Parmar, 2024).

For individuals aged 15 to 45 at the time of their first HPV vaccination, the CDC recommends a three-dose IM schedule of 0.5 mL each, with the second dose given 2 months after the first and the third dose administered 6 months after the first dose (Soca Gallego, Alvio and Parmar, 2024). This dosing regimen is supported by immunogenicity studies, which show that antibody titers in females vaccinated at age 14 are higher than those vaccinated at age 15. To compensate for this immunological difference, a three-dose schedule is recommended for individuals initiating vaccination at age 15 or older (Castle and Maza, 2016; Ashique *et al.*, 2023).

Effectiveness of the HPV Vaccine

HPV vaccines are highly effective in preventing a wide range of HPV-related diseases. Their efficacy approaches 100% in preventing persistent infections with specific HPV types, as well as Cervical Intraepithelial Neoplasia (CIN) grades 2/3 and adenocarcinoma in situ (AIS) in individuals who were HPV-naïve at the time of vaccination (Kanan *et al.*, 2024a). The quadrivalent vaccine also demonstrates 99% efficacy in preventing genital warts (condyloma acuminata). Among men who have sex with men (MSM), the quadrivalent vaccine has been shown to prevent Anal Intraepithelial Neoplasia (AIN) grades 2/3 (Yousefi *et al.*, 2022). With the inclusion of HPV vaccines in routine national immunization programs, it is expected that herd immunity or herd protection may develop over time, potentially offering indirect protection even to unvaccinated individuals (Restrepo *et al.*, 2023). However, this remains a subject of debate in several countries, particularly due to the common practice of targeting only females for HPV vaccination—a decision often driven by cost-effectiveness considerations.

A recent study by the International Agency for Research on Cancer (IARC) revealed that a single dose of the quadrivalent HPV vaccine provides comparable protection to two or three doses, even 15 years after initial vaccination. This prospective cohort study, conducted in India, involved 17,000 female participants aged 10–18 years who received the HPV vaccine during 2009–2010. The vaccine's efficacy against HPV types 16 and 18 was 92%, showing no significant difference between one, two, and three doses (Malvi *et al.*, 2024).

The study concluded that long-term protection of at least 15 years can be achieved with a single-dose schedule. Similarly, Setiawan et al., (2024) conducted a systematic review and meta-analysis of 23 articles related to HPV vaccine dosing. Their findings support the conclusion that one-dose HPV vaccination is equally effective as two- or three-dose regimens, offering protection for at least 8 years. Nevertheless, the researchers emphasize the need for longer-term studies to fully validate this recommendation. Research on HPV vaccination continues to evolve and remains an active field of global public health inquiry.

Conclusion

There are three types of HPV vaccines: bivalent, quadrivalent, and nonavalent, all of which provide protection against human papillomavirus (HPV) types associated with cervical cancer. Currently, the Government of Indonesia has included HPV vaccination as part of the national routine immunization program, administered to 9-year-old girls. The recommended number of doses depends on the age at initiation: individuals who begin vaccination at an early age are advised to receive two doses, while those who start at age 15 or older are recommended to receive three doses.

Recent studies have focused on the potential of a single-dose HPV vaccine to offer comparable protection to two- or three-dose regimens. However, further research is needed to substantiate this approach and to support global vaccination policy changes.

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