How HPV Vaccines with Various Compositions Work for Humans

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Abstract: Human papillomavirus (HPV) is the main cause of genital infection, which further causes cervical cancer and other HPV-related diseases. These diseases severely affect the physical and psychosexuals of both males and females. Cancer vaccines have contributed significantly to cancer prevention or therapy these years, especially for cervical cancer. In this review, the topics of what HPV is and how the innate immune system fights against it have been introduced. Furthermore, the mechanisms of three prophylactic HPV vaccines- Gardasil®, Cervarix® and Gardasil® 9- that contain various virus-like particles (VLP) have also been discussed. In addition, this paper discusses and compares the composition of each of these HPV vaccines and how effective they are in prevention of cervarix cancer, how the body reacts to immunization of these vaccines. Lastly, the achievements and the future of the vaccination programmes are investigated.

1 INTRODUCTION

Over 570,000 women are affected by cervical cancer, and about 311,000 women pass on each year worldwide, with almost 90% of them living in low and middle- low-income countries (Okuhara et al., 2021). The International Agency for Research on Cancer has accepted a direct causative association between HPV and genital infections, such as in the cervix, penis, vulva, but the severity of the correlation varies. As a result, HPV is widely regarded as the most important oncogenic virus affecting humans and the leading cause of uterine cervical cancer. The direct relationship between the prevalence of HPV and women is all around depicted, with rates peaking in younger women and then steadily declining. HPV prevalence in males is higher than in women overall and remains stable over time among different age groups. In certain male populations, like who have sex with men,especially those with HIV infection, the HPV prevalence can be exceedingly high (over 70 percent) and is commonly linked to anal carcinoma (Mariani et al., 2017).

In recent years, cancer immunotherapy has been utilizied more frequently, with cancer vaccines emerging as a novel approach to cancer treatment. The development of therapeutic vaccines capable of activating cytotoxic T cells or generating antibodies, so initiating an immunological response, has been aided by a better understanding of how cancer cells avoid detection and are targeted by the immune system. In clinical trials, cancer vaccines are commonly combined with other forms of therapy, such as surgery and chemotherapy, to improve efficacy. Cell immunizations (cancer or safe cell), protein/peptide antibodies, and hereditary (DNA, RNA, and viral) immunization are a few of the major categories of clinical studies (Mannan et al. 2016). Almost all high-resource nations have been building HPV vaccination programs since 2007. The Global Alliance for Vaccines and Immunization (GAVI) is coordinating and sponsoring several pilot projects in low- and middle-income countries. Cervical cancer incidence and death rates are higher in disadvantaged areas where immunization efforts are almost non-existent (Mariani et al., 2017).

This review mainly focuses on the mechanisms and clinical trials of the three prophylactic HPV vaccines, including their compositions. There is also including the effect of cancer vaccines on males and females of all ages.

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2 THE DISCOVERY AND DEVELOPMENT OF HPV

HPV are double-stranded circular tiny DNA viruses that infect epithelial tissues such as the basal epidermis (skin or mucosal) cells and the upper respiratory and anogenital tract epithelial linings (Figure 1). HPVs are classified into low-risk and high-risk types based on their ability to cause malignant transformation. According to the international agreement, "high-risk" genotypes such as 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 have been associated to cervical cancer and other mucosal anogenital malignancies. Low-risk infections can cause benign or low-grade cervical tissue changes and genital warts, which are growths on the cervix, vagina, vulva, or anus in women and the penis, scrotum, or anus in men (Cutts et al., 2007). HPV16 and 18 are the two most frequent cancer-causing DNA subtypes, accounting for around 79% of carcinomas in North America and 68% in Africa, respectively, whereas HPV 6 and 11 lead to 90% of recurrent respiratory papillomatosis (RRP). These papillomaviruses are the only known viral infections that start spontaneously by interacting with the cell surface when they assault. From then, HPV requires a simple 24 hours to thoroughly acclimatize the nuclear DNA of the basal cell with its own. As a result, the infectious genetic material is transcribed and translated, enabling viral proteins to be synthesized that interact with the infection. The genome encodes six early regulatory proteins (E1, E2, E4, E5, E6, and E7), as well as two late structural proteins (L1 and L2). The early genes code for viral DNA replication, transcription, and oncogenic transformation proteins, whereas the late genes code for virus capsid proteins. The late viral genes *L1* and *L2* are translated when the infected basal cells go up and separate, accordingly provoking the vegetative phase of the virus life cycle, which is marked by substantial genome expansion (Ferreira et al., 2020). When the cell arrives at the peripheral layer of the epithelium, the recently generated viral DNA is exemplified to shape new virions, which are delivered, and the existence cycle is rehashed (Thomas T. L. 2016).

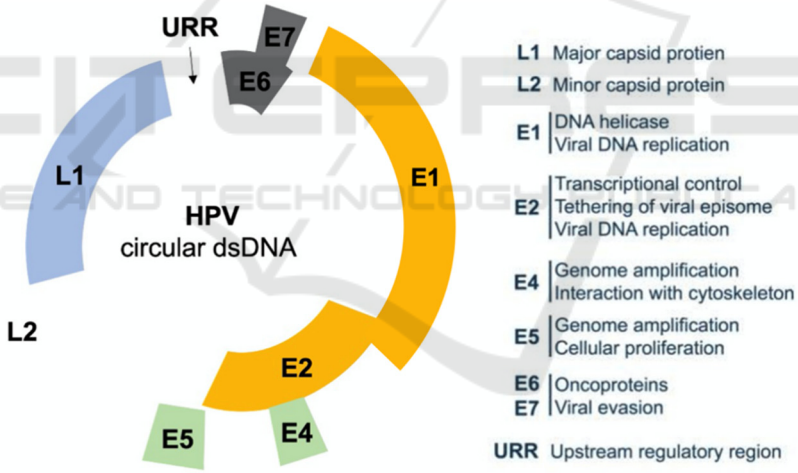

Figure 1: Illustration of HPV circular dsDNA (Ferreira et al., 2020).

The HPV vaccine is a crucial strategy for preventing cervical cancer, primarily when used with a healthy sexual way of life and appropriate contraception. Scientists started to examine the possible role of HPV in cervical cancer in the range of 1974 and 1976. In 1976, Meisels and Fortin found the presence of Koilocytes in cervical smears, which demonstrated the presence of papillomavirus disease. In 1983 and 1984, the scientists secluded cervical cancer-related HPV type, HPV16, and HPV18, from cancer biopsies of the cervix, separately. In 1987, de Villiers *et al.* led the first epidemiological investigation of HPV infections. The first virus-like particles (VLPs), which are collected from recombinant HPV capsid proteins and are non-irresistible because of the absence of viral DNA were produced in 1991. HPV was first proposed as an important reason for cervical malignant growth improvement in 1999. Harro *et al.* revealed the wellbeing and immunogenicity of VLP immunizations in people in 2001 (Figure 2) (Wang et al., 2020). There are three authorized prophylactic HPV vaccinations available now. In June 2006, a quadrivalent HPV (4xHPV; Gardasil®) vaccine that

protects against HPV6, HPV11, HPV16, and HPV18 was authorized in the United States and afterward in the European Union (September 2006). The Food and Drug Administration (FDA) approved a bivalent HPV (2xHPV; Cervarix®) vaccination (GlaxoSmithKline) in October 2009, which protects against HPV16 and HPV18. The nonavalent HPV (9xHPV; Gardasil 9®) vaccine (Merck & Co) was licensed in 2014 that covers five more HPV types, which are HPV31, HPV33, HPV45, HPV52, and HPV58 (Wang et al., 2018).

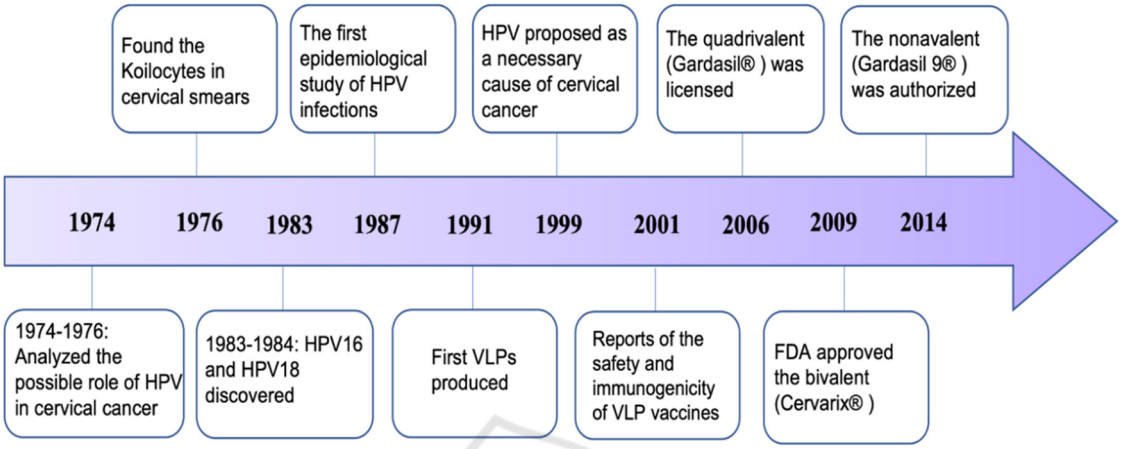

Figure 2. The research chronology for HPV and HPV vaccines (Wang et al., 2020).

Despite the fact that prophylactic or preventive HPV vaccinations have been a huge step forward in preventing HPV infections and diseases, there is such an unresolved HPV-related infection problem throughout the world that there are no therapeutic HPV vaccines approved for use in humans. Furthermore, the majority of nations having national HPV inoculation programs are high or upper-middle-income countries. There is also concern that traditional expression techniques may result in more expensive products, making them unavailable to be utilized in the low-income countries with the most significant rates. Thus, medications for managing, controlling and eliminating existing HPV infections and related diseases are earnestly needed.

3 NATURE IMMUNE RESPONSE

Cell-mediated immunity (CMI) is an effective immune response to the genital HPV infections. The innate immune system detects the damage via local antigen-presenting cells (APCs), then the pro-inflammatory cytokines and chemokines move to part of the lymph nodes to uphold the viral antigen processing. Activated APCs can stimulate CD4+ T cells to either help activation of CD8+ T cells. Effector T cells get response to the early proteins, mainly E2, E6 and E7, which can attack the virus-infected cells. Helper T cells that recognize L1 major capid protein help induce neutralizing antibodies (nAbs), thereby preventing virus spread and host reinfection. However, the expressions of E6 and E7 proteins are depressed with HPV persistence. This may arise from methylation of the E2 promoter but is usually associated with viral integration that can drive lesion growth.

4 VLP IMMUNOGENICITY

Virus-like particles (VLPs) are a more effective technique to develop highly immunogenic vaccinations. They combine safety, ease of production, and the presense of both high-density B cell epitopes and intracellular T cell epitopes to produce potent humoral and cellular immune responses. VLPs are similar to native HPV particles. The VLPs are fully non-infectious and non-oncogenic due to the lack of viral genes, forming a structure that resembles the outer shell of the HPV virus. They activate antibody synthesis in response to infection and contain conformational epitopes that contribute in the development of neutralizing antibodies by limiting target cell uptake (Stanley et al., 2010) (Dadar et al., 2018).

Antigens from HPV's capsid can trigger a range of type-specific antibodies, the majority of which can bind to the local virion, but not all of them can eradicate the infection by preventing uptake by the

target cell. The non-neutralizing antibodies (non-nAbs) are unable to directly affect the infectivity of the virus. The nAbs generated by L1 VLP can, however, prevent the binding to heparin sulfate proteoglycans (HSPGs) on the basement membrane (BM), but they cannot stop the infection completely. After a conformational shift in the capsid and cleavage of L2 by extracellular furin, the nAbs generated by L2 vaccination can neutralize the virion and deliver L2 defensive epitopes (Figure 3) (Roden et al., 2018)

The quadrivalent vaccination comprises a combination of four different VPLs obtained from the major capsid protein L1 of HPV 6, 11, 16, and 18. The nonavalent vaccine contains nine VPLs of HPV6, 11, 16, 18, 31, 33, 45, 52, and 58. These type specific L1 VLPs are synthesized by recombinant expression of major capsid antigen L1 in the *Saccharomyces cerevisiae (S. cerevisiae)* yeast with the amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant. In females and males aged 9 to 26 years, the quadrivalent HPV vaccination protects against genital warts, precancerous or dysplastic lesions, and cervical cancer. The nonavalent HPV vaccine is prescribed to avoid genital warts, precancerous lesions, cervical, vulvar, vaginal, and anal cancer in females and males aged 9 to 45 years. The bivalent vaccine has been authorized to prevent cervical and anogenital infection against HPV16 and 18. It is produced in the *baculovirus* expression vector system with the AS04 adjuvant containing aluminum hydroxide and 3-deacylated monophosphoryl lipid A (MPL) (Wang et al., 2020).

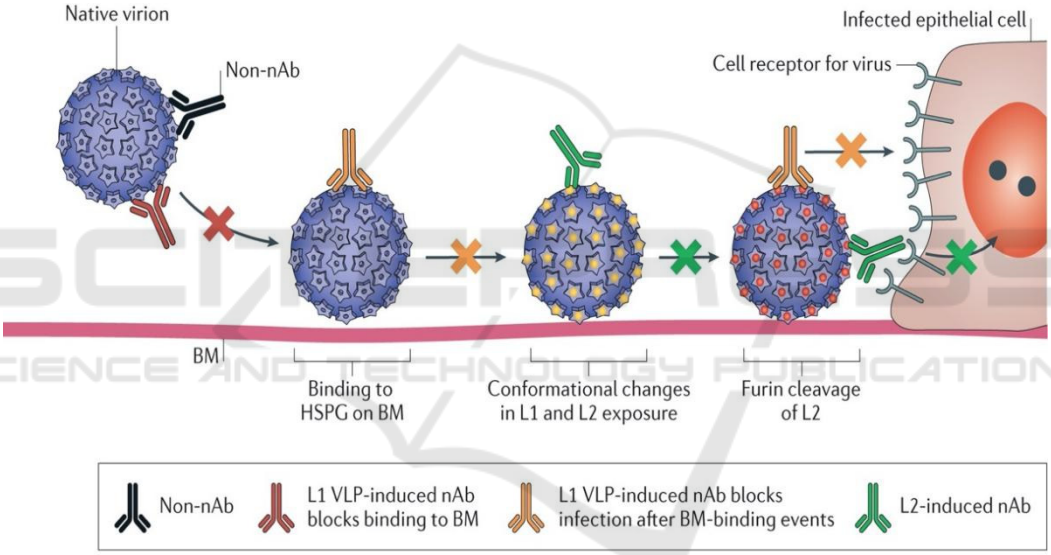

Figure 3: Antibody-mediated protection (Roden et al., 2018).

5 CLINICAL TRIALS

Several clinical investigations have been conducted to demostrate the advantages of the vaccine. A total of 14,000 girls aged 16 to 26 years old took part in a Gardasil 9 HPV vaccination phase III clinical research study. This study showed the significant differences between the result of Gardasil that only 1 out of 6,016 females who received three doses of Gardasil 9 acquired illnesses caused by HPV types 31, 33, 45, 52, and 58, contrasted with 30 out of 6,017 women who received three dosages of Gardasil. Epidemiological research in Europe attempted to quantify the advantages of the nonavalent vaccination over the quadrivalent vaccine. According to the findings, the nonavalent vaccination can prevent 19% more cervical cancers than the quadrivalent vaccine, and vaccine coverage for precancerous lesions of the vagina, vulva, cervix, and anus is expected to be 75% (Manini et al., 2018). The result of a long-term bivalent HPV vaccine study that involved 7466 women aged 18-25 years was characterized histopathologically affirmed CIN2+ or cervical intraepithelial neoplasia grade 3 or more terrible related with HPV 16/18 cervical contamination distinguished at colposcopy reference.

These vaccines have components that are manufactured through biochemical synthesis. These

components are part of the epitope of L1. Gardasil 9 is found to contain more virus-like particles that are double the amount of the antigens and higher than a double portion of aluminum hydroxide that is found in Gardasil. The amount of concentration of virus-like-particles in Gardasil 9 makes it more efficient in protection against and treatment of HPV 16 and HPV 18 since it can effectively introduce inferior responses of the antibodies as compared to Gardasil.

In addition, Cervarix contains antigens of a lower concentration when compared with these other two vaccine composition that is highly integrated and of greater enhancement. These look similar to receptors that inhibit antigens to stimulate and make an improvement in the human immune responses and as a result, long-lasting action of response by antibodies is built up.

Table 1: Vaccine composition of a 0.5 ml dose of the HPV vaccine (Hildesheim et al., 2020).

	Gardasil	Gardasil9	Cervarix
Oncogenic protein subunit			
HPV 16	41	60	21
HPV 18	22	41	20
HPV 31		22	
HPV 33		20	
HPV 45		23	
HPV 52		23	
HPV 58		23	
Verrucouis protein subunit			
HPV 6	22	30	
HPV 11	40	41	
Sodium Chloride	9.55	9.55	4.4
Sodium borate	34	34	
Sodium dihydrogen phosphate dihydrate			0.625
Amorphous aluminum hydroxyphosphate sulfate	224	224	
3-*O*-Desacyl-4′-monophosphoryl lipid (MPL) A adsorbed on			50
Aluminum hydroxide			500

The trials that were conducted on women of ages between 16 and 26 years and the findings showed for the ones under 16 years, as shown by the standard of WHO, this lack of superiority is acceptable and especially at the endpoint. The individuals who were over 26 years of age showed that the persistent of this infection can be protected against for utmost 6 months given some specific vaccine and subjected to a certain certified treatment and attention required was found fit and accepted to be used in preventing abnormal growth of cells in the female cervical areas. The ability of the vaccine to protect against the disease occurring in the vagina gives it the approval to be used in the treatment and defined as16/18 HPV and 2/3 HPV intraepithelial neoplasia.

There is not a clearly defined bare maximum level regarding protection that antibody titers offer against the cancer-causing and the disease itself in response to these studies of how cervical cancer vaccines define the endpoint of these VLPs. However, since this HPV-causing cancer is found to be one of the most dangerous and its treatment is limited, and is also a long-term disease as shown by the studies. As a result, they are used in the estimation of the appropriate amount of time it would take to offer protection to individuals of a certain age. Therefore, there timing of a vaccine is very important and very necessary since it determines the effect on the antibody titers.

Giving three doses of the vaccine tends to be considered a complete dose especially in women who are between the age of 12 and 15 years. The seropositivity that is realized in the response to the titers of anti- HPV 16 is seen to be high after vaccination for Cervarix and Gardasil vaccines (Kumar et al., 2011). The long-term protection that is expected for the specific vaccine is most of the time is affected by the decrease in titers, especially the Gardasil vaccine. Cervarix has higher retention for seropositivity when compared with Gardasil and therefore Cervarix shows an ability to bind serum and response of the antibody for HPV 16 and HPV 18 than Gardasil. Both Gardasil and Gardasil 9 have shown similar anti-A HPV 16 and 18 responses. In terms of geometric mean numbers, Cervarix tends to be superior when put in comparison with Gardasil.

When Gardasil 9 is administered in three doses, it shows a similar reduction in geometric mean number and an equal loss of seropositivity when taken for protection against HPV 18 like Gardasil. However, in 22 months after giving the vaccine, a reduction of the observable titers. In 1.4 years of vaccination, over

12% of female individuals showed no presence of detectable titers while 255 of women could show the absence of observable titers after 3 years of vaccination and 35% women after 5 years.

After 24 months of administering the Gardasil 9 vaccine, 15% of women shoed to have lost the detectable titers for HPV 45. The loss of these antibody titers for HPV 45 is considerably larger than the lowest percentage loss shown by the same vaccine for HPV 16 type and shows direct protection. The intervals that the doses of the vaccines are taken are also termed to be very important and help in the determination of the GMT.

Two doses of Gardasil 9 and Cervarix were given at an interval of six months thereafter followed by a booster for the adolescents between 9 and 10 years of age showed that hat Gardasil maintained a lower amount of HPV 16 and 18 titers than for the dose of Cervarix in one month of vaccination.

Three doses of Gardasil when given to pre-adolescent girls tend to show an absence of antibodies for different HPV types different from those administered with Cervarix. A random test was conducted for three doses of Gardasil 9 that showed a higher number of HPV titers which was higher than those administered with Gardasil 9 (Arbyn et al., 2018). Both Gardasil and Cervarix have similar antibody titers when administered at an interval of six months and only two doses given. Women who are above the age of 25 have inferior antibodies unlike those who are below 18 years.

Vaccines need to be examined and their safety determined and create an assurance that they will provide the maximum protection to the recipients against the different types of HPVs (Pennella et al., 2020). Administering the most efficient of these vaccines to women enhances protection against pre-cancer infections. Surveillance that was carried out by the Vaccine Safety Datalink depicted that these three vaccines are safe for use by the recipients and offer the most effective protection against these types of HPV infections. Before any vaccine is licensed and is accepted to be used, its safety is evaluated. In am examination to determine how safe these vaccines are, a similarity in the safety image of Gardasil and Gardasil 9 which was the earlier version of Gardasil 9. However, the latter was found out to show more side effects than Gardasil which however disappear away after some time.

Through the program for vaccination, the government has attained a significant decrease in the occurrence of the various HPV causing disease types that lead to the development of cervical cancer. An approximately 50% in the go down of appearance of abnormalities to teenage girls whose age is below 18 years. Through this, society is able to create assurance to both men and women that vaccination is important to their health and help them get away from this dangerous disease. This also helps them to avoid the expensive treatment of these long-term diseases by just prevention them by taking a vaccination. Since cancer is one of the fatal and dangerous and is becoming a threat in society today by the number of deaths it contributes to. Due to this, society today together with the government has enabled individuals to receive special attention and experienced medical care by enabling the introduction and inputting the required equipment for treatment and screening of cancer cells to help determine early detection and early treatment and later these have led to the achievement of a healthy society (Kumar et al., 2011).

6 FUTURE AND GOALS

The vaccination programs today are working in hands with the various respective governments to give more quality care to the individuals who are at a high risk of contracting the cancer disease. It, therefore, aims to achieve an educated society with people who are aware of the danger of these diseases and are aware of the importance of seeking early checkups and treatment. Through this, a healthy society and the number of deaths from this disease is achievable

7 CONCLUSION

In conclusion, cancer vaccines have been realized to be a very important aspect in both the health sector and even in the society at large. This is because they enabled the finding of the solution to one of the threats to individuals in the world today. Scientists and research centers through the World Health Organisation put these vaccines into place to help in the fight to eradicate this deadly disease. Though the cure has not yet been found, protection through these vaccines saves a great deal. Even though these vaccines bring different side effects to the body and tend to react with different types of bodies of diverse ages. More research enables determine which is the most effective vaccine to administer to what age and gender will work with their bodies without causing diverse effects and abnormalities.

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