Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

HUMAN PAPILLOMA VIRUS, ITS VACCINE SIGNIFICANCE, SIDE EFFECTS, AND COMPLICATIONS

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ARTICLE INFO

Received:
10 Apr 2021
Received in revised form:
20 Jul 2021
Accepted:
23 Jul 2021
Available online:
28 Aug 2021

Keywords: Human papillomavirus (HPV), Cervical cancer, Vaccine, Effectiveness, Side effects, Healthcare

ABSTRACT

Human papillomavirus (HPV) is the most common causative agent of cervical cancer, national and international decisions are made regarding HPV vaccines and the prevention of cervical cancer. Risk-benefit assessments and critical data analyses are significant for reaching consensus. Much controversy is still present over whether the benefits of the available 'HPV' vaccines outweigh its risks. It has reduced the acceptance of the 'HPV' vaccines compared to other various vaccines. Concerns regarding the safety of the 'HPV' vaccines have resulted in many physicians/healthcare providers and parents refusing the HPV vaccine. The most typical cause for not taking the prophylactic HPV vaccine was concerns regarding it is side effects. However; It is recommended that a different independent system for monitoring vaccines immunogenicity as well as side effects is established for addressing possible conflicts of interest via qualified professionals to accurately assess the side effects related to HPV vaccines. Eventually, it is recommended that expanded usage of HPV vaccines to further various populations, especially those who live within poor settings, may provide various health benefits using preventing HPV-related diseases. This review aims to assess the scientific peer-reviewed data associated with assessable outcomes from the usage of 'HPV' vaccines worldwide with more attention on the possible side effects.

To Cite This Article: Gari A. Human Papilloma Virus, its Vaccine Significance, Side Effects, and Complications. Pharmacophore. 2021;12(4):36-40. https://doi.org/10.51847/1cs1tXYKp8

Introduction

Human papillomavirus (HPV) is the causative agent of numerous severe illnesses among women and men, involving pre-cancerous and cancerous lesions of the cervix, vagina, vulva, oropharynx, anogenital area, and penis [1, 2]. It also plays a critical etiological role in developing anogenital warts among women and men. Anogenital warts, also known as venereal warts, are the most common manifestation of infection by HPV clinically. Over 90% of anogenital warts cases are caused by '11' and '6' types of HPV. Those types are responsible for the development of recurrent respiratory papillomatosis [3].

Various risks for acquiring HPV infection have been determined and involves low immunity, smoking, and being co-infected with other diseases that are transmitted sexually. Maintained infection with that virus is accompanied by cervical squamous carcinoma, cancer of the oropharynx, genitalia as penis, vagina, and vulva, anus, as well as head and neck. About 90% of HPV infections the virus spontaneously resolved via immunity. Although persistent infection is usually with high-risk strains as type '16' which leads to 20% of cervical cancers and type '18' leads to 50% of the cervical cancers [4]. Therefore, it is not surprising that the initial vaccines for HPV are directed to those genotypes. There are at least other 13 genotypes of high-risk strains, which involve '31', '33', '35', '39', '45', '51', '52', '56', '58', '59', '68', '73' as well as '82'. that their presence among particular populations within Latin America, might justify the differences between prevalence of '16' and '18' genotypes, as well as justify the cervical cancer incidence. A nine-valent vaccine has been recently approved by the Food and Drug Administration (FDA) for combating infections by seven genotypes of human papillomavirus of high risk, which are '16', '18', '31', '33', '45', '52', and '58' types plus it is coverage against HPV 6 and 11 (non-oncogenic strains) [5].

Vaccines for HPV have been globally introduced for preventing cervical and uterine cancers. In 2006, the FDA approved Gardasil as a recombinant papillomavirus quadrivalent vaccine, followed by the approval of Cervarix in 2009, a recombinant

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papillomavirus bivalent vaccine. Both vaccines were introduced widely for usage among Japanese female teenagers, as that vaccination's cost was borne largely by numerous regional governments. Then, in April 2013, adolescent females aged between 13 and 16 years were legally required to take that vaccination, and its costs were covered totally by the government [6].

Search Strategy

This project is a review of the literature concerning the human papilloma virus 'HPV' vaccines, its advantages and potential side effects.

The literature search has been guided primarily via Trip Database, Google Scholar and PubMed advanced search builder with the following keywords: Human papillomavirus, cervical cancer, vaccine, effectiveness, and side effects. The search was limited to English language, and full text. Moreover, the search was limited to recent studies from 2016 to 2021 on the topic. The relevant articles have been included in this review as per the following: HPV-related diseases and cancers (2 articles [7, 8]), viral cytology (2 articles [9, 10], current vaccines and their development (3 articles [4, 11, 12]), and vaccine safety concerns and potential side effects (7 articles [13-19]). (See References). However, there was scarcity of literature in Saudi Arabia, so the researcher depended on the available literature in different countries.

The Burden of Human Papilloma Virus

HPV Infection is one of the most common diseases transmitted sexually. It is related to many cancers as cervical cancers, anal cancers, and squamous cell carcinoma of the head and neck. Brianti *et al*. stated that, till now, over 200 types of HPV had been determined. HPV infections are transmitted primarily by skin to mucosa or skin to skin contact. Some types of human papillomavirus infect cutaneous tissues and stimulate warts mainly, while other types of the virus target mainly mucosal oral and cervical tracts tissues [7].

Although most HPV infections cases do not lead to illness, persistent infections might lead to disease. According to the World Health Organization (WHO); in 2012, there were about 266,000 deaths because of cervical cancer caused by HPV among women globally, where more than 85% of those deaths took place within less-developed regions. Cervical cancers form about 84% of all cancers related to HPV worldwide [20]. Various factors may influence infections and cancers related to HPV as getting infected by the virus or clearance of its infection, including immune status, earlier age of sexual intercourse, usage of oral contraceptive pills and intrauterine devices, multi-parity, history of previous infections, smoking, low socioeconomic status, alcoholism, deficient diet in vitamins, ethnicity, as well as genetic causes.

Bihl *et al*. stated that, according to the oncogenic capacity, different types of HPV are either classified as high-risk oncogenic types, that might be possibly carcinogenic as '16', '18', '31', and '33' types, or low-risk non-oncogenic types, that are found mostly within warts, as '6' and '11' types [9]. HPV infections were thought initially to be transmitted uncommonly from mothers to infants during labor; but, a lot of evidence identified that as a potential route for transmission if the mother was affected by genital warts during labor. Skoczyński *et al*., also have identified the presence of '16' and '18' types of HPV among newborns of asymptomatic mothers infected by '16' and '18' types of the virus. That identifies the risk for mother to fetus transmission of HPV [8].

The Development of Vaccine and its Significance

Fortunately, two HPV vaccines were developed, indicating powerful protection against cervical infections caused by the specific types of HPV included in these vaccines ie. condylomas and some cancers related to the virus. There are various reviews on the infections caused by HPV and their association with various cancers, including head and neck, penile, vaginal, vulvar, and anal cancers.

Recent vaccines for HPV are built on viral-like particles and include self-arranged pentamers of the L1 capsid's bigger protein. HPV vaccines are used for prophylaxis and not for therapy. HPV vaccines aim to avoid continuing infections that may progress to invasive carcinomas. These vaccines are not intended for treating cancers because the cancerous cells do not show significant L1 levels. Skeate *et al*. stated that immunotherapy is used to treat cancers originating from the HPV, introducing a cellular immune response for combating antigens related to cells' transformation [4].

These vaccines don't affect the cellular immune response, eliminating the virally infected cells; however, it stimulates the antibodies production against L1 protein within blood. The two main approved vaccines are the bivalent one, Cervarix, which prevents '16' and '18' infection types, and the quadrivalent one, Gardasil, prevents '18', '16', '11', and '6' infection types. These two vaccines protect the females from pre-cancerous lesions of the cervix, so it is still hard to predict their efficacy in the long term. The latest vaccine approved was Gardasil 9 which covers against HPV types 6,11,16, 18, 31, 33, 45, 52, 58. The vaccine showed non-inferior protection against HPV 6, 11, 16, 18 in addition to the other 5 HPV strains but no other HPV types (9).

Numerous studies have stated that bivalent, quadrivalent, and 9 valent vaccines are mostly considered to be safe. Malagon *et al*. noted that each of the vaccines did show long-term durability for protecting from primary infections caused by targeted HPV types through the vaccines accompanied by an average cross-protection degree from many non-targeted HPV, most significantly '31', '33', and '45' types [12].

Regarding the efficacy of the vaccine, Ozawa *et al*. has stated that HPV vaccines cause a significant decrease in the incidence of abnormal cytological findings of the cervix compared to females who weren't vaccinated. More significantly, a

significant reduction has also been observed within the diagnosis of cervical intraepithelial neoplasia-2 or worse, histologically [10].

An active HPV infection reduction has also been observed within the year-to-year rate of screening and finding abnormal results as a result of the HPV vaccine. For example; the birth year-dependent alteration within risk for cervical cancer. As Ueda *et al*. stated, the targets between 2014 and 2019 for those born between 1994 and 1999, the abnormal results' rate within the cervix cytology slightly increased from 3.68% in 2010 up to 4.35% in 2013. But, it dropped dramatically to 2.99% in 2014 and 3.03% within 2015. Thus, the mean rate between 2010 and 2013 was 3.96%, but it significantly dropped to 3.01% between 2014 and 2015 (p-value = 0.014) [21].

Within a global scale, maximal drops of about 90% HPV '6', '11', '16' and '18' types, and 45% reductions for low-grade cervical cytological abnormalities, in addition, up to 85% drops for cervical histological high-grade abnormalities have been observed. The 'Global Advisory Committee on Vaccine safety has systematically investigated the safety issues with HPV vaccines and indicated that it had not observed any safety concerns that would change its recommendations for using the HPV vaccine [13]. Nevertheless, there are various continuing controversies regarding the compliance with the vaccine recommendation, which at certain times has included health governmental agencies. The HPV vaccines are not therapeutic for any associated diseases with HPV (active infections) which might present at the vaccination time, nor protecting from diseases caused by other types of HPV. Moreover, 'HPV' vaccines aren't recommended for girls younger than nine years or during pregnancy.

The Vaccine Side Effects and Complications

Arbyn *et al*., in Cochrane review (2018), and the majority of large epidemiological studies did not state severe nor general harms related to the HPV vaccines. That review was based mainly on publications that are often affected by the reporting bias and the epidemiologic studies that are affected by the confounding bias [14]. There are rare harms that involve syncope and anaphylaxis. Several case studies stated rare neuronal harms as orthostatic postural tachycardia syndrome and regional complex pain syndrome. According to Chandler *et al*., some analyses of case safety individual reports from WHO showed more serious harms that overlapped with postural tachycardia syndrome symptoms and the regional complex pain syndrome [22]. Weber & Andersen stated that despite the European Medicines Agency (EMA), investigations of postural tachycardia syndrome and the regional complex pain syndrome did not show a relationship with HPV vaccines. The EMA investigations were dependent on the assessments of the manufacturers of the vaccines, and nearly 30 cases of postural tachycardia syndrome and regional complex pain syndrome were not recognized within the trials of the manufactures of the HPV vaccines [23].

Suzuki & Hosono in Nagoya concluded in their study the possible association between HPV vaccine and the observed symptoms, it didn't show a significant increase within the occurrence of any of the observed symptoms of post-HPV vaccination. The vaccines were associated with increased medical visits for severe headaches, abnormal menorrhagia, irregular menstruations, and chronic abnormal menorrhagia. None of those symptoms influenced attendance at school significantly. Thus, it recommended no correlation between the HPV vaccine and any of the side effects reported previously [15].

However, a report by Tomljenovic *et al*. indicated post-mortem findings of the viral components included within the Gardasil vaccine could cross the blood-brain barrier, which was claimed to cause cerebral vasculitis, which is a severe inflammation within the blood vessels of the brain that may even lead to death. Also, Tomljenovic *et al*. presented two cases of young-age females who died in months during or following the Gardasil vaccination. Still, the source of the HPV capsid proteins detected within the brain's blood vessels could not be attributed directly to the Gardasil vaccine [16]. Moreover, a 10-year follow-up study conducted by Huh *et al*. indicated that Gardasil stimulates immune responses, is effective clinically, and is well-tolerated generally among pre-adolescents and adolescents. In addition, Cervarix showed significant tolerance and antibodies sustenance following vaccination up to 9.4 years. The same for Gardasil-9 for up to 6 years, which is a recent version of the 'Gardasil' vaccine [17].

Gonçalves *et al*. stated that the vaccines' most commonly reported side effects were reactions at the injection site, including swelling and pain, potentially because of the inflammation process related to the viral-like particles. 'Cervarix' may also result in systemic symptoms like fever, dizziness, nausea, diarrhea, vomiting, and myalgia. Fatigue and headache are the most common systemic side effects of the Cervarix vaccine, which are observed among about 50 to 60% of vaccinated females. Recipients of the Gardasil and Gardasil-9 vaccines may also suffer from general side effects, but there were no observed increased risks of systemic side effects among these recipients [18].

Also, some safety issues are present regarding aluminum, which is used widely as an adjuvant to the HPV vaccines. Currently, mice experiments, as the one conducted by Khan *et al*. for assessing the bio-distribution of aluminum related to the vaccine, have shown that continuously raising the doses of the badly bio-degradable aluminum adjuvant may become insidiously harmful, especially among cases of closely-spaced, repetitive vaccinations which may cross the blood-brain barrier [19]. Other animal experiments have stated that injected adjuvant nano-aluminum particles may travel from the site of injection to body organs like the brain and the spleen. Furthermore, other past studies, like the one conducted by Petrik *et al*., showed the generation of harmful immunological-inflammatory responses within nerves tissues [24].

Conclusion

Human papillomavirus vaccines Cervarix (the bivalent vaccine) and Gardasil (the quadri-valent and 9 valent vaccines) are used for prophylaxis and don't treat pre-existing infections by the virus nor its associated conditions. Many researchers are still working on developing therapeutic vaccines which trigger and stimulate cellular immune responses for treating known 'HPV' infections as well as cancers.

There are also many trials working on various potential therapeutic vaccines, besides combination therapies. But unfortunately, till now, despite the tested potentially therapeutic vaccines, none of them proved complete regression of cancers associated with the human papillomavirus.

Further Recommendations

The main aim of developing the HPV vaccine was the prevention of cervical cancers. Thus, each country must introduce or strengthen population-based comprehensive tumor registries for tracking trends of cervical cancers. Registries of cancers, as well as other administrative information resources, can evaluate the long-term effect of a comprehensive prevention strategy of cervical cancer involving 'HPV' vaccines, pre-cancer screening of cervix as well as a cancer treatment. But, the total impact upon the 'HPV' burden and cancer wouldn't be observed except for 100 years following the development of the vaccines.

Vaccines for human papillomavirus significantly reduced 'HPV' infection as well as its associated illnesses. With the developments within the coverage of the vaccine and the development of vaccination programs for both males and females, enhanced protection from 'HPV' and fewer cervical cancer cases are predicted. For fulfilling that, educational programs describing the risk of human papillomavirus as well as the vaccine benefits are significant, particularly within the low-as well as middle socio-economic class.

Another critical issue is that the types of the human papillomavirus which are not covered by the developed vaccines are prevalent across younger females. The next generation of the 'HPV' vaccines must concern with vaccines with broad-spectrum protection. Besides, clinical studies are significant for evaluating the impact of 'HPV' vaccines on all the cancers related to it. Tota *et al*. stated that the therapeutic vaccines for treating 'HPV' cancers are very important and carry an assuring future for treating human papillomavirus and its related illnesses from prevention up to complete clearance [25]. The absence of sufficient evidence regarding the exact doses of 'Gardasil-9' is probably concerning. Thus, there's a need for more evidence involving all the present confounders as to whether one vaccine is more appropriate than the other, tolerated better, and with lesser costs.

Also, the cost-effectiveness studies must consider the vaccines as well as other social possible modifications as to whether supplementation of probiotics or vitamin D, or whether using contraceptive pills or intrauterine devices, is safer and more cost-effective than the human papillomavirus vaccine.

Acknowledgments: I would like to express my special thanks to the senior pharmacists Ghufran Rawas and Abrar Alhazindar, who helped me out with this review in the literature and manuscript reviewing.

Conflict of interest: None

Financial support: None

Ethics statement: None

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