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HPV Vaccine Optimization Concerning Cervical Cancer

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Abstract. Cervical cancer, associated with human papillomavirus (HPV), is currently the fourth most prevalent cancer among women in the world. Though nowadays there are HPV vaccines available on the market, more strategies need to be taken to improve them and develop more therapeutic vaccines. Recent research has mostly concentrated on the state of HPV vaccinations, including their mechanisms, clinical efficacy, and room for improvement. However, there is a significant research deficit in the field of therapeutic HPV vaccination development. This paper analyzes the mechanisms of both prophylactic and therapeutic HPV vaccines, analyzes the clinical efficacy of five major vaccines in China, and discusses strategies for optimizing HPV vaccines through adjuvants and targeted antigen design. This thorough analysis offers insightful perspectives on the efficacy and safety of the HPV vaccine and makes recommendations for further study and immunization campaigns. However, the problems about the impact of vaccination programs and HPV-related diseases in men haven't been solved yet. Therefore, future studies should target developing therapeutic HPV vaccines, improving HPV vaccines in the next generation, increasing the awareness of the public, and increasing accessibility of vaccines to release the burden of cervical cancer globally.

Keywords: Cervical cancer; human papillomavirus; HPV vaccines; optimization.

1. Introduction

According to Burmeister et al, cervical cancer is the fourth most prevalent cancer among women in the world, ranking after breast cancer, colorectal cancer, and lung cancer. Since cervical cancer contributes to a high rate of morbidity and mortality among women, it is believed to be a global health concern. Every year, more than 500,000 women are diagnosed with cervical cancer globally, and the number of deaths is up to 300,000 [1]. In 2018, cervical cancer became the primary cause of fatalities among women in eastern, western, middle, and southern Africa. Among them, Eswatini showed the highest incidence with approximately 6.5% of women developing cervical cancer before turning 75 years old. The average global age of cervical cancer-associated mortality was 59 [2].

By attaching to the virus and stopping it from infecting the epithelium when exposed to HPV, HPV vaccinations aid in the prevention of cervical cancer. However, the antibodies produced during the process are not sufficient to stop the subsequent reinfection. Thus, the optimal HPV vaccine ought to promote an improved immune response [3].

Currently, there are three kinds of prophylactic HPV vaccines available on the market: Gardasil®, varix®, and Gardasil 9®. Gardasil is a quadrivalent HPV (4vHPV) vaccine; Cervarix is a bivalent HPV (2vHPV) vaccine; Gardasil 9 is a nonavalent HPV (9vHPV) vaccine. The HPV L1 capsid protein is the target of all currently available vaccines, yet infected basal epithelial cells do not express the protein. This that these vaccinations cannot be used to treat infections that already exist, which presents a problem for the development of HPV vaccines in the future.

It is a pity to know the fact that in mainland China, only a minority of people are willing to be vaccinated. According to Yu et al., among the 91762 who participated in the survey, only 66.4% have the intention to vaccinate against HPV. Reasons that people stand against the vaccine include a lack of knowledge about the HPV vaccine and concerns about being misled by false interpretations. To prevent cervical cancer, mainland Chinese residents' awareness of the HPV vaccine should be improved [4].

It is essential to comprehend the mechanics behind HPV vaccines and investigate ways to improve them. Progress in vaccine formulation could be used as an optimization method, such as creating next-generation vaccines that target a wider range of HPV strains, and better vaccine delivery systems for higher immunogenicity and long-term protection. Furthermore, barriers to vaccination accessibility, such as expenses and availability, should be eliminated to provide universal access to preventative interventions against cervical cancer.

A comprehensive review of the mechanisms of HPV vaccines will be discussed, highlighting their immunogenicity, efficacy, and safety profiles. In addition, the most recent developments in HPV vaccine research and the possible significance of improving these vaccinations in terms of avoiding cervical cancer will be investigated. Moreover, some challenges related to vaccine implementation concluded, and strategies to overcome these barriers to support continued initiatives to lower the incidence of cervical cancer worldwide will be proposed.

2. Mechanism of HPV Vaccines

HPV vaccines work by triggering the immune response to combat most types of HPV. Depending on the different purposes of dealing with infections, HPV vaccines can be distinguished into two types: prophylactic and therapeutic. These two types of HPV vaccines have diverted mechanisms of action.

Prophylactic HPV vaccines intend to prevent the HPV infection before the patient is exposed to the virus. These vaccines contain virus-like particles (VLPs) that mimic the structure of the HPV virus, specifically the capsid proteins [5]. They are derived from the outer coat of VLPs spontaneously self-assembled by L1 proteins, the origin of antigens. However, since VLPs do not contain the genetic material of viruses, they do not lead to any illness. When the vaccines are administered, antigen-presenting cells (APCs) present antigens to stimulate the activation of B cells and T cells. While CD4+ T cells help to coordinate the immune response and CD8+ T cells specifically target and kill HPV-infected cells, B cells are able to identify and neutralize antibodies. Following activation, B cells undergo differentiation into plasma cells, which have the capacity to generate large quantities of particular HPV anti-L1 VLP antibodies. When genuine HPV enters the body, antibodies made possible by B cells and T cells are able to identify the virus rapidly and stop it from infecting further human cells. This prevents HPV infection from progressing to a disease.

With the goal of generating cell-mediated immunity, therapeutic HPV vaccines are used to treat current HPV infections and related illnesses [6]. The mechanism of therapeutic vaccines includes a sequence of steps: Initially, the vaccines transmit HPV antigens such as E6 and E7 proteins to APCs through DNA or RNA vaccines, protein-based vaccines, peptide-based vaccines, dendritic cell-based vaccines, etc. Following this, T cells are stimulated in a manner similar to that of preventative vaccinations, specifically aiming to destroy HPV-infected cells. Subsequently, activated T cells undergo clonal proliferation and develop into effector T cells, which target HPV-infected cells. A portion of these cells also give rise to memory T cells, which offer long-term immunity against HPV infection. Finally, effector and memory T cells travel to the lesion or HPV-infected location and infiltrate the tumor microenvironment. There, they identify and eliminate HPV-infected cells that express the E6 and E7 oncoproteins.

3. Review of Clinical Data for Prophylactic Vaccines

Currently, in China, five types of HPV vaccines have been tested through clinical trials for use in females. Three of them are bivalent (bv): Cervarix (AS04-HPV-16/18), Cecolin (Escherichia coli), and Walrinvax (Pichia pastoris) target HPV16 and HPV18. In addition, a quadrivalent (qv) HPV vaccine, Gardasil, is designed to prevent against HPV6, HPV11, HPV16 and HPV18. Furthermore, there is a nonavalent (9v) HPV vaccine, Gardasil-9, aiming at HPV 6, HPV11, HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, and HPV58. It has been demonstrated that all of these vaccinations are highly immunogenic, generally well-tolerated, and effective against genital precancerous lesions

and recurrent infections in Chinese women. In international studies, they have also demonstrated a respectable safety profile.

A total of 6,051 women were involved in and followed for up to 72 months in a large-scale randomized clinical trial (NCT00779766) carried out in China to assess the efficacy, safety, and immunogenicity of the bivalent HPV vaccine (AS04-HPV-16/18) in preventing HPV infection and related cervical precancers [7]. The overall aim of the research was the effectiveness of the vaccine against cervical intraepithelial neoplasia grade 2 or above (CIN2+). Various cohorts were included in the analysis, including TVC-naïve, ATP-E, and TVC-E, the according-to-protocol cohort for efficacy. The effectiveness of ATP-E in preventing HPV-16/18-associated CIN1+ is 97.1%. The effectiveness of the vaccine against other endpoints, such as incident infection, 6-month persistent infection (6MPI), 12-month MPI, and atypical squamous cells of unknown significance (ASC-US+), was also noted. Researchers found that the vaccination can remain effective for up to 72 months as a result of this investigation. In addition, prophylactic HPV vaccination combined with screening may lessen the incidence of HPV infection and cervical cancer in China.

The HPV bivalent vaccine generated by Escherichia coli was the subject of another investigation carried out in China (NCT02562508) [8]. In the trial, 301 girls aged 9 to 14 received two doses, 304 girls received three doses, 149 girls aged 15 to 17 received three doses, and 225 women aged 18 to 26 received three doses. Participants in the trial were split up into age groups and administered vaccination doses at predetermined intervals. Using the pseudo virion-based neutralization assay (PBNA) and the enzyme-linked immunosorbent assay (ELISA), HPV-16 and HPV-18 specific IgG antibodies and neutralizing antibodies were found. The outcome showed that the proposed HPV bivalent vaccination was efficient in eliciting an immune response in girls between the ages of 9 and 17 and equivalent to that of women between the ages of 18 and 26.

In women and girls aged 18 to 30, as well as those aged 9 to 17, the HPV bivalent vaccine made by Pichia pastoris elicited an antibody response against HPV16 and HPV18 in Phase III-IIIB studies. In each of these groups, neutralizing antibodies were greater than 99.77% during the experiment. According to international research, the vaccination works well against genital precancerous lesions and chronic HPV-associated illnesses. Notably, the Pichia Pastoris HPV bivalent vaccine and other HPV vaccines authorized in China have a satisfactory safety profile in international trials [7].

In Wuzhou, Guangxi, China, a study was carried out from July to August 2008 to assess the safety and immunogenicity of the quadrivalent HPV vaccine in Chinese men and women. In this study, 500 Chinese women and 100 Chinese males in good health, ages 9 to 15, participated [9]. Participants in this technique were randomized to receive either the adjuvant-containing placebo or the quadrivalent HPV vaccination. On days 1, 2, and 6, the vaccination group received three doses of the vaccine; at the same time, the placebo group received a placebo injection. The findings demonstrated that systemic adverse responses associated with vaccination that Chinese participants reported were comparable between the vaccination and placebo groups. The percentage of patients in both the vaccinated and placebo groups who experienced fever following vaccination was similar. The findings back up immunizing Chinese men and women against cervical cancer in an effort to lower the disease's incidence.

A Phase III open-label study (NCT03903562) was developed, aiming to test the immunogenicity of the 9-valent human papillomavirus (9v-HPV) vaccine. The study involved 1,990 women, including different age groups 9-19 years (n=690), 20-26 years (n=650), and 27-45 years (n=650) [10]. The results of the study showed that one month after receiving 3 doses of the vaccine, 99% of participants had seroconversion on the corresponding HPV type, with an overall seroconversion rate of 100% for all participants and only a slightly lower HPV18 seroconversion rate (99.8%) in the 20-26-year-old group. In addition, 9-19 and 27-45 Chinese women for HPV6/11/16/18/31/33/45/52/58 serum conversion rate of not less than 20 to 26-year-old women. These results are based on a review by the NMPA (China's National Medical Products Administration), which gave its approval to the 9v-HPV vaccine's August 2022 age range extension to women ages 9 to 45.

According to the 5 studies above, all of the five major HPV vaccines in China showed great efficacy and safety in preventing HPV infection and correlated precancerous lesions. Strong immune responses were elicited by the vaccines in individuals of various ages, indicating their long-term advantages and justifying their inclusion in the vaccine to lower the incidence of cervical cancer. The findings offer a strong scientific foundation for HPV vaccination usage and promotion in China.

4. Possibilities of HPV Vaccine Optimization

Due to the progress of technology and innovative approaches, the HPV vaccine appears to have a promising future of optimization. Many cutting-edge technologies and new methods are being developed to improve the effectiveness and safety of HPV vaccines. Having methods from adding adjuvants to targeted antigen design, the potential for optimizing HPV vaccines is tremendous and transformative. All these possibilities are the key to increasing vaccination accessibility, scalability, and efficacy in the fight against HPV-related infections and associated cancers.

An adjuvant is a material that enhances a vaccine's immunogenicity. The strength and durability of the immune response brought on by HPV vaccinations can be greatly increased by the creation and application of new adjuvants. Adjuvants stimulate several immune cell types, or signaling, to enhance the immune system's long-lasting and comprehensive response to the HPV vaccine. The possible effectiveness of adjuvant HPV vaccination following surgical excision for cervical intraepithelial neoplasia (CIN) 2 or greater was examined by Lichter, K. et al. [11]. According to their research, adjuvant HPV vaccination may lessen the chance of future CIN and disease recurrence. Since the primary purpose of HPV vaccinations was primary prevention, the mechanism underlying their efficacy remains unclear. Nonetheless, it is hypothesized that the preventive vaccine may be successful in a new backdrop that is comparable to that of an unexposed patient due to the alteration in the immune microenvironment brought about by surgery. Furthermore, research has indicated that vaccination against HPV strains other than HPV 16,18 may offer cross-protection against them.

With focused antigen design, the HPV vaccination can be made even better. At present, clinically developed HPV therapeutic vaccines primarily target the two HPV oncoproteins, E6 and E7. To improve efficacy, additional HPV antigens must be included to upcoming therapeutic HPV vaccinations. Research has indicated that novel targets for therapeutic vaccinations could include antigens like E1 and E2, which are expressed from the early stages of infection until they change into malignancy [12]. By focusing on these antigens, it may be possible to eradicate the underlying infection and lower the likelihood that neoplastic alterations would return. Additionally, attempts have been made to develop a broadly reactive therapeutic vaccine that encodes conserved portions of the E1, E2, E4, E5, E6, and E7 proteins, which represent several HPV genotypes and are capable of targeting and curing infection from multiple HPV types [13]. Although the goal of this approach is to offer cross-type coverage, not all patients will benefit from it. Lastly, immunogenicity, weariness over various stages and varieties of HPV-associated lesions and malignancies, and patterns of HPV protein expression should all be taken into account when developing future therapeutic vaccines against the virus.

5. Challenges and Strategies in Vaccine Implementation

While the HPV vaccines are being invented and improved, there are lots of challenges to implementing them in the public. Several factors are affecting the condition, including social, cultural, and economic factors. Therefore, more strategies need to be taken to better popularize the HPV vaccine among the public.

The public's lack of knowledge about the HPV vaccine is one of the main issues at hand. In a survey of 172 undergraduate students from King Saud University's College of Medicine and the Arts and Business colleges in Riyadh, Saudi Arabia, Azer, S. A. et al. found that medical students knew more about cervical cancer and the HPV vaccine than non-medical students did. Because of their educational background, medical students were more likely to obtain the HPV vaccine and had a

more positive attitude toward it. Consequently, it is critical to increase knowledge about HPV, cervical cancer, and cervical cancer screening at educational institutions, community outreach programs, and schools [14].

Another issue that individuals are currently dealing with is vaccine disparity. According to a study by Hirth J. (2019), there has been a general success in increasing vaccination rates; nevertheless, there is still limited completion of the HPV vaccine series, particularly in some populations [15]. The US's southern states have lower immunization rates than other regions. These areas put people at risk due to high incidence of cervical cancer mortality and limited access to HPV vaccinations. Additionally, there are variations in the vaccination rates among various racial and cultural groupings. Governments must address these gaps and guarantee high vaccination rates in order to lower the cost of illnesses and malignancies linked to HPV.

The price of vaccinations is a significant consideration in addition to the first two. Cost-effectiveness study revealed that careHPV screening with vaccination once every five years was the most economical approach found in China [16]. Moreover, combined techniques would be more economical than screening-only procedures at all WTP levels if the vaccination cost was further lowered to $10 for two doses. With HPV screening administered every five years and vaccination being the most cost-effective approach at a WTP of three times the per-capita GDP, the study shows the value of combination screening and immunization strategies for preventing cervical cancer in China.

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