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The Role of Recombinant Protein Technology in the Development and Global Impact of Gardasil: Addressing HPV-Induced Cancers and Advancing Vaccine Strategies

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Abstract:

HPV (Human Papilloma Virus) is classified into low or high-risk genotype. It is responsible for nearly 5% of all human cancers in both sexes worldwide; certain high-risk genotypes can cause cervical cancer in women. Gardasil vaccine is designed to prevent HPV infections in people aged 9 to 45. By utilizing virus-like particles (VLPs), which are non-infectious mimics of the virus, the vaccine triggers a robust immune response without the risk of causing the disease. One of the major advantages of using recombinant proteins in vaccines like Gardasil is that they are highly immunogenic and allow for precise targeting of specific viral strains. Researchers have proven that Gardasil is safe and effective in clinical trials, although such data is limited for pregnant women. Promoting Gardasil globally will require continued efforts to raise awareness about the vaccine's benefits, address vaccine hesitancy, and ensure equitable access, particularly in regions where HPV-related cancers are most prevalent.

Keywords: HPV Vaccine; Gardasil; Recombinant protein; Immunity; Vaccine hesitancy.

1. Introduction

HPV (Human Papilloma Virus) is a double-stranded DNA virus in the Papillomaviridae family. It can develop into benign and malignant conditions in both sexes, including warts and various cancers such as cervical, anal, and oropharyngeal cancers. HPV can be classified as low or high-risk genotype according to its association with malignant transformation of cells [1]. Certain high-risk genotypes can cause cervical cancer in women, which is the 4th most common cancer among women globally [2]. With over 200 identified HPV genotypes, certain strains, particularly high-risk types, are responsible for nearly 5% of all human cancers worldwide. Due to its status as the most common sexually transmitted infection

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globally, there has been a significant focus on developing preventive measures, most notably vaccines, to reduce HPV-related disease burden [1].

Protecting people aged 9 to 45, Gardasil is a breakthrough vaccine designed specifically to prevent infections caused by HPV. There are two types of Gardasil: One is quadrivalent; the other nonavalent. Gardasil quadrivalent is manufactured by Merk & Co., and targets 4 HPV genotypes. Marketed internationally by Merk & Co. in 2015, Gardasil 9 targets 9 prevalent HPV genotypes. Gardasil uses recombinant protein technology, creating virus-like particles (VLPs) that resemble the virus but do not cause infection. These particles stimulate the body‘s immune system to produce neutralizing antibodies, providing protection against future HPV infections [3]. Thus, the body is able to develop immune mechanism against the virus. Introduced in 2006 and expanded with Gardasil 9 in 2015, this vaccine has significantly reduced HPV-related infections and associated cancers globally.

It is evident that HPV infection has a huge impact on the health of people all over the world. Studying Gardasil and its underlying technology is crucial not only for understanding its role in preventing HPV-related diseases but also for advancing vaccine development. The immune responses triggered by Gardasil, its effectiveness in clinical trials, and the potential for future innovations make it a key focus for medical research. By exploring its use and promoting global vaccination efforts, we can continue to reduce the incidence of HPV-related cancers and improve public health outcomes and might develop a more refined and advanced HPV vaccine, which benefits people by lowering infection risks and reducing side effects.

2. Recombinant Protein Technology in Gardasil

Gardasil vaccine uses recombinant proteins in its production process. The technology of producing recombinant proteins is mature today. Recombinant proteins are encoded by recombinant DNA, which combines DNA from different sources to form a recombinant DNA molecule [4]. Modification of the gene by recombinant DNA technology can lead to expression of a mutant protein, which is successful in modifying gene sequences. Recombinant proteins have the advantage of being cost-effective, simple, and fast in producing large yields, which are the reasons they are used extensively in research to treat diseases [5].

Recombinant protein technology has been used in quadrivalent Gardasil vaccine, which contains the VLPs derived from L1 capsid proteins of HPV type 6, 11, 16, and 18, which are responsible for most cervical cancer and genital warts cases [6]. After injection into the patient’s arm muscle, the vaccine stimulates the immune system to produce antibodies against L1 proteins. Therefore, when the virus actually invades into the human body, its immune system can respond more quickly to the virus.

Recombinant protein technology used in the Gardasil vaccine represents a significant advancement in vaccine development. By utilizing virus-like particles (VLPs), which are non-infectious mimics of the virus, the vaccine triggers a robust immune response without the risk of causing the disease. The L1 protein, a major structural component of the HPV virus, is expressed in yeast cells using recombinant DNA technology. This allows for the production of large quantities of VLPs, which self-assemble into structures resembling the outer shell of the HPV virus but do not contain its genetic material, ensuring safety.

One of the major advantages of using recombinant proteins in vaccines like Gardasil is that they are highly immunogenic, meaning they effectively stimulate the immune system to produce long-lasting protective antibodies. Furthermore, recombinant protein technology allows for precise targeting of specific viral strains, such as HPV types 6, 11, 16, and 18 in the quadrivalent vaccine.

Additionally, recombinant protein vaccines like Gardasil have a proven safety profile, as they do not involve live viruses, reducing the risk of adverse reactions commonly associated with traditional vaccines. The scalability of recombinant protein production also means that vaccines can be manufactured in large quantities at a relatively low cost, making them more accessible for widespread public health use.

In conclusion, recombinant protein technology in Gardasil not only enables efficient production but also ensures high safety and efficacy, marking it as a key advancement in preventative healthcare, particularly in combating HPV-related diseases.

3. Immunity Effects, Effectiveness, and Side Effects of Gardasil

Gardasil’s immunity effects, effectiveness, and safety profile make it a critical tool in the prevention of HPV-related diseases. Understanding the specific immune response triggered by Gardasil provides insight into how this vaccine protects against multiple HPV strains and helps reduce the risk of HPV-associated cancers and conditions. Below, we explore Gardasil‘s mechanism of inducing immunity in detail.

3.1 Immunity Effects of Gardasil

Gardasil, a recombinant vaccine, provides immunity

against multiple strains of HPV by using virus-like particles (VLPs). These particles resemble the structure of HPV but do not contain viral DNA, making them non-infectious. Upon vaccination, these VLPs are recognized by the immune system, which triggers the production of antibodies specifically targeting the L1 protein of HPV. These antibodies remain in the system, providing long-term immunity against future HPV infections. Studies conducted by Carlos et al. have shown that antibody responses to the valence 9 vaccine-targeted HPV types sustained for 10 years post-dose, and, among the 301 male and 971 female participants, no cases of cancer and genital warts related to the HPV types covered by the vaccine were diagnosed [6].

3.2 Effectiveness of Gardasil

Clinical trials, such as those conducted by Joura et al., have demonstrated that Gardasil is highly effective at inducing a strong immune response. In trials comparing the 9-valent Gardasil to the quadrivalent version, the geometric mean titers (GMTs) for HPV types 6, 11, 16, and 18 remained high in both groups, indicating similar immune responses for the shared HPV types [7]. Additionally, the 9-valent vaccine showed greater efficacy for HPV types 31, 33, 45, 51, and 58, providing broader protection.

Studies also show that the immune response generated by Gardasil is durable, with protective antibody levels persisting for at least 10 years after vaccination. This long-lasting immunity helps prevent cervical cancer, genital warts, and other HPV-related diseases.

Moreover, the effectiveness of Gardasil has been demonstrated in various populations, including young men and women, with studies suggesting that two doses of the vaccine provide comparable immunity to the traditional three-dose regimen in younger age groups. In conclusion, Gardasil leverages recombinant protein technology to generate a potent and lasting immune response, protecting individuals from the most harmful HPV strains and significantly reducing the risk of HPV-related diseases.

Additionally, Gardasil has shown efficacy across diverse geographical regions and populations, further reinforcing its global potential in HPV prevention. Studies have indicated that Gardasil is effective not only in developed countries but also in low- and middle-income regions where HPV-related cancers, particularly cervical cancer, are more prevalent. By reducing the incidence of high-risk HPV strains, Gardasil contributes to a significant decline in pre-cancerous lesions, thereby lowering future cancer burden. This broad efficacy highlights Gardasil‘s role as a cornerstone in global public health initiatives aimed at reducing HPV-related disease rates, especially in underserved populations where access to healthcare and regular screening may be limited.

3.3 Side Effects

After Gardasil’s launch into the market, using clinical trials, researchers found that two doses of HPV vaccine were comparable with three doses [8]. Joura et al. conducted a study to check the efficacy and immunogenicity of the 9-valent Gardasil, comparing it to the immunogenicity of 4-valent Gardasil. They divided the women into two groups: one vaccinated with 9-valent Gardasil; the other vaccinated with 4-valent Gardasil. The study found that the immunogenicity for HPV 6, 11, 16, and 18 was similar between the 2 groups, and geometric mean titers (GMTs) remained similar as well about 2 years after the vaccination. The 9-valent vaccine efficacy for HPV 31, 33, 45, 51, and 58 was superior with the results of 97.4% [9]. And other studies have shown that Gardasil 9 is effective in preventing infection of 9 types of HPV. After assessing its immunogenicity, another question arises: is 9-valent Gardasil safe for women? Side effects found in the previous study include pain, rash, fever, fatigue, and itching sensation at inoculation site [9]. But other than those, no significant side effects were spotted. And the study included 72 breastfeeding women in clinical trials, and no adverse effects were found [9].

Because of inadequate study of pregnant women exposed to Gardasil vaccination, Gardasil is not recommended for pregnant women. However, according to limited clinical trial data, Gardasil is not found to cause adverse pregnancy outcomes, such as major malformations. Therefore, if a woman inadvertently took the vaccine during pregnancy, it is not necessary to consider termination of pregnancy [10].

4 Promoting Gardasil Worldwide

4.1 Specific Strategies to Promote the Gardasil Vaccine

As previous studies have shown, Gardasil is extremely effective in preventing targeted types of HPV. The immunogenicity and safety of Gardasil are its main attraction to the market. And the potential market for Gardasil is quite large: it is estimated that 85% of sexually active women and 91% of sexually active men acquire HPV at some point during their lifetime [11]. Since Gardasil vaccine has proven its effectiveness, and HPV can cause multiple types of cancer in both male and female, it is recommended that boys and girls take the vaccine before they start their sex-life (the earliest possible age for vaccination is 9).

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There are some districts in the United States that require HPV vaccination for school entry. By May 2024, HPV vaccine is required for secondary school in DC, Virginia, Rhode Island, and Hawaii. The goal set by the US Department of Health and Human Services is to achieve 80 percent of adolescents who receive recommended doses of the HPV vaccine [12]. These mandates reflect the growing recognition of Gardasil's critical role in reducing HPV transmission and preventing HPV-related cancers.

Expanding Gardasil's global reach will require continued efforts to raise awareness about the vaccine's benefits, address vaccine hesitancy, and ensure equitable access, particularly in regions where HPV-related cancers are most prevalent. This paper recommends several specific strategies to promote Gardasil vaccination. Over the past ten years, there has been an increase in the percentage of parents reporting safety concerns as the reason for HPV vaccine hesitancy [13]. Strategies to promote Gardasil should be able to address this concern, directly pointing out there is no scientific evidence that suggests Gardasil is not safe.

Social media has gained momentum in recent years, influencing and reaching more and more people worldwide. Thus, posting information about HPV and Gardasil vaccine via social media platforms is a good way to promote the Gardasil vaccination. This has been done before and produced good results. In 2012, PDPH (Philadelphia Department of Public Health) launched an advertising campaign called *3forME* on Facebook, which encouraged adolescents to take 3 doses of HPV vaccines. This project reached 155,110 adolescents, engaged 2107 adolescents per advertising campaign, and gained more than 3400 unique fans over the course of the project, showing the great potential for similar online campaigns [14]. The campaign has certainly raised awareness of HPV vaccination among Philadelphia adolescents. However, relying solely on an online campaign to get adolescents vaccinated is not effective enough.

Community workers can go door-to-door to talk with parents about HPV vaccines and make regular calls to people reminding them to get vaccinated. During these conversations, the use of personal experience and scientific data is recommended to address vaccine hesitancy [15]. Schools should utilize educational interventions such as pamphlets, movies, workshops, and consulting sessions to educate students on HPV vaccination [16]. This approach is highly recommended because of its significant effectiveness in improving vaccine acceptance [17].

Additionally, governments can consider providing financial incentives or free vaccination to low-income households, lowering the barrier of vaccination. Free vaccination was proven to be the most effective measure in Australia, and it will be especially helpful for developing countries [16].

4.2 Preventing Sexually Transmitted Infections

There are many other types of STIs (Sexually Transmitted Infections) besides HPV that are affecting people worldwide, including HIV (Human Immunodeficiency Virus), Syphilis, and Chlamydia. To prevent STIs, people should get vaccination when it is available.

In addition to vaccination, practicing safe sex is crucial. Correct and consistent use of condoms has been proven to lower the transmission risk for infections like HIV and chlamydia. Public health initiatives should reinforce these practices through education programs, particularly targeting youth and young adults, and provide easy access to condoms and STI testing. For at-risk populations, regular screenings and timely treatment are recommended to prevent further transmission, with healthcare providers and community organizations working to ensure these services are affordable and accessible, thereby supporting better overall sexual health.

5 Conclusion

HPV infection, responsible for 5% of human cancers, underscores the importance of prevention, with Gardasil emerging as a key vaccine. Using virus-like particles (VLPs) to stimulate antibodies against HPV's L1 protein, Gardasil offers immunity lasting at least 10 years. Clinical trials confirm that 9-valent Gardasil is as effective as the 4-valent version, offering broader protection against additional HPV strains. However, vaccine hesitancy remains a challenge. Strategies to increase vaccination rates include social media campaigns, community outreach, educational initiatives, and government-supported incentives, particularly in high-risk areas. Future research should focus on Gardasil's effects in specific groups, like pregnant women and transgender individuals, and assess its safety alongside other vaccines.

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