Proceedings of the 2nd International Conference on Environmental Geoscience and Earth Ecology
DOI: 10.54254/2753-8818/47/2024PJ0106

HPV vaccine development: Cervical cancer and broader implications for HPV-related malignancies

Xiaopeng Zhao

School of Life Sciences, Capital Normal University, Beijing, China

xxgk@cnu.edu.cn

Abstract. Cancer of the cervical region, which is caused by highly susceptible HPV types and serves as the fourth leading malignancy to develop in women worldwide, is the main public health objective of the HPV vaccine. Furthermore, it is imperative that you prevent genital warts and malignancies, including anal, oral, and vaginal cancers, that are associated with high risk HPV. Currently, nevertheless, there exist regional and national differences in the prevalence of HPV infection and vaccination as well as within various populations. In order to provide relevant recommendations for future research on the relevant situation, this paper analyzes the literature on the mechanism of action and application of the nine-valent and quadrivalent HPV vaccines, in addition to the technological innovation and development of vaccine R&D, challenges associated with vaccine R&D, and future development trends. Though future research can concentrate on the study of other cancers produced by HPV in other pertinent directions, this publication concentrates on the study of cervical cancers caused by high-risk HPV strains. Future research can look on linked cancers.

Keywords: HPV vaccine, nine-valent and quadrivalent HPV vaccines, mechanism, challenges, future development trends.

1. Introduction

A related study done in 2020 with data from 185 countries found that there were about 311,000 cancers of the cervical cavity deaths while 570,000 newly identified instances of the illness globally in 2018. Cancer of the cervical cavity is the 4th most common disease in women. At the same time, women in Eastern, Central, Southern, a`nd Western Africa die from cervical cancer at the highest rate. With a combined share of over one-third of cases and fatalities worldwide, China and India bear the largest burden of cervical cancer. This demonstrates how important it is to stop cervical cancer from developing.

2. Mechanism of action and related vaccines

The genetic code of HPV, a circular double-stranded DNA virus, has roughly 8,000 pair of bases. Two late structural proteins, L1 along with L2, as well as six early regulatory proteins, termed E1, E2, E4, E5, E6, and E7, are encoded by this genetic material [1]. The WHO encourages that countries vaccinate teenage girls toward HPV because secure and efficient vaccines have been available since 2006. The WHO has pre-qualified vaccines for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58, which are nine-valent and quadrivalent respectively [2]. While the HPV bivalent, quadrivalent, and nine-valent vaccinations protect against distinct HPV strains, their methods of action are largely similar. The following discussion

DOI: 10.54254/2753-8818/47/2024PJ0106

will center on the quadrivalent and nine-valent vaccines because they were the first to be licensed and because the nine-valent vaccine is the most complete.

2.1. Quadrivalent vaccine

90% of genital warts brought on by low-risk HPV6/11 viruses and almost 70% of cervical cancers brought on by HPV16/18 viruses are the targets of the quadrivalent vaccine. It contains HPV6, HPV11, HPV16, and HPV18 virus-like particles.

2.1.1. Safety assessment of HPV quadrivalent vaccine.

A comprehensive study conducted in Sweden involved 1,672,983 women aged between 10 and 30. The research demonstrated that the incidence of cervical cancer significantly decreased among those who received the quadrivalent HPV vaccine. The research data indicates that women who were vaccinated before turning 31 had a significantly lower cumulative incidence of cervical cancer, totaling 47 cases per 100,000 individuals. 94 cases of cervical cancer per 100,000 individuals were observed in women who were not vaccinated before reaching the age of 31, on the other hand. The incidence rate for women who were vaccinated and those who were not was 0.51 with a 95% confidence interval of 0.32-0.82 after age adjustment. Following the other variables' adjustment, the rate decreased to 0.37 with a 95% confidence interval of 0.21-0.57. The incidence rate for women who received vaccinations before the age of 17 had been 0.12, alongside a 95% CI that went from 0.00 to 0.34, and for women who received vaccinations between the ages of 17 and 30, the incidence rate was 0.47, alongside a 95% assurance duration spanning coming from 0.27 to 0.75, after all confounders were taken into account [3]. Although it is not a global relevant study, it can also generally indicate that the quadrivalent HPV vaccine can play a significant inhibitory effect on the prevention of cervical cancer, especially for young women. It provides relevant data support and foundation for the subsequent development of related HPV vaccines. Furthermore, the Cochrane study indicates that the quadrivalent vaccine may help males with anogenital warts and external genital lesions [4].

2.1.2. Mechanism of action of HPV quadrivalent vaccine

The quadrivalent HPV vaccination contains virus-like fragments (VLPs), which self-assemble from the L1 protein of each type of HPV. VLPs resemble actual viruses in structure, but they are not contagious because they lack viral genetic material. Because of their structure, VLPs can be identified by the immune system as foreign invaders, which sets off an immunological reaction. The immune system starts to create antibodies against these particular HPV kinds as soon as the vaccine is given because it detects the VLPs. By keeping the virus from penetrating the body's cells, these antibodies function by circulating throughout the bloodstream. When the right HPV type is exposed to them, their bodies react swiftly to neutralize the virus and stop it from entering the cells. This stops certain virus types from causing diseases like cervical cancer. Additionally, the vaccination aids in the development of memory immune cells, which, when coming into contact with the same virus a second and later times, activate and mount a potent defense.

2.2. Nine-valent vaccine

In addition to the four HPV strains (6, 11, 16, and 18) covered by its predecessor, the nine-valent HPV vaccine provides immunity against five more strains, including 31, 33, 45, 52, and 58, which is an extension of the quadrivalent version. The enhanced vaccine is capable of protecting against a wider variety of cancers, including cervical, vulvar, anal, and vaginal cancers, as well as genital warts. The additional types boost the effectiveness of prophylaxis against cervical cancer to ninety percent. The nine-valent vaccine received US FDA approval to be marketed in December 2014 [5].

A different approach VLP approach which incorporates the L1 proteins of all nine HPV strains is the septavalent vaccination. Following vaccination, the vaccine stimulates the production of certain antibody responses by the immune system against these HPV strains. These antibodies aid in preventing viral infections and the health problems they can bring in the future.

DOI: 10.54254/2753-8818/47/2024PJ0106

3. Global Status of HPV Vaccine Adoption

TA global appeal for the elimination of cervical cancer was initiated by the Director-General of the World Health Organization (WHO) in May 2018. The emphasis of the call was on the renewed dedication of global leaders to reach this objective and the encouragement of collaboration among all stakeholders involved. The announcement sparked a movement to unify efforts and resources for eradicating this disease worldwide. The World Health Assembly approved the Global Strategy for the Elimination of Cervical Cancer in August 2020.

3.1. Global status of vaccination and its impact on public health

Over the past ten years, there has been a notable increase in HPV vaccination rates worldwide [6]. More are in affluent nations where the HPV vaccine is part of regular immunization regimens. Widespread vaccination can significantly reduce the number of cases of HPV infection, cancer of the cervical cavity, and other cancers associated with the virus (including pharyngeal as well as anal cancer). Australia currently has a comprehensive immunization and cervical screening program in place. Studies indicate that the initiative has led to notable declines in both the occurrence and fatality rates associated with cervical cancer. This positive trend underscores the effectiveness of the program in combating this particular form of cancer [7].

Numerous vaccination initiatives have been put in place by various nations. In order to develop immunological protection prior to exposure to the virus, the majority of countries advise vaccination in early adolescence. Girls typically get vaccinated among the ages of 9 and 14. For the purpose of to help stop the spread of HPV and the malignancies it is linked to, some nations have also started to provide males with the HPV vaccine. By providing extra doses to older age groups or adults who had not had the vaccine before, several nations have increased the age range that the vaccine is effective against [8,9].

The necessity for all those under 26 that have yet to receive their entire dosage of the vaccine to obtain a catch-up shot is highlighted in the HPV immunization guidelines. While catch-up immunization is not always advised for adults between the ages of 27 and 45, it is advised that patients and healthcare professionals jointly decide whether to receive the vaccine. These updates highlight the value of vaccination, especially for younger people who have not yet contracted HPV, and the benefits of the vaccine in avoiding HPV infection and related malignancies. Studies on the health economics of adult vaccination in the current immunization programs have demonstrated that expanding vaccination coverage to older age groups results in lower cost savings [10].

3.2. Challenges of vaccination

SA study that addresses the obstacles and problems of Women that reside in countries with low or middle incomes (LMICs) ought to receive screening for cervical cancer suggests policies and initiatives to deal with these issues. The study demonstrates that there are a variety of human, societal, cultural, architectural obstacles to cervical cancer screening within the healthcare sector. In order to increase screening coverage, the conversation focused on the necessity of comprehensive legislative support, bolstering the capacity of the health system and community involvement. As the discourse draws to a close, it is imperative that clear policies be put in place to improve women's health equality through robust support from the healthcare sector, comprehensive community education, and campaigning to lower the disproportionate prevalence of cancer of the cervical cavity in LMICs as search.

In order to move closer to the objective of eradicating cervical cancer as a worldwide public health concern, the findings highlight the necessity of designing interventions specifically to meet the particular difficulties in these contexts [11].

This indicates that, even with the apparent benefits of HPV vaccination in the modern world, considerations regarding worldwide vaccine coverage remain. First, the expensive cost of the HPV vaccine can restrict the quantity that can be administered in low- and middle-income nations, as well as hinder its distribution and transportation [12].

DOI: 10.54254/2753-8818/47/2024PJ0106

The second concern is the level of HPV awareness. There are several nations where HPV is not well known. For instance, the HPV vaccine is not widely known in Indonesia. Nevertheless, relatively few people in Ethiopia are aware that sexual contact can spread infections caused by HPV, which is the main trigger of cancer of the cervical cavity [13,14].

The third argument is that varying cultural backgrounds could have influenced how various people view the HPV vaccine. In a multicultural neighborhood in Los Angeles, rejection of HPV vaccination was caused by false information about the vaccine and concerns about its side effects, which increased throughout the COVID-19 pandemic [15].

4. HPV Vaccine Research and Development

4.1. HPV Vaccine R&D Technology Innovation and Development

A nine-valent vaccine that covers more HPV types and provides more thorough and widespread protection has developed over time from the original bivalent and quadrivalent vaccines. Notable are a few of the active clinical trials for therapeutic HPV vaccinations. The design goals of such vaccines revolve around eliminating pre-existing infections caused by viruses and triggering a Th1-based cellular immune system response in the host, which delays or inhibits tumor progression. Clinical trials are currently being conducted for these vaccinations [16]. Furthermore, advancements have been achieved in developing the production of HPV vaccinations utilizing the utilization of the E. coli expression system. This approach to vaccine development has the advantage of being low cost and high yield, which provides up an exciting new path for HPV vaccine being adopted [17].

4.2. Challenges and future trends in vaccine development

The world's unequal distribution of HPV infection rates, which differ throughout populations and countries, is a major problem. As an illustration, sub-Saharan Africa, East Africa, and the Caribbean have the greatest number of people with HPV infection [18].

The second issue is the wide range in immunization status throughout nations worldwide.2019 saw 50% of women in high-income countries receive their first vaccination, and 40% of those women completed all recommended vaccinations. In contrast, women in middle- and low-income countries received their first vaccinations at 16% (95% CI: 8-31%), and 12% (5%-24%) of them accomplished all recommended vaccinations. Pilot or demonstration projects are among these initiatives that are frequently funded by different organizations in nations with low to middle incomes. Although the area covered is limited (which are usually a region of a country), the percentage of patients who complete of one dose can reach 93%, and the completion rate of two or three doses can achieve 70%–90%.The median HPV vaccination rate for the first dose was slightly higher (80%) in middle-income and low-income nations than it was in high-income countries (72%). Nonetheless, in comparison with high-income countries, the mean proportion of people in these nations who stopped taking their following doses after getting the first dose had been greater (18 percent vs. 11 percent) [19]. Furthermore, the nine-valent vaccine presently protects against most highly dangerous HPV strains; however, several HPV types are still unprotected. Future efforts to boost HPV vaccination rates worldwide, improve vaccination schedules, and advocate for immunization everywhere will be essential, particularly in regions with high infection rates. Public health is directly impacted by these initiatives, especially in the field of cervical cancer prevention and control. WHO has provided recommendations for HPV vaccination programs that could enhance vaccine access and coverage, including the potential for single-dose regimens [20].

It is expected that more effective vaccinations covering a wider range of HPV types will soon be created as science and technology continue to progress. Global collaboration is necessary in the interim to boost vaccination rates. Global disease surveillance should be carried out by international organizations to give WHO a strong platform on which to organize vaccination distribution programs. Low- and middle-income nations can receive financial assistance from international financial

DOI: 10.54254/2753-8818/47/2024PJ0106

institutions to buy vaccines or bolster technical support. Diversification of vaccines can be encouraged by means of international collaboration and experience sharing.

There are several obstacles to HPV vaccination across the globe in various nations and areas. An era of continuous technological innovation and progress, adherence to the WHO's recommendations and updates, international cooperation, and people's tenacious efforts will soon see an increase in rates of immunization and penetration of the HPV vaccine.

5. Conclusion

Preventing high-risk HPV variants from causing cervical cancer, which is the four most prevalent malignancy in women worldwide, is the primary goal of the HPV vaccine in terms of public health. Nevertheless, it's also critical to avoid malignancies including those of the mouth, throat, and vagina, as well as other genital warts brought on by high-risk HPV strains. The present state of the effectiveness mechanism and use of the nine-valent and quadrivalent HPV vaccines is covered in this publication. Future studies on the development of linked contents may find it useful as a reference. Vaccination against HPV has emerged as a global strategy for avoiding HPV infection and associated malignancies. However, there are differences in different nations, areas, and demographic groups when it comes to the prevalence of HPV infection and vaccination. This article provides an overview of current developments in HPV vaccine technologies, discusses potential obstacles and development trends in the future, and offers recommendations for how to effectively raise the worldwide HPV vaccination rate. Future research may concentrate on different aspects of other related HPV-caused malignancies, as this work concentrates on cervical cancers brought on by high-risk HPV strains. The goal of future international HPV vaccine research should be to raise vaccination rates and vaccine coverage, particularly in high-infection areas. In order to guarantee the vaccine's long-term efficacy, vaccination tactics must also be further investigated and improved. Research on public health interventions and policies is also crucial. Global cervical cancer prevention and control will undoubtedly prove greater in effectiveness.

References

[1] Wang R Pan W Jin L Huang W et al 2020 Human papillomavirus vaccine against cervical cancer: Opportunity and challenge Cancer Letters 471 88-102

[2] Porras C Tsang S H Herrero R et al 2020 Efficacy of the bivalent HPV vaccine against HPV 16/18-associated precancer: Long-term follow-up results from the Costa Rica Vaccine Trial Lancet Oncology 21 12 1643-1652

[3] Lei J Ploner A Elfström K M Wang J Roth A Fang F Sundström K Dillner J & Sparén P 2020 HPV vaccination and the risk of invasive cervical cancer New England Journal of Medicine 383 14 1340-1348

[4] Bergman H Buckley B S Villanueva G et al 2019 Comparison of different human papillomavirus HPV vaccine types and dose schedules for prevention of HPV-related disease in females and males Cochrane Database of Systematic Reviews 2019 11 Art No CD013479

[5] Vaccine Delivery Research and Innovation Laboratory 2023 Efficacy and safety of HPV vaccines

[6] Markowitz L E & Schiller J T 2021 Human papillomavirus vaccines Journal of Infectious Diseases 224 12 Suppl 2 S367-S378

[7] Garland S M Kjaer S K Muñoz N et al 2016 Impact and effectiveness of the quadrivalent human papillomavirus vaccine: A systematic review of 10 years of real-world experience Clinical Infectious Diseases 63 4 519-527

[8] Villa L L & Richtmann R 2023 HPV vaccination programs in LMIC: Is it time to optimize schedules and recommendations? Journal of Pediatrics Rio J 99 Suppl 1 S57-S61

[9] Bergman H Buckley B S Villanueva G Petkovic J Garritty C Lutje V Riveros-Balta A X Low N & Henschke N 2019 Comparison of different human papillomavirus HPV vaccine types and dose schedules for prevention of HPV-related disease in females and males Cochrane Database of Systematic Reviews 2019 11

DOI: 10.54254/2753-8818/47/2024PJ0106

[10] Meites E Szilagyi P G Chesson H W Unger E R Romero J R & Markowitz L E 2019 Human papillomavirus vaccination for adults: Updated recommendations of the Advisory Committee on Immunization Practices MMWR Morbidity and Mortality Weekly Report 68 32 698-702
[11] Petersen Z Jaca A Ginindza T G et al 2022 Barriers to uptake of cervical cancer screening services in low-and-middle-income countries: A systematic review BMC Women's Health 22 486
[12] Guillaume D Waheed D E Schleiff M Muralidharan K K Vorsters A & Limaye R J 2024 Global perspectives of determinants influencing HPV vaccine introduction and scale-up in low- and middle-income countries PLOS One 19 1 e0291990
[13] Khatiwada M Kartasasmita C Mediani H S Delprat C Van Hal G & Dochez C 2021 Knowledge attitude and acceptability of the human papilloma virus vaccine and vaccination among university students in Indonesia Frontiers in Public Health 9 616456
[14] Dereje N Ashenafi A Abera A et al 2021 Knowledge and acceptance of HPV vaccination and its associated factors among parents of daughters in Addis Ababa Ethiopia: A community-based cross-sectional study Infectious Agents and Cancer 16 58
[15] Shin M B Sloan K E Martinez B et al 2023 Examining multilevel influences on parental HPV vaccine hesitancy among multiethnic communities in Los Angeles: A qualitative analysis BMC Public Health 23 545
[16] Xu X Q You T T Hu S Y Qiao Y L Zhao F H 2021 Global development of human papillomavirus vaccination guidelines: A systematic review Chinese Medical Journal 101 1890-1898
[17] Zhang S Y Wang Z P Gu R et al 2023 Progress in the development of human papillomavirus vaccines based on the E coli expression system China Food and Drug Regulation 12 42-49
[18] HPV Centre Statistics on HPV infection Retrieved from https: / / hpvcentre. net/ statistics/ reports/ XWX. pdf?t= 1716157527932
[19] VaxLab Evidence on HPV vaccination and inclusion in national immunization programs Retrieved from https://vaxlab.dukekunshan.edu.cn/evidence-db-media/hpv-vax-media/hpv-vaccination-and-inclusion-in-national-immunization-programs/
[20] World Health Organization 2022 WHO updates recommendations on HPV vaccination schedule Retrieved from https://www.who.int/zh/news/item/20-12-2022-WHO-updates-recommendations-on-HPV- vaccination- schedule