Proceedings of the 2nd International Conference on Biological Engineering and Medical Science (ICBioMed 2022), Part I
DOI: 10.54254/2753-8818/3/20220486

HPV Relevant Diseases and Vaccines, Analysis of Willingness to Vaccinate in Chinese Population and the Significance of Male Vaccination

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Abstract. As a virus that commonly infects various populations, HPV has many types and can lead to many diseases and even malignant tumors. In this paper, the author mainly introduces HPV typing, the diseases that will cause it, and the current situation of HPV preventive vaccines, including the mechanism and types of preventive vaccines, as well as the willingness to vaccinate specific groups in some areas of China. At the end of this paper, the importance and necessity of HPV preventive vaccination for men are introduced. This paper can provide some help for future scholars in the improvement and innovation of HPV preventive vaccines, and provide some ideas and help in the direction of vaccination for male groups.

Keywords: HPV, HPV vaccine, Vaccination intention, Male vaccination, HPV Relevant Diseases

1. Introduction

HPV refers to the human papillomavirus, one of the most prevalent viruses in the world. Its classification is very much, divided into high-risk and low-risk types. The probability of HPV infection in women 's life is 80 %. And 80 % of the infected people who are infected 8 months - 1 year can rely on their immune system to clear the virus. Only persistent infection of high-risk HPV may cause malignant tumors. Cervical cancer caused by high-risk HPV is one of the major malignant tumors that endanger women 's health. Cervical cancer is the second most common female malignancy in China, with an annual incidence of about 25 % of new cases worldwide [1].

For people infected with HPV caused by a variety of diseases, there are many ways to treat it. Such as cervical cancer, and skin tumors can be removed by surgery. For patients who cannot tolerate surgery or diseases that occur in special sites, photodynamic therapy can be selected [1]. In addition, there are HPV therapeutic vaccines. Although there are many different treatments for different diseases, some diseases are prone to relapse, and therapeutic vaccines progress slowly relative to preventive vaccines. Therefore, for HPV, prevention is greater than treatment, and vaccination can effectively prevent HPV.

According to the follow-up results of a randomized clinical trial in the United States, the preventive effect of Cervarix on CIN II and above caused by HPV16,18 was 100 %, and the preventive rate of cervical precancerous lesions was 97.4 % [2]. According to statistics on vaccination of U.S. nationals in 2018 and 2019, the HPV vaccination rate reached 68.1 % [3] among women aged 13-17 and 53.6 %

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DOI: 10.54254/2753-8818/3/20220486

[4] among women aged 18-26. This shows the universality and importance of vaccination. In China, due to the small number of vaccines on the market and the large population of the right age, vaccines are in short supply. Even if most people are willing to get vaccinated, they are deterred by the lack of vaccine supply and the high cost of vaccination. The main content of this article outlines the typing of HPV, the status of vaccines, and the willingness of Chinese nationals to vaccinate, and the need for men to be vaccinated.

2. Diseases caused by HPV

HPV is a very large family, so far found more than 200 HPV subtypes. HPV virus is a double-stranded DNA virus that can specifically infect epithelial cells of skin and mucosa. About 70 % of HPV infection is only transient infection. Only when the cervical epithelial cells are continuously infected for more than ten years, the abnormal hyperplasia of cervical epithelial tissue will eventually develop into cervical cancer. Different types of HPV can cause different clinical manifestations. According to the different sites of invasion, it can be divided into low-risk skin type, high-risk skin type, low-risk mucosal type, and high-risk mucosal type (TABLE 1).

Table 1. HPV typing and diseases.

Categories	HPV typing	Diseases
Low-risk skin type	1,2,3,4,7,10,12,15 etc.	causing common warts, flat warts, plantar warts, and other symptoms
High-risk skin type	5,8,14,17,20,36,38 etc.	causing vulva cancer, penile cancer, anal cancer, prostate cancer, bladder cancer
Low-risk mucosal type	6,11,13,32,34,40,42,43,44,54 etc.	causing condyloma acuminatum; infected genital, anal, oropharyngeal, esophageal mucosa
High-risk mucosal type	16,18,30,31,33,35,53,39 etc.	causing cervical cancer, rectal cancer, oral cancer, tonsil cancer

It is well known that women can be infected by HPV. For women, the susceptible sites include the cervix, anus, rectum, vagina, vulva, etc. In many types of the most serious is HPV 16,18, high risk of cancer, easy to cause cervical cancer in women. In addition, women may also suffer from vaginal cancer, vulvar cancer, etc. Although HPV6, 11 is a low-risk type, also needs to be alert, they can cause a person to suffer from condyloma.

Besides women can be infected by HPV, HPV can also infect men, male susceptible sites include the anus, penis, oropharynx, etc. According to statistics, adult healthy men who can detect HPV in the penis account for about 16 % to 69 % of the total [5]. More than 90 % of genital warts are caused by HPV type 6 and 11 infections, and 25 to 29 years old is the most common age for men to develop genital warts [6]. Most warts form within 2-3 months after HPV infection, and about 30 % will automatically subside. In addition to genital warts, men are also at risk of HPV-related cancers such as penile cancer, anal cancer, and oral cancer. Some statistical results show that the incidence of oropharyngeal cancer and other oropharyngeal-related cancers caused by HPV infection in male groups in some countries has increased dramatically [7]. Compared with the prevalence of HPV in women, the prevalence of HPV-positive oropharyngeal cancer and oral cancer in men was significantly higher than that in women [8]. There is a big gap between the prevalence of men and women, probably because of the differences between men and women in sexual behavior and some personal hobbies are not the same. In addition, because HPV infection is mainly transmitted through sexual behavior, among all-male groups, homosexuals and HIV-infected men have a higher proportion of HPV anal infections (≥ 90 %) than heterosexual men [9].

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3. Preventive HPV vaccine

Preventive HPV vaccination is an economical and effective means of preventing a range of diseases caused by HPV, especially cervical cancer in women. According to the data and results of a large number of studies, the immune response of HPV hosts can play an important role in the control of HPV infection and related diseases [10]. Therefore, the mechanism of HPV preventive vaccine is mainly VLPs assembled by L1 proteins obtained from different expression systems, with virus-like particles as target antigens [11], thereby inducing virus neutralizing antibodies and memory effects in vivo, and ultimately protecting the body from HPV infection. VLPs are non-enveloped viroid particles with neutralizing epitopes on the surface, which can induce the body to produce high titers of anti-L1 antibody IgG and IgA, thereby protecting the body from viral infection. After vaccination, the antibody response reached the expected peak, and the antibody concentration decreased after 12-18 months, and then stabilized at an effective level, thereby achieving protection against viral infection [10]. The preventive HPV vaccines that have been marketed are all based on this mechanism. At present, there are three kinds of HPV preventive vaccines that have been marketed globally, namely the bivalent vaccine Cervarix, the tetravalent vaccine Gardasil and the nine-valent vaccine Gardasil 9.

The earliest cervical cancer vaccine was Gardasil, a tetravalent HPV vaccine produced by Merck, which was approved by the US FDA in June 2006. The tetravalent vaccine includes VLPs of two high-risk HPV (16,18) and two low-risk HPV (6,11). It can prevent genital cancer and precancerous lesions and condyloma. This vaccine is suitable for women aged 20-45 years. According to a large number of clinical data, about 70 % of cervical cancer can be prevented by Gardasil [2].

GlaxoSmithKline's bivalent HPV vaccine Cervarix was approved by the US FDA in October 2009. Different from the tetravalent HPV vaccine Gardasil, the bivalent vaccine is made of virus-like particles composed of L1 proteins on the two most pathogenic high-risk HPV types 16 and 18. This protein cannot replicate itself and cannot further infect living cells [10]. Therefore, Cervarix can only prevent two high-risk HPV types - HPV16,18. In December 2019, the first domestic bivalent HPV vaccine produced by Xiamen Wantai Canghai Biotechnology Co. Ltd was approved. As a result, China became the third country to independently supply HPV vaccines after the United States and the United Kingdom. The first domestic HPV vaccine in China uses E. coli as the expression system, which is efficient and simple and reduces production costs [2]. According to clinical trial data, the Chinese domestic bivalent vaccine for HPV16,18-related precancerous lesions protection rate of 100 %, and in the prevention of HPV16,18 persistent infection, a protection rate of 97.7 % [12].

Nine-valent vaccine covers HPV16,18,6,11,31,33,45,52,58, a total of nine types. It is the most comprehensive HPV vaccine covering the HPV virus spectrum, but it is also relatively expensive. The nine-valent vaccine Gardasil 9 produced by Merck was approved by the US FDA in December 2014. Gardasil 9 prevents five high-risk HPV types not included in Cervarix and prevents approximately 90 % of cervical cancer in women and approximately 80 % to 95 % of other HPV-related anal genital cancers in women aged 16-26 years [2].

The nine-valent HPV vaccine was launched in mainland China in April 2018. However, China’s domestic nine-valent vaccine, the optimistic estimate will not be approved after 2025. Although there is no possibility for China's domestic nine-valent vaccine to be marketed, the approval of the new nine-valent vaccine issued on August 30, 2022, has attracted the attention of the whole society. According to the website of the State Drug Administration of China, the nine-valent human papillomavirus vaccine (Saccharomyces cerevisiae), also known as the nine-valent HPV vaccine, has been expanded in indications, and the applicable population has been expanded to 9-45 years old women. On the same day, Merck Sharp & Dohme also released the same message. The approval of this new indication means that women aged 9-15 and 27-45 can also choose a nine-valent HPV vaccine, and the age of vaccination is extended to a wider range. This has given more women in China the opportunity to be vaccinated and has also helped more women in China to stay away from the invasion of HPV infection-related diseases, including cervical cancer.

DOI: 10.54254/2753-8818/3/20220486

4. Vaccination intention

According to the survey data of multiple groups on the vaccination willingness of various populations, there are significant differences between men and women.

For example, Hu Shuyi and others investigated the cognition of HPV and its vaccine among female college students in Shanghai, China [13]. The survey of HPV and HPV vaccines among female college students (average age 18-22) in four universities in Shanghai yielded the following findings (TABLE 2).

Table 2. Awareness rate of HPV and its vaccine (female college students) (redrawn from [13]).

Relevant question	Awareness rate
Know HPV	69.3%
Know that HPV can cause some diseases	58.7%
Know the main route of transmission of HPV	41.4
Know HPV vaccine	67.7%
Know the type of HPV vaccine	79%（ nine-valent ）
Vaccinated	8.4%
Willing to vaccinate HPV vaccine (unvaccinated)	79.6%
Reasons for reluctance to vaccinate against HPV (unvaccinated)	Concerns about vaccine safety and timeliness 54.2% Unaware of the HPV vaccine 44.5% Not clear where to vaccinate 29% Higher price 27.6%

It can be seen from the table that some female college students in Shanghai, China, have a very low understanding of HPV-related information. The proportion of people who have heard of HPV is similar to the proportion of people who know about HPV vaccines. While most students know there's a nine-valent vaccine, a small number don't understand the other types. Although there are not a few students who know the vaccine, the vaccination rate is still very low. Among all the female college students surveyed, the number of people who have been vaccinated is even less than one-tenth of the total number. Among those who have been vaccinated, 79 % have been vaccinated with the nine-valent vaccine. Although most students are not vaccinated, many of them want to be vaccinated in the future, and they clearly express their willingness to be vaccinated. Among the unvaccinated, the general reason for the reluctance to vaccinate is to worry about the potential dangers of the vaccine or not understand the vaccine, there is also part of the reason that is not yet universal in China, the vaccine is more expensive, and other issues.

In Zhang Hong et al 's survey of HPV vaccine cognition and vaccination attitude of obstetrics and gynecology nurses in Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology [14], the average age of the nurses surveyed was 21-47 years old. The results of the survey are as follows (TABLE 3).

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Table 3. HPV Vaccine Awareness and Attitude (obstetrics and gynecology nurses) (redrawn from [14]).

	Relevant question	Rate of the right answer
Awareness of HPV vaccines	Know that the HPV vaccine can prevent disease	Cervical cancer (98.62 %) Laryngeal papilloma (5.53 %) Genital warts (4.61 %) Penile cancer (3.23 %)
	Know the HPV vaccination population	Non-pregnant women (98.16 %) Males (28.57 %)
	Know the best age for vaccination	68.66%
	Know the HPV vaccination process	34.1%
Attitude towards HPV vaccination	Willing to vaccinate HPV vaccine	66.82%
	Willing to suggest other people get vaccinated	31.8%
	Can accept HPV vaccine as the age-appropriate population must be vaccinated vaccine	67.74%
	Reasons for reluctance to vaccinate	Suspected vaccine effectiveness (70.83 %) Worried about adverse reactions (66.67 %) Expensive (22.22 %)

According to Zhang Hong et al 's research on the cognition and vaccination attitude of obstetrics and gynecology nurses on the HPV vaccine, almost half of the people have an understanding of the function of the HPV vaccine, the population of vaccination, and the age of appropriate vaccination. But generally speaking, the understanding of the HPV vaccine has been relatively good. In the survey of attitudes towards HPV vaccination, most people expressed their willingness to be vaccinated against HPV, but only a small number of people were willing to recommend vaccination to those around them. Among the people who are unwilling to vaccinate, the main reason maybe is that they are worried about the effectiveness and safety of the vaccine.

These surveys show that even in an international metropolis like Shanghai in China, very few women know the basics of vaccines and have been vaccinated. Of course, doctors, nurses, and other professional medical workers know more about the HPV vaccine than other people. And whether nurses or female college students, there are more than half of the people expressed their willingness to HPV vaccination, and the existence of the vaccine is very easy to accept. Although there is a problem with low vaccination rates, it may be because in China HPV vaccine is not fully universal to every region and the vaccine supply is not sufficient to support such a large demand for vaccination age groups. For some women, they are generally concerned about the safety and effectiveness of the vaccine, as well as the high price of the vaccine, so they choose not to vaccinate or are unwilling to vaccinate.

In addition to the above research based on women as the research object, there are also research surveys for male groups. Wu Yinji et al investigated the cognition of adult males in the Lishui District of Nanjing City, China on the HPV vaccine and the influencing factors of vaccination willingness [15]. In the survey, adult males over 18 years old were investigated. In the form of questions, the survey

DOI: 10.54254/2753-8818/3/20220486

investigated men's knowledge of HPV, HPV disease, HPV vaccine, and so on. 90 % of people answered the question about whether cervical cancer screening should be done after vaccination. The lowest rate of correct answers is about the difference between different types of the HPV vaccine, whether men and women can be injected with the HPV vaccine, HPV, and what diseases.

Most men know HPV and its vaccines, but they do not know too much about it. According to the survey results on the willingness to vaccinate, 48.61 % of the men had the willingness to vaccinate, and the willingness to vaccinate was significantly different from the age, education, occupation, and whether they had heard of the HPV vaccine.

According to the results of the above survey, the willingness of men to vaccinate is generally lower than that of women. The possible reasons are that men do not know about the HPV vaccine, do not think that men should be vaccinated against the HPV vaccine, and the cost of vaccination is too high. And because most men do not understand HPV and its hazards, they are not aware of the necessity of vaccination.

5. Importance of HPV vaccination for men

With the development of HPV vaccines, people have realized the impact of HPV on women's health and the necessity of vaccination. When it comes to HPV, it is often only considered that only women will be infected, so male HPV infection is rarely concerned, and the harm of HPV to men cannot be ignored. With the increasingly free and open sexual orientation and sexual behavior in modern society, the male HPV infection rate is increasing year by year [16]. The results of HPV infection in men are no less than those in women. Men will develop genital warts, affect the function of male reproductive organs, and even lead to infertility or some malignant tumors.

HPV infection in men will reduce the fertility of men and increase the abortion rate of female partners. Because HPV can reduce sperm motility by infecting sperm, resulting in normal sperm morphology changes, and ultimately lead to poor semen quality, thus affecting male fertility. Therefore, sometimes a considerable part of the population of infertility is due to men [16]. HPV infection in men addition leads to decreased sperm motility, and even men are at risk of oropharyngeal cancer, anal cancer, and penile cancer. Therefore, male vaccination is particularly important.

According to the results of a study, the HPV vaccine for the prevention of male anal genital infection caused by HPV16 (continuous contact > 6 months) the effective rate was 46.9 %, and for the prevention of persistent oral HPV infection effective rate was 88 %, prevention of anal intraepithelial neoplasia grade 2 and grade 3 effective rates were 61.9 %, 46.8 % [17]. This shows that the HPV vaccine can effectively prevent male HPV infection [16].

According to a survey of 1767 young people in the United States, the experimental group was given a quadrivalent vaccine, and the HPV infection rate in the mouth and anus of the vaccinated group (22.9 %) was lower than that of the unvaccinated group (31.6 %), and the study showed that the effectiveness of HPV vaccine decreased with age, so this shows the effectiveness of HPV vaccine for men and the necessity of early vaccination [18].

It is necessary for men to vaccinate not only for their safety but also for the health of their female partners. Because men are the main disseminators of the HPV virus, men are more active in spreading the HPV virus, so men vaccinated with the HPV vaccine can protect their partners. According to relevant research results, only when both men and women are vaccinated with the HPV vaccine and the vaccination rate reaches 75 %, it is possible to eliminate HPV16 and 18 viruses that cause cervical cancer as soon as possible [15].

Now the United States, Australia, Scotland, Austria, Canada, and other countries, have recommended to men should be vaccinated against HPV. In Australia, HPV vaccine universal coverage is very high, with female vaccine coverage of up to 80 %, male coverage of 76 % of its population HPV infection, and the incidence of related diseases decreased significantly [18]. As early as October 5, 2018, the FDA approved a supplementary application for Gardasil 9 to be administered to women and men aged 27 to 45 [19].

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The above research and results show the necessity and importance of vaccination for male groups. Just because many men do not understand the importance of HPV vaccination, lack of awareness of HPV can lead to male diseases and cancer, more importantly, the current domestic HPV vaccine in short supply led to the current Chinese domestic those suitable for vaccination of men and women have no chance to play a rare vaccine. In the future, when more Chinese HPV vaccine market, will eventually usher in both men and women can be vaccinated.

6. Conclusion

Due to the prevalence of HPV, HPV preventive vaccination is increasingly important. At present, the HPV vaccine has been very popular in many countries, and the vaccination rate is very high. It is only because of the insufficient supply and a large number of people in China that the vaccination rate is low.

This paper summarizes the situation of male and female vaccination in China and analyzes other scholars ' research on the cognition, vaccination, and vaccination willingness of some male and female groups. This paper also summarizes the problem of men's low willingness to vaccinate and analyzes the possible reasons for this problem due to men's low understanding of HPV. It also summarizes and analyzes the recent news of the new nine-valent vaccine in China. Extending the vaccination age is tantamount to good news so that more people can get the opportunity to prevent HPV. Because HPV infection in men is usually not paid much attention to and men do not have awareness of HPV vaccination, the male vaccination rate and willingness to vaccinate are very low. Therefore, the paper also summarizes the importance of male vaccination, both to protect their health and reduce the risk of female partners infected with the virus.

Through this paper, the author hopes that more men and women of age in remote areas can be vaccinated against HPV. It can promote and even establish relevant policy systems for future male vaccination. And the country can carry out the popularization of HPV-related knowledge nationwide according to the current situation so that more people can understand the virus. Countries can also formulate relevant laws and regulations to promote the development and circulation of more vaccines and even reduce the cost of vaccination so that more people can be vaccinated against HPV, reduce the incidence of HPV-related diseases, and ultimately eliminate HPV as much as possible.

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