

Research progress of HPV vaccine for preventing damage from HPV infection

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Abstract. Human papillomavirus virus is one of the common infectious diseases in the world. HPV causes around 90% of the cervical cancers [1] and other diseases in males, females and bisexuals. In this article, the HPV vaccine is discussed as an effective way to prevent HPV intervention. The currently available HPV vaccines are 2, 4 and 9 valent which are all included in this article. The 2-valent targets 16, 18 types of HPV, the 4-valent and 9-valent can target 6, 11, 16, 18; 6, 11, 16, 18, 31, 33, 45, 52, and 58 types of HPV. The target populations of these 3 HPV vaccines are similar. Need to mention that many gender populations (males, females and bisexuals included) are all encouraged to take HPV vaccine at certain ages. The limitations of HPV vaccines cause the inhibition of the prevention of HPV and low inoculation rates worldwide, especially in developing countries. Limitations include inoculation age, target HPV types and vaccine price. This article also proposes a future tendency of research may on resolving these restrictions and promoting HPV vaccines in teenagers.

Keywords: HPV, Clinical, Vaccines, Treatment.

1. Introduction

Human papillomavirus virus (HPV) is an infectious disease. Definition of HPV is a collection of more than 200 types of branched viruses. HPV mostly has no symptoms unless it causes certain diseases. Serious consequences include cervical, vaginal, vulvar, penile, anal, oropharyngeal cancers and reproduction organs warts [1]. HPV is a virus that, in the vast majority of instances (90%), fades away on its own within two years without causing any health consequences. However, if HPV does not go away, it can lead to health issues such as genital warts and cancer (CDC 2). After a person contracts HPV, cancer can more than 10 years to develop into noticeable diseases. It seems impossible to predict a certain population may acquire cancer or other health issues as a result of HPV. People with weakened immune systems (such as HIV carriers) may easier be infected with HPV and are more susceptible to HPV-related health issues.

Unfortunately, HPV is not curable till today. There is no medical technique to destroy or remove HPV in the human body once people got infected. However, the prevention of HPV is highly efficient for the majority population. Based on it sexually transmitted, condoms used during sexual activities between heterosexuals and homosexuals are showing positive effects. In Winer's (2006) study, the risk of being infected by HPV type 6, 11, 16, 18 of women in condom-protected relationships is 51.5% lower than in unprotected heterosexual sexual activities relationships [1]. Consistent condom usage by sexually active women's partners appears to minimize the incidence of cervical HPV infection.

Another way efficiently prevents HPV, there are vaccines available. The HPV vaccine is first approved in 2006 in the United State [2].

In this article, different types of vaccines are discussed, 2, 4 and 9-valent. Also, include the effectiveness and applications of these three types of vaccines. Limitations of vaccines will be explained and initiate research area in the future.

2. General mechanism

HPV is a double-stranded DNA virus with early and late-stage genes that relate to different phases of viral infection. These vaccines are primarily intended to stimulate the body's cell-mediated immune

system response to respond against the E6 and E7 proteins, which are generated early in the infectious cycle and would allow for prompt treatment [3].

HPV vaccinations for prevention focus on humoral immunity. Preventive HPV vaccinations provide L1 and/or L2 viral capsid proteins encoded by HPV virus-like particles (VLPs). B cells attach to HPV VLPs and are stimulated to become plasma cells, which release antibodies, by TH2 (differentiated CD4+ T helper cells). These neutralizing antibodies prevent HPV infection in the first place, resulting in HPV protection [4].

Non-infectious recombinant type-specific L1 capsid proteins packaged into viral-like particles (VLPs) serve as immunogens in all three vaccinations. The produced recombinant L1 capsids self-assemble into 72 pentamers with an external surface that closely resembles HPV virions, and it is this multiplicity of L1 domains that confers immunogenicity to the VLP antigen, even in the absence of immune modulators [5].

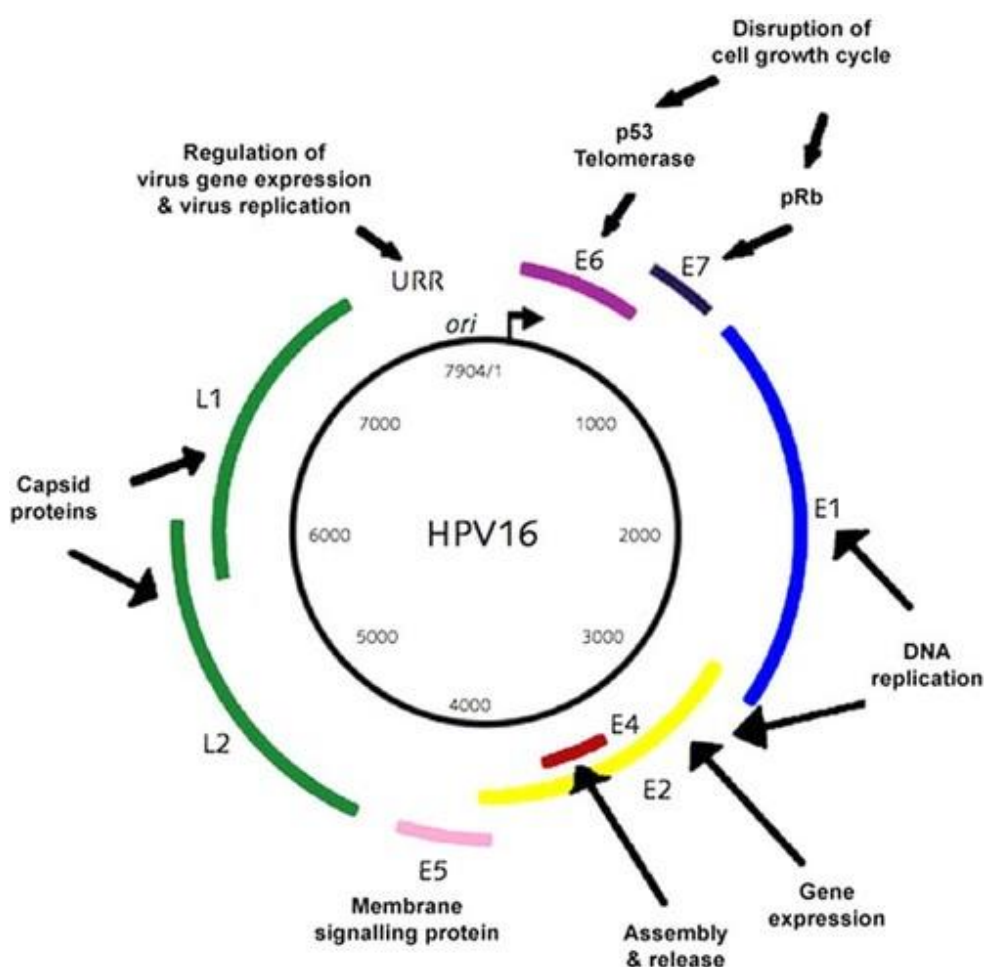


Figure 1. General structure of HPV [3].

Preventive HPV vaccinations that are now available on the market. Quadrivalent HPV L1 VLP vaccination that includes L1 VLP from HPV-6, 11, 16, and 18. It has been demonstrated to be particularly effective in protecting people against four of the most clinically important HPV strains, including HPV-6 and 11 for benign genital warts and HPV-16 and 18 for cervical malignancies [4].

To conclude, the aim of the HPV vaccine is to create a prevention system in the human body to avoid the infection of HPV.

The picture shows the mechanism of HPV preventive vaccine manufacturing. Based on the domain of the HPV L1 coding sequence, the sequence is amplified in eukaryote, and prokaryote. Yeast and *E. coli* is used as eukaryote and prokaryote. CervarixTM (2-valent), GardasilTM-9 (9-valent) are developed in eukaryotic system; CecolinTM and GelcolinTM are in prokaryotic system. And then HPV-VLP is made that could use on human body.

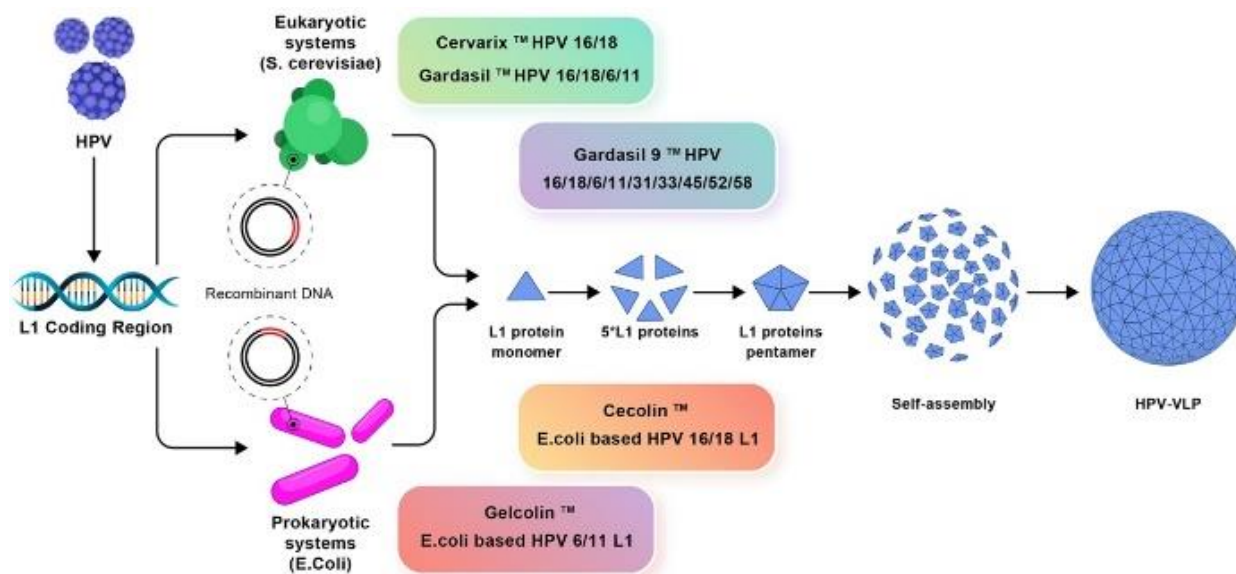


Figure 2. The mechanisms of preventive vaccine manufacturing [6].

3. Types of HPV vaccine

2-Valent

The 2-Valent vaccine is commonly known as Cervarix™, made by GlaxoSmithKline, Rixensart, Belgium. It was approved by Food and Drug Administration (FDA) in 2009 for female between 9 to 26 years old [7]. Actually, bivalent vaccine is produced 3 years after 4-valent vaccine. Type 16 and 18 is overlapping in these two vaccines, but FDA mentioned that 2-valent is specific on preventing cervical cancer for female between 9-26 years old.

It mainly targets type 16, 18 HPV which are the major cause of invasive cervical cancer [8]. Bivalent is now not the first for people to choose because of the success 4-valent and 9-valent vaccines. However, it is still an effective way for the countries do not have enough supply for 4-valent and 9-valent vaccines. Since bivalent can prevent type 16, 18 which are the high-risk types cause many cancers and 50% of cervical malignancies. In China, most people choose to take 2-valent vaccines to get projection while waiting for 4-valent and 9-valent vaccines. 2 and 3 doses of 2-valent are both accepted.

4-Valent

Both the 4-Valent and 2-Valent HPV vaccines are made up of capsid antigen L1 virus-like particles that appear like natural virions and produce immunity, but they are not infectious [4].

The quadrivalent vaccine to the public is Gardasil®, produced by Merck & Co, Inc., Whitehouse Station, New Jersey. FDA approved it first in 2006 for female between 9 to 26 years old [9].

It also targets type 16, 18 HPV, but also HPV 6 and 11. Type 6, 11 are the main cause of external genital warts [10]. Compare to bivalent vaccine, genital warts are prevented which 90% cause by type 6 and 11 HPV [11]. There are 3 doses for Gardasil® and it is recommended to take all 3 doses to have nearly 100% protection [12]. However, it is same with 2-valent vaccine, both 2 and 3 dosages of 2-valent work functionally.

9-Valent

Gardasil®9 is the known vaccine that can target the most types of HPV. The FDA authorized it in 2014 for use in girls 9 to 26 years old and men 9 to 15 years old [9]. They are included but are not limited to types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Accepting 3 doses is defined as a full vaccination.

HPV vaccination has been included in an increasing number of national immunisation regimens since the vaccine became available in 2006. HPV vaccine was originally introduced in the United States, Canada, Australia, and the United Kingdom, and was shortly followed by other European and high-income nations.

According to the previous study, 18-24 years old females in Australia decrease 75-80% risk of 4 types of HPV (HPV 6, 11, 16, 18) after getting full doses of the 4-valent vaccine [13]. Also in previous research, nearly 90% of people were protected against these two kinds of cervical cancer, which account for roughly 70% of all cervical malignancies [14]. In further development, 9-valent vaccine shows around 71% declining risks of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 [15]. Furthermore, by combining the direct action of the nonvalent vaccination with the cross-protection of bivalent and quadrivalent vaccines, HPV 6/11/16/18/31/33/45/52/58 is reduced. Data of the effectiveness of males are still not available since the small number of participants and samples.

HPV has been established as the leading cause of cervical cancer and dysplasia in clinical and molecular epidemiologic studies (5,6). The genes of high-risk HPVs (most typically, types 16, 18, 31, and 45) are detected in virtually all cervical malignancies, and the relative frequency with which these kinds are found is very comparable in most locations of the world (6,7). HPV16 is identified in around 50% of cervical malignancies, with HPV18, 31, and 45 accounting for the remaining 25%–30% of HPV-positive cancers [5]. The table shows approved years of types of vaccines in the US by The U.S. FDA. The main HPV types that different vaccines can prevent. Decreased risk shows the vaccine effectiveness in adult female based on previous research [2].

Table 1. Summary of 2, 4, 9 valent HPV vaccines.

HPV Vaccine	Approved Year	Main Target HPV Types	Decreased Risk
9-valent	2014	HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58	71% [15]
4-valent	2006	HPV 6, 11, 16, 18	75-80% [13]
2-valent	2009	HPV 16, 18	90% [14]

The bivalent, quadrivalent, and 9-valent HPV vaccinations are typically well accepted, with the most frequent adverse event being a moderate and self-limited injection site response. Other commonly reported occurrences do not appear to be more common in vaccination receivers compared to non-vaccine recipients, nor in HPV vaccine recipients compared to non-vaccine recipients [16].

4. The Population Targeted

The Advisory Committee on Immunization Practices (ACIP) encouraged 11-12 years old females to get the HPV vaccine in 2006. Males were added and encouraged in 2011. In vaccinated people, VLP vaccinations minimize the risk of HPV-related illness. HPV vaccinations that protect against cervical cancer and genital warts should preferably be given before sexual activity begins in order to achieve the greatest public health benefit [17].

There was a misunderstanding that males do not need to take the HPV vaccine in 2009 in the US [2]. But now male is also encouraged to have completed 3 doses of vaccines [2]. In adolescents and males 16 to 26 years old, preventive treatment of quadrivalent HPV vaccination is effective in avoiding the occurrence of external genital lesions caused by infection with HPV-6, 11, 16, or 18 [18]. Males can be infected with the human papillomavirus (HPV) and develop HPV-related illnesses. Examples of diseases are external genital warts, anogenital infection and penile cancers. Also, males may transmit HPV to their partners (this includes homosexual and heterosexual partners) which can make them sick.

Table 2. ACIP recommendations of 4-valent HPV vaccine which was licensed in the US [2].

Recommendation Year	Female	Male
2006	11 or 12 years to 26*	/
2009	11 or 12 years to 26*	9-26 years*
2011	11 or 12 years to 26*	11 or 12 years to 21* Vaccination is suggested for males who have homosexual sex and are immunocompromised (including HIV infection) until they are 26 years old. *

* ACIP recommended 3 doses for vaccines at 0, 1–2, and 6-month intervals

5. Limitations

HPV is one of the frequent sexually transmitted illnesses among sexually active teenagers and young people all over the world. HPV is transferred mostly through sexual intercourse and direct skin-to-skin contact, with penetrative sex being the most prevalent mode of transmission [19]. However, vaccines cannot prevent HPV in the population already exposed to HPV. HPV vaccines are encouraged for both girls and boys to inoculate early from 9-11 years old. The main purpose is to get HPV vaccine protection before having sexual activities. The HPV vaccine does not protect against infection caused by HPV types that a person has been exposed to before immunization. Based on early study, Individuals who have already been infected with the matching HPV type see a significant reduction in vaccine efficacy. This confirms the suggestion that boys to be vaccinated early in order to get maximum immunization coverage before they begin sexual activity [20].

The vaccination also has no effect on the development of HPV infection or illness caused by HPV. The basic mechanism shows that HPV vaccines cannot destroy HPV in the human body. Prevention is the main purpose of HPV vaccines. In future encounters with HPV, vaccinations drive the body to create antibodies that attach to the virus and prevent it from infecting cells. Therefore, if the human bodies already get infected by HPV and cells are damaged, HPV vaccines are not proper treatments. Instead, treatments object to certain diseases or cancers are needed.

Vaccines do not protect against all HPV types (more than 200 types). The majority of presently available vaccinations may primarily target 9 types of HPV. Luckily to see these 9 types are the main HPV types that cause diseases and cancers in the human body. However, there is still a limit to the sorts of viruses that may cause diseases and need to be prevented. In other words, HPV cannot be fully prevented based on current vaccine technology.

Geographic, policies, and storage reasons limit the inoculation rate even in developed countries. In the National Immunization Survey of 2014 statistics, in teenagers, only 38% of 13- to 17-year-old females and 31% of 13- to 17-year-old boys in Hawai'i have received the HPV vaccination [21]. Refrigerate between 2 and 8°C (36 and 46°F) [22]. Do not allow yourself to get frozen. If the vaccination has been frozen, it should be discarded. Protect yourself from the sun. The high requirement of storage creates restrictions in many areas [22].

The high cost of transport and storage lead to the high price of vaccines for both individuals and society, especially in developing countries. In China, the HPV vaccine is not included in health insurance coverage. 3 doses of a 9-valent HPV vaccine cost around 360 dollars [23]. Cost \$360 million at \$5 per dosage in the 33 Latin American and Caribbean countries, and \$1.25 billion at \$19.50 per dose. This amount of money will barely be enough to vaccinate 70% of 12-year-olds [24]. High costs to people and countries inhibit the promotion of HPV in many developing countries, in order to cause a low inoculation rate and less prevention from HPV. Also causes a constrain on HPV interventions.

6. Future Development And Suggestion

High-risk HPVs can lead to a variety of cancers. HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 are among the 14 high-risk HPV kinds. 9-valent HPV prevention covers type 6, 11, 16, 18, 31, 33, 45, 52, and 58. In the future, the new research area could be focused on discovering new techniques to improve vaccines to prevent more types of HPV.

Also, finding ways to decrease the cost of storage and transportation of vaccines in developing countries is significant for providing efficient vaccine inoculations. The goal is to let everyone under any social determination can afford HPV vaccines and access the capacity to vaccines in all countries.

Promoting vaccines in young age population groups is essential. A study showed, young female teenagers in the US have a low inoculation rate. The methodologies used in the research resulted in increased levels of HPV-related awareness, vaccination intentions, and vaccination rates among female teenagers in the US [25].

7. Conclusion

According to previous studies, HPV vaccines show significant roles in the prevention and control. The effectiveness is high for the types of HPV that cause the majority of diseases and cancers. However, there the inoculation rate is low in developing and developed countries. HPV vaccines are faced by populations of all genders (including bisexuals) in any relationship. HPV is one of the most powerful methods to prevent HPV currently. The research illustrated that there are many restrictions on vaccines. These limitations include early inoculation and storage requirements. These might be the reasons for the low inoculation rate in the world. The other reason is the less information on teaching and promotion of HPV vaccines, there are many studies that show education to college students gave the positive outcome.

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