**REVIEW ARTICLE :**

# HPV vaccine development after more than ten years approval

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## ABSTRACT

At present, ten years have passed since the human papillomavirus (HPV) vaccine was first approved for use in humans. Research related to HPV vaccine, both in terms of effectiveness and immugenicity in its development, has been widely carried out, such as in terms of the indications of the HPV vaccine use that is not only for preventing cervical cancer, the guidelines for administering 2-dose HPV vaccines for those under 15 years of age, and the discovery of the latest HPV vaccine types: nonavalent HPV vaccine. This review literature discusses all aspects of the development of HPV vaccine since it was first approved for use in humans in 2006.

**Keywords:** HPV; effectiveness; immunogenicity; HPV nonavalent

## ABSTRAK

Saat ini, sepuluh tahun telah berlalu sejak vaksin human papillomavirus (HPV) pertama kali disetujui untuk digunakan pada manusia. Penelitian terkait vaksin HPV, baik dari segi effectiveness dan immugenicity dalam perkembangannya, telah banyak dilakukan, seperti dalam hal indikasi penggunaan vaksin HPV yang tidak hanya mencegah kanker serviks, panduan pemberian vaksin HPV 2 dosis untuk usia dibawah 15 tahun, dan penemuan jenis vaksin HPV terbaru: vaksin HPV nonavalent. Literatur review ini membahas semua aspek perkembangan vaksin HPV sejak pertama kali disetujui untuk digunakan pada manusia pada tahun 2006.

**Kata kunci:** HPV; efektivitas; imunogenisitas; HPV nonavalent

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## INTRODUCTION

The United States Food and Drug Administration (FDA) approved the use of quadrivalent HPV vaccines in 2006 to prevent cervical cancer and genital warts, followed by the use of bivalent HPV vaccines to prevent cervical cancer in 2009. Since 2006 until now there have been many research developments and guidelines use of HPV vaccine. Indications for the administration of HPV vaccines have also experienced a lot of development. The FDA approved the use of a quadrivalent HPV vaccine to prevent anal cancer (2010) and approved the administration of a quadrivalent HPV vaccine for boys (2009). The administration method has also developed. At present adolescents of less than 15 years obtained only 2 injections, no more 3 injections. Studies are also developing to observe the immunogenicity and effectiveness of HPV vaccine. The latest development is the approval of a nonavalent HPV vaccine by the FDA in 2014 which is able to provide protection against 9 types of HPV. There are currently three vaccines available: bivalent (HPV 16 and 18), quadrivalent (HPV 6,11,16 and 18) and nonavalent (HPV 6,11, 16, 18, 31,33,45, 52,58).

## IMMUNOGENICITY AND EFFECTIVENESS

Immunogenicity is the ability of a vaccine to evoke an immune response, while effectiveness is the amount of decrease in the incidence of a disease after the administration of a vaccine. A study conducted by Einstein shows that the administration of a bivalent vaccine induces a higher immune response than the administration of a quadrivalent vaccine in all age groups between 18-45 years.[1] However, the results of the study did not illustrate the correlation with protection against clinical abnormalities in the cervix because the end-point of this study was not an abnormality in the cervix, but only measured antibody titers after the vaccine administration. Whether bivalent vaccine is more effective in reducing the incidence of cervical cancer than quadrivalent vaccine, still needs further research

A study conducted by Zhu shows that seroconversion occurs in 99-100% of women who receive HPV vaccine.[2] After a natural infection, seroconversion only occurs in 70-80% and the produced antibodies are not effective in preventing cervical abnormalities. This further supports the importance of vaccines in preventing HPV infections.

Several studies have shown that the administration of HPV vaccine is effective in reducing the incidence of cervical lesions. A study conducted by Herweijer in Sweden on more than a few million women aged 13-29 years who received HPV showed that the administration of HPV vaccine reduced the incidence of high-grade cervical lesions by 75% in women who received the vaccine before the age of 17 years and by 46% in women who received the vaccine in age 17-19 years.[3] A study by Konno in Japan on women aged 20-29 years showed that vaccinated women had a 69% lower risk of the incidence of high-grade pre-cancerous lesions than women who were not vaccinated.[4] A meta-analysis conducted by Drolet in 14 countries, with a sample of more than 60 million women vaccinated with HPV, showed HPV infections 16 and 18 decreased by 83% in women aged 15-19 years and decreased by 66% in women aged 20-24 years. The prevalence of cervical pre-cancerous lesions decreased by 51% in women aged 15-19 years and decreased by 31% in women aged 20-24 years.[5] Hariri's study involving more than 7,000 women showed a decrease in high-grade cervical pre-cancerous lesions in the vaccinated group. The reduction in the incidence of high-grade cervical pre-cancerous lesions reaches 72% in vaccinated women.[6]

To date, studies have shown good immunogenicity after the administration of HPV vaccine and effective administration of the vaccine reduces the risk of cervical pre-cancerous lesions. The effect of HPV vaccine on decreasing cervical cancer incidence still cannot be observed considering the natural course of change from normal cervix to cervical cancer requires a very long time. However, at least until now the HPV vaccine has been able to reduce the incidence of pre-cervical cancerous lesions, which are the stages before becoming cervical cancer.

Several studies have shown the effectiveness of the HPV vaccine in reducing the risk of genital warts. A study conducted in Spain on female adolescents aged 14-19 years showed a reduction in the incidence of genital warts by 77% after administering 3 doses of quadrivalent vaccine.[7] A study conducted in Sweden showed a decrease in genital warts by 80% in female adolescents who were given with quadrivalent HPV vaccines at the age of 14-16 years and by 93% in female adolescents who were given with quadrivalent HPV vaccines before the age of 14 years.[8] A study conducted in Australia showed a decrease in the incidence of genital warts after quadrivalent HPV vaccine delivery by 81.8% in women under 21 years of age and by 51.1% in women aged 21-30 years.[9]

Until now, the administration of HPV vaccine does not need to be repeated after complete administration. Another study shows that antibody titers against HPV last a long time. Antibodies to HPV after HPV vaccine administration are estimated to last up to 15 years, even

the level of these antibodies in the 15th year remains higher than antibodies after natural HPV infection.[10]

## HPV VACCINE FOR MALE ADOLESCENTS

Since 2009, the FDA has approved the use of HPV vaccine in male adolescents to prevent genital warts. About 90% of genital warts are caused by HPV 6 and 11. In 2010, the FDA approved the administration of HPV vaccines for women and men to prevent anal cancer and at this time the United States, Canada, the United Kingdom and various other countries recommend administering HPV vaccine to male adolescents.

A randomized controlled trial study involving 4065 men aged 16-26 in 18 countries showed that HPV vaccine reduced 89.4% of the incidence of condyloma accuminata. In addition, this study also showed a decrease in the incidence of genital lesions (including condyloma accuminata, penile intraepithelial lesions, perianal intraepithelial lesions, perium intraepithelial lesions, penile cancer, perianal cancer, and perineal cancer) by 65.5%.[11]

The Advisory Committee on Immunization Practices (ACIP), the body responsible for immunization, provides guidance on the administration of quadrivalent vaccines to male children aged 11-12 years and male adolescents aged 13-26 years who have not received HPV vaccination. For ages 27 years and older ACIP does not recommend routine HPV vaccine administration, but it is adjusted according to individual needs.[12] Guidelines for administering HPV vaccines in the UK recommend vaccinating all male adolescents aged 13-25 years.

Indications for providing HPV vaccine to males are not intended to prevent cervical cancer, but rather to prevent diseases caused by HPV such as genital warts, anal cancer, perianal cancer, and penile cancer. In its development, the administration of HPV vaccine to males can also be given to males aged over 26 years. A study shows that the quadrivalent HPV vaccine given to males aged 27-45 years is able to generate immune response, and seroconversion was found in all study samples.[13] However, further studies are still needed to determine the effectiveness of HPV vaccine in males over the age of 26 years. Various guidelines for administering HPV vaccines in several countries recommend the administration of quadrivalent HPV vaccines for males up to the age of 26 years. For ages over 26 years, it is adjusted for special needs.

## HPV VACCINE IN A DOSE OF TWO INJECTIONS

When HPV was first approved for use in humans, the vaccine, both bivalent and quadrivalent, was given in three doses. In 2013, Dobson conducted a study on 830 women divided into girls (aged 9-13 years) and adolescent girls (aged 16-26 years) and gave a 3-dose quadrivalent HPV vaccine (0-2-6) to a group of adolescent girls and 2 (0-6) or 3 doses (0-2-6) for groups of girls, and then antibody levels were observed up to 36 months post-vaccination. The results of this study indicated that the group of girls who received 2 doses was not more inferior than the group of girls who received 3 doses. In fact, a group of girls who received 2 doses produced the same level of antibodies as those who received 3 doses.[14]

A study on 2-dose injections for bivalent vaccines shows that the 9-14 years age group receiving 2 doses (0-6 or 0-12) produce antibody level similar to that in 15-25 years age group receiving 3 doses (0-1- 6). In this study, the administration of 2 doses of the vaccine were divided into 2 groups: the group receiving vaccine at 6-month intervals and the group at 12-month intervals. Both 2 doses groups of produced antibody levels similar to the group receiving 3 doses.[15]

At present, various guidelines from world professional organizations recommend the provision of 2-dose vaccines for women aged less than 15 years, both by administering bivalent HPV vaccine, quadrivalent HPV vaccine, and nonavalent HPV vaccine. The World Health Organization provides guidelines for administering 2-dose HPV vaccines with all three types of vaccines available (bivalent, quadrivalent and nonavalent) for females aged 9-14 years. The interval of 2 doses administration is 6 months and the maximum interval is 12-15 months. If the second interval of the dose is less than 5 months, then a third injection should be given at a minimum interval of 6 months from the first injection.

## NONAVALENT HPV VACCINE

The development of a 9 valence (9v)/nonavalent HPV vaccine started with clinical trials in 2009, and was then approved by the FDA in 2014. The 9v HPV vaccine provides protection against 9 types of HPV: 2 types of low risk HPV (HPV 6 and 11) and 7 types of high risk HPV (16, 18, 31, 33, 45, 52, 58). The HPV9v vaccine can prevent genital warts and cancers caused by HPV. In the United States, quadrivalent vaccines have been withdrawn from circulation since 2016 and replaced by nonavalent HPV vaccines.

A study showed that after vaccination with a nonavalent HPV vaccine, seroconversion occurs in 100% of studied participants and the antibodies produced at that time showed a survival of up to 2 years. The resulting antibody titer is still being followed-up in further studies.[16] Another study involving 1935 research samples showed that antibody titers against 9 types of HPV contained in nonavalent HPV vaccines lasted for 60 months in 77.5-100% of the study sample.[17]

A randomized controlled trial study of 14,215 women aged 19-26 showed that the levels of antibodies against HPV 6, 11, 16 and 18 produced by nonavalent HPV vaccine were the same as those produced by quadrivalent vaccine. The incidence of high-grade intraepithelial neoplasia, adenocarcinoma in situ and cervical cancer caused by HPV 31, 33, 45, 52 and 58 (additional types of HPV in nonavalent HPV vaccines, which are not present in quadrivalent HPV vaccines) are smaller in group receiving nonavalent HPV vaccine (1/5945) compared with those receiving quadrivalent HPV vaccine (27/5943).[18]

The number of virus-like particles (VLP) and adjuvants in nonavalent HPV vaccines is higher than quadrivalent HPV vaccines and can have greater side effects. Research shows that the group receiving nonavalent HPV vaccine had more side effects at the injection site than the group receiving quadrivalent vaccine (90.7% vs 84.9%). These side effects are mild such as: pain, swelling, erythema and itching at the injection site.[18]

Food and drug administration of the United States of America approves the use of nonavalent HPV vaccines for use in females of 26-45 years. The effectiveness of vaccines given to females over 26 years of age is still underway. The advantages and disadvantages of HPV vaccine for people over 26 years must be discussed in depth. At present the guidelines for administering HPV vaccine are that three doses should be administered to females aged 15-26 years (0-1-6) and two doses (0-6) should be administered to females aged 9-14 years.

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