

Listing and Comparing the Immunogenicity, Safety, and Effectiveness of 9vHPV Vaccinations for Different Age Groups: 9-15 Years Old, 16-26 Years Old, 27-45 Years Old

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Abstract. The effectiveness of the Human Papillomavirus (HPV) vaccination in preventing high-risk HPV infections and accompanying serious vaginal, cervical, and vulvar disorders was verified. The development of the 9-valent HPV(9vHPV) vaccine yields greater coverage versus the quadrivalent (qHPV) vaccine. This study aims to assess the 9vHPV from immunogenicity, safety, and effectiveness in three different age groups respectively: 9-15 years old, 16-26 years old, and 27-45 years old. This paper searched PubMed and Embase databases to include related clinical trials of these three age groups and ensure a large-scale study population. Immunogenicity analysis for different age groups reported that the geometric mean titers (GMTs) decreased with age but could still stimulate robust and effective immune responses. The antibody levels of the subjects significantly increased to reach protective levels and persisted for a long time after vaccination. Besides, the 9vHPV vaccine has a high protective effect against the infection of nine subtypes of HPV. Both HPV infection rates and rates of associated diseases significantly decreased versus those who did not receive the vaccine. Additionally, the outcomes also demonstrated that the safety of the 9vHPV vaccines was good across all age groups. The intensity of most reported injection-site adverse events (AEs) and vaccine-related systemic AEs were not serious. Serious adverse reactions are very rare. In total, immunogenicity, efficacy, and safety in different age groups of the 9vHPV vaccination are overall good. These findings provide scientific evidence for the immunization of the 9vHPV vaccine and recommend the optimal age for vaccination.

Keywords: HPV vaccine; nine valent; effectiveness; immunogenicity; safety.

1. Introduction

HPV infection, a frequently occurring disease which can be transmitted by sex, is able to result in various types of cancers. Bivalent, quadrivalent, and nine-valent vaccines are being used to prevent related diseases. Among these three vaccines, the nine-valent vaccine is an important preventive measure, providing broad-spectrum protection against nine types of HPV [1].

Advisory Committee on Immunization Practices (ACIP) suggests that the encouraged age range for HPV vaccination is from 11 to 12, but the vaccine can be given at the age of 9. For people younger than the age of 26, if the first vaccine was given before the age of 15 and the following vaccine was administered 5 months later, only two doses in total are needed, otherwise, three doses in total are needed. However, for people who are immunocompromised and/or HIV-infected, three doses are needed. For people older than age 26 years, vaccination is not recommended because most people have already been exposed to HPV, which can weaken the effectiveness of the vaccine [2].

The nine-valent vaccination, one of three varieties, received commercial approval for the first time in 2014, and many post-market studies were conducted after the approval, assessing safety, effectiveness as well as immunogenicity by monitoring vaccine recipients. Till now, many short-term studies and some interim analyses (often 8 years) of long-term studies were published, but a review of all these studies is lacking. Furthermore, there are variations in the HPV nine-valent vaccine's safety, efficacy, and immunogenicity when given to different age groups, but there is little article that reviews the three groups comprehensively. In order to better understand how the vaccine is used

across a variety of age groups, this article will evaluate pertinent information on its administration in the age categories of 9-15, 16-26, and 27-45.

To ensure a comprehensive and high-quality review, PubMed and Embase databases were used to collect relevant information. All included papers were written in English. Papers were excluded when they did not meet the grouping conditions of this study (9-15, 16-26, 27-45). The integration of current research that were published within the last five years is the main goal of this review, although some papers published earlier than five years ago are also included to gather important information. This review focuses three aspects of the nine-valent HPV vaccination in three age groups. Besides, this review discusses possible reasons why immune responses are different when 9-valent vaccines are administered to different age groups.

2. Immunogenicity, Safety, and Effectiveness of the 9-valent Vaccine among 9-15 age group

2.1. Immunogenicity

When given to the 9–15 age range, the vaccination results in high seroconversion rates and strong immune responses. The highest GMTs are always be seen at Month 7 post-vaccination and gradually decline over time. These results confirm the 9-valent HPV vaccine's capacity to produce a protective immunity against relevant diseases.

The result of an interim analysis (8 years) of a long-term study supported the common time (Month 7) when the highest GMTs are induced. The study also found seropositivity rates remained >90% at month 90 [3]. An RCT done in Tanzania found more than 98% participants were seropositive to both HPV16 and HPV18 [4]. Because this RCT focused on one dose vaccination, the corresponding result could be used to evaluate if the one-dose vaccination strategy is valid. A phase III study conducted in Latin America found that over 99.3% of the PPI (per-protocol immunogenicity) population who got the vaccine experienced seroconversion to the 9 HPV types by the common time. Besides, GMTs peaked at the common time and then steadily fell over the following months, plateauing for all individuals at month 36 [5]. The majority of girls and boys in an Indian clinical study who received the vaccination by month 7 seroconverted to each nine HPV type. After the common time, anti-HPV GMTs decreased, with the biggest drops happening between months 7 and 12 [6]. All PPI individuals achieved seroconversion for each HPV type by the common time, based on the study carried out in Vietnam. And at that time, strong GMTs were also seen for all nine HPV types [7]. Similarly, an open-label phase III study conducted in Japan showed that the seroconversion rate for the included 100 girls was 100% at the common time, and this high rate was maintained for two years (month 30). The GMTs for each type of HPV vaccine peaked at month 7 and gradually declined through month 30 [8].

2.2. Safety

The studies consistently show that the 9-valent HPV vaccination typically has a good safety characteristic. Injection site responses and transitory systemic symptoms are two frequently happening AEs. It is important to note that serious AEs are rare and the reported events are manageable.

During the long-lasting monitoring period in one study, no SAEs connected to vaccines or medical procedures were reported. There were also no instances of participant mortality [3]. The three-dose course of the vaccine was safe, according to the results of the phase III research carried out in Latin America. In this study, the injection site was the site of the most frequent AEs, which were recorded in 86.0% of girls and 76.9% of boys who received the 9vHPV vaccination. The most frequently observed injection-site reaction was pain. Swelling and erythema were two less common injection-site responses. Additionally, systemic AEs of the vaccine were reported by around 30% girls and boys, with headache and pyrexia being the most common. It is noteworthy that a Peruvian kid aged

10 suffered an asthma attack the day after getting the first dose of the 9vHPV vaccination. The next day, this youngster was admitted to the hospital for treatment, and one day later, he was fully recovered [5]. In the clinical study conducted in India, AEs were reported within 15 days following vaccinations by 85 out of 122 girls (69.7%) and 42 out of 72 boys (58.3%). Injection-site responses were the most typical AEs, and pyrexia took up the greatest proportion of systemic AEs. No death or other serious outcomes due to the vaccination were reported [6]. The open-label phase III study conducted in Japan reported a 96.0% incidence of vaccine-related clinical AEs. Injection-site pain (93%) was the most prevalent, followed by swelling (42%) and erythema (33%) at the injection site. The majority of the AEs were modest in severity, and no negative outcomes materialized [8]. Out of 266,647 doses given, a total of 22 AEs after vaccination (AEFIs) were documented in a real-life study done in Puglia, Italy. Of these AEFIs, about 77% were recorded in participants between the ages of 9 and 15, and three of these events were considered severe. However, only one of three events were deemed as vaccine-related [9].

2.3. Effectiveness

The 9-valent vaccine demonstrates high efficacy against specific diseases.

The interim analysis revealed that no incidences of genital warts or high-grade intraepithelial neoplasia related to the nine HPV types were documented. Over a six-month period, the incidence rates of these nine types related persistent infection were below 50 per 10,000 person-years both for male and female [3]. An immunobridging analysis found one dose of vaccination could generate sufficient protection against HPV related-diseases for girls, providing positive information for one-dose strategy [4].

3. Immunogenicity, Safety, and Effectiveness of the 9-valent Vaccine among 16-26 age group

3.1. Immunogenicity

The 16-26 age group always shows strong seroconversion rates and robust GMTs one month after the third vaccination. Most noteworthy is the higher GMTs when 9-valent vaccines are administered to younger women or girls.

Almost all individuals seroconverted to nine HPV types at the common time, according to a phase 3 open-label research. Subgroup analysis based on age (16-20, 21-26) within the research demonstrated higher GMTs among the younger age group [10]. Another open-label, phase 3 trial conducted in Vietnam indicated that all PPI-eligible participants achieved seroconversion for each HPV type at the scheduled time. Robust GMTs were also observed at that time [7]. It worths mentioning concentrations of GMTs in 9-15 age group is slightly higher compared with 16-26 age group. According to a clinical experiment conducted in India, all 25 participants achieved seroconversion for each targeted HPV type, and strong GMTs were seen [6]. Besides, a study done in Latin America found that over 99% of the PPI population seroconverted by month 7, with peak GMTs at this time point. In this study, the seropositive rate remained high at month 60, ranging from 77% to 100% [5].

3.2. Safety

In general, the 9-valent vaccine is safe for 16-26 women and men. Pain, swelling, as well as erythema, are the three most frequently happening injection-site AEs. Although AEs happened, most of them were not serious in severity. Additionally, only a small number of SAEs were thought to be vaccine-related. Also, no fatality was thought to be germane to vaccinations.

In a phase 3 international open-label study, no vaccine-related SAEs or deaths were reported. Pain (82.8%), swelling (23.3%), and erythema (16.9%) were the three most commonly seen injection-site AEs. Meanwhile, headache (12.6%), pyrexia (3.0%), and fatigue (2.8%) were the three dominant

vaccine-related systemic AEs. Within five days of receiving any immunization, 3.5% of women reported elevated temperatures, with the majority of those readings falling between 37.8°C and 38.9°C [10]. Injection-site AEs were recorded in 50.5% of Chinese women aged 20 to 26 in another phase 3 research conducted in China, while 57.1% of the participants suffered systematic AEs. There were no SAEs, withdrawals owing to AEs, or fatalities associated with vaccinations [11]. In a clinical trial done in India, 56.0% of women experienced AEs within 15 days after receiving any 9-valent HPV vaccination [6]. Based on the research conducted in Latin America, the majority of AEs occurring within 15 days of vaccination were injection-site-related (89.6%). Consistent with other studies, pain, swelling, and erythema were commonly seen as injection-site related events, with intensities ranging from mild to moderate. After receiving the 9-valent vaccination, 31.4% of participants reported having vaccine-related systemic AEs, with headache and pyrexia dominating. It is worth mentioning that one serious vaccine-related AE was reported. 11 hours after taking the third dose, a 26-year-old Brazilian lady reported having a high temperature (38.6°C), headache, bodily discomfort, and lethargy. Symptoms of this girl worsened over the next 12 hours but she recovered the following day after receiving symptomatic treatment [5].

3.3. Effectiveness

In summary, the 9-valent vaccine demonstrates high effectiveness against certain diseases in 16-26 age group. When compared to a quadrivalent vaccination, the 9-valent vaccine's effectiveness is likewise quite high.

Women who were negative for the studied HPV types before vaccination proved the 9-valent HPV vaccine's high efficacy, which was recorded in a review of three worldwide, randomized, double-blind studies. The incidences of high-grade CIN, cervical surgeries, and high-grade vulvar and vaginal diseases were significantly reduced by about 98.2%, 97.8% and 100%, compared to placebo [12]. The vaccine is quite useful in reducing incidences of relevant diseases. Moreover, a study conducted in Scandinavia found the vaccine was efficacious due to the fact that no newly developed serious disease was found. The vaccine's effectiveness was believed to sustain for at least 6 years, as evidenced by control chart analysis showing no points crossing the pre-specified sigma limits [13]. Another study found the 9-valent vaccine demonstrated an efficacy of 92.3% (95% CI 54.4, 99.6) compared to the quadrivalent vaccine for high-grade cervical, vulvar, and vaginal diseases associated with HPV types that can only be covered by the 9-valent one (HPV31/33/45/52/58). Cervical diseases regardless of the grade, the efficacy reached 98% (95% CI 88.9, 99.9). Furthermore, the vaccine's effectiveness against 6-month persistent infection of the five HPV types was approximately 95% [5].

4. Immunogenicity, Safety, and Effectiveness of the 9-valent Vaccine among 27-45 age group

4.1. Immunogenicity

Most participants of this age group seroconverted at Month 7. Some studies presented non-inferiority of GMTs when compared with younger age groups.

An international open-label phase 3 study found seroconversion percentages were more than 99% for each HPV type. Besides, results of GMTs showed non-inferiority when compared with the 16-26 age group (HPV16/18/31/33/45/52/58), because the lower limit of GMTs ratio's 95% confidence interval was from 0.60 to 0.67 [10]. More than 99% of participants in a phase 3 open-label trial seroconverted by the same month. Chinese women's immune responses to a three-dose course of the 9vHPV vaccination in this age group were comparable to those of Chinese younger women in the age range 20-26 [11].

4.2. Safety

In general, the 9-valent vaccine is well tolerated for 27-45 years old people

Injection site AEs happened to slightly more than 85% participants, while systemic AEs that were relevant to the vaccine happened to slightly lower than 25% participants, proved by an international open-label phase 3 research. The most frequent injection AEs were pain (82.8%), edema (23.3%) and erythema (16.9%). AEs were not serious in severity. Throughout the trial, no SAEs or fatalities linked to vaccinations were noted. Headache (13.6%), pyrexia (1.7%), and tiredness (3.4%) were the most frequent systemic AEs associated with vaccinations. Within 5 days after receiving any immunization, 2.5% of participants reported having raised temperatures, most of them were from 37.8°C to 38.9°C [10].

4.3. Effectiveness

Because studies proved non-inferiority in the 27-45 age group versus the 16-26 age group, some researchers reckon that findings about the effectiveness of the 9-valent vaccine in the younger group can be bridged to the older group. However, since many women was infected by HPV at 27 years old, the effectiveness may be limited. In fact, there is little study testing the effectiveness of the 9-valent vaccine in the 27-45 age group.

5. Age-dependent Differences in Immune Responses for Two Main Reasons.

5.1. Differences in Immune Response

The most striking feature of in lymphatic system is the depletion of immature T cells and a significant imbalance in mutual effect of T cell and B cell in old age [14]. The gradual decrease of new T cells and memory T cells bring out the overall shrinkage of T cell repository. Therefore, the immune system cannot respond to neoantigens in a timely and effective way [15]. The efficacy and effectiveness of vaccines decline for immune functions decreasing with age [16]. The immune system of young people versus the old is usually more sensitive, with higher immunogenicity to vaccines and the ability to produce a stronger immune response. Therefore, younger people can establish a lasting immunological memory after vaccination. This means they may be more likely to receive long-term immune protection.

5.2. Effects of Previous Infections

There are multiple subtypes of human papillomavirus, and the 9-valent vaccination can prevent nine common high-risk HPV infections (HPV 6/11/16/18/31/33/45/52/58). However, people growing with age are more likely to have been infected with certain HPV subtypes before vaccination. Up to 63% of women possibly have HPV infection 4 years after sexual debut [17]. It is recognized that there is no efficacy of HPV vaccinations against existing HPV, but they are preventive. (6/11/16/18/31/33/45/52/58) infection or disease [18]. Therefore, vaccines may not provide complete protection for previously infected individuals, and the immune effect on this specific subtype may be reduced.

6. Discussion

The 9vHPV vaccine can protect against HPV6/11/16/18 as the qHPV vaccine. And the 9vHPV prevents persistent infections linked to HPV31-, 33-, 45-, 52-, and 58, as well as high-grade cervical, vulvar, and vaginal diseases [5]. Persistent infection outcomes associated with high-risk HPV types and illnesses were effectively prevented by the vaccination (Table 1). In 2016, the World Health Organization revised its stance by recommending that HPV vaccines be administered to girls in multiple age groups (9-14 years old) when introducing vaccines in a country, rather than to a single cohort [19]. The combined immunogenicity analysis of five studies about nine-valent HPV vaccine also revealed that GMT decreased with age in female aged 9 to 26 years old [20]. There is the greatest vaccine utility when the nine-valent HPV vaccination is given to those individuals who are susceptible people as a means of prophylaxis. Both girls and boys are supported to entail

immunization before sexual debut because they are unlikely to be exposed to HPV [21]. Expanding the target population for vaccination may help accelerate the impact of vaccination plans on public health.

Table 1. Vaccine efficacy of women aged 16-26.

Author year	Location	Endpoint	Vaccine efficacy (95% CI)
Susanne K. Kjaer et al.	Denmark, Norway, and Sweden	HPV16/18/31/33/45/52/58-related diseases	100 (79.4–100)
Warner K Huh et al.	18 countries	HPV31/33/45/52/58-12 months' persistent infection	96.7 (95.1 to 97.9)
Ángela María Ruiz-Sternberg et al.	Latin American	HPV31/33/45/52/58-persistent infection	95.2 (92.7, 97.0)
S. M. Garland et al.	Asian participants	HPV-31/33/45/52/58-persistent infection ≥ 12 months	93.9 (81.4–98.4)

7. Conclusion

To sum up, the 9-valent vaccine demonstrates good safety, immunogenicity, and effectiveness among the three age groups. In all studies, the 9-valent vaccine induced high seroconversion percentages (>95%) and robust GMTs for each nine HPV type. It worths to mention that GMTs always peak at Month 7 and then decline in the following months but maintain high levels around Month 60. There is evidence that shows one-dose strategy for girls under 15 years old is sufficient, but more results regarding comparing one dose vaccine with two-dose or three-dose vaccine are needed.

Not so many studies focus on people older than 26. The first explanation is the high incidence of past HPV exposure. Besides, women of this age group tend to get vaccination because they are at a higher risk, so confounders are difficult to control. Additionally, people older than 27 are not recommended to administer 9-valent vaccines.

Although a proportion of participants suffer from AEs, it's undeniable that the 9-valent vaccine demonstrates safety. The most typical injection-site AE is pain, whereas the most typical systematic AE is headache. SAEs are seen from time to time, but few of them are considered to be vaccine-related. Also, no death is considered to be relevant to the vaccine.

The 9-valent vaccine is effective since it can significantly reduce incidence rates of certain diseases. When the 9-valent vaccine is contrasted with other types of vaccine, the same or higher efficacy is also observed.

This review has some advantages. Firstly, the review is quite comprehensive since we include three age groups (9-15, 16-26, 27-45) as well as three evaluation yardsticks (immunogenicity, safety, and effectiveness). Besides, most included articles are newly published (within 5 years), so a high level of timeliness is ensured. Moreover, this review examines the rationale behind recommending the administration of the 9-valent vaccine to younger individuals.

This review also encounters several disadvantages. Firstly, due to the exacting grouping criteria, not so many papers are included. As a result, the reliability is affected. Apart from that, heterogeneity is not considered.

In the future, more studies regarding one dose of 9-valent vaccination should be done to evaluate if we could save money and time in this way. This one-dose vaccination strategy could be taken into practice for people who can't receive vaccinations easily first.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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