*Section: Research Paper*

# COMPARISON OF LONG-TERM OUTCOMES OF BIVALENT, QUADRIVALENT AND NONAVALENT HUMAN PAPILLOMAVIRUS VACCINE: A SYSTEMATIC REVIEW

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## SUMMARY

**Objective:** To compare the long-term outcomes of bivalent, quadrivalent and nonavalent human papillomavirus vaccines.

**Introduction:** The human papillomavirus is the most frequent sexually transmitted infection in the world and can cause benign and malignant processes in both men and women. Cervical cancer is its main complication and one of the leading causes of death worldwide. The HPV vaccine is the best method of preventing lesions and other complications caused by this virus, there are three types of vaccines: bivalent, quadrivalent and nonavalent that target different types of HPV, mainly HPV 16 and 18 that are considered high risk.

**Methodology:** A systematic review was carried out applying the PRISMA 2020 criteria, original articles were collected, both in English and Spanish, in scientific databases such as Pubmed, SCOPUS and Web of Science, between the years 2017 to the present year.

**Results:** After applying the inclusion and exclusion criteria, six articles were obtained that responded to the objectives of the research. The nonavalent vaccine demonstrated greater than 97% efficacy in reducing and occurring incident HPV infections 31, 33, 45, 52, 58. The bivalent and quadrivalent

vaccines are more than 90% effective in preventing persistent infections. In relation to precancerous lesions, the three vaccines prove to be 100% effective, preventing the development of CIN 1 and CIN 3.

**Conclusion:** Although the three vaccines are effective and beneficial, it was evidenced that nonavalent has greater efficacy compared to quadrivalent because it offers protection not only for HPV 6, 11, 16, 18 but also for HPV 31, 33, 45, 52 and 58.

**Key words:** Cervarix, efficacy, Gardasil, Gardasil 9, human papillomavirus, vaccines.

## INTRODUCTION

The human papillomavirus (HPV) is considered one of the most common causative agents of sexually transmitted diseases worldwide. So far more than 200 types of viruses are known and, of these, more than 40 types are sexually transmitted and can cause premalignant and malignant lesions of the cervix, anal, vulvar, vaginal, penile, oropharyngeal cancer and genital warts (1). In 2017, the World Health Organization (WHO) estimated that the prevalence of human papillomavirus in women is 11.7% worldwide. Latin America and the Caribbean had a prevalence of 16.1%, the second highest in the world after Sub-Saharan Africa with 24% (2).

This is an extremely frequent infection worldwide and its transmission is mainly due to sexual contact, it is estimated that 80% of sexually active people will be infected with HPV at some point in their lives. (3). Although HPV oncogenesis is now known, there are powerful methods of diagnosis, treatment and prevention of HPV-associated precancerous lesions, more than 270,000 women die annually from cervical cancer (4,5).

The incorporation of HPV vaccines has revolutionized the prevention of cervical cancer; because they are very effective in preventing infection against different types of HPV and the pathologies associated with infection when administered to prepubertal girls and boys, but they do not eliminate or reduce the persistence of the virus in women with ongoing infections (6).

Worldwide, HPV-16 is thought to be the most prevalent genotype, followed by HPV-18, although this prevalence varies greatly by geographic region. HPV-16 and HPV-18 are high-risk for the vulva, penis, vagina, anus, and oropharynx, while genotypes 6 and 11 play a role in genital warts. These cancers are less prevalent than cervical cancers, but many of these cancers represent high morbidity and mortality rates. Prevention of HPV infection and therefore these associated conditions is important for global public health (7,8).

The HPV vaccine was first recommended for use in the United States for adolescent and young adult women in 2006; and, for adolescent men and young adults in 2009 (6). Currently, there are three types of vaccines for the prevention of HPV: bivalent (coverage for HPV16 and HPV18), quadrivalent (genotypes 6, 11, 16 and 18) and nonavalent (6, 11, 16, 18, 31, 33, 45, 52 and 58). In Ecuador, vaccination is approved and vaccination is recommended for girls from nine years of age by means of two doses, with a time of two months between the first and second doses (9,10).

Vaccination and cytology are the main strategies for HPV prevention. Immunization has been successful in reducing HIV infection rates in countries with high vaccination coverage, as well as reducing the incidence of cervical cancer (3). For this reason, the present research work aims to compare the long-term results of the bivalent, quadrivalent and nonavalent vaccine against the human papillomavirus.

## METHODOLOGY

A systematic review of scientific literature on HPV vaccines and their long-term effects was conducted. For its preparation, the guidelines have been followed and reported according to the guidelines of the statement Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 (11), for conducting systematic reviews. For a study to be eligible, it had to meet the inclusion criteria and exclusion criteria.

### Inclusion criteria

- Randomised controlled trials (RCTs), non-RCTs and post hoc analyses.
- Studies where Cervarix, Gardasil and Gardasil-9 vaccine have been applied.
- Studies that have recruited women who test negative or positive for HPV.
- Articles in English and Spanish.
- Trials that report on the effectiveness of vaccines.
- Trials where patients have received 3 doses of vaccines.
- Studies of vaccines using or not using adjuvant.
- Studies with a follow-up duration of 5 years and older.
- Studies that report at least any of the following outcomes based on the objectives of the study: 1) incident lesions, 2) persistent lesions), 3) precancerous lesions, 4) genital warts.
- Articles that have been published between 2017 – 2023.
- The control group had to be women who were not vaccinated or who had received a placebo or a different HPV-targeted vaccine than the one in the study.

### Exclusion criteria

- Studies in which a vaccine for another pathogen has been given.
- Studies evaluating the non-prophylactic administration of bivalent, quadrivalent and nonavalent vaccines.

### Search strategy

The systematic search was performed again on April 29, 2023, in PUBMED, Web of Science and SCOPUS, taking into account the results of the publications of the year 2017 until the date of search.

La combinación de términos con los que se obtuvo mejores resultados para PUBMED fue: ((((((human papillomavirus) AND (vaccines)) AND (efficacy)) OR (persistent HPV infections)) OR (recurrent HPV lesions)) OR (HPV cervical cancer)) OR (HPV genital warts). Mientras que, para Web of Science fue: ((((((((((ALL=(human papillomavirus)) AND ALL=(vaccines)) AND

ALL=(efficacy)) OR ALL=(persistent HPV infections)) OR ALL=(recurrent HPV lesions)) OR ALL=(HPV cervical cancer)) OR ALL=(HPV genital warts)) AND ALL=(Controlled Clinical Trial)) AND ALL=(Randomized Controlled Trial)) AND ALL=(humans)) AND ALL=(female). Para SCOPUS se empleó la búsqueda: ("human papillomavirus") AND vaccines AND efficacy OR ("persistent HPV infections") OR ("recurrent HPV lesions") OR ("HPV cervical cancer") OR ("HPV genital warts") AND ("Controlled Clinical Trial") AND ("Randomized Controlled Trial").

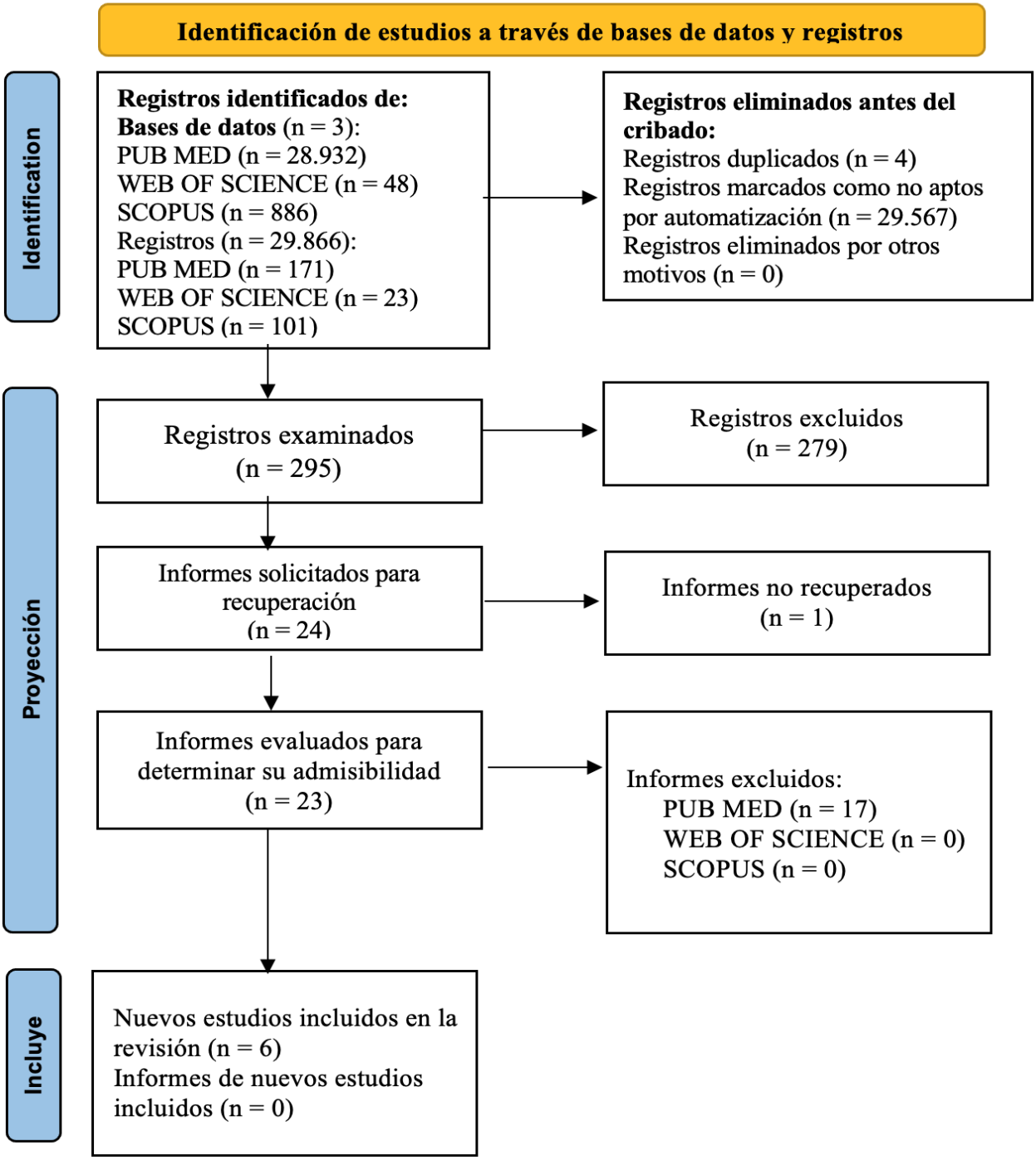
**Data extraction**

Initially, of the eligible studies, two review authors independently reviewed the articles to extract the characteristics of the study and assess methodological quality and whether the results provided information for the development of the systemic review. Then, with the help of an outside researcher, a final decision was made by consensus, especially when there were disagreements. Data were collected such as: author, year of publication, type of study, inclusion criteria, exclusion criteria, duration of follow-up, vaccine used, comparator, results and conclusions.

## RESULTS

We identified a total of 29866 articles related to our search strategy from the different databases. After applying the eligibility criteria and exclusion criteria, we obtained a total of 295 articles for the selection of articles through titles and abstracts. Subsequently, we evaluated the full text of the 24 articles chosen. Of these, 24 were excluded due to lack of relevant data, studies that do not present final results of their research, or not being a vaccination study with the types of vaccines to be compared. Therefore, we finally included 6 studies in the analysis (a flowchart describing the study selection process is presented in Figure 1).

**Figure 1: PRISMA 2020 flowchart.**




**Assessment of risk of bias and quality of evidence**

For risk of bias assessment, we used the Cochrane 'Risk of Bias 2 (ROB 2)' tool to assess the risk of bias of RCTs (12,13). We analysed selection bias in the six included studies; All of them adequately described the methods used to generate the randomisation sequence and were therefore considered to be at low risk of bias. Four trials were at low risk of bias because they had no deviations in their

studies, i.e. they were based on follow-up of the base study population and in case of loss of participants, these data did not interfere with the results (14–17), we judged the other two trials to be at unclear risk of bias because the authors analysed trials from different populations when conducting their study (18,19). Four studies were at low risk of bias, as there was no loss of data on the outcomes (14–17), while two trials are at high risk as there was data loss when collecting information from baseline studies (18,19). All six studies analysed were at low risk of bias in outcome measurement (14–19). Four studies demonstrated a low risk of bias in reported outcomes (14–17), however, there was a high risk of bias in two studies as not all data were analysed and only those that were eligible for research were used. (18,19).

**Figure 2: Analysis on each element of risk of bias for each included study.**

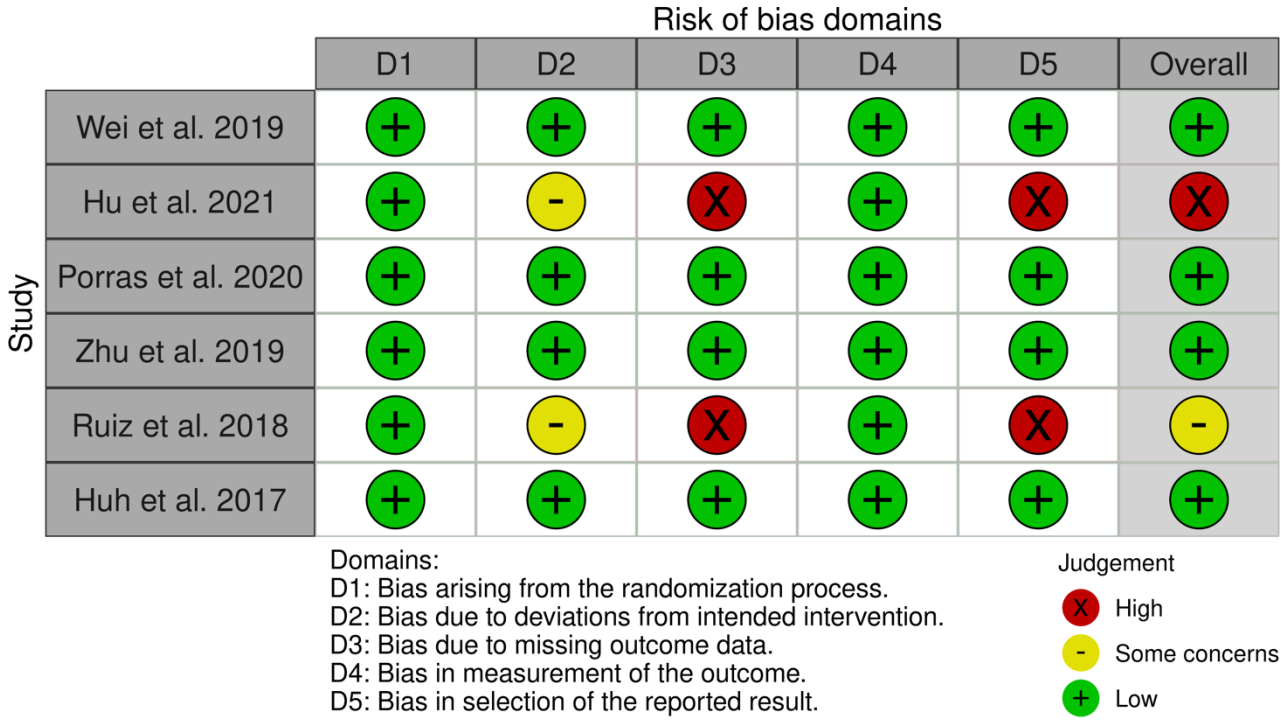
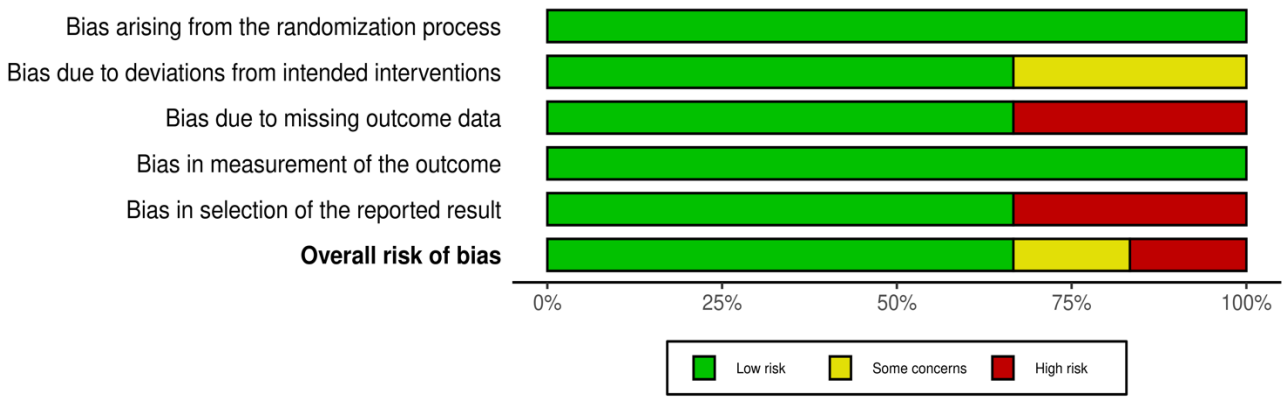



**Figure 3: Risk of bias analysis.**



Summary data were presented in tables; incident lesions, persistent lesions, precancerous lesions and genital warts were presented as #events/total participants and vaccine efficacy was represented by 95% confidence intervals (95% CI) extracted from publication results. Where we will find the author, year of the article, the type of vaccine, the follow-up time in years, the selection variables, the events and participants where the event is the number of cases of patients with pathological alterations in reference to the total number of participants and vaccine efficacy (EV) represented with a 95% confidence index (data detailed in Table 1).

**Table 1. Results of bivalent, quadrivalent, nonavalent HPV vaccines from studies that provided efficacy data for participants who received three doses of the vaccine, compared with participants who were unvaccinated or who received a different vaccine.**

| **Author/year** | **Type of vaccine** | **Follow-up time (years)** | **Variable** | | **# events/ total participants** | | **VE % (95% confidence interval)** |
|---|---|---|---|---|---|---|---|
| | | | | | Vaccinated group | Control group | |
| Wei et al (14), 2019 | Tetravalente (Gardasil) | 6,5 | Precancerous lesions | NOTHING 1 | 0/1272 | 14/1243 | 100 (70,9 - 100) |
| | | | | NOTHING 2 | 0/1272 | 7/1243 | 100 (32,2 - 100) |
| | | | Persistent infections | 12 M - IP cervical | 1/1275 | 38/1246 | 97,5 (85,1 - 99,0) |
| | | | | 12 M - IP no cervical | 4/1277 | 46/1245 | 91,7 (77,2 - 97,8) |
| Hu et al (18), 2021 | Bivalent (Cervarix) | 6 | Incident infection | HPV 16/18 | 4/121 | 9/102 | 66,8 (−18,9 - 92,5) |
| | | | | HPV 16 | 1/28 | 2/23 | 61,2 (−646,2 - 99,3) |
| | | | | HPV 18 | 3/93 | 7/79 | 68,4 (−38,5 - 94,7) |
| Porras et al (15), 2020 | Bivalent (Cervarix) | 11 | Precancerous lesions | NOTHING 2 | 0/1913 | 34/2233 | 100% (89,2 - 100,0) |
| | | | | NOTHING 3 | 0/1913 | 18/2237 | 100% (78,8 - 100,0) |
| Zhu et al (16), 2019 | Bivalent (Cervarix) | 6 | Incident infection | HPV 16/18 | 49/2610 | 184/2639 | 73,5 (63,6 - 81,1) |
| | | | Persistent infection | 6M | 4/2551 | 80/2571 | 95,0 (86,7 - 98,7) |
| | | | | 12 M | 3/2518 | 41/2536 | 92,6 (76,9 - 98,5) |
| | | | Precancerous lesions | NOTHING 1 | 2/2567 | 17/2587 | 88,1 (49,7 - 98,7) |
| | | | | NOTHING 2 | 1/2567 | 9/2587 | 88,7 (18,5 - 99,7) |
| Ruiz et al (19), 2018 | Nonavalente (Gardasil 9) | 5,4 | Persistent HPV-related infection 31-/33-/45-/52-/58 ≥6 months | | 22/2010 | 414/2029 [t] | 95,2 (92,7 - 97,0) |
| | | | Incident HPV infection 31-/33-/45-/52-/58 | | 2/2032 | 64/2052 [t] | 96,9 (89,2 - 99,5) |
| | | | Precancerous lesions | NOTHING 1 | 0/2009 | 45/2018 [t] | 100 (92,5 - 100) |
| | | | | NOTHING 3 | 1/2032 | 13/2052 [t] | 92,3 (54,4 - 99,6) |
| | | | Genital warts | Condyloma | 0/2028 | 3/2051 [t] | 100 (−72,3 - 100) |
| Huh et al (17), 2017 | Nonavalente (Gardasil 9) | 6 | Persistent infection | 6M HPV 6, 11, 16, 18 | 68/5812 | 95/5830 [t] | 28,5 (1,8 - 48,4) |
| | | | | HPV 31, 33, 45, 52, 58 | 41/5941 | 946/5955 [t] | 96,0 (94,6 - 97,1) |

| | | | | | |
|---|---|---|---|---|---|
| Incident infection | 12M | HPV 6, 11, 16, 18 | 25/5812 | 35/5830 [t] | 28,5 (–22,9 - 57,7) |
| | | HPV 31, 33, 45, 52, 58 | 23/5941 | 657/5955 [t] | 96,7 (95,1 - 97,9) |
| | HPV 6, 11, 16, 18 | | 6/5883 | 9/5898 [t] | 33,1 (–101,6 - 76·3) |
| | HPV 31, 33, 45, 52, 58 | | 3/6016 | 127/6017 [t] | 97,7 (93,3 - 99·4) |
| Precancerous lesions | NOTHING 1 | HPV 6, 11, 16, 18 | 0/5824 | 2/5832 [t] | 100 (–248,1 - 100) |
| | | HPV 31, 33, 45, 52, 58 | 1/5949 | 87/5943 [t] | 98,9 (94,1 - 99,9) |
| | NOTHING 2 | HPV 6, 11, 16, 18 | 1/5824 | 0/5832 [t] | ON |
| | | HPV 31, 33, 45, 52, 58 | 1/5949 | 32/5943 [t] | 96,9 (81,5 - 99,8) |
| | NOTHING 3 | HPV 6, 11, 16, 18 | 0/5824 | 1/5832 [t] | 100 (–∞ - 100) |
| | | HPV 31, 33, 45, 52, 58 | 0/5949 | 7/5943 [t] | 100 (39,4 - 100) |
| Genital warts | Condyloma | HPV 6, 11, 16, 18 | 5/5876 | 2/5893 [t] | –150,9 (–∞ - 48,0) |
| | | HPV 31, 33, 45, 52, 58 | 0/6009 | 4/6012 [t] | 100 (–11,5 - 100) |

t: tetravalente

**Incident infections**

We included 4 studies to report outcomes for incident HPV infection for participants who received three doses of HPV vaccine relative to the control group. Of these studies, three (16–18) report results up to 6 years after vaccination, and one (19) up to 5.4 years. In addition, two studies (16,18) evaluate the bivalent vaccine, while the other two study the nonavalent vaccine (17,19).

The results of the efficacy of the bivalent vaccine with respect to incident infections were presented in percentage % (Confidence index 95%). In the studies of Hu et al (18) y Zhu et al (16) An efficacy of the 66.8 (−18.9 to 92.5) and 73.5 (63.6 - 81.1), respectively, for the cumulative incidence of HPV 16/18 infection, while for HPV 16 and HPV 18 efficacy between 60 and 75% was obtained. Between 5 and 6 years of follow-up after nonavalent vaccination, when participants were between 16 and 26 years old, Huh et al (17) and Ruiz et al (19) report in their results an efficacy greater than 95% for incident infections caused by HPV 31, 33, 45, 52, 58 with respect to the control group in which the quadrivalent vaccine was used. However, for HPVs 6, 11, 16, 18, the incidence of these infections was 33.5% (95% CI: (–101,6 – 76,3%).

**Persistent infections**

The results of this review include 4 articles that analyze the long-term effect of persistent infections against patients vaccinated for different types of HPV, two studies present their results 6 years after vaccination and the other two up to 5.4 and 6.5 years after vaccination. The efficacy results of these articles differ based on the vaccinated group and the control group that in two articles is represented by another equal vaccine for HPV while in the other two articles the control group are patients not vaccinated against HPV. Wei et al (14) reports that persistent infections in patients vaccinated against HPV 6/11/16/18 (Tetravalent-Gardasil) at 12 months with persistent cervical infection was 97.5% (95% CI: 85,1 %: 99,0 %) while the group of persistent non-cervical infections was 91.7% (95% CI: 77,2 %: 97,8 %) at 6.5 years after vaccination.

Zhu et al (16) evaluates persistent infections in patients vaccinated against HPV 16/18 (Bivalent-Cervarix) versus the control group who were not vaccinated in 6 months of 95.0% (95% CI: 86.7 %: 98,7 %) as opposed to 12 months of 92,6 % (95% CI: 76.9% - 98.5%) at 6 years after vaccination. Ruiz et al (19) shows that patients vaccinate against HPV 6/11/16/18/31/33/45/52/58 greater than or equal to 6 months (Nonavalente- Gardasil9) versus patients vaccinated against HPV 6/11/16/18 (Tetravalent-Gardasil) is 95.2% (95% CI: 92.7% - 97.0%). Huh et al (17) reports that patients vaccinate against HPV 6/11/16/18/31/33/45/52/58 (Nonavalente- Gardasil9) against HPV vaccine patients 6/11/16/18 (Tetravalent-Gardasil) at 6 months represents 28.5% (95% CI: 1.8% - 48.4%) for HPV 6/11/16/18/ while for HPV 31/33/45/52/58 represented 96.0% (95% CI: 94.6% - 97.1%) versus the control group after vaccination to 6 years. At 12 months of persistent HPV infections 6/11/16/18 compared to their control group was obtained 28.5 % (95% CI: -22.9% - 57.7%), while the HPV 31/33/45/52/58 represents 96.7% (95% CI: 95.1% - 97.9%).

**Precancerous lesions**

We included 5 studies reporting on precancerous lesions in patients vaccinated against HPV. Of these studies, two report outcomes up to 6 years after vaccination, one study up to 11 years while another study up to 6.5 years as opposed to the last study which is 5.4 years.

According to the results of three studies by Wei et al (14), Ruiz et al (19) and Huh (17) have an efficacy of 100% against CIN 1, while in the study of Zhu et al (16) CIN1 had an efficacy of 88.1%. In the studies of Wei et al (14), Porras et al (15) it also has an efficacy of 100% against CIN 2, however, the study by Zhu et al (16) compared to IAS 2 presented an efficiency of 88,7% (IC 95%: 18.5% - 99.7%), while CIN 2 in the Huh 2017 study was 96.9% (95% CI: 81.5% to 99.8%). In the studies of Porras et al (15) and Huh (17) an efficacy of 100% was presented against CIN 3, while in the Ruiz study (19) was 92.3 % (95% CI: 54.4% - 99.6%) at 6.5 years after vaccination.

**Genital warts**

Results for the occurrence of HPV genital warts for participants who received three doses of the vaccine (Nonavalente-Gardasil9) compared to the control group that in the two studies received the vaccine (Tetravalent-Gardasil) where Ruiz et al (19) has an efficacy against condylomas of 100% (95% CI -72.3% - 100%) as opposed to Huh (17) that has an efficacy against HPV 6/11/16/18 from -

150.9% (95% CI: –∞ - 48.0%) versus their control group, instead, for HPV 31/33/45/52/58 represents 100% efficacy (95% CI -11.5% - 100%).

## DISCUSSION

The present systematic review presents clear data on the efficacy of HPV vaccines in patients with three doses. The 6 studies analyzed in this research report data on the criteria evaluated and on the three vaccines compared. The nonavalent vaccine was shown to have an efficacy of more than 97% for HPV types 31, 33, 45, 52, 58, decreasing the occurrence of incident infections by these types of viruses; whereas, the bivalent and quadrivalent vaccine did not present significant efficacy for any type of HPV. Compared to the variable of persistent infections, it is demonstrated that with the bivalent and quadrivalent vaccine there is an efficacy greater than 90% unlike the nonavalent vaccine that only proved to be effective in preventing the development of a persistent infection by HPV types 31, 33, 45, 52, 58. The third study variable corresponding to precancerous lesions has demonstrated a 100% efficacy for the development of CIN1 and CIN3 in the 3 types of vaccines. On the other hand, in the variable on the appearance of genital warts, efficacy per vaccine could not be evaluated; However, one study showed that the nonavalent vaccine demonstrated 100% efficacy.

Whitworth et al (20), conducted a systematic review where they found that incident, persistent and prevalent infections with HPVs 16 and 18 were extremely low in participants who received any of the HPV vaccines relative to patients who were not immunized or who received another type of vaccine. All studies included in this research reported comparable efficacy against HPV 16 and 18 infection, regardless of the number of doses. In one of the studies analyzed on the bivalent vaccine, efficacy greater than 74% against persistent HPV 16 or 18 infection was demonstrated at 12 months at four years after vaccination, an efficacy of 80.9% in people who received 3 doses, 84.1% in those who received 2 doses and 100% in people who received only one dose.

Similarly, the results presented in the present research have shown that vaccination prevents the incidence of both persistent and incident lesions compared to the unvaccinated group; however, the efficacy of the bivalent vaccine against persistent infections was evaluated over a longer period of time (6 years) demonstrating an EV at 6 and 12 months greater than 90% with the application of three doses of the vaccine. This efficacy can be explained by the formation of antibodies and cross-protection offered by the Cervarix vaccine. A 3-dose study on bivalent vaccine conducted in girls who were 10 to 14 years old, antibody titers against HPV 16 and HPV 18 at month 120 were 53.4 times and 26.3 times higher, respectively than those observed after natural infection in subjects 15 – 25 years of age, and 3.8-fold and 2.5-fold higher than those measured 9.4 years after vaccination in vaccinated subjects at ages 15 to 25 years. That is, all three doses of the vaccine generated a high and sustained antibody response against HPV-16, 18, 31 and 45 in girls aged 10 to 14 years during the 10 years of follow-up, with an acceptable long-term response. (21).

Moreover, the research conducted by Hoes et al (22), demonstrated that vaccination after 10 years with the bivalent vaccine is effective for incident and persistent infections. The EV was 95.8% against persistent HPV type 16/18 infections and 64.6% against persistent infections cross-protection against HPV type 31/33/45. Likewise, another study that evaluates the cross-protection of the

bivalent vaccine is a controlled trial, where they obtained the efficacy of different vaccination schedules up to 11 years after immunization, obtaining as a result that 3 doses of this vaccine offers cross-protection against HPV 31/33/45 with an average EV of 64.4%, for HPV 35 with an average EV of 23.2% and for HPV 58 with an average EV of 21.2%. Demonstrating in this way that the bivalent vaccine provides cross-protection for HPV 31/33/45 and to a lesser extent for HPV 35 and 58 (23).

With regard to the nonavalent vaccine, in the study Giuliano et al (24), efficacy was demonstrated by analyzing 3 international, randomized, double-blind studies to evaluate their efficacy against all 9 HPV types. (6/11/16/18/31/33/45/52/58) and cervical surgeries. The nonavalent vaccine was shown to prevent 98% of high-grade cervical dysplasia and 98% of cervical surgeries related to the 9 HPV types covered by the vaccine. The overall reduction in vulvar and vaginal disease of any grade was 94.9% and for high grade it was 100%. A high efficacy (94.3%) against the appearance of vulvar and vaginal condylomas was also observed. In addition, cervical biopsy related to nonavalent vaccine types was reduced by 95.1% and definitive cervical therapy (loop electrosurgical excision procedure, conization) by 97.8%.

Also, the results of our research have shown that precancerous lesions have an EV of 100% by the nonavalent vaccine, because in the study by Garland et al (25), it was evidenced that the application of this prophylactic vaccine markedly reduced the risk of persistent HPV-related infection 31/33/45/52/58, cytological abnormalities of the cervix, diseases and medical procedures in Asian participants, with an efficacy of 91.3% to 100% for all HPV types. Geometric titer measurements (GMT) for HPV 6/11/16/18 were comparable between nonavalent and quadrivalent vaccine recipients, although GMTs for HPV-11 tended to be lower with nonavalent vaccine, with participants $\geq$ 97.9% experiencing seroconversion within 1 month after last vaccination. This suggests that the efficacy of the vaccine and the duration of protection of this depends on the degree of immunogenicity of the same.

Regarding the quadrivalent vaccine, in the study by Mikamo et al (26), efficacy against the incidence of persistent HPV-related infection 6/11/16/18 was shown to be 85.9%. Among the subgroups of heterosexual men (MH) and men who have sex with men (MSM), efficacy was 87.4% and 83.6%. There were no cases of HPV6/11/16/18-related external genital lesions in the vaccine group. Two cases of HPV6/11/16/18-related external genital lesions were observed in the placebo group: one case of condyloma and one case of penile/perianal/perineal intraepithelial neoplasia, or penile, perianal or perineal cancer (PIN 1). Therefore, efficacy against the combined incidence of persistent HPV-related lesions 6/11/16/18 infection and external genital lesions was 86.5%. On the contrary, in the present study it was shown that the nonavalent vaccine is superior to the quadrivalent vaccine since it presented a 100% efficacy to prevent the appearance of condylomas, regardless of the type of HPV, but in one of the studies analyzed a 100% efficacy was demonstrated only against HPV 31, 33, 45, 52, 58 (17).

The three vaccines confer almost 100% protection against infection by the HPV genotypes included in the vaccine formulations and this protection against infection by the different types of HPV is mediated by neutralizing antibodies against the HPV L1 capsid protein, even the specific antibodies against HPV induced by the prophylactic vaccines administered in people with HPV generate

memory responses of B cells that are 100 to 1000 times greater than pre-existing endogenous antibody titers. While these antibodies do not have a therapeutic effect, there is literature on the post-treatment use of established HPV disease, to decrease the likelihood of recurrences. (27). However, in a study by Karimi et al (28), it has been shown that these vaccines can be used as a therapeutic vaccine in the presence of precancerous lesions, it has been shown that 2 years after follow-up the effectiveness of the vaccine (two or more doses) in women with CIN 1, 2, 3 was 54.9, 63.3 and 52.5%, respectively. The efficacy with respect to two and three doses of HPV vaccine in the treatment of CIN 1 was 38.6% and 63.1%, and its efficacy in the treatment of CIN 2 was 50% and 72.2%, respectively. The difference between the efficacy of different doses of vaccine for the treatment of residual/recurrent CIN 1 and CIN 2 was statistically significant ($p = 0.012$, $p = 0.042$).

The three prophylactic HPV vaccines (Cervarix, Gardasil, and Gardasil 9) are based on L1 capsid proteins assembled into virus-like particles (VLPs). Of these vaccines, Gardasil and Gardasil 9 are generated in yeast and amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant are added to them, so they have a high ability to adhere to L1 VLPs compared to other adjuvants. Whereas, the Cervarix vaccine is generated in insect cells "baculovirus" and uses the adjuvant AS04 which is composed of aluminum hydroxide plus an additional immunostimulant (3-O-desacil-4'-monophosphoryl lipid A); AS04 has been shown to improve innate, humoral and cellular immune system responses, because of this, it is responsible for differences in immunogenicity compared to other vaccines. Another difference is related to the concentration of L1 VLPs; Gardasil has a high concentration, 2 times higher, of HPV16 and 18 VLP L1 compared to Cervarix. In contrast, Gardasil 9 contains twice the L1 VLP for HPV 16 and 18, and contains twice as much adjuvant as the quadrivalent vaccine. (29).

## CONCLUSION

The present study showed that the application of prophylactic vaccines is of great importance, because it prevents the appearance of lesions caused by the spread of HPV. It is also important to mention that all three types of vaccines are effective in preventing precancerous lesions such as CIN 1 and CIN3. Although all vaccines prove to be effective and beneficial in avoiding complications caused by any type of HPV to which the vaccine is directed, it was evidenced that the nonavalent vaccine has greater efficacy with respect to the quadrivalent vaccine, because it offers protection for both HPV 6, 11, 16, 18 and also for 31, 33, 45, 52, 58 demonstrating an efficiency greater than 95%.

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