SYSTEMATIC REVIEW

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Papillomavirus vaccine in Peru
Vacuna del papilomavirus en el Perú

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ABSTRACT
Cervical cancer is a public health concern. The human papillomavirus (HPV) vaccine protects against infection with HPV. The vaccine has been shown to be effective in preventing premalignant lesions and cervical cancer, as well as lesions of the vulva, vagina, anal canal, penis, and oropharynx. It has also proven to be cost effective and supports the idea of introducing a national vaccination strategy. The HPV vaccine could be the ideal tool for health systems where secondary prevention has not been successful over time. The implementation of the vaccination program in Peru began in 2011. Currently, in Peru, the indication for vaccination is with the quadrivalent vaccines for 5th grade girls from public and private schools. It is administered in 2 doses, 0-6 months. In 2019, coverage in Peru was 87% (234 535 girls) for the first dose and 78% (211 339 girls) for the second dose.
Key words: Human papillomavirus, Vaccination, Human papillomavirus recombinant vaccine, *Papillomaviridae*, Peru.

RESUMEN
El cáncer de cuello uterino es un problema de salud pública. La vacuna contra el virus del papiloma humano (VPH) protege contra la infección por el VPH. Ha mostrado ser efectiva para prevenir lesiones premalignas y cáncer de cérvix, así como lesiones de la vulva, vagina, canal anal, pene y orofaringe. Forma parte del calendario nacional de vacunación, es costo efectiva en la introducción de la estrategia nacional de vacunación y es la herramienta ideal ante sistemas de salud donde la prevención secundaria no ha dado resultado a lo largo del tiempo. La implementación del programa de vacunación en Perú se inició en el 2011. Actualmente, la indicación de la vacunación es con la vacuna tetravalente a niñas del 5° grado de primaria de los colegios públicos y privados, en 2 dosis a los 0 y 6 meses. En el 2019, la cobertura fue de 87% (234 535 niñas) para la primera dosis y 78% (211 339) para la segunda dosis.
Palabras clave. Papillomavirus humano, Vacunación, Vacuna recombinante del Papilomavirus humano, *Papillomaviridae*, Perú.

Introduction

Worldwide, about half a million cases of cervical cancer are estimated. In developed countries, screening intervention strategies have decreased the mortality rate. In Peru, cervical cancer is the second cause of cancer in women, a serious public health issue[1]. In developing countries, cases have not decreased despite the strategies implemented. For many years, the intervention tool has been conventional cytology. Currently, it is known that cytology sensitivity is about 50% in research scenarios, and about 22.1% in real scenarios[2].

In Latin America, nearly 69 000 new cases of cervical cancer and approximately 29 000 deaths associated with this disease are reported annually[3]. Cancer rates associated with HPV have varied over time based on each region. Decreasing cases of cervical cancer were found in developed countries, but the incidence of cancer of the anus, oropharynx, and vulva of the squamous type has increased. HPV 16 and 18 are estimated to be responsible for more than 90% of oropharynx, cervix and anal canal cancer cases[4]. In 2015, HPV-associated oropharynx cancer was the most frequent in the United States, above cervical cancer[5].

Intervention strategies for cervical cancer are based on:

a) Primary prevention with vaccines

b) Secondary prevention with diagnosis and treatment of premalignant lesions and early clinical cancer stages.

HPV vaccine was introduced in 2006. In order to monitor the impact of HPV vaccination, three levels of evaluation have been used over time. The first evaluation is at short term, in months, measuring the HPV infection prevalence and the presence of genital warts. In the intermediate term, in years, reduction in the incidence of cervix, vulva, vagina, and anus premalignant lesions. Finally, in the long term, in decades, with incidence of cervical, vulva, vaginal and anal cancer[6].

Methodology

Search of PUBMED database was performed using the following key words: HPV vaccine, cervarix, gardasil, nonavalent HPV vaccine, cervical cancer. Available data from the Ministry of Health (MINSA) was accessed through the OGTI (General Office of Information Technology).

Human papilloma virus

The human papilloma virus (HPV) is a double stranded DNA with more than 120 different genotypes[7]. It is the cause of the most frequent sexually transmitted infection. HPV types are categorized as low risk (types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81) and high risk (types 16, 18, 31, 33, 35, 45, 51, 52, 56 and 58). Those high risk or oncogenic are related to persistent HPV infection and able to generate premalignant lesions and cervical cancer; the low risk or non-oncogenic could develop genital warts, condylomata acuminata, papillomas, and laryngeal papillomatosis[7,8].

Three vaccines have historically been developed to prevent HPV-associated diseases.

Bivalent vaccine

The United States Food and Drug Administration (FDA) approved the Cervarix vaccine in 2009, produced by Glaxo (GSK), which protects against HPV 16 and 18 infections, with results that are close to 100% effective against pre-malignant cervical lesions and with levels of antibodies that exceed 80% against natural infection, as well as protection by cross-reaction for HPV 45 and 41[8].

In the PATRICIA study (Papilloma Trial against cancer in Young adults), the efficacy and immunogenicity of HPV 16 and 18 were evaluated in young women between the ages of 15 and 25, finding that vaccination in adolescents before sexual debut has been shown to have a significant impact on the incidence of high-grade injuries[9].

Tetravalent (G4) and nonavalent (G9) vaccine

The FDA approved in 2006 the quadrivalent vaccine produced by Merck & Co (MSD) called Gardasil to prevent infection of viral types 6, 11, 16, 18, and in 2014 the nonavalent vaccine or Gardasil-9 that contains specific proteins for HPV L1 6, 11, 16, 18, 31, 33, 45, 52 and 58. The G4 vaccine has been shown to be safe, efficient, and effective with minimal side effects. The first studies of the G9 vaccine seeked to demonstrate non-inferiority compared to the tetravalent. For this, study 001 (Protocol V503-001), a phase II / III double-blind, randomized, controlled study of the G9 vaccine versus the G4 vaccine, was developed in women between 16 and 26 years old. Efficacy was evaluated at 7 months in 14 215 participants from 18 countries, 33.4% were from Latin America, including Peru with 2 research centers. Also phase III study 002 (Protocol V503-002) where the safety and immunogenicity of G9 were evaluated in women and children from 9 to 15 years of age compared to young women from 16 to 26 years of age. The number of participants enrolled was 3 074 from 17 countries. The efficacy result of the G9 vaccine with respect to HPV 31, 33, 45, 52 and 58 was 92.3% (95% CI: 54.4 to 99.6) for high-grade cervical, vulvar, vaginal, and 98% (95% CI: 88.9 to 99.9) for any type of cervical disease; the efficacy of the vaccine was robust in reducing disease. The G9 vaccine reduced the number of abnormalities of the Papanicolaou test and cervical procedures related to HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 as well as cases of CIN 2+. In the follow-up from 7 to 36 months, the mean geometric titers of antibodies remained high in girls and boys between 9 and 15 years old. In addition, most girls and boys in this age group maintained seropositive levels for 60 months in the G9 vaccine group[10].

Efficacy

The World Health Organization (WHO) defines vaccination efficacy as the percentage reduction in the incidence of the disease in the vaccinated subjects compared to a group that does not

receive the study vaccine[11]. G4 vaccinated patients have a high possibility of seroconversion for vaccine types 6, 11, 16 and 18 compared to patients who received any placebo or hepatitis "A" vaccine, showing the reduction of the infection rate and persistence among the vaccinated groups compared to the non-vaccinated ones.

The systematic review of 6 reports described a lower risk of developing genital condylomas in the vaccinated population. In each meta-analysis reviewed, HPV vaccination shows a protective effect for pre-malignant lesions. The size of the protection effect for CIN3 + showed RR 0.01 (95% CI: 0.0 to 0.1) and for CIN2 + RR 0.8 (95% CI: 0.62 to 1.02)[12]. The efficacy of the quadrivalent vaccine is 70% against premalignant lesions and cancer, which increases by 20% with the nonavalent vaccine, reaching up to 90%.

Effectiveness

Vaccine effectiveness is the ability of a vaccine to protect against disease when applied under field conditions, actual or routine conditions of daily clinical practice in public health programs. It should be evaluated when the vaccine has previously shown to be effective in a controlled clinical trial[11]. Collective evidence of efficacy of HPV vaccines, in systematic reviews and controlled studies, demonstrates effectiveness against HPV vaccine types including pre-malignant and benign lesions[13].

The systematic review and meta-analysis of 20 ecological studies from developed countries (7 from HPV infection, 11 from ano-genital warts, and 2 from high-grade lesions) reports a 68% decrease in HPV infection 16 and 18, and a 61% decrease in ano-genital warts between the pre-vaccination and post-vaccination era with bivalent and quadrivalent vaccine among women aged 13 to 19 in countries with vaccination coverage of at least 50%[14].

Side effects

Side effects may occur from the first to the fifteenth day after vaccination. Based on protocol 001, it was determined that patients who received G9 were more likely to experience adverse events than those who received G4 at the injection site. The most common injection-site adverse events were pain, swelling, erythema, and itching. Systemic adverse effects were similar between the two vaccine groups, G4 and G9. These effects were found in 27.2% of girls, 37.5% of boys, and 31.4% of women when the G9 vaccine was used. Then, the most common systemic adverse effects were headache (14.6%), fever (5%), nausea (4.4%), dizziness (3%)[11].

Dosage and schedules

The vaccine started with three application doses, 0-1-6 and 0-2-6 months for each vaccine; but studies have shown changes over time.

Two doses versus three doses of quadrivalent HPV vaccine in women aged 9 to 15

The immunogenicity of two doses versus three doses based on neutralizing antibodies in young women is comparable. The antibody response after vaccination with two doses and three doses was similar at the 5-year follow-up. Side effect studies comparing two versus three doses show that there is a very low difference between the two[15]. Therefore, two doses for primary immunization programs is recommended in adolescents aged 9 to 13[16].

Interval between doses of HPV vaccine in women and men aged 9 to 14

The antibody response with G4 is strong with an interval between 6 to 12 months after the first dose; while, for less than 6 months, it had a moderate antibody level response. Therefore, it is suggested that the minimum interval between both doses be 6 months. Side effects were similar in both groups.

Vaccination among men 10 to 26 years old

The G4 vaccine reduces external genital lesions and ano-genital warts compared to the control group (control 36/3 081 patients, quadrivalent 6/3 173 patients per year). Pain at the application site level was presented as a major adverse effect.

Nonavalent versus quadrivalent vaccination in women and men aged 9 to 26 years

The G9 vaccine's geometric mean titers of antibodies for heterosexual men were not lower than those for women aged 16-26. These results

were found with G9 after 3 doses. No differences were found between the vaccinated groups between 9 to 15 versus 16 to 26 years of age in the geometric titers of antibodies or in the incidence of high-grade CIN of the cervix, vagina, vulva, adenocarcinoma in situ or cervical cancer. Side effects occurred between 1 and 15 days after G9 application[17].

HPV vaccination for population living with HIV

The antibody rate was high followed by bivalent or tetravalent vaccination compared to the control and they remained high for the following 24 months; but, the evidence on efficacy in this population is limited[16].

Recommended dose

Two doses (0-6 months) for 9 to 14 years old.

Three doses (0-2-6 months) for 15 to 26 years old.

FDA approval October 2018

Expand the use of the HPV9 vaccine (Gardasil9) and include men and women aged 27 to 45 years.

Recommendation according to Ministerial Resolution June 26, 2019 for Peru

- Girls and adolescents in the 5th grade of public and private elementary school.
- Girls from 9 years to 13 years, 11 months and 29 days, who for some reason are not physically attending school.
- Women living with HIV under the age of 20, with a negative HPV molecular test, will be able to receive the vaccination according to the evaluation of their immunological status, which depends on the treating specialist physician.

HPV9 and pregnancy

For the study of the G9 vaccine, no specific studies were performed in pregnant women. It should be postponed until the end of pregnancy and lactation. But, the subsequent sub-analysis on pregnant women does not indicate teratogenic effects, nor fetal or neonatal G9 toxicity.

Screening in vaccinated women

The screening in vaccinated women against HPV is a new screening scenario, and the evidence suggests that ideal screening should be done with the HPV Test[15,18].

Contraindications

- Gestation
- Lactation
- Vaccine hypersensitivity.

Vaccination in Peru

In Peru, on January 28, 2011, the HPV vaccine was incorporated as part of the national vaccination scheme, according to Technical Health Standard N° 080-MINSA / DGSP V.02 "Technical Health Standard that establishes the National Vaccination Scheme", approved with Ministerial Resolution No. 510-2013 / MINSA[19]. By using the bivalent recombinant vaccine at 0.5 mL intramuscular dose, 3-dose schedule 0-2-6 months, the recommendation was for 10-year-old girls and, as captive population strategy, for girls not older than 15 years at schools, and on demand in health facilities.

On April 22, 2015, the Ministry of Health (MINSA) approved the Health Directive No. 064-MINSA / DGSP V.01 for the administration of the Vaccine against the Human Papilloma Virus (HPV) [20], with a recombinant quadrivalent vaccine to cloudy white suspension, in 0.5 mL single dose vial, intramuscular. The vaccination strategy was recommended in a 3-dose schedule, 0-2-6 months. It was administered to 5th graders (girls aged 10 to 13), as well as on a house-to-house basis and or vaccination facilities.

Girls who had not completed the three doses of vaccines had to complete the vaccination schedule in order to close the gap for years 2011, 2012, 2013 and 2014, considering the vaccination schedule established in NTS N° 080- MINSA / DGSP V.03. This directive recommended the vaccination scheme for girls in the 5th grade of public and private elementary schools. In excep-

tional cases, for those girls (10 to 13 years old), who were not vaccinated, it was recommended to attend a health facility to request such a vaccine[21].

In reference to the interchangeability of the bivalent HPV vaccine with the quadrivalent HPV vaccine, MINSA followed the recommendation from USCDC's ACIP (the Advisory Committee on Immunization of the US Center for Disease Control and Prevention). They recommend: "in case of not knowing which vaccine was previously applied or the corresponding one was not available; any vaccine can be applied to complete the scheme to protect against genotypes 16 and 18".

On August 31, 2016, the Technical Health Standard No. 080-MINSA / DGIESP-V.04 "Technical Health Standard establishing the National Vaccination Scheme" was approved, with Ministerial Resolution No. 651-2016 / MINSA that establishes vaccination against HPV for girls of 5th and 6th grade of public and private elementary educational institutions as well as for girls of 9 to 13 years with 11 months 29 days of urban and rural population who for some reason are not studying. They must be registered and vaccinated in health establishments and / or vaccination brigades[22]. The new vaccination scheme is with two 0.5 mL doses intramuscularly (0-6 months). Girls and adolescents who have already started vaccination with the previous scheme (3 doses) will continue and complete the vaccination or gap closure scheme with the three doses of vaccines, during the years 2011, 2012, 2013, 2014, 2015 and 2016.

On August 1, 2018, the Technical Health Norm No. 141-MINSA / 2018 / DGIESP "Technical Health Norm that establishes the National Vaccination Scheme" was approved with Ministerial Resolution No. 719-2018 / MINSA. This resolution did leave without effect Ministerial Resolution No. 651-2016 / MINSA, of August 31, 2016, which described the vaccination scheme for girls and adolescent women in the 5th grade of both public and private elementary school, and for adolescent female girls from 9 to 13 years old with 11 months 29 days that for some reason were not attending school[23].

On December 29, 2016, the Technical Guide: "Clinical Practice Guide for the prevention and management of cervical cancer" was approved, with Ministerial Resolution No. 1013-2016 / MINSA, establishing HPV vaccination as part of the primary prevention of cervical uterine cancer [24].

On June 26, 2019, the Health Directive No. 085-MINSA / 2019 / DGIESP "Health Directive for the prevention of cervical cancer through the early detection and treatment of pre-malignant lesions including carcinoma in situ" was approved by Ministerial Resolution No. 576-2019 / MINSA which derogated Ministerial Resolution No. 1013-2016 / MINSA. This new Ministerial Resolution establishes, as part of the primary prevention of cervical cancer, vaccination against HPV, according to Technical Health Standard No. 141-MINSA / 2018 / DGIESP "Technical Health Standard that establishes the National Vaccination Scheme": in women living with HIV under 20 years old with a negative HPV molecular test, may receive vaccination according to the evaluation of their immunological status which depends on the treating specialist physician[25].

The HPV vaccination goal initially projected by the Ministry of Health for 2019 according to the nominal registry of HPV vaccination, was 269 316 girls; 234 535 (87%) and 211 339 (78%) were applied as the first and second dose respectively. However, the nominal record of the 5th grade indicated by the Ministry of Education for June 17, 2019 was 232 318 girls, establishing a different denominator. Finally, based on the new data on the nominal standard, the Ministry of Health established a higher coverage than that described. It is also noted in the OGTI (General Information Technology Office) that vaccination was completed in older girls in the same campaign. The difference in the denominator value in this calculation allows us to understand the reported values.

Discussion

HPV is the main risk factor for the formation of pre-malignant lesions and cervical cancer. The HPV family are a group of viruses that infect the skin and mucous membranes; most of these infections are cleaned by the effect of the immune system. But some people can have persistent infection and certain types of viruses could cause abnormalities in cells. These changes are called pre-malignant lesions and they could eventually develop cancer of cervix, vagina, vulva, anal canal, penis, head and neck, as well as develop genital warts[7].

There are two approaches to cervical cancer prevention: A primary prevention through HPV vaccine, the causative agent of the disease; and a secondary prevention through screening, detection, and treatment of pre-malignant lesions before they become invasive cancer[16]. In low-income countries, where cancer control is a challenge due to funding, technical resources, and limited human resources, prevention through cervical screening and early detection can provide great benefits in cancer control[20,21]. In places where screening strategies have not been successful, intervention through immunization with HPV will play a significant role in controlling the disease[26]. A special population is patients treated with CIN2 + with LLETZ (large loop excision of the transformation zone), where the quadrivalent vaccine was applied after the procedure in doses 0-2-6, finding that it could reduce the risk of recurrence by 80%.

Genital warts represent another frequent pathology that also has an impact on the morbidity of women. Genital warts are generally associated with under registration; the prevalence is 2.28% (CI 95%: 2.02 to 2.56) in Peru and apparently these are cases usually seen in medical offices[27].

Screening with HPV is the ideal test as primary screening. This test should be used especially in places where no response has been found with other strategies[28]. The HPV test has high sensitivity and reproducibility compared to cytology. Additionally, the HPV test could be used in the future with self-sampling[18,24]. Another benefit is that the interval between a HPV test and the next screening can be extended to 5 years[28]. A drawback of the HPV test is the high prevalence compared to cytology. This, in turn, increases the number of patients referred to colposcopy. For this reason, a prior triage test must be found. This unknown triage test is intended to be found by the ESTAMPA study[29].

It can be concluded that there is scientific evidence of the efficacy of the HPV vaccine against pre-malignant lesions and genital warts; but, given the long latency time between HPV infection and invasive cancer, the real effect of the impact of vaccination on incidence of cervical cancer will show up after several years[16]. Australia was one of the first countries to include the vaccine as a national vaccination program in April 2007 with girls 12-13 years old and with catch-up in women younger than 26 years; in 2013 it included children 12-13 years with catch-up in children up to 15 years; the coverage achieved was 70%. Currently, if the high vaccination and screening coverage is maintained, it could be considered that cervical cancer will be a disease of the past for that country.

The vaccination strategy in Peru is for girls in the 5th grade of elementary schools, chosen as the target population. This intervention strategy depends on each country.

Given the coronavirus pandemic, it is expected that the vaccination schedule will have to be modified. So, moving to a 2-dose strategy (0-12 months) in schools would be an option, because it would allow a single visit for the first dose in the 5th grade of elementary and a second dose in the 6th grade of elementary, a vaccination scheme that is managed in different countries.

With the implementation of vaccination in Latin America, a high impact is expected in the reduction of cases with cervical cancer, but the efficacy of the vaccination program is still a challenge at the regional level. The cost-effectiveness studies of the HPV vaccine in women in Peru after 10 years of implementation suggest that they are cost-effective compared to the unvaccinated group[28]. The HPV vaccine is a very cost-effective strategy in Peru according to the WHO's recommendations. In conclusion, screening and vaccinating is more cost-effective than screening only. In a systematic review of cost-effectiveness studies on gender-independent G9 vaccine, it was confirmed the health and economic benefit of the introduction of vaccination programs because the increase in the cost-effectiveness rate does not exceed the respective local economic limits in any of the studies.

We should use formative research as an introduction strategy for the HPV vaccine, which aims to understand the sociocultural environment of the health system and provide the research keys to share the HPV vaccine introduction programs. We should also use participatory community-based research, which will provide techniques to help implement cervical screening, treatment and vaccination processes[30,31]. The next genera-

tion of vaccines could increase the range of protection against HPV[16] and perhaps decrease the regimen to a single dose.

Finally, the HPV vaccine has been shown to be effective, safe, and well tolerated. The coverage against cervical cancer with G4 is 70% of protection; while the coverage with G9 vaccine is 90% of protection. There are challenges in the HPV vaccine intervention strategy to achieve greater coverage. It is important to emphasize that the incidence of cervical cancer has not changed in the last 10 years despite efforts in secondary prevention. Therefore, in these scenarios, the implementation of an adequate vaccination program with high coverage could decrease the incidence of the disease. We must continue to use for prevention:

- Strengthen the education of the population about cervical cancer and the benefit of prevention[32]
- Implement vaccination programs with coverage of at least 90% by the age of 15
- Implement screening programs with coverage of at least 70% with a high performance test by the age of 35 and 45
- Incorporate the use of the *Papillomavirus* molecular test for the primary screening of cervical cancer
- Ensure the treatment of premalignant and malignant lesions of at least 90% of patients[33]
- Identify the triage test after the positive HPV test to adequately direct the cases and adequately refer the cases to colposcopy.

The main multifactorial barriers to HPV vaccination are limited knowledge of HPV and misguided safety concerns. The implementation of the HPV vaccine in Latin American countries will need to adapt to a school-based vaccination program, followed by integrated monitoring to be able to reach the expected coverage[34].

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