Review article
Ginecol Obstet Mex 2024; 92 (6): 200-206.

https://doi.org/10.24245/gom.v92i6.

Nonavalent vaccine against human papillomavirus: a strategy to prevent cervical cancer.

Vacuna nonavalente contra el virus del papiloma humano: una estrategia para prevenir el cáncer de cuello uterino

Andrés Felipe Anaya Rodríguez

Abstract

BACKGROUND: Cervical cancer is a public health problem due to its high incidence. Its main cause is the human papillomavirus transmitted by sexual contact. One prevention tool is immunization. At present there are three vaccines, and the nonavalent is the most recent.

OBJECTIVE: To analyze the recent literature and describe the findings with the application of the nonavalent vaccine in patients with cervical cancer.

METHODOLOGY: Search of articles in the Pubmed database with the descriptor "nonavalent", and the MeSH terms "recombinant nonavalent human papillomavirus vaccine", "human papillomavirus vaccines" and "cervical cancer", with adverse reactions, effectiveness, and impact of the nonavalent vaccine against cervical cancer.

RESULTS: We found 107 articles, of which 80 were excluded due to duplicates, confusing titles and incomplete abstracts, and lacking data related to the study. In the end, only 27 sources were analyzed.

CONCLUSIONS: The nonavalent vaccine protects against five high-risk genotypes, which is more than other vaccines. It is effective against diseases caused by human papillomavirus, including cervical intraepithelial neoplasia and cervical cancer. It also has a safety profile like that of its predecessor vaccines, although its effectiveness is linked to other factors.

KEYWORDS: Human papillomavirus nonavalent vaccine; Uterine cervical cancer; Effectivity, Safety.

Resumen

ANTECEDENTES: El cáncer de cuello uterino es un problema de salud pública debido a su alta incidencia. Su causa principal es el virus del papiloma humano trasmitido por contacto sexual. Una herramienta de prevención es la inmunización. En la actualidad existen tres vacunas; de ellas, la nonavalente es la más reciente.

OBJETIVO: Investigar la bibliografía reciente y describir los desenlaces con la aplicación de la vacuna nonavalente a pacientes con cáncer de cuello uterino.

METODOLOGÍA: Búsqueda de artículos en la base de datos Pubmed con el descriptor "nonavalente" y los términos MeSH "vacuna recombinante nonavalente contra el virus del papiloma humano", "vacunas contra el virus del papiloma humano" y "cáncer de cuello uterino"; lo anterior con las reacciones adversas, efectividad y repercusión de la vacuna nonavalente contra el cáncer de cuello uterino.

RESULTADOS: Se encontraron 107 artículos de los que se excluyeron 80 por duplicados, títulos confusos y resúmenes incompletos, sin aporte de datos referentes al estudio. Al final, solo se analizaron 27 fuentes.

Surgeon physician, FOSCAL Clinic, Bucaramanga, Santander, Colombia.

Received: March 2024

Accepted: May 2024

Correspondence
Andrés Felipe Anaya Rodríguez
andresfar061@gmail.com

This article should be cited as: Anaya-Rodríguez AF. Vacuna nonavalente contra el virus del papiloma humano: una estrategia para prevenir el cáncer de cuello uterino. Ginecol Obstet Mex 2024; 92 (6): 200-206.

CONCLUSIONES: La vacuna nonavalente tiene alcance en contra de cinco genotipos de alto riesgo: más que otras vacunas. Es efectiva contra las enfermedades provocadas por el virus del papiloma humano, incluidas las neoplasias intraepiteliales cervicales y el cáncer de cuello uterino. Además, tiene un perfil de seguridad similar al de las vacunas predecesoras, aunque su efectividad está ligada a otros factores.

PALABRAS CLAVE: Vacuna nonavalente contra el virus del papiloma humano; cáncer de cuello uterino; efectividad; seguridad.

BACKGROUND

The human papilloma virus is a DNA type virus which comes from the *Papillomaviridae* family, with a significant tropism for squamous epithelial cells. For this virus to infect, it requires to enter the epithelial base stem cells, which are covered by layers of differentiated cells; hence the virus must enter and infect each one of these layers until it reaches basal cells.

The cervix's squamocolumnar junction is very vulnerable, and it is there where the infection can easily reach its target.[1] Independently of its genotype, 90% of the infections from this virus are cured within the first two years of acquiring it.[2] The human papillomavirus can be carcinogenic, because of its viral components, especially E6 and E7, which cause abnormal cell growth and chromosome instability. This not only depends on the virus, but also on the infection site and the persistence, because when the infection starts at the squamocolumnar junction there can't be an adequate control of basal cells. Also, other factors are necessary to influence the natural history of the disease, such as the immune state of the patient, smoking, the use of oral combined contraceptives, multiparity, and a history of other sexually transmitted diseases.[3]

Cervical cancer is still a public health issue due to its important repercussions in society, despite multiple programs and existing prevention strategies. From a global point of view, cervical cancer is the fourth most frequent type of neoplasia.[4] However, its epidemiology largely depends on each county's development, given that in low and mid income countries, it is the second most frequent cancer.[5] Because the main cause for cervical cancer is the human papillomavirus, which is a pathogen transmitted by sexual contact, one of the main prevention strategies is vaccination.[6] The human papillomavirus is also a factor for other diseases, and vaccination contributes not only to the protection of women, but also of men.[7] There are bivalent vaccines (strains 16 and 18), and tetravalent vaccines (strains 6, 11,16, and 18), which have showed to be effective, even in high risk populations.[8] At the end of the year 2014, the Food and Drug Administration (FDA) approved the nonavalent vaccine,[9] which also has an effect of strains 31,33,45,52, and 58.[5] So, considering its recent development, it is necessary to review what has been published and analyze the different outcomes, adverse reactions, effectivity, and repercussions as a preventive method for cervical cancer.

METHODOLOGY

Retrospective study conducted by means of a literature review in the PubMed database, with the "nonavalent" search word, and the MeSH terms

"human papillomavirus recombinant vaccine nonavalent", "human papillomavirus vaccines", and "cervical cancer". *Inclusion criteria*: observational studies, cases and controls, systematic reviews, and meta-analyses. The applied filters were date of publication within the last 10 years, conducted on humans, and written in English or Spanish. The titles of the articles were evaluated, and those which were related to the subject under study were selected. The abstracts of each article were reviewed, and those considered relevant were selected. *Exclusion criteria*: research protocols and articles which did not study the application of the nonavalent vaccine in relation to cervical cancer prevention.

RESULTS

Thirty-three articles that met the inclusion criteria were selected for their analysis. From among these, those conducted in developed countries showed evidence for the potential of the vaccine to not only prevent cervical cancer, but also intraepithelial cervical neoplasms, and other diseases related with the human papillomavirus. Compared with previous vaccines, the nonavalent, which is active against other high-risk strains, can diminish the incidence of cervical cancer between 15-20%,[10-12] and a 17% of cervical intraepithelial neoplasms. This last finding has been underestimated because the genotypes covered by the vaccine cause 82% of these lesions.[11] This means that it could protect against 25 to 33% of high-grade cervical neoplasms, and 12 to 22% of the low-grade ones.[13] A study conducted in Brazil, Mexico, India, and China found that when the coverage against strains 31, 33, 45, 52, and 58 is added, the preventive percentage against invasive cervical cancer increases 12 to 19%.[14]

With the current reach of bivalent and tetravalent vaccines, the incidence of cervical cancer could be reduced in 73%, and its mortality in 49%.[10] With adequate prevention programs and a reach of 60% of girls, the incidence of cervical cancer could decrease in 92%, and 96% for cervical intraepithelial neoplasms.[11]

A study conducted in Sweden concluded that the nonavalent vaccine could cover up to 90% of the grade 3 cervical intraepithelial neoplasms, and 97% of invasive cervical cancer, while its predecessors have only a 62 and 73% effectiveness, respectively.[15] Another study showed the same coverage percentage of the nonavalent vaccine for grade 3 cervical intraepithelial neoplasms.[16] This could have a positive impact on public health systems by reducing costs related to the treatment of theses lesions.[17] It is estimated that a sevenfold decrease of mortality could be reached with nonavalent programs, unlike screenings which only achieve a two to fourfold decrease.[18] The cost-benefit of the application of the nonavalent vaccine is calculated in approximately 65 thousand American dollars per quality-adjusted life year. For this to be the same for other vaccines, it would be necessary to increase their reach in 11%, which would imply an expense of millions.[10] Something to keep in mind is that one of the criteria for the change of vaccination scheme with the nonavalent vaccine to be cost-effective, is that its price per dose not be above 13 dollars, as that of the tetravalent, nor 18 dollars of the bivalent.[19-21]

Regarding the vaccination scheme, less than three doses are suggested to be enough to protect against the human papillomavirus infection, but the length of the effect is unknown. Because of this, 1 or 2 doses can be effective, but insufficient.[10] Also, the vaccination after 18 years of age is less cost-effective.[21] About the application of the vaccine in previously immunized patients with three doses of the tetravalent vaccine, it has been observed that the immune response is higher for the included serotypes, while the 5 newly introduced ones had a relatively low response,[22] which may be due to the lack of signs of a cross-reaction.[11]

https://doi.org/10.24245/gom.v92i6.

Repercussions on health and society

In the past 50 years, the prevalence of human papillomavirus infection has increased because of changes in sexual behavior.[18] Thus, the prevalence of neoplastic lesions and cervical cancer has increased as well, situation which calls for the implementation of strategies with better and broader reach. Several studies show that the cost-effectiveness of the nonavalent vaccine is better than previous ones,[10,11,13,17,20,23-24] and this is associated with the prevalence of diseases caused by the 5 new genotypes.[22] Despite the aforementioned, a study conducted in China did not find the same results in young women not previously infected by the human papillomavirus (unless it is considered not only for cervical cancer prevention but for other lesions caused by this virus).[25] Similarly, another study from Singapore found evidence that the nonavalent vaccine doesn't represent a cost-effective option when compared to the bivalent vaccine. Despite it reducing the incidence and mortality of cervical cancer, its inclusion would be justified if the cost were reduced.[26]

In a study made with a mathematical model, an absolute risk of 2 for every 100,000 vaccinated women was calculated, compared to 20 for every 100,000 non-vaccinated women with the nonavalent vaccine, having a reach of 60%. It is necessary to consider the population being vaccinated, and its reach, because this can favor the vaccination with the biological predecessors.[27] It is also necessary to analyze the repercussions of the new vaccine in relation with the broad spectrum of diseases against which it is useful. For example, it was found in Spain that the vaccine is cost-effective if it is applied to men and women, because besides preventing cervical cancer, it decreases the number of cases of genital warts, and the incidence of anal cancer.[28]

Because of not counting with the indirect costs and the loss of income due to cancer incapacitation, there is an underestimation of the economic advantages that this preventive strategy would provide. Also, because its reach is 20% higher than that of the first-generation vaccines, there would be a decrease in cytology samples, which has a repercussion in public health.[11] This way, it provides more advantages with the same, or lower social cost. The incidence of cervical cancer is diminished, as well as the cost of health care services.[10] Epidemiological achievements are reachable if it is possible to immunize more than 80% of a population.[13]

Among the risks that may arise, unprotected cases could be detected late if screenings for precancerous lesions and cervical cancer are reduced, overestimating the effectiveness of the vaccine. Therefore, immunization is advised first, and then the continuation of screening programs to mitigate residual risks.[18] There is evidence that if the reach of the vaccine is broad, screening could be eliminated, or only 1 or 2 check-ups in a patient's life would be necessary.[29]

Regarding the social sphere, the emotional suffering related with screening reports, worries about fertility potential, the possibility of a life-long incapacity, medical treatments, follow-ups, and the possibility of requiring a surgical intervention, can be reduced.[11,17]

Vaccine safety: effects and adverse reactions

The nonavalent vaccine has showed that its safety profile is comparable to that of the tetravalent vaccine,[22] although with a higher likelihood of local reactions, or reactions related with the injection site, because of the excipients with which the vaccine is made;[12] the difference being of 6%.[19,30] The adjuvant used in the nonavalent vaccine is more than double that of the tetravalent, and it also has more particles which are similar to the virus.[31] The most common adverse reactions in the injection site were pain, edema, erythema, and pruritus.[30]

The most frequent systemic symptoms with the nonavalent vaccine were headache, fever,[22]

nausea, dizziness, and fatigue.[30] Other relevant effects were Guillain-Barre, anaphylaxis, seizures, and thromboembolisms, from which no relation was found.[32] Regarding the application of the vaccine to pregnant women, the proportion of live births, obstetric complications, spontaneous abortions, and late fetal deaths, were observed to happen with either vaccine.[30] A cohort observational study analyzed the exposure to the vaccine shortly before pregnancy and after it, and no association was found with spontaneous abortions or birth adverse outcomes, such as pre-term birth, small size for gestational age, and anatomical defects.[33]

Regarding immunization with the nonavalent vaccine in patients previously vaccinated with the tetravalent vaccine, a higher rate of edema and erythema at the site of injection was found ,[21] and about the concomitant administration of other vaccines, a slight increase of local reactions was observed.[22]

DISCUSSION

The human papillomavirus is increasingly frequent because of changes in sexual habits and unsafe practices,[18] and this has increased the incidence of pre-neoplastic lesions and cervical cancer, which is a disease of public health interest, because it is susceptible of being prevented with different strategies. After the creation of bivalent and tetravalent vaccines, the nonavalent vaccine was developed, providing immunization against L1 proteins (which are important for the entrance of the virus) of 2 genotypes of low (6 and 11) and high (16 and 18) risk, which the predecessors already contained, and 5 new genotypes of high risk (31, 33, 45, 52, and 58),[31] which protect against 90% of the cervical cancers.[19]

The nonavalent vaccine is a cost-effective strategy because of the percentage of preventable cases.[10-11,13,17,20] However, for the vaccine to show its full potential, it is necessary to increase its population reach, for the effect to be reflected in savings in the cancer treatment budget. Individually, it would improve the quality of life of women, and it would diminish emotional distress.[11]

The nonavalent vaccine has a safety profile like that of its predecessors,[22] although it causes local reactions such as pain, erythema, pruritus, and edema more frequently,[30] perhaps because of the composition of the vaccine. The most frequent systemic adverse reactions are headache and fever.[22] Currently, no important side-effect is known that can affect the integrity of the population.

The present study was aimed at analyzing the vaccine's impact on cervical cancer, because of its global importance, but the nonavalent vaccine can prevent other conditions such as genital warts, and anal cancer,[28] so the knowledge and application of these strategies is also important.

CONCLUSIONS

Immunization with the nonavalent vaccine is an effective strategy against cervical cancer. Said immunization is achieved by reaching high-risk human papillomavirus genotypes, just as it is with the application of the bivalent, and tetravalent vaccines, and the safety profile of the nonavalent one is similar to that of the predecessor vaccines. However, it requires of a broad reach, ease of access to the population, education to promote its acceptance, and the concomitant application of other public health strategies.

REFERENCES

1. Harden ME, Munger K. Human papillomavirus molecular biology. Mutat Res - Rev Mut Res 2017; 772: 3-12. https://doi.org/10.1016/j.mrrev.2016.07.002
2. Gravitt P, Winer R. Natural history of HPV infection across the lifespan: role of viral latency. Viruses 2017; 9: 267. http://dx.doi.org/10.3390/v9100267

https://doi.org/10.24245/gom.v92i6.

3. Graham SV. The human papillomavirus replication cycle, and its links to cancer progression: a comprehensive review. Clin Sci 2017; 131 (17): 2201-21. https://doi.org/10.1042/CS20160786
4. Buskwofie A, David-West G, Clare CA. A Review of Cervical Cancer: Incidence and Disparities. J Natl Med Assoc 2020; 112 (2): 229-32. https://doi.org/10.1016/j.jnma.2020.03.002
5. Vu M, Yu J, Awolude OA, et al. Cervical cancer worldwide. Curr Probl Cancer 2018; 42 (5): 457-65. https://doi.org/10.1016/j.currproblcancer.2018.06.003
6. Yousefi Z, Aria H, Ghaedrahmati F, Bakhtiari T, et al. An Update on human papilloma virus vaccines: History, types, protection and efficacy. Front Immunol 2022; 12. http://dx.doi.org/10.3389/fimmu.2021.805695
7. Aranda-Flores CE. Infección por el virus del papiloma humano en varones. Ginecol Obstet Mex 2015; 83: 697-706. https://ginecologiayobstetricia.org.mx/articulo/infeccion-por-el-virus-del-papiloma-humano-en-varones
8. Lazcano-Ponce E, Salmerón J, González A, et al. Prevention and control of neoplasms associated with HPV in high-risk groups in Mexico City: The Condesa Study. Salud Publica Mex 2018; 60 (6): 703-12. https://doi.org/10.21149/10034
9. Johnson CA, James D, Marzan A, Armaos M. Cervical cancer: an overview of pathophysiology and management. Semin Oncol Nurs 2019; 35 (2): 166-74. https://doi.org/10.1016/j.soncn.2019.02.003
10. Durham DP, Ndeffo-Mbah ML, Skrip LA, Jones FK, et al. National and state-level impact and cost-effectiveness of nonavalent HPV vaccination in the United States. Proc Natl Acad Sci USA 2016; 113 (18): 5107-12. https://doi.org/10.1073/pnas.1515528113
11. Boiron L, Joura E, Largeron N, Prager B, et al. Estimating the cost-effectiveness profile of a universal vaccination programme with a nine-valent HPV vaccine in Austria. BMC Infect Dis 2016; 16: 153. https://doi.org/10.1186/s12879-016-1483-5
12. Forster AS, Waller J. Taking stock and looking ahead: Behavioural science lessons for implementing the nonavalent human papillomavirus vaccine. Eur J Cancer 2016; 62: 96-102. https://doi.org/10.1016/j.ejca.2016.04.014
13. Riethmuller D, Jacquard AC, Lacau St Guily J, Aubin F, et al. Potential impact of a nonavalent HPV vaccine on the occurrence of HPV-related diseases in France. BMC Public Health 2015; 15: 453. https://doi.org/10.1186/s12889-015-1779-1
14. Serrano B, Alemany L, Alonso de Ruiz P, Tous S, et al. Potential impact of a 9-valent HPV vaccine in HPV-related cervical disease in 4 emerging countries (Brazil, Mexico, India and China). Cancer Epidemiology 2014; (38): 748-56. https://doi.org/10.1016/j.canep.2014.09.003
15. Egli-Gany D, Spaar Zographos A, Diebold J, Masserey Spicher V, et al. Human papillomavirus genotype distribution and socio-behavioural characteristics in women with cervical pre-cancer and cancer at the start of a human papillomavirus vaccination programme: the CIN3+ plus study. BMC Cancer 2019; 19 (1): 111. https://doi.org/10.1186/s12885-018-5248-y
16. Inturrisi F, Lissenberg-Witte BI, Veldhuijzen NJ, Bogaards JA, et al. Estimating the direct effect of human papillomavirus vaccination on the lifetime risk of screen-detected cervical precancer. Int J Cancer 2021; 148 (2): 320-28. https://doi.org/10.1002/ijc.33207
17. Capra G, Giovannelli L, Matranga D, Bellavia C, et al. Potential impact of a nonavalent HPV vaccine on HPV related low-and high-grade cervical intraepithelial lesions: A referral hospital-based study in Sicily. Hum Vaccin Immunother 2017; 13 (8): 1839-43. https://doi.org/10.1080/21645515.2017.1319026
18. Petry KU, Bollaerts K, Bonanni P, Stanley M, et al. Estimation of the individual residual risk of cervical cancer after vaccination with the nonavalent HPV vaccine. Hum Vaccin Immunother 2018; 14 (7): 1800-6. https://doi.org/10.1080/21645515.2018.1450125
19. Mariani L, Preti M, Cristoforoni P, Stigliano CM, et al. Overview of the benefits and potential issues of the nonavalent HPV vaccine. Int J Gynaecol Obstet 2017; 136 (3): 258-65. https://doi.org/10.1002/ijgo.12075
20. Ng SS, Hutubessy R, Chaiyakunapruk N. Systematic review of cost-effectiveness studies of human papillomavirus (HPV) vaccination: 9-Valent vaccine, gender-neutral and multiple age cohort vaccination. Vaccine 2018; 36 (19): 2529-44. https://doi.org/10.1016/j.vaccine.2018.03.024
21. Chesson HW, Laprise JF, Brisson M, Markowitz LE. Impact and cost-effectiveness of 3 doses of 9-valent human papillomavirus (HPV) vaccine among US females previously vaccinated with 4-Valent HPV Vaccine. J Infect Dis 2016; 213 (11): 1694-700. https://doi.org/10.1093/infdis/jiw046
22. Lopalco PL. Spotlight on the 9-valent HPV vaccine. Drug Des Devel Ther. 2017; 11: 35-44. https://doi.org/10.2147/DDDT.S91018
23. Mahumud RA, Alam K, Dunn J, Gow J. The cost-effectiveness of controlling cervical cancer using a new 9-valent human papillomavirus vaccine among school-aged girls in Australia. PLoS One 2019; 14 (10): e0223658. https://doi.org/10.1371/journal.pone.0223658
24. Michaeli DT, Stoycheva S, Marcus SM, Zhang W, et al. Cost-effectiveness of bivalent, quadrivalent, and nonavalent HPV Vaccination in South Africa. Clin Drug Investig 2022; 42 (4): 333-43. https://doi.org/10.1007/s40261-022-01138-6
25. Jiang Y, Ni W, Wu J. Cost-effectiveness and value-based prices of the 9-valent human papillomavirus vaccine for the prevention of cervical cancer in China: an economic modelling analysis. BMJ Open 2019; 9 (11): e031186. https://doi.org/10.1136/bmjopen-2019-031186
26. Phua LC, Choi HCW, Wu J, Jit M, et al. Cost-effectiveness analysis of the nonavalent human papillomavirus vaccine for the prevention of cervical cancer in Singapore. Vaccine. 2022; 39 (16): 2255-63. https://doi.org/10.1016/j.vaccine.2021.03.040

27. Naslazi E, Hontelez JAC, Naber SK, van Ballegooijen M, et al. The differential risk of cervical cancer in HPV-vaccinated and -unvaccinated women: a mathematical modeling study. Cancer Epidemiol Biomarkers Prev 2021; 30 (5): 912-19. https://doi.org/10.1158/1055-9965.EPI-20-1321

28. De la Fuente J, Aguado JJH, Martín MS, Boix PR, et al. Estimating the epidemiological impact and cost-effectiveness profile of a nonavalent HPV vaccine in Spain. Human Vaccines & Immunotherapeutics 2019; 15 (7-8) 1949–61. http://dx.doi.org/10.1080/21645515.2018.1560770

29. Simms KT, Smith MA, Lew JB, Kitchener HC, et al. Will cervical screening remain cost-effective in women offered the next generation nonavalent HPV vaccine? Results for four developed countries. Int J Cancer 2016; 139 (12): 2771-80. https://doi.org/10.1002/ijc.30392

30. Joura EA, Giuliano AR, Iversen OE, Bouchard C, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015; 372 (8): 711-23. https://doi.org/10.1056/NEJMoa1405044

31. Toh ZQ, Kosasih J, Russell FM, Garland SM, et al. Recombinant human papillomavirus nonavalent vaccine in the prevention of cancers caused by human papillomavirus. Infect Drug Resist 2019; 12: 1951-67. https://doi.org/10.2147/IDR.S178381

32. Logroño IEN, Macías ACC, Macías LGC. Eficacia de la vacuna nonavalente en la prevención de la infección por virus papiloma humano (HPV) y cáncer cervical. La Ciencia al Servicio de la Salud 2019; 9 (2): 30-7. http://revistas.espoch.edu.ec/index.php/cssn/article/view/88

33. Kharbanda EO, Vazquez-Benitez G, DeSilva MB, Naleway AL, et al. Association of inadvertent 9-valent human papillomavirus vaccine in pregnancy with spontaneous abortion and adverse birth outcomes. JAMA Netw Open 2021; 4 (4): e214340. https://doi.org/10.1001/jamanetworkopen.2021

https://doi.org/10.24245/gom.v92i6.