

Vaccination against human papilloma virus in men: situation and proposals

Vacunación contra el virus del papiloma humano en hombres: situación y propuestas

Javier Cortés¹ , **Ángel Gil²** , **Federico Martín³** , **Francisco Xavier Bosch⁴** , **José Manuel Ramón y Cajal⁵**

1. Royal Academy of Medicine of the Balearic Islands.

2. Professor of Preventive Medicine and Public Health at the Rey Juan Carlos University.

3. Coordinator and Head of the Pediatric Service. University Clinical Hospital of Santiago de Compostela. Coordinator Group of Genetics, Vaccines, Infections and Pediatrics. Sanitary Research Institute of Santiago de Compostela.

4. Consultant Catalan Institute of Oncology. Associate Professor Open University of Catalonia.

5. Gynecology Service. Hospital of San Jorge, Huesca

Corresponding author

Javier Cortés

E-mail: ortes@oceca.es

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Abstract

The causal epidemiology of papillomavirus pathology in man and its incidence and the status of its preventive activity in Spain are described, which does not conform to the recommendation that scientific evidence has formulated and that many countries in our environment are following. Lines of action are detailed in this regard that are considered preferred from the point of view of health political action.

Keywords: Vaccination, human papilloma virus, prevention.

Resumen

Se describe la epidemiología causal de la patología papiloma virus causal en el hombre y su incidencia y la situación de su actividad preventiva en España, no conforme con la recomendación que la evidencia científica ha formulado y que numerosos países de nuestro entorno sí están siguiendo. Se detallan líneas de acción al respecto que se consideran preferentes desde el punto de vista de acción político – sanitaria.

Palabras clave: Vacunación, virus papiloma humano, prevención.

Introduction

The human papillomavirus (HPV) is a transmission virus associated with sexual activity, not necessarily coital: transmission by skin-to-mucosal contact is an essential condition for contagion to occur¹. The World Health Organization² reports that In the world more than 290 million women are infected with HPV. Actually, it is a universal pathogenic microorganism, since it affects both men and women: around 80-85% of sexually active individuals will be in contact with HPV at some point in their lives. Most of these infections will be controlled by the infected person's immune system, but in general, in 1 or 2 cases out of 10, the infection will persist and put the carrier at risk of developing HPV-dependent disease. At the time, the CLEOPATRE³ study reported

that in Spain 14% of women over 30 years of age were positive for HPV. Right now, the prevalence of HPV DNA in Spanish women is estimated to range between 1.3 and 5%,⁴ which represents a number of female carriers between 350,000 and 900,000.

Knowledge of the structure of HPV and the mechanisms of its oncogenic action⁵ have allowed the development of very effective, safe, effective and efficient strategies for primary and secondary prevention of the pathology it causes, cervical cancer in women –also of the vulva and vagina–, of the penis in men and of the oro-pharynx and anus in both, in addition to skin warts and recurrent respiratory papillomatosis.

This volume of disease constitutes a significant oncological burden⁶. For the National Health System, its treatment represents an annual cost of slightly more than €150 million⁷. Consequently, establishing guidelines and recommendations for population application for its prevention must be a priority. The World Health Organization (WHO) has declared cervical cancer – caused in 100% of cases by HPV⁸– as the first eradicable cancer in our world⁹. To achieve this, implement preventive action in women –very consolidated and in majority application in clinical practice¹⁰– with actions also in men seems absolutely essential.

This work updates and summarizes the evidence in this regard and, in its conclusions, establishes recommendations for preventive action.

Epidemiology of HPV in men

The evidence indicates that the prevalence of genital HPV infection in healthy men is relatively higher than in women, with very important differences published that reach 73% in reference works¹¹, differences attributable to the different populations studied, to the anatomical sites used for the determination and the different HPV detection methods used. Everything shows that the study of HPV infection in men is far from having obtained the solidity of the data obtained in women: we cannot at this time offer a man a solid recommendation on how and in what way to detect HPV.

In prospective multinational studies, it has been observed that up to 50.5% of the men studied were positive for at least 1 type of HPV, oncogenic or not. HPV type 16 was the most commonly detected, up to 6.5%¹², a relevant fact since it is the type most involved in oncological damage¹³. In asymptomatic heterosexual men, the penis and scrotum were the sites in which almost 95% of genital HPV¹¹ infections were detected.

An important aspect is that in men the risk of acquiring an HPV infection does not change with age. This lack of association with age suggests that the prevalence of male HPV infection is relatively constant and may be due to the continual acquisition of new infections throughout life. The good news is that infections in men are less likely to persist than in women: the median time to clearance of an infection in men is 5.9 months, with 75% of infections cleared within¹² months post infection¹⁴, a risk of persistence that decreases more among circumcised men¹⁵.

In relation to the most important locations of causal HPV cancer mentioned above in men, anus and oropharynx, it should be noted that in the “HPV Infection in Men” study, the prevalence of anal HPV in heterosexual men was 12% and the rate of the incidence of anal cancer was 8.1%, a prevalence that was markedly higher –47.2%– among men who had sex with men¹¹.

The incidence of oral HPV infection is higher in adults aged between 31-50 years, and, as in other locations, the persistence of HPV infection in the oral cavity increases with age¹⁶, with a prevalence of HPV infection in the oropharynx in men between 18 and 65 years of 11.5%. It is noted that oral infection is more prevalent in men than in women, with a bimodal distribution throughout life in men, higher in adulthood.

Another characteristic of HPV infection in men is that only 7.7% have antibodies against HPV 6-11-16-18 at 36 months post-infection, with titers 4 to 10 times lower than those of women. This weak seroconversion does not protect against subsequent infections, a protection that is manifested in women¹⁷.

HPV disease in men

A recent publication¹⁵ reports that HPV causes 118 penile cancers in Spain each year and, in men, 522 high-grade intraepithelial lesions of the anus or anal cancers, 603 oropharyngeal cancers, and 28,047 genital warts.

The estimate for Europe is that 325,700 cases of genital warts and 12,700 of oropharyngeal, 1,700 anal, and 1,090 penile cancers are diagnosed annually in men¹⁸. There are no secondary prevention programs against any of these cancers, so primary prevention, vaccination against HPV, is the only possible alternative.

Vaccines against HPV

Once the infectious cause of a disease is known, the primary preventive measure to apply preferentially if available is vaccination against the causal agent. The two HPV vaccines currently available, Cervarix® and Gardasil9®, do not include a gender difference in the indication for their administration in their technical data sheet approved and disseminated by the European Medicines Agency: both are said to be vaccines indicated for immunization of people from the age of 9 years^{19,20}. Consequently, male vaccination against HPV is approved by all European national regulatory agencies.

The degrees of efficacy of both vaccines against pre-cancerous lesions of the cervix, vulva, vagina and anus are very high, always greater than 90–95%^{19,20}. In addition, on June 15, 2020, the Food and Drug Administration of the United States specifically approved the indication of Gardasil9® for the primary prevention of oropharyngeal cancers caused by HPV²¹.

We therefore have highly effective vaccines against cancers caused by HPV, but are they safe? Is their application to men efficient?

Although it is true that at some point adverse reactions occurred that initially seemed associated and only initially raised some doubts, the safety of HPV vaccines is unquestionable after more than 15 years of use and hundreds of millions of doses administered. The latest review by the WHO is forceful in its report²²: its vaccine safety review committee reaffirms that no doubt should be raised about the safety of HPV vaccines and that political decisions based on unverified data that induce doubt about its safety and that consequently lower the quality of the recommendation for its use can cause considerable damage to the health of the affected community.

The most recent reports on the cost/benefit of the application of HPV vaccines in population-based Public Health programs for boys, from France²³ and the Netherlands²⁴ and from other countries and scenarios²⁵, demonstrate their high efficiency: to the benefit of Prevention of HPV lesions in them adds to the impact on transmission to girls. Collecting this evidence, already 53 countries from the five continents – 28 Europeans – include financed vaccination against HPV in children in the vaccination schedules of their Public Health programs²⁵. An associated benefit that has been highlighted of male vaccination is that HPV could be eradicated even in conditions of low coverage in female vaccination²⁶.

In Spain, the vaccination calendar published by the Ministry of Health 27 includes HPV vaccination for adolescent women according to the following guideline:

- Vaccination at 12 years of age: 2 doses will be administered at least 5-6 months apart (depending on the vaccine used).
- Vaccination between 13 and 18 years: Only adolescents who have not been vaccinated, or who have not received the complete schedule, will be vaccinated. Two doses will be administered at least 5-6 months apart (depending on the vaccine used).
- If vaccination is started after 14 or 15 years of age, 3 doses will be administered with a schedule of 0, 1-2, 6

The Advisory Committee on Vaccines of the Spanish Association of Pediatrics states that vaccinating boys within the current Spanish vaccination calendar should be an immediate recommendation, in line with the proposal of the European Center for Diseases Prevention and Control²⁷. This recommendation has not been collected, however, in the latest edition of the "Cancer Strategy of the National Health System"²⁸, unlike the European plan against Cancer, published in the same year, which not only includes the indication of male vaccination, but also establishes vaccination against HPV in girls and boys as one of the emblematic initiatives of plan²⁹.

HPV vaccination coverage in Spain

A crucial aspect of all vaccination procedures in Public Health is to achieve sufficient coverage to, in addition to protecting the vaccinated, achieve herd immunity and block and perhaps prevent the circulation of the virus. Coverage greater than 70% would be required to achieve these objectives³⁰. In Spain, the latest report available from the Ministry of Health³¹ details that in 2019 a satisfactory coverage of 79% was achieved in the administration of the second dose of the HPV vaccine to girls born in 2006, with a range that goes from 75.4% in Andalusia to 91% in La Rioja, although it should be noted that the table does not include the data on the coverage achieved in Aragon, Asturias, the Balearic Islands and the Canary Islands. Working to maintain or improve this coverage when –as soon as possible– the boys are included in the program, constitutes a priority and a victory for equality³², as Kevin Pollock titled in his very recent article communicating the inclusion of the males in the UK vaccination programme. Along these lines is the publication of the Evaluation Service of the Canary Islands Health Service, supported by the Spain Ministry of Health³³, in which it is stated verbatim that "it would be advisable to introduce the universal vaccination strategy against HPV with a vaccination schedule of two dose at 12 years of age for both sexes in Spain, with the condition of reviewing its cost-effectiveness with new evidence on the effectiveness, costs or alternative guidelines".

A review of the vaccination calendar in execution in all the Spanish Autonomous Communities and the two Autonomous Cities carried out in September 2021, was able to document that only in Euskadi³⁴, Cantabria³⁵, Catalonia³⁶ and Castilla y León³⁷ is it implemented, with different age indications and circumstances, vaccination of males.

Conclusions

1. The human papillomavirus is the most common sexually transmitted infection, and is considered a universal pathogen, since it affects both women and men.
2. In recent years, progress has been made in understanding the burden of disease associated with HPV: it is currently estimated that HPV is responsible for 5% of cancer that occurs in humans.
3. Men can develop cancers of the anus, penis, head, and neck that are related to HPV.
4. The prevalence of genital warts is high and similar in both sexes.
5. Unlike what happens with cervical cancer, cancers that affect men lack secondary prevention methods (screening).
6. The available vaccines against HPV have proven to be effective, safe, effective and efficient in their application to women and men.

7. A gender-independent HPV vaccination program would be more equitable than the situation that currently exists in access to this vaccine in our country, it could provide direct health benefits not only for women, but also for men and women, it would maximize the prevention of cervical cancer, accelerating the global control of HPV infection, in addition to helping to mitigate the negative impact on the prevention of possible low female vaccination coverage.

Definitely, the WHO has formally requested³⁸ that HPV vaccination be extended immediately to all eligible populations, saying that "...there is also a clear risk in terms of missed opportunities for the expansion of other immunization services, for example, the safe and effective implementation of HPV vaccines. Low-income countries need timely access to vaccines at sustainable prices and timely financial support", a position also defended by the European Center for Disease Control and Prevention in a recent publication³⁹. On the other hand, international reference sources⁴⁰ call for a global solidarity policy aimed at the elimination of HPV-dependent pathology.

The authors of this work formally align themselves with these requests and make them their own, hoping that the Spanish Health Institutions will take the appropriate measures to comply with them.

Conflict of interests

JC has received travel and/or research grants and/or speaking and/or consulting fees from Genomics, GSK, Merck, Procare Health, Qiagen, Roche, and SPMSD.

AG has received grants for travel and/or fees for conferences and/or sponsorship of projects and/or consultancies from Sanofi Pasteur, MSD, GSK, Seqirus and Pfizer.

FM has received fees from Biofabri, GSK, Pfizer, Sanofi Pasteur, MSD, Seqirus, Novavax and Janssen as advisor, consultant or speaker outside the scope of this work and has worked as principal investigator in clinical trials promoted by the aforementioned pharmaceutical companies and , in addition, Ablynx, Regeneron, Roche, Abbott and MedImmune, with fees paid to the Institution. FXB is International Consultant of MSD.

JMRyC has received professional fees for work carried out, conferences and scholarships for assistance in training activities from Roche Diagnostics, Qiagen, GSK and MSD

Bibliography

1. Kjaer SK, Chackerian B, van den Brule AJ, Svare EI, Paull G, Walbomers JM et al.: High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse). *Cancer Epidemiol Biomarkers Prev* 2001; 10: 101-6
2. Available in [https://www.who.int/es/news-room/fact-sheets/detail/sexually-transmitted-infections-\(stis\)](https://www.who.int/es/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis)) Access 01.08.2021.
3. Castellsagué X, Iftner T, Roura E, Vidart JA, Kjaer SK, Bosch FX et al.: Prevalence and genotype distribution of human papillomavirus infection of the cervix in Spain: the CLEOPATRE study. *J Med Virol.* 2012; 84: 947-56.
4. Spanish Society of Epidemiology. Papilloma Virus and Cancer. Available in: <https://www.seepidemiologia.es/documents/dummy/4monografiaVirusPapilomaYCancer.pdf>. Access 02.08.2021
5. Szymonowicz KA, Chen J.: Biological and clinical aspects of HPV-related cancers *Cancer Biol Med.* 2020; 17: 864-78.
6. Available in: <https://www.aecc.es/es/todo-sobre-cancer/que-es-cancer/factores-riesgo> Access 02.08.2021.
7. López, N, Torné A, Franco A, San-Martín, M, Viayna E, Barrull C et al.: Epidemiologic and economic burden of HPV diseases in Spain: implication of additional 5 types from the 9-valent vaccine. *Infect Agent Cancer.* 2018; 13: 15.
8. Walbomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV et al.: Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol.* 1999; 189: 12-9.
9. Ghebreyesus TA, Director General.: Reunión Ejecutiva OMS Intercontinental Hotel, Genève, Confédération Suisse. 19 May 2018.
10. Cortés J, Bosch X, Concha A, González A, Martínón F, Ortiz de Lejarazu R et al.: Asociación Española contra el Cáncer: Documento de posición sobre prevención del Cáncer de Cuello de Útero. *Prog Obstet Ginecol* 2019; 61: 510-44.
11. Giuliano AR, Lazcano-Ponce E, Villa LL, Flores R, Salmeron J, Lee J-H et al.: The human papillomavirus infection in men study: human papillomavirus prevalence and type distribution among men residing in Brazil, Mexico, and the United States. *Cancer Epidemiol Biomarkers Prev.* 2008; 17: 2036-43
12. Ingles DJ, Lin HY, Fulp WJ, Sudenga SL, Lu B, Schabath MB et al.: An analysis of HPV infection incidence and clearance by genotype and age in men: The HPV Infection in Men (HIM) Study. *Papillomavirus Res* 2015; 1: 126-35
13. Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX, de Sanjosé S.: Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *J Infect Dis.* 2010; 202: 1789-99.

14. Giuliano AR, Lee J-H, Fulp W, Villa LL, Lazcano-Ponce E, Papenfuss MR, Abrahamsen M et al.: Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. *Lancet* 2011; 377: 932-40.
15. Albero G, Villa LL, Lazcano-Ponce E, Fulp W, Papenfuss MR, Nyitray AG et al.: Male circumcision and prevalence of genital human papillomavirus infection in men: a multinational study. *BMC Infect Dis.* 2013; 13: 18.
16. Chatuverdi AK, Engels EA, Pfeiffer RM, Hernández BY, Weihong X, Kim E et al.: Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011; 29: 4294-301.
17. Giuliano AR, Viscidi R, Torres N, Ingles DJ, Sudenga SL, Villa LL et al.: Seroconversion Following Anal and Genital HPV Infection in Men: The HIM Study. *Papillomavirus Res.* 2015; 1: 109-15.
18. Stanley M.: Program Research Epidemiology of Cancer. Cambridge Univ. Presented at EUROGIN 2018. 2-5 December. Lisbon. Portugal.
19. Cervarix® summary product characteristics. Available in https://cima.aemps.es/cima/dochtml/ft/07419004/FT_07419004.html Access 03.08.2021.
20. Gardasil9® summary product characteristics. Available in https://cima.aemps.es/cima/dochtml/ft/1151007002/FT_1151007002.html Access 03.08.2021.
21. Available in: <https://search.usa.gov/search?query=gardasil9+expanded&affiliate=fda1> Access 03.07.2021
22. Global Advisory Committee on Vaccine Safety (GACVS). *Weekly Epidemiological Record*: 92; 28. 14 de julio de 2017.
23. Majed L, Bresse X, El Mouaddin N, Schmidt A, Daniels VJ, Pavelyev et al.: Public health impact and cost-effectiveness of a nine-valent gender-neutral HPV vaccination program in France. *Vaccine.* 2021; 39: 438-46.
24. Simons JJM, Vida N, Westra TA, Postma MJ.: Cost-effectiveness analysis of a gender-neutral human papillomavirus vaccination program in the Netherlands. *Vaccine.* 2020; 38: 4687-94.
25. Qendri V, Bogaards JA, Baussano I, Lazzarato F, Vänskä S, Berkhof J.: The cost-effectiveness profile of sex-neutral HPV immunisation in European tender-based settings: a model-based assessment. *Lancet Public Health.* 2020; 5: e592 – e603.
26. Vänskä S, Luostarinen T, Baussano I, Apter D, Eriksson T, Natunen K et al.: Vaccination With Moderate Coverage Eradicates Oncogenic Human Papillomaviruses If a Gender-Neutral Strategy Is Applied. *J Infect Dis.* 2020; 222: 948-56.
27. Available in <https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/vacunas/profesionales/vph.htm> Access 27.08.2021.
28. Available in: <https://vacunasaep.org/profesionales/noticias/VPH-informe-ECDC-vacunacion-varones-y-otros-temas> Access 03.08.2021.
29. European Commission. Europe's Beating Cancer Plan. Communication from the Commission to the European Parliament and the Council 2021. Available in: https://ec.europa.eu/health/sites/default/files/non_communicable_diseases/docs/eu_cancer-plan_en.pdf Access 27.08.2021
30. Marra F, Cloutier K, Oteng B, Marra C, Oglivie G.: Effectiveness and cost effectiveness of human papillomavirus vaccine: a systematic review. *Pharmacoeconomics* 2009; 27: 127-47.
31. Available in: <https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/calendario-y-coberturas/coberturas/docs/Tabla11.pdf> Access 03.08.2021.
32. K Pollock (2019). Adolescent male vaccination in the United Kingdom - a victory for equality. *www.HPVWorld.com*, 94.
33. Linertová R, Guirado Fuentes C, Toledo Chávarri A, Vallejo Torres L, García Pérez L, Delgado Rodríguez J et al.: Vacuna frente a VPH en varones adolescentes: coste-efectividad e impacto presupuestario. Ministry of Health, Consumption and Social Welfare. Evaluation Service of the Canary Islands Health Service; 2020. Health Technology Assessment Reports.
34. Available in <https://www.euskadi.eus/informacion/vacuna-contrael-virus-del-papiloma/web01-a2adik/es/> Access 10.09.2021
35. Available in: <https://saludcantabria.es/index.php?page=vacunaciones> Access 10.09.2021
36. Available in: https://salutpublica.gencat.cat/web/.content/minisite/aspacat/promocio_salut/vacunacions/00manual_de_vacunacions/capitols_i_annexos_manual/apartat_4_vacunes_disponibles/Manual-Vacunacions-apartat-4_12.pdf Access 11.09.2021
37. Available in: <https://www.saludcastillayleon.es/es/vacunaciones/vacunacion-frente-virus-papiloma-humano-vph-2019> Access 11.09.2021
38. Available in <https://www.who.int/news/item/22-07-2021-vaccine-inequity-undermining-global-economic-recovery> Access 02.09.2021.
39. Colzani E, Johansen K, Johnson H, Celentano LP.: Human papillomavirus vaccination in the European Union/European Economic Area and globally: a moral dilemma. *Euro Surveill.* 2021; 26(50).
40. Lehtinen M, Baussano I, Paavonen J, Vänskä S, Dillner J.: Eradication of human papillomavirus and elimination of HPV-related diseases - scientific basis for global public health policies. *Expert Rev Vaccines.* 2019; 18: 153 – 160.