SPECIAL ARTICLE

Vaccination against human papilloma virus in men: situation and proposals
Vacunación contra el virus del papiloma humano en hombres: situación y propuestas

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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 burden. For the National Health System, its treatment represents an annual cost of slightly more than €150 million. Consequently, establishing guidelines and recommendations for population application for its prevention must be a priority. The World Health Organization (WHO) has declared cervical cancer—a 100% of cases by HPV— as the first eradicable cancer in our world. To achieve this, implement preventive action in women—very consolidated and in majority application in clinical practice—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 75% in reference works, 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 one type of HPV, oncogenic or not. HPV type 16 was the most commonly detected, up to 6.5%, a relevant fact since it is the type most involved in oncological damage. In asymptomatic heterosexual men, the penis and scrotum were the sites in which almost 95% of genital HPV 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 within 12 months post-infection, a risk of persistence that decreases more among circumcised men.

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 men.

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 age, 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 women.

**HPV disease in men**

A recent publication 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 men. 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 Gardasil®®, 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.

Consequently, male vaccination against HPV is approved by all European national regulatory agencies.

The degrees of efficacy of both vaccines against precancerous lesions of the cervix, vulva, vagina and anus are very high, always greater than 90-95%. In addition, on June 15, 2020, the Food and Drug Administration of the United States specifically approved the indication of Gardasil® for the primary prevention of oropharyngeal cancers caused by HPV.

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 report[23], 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 France[23] and the Netherlands[24] and from other countries and scenarios[25], 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 programs[25]. An associated benefit that has been highlighted of male vaccination is that HPV could be eradicated even in conditions of low coverage in female vaccination[26].

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 Control[27]. 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 plan[29].

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 objectives[22]. In Spain, the latest report available from the Ministry of Health[27] 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 equality[22], 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 Health[23], 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 Euskadi[34], Cantabria[35], Catalonia[36] and Castilla y León[37] 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 requested\(^\text{38}\) 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 publication\(^\text{39}\). On the other hand, international reference sources\(^\text{40}\) 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 SPF MSD.

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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.

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Bibliography


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