HPV vaccine for men: Where to? (Review)

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Abstract. Human papillomavirus (HPV) is one of the most widespread human pathogens. For a long time, it was treated as an opportunistic infection, but it is in actuality one of the most dangerous carcinogens. It is responsible for numerous malignancies: Cervical, penile, oropharyngeal, vaginal, vulvar and some anal neoplasia. The need for a long-term solution was evident and thus HPV vaccines were proven to be a viable solution. Women and men who have sex with men, and young men are included in the vaccination template. A thorough review using PubMed and other databases that included articles on vaccine templates and targeted male patients was carried out. After review of all of the studies conducted on this subject, there is a clear benefit for HPV vaccination for men. Yet, even with the introduction of a national vaccine program for HPV for women and girls in most developed countries, regarding the male vaccine program, few countries have established a national program. Still, a gender-neutral vaccine remains a controversial issue. It is important to monitor the impact of HPV vaccine in men and the benefits that occur, to inform and spread the results in order to implement this vaccine program worldwide. Any monitoring plan regarding the HPV vaccination must include HPV prevalence, anogenital warts, and anal cancer. The largest impact regarding the range of this type of vaccine is the surveillance of the specific targeted population. HPV vaccine is a very efficient immunization method. Women are obviously the first target, but there are still many contradictions regarding men. Most of the reasons reside in the cost-efficiency aspect, but there is still great debate regarding the most efficient vaccine in the male population.

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Contents

1. Introduction

Human papillomavirus (HPV) is one of the most significant carcinogens in humans, classified in Group 1: 'Carcinogenic to humans' by the International Agency for Research on Cancer (IARC). Its implication in neoplasia has been demonstrated. A vaccine was created due to the need for a cure. Currently, there are more types of vaccines targeting from 2 up to 9 viral strains. Some of them, like the two strain type, have proven effective in women. Others, like the 9 strain type, seem to have higher efficiency in men. The bivalent vaccine has proven its effectiveness in anogenital neoplasia (HPV16 and 18 strains) at present, the nonavalent vaccine adding the HPV31, 33, 45, 52 and 58 strains (1,2).

Overall, this vaccination was initiated in 2006 for women and in 2011 for men. The Advisory Committee on Immunization Practices (ACIP) has also made recommendations for men who have sex with men, and for men and women over 26 and 21 years, respectively (3,4).

The most significant issue is that every country has introduced and applied their variant of the vaccination program. The Nordic countries from Europe have adhered to HPV vaccination and many studies have been conducted there.

Some countries use the bivalent, the quadrivalent and the nonavalent vaccine. For example, the US has used the nonavalent vaccine from 2015. The country that adhered the most to using the HPV vaccine is Australia. This country has a proper vaccination program. The proportion of those vaccinated with three doses is 30 and 70%, respectively, representing women

in the age range of 20-26 and 12-14. In contrast, vaccination with at least one dose of the vaccine in the cohorts of women is 52 and 83% (5).

There is still no consensus regarding the dose that should be used. In some countries such as Japan, the quadrivalent vaccine comprising strains 6, 11, 16 and 18 is the most frequently used.

2. Data collection process

PubMed and Scopus databases were searched for reviews and original articles regarding HPV vaccination in men. The time period for this research was the last 10 years. The aim was to find information concerning the cost effectiveness and efficacy. Side effects were also taken into consideration.

3. Study characteristics

Vaccination of the female population is a well-established point in the vaccination agenda. There are still age-related debates, but most of the issues have been addressed. In contrast, many questions appear regarding the HPV vaccination in men. There are many discussions related to men who have sex with men (MSM). They are prone to more frequent HPV infections and HPV-related neoplasia than other population groups.

4. Results of the individual studies

The HPV vaccine is used in more than 70 countries (6).

The quadrivalent vaccine was tested in a study that included more than 1,000 men aged 16-26, from Japan. Most of the participants were heterosexual, but the study also included a small group of MSM. The efficacy was 83.3% at more than six months. Local side effects including pain and swelling were present in 59.6% of the cases. Systemic side effects such as headache and pyrexia were present in 14.4% of the cases. The immune response was strong in most of the participants, with more than 97% maintaining it in the 36th month. More importantly, the authors noted that a strong decline in immunization appeared after 2013, when some side effects were suspected. Still, other long-term studies (more than 10 years) supported the safety of this vaccine (7). The authors acknowledged the major limitation of their study, which was the short timeline. They emphasized the need for male vaccination, given the low rate of vaccination of Japanese women (7).

In a long-term study (10 years), Goldstone and colleagues found an 85.6% efficacy. They also noted a high efficacy against external genital lesions and external warts not only short term but also long term: 10 years. In addition, the immune response was strong and sustained over time. Systemic side effects were present in a relatively higher proportion than that noted in the Japanese study-31.6% (1,2,8).

As already mentioned, Australia is one of the countries that has fully implemented the vaccination. Males are included in the vaccination program for numerous reasons, such as equity in gender (ethical reason); the real reason was the expected incremental reduction of disease burden in women, given the fact that men are the real reservoirs for this disease. HPV is also an oncogene for other types of neoplasia: Penile, anal, and oropharyngeal. Up to 95% of anal cancers are associated with HPV, and a great proportion of oropharyngeal neoplasia is HPV associated. In addition, a gender-neutral vaccination program assured the general acceptance of the population (9,10).

One specific category of male patients is that of the MSM population. In heterosexual patients, the herd effect is useful, but, for this segment, there are no real benefits from the women vaccination program. Furthermore, MSM are more prone to other HPV-related infection diseases such as genital warts and anal cancer. Some countries such as the UK have implemented pilot studies, in which this category also received the vaccination. It is estimated that there were 3.1% gay or bisexual males in UK, in 2014 (11).

In addition to the real benefits of HPV vaccination, there are also benefits regarding the bisexual population. Not all countries have implemented this vaccination program. In fact, in April 2018, the UK for instance, started a gender-neutral vaccination, which has proven convenient; this way also covering the bisexual population (12).

Another issue that has appeared is the population adherence to this program. In their study, Adjei Boakye *et al* discovered that young adults from the US, who have an education level of high school or lower, or those born outside the country, were more apt to adhere less to the vaccination program. They studied young adults between 18 and 26 years of age from 2014 to 2015, from the National Interview Survey. Apparently, according to sex, men were less willing to participate in the vaccination program (13).

In their work, Soe *et al* (14) approached the financial aspect of expanding the vaccination to women over 26 years of age, heterosexual men and MSM. They split the countries into two categories: Those with high income and those with low income. From the 26 studies selected, three were from low-income countries and the rest from high income countries. Most of the studies concerned the quadrivalent vaccine, while the rest were split into two for the dual vaccine and four for the nonavalent. A total of 16 out of 26 proved cost effective. What the authors noted was that all 4 studies on nonavalent vaccine proved cost effective. Moreover, they observed that the more recent, the more the cost-effectiveness increased.

Age also seemed to be an important factor in these studies. Some of them supported the need to extend vaccination to school-age boys, others did not if the vaccination of women was extended to up to 26 years. Other studies underlined the uselessness of vaccination in heterosexual men and boys if the vaccination in women was 75% or more (14-26).

Their conclusion was that the vaccination in women over 26 years of age would not be cost effective. They stressed the need for vaccination for MSM and the need to attain higher rates of vaccination in this population. Unfortunately, the cost of the vaccine is a milestone, and thus are the number of doses and the length of coverage of the vaccine (14-26).

One interesting study comes from Jach *et al* (27). Their approach in terms of limitations and shortcomings is realistic. They underlined the surrogate cut-off value of all these studies as being the appearance of cervical intraepithelial neoplasia (CIN) lesions, which is a reasonable end point but not ironclad. Also, the monitoring of different sites and HPV strains differ from one study to the other and no study can rule out all sites and strains; henceforth, the need for a protocol that is not ready. From all the manifestations of HPV, genital warts are

the easiest to follow up and the results are encouraging even in men without vaccination; a reduction of 81.8 and 51.1% in men under 21 and between 21- and 30-years is impressive. The information is contradictory since one study from the Nordic countries failed to report any improvement regarding genital warts in heterosexual men. Given the risk of anal cancer, the authors of the study supported the idea of male vaccination, especially of the MSM population (28). Recent studies have demonstrated that anogenital warts have decreased in incidence since the initiation of vaccination for HPV in females in more developed countries. This concept reflects the herd protection as this disease is usually transmitted from females to their male sex partners. Therefore, the disease reduction in male patients is directly proportional to the vaccination of females. This is the reason why it is difficult to implement the vaccine against HPV in the male population, as the results are influenced by the female vaccination rate, therefore the need for an overall increase in vaccination programs that cover both sexes (27-29).

There is also a very comprehensive study regarding the cost effectiveness of the vaccination of men aged 21 to 26 in the US. Chessona *et al* studied the cost effectiveness of the nonavalent HPV vaccination for an age-specific male population. The hypothesis was the age harmonization vaccination between men and women by increasing the upper recommended catch-up age of HPV vaccination for males aged 21 to 26. Their conclusion was catastrophic in financial terms; the cost for implementing such a change would be almost 10 times more per year than the actual vaccination scheme. Still, they recognized there were many limitations to their study starting with the fact that there was no financial limit established by the Advisory Committee on Immunization Practices (ACIP). The potential differences in the immunity status between male and female seems to be in favor of the latter, thus the efficiency of male vaccination in terms of protection could be much lower, therefore the cost could escalate. Finally, yet importantly, besides financial considerations, ACIP must also consider other problems such as logistics for example, which may seem simple but, in the end, turn out to be a very bothersome matter (30).

An interesting comment from Kwan *et al* (31) underlined the other side of the HPV burden that is left behind. HPV is also responsible for other neoplasia such as oropharyngeal carcinoma, which has lately become an issue in developed countries. It is 5 times more common in middle aged men than in middle aged women and its incidence is steadily increasing. There is a grim prediction that in four years, the incidence of this type of neoplasia will surpass the incidence of cervical cancer in the US. In fact, there is proof that this has already occurred. Unfortunately, there is no screening method for this type of cancer, thus prevention is the best measure of defense. Authors highlight the fact that there is a true possibility that the costs of treating this type of cancer greatly exceed the actual estimations (31-33).

On the other hand, based on a Bayesian synthesis framework and assuming equal vaccine coverage in both sexes, Qendri *et al* reached a very troublesome conclusion in their study: Below 60% of the women benefit the most from the vaccine; at 80% coverage, only 15% goes to heterosexual men and 35% goes to MSM. Even if a hypothetical 90% coverage is reached, 85-100% of the male gain goes to MSM, given the fact that they are the most prone to oropharyngeal and anal neoplasia. The authors recognize that this is a simple iteration but it is still based on real models. They consider that the most important effect of this vaccination is the herd effect (34).

It is known that the primary objective of male vaccination against HPV is to document the possible changes regarding the appearance of HPV infection or the diseases that occur from this disease. The second objective is, of course, the investigation of the effectiveness of the vaccine on male subjects regarding the infection with HPV of female and the diseases that it can produce. This information can be of use in order to extend and support the male vaccination program. It is an important program because these changes may be entirely new, if the program targets both sexes or females and MSM (34).

There are some challenges regarding the impact of the HPV vaccine on male individuals. Anogenital warts and respiratory papilloma can be well surveilled in the male populations because the diagnosis and reports are the same as for female patients.

Regarding the surveillance of sexually transmitted infections in women, which includes large population screening, opportunistic testing in different laboratories that also includes HPV surveillance for men, a problem may arise because these tests are not routinely performed, as there are no national screening programs regarding HPV in males.

Kim performed a study in which she analyzed the cost-effectiveness of targeted HPV vaccination of MSM in the US. It is well known that 80% of anal cancers are associated with type 16 and 18 HPV infection, with a high incidence in the male population. Therefore, the high-risk populations that are represented by homosexuals can benefit from the HPV vaccination. This study discovered that HPV vaccination had a cost of 15.290 US dollars per quality adjusted life year gained, compared to no vaccination. Also, if homosexuals are vaccinated earlier in life, when the risk of being already infected with HPV is higher, the cost-effectiveness ratios become less attractive. All the results demonstrated a sensitivity to rates of anal cancer incidence and the duration of vaccine protection (35).

5. Synthesis of the results

In light of all the studies performed on this subject, there is a clear benefit for HPV vaccination for men, Yet, even with the introduction of a national vaccine program for HPV for women and girls in most developed countries, regarding the male vaccine program, few countries have established a national program. Still, a gender-neutral vaccine remains a controversial issue. If the only public health benefit considered is a reduction in female cancer, then all the mathematical models indicate that male vaccine effectiveness is low and adds only a small benefit to the disease reduction. It is considered that if the female mass is immunized, with time, the herd immunity could block some sexually transmitted diseases (36). Nevertheless, men also develop cancers due to HPV infection (anus, oral cavity, and oropharynx). In their study, Canfell *et al* demonstrated that if there is a high female vaccine program, the vaccination for HPV in men and boys is

not cost effective (37). The only downfall of this case is for the MSM population, where there is basically no herd protection, therefore they remain vulnerable to HPV-associated diseases.

6. Acceptance of the HPV vaccine

Despite all the studies that suggest the benefit of the HPV vaccine in men, there is also the problem of acceptability of these individuals. Hoefer *et al* performed a study among high-risk Greek men on a cohort of 298 subjects, on the willingness to vaccinate against HPV. This high-risk group was represented by men between 18 and 55 years of age, usually unmarried. From all the patients, 30% were MSM. Among all the participants in the study, 90% were aware that this virus is present in both men and women, but they were unaware that it can cause cancer in both sexes and not only in women, and that the vaccine can protect both men and women. The mean age of the participants in this study was 33 years. From all the participants, 69% reported a history of genital warts, and 20% were HIV positive. A total of 76% all agreed to be vaccinated against HPV even if they had to pay for it. This study also demonstrated that the willingness to vaccinate against HPV was highly associated with a high-income level, HIV positivity, and a history of genital warts, while a low income, economic instability, and low education level were associated with a negative response regarding vaccination. Another factor highly related to the willingness to vaccinate was the participants' beliefs about the safety and efficacy of the vaccine. One of the most common factors that increased the willingness to vaccinate was the belief that the vaccine could protect against cancer and other sexual transmitted diseases (STDs) and a recommendation from the healthcare provider that the side effects would be minimal. The most important factors that made a participant unwilling to vaccinate were the fear of side effects, insufficient knowledge about the vaccine and some of them reported that a high cost for the vaccine would make them less likely to vaccinate. In conclusion, the study reported that high-risk Greek men have a high acceptability rate for vaccination against HPV, for themselves or for their sons and daughters (38).

7. Summary of the evidence

All the studies performed concerning the efficacy of the HPV vaccine demonstrated that it has a beneficial effect on HPV6/11/18 infection. There are little to no cases concerning extra-genital lesions.

The objective of all the meta-analyses on all researched articles was to assess the efficacy and benefit of HPV vaccine in men.

8. Contraindication for the HPV vaccine?

Regarding HPV vaccine administration, reports have shown that it is usually safe, and adverse effects are usually rare; the benefits of the vaccine being well beyond the risks of the adverse effects. Thus, many studies regarding the vaccine shot and the appearance of the disease, made the use of the vaccine against HPV controversial (39). There is a high risk of vaccine refusal when the HPV vaccine is associated with an autoimmune disease because the vaccine is usually recommended for young men and women, in whom the incidence for such an autoimmune disease is high.

There was a report that suggested that there is a possible role of a genetic predisposition to vaccine-induced autoimmune disease (40). This is a possible and accepted risk compared to the benefit that this vaccine offers against different cancers.

These types of problems can make the parents decline the recommendation for vaccination against HPV for their children, which can lead to the spread of the disease in both men and women.

Regarding the MSM population, one of the most important benefits of the vaccine is the decrease in anal cancer cases. The effectiveness of vaccination has proven to have a good cost-efficiency result. The fact that this vaccine in men can be efficient against other types of cancer, such as oral or penile cancer, make it even more attractive, even though its contribution to this type of cancer is lower than for anal cancer and genital warts.

It is important to monitor the impact of the HPV vaccine in men and the benefits that occur, to inform and spread the results in order to implement this vaccine program worldwide. Any monitoring plan regarding the HPV vaccination must include HPV prevalence, anogenital warts, and anal cancer. The largest impact regarding the spreading of this type of vaccine is the surveillance of specific targeted populations, such as MSM, and HIV-infected men, who have the highest benefit from the vaccination.

9. Conclusions

Indications for HPV vaccine are continuously changing. Unfortunately, the main factor for this change seems to be the financial one.

In some countries, efforts have been made to enlarge the indication of vaccination in men. They seem to be trying to standardize the age for men and women alike. Evidence continues to accumulate and time is needed to decide which is the better vaccination scheme. The nonavalent vaccine seems to provide the best results in men, but it is still a work in progress. Financial issues are addressed one by one in the hope of lowering the price of immunization. The problem is that all the studies are based on surrogate indicators, and only the timeline will confim if there is any beneficial aspect.

Moreover, the level of adherence to vaccination differs from country to country and depends solely on the individual perspective. Guidelines are still changing and must consider other issues including logistics, if another population subset in the vaccination scheme is introduced.

Almost all of the evidence points to cervical cancer but there are also other types of neoplasia that are not specific solely to women. One can argue that the herd effect is enough; yet, given the variable rate of vaccination, the results are doubtful. There is also the MSM population subset who gains little from the herd effect and they should also be considered.

At this point, it can be stated that there are firm indications for women, MSM, and men over 26 years of age. The main counter-argument for expanding the immunization to men is the herd effect and the fact that vaccinated women act as a protective umbrella also for men. Only time-based evidence

will prove if this is enough. The decision to expand or not to provide immunization to other segments of the population is open for debate.

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ADS and RFA collected, analyzed and interpreted the patient data regarding HPV vaccination in men. DRM, DLI, AC and DLDM made substantial contributions to the conception of the work and interpretation of data; also, they drafted the manuscript and contributed substantially to writing the manuscript. All authors read and approved the final manuscript for publication.

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Competing interests

The authors declare that they have no competing interests.

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