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Towards the eradication of HPV infection through universal specific vaccination

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Abstract

Background: The Human Papillomavirus (HPV) is generally recognized to be the direct cause of cervical cancer. The development of effective anti-HPV vaccines, included in the portfolio of recommended vaccinations for any given community, led to the consolidation in many countries of immunization programs to prevent HPV-related cervical cancers. In recent years, increasing evidence in epidemiology and molecular biology have supported the oncogenic role of HPV in the development of other neoplasm including condylomas and penile, anal, vulvar, vaginal, and oro-pharyngeal cancers. Men play a key role in the paradigm of HPV infection: both as patients and as part of the mechanisms of transmission. Data show they are affected almost as often as women. Moreover, no screening procedures for HPV-related disease prevention are applied in men, who fail to undergo routine medical testing by any medical specialist at all. They also do not benefit from government prevention strategies.

Discussion: A panel of experts convened to focus on scientific, medical, and economic studies, and on the achievements from health organizations' intervention programs on the matter. One of the goals was to discuss on the critical issues emerging from the ongoing global implementation of HPV vaccination. A second goal was to identify contributions which could overcome the barriers that impede or delay effective vaccination programs whose purpose is to eradicate the HPV infection both in women and men.

Summary: The reviewed studies on the natural history of HPV infection and related diseases in women and men, the increasing experience of HPV vaccination in women, the analysis of clinical effectiveness vs economic efficacy of HPV vaccination, are even more supportive of the economic sustainability of vaccination programs both in women and men. Those achievements address increasing and needed attention to the issue of social equity in healthcare for both genders.

Keywords: HPV infection, Condylomas, Cervical cancer, Genital cancer, Oro-pharyngeal cancer, Anti-HPV vaccines, Universal vaccination, Vaccination programs, Incremental cost-effectiveness ratio

Background

Human Papillomavirus (HPV) infection is the most widely spread sexually transmitted infection in some areas of the world, with up to 70% of the population expected to become infected at some point of their lifetime [1,2]. The majority of these infections are subclinical, unrecognized, and benign [3,4]. Since HPV was discovered to be the direct cause of cervical cancer [5,6],

scientific data paired to the development of effective anti-HPV vaccines, accepted by health organizations, and included in the portfolio of recommended vaccinations for the community, have led to the consolidation in many countries of immunization programs to prevent HPV-related cervical cancers. Knowledge and experience accrued thus far, support and better address prevention programs in utilizing HPV vaccination for the benefit of the community. HPV infection, earlier correlated only to cervical carcinoma, today is acknowledged to be primarily responsible for cancerous and precancerous lesions of the genital area in both males and females and, in a

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lower percentage but with a not indifferent burden, of head and neck cancers [7,8]. Although HPV infections are known to be mainly a sexually transmitted disease, recent studies in non-sexually abused children infected with HPV suggest different forms of transmission [9,10]. Reports on the non-sexual transmission of anogenital warts, e.g. by prenatal mode, show the importance of maternal gynecologic history [11], and can help to understand better suspected sexual abuse in children [12]. Hand-genital transmission in adults should also be considered as a non-sexual means of transmission of HPV [13,14] although it has yet to be confirmed [15].

Until today, HPV prevention strategies through vaccination have targeted women mainly against cervical cancer. HPV vaccination, as efficacious means to reduce the development of cervical cancer in women in primary intervention strategies, has already been shown to be highly effective in reducing HPV-related lesions, such as genital warts as well as CIN 2/3 [16,17]. The significant declines in the proportion of young women found to have genital warts and the absence of genital warts in vaccinated women in 2011 suggests that the human papillomavirus vaccine has a high efficacy outside of the trial setting. Vaccination is undoubtedly a primary prevention tool; furthermore the expected eradication of the most prevalent HPV types will decrease the need of intense screening (secondary prevention) and cervical excisions for high grade disease (tertiary prevention). Now increasing evidence demonstrates how important the burden of HPV-correlated diseases also is in men. Epidemiological data show that in Europe and the USA, the burden of HPV-related head and neck cancers is carried mainly by men (4 times more than women), which shows that males are more than mere vectors [18,19]. Between 2006 and 2007 many countries have implemented HPV vaccination programs only for girls around 12 years of age. In the beginning the two available and approved vaccines were intended to target females only. After the approval of the quadrivalent vaccine (HPV4) indications for men, the USA, Canada, and Australia now recommend routine vaccination for both men and women. Men however are not yet included in nationally funded routine HPV vaccination programs in Europe (except Austria) and in many other countries.

Data on disease burden, vaccine efficacy, vaccine safety, cost-effectiveness, and social and ethical factors need to be taken into consideration when authorities decide to add men to European HPV vaccination programs. This paper summarizes the topics debated by a panel of experts convened to focus on scientific, medical, and economic studies, and on achievements from health organizations' intervention programs on the matter. The goal is to better develop a knowledge platform to be

used to further support and promote eradication of HPV infections in both women and men. The discussion was structured to identify contributions which could overcome common barriers that impede or delay effective vaccination programs whose purpose is to eradicate the HPV infection in both women and men.

Discussion

Natural history of HPV infection in women and men

The increased understanding of the natural history of HPV infection recently supported one of the main breakthroughs of medical science. HPVs are double-stranded DNA viruses that replicate within stratified squamous epithelia that need micro-abrasions or areas of transitional epithelium, such as in the cervix, anus, and tonsils, to be able to infect epithelial cells [20]. After infection, the virus makes use of the cells' normal DNA replication machinery to produce further viral genetic fragments at the supra-basal layer of the epithelium [20,21]. Like all papillomaviruses, HPVs establish productive infections only in keratinocytes of the skin or mucous membranes. While the majority of the known HPV infections cause no symptoms in most people and are usually spontaneously cleared by the host, some types can cause warts while others may lead – in a few cases – to cancers of the cervix, vulva, vagina, penis, anus, and oro-pharynx. More than 130 genotypes of HPV have been described; types are divided into high risk and low risk according to their ability to produce benign or malignant lesions over time. The main high risk HPV types, classified as carcinogenic to humans by the International Agency for Research and Cancer (IARC) since 1995 [22], are HPV types 16 and 18, which are responsible of about 70% [2,23] of cervical cancers worldwide and most HPV-related pre-cancerous lesions in other anatomical regions whether genital or not [24,25]. Among the low risk types, HPV types 6 and 11 account for approximately 90% of genital warts. Seventy percent of infections are usually cleared after one year and 90% in two years [20,26]. However, when the infection caused by high risk (HR) genotypes of HPV, persists – in 5% to 10% of infected women – there is a high probability of developing precancerous lesions of the cervix, which can progress to invasive cervical cancer. This process usually takes 10-15 years, providing many opportunities for prevention, detection, and treatment of the pre-cancerous lesion involved [21]. Several models show that what one may consider today as remission of infection might not be remission at all [20]. As already mentioned, increasing evidence in epidemiology and molecular biology have supported the oncogenic role of HPV in the development of other genital cancers including penile, anal, vulvar, and vaginal cancers [27,28] and some oro-pharyngeal cancers [8,29-31] that share

mucosal junction similarities, such as the anal and cervical areas [32]. Several risk factors seem to affect HPV infection, from the number of sexual partners [33,34] and oral contraceptive use [35] to smoking and alcohol: the latter ones particularly related to head and neck cancers [36]. Other risk factors have been studied including condom use [37] and circumcision [38,39]. In women, evidence suggests two HPV incidence high peak points at < 25 and around 45 years of age [40]. On the other hand, in men, HPV prevalence and incidence seem to be constantly high at all ages [41,42]. The most common lesions in both sexes are anogenital warts (AGW), mainly attributable to HPV types 6 and 11 (> 90%). Of these cases, 20-50% involve co-infection with other high risk HPV types [27,43]. In fact, studies have demonstrated that both in females and males, AGW patients have a higher risk of developing HPV-related cancers [44]. These results seem to contradict statements from the American Centers for Disease Control (CDC) (2010) which indicate that AGW, except in very rare and unusual cases, will not turn in cancer. The types of HPV that cause AGW are different from the types that can cause anogenital cancer; however, subjects with low risk (LR) HPV types should be considered at higher risk of having cancer by HPV 16 in the future. Knowledge of natural history and epidemiology of HPV in men is constantly increasing although it still remains less extensive than in women. Cancers related to HPV diagnosed every year in males have been shown to be approximately half the number of HPV-related cancer cases in women. This proportion of 1:2 (not 1:100 or 1:1000) is significant, without taking into account other less severe HPV-related diseases that have a higher incidence and life-long-prevalence in men than in women. HPV-16 and -18 are found to account for 90% of all HPV-related cancers in men [45]. The most recent studies in Europe show that 17,403 cancer cases in men are expected to be HPV-related, 15,497 of which are attributable exclusively to HPV types 16 and 18 vs 32,562 which are expected to be related to these two types in women [19]. In addition it has also been estimated that there will be around 650,000 new cases each year of genital warts, more than 50% of which are expected in men. Similar data are confirmed by the most recent WHO (World Health Organization) statistical report on HPV in Europe [46]. A recent study conducted by Baio et al. [47] showed that the burden of HPV-related disease in Italy behaves similarly to that in Europe, with males playing an important role. The latest CDC data [18] on burden of disease in males display the same trend as Hartwig et al. [19] with almost half the number of cases of HPV-related cancer as women determined in Europe. Overall an average of 33,369 HPV-associated cancers (10,8 per 100.000 population), were diagnosed annually: 21,290 among women

(13,2 per 100.000 population) and 12,080 among men (8,1 per 100.000 population). Cervical cancer was the most common, and oropharyngeal cancer ranked as the second most common. HPV-related head and neck cancer incidence in the USA is already higher in men, and should no action be taken, is expected to exceed that of cervical cancer by 2020 [18]. Anal cancer is a rare cancer; however, it has a very high incidence in men who have sex with men (MSM), where the incidence is estimated to be equivalent to that in women with cervical cancer, ranging from 32.8% to 93.5% [48-50], with an estimated risk of anal cancer 30 times [51,52] and genital warts around 10 times [53] higher than in heterosexual men. However not all cancers termed "HPV-associated" reflect actual infections and the numbers judged to be HPV-attributable are only estimates. The same MMWR editorial concludes: "Population-based screening for non-cervical HPV-associated cancers is not recommended" [18].

Critical issues in HPV vaccination

Immunogenicity, safety, and clinical significance represent the critical issues on which to base the prospective of the eradicating HPV-related diseases through a global implementation of multivalent HPV vaccination.

Two vaccines are currently available to prevent HPV infection. The bivalent vaccine (HPV2) targets HPV types 16 and 18 [54], while the quadrivalent vaccine (HPV4) targets HPV types 6, 11, 16, and 18 [55]. Both vaccines have demonstrated high efficacy in the prevention of cervical precancerous lesions, long-term immunogenicity and efficacy, and to be safe and well tolerated in females up to 25 years of age. HPV4 vaccine has also demonstrated, together with the protection against cervical cancer, high efficacy against genital warts from HPV types 6 and 11, against vaginal and vulvar precancerous lesions, re-infection, persistent infection, and anal precancerous lesions (AIN 1,2,3 studied in an MSM population) [56-58]. HPV4 vaccine is also indicated for the use in females up to 45 years of age and in males up to 26 years of age by the European Medicines Agency (EMA) in Europe. Both vaccines are currently employed in girls in many national vaccination campaigns and have proven to be safe, well tolerated, and highly efficacious in preventing persistent infections and cervical diseases associated with specific HPV types among females [59]. Studies about long-term duration of efficacy are still ongoing for both vaccines, and are around 9 years without breakthroughs. Time is needed to clarify the issues of long-term duration of efficacy and immunogenicity and whether a vaccine boost will be required or not [60-62]. Through mathematical modeling Fraser et al. evaluated the long-term anti-HPV-16 responses following administration of a three-dose

regimen of HPV-16 vaccine in women aged 16-23 years. Using a conventional power law model a median duration of detectable antibody (> 5.9 mMU/mL) of 32 years has been estimated; whereas the modified power law model predicted a long-term plateau of antibody duration with a nearly life-long persistence above the level of detection (> 5.9 mMU/mL) [63].

As mentioned before, the HPV burden of disease has been demonstrated to be quite high in men as well. Recent randomized studies have been conducted in order to assess efficacy, immunogenicity, and safety of the quadrivalent vaccine in men and included 4,065 young male subjects aged between 16 and 26 years of age, 602 of which self-declared to have sex with other men. Vaccine efficacy against external genital lesions (EGL) was found to be 90.4% and 89.4% against genital warts [56] (Table 1). The study by Giuliano and colleagues showed efficacy of 92.4% against genital warts in the heterosexual male population and 79% in the MSM population; for persistent infection the vaccine proved to have an efficacy of 50.4% for heterosexual males and 43.6% for MSM [56]. The same trial conducted to evaluate any grade of anal intraepithelial neoplasia (AIN) in MSM showed an overall efficacy on the per protocol population of 77.5% [57]. An exclusively post-hoc efficacy analysis for vaccine types of 92% was reported [58]. The studies [56-58] on male vaccine efficacy are summarized in Table 2. Efficacy of vaccine was bridged to males 10-15 years old with an immune-bridging study that demonstrated non-inferiority immune response compared to females aged 16 to 23 [64]. These studies are the basis for vaccine approval for males and male vaccination recommendations by EMA and FDA (Food and Drug Administration).

HPV vaccines have been demonstrated to be safe over the last 10 years. Most available data is on women, as they were the primary target of vaccination. Data on immunogenicity and safety are available however also for men and demonstrated that both HPV2 and HPV4 have immunogenicity and favorable safety profile similar to the studies conducted in women [65]. Both HPV vaccines are closely monitored worldwide and post-

licensure studies have shown good safety profiles [66,67].

The clinical significance of HPV vaccination has been extensively studied in specific communities.

In the province of Victoria (Australia) an ecological study compared the incidence of high-grade pre-neoplastic and cancers (CIN 2+) lesions detected in women < 18 years of age examined before and after the start of an HPV4 vaccination program in young girls aged 12-to-13 years old [16]. A progressive decrease in the incidence of high-grade lesions by 0.38% has been observed in the girls younger than 18 years in a region where the vaccination coverage was between 71% and 79%. Another Australian ecological follow-up study [17] showed that after 5 years from the beginning of the vaccination program, genital incidence of new cases of genital wart dropped by 93%. Some herd immunity was also observed in males of the same age group, although incidence remained high in the MSM population [17]. Two other studies conducted in New Zealand [68] and California (USA) [69] – where the coverage of vaccination programs of the target population was rarely over 50% – showed around 60% and 30% reduction of genital warts, respectively. Evidence seems to support vaccine efficacy and reduction of disease with some herd immunity effect in heterosexual males but not in MSM. A rapid and marked reduction in the incidence of genital warts occurred among vaccinated women, and this reduction could mean some benefit being conferred to heterosexual men [70], but not to MSM. A rapid decline in presentation of genital warts was observed after implementation of a national program with HPV4 vaccine [70]. Given the success of Australia's catch-up program, it will not be long before we know if the basic reproductive number for genital warts holds the prospect of elimination. However, if genital warts stabilize at a lower, but not very low, rate we will know that elimination will not be possible without vaccination of males [71].

International policies and recommendations

Vaccination and vaccines are undoubtedly one of the most innovative procedures with the greatest impact on

Table 1 HPV4 vaccine efficacy study against external genital lesions and persistent HPV infection in men 16-26 years of age (n = 4065) [56]

Endpoint	HPV4 (n = 1397)	Placebo (n = 1408)	Efficacy (%)	95% CI
	N° cases	N° cases		
All external genital lesions	3	31	90.4 (all HPV types)	62.2-97.9
Condyloma	3	28	89.4	65.5-97.9
Penile/perianal/perineal intraepithelial neoplasia	0	3	100	0-100
Persistent infection (all HPV types)	15	101	85.6	73.4-92.9
DNA detection	136	241	44.7	31.5-55.6

Table 2 Summary of HPV4 vaccine efficacy studies in men [56-58]

	Giuliano	Palefsky	Goldstone
Population	Per-protocol (16-26 years)	Per-protocol (16-26 years)	Per-protocol* (16-26 years)
External genital lesions	90.4% (95% CI: 69.2-98.1)		
Anal intraepithelial neoplasia		77.5% (95% CI: 39.6-93.3)	91.7% (95% CI: 44.6-99.8)
Condylomata acuminata	89.4% (95% CI: 65.5-97.9)		

* Post-hoc analysis.

population health protection. Well-implemented vaccine policies achieve almost complete eradication of diseases once thought to be lethal.

In Europe, recommendations for HPV vaccination in females have been introduced in nearly all Western European countries with some of them also offering national or regional funding programs. It was first introduced in 2007 in Belgium, France, Germany, and Italy. In 2008 other countries also recommended vaccination, such as Greece, Luxembourg, the Netherlands, Romania, Spain, Switzerland, and the UK. Other European countries followed (Denmark, Norway, Portugal, San Marino, and Macedonia). The latest to start were Sweden and Ireland in 2010. As of today the vaccination advisory boards in 21 of the 29 countries of the EU have recommended and have in place active HPV vaccination programs [72]. In other countries (Czech Republic, Slovenia, Latvia, and Iceland), HPV vaccination has been recommended but has not been actually integrated in the national immunization programs. Some countries not only initiated their programs with the primary cohort of females but also have implemented different vaccination cohorts or catch-up programs. In Italy, the Basilicata region started in 2007/08 with a 4-cohort strategy covering females up to 25 years of age and assuring coverage of all females up to 21 years of age in 2012. This has resulted in average coverage rates in the primary cohort of around 80% and represents an excellent paradigm. Data collected by the VENICE2 Group in 2010 [72] registered a high heterogeneity in the strategies for implementation of the HPV vaccination in European countries. Recommendations for the vaccination starting age range from 10 to 18 and the catch-up rounds from age 12 to 24. So far the targets are girls/women in all European countries except Austria, which already targets but does not fund vaccination in males as well as females.

Today, in fact, the HPV4 vaccine is also indicated by the main health organizations (e.g. FDA, EMA) for males up to 26 years of age.

The US initially recommended routine vaccination of females between 11 and 12 years of age, with catch-up programs up to 26 years of age. Although the private American health system is not comparable to most public European health systems, the vaccine was offered for free both to the health-insured population and to the uninsured through Medicaid and the Vaccine for Children (VFC) program that offered the vaccine for free to girls up to 18 years of age. Even so, the US found several obstacles to reach high rates of vaccine coverage effectively in all regions, with an average coverage of only around 20% [73]. In 2011, the CDC Advisory Committee on Immunization Practices (ACIP) took into account new efficacy data on the vaccines, the low coverage rates, and the updated burden of disease knowledge and decided to recommend routine vaccination for both men and women, a gender-neutral vaccination offered free of charge, both to insured and uninsured people up to their 18th birthday [74]. To support this decision, the American Academy of Pediatrics [75] recommended the vaccination of males as well as females. This new strategy is expected to further reduce the burden of the disease. In 2007 Canada and Australia which have national health systems decided to vaccinate women at the start of the program through school-based programs. Doing so, vaccine coverage reached higher coverage rates, ranging from 63.7% to 79.6% in Australia and from 50% to 85% in Canada [76-78]. The latest epidemiological studies in Australia show an almost complete disappearance of genital warts diagnosis: with a coverage of 83% of women < 21 years who received the first dose of the vaccine, the diagnosis of genital warts declined by 93% by the fifth year of the national quadrivalent HPV vaccination program [17]. In late 2011 and early 2012, both PBAC (Pharmaceutical Benefits Advisory Committee) and the NACI (National Advisory Committee on Immunization) [78] vaccine bodies in Australia and Canada have decided to recommend routine HPV vaccinations for males and females; the program started in Australia in January 2013.

Since the EMA approval in 2011 of male vaccination with the HPV4 vaccine, no European country (except Austria) has developed and implemented a program for routine vaccination in boys.

Clinical effectiveness vs economic effectiveness

An overview of the results of many economic studies shows that vaccination against HPV produces immediate benefits from epidemiological points of view and in terms of avoided costs for country-specific National Health Systems (NHSs) [79-82]. Although estimates vary depending on the assumptions made, the cost-effectiveness of vaccination against HPV has been confirmed by a large body of modeling studies, which have been designed to evaluate different vaccination strategies [83,84]. In general, these studies compared a single cohort of women who underwent vaccination, plus optional catch-up cohorts, with women who underwent screening alone; the cohorts varied in age of immunization among studies. Studies evaluated the cost-effectiveness of vaccinating women of a particular age (e.g. 35 years) who had been participating in a specific screening strategy (e.g. biennial cytology) [85]. Two studies evaluated the implementation and economic consequences of a multi-cohort vaccination strategy [86,87]. At present, to be considered efficient from an economic point of view, health intervention should have an ICER (Incremental Cost Effectiveness Ratio) per QALY (Quality Adjusted Life Year) gained of less than £ 20,000 to £ 30,000 [88,89] (approximately € 30,000 to € 45,000). It should be noted that the threshold of £ 30,000 as defined by the National Institute for Health and Clinical Excellence (NICE) is not transferable to the specific policies on vaccines. The Canadian Agency for Drugs and Technologies in Health evaluated the cost-effectiveness of HPV vaccination in women and calculated a cost per QALY gained amounting to € 14,224 for the HPV4 vaccine and € 21,540 for the HPV2 vaccine [89]. Another study calculated QALY gained for HPV4 vaccines in Italy of € 9,569 [84]. In a recent study [87], results from a multi-cohort (12, 15, 16, and 25 years old) vaccination strategy of women confirmed the cost-effectiveness of HPV vaccination.

Several economic evaluations have assessed various HPV vaccine scenarios for men and women, on a cost-effectiveness basis in terms of QALY gained [79-81]. Even so, most cost-effectiveness studies of male vaccination tend to be centered on exclusively reducing cervical cancer in women and lack further important economic considerations – only lately have some studies started to take into account other vaccine benefits.

The published mathematical models using both men and women are based on assumptions that are not fully evidence-based. There are few studies that include males

and those that are available also do not include all HPV-related diseases in both sexes and the coverage and compliance rates. Increasing coverage rates in females is a real challenge in most countries and is unlikely to be realized, unless a considerable budget effort is made by health authorities (public health campaigns, etc). The CDC recommendation (in November 2011) that young boys, as well as girls, should get immunized against HPV was based on the statement that male inclusion is cost-effective when coverage rates in females are low, such as is the case in the United States. In Australia, where the HPV vaccine coverage in female is high (> 80%), the decision to include routine vaccination of boys 12/13 years of age (recommended by the Pharmaceutical Benefits Advisory Committee (PBAC) [90]) was supported by showing that male inclusion could be cost-effective in Australia [91]. Following the Australian example, in January 2012 the National Advisory Committee on Immunization (NACI) in Canada recommended extension of the HPV4 vaccine to males between 9 and 36 years of age and routine vaccination of 12-year-old boys [78]. When more non-cervical diseases are included, cost per QALY gained decreased significantly. Moreover, not incorporating the reduction of number of non-cervical cancer cases in both sexes leads to a substantial underestimation of the cost per QALY gained of extending the vaccination to males. Elbasha et al. [92] presented all epidemiological outcomes and the number of cases avoided by vaccinating males in addition to females. The most oncogenic HPV type causing the greatest burden may be the most difficult to eliminate through vaccination of girls only; more substantial incremental benefits are expected by adding boys to vaccination programs when the HPV vaccine coverage is < 50% among young girls [93]. The cost/effectiveness of the impact on the overall population of including routine vaccine to MSM is still to be better defined. Boys and girls will mostly benefit from HPV vaccination if vaccinated routinely before becoming sexually active. In addition to protecting heterosexual males and their female partners, routine vaccination of boys at a young age is also the best way to reach MSM at an age when they could most benefit [74]. Furthermore, in the early stages of sexual life for a significant number of MSM, heterosexual activity is not uncommon thus contributing to the transmission of the virus [94]. Burden of disease in men seems to be quite significant, because genital warts alone have an important economic and psychological burden. Models taking into consideration several factors such as other HPV-related diseases seem to prove that male vaccination is expected to be cost effective.

Introduction to male vaccination

One of the main goals of vaccination programs is to stop the transmission of an infective agent. In the case of

HPV a single gender vaccination will not achieve such a goal. Moreover, why should vaccination programs target only one single disease such as cervical cancer, when vaccine benefits have also been proven to be high against other HPV-related diseases? Vaccinating boys is expected to facilitate the eradication of the cervical cancer, reduce the transmission of the virus, increase herd immunity, and contribute to the prevention of HPV-associated diseases in both genders. In fact more incremental benefits are expected by adding the boys in the vaccine program [93].

Neither the EMA nor the European Centre for Disease Prevention and Control (ECDC) guidelines [95] formally recommend vaccinating programs in boys or men. Among the scientific endorsements of an inclusion of males into vaccination programs for females, two different multidisciplinary panels of experts were convened between 2010 and 2012 in Italy. The Italian Society of Andrology, the Italian Society of Urologists, and the Italian Society of Andrology and Sexual Medicine created a panel of experts which developed a consensus statement arguing that the vaccine should be offered to males [96]. The second panel developed a commitment platform among scientists that is the basis of this paper. Italy is now also offering the vaccine on demand to males with a strategy of co-payment although informational and promotional campaigns have not been finalized yet.

Men play a key role in the paradigm of HPV infection: both as patients and as part of the mechanisms of transmission. As mentioned before, data show men are affected almost as frequently as women. Moreover no screening procedures for HPV prevention are currently ongoing in men, who do not receive routine medical testing by any medical specialist; in general the attitude in men towards prevention is low. They also do not benefit from government prevention strategies. It is well known that flat penile lesions play an important role in the transmission of high risk HPVs. In women the anal mucosa is a reservoir of HPV, which can be a source of re-infection for the cervix [97]. However, as observed in the mentioned study, there was not a significant association between the anal sex practice and the prevalence of anal cytological abnormalities. Including men in HPV vaccination programs increases its ranking on the list of urgent decisions to be taken by policy makers [98-101]. Information on HPV-related diseases is low or lacking in men; however, from studies focused on the acceptance by parents of vaccination of boys, it appears they would be willing to vaccinate their male children [102-104] and inclusion of men in the vaccine program will also increase coverage in women [105-107]. Discussion regarding the introduction of male vaccination is ongoing. Several key points could help in the extension of HPV vaccination programs to men such as: female-only

vaccination will not protect all men; HPV-related head and neck cancer burden is carried mainly by men; it is the fastest way to achieve female protection by means of herd-immunity; vaccinating males is a more gender-equitable public health policy; men seem to accept vaccination as do parents of boys; vaccine seems to elicit the same if not a higher degree of immunogenicity in boys than in girls; genital warts and HPV-related cancers in men represent costly and emotionally burdensome and preventable conditions; lessons from the past with other vaccines show that single-gender-based vaccination policies are less effective.

“...there is a good chance of drastically reducing cervical cancer by vaccination.... HPV-16 and -18 could probably be eliminated if we have a global program. You could theoretically achieve this by vaccinating only girls, but you would need very high coverage. I'm a strong advocate for vaccinating boys as well: we'll reach the goal much faster by vaccinating both sexes. The disadvantage is that the cost is very high...” [108].

The HPV4 vaccine has proved to be effective and safe in men, but whether this is enough to recommend inclusion of males in NHS prevention strategies is still being debated. Several factors such as vaccine efficacy, herd immunity, vaccine coverage rates in females, burden of disease in men, and cost-benefit ratios need to be further evaluated when including men into the formula.

Summary

Achievements, pending questions, next steps

Vaccines are among the few medical interventions capable of achieving almost complete eradication of a disease. Today's available epidemiological data show that HPV do not affect men and women differently and that men carry a considerable burden of the disease, enough to justify being included in national recommendations for immunization programs against HPV-associated lesions. Both the EMA and the FDA have approved HPV4 vaccine indication in males 9-26 years of age. Some national public health authority boards, such as in the USA, Canada, and Australia, already recommend men being included in their anti-HPV national routine immunization programs. So far, except for Austria, it is not yet recommended in Europe.

Taking advantage of the increasing opportunity to reduce HPV infection and transmission among sex partners, and of the increasing evidence on the effectiveness/efficacy of the HPV vaccines in preventing the development of HPV-related diseases, will decrease the burden of disease and increase the quality of life in the communities.

Including boys in vaccination programs can produce more incremental benefits globally to the currently unsolved and severe problem of HPV infection [93,109].

Those achievements pose questions for decision-makers as to their duty to overcome any barrier that impedes the achievement of health protection for both women and men against HPV infection. The issue of social equity in healthcare for both men and women is also one that must be addressed.

Future evaluation by the decision-makers in various countries of the results obtained by the next generation of intervention programs will focus on the critical issues that still exist: a) previous experience in gender-restricted vaccination programmes has demonstrated a substantially lower effectiveness than universal vaccination; b) limiting vaccination to women might increase the psychological burden on women by confirming a perceived inequality of the sexes; c) even if all women were immunized, the HPV chain of transmission would still be maintained through MSM; d) the cost-effectiveness of including boys in HPV vaccination programs should be re-assessed in view of the increased reduction, due to universal vaccination, of the economic burden of HPV related diseases in men and women [110].

Therefore steps must be taken by recommendation bodies and stakeholders to achieve the expected results of universal vaccination - the eradication of HPV infection. The goal to eradicate sexually transmitted carcinogenic viruses can be accomplished jointly by women and men within a few decades [111].

Abbreviations

ACIP: Advisory committee on immunization practices; AGW: Ano genital warts; AIN: Anal intraepithelial neoplasia; CDC: Centers for disease control and prevention; CIN: Cervical intraepithelial neoplasia; ECDC: European centre for disease prevention and control; EGL: External genital lesions; EMA: European medicines agency; FDA: Food and drug administration; HPV: Human papilloma virus; HPV2: HPV bivalent vaccine; HPV4: HPV quadrivalent vaccine; IARC: International agency for research and cancer; MSM: Men who have sex with men; NACI: National advisory committee on immunization; NHS: National health systems; PBAC: Pharmaceutical benefits advisory committee; QALY: Quality adjusted life year; VENICE: Vaccine european new integrated collaboration effort; VFC: Vaccine for children; WHO: World health organization.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The manuscript is a result of numerous discussions among the authors during three Workshops organized and moderated by the Fondazione Giovanni Lorenzini Medical Science Foundation (Milan, Italy and Houston, TX, USA). All authors have participated in writing the manuscript. All the authors have read and approved the final manuscript.

Acknowledgement

The manuscript is a result of the activity of a panel of experts convened by the Fondazione Giovanni Lorenzini Medical Science Foundation (Milan, Italy and Houston, TX, USA).

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Received: 17 January 2013 Accepted: 22 May 2013

Published: 11 July 2013

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doi:10.1186/1471-2458-13-642

Cite this article as: Crosignani et al.: Towards the eradication of HPV infection through universal specific vaccination. *BMC Public Health* 2013 **13**:642.

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