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Public health value of universal HPV vaccination

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ABSTRACT

Background: The story of Human Papillomavirus vaccination demands reflection not only for its public health impact on the prophylactic management of HPV disease, but also for its relevant economic and social outcomes. Greater than ever data confirm the efficacy and support the urge for effective vaccination plans for both genders before sexual debut.

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Methods: A review of previous experience in gender-restricted vaccination programs has demonstrated a lower effectiveness. Limiting vaccination to women might increase the psychological burden on women by confirming a perceived inequality between genders; and even if all women were immunized, the HPV chain of transmission would still be maintained through men.
Results: The cost-effectiveness of including boys into HPV vaccination programs should be re-assessed in view of the progressive drop of the economic burden of HPV-related diseases in men and women due to universal vaccination. The cost of the remarkable increase in anal and oropharyngeal HPV driven cancers in both sexes has been grossly underestimated or ignored.
Conclusions: Steps must be taken by relevant bodies to achieve the target of universal vaccination. The analysis of HPV vaccination's clinical effectiveness vs. economic efficacy are supportive of the economic sustainability of vaccination programs both in women and men.
In Europe, these achievements demand urgent attention to the social equity for both genders in healthcare. There is sufficient ethical, scientific, strategic and economic evidence to urge the European Community to develop and implement a coordinated and comprehensive strategy aimed at both genders and geographically balanced, to eradicate cervical cancer and other diseases caused by HPV in Europe.
Policymakers must take into consideration effective vaccination programs in the prevention of cancers.

1. Clinical prospects on efficacy

1.1. HPV vaccines today

Until recently, infection with high risk or oncogenic HPVs seemed to correlate solely to cervical carcinoma, while today it is known to be primarily responsible for cancerous and precancerous lesions of the ano-genital area in both males and females; it is also responsible, at a lower but not negligible rate, for head and neck cancers (Giuliano et al., 2015). HPV was ascribed to cause effectively 100% of cervical cancer cases, 88% of anal cancer cases, 43% of vulvar cancer cases, 70% of invasive vaginal carcinomas, 50% of all penile cancers worldwide (de Martel et al., 2012). The exact proportion in Head and Neck (H&N) cancer is unknown but the anatomical site specific cancer "oropharyngeal squamous cell carcinoma (OPSCC)" is increasing in the UK (were data are available) at a rate of 15% per annum. In England, USA and Canada around 70% of OPSCC is thought to be HPV driven, and oropharyngeal cancer constitutes about one third of the over 9.000 cases of H&N cancer in England in Wales per annum (Jones, 2014). It is unclear why the dramatic increase in both oropharyngeal and anal cancer driven by HPV affecting both sexes which now exceeds the incidence of cervical cancer has received so little attention from policymakers (Mitchell, 2015).

One third of HPV-16 and HPV-18-induced cancers in Europe (Hartwig et al., 2012) and the US (MMWR, 2013) appears to affect men, while low-risk viruses such as HPV-6 and -11 cause genital warts, representing a huge disease burden in both men and women (Stanley et al., 2014). Squamous cell cancers of the oral cavity (OCC) and of the oropharynx (OPSCC) are the sixth most prevalent cancers worldwide with an estimated 400.000 cases per annum and 230.000 deaths (Ferlay et al., 2010): around 30% of these are estimated to be caused by HPV. Currently a three-yearly smear test is recommended for women aged 21–29; HPV testing is not recommended in this age group since HPV infections are common during the second decade of life (although they do not persist in most cases) (McCarthy, 2014). For women, aged 30–65, 3-yearly cytology screening is recommended or 5-yearly cotesting (Pap smear + HPV test) (McCarthy, 2014). Although already approved only in the Netherlands, most of European countries are moving to cervical cancer screening with primary HPV-DNA test, with further cytological triage if necessary. There are no screening programs for all other HPV related cancers in both men and women.

Table 1
Efficacy of vaccines.

	Target	HPV-6,-11,-16,-18 infection	Efficacy (%)
Quadrivalent	Female 16–26 years	CIN 2/3	98.2
		VIN 2/3	100
		VaIN 2/3	100
		Genital warts	99.0
	Female 24–45 years	CIN, LGE	95.7
	Males 16–26 years	LGE	90.4
		AIN	77.5
Bivalent	Female 15–25 years	CIN 2+	94.9
		CIN 3+	91.7

Giuliano et al. (2011), Anon. (2015a,b), Lehtinen and Dillner (2013), Van de Velde et al. (2012) and Serrano et al. (2012).

In males, the quadrivalent HPV (qHPV) vaccine efficacy against ano-genital lesions related to HPV 6,11,16 and 18 has been reported by Giuliano et al. (Giuliano et al., 2011) up to 90% in per-protocol (PP) population and 65.5% in intention-to-treat (ITT) group. In the same study, vaccine efficacy against incident infection and HPV-DNA detection was 47.8% and 27.1% in PP and ITT population, respectively.

Both vaccines (Table 1) are considered highly effective against cervical cancer and pre-cancerous lesions caused by HPV 16 and 18. Both vaccines provide some cross-protection against HPV genotypes which are not included in the vaccines (Anon., 2014b). The increased importance of vaccinating both girls and boys is underlined by the mostly low coverage of national, girls-only vaccination programs (Lehtinen and Dillner, 2013). The European Centre for Disease Prevention and Control (ECDC) acknowledged that the most effective strategy to prevent HPV-related morbidity would be universal coverage of both females and males (ECDC, 2012).

Cross-protection against non-vaccine HPV types is an important consideration since non-vaccine HPV types are associated with 30% approximately of cervical cancer (Schiller et al., 2012). Data on cross-protection against persistent infection and against disease endpoints are not easy to be evaluated so far for the differences in the experimental approaches and differences in the evaluation of efficacy results (Schiller et al., 2012). Furthermore, data from clinical studies show that the supposed cross-protection specially against non-vaccine HPV types 31, and 45, decreases during an increased follow-up, suggesting a waning of cross-protection (Malagón et al., 2012).

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1.2. New vaccine against HPV-diseases

The 9vHPV (nine-valent or nonavalent) vaccine, recently approved by FDA on December 2014, and in Europe by EMA first approval given by CHMP the 27th of March 2015 and approved finally on 10/06/2015 (Anon., 2015d), it is expected to prevent compared to bivalent and quadrivalent vaccine from 40% to 70% of CIN2, from 58% to 84% of CIN3, and from 90% to 94% of AIS (adenocarcinoma in situ): these data have been highlighted by Joste et al. (2015) after they analyzed a population-based sample of 6.272 tissue specimens tested for HPV genotypes. In a total of 14.215 randomized participants population the 9vHPV vaccine has been studied: this study showed that the 9vHPV vaccine prevented cervical, vulvar, and vaginal disease and persistent infection associated with HPV-31,-33,-45,-52,-58, and generated antibody response to HPV-6,-11,-16, -18 that was not inferior to that generated by the qHPV vaccine. The 9vHPV vaccine did not prevent infection and disease related to HPV types beyond the nine types covered by the vaccine (Joura et al., 2015).

Changing from a bivalent or quadrivalent to a nonavalent HPV vaccine is predicted to reduce the cumulative number of anogenital warts (AGWs) episodes by an additional 66.7% (compared with bivalent) or 0.0% (compared with quadrivalent), CIN2 and CIN3 episodes by an additional 9.3% (compared with bivalent) or 12.5% (compared with quadrivalent), and squamous cell carcinoma (SCC) cases by an additional 4.8% (compared with bivalent vaccine) or 6.6% (compared with quadrivalent vaccine) in the cumulative incidence up to 70 years (Van de Velde et al., 2012).

The potential impact of 9vHPV vaccine (Serrano et al., 2012) estimated through the relative contribution (RC) towards invasive cervical cancer (ICC) and the precancerous cervical lesions of the nine HPV types in ICC, was 89.4% and varied by histology, ranging between 89.1% in SCC and 95.5% in adenocarcinomas (ADC). The overall safety profile of the 9vHPV vaccine was comparable to the qHPV vaccine (Chatterjee, 2014) across multiple studies and different populations. Few multinational studies show (Pimenta et al., 2013) how vaccines protective against HPV-16 and HPV-18 could potentially prevent 44.702 cases (79%) of ADC per year, assuming 100% vaccine coverage. An efficacy and immunogenicity study of 9vHPV vaccine (Joura, 2013) conducted in young women from 16 to 26 years of age demonstrates that the immunogenicity of 9vHPV vaccine is non-inferior to that of qHPV vaccine; it was also demonstrated how 9vHPV vaccine is highly effective when compared to qHPV vaccine in preventing HPV-31,-33,-34,-52,-58-related persistent infections and conditions.

1.3. Anogenital warts

Genital Warts-GWs are part of a hidden world which is not overtly targeted by national health plans; patients are thus, obliged to hide their condition. In some countries, such as in Italy, their treatment is thus, missing from epidemiology databases and economic records. Mariani et al. (2015) identified 13 publications from 9 sources in 6 countries (Australia, New Zealand, US, Denmark, Germany and Sweden) revealing the real-world impact of qHPV vaccine on the incidence of GWs. These results provide evidence for a rapid, strong impact on GW incidence in vaccine-target populations and a smaller, but substantial, indirect impact in non-targeted populations. These data have been further confirmed by Hariri et al. (2013): about 90% of cases of GWs were caused by HPV-6 and -11 (Ali et al., 2013). Reductions in the incidence of genital warts have been documented in several countries, depending on the level of coverage with qHPV vaccine.

2. Safety

The WHO Global Advisory Committee for Vaccine Safety (GACVS) has regularly reviewed the evidence on the safety of HPV vaccines (Table 2).

2.1. Local reactions

Injection site reactions included pain (92.9% bivalent, 71.6% quadrivalent), redness (44.3% bivalent, 25.6% quadrivalent) and swelling (36.5% bivalent, 21.8% quadrivalent) (Einstein et al., 2011). In both vaccines injection site reactions, particularly pain, are usually of short duration and resolve spontaneously (Macartney et al., 2013).

2.2. Systemic reactions

Pyrexia, headache, dizziness, myalgia, arthralgia are observed. Post-vaccination syncope has been reported, as for many other vaccines, but can be minimized and its complications avoided with appropriate care (Macartney et al., 2013).

In *pre-licensure trials* of the quadrivalent vaccine (Anon., 2015c), in vaccine recipients not already infected with HPV, systemic adverse events were monitored for the first 15 days post vaccination. Pyrexia was the only reported adverse event that occurred in >10% of vaccinees and more frequently than in placebo groups (10.1% and 8.4%, respectively).

In *post-licensure clinical trials* which enrolled 997.585 girls aged 10–17 years old, no serious adverse events ascribable to the vaccine were recorded for the quadrivalent as well as the bivalent vaccine (Arnheim-Dahlström et al., 2013).

In post-licensure clinical trials a review of post-licensure safety surveillance during >4 years of routine use of the bivalent vaccine found no patterns or trends for potential immune-mediated diseases after vaccination (Angelo et al., 2014).

2.3. Pregnancy

In the absence of well-controlled studies in pregnant women, vaccination with HPV vaccine is not recommended in pregnancy as a precautionary measure. However, some data are available from pregnant women inadvertently enrolled in Phase III clinical trials with known pregnancy outcomes, and through the establishment of pregnancy registers. The rate of major congenital anomalies was within the expected background population rate of 2–3%. No trends were observed, and the rate of spontaneous abortion was in line with reported rates in the UK and USA (Angelo et al., 2014).

The 9vHPV vaccine was generally well tolerated among women aged 16–26 years and boys/girls aged 9–15 years. Vaccine-related serious adverse experiences (SAEs) were rare. The 9vHPV vaccine displayed an adverse event profile generally comparable to that of 4vHPV. Vaccine-related adverse experiences (AEs) were largely ascribable to injection-site experiences, most of which were of mild or moderate intensity. These considerations were based on 3.066 boys and girls (Van Damme, 2015), 600 boys and girls (Van Damme et al., 2015) and 14.204 women aged 16–26 and 3.011 preadolescent and adolescent boys and girls (age 9–15) (Giuliano, 2015).

Case reports have suggested a link between human papillomavirus (HPV) vaccination and development of *multiple sclerosis* and other demyelinating diseases. Scheller et al. (2015) with their study have demonstrated that qHPV vaccination was not associated with the development of multiple sclerosis or other demyelinating diseases. These findings do not support concerns about a causal relationship between qHPV vaccination and demyelinating diseases (Scheller et al., 2015).

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Table 2
HPV vaccines control by the WHO Global Advisory Committee on Vaccine Safety (GACVS) (Anon., 2013, 2014b,c).

When	Starting points	Issues	Statement
GACVS update on HPV Vaccines 19 July 2013 (Anon., 2013)	In 2013, GACVS noted that growing evidence on the safety of HPV vaccines was reassuring; studies on HPV immunization had started, along with capacity-building for adverse events monitoring. GACVS places a high priority on the ongoing collection of high-quality safety data in settings where the vaccine is being introduced	4 years after the last review of HPV vaccine safety and with more than 170 million doses distributed worldwide and more countries offering the vaccine through national immunization programs, the Committee continues to be reassured by the safety profile of the available products	A timely clinical assessment and diagnosis of each case followed by appropriate treatment is therefore essential
GACVS Statement on the continued safety of HPV vaccination March 12, 2014 (Anon., 2014c)	As with all new vaccines, the GACVS has been reviewing the safety of HPV vaccines since they were first licensed in 2006	Safety concerns about HPV vaccines have systematically been investigated: to date, the GACVS has not found any safety issue that would alter any of the current recommendations for the use of the vaccine and its introduction is programmatically feasible	It is important to highlight and reiterate this work because a number of national immunization programs have been facing real and potential public losses of confidence in their programs as a result of increased negative publicity, even from safety issues that have been addressed
WHO Weekly epidemiological record 24 October 2014 (Anon., 2014b)	WHO recognizes cervical cancer and other HPV-related diseases as global public health problems and reiterates its recommendation that HPV vaccines should be included in national immunization programs	Prevention of cervical cancer and/or other HPV-related diseases constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost-effectiveness of vaccination strategies in the country or region is considered	Both the quadrivalent and bivalent HPV vaccines have excellent safety and efficacy profiles

3. Economic evaluation

3.1. Recommended immunization

The recommended immunization schedule for HPV by the European Center for Disease Control and Prevention—ECDC is presented in Table 3.

Cost-effectiveness studies of universal HPV vaccination present a small portion of the large data retrieved. Part of the information is excluded from most investigations including, but not limited to, impacts on productivity, patient's time and costs, caregivers and family costs, and broader social values such as the right to access treatment. Consideration should be given to provide alternative approaches to capture a broader set of values in a way that might be useful to decisions-makers, such as multi-criteria decision analysis (Marsh et al., 2014). However, in the analysis of countries or regions the multi-parametric evaluations are not always based on comparable data.

Jiang et al. (2013) conducted a critical review of available cost-effectiveness analysis for HPV vaccination in males and nine studies were identified from different countries. Key factors such as vaccine coverage rate and studies considered the epidemiological trend of HPV-related diseases, such as the observed increase in the incidence of anal or head and neck cancers (Jiang et al., 2013). Using 2011/2012 times and prices for England and Wales about 3.000 people had oropharyngeal cancer which cost approximately £115 million to treat. 70% of those cancers could reasonably be expected to be HPV driven. This equates to roughly £80 million in treatment costs. The all party UK parliamentarian health group estimated it would cost about £20–22 million to vaccinate boys in a gender neutral vaccination policy. Even at rough but reasoned estimates on Office for National Statistics (ONS) derived statistics and public domain Payment by Results (PbR) figures there is a fourfold saving for vaccinating just in financial terms (Baron et al., 2014; Upile et al., 2014).

Official bodies including WHO and other supervisory authorities recommend that the decision-making process should be based on both the quality of goods and services as well as the analysis of the best achievable price, economic impact and cost-effectiveness (Mennini et al., 2009a).

3.2. Cervical cancer treatment

The combined use of administrative and clinical databases allowed assessing the costs relevant to cervical cancer. The management of patients affected by locally advanced cervical cancer (LACC) is associated with higher costs due to the utilization of several therapeutic strategies and a more frequent appearance of disease

Table 3
The European Vaccine Schedule at the start of 2015, as it is in the European Center for Disease Control and Prevention-ECDC and in other publications.

	Gender	Ages of vaccination	Doses	Notes
Austria	F & M	9 and 12	2	Boys and Girls. Free of charge in school programs. At 13 years partially subsidized. http://bmg.gv.at/cms/home/attachments/8/9/4/CH1100/CMS13893658600013/impfplan.pdf Vienna, January 2015
Belgium	F	10	3	Recommended for girls 10–13 years old with 3 doses (schedule 0, 1, 6 months (2vHPV) or 0, 2, 6 months (4vHPV)
Bulgaria	F	12		HPV vaccination is not included in the National Immunization schedule. The vaccination is voluntary, but free of charge for 12-year-old girls
Croatia				
Cyprus				
Czeck Rep	F	13 and 18	3	Recommended only Females only. Three doses
Denmark	F	12 and 19		Females only. Denmark's childhood vaccination program 2014
Estonia				
Finland	F	11 and 13		HPV catch-up during the first 2 years of introduction to girls 13–15 years of age
France		11 and 15	2 and 3	11–13/14 2 doses Three doses in a 0, 1 or 2, 6 month schedule (girls aged 15–19 years) Haut Conseil de la santé publique
Germany	F	9–13/14 and 15	2 and 3	Two doses at 6 months interval. Females only. If the interval between two doses is <6 months, a 3rd dose may be recommended. Empfehlungen der Standigen Impfkommission (STIKO) am Robert Koch-Institut/Stand: August 2014
Greece	F	11 and 19	2 and 3	Females only. Vaccination recommended up to 26 years of age from January 2015 New NVC 01/2015 (2D in girls 11–<15 years)
Hungary				
Iceland	F	12		Females only. 7th grade
Ireland	F	11	2 and 3	First year second-level school (females 12–13 years of age), 3 doses given between 6 and 12 months NIAC 08/2014 (2D Girls 9–<15years; 0–6 months)
Italy	F & M	11	2 and 3	2 doses up to 13/14 years of age. Three doses all other ages. Females in all regions, males included in 7 regions
Latvia	F	12		Females only
Liechtenstein	F	11 and 15	2	Two doses. Females only. Catch-up vaccination recommended before the 20th birthday
Lithuania				
Luxembourg	F	12 and 15		Females only
Malta	F	12	3	For females born from the year 2000 onwards. 3 doses in a 0, 1, 6 month schedule
Netherlands	F	12	2	For girls under age 15, 2vHPV can be administered in a 2 dose schedule instead of 3 previously. The 0-1-6-schedule in under 15's is replaced by two doses in a 0-6-schedule (Jit et al., 2015)
Norway	F	12	3	Females only. 7th grade Plan to maintain 3D
Poland				
Portugal	F	13	2 and 3	Three doses. Females only DGS 10/2014: New vaccine schedule published with 2D and lowering age to 10–13 years
Romania	F	11	3	3 doses. Recommended, but not mandatory
Slovakia	F	12		Recommended only. Not included in the national immunization schedule. Partial reimbursement by the national healthcare system
Slovenia	F	11		Girls only
Spain	F	14	3 or 2	Three doses. Females only. 2D from Q3 2014 in some regions http://www.msssi.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/docs/PapilomaVPH.pdf Consejo Interterritorial 01/2015—Common pediatric vaccination calendar Lowered age at 12 years (girls)
Sweden	Children	10	3	Three doses. Children. Social styrelsen Tvadoschema den 8 september 2014 kl. 13:58 Nyhet children applies only to children 9–13 years: it must continue to be given to older children and adults, as well as immunosuppressed children
Switzerland	F	11–14	2	In the transition period also girls aged 15–19 should be included (Chastonay, 2007). Switched from three dose to two dose vaccination schedules for girls aged 9–14 years on the basis of such risk-benefit considerations (Jit et al., 2015)
UK	F and MSM	12 and 16–40	3	Females only. First dose can be given at any time during school year 8, to girls who are usually 12–13 years old. Second dose to be given around 12 months after the first. Implementing a catch-up campaign of girls up to age 18 is likely to be cost-effective (Jit et al., 2015) Free of charge vaccination 3 doses for Males who have sex with Males (MSM) up to 40 years of age (Anon., 2014a)

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progression/recurrence. As far as treatment is concerned, patients with early stage cervical cancer are triaged to exclusive radiotherapy or radical surgery with comparable results in terms of clinical outcome, although with different rates of complications and severity of side effects (Ferrandina et al., 2010). Although chemoradiation currently represents the gold standard in the treatment of locally advanced cervical cancer patients (Eifel et al., 2004; Eifel, 2006), the prognosis of this group of patients remains dismal, and there is still room for improving the treatment plan according to its different stages. Difficulties in assessing the formal cost of cervical cancer management is explained by the fact that clinical and administrative databases are often not linked. Some of the data has been collected analyzing patients diagnosis, treatment and follow-up in various (although similarly-organized) venues linked to the Italian Network of Cancer Registries: this has provided a comprehensive set of clinical and pathological information on characteristics and outcomes, with a relatively high degree of homogeneity (i.e.: diagnostic procedures, treatment protocols, surveillance etc.). Mean management costs (estimated by the International Federation of Gynecology and Obstetrics-FIGO) for incident cases (including 10 years of follow-up) were: €6,024 (FIGO I); €10,572 (FIGO II); €11,367 (FIGO III); €8,707 (FIGO IV); and €5,854 for the terminal phase (1 month) (Ricciardi et al., 2009). Another analysis (Ferrandina et al., 2010) pointed out that the mean cost by patient amounted in Italy to almost €29,000 and €12,300 for a patient with locally advanced cervical cancer and early stage cervical cancer, respectively. As a different methodology was applied, these findings are hardly comparable with the results previously reported in studies conducted in other countries (such as the France, United Kingdom and United States) (Arveux et al., 2007; Brown et al., 2006; Costa and Favato, 2008).

3.3. Anogenital warts

GWs event is highly variable in relation to its occurrence, management, and medical approach (general practice vs hospital-based dermatology, genitourinary, etc.). The annual cost in Italy of the treatment of genital warts is approximately €37 million for females and about €33 million for males (Baio et al., 2012). An economic analysis showed that the costs associated with GWs in men and women represented 24.3% (€70.9 million) of the total costs associated with HPV-6,-11,-16 and -18 diseases in Italy; preventing GWs and the associated costs alone would cover most of the costs for qHPV vaccination (Baio et al., 2012).

3.4. Preventive measures

In Italy, the Basilicata Region was the first to implement preventive measures in 2007; this was soon followed by other regions and provinces with different covering profiles in the following 5 years. Based on a coverage rate of 80%, assuming lifetime duration of protection and discount rates of 1.5% and 3% for health benefits and costs respectively, the implementation of HPV vaccination in Italy among a cohort of girls aged 12 years has been evaluated to avoid 1.432 incremental cases of cervical cancer (−63.3%) and 513 related deaths (−63.4%) compared to screening program only (Mennini et al., 2009b). In this study, the impact of vaccination was evaluated considering the current screening strategy on women only. This evaluation provides estimates of cost-effectiveness for HPV vaccination in Italy which were consistent with data reported by another Italian study (Capri et al., 2007) highlighting similar conclusions on the cost-effectiveness of HPV vaccination alongside screening strategies in Italy, but with ICERs (incremental cost-effectiveness ratios) slightly higher (€34,676 per life year gained-LYG and €26,361 per QALY gained). The main objective of the evaluation of the substantial burden of direct costs in the Italian National Health Service is to estimate the total direct medical costs associated with nine major HPV-related diseases, namely invasive cervical cancer, cervical dysplasia, cancer of the vulva, vagina, anus, penis, and head and neck, anogenital warts, and recurrent respiratory papillomatosis, and by providing an aggregate measure of the total economic burden attributable to HPV-6,-11,-16, and -18 infection. The total direct costs (related to 2011) associated with annual incident cases of the nine HPV-related conditions included in the analysis were estimated to be €528.6 million, with a plausible range of €480.1–686.2 million. The fraction attributable to HPV-6, -11,-16, and -18 was €291.0 (range €274.5–315.7 million), accounting for approximately 55% of the total annual burden of HPV-related disease in Italy. The fraction of the total direct lifetime costs attributable to HPV-6,-11,-16, and -18 infections and the economic burden of non cervical HPV-related diseases carried by men were found to be cost drivers relevant to the making of informed decisions about future investments in programs of HPV prevention (Baio et al., 2012).

The difficulty of studying the pathophysiology of HPV in men is well addressed by Zuccotti et al. (Zuccotti and Mameli, 2013). The authors show that there is a wide range of variability in the prevalence of the infection, related to the different methods of sampling used, the geographical area where the study was performed (in Europe and East Asia prevalences have been observed to be lower than in countries of the African continent), the anatomical site in which the virus has been researched, the number of sites considered in the study, the difficulty of having a population representative of the general population, and the risk group. Prue showed that the economic cost of HPV-related diseases is considerable and also that any decision about whether to vaccinate boys should not be based solely on cost effectiveness. Public health, equity, and the human costs of HPV-related disease for both sexes must be the main concern (Prue, 2014). The cost-effectiveness evaluation of vaccination is based also on the design of developed programs. Indeed, depending on the number (1, 2, or 3) of eligible cohorts, the cost of HPV vaccination in Italy might be assumed in a range between €55 and €120 million (Favato et al., 2007). On the other hand, annual costs associated with HPV-related diseases amount to about €250 million (Mennini et al., 2009a). With the HPV vaccination, the overall reduction of HPV-related events over time would produce a total decrease in costs of approximately €132 million (Mennini et al., 2009a). In order to optimize the use of public financial resources, a multi-cohort vaccination program should be considered in order to reach a positive balance point between the need to accelerate the cost reduction of the invasive cervical cancer and the rational management of healthcare demand. The PRIME (Papillomavirus Rapid Interface for Modelling and Economics) effectiveness model (Jit et al., 2014) developed to evaluate the impact on public health by the vaccination of 58 million girls (12 years old) in 179 countries before their first sexual debut, would prevent 690.000 cases of cervical cancers and 400.000 linked deaths, with an estimated cost of US $4 billion. The current proposed and in some countries accepted two-dose vaccination with expected similar positive outcomes in terms of health efficacy and safety will hugely decrease the total cost.

3.5. At European level

The objective of the study of Marty et al. (2013) was to estimate the incremental benefit of vaccinating boys and girls using the qHPV vaccine in Europe versus girls-only vaccination. Incremental benefits in terms of reduction in the incidence of HPV-6,-11,-16 and -18-related diseases (including cervical, vaginal, vulvar, anal, penile, and head and neck carcinomas and genital warts) were assessed. Compared with screening alone, girls-only vaccination led to 84% reduction in HPV-16,-18-related carcinomas in females

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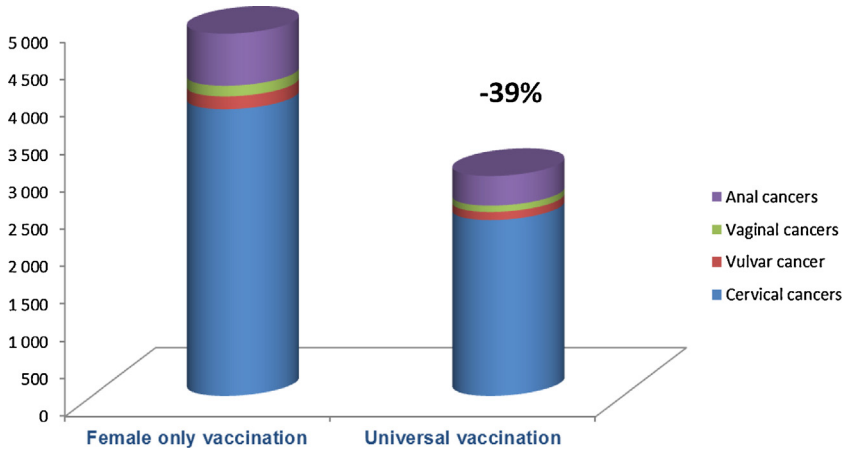

Fig. 1. Estimate of the reduction of the remaining HPV-16,-18-genital and anal cancers burden in females in Europe through female-only HPV vaccination and universal HPV vaccination (age 12 years, 70% VCR).

and a 61% reduction in males. Vaccination of girls and boys led to a 90% reduction in HPV-16, -18-related carcinomas in females and 86% reduction in males versus screening alone. Relative to a girls-only program, vaccination of girls and boys led to a reduction in female and male HPV-related carcinomas of 40% and 65%, respectively and a reduction in the incidence of -HPV-6, -11-related genital warts of 58% for females and 71% for males versus girls-only vaccination.

Further analyses should be performed taking into account the country-specific situation. In addition to clinical benefits, substantial economic benefits are also anticipated and warrant further investigation as do the social and ethical implications of including boys in vaccination programs (Marty et al., 2013). When talking about cancer as a preventable endpoint we have to question ourself twice if economic evaluation analysis of cost effectiveness is acceptable, the disease has an important economic and health impact in males with possible reduction of several thousand cases of anal cancer in males, this should be enough to justify male vaccination.

3.6. Universal vaccination

The economic impact of the gender-neutral vaccination has been assessed through several studies (Marsh et al., 2014) focusing on the health prevention. Unfortunately several investigations fail to take into consideration the impact on the family costs to save presence of the person within the labor areas, and social values. The Bayesian model has been largely evaluated (Haeussler et al., 2014): the results confirm that the universal vaccination against HPV is cost-effective in comparison to the screening and the vaccination only of the women cohorts. Other studies have evaluated the effects of herd immunity and other variables (such as number of partners, smoking, and socio-cultural levels) and the potential of the universal vaccination has been confirmed (Haeussler et al., 2014). The principle of equity and equal access to healthcare to maximize a population's health is a cornerstone for all health systems, therefore universal vaccination would give men and women the same rights to protection. Targeting both boys and girls, in through routine universal HPV vaccination, would:

- protect females and males against HPV-related cervical, vulvar, vaginal and anal (pre) cancers, and genital warts and, significantly reduce the remaining burden in both genders (Marty et al., 2013);
- accelerate the control of HPV vaccine types circulation and related cancers and diseases with quasi-elimination of vaccine HPV strains in the population (Brisson et al., 2011; Bresse et al., 2014; Korostil et al., 2013);

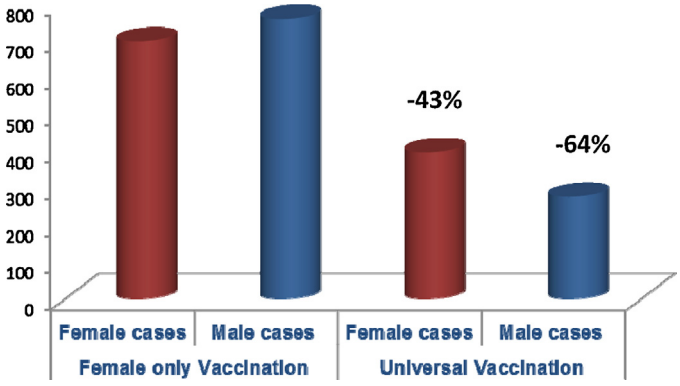

Fig. 2. Reduction of the remaining HPV-16,-18-anal cancer burden in females and males in Europe through female-only HPV vaccination and universal HPV vaccination (age 12 years, 70% VCR).

- normalize HPV vaccination to become a standard vaccination in pre-adolescents;
- reduce gender and social health inequalities by protecting men exposed to unvaccinated female or male partners (increased risk with population movements) and protecting the most vulnerable people.

It has been estimated that universal HPV vaccination programs can significantly reduce the remaining burden of HPV-vaccine types related (pre) cancers and genital warts in both females and males, as also shown by internal modelling exercise based on a European adaptation of the Marty et al. (2013) model (Figs. 1–3).

As already discussed, HPV vaccination is a highly valuable investment which contributes to more sustainable and efficient health systems with economic benefits. Incremental cost-effectiveness ratios are generally lower for the quadrivalent vaccine versus the bivalent vaccine, mainly due to additional benefits of genital wart prevention (Jit et al., 2011). The full economic benefits of HPV vaccination are difficult to be quantified in monetary terms (e.g.: decrease of the burden for the caregiver, psychosocial impact, impact on fertility, productivity loss) and therefore the cost-effectiveness is likely not to be the most relevant measure, based on existing guidelines, when assessing the broad economic value of HPV universal vaccination (Marsh et al., 2014). At a national and European level, it is observed that:

- on the short-run, an early return on investment is observed due to the prevention of genital warts with 4vHPV vaccination with

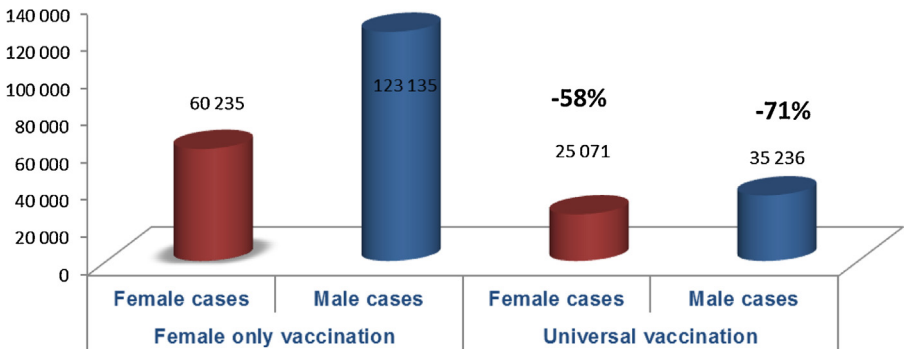

Fig. 3. Reduction of the remaining HPV-6,-11-genital warts burden in females and males in Europe through female-only vaccination and universal vaccination (excluding HPV-related head/neck cancers) (age 12 years, 70% VCR).

the majority of costs saved over 5–10 years following vaccination due to genital warts prevention (Dasbach et al., 2008);

- on a long-term basis, a broad benefit-cost analysis in Germany showed that universal HPV vaccination (1 cohort of 12-year-old girls and boys) resulted into a positive net economical value. Every Euro spent on universal vaccination provides €1.81 of revenue to the government (Kotsopoulos et al., 2013).

It is important to underline that HPV vaccination represent a low-cost and efficient intervention for HPV-related cancers not only in comparison with other oncologic treatments. It also represents a sustainable solution thanks to its long term duration of protection.

4. Are there new political positions in the prevention of HPV infection?

4.1. Upgraded positions

In 2012, about 40 countries (22 in Europe, 6 in the Americas, 1 in Eastern Mediterranean, 10 in Western Pacific, 1 in South East Asia, and 1 in Africa) were delivering immunization programs against HPV, although with different approaches, with a starting target group of girls at 11 or 12 years of age and with variable catch up group till 26 years of age. USA and Austria had started in 2006, and Sweden entered the group in 2012. Worldwide the delivery of the vaccination was carried out either in the schools or in health centers. By August 2014, 58 countries have had introduced HPV vaccine in their national immunization programs for girls, and in some countries also for boys (Anon., 2014b). The European Medical Agency in 2011 introduced boys/men in the HPV target but limited to genital areas; some European countries started with a vaccination aimed at men, delivering it free of charge to young male people; as of today in Italy, 7 regions out of 21 have decided to include free males active vaccination. The qHPV vaccine has been approved for the prevention of anal cancer in June 2014. The qHPV vaccine, which includes HPV-6 and HPV-11, the HPV types that most commonly cause ano-genital warts, when given in a 3-dose schedule provides high-level protection against anogenital warts in males and females and anogenital precancerous lesions in susceptible males aged 16–26 years. Some studies in high income settings have reported that vaccinating adolescent girls for cervical cancer prevention might potentially be cost-effective if vaccine coverage in girls is high. Other investigations in high-income settings (Norway) have reported that expanding the HPV vaccination programs to boys, may be cost-effective and may warrant a change in the current female-only vaccination policy in the country (Burger et al., 2014). In vaccinees who were seronegative in the vaccines currently employed, high seroconversion rates and high levels of anti-HPV antibodies against HPV-6 and HPV-11 virus-like particles were observed in females aged 9–45 years and in males aged 9–26 years (McCormack, 2014). In a number of industrialized countries (Australia, Sweden, Denmark and the United States of America), substantial decreases in cases of genital warts have been observed following the introduction of a national HPV vaccination program using qHPV vaccine (Ali et al., 2013). From analyzing eighteen studies including between 897 and 46.900 women, De Vuyst et al. (2009) have demonstrated that in female the prevalence of HPV is high in the first years of the sexual debut and lowers later on, while in male it remains high throughout life (De Vuyst et al., 2009). A comprehensive cost analysis should capture the full economic value of vaccination management programs in both genders including the quality-adjusted life-year gained in several cohorts. In health care this approach is a non ending evolutionary process that creates a new responsibility for decision-making choices globally (Favato et al., 2013).

Table 4
Incremental cost of HPV vaccination in women protection against cervical cancer.

Austria	€26,701 QALY
Belgium	€10,546 QALY
France	€8,408 QALY per TPP or 13,809 per DCP
Germany	€10,530 QALY
Hungary	$27,588 QALY
Italy	€9,569 ICER per QALY
Netherlands	€53,500 QALY € 5,815 ICER per QALY
Norway	€8,272 QALY
Slovenia	€23,178 ICER per QALY
Switzerland	CHF 26,005 ICER per QALY
UK	£21,059 ICER per QALY varying discount rates from 3,5% for medical benefits to 1,5% would decrease the ICER to £9,653 per QALY

Legenda: QALY quality-adjusted life years. ICER QV incremental cost-effectiveness ratio. TPP: third-party payer perspective quality-adjusted life-year. DCP direct healthcare cost perspective for quality-adjusted life-year for Data.

4.2. Incremental cost of HPV vaccination

The analysis of incremental cost of HPV vaccination in women protection against cervical cancer opens a series of questions marks. The reported data from the literature show a different economic interpretation in the mentioned countries (see Table 4) of a substantial answer to a correct interpretation of the concepts on health rights (Giraldi et al., 2014; Bresse et al., 2014; Hillemanns et al., 2008; Vokó et al., 2012; Mennini et al., 2009b; Bergeron et al., 2008; Szucs et al., 2008; Obradovic et al., 2010; de Kok et al., 2009).

Published studies on cost effectiveness of HPV vaccination suggest that vaccination against HPV can be used and can be cost effective. Over 64 countries around the world were included in cost effectiveness analyses of HPV vaccination (Čavaljuga et al., 2013). In this study the mean value of ICER was $28,399, with a median

$15,600. Data on men are not sufficient and not comparable to data on women in the cervical cancer. The studies included in this mentioned review used different methodologies and had various assumptions but were consistent in the conclusion that preadolescent female vaccination is cost effective compared to screening alone. Values of cost effectiveness ratios are not static and can change in time. It is clear that the evaluation changes from country to country.

In the United Kingdom and in Italy, with competitive tendering, tender prices for vaccines can be substantially lower than their list price.

The recent introduction in some countries (such as United Kingdom and Italy) of the two doses vaccination schedule is opening questions on the long lasting protection against infection, and that means that the cohorts given two doses should be monitored (Jit et al., 2015). This approach is asking more studies with the introduction of the 9vHPV vaccine.

An economic evaluation is expected to assess the cost-effectiveness of the introduction of boys in the vaccination schedules.

During its February 2015 meeting, the Advisory Committee on Immunization Practices (ACIP) recommended 9-valent human papillomavirus (HPV) vaccine (9vHPV) as one of three HPV vaccines that can be used for routine vaccination (Petrosky et al., 2015). This introduction is proposing a new evaluation of the HPV vaccine use within the countries.

In this mutable scenario the added long term value for public policy purposes remains untested: the use of forecasting models is limiting the uncertainty of assumptions, although it is not comparable to long term epidemiological studies (Garattini et al., 2015).

5. Conclusions

Epidemiological data show how HPVs affect both men and women, with men carrying a considerable burden of disease, enough to justify amendments of the national recommendations for immunization programs against HPV-associated lesions. There is an increasing opportunity to decrease the burden of the disease and to increase quality of life (Čavaljuga et al., 2013), taking advantage of the increasing opportunity to reduce HPV infection and its transmission among sexual partners, as much as of the strong evidence in favour of the efficacy and effectiveness of HPV vaccines in preventing the development of HPV-related diseases.

The cost-effectiveness of including boys into HPV vaccination programs should be re-assessed in every country in view of the progressive drop of the economic burden of HPV-related diseases in men and women due to universal vaccination. These achievements demand urgent attention to the social equity for both genders in healthcare (Crosignani et al., 2013); advocating and educating the general public and the medical community on HPV vaccination is a top priority (Odone et al., 2015).

Unfortunately the organization and quality of HPV vaccination programs differ across countries and, in some instances, even across regions within the same country. The majority of countries had some level of vaccination activity, and half of them report an organized vaccination program. Costs of organization and monitoring are difficult to estimate and varied significantly. In many cases it is difficult to compare systems and infrastructures among them, as some countries were able to use existing infrastructures while others had to create new systems, incurring greater costs (Elfström et al., 2015). The cost of organization is a point of large discussion not only in Europe (Isshiki, 2014; Arakawa et al., 2015).

The comparison of the different approaches among European countries confirms the need to develop and implement a common policy of HPV vaccination within the frame of the concept of a "one only" European health system. From the above-mentioned evaluations it is clear that, thanks to HPV vaccination, the economic management of related tumor prevention must be seen in a larger European context, rather than in a single region or a single country. The importance of HPV related diseases is recognized by WHO, which considers the prevention of cervical cancer and/or other HPV-related diseases as a public health priority, through the programmatically feasible introduction of HPV vaccine. However, WHO so far has not been able to secure a sustainable financing and to implement cost-effective vaccination strategies in most countries or regions (Anon., 2014b). The following strategy suggested by WHO should become an urgent executive policy for the European Union including: education about reducing behaviors that increase the risk of acquiring HPV infection; training health workers and providing information to men and women on screening, diagnosis and treatment of HPV associated tumors. HPV vaccination should be considered as a primary prevention tool, although it does not eliminate the need for further screening later in life, since currently available vaccines do not protect against all high risk HPV types.

The full effect of HPV vaccination is expected to be seen only in 30–40 years time (Lynge et al., 2014). Given the future of a heterogenous target population it would be reasonable to replace the "one-model-fits-all" today screening schedule with stratified algorithms. The introduction of 2-doses, as it is going to be in some countries in Europe, will open a new evaluation of the cohort and screening programs selection. The European healths authorities (EMA) have licensed the bivalent and quadrivalent vaccines for a 2-dose application with suggested interval with 6–12 months (Pils and Joura, 2015). The future of cervical cancer screening is linked to the modification of screening programs where the HPV-DNA testing will be added or will substitute the Papanicolau testing or co-testing. In USA, the primary HPV screening is considered to be an alternative of the Papanicolau testing or co-testing. The Netherlands and Australia plan to replace Papanicolau testing with primary HPV testing in 2016 (Pils and Joura, 2015). This changing will ask a confirmation by the general implementation of the HPV-DNA tests that are modifying the traditional HPV screening through cytology. In this field, the scientific results are expected to confirm or modify the today approach in the vaccination policies within the countries.

The European Union is asked to equally spread support across all country members in: reaching cost-effective vaccination programs in boys and girls; delivering affordable control policies of the results of the vaccination programs; empowering the population in defending their health values in front of HPV linked diseases. If countries consider phased introduction, priority should be given to strategies that include those European populations who are likely to receive less access to screening for cervical cancer later in life. With currently effective vaccines, the focus of organized HPV vaccination programs should change from the reduction of HPV disease burden to the control of high-risk HPV and low-risk HPV types (Lehtinen and Dillner, 2013). There is sufficient ethical, scientific, strategic and economic reasons to urge the European Community to develop and implement a coordinated and comprehensive strategy aimed at both genders and geographically balanced, to eradicate cervical cancer and other diseases caused by HPV in Europe.

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Biography

Andrea P Peracino: Vice President and Member of the Scientific Committee of the Fondazione Giovanni Lorenzini Medical Science Foundation (Milan, Italy-Houston, TX, USA). The Lorenzini Foundation has the mission to transfer the most recent developments and results in the experimental sciences to clinical and applied research, including health economy evaluations, to be used for the single patient and for the community. The Foundation collaborates with academia, basic and clinical scientific societies, health organizations, regulatory agencies, industry, to ensure the constant updating of the health experts. The Lorenzini Foundation is used to combine multi-faceted interests and experiences to solve complex problems at national and international level.

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