Human papilloma virus vaccination: impact and recommendations across the world

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***Abstract*:** Human papilloma virus (HPV) vaccination has been implemented in several countries for about the past 7 years, mainly in the adolescent female population, with varying coverage results. Although the impact of immunization on cervical and other HPV-related cancers will be evident in the next decades, a marked decrease of prevalent HPV infections, precancerous lesions and genital warts is already dramatic in the vaccinated cohorts, and also in their sexual partners, thus providing clear evidence of the effectiveness of HPV vaccination, including a herd-protection effect. Today, recommendations and implementation of universal HPV vaccination for adolescent girls are a public-health priority in all countries of the world. Countries with limited resources are presently involved in demonstration projects and, in some cases, have launched national programmes with the help of international agencies and alliances. Extension of immunization offer to young women and to adolescent male subjects has become an important additional opportunity for several countries, with a special focus needed on homosexual men with HIV infection who are at particularly increased risk of HPV-related diseases. Public-health authorities are confronted with the need to enlarge HPV-vaccination offer to all target groups, especially pre-adolescent girls, so that they can be saved from dreadful cancers by reaching high immunization coverage.

Keywords: coverage, human papilloma virus, impact, recommendations, vaccination

Introduction

The human papilloma virus (HPV) is one of the most important carcinogenic factors, classified as a group 1 carcinogen according to the criteria of the International Agency for Research on Cancer. Different high-risk HPV types are causally associated with about 5% of all cancers, 10% of female cancers, and 16% of cancers of women in countries with limited resources [De Flora and Bonanni, 2011; de Martel *et al.* 2012; Forman *et al.* 2012] (Table 1).

The development of two vaccines able to prevent persistent HPV infections and the evolution to precancerous lesions has opened a new era in vaccinology and oncology. HPV vaccines are actually perceived as the first anticancer vaccines (those against hepatitis B were in reality the first vaccines directed against a tumour).

Due to the impossibility of measuring direct efficacy against cancer for both ethical and time reasons, prevention of cervical intraepithelial neoplasia lesions of grades 2 or 3 (CIN2+) was considered as the best surrogate endpoint for protection. Clinical trials of both the quadrivalent (type 16, 18, 6 and 11 containing vaccine) and the bivalent (type 16 and 18 containing vaccine) reported results mainly as efficacy against the above endpoint [Future II Study Group, 2007; Paavonen *et al.* 2009].

Since 2007, recommendations have been issued in many industrialized countries on subjects to whom vaccination should actively be offered. Actual implementation was highly dependent on national factors, such as organization of the healthcare system and ways chosen to fund or reimburse vaccination offer [Bonanni *et al.* 2011].

In this review, we aim to provide evidence of the first results of the effectiveness of HPV immunization on HPV-related diseases, outline different recommendations from around the world, and

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Table 1. Proportion of cancers attributable to persistent human papilloma virus infection.

5% of cancers
10% of cancers in women
16% of cancers in women living in developing countries

also identify priority subjects to whom vaccination is proposed and administered.

HPV vaccination effectiveness: general aspects

HPV vaccines are intended to prevent, as their primary objective, cervical and other genital cancers. As such, their effectiveness will be measurable only in the long term, when sufficiently numerous cohorts of immunized adolescents will have reached the age when cancers are more frequently diagnosed.

Since the natural history of the evolution from persistent infection to precancerous (CIN1–3) and cancerous lesions is well known [Goldie *et al.* 2003], several model-based projections have been made about the impact of HPV-vaccination programmes on disease incidence, thus allowing the forecast of both clinical and economic outcomes of immunization before the two HPV vaccines were available on the market. Different modelling approaches were used (e.g. cohort, population dynamic and hybrid), but all simulations demonstrated that universal pre-adolescent female immunization coupled with screening invariably substantially impacted on the incidence of cervical precancers and cancers, and was cost-effective even when only cervical cancer was considered, without also taking into account impact on the rarer cancers associated with HPV [Dasbach *et al.* 2006]. Papers on impact models of HPV vaccination are continuously being produced to explore new possible target groups, such as adolescent males [Smith and Canfell, 2014] or, recently, the use of a reduced number of doses [Jit *et al.* 2014].

However, it must not be forgotten that the impact of HPV vaccination on conditions with a shorter natural history compared with cancer is already possible a few years after universal immunization was implemented. In particular, comparison between vaccinated and nonvaccinated subjects with regard to persistent HPV infection, genital warts (for the quadrivalent vaccine), and precancerous lesions (CIN2+) has started to supply intriguing data on the effectiveness of HPV vaccination.

Caution in the evaluation of results is always needed, since sources of bias and misinterpretation are possible. As a matter of fact, monitoring prevalent infections implies sampling, detecting and genotyping HPV from the infection site, and the recent changes occurring in many countries in the recommendations on the age of initiation of screening, its intervals and tests to be used can affect the possibility of detection of infections and lesions, especially when methodological changes occur during the follow-up time. In addition, with regard to impact on genital warts, it is worth underlying that such lesions are not subject to notification in many countries, and their diagnosis is highly variable and dependent on health organization and social factors [Hariri *et al.* 2013]. However, despite such limitations, data are accumulating in several countries that provide proof of the effectiveness of HPV vaccination.

Effectiveness of HPV vaccination: examples across the world

Examples of the effectiveness of HPV vaccination are available from different countries, but there is no doubt that Australia is the country where immunization programmes were most comprehensive, and where high coverage in a considerable number of young females was reached in a short time. Coverage with three doses of quadrivalent HPV vaccine in female cohorts ranged from 30% in the age groups 20–26 years and 73% in 12–13-year-old groups, respectively (with intermediate age groups showing progressively higher coverage with decreasing age). The corresponding figures for uptake of at least one dose were 52% and 83% [Gertig *et al.* 2011].

A comparative study on HPV-type prevalence in Pap smears in Australian women aged 18–24 years in the prevaccination period (2005–2007) and in the postvaccination period (2010–2011) using the same recruitment and testing strategies showed that the prevalence of vaccine HPV genotypes (6, 11, 16 and 18) was significantly lower in the postvaccine sample than in the prevaccine sample (6.7 *versus* 28.7%; $p < 0.001$), with a lower prevalence observed in both vaccinated and unvaccinated women compared with the prevaccine population (5.0% [adjusted odds ratio (OR): 0.11; 95% confidence interval (CI): 0.06–0.21]

and 15.8% [adjusted OR: 0.42; 95% CI: 0.19–0.93], respectively) [Tabrizi *et al.* 2012].

Also the impact on genital warts was clear. In a study evaluating the trend of Australian national surveillance data between 2004 and 2011 in more than 85,000 subjects, a dramatic decline was observed in the proportions of women younger than 21 years and those aged 21–30 years diagnosed with genital warts which, respectively, changed from 11.5% in 2007 to 0.85% in 2011 (a 92.6% decline; $p < 0.001$), and from 11.3% in 2007 to 3.1% in 2011 (a 72.6% decline; $p < 0.001$). By contrast, no significant decrease in genital warts diagnoses was registered in women older than 30 years. The indirect effect of universal immunization was also detected in heterosexual men younger than 21 years and those aged 21–30 years, for whom a 81.8 and 51.1% decrease of genital warts, respectively, was detected in the same period ($p < 0.001$). No decline in wart diagnoses was registered in heterosexual men over 30 years of age [Ali *et al.* 2013].

A third study from Australia was also able to show the decrease of high-grade cervical abnormalities (HGA) (CIN2+ or adenocarcinoma *in situ*) in women younger than 18 years involved in the vaccination programme when comparing the period 2003–2007 (prevaccination) with the period 2007–2009 (postvaccination). Such a decline from an incidence of 0.85% in 2006 to 0.22% in 2009 represents a more than 50% decline in incidence ($p = 0.003$). A quantitative comparison of linear trends also showed a significant decrease in HGA incidence after the introduction of the vaccination programme in individuals aged 17 years or younger, but no significant decrease in those aged 18–20 years. Although the ecological nature of the study does not prove a causal link between the decrease of HGA incidence and implementation of HPV vaccination, it is nevertheless very plausible that the two phenomena are strongly related, since no change was recorded in nonvaccinated cohorts [Brotherton *et al.* 2011].

Evidence of the early impact of HPV vaccination is available not only from Australia, but also from northern European countries. A study in Denmark demonstrated that, whereas a 2% annual increase of genital warts had been registered in the years preceding immunization, they virtually disappeared in girls aged 16–17 years when, after the introduction of vaccination, coverage reached 85% in a short time. No indirect impact on warts in males has been registered up to now [Baandrup *et al.* 2013].

All Nordic countries have implemented a long-term surveillance system to follow up women vaccinated in the first vaccine trials of the quadrivalent HPV vaccine. Since all women in the placebo arm of the Future II vaccine trial were immunized after 60 months of observation for ethical reasons [Olsson *et al.* 2007], it is no longer possible to calculate vaccine efficacy (VE). However, it is noteworthy that no case of breakthrough HPV 16/18-related CIN2+ occurred in women belonging to the vaccine arm up to 8 years after immunization [Kjaer *et al.* 2012].

In the USA, coverage with HPV vaccine is low in girls targeted by the vaccination recommendations (three-dose coverage in 2010 was only 32% among 13–17-year-olds). Nevertheless using data from the National Health and Nutrition Examinations Surveys, a clear decline (56%) of vaccine-type HPV infections between 2003–2006 and 2007–2010 was registered in those aged 14–19 years. Vaccine effectiveness of at least one dose against such an endpoint gave results as high as 82% [Markowitz *et al.* 2013].

HPV vaccines have shown a variable degree of cross protection in clinical trials. However, an unexpected effect on 6-month persistent infections has been recently described in the Papilloma Trial Against Cancer In Young Adults (PATRICIA) study for the bivalent vaccine against HPV types responsible for genital warts. VE was 34.5% against combined HPV 6/11, 34.9% against HPV 6, and 49.5% for HPV 74 (all statistically significant results). An ecological study on the impact of the bivalent vaccine on genital warts incidence in the UK seems to confirm the trial data. As a matter of fact, between 2008 and 2011, a universal programme with the bivalent HPV vaccine was implemented in 12-year-old girls, reaching more than 80% coverage, supplemented by a catch-up strategy up to 18 years (more than 40% coverage). Genital warts, which had increased steadily from the 1970s until 2009, showed a decrease since then, with a calculated 11–16% effectiveness of the vaccine in young women aged 18 years and 15 years, respectively [Howell-Jones *et al.* 2013; Szarewski *et al.* 2013].

HPV is not only responsible for genital lesions, but is also a considerable cause of morbidity and

mortality for head and neck cancers. More than 11,000 such cancer cases attributable to HPV are estimated to occur every year in the USA, with a 4/1 rate for males compared with females. Whether HPV vaccines will be able to prevent HPV-related head and neck cancers still remains undemonstrated. Actually, it is not possible to perform clinical trials due to the absence of an early marker of disease, and therefore only population-based epidemiological studies will be able to address this issue in the next 1–2 decades. However, vaccine coverage has been foreseen by the scientific community as well as by the Centers for Disease Control and Prevention (CDC) to have an impact on the incidence and mortality of more exploratory outcomes, such as head and neck cancers [Brotherton and Gertig, 2011; CDC, 2012].

A first positive indication of the potential role of HPV immunization comes from a recent study performed during a clinical trial of the bivalent vaccine in Costa Rica. At the final study visit, 5840 participants provided oral specimens (91.9% of eligible women) to evaluate VE against oral infections. Primary analysis evaluated prevalent oral HPV infection among all vaccinated women with oral and cervical HPV results. Approximately 4 years after vaccination, there were 15 prevalent HPV 16/18 infections in the control group and one in the vaccine group, for an estimated VE of 93.3% (95% CI: 63–100%). Corresponding VE against prevalent cervical HPV 16/18 infection for the same cohort at the same visit was 72.0% (95% CI: 63–79%) (*p versus* oral VE = 0·04).These results suggest that the bivalent HPV vaccine affords strong protection against oral HPV 16/18 infection, with potentially important implications for the prevention of increasingly common HPV-associated oropharyngeal cancer [Herrero *et al.* 2013].

Studies have been committed by regulatory agencies to exclude the possibility that, under immunological pressure in highly vaccinated populations, types of HPV not included in vaccines might emerge as a cause of precancerous and cancerous lesions, thus filling an ecological niche left open by immunization programmes. Such researches are under way and will add important information in the near future. However, some characteristics of HPV viruses (like the frequent possibility of being infected simultaneously by different HPV types) make it very unlikely that a replacement effect like that described for some encapsulated bacteria might occur after the implementation of routine HPV vaccination programmes.

The new two-dose vaccination schedule

The opportunity to reduce the number of doses needed to confer protection against HPV-related diseases has a double potential advantage: it makes coverage targets easier and saves money that could be used to expand target cohorts for immunization.

Two studies were performed on the potential use of a two-dose schedule with the bivalent vaccine, firstly a 'proof of concept' phase I/II trial (HPV-048) [Romanowski *et al.* 2011], and subsequently a confirmatory, phase III trial (HPV-070) [Puthanakit *et al.* 2013]. The first study investigated the two-dose schedules using the licensed 20/20 μg of HPV 16 and HPV 18 L1 protein virus-like particles or an alternative formulation containing 40 μg of each antigen, compared with the licensed three-dose schedule. Healthy females stratified by age (9–14, 15–19, 20–25 years) were randomized to receive two doses of 20/20 vaccine at months (M) 0,6 (n = 240), 40/40 vaccine at M0,6 (n = 241), or 40/40 vaccine at M0,2 (n = 240), or three doses of 20/20 vaccine at M0,1,6 (licensed schedule/formulation, n = 239). One month after the last dose, the three-dose schedule was not immunologically superior to the two-dose schedules except in the 40/40 vaccine M0,2 group for HPV 16 (lower limit of 95% CI geometric mean antibody titre [GMT] ratio [two-dose/three-dose] < 0.5). For both HPV 16 and HPV 18, the two-dose schedules in girls 9–14 years were immunologically noninferior to the three-dose schedule in women 15–25 years (the age group in which efficacy has been demonstrated) (upper limit of 95% CI for GMT ratio [three-dose/two-dose] < 2) 1 month after the last dose. At month 24, noninferiority was maintained for the two-dose M0,6 schedules in girls 9–14 years *versus* the three-dose schedule in women 15–25 years [Goldie *et al.* 2003]. Antibody response was recently reported to be still high at the 48-month follow-up visit in all groups [Romanowski *et al.* 2013].

The confirmatory phase III trial aimed, as a primary objective, at demonstrating noninferiority in enzyme-linked immunosorbent assay (ELISA) for the two-dose schedule (M0,6) in 9–14-year-old girls *versus* the three-dose schedule (M0,1,6)

in 15–25-year-old women for both seroconversion rates and GMTs. Secondary objectives were to measure functional antibody response through pseudovirion-based neutralization assay (PBNA) and cell-mediated immunity (CMI) including, for the latter evaluation, cross-protective antibodies against HPV 31/45. In the according-to-protocol population, noninferiority of the two-dose schedule in 9–14-year-olds *versus* the three-dose schedule in 15–25-year-olds was demonstrated for HPV 16/18 ELISA antibody response. At least 98.9% of initially seronegative subjects seroconverted for anti-HPV 16/18/31/45 antibodies (ELISA). Anti-HPV 16/18/31/45 GMT (ELISA) and CMI responses were similar (descriptive analysis) between two-dose and three-dose groups. HPV 16/18 neutralizing antibody responses (PBNA) appeared higher in the two-dose group than in the three-dose group. The European Medicine Agency (EMA) approved the change for the indication of the bivalent HPV vaccine to a two-dose schedule for girls aged 9–14 years on 20 December 2013.

With regards to the quadrivalent HPV vaccine, no '*ad hoc*' study was planned by the producer to support a change of schedule in young girls. However, some countries independently opted for an off-label use of the vaccine, proposing the use of a two-dose schedule, possibly followed by a booster dose some years later. In particular, a randomized, phase III postlicensure noninferiority study was conducted in Canada on 830 age-stratified female subjects [Dobson *et al.* 2013]. Girls aged 9–13 years were randomized 1:1 to receive three doses of quadrivalent HPV vaccine at M0, 2, 6 (n = 261) or two doses at M0,6 (n = 259). Young women (16–26 years) received three doses at M0,2,6 (n = 310). Antibody levels were measured at M0,7,18,24,36. The results showed that the GMT ratios were noninferior for girls (two doses) to women (three doses): 2.07 (95% CI: 1.62–2.65) for HPV 16 and 1.76 (95% CI: 1.41–2.19) for HPV 18. Girls (three doses) had GMT responses 1 month after the last vaccination for HPV 16 of 7736 mMU/mL (95% CI: 6651–8999) and HPV 18 of 1730 mMU/mL (95% CI: 1512–1980). The GMT ratios were noninferior for girls (two doses) to girls (three doses): 0.95 (95% CI: 0.73–1.23) for HPV 16 and 0.68 (95% CI: 0.54–0.85) for HPV 18. The GMT ratios for girls (two doses) to women (three doses) remained noninferior for all genotypes at month 36 of follow up. Antibody responses in girls were noninferior after two doses *versus* three doses for all four vaccine genotypes at month 7, but not for HPV 18 by month 24 or HPV 6 by month 36. Based on the presentation of the comparative results with the two-dose schedule in 9–13-year-old girls *versus* the three-dose schedule in young women, on 27 February 2014, the Committee for Human Medicinal Products of the EMA granted a positive opinion on the possibility of adopting a two-dose schedule with the quadrivalent HPV vaccine in girls in the age range 9–13 years. The new EMA indications for the quadrivalent HPV vaccine allow for a two-dose (M0,6) or three-dose (M0, 2, 6) schedule in subjects aged 9–13 years.

HPV vaccination recommendations in different countries

Recommendations for HPV vaccination of the primary cohort have been issued in nearly all western European countries, and nationally/regionally funded vaccination programmes for HPV have been introduced in most western European countries, with some exceptions (e.g. Austria was the first country to issue national recommendations in November 2006, but never publicly funded the programme).

In Europe, universal HPV vaccination of female adolescents was first introduced in 2007 in Belgium, France and Germany. In the subsequent year, programmes were also started in Greece, Luxembourg, the Netherlands, Italy, Romania, Spain and Switzerland; in 2009 in Denmark, Norway, Portugal, San Marino, Macedonia and the UK [Bonanni *et al.* 2011].

As of May 2013, 45 countries have introduced HPV vaccination at the global level (Figure 1) [World Health Organization, 2014]. Most of these are developed countries, but given that the global burden of cervical cancer falls heaviest on developing countries, there is still a great need for more countries to introduce HPV vaccination as part of a national public-health strategy that includes a comprehensive approach to prevention and control of cervical cancer.

In 2013, a record-low price for HPV vaccines was negotiated by the Global Alliance for Vaccines and Immunization (GAVI) for countries eligible for support, opening the door for millions of girls in the world's poorest countries to be immunized against HPV. The US$4.50 vaccine represents a two-thirds decrease on the lowest previously available public price. GAVI's support for HPV

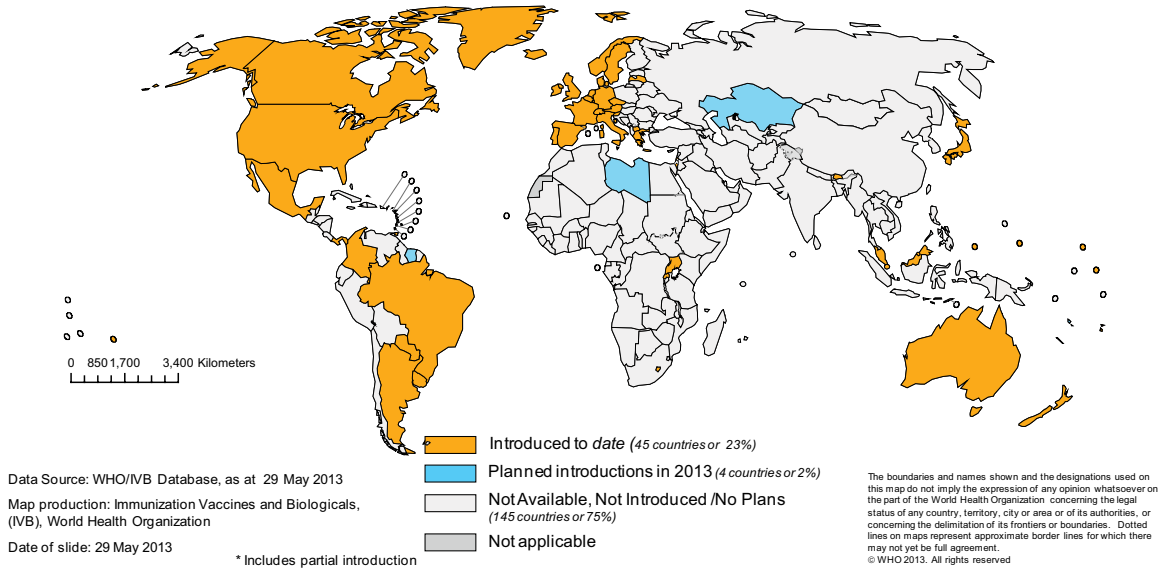

Figure 1. Countries with human papilloma virus vaccine in the national immunization programme and planned introductions, 2013 (source: World Health Organization).
Introduced: Argentina, Australia, Austria, Belgium, Bhutan, Brazil, Brunei Darussalam, Canada, Colombia, Cook Islands, Czech Republic, Denmark, Fiji, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Kiribati, Latvia, Lesotho, Luxembourg, Macedonia, Malaysia, Marshall Islands, Mexico, Micronesia (Federated States of), the Netherlands, New Zealand, Norway, Palau, Panama, Paraguay, Portugal, Rwanda, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, Trinidad and Tobago, Uganda, UK, USA, Uruguay.
Partial introduction: Brazil, Kiribati, Uganda.
2013 planned introductions: Kazakhstan, Libya, Suriname, Vanuatu.
Peru introduced the vaccine in 2011, then it was suspended, possible re-introduction in the next 2 years.
Some countries are running demonstration projects. They are not included.

vaccines will enable a bridging of the gap between rich and poor countries, by making HPV vaccines available where girls need them the most, thus preventing the infection that causes this disease.

Eleven mainly sub-Saharan African countries were approved in 2013 to introduce HPV vaccines with GAVI support: Ghana, Kenya, Laos, Madagascar, Malawi, Mozambique, Niger, Sierra Leone, Tanzania and Zimbabwe, with Rwanda being the first country to roll out HPV vaccines nationally with GAVI support in 2014. Another 10 countries are running or will run demonstration programmes over the next 3 years: Benin, Burundi, Cameroon, Cote d'Ivoire, Gambia, Liberia, Mali, Senegal, Solomon Islands and Togo (Figure 2). The demonstration projects provide countries with an opportunity to gain experience in reaching girls with vaccines outside the usual routine immunization schedule and to make informed decisions about whether to apply for a national introduction. The wide reach of the immunization programmes also provides an opportunity for countries to implement other health interventions that may benefit young adolescent girls.

By 2015, GAVI plans to support the vaccination of 1 million girls in more than 20 countries and expects these numbers to accelerate dramatically, with the goal of more than 30 million girls vaccinated in over 40 countries by 2020.

Coverage data are highly variable among industrialized countries with consolidated programmes, with higher coverage usually being reached in countries providing vaccination through a well-organized school-health system. However, good results were obtained also in some countries where girls were invited to vaccination services outside schools [Bonanni *et al.* 2011]. Nevertheless, more efforts are needed to make HPV vaccine uptake nearly universal in target groups. Communication should clearly highlight that severe forms of cancer can be avoided by vaccination, an opportunity that should not be missed.

Vaccination acceptance and coverage rates: an open issue

In spite of the excellent efficacy, effectiveness and safety profile of HPV vaccines, acceptance and coverage rates are still far from optimal in the

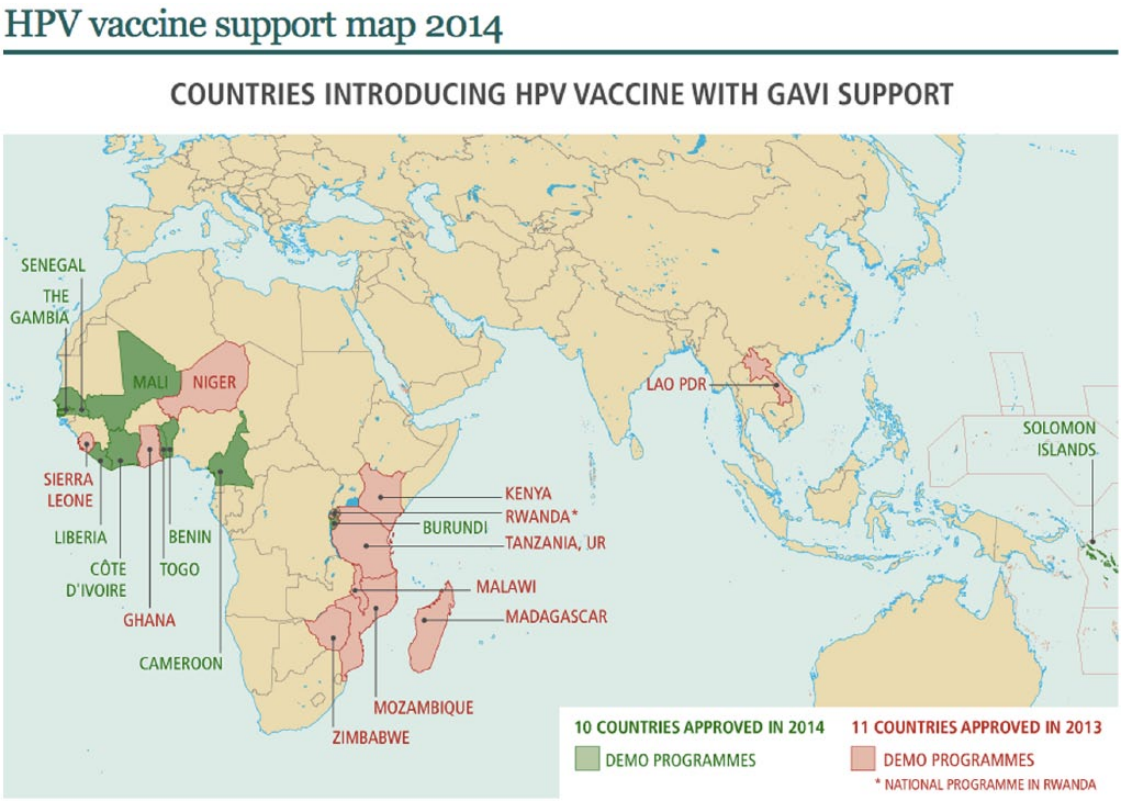

Figure 2. Countries introducing human papilloma virus vaccination with the support of the Global Alliance for Vaccines and Immunization, 2014.

majority of countries that introduced routine active immunization programmes.

According to the updated European Centre for Disease Prevention and Control (ECDC) guidance on the introduction of HPV vaccines in European countries (2012), there are several reasons for such low uptake. Among them, the most relevant seem to be the scarce knowledge of HPV and the HPV vaccine, the high costs of vaccination where they are covered by the recipient, a perceived low efficacy of the vaccine, and alleged and real adverse events to vaccines. Moreover, many studies underlined the factors that are barriers to parental acceptance of HPV immunization including a decreasing awareness of vaccination after the initial knowledge when immunization programmes were introduced, persisting concerns regarding safety and side effects, a perception of the vaccine in a similar vein to the oral contraceptive pill, with preference to postpone vaccine administration until their children are sexually active [ECDC, 2012]. In this respect, it is worth underlining that a study on girls immunized at 11–12 years of age in a large managed care organization and followed for up to 3 years showed that HPV vaccination at the recommended ages was not associated with increased sexual activity-related outcome rates [Bednarczyk *et al.* 2012].

In order to increase coverage rates in all countries, necessary to obtain the crucial public-health results of HPV vaccination, parents need more information and reassurance from healthcare workers on the safety and effectiveness of HPV vaccines. Policy programmes need to face parents' concerns and communicate the appropriate information in a simple and easily understandable way. Moreover, attitudes, knowledge and practices of healthcare professionals towards vaccination should be studied and properly addressed through formative initiatives whenever needed [ECDC, 2012].

Vaccination of older women and males: opportunities and limits

Vaccination of naïve adolescent girls is without doubt the priority use of HPV vaccines, given their nearly 100% efficacy in this population.

However, vaccination of young women and also, from an individual perspective, relatively older women is an attractive option to confer protection against precancerous and cancerous lesions [Muñoz *et al.* 2009; Schwarz *et al.* 2009].

Immunizing catch-up cohorts of women is useful because: (a) the chance of being infected by all four or two HPV types included in the quadrivalent or bivalent vaccine is extremely low (< 1%); (b) HPV vaccines are effective against HPV types for which the subject has never been infected at the time of immunization; (c) there is evidence that vaccination is protective against HPV types for which women had a previous resolved infection (seropositive, but DNA negative).

All sexually active women are permanently exposed to new infections and it is not feasible to identify those at higher risk. HPV infections can recur, even with the same type. Moreover, given the decreasing effectiveness of the immune system with aging, persistent infections may increase with relative frequency [Castle *et al.* 2005].

Past Health Technology Assessment evaluations have shown that a universal, free-of-charge offer of HPV vaccination may be a cost-effective option to enlarge immunization offer beyond adolescent girls [Capri *et al.* 2007]. The decline in public-health costs of a HPV vaccine dose registered in the last few years is progressively increasing the age limit for a cost-effective vaccination programme in women.

With regard to male vaccination, it has been demonstrated that the vaccine is able to prevent external genital lesions (particularly genital warts) with more than 90% efficacy [Giuliano *et al.* 2011]. The impact and relevance of male vaccination is extremely high in homosexual men. The efficacy against intraepithelial anal lesions was calculated to be 92% after assignment of aetiology to vaccine HPV types [Palefsky *et al.* 2011], and therefore active offer of HPV immunization to homosexual men is a priority. However, given the clear difficulties in identifying sexual orientation in adolescent males and the traditional failures of risk-based approaches for all vaccinations [Bonanni, 2007], it seems that only through a universal approach to male HPV vaccination will it be possible to confer substantial protection to such a high-risk category.

In this respect, regarding universal adolescent male vaccination, economic evaluations performed some years ago suggested that, compared with adolescent female immunization, vaccination of boys would be economically unattractive, unless the impact of immunization on infection transmission is proven, and coverage with three doses in girls is low [Brisson *et al.* 2011]. However, in the meantime, vaccination costs have decreased dramatically, making the HPV vaccine a tool for broader application.

Presently, there are still disadvantages, but also relevant advantages concerning the addition of a cohort of adolescent boys to the current recommendation of girl vaccination. The weaknesses of adolescent boy immunization are the inferior cost-effectiveness compared with girls, the official indication restricted to external genital lesions (warts), the difficulty of demonstrating HPV vaccine efficacy and effectiveness against head and neck cancers (that are more incident in males than in females, with a proportion of 2:1), the lack of any data on the potential uptake of HPV vaccination in males. The advantages would be the improved cost-effectiveness with lower costs of each dose, the increasing evidence on HPV-related burden of disease in males, the likely (although undemonstrated) impact on male cancers and precancers, the lack of any alternative early diagnosis for males (no screening available) and the potentially easier acceptance of a gender-neutral immunization programme.

Conclusion

HPV vaccination represents a landmark in the history of both vaccination and cancer prevention. Immunization of adolescent girls has the potential to decrease dramatically cervical cancer incidence and mortality, both in the industrialized world and the developing world, where screening programmes for early detection of precancerous lesions are often impossible to set up. However, even in the Western world, there are ample sectors of the female population where periodical screening for cervical cancer detection is not performed regularly or at all. The only real hope of defeating cervical cancer is to implement universal girl immunization in all countries, and to carry out all possible efforts, including strong communication initiatives, to convince parents and girls that acceptance of HPV vaccination offer is a fundamental step for better prevention in women. Moreover, evidence is accumulating that cervical cancer, with no doubt the most important HPV-related disease, is not the only

potential public-health objective of immunization. Public-health authorities are therefore confronted with the importance of evaluating every possible positive impact that HPV immunization can have on the health of the population, trying to invest in a larger target for vaccination programmes.

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Conflict of interest statement

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