HPV vaccines and cervical cancer

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**Introduction**

Human papillomavirus (HPV) vaccines have opened a new perspective on the prevention of cervical cancer, one of the most paradigmatic long-term goals of the cancer prevention field. For decades, prevention has been and still is partially fulfilled by the expansion of the practice of cervical cytology (the Pap smear) repeated frequently in tens of millions of asymptomatic women worldwide. The practice and the programmes of cervical cytology were also instrumental in developing the concept of screening for pre-cancerous lesions, helped in developing the methodology for programme evaluation, comprehensively developed the public health interactions between early diagnosis, clinical diagnosis, pre-cancer treatment, cancer treatment requirements and follow-up and provided some of the first models of cost–benefit evaluation of massive public health interventions. Most importantly, cervical pre-cancer screening using repeated cytology significantly contributed to the reduction of cervical cancer incidence and mortality in the areas of the developed world in which coordinated programmes were implemented and sustained for extended periods of time. Now is the time to introduce HPV vaccination in the everyday setting.

**The rationale for HPV vaccination**

HPV has been unequivocally linked to cervical cancer and is being linked to several other cancers of the female genital tract, the male genital tract, the oral cavity and the oropharynx in both sexes. The evidence for cervical cancer includes prevalence studies showing that under adequate conditions, HPV DNA can be recovered from all cervical cancer cases. Case–control studies have shown consistently high relative risks and attributable fractions and cohort studies have documented that HPV infection precedes the development of both cancer precursors and advanced cancerous lesions. Taken together, these pieces of evidence helped the recognition of HPV as a necessary cause of cervical cancer and therefore, preventive strategies based upon novel human HPV technology for screening and vaccination should effectively target all cases worldwide [1].

**Two vaccines, two rationales**

There are currently two vaccines that have contributed phase III trial results, have been licensed in over 80 countries in the world, have been granted European Medicines Agency (EMEA) licences and Food and Drug Administration (FDA) licence (one vaccine as of January 2008) and several million doses have already been distributed and administered. The most advanced results are from a quadrivalent vaccine (Gardasil, MSD) that targets four HPV types (6, 11, 16 and 18) and interim results are available from a bivalent vaccine (Cervarix, GSK) that targets two HPV types (16 and 18). Final results of the pivotal phase III trial are awaited in 2008.

HPV types 16 and 18 are responsible for at least 70% of cervical cancer worldwide and for some 50% of the pre-neoplastic lesions cervical intraepithelial neoplasia (CIN) 2/3. HPV 6 and 11 are responsible for a small proportion of the CIN 1 lesions and for the majority of the genital warts, a non-malignant condition that is frequent in young sexually active populations. The condition requires clinical or surgical treatment and represents a significant health burden. Occasionally HPV 6 and 11 are transmitted from mothers to infants and in rare occasions they induce a persistent infection of the upper respiratory tract known as recurrent respiratory papillomatosis (RRP) a condition that might be devastating to children and families.

The rationale behind the quadrivalent vaccine includes the combination of two objectives: one is to cover the two most important oncogenic HPV types and the second is to cover the most important types related to genital warts and to RRP. The former is a medium- and long-term goal and the latter a goal that should offer shorter term results and has an additional attraction to the male population.

The rationale behind the bivalent vaccine is focused on the oncogenic types 16 and 18 and aims to ensure a prolonged immune response by means of their adjuvant, specifically designed to enhance the antibody titres and to stimulate cellular immune response.

Although there are at present no correlates of protection that can be used to predict the long-term effects of each of the vaccines, there are a number of interesting secondary objectives that are important to follow in the future. These are the persistence of the antibody titres, the correlation of the antibody titres with vaccine efficacy, the presence of antibodies at the genital mucosa surface, the extent of protection offered against non-vaccine types and the characteristics of the vaccine failures if they appear in the future. Continued surveillance of women entered in the trials and phase IV surveillance post introduction are being put into place to provide some of these answers as well as to monitor the essential traits of the
programmes, ensuring efficacy and duration of protection, monitoring safety and helping to define the integration of these vaccines with the screening practices.

As anticipated by the long-term natural history between HPV infections and cervical pre-cancer and cancer, paired with the excellent results of these two vaccines in the trial phase, the full potential of each of them will not be clearly perceived until some additional years of follow-up of carefully controlled vaccinated populations has elapsed.

**key results and implications of phase III HPV vaccination trials**

While recognizing the limitations of the still moderate (5–6 years) follow-up in a few tens of thousands of young women, these two vaccines to date have shown high efficacy, safety, immunogenicity, long-term duration of protection and a strong suggestion of induction of immune memory [2–5].

The currently available vaccines offer HPV 16- and 18-naïve women (women who are found to be HPV DNA 16 and 18 negative and negative to HPV type-specific antibodies) full protection (>95%) from the two HPV types that cause an estimated 70% of cervical cancer cases and a slightly lower fraction (close to 50%) of its precursors. A moderate impact on HPV infections and associated lesions related to other HPV types has been reported or published. These relate to types that are closely related in their phylogeny (i.e. HPV 18 and 45 and HPV 16 and 33) but precise estimates of the extent and duration of the cross-protection and potential differences between the two vaccines remains a research issue. Once the cross-protection impact is fully described and the geographical variation of the HPV types in cervical cancer is better known, these estimates will likely increase in some areas to perhaps 75–80%. HPV 16, 18 and 45 account for a higher proportion of cervical adenocarcinomas, in the range 80–85% [6] the histological subgroup that more easily escape detection by cytology-based screening practices. These vaccines have not shown any ability to modify the prognosis of established HPV infections or CIN lesions. Therefore, the clinical indications are strictly prophylactic [7].

Further, one of the HPV vaccines has already shown that current HPV 16 and 18 vaccines are capable of offering almost complete protection against the precursor lesions of the vulva [vulvar intra-epithelial neoplasia (VIN) 2/3] and the vagina [vaginal intra-epithelial neoplasia (VAIN) 2/3]. Although not directly assessed in the current trials, it is likely that protection against other HPV 16- and 18-induced cancers will also be shown in the future. These include anal cancer and a significant fraction of the cancers of the oral cavity, the oropharynx and the larynx. If protection in males is similar to that in women, prevention of significant fractions of penile cancers might be achieved as well. The quadrivalent vaccine has also shown high protection against the HPV 6- and 11-induced external lesions genital warts.

A number of clinically relevant issues remain to be fully described, including the magnitude and the HPV spectrum included in the cross-protection effect, and the long-term effects of HPV vaccines on cancer protection and safety. However, to answer these questions longer follow-up is required and the organization of large phase IV studies, some of which are already ongoing.

With these results, the priority indications of HPV vaccines have been established with remarkable consistency worldwide [8–10]. Priority vaccination has been recommended for pre-adolescent and young adolescent girls, a surrogate indicator of pre-sexual initiation and therefore of non-exposure to HPV. Trials have also shown efficacy, safety and immunogenicity in women up to 26 years of age and therefore the indication in the regulatory documents has also adopted this artificial age limit. However, as young women are increasingly sexually active, some of them would have been exposed to HPV 16 or 18 and a fraction of them would remain as chronic carriers of the viral infection. In these women, the type-specific prophylactic potential of the vaccine is lost and the global efficacy of a vaccination programme including sexually active women will be reduced accordingly. Ongoing trials will show in the future the potential for prevention in women beyond 26 years of age. Preliminary results of trials including women up to 45 are very encouraging.

**the size of the cervical cancer problem and the requirements of the solution**

There are currently some 500 000 cases of cervical cancer diagnosed every year and some 40 000 cases of cancers of the vulva and vagina. The number of cases is driven both by the underlying incidence rates and by the size of the population in the relevant age groups. Thus for these cancers that typically cluster in the 40–60+ age groups, the expected duration of life is critical. Further, given the absence of screening programmes and the limitations of medical resources, at least 75% of the cancer cases cluster in developing countries as does the attributable mortality.

Following an explosive increase in population in developing countries in the 20th century, the demographic predictions for the period 2000–2050 indicate a stabilization of the female population (ages 15+) in developing and in developed countries. For girls aged 10–14 and women 15–24 years a plateau in developing countries and a slight decrease in developed countries are predicted. These population estimates are largely attributable to increased life expectancy in women in developing countries. As a consequence, the International Agency for Research on Cancer (IARC) predictions on the number of cases of cervical cancer anticipated by 2020, all other things being equal, is of an increase of 40% globally. The 40% increase in cervical cancer cases is dramatically driven by socioeconomic status, and countries in Africa, Latin America and Asia are predicted to increase the number of cases by 50–55%. Europe and North America will also experience a modest increase in the number of cases of the order of 6% in Europe and of 23% in Northern America [11].

The number of women in any 1-year age cohort between 10 and 14 years has been estimated to be close to 60 million. Of these, some 52 million (87%) live in developing countries. Vaccination of the 5-year pre-adolescent cohorts aged 10–14 years would require approximately 1 billion doses of HPV.
vaccine (accounting for a 10% wastage). Should a catch-up strategy be put in place, increasing the vaccination target to women aged 10–25 years would increase the vaccine requirements for the initial vaccination rounds to a target of up to 15 billion doses. There is a clear need to address early in the process the phasing stages of this introduction and most importantly, to understand with vaccine manufacturers how these quantities can be produced, where are the strategic production countries and the time it will take to put vaccines into their target delivery points in order to anticipate the time scale in which worldwide HPV vaccine introduction will realistically be an achievable goal.

HPV vaccines have a cost in 2007 that exceeds the current possibilities of many countries. It is thus anticipated that for some time after introduction, access to vaccination will also reflect the different opportunities related to socioeconomic status. Previous experience with the introduction of the hepatitis B virus (HBV) vaccine in developing countries has documented that vaccine cost is an essential component of a successful introduction and a determinant of the time to introduction in many parts of the world [12]. It is thus plausible that, unless a definite and specific massive international intervention occurs, a meaningful introduction of HPV vaccines worldwide will take decades. As a sequitur, for most living women to day, screening remains their primary option for cervical cancer prevention. Continuation of screening activities will be required because of the limitations of current HPV vaccines both in their lack of therapeutic effect (thus not protecting women with an ongoing neoplastic status. Previous experience with the introduction of the hepatitis B virus (HBV) vaccine in developing countries has documented that vaccine cost is an essential component of a successful introduction and a determinant of the time to introduction in many parts of the world [12]. It is thus plausible that, unless a definite and specific massive international intervention occurs, a meaningful introduction of HPV vaccines worldwide will take decades. As a sequitur, for most living women today, screening remains their primary option for cervical cancer prevention. Continuation of screening activities will be required because of the limitations of current HPV vaccines both in their lack of therapeutic effect (thus not protecting women with an ongoing neoplastic status). Previous experience with the introduction of the hepatitis B virus (HBV) vaccine in developing countries has documented that vaccine cost is an essential component of a successful introduction and a determinant of the time to introduction in many parts of the world [12]. It is thus plausible that, unless a definite and specific massive international intervention occurs, a meaningful introduction of HPV vaccines worldwide will take decades. As a sequitur, for most living women today, screening remains their primary option for cervical cancer prevention. Continuation of screening activities will be required because of the limitations of current HPV vaccines both in their lack of therapeutic effect (thus not protecting women with an ongoing neoplastic status).

the time of introduction of HPV vaccines

The evolving field of cervical cancer prevention calls for a fast and widespread introduction of HPV vaccines and an acceleration of the arrival of the current vaccines to the developing parts of the world. The criteria developed for regulatory agencies to issue evaluations and recommendations were intensively discussed in the early years of the 2000 decade. At the time, World Health Organization (WHO) expert groups, FDA, the EMEA groups and subsequently all regulatory agencies over 80 countries in the world concluded that showing efficacy against histologically proved CIN 2/3 was the threshold requisite to claim prevention against cervical cancer. The endpoint clearly recognized the complexity of the very long natural history and the insurmountable difficulties in logistics cost and feasibility of a randomized trial that defined cervical cancer as the endpoint and required adequate screening in the control group. This requisite has been clearly satisfied by phases II and III of the trials by both vaccines, and licensing was granted accordingly.

Currently additional discussions are underway to define the terms of reference to prove independent efficacy against other HPV types (individual type-specific cross-protection) and will continue when trials of multivalent vaccines are designed. The discussion is driven by the lower frequency of exposure to any of the remaining types and the longer time required to develop CIN 2+ cases as compared with HPV 16- and 18-related CIN 2+ cases. As a consequence it is now clear that short-term (4–5 year) trials of the size of 15–20 000 young women (15–26 years) have been highly informative in assessing efficacy against any HPV 16 and 18 endpoints but will be largely insufficient to assess efficacy against any other type with the same histological endpoint. The difficulties are even increased because any future trials will require HPV vaccination of the control group. Therefore composite endpoints (virological and histological endpoints) and combined endpoints (protection against groups of several HPV types) will be increasingly important.

For several reasons other than having shown the required levels of efficacy and safety, several considerations indicate the importance of a prompt introduction of HPV vaccines. The first consideration is that vaccines offer protection immediately after the 6-month completion of the vaccination programme (under the assumption that a three-course vaccination will offer sufficient long-term protection). Therefore the claims that cancer reduction will not be observable until several decades after vaccination only applies to the documentation of the cancer endpoint protection; the benefits of protection are immediate after vaccination is completed.

Secondly, these vaccines also apply to the prevention of pre-neoplastic cervical lesions CIN 2 and 3 (and to some extend to CIN 1). This will translate into a reduction of the number of repeat cytology because of ambiguous results [inadequate, atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions (LSIL)]. It will also reduce significantly (40–50%) the referrals and associated colposcopies and the number of biopsies and conizations. Apart from the economic cost of these interventions and the obstetric consequences of the cervical surgery, there is considerable suffering and concern among women undergoing these processes, which underline the superiority of primary prevention over current forms of secondary prevention.

Thirdly, one of the HPV vaccines has shown protection against the relevant pre-neoplastic lesions of the vulva and the vagina. Presumably the second vaccine will show similar results in the future. These cancers have been unaffected by cervical screening efforts and in the advanced forms require complicated and mutilating surgery. Therefore, the arrival of a primary preventive option represents a net benefit.

Fourthly, HPV 16 and 18 vaccines have a putative (still undemonstrated) potential for prevention of other HPV 16- and 18-induced cancers. These include some 25% of the cancers of the oral cavity and the oropharynx, 40% of cancers of the penis and >80% of the cancers of the anal canal. The assessment of this interesting outcome will probably result from vaccine surveillance studies in the decades to come and specific studies of vaccine efficacy in males. None of these cancers have currently any preventive option other than smoking cessation.

Fifthly, the use of the quadrivalent vaccine has shown protection against genital warts, a condition that is relevant to both males and females and has little preventive options other than sexual abstinence and to some extend regular condom use.
Finally at the current level of development, novel vaccines are likely to replace current ones sometime in the future. These will include polyvalent options that could potentially eliminate the need for subsequent screening in developed countries as well as formulations that will make them more sustainable in developing countries. All efforts that are developed today in preparation for the introduction of currently available vaccines will greatly facilitate the introduction of more powerful vaccine products while already offering immediate protection to entire generations of vaccinated women.

conclusions

There is a need to join international efforts to accelerate the introduction of HPV vaccines in the world with focal interest in facilitating the massive arrival to developing countries.

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disclosures

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references