Evaluating the potential benefits of universal worldwide human papillomavirus vaccination

Human papillomavirus (HPV) vaccines have opened a new perspective to the prevention of many cancers, mainly 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), which is repeated frequently in tens of millions of asymptomatic women worldwide. The practice and the programs of cervical cytology were also instrumental in developing the concept of screening for precancerous lesions, helped in developing the methodology for program evaluation, comprehensively developed the public-health interactions between early diagnosis, clinical diagnosis, precancer 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 precancer 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 programs were implemented and sustained for extended periods of time. In these variable contexts, HPV vaccines have to find their space and integration, and decisions regarding the appropriate time to introduction is a key consideration.

Two vaccines, two rationales

There are currently two human papillomavirus (HPV) 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) licenses and US FDA license (Gardasil®), and of which several million doses have already been distributed and administered. The Phase III results are available from a quadrivalent vaccine (Gardasil, Merck & Co., Inc., NJ, USA), which targets four HPV types (6, 11, 16 and 18), and from a bivalent vaccine (Cervarix®, GlaxoSmithKline Biologicals, Rixensart, Belgium), which targets two HPV types (16 and 18). Further results of some of the pivotal Phase III trials are awaited in 2008 for both vaccines.

HPV types 16 and 18 are responsible for approximately 70% of cervical cancer worldwide, for some 50% of the preneoplastic lesions of cervical intraepithelial neoplasia (CIN) grades 2/3, and for a fraction of high-grade vulval intraepithelial neoplasias (VIN) and vaginal intraepithelial neoplasias (VaIN). HPV types 6 and 11 are responsible for a small proportion of low-grade CIN, and for the majority of cases of 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 in those infants, and in young adults, of the upper respiratory tract, known as recurrent respiratory papillomatosis (RRP), a condition that can 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 two 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 advantage of being potentially beneficial for the male population.

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

Although there are at present no immunological 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 titers, the correlation of the antibody titers with...
the vaccine efficacy, the presence of antibodies in the vaginal mucus, the extent of protection against lesions and persistent infections offered against nonvaccine 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. Such surveillance will also help in the monitoring of the essential traits of the programs, ensuring efficacy, duration of protection and safety, and aiding in defining the integration of these vaccines into the screening practices.

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

Key results & implications of Phase III human papillomavirus vaccination trials

While recognizing the limitations of the still moderate (5–6 years) follow-up in a few tens of thousand young women, to date, these two vaccines have shown high efficacy, safety, immunogenicity, long-term duration of protection and a strong suggestion of induction of immune memory [1–6].

The currently available vaccines offered to HPV 16- and 18-naïve women (women who are found HPV DNA 16- and 18-negative and negative to HPV type-specific antibodies) provide full protection (>95%) from the two HPV types that cause an estimated 70% of cervical cancer 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 types within the A7 or A9 family, such as HPV 18 and 45, and HPV 16 and 33). However, 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 (there are still weak data for these types in certain regions of the world) [7], 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 of 80–85% [8]), the histological subgroup that more easily escapes detection by cytology-based screening practices. These vaccines have not shown any ability to modify the prognosis of established HPV infections or CIN lesions related to vaccine HPV types. Therefore, primary clinical indications are strictly prophylactic [9], although some benefit has already been shown in women with past infection and, in fact, many countries recommend the vaccine for persons who have already been infected.

One of the HPV vaccines has already shown almost complete protection against the precursor lesions of the vulva (VIN 2/3) and the vagina (VaIN 2/3) [3,10]. 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 the protection afforded in males is similar to that afforded in females, prevention of significant fractions of penile cancers might also be achieved. The quadrivalent vaccine has also shown high protection against the HPV 6- and 11-induced external genital lesions.

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 solve these questions, additional follow-up time and the organization of large Phase IV studies is required, some of which are already in place.

Table 1 shows a selection of the established qualitative findings thus far for both vaccines, focusing on the evaluations reported in adolescents and in HPV DNA-naïve women at study entry.

With these results, the priority indications of HPV vaccines have been established with remarkable consistency worldwide [101,102,103]. Priority vaccination has been recommended for preadolescent and young adolescent girls, a surrogate indicator of presexual initiation or early sexual activity, and therefore of non- or minimal exposure to HPV. Trials have also shown efficacy, safety and immunogenicity in women aged up to 26 years, 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 will already 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 program including sexually active women will be reduced accordingly. Preliminary data from ongoing trials are already showing a potential for prevention of lesions in women aged over 26 years.

**Size of the cervical cancer problem & 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 [7,11]. The number of cases is driven both by the underlying incidence rates and by the age structure and size of the population in the relevant age groups. Thus, for these cancers, which typically cluster in the 40–60+ years age groups, the expected duration of life is critical. Furthermore, given the absence of screening programs and the limitations of medical resources, at least 75% of the cancer cases cluster in developing countries, as does the attributable mortality and the impact on years of life lost.

Following an explosive increase in the population in developing countries in the 20th century, the demographic predictions for the years 2000–2050 indicate a stabilization of the female population (age 15+ years) in developing and developed countries. For girls of 10–14 years of age, and women 15–24 years of age, a plateau in the developing countries and a slight decrease in the developed countries are predicted. These population estimates are largely attributable to the increased life expectancy in women in developing countries. As a consequence, the International Agency for Research on Cancer (IARC) prediction 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

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**Table 1. Key results from trials of human papillomavirus vaccines.**

<table>
<thead>
<tr>
<th>Vaccine name</th>
<th>Gardasil®</th>
<th>Cervarix®*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of follow-up</td>
<td>36 months (advanced)</td>
<td>15 months (interim)</td>
</tr>
<tr>
<td>HPV types included</td>
<td>6, 11, 16, 18</td>
<td>16, 18</td>
</tr>
<tr>
<td>Antigen dose</td>
<td>20/40/40/20 µg</td>
<td>20/20 µg</td>
</tr>
<tr>
<td><strong>Efficacy on HPV 16 or 18 CIN2+</strong></td>
<td><strong>Proven</strong></td>
<td><strong>Proven</strong></td>
</tr>
<tr>
<td>– Efficacy on HPV 16 CIN2+</td>
<td>Proven</td>
<td>Proven</td>
</tr>
<tr>
<td>– Efficacy on HPV 18 CIN2+</td>
<td>Proven</td>
<td>Proven</td>
</tr>
<tr>
<td>– Efficacy on HPV 16 or 18 CIN2</td>
<td>Proven</td>
<td>Proven</td>
</tr>
<tr>
<td>– Efficacy on HPV 16 or 18 CIN3</td>
<td>Proven</td>
<td>Not yet reported</td>
</tr>
<tr>
<td>Efficacy on HPV 16 or 18 VIN 2/3</td>
<td>Proven</td>
<td>Not yet reported</td>
</tr>
<tr>
<td>Efficacy on HPV 16 or 18 VaIN 2/3</td>
<td>Proven</td>
<td>Not yet reported</td>
</tr>
<tr>
<td>Efficacy on HPV 6 or 11 genital warts</td>
<td>Proven</td>
<td>Not in target</td>
</tr>
<tr>
<td>Therapeutic efficacy</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Safety at 6 years’ follow-up</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Tolerability</td>
<td>Well tolerated</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>Protection against 6-month persistent HPV infections of types other than 16 or 18</td>
<td>Against combined types 31/33/45/52/58</td>
<td>Against specific types 45, 31 and 52</td>
</tr>
<tr>
<td>Protection against CIN 2/3 related to HPV other than types 16 or 18</td>
<td>Reported</td>
<td>Not yet reported</td>
</tr>
<tr>
<td>Duration of protection</td>
<td>5–6+ years</td>
<td>5–6+ years</td>
</tr>
<tr>
<td>Immunogenic in pre-adolescents and older women</td>
<td>Proven</td>
<td>Proven</td>
</tr>
<tr>
<td>Immunogenic in boys</td>
<td>Proven</td>
<td>Not yet reported</td>
</tr>
<tr>
<td>Evidence of immune memory</td>
<td>Booster effect of a fourth dose at year 5</td>
<td>Enhanced production of memory B cells</td>
</tr>
</tbody>
</table>

*Expected results from Phase III trial in 2008.
†Proven in long-term follow-up of Phase II trials.
‡In clinical trials and post-licensing evaluation [103].
§Corresponds to duration of trials in 2007.
CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus; VaIN: Vaginal intraepithelial neoplasia; VIN: Vulval intraepithelial neoplasia.
experience a modest increase in the number of cases of the order of 6% in Europe and 23% in Northern America [11].

The number of women in any 1 year age cohort of 10–14-year-olds has been estimated to be close to 60 million. Of these, some 52 million (87%) live in developing countries. Vaccination of the 5-year preadolescent cohorts aged 10–14 years would require approximately 1 billion doses of HPV vaccine (accounting for a 10% waste). 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 approximately 3 billion doses. There is a clear need to address the phasing stages of this introduction early in the process 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 timescale in which worldwide HPV vaccine introduction will, realistically, be an achievable goal. Beyond production capacity, the major challenge is implementing a vaccination program targeting preadolescent girls.

In 2007, HPV vaccines had a cost that exceeds the current possibilities of many countries, unless innovative financing mechanisms are envisioned and made available. 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 vaccine in developing countries has documented that vaccine cost is an essential component of a successful introduction, and a determinant of the time of 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. Major international efforts (i.e., GAVI, Advanced Market Commitments, UNICEF) are being organized to accelerate the introduction of HPV vaccines in developing countries [13]. As a consequence, for most women living in the developed world, 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 ongoing neoplastic processes) and in their limited number of HPV types (thus leaving to evolve between 25 and 30% of cervical cancer cases related to HPV types other than 16 or 18). The exact proportion will ultimately depend on the degree of cross-protection, which will be confirmed in the ongoing vaccination trials of both vaccines.

**Singularity of human papillomavirus vaccines**

In relation to HPV vaccines, at least three characteristics are worth considering. These are discussed in the sections below.

**Vaccinating adolescents versus vaccinating infants**

The priority age of vaccination is the pre- and young-adolescent female groups. In many parts of the world, an adolescent platform is not ready to operate, whereas the infant vaccination programs are universal. The Expanded Program of Immunization (EPI) is probably one of the most successful public-health efforts in place. Globally, the program ensures vaccination of 70–75% of children with three doses of diphtheria, tetanus and pertussis (DTP). Furthermore, the socioeconomic gap between the wealthiest and the poorest countries is in the order of 25–30%, while the gap in terms of, for example, gross national product (GNP) and other health indicators is several-fold higher. Vaccination of infants is thus feasible in developing countries and vaccination programs, such as the EPI, have developed and maintain in place a considerable infrastructure and logistics network. In contrast, vaccination of adolescents might represent the greatest challenge in many developing populations, and several exploratory and demonstration projects are now underway [104]. Introduction of HPV vaccines into the EPI program will first require confirmation of safety in infants and the ability of the vaccines to afford long-term and sustained protection against HPV. In contrast, the EPI structure will ensure fast and widespread coverage in all settings in the world. Alternatives, such as the deployment of a platform for vaccination of adolescents (i.e., based in schools), could be considered in some countries with adequate infrastructure.

**Vaccination against sexually transmitted viral infection versus a cancer-causing agent**

HPV is a sexually transmitted virus and the risk factors for infection relate to the number of sexual partners, the number of partners of the male, early age at first sexual exposure, and other aspects of sexual behavior. As such, some concerns have been
raised in discussions with different societies and cultural environments. Essentially, more conservative societies tend to perceive that introduction of HPV vaccines would represent either recognition of sexual activity in age groups that are socially requested to abstain (denial societies) or to grant tolerance towards early sexual initiation. The discussions that have taken place in relation to making these vaccines a mandatory requirement in the schooling system in the USA are a clear example of the latter. In general terms, some sociological surveys and the experiences in the countries that have initiated HPV vaccination, including the USA, Canada and, most importantly, Australia, tend to indicate that sexual behavior in adolescents is influenced in a limited way by the information that is transferred at the time of vaccine proposition [14,15]. Furthermore, some health educators are seeing this vaccine as a relevant opportunity to introduce sexual education, and as a method of prevention of a sexually transmitted infection in the adolescent population.

**Vaccination versus alternative screening options**

Third, screening options for cervical cancer prevention are also under significant evolution and change. Because in many developed countries screening programs have become established, significant efforts in terms of organization, professional training, financial mechanisms and improvements of the screening strategy are important options that might challenge the need for the introduction of HPV vaccines. More specifically, HPV vaccines should offer interesting health benefits other than and above the current results of screening programs (i.e., up to 70% reductions in cervical cancer mortality in a few countries). Cost–benefit analyses are critical in clearly estimating the most adequate strategies to combine vaccines and screening efforts.

Among the developments in screening technology, one can consider both highly sophisticated technologies and low-technology options to be sustainable in the developing parts of the world.

Highly sophisticated technologies include liquid-based cytology, computer-aided cytology reading, HPV DNA and RNA screening tests, and the use of other biomarkers that can signal early changes in the tissue with prognostic value. Of these, several international reviews have consistently shown that the use of HPV DNA tests as the primary screening method is significantly more sensitive than cytology-based screening, either conventional or liquid-based [16–18]. Centralized HPV-based screening programs might be considered complementary to HPV vaccination, notably while current vaccines still require continuation of some form of screening efforts.

Low-technology options are also under active investigation to introduce screening in populations that lack the essential social and health structures required to make screening a success. Research on visual inspection methods (visual inspection with acetic acid [VIA]), self-sampling strategies for HPV DNA, reduction of screening protocols to two-step (screen and treat) rather than three-step (screen, diagnose and treat) methods, and development of lower-cost, lower-technology screening tests for HPV are ongoing. For example, in India, a VIA program was effective in reducing the incidence of cervical cancer, of advanced cervical cancer and of mortality owing to cervical cancer [19]. Operational research should carefully consider strategies that would broaden the age ranges of the preventive interventions; for example, programs could jointly offer HPV vaccine to adolescents (or to infants) and some form of screening to their mothers during the vaccination sessions already in place in most developing countries. These options are clearly alternatives while the costs of the vaccine remain inaccessible.

**Time of introduction of human papillomavirus vaccines**

The evolving field of cervical cancer prevention calls for a fast and widespread introduction of HPV vaccines, and the 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 2000s. At the time, WHO expert groups, the US FDA and the EMEA groups, and subsequently all regulatory agencies from over 80 countries in the world, concluded that showing efficacy against histology-proven CIN 2/3 was the threshold requisite to claim prevention against cervical cancer. The end point 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 end point and required adequate screening in the control group. This requisite has been clearly satisfied by the Phase II and III of the trials of 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 years) trials including in the region of 15–20,000 young women (of 15–26 years of age) have been shown to be highly informative in assessing the efficacy against any HPV 16 and 18 end points, but will be largely insufficient to assess efficacy against any other type with the same histological end point. These difficulties may even be increased, because any future trials will require HPV vaccination of the control group. Therefore, composite end points (virological and histological end points) and combined end points (protection against groups of several HPV types) will be increasingly important.

Other than having shown the required levels of efficacy and safety, several other reasons 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 program (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 end point protection, as the benefits of protection are immediate after vaccination is completed.

Second, these vaccines also apply to the prevention of pre-neoplastic cervical lesions CIN 2 and 3 (and to some extent, CIN 1). This will translate into a reduction in the number of repeated cytologies due to ambiguous results (inadequate, atypical squamous cells of undetermined significance [ASCUS] and low-grade squamous intraepithelial lesion [LSIL]). It will also significantly reduce (by 40–50%) the referrals and the associated colposcopies, in addition to the number of biopsies and conizations. The reduction in the number of abnormal cytologies will negatively affect the value and efficiency of cytology screening, as it will cause a significant reduction in the positive predictive value of cytology [20]. Other than 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 that underlie the superiority of primary prevention over the current forms of secondary prevention.

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

Fourth, HPV 16 and 18 vaccines have a putative (still non-demonstrated) 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 over 80% of cancers of the anal canal. The assessment of this interesting outcome will probably result from vaccine surveillance studies in the decades to come, and the specific studies of vaccine efficacy in males. None of these cancers currently has any preventive option other than smoking cessation.

Fifth, the use of the quadrivalent vaccine has shown protection against genital warts, a condition that is relevant to both males and females and has few preventative options other than sexual abstinence and, to some extent, 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 the 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.

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

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FX Bosch has acted on Advisory Boards for GlaxoSmithKline, Merck Sharp & Dohme and Sanofi-Pasteur MSD, on the Speakers Bureau for GlaxoSmithKline, and received research grants from Merck Sharp & Dohme and Sanofi-Pasteur MSD.
Executive summary

- Two type-specific human papillomavirus (HPV) vaccines, Gardasil® and Cervarix®, have been tested in Phase III trials for the prevention of infection by HPV 16 and 18 (both vaccines) and HPV 6 and 11 (Gardasil).
- Both vaccines are safe and able to induce high antibody titers and to protect against cervical precancer and cancer for a period of at least 5 years.
- Gardasil has also shown protection against vulvar and vaginal precancers and against genital warts.
- Cervarix has the potential to also prevent vulvar and vaginal precancers but not genital warts.
- Recommendations to introduce HPV vaccines are being generally developed.
- The priority population targets for vaccination are the pre- and young-adolescent female groups.
- The evolving field of cervical cancer prevention calls for a fast and widespread introduction of HPV vaccines, and the acceleration of the arrival of the current vaccines to the developing parts of the world.

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