Chapter 30: HPV vaccines and screening in the prevention of cervical cancer; conclusions from a 2006 workshop of international experts

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Abstract

The finding that cervical cancer only occurs in women infected with specific, “high-risk” types of the human papillomavirus (HPV) has led to the development of novel, non-cytology-based cervical cancer prevention strategies. We now have sensitive molecular methods for detecting HPV that dramatically improve our ability to detect high-grade cervical cancer precursor lesions. Perhaps more importantly, prophylactic HPV vaccines have been developed that are protective against cervical cancer precursors caused by HPV 16 and 18. In the Spring of 2006, over 100 experts in HPV, cervical cancer screening, and vaccination worked together to define how best to incorporate HPV DNA testing and the HPV vaccines into cervical cancer prevention efforts. In this summary, we summarize the opinions of this expert group on how these advances can be introduced to provide the maximum benefit to women and to reduce the global burden of cervical cancer.

Keywords: Cervical cancer; Human papillomavirus; Vaccine; Screening; Cytology; Prevention; Health economics; Models

1. Introduction

A quadrivalent HPV vaccine protective against both cervical cancer precursors and external genital lesions caused by HPV types 6, 11, 16, 18 was licensed for use in the United States by the Food and Drug Administration in June of 2006. An application for a bivalent vaccine targeting HPV-16 and -18 was also submitted for European licensure in 2006. The successful licensure of HPV vaccines can be considered to be a major new milestone in our efforts to reduce the impact of cervical cancer.

The effort to eliminate cervical cancer began over 50 years ago with the introduction of the Pap test. Cytology-based screening has reduced the incidence of cervical cancer by up to 75% in countries that have been able to implement and sustain centralized, quality-controlled screening programs [1]. The next significant milestone in cervical cancer prevention came in the 1980s with the discovery of a link between cervical cancer and HPV [2]. During the following 20 years epidemiologic studies clearly demonstrated that infection with specific “high-risk” or “carcinogenic” types of HPV is essential for the development of cervical cancer [3]. Today, 12–18 types of HPV are classified as “known human carcinogens” [4]. The finding that cervical cancer only occurs in women who are infected with specific “high risk” or “carcinogenic” types of HPV led to the development of sensitive molecular methods for detecting HPV that are now being used to dramatically improve our ability to detect high-grade cervical cancer precursor lesions [5]. It also provided
the basis for vaccination-based strategies for the primary prevention of cervical cancer. Because of the enormous burden of HPV-16 and -18-related cancer globally and the limitations of cytology-based screening, it is expected that HPV vaccination will be rapidly adopted by many countries.

The introduction of HPV vaccines presents several somewhat unique challenges. HPV is a sexually transmitted infection and almost all individuals become infected with HPV within 2–5 years of initiating sexual activity [6,7]. In order to obtain maximum effectiveness, vaccination will need to occur prior to the onset of sexually activity, which means vaccinating young adolescents (9–13 years of age) in many countries. Already, concerns have been raised about the propriety of vaccinating adolescent girls for a sexually transmitted infection. The fact that the HPV vaccines are likely to be perceived as cancer prevention vaccines also presents unique challenges since it may be difficult for parents to reconcile vaccinating 9–13 year old girls for a cancer that they are unlikely to develop for at least two to three decades. This problem is exacerbated by the fact that the duration of protection afforded by vaccination is not yet known. Another challenge is that the two vaccines that will be licensed and available for use over the next several years will have different compositions. Although both are expected to provide excellent protection against cervical cancer caused by HPV 16 and 18, ongoing trials will provide additional information on their comparative efficacy, safety, and duration of protection.

In the Spring of 2006 over 100 experts in HPV, cervical cancer screening, and vaccination worked together to define how best to incorporate HPV vaccines into cervical cancer prevention efforts. The goal was to avoid many of the mistakes and delays that occurred with the introduction of other vaccines, such as that for Hepatitis B, through careful planning prior to the introduction of the HPV vaccines. In this summary we review what is known, and perhaps more importantly, what is not known about the new HPV vaccines. We also have attempted to summarize the opinions of this expert group expressed in the specific overviews in this monograph on how the new HPV vaccines can be introduced into existing screening programs, to provide the maximum benefit to women and to reduce the global burden of cervical cancer.

2. Human papillomaviruses

Human papillomaviruses are small DNA tumor viruses that have a circular genome of approximately 8000 base-pairs and an icosahedral viral capsid composed of two proteins, L1 and L2. More than 100 HPV types have been characterized molecularly, of which over 40 are considered genital types because they preferentially infect stratified squamous epithelium of mucosa and genital skin of the cervix, vagina, vulva, penis, and perianal areas and infrequently infect epithelial outside the genital area. The most common types of genital HPV are listed in Table 1. The genital HPV types can be divided into three groups: “high-risk” or “carcinogenic” types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) associated with a high relative risk of cervical cancer; “low-risk” viruses associated with benign epithelial proliferations in the genital area, but not associated with invasive cervical cancer (6, 11, 40, 42, 43, 44, 54, 61, 67, 72, 81, 89); and a group of six types (26, 53, 66, 68, 73, 82) that is classified as “probably carcinogenic” since there is limited data associating these HPV types with cervical cancer [8,9].

3. Epidemiological evidence linking HPV to cervical cancer

The epidemiological evidence linking the “high-risk” or “carcinogenic” viruses with cervical cancer includes case series of women with cervical cancer. One of the largest of these series identified “high-risk” HPV-DNA in over 99% of approximately 1000 invasive cervical cancers collected from 22 countries around the world [10,11]. The distribution of HPV types associated with invasive cervical cancer globally has been evaluated in a recent meta-analysis including approximately 10,000 cases [12]. The eight most common HPV types detected in descending order of frequency are: HPV 16, 18, 45, 31, 33, 52, 58, and 35. These eight types of HPV are responsible for about 90% of all cervical cancers worldwide. Further evidence comes from case-control studies that allow the estimation of the relative risk linked to each individual HPV type. The largest of these studies pooled data from 11 case-control studies from different countries that used the same methodology to test for HPV [8]. It included about 2500 women with cervical cancer and 2500 control women and reported extraordinarily high odds ratios for infections with “high-risk” types of HPV, Fig. 1. HPV-16 and -18 are the two most common types found in association with either squamous cell carcinomas or adenocarcinomas. The fraction of squamous cell carcinomas or adenocarcinomas attributable to HPV-16 and -18 was 70% and 86%, respectively [12].

High-grade cervical cancer precursor lesions, referred to as cervical intraepithelial neoplasia grades 2 and 3 (CIN-2/3), as well as histologically similar lesions of the vulva, penis, and anus, are also usually associated with “high-risk” types of HPV [13]. A meta-analysis of associations between HPV and CIN-2/3 concluded that “high-risk” HPV-DNA is detected in 84% of CIN-2/3 lesions [14]. The eight most common HPV types detected in descending order of frequency are: HPV 16, 31, 58, 18 33, 52, 35, and 51. Prospective and retrospective cohort studies have demonstrated that women who are HPV-DNA positive have a higher risk of subsequently devel-
Fig. 1. Type-specific odds ratios (OR) and 95% confidence intervals (CI) for cervical carcinoma (squamous-cell and adenocarcinoma). Subjects with HPV-DNA negative results were used as the reference category. ORs are adjusted by country and age-group. HR: high-risk; LR: low-risk. HPV type X denotes undetermined type (i.e. specimens that were positive with GP5+/6+ system but that did not hybridize with any of the 33 type-specific probes). Adapted and expanded from [12].

opining CIN-2/3 during follow-up than do HPV-DNA negative women [15–17]. Some long-term follow-up studies indicate that this risk is particularly high for women with HPV 16 or 18 compared to women with any of the remaining “high-risk” types [17].

4. Natural history of HPV infections

Genital infection with HPV is the most common sexually transmitted infection. In many populations over half of sexually-active women, and probably an equal percentage of men, are infected with HPV at some point in their lives. HPV infections are both extremely common and readily transmitted between sexually active adolescents and young adults. Prevalence surveys of adolescent or college-age women in certain populations have reported that approximately 20–25% are HPV-DNA positive [18]. After 2–3 years of follow-up, the cumulative detection of HPV in sexually-active young women is 59–82% [7,19]. In one study, 20% of young women became infected with HPV within 12 months of initiating sexual intercourse [7]. The majority of HPV infections in young women are “transient” or self-limited. Only approximately 10–20% of HPV-infected women develop a persistent infection and continue to shed HPV-DNA from the genital tract for 24 or more months [18]. As a result, HPV prevalence and incidence peak in women under 20 years of age and decline dramatically in women 30 years and older, Fig. 2 [20].

Persistence is the single most important determinant of whether or not a HPV-infected woman will develop a clinically significant sequel. Only women who develop persistent “high-risk” HPV infections are at risk for developing CIN-2/3 and invasive cervical cancers [18]. Time to progression from HPV infection to CIN-2/3 among HPV persistent carriers is highly variable with a significant fraction of cases occurring within the first years of persistency [21,22]. Unfortunately, the biological determinants of HPV persistence are not well characterized. There is some data to suggest that HPV 16 persists longer, on average, than do other types of HPV. Infection with Chlamydia trachomatis increases persistence and use of condoms reduces persistence in some studies [18].
5. Global burden of HPV-associated disease

The global burden of HPV-associated disease is very high. Cancer of the cervix is the second most common cancer among women worldwide and it is estimated that in 2002 493,000 women were diagnosed with cervical cancer and 274,000 died from it [23]. There is considerable uncertainty with respect to estimates of the global burden of cervical cancer. The majority of cases (83%) occur in developing countries where cytological screening programs have not been successfully implemented. Tumor registries in these regions are frequently inadequate, making it difficult to estimate the number of cervical cancers and as a result the number of cases may be greater than estimated. The social impact of cervical cancer is even greater than the number of cases suggests. This is because cervical cancer frequently affects relatively young women and because of this it is the largest single cause of years of life lost (YLL) from cancer in developing countries [24]. Other cancers associated with HPV are much less common, reducing the number of women with abnormal cervical cytology results and CIN-2/3 will be an important goal of HPV vaccination. In the U.S., for example, we estimate that approximately 750,000 women are diagnosed yearly with CIN-2/3, 60% of which are caused by HPV 16 and 18 [25–27]. Most of these women undergo outpatient surgical therapy, which is relatively expensive and has a potential negative impact on subsequent pregnancy outcomes [28]. The costs of evaluating women with abnormal cervical cytology and treating women with CIN-2/3 are enormous. Each year approximately 3.6 billion dollars are spent on this in the U.S. [29].

Almost 100% of external genital warts are found in association with HPV 6 and 11. Although genital warts are not a serious medical condition, they affect a large number of individuals and cause significant psychological morbidity and account for substantial healthcare costs [30]. For example, a UK survey in 2000 reported that 3.6% of men and 4.1% of women 16–44 years of age reported having been diagnosed with genital warts [30]. HPV 6 and 11 also cause recurrent respiratory papillomatosis (RRP), a rare condition characterized by the recurrent growth of benign papillomas in the respiratory tract.

6. Immunologic basis for vaccination

In the majority of individuals, HPV infections presumably induce strong, local, cell-mediated immunity that results
in clearance of HPV-induced lesions and protection against subsequent infection with the same HPV type [31]. In many, but not all, infected individuals serum antibodies (humoral immunity) are also induced that are directed against conformational epitopes on the major viral capsid protein (L1) displayed on the outer surface of the virion. The L1 antibody responses occurring after natural infection are delayed and are present at low titers [32]. This is presumably because the viral capsid proteins are only expressed in the upper layers of the HPV infected epithelium and are not efficiently presented to the systemic immune system. Antibodies directed against the L1 capsid proteins of a given HPV type appear to neutralize that HPV in various in vitro and in vivo models [33]. Despite the low titers of neutralizing antibody produced during natural infection, animal models indicate that neutralizing antibody confers protection against subsequent infection, perhaps for life. It is unclear what proportion of naturally occurring immunity is mediated through humoral immunity and how much though cell-mediated immunity directed against structural and non-structural viral proteins.

7. Current HPV L1 VLP vaccines

It is expected that two HPV prophylactic vaccines will soon be widely available for clinical use. One is a bivalent HPV-16/18 vaccine that is being produced by GlaxoSmithKline (Cervarix). The other is a quadrivalent HPV-6/11/16/18 vaccine that is being produced by Merck (Gardasil). Both prophylactic HPV vaccines are generated by recombinant technologies and are composed of viral-like particles (VLPs). The VLPs are produced by cloning the major viral capsid genes (L1) from the different HPV types, inserting them into yeast or baculovirus vectors, and then producing large amounts of the L1 proteins of each of the HPV types separately in a eukaryotic tissue culture system [31]. The bivalent vaccine is produced using an insect cell culture system whereas the quadrivalent vaccine is produced in yeast. The recombinant L1 proteins are subsequently purified and self-assemble into VLPs that appear structurally similar to infectious HPV virions, but which lack viral DNA or RNA. Therefore the VLPs are completely non-infectious and non-oncogenic. The purified VLPs are then mixed with an adjuvant to produce the final vaccine that is administered intramuscularly as three injections over a 6-month period. The bivalent vaccine utilizes a relatively novel ASO4 adjuvant comprised of aluminium hydroxide and 3-deacylated monophosphoryl lipid a. The quadrivalent vaccine utilizes a proprietary alum adjuvant.

Both vaccines are highly immunogenic and when parenterally injected into humans produce levels of neutralizing antibody that are substantially greater than those produced during natural infections. In the clinical trials immunogenicity has been excellent. Virtually 100% of vaccine recipients seroconverted [21,22,33]. Antibodies produced in response to parenterally injected VLPs predominantly recognize conformation-dependent and type-specific L1 epitopes. The duration of protection that will be achieved is currently unknown, but titers of neutralizing antibody remain significantly higher for at least 42 months after vaccination than those produced after natural infection [21,22].

8. Phase I to III trials of the HPV vaccines

Phase I and II trials have been completed with both the bivalent (16, 18) and the quadrivalent (6, 11, 16, 18) HPV vaccines. Two of the large Phase III trials of the quadrivalent vaccine have been completed and other Phase III trials are still underway, as are the Phase III trials of the bivalent vaccine. Safety of both vaccines has been excellent. In five clinical trials that included 5088 women 9–26 years of age who were administered the quadrivalent vaccine, only 0.1% of the vaccine recipients discontinued due to adverse experiences [34]. Vaccine recipients more frequently experienced injection site discomfort compared to placebo, but most vaccine recipients judged the injection site discomfort as mild to moderate. Slightly more vaccine recipients experienced fever (10.3%) 1–15 days post vaccination compared to placebo recipients (8.6%) [34].

Both the bivalent and quadrivalent HPV vaccines have demonstrated truly remarkable efficacy in the Phase II and Phase III trials. The quadrivalent vaccine has been studied in three clinical trials, Protocol 007, FUTURE I, and FUTURE II, Table 2 [34,35]. In these trials the “per-protocol-population” (PPP) was defined as women who were (1) naive to the HPV types included in the vaccine through 6 months after entry, (2) received all three vaccinations, and (3) had no significant protocol deviations. In the “per-protocol-population”, persistent infection with the HPV types included in the vaccines was reduced by 89% in Protocol 007, Table 2. CIN-2/3 and adenocarcinoma in situ (AIS) associated with HPV 16, 18, were reduced by 100% in vaccine recipients compared to placebo recipients in all three trials, Table 2. Similarly, biopsy-confirmed genital warts associated with HPV-6, -11, -16, -18 were reduced by 100% in vaccine recipients compared to placebo recipients in Protocol 007 and FUTURE I, and by 98% in FUTURE II.

The Phase II trial of the bivalent HPV-16/18 vaccine was divided into an initial follow-up period that had a median follow-up of 2.2 years and a subsequent follow-on study of a subset of the original enrollees with a median follow-up of 4.0 years [21,36]. In both study periods persistent infection with HPV-16 or -18 was reduced in the “per-protocol-population” by 100% in vaccine recipients compared to placebo recipients, Table 3. In order to evaluate efficacy of the bivalent vaccine for reducing HPV-16 or -18 associated CIN-2/3, data from both follow-up periods were combined. After 2 and 4 years of follow-up, biopsy-confirmed CIN-2/3 associated with HPV-16 or -18 was reduced by 100% in vaccine recipients compared to placebo recipients. Recently it has been shown that women vaccinated with the bivalent HPV vaccine show cross-protection against incident infection with
### Table 2
Efficacy of the quadrivalent HPV vaccine

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Median follow-up</th>
<th>Cases in vaccine recipients</th>
<th>No.</th>
<th>Cases in placebo recipients</th>
<th>Efficacy (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent infection with HPV-6, -11, -16, or -18&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol 007</td>
<td>235</td>
<td>3.0</td>
<td>4</td>
<td>233</td>
<td>35</td>
<td>89</td>
<td>70–97</td>
</tr>
<tr>
<td>HPV 16 or HPV 18 associated CIN-2, -3 and AIS&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol 007</td>
<td>231</td>
<td>3.0</td>
<td>0</td>
<td>230</td>
<td>1</td>
<td>100</td>
<td>−3735–100</td>
</tr>
<tr>
<td>FUTURE I</td>
<td>2,200</td>
<td>2.4</td>
<td>0</td>
<td>2,222</td>
<td>9</td>
<td>100</td>
<td>79–100</td>
</tr>
<tr>
<td>FUTURE II</td>
<td>5,301</td>
<td>2.0</td>
<td>0</td>
<td>5,258</td>
<td>21</td>
<td>100</td>
<td>81–100</td>
</tr>
<tr>
<td>Combined</td>
<td>7,732</td>
<td></td>
<td>0</td>
<td>7,701</td>
<td>53</td>
<td>100</td>
<td>93–100</td>
</tr>
<tr>
<td>HPV-6, -11, -16, or -18 associated genital warts&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Protocol 007</td>
<td>235</td>
<td>3.0</td>
<td>0</td>
<td>233</td>
<td>3</td>
<td>100</td>
<td>−140–100</td>
</tr>
<tr>
<td>FUTURE I</td>
<td>2,261</td>
<td>2.4</td>
<td>0</td>
<td>2,279</td>
<td>29</td>
<td>100</td>
<td>86–100</td>
</tr>
<tr>
<td>FUTURE II</td>
<td>5,401</td>
<td>2.0</td>
<td>1</td>
<td>5,387</td>
<td>59</td>
<td>98</td>
<td>90–100</td>
</tr>
<tr>
<td>Combined</td>
<td>7,897</td>
<td></td>
<td>1</td>
<td>7,899</td>
<td>91</td>
<td>99</td>
<td>94–100</td>
</tr>
</tbody>
</table>

<sup>a</sup> Per-protocol-population is defined as women naïve to HPV types included in the vaccine through 6 months after entry, that received all three vaccinations, and who showed no significant protocol deviations.

<sup>b</sup> Modified from ref. [34].

<sup>c</sup> Modified from ref. [33].

### Table 3
Efficacy of bivalent HPV vaccine

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Median follow-up</th>
<th>Cases in vaccine recipients</th>
<th>No.</th>
<th>Cases in placebo recipients</th>
<th>Efficacy (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent infection with HPV-16, or -18</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harper et al.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>366</td>
<td>2.2</td>
<td>0</td>
<td>355</td>
<td>7</td>
<td>100</td>
<td>77–100</td>
</tr>
<tr>
<td>Harper et al.&lt;sup&gt;c&lt;/sup&gt;</td>
<td>311</td>
<td>4.0</td>
<td>0</td>
<td>295</td>
<td>7</td>
<td>100</td>
<td>34–100</td>
</tr>
<tr>
<td>HPV-16 or HPV-18 associated CIN-2, -3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harper et al.&lt;sup&gt;c&lt;/sup&gt;</td>
<td>481</td>
<td>2–4</td>
<td>0</td>
<td>385</td>
<td>5</td>
<td>100</td>
<td>−7.7–100</td>
</tr>
</tbody>
</table>

<sup>a</sup> Per-protocol-population is defined as women naïve to HPV types included in the vaccine through 6 months after entry, that received all three vaccinations, and who showed no significant protocol deviations.

<sup>b</sup> Modified from ref. [35].

<sup>c</sup> Modified from ref. [20].

HPV types 45 and 31 [21]. Women who were vaccinated with the HPV-16 or -18 vaccine had a 94% (95% CI 63–100%) reduction in incident infections with HPV-45 and a 55% (95% CI: 12–78%) reduction in incident infections with HPV 31, compared to placebo recipients.

### 9. Potential impact of HPV vaccination

It is likely to be decades before we will be able to evaluate the impact of HPV vaccination on the incidence of cervical cancer using empirical data. Moreover, because of the factors that will vary from setting to setting, such as the incidence of cervical cancer, temporal patterns in sexual behavior and parity, presence of ongoing cytology screening, and resources available for investments in health, it is going to be very difficult to determine what the impact of vaccination will be in any given setting using empirical data alone. Mathematical models that integrate biologic, epidemiologic, economic, and behavioral data offer a quantitative and systematic approach to predicting the impact of HPV vaccination in different settings [37].

Several groups have developed mathematical models of cervical cancer natural history and evaluated preventive options. When compared, these models reveal at least three common themes [38]. The first is that a vaccine for HPV-16/18 will reduce, but not eliminate, the risk of cervical cancer. The second is that in countries with cervical cancer screening programs, such a vaccine may significantly reduce HPV 16/18 associated CIN-2/3 lesions and invasive cervical cancer, although the potential magnitude of the clinical benefits will depend on the underlying effectiveness of the screening program. In the U.S., the cost-effectiveness of vaccination will depend heavily on whether or not it will be acceptable to initiate cytological screening at a later age, screen less frequently, and adopt a conservative approach to managing equivocal and mildly abnormal screening test results [39]. The third is that the age of vaccination is likely to be influential on the relative benefits and costs of primary prevention. Vaccination of young adolescents prior to sexual activity, while producing the greatest long-term impact, delays the impact of vaccination and could present challenges in terms of achieving widespread coverage. On the other hand, programs that target older women, who are more likely...
to have been previously exposed to HPV types 16 and 18, will be less effective.

The models also indicate that the benefits of using a type restricted HPV 16 and 18 vaccine are likely to be substantial in developing countries that lack cervical cancer screening programs [40], compared with the status quo. Although the optimal prevention strategy will be heavily influenced by a particular country’s resource constraints (monetary, human, and health infrastructure) and ability to achieve widespread coverage, vaccination and screening strategies have been identified in a wide variety of settings that would be as cost-effective as other well accepted public health interventions. In the poorest countries, these include vaccination alone in adolescence and cervical cancer screening in women age 35–40 using strategies that enhance the linkage between screening and treatment (e.g., HPV-DNA testing followed by treatment of screen-positives in a second visit). In countries such as Brazil, a combination of vaccination of young girls together with provision of two cervical cancer screenings between 35 and 45 years of age, appears promising [38], and at a cost per-vaccinated woman of less than $25 is likely to be cost saving. The cost-effectiveness of vaccination in poor countries is most influenced by the vaccine price, costs associated with achieving widespread population coverage, feasibility of delivering three doses of vaccine to a young adolescent population, and duration of vaccine-induced immunity.

10. Unresolved issues

10.1. Target populations

10.1.1. Optimal age groups for vaccination

The optimal target populations for the HPV vaccines have not yet been clearly defined and are likely to vary from country to country because of differences in age at first intercourse/exposure to HPV, epidemiology, and available vaccination platforms. Both HPV vaccines prevent persistent infections and the development of HPV-associated lesions due to the vaccine HPV types in women 15–26 years of age who are both HPV-DNA negative and serologically negative for the vaccine HPV types. Immunological “bridging studies” have documented better serological responses to the quadrivalent vaccine among 9–15 year old females than among older adolescents and women [34]. Based on this, the U.S. FDA recently approved the quadrivalent vaccine for use in women 9–26 years of age.

The two HPV vaccines under consideration are considered “prophylactic” rather than “therapeutic” vaccines and optimally should be administered prior to natural exposure to the vaccine HPV types. HPV infections are both extremely common and readily transmitted between sexually active adolescents and young adults. The majority of females become infected with at least one type of HPV within 2–5 years of initiating sexual activity [7,19]. Since HPV 16 and 18 are among the most common HPV types found in adolescents and young adults, maximum benefit will be achieved by vaccinating prior to initiating sexual activity [7,19,40]. The age at which girls initiate sexual activity varies considerably between different countries and cultures. The average reported age of first sexual intercourse varies in EU countries from 15 years for women in the Czech Republic to 20+ years in Italy [41]. In Portugal only 25% of 18 year old women have been sexually active, whereas in Iceland 72% have been. Surveys in the U.S. indicate that the percentage of adolescents who self-report having been sexually active varies considerably between different regions [42].

Based on these considerations, priority should be given to vaccination of females 9–13 years of age. This raises a number of issues for the vaccination community. Although some countries have successful school-based programs that deliver Hepatitis B (HBV) vaccine to adolescents, many do not. In countries such as Belgium, Croatia, the Netherlands, and Slovenia which have school-based programs, the coverage rate for adolescent HBV vaccination programs ranges from 70–85% [43]. However, in countries such as France, Germany, Italy, and the U.S. that do not have school-based programs, it may prove difficult to obtain high coverage rates for HPV vaccination in 9–13 year old females. Ten years after the introduction of recommendations and funding for HBV vaccination in adolescents, the coverage rate in Germany remains below 30% [43].

10.1.2. Other age groups for vaccination

If only 9–13 year old females are targeted for vaccination it will take 20 years before any impact of the HPV vaccine on cervical cancer is observed. Full effects of vaccination on cervical cancer would likely take 30 or 40 years. This may be too long for many countries, which will want to introduce “catch-up” vaccination for sexually-active females. There are a number of issues that need to be taken into account when considering vaccination of sexually-active women. One is whether these women will benefit from vaccination. Although the HPV vaccines have already been demonstrated to be effective in sexually-active females 15–26 years of age, to date, benefit has only been documented for women who are HPV-DNA negative and serologically negative for the vaccine HPV types. Thus, older, sexually-active women who have been infected with one or more of the vaccine types of HPV may either not benefit, or have a reduced benefit, from vaccination. It is important to note that vaccination of women already naturally infected with vaccine HPV types has not been associated with any adverse effects in the clinical trials.

Vaccination of sexually-active women raises another issue: should pre-vaccination testing for HPV be performed. It is unlikely that pre-vaccination testing for HPV will provide clinically useful information since neither HPV serological assays nor HPV-DNA tests are good measures of infection with HPV. Approximately one-half of HPV-infected individ-
uals remain serologically negative and the detection threshold of commercially-available HPV-DNA tests has been adjusted to identify women with cervical neoplasia, rather than women who are infected with HPV [5,32]. After considering all of these issues, the U.S. Advisory Committee on Immunization Practices (ACIP) recently recommended that even though the primary target population is females 11–12 years old, sexually active females 13–26 years old should also be vaccinated in the U.S. [44].

10.1.3. Vaccination of males

Although encouraging immunogenicity trials of the HPV vaccines in males have been conducted, to date there is no data documenting efficacy. If efficacious in males, there may be considerable interest in some industrialized countries in vaccinating adolescent males with the quadrivalent vaccine in order to reduce risk for anogenital warts. There is less of a compelling argument for vaccinating males with the bivalent HPV 16, 18 vaccine. Even though the burden of HPV 16 and 18 associated penile, anal, and oropharyngeal cancers in males is not insignificant, it is considerably less than the burden of HPV 16 and 18 associated cervical disease in women [13].

Mathematical models can also be used to evaluate the incremental benefits and cost-effectiveness of vaccinating males. In contrast to vaccinating against common childhood infectious diseases, vaccinating against a sexually transmitted disease requires consideration of the heterogeneity in risk and the nature of contacts between men and women [38]. The value of vaccinating both men and women depends upon how well vaccinating women alone controls the spread of infection. With moderate heterogeneity in risk behaviour and high vaccination coverage of women, the benefits of vaccinating men is predicted to be limited for the purpose of cervical prevention [45], and may not be cost-effective. Herd immunity effects of vaccination can protect unvaccinated individuals in the population, but are only fully protective at high levels of vaccination coverage. Even at high levels of coverage, the existence of high-risk groups can make elimination of the disease difficult and lead to diminishing returns of increased vaccination coverage.

10.2. Need for boosters

The durability of the immune response engendered by the HPV vaccines is unknown. Both a monovalent HPV 16 vaccine and the bivalent HPV-16/18 vaccine result in levels of neutralizing antibodies that are considerably higher than those encountered after natural infection. In addition, the antibody responses that are produced through vaccination appear to be quite durable, lasting for at least 42 months [21,33]. Over the next several decades it will be important to monitor antibody levels and HPV infections in immunized subjects to determine whether boosters will be needed and if so, how many years after vaccination.

10.3. Introduction in developing countries

Approximately 80% of cervical cancer occurs in less developed countries, predominantly due to the fact that women have limited access to screening and treatment [23]. Thus, the need for vaccination is much greater in developing countries than in industrialized countries and the real public health potential of the HPV vaccines will only be realized if they can be provided in these settings. Unfortunately, the introduction of other new vaccines such as HBV vaccine and Hemophilus influenzae type b (Hib) has generally taken 10–20 years to reach the public sector in developing countries. In large part this delay has been due to the costs of new vaccines. New vaccines tend to be relatively expensive because of advanced technologies and regulatory requirements compared to older, more established vaccines. With HBV and other vaccines, manufacture in second tier industrializing countries such as India has significantly reduced the costs of vaccination. If the HPV vaccines can be made available to developing countries at a significantly reduced cost it would greatly improve the chances of a rapid and widespread introduction. Work is already underway with The Global Alliance of Vaccines and Immunization (GAVI) and other donor institutions to determine whether novel-funding mechanisms might be utilized for providing HPV vaccines to developing countries. One new mechanism is referred to as Advanced Market Commitments (AMCs) [46]. AMCs provide a legally-binding commitment by donor institutions to vaccine manufacturers to pay a price for a future vaccine that would provide revenues matching those of other health products in the global marketplace. Donors agree to pay this price for a certain number of doses. When this number of doses is met, the manufacturers are obligated to sell the vaccine to developing countries at a low price that is affordable. This provides the vaccine manufacturers with some assurance that they will earn a reasonable return on their investment if they provide vaccines to the poorest developing countries.

Because of an infusion of resources from donors over the last decade, vaccine delivery systems are now among the most advanced healthcare systems in many developing countries. Despite this, even if the HPV vaccines can be made available at an acceptable cost, there remain a number of additional barriers to their introduction. One is the need to bridge the pediatric immunization, sexual and reproductive health, and cancer communities to develop an efficient delivery system for providing the HPV vaccines to 9–13 year old females and other potential target groups. These groups frequently do not communicate directly with each other and will need to do so if they are to effectively approach the introduction of HPV vaccines. Another potential barrier is that there are a number of new vaccines being introduced against infections such as such as rotavirus, Japanese encephalitis virus, and pneumococcal disease. These other vaccines will most likely compete for limited immunization resources in developing countries. It is quite possible that pediatricians and infectious disease specialists who usually determine vaccination policies will
10.4. Impact of vaccination on screening programs

Even after vaccination programs have been instituted and reasonable levels of coverage obtained, cervical cancer screening programs cannot be discontinued. There are a number of reasons why screening will need to continue for the foreseeable future. One is that the primary target population for vaccination is 9–13 year old females. Although some “catch-up” vaccination of older, sexually active women will occur in many countries, much lower rates of coverage will likely be achieved through “catch-up” vaccination efforts compared to a targeted cohort vaccination of young adolescents. Another reason why screening programs have to be maintained is that vaccination will not protect, against the HPV types not included in the vaccines. Depending on geographic location, HPV 16 and 18 account for only 62% to 77% of all cervical cancers [12]. In addition, although a dramatic 100% protection against HPV 16 and 18 associated CIN-2/3 was observed in the Phase II and Phase III trials of the HPV vaccines, it is very likely that with longer follow-up protection will begin to decline. Although there may be some cross-protection against other “high-risk” types of HPV achieved by vaccinating against HPV 16 and 18, the extent and duration of cross-protection is currently unclear.

Given that screening will need to continue after the introduction of HPV vaccination programs it will be important to eventually re-evaluate how we screen [47]. It is likely that the current approach of frequent screening utilizing cytology efforts will prove to be too expensive and inefficient for many countries. Most countries that introduce HPV vaccination will eventually want to switch to HPV-DNA testing as the primary screening test since not only does it have better performance characteristics than cervical cytology, but using HPV testing for screening coupled with HPV genotyping will provide a simple strategy to monitor long-term protection among vaccinated women [47]. HPV testing systems amenable to use in areas with limited health infrastructures are currently being developed and evaluated.

11. Next steps

It is important to recognize that receiving regulatory approval does not mean that the HPV vaccine will be widely used, even in industrialized countries. Developing recommendations for use of the vaccine, assuring a mechanism for service delivery, providing funding for vaccination, surveillance of vaccine coverage and safety, sustaining and improving coverage rates, and creating awareness of the need for vaccination in the professional, public, and political communities through advocacy efforts in order to generate the political will to support vaccination are all critical for a successful vaccination system, Table 4 [43].

11.1. Developing recommendations for use

Primary cervical cancer prevention efforts through vaccination and secondary prevention efforts through screening clearly impact each other and recommendations for both will need to be closely coordinated. This means that national immunization programs will have to partner with sexual and reproductive health programmes as well as national cancer control programmes to develop coordinated recommendations and approaches to health education, immunization, and screening to reduce the burden of morbidity and mortality associated with cervical cancer. This will require difficult decisions with respect to prioritizing between primary and secondary prevention efforts.

11.2. Assuring mechanisms for delivery

Obtaining high coverage rates in adolescent females should be relatively easy in countries with school-based HBV vaccination programs. However, assuring a mechanism for service delivery to this target population will be challenging in other countries. These countries will need to either establish school-based programs or develop alternative approaches to reaching young adolescents. Alternative vaccination approaches for adolescents have not been highly successful in the past [43]. The target age group also presents programmatic challenges to developing countries, many of which have only recently been able to achieve high coverage rates for their infant and early childhood vaccination programs. The introduction of the HPV vaccines means that already under-resourced national immunization programs will have to enter into the arena of schoolchild and adolescent vaccination. In some developing countries young girls frequently do not attend school so non-school-based vaccination programs will have to be developed.
11.3. Providing funding for vaccination

The quadrivalent HPV vaccine is one of the most expensive vaccines ever and assuring that there is funding for the HPV vaccines will also be challenging. The non-discounted U.S. price for three doses of the quadrivalent vaccine is $360, exclusive of vaccination costs. The high cost of the first generation HPV vaccines may provide an insurmountable barrier to introducing them in the world’s poorest countries where they are needed most. 2.2 billion people live in the world’s lowest income countries which have a gross national income (GNI) of less than $825 per capita [48]. Even though novel approaches to providing vaccines have reduced the cost of immunizing a child in these regions of the world to only $30, roughly one child in four still does not receive any vaccinations [49]. The vaccine for diphtheria, tetanus, and pertussis (DPT) is the most accessible and affordable childhood vaccine, but the DPT vaccination rate for sub-Saharan Africa has remained at only about 50% for the last 15 years [50]. Clearly we need to develop not only unique funding mechanisms to assure that HPV vaccines are available to the countries where they are needed most, but also approaches to decrease the cost of vaccination programs such as regional manufacturing and/or development of second generation vaccines [46].

12. Concluding remarks

The registration of the first generation of HPV vaccines represents a highly significant milestone in our efforts to reduce the impact of cervical cancer globally. We now have the capacity to prevent cervical cancer not only through secondary prevention by screening and treatment of CIN-2/3, but also through primary prevention. Careful integration of primary and secondary prevention programs should lead to greater reductions in cervical cancer compared to what can be achieved by screening alone. As Editors of this monograph we have attempted to synthesize the key messages for policy makers and healthcare providers with respect to integrating HPV vaccination into cervical cancer prevention programs. Although the link between HPV infection and cervical cancer and the interactions between screening and vaccination are complex, in few areas of cancer control do we have such a wealth of information coming from multidisciplinary research We must caution, however, that there are considerable barriers to the implementation of effective HPV vaccination programs. The success of HPV vaccination programs will require the full endorsement of public health authorities, healthcare workers, and the general population. Improving public and provider awareness regarding HPV, cervical cancer, and the benefits of HPV vaccination will be an important step in obtaining this endorsement. Another barrier will be paying for the vaccines. In the real world of competing healthcare priorities, making the vaccines available to the poorest countries with the greatest need will require that vaccine manufacturers and donors work together to provide vaccination at an affordable cost. Only through such efforts can the real potential of the HPV vaccines be achieved—making cervical cancer a disease of the past.

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References


