This issue of the Journal presents the results of an experimental project describing the technology and the model system to generate novel human papillomavirus (HPV) vaccines. Rather than using the immune capacity of the L1 capsid epitopes, these prototypes are based on the unique properties of the L2 protein of the capsid to induce broad-spectrum (BS) HPV antigenic recognition and the formation of neutralizing antibodies to a large number of HPV types. The results open the door to a novel family of second-generation HPV vaccines with substantial potential value in the public health horizon.

The developments and the clinical program will still require years of investigation, but the concept addresses in a meaningful way some of the recognized limitations of current vaccines, including the continuous screening requirements and at least partially the difficulties related to the current vaccine cost.

**Phase III Results: HPV Type-Specific Protection and Cross-Protection**

There are currently two vaccines that have contributed phase III clinical trial results: Gardasil (Merck & Co., Inc., Whitehouse Station, NJ), which targets two oncogenic HPV types (16 and 18) and two nononcogenic HPV types (6 and 11) responsible for genital warts and respiratory papillomatosis, and Cervarix (GlaxoSmithKline Biologicals, Rixensart, Belgium), which targets two oncogenic HPV types (16 and 18) and is formulated with a novel adjuvant AS04. These vaccines are currently licensed in more than 120 countries and have been introduced into routine vaccination programs in many developed countries (1–3). More than 40 million doses have already been distributed.

Most of the critical phase III results are available for Gardasil, and final results of the pivotal trial with Cervarix will be available in 2009. These two vaccines have shown to date high efficacy against the predefined endpoint lesions (cervical intraepithelial neoplasia of grade 2 or more [CIN 2+]), adequate safety and tolerability profiles, high immunogenicity, long-term duration of protection in the range of 6–7 years, and strong indications of its ability to induce immune memory [reviewed in (3–5)].

The global estimates of the protection against cervical cancer of the currently available vaccines range from 70% attributed to HPV-16 and HPV-18 to 75%–85% related to a relatively small geographical variation and to additional nonvaccine-type cross-protection. None of the vaccines have shown therapeutic activity.

**Recognized Limitations of Current HPV Vaccines**

Some of the limitations of current vaccines are presented in Table 1. Also shown are areas that could be, at least theoretically, overcome by BS HPV vaccines (Table 1) (6–9).

**New Technology in HPV Vaccine Development**

The experiments presented by Jagu et al. (10) are encouraging. Novel vaccine formulations based on multiple concatenated fragments of L2 of HPV of both cutaneous and mucosal types are tested in rabbit and mouse model systems. A series of adjuvants are also investigated, allowing for a systematic exploration of the optimal vaccine formulation for phase I studies in humans. Responses in the vaccinated animals were measured as induction of HPV type-specific and neutralizing antibody titers. As a surrogate of vaccine efficacy, a challenge trial with cutaneous HPV-16 pseudovirions was conducted. Finally, comparisons are made with the type-specific and cross-reactive antibody responses obtained in vaccinated animals with Gardasil.

Vaccinated mice and rabbits showed substantial and robust antibody responses against multiple HPV types (up to 22) pertaining to the cutaneous and mucosal types. All of the 15 high-risk types identified in cervical cancer and two of the low-risk types are represented in one of the formulations. The experiments also suggest that the adjuvants used are relevant in modulating the immune response, as has also been shown for current HPV vaccines, and might prove to be critical if high titers of type-specific antibodies are required for ensuring long-term BS HPV protection. The quality of the antibody response has not yet been tested or reported.

As soon as appropriate, phase I trials in humans should be initiated. These trials are designed to explore whether L2-based concatenated multiple-type vaccines can 1) induce immune responses against all antigens represented, 2) show noninterference with the responses required against HPV-16 and HPV-18, and 3) evaluate local reactions and tolerability.

If results from such phase I studies are encouraging, a clinical program will follow, and challenges can already be anticipated. The novel clinical trials will ethically require HPV vaccination of the control groups, thus substantially reducing the incidence of CIN 2/3 lesions in the reference. Furthermore, given the relatively low prevalence of HPV infections of many of the non–HPV-16 and HPV-18 oncogenic types and their slower progression rate, the trials will have to be differently designed. Virological endpoints (ie, seroconversion, antibody titers and profiles over time, allowance for a systematic exploration of the optimal vaccine formulation for phase I studies in humans. Responses in the vaccinated animals were measured as induction of HPV type-specific and neutralizing antibody titers. As a surrogate of vaccine efficacy, a challenge trial with cutaneous HPV-16 pseudovirions was conducted. Finally, comparisons are made with the type-specific and cross-reactive antibody responses obtained in vaccinated animals with Gardasil.

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HPV type–specific persistency), composite endpoints (virological and histological), and combined endpoints (protection against groups of several HPV types) will be increasingly important as will the methodology to address causality in the presence of multiple concurrent HPV infections and multiple lesions in a given specimen. Study groups of larger sizes and extended follow-up times are likely to be necessary. In anticipation, the scientific community and the regulatory agencies could examine these issues and formally update the recommendations made in 2004 (11).

**Implications of BS HPV Vaccines on Production Cost**

An interesting feature of the trials presented is the opportunity for vaccine production in a bacterial model system that might as a result be less sophisticated and expensive than current or future polyvalent HPV L1 virus-like particle–based vaccines. The cooperation shown between researchers in India and the United States and the presumable technology transfer that has occurred reflects a promise of massive production of BS HPV vaccines in India. It has been estimated that out of the close to 500,000 new cases of cervical cancer worldwide per year, approximately 150,000 are generated in the population of the Indian subcontinent, with a high impact on cancer mortality (12,13). Locally produced vaccines have a unique opportunity to substantially reduce the cancer burden in India and neighboring populations. The generous implication and the support to the program by the major vaccine production industries will be critical.

**Table 1.** Recognized limitations of current HPV vaccines that could be overcome by novel broad-spectrum HPV vaccines*

<table>
<thead>
<tr>
<th>Rubric</th>
<th>Limitations of current HPV vaccines</th>
<th>Potential impact of BS HPV vaccines</th>
<th>Alternatives under research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost and/or price</td>
<td>High</td>
<td>Technology transfer</td>
<td>Tier pricing for developing countries Financing strategies†</td>
</tr>
<tr>
<td>Continuous screening requirements for HPV-vaccinated women</td>
<td>Two oncogenic HPV types included Limited impact of cross-protection No therapeutic effect</td>
<td>BS HPV prophylaxis, including all HPV oncogenic types</td>
<td>Multiple additional types added to current L1 VLP HPV vaccines‡ Other vaccine constructs§</td>
</tr>
<tr>
<td>Management of sexually active adult women</td>
<td>Reduced vaccine efficacy due to prevalent HPV type–specific infected women No therapeutic effect</td>
<td>Facilitate general adoption of HPV testing for primary screening and “screen and vaccinate” protocols (Figure 1)</td>
<td></td>
</tr>
<tr>
<td>Vaccine acceptability and introduction</td>
<td>Limited perception of burden of disease in females and males</td>
<td>Inclusion of cutaneous types</td>
<td>Professional education Population education Community involvement</td>
</tr>
</tbody>
</table>

* HPV = human papillomavirus; VLP = virus-like particle; BS = broad spectrum.
† See also (6) and (7).
‡ Phase III trials are ongoing.
§ See also (8).
|| See also (9).

**Figure 1.** Forward looking views on cervical cancer prevention strategies should broad spectrum HPV Vaccines become available. BS = broad spectrum; HPV = human papillomavirus; VIA = visual inspection with acetic acid.
†, see also (14, 15)
‡, details of such protocols would require additional clinical research.
Implications of BS HPV Vaccines on Screening Requirements

The use of BS HPV vaccines might alleviate the requirement of continuous screening among vaccinated women and change the strategy for cervical cancer prevention in sexually active adult women in both developed and developing countries (Figure 1) (14,15). Adolescents who receive BS vaccines would not need further screening, and sexually active women could move into a strategy of HPV screening (with or without cytology), followed by vaccination if they are HPV negative and active diagnostic and follow-up (with or without vaccination) if they are HPV positive.

Developing countries have proven to be able to efficiently execute preventive strategies that require one-time population campaigns (ie, Polio vaccination) while repeatedly failing to sustain the requirements imposed by repetitive screening protocols (16). Strategies combining low-cost HPV screening of adult women and mass vaccination with BS HPV vaccines have a theoretical chance of feasibility in developing countries. They might also represent the technical requirement to begin closing the equity gap in cervical cancer prevention between developed and developing countries.

As soon as it is appropriate, modeling studies should explore the costs and benefits of these novel options.

The Benefits Offered Today by HPV Vaccines and the Responsibility of Deciding the Time to Intervention

While second-generation vaccines are being investigated, available HPV vaccines should be introduced as intensively and as widely as is possible. It is critical to recognize that continued developments in research should evolve in parallel to (and learn from) the public health preventive efforts.

The first consideration is that animal models do not always translate linearly to results in humans. To complete a clinical HPV vaccine research program, 5–10 years of development and clinical research are likely to be necessary.

Second, currently available vaccines offer protection immediately after the completion of the vaccination program, even if empirical proof of cancer reduction will take decades. Within a short interval, current vaccines will effectively prevent ambiguous cytology results and preneoplastic cervical lesions in the cervix, extending for Gardasil to the preneoplasias of the vulva and vagina and to genital warts. It is likely that Cervarix will show similar results for vulvar and vaginal lesions. Both vaccines have the additional potential to prevent other HPV-16– and HPV-18–induced genital and nongenital cancers. Finally, the introduction of HPV vaccines, currently targeting female adolescents, poses complex problems that are often culturally dependant. These include professional and general population education, political persuasion, financial continuity, logistical deployment, and the organization of monitoring and evaluation programs (17). All the efforts that are developed today for the introduction of currently available HPV vaccines will greatly facilitate the introduction of BS vaccines in the future.

For several generations of women, access to currently available vaccines will be their best and unique chance of lifetime protection against cervical cancer, and it would be unjustified to delay it on the grounds of the promise of better vaccines on the horizon.

References


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