Chapter 17: Second generation HPV vaccines to prevent cervical cancer

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Abstract

Prophylactic human papillomavirus (HPV) vaccines based on intramuscular injection of non-infectious L1 virus-like particles (VLPs) are undergoing intense clinical evaluation. As documented in preceding chapters of this monograph, clinical trials of these vaccines have demonstrated their safety and high efficacy at preventing type-specific persistent cervical HPV infection and the development of type-specific cervical intraepithelial neoplasia (CIN) cervical neoplasia. There is widespread optimism that VLP vaccines will become commercially available within the next few years. The prospects for development of alternative HPV vaccines must be considered in light of the likelihood that a safe and effective prophylactic HPV vaccine will soon be available. Three questions need to be addressed: (1) Is there sufficient need for a second generation vaccine? (2) Are there sufficiently attractive candidates for clinical trials? (3) Is there a realistic development/commericalization path?

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1. Is there sufficient need for a second generation vaccine?

From a worldwide public health prospective, reducing deaths from cervical and other HPV-induced cancers is arguably the most important goal of an HPV vaccination program. Sustainable vaccination programs that protect as many women as possible from persistent infection by at least HPV-16 and -18 would seem to be the most practical means of approaching this goal. The current VLP vaccines have fundamental weaknesses for achieving this purpose, particularly for widespread distribution in developing countries, where most cervical cancers occur. First, VLP vaccines are expensive to manufacture, since they are produced in eukaryotic cell culture and extensively purified. Second, they are, like many current vaccines, relatively expensive to distribute as they involve intramuscular injections of a vaccine that requires a cold chain for storage. In addition, the primary target group for vaccination is pre-adolescent girls, a group that will not be easily enrolled in a vaccination program that involves three needle injections over a 6-months period. Third, protection may well be predominately type-specific, and so the current vaccines are not expected to protect against the almost 30\% of cervical cancers that are HPV-16- and -18-independent. Incomplete type coverage is especially problematic for developing countries because most do not have effective screening programs as an alternative to reduce cervical cancer risk from minor oncogenic types. Fourth, the L1 VLP vaccines are not expected to induce regression of established HPV-induced neoplasia. Because it generally takes more than a decade for incident HPV infection to develop into cervical cancer, the major public health benefit of VLP vaccines will be substantially delayed. It might prove easier to convince public health officials to invest in a vaccine with therapeutic, as well as prophylactic, potential, since it could afford protection for the current generation of women.
2. Are there sufficiently attractive candidates for clinical trials?

An ideal HPV vaccine would be inexpensive to manufacture and distribute, protect against all oncogenic types after a single vaccination, and act both therapeutically and prophylactically. None of the second generation vaccines currently under development is designed to meet this ideal, therefore either new candidates will need to be developed or decisions will need to be made as to which characteristics are most important and most feasible. Public sector support should be directed to candidates that have a potential for making large differences in the number of women effectively vaccinated. Support for development of strategies that could, at best, make incremental increases must be weighed against devoting these resources to the vaccination of women with the vaccines that are expected to soon be available. Second generation vaccines can be divided into several, in some cases overlapping, categories, as discussed below. Table 1 provides a partial list of vaccine approaches under development and summarizes their potential strengths and weaknesses.

2.1. L1 protein vaccines

The most straightforward approach to a second generation vaccine would be to simply increase the valency of the current VLP vaccines. Given the expectation that two companies (Merck and GlaxoSmithKline) will soon be selling competing VLP vaccines, it would be surprising if a race to increase market share by increasing the number of VLP types in the vaccine did not take place. Importantly, there is no indication that increasing valency decreases type-specific antibody induction. The central question from a public health perspective is whether the added type coverage would be worth the additional cost. Going from an HPV-16/18 bivalent vaccine to a vaccine containing seven types would modestly increase the cervical cancer prevention potential from 71% to 87%, assuming type-specific protection [1]. Therefore, in settings with limited resources, increasing the valency would be effective only if it resulted in a small increase in the overall cost of the vaccination program; otherwise, it would be preferable to use the resources to vaccinate a greater number of women with a less expensive HPV-16/18 vaccine.

More novel second generation L1 protein-based vaccines can be divided into strategies that seek to reduce the cost of production and those that seek to reduce the cost of delivery. The cost of VLP production might be reduced by production in bacteria or plants. Most of the L1 produced in commonly used bacteria, such as E. coli, is either found in a denatured form in inclusion bodies or associated with a bacterial chaperone, and therefore most is not assembled into VLPs [2]. However, schemes have been derived to efficiently produce L1 pentameric capsomers that can induce neutralizing antibodies from recombinant E. coli extracts [3]. Whether they would induce the remarkably consistent high titer neutralizing antibody responses observed after low-dose VLP injection in humans is unclear. In addition, the relatively complicated process of purification may not lead to a substantially less expensive vaccine than, for instance, yeast-derived VLPs.

L1 VLPs can also be produced in L1 transgenic plants or after transient L1 expression in plants. However, L1 production has been disappointingly low in published studies—0.5% of soluble protein at best—despite efforts to increase expression by codon modification of the gene [4]. Industrial-scale

Table 1
Second generation HPV vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Potential advantages</th>
<th>Potential limitations</th>
<th>Ref.</th>
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<tr>
<td>Additional VLP types (HPV-31, -45, -53, -52, etc.)</td>
<td>Established technology</td>
<td>Increased cost, modest increase in protection from cervical cancer</td>
<td>[1]</td>
</tr>
<tr>
<td>Heat stabilization of VLPs</td>
<td>Decreased implementation costs</td>
<td>Unproven technology for HPV VLPs</td>
<td>[6,10]</td>
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<tr>
<td>Slow release formulation</td>
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<td>Upper respiratory tract delivery of purified VLPs</td>
<td>Needle free delivery; Induction of sIgA; lower cost of implementation?</td>
<td>Consistency of immune response? Safety?</td>
<td>[9]</td>
</tr>
<tr>
<td>Oral delivery of VLP in crude plant or yeast extract</td>
<td>Low cost production and administration; induction of sIgA</td>
<td>Low level expression in plants; low immunogenicity in animal models</td>
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</tr>
<tr>
<td>L1 DNA</td>
<td>Standard production procedures</td>
<td>Less immunogenic than VLPs? Unknown oncogenic potential of injected vectors</td>
<td>[17]</td>
</tr>
<tr>
<td>L1 pentameric subunits</td>
<td>Lower cost of production (made in bacteria)</td>
<td>Less immunogenic than VLPs?</td>
<td>[3]</td>
</tr>
<tr>
<td>L1 recombinant bacteria</td>
<td>Low cost of production and administration if mucosal</td>
<td>Regulatory issues with GM organisms; safety/immunogenicity uncertain</td>
<td>[22–26]</td>
</tr>
<tr>
<td>L1 recombinant virus</td>
<td>Lower cost of administration if mucosal; lower cost of production?</td>
<td>Regulatory issues GM organisms; safety/immunogenicity uncertain</td>
<td>[18–20]</td>
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<tr>
<td>Chimeric VLPs</td>
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<td>[28]</td>
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<tr>
<td>VLPs combined with a therapeutic HPV vaccines</td>
<td>Combined prophylactic/therapeutic efficacy; earlier benefits</td>
<td>Efficacy of current therapeutic vaccines limited; interaction with VLPs uncertain</td>
<td>[29]</td>
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<tr>
<td>L2 protein or peptide</td>
<td>Induction of broadly type cross-neutralizing antibodies; lower production costs</td>
<td>Lower titers of neutralizing antibodies than VLPs</td>
<td>[27]</td>
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</tbody>
</table>

VLP (virus-like particle); sIgA (secretory immunoglobulin A); GM (granulocyte macrophage)
purification of VLPs from plants with this level of production would therefore be a difficult proposition. However, plant expression is an area of active research, and there is an encouraging unpublished finding that higher levels of L1 (>10% of total soluble protein) can be produced by directing L1 expressed from a “humanized” L1 gene to chloroplasts (E.P. Rybicki, personal communication, May 24, 2006).

Perhaps the simplest approaches for making a significant impact on delivery would be to remove the need for a cold chain or to reduce the number of doses required for the existing L1 VLP vaccines. One strategy would be to lyophilize the vaccine to a powder that could be reconstituted on site. Recovery of the conformation-dependent epitopes that induce neutralizing antibodies will be the critical outcome to monitor when developing this approach. Papillomavirus virions are resistant to desiccation, so there is reason to hope that VLPs might also retain their native conformation after lyophilization [5]. An alternative approach would be to add a protein-stabilizing agent such as the non-ionic block co-polymer Pluronic [6]. This compound has the interesting property of reverse thermal gelation: it is liquid at ambient temperature but forms a gel at body temperature. Therefore, in addition to heat stabilization, this approach might also decrease the number of doses required by providing a sustained release depot effect after injection. Alternatively, microsphere approaches might be tried for slow release of VLPs [7].

Needle-free mucosal vaccination might substantially reduce the cost of VLP vaccine delivery and the complexity of vaccination programs. For instance, it might facilitate school-based vaccination programs of early adolescents, whereas needle-based programs are more likely to require clinic visits. Mucosal vaccination might also prevent infectious disease transmission that can occur through improper parenteral immunization practices and reuse of needles. Mucosal delivery, unlike parenteral injection, would induce, in addition to serum immunoglobulin G (IgG), secretory IgA (sIgA). In theory, this added arm of the immune response might increase vaccine efficacy or duration of protection by compensating for the decrease in VLP-specific IgG during ovulation [8]. However, it is clear from the clinical trials to date that specific induction of VLP sIgA is not required for very strong protection from cervical infection and dysplasia, at least in the short term. Therefore, while the potential value of mucosal vaccination for implementation is clear, the added value for protection is uncertain.

The central challenges for mucosal delivery are minimizing the dose required and maximizing the consistency of response. The immunogenicity of VLPs after mucosal delivery has been examined in a clinical trial. In a small pilot study, half of the women receiving two 50-µg doses, and all the women receiving two 250-µg doses, of HPV-16 L1 VLPs in aqueous solution to the upper respiratory tract (using a cold ultrasound nebulizer) produced neutralizing antibody responses that were similar to those produced by two intramuscular injections of 50 µg [9]. These are encouraging results given that VLP delivery to the lower airways was unlikely to have been optimal. Devices exist for varying the droplet size and pressure for respiratory delivery and these could be evaluated to optimize the consistency and strength of antibody induction at doses similar to those used for parenteral injection. Lyophilized VLPs in a powder formulation might be an alternative to aqueous droplets for mucosal delivery. This would overcome the need for a cold chain as well. Powder formulations have been developed for aerosol delivery of the measles vaccine [10]. One interesting approach might be to combine the VLPs with an anion polysaccharide vehicle that changes from a powder to a mucosal gel after delivery (www.delsite.com). Added retention might increase immunogenicity after aerosol or nasal delivery. L1 capsomers are immunogenic after nasal delivery in mice, but have not been tested in humans [11].

Oral delivery of purified VLPs can be immunogenic in mice, but it takes approximately 100-fold more VLPs to induce a strong antibody response compared to parenteral injection. This high dose requirement would almost certainly make oral delivery of purified VLPs prohibitively expensive. This inefficiency may be partially overcome by adding a mucosal adjuvant, such as mutant forms of LT or CpG oligonucleotides [12], but this strategy would further add to the cost of the vaccine and could raise safety concerns. An oral immunization approach might be practical if inexpensive crude extracts of yeast or a plant expressing L1 VLPs were used. Oral immunization using crude L1-containing plant or yeast (Saccharomyces cerevisiae) extracts has been attempted in mice, but the extracts were poorly immunogenic, presumably because of their low L1 content [13,14]. However, Saccharomyces cerevisiae extracts, such as those used to produce the Merck vaccine, presumably contain higher concentrations of VLPs. Extracts of this baker’s/brewer’s yeast are commonly taken as vitamin supplements, and so L1 recombinant yeast extracts might be a widely acceptable and inexpensive oral vaccine provided they can consistently induce strong immune responses. It would seem well worth the effort to examine this possibility in clinical trials.

Intravaginal vaccination was successful at inducing both systemic IgG and mucosal IgA in mice if high dose VLPs (100 µg) were formulated in Pluronic containing the mucosadhesive polymer, polyethylene oxide plus cholera toxin as a mucosal adjuvant [15]. However, intravaginal administration to early adolescent girls would likely be unacceptable to many parents. It is unlikely that this route of administration would be practical for primary immunization, although it might be considered for a later booster dose, should it be required.

2.2. L1 genetic immunization

Genetic immunization with naked DNA has the theoretical advantage of simple production. However, it would not overcome the requirement for multiple parenteral injections. Naked DNA vaccination with L1 expression plasmids can
induce neutralizing antibody responses in animal models, and responses are increased if codon-modified genes are used to increase expression [16]. However, this approach has several potential liabilities. First, antibody responses to other DNA vaccines have been disappointing in humans [17]. Second, it is unclear whether plasmids expressing different L1 genes can be co-injected. Co-expression of the L1 of more than one type in a cell may lead to co-assembly of hybrid VLPs that fail to efficiently display the neutralizing epitopes of any of the types. Third, the long-term risk of promoter insertion mutagenesis by the injected DNA is difficult to evaluate. Individual risk may be very small, but cumulative risk would be magnified by the administration of millions of doses of a prophylactic vaccine to healthy young people, the vast majority of whom are not destined to acquire an HPV-induced cancer. Regulatory approval for a DNA-based vaccine may therefore be difficult, particularly in settings where the current protein-based vaccine is a practical alternative. However, the risk/benefit equation might be quite different in a setting with inadequate resources for either screening or the current vaccines.

Transfer of the genes for target antigens can be facilitated by incorporating them into recombinant viruses. Viral vectors could not only deliver the L1 gene more efficiently, but in many cases would be compatible with mucosal delivery. HPV-16 L1 recombinants of two DNA viruses, adenovirus 5 [18] and Adeno-associated virus (AAV) [19], have been developed as prophylactic vaccine candidates. Encouragingly, the AAV vector produced high levels of VLP antibodies after a single injection in mice, and the titers could be enhanced by co-injection with a recombinant adenovirus expressing granulocyte macrophage colony stimulating factor (GM-CSF). RNA viruses without a DNA intermediate in their life cycle would not have the associated issue of promoter insertion mutagenesis. It is therefore interesting that a single injection of a cottontail rabbit papillomavirus (CRPV) L1 recombinant vesicular stomatitis virus (VSV, a negative-strand RNA rhabdovirus) induced complete protection against high dose experimental CRPV challenge of domestic rabbits [20]. There are also several other attractive RNA viral vectors, including alphavirus vectors, which are currently under investigation for other antigens, mostly as therapeutic vaccines [21]. Generating viruses in mammalian cells is inherently expensive and so the overall production cost could be high, depending upon the titer of the stocks produced, the amount needed to generate a potent immune response, and the number of immunizations required. The other important concern with viral vectored vaccines for general distribution is safety in immunocompromised individuals. This could vary considerably depending on the vector.

2.3. Live recombinant bacteria

Live bacteria vaccines are potentially simple and inexpensive to manufacture. They also can be relatively inexpensive to deliver if administered mucosally. Replication-competent bacterial vectors may pose less of a threat to immunocompromised vaccinees than viral vectors because breakout infections can be effectively treated with inexpensive antibiotics. A concern during development of recombinant live bacteria vaccines, and also live viral vaccines, is environmental spread. Therefore, initial studies often require strict containment of vaccinees, initially to monitor shedding of infectious recombinant microbes. This can substantially increase the cost and logistics of early-phase trials. Four distinct L1 recombinant bacteria vaccines have been developed and tested for immunogenicity in animal models. L1 recombinant bacille Calmette–Guerin (BCG) produced relatively weak antibody response in mice [22]. However, in rabbits, three subcutaneous injections of 10^7 CRPV L1 recombinant BCG protected the animals from CRPV challenge, although L1 antibody titers were lower than after VLP injection [23]. Recombinant Lactobacillus casei generated VLP antibody responses after subcutaneous injection, but mucosal immunization has not yet been reported [24]. An attenuated Shigella flexineri strain expressing L1 was recently evaluated for immunogenicity in a guinea pig conjunctiva inoculation model [25]. IgG and IgA VLP antibody responses were detected in serum, intestinal lavage, and vaginal lavage, and the serum antibodies were shown to inhibit VLP hemagglutination of mouse red blood cells, a proxy for virus neutralization. Finally, L1 recombinant clones of attenuated Salmonella enterica serovar Typhimurium and Typhi strains were shown to induce strong neutralizing antibody responses after a single intranasal or oral application in mice [26]. L1 plasmid stability and immunogenicity was substantially increased by using a codon-modified L1 that matched enteric bacteria codon usage. Significantly, a clone of the attenuated Ty21 strain Vivotif expressing L1 induced a strong neutralizing antibody response. Ty21 (Vivotif) has an excellent safety record, based on its use as an oral vaccine to prevent typhoid fever in tens of millions of individuals worldwide. Therefore, this clone could potentially serve as a combined HPV/typhoid fever vaccine. A phase I clinical trial of this vaccine seems warranted.

2.4. L2 minor virion protein

Prophylactic vaccines based on the L2 minor capsid protein are also under development. The neutralizing antibody response to L1 or L1/L2 VLPs is type-restricted, such that cross-neutralization in in vitro assays is only detected for closely related HPV types such as HPV-18 and -45. Even then, cross-neutralization titers are much lower than titers against the homologous type. In contrast, L2 can induce very broadly cross neutralizing antibodies, when taken out of the VLP context, as measured using mouse and rabbit sera in in vitro pseudovirus-based assays [27]. The broadly cross-neutralizing epitopes are presumably buried or subdominant when L2 is assembled into capsids. Remarkably, the highest cross-neutralizing titers against a diverse group of genital HPVs, including 6, 16, 18, and 31 have been generated by
the amino-terminal peptide of BPV1 L2, a distantly related bovine cutaneous type. These results raise the possibility that a monovalent vaccine could protect against a broad range of genital types. The same antibodies also prevented HPV-5 and CRPV infection, which are human and rabbit cutaneous types, respectively. If cross-protection were to extend to the cutaneous HPVs that cause common and plantar warts, then it would provide an impetus to vaccinate infants to prevent skin warts. Even if an adolescent booster was required, this vaccination scheme might remove much of the sexually transmitted infection stigma associated with the current vaccines. In addition to broad cross-type protection, L2 polypeptides have the advantage that they could be produced in E. coli, and therefore manufacturing would be relatively inexpensive compared with VLPs. The potential problem with the L2 vaccines is that the homologous and cross-neutralizing titers that current candidates generate are much lower than the homologous titers generated by L1 VLPs, so it is unclear whether they would match the outstanding efficacy of the VLP vaccines. Additional preclinical work may be needed to increase the immunogenicity of L2-based vaccines before these vaccines can be considered promising candidates for clinical trials.

2.5. Combined prophylactic/therapeutic vaccines

A vaccine that could induce regression of established HPV lesions, in addition to preventing them, could help to protect this generation of women from cervical cancer, in addition to providing maximal protection for the next. The most advanced candidates for this type of vaccine are chimeric VLPs which incorporate peptides of early proteins as fusions of L1 or L2. Chimeric VLPs induced both neutralizing antibodies to L1 and T-cell responses to the inserted polypeptide in mouse studies [28]. A HPV L1-E7 chimeric VLP was tested in a Medigene-sponsored, randomized, placebo-controlled clinical trial targeting HPV-16-associated high-grade cervical dysplasia. T-cell responses were induced in most vaccinees and there was a trend toward increased clinical responses in the vaccinees compared to controls, although clinical responses did not correlate with T-cell responses in vitro [29].

The only other combined vaccine to be tested in clinical trials was Cantab/Xenova’s TA-CIN, which consists of an HPV-16 L2-E6-E7 fusion protein. The safety and T-cell responses to this vaccine, administered without adjuvant, were established in a phase-I trial [30]. The trial was conducted before the ability of L2 to induce broadly cross-neutralizing antibodies was known, and the neutralizing activity of vaccinees sera was only recently examined. Immune sera from initially HPV-16 and -18 seronegative vaccinees neutralized both HPV-16 and -18 pseudovirions in in vitro assays, although the titers were relatively low, as expected for a simple protein vaccine injected without adjuvant [31]. The therapeutic efficacy of this vaccine has been tested only as part of a heterologous prime/boost strategy with a recombinant vaccinia virus that expresses E6 and E7 from HPV-16 and -18. While T-cell responses were consistently detected, clinical responses were not.

The therapeutic results of the above trials are in keeping with the results of clinical trials involving strictly therapeutic HPV vaccines and patients with persistent HPV lesions [32]. Therefore, the development of a combined vaccine may need to await the development of a consistently effective therapeutic vaccine. It might then be possible to combine an effective therapeutic vaccine with the VLPs, especially if it were protein-based. VLPs might even provide a beneficial adjuvant effect in that they activate professional antigen-presenting cells and induce a potent T-helper response in humans [33]. However, reconciling dosing, scheduling, and adjuvants to maximize both T- and B-cell responses in the combined vaccine may prove challenging.

3. Is there a realistic development/commercialization path?

There are a number of hurdles to the successful manufacture and commercialization of a novel second generation HPV vaccine. There are also several reasons why development may be facilitated by the success of the first-generation vaccines. It will be difficult to conduct placebo-controlled trials once there is a commercial vaccine. However, the demonstration, for the first time, that a prophylactic vaccine against a sexually transmitted infection can be highly effective could encourage wider corporate interest in this prevention strategy. The current efficacy trials should formally establish protection from persistent infection as a surrogate for protection from high-grade cervical dysplasia, thereby raising the possibility that the former can be used as the primary end point in a phase III trial. A trial with a virological endpoint would require fewer women and/or a shorter duration. It is also possible that neutralizing antibody titers will be found to be an immune correlate of protection, which would be very helpful in guiding early-phase clinical development of alternative vaccine approaches.

It may prove difficult to attract sufficient development funding once an effective HPV vaccine is commercially available. Public funding sources in richer countries might be difficult to obtain if there is the perception that the problem is already solved for these countries. Private foundations may choose the surer bet of purchasing and distributing the existing vaccine rather than the more speculative investment in alternative approaches, even if they could potentially reach more women in the long run. Corporate interest may well be muted because intellectual property constraints will make it difficult, if not impossible, for competitive commercialization of a VLP-based second generation vaccine in most of the major industrialized countries. Merck and GSK have signed a financial agreement to cross-license the competing VLP/L1 patents and patent applications of the major parties, including the United States government. The purpose is to assure
unimpeded market access for the two companies and exclude other potential manufacturers. Given their enormous investment in the current vaccines, it is unlikely that Merck and GSK will be interested in the development of substantially different second generation vaccines.

If a substantially different second generation vaccine is commercially developed in the next twenty years, it probably could be marketed only in countries in which the dominant VLP/L1 patent applications were not initially filed, the same countries in which the majority of cervical cancer cases occur [34]. An exception to this restriction would be L2-based vaccines, as this approach is not included in the intellectual property cross-licensed in the Merck/GSK agreement. While markets excluding Europe, North America, and Japan may be insufficient incentives for commitments from the largest pharmaceutical companies, they may be sufficient for regional manufacturers in Asia and Latin America. Regional manufacturers produce many of the vaccines currently in use. It may be worthwhile to inform these companies of the opportunities that might exist for developing second generation HPV vaccines, or manufacturing the current VLP vaccines, and to facilitate transfer of technology and clinical trial expertise to them.

4. Conclusions

It will almost certainly be difficult to develop sustainable broad-coverage vaccination programs in many parts of the world with high rates of cervical cancer if they are based on the current L1 VLP candidates. These vaccines are in many ways analogous to the hepatitis B vaccine, which is also a purified virus-like particle that requires three intramuscular injections. That vaccine remains under utilized in many parts of the world, despite 20 years of effort in implementation and a more than 100-fold reduction in price in the developing world (mostly due to production in developing countries) [35]. Several of the strategies currently being developed have the potential to significantly increase access of poorer women to an effective HPV vaccine. However, if a substantially different second generation vaccine becomes a reality, it will likely require continued public-sector support of preclinical and early-phase clinical development to identify the most attractive candidate(s) for efficacy trials; such trials would probably require corporate sponsorship. In our opinion, it would be a mistake to look only to the large vaccine manufacturers in the most developed countries for production of a second generation vaccine. Because they would likely be less constrained by intellectual property issues, developing country manufacturers might see more opportunities in commercial development of an HPV vaccine, especially if it was less technically demanding to mass produce and deliver than the current VLP vaccines. However, it would also be a mistake to delay introduction of current vaccines in the hope that a better one might be forthcoming. None of the candidates discussed above are ready for clinical efficacy trials, and even if they were, their chance of success would be uncertain and the time line for commercialization relatively long.

Disclosed potential conflict of interest

JTS: Patents (U.S. government owned and licensed to GlaxoSmithKline and Merck and Co., Inc.)
DN: Patents (Indian Immunological Ltd.)

References


