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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/commericialization 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.

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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 straight forward 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

Vaccine	Potential advantages	Potential limitations	Ref.
Additional VLP types (HPV-31, -45, -33, -52, etc.)	Established technology	Increased cost, modest increase in protection from cervical cancer	[1]
Heat stabilization of VLPs	Decreased implementation costs	Unproven technology for HPV VLPs	[6,10]
Slow release formulation	Lower cost of administration, if fewer injections required	Unproven technology for HPV VLPs	[7]
Upper respiratory tract delivery of purified VLPs	Needle free delivery; Induction of sIgA; lower cost of implementation?	Consistency of immune response? Safety?	[9]
Oral delivery of VLP in crude plant or yeast extract	Low cost production and administration; induction of sIgA	Low level expression in plants; low immunogenicity in animal models	[14,16]
L1 DNA	Standard production procedures	Less immunogenic than VLPs? Unknown oncogenic potential of injected vectors	[17]
L1 pentameric subunits	Lower cost of production (made in bacteria)	Less immunogenic than VLPs?	[3]
L1 recombinant bacteria	Low cost of production and administration if mucosal	Regulatory issues with GM organisms; safety/immunogenicity uncertain	[22–26]
L1 recombinant virus	Lower cost of administration if mucosal; lower cost of production?	Regulatory issues GM organisms; safety/immunogenicity uncertain	[18–20]
Chimeric VLPs	Combined prophylactic/therapeutic efficacy; earlier benefits	Modest therapeutic effect in a clinical trial	[28]
VLPs combined with a therapeutic HPV vaccines	Combined prophylactic/therapeutic efficacy; earlier benefits	Efficacy of current therapeutic vaccines limited; interaction with VLPs uncertain	[29]
L2 protein or peptide	Induction of broadly type cross-neutralizing antibodies; lower production costs	Lower titers of neutralizing antibodies than VLPs	[27]

VLP (virus-like particle); sIgA (secretory immunoglobulin A); GM (granulocyte macrophage)