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Opportunities to improve immune-based prevention of HPV-associated cancers

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ABSTRACT

Immunization of adolescent girls with VLP vaccines, made of L1 proteins from the most medically significant high risk HPV types, is a major strategy for prevention of cervical cancer plus other HPV-associated cancers. Maximal population impact, including through herd immunity, requires high vaccination coverage. However, protection of unvaccinated women requires secondary prevention through cytology screening. Unfortunately in countries with the highest incidence/mortality due to cervical cancer HPV vaccination (or cytology screening) is not sufficiently available. Vaccination programme costs and a lack of accessibility of the populations for immunization remain significant hurdles. Several approaches could increase effective implementation of HPV vaccination. 1) Use of a single immunization of the current VLP vaccines. 2) Vaccination bundled with other paediatric vaccines with lower dosage to facilitate delivery, improve coverage and reduce costs through established logistics. 3) Local manufacture with lower cost systems (e.g. bacteria) for VLP or capsomer based vaccine production and utilization of additional protective epitopes (e.g L2) for increasing breadth of protection. However, all the latter need appropriate clinical validation. Gender neutral vaccination and extending routine vaccination strategies to women up to age 30 years in combination with at least one HPV screening test can also hasten impact on cancer incidence.

1. Introduction

Typical preventative vaccines act to limit rather than stop initial natural infection. Such contained infection elicits early and efficacious immune memory responses in the exposed vaccinated individual to prevent the development of clinical disease [1]. Because of the slow infectious process and spatially-separated productive virus life cycle of HPV, the VLP vaccines may differ from this paradigm in that L1-specific antibody can fully neutralize the inoculum to confer sterilizing immunity against the vaccine related types.

The available 2v- and 4v-vaccines both target the HPV 16 and 18 types, which account for about 70% of cervical cancers and 90% of HPV-related cancers at other sites, and the 4v-vaccine also contains VLPs for HPV 6/11, which cause benign genital warts. However, cross protection against other 16/18 related oncogenic HPV types is most evident with the 2v-vaccine, and the levels of protection against high grade cervical intraepithelial neoplasia in clinical trials was about 93%. Trial data on a 9v-vaccine (4v-vaccine plus VLPs for HPV types 31, 33, 45, 52, 58) documented a similar level of protection against high grade disease. Time will tell if this robust efficacy mediated by type-specific and/or via cross protection show similar longevity. None of these VLP vaccines provide comprehensive protection against all oncogenic types, but they target the most medically impactful in cancer worldwide. Prevention of cervical cancer (~0.5 million cases per annum), accounting 90% of HPV associated cancers in females, is a principle goal although there will undoubtedly be an impact on other HPV-associated anogenital and oropharyngeal cancers. With the focus on cervical cancer, the general vaccination strategy has been the immunization of adolescent girls twice 6 months apart. The available evidence suggests that the levels of neutralizing antibodies may provide life long protection [2]. Older individuals may also benefit from VLP vaccination as the majority are not infected, and for those already exposed there are obviously multiple additional HPV types where protective immunity would be valuable.

Abbreviations: VLP, virus-like-protein; L, late protein; high risk, hr; bivalent, 2v; quadrivalent, 4v; 9v, nonavalent; AS04, adjuvant system 04; E, early protein; GAVI, Global alliance for Vaccines and Immunization; BEVS, baculovirus expression vector system; CIN, cervical intraepithelial neoplasia

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Table 1
Summary of prophylactic HPV L1 VLP-based vaccines in advanced phase testing. For recent indexing of studies see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5774129/.

L1 VLP types	System	Adjuvant	Status/Name	Party
HPV16/18	BEVS	Aluminium hydroxide + MPL	Licensed/Cervarix	GSK
HPV6/11/16/18	*S. cerevisiae*	AHSS	Licensed/Gardasil	Merck
HPV6/11/16/18/31/33/45/52/58	*S. cerevisiae*	AHSS	Licensed/Gardasil9	Merck
HPV16/18	*E. coli*	Aluminium hydroxide	Phase III	Innovax, Xiamen
HPV6/11	*E. coli*	Aluminium hydroxide	Phase II	Innovax, Xiamen
HPV16/18	P. pastoralis	Alum	Phase III	Zerun/Walvax
HPV6/11/16/18	H. polymorpha	Aluminium hydroxide	Phase II/III	Serum Institute of India

2. Limitations of current HPV vaccination

A key aspect of maximizing population protection is herd immunity for which vaccination coverage needs to be at least 70–80%. A gender-neutral strategy can enhance the effectiveness of HPV vaccination for cross-protected HPV types with low to moderate coverage. Indeed, high coverage in males might be the key to a substantial public health benefit against anogential and oropharygeal cancers of men, and indirectly in unvaccinated females [3]. However, there is a considerable lag time of > 20 years for approaching the full impact on cervical cancer rates even with very efficient national HPV vaccination programs. Such programs are usually school based although this not be suitable in the context of the social structures of all countries [4]. HPV-FASTER aims to extend routine vaccination in women up to the age of 30 which in conjunction with a least HPV screening test at older ages has been modelled and predicts an accelerated cervical cancer reduction [5]. Secondary prevention through organized cervical screening will remain central to reduction in cervical cancer rates even in developed countries during this phase because the vaccines do not impact prevalent infection and disease [6]. While many women from high-income and upper-middle-income countries have or are being vaccinated against HPV, women from countries afflicted by the highest incidence and mortality of disease remain largely unreached [7]. Unfortunately, sufficiently organized screening/treatment programmes are also not widely available where there are the highest HPV associated cancer rates. While routine vaccination can provide for comprehensive protection against HPV associated disease, accessibility of populations for vaccination (school, gynaecologist, other), the lack of infrastructure in non-developed countries and the prioritisation of funding for this purpose (and competition for resources for cervical screening) remain imposing barriers. Bundling of HPV vaccine with other childhood vaccines might help address some of these challenges, given evidence of durable immunity.

3. Strategies for increasing HPV vaccination impact

There are inherent limitations to the current VLP type vaccines as they do not protect against all hr HPV types, require a cold chain and are relatively expensive to manufacture. Extending the type specific coverage by adding more VLP types may not be sufficiently more efficacious or cost effective; for example, in terms of cancer prevention the 2v Cervarix vaccine adjuvanted with AS04 could possibly provide a similar impact on rates of cervical cancer as the 9v Gardasil, although the latter also targets benign genital warts. Only time will tell whether the cross protection has sufficient longevity. While VLP HPV vaccines are not designed to be therapeutic 9v Gardasil is being examined in a phase 3 study (NCT03848039) as adjuvant treatment after lesion excision to prevent recurrence or guard against another HPV type infection [8].

There are observations that indicate that a single immunization with an HPV VLP vaccine can provide efficacious protection [9]. This may result from the nature of the repetitive VLP protein structure, an optimal size for trafficking to the lymph nodes and subsequent acquisition by follicular dendritic cells with an optional spacing of the epitopes to engage the B cell receptors. These features provide for the generation of a pool of long-lived plasma cells able to provide long-term protection [10]. If single dose protection is validated in on-going clinical trials this could improve vaccination coverage, although the longevity of protection, especially if delivered in a paediatric setting, and the impact on cross-protection will also need careful assessment.

While sufficient herd immunity can impact HPV-associated cancers in males there are around 34,000 cases per annum including those involving the oropharynx, which are 2.5 fold more prevalent than in females. Increasing the vaccination of boys before first exposure can therefore also impact disease rates and promote herd immunity [11].

In the history of successful implementation of vaccination, successive developments have provided for increased range of specificity, improved coverage and logistics underwritten by improved cost effectiveness. Such potential opportunities are being investigated through different VLP production (e.g. in bacteria or the use of capsomere subunits) with selective adjuvantation and local manufacture. Extending the protection to more hr HPV types and beyond may also be achieved by increasing valency, or inclusion of the broadly cross-reactive and protective epitopes (e.g. RG-1) of the amino-terminal of L2 [2]. Table 1 summarizes the current VLP based vaccines that are in advanced clinical trials.

Sufficiency of population coverage is central to vaccine impact, and this remains the most formable obstacle to worldwide elimination of cervical cancer. While approaching this goal may eventually be achievable in countries with both high coverage cervical screening and vaccination (usually school based) programmes [Brotherton & Bloem; Canfell both this issue], this remains unfeasible in the poorest countries with inadequate infrastructure for repeat vaccination of young adults. By contrast, paediatric immunization against a variety of pathogens has achieved high levels in global routine vaccination coverage [12]. If HPV vaccination could be given as a single dose in infants, or bundled with other standard multi-dose childhood immunizations, the prospects for delivering substantial worldwide protection would be significantly improved (see Table 2A, B). This will require the appropriate bridging, dose-ranging and safety studies in infants and very long term follow up. Lower paediatric dosages may provide cost savings in addition to improved logistics for administration. Current generations would continue to rely on adolescent vaccination and screening in the meantime. Resource poor countries with no HPV vaccination or screening are those with the greatest need and the most to gain, and GAVI is one tool for helping to extend the benefits of HPV vaccination but this demands commitment from governments to sufficiently prioritize cervical cancer prevention.

4. Therapeutic vaccines

HPV therapeutic vaccine strategies have mostly focused on generating specific effector T-cells against the constitutive and functionally obligate expression of E6 and/or E7 oncogenes. Recently, several clinical trials of therapeutic HPV oncogene vaccines tested in patients with HPV-associated high-grade anogenital lesions have shown encouraging

Table 2
Speculations on the impacts of early versus late childhood vaccination against HPV.

Potential Benefits	Hurdles to climb	Best outcome	Other impacts	Therapeutic considerations
A: Current adolescent female multi-dose HPV VLP vaccination primarily aimed at preventing cervical & other anogenital neoplasia				
There is a validated vaccination procedure that with sufficient population coverage can impact significantly on HPV associated disease. Schools based vaccination is so far the most successful at achieving high coverage. Vaccination of boys, certain special risk populations & older women can accelerate the reduction of disease risk in wider populations. Herd immunity improves real-world effectiveness. Logistic efficiency & overall coverage could be helped by establishing that a single dose can provide efficacious protection.	Coverage in populations most at risk & who would benefit most is likely to remain at low levels. Targeting adolescent girls in many countries has additional cultural & access difficulties. There is no systematic worldwide implement-ation of vaccination of special risk populations, boys or older women. Managing limited resources in trade-off between immediate benefits of screening & longer-term impact of vaccination. In long term, provision of a cheaper vaccine with less cold chain dependence & maximal protection against hr types is likely to impact on vaccination success. Local & low cost production systems (bacterial) for of L1 VLPs or capsomers, &/or incorporating broadly cross protective L2 epitopes may provide significant cost reductions & breadth of protection respectively. Understanding the precise immune correlates of protection would be of great value in design improvements & allow define successful immunized. All these need to validated by clinical trials.	A significant reduction in HPV associated cancers in countries that can deliver & sustain sufficient population vaccination coverage is predicted. Herd immunity will provide some level of protection to the unimmunized populations & even high-risk populations (HIV+, organ transplant etc). HPV vaccination of adolescent girls will directly impact on established cervical screening programs. This is likely to result in an increased screening interval & the use of primary HPV testing. In developed countries it will take a long time before screening can be abandoned, if ever, but the overall costs will diminish in the long term.	Those countries with effective national cervical screening programs will continue to provide this service because of the prevalence of HPV infections in unvaccinated women. Current algorithms plan to exploit the negative predictive value of hr HPV testing to reduce the number of lifetime screens. HPV + individuals will be referred for cytology & treated surgically if necessary. There will be a significant number of individuals who present as HPV + but cytology negative & if this is sustained then they will be referred for colposcopy but that may not identify any lesion.	Current VLP vaccines are not designed to be therapeutic. For those in developed countries prospects are improving with new treatments for cervical neoplasia in development. Recent data on the efficacy of E6/E7 therapeutic HPV vaccines in treating high grade CIN suggest that with some further improvements this might be an alternative to surgical treatment. Indeed those with HPV + tests following screening could potentially also be treated by such a therapeutic vaccination. Overt cancer treatment using immunotherapy approaches including vaccines is under intense investigation & is likely to provide improved options for patients in some developed countries
B: Universal paediatric multi (low) dose HPV vaccination for cancer prevention				
Increased coverage worldwide using established logistics. HPV vaccines might be bundled with other paediatric vaccines (e.g. Hepatitis B vaccine) to facilitate delivery & reduce costs. Targets all genders & separates vaccination from sexual debut. Could protect against childhood exposure to hr HPV. Current VLP type vaccines could be tested with lower 'paediatric' doses to provide product cost savings equivalent to one dose adult vaccination.	Key issue is will immunity last for an additional decade? A single booster could be used in adolescence if needed. In the long term, provision of a cheaper vaccine with less cold chain dependence & maximal protection against hr types is likely to impact on vaccination success. Characteristics of a useful paediatric vaccine may also seek to include low risk HPV types. All improvements need to be validated by clinical trials. Demonstration will initially depend on bridging studies for immunogenicity and longevity of relevant immune responses Impact of vaccines on cancer rates delayed by a further decade (although the missed generations could be vaccinated as adolescents)	Potential to provide maximum coverage & thus protection worldwide against hr HPV associated cancers with lowest implementation costs if the vaccines are bundled with existing paediatric vaccines & delivered with lower doses of antigen	In the non-developed world, it could provide for a focus of resources on primary compared to secondary prevention. The latter may remain effectively undeliverable for significant numbers in the poorest countries In the developed world. This type of vaccine could increase/sustain vaccination population coverage and be a more cost effective way to save more lives	This type of vaccination is not designed to be therapeutic. In the non-developed world there are generally insufficient resources to diagnose & treat even early premalignant lesions. Lack of early diagnosis & of any significant capacity to treat overt cancer patients condemns many individuals to a very poor prognosis.

clinical impact [13]. In the natural history of hr HPV infection, E6/E7 oncogene expression drives immune escape pathways that alter innate responses of immune and other lesion-associated cells which combine to blunt adaptive immunity, enabling the persistence and subsequent neoplastic transformation of HPV lesions [14], (Smola this issue). Thus further optimization will be required to improve efficacy. This is in progress through vaccine immunogen design (e.g. addition of E1/E2), co-administration with adjuvants/cytokines/chemokines (to maximize antigen presentation/T cell activation/migration) and optimization of the delivery vehicles [10]. However, the influences of local and systemic immune suppressive factors remain significant hurdles to efficacy, especially in more advanced disease. Novel strategies for targeting such immunosuppressive components, including a reevaluation of the functions of standard of care treatments in this context, are being investigated to provide for the maximum impact in tandem with therapeutic HPV vaccination [15].

Such vaccines would be particularly impactful for cancer patients and also when combined with screening and HPV testing. A combination of the remarkably successful prophylactic HPV vaccines with a therapeutic component remains an attractive goal, especially for implementation in sexually experienced populations, as this could achieve reductions in HPV-associated cancers sooner.

Conflicts of interest

RBSR is a member of Papivax LLC, has Papivax Biotech Inc. stock options and is a member of Papivax Biotech Inc.'s Scientific Advisory Board. Under a license agreement between Bravovax and the Johns Hopkins University, RBSR is entitled to distributions of payments associated with an L2-based invention described in this review. Under a license agreement between PathoVax LLC and the Johns Hopkins University, RBSR is entitled to distributions of payments associated with an invention described in this review. RBSR also owns equity in PathoVax LLC and is a member of its scientific advisory board. These arrangements have been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies.

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References

[1] A.L. Cunningham, N. Garçon, O. Leo, L.R. Friedland, R. Strugnell, B. Laupèze, M. Doherty, P. Stern, Vaccine development: from concept to early clinical testing, Vaccine 34 (2016) 6655–6664 https://doi: 10.1016/j.vaccine.2016.10.016.
[2] R.B.S. Roden, P.L. Stern, Opportunities and challenges for human papillomavirus vaccination in cancer, Nat. Rev. Canc. 18 (2018) 240–254 https://doi: 10.1038/nrc.2018.13.
[3] M. Lehtinen, A. Söderlund-Strand, S. Vänskä, T. Luostarinen, T. Eriksson, et al., Impact of gender-neutral or girls-only vaccination against human papillomavirus-Results of a community-randomized clinical trial (I), Int. J. Cancer 142 (2018) 949–958, https://doi.org/10.1002/ijc.31119.
[4] J.M.L. Brotherton, P.N. Bloem, Population-based HPV vaccination programmes are safe and effective: 2017 update and the impetus for achieving better global coverage, Best Pract. Res. Clin. Obstet. Gynaecol. 47 (2018) 42–58, https://doi.org/10.1016/j.bpobgyn.2017.08.010.
[5] F.X. Bosch, C. Robles, M. Díaz, M. Arbyn, I. Baussano, et al., HPV-FASTER: broadening the scope for prevention of HPV-related cancer, Nat. Rev. Clin. Oncol. 13 (2) (2016) 119–132, https://doi.org/10.1038/nrclinonc.2015.146.
[6] A. Castanon, R. Landy, F. Pesola, P. Windridge, P. Sasieni, Prediction of cervical cancer incidence in England, UK up to 2040, under four scenarios: a modeling study, Lancet Public Health 3 (2018) e34–43.
[7] L. Bruni, M. Diaz, L. Barrionuevo-Rosas, R. Herrero, F. Bray, F.X. Bosch, S. de Sanjosé, X. Castellsagué, Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis, Lancet Glob. Health. 4 (2016) e453–e463 https://doi: 10.1016/S2214-109X(16)30099-7.
[8] W.D. Kang, H.S. Choi, S.M. Kim, Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2-3)? Gynecol. Oncol. 130 (2) (2013) 264–268, https://doi.org/10.1016/j.ygyno.2013.04.050.
[9] A.R. Kreimer, R. Herrero, J.H. Sampson, C. Porras, D.R. Lowy, et al., Evidence for single dose protection by the bivalent HPV vaccine-Review of the Costa Rica HPV vaccine trial and future research studies, Vaccine 36 (2018) 4774–4782.
[10] D.R. Lowy, HPV vaccination to prevent cervical cancer and other HPV-associated disease: from basic science to effective interventions, J. Clin. Investig. 126 (2016) 5–11 https://doi: 10.1172/JCI85446.
[11] S.L. Ranjeva, E.B. Baskerville, V. Dukic, L.L. Villa, E. Lazcano-Ponce, A.R. Giuliano, G. Dwyer, S. Cobey, Recurring infection with ecologically distinct HPV types can explain high prevalence and diversity, Proc. Natl. Acad. Sci. U.S.A. 114 (2017) 13573–13578 https://doi: 10.1073/pnas.1714712114.
[12] L.R. Feldstein, S. Mariat, M. Gacic-Dobo, M.S. Diallo, L.M. Conklin, A.S. Walace, Global routine vaccination coverage, MMWR (Morb. Mortal. Wkly. Rep.) 66 (2017) 1252–1255.
[13] A. Yang, E. Farmer, J. Lin, T.C. Wu, C.F. Hung, The current state of therapeutic and T cell-based vaccines against human papillomaviruses, Virus Res. 231 (2017) 148–165 https://doi: 10.1016/j.virusres.2016.12.002.
[14] S. Smola, C. Trimble, P.L. Stern, Human papillomavirus-driven immune deviation: challenge and novel opportunity for immunotherapy, Ther. Adv. Vaccines. 5 (2017) 69–82 https://doi: 10.1177/2051013617717914.
[15] A.G. Dalgleish, P.L. Stern, The failure of radical treatments to cure cancer: can less deliver more? Ther. Adv. Vaccines Immunother. 6 (5–6) (2018) 69–76.