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Overview

Human Papillomavirus Vaccines versus Cervical Cancer Screening

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ABSTRACT:
Prophylactic vaccination with human papillomavirus (HPV) virus-like particle (VLP) vaccines against HPV 16 and HPV 18, which are the cause of 70% or more of cervical cancers in women, has transformed our prospects for reducing the incidence of this disease on a global scale. HPV VLP vaccines are immunogenic, well tolerated and show remarkable efficacy, achieving >98% protection in randomised clinical trials against the obligate precursor lesions cervical intraepithelial neoplasia grade 2/3 (CIN2/3) and adenocarcinoma *in situ*. The implementation of these vaccines as a public health intervention is, however, complex. Cervical cancer screening can be a highly effective secondary intervention, but in the developing world these programmes are either not available or are ineffective. HPV vaccination represents the most effective intervention in that scenario. In countries with successful well-organised cervical cancer screening programmes, such as the UK, the cost-effectiveness of vaccination as opposed to screening is a major factor. Screening will have to continue, as only two of the 15 oncogenic HPV types are in the vaccines and for two to three decades at least unvaccinated sexually active women will remain at risk for the disease. However, if both vaccination and screening are combined then the virtual elimination of cervical cancer and the other HPV 16 and 18-associated cancers is possible. Stanley, M. (2008). *Clinical Oncology* ■■, ■–■
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Key words: Cervical cancer, CIN, HPV, prophylactic vaccines, screening programmes, VLPs

Statement of Search Strategies Used and Sources of Information

PubMed was searched for publications relating to cervical cancer screening, HPV vaccines, HPV 16/18 and serology, HPV testing, HPV typing. The author has a literature database containing 57 000 items from PubMed relating to these search items. Google was searched for ACIP, WHO and UNICEF websites.

Vaccines vs Screening?

The obvious answer to this question is both are needed, but implementation as a rational public health intervention will be complex and depend upon social and economic factors. Invasive cervical carcinoma of the cervix in women is the second most common malignancy in women worldwide, with an estimated incidence of 500 000 cases per year and 250 000 deaths [1]: 80% of cases and deaths are in developing countries. This discrepancy in disease between the developed and developing world can be attributed very largely to cervical cancer screening programmes in developed countries. Invasive cervical cancer is preceded by epithelial atypia: cervical intraepithelial neoplasia (CIN) in squamous cell carcinoma and adenocarcinoma *in situ* (AIS) in adenocarcinoma. CIN represents a spectrum of atypia in squamous epithelia ranging from mild (CIN1), moderate (CIN2) to severe or high grade (CIN3); CIN3 and AIS are usually accepted as the obligate precursor lesions of invasive cervical cancer. The objective of cervical cancer screening is to detect these high-grade lesions and to remove them by ablative or excisional procedures, thus interrupting progression to malignant disease in the screened population.

Persistent infection with one of a subset of human papillomaviruses (HPVs) that infect the anogenital epithelium of men and women is the cause of CIN and AIS and by inference, therefore, is the necessary cause of invasive cervical cancer [2,3]. Because an infectious cause for cervical cancer has been established [4] there is a realistic opportunity for primary intervention to prevent invasive cervical cancer.

What are Human Papillomaviruses?

HPVs are a large family (greater than 100 different HPV types known) of small, double-stranded DNA viruses that infect squamous epithelia or cells with the potential for squamous maturation. These viruses have two key characteristics: they are absolutely host and tissue specific and

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a complete infectious cycle occurs only in a fully differentiating keratinised squamous epithelium [5]. Despite their very large numbers, HPVs can be classified into two major groups, those that infect skin or cutaneous surfaces and those that infect the internal wet squamous mucosae [6]. Within these groups there are low-risk types, which generate benign lesions, in other words warts, and high-risk or oncogenic types, which are associated with cancers and their precursor lesions [7]. In the genital tract, about 40 HPV types regularly or sporadically infect the mucosal epithelial surfaces. Low-risk HPV types, HPV 6 and 11, cause more than 90% of genital warts, with minor types (HPV 42, 44) and assorted high-risk types contributing to about 10% of these lesions [8]. Oncogenic HPVs in the genital tract are dominated by HPV 16 and HPV 18, which, with their close relatives 31, 33, 35, 52, 58, 39, 45, 59, 56, 66 and 51, are the cause of cervical cancer. Thus, in 99% or more of biopsies of invasive cervical cancer worldwide, HPV DNA sequences can be detected [9] and in CIN3 and AIS about 90% contain high-risk HPVs [10]. HPV 16 dominates, with at least 50% of cancers, irrespective of geographical location, containing HPV 16, followed by HPV 18 (7–20%).

The evidence that HPV infection is the necessary cause of invasive carcinoma of the cervix is compelling. Case control studies show odds ratios and relative risks of the order of 250 or more for infection with oncogenic HPVs and cervical cancer [11]: natural history studies show that CIN of any grade is caused by infection of genital HPVs [12], with high-risk HPVs, particularly HPV 16, becoming increasingly dominant as the grade of CIN increases [13]. Laboratory studies show that the oncogenic genital HPVs encode two potent oncogenes, E6 and E7, that, respectively, disable cell cycle control mediated by p53 and pRB [14]. HPV infection does not only cause cervical cancer, oncogenic HPV DNA sequences are found in a proportion of anal, vulva, vaginal, penile and head and neck cancers (Table 1). HPV 16 is again the dominant oncogenic type, followed by HPV 18, and overall the malignant burden attributable to HPV infection is calculated to be 3.7% of all cancers [1].

Table 1 – The burden of cancer attributable to human papillomavirus (HPV) infection [1]

		Developed countries		Developing countries	
Site	Attributable to HPV (%)	Total cancers	Attributable to HPV	Total cancers	Attributable to HPV
Cervix	100	83 400	83 400	409 400	409 400
Penis	40	5200	2100	21 100	8400
Vulva, vagina	40	18 300	7300	21 700	8700
Anus	90	14 500	13 100	15 900	14 300
Mouth	≥ 3	91 200	2700	183 100	5500
Oropharynx	≥ 12	24 400	2900	27 700	3300
Other	0				
All sites		5 016 100	111 500	5 827 500	449 600

Human Papillomavirus Vaccines

Prophylactic vaccines have been and continue to be the most effective strategy for controlling viral infections and the evidence is accumulating that HPVs are no exception to this. Papillomaviruses are exclusively intraepithelial and serum neutralising antibody concentrations in natural infections are low [15,16]. Despite this, it has been known for more than 70 years, from the pioneering studies of Shope [17] in rabbits, that serum neutralising antibody is protective against viral challenge. Neutralising antibodies are directed against the major viral coat protein L1 assembled in the native or tertiary structure. HPVs cannot be grown in bulk in tissue culture and thus conventional killed or attenuated viral vaccines are not possible. HPV vaccines are subunit vaccines consisting only of the L1 protein assembled into macromolecular structures known as virus-like particles (VLPs). HPV L1 VLPs are conformationally correct empty capsids that are morphologically and antigenically almost identical to the virus particle. They contain no DNA and therefore are not infectious. Two HPV L1 VLP prophylactic vaccines have been developed. These are Cervarix®, a bivalent HPV 16, 18 VLP vaccine from GlaxoSmithKline and Gardasil® also known as Silgard, a quadrivalent HPV 16/18/6/11 vaccine from Merck Vaccines (Table 2). Both vaccines have undergone randomised placebo-controlled double-blind clinical trials (RCTs) in women in North America, Latin America, Europe and Asia Pacific and have been granted a licence in many countries and for the European Union by the European Medicines Evaluation Agency. The quadrivalent vaccine has been licensed by the Federal Drugs Agency of the USA since June 2006.

An important issue for the RCTs for the HPV vaccines was how to ascertain vaccine efficacy for the oncogenic HPV VLP types as the conventional measurable end point of efficacy, disease incidence, was not feasible for cervical cancer for

Table 2 – Human papillomavirus (HPV) L1 virus-like particle (VLP) vaccines

	Gardasi®	Cervarix®
L1 VLP antigens	HPV 6 (20 μg) HPV 11 (40 μg) HPV 16 (40 μg) HPV 18 (20 μg)	HPV 16 (20 μg) HPV 18 (20 μg)
Expression system	Yeast (*S. cerevisiae*)	Baculovirus
Adjuvant	Proprietary aluminium hydroxyphosphate sulphate (225 μg)	ASO4 Aluminium hydroxide (500 μg) plus 50 μg 3-deacylated monophosphoryl lipid A
Injection volume and immunisation schedule	0.5 ml intramuscularly 0, 2 and 6 months	0.5 ml intramuscularly 0, 1 and 6 months
Adolescent safety/ immunogenicity bridging trials	Females and males 9–15 years	Females 10–14 years

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both practical and ethical reasons. Cervical cancer is a disease with a long interval between viral infection and clinical presentation and, furthermore, is one that can be prevented substantially by secondary intervention in terms of detection and treatment of precancerous lesions. Therefore, invasive cervical cancer could not be an end point and disease-relevant end points acceptable to national regulatory authorities had to be identified. Both virological and clinical end points were considered. As HPV infection is necessary for the full development of almost all cervical cancers [9] it could be argued that preventing HPV infection was an adequate measure of efficacy. Genital HPV infection can be incident, defined as new detection of HPV DNA and vaginal cells in a woman previously HPV DNA negative, or persistent, HPV DNA of the same type detected on two successive occasions, 6 or 12 months apart in a woman previously HPV DNA negative. The available evidence suggests that persistent HPV infection is the most significant predictor of progression to CIN3 [18] and, by implication therefore, invasive cervical cancer, suggesting that prevention of persistent HPV infection could be a suitable surrogate. However, there is no real evidence that preventing persistent infection affects cervical cancer development and, furthermore, prevention of infection had not been previously accepted as a vaccine end point. High-grade CIN (CIN2/3 or AIS) are accepted as the immediate precursors of invasive cervical cancer and for vaccine licensure the end point of CIN2/3 or AIS or worse has been accepted widely as the ethically acceptable proxy for efficacy against cervical cancer by these vaccines [19].

Vaccine Efficacy

In women who have no evidence of exposure or infection with the HPV genotypes that are present in the vaccine, both vaccines show very high efficacy, with over 90% reduction in persistent infection and greater than 98% reduction in high-grade cervical lesions [20–23]. The quadrivalent vaccine has shown in the per protocol efficacy group, that is women 16–26 years old with five or fewer lifetime sex partners and who were HPV 6 or HPV 11 or HPV 16 or HPV 18 negative at entry, 100% efficacy against vulval intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), genital warts [24] and 98% efficacy against CIN3 and AIS [25,26] caused by any of the vaccine HPV types over a 3-year follow-up period. The bivalent vaccine has shown, in an interim analysis with a mean follow-up of 14.8 months of women 15–25 years of age with six or fewer lifetime sex partners and who were DNA negative for the relevant oncogenic HPV type in the vaccine, 90.4% efficacy against HPV 16/18 CIN2+, two cases in the vaccine group, 21 cases in the placebo [23]. It is unlikely that the HPV 16 or 18 infection detected in the two cases in the vaccine group caused the CIN2+ lesions. HPV 16 or 18 DNA was detected only in the biopsy sample taken, but not in any of the preceding cervical cytology samples. Another non-vaccine oncogenic HPV type was present in all sections of the diagnostic biopsy and in the preceding cytology samples, including that taken at day 0. The one case of CIN3 in the quadrivalent trial exhibited a similar profile. HPV 16 was detected only the biopsy, but another non-vaccine oncogenic HPV type was present in the cytology samples at day 0 and was detected in every section of the Loop electrosurgical excision procedure (LEEP) biopsy. In these cases from trials of the two different vaccines there was persistent infection with an oncogenic type other than the vaccine type preceding the CIN2+ lesion the same type was present in the diagnostic biopsy, and probably caused the CINs detected. If this interpretation is accepted then both these vaccines show 100% efficacy against HPV 16/18-associated high-grade cervical disease in women naive for HPV 16 or 18 when immunised. In the USA, the quadrivalent phase III RCT has been terminated after a 4-year follow-up. The data safety monitoring board for the vaccine concluded that there was overwhelming evidence of efficacy and all placebos are being immunised (Table 3).

It must be emphasised that HPV VLP vaccines are prophylactic, not therapeutic, and have no efficacy against existing HPV 16/18 infection or disease. Analysis of the FUTURE II data [25] clearly reveals this. The quadrivalent vaccine showed 98% efficacy in women HPV 16 or 18 negative at trial entry, but only 48% efficacy in all women randomised at entry. The potential efficacy of HPV VLP vaccines is illustrated by the 001/007 trial of the bivalent vaccine [21]. Women in this phase IIb immunogenicity and efficacy trial were naive for 14 high-risk oncogenic HPV types at trial entry and after 4.5 years efficacy of 69% against all CIN2+ was shown in the vaccine group. Although the numbers were small and it could be argued that this population represents in some way a cohort naturally resistant to HPV infection, this cohort is the closest comparison to the peripubertal adolescent population (virtually all of whom will be HPV naive) that would be the optimal group for immunisation. The results suggest that the VLP vaccines, if delivered to young adolescents, will achieve in the long term at least the same, but probably greater, impact on cervical cancer incidence that is currently achieved by screening.

Table 3 – Phase III randomised clinical trials: outcomes to date [22,23]

Vaccine	Gardasil®	Cervarix®
Follow-up	3 years	15 months (interim analysis)
Prophylactic efficacy		
HPV 16 CIN2/3+	Established	Established
HPV 18 CIN2/3+	Established	Positive trend Not yet at statistical significance
HPV 16/18 VIN3	Established	Not reported
HPV 16/18 VaIN3	Established	Not reported
6/11 anogenital disease	Established	Not a target
Tolerability	Well tolerated	Well tolerated
Therapeutic efficacy	None	None
Duration of protection	5–6 years	5–6 years

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Duration of Protection

Although the HPV L1 vaccines have shown remarkable efficacy against HPV-related disease in women in the 15–26-year-old age group who were naive for the relevant vaccine type, a key issue is how long this protection will last. At the present there are no immune correlates of protection, as sero-conversion has occurred in virtually 100% of vaccinees and there have been no obvious breakthroughs of disease in the vaccinated cohorts in the RCTs. The VLP vaccines result in high levels of serum neutralising anti HPV L1 immunoglobulin G that at peak concentrations (1 month after the third immunisation) is up to 1000 times and at 5–6 years after immunisation up to 10–12 times that measured in natural genital HPV infections [21,27]. Mathematical modelling of the kinetics of antibody decay indicates that antibody (at least for yeast-derived HPV 16 VLPs) could persist for 30 years [28]. Importantly there is good evidence that robust immune memory is generated by these vaccines. The quadrivalent vaccine has shown an impressive recall response to antigen challenge, the functional read out for memory, 5 years after immunisation [29] and circulating B memory cells can be detected 1 month after the third and final immunisation with the bivalent vaccine [30]. Furthermore, the persistence of antibody levels in excess of that found in natural infection strongly suggests robust B and T memory induction. Immune memory is fundamental to successful immunisation and the observations of persistence of antibody and robust recall from the VLPs in the trials leads to optimism that the duration of protection might be measured in decades, as for example, has been shown for hepatitis B subunit vaccines. HBV antibody levels wane in a proportion of subjects over time, but protection against disease is sustained and strong recall responses and T and B cell memory can be shown even 20 years after immunisation [31–33]. HPV 18 antibody concentrations fall to background levels in about 20% of subjects immunised with the quadrivalent vaccine [34], but efficacy against HPV 18-associated CIN2/3 and VIN/VaIN3 remains at 100% over a 4-year period, irrespective of antibody level (Ault, pers. commun. 2008). Attack rates of HPV 18 in the placebo group remain constant over the 4 years. The measurement of antibody to HPV VLPs is not standardised and completely different methods and units of measurement are used for the two vaccines. A conventional enzyme-linked immunoassay (ELISA) that measures total anti-VLP antibody is used for Cervarix, but a competition Luminex bead assay is used for Gardasil. The competition assay measures only one monoclonal neutralising antibody, representing the data in assay-specific units, completely different from those used for ELISA. The problem with the competition assay is that the mechanism by which HPV entry into cells is neutralised by antibody is not known and which of the several neutralising antibodies generated to HPV VLPs are important in this function is also not known and therefore the relevance or otherwise of the fall off in antibody concentration for HPV 18 cannot be determined. The only solid data at the present is that efficacy against HPV 18-associated high-grade intraepithelial disease remains at 100% 4 years after immunisation irrespective of antibody level. At the time of introduction of a vaccine the duration of protection when the vaccine is delivered in field conditions to millions of individuals cannot be predicted. Post-vaccine surveillance and monitoring are essential – time will tell us about the duration of protection and the relevance of antibody levels.

Cross-protection

In natural HPV infections, the humoral immunity induced is type specific and type-specific neutralising antibodies seem to be the predominant species generated by the VLPs. However, the VLP vaccines induce very much higher concentrations of antibody than natural infection. There is considerable amino acid sequence homology in L1 between closely related HPV types [35], implying that there could be cross-neutralising epitopes and that cross-neutralising antibodies could be present in the polyclonal response. There is evidence from the phase III trial of the bivalent vaccine that HPV 16/18 vaccinees are partially protected against persistent infection (detection of the same HPV type over a 12 month interval) with non-vaccine oncogenic HPV types, including HPV 31, 33, 52 and HPV 45 [21], although the data are not statistically significant. It has been reported that subjects immunised with the quadrivalent vaccine showed protection against CIN2+ disease caused by several HPV types, including HPV 31, 33, 35, 52 and 58. However, cross-protection is partial (at best 59%) and cross-neutralising antibody concentrations are 1–2 logs lower than that achieved for type-specific antibodies [36]. Second-generation vaccines will probably need to consist of, or include, other oncogenic HPV types, raising a frequently asked question 'will we need different cocktails of HPV types for different populations?' This seems unlikely. HPV 16 and HPV 18 are the dominant types worldwide, consistently detected in 70% of all cervix cancers [1]. A further six types, HPV 45/31/56/52/35 and 33, consistently make up the remaining 20–30%, irrespective of the geographical region and a polyvalent vaccine that contained these eight types would effectively protect against more than 90% of all cervix cancers [37].

Who and When to Vaccinate

In the European Union, the vaccines are licensed for 9–26 year olds (Gardasil®) and 10–25 year olds (Cervarix®). The licence is gender neutral and both men and women in those age groups could be immunised. Many countries have issued recommendations as to the cohorts to be vaccinated and most countries have opted for peripubertal immunisation with no or varying age groups as a catch up group. Only Australia has recommended immunisation of boys in the 9–15 age group. There are no efficacy data for men at present. Recently an announcement from the UK Minister of Health stated that he had accepted the recommendations of the UK Joint Committee on Vaccination and Immunisation

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that the HPV L1 VLP vaccine be offered to 12—13-year-old females via a school-based immunisation delivery programme starting in September 2008, with a catch up programme for females up to 18 years old over a 2-year period commencing in 2009. Such a recommendation makes sense from several perspectives — the natural history of HPV infection and disease, the immune response, public health criteria and cost-effectiveness.

The HPV L1 VLP vaccines are prophylactic, not therapeutic, preventing, not treating, infection and the available evidence is clear that immunisation with them will not be effective in individuals with established HPV infections of the types included in the current vaccines [38]. Genital HPV infection is usually, but not always, sexually transmitted. The most important at risk period for acquisition of genital HPV infection seems to be the mid- to late teens and early adulthood, soon after the onset of sexual activity [39]. To maximise vaccine benefit, the vaccine should be delivered before the sexual debut. Immunologically the optimal time for immunisation with the VLP vaccines is before puberty. Immunogenicity bridging studies for the quadrivalent vaccine determining antibody concentrations achieved after immunisation in 9—15-year-old girls and boys show that antibody levels after HPV VLP vaccination are higher in 9—15-year-old boys than in 9—15-year-old girls and 9—15-year-old girls have higher concentrations than 16—23-year-old women [40,41]. Antibody concentrations in girls and boys remain at constant levels over the 9—11-year-old range, but fall quite sharply at 12—13 years, the average age of puberty, with a shallow decline thereafter. This shallow decline continues on through the decades. These considerations imply that the target groups for vaccination should be, in the first instance, preadolescent girls in the 12—13-year-old age group.

Vaccines are public health interventions, not medicines, and their efficacy in preventing disease and, hence, their cost-effectiveness, depends upon achieving a wide coverage of the unexposed population. This objective will probably be achieved with a school-based vaccination programme for peripubertal females, providing it is accompanied by effective education and information for both the medical community and the general public of HPV-associated disease. If school-based delivery of the vaccine programme were to be delayed to mid- or late adolescence, then it would be unlikely to provide the coverage necessary for cost-effective immunisation, as this age group participate poorly in vaccination programmes.

Vaccination in Sexually Active Women

But what about sexually active women who will almost certainly have been exposed to HPV? Will these vaccines have any benefit? The RCTs of the two vaccines have shown that in women aged 15—26 years with fewer than five to six lifetime sex partners who were HPV 16/18 negative at trial entry the VLP vaccine did protect against the development of HPV 16/18-related disease and also in the case of the quadrivalent vaccine, against HPV 6/11-related disease. There are no published data on vaccine efficacy in women older than 26 years, but antibody levels induced by the VLP vaccines in 26—55-year-old women are much higher than natural infection, although lower than in the younger age groups. The level of protection that might be afforded in this group is not known and in the context of an organised cervical cancer screening programme is unlikely to be cost-effective [42].

Screening and Vaccines

Cervical cancer screening is a highly effective secondary prevention in the UK. Since the programme was centrally organised in 1988, invasive cervical cancer incidence and mortality in the UK has fallen by more than 50% [39,43]. This is despite an escalating risk of disease across Europe in the birth cohorts of women born since the 1940s. Screening starts to impact on fully invasive cervical cancer (excluding microinvasive carcinoma) in women over 30 years old [44]. It has no effect on invasive cervical cancer in the under 30 years age group, but probably has an effect on microinvasive cancer [45]. The current vaccines include only two of the 15 oncogenic genital HPV types and even if delivered optimally with 100% coverage of the target age group, would prevent only 70—75% of cancers in the long term (and this takes into account some contribution from cross-protection). Therefore, screening will have to continue for the foreseeable future for the following reasons. In the UK, only 12—13 year olds will form the vaccinated cohort as from September 2008. Vaccine coverage will probably be patchy in the catch up group (i.e. those under 18 years targeted in a 2-year programme from 2009) and there will be the large unvaccinated population over 18 years of age who remain at risk for the development of premalignant and malignant disease. Both immunised and non-immunised birth cohorts will have to continue in the screening programme, as the immunised group will continue to be at risk for the non-vaccine oncogenic types.

Screening will have to continue, but it can be predicted that screening protocols will change and be based upon HPV detection (and probably typing) as the first-line screening test [46]. HPV testing has been shown consistently to be superior to cytology in terms of sensitivity and positive predictive value [47]. Furthermore, in a scenario where HPV 16 and 18 are virtually eliminated from the spectrum of cervical intraepithelial lesions in the cohorts of vaccinated women entering the screening programme, the performance of cytology as a screening tool will be significantly reduced [48]. What is critical after the introduction of HPV vaccination is that young women do not perceive the vaccine as a 'magic bullet' giving complete protection against cervical cancer. They must continue in the screening programme, vaccinated or not. Vaccination plus screening could virtually eliminate cervical cancer in the UK, but how the programmes are managed and interact will be crucial and presents a major, but exciting, public health challenge.

Vaccination plus screening should, in theory, prevent almost 100% of cervical cancers, but this could only apply in countries with organised screening programmes [49]. In populations without adequate screening, HPV vaccines, providing they are at affordable cost, are the only answer.

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Immunisation as a public health intervention is highly effective, even in countries with very low resources. The expanded programme for immunisation ensures primary vaccination of 70—75% of children worldwide, even in the poorest countries, and in campaigns can reach greater than 90%. The infrastructure and organisation for population immunisation are in place in developing countries, but not for cervical cancer screening programmes [50]. The effectiveness of screening in low resource countries in Latin America, Africa and South East Asia is poor, with the fraction of the population regularly screened being less than 5% and restricted to the affluent classes [51]. HPV vaccines are the only realistic intervention in such situations.

Summary

The ability to generate HPV VLPs by the synthesis and self-assembly *in vitro* of the major virus coat protein L1 has transformed our prospects for preventing benign and malignant anogenital disease caused by the common genital HPV types. Two HPV L1 vaccines have been developed, a quadrivalent HPV 6/11/16/18 and a bivalent HPV 16/18 product. Both vaccines are very immunogenic and well tolerated. They have been shown in the various RCTs to be very effective at preventing infection and premalignant disease related to the vaccine HPV genotypes in women who were DNA negative and sero-negative for the vaccine HPV types at baseline. The protection generated by the vaccine persists for at least 5 years, and because antibody levels remain high after 5 years and there is evidence of good immune memory, protection will probably be long lasting. HPV vaccines containing HPV 6/11 will almost eliminate genital warts in the medium term. The vaccines will reduce, but not eliminate, the risk of cervical cancer, as at present they only target two of the oncogenic genital types. They will also reduce the incidence of other HPV-associated cancers. Cervical cancer screening programmes will remain as important secondary interventions for cervical cancer in vaccinated populations, although screening protocols will almost certainly change with HPV testing becoming the first-line screening test. The primary target group for immunisation with HPV vaccines are the peripubertal female population. There may be benefit in vaccinating other groups (men, sexually active women of all ages), but the cost-effectiveness of these interventions will need to be evaluated. In societies in which organised screening programmes are not available, HPV vaccines are probably the most realistic intervention against HPV-associated disease. In the longer term, if protection against most of the oncogenic types can be achieved, HPV vaccines will be the only intervention needed against genital HPV-associated disease.

Conflict of Interest

The author is a consultant for Merck Research Laboratories, Philadelphia, USA, GSK Biologicals, Rixensart, Belgium and Sanofi Pasteur MSD, Lyon, France.

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