HPV vaccines: are they the answer?

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Background: The burden of human papillomavirus (HPV)-associated ano-genital disease is significant but the ability to generate HPV virus-like particles by the synthesis and self-assembly in vitro of the major virus coat protein L1 has transformed our prospects for preventing benign and malignant ano-genital disease caused by the common genital HPV types.

Sources of data: Peer reviewed journals.

Areas of agreement: 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 randomized Control trials 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 base line. The protection against disease generated by the vaccines persists for at least 5 years. HPV vaccines containing HPV 6/11 will reduce the incidence of genital warts by 80–90% in the medium term. The vaccines will reduce but not eliminate the risk of cervical cancer since at the present they only target two of the oncogenic genital types. Cervical cancer screening programmes will remain as important secondary interventions for cervical cancer even in vaccinated populations.

Areas of controversy: The duration of protection remains unknown but there is evidence of good immune memory, it is possible that protection will be long lasting. The primary target group for cost effective immunization with HPV vaccines are peri-pubertal females. 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 organized screening programmes are not available, HPV vaccines are probably the most realistic intervention against HPV-associated disease.

Areas timely for developing research: Second generation vaccines that offer protection against additional types, are thermostable and delivered by non-injection methods are an important area of investigation.

Keyword: HPV 16/18/6/11/VLP/vaccines/antibody/cervical cancer/genital warts
Introduction

If surveys in both the medical and lay press are to be believed human papillomaviruses (HPVs) do not figure on the radar of most readers. HPVs were long assumed to be unimportant, the cause of warts which although cosmetically unsightly excrescences were of trivial significance. However this large family of small DNA viruses, it turns out, include individual types that are major global carcinogens causing an estimated 3.7% of cancers mainly in the ano-genital tract.\(^1\) Even the so-called trivial warts, particularly if they occur on the ano-genital skin,\(^2\) or in the larynx\(^3\) have significant morbidity and are a substantial health economic burden\(^4\) for their management and treatment.

The development of vaccines to prevent HPV-related diseases has therefore been an important objective. This has not been an easy task. The absolutely restricted host range (no animal papillomavirus infects humans and no HPV infects any other species but man) together with our inability to efficiently propagate these viruses in tissue culture were serious impediments. Despite this, over the past two decades huge progress has been made in the development of prophylactic HPV vaccines culminating in the widespread licensing of two vaccines. Both vaccines prevent infection and disease caused by the major oncogenic HPV types 16 and 18 and one of the vaccines, in addition, targets the commonest causes of genital warts HPV types 6 and 11.

With the advent of these HPV vaccines the prospects for the prevention of infection by the major genital HPVs have never looked more encouraging but the decision to introduce a new vaccine depends upon a number of factors including:

(i) The burden of disease – the public health priority.
(ii) Effectiveness and safety of the vaccine.
(iii) Availability of other interventions and cost effectiveness vis a vis the vaccine.
(iv) The ability of the health infrastructure to effectively deliver the vaccine to achieve the public health benefit.

In view of these criteria is the optimism surrounding these vaccines justified, do these vaccines tick the boxes for the public health benefit? This brief review attempts to address some of these issues.

Burden of disease

HPVs are a large family (>100 different HPV types known) of small, double-stranded DNA viruses that infect squamous epithelia or cells with the potential for squamous maturation.\(^5\) They are classified as
genotypes on the basis of their DNA sequence and are numbered in order of their discovery. Despite their very large numbers HPVs fall into two major groups, those that infect skin or cutaneous surfaces and those that infect the internal wet squamous mucosae. Within these groups there are low risk types which generate benign lesions, in other words warts, and high risk or oncogenic types that are associated with cancers and their precursor lesions. In the genital tract ~40 HPV types regularly or sporadically infect the mucosal epithelial surfaces. Low risk HPV types, HPV 6 and 11, cause >90% of genital warts with minor types (HPV 42, 44) and assorted high risk types contributing to ~10% of these lesions. Benign disease caused by the genital low risk HPVs is not trivial. Genital warts are the most common viral sexually transmitted disease in the UK with 79,618 new cases reported from STD clinics in 2004. Incidence rates rise sharply in girls aged 15–24 years and in boys aged 20–29 years; peak rates are in 20–29-year-olds in both sexes then fall sharply in females but remain high in males to age 40 years. Almost 50% of women with an incident infection with HPV 6/11 will develop genital warts within a period of 12 months, and 64% in 36 months. Consistent use of condoms decreases the risk of genital warts by 60–70%: HIV infection is associated with an increased prevalence. The low risk HPVs that cause genital warts are highly infectious, result in significant morbidity and cost the UK healthcare system of the order of £25–30 million per annum.

A maternal history of genital warts is associated with a 231-fold risk for recurrent respiratory papillomatosis (RRP) an uncommon but potentially devastating disease, characterized by the growth of wart-like benign neoplasms throughout the aero-digestive tract that often requires repeated surgeries.

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% of biopsies of invasive invasive carcinoma of the cervix (CaCx) worldwide, HPV DNA sequences can be detected and in the obligate cervical cancer precursor lesions cervical intra-epithelial neoplasia (CIN) grade 3 (CIN 3) and adenocarcinoma in situ (AIS) ~90% contain high risk oncogenic HPVs. 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 CaCx is compelling. Case–Control studies show odds ratios and relative risks of the order of ≥250 for infection with oncogenic HPVs and cervical cancer: natural history studies show that CIN of any grade is caused by infection of genital HPVs with high risk HPVs, particularly HPV 16 becoming increasingly dominant as the grade of CIN...
increase. Laboratory studies demonstrate that the oncogenic genital HPVs encode two potent oncogenes, E6 and E7 that, respectively, disable cell cycle Control mediated by p53 and pRB. HPV infection is associated with cancers other than cervix. This oncogenic HPV DNA sequences are found in a proportion of anal, vulval, vaginal, penile and head and neck cancers and the precursor intra-epithelial lesions. 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.

## Prophylactic HPV vaccines

The HPV DNA genome is enclosed in a shell or capsid comprised of two proteins L1 and L2; in natural infections serum neutralizing antibodies are made only to the L1 protein. It has been known for >70 years from the pioneering studies of Shope in rabbits that serum neutralizing antibody is protective against viral challenge suggesting that prophylactic vaccines would be protective against HPV infections in humans. HPVs, however, cannot be grown in bulk in tissue culture and thus conventional killed or attenuated viral vaccines were not feasible. The currently available HPV vaccines are subunit vaccines consisting only of the L1 protein assembled into macro molecular 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 L1 VLP vaccine from GlaxoSmithKline Biologicals and Gardasil® also known as Silgard, a quadrivalent HPV 16/18/6/11 L1 VLP vaccine from Merck & Co. Inc. (Table 1). Both vaccines have undergone randomized, placebo-controlled,

<table>
<thead>
<tr>
<th>Table 1 HPV L1 VLP Prophylactic vaccines</th>
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<tbody>
<tr>
<td><strong>Gardasil®</strong></td>
</tr>
<tr>
<td><strong>L1 VLP Antigens</strong></td>
</tr>
<tr>
<td>HPV 6 (20 μg)</td>
</tr>
<tr>
<td>HPV 11 (40 μg)</td>
</tr>
<tr>
<td>HPV 16 (40 μg)</td>
</tr>
<tr>
<td>HPV 18 (20 μg)</td>
</tr>
<tr>
<td><strong>Injection volume and immunization schedule</strong></td>
</tr>
<tr>
<td>0.5 ml i.m.; 0, 2 and 6 months</td>
</tr>
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<td></td>
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double-blind clinical trials (RCTs) in women in North America, Latin America, Europe and Asia Pacific. Both have been licensed in many countries including the nation states of the European Union. Gardasil® has been licensed by the Federal Drugs Agency (FDA) of USA since June 2006.

**Vaccine endpoints**

Clinically relevant and ethically acceptable endpoints were important issues for the HPV vaccine RCTs. Cervical cancer is not an ethically acceptable endpoint; it is a disease with a long interval between viral infection and clinical presentation and, furthermore, one that can be prevented substantially by secondary intervention via cervical cancer screening programmes with the detection and treatment of precancerous lesions. Both virological and clinical endpoints were potential vaccine trial endpoints and the advantages and disadvantages of these for HPV vaccines have been reviewed in depth.\(^\text{16}\) High grade intra-epithelial lesions (CIN 2/3 or AIS) are recognized as the immediate precursors of invasive cervical cancer and for vaccine licensure the endpoint of CIN 2/3 or AIS or worse has been accepted widely as the ethically acceptable proxy for vaccine efficacy against cervical cancer. This endpoint can be evaluated among young women but in children or young adolescents, however, CIN as an endpoint is ethically unacceptable since cervical specimens would be required. Bridging studies have therefore been conducted in children and young adolescents by comparing antibody responses in these cohorts with those in the women for whom efficacy has been evaluated using the CIN endpoint.

**Vaccine efficacy**

Vaccine efficacy is calculated by comparing the incidence in women who received the vaccine and women who received placebo (the Control group). The results are expressed as a percentage with the corresponding 95% confidence limits. The primary analyses for trials are conducted usually in the per protocol (PP) or according to protocol groups, i.e. women in the specified age group who had no evidence of infection with the HPV genotypes in the vaccine at trial entry, received three doses of vaccine or placebo and did not deviate from the protocol.

Both vaccines have shown very high efficacy against cervical intra-epithelial neoplasia in the RCTs.\(^\text{17–23}\) In the Phase III RCTs of the quadrivalent vaccine the PP group were women aged 16–24 years.
with <4 lifetime sex partners and naïve for ≥1 HPV vaccine genotypes at enrolment through 1 month post the third immunization. In the FUTURE I RCT designed to evaluate efficacy of the quadrivalent vaccine in preventing HPV 6/11/16/18 caused ano-genital disease, vaccine efficacy in the PPG was 100%, i.e. no cases of HPV 6/11/16/18 caused CIN, VIN, VaIN or external genital warts detected in the vaccine group over a 3-year period. A combined analysis of RCTs (Phase IIb and Phase III trials) of the efficacy of the quadrivalent vaccine against HPV 16/18 caused cervical intra-epithelial disease has been published. In these trials involving 20 583 women efficacy against HPV 16/18 caused CIN 2/3 was 99% (one case in the vaccine group) and 100% for HPV 16/18-related AIS.

The bivalent vaccine in the Phase III RCT has shown, in an interim analysis with a mean follow-up of 14.8 months of women 15–25 years of age with ≤6 lifetime sex partners and who were DNA negative for the relevant oncogenic HPV type in the vaccine at trial entry, 90.4% efficacy against HPV 16/18 CIN 2+, two cases in the vaccine group, 21 cases in the placebo. It is unlikely that the HPV 16 or 18 infection detected in the two cases in the vaccine group caused the CIN 2+ lesions. HPV 16 or 18 DNA was detected only in the biopsy sample taken, but not in any of the preceding cervical cytology samples. Persistent infection with a non-vaccine oncogenic HPV type could be shown; this type was present in all sections of the diagnostic biopsy and in the preceding cytology samples including that taken at day zero. Furthermore immunohistochemical analyses found no evidence of HPV 16 or 18 type specific viral gene expression in these two cases. The one case of CIN 3 in the vaccine group in the combined RCT analysis of the quadrivalent vaccine exhibits a similar profile; there was persistent infection with a non-vaccine oncogenic type preceding the CIN 2+ lesion and the same type was present in the diagnostic biopsy. Persistent infection with an oncogenic HPV is the most significant predictor of progression to CIN 3 and the persistent non-vaccine oncogenic HPV types detected in these cases were the most likely cause of 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 naïve for HPV 16/18 infection at the time of immunization. In the USA the phase III RCT for Gardasil 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 immunized.

HPV VLP vaccines are prophylactic not therapeutic and have no efficacy against existing HPV 16/18 infection or disease. This is clear from the RCTs of the quadrivalent vaccine. In the PP group (women who are naïve at entry for HPV 16/18) efficacy against high grade cervical
disease is >98%. However in the intention to treat group (women entering the trial irrespective of baseline HPV status or evidence of HPV-related disease of any grade and for whom endpoint follow-up started 1 day after trial entry) efficacy against 16/18-related CIN 2+ or AIS was 44%.21 The 001/007 trial of the bivalent vaccine provides some evidence of the potential efficacy of HPV 16/18 VLP vaccines against cervical neoplasia.19 Women in this Phase IIb immunogenicity and efficacy trial were naïve for 14 high risk oncogenic HPV types at trial entry. Four and a half years post-vaccination, an efficacy of 69% against all CIN 2+ (not only HPV 16/18 related but any HPV) was shown in the vaccine group. Although the numbers are small and it could be argued that this population represents in some way individuals naturally resistant to HPV infection or behaviourally distinct, this cohort is the closest comparison with the peri-pubertal adolescent population (virtually all of whom will be HPV naïve) that would be the optimal group for immunization. The results suggest that the HPV VLP vaccines if delivered to young adolescents will achieve in the long term, at least the same impact on cervical cancer incidence that is currently achieved by screening in the best organized programmes.

Vaccine immunogenicity

The vaccines are highly immunogenic inducing high levels of serum antibodies in virtually 100% of individuals.19,28 The current assumption is that the major basis for protection is neutralizing antibody and this assumption is supported by animal models that demonstrate protection against viral challenge in animals immunized by passive transfer of antibody.29,30 To date there is no immune correlate of protection, no antibody threshold has been defined that correlates with protection. In the Phase IIb immunogenicity trial 001/007 of the bivalent vaccine anti-HPV 16 and 18 antibody persisted at levels ~10× that observed in natural infections for at least 6 years post-immunization.19 Antibody levels induced by the quadrivalent vaccine persist in most vaccinees 5–6 years post-vaccination and mathematical modelling of the kinetics of antibody decay suggests that detectable antibody (at least for yeast derived HPV 16 VLPs) could persist for 30 years.31 In ~20% of subjects immunized with the quadrivalent vaccine HPV 18 antibody concentrations fall to background levels28 but efficacy against HPV 18-associated CIN 2/3, AIS and VIN/VaIN3 remains at 100% over a 4-year period irrespective of antibody level.32 Attack rates of HPV 18 in the placebo group remain constant over the 4 years. A competition Luminex bead assay that measures only one monoclonal neutralizing antibody species is used in the quadrivalent vaccine trials unlike the
conventional ELISA that measures total antibody used in the bivalent vaccine trials (reviewed in 33). The problem with the competition assay is that the mechanism by which HPV entry into cells is neutralized by antibody is not known and which of the several neutralizing antibodies generated to HPV VLPs are important in this function is also not known; the relevance or otherwise of the fall off in antibody concentration for HPV 18 cannot be determined at the present. The only solid data at the present is that efficacy against HPV 18-associated high grade intra-epithelial disease remains at 100% 4 years post-immunization irrespective of antibody level.

Importantly there is good evidence that robust immune memory is generated by these vaccines. The quadrivalent vaccine has shown an impressive anamnestic/recall response to antigen challenge, the functional read out for memory, 5 years post-immunization and circulating B memory cells can be detected 1 month after the third and final immunization with the bivalent vaccine. Furthermore, the persistence of antibody levels in excess of that found in natural infection strongly suggests robust induction of B and T cell memory. Immune memory is fundamental to successful immunization 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 has been shown for hepatitis B subunit vaccines.36,37

Cross-protection

In natural HPV infections, the humoral immunity induced is type specific and type specific neutralizing antibodies appear 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 implying that there could be cross-neutralizing epitopes and that cross-neutralizing antibodies could be present in the polyclonal response. Subjects in the Phase III RCT of the bivalent vaccine 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 4522 although the data are not statistically significant. Subjects immunized with the quadrivalent vaccine showed protection against CIN 2+ disease caused by several HPV types including HPV 31, 33, 35, 52 and 5839 http://www.cdc.gov/vaccines/recs/ACIP/downloads/mtg-slides oct07/20HPV.pdf.

However, cross-protection is partial (at best 59%) and cross-neutralizing antibody concentrations are one to two logs lower than
that achieved for type specific antibodies. It seems likely that second generation vaccines will 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. A further six types, HPV 45/31/56/52/35 and 33, consistently make up the remaining 20–30%, irrespective of the geographic region and a polyvalent vaccine that contained these eight types would effectively protect against >90% of all cervix cancers.

**Immunogenicity in young adolescents: immunobridging studies**

Immunogenicity bridging studies for the quadrivalent vaccine determining antibody concentrations achieved after immunization 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 9–15-year-old girls and 9–15-year-old girls have higher concentrations than 16–23-year-old women. 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 9–13-year-old age group.

The HPV L1 VLP vaccines are prophylactic not therapeutic, preventing, not treating, infection and the available evidence is clear that immunization with them will not be effective in individuals with established HPV infections of the types included in the current vaccines. Genital HPV infection is usually, but not always, sexually transmitted. The most important at risk period for acquisition of genital HPV infection appears to be the mid to late teens and early adulthood, soon after the onset of sexual activity. To maximize benefit, HPV vaccines should be delivered before the sexual debut and as the immunobridging studies reveal, immunologically, the optimal time for immunization with the VLP vaccines is before puberty.

**Safety**

Both vaccines appear to be generally well tolerated. No increase in serious adverse events has been found in any of the trials. In RCTs of
both vaccines, injection site pain, erythema and oedema were common, and occurred significantly more often for vaccine recipients than placebo recipients. For the quadrivalent vaccine, detailed safety data reviewed by the US FDA, are included in the label. Few subjects (0.1%) discontinued due to adverse experiences. Seventeen deaths were reported in 21,464 male and female subjects. The events reported were consistent with events expected in healthy adolescent and adult populations. The most common cause of death was motor vehicle accident.

Vaccines and screening

Cervical cancer screening is a highly effective secondary prevention in many developed countries. In the UK since the programme was centrally organized in 1988 invasive cervical cancer incidence and mortality has fallen by >50% despite an escalating risk of disease across Europe in the birth cohorts of women born since the 1940s. Screening starts to impact on the incidence of invasive cervical cancer (excluding micro invasive carcinoma) in women >34 years old. It has little or no impact on incidence of invasive cervical cancer in the <30 years age group.

In countries with effective screening programmes the cost effectiveness of adding an HPV vaccine to the existing screening programme needs to be evaluated and this has been accomplished using modelling techniques. The expected benefits from introduction of HPV vaccine include the reduction in morbidity and costs associated with follow-up of mild or equivocal cervical lesions, the treatment of CIN 2+ and invasive cancer and modifications to the screening programme that would result in cost savings. In countries where the burden of disease from conditions other than cervical cancer (including genital warts, RRP) is well documented their treatment is costly and impacts significantly on the quality of life. Models that include these outcomes predict greater benefits from the quadrivalent vaccine than do models focusing only on prevention of cervical cancer but the quadrivalent vaccine may not necessarily be as cost effective if the cost per dose is significantly greater than that of the bivalent. In a recent analysis it was shown that for the UK a cost difference of £13–£20/dose would have to exist between the two vaccines for the bivalent vaccine to be as, or more, cost effective and this presumably was the major factor in the choice of Cervarix for the UK school immunization programme.
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) approximately the same reduction that is achieved currently by the UK screening programme [http://www.ic.nhs.uk/statistics-and-data-collections/screening/cervical-cancer/cervical-screening-programme-2006-07-5Bns%5D. Even if vaccination coverage reaches the 85–90% levels normal in the UK, screening will have to continue for the foreseeable future for the following reasons. In the UK only 12–13-year-olds will form the regularly vaccinated cohort as from September 2008. Vaccine coverage may be patchy in the catch-up group (i.e. those <18 years targeted in a 2-year programme from 2009) and there will be the large unvaccinated population >18 years of age who remain at risk for the development of premalignant and malignant disease. Both immunized and non-immunized birth cohorts will have to continue in the screening programme, since the immunized group will continue to be at risk for the non-vaccine oncogenic types.

Reduction in disease burden: primary and secondary intervention

Vaccination plus screening could, in theory, prevent almost 100% of cervical cancers but this could only apply in countries with organized screening programmes. It is important to remember that 80% of cervical cancers occur in the developing world.1 In these populations without adequate screening programmes and the sophisticated infrastructure to support diagnosis and treatment of pre-invasive disease HPV vaccines, providing they are at affordable price, are the only realistic intervention. This is supported by data from recent studies showing the positive population impact of the quadrivalent vaccine in Latin American women.53 Immunization as a public health intervention is highly effective, even in countries with very low resources since the infrastructure and organization for population immunization are in place in developing countries whereas that for cervical cancer screening programmes is not.54 The huge challenge in these countries will be to implement adolescent immunization programmes since no platform for this exists at the present.

Vaccination in sexually active women and men

Sexually active women will almost certainly have been exposed to HPV, although not necessarily infected, and a frequently asked
question is whether these women would benefit from vaccination. This population will include:

(i) Women who have not been infected, immunizing these women will protect against infection with a vaccine HPV type.

(ii) Those who have been infected and cleared their infection, immunizing these women will be beneficial in that an existing humoral response will be boosted.

(iii) Those who have been infected but have made an inadequate immune response, these women will be DNA positive and may be seropositive, immunizing these women will have no effect on the established infection but would confer protection against the other type(s) in the vaccine.

(iv) Women who are infected but who have not made as yet an immune response, immunizing these women will have no effect on the progress or otherwise of that infection but would confer protection against the other types(s) in the vaccine.

The randomized Control trials of the two vaccines have shown that in women 15–26 years old with <4–6 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 is no published data on vaccine efficacy in women >26 years of age, 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 http://www.cdc.gov/vaccines/recs/ACIP/downloads/mtg-slides-oct07/21HPV.pdf. The level of protection that might be afforded in this group is not known and in the context of an organized cervical cancer screening programme is unlikely to be cost effective.55

Another frequently raised issue is immunization of boys and men. Certainly if herd immunity, in the heterosexual population, against HPV is to be achieved, and virus transmission interrupted effectively, then boys, as well as girls, should be immunized. The quadrivalent vaccine is immunogenic in boys and antibody levels are higher in 9–15-year-old boys than in 9–15-year-old girls, suggesting that male immunization will be effective.43 However, all the efficacy trials have included women only and there is no efficacy data in men available although trials are ongoing. The arguments against vaccinating boys for the oncogenic HPVs are based on health economic considerations and cost effectiveness. In a heterosexual population the spread of HPV infection can be stopped entirely by complete protection of one sex alone and dynamic simulation models of HPV transmission show that if high coverage of females can be achieved, there is little to be gained in the additional reduction of cervical cancer by vaccinating males.56
Anal HPV infection is very common in men who have sex with men and in the absence of male vaccination could act as a reservoir for vaccine HPV types. These data together with the accumulating evidence for HPV as a major risk factor in the aetiology of some head and neck cancers may change the position of politicians and public health decision makers on male vaccination despite the cost effectiveness evidence.

Future developments

Prophylactic HPV L1 VLP vaccines have been shown, in large clinical trials, to be very immunogenic, well tolerated and highly efficacious against ano-genital disease caused by the vaccine HPV types (Table 2). These products are being delivered now in many countries mainly to cohorts of adolescent females but they are not the total answer to HPV-induced ‘disease. The vaccines, at the present, protect against only two of the 15 oncogenic genital HPV types, they are expensive, delivered by intra muscular injection and require a cold chain all of which inhibits their uptake in the developing world where cervical cancer is common and unlikely to be controlled by any strategy other than primary intervention. Furthermore the efficacy and immunogenicity of these products in immunocompromised individuals such as HIV infected subjects is not known and this is an important research question. The challenges for second generation vaccines are to develop cheap, thermostable products that can be delivered by non-injectable methods and provide long term (decades) protection at mucosal surfaces to most if not all oncogenic HPV types that is as good as the current VLP vaccines.

Table 2 Prophylactic HPV L1 VLP vaccines (phase III RCTs: outcomes to date)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Gardasil®</th>
<th>Cervarix®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>3 years</td>
<td>15 months (interim analysis)</td>
</tr>
<tr>
<td>Prophylactic efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 16 CIN 2/3+</td>
<td>Established</td>
<td>Established</td>
</tr>
<tr>
<td>HPV 18 CIN 2/3+</td>
<td>Established</td>
<td>Positive trend (not yet at statistical significance)</td>
</tr>
<tr>
<td>HPV 16/18 VIN3</td>
<td>Established</td>
<td>Not reported</td>
</tr>
<tr>
<td>HPV 16/18 VaIN 3</td>
<td>Established</td>
<td>Not a target</td>
</tr>
<tr>
<td>6/11 Ano-genital disease</td>
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<tr>
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<td>Well tolerated</td>
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<tr>
<td>Therapeutic efficacy</td>
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<td>None</td>
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<tr>
<td>Duration of protection</td>
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Conflict of Interest

Consultant Merck Research Laboratories, Philadelphia, USA; GSK Biologicals, Rixensart, Belgium; Sanofi Pasteur MSD, Lyon, France.

References


