Human papilloma virus (HPV) prophylactic vaccination: Challenges for public health and implications for screening

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Abstract

Prophylactic vaccination against high risk human papilloma virus (HPV) 16 and 18 represents an exciting means of protection against HPV related malignancy. However, this strategy alone, even if there is a level of cross protection against other oncogenic viruses, cannot completely prevent cervical cancer.

In some developed countries cervical screening programmes have reduced the incidence of invasive cervical cancer by up to 80% although this decline has now reached a plateau with current cancers occurring in patients who have failed to attend for screening or where the sensitivity of the tests have proved inadequate. Cervical screening is inevitably associated with significant anxiety for the many women who require investigation and treatment following abnormal cervical cytology. However, it is vitally important to stress the need for continued cervical screening to complement vaccination in order to optimise prevention in vaccinees and prevent cervical cancer in older women where the value of vaccination is currently unclear.

It is likely that vaccination will ultimately change the natural history of HPV disease by reducing the influence of the highly oncogenic types HPV 16 and 18. In the long term this is likely to lead to an increase in recommended screening intervals. HPV vaccination may also reduce the positive predictive value of cervical cytology by reducing the number of truly positive abnormal smears.

Careful consideration is required to ensure vaccination occurs at an age when the vaccine is most effective immunologically and when uptake is likely to be high. Antibody titres following vaccination in girls 12–16 years have been shown to be significantly higher than in older women, favouring vaccination in early adolescence prior contact with the virus. Highest prevalence rates for HPV infection are seen following the onset of sexual activity and therefore vaccination would need to be given prior to sexual debut. Since 20% of adolescents are sexually active at the age of 14 years, vaccination has been suggested at 10–12 years. However, parental concerns over the sexual implications of HPV vaccination may reduce uptake of vaccination thereby reducing the efficacy of an HPV vaccination programme. Concerns have already been raised over the acceptability of a vaccine preventing a sexually transmitted infection in young adolescents, particularly amongst parents or communities who consider their children to be at low risk of infection. This may be a particularly sensitive issue for ethnic minority groups.

This paper considers the factors which will influence the efficacy of a public HPV vaccination programme and its impact on cervical screening.

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1. Introduction

The recognition of the central role of high-risk high papilloma viruses in the aetiology of cervical cancer worldwide [1] has led to the development of prophylactic vaccination as a new means of cervical cancer prevention. Two vaccines based on the L1 capsid protein of human papilloma virus (HPV) 16 and 18 have demonstrated almost 100% efficiency in preventing persistent infection and related HPV pre-malignancy with these viruses in late stage trials [2,3]. The licensing of the first vaccine, Gardasil (Merck/Sanoﬁ Pasteur MSD), by EMEA in 2006 and the imminent licensing of the second vaccine Cervarix (Glaxo Smith Kline, GSK) in 2007 offers the prospect of prophylactic vaccination programmes with
the ultimate potential of preventing approximately 70% of cervical cancer.

In countries lacking a cervical screening programme a strategy of vaccination alone could have a major impact on the burden of HPV malignancy, providing funding for vaccine and the necessary infrastructure for vaccination was available. However, in a number of developed countries such as the UK, Canada and Scandinavia, the introduction in the 1980s of highly organised, systematic cervical screening programmes based on cervical cytology has led to a major reduction in mortality from cervical cancer. In the UK a comprehensive cervical screening programme based on cervical cytology is considered to have prevented an epidemic of cervical cancer and projected to have reduced mortality by up to 80% [4].

2. Limitations of cervical screening

Despite the major success of cervical screening programmes based on cervical cytology, important limitations have to be recognised.

(a) Poor sensitivity of cervical cytology

Whilst many cervical screening programmes claim sensitivity for cervical cytology of 60–70%, results may vary considerably. A metaanalysis [5] suggested that in some countries the sensitivity of cervical cytology was as low as 51% for CIN1 although the average specificity was 98%. Limited sensitivity of cervical cytology may partly explain why 66% of women presenting with cervical cancer in 2003 had been screened [6]. The high false negative rate for a cervical smear has been the most important limitation of the test as false negative diagnoses may have major medical and medicolegal implications. It is the frequency of cervical cytology testing, i.e. three to five yearly, which ensures cervical screening programmes have achieved an acceptable level of sensitivity.

(b) Anxiety and morbidity of screening investigations

The investigation of abnormal cervical cytology inevitably causes significant morbidity and anxiety for large numbers of screened women, since up to 10% of all cervical smears will be found to be abnormal, albeit often with low-grade borderline atypia [7]. For a population of 20 million in England 2004/2005 almost 4 million smears were performed, resulting in 124,238 referrals for colposcopy following abnormal results [8]. Similarly, in Wales with a population of 1.5 million women, 200,000 smears were performed resulting in 22,000 colposcopy clinic visits in order to detect 3218 women with high-grade CIN and 41 cancers [9]. Women with low-grade abnormalities have been shown to experience similar anxiety to those with high-grade results and anxiety is greatest in young women who are likely to be highly concerned about future fertility [10].

(c) Poor uptake by some communities

Even the most highly organised screening programmes may not reach 20–25% [8,9] of women, including women who may be particularly vulnerable to HPV associated malignancy from disadvantaged and ethnic minority communities. Women from ethnic minority communities may find it more difficult to access screening services particularly where there are language barriers. It has been demonstrated that the most important predictor of non-attendance is fear of the consequences of investigation. This may be a particular issue amongst less informed younger women [10].

(d) Falling screening coverage in the UK

Recently, concern has been expressed about the fall of coverage for the screening programme in England from 77 to 71.6% amongst women age 25–29 [11]. The discomfort and embarrassment of the procedure and adverse experiences of other women may influence attendance.

(e) Poor predictive value for adenocarcinoma

Adenocarcinoma in situ (ACIS) is frequently missed by cervical cytology as a consequence of reduced accessibility to the cervical canal and the failure to recognise these lesions. In contrast to a declining incidence of squamous carcinoma the incidence of adenocarcinoma of the cervix has remained stable or has increased in some countries despite well organised screening programmes [12–14].

Prevention of HPV 16 and 18 infections by prophylactic vaccination in conjunction with cervical screening may be a means to further improve cervical cancer prevention. However, the size of the impact of this strategy on cervical cancer prevention and cervical screening is unclear at present.

3. Current commercial prophylactic HPV vaccines

Both current commercially developed vaccines Gardasil (Sanofi Pasteur MSD/Merck) and Cervarix (GSK) consist of recombinant proteins of the L1 capsid of HPV 16 and 18 viruses which self assemble to form virus like particles (VLPs), combined with an adjuvant. The key differences and characteristics of the vaccines are summarised in Table 1. Gardasil (Sanofi Pasteur MSD/Merck) is a quadrivalent vaccine, which contains the VLPs for 6 and 11 in addition to VLPs for 16 and 18 prepared with conventional alum adjuvant. HPV 6 and 11 are low risk human papilloma viruses responsible for 90% of genital warts and a proportion of low-grade cervical cytology abnormalities.

Cervarix (GSK) is bivalent vaccine containing VLPs for 16 and 18 combined with a novel adjuvant AS04, containing 3D monophosphoryl lipid A (MPL). MPL acts as a toll-4 ligand and has been shown to enhance the titre of neutralising antibodies [16,17]. The combination of MPL and aluminium salts has been shown to induce enhanced humoral and cellular responses as compared with antigen alone or in combination with alum adjuvant [19]. This novel adjuvant has been...
Table 1
Comparison of commercial vaccines (randomised phase 2 studies)

<table>
<thead>
<tr>
<th></th>
<th>GSK</th>
<th>Merck</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV types</td>
<td>16/18 high risk</td>
<td>16/18 high risk; 6/11 genital wart types</td>
</tr>
<tr>
<td>Expression system</td>
<td>Baculovirus</td>
<td>Yeast</td>
</tr>
<tr>
<td>Vaccination schedule</td>
<td>0, 2, 6 months</td>
<td>0, 1, 6 months</td>
</tr>
<tr>
<td>Antigen dose</td>
<td>VLP 16,18 (20, 20 μg)</td>
<td>VLP 16, 18, 6, 11 (40, 20, 20, 40 μg)</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>AS04 [500 μg Al(OH)3 + 50 μg MPL]</td>
<td>Alum 225 μg [Al(PO4)]</td>
</tr>
<tr>
<td>Trial size</td>
<td>560 vaccinees; 553 placebo</td>
<td>227 vaccinees; 275 placebo</td>
</tr>
<tr>
<td>Trial countries</td>
<td>United States of America, Canada, Brazil</td>
<td></td>
</tr>
<tr>
<td>Age, trial subjects</td>
<td>15–25 years</td>
<td>16–23 years</td>
</tr>
<tr>
<td>Duration of follow up</td>
<td>Up to 54 months</td>
<td>Up to 36 months</td>
</tr>
<tr>
<td>Efficacy (% CI intervals)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) HPV infection</td>
<td>96.9 (81.3–99.9)</td>
<td>Not available</td>
</tr>
<tr>
<td>Persistent infection intention to treat</td>
<td>94% (63–99)</td>
<td>89% (73–96) [composite infection and lesion endpoint]</td>
</tr>
<tr>
<td>(b) Cytological abnormalities</td>
<td>97% (84–100)</td>
<td>Not published</td>
</tr>
<tr>
<td>(c) HPV 16/18 pre-malignancy</td>
<td>100% (42–100)</td>
<td>100% (32–100)</td>
</tr>
<tr>
<td>Serious adverse events reported</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Immune response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Seroconversion</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>(b) Antibody titres</td>
<td>50–80 times natural infection</td>
<td>10–20 times natural infection</td>
</tr>
</tbody>
</table>

Both HPV 16/18 commercial vaccines would be expected to protect against approximately 70% of high risk HPV in most regions worldwide [21] and thus 70% of cervical cancer.

To date clinical trial intention to treat analysis has suggested almost 100% efficacy against persistent HPV 16/18 infection in phase 2 studies in according to protocol analysis with the bivalent and similar results for overall analysis for the quadrivalent vaccine. All patients have sero-converted following vaccination in phase 2 studies. The titres of neutralising antibody observed were 10–80 times higher than observed in natural infection. However, the minimum serum antibody titre to protect from persistent HPV infection remains to be defined. Both vaccines appear safe and highly effective with almost 100% protection against persistent HPV infection 16/18 and related HPV pre-malignancy (see Table 1). A recent most interim analysis of the phase 3 quadrivalent vaccine has confirmed the efficacy for the prevention of CIN2/3 observed in the phase 2 trials [18,19]. Based on these results Gardasil has received approval of the European Agency for the Evaluation (EMEA) of medical products and the FDA in the United States of America.

4. Potential coverage HPV type coverage of current commercial vaccines

In order to provide protection against greater than 90% of high HPV types responsible for cervical cancer a vaccine would have to contain LI VLPs for the eight most prevalent types of high risk human papilloma viruses [20]. The prevalence of these high risk HPV types is as follows:

- HPV 16 (53%), HPV 18 (17.2%), HPV 45 (6.7%), HPV 31 (2.9%), HPV 33 (2.6%), HPV 52 (2.3%), HPV 58 (2.2%), HPV 35 (1.4%) [17].

Whilst VLP vaccines would be expected to be type specific Harper et al. [15] have reported a degree of cross protection against cyto-histological outcomes beyond that anticipated from an HPV 16/18 vaccine. The vaccine provided 94% (95% CI 63.9–99.9) protection against HPV 45 and 54% (95% CI 11.5–77.7) protection against HPV 31. This may be the result of overlapping epitopes of HPV genotypes 16, 31, 18 and 45 which have similar sequencing [23]. Consequently, coverage of high-risk HPV types could rise from 70 to 75–80% by an HPV 16/18 vaccine.

5. Potential health gain for vaccination with current commercial vaccines

Whilst promising phase 2/3 trials for HPV 16/18 vaccines have shown very high efficacy for vaccination it is difficult to predict the precise effect of vaccination on the incidence of pre-invasive and invasive cancer in the community, particularly when public vaccination is provided alongside a high quality cervical screening service. Nevertheless, mathematical models [24,25] support a high level of public health gain for the prevention of HPV malignancy in women for most
countries. The added value of male vaccination to attempt to improve herd immunity and further reduce female HPV malignancy is unknown. Mathematical modelling suggests there is little added advantage if HPV vaccination coverage in the females exceeds 70% [24].

In the UK Kohli et al. [25] have performed a cohort analysis to estimate the lifetime impact of an HPV 16/18 prophylactic vaccine on the burden of cervical disease in the UK according to different scenarios. They estimated that a 70% reduction of in the prevalence of high-grade cervical lesions and a 76% reduction in cervical cancer cases and deaths would be seen in the lifetime of a cohort of 12-year-old females if 100% coverage was achieved. If vaccination did not occur until 18 years the preventative effect of vaccination on the population would be diminished. In addition, there would be a proportionate fall off in population health gain for reduced vaccination coverage (see Table 2).

The number of abnormal cytology results diagnostic tests, biopsies and colposcopies could fall by a half (see Table 3).

Thus, HPV vaccination could lead to a substantial reduction in the morbidity and anxiety associated with cervical screening.

6. Factors which may influence vaccination health gain outcome

It is likely that the following the key factors will exert a significant impact on the level of benefit in the population in terms of reduction of the burden of HPV malignancy and the morbidity of screening.

(a) Age of vaccination

There is no evidence to date that HPV LI VLPs have any therapeutic activity against persistent HPV infection. Consequently, for prophylactic vaccination to be most effective it should occur prior to sexual debut. The majority of girls will become infected with HPV, most commonly HPV 16 and 18, within 2–3 years of the onset of sexual activity [26]. HPV 16 is particularly carcinogenic and the absolute risk of CIN approaches 40% 5 years after persistent infection [27], other HPV types being significantly less oncogenic [21]. HPV prevalence and incidence peak around 20 years and decline rapidly in women 30 years and older [26]. Persistent HPV infections occurring in the older teens or early twenties give rise to peak of CIN in the 25–30 year age group and cervical cancer at a later age [26]. The duration of induced HPV immunity needs therefore to be at least 10 years after adolescent vaccination to protect against persistent HPV infection in the late teens and twenties age group and the subsequent development of CIN2/3.

Twelve-year-old girls have been shown to have a better serological response to the HPV vaccine as compared with older women which could theoretically lead to longer lasting immunity [28]. However, there is no definite evidence of this at present. The projected impact on life time risk of HPV malignancy of vaccinating a cohort of 12 year olds is likely to be greater than a cohort of women 18 years or more (see Table 2 above), largely because they have not been exposed to HPV infection.

For women over the age of 25 years the level of benefit of HPV is unknown and awaits the results of ongoing trials. However, from available evidence to date one can project that for the small group of over 25s who have not been exposed to HPV there will be clear benefit. However, for women who have been exposed to infection and have detectable HPV DNA benefit is unlikely. The potential benefit of vaccinating women who have successfully eradicated infection with their natural immunity to prevent re-infection occurring in later life is unknown.

If only cohorts of 12 year olds are vaccinated it will take at least 15 years before a major significant impact on the incidence of CIN2/3 and at least 30 years before an impact on cervical cancer incidence is observed. Therefore, a catch up vaccination programme may be appropriate for older adolescent girls and women.

(b) Acceptability of vaccination

Parental acceptance of adolescent HPV vaccination is unknown.

Whilst there is a clear rationale for vaccination in adolescence, this may provoke concern in some parents that adolescent HPV vaccination will promote adolescent promiscuity or early sexual activity. This may be a consideration for parents in communities that consider their children to be at low risk of HPV infection, particularly in some religious and ethnic minority communities.

Table 2

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Reduction in CIN2/3 (%)</th>
<th>Reduction in cervical cancers (%)</th>
<th>Reduction in cancer deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 10 years at vaccination with high coverage</td>
<td>70.2</td>
<td>76.0</td>
<td>76.1</td>
</tr>
<tr>
<td>Age 18 years at vaccination with low coverage</td>
<td>54.5</td>
<td>66.0</td>
<td>63.9</td>
</tr>
<tr>
<td>80% vaccine coverage</td>
<td>53.1</td>
<td>60.8</td>
<td>60.9</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Abnormal cervical cytology</th>
<th>Colposcopies</th>
<th>Treated CIN lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vaccine</td>
<td>124,701</td>
<td>68,957</td>
<td>26,773</td>
</tr>
<tr>
<td>100% vaccination coverage</td>
<td>59,411</td>
<td>31,160</td>
<td>10,876</td>
</tr>
<tr>
<td>Reduction due to vaccine (%)</td>
<td>52.4</td>
<td>54.8</td>
<td>59.4</td>
</tr>
</tbody>
</table>
To date information regarding acceptance is based on research questionnaires largely carried out in the United States of America indicating an acceptability level in most studies of 80% [28] or more. There is some evidence that educational intervention can improve the level of acceptability in undecided parents [29].

The only study performed in the UK in Manchester found that 81% of parents would probably or definitely would have their child vaccinated and 84% thought it would be important to vaccinate children before they were sexually active [30]. Parents worried about vaccine safety and with strong religious convictions were less likely to support adolescent vaccination [30].

The availability of a health care professional such as a school nurse to address parental and adolescent concerns over HPV vaccination may prove particularly important to alleviate the anxiety of undecided parents. Reduction of vaccination uptake to 80% or less as a result of limited acceptability of adolescent vaccination could reduce the lifetime impact of vaccination on CIN2/3 and cervical cancer incidence to 53.1 and 63.9%, respectively (see Table 2).

(c) Duration of immunity

Current evidence from clinical trials suggests that the immunity following vaccination exceeds 4 years and appears to be sustained [28]. At present there is no evidence of a falling immunity with time and whether vaccination boosting will be required is a key unknown. It is possible that re-infection will provide a means of naturally sustaining immunity in the absence of vaccine boosting. However, currently this is speculative and to what extent VLP vaccines, which are inherently highly immunogenic, together with the enhanced immunity of novel adjuvants will provide long HPV term immunity remains to be demonstrated. Continued monitoring of efficacy will be essential to determine the need or otherwise for booster doses.

(d) Place and method of vaccine delivery

One means of delivering the HPV vaccine would be by the school health service immunisation programme. School nurses in some parts of the UK are currently responsible for immunisation with dTap-IPV (diphtheria, tetanus, pertussis and inactivated polio) in adolescence with back up from primary care. Such programmes have traditionally achieved coverage of 80–90%. These nurses could also be a source of advice for both parents and adolescents on HPV vaccination as they usually have considerable experience in sex education and managing female adolescent issues which are relevant to HPV vaccination.

A particular problem will be maximising compliance for three doses over a 6-month period. The immunisation programme will need to be timed to minimise disruption of school and pupil studies. Countries without school health services, such as France and Italy, have frequently been unable to introduce vaccination with high coverage [27].

A recent study [31] has assessed the feasibility of HBV vaccination in Greater Glasgow Scotland through a school health system. Vaccine uptake was 91.3, 89.3 and 80.2% for first and second and third doses, respectively, giving some optimism for the prospects of high compliance for three dose immunisation in the school environment.

For older women the optimum service delivery for HPV vaccination is less clear and achieving high coverage in a catch up campaign may be more difficult. The potential source of vaccination includes primary care family planning clinics, possibly obstetricians and gynaecologists and the private sector.

(e) Effect on cervical screening

Cervical cancer screening based on cytology has had a major impact on cervical cancer incidence and mortality. Screening will need to continue in the post vaccination era to ensure the continued surveillance of the large cohort of women who have been exposed to HPV infection prior to vaccination and to screen the 25–30% of HPV infections not prevented by the current HPV 16/18 vaccines.

Whilst HPV vaccination in conjunction with cervical screening is projected to reduce abnormal cytology by 50–60% [25] paradoxically it may adversely affect the performance of screening as a result of:

(i) Fall in screening population coverage: already the coverage of cervical screening is falling in some groups in younger women [11]. There is a danger that coverage could fall further if the public developed the misconception that HPV vaccination had removed the need for screening. Therefore any vaccination programme needs to be supported by public education to reinforce the continued role of screening for the foreseeable future.

(ii) Reduced sensitivity and specificity of cervical cytology: reduction in the number of squamous abnormalities as a result of vaccination could lead to a fall in the negative predictive value of cytology as calculated in Table 4 below.

In most developed countries the current prevalence of cytological abnormality is between 5 and 10%. Following vaccination a reduction of 50–60% in the prevalence of cytological abnormalities could ultimately lead to a fall in predictive value of between 10 and 20% when most of the population have been vaccinated.

<table>
<thead>
<tr>
<th>Cytological abnormality prevalence rate</th>
<th>0.5</th>
<th>1</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative predictive value of cervical cytology (%)</td>
<td>11.4</td>
<td>20.5</td>
<td>57.3</td>
<td>73.9</td>
<td>86.4</td>
<td>96.2</td>
</tr>
</tbody>
</table>
may also be concern over missing abnormalities leading greater identification of inflammatory changes. Such loss of specificity for cervical cytology could lead to an increase in unnecessary screening investigations.

Ultimately, HPV testing with its greater sensitivity but lower specificity could become the primary screening test, with HPV testing followed by cervical cytology in the presence of a positive HPV test. This would provide a population based means of monitoring the efficacy of HPV vaccination. The use of HPV/cytology triage would reduce the number of cervical smears overall but would artificially increase the prevalence and the predictive value of cytology. If only HPV positive individuals were subjected to cytology the prevalence of cytological abnormalities would artificially increase to up to 50% and the negative predictive value would rise (see Table 4).

The use of HPV testing which could distinguish HPV genotype would be preferred for the future, which would enable changes in the natural history of HPV malignancy to be monitored. Reduction of prevalence of the highly malignant types, e.g. HPV 16 could lead to a predominance of less malignant HPV types leading to a more indolent natural history after many years which could lead ultimately to a prolonged screening interval.

7. Conclusions

HPV vaccination in adolescence with continued cervical screening could ultimately lead to a 76% lifetime reduction in cervical cancer deaths after many years and a 50% reduction in cervical screening abnormalities if high coverage of vaccination was achieved. However, integrating HPV vaccination with screening is complex and it is difficult to anticipate the impact in the population from the phase 2/3 HPV trials. Therefore, large phase 4 population studies are needed to monitor the true efficacy of HPV vaccination. Cervical cytology screening programmes will in time require modification but could develop a new role in monitoring the long term efficacy of vaccination and the changes in the natural history of HPV malignancy, ultimately increasing the screening interval.

References


