Prophylactic human papillomavirus vaccines may protect against cervical cancer

Sexual transmission of certain human papillomavirus (HPV) subtypes is strongly associated with development of cervical cancers in females and anal cancers in males, while other subtypes can lead to genital warts. In a rational attempt to reduce the incidence of these sexually transmitted diseases vaccines have been developed against these HPV subtypes as explained by Anne Szarewski

Cervical cancer is a major cause of morbidity and mortality worldwide. Each year an estimated 400,000 women develop cervical cancer and 270,000 die of the disease, 85% of those being in the developing world.[1] Cervical cancer is common between the ages of 30 and 45 years, thus affecting women with young families.

In the UK, the incidence of cervical cancer has dropped substantially since 1988, when the UK national call-recall system began. It has been estimated that the UK screening programme saves approximately 4,500 lives every year, but despite this, approximately 2,800 women per year still develop cervical cancer.[2] Meanwhile, the diagnosis and treatment of pre-cancerous cervical abnormalities results in significant anxiety,[3,4] as do even inadequate cytology results.[3] Cervical screening programmes are expensive: the programme in the UK, including the treatment of cervical abnormalities, costs an estimated £150 million per year.[5]

Human papillomavirus infection is the main cause of cervical cancer

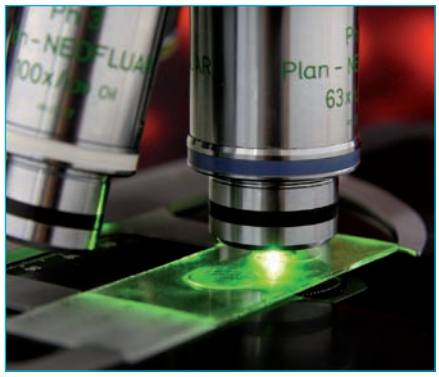
Infection with certain types of sexually transmitted human papillomavirus (HPV), in particular HPV 16 and HPV 18, is the main cause of cervical cancer. It has been shown that 99.7% of cervical cancers contain HPV DNA.[6] HPVs are members of a large family of viruses: the so-called low risk types (chiefly 6 and 11) are responsible for genital warts, while the high-risk types (mainly 16, 18, 31, 33, 35, 45, 52, 56) are implicated in cervical cancer. Of these, types 16 and 18 together account for approximately 70–80% of cervical cancers, around 80% of anal cancers and approximately half of all vulval and vaginal cancers.[7,8] Infection with HPV is extremely common in young people, but is usually transient.[9]

Genital warts are a manifestation of infection with low-risk HPV types, mainly 6 and 11. Genital warts are the most common viral sexually transmitted disease in the UK with 81,000 new diagnoses in 2005, and a 30 per cent increase in the last ten years.[10] HPV types 6 and 11 are also responsible for virtually all cases of recurrent respiratory papillomatosis (RRP), a rare, but extremely distressing condition in young children.[10]

Logical primary prevention strategy

Screening tests detect cellular abnormalities early, but this is still only secondary prevention. Since a virus (HPV) is known to be necessary for the development of these cancers, primary prevention, with a vaccine, is an obvious goal. In contrast to most viral vaccines, which are based on an attenuated form of a virus, (for example, polio) the development of an attenuated HPV vaccine has been difficult because there is no effective culture system to propagate HPV. An attenuated vaccine could also potentially cause disease in vaccinated subjects, particularly if they were immunocompromised. The solution has therefore been to manufacture virus-like particles (VLPs) using the L1 and/or L2 virus coat proteins. VLPs have the outward appearance of the actual virus and generate a powerful immune response, but contain no DNA.

A feature of HPV infection is that the virus is very successful at avoiding the host's immune system, and therefore antibody levels following natural HPV infections are low. Both the LI VLP vaccines, probably due to addition of an adjuvant (aluminium hydroxyphosphate sulfate in the quadrivalent vaccine, aluminium hydroxide with monophosphoryl lipid A — ASO4 — in the bivalent vaccine) result in antibody titres that are enormously (60–100 times) higher and longer lasting (10–16 times higher at 18 months) than those generated by natural infection.[11,12] The ASO4 adjuvant has been used previously in a Hepatitis B vaccine, where it was shown to generate a stronger and longer lasting immune response than the vaccine containing aluminium hydroxide alone.[13] This is the rationale (as



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> Antibody responses induced by all vaccines are higher pre-puberty compared to post-puberty, a feature which has also been shown for the HPV vaccines.

yet, however, not proven) for its use in the bivalent HPV vaccine.[14]

Two prophylactic L1 VLP vaccines against types 6, 11, 16 and 18 have shown great promise in clinical trials.[11,15–19] HPV infection and persistence rates are end-points, which are obviously not as robust as cervical cancer rates, but given that there are virtually no cervical cancers without HPV, it has been considered reasonable to use these initially.

Licensed vaccines

Gardasil®, which contains all four HPV types and would thus protect against genital warts (types 6 and 11) as well as the commonest cervical cancer HPV types (16 and 18) has been approved by the EMEA. Gardasil® is licensed for adolescents aged nine to 15 years and women aged 16 to 26 years. Cervarix® which contains types 16 and 18, and thus targets cervical cancer alone, was approved by the EMEA in September 2007 and is licensed for girls and women from the age of nine years upwards. In the UK, the National Health Service cost of one dose of either vaccine is £80.50; three doses are required to provide protection.

In clinical trials Gardasil® showed 99% (95% CI 93 to 100) efficacy in the prevention of cervical intraepithelial neoplasia-2/3 (CIN2/3) related to HPV 16 and 18.[17] Gardasil® was also 100% (95% CI 72 to 100) effective in preventing vulval intraepithelial neoplasia-2/3 (VIN2/3) and vaginal intraepithelial neoplasia-2/3 (VaIN2/3) related to HPV 16 and 18.[18] Gardasil® has shown 100% (95% CI 94 to 100) efficacy in the prevention of genital warts related to HPV types 6,11,16 and 18.[19]

Younger people have bigger responses

Immunogenicity studies have been carried out in 10–15 year-old boys and girls.[20] Anti-HPV responses at month seven among nine- to 15-year-old girls and boys were non-inferior to anti-HPV responses in 16- to 26-year-old young women for whom efficacy was established in the phase II and III studies. Immunogenicity was related to age and month seven anti-HPV levels were significantly higher in younger individuals below 12 years of age than in those above that age.

Evidence of an anamnestic response (a secondary immune response occurring on subsequent exposure to a previously encountered antigen) was seen in vaccinated individuals who were seropositive to relevant HPV type(s) prior to vaccination. In addition, a subset of vaccinated individuals who received a challenge dose of Gardasil® five years after the onset of vaccination, exhibited a rapid and strong anamnestic response.[20]

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In a phase II efficacy study with extended follow-up to 53 months in women 15–25 years of age, vaccination with Cervarix® conferred 100% (95% CI 33.6 to 100) protection against HPV-16/18-related persistent infection and 100% efficacy (95% CI 42.4 to 100) against associated histological lesions up to 4.5 years.[11,15] In addition, broad protection has been observed against cytohistological outcomes beyond that anticipated for HPV-16/18, and protection against incident infection with HPV 45 (94%) and HPV 31 (54%).[11,15,16]

Immunogenicity of Cervarix® has been assessed in younger and older age groups. Immunobridging studies have been carried out in adolescent girls (10–14 yrs versus 15–25 yrs), and in mature women (15–25 yrs versus 26–55 yrs). The results of these age-stratified studies showed that all the subjects had seroconverted at the first post-vaccination sample. Geometric mean antibody titres (GMTs) for both HPV 16 and 18 were at least 2-fold higher in the 10–14 year old girls.[14] In the young women versus mature women study, all initially seronegative women became seropositive for both HPV-16 and HPV-18 at month two.[21] As observed with other vaccines, GMTs decreased with advancing age. However, the month 7 post-vaccination antibody levels in the oldest age group (46–55 yrs) were still 3–4 times higher than those observed during a study where sustained efficacy has been shown over a period of 4.5 years. The bivalent vaccine has also been shown to induce high levels of memory B cells, implying an anamnestic response.[22]

Unanswered questions

Despite the optimism surrounding the introduction of these vaccines, there are still a number of unanswered questions. These can be summarised as follows:

1. Cross-protection:

It had been thought unlikely that this would occur, yet both vaccines have shown early evidence of such an effect.[15,23] The extent of sustained cross-protection against persistent infections, abnormal cytology and pre-cancerous lesions remains to be determined. Cross-protection is potentially extremely important, because it may raise the overall protection level significantly.

2. Effect of a vaccine in HIV positive people:

In many developing countries both HIV and HPV are common and likely to occur together, so the outcomes of these studies are eagerly awaited.

3. Effect of HPV vaccines administered during pregnancy:

Inadvertent vaccination of pregnant women

is bound to occur. So far the trials have not revealed any increase in miscarriage rates or foetal abnormalities,[15,24] but monitoring needs to continue.

4. How long the immunity conferred by these vaccines lasts:

For optimal protection, the vaccines should be administered prior to the onset of sexual activity. Antibody responses induced by all vaccines are higher pre-puberty compared to post-puberty, a feature which has also been shown for the HPV vaccines.[14,20] Data on immunity are available only up to five years.[15,24] Ideally a vaccine would be administered with other childhood vaccines, removing any link with sexual activity in the minds of parents.[25] However, that would depend on the immunity lasting for decades, or boosters being given.

Vaccination programme plans in England

In England, the Department of Health recently announced that it will fund a vaccination programme for 12–13 year olds, with a catch-up to age 18. The basic programme is to start in Autumn 2008, with the catch-up programme commencing in Autumn 2009.

5. The benefits of vaccinating boys as well as girls

Efficacy studies in men, both heterosexual and homosexual are lacking. Most mathematical models suggest that vaccination of girls alone is the most cost-effective strategy, assuming high uptake among girls.[26,27] However, if boys are not vaccinated, men who have sex with men, and who are at increased risk of HPV infections and anal cancer, will not benefit from the vaccine.[28]

Another unfortunate aspect of restricting vaccination to girls is that it focuses attention on women in relation to a sexually transmitted virus. This is not a useful social message in any context and there are some cultures in which the strategy may prove unacceptable.

6. Development of resistance to a vaccine:

A fundamental issue underpinning the potential resistance to an HPV vaccine is the lack of education of both the public and health professionals about HPV.[29] Possibly the most important aspect will be how the information is presented, and work needs to be done to ascertain the most effective ways of doing this.

7. Vaccinating previously infected women:

Studies are commencing to evaluate the benefit of vaccinating previously infected women (ie. those more than 25 years old), preventing not only re-infection, but also persistence of infection. If this is indeed shown to be the case, vaccination of a wider age range could have a more immediate impact on cervical cancer. Although the prevalence of HPV infections declines with age, studies from South America have suggested an incidence of high risk HPV of approximately 5% per year in women who are more than 35 years of age.[30,31] Studies in Canada and the UK have found that acquisition rates of HPV appear to be similar in both young and older women.[32,33]

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The rates seen in women aged more than 45 years may reflect the increasing social trend towards breakdown of marriages and new partnerships forming at around that age.

Should we screen for HPV before vaccinating 'older' women, who are likely to have been exposed to HPV?

In practice, this is likely to be impractical and unnecessary. There is currently no officially approved genotyping test for HPV and it is unlikely that women will have been exposed to all the HPV types in the vaccines or indeed even to both HPV 16 and 18.[16,34] HPV testing is expensive and the psychosocial sequelae of testing positive can be very damaging.[29] In my view, all these considerations mitigate against HPV testing prior to vaccination.

> Ideally a vaccine would be administered with other childhood vaccines, removing any link with sexual activity in the minds of parents. However, that would depend on the immunity lasting for decades, or boosters being given.

Need for cervical screening:

In theory, an HPV vaccine could prevent almost all cervical cancer, eventually removing the need for cervical smears. It is noteworthy that the vaccines should be effective against cervical adenocarcinoma, which is not detected effectively in current screening programmes, and which appears to be increasing in incidence.[7] There is potential for a very significant reduction in this cancer, which now accounts for up to 20% of cervical cancers. However, until the number of HPV types in the vaccine is increased, there will still be cancers not prevented by vaccination. In addition, as mentioned above, there is at least one whole generation of women for whom the vaccines have come too late to precede sexual activity, and who will continue to require screening. It is, however, clear that screening programmes, where they exist, will need to adapt when HPV vaccination becomes widespread. ✣

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