Distinguished Expert Series

Prophylactic HPV vaccines

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Summary

Infection with human papillomavirus (HPV), in particular HPV 16 and HPV 18, is the main cause of cervical cancer. Two prophylactic vaccines against types 6, 11, 16 and 18 have shown great promise in clinical trials, with recent results demonstrating 100% efficacy against persistent HPV infection and development of CIN up to five years of follow-up. One of these (Gardasil, recently licensed) contains all four HPV types, offering protection against genital warts (types 6 and 11) as well as cervical cancer. The other (Cervarix) contains types 16 and 18, targeting cervical cancer alone. Recent data suggest a degree of cross-protection, against types 31 and 45; this could significantly increase the level of protection afforded by the vaccines. It is envisaged that girls between 11 and 12 will be the target, and this is what has been recommended in the United States. There is still debate about the issue of vaccinating boys.

A fundamental issue is the lack of education of both the public and health professionals about HPV. In theory, an HPV vaccine could prevent almost all cervical cancer, eventually removing the need for cervical smears. However, there is at least one whole generation of women for whom the vaccine will come too late, and who will continue to require screening.

Key words: Human papillomavirus; Cervical cancer; Vaccines.

Introduction

Cervical cancer is a major cause of morbidity and mortality worldwide, particularly in countries which do not have organised screening programmes. It is the second most common cancer and the third leading cause of death in women worldwide after breast and lung cancer [1]. Each year an estimated 400,000 women develop cervical cancer and 270,000 die of the disease. Worldwide, every two minutes a woman dies of cervical cancer, and 85% of those are from the developing world [1]. Cervical cancer is common between the ages of 30 and 45, thus affecting women with young families. As a result, its combined social, economic and emotional burden is immeasurable.

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 precancerous 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]. This is beyond the reach of many countries [6, 7].

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 [8]. 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 [9, 10]. Infection with HPV is extremely common in young people, but is usually transient [11]. It appears that the presence of HPV is more meaningful in older women (over 30), who have persistent infection.

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% increase in the last ten years [12]. Treatments can be painful, and recurrence is frequent. The estimated cost of genital wart treatment in genitourinary medicine clinics in 2003 in the UK was around £23 million [13]. 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 [12].

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 the virus, (e.g. polio) the development of an attenuated HPV vaccine has been difficult because there is no effective culture system to propagate HPV, nor will the viruses infect non-human species. An attenuated vaccine could also potentially cause disease in vaccinated sub-

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jects, 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 are harmless as they contain no DNA. Another problem is the number of cervical cancer HPV types which need to be included (potentially 15).

A feature of HPV infection is that the virus is very successful at avoiding the host immune system, and therefore causing natural immunity. HPV infects primitive basal keratinocytes, which are cells already destined to die. The virus does not speed up or change the life-cycle of the keratinocytes; there is no inflammation or any provocation of immune messengers. As a result, the immune system simply does not notice that the virus is present, potentially allowing chronic, persistent infection to occur [14]. When the epithelial cells containing HPV are shed as a natural event, the virus travels on to a new destination. Despite the ability of HPV to impede host defences, a successful immune response to genital HPV infections does seem to occur in most people. The mechanism appears to be a local cell-mediated immune response associated with lesion regression and the generation of serum neutralising antibody [14]. However, antibody levels following natural HPV infections are low. Both the LI VLP vaccines, probably due to addition of an adjuvant (aluminium hydroxyphosphate sulphate 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 [15, 16]. 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 [17]: this is the rationale (however, as yet not proven] for its use in the bivalent HPV vaccine [18].

Two prophylactic L1 VLP vaccines against types 6, 11, 16 and 18 have shown great promise in clinical trials [15, 16, 19, 29]. HPV infection and persistence rates are endpoints 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 do so initially. Gardasil®, (Sanofi Pasteur MSD) 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 recently been approved by both the United States FDA and the EMEA in Europe. Gardasil® is licensed for children and adolescents aged 9 to15 years and adult females aged 16 to 26 years. In the UK, the National Health Service cost of one dose of the vaccine is £80.50 (123 Euros), three doses are required to provide protection.

In clinical trials Gardasil® showed 100% (95% CI 92.9-100) efficacy in the prevention of CIN2/3 related to HPV 16 and 18. Gardasil® was also 100% (95% CI 41.4-100) effective in preventing VIN2/3 related to HPV 16 and 18. In addition, there were no cases of high-grade vaginal lesions (VaIN2/3) due to HPV types 16 and 18 in those who received Gardasil®, compared to five in those who received placebo (however, this was not statistically significant). Gardasil has shown 98.9% (95% CI 93.7-100) efficacy in the prevention of genital warts related to HPV types 6 and 11 [21]. An extended follow-up study showed that at five years, the vaccine was effective in preventing 95.8% (95% CI 83.8-99.5) of cases of persistent HPV infection or disease [20].

Immunogenicity studies have been carried out in 10-15 year old boys and girls [21]. Anti-HPV responses at month 7 among 9- 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 III studies. Immunogenicity was related to age and month 7 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 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 [21].

The other vaccine (Cervarix, GSK) contains types 16 and 18, and thus targets cervical cancer alone. In an efficacy study with extended follow-up to 53 months in women 15-25 years of age, vaccination conferred 100% protection against HPV-16/18-related persistent infection and associated histological lesions up to 4.5 years [15, 19] In addition, broad protection was observed against cytohistological outcomes beyond that anticipated for HPV-16/18, and protection against incident infection with HPV 45 (94%) and HPV 31 (54%) [15, 19].

Immunogenicity of Cervarix has been assessed in younger and older age groups: immunobridging studies have been carried out in adolescent girls (10-14 yrs vs 15-25 yrs), and in mature women (15-25 yrs vs 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 [18] In the young women vs. mature women study, all initially seronegative women became seropositive for both HPV-16 and -18 at month 2 [22]. 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 three to four times higher than those observed during a study where sustained efficacy was 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 [23].

Despite the optimism surrounding the introduction of these vaccines, there are still a number of unanswered questions. An issue on which further information may be available fairly soon is that of cross-protection. It had been thought unlikely that this would occur, yet both vaccines have shown early evidence of such an effect. The bivalent vaccine trial showed a 94% protection against incident infections with HPV-45, which is HPV-18-related, and 55% protection

against incident infections with HPV-31, which is HPV-16-related [19]. Protection against HPV types 33, 52, and 58, which are also HPV-16-related high-risk types, was not observed. The extent of sustained cross-protection against persistent infections, abnormal cytology and precancerous lesions remains to be determined. A laboratory study of antibody cross neutralization with Gardasil suggests there may be cross protection against types 31, 45, 52 and 58 [24]. Cross-protection is potentially extremely important, as it may raise the overall protection level significantly. If one assumes 94% protection against HPV-45 and 54% protection against HPV-31, the efficacy of the bivalent vaccine could be increased from 71% to 77%. At this point (assuming 100% vaccine uptake) the efficacy would become comparable to that offered by the cervical screening programme in the UK, which is one of the best in the world. Such issues need to be considered by existing screening programmes.

If we eliminate cancer due to HPV types 16 and 18, will other types take their place? This is thought unlikely, in view of the fact that HPV infections are independent of each other [25], but evidence either way is lacking.

Will we need different vaccines for different populations? Although HPV-16 is by far the most common HPV type worldwide, the frequency of the others varies [26]. For example, while type 45 accounts for around 7% of cancers in most areas, in sub-Saharan Africa it accounts for 15%. HPV-31 is more prevalent in South America than other countries and HPV types 52 and 58 are more common in Japan and China than elsewhere [27]. It is possible that slightly different vaccines would benefit different countries.

What might the effect be of a vaccine in HIV-positive people? The initial studies excluded immunocompromised individuals, but studies are now underway looking specifically at HIV-positive people. In many developing countries both HIV and HPV are common and likely to occur together, so the outcomes are eagerly awaited. Safety is not likely to be an issue, since the vaccines contain no viral DNA. However, there are no efficacy data as yet.

What is the effect of HPV vaccines administered during pregnancy? Clearly, this would not be done knowingly, but as more women are vaccinated, inadvertent vaccination of pregnant women is bound to occur. So far the trials have not revealed any increase in miscarriage rates or foetal abnormalities [19, 20], but monitoring needs to continue.

A contentious issue is the age at which HPV vaccines should be given, since for optimal protection, they should be administered prior to the onset of sexual activity. It is also important to note that 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 [18,21]. We do not know at present how long the immunity conferred by these vaccines lasts, as data are available only up to five years [19,20]: ideally, such a vaccine would be administered with other childhood vaccines, removing any link with sexual activity in the minds of parents [28]. It would also be much simpler logistically, particularly in developing countries, where girls are less likely to be attending school in adolescence. However, that would depend on the immunity lasting for decades, or boosters being given. Another issue is whether boys as well as girls should be vaccinated.

Parental attitudes to vaccination have started to be evaluated. Studies, mainly of white, Afro-Caribbean or Hispanic groups in the American subcontinent, have found generally positive responses to the vaccine and a willingness to allow young girls to be vaccinated [29, 30, 31, 32]. Similarly, there have been a couple of small studies in the UK, again with limited ethnic mix, which have elicited positive responses [33, 34]. However, parents seem to have considerable reservations about the age at which children should be vaccinated. Studies in the UK [34, 35] suggest that parents feel that below the age of 10 or 11, girls have not had much, if any, sex education at school, and that therefore discussing a sexually transmitted disease with them would be difficult. Ideally, parents would like babies to be vaccinated, removing the need for discussion altogether [34]. However, as mentioned above, this approach would require long-lasting immunity. There appears to be a general consensus, both in the UK and in the United States, that by age 11, when girls are entering puberty and moving to secondary school, it would be possible to explain HPV to them, and indeed, the FDA has recommended vaccination of 11-12 year olds in its programme [9].

Most mathematical models suggest that vaccination of girls alone is the most cost-effective strategy. However, this assumes high uptake of the vaccine by girls, of which there is no guarantee. The rubella vaccination programme has provided evidence of the benefit of vaccinating both sexes despite the consequences of infection being a predominantly female problem. In Sweden the programme (as in many places) began only with girls. However, it was found to be ineffective and rubella syndrome was only eradicated when both boys and girls were included in the programme [36]. It is very unlikely that uptake of the vaccine by girls will even approach 100%, thus for herd immunity to develop both sexes will need to be vaccinated: even assuming 90% coverage mathematical modelling suggests a significant improvement with vaccination of both sexes [37, 38]. A recent model has suggested that if coverage of girls falls below 75%, it becomes cost-effective to include boys in the programme [39]. In addition, 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. Anal cancer is the only cancer with a greater prevalence among men who have sex with men (MSM) than in the general population. About 35 in every 100,000 MSM develop anal cancer, compared to less than one in every 100,000 heterosexual men [40]. Studies in men, both heterosexual and homosexual, are lacking, a deficiency which should be addressed.

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. Such cultures try to ignore the role and sexual behaviour of men as vectors of infection, but may acknowledge that even women who are virgins at marriage are often infected by their husbands. In addi-

tion, immunisation programmes in the past have been impeded by the suspicion that vaccines were covertly trying to sterilise women [41]. It is essential to evaluate responses to the HPV vaccine in different ethnic groups and assess whether vaccination of both sexes may be the most effective way of achieving uptake. In developing countries, where screening services are sporadic because of unpredictable funding and poor infrastructure, HPV vaccination represents a great hope in the fight against cervical cancer. For a vaccination programme – in any country – to have public health benefits, the acceptability and uptake of the vaccine is as important as its efficacy, so investigating attitudes to the vaccine and likely uptake are crucial.

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 [42]. 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. This has been a woefully neglected aspect of strategies proposed for the introduction both of HPV testing and vaccines.

Studies are commencing to evaluate the benefit of vaccinating previously infected women (i.e., over 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 over 35 years of age [43, 44]. Studies in Canada and the UK have found that acquisition rates of HPV appear to be similar in both young and older women [45, 46]. The rates seen in women over 45 may reflect the increasing social trend towards breakdown of marriages and new partnerships forming at around that age.

Should we screen for HPV prior to 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 [26]. They will then derive benefit from protection against the types to which they have not been exposed, and indeed, there is a suggestion that in women who have in fact developed natural immunity to an HPV type, the vaccines may act as a 'booster' [25]. HPV testing is expensive and the psychosocial sequelae of testing positive can be very damaging [42]. In my view, all these considerations mitigate against HPV testing prior to vaccination.

As always, it is the developed countries which will have the earliest benefit from prophylactic vaccines. The current vaccines are expensive, require three intramuscular injections and refrigeration. All these factors are likely to impede their introduction into developing countries. However, organisations such as the Global Alliance for Vaccines and Immunization (GAVI) could help poorer countries set up vaccination programmes. Research should also be encouraged into more easily delivered vaccines, for example heat stabilisation, needle-free mucosal administration and oral administration [47]. However, progress in these areas is still at a very early stage and a more realistic prospect is the provision of the current vaccines to developing countries at reduced and subsidised prices.

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 [9]. 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. How this is done will depend on many factors, including the uptake of the vaccine, the current success of the existing screening programme and women's attitudes to attending for cervical smears. A crucial deciding factor will be financial, and this, of course, is subject to the vagaries of politics, public opinion and government priorities. Interesting times lie ahead.

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