EDITORIAL

Prophylactic vaccines for human papillomavirus: a bright future for cervical cancer prevention

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Cervical cancer affects nearly half a million women each year, and nearly half of them die of the disease. The greatest problem is in the developing world, though even in the UK around 3000 women develop cervical cancer each year.

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.[1] 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 and 56) are implicated in cervical cancer. Of these, types 16 and 18 together account for approximately 70–80% of cervical cancers.[2] Infection with HPV appears to be extremely common in young people, but is usually transient.[3] It appears that the presence of HPV is more meaningful in older women (over 30 years old), who have persistent infection.

Screening tests detect cellular abnormalities early, but the ultimate solution to a viral disease is obviously a vaccine. In contrast to most viral vaccines, which are based on an attenuated form of the virus (for example polio vaccine), the development of an attenuated HPV vaccine has been difficult because there is no effective culture system to propagate the virus. 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 as they contain no DNA they are harmless. Another problem is the number of cervical cancer HPV types which need to be included (potentially 15). However, two prophylactic vaccines against types 6, 11, 16 and 18 are showing great promise in clinical trials.[4,5] One of these contains all four HPV types and would thus protect against genital warts (types 6 and 11), as well as the most common cervical cancer HPV types (16 and 18). The other contains types 16 and 18 and thus targets cervical cancer alone. Both vaccines are currently in large, multicentre, worldwide Phase III clinical trials and have shown excellent tolerability, safety and efficacy. So far, the bivalent vaccine appears to be 90–100% effective in preventing both incident and persistent HPV 16 and 18 infection,[4] and similar results have been reported for the quadrivalent vaccine.[5] A feature of HPV infection is that the virus is very successful at avoiding the host immune system, and therefore causing natural immunity. Both vaccines, however, probably due to the addition of an adjuvant, 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.[4,5] 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 is considered not unreasonable to use these endpoints initially.

A vaccine against cervical cancer is a very exciting prospect, but there are a number of unanswered questions.[2] Will there be any cross-protection against HPV types not included in the vaccines? This has always been thought unlikely, but very recent data have suggested otherwise. In the trial of an HPV 16/18 L1 VLP vaccine, preliminary results suggest a high level of cross-neutralization against HPV types 31, 52 and 45.[6] This is potentially extremely important, as it may raise the overall protection level significantly.

If we eliminate cancer due to HPV types 16 and 18, will other types take their place? Will we need different vaccines for different populations? What might be the effect of a vaccine in HIV-positive women? There are no answers to these questions at present.

Does the method of contraception have any effect on vaccine efficacy? A recent study demonstrated significant differences in cervical IgG vaccine-specific antibodies between ovulating women and those using the oral contraceptive pill.[7] In women using the pill, titres were relatively constant (and high) throughout the month. However, in ovulating women titres varied during the menstrual cycle, being highest during the proliferative phase, decreasing approximately nine-fold around ovulation and increasing approximately three-fold during the luteal phase. In addition, serum- and cervical-specific IgG levels were correlated in pill-using women but not in ovulating women. This may have practical implications when the vaccines are publicly available, since women in the trials have been required to use effective contraception (albeit not necessarily ovulation-inhibiting methods). It has been pointed out that, despite this, the vaccines have so far shown very high efficacy, both in ovulating and non-ovulating women;[8] however, larger, longer-term studies may be needed for certainty.

A tricky issue is deciding at which age a vaccine should be given, since it is best administered prior to the onset of sexual activity. We do not know at present how long the immunity conferred by these vaccines lasts: ideally, such a vaccine would be administered with other childhood vaccines, removing any link with sexual activity in the minds of parents.[9] However, that would depend on the immunity lasting for decades, or boosters being given. And should we not vaccinate boys as well as girls?

Currently, there is interest only in vaccinating girls (for financial reasons), but this is a shortsighted and potentially damaging strategy. 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.[10] It is very unlikely that uptake of the vaccine by girls will even

approach 100%; therefore 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.[11,12]

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.[13–15] However, restricting vaccination to girls has the effect of focussing attention on women in relation to a sexually transmitted virus; there are some cultures in which this may prove unacceptable. In those communities, the role and sexual behaviour of men as vectors is ignored, but it would only be by vaccinating men that women could be protected. The quadrivalent vaccine (containing the types causing genital warts as well as cervical cancer) may be the solution in such societies, as it can be presented as primarily protecting men from warts. There is evidence that social norms around sexual behaviour and sexual health vary between different ethnic communities within the UK,[16] and there appear to be ethnic differences in attitudes to HPV and self-sampling for the virus.[17,18] It is therefore essential to evaluate responses to the HPV vaccine in different ethnic groups.

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.[19–21] 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 of both HPV testing and vaccines.

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.

As always, it is the developed countries which will have the earliest benefit from prophylactic vaccines. Preliminary estimates suggest that the three-injection course will cost around US$200 for the vaccine alone; although modelling suggests that vaccination will be cost-effective,[22,23] this is clearly unaffordable in poor countries. However, organizations such as the Alliance for Cervical Cancer Prevention, the WHO and the Bill and Melinda Gates Foundation have all contributed to developing world projects, and could choose to help these countries set up vaccination programmes. An exciting possibility, particularly for developing countries, is an oral vaccine, as this would be cheap and remove the need for refrigeration. Studies in transgenic plants have shown that both transgenic potatoes and tobacco can express the L1 HPV 16 gene, and that an immune response can be generated.[24–26] Potatoes have frequently been used, but a more palatable system is preferred, as the vaccine must be consumed raw to prevent heat denaturation of the antigens. Both tomatoes and bananas are attractive alternatives and are currently under study. However, it is obvious that an oral vaccine is still many years away from becoming a reality.

In theory, an HPV vaccine could prevent almost all cervical cancers, eventually removing the need for cervical smears. However, until the number of HPV types in the vaccine is increased, there will still be cancers not prevented by vaccination. In addition, there is at least one whole generation of women for whom the vaccine will come too late, and who will continue to require screening. 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 effective, vaccination of a wider age range could have a more immediate impact on cervical cancer. The exact point at which vaccination supersedes screening will depend upon the percentage of cancers preventable by the vaccine, the percentage being prevented by the existing screening programme, the attitude of women to having smears and the attitude of the society in which they live to vaccination against a sexually transmitted virus. It is therefore clear that this will vary considerably in time and place.

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