Vaccines against human papillomavirus: the future is bright

Every year in the UK over 2800 women develop invasive cervical cancer and almost 1100 die (Cancer Research UK, 2006). Until recently, the main way to prevent cervical cancer was through cervical screening programmes. This is set to change. In September 2006, the first vaccine that can prevent cervical cancer (Gardasil, Merck and Co, Inc. New Jersey) was granted a European licence and a second vaccine (Cervarix, GlaxoSmithKline, Rixensart) should be licensed early in 2007. Both vaccines protect against HPV 16 and 18, the types of human papillomavirus (HPV) that account for about 70% of cervical disease (Harper et al, 2004; Villa et al, 2005). Gardasil additionally protects against HPV types 6 and 11 that cause genital warts. The United States Centers for Diseases Control has already recommended routine vaccination with Gardasil for 11- and 12-year-old girls, and for 9–10-year-old girls at the discretion of their physician. In the UK the Joint Committee on Vaccination and Immunisation is reviewing the use of HPV vaccines and their potential benefits.

The challenge of vaccinating against HPV

Introduction of HPV vaccines presents an exciting public health challenge, requiring decisions on which vaccine to introduce (if at all), who to vaccinate and how to ensure high coverage (Bosch et al, 2006).

Choice of vaccine

Both vaccines are more than 90% protective against type-specific persistent HPV infection and 100% effective in preventing moderate or pre-cancerous lesions. Both are given in a series of three 0.5 ml intramuscular injections over a 6-month period. After three doses, detectable antibody levels to each HPV genotype are 10–104 times higher than in natural infections and persist at high levels for at least 5 years post-vaccination. No serious vaccine-related events have been recorded for either vaccine, nor for pregnant women who were vaccinated inadvertently with Gardasil. One clinical advantage of Gardasil is that it prevents genital warts. This is an important consideration because in 2001 in the UK there were 32 185 diagnoses of genital warts in females, 29% of which occurred in adolescents (Public Health Laboratory Service, 2002). Although they do not usually result in mortality, genital warts cause significant morbidity and substantial health-care costs. However, the risk of stigmatization is potentially greater for a quadrivalent vaccine as it is more likely to be perceived as a vaccine against sexually transmitted infections rather than a cancer vaccine.

The other main consideration in choice of vaccine will be the cost. Where it has been licensed, Gardasil is over US $100 per dose and both drug companies will operate a variable pricing scheme for developed and developing countries. Cost is a major factor in the UK, because infant and childhood vaccinations are provided by government, rather than by the private sector.

Who to vaccinate

The protection afforded by these vaccines is demonstrated for women with no evidence of current or prior HPV infection at recruitment. Effectiveness is uncertain among women with current HPV infection. For this reason it is recommended to administer preventive vaccines to (pre)-adolescent girls before they become sexually active and exposed to HPV. The risk of infection is highest soon after onset of sexual activity and in the UK, 25% of adolescents will initiate sex before the age of 16 years (Wellings et al, 2001).

In the largest study population to have undergone routine cervical screening with both liquid-based cytology and HPV testing in the UK, HPV prevalence was 40% among women aged 20–24 years (Kitchener et al, 2006). Among adolescents attending genitourinary medicine clinics in the same geographical location, 65% were HPV DNA positive (Brabin et al, 2005). These data support the view that in the UK, the primary target group for vaccination should be girls aged 10–14 years. For immunological reasons, antibody responses induced by vaccines are also higher when they are administered pre-pubertally.

The potential gains from vaccinating males need to be considered, including indirect (reduced HPV transmission) as well as direct effects (prevention of male cancers). So far, results of dynamic simulation models of HPV transmission suggest that if high coverage of females can be achieved, there is little additional reduction in cervical cancer gained by vaccinating males. This economic argument needs to be clearly explained to the general public to whom a single-sex vaccine policy may seem inequitable.

Ensuring high coverage of female adolescents

A number of studies, mostly conducted in the US, indicate considerable interest in adolescent HPV vaccination among parents. Sociodemographic factors do not strongly affect vaccine uptake as opinions cut across ethnic, socioeconomic and religious divisions. In a population-based study conducted in Manchester, 81% of parents of 11–12-year old pupils said they would consent to future HPV vaccination, although only 38% were definite in their approval (Brabin et al, 2006). Long-term safety of the vaccine was an important issue, and a minority of parents would refuse on grounds that vaccination could encourage early sexual debut or riskier sexual behaviour. Perhaps most worrying was some parents' failure to accept the possibility that their child might be at risk of a sexually transmitted infection, as well as over-estimation of young people's efficacy in using condoms, which may partly protect against HPV.

There will be large differences between countries in how vaccination is implemented. School vaccination programmes would be feasible in the UK but more certainty about the acceptability by the

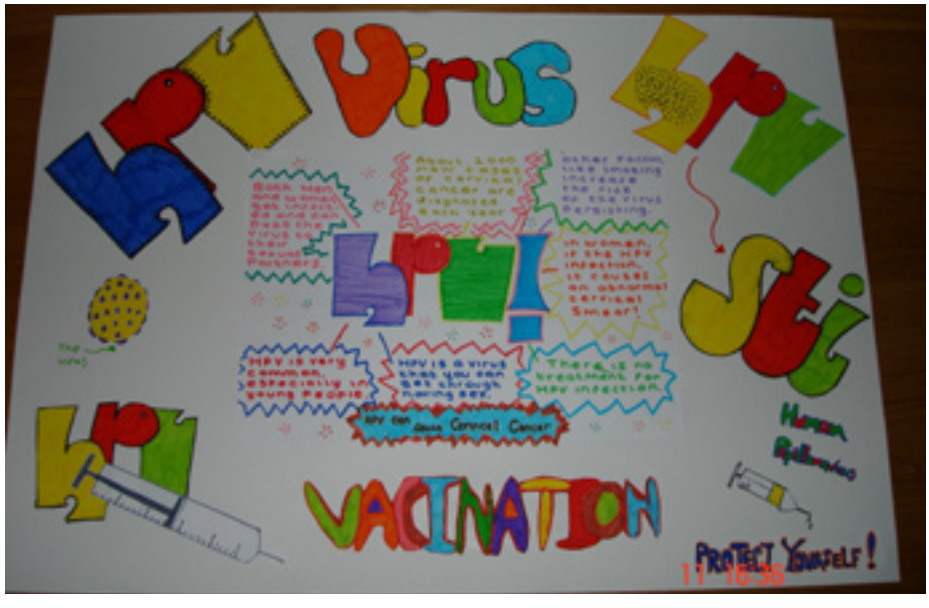
public of routine vaccination against a sexually transmitted infection is required. A study in Glasgow showed the feasibility of introducing adolescent hepatitis B vaccination, where it was offered to 10 800 11–12-year-old pupils through the school system (Wallace et al, 2004). Vaccine uptake was 91.3%, 89.3% and 80.2% for one, two and three doses respectively.

HPV vaccination of young adolescents is seized upon by the media as a controversial issue, and needs to be counter-balanced by a carefully prepared education and information strategy that fosters initially favourable views of parents. Many studies show that women want more information about HPV. They also want their health providers to be well informed and to be able to answer their questions. One study of paediatricians found that varicella vaccine acceptance was directionally proportional to the strength of the doctor's recommendation (Ehresmann et al, 2000). Unfortunately many health professionals have limited knowledge about HPV, cervical cancer and HPV vaccines. US studies have also shown some reluctance of health providers to vaccinate young adolescents as well as to address sexuality issues with adolescent patients who should understand the link between HPV and cervical cancer (*Figure 1*).

Implications of HPV vaccination for future cancer prevention

Targeting 10–14-year-olds (and perhaps time-limited catch-up programmes for young women aged 15–26 years) means that it will be 15–20 years before any impact on cervical cancer rates is observed. This allows time to anticipate and introduce changes to the cervical screening programme. It can be assumed that women receiving the full three doses will have lower rates of mild to severe cervical intra-epithelial neoplasia. This should translate into savings to the health-care system but may lead to some reduction in cytology caseload and, indeed, to a decrease in the positive predictive value of Pap cytology. In other words increasingly larger proportions of women who screen positive will have a false-positive diagnosis. It is likely that in the post-vaccination era there will be re-structuring based on HPV screening and triaging with the Pap smear. In the meantime, vaccinated and unvaccinated women should be reminded of the importance of regular attendance for cervical screening. **BJHM**

Figure 1. Educating school children about prevention of cervical cancer.



KEY POINTS

- Two vaccines, Cervarix and Gardasil, can prevent cervical cancer.
- In the UK, the main target for vaccination should be girls aged 10–14 years.
- Research indicates that the majority of parents will be receptive to human papillomavirus (HPV) vaccination.
- High coverage could be achieved through school vaccine programmes.
- Health practitioners must be ready to advise parents and adolescents about HPV and cervical cancer prevention.

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Figure 1 *is reproduced courtesy of Lorraine Vallely.*

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