Preventing cervical cancer by vaccinating against HPV

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There was widespread media interest in a report on the successful results from a trial of a vaccine against virus strains responsible for cervical cancer. This article examines the background to the report, considers the actual outcomes and comments on the significance and likely impact of the vaccine.

Cervical cancer is the second most common gynaecological cancer after ovarian cancer. Research has found that human papilloma viruses (HPVs) are responsible for most, possibly all, cases and are also implicated in other anogenital cancers and in a subset of head and neck cancers (zur Hausen, 2002).

A relatively limited number of HPV genotypes are classified as high risk and these have been isolated from almost all cervical cancers studied (Bekkers et al, 2004). Unfortunately, while condoms are highly effective in preventing transmission of most sexually transmitted diseases, they are less effective in preventing spread of HPV (Cotran and White, 2002). This means the only strategy likely to disrupt spread of HPV is an effective immunisation programme. At least 50 per cent of sexually active adults will acquire genital HPV infection (Valdiserri, 1999).

**The vaccine**

The idea of a vaccine to protect against HPV has existed for almost two decades. Widespread availability of an effective vaccine against the high-risk subtypes of HPV would offer the potential to greatly reduce global mortality due to cervical cancer, particularly in developing countries where large-scale screening and early treatment may not be feasible.

On the basis of animal studies it has been suggested that an HPV vaccine would be effective in humans. If globally applied, prevention of infection by the most high-risk HPV types could prevent more than 300,000 cases of cervical cancer per year worldwide (zur Hausen, 2002).

The proteins on the surface of the virus (capsids) differ between strains. Under suitable conditions they will self-assemble into virus-like particles (VLPs) – in effect ‘empty’ virus shells. These have been shown to be capable of inducing a potent, specific and durable immune response that is protective against infection with the specific HPV strain from which the VLP is derived. The vaccine used in the current trial is effective against HPV strains 6, 11, 16 and 18. Strains 16 and 18 are the most frequently implicated as causes of cervical cancer (Franceschi, 2005), and strains 6 and 11 are strongly associated with (benign) genital warts and were probably included to encourage uptake of vaccination by men, who have a lower incidence of HPV-induced malignancy, but may be vectors for the high-risk strains (Castellsague et al, 2001).

**The study**

The study, called Future II, was a phase-III trial of a vaccine called Gardasil. The participants were 20,559 women in 13 countries who were aged between 16 and 26 and seronegative for infection with HPV strains 16 and 18. Half of the group received three doses of the vaccine, while the remainder received a placebo.
The results of the trial have so far only been presented as an abstract at the annual conference of the Infectious Diseases Society of America, and no paper has yet been published giving full details of the trial and outcomes. Published results of previous trials indicate that the vaccine is safe, well tolerated and effective, but only short-term follow-up data is available at present.

The phase II trial has a maximum follow-up of three years, while the current phase III trial has only two years’ follow-up. Epidemiological studies suggest that, in unprotected women, most HPV infections are acquired in the late teens or early 20s, premalignant lesions peak in incidence around 30 years of age, while women with invasive cancer tend to be about 10 years older (Heard, 2005). The natural history of the disease clearly shows that, to be fully effective, the vaccine must induce long-lasting immunity to HPV infection. Over a two-year follow-up period no cases of cervical cancer or precancerous lesions occurred in the women who received all three doses of the vaccine, whereas 22 cases occurred in the placebo group. One case of cervical cancer occurred in the small group of women who received only one dose of vaccine, but this still represents 97 per cent efficacy, according to Dr Eliav Barr, Merck’s head of clinical development for the vaccine. The most common side-effects were mild discomfort at the injection site and mild headache. No woman left the trial because of adverse effects.

The future

Clearly the results of the vaccine trial are impressive and offer great hope for the future. However, important questions need to be answered before the vaccine can be approved for general use. It is certainly not the case that smear tests can be abandoned in the near future and health planners will have a difficult task deciding when, if ever, this can be done. In the immediate future there are millions of women who are already infected with HPV, or who will become infected before a vaccine is routinely available. Prevalence studies suggest that fewer than one per cent of women with clinically detectable infection develop invasive cervical cancer (Tindle, 2002) but even at this low level of progression virtually all developed countries deem that the cost of cervical screening to health care providers and its inconvenience to women can be justified and have set up universal screening programmes.

One question to be answered is what will happen to the cost-benefit ratio of these screening programmes when the incidence of HPV infection is much lower and so also is the rate of progression. At what point will a screening programme cease to be viable? The decision to cease screening may not arise since the high-risk strains in the vaccine (HPV 16/18) account for only about 72 per cent of all cases of cervical cancer (Lowy and Frazer, 2003); the remainder are caused by other strains or, in about five per cent of cases, have no viral component in their aetiology. The level of disease that will persist when protection against HPV 16 and 18 is complete cannot be predicted – it may be high enough to justify continuing with routine screening.

A particularly sensitive issue is the age at which vaccination should occur, since it should be given before sexual activity commences if it is to be optimally effective. The average age of first sexual intercourse is falling in most western countries and is commonly below the age of legal consent for females. This means it will be necessary to set the vaccination age below the age of consent, which clearly invites accusations of condoning underage sexual activity. Some groups fear that vaccinating girls against a virus that is predominantly sexually transmitted will encourage promiscuous behaviour. However, this argument may be countered by the fact that HPV vaccine protects only against cervical cancer in later life and not against other consequences of sexually reckless behaviour. There may be difficulty in persuading populations to vaccinate young boys, since they are at low risk of HPV-associated anogenital malignancy unless they have HIV infection. However, the inclusion in the vaccine of HPV 6 and 11, which cause benign anogenital lesions in boys, may encourage uptake. It should be recalled that rubella vaccination of boys is undertaken chiefly to maintain high herd immunity and thus to protect pregnant women – and therefore unborn babies – from exposure to rubella (Lowy and Frazer, 2003).

**TABLE 1. RESULTS FROM TRIAL OF GARDASIL VACCINE**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Placebo</th>
<th>Efficacy</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Cases</td>
<td>Rate †</td>
<td>n</td>
</tr>
<tr>
<td>PP</td>
<td>5301</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>MITT</td>
<td>5736</td>
<td>1</td>
<td>&lt;0.1</td>
</tr>
</tbody>
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†(n/subject years at risk) × 100  ‡multiplicity adjusted (interim analysis)

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