

Cervarix, a bivalent HPV vaccine to prevent cervical cancer

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KEY POINTS

- Cervarix is a bivalent vaccine against HPV-16 and HPV-18, which account for over 80 per cent of cases of cervical cancer in the UK
- licensed for the prevention of high-grade cervical intraepithelial neoplasia and cervical cancer causally related to HPV-16 and HPV-18, and has been selected for the NHS HPV immunisation programme
- administered as a course of three injections over six months
- seroconversion is virtually complete and sustained for over four years
- in the pivotal trial, persistent infection in women with no evidence of infection at baseline was reduced by 84 per cent for HPV-16 and 74 per cent for HPV-18
- interim analysis of this trial suggests that Cervarix may prevent all new high-grade cervical lesions associated with HPV-16 and HPV-18
- the commonest adverse events were injection-site pain and transient arthralgia and myalgia



Cervarix, a bivalent vaccine against HPV-16 and -18, is licensed for the prevention of cervical cancer and has been chosen for the HPV immunisation programme. In our New products review, Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Mr Nick Nicholas comments on its place in HPV protection.

Human papilloma virus (HPV), one of the commonest sexually transmitted infections, causes cervical cancer. Sixteen of the 40 viral genotypes are highly oncogenic – the two most frequently associated with cervical cancer are HPV-16 and HPV-18, accounting for 82 per cent of invasive cervical cancers in the UK.¹

According to the WHO, approximately 7 per cent of women in the UK have HPV infection; almost 3200 women are diagnosed with cervical cancer each year and over 1500 die from it.¹ Recent UK data from 1483 girls and women aged 10-29 suggest a prevalence of 12 and 5 per cent for HPV genotypes 16 and 18 respectively.²

The government has announced that all girls aged 12-13 will be routinely offered HPV vac-

ination with Cervarix from September 2008. A two-year catch-up programme to vaccinate girls under the age of 18 will start in Autumn 2009.³

The first HPV vaccine introduced in the UK was Gardasil, a quadrivalent vaccine conferring immunity against genotypes 6, 11, 16 and 18. Cervarix is a bivalent vaccine against genotypes 16 and 18.

The technology

Like Gardasil, Cervarix contains virus-like protein produced by recombinant DNA technology, though using a different expression system. Whereas Gardasil is formulated with a conventional aluminium hydroxide adjuvant, Cervarix includes a modified adjuvant (ASO4) associated with an enhanced immune response.⁴

Cervarix is licensed for the prevention of high-grade cervical intraepithelial neoplasia (CIN grades 2 and 3) and cervical cancer causally related to HPV-16 and HPV-18. Gardasil is additionally licensed for the prevention of high-grade vulvar dysplastic lesions and external genital warts. Cervarix is administered by intramuscular injection at 0, 1 and 6 months. In clinical trials, it was associated with virtually complete seroconversion against HPV-16 and HPV-18 for up to four years.⁴ It is contraindicated during pregnancy, though limited experience does not suggest a risk.

Clinical trials

Two randomised trials and one extension study provide the key data for the efficacy and safety of Cervarix.⁵⁻⁷

The first trial⁵ randomised 1113 women aged 15-25 who were seronegative for HPV-16 and HPV-18 and negative for HPV infection and had normal cytology. The primary end-point was the incidence of cervical HPV infection, which is not the licensed indication. However, cervical cancer was included among the secondary end-points. After 27 months' follow-up, the vaccine reduced cervical infection by HPV-16 and HPV-18 by 95 per cent and associated cervical cytological abnormalities by 93 per cent compared with placebo.

The extension study included 776 women with an average follow-up of 54 months after completing the course of vaccination (see Figure 1).⁶ Protection against infection was maintained. Combined analysis of the original and extension studies showed complete protection against CIN associated with HPV-16 and HPV-18.

The pivotal trial involved 18 644 women aged 15-25 randomised to Cervarix or hepatitis A vaccine (HAV); 74 per cent had no evidence of infection by HPV-16 or HPV-18, and 22 per cent had abnormal low-grade cytology or evidence of infection by oncogenic HPV at baseline.

The primary end-point was protection against CIN2+ lesions associated with HPV-16 or HPV-18 among women who were originally seronegative. Only an interim analysis (mean follow-up 15 months) is currently available. This was conducted when at least 23 cases of CIN2+ associated with HPV-16 or HPV-18 had been identified. By this time, 954 women had withdrawn, equally divided between the groups, mostly lost to follow-up.

Vaccine efficacy in preventing CIN2+ lesions was 90 per cent – two cases in the Cervarix cohort and 21

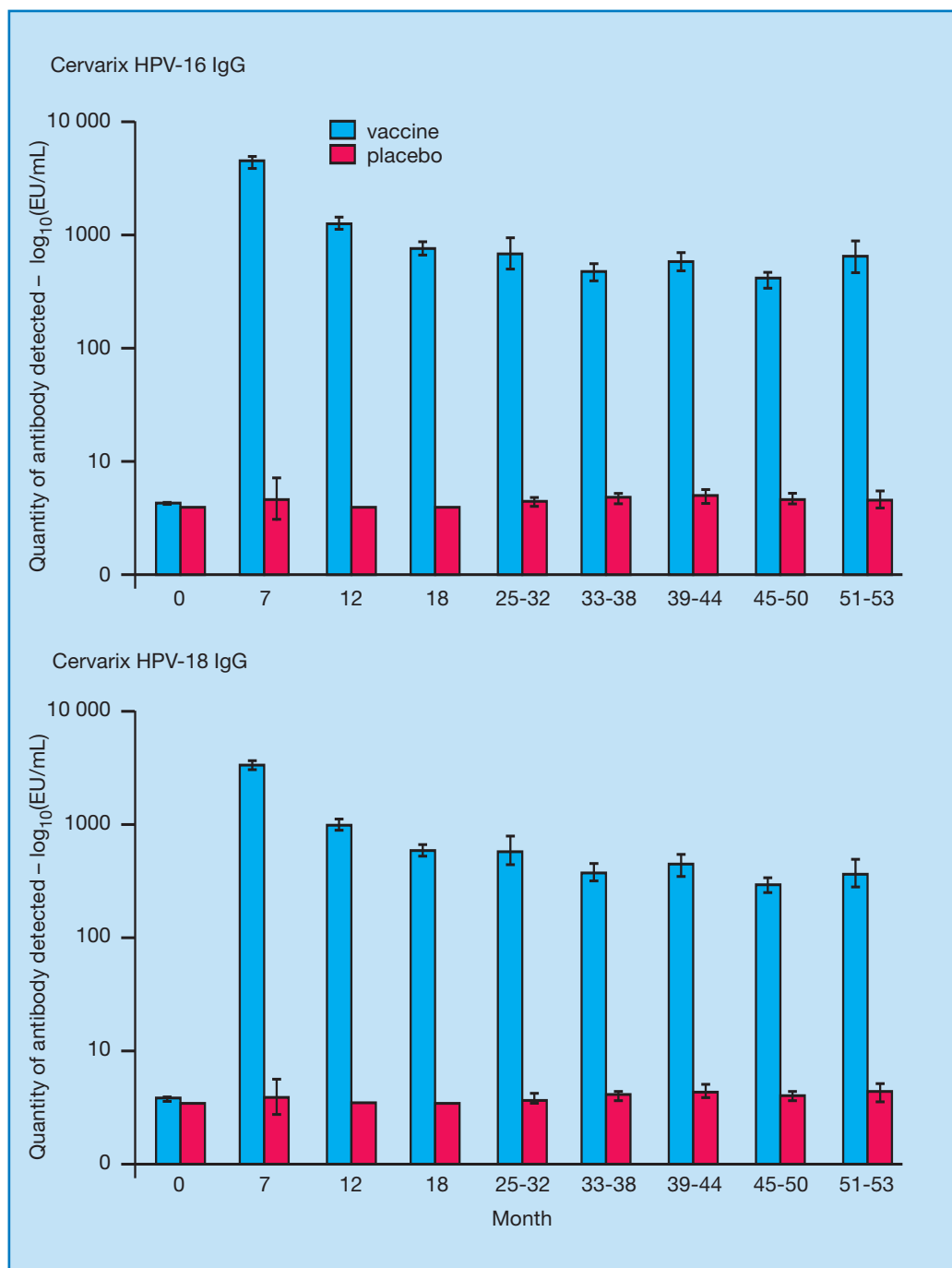


Figure 1. Long-term persistence of HPV-16 and -18 antibodies in blood samples, determined by enzyme-linked immunosorbent assay (ELISA), following vaccination with Cervarix

in the control group (see Table 1). *Post-hoc* analysis excluding lesions not likely to have been due to HPV-16 or HPV-18 excluded both lesions in the Cervarix cohort and one in the control group, implying complete protection against CIN2+

lesions. Persistent infection in women with no evidence of infection at baseline was reduced by 84 per cent for HPV-16 and 74 per cent for HPV-18. Protection rates were similar when baseline serological status was ignored.

Event type	Group	N	n	% vaccine efficacy	p-value
HPV-16/18	HPV	7788	2	90.4	<0.0001
	HAV	7838	21	-	-
HPV-16	HPV	6701	1	93.3	0.0005
	HAV	6717	15	-	-
HPV-18	HPV	7221	1	83.3	0.1249
	HAV	7258	6	-	-

Table 1. Incidence rates (n) and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (determined by polymerase chain reaction) in HPV DNA negative and seronegative subjects at baseline; HAV = hepatitis A vaccine (control group)

Adverse effects

The commonest adverse event reported in the clinical trials programme, which included 16 142 women and girls who received at least one dose of Cervarix, was injection-site pain (78 vs 41-59 per cent with adjuvant alone or HAV). Arthralgia (10.2 vs 8.6 per cent) and myalgia (28.1 vs 26.5 per cent) were slightly more common with Cervarix than controls but were short lived and not severe.

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By Steve Chaplin, a pharmacist who specialises in writing on therapeutics

Place in therapy

Although cervical cancer mortality rates in 2006 (2.4 per 100 000 females) are nearly 70 per cent lower than they were 30 years ago (7.6 per 100 000 females), cervical cancer is still a condition that has major worldwide impact on women's health. According to the WHO, there were around 500 000 new cases of cervical cancer in 2005.

In the UK, cervical cancer is the second most common cancer in women under 35 years old. About 6 per cent of cervical cancer deaths occur in women under 35, with the majority occurring in women over

75. This condition is therefore a disease that affects women in the reproductive age.

HPVs comprise a large group of virus types, some of which are 'low risk' causing benign warts and flat papillomas, while others are 'high risk' and associated with cervical cancer in women; these are referred to as oncogenic or carcinogenic HPVs, the commonest being types 16 and 18.

HPVs are sexually transmitted and it is estimated that by the age of 50, 80 per cent of all women will have become infected at some time. Not all HPV infections cause cervical cancer. However, persistence of HPV infection is thought to be the main cause.

Refraining from genital contact and sex, or perhaps more realistically having fewer sexual partners and using condoms, can reduce HPV infection risk, but does not eliminate it.

Natural infection with HPV does not confer sufficient immunity to further HPV infections, hence the need for immunisation.

Cervarix is one of two vaccines currently available for vaccination against HPV and thus cervical cancer. Implementation of vaccination has the potential to reduce the incidence of cervical cancer by at least 70 per cent, since there is some early indication that cross-reactivity with other high-risk oncogenic HPVs

may also occur.

Protection against HPV-16 and -18 with the Cervarix vaccine lasts at least four years and further work is ongoing to determine whether booster vaccinations will be necessary.

The UK's Joint Committee on Vaccination and Immunisation, which provides independent expert advice to ministers on vaccination, recommended in June 2007 that the government should implement an HPV vaccination programme. However, the dilemma was which of the two vaccines should be adopted.

The choice was between the quadrivalent Gardasil and the bivalent Cervarix. Both vaccines were assessed on a wide range of criteria, especially their scientific qualities and cost effectiveness. Cervarix was selected in preference to Gardasil, and contrary to the more common decision to use Gardasil taken by many EU countries.

The main reasons for choosing Cervarix were price and the possibility that the adjuvant used appears to be more immunogenic, thereby potentially reducing the need for further booster injections (also see Editorial, pages 7-11). However the long-term efficacy of both vaccines is thought to be the same, and the Gardasil vaccine provides additional protection against genital warts.

The impact of worldwide vaccination will take 20 years to realise. Since Cervarix does not protect against all HPVs, it is very important that the message gets to all women between 25 and 64 years in the UK that the National Cervical Screening Programme must continue in its current form.

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