

HPV Vaccination advice – BASHH HPV Special Interest Group

Two prophylactic HPV vaccines are currently available in the UK. Gardasil[®] is a quadrivalent virus-like particle (VLP) vaccine developed by Sanofi Pasteur MSD and was licensed in the UK in October 2006. The vaccine provides protection against infection with HPV types 6, 11, 16 and 18 and is licensed in Europe (by the EMEA) for the prevention of high-grade CIN and VIN, cervical carcinoma and external genital warts causally related to HPV 6, 11, 16 and 18. The indication is based on the demonstration of efficacy of Gardasil[®] in adult females 16 to 26 years of age and on the demonstration of immunogenicity in 9 to 15 year old children and adolescents. Considering pooled results from four studies for the per-protocol population (i.e. those who had no vaccine-type HPV infection at baseline and went on to receive all doses of the vaccine or placebo and had no protocol violations) for the primary outcome measure (the combined incidence of HPV 16- or 18-related CIN 2 or 3 or worse) showed 1 case (of CIN 3) with the vaccine compared to 85 cases with placebo, equivalent to 99% efficacy (95% CI 93% to 100%). This single case may have been caused by HPV 52. There were no cases with the vaccine of anogenital disease (i.e. anogenital warts, or premalignant lesions of the vulva or vagina) associated with the vaccine HPV types compared to 60 with placebo (100% efficacy, 95% CI 94% to 100%). Gardasil[®] has also shown efficacy in decreasing the incidence and persistence of infection with HPV 6/11/16/18 in men aged 16-26 years.

Cervarix[®] is a bivalent VLP vaccine developed by GlaxoSmithKline and was licensed in the UK in September 2007. The vaccine provides protection against infection with HPV types 16 and 18 and is licensed in Europe for the prevention of premalignant cervical lesions and cervical cancer causally related to the vaccine HPV types, but not for prevention of genital warts. Cervarix[®] has demonstrated 100% efficacy in preventing cervical pre-cancerous lesions due to HPV types 16 and 18 in women 15-25 years of age in per-protocol analyses.

GSK have conducted a head-to-head study of Cervarix[®] and Gardasil[®] whose primary objective was to compare immune responses to HPV types 16 and 18. Cervarix was shown to

produce 2.3 - 4.8 fold higher neutralising antibodies against HPV16, and 6.8 - 9.1 fold higher antibodies against HPV 18. This was associated with a 2.7 fold higher induction of memory B-cells. However, the correlation between these differences in immune response with long term protection against disease remains a subject of debate.

A national programme using Cervarix^R to vaccinate girls aged 12–13 years began in the UK in September 2008 with a 2 year 'catch up' programme for those under the age of 18.

Both Gardasil^R and Cervarix^R are given as 3 injections over 6 months. Practitioners may prescribe Gardasil^R and Cervarix^R, taking into consideration trial data and the subsequent indications for vaccination arising from these data. Vaccination on the NHS of people at risk who are not included in the national vaccination programme is at the clinical discretion of GPs and other medical practitioners. The cost to the NHS of three doses of either vaccine outside the national vaccination programme is currently £241.50. This would be more costly for a patient receiving private prescription.

A few general points:

As HPV is such a common infection, sexually active individuals requesting vaccination may well have been previously infected. HPV serology is not generally available and may not provide helpful information for individual patients. The low sensitivity of the assays used to detect antibodies and the variable time interval between infection with HPV and seroconversion suggest that serology is best restricted to use as a marker of past or current HPV infection in population-based studies.

Obtaining genital swabs for HPV detection by nucleic acid amplification tests (NAATS) should detect current infection but not 'past and cleared' infection and only provides information for the site tested, which would represent a small part of the entire genital epithelium. For these reasons, HPV testing prior to offering vaccination would appear unhelpful.

Vaccination of boys as part of the national immunisation programme appears not to be cost effective and therefore has not

been recommended by government. However, immunogenicity data from the Gardasil^R trials show excellent antibody responses in boys aged 9 -15 years and protection against external genital warts and intraepithelial neoplasia.

Women with a past history of genital warts may request vaccination. Although this suggests previous (or current) infection with HPV 6/11, these patients may still be at risk of acquiring HPV 16/18 and would therefore benefit from vaccination. Similarly, women with a history of CIN 2/3 or high grade VIN may be at ongoing risk of acquiring HPV 6/11/16/18.

The role of vaccination to prevent re-infection after successful treatment (i.e. clearance of lesion +/- HPV DNA negative post treatment) of genital warts, VIN or CIN is unknown.

The currently licensed HPV vaccines are prophylactic and not therapeutic. They are therefore not indicated as adjunct treatment for HPV associated ano-genital disease.

Women who have been vaccinated should participate in the cervical screening programme when eligible/invited to do so. Both vaccines do give some cross protection against some related HPV types (e.g. HPV types 31, 33, 45, 52, 58), and there is evidence that Cervarix induces a greater degree of cross-protection than Gardasil. However, the protection against all HPV types associated with cervical cancer is less than 100%.

As with all medications, practitioners should be aware of the potential implications of prescribing a vaccination beyond license indications.

The duration of vaccine induced protection is not yet known. Booster doses of vaccine may be required but further data are being collected to address this. The immune response to a 'booster dose' of vaccine would appear to be superior to naturally acquired infection following a course of vaccination.

A review article in the Drug and Therapeutics Bulletin (December 2008; 46: 89 – 93) concluded that the quadrivalent vaccine should be offered to those people requiring protection against HPV infection outside the national vaccination programme.

