Human Papillomavirus (HPV) Vaccination

Human papillomavirus (HPV) vaccination was introduced into the immunisation schedule for females aged 12-13 years in September 2008[1].

**NB:** all women, whether vaccinated or not, should be strongly encouraged to attend routine cervical screening at the scheduled age, as vaccination will protect against most, but not all, potentially cancer-causing strains of HPV.

Pathogenesis

HPV is a double-stranded DNA virus, which infects squamous epithelia, including the skin and mucosae of the upper respiratory and anogenital tracts. There are approximately 100 types of HPV, of which about 40 infect the genital tract. Although most infections are asymptomatic and self-limiting, genital infection by HPV is associated with genital warts and anogenital cancers, both in men and in women. It has also been more recently shown that HPV can cause oropharyngeal cancers, and prevalence of these tumours is rising[2].

HPV viruses are classified as either 'high-risk' or 'low-risk' types depending on their association with the development of cancer:

- Genital HPVs are transmitted by sexual contact with an infected individual, usually through sexual intercourse.
- The risk increases with the number of sexual partners, the introduction of a new sexual partner or because of the sexual history of a new partner. The use of condoms reduces but does not eliminate the risk of sexual transmission.
- Non-sexual routes of HPV transmission include vertical transmission from mother to newborn baby.

Of the high-risk types, HPV16 and HPV18 are responsible for more than two thirds of all cervical cancers globally[3, 4]. The majority of high-risk HPV infections are transient and cause no clinical problems. Persistent infection by a high-risk HPV type is the most important causal factor for the development of cervical pre-cancerous and cancerous lesions. Persistence and disease are more common for infections by HPV types 16 and 18 than for other high-risk types. The reduction of cervical cancer was the original aim in the widespread introduction of HPV vaccination, but other benefits have rapidly become apparent.

HPV testing is rapidly becoming a part of the cervical cancer screening programmes across the UK as studies have shown the benefits[5].

Prevention of HPV infection in those eligible for vaccination and in others outside of the routine programme should include advice on safer sex.

Epidemiology

Surveillance of HPV is complex due to the high proportion of asymptomatic infections, the variable presentation of the different viral types and the long period between infection and disease.

A UK seroprevalence study in an unselected population showed that HPV prevalence was extremely low in girls aged 14 years but HPV infections rise sharply in the mid-teens[3].

Prevalence of any HPV type, and particularly of HPV16 or HPV18, is higher in women who have abnormal cytology. HPV is detected in 99% of cervical tumours[4].

Vaccines

There are two HPV vaccines available in the UK: Cervarix® and Gardasil®.

Cervarix® is known as a bivalent vaccine, meaning it protects against two strains of HPV. Cervarix® protects against HPV16 and HPV18 and so is aimed to reduce (in time) the number of cases of cervical cancer. When the UK first started immunising young women against HPV, this was the vaccine chosen.

Gardasil® is a quadrivalent vaccine, meaning it protects against four strains of HPV. Gardasil® protects against HPV16, HPV18 and HPV6 and HPV11. This means that it also protects against genital warts as well as cervical cancer, as HPV 6 and 11 cause the majority of cases of genital warts.
In November 2011, the Department of Health announced that from September 2012 the UK HPV immunisation programme would switch to using Gardasil®.

**Efficacy**

HPV vaccines are highly effective at preventing the infection of susceptible women with the HPV types covered by the vaccine. In clinical trials, both vaccines are over 99% effective at preventing pre-cancerous lesions associated with HPV types 16 or 18 in young women[6]. Current studies suggest that protection is maintained for at least ten years[7]. Based on the immune responses, it is expected that protection will be extended further; long-term follow-up studies are in place[8].

A World Health Organization-funded study on cost-effectiveness of the HPV vaccination across 179 countries showed it was very cost-effective in the majority of countries[9]. Vaccination of 58 million 12-year-old girls in 179 countries had prevented 690,000 cases of cervical cancer and 420,000 deaths.

Gardasil® is also 99% effective at preventing genital warts associated with vaccine types in young women[10]. Australia was the first country to introduce national HPV vaccination with the quadrivalent vaccine, and results after five years from sexual health clinics showed a marked reduction of genital warts in women and also heterosexual men in the vaccinated age group[11]. Between 2007 and 2011, the percentage of women having genital warts in sexual health clinics in the relevant age group dropped from 11.5% to 0.85%. In 2011 no diagnoses of genital warts were made in girls who had been vaccinated. The UK can expect similar reduction, but results will be delayed as the bivalent vaccine was used until 2012.

**Administration dosage and schedule[7]**

Since the immunisation programme began, on a three-dose schedule, it has been established that a two-dose schedule is as effective as a course of three. From 2014, a two-dose schedule has been recommended, as long as vaccination is started before the girl's 15th birthday. This will start at age 11-13 from September 2014 (school year 8 in England and Wales, 9 in Northern Ireland, S2 in Scotland). For either vaccine, a 0.5 ml dose is given first, with the second 0.5 ml dose given 6-24 months later.

The three-dose schedule for girls over the age of 15 is as follows:

- **Schedule for Gardasil®:**
  - First dose of 0.5 ml.
  - Second dose of 0.5 ml at least one month after the first dose.
  - Third dose of 0.5 ml at least three months after the second dose.

- **Schedule for Cervarix®:**
  - First dose of 0.5 ml.
  - Second dose of 0.5 ml, one to two and a half months after the first dose.
  - Third dose of 0.5 ml at least five months after the first dose.

If vaccination has been started before September 2014, if the three-dose schedule has been started, it should be completed as per the schedule above. If the second dose has been given within six months of the first, two doses are not considered to confer adequate long-term immunity. Therefore, a third dose should be given.

Vaccines are given intramuscularly in the upper arm or anterolateral thigh.

**HPV immunisation programme cohort[7]**

The objective of the HPV immunisation programme is to provide three doses of HPV vaccine to females before they reach an age when the risk of HPV infection increases and they are at subsequent risk of cervical cancer.

**Females aged 9 to 11 years**

Gardasil® and Cervarix® are licensed for individuals from the age of 9 years. Vaccination is not routinely recommended for those aged 9 to 11 years and is not covered by the national immunisation programme.

**Females aged 11 to 18 years**

HPV vaccination is routinely recommended for all girls at 11 to 14 years of age with the first dose offered in school year 8 in England and Wales, S1/S2 in Scotland, and school year 9 in Northern Ireland.

If the course is interrupted then it should be resumed but not repeated, ideally allowing the appropriate interval between the remaining doses. For girls who miss starting a course of vaccination in the first target year, those less than 15 years of age should still start on a two-dose schedule. Those aged 15 or less than 18 years of age should start a three-dose schedule.

**Females aged 18 or over**

Vaccination against HPV is not part of the routine immunisation programme for those aged 18 years or over. However, for those who did not complete their vaccinations during the catch-up programme it is reasonable to do so after the age of 18.
Vaccination of females with unknown or incomplete immunisation status

Where a female in the target cohort aged over 12 and under 18 years presents with an inadequate vaccination history, every effort should be made to clarify what doses they have had. A female who has not completed the schedule should complete the vaccination course at the minimum interval (see above) where possible. Females coming to the UK from overseas may not have been offered protection against HPV in their country of origin and should be offered vaccination where appropriate.

Vaccination of boys

Males of any age are not currently covered by the national immunisation programme. This is currently the subject of much debate and controversy[2, 12]. Gender-neutral vaccination has been recommended in other countries, such as the USA, Canada, Australia and Austria. This is because, although there may be a herd immunity effect in reducing genital warts in heterosexual men, it discriminates against men who have sex with men. It is thought that where both boys and girls are routinely vaccinated this will also help significantly reduce other anogenital and oropharyngeal cancers.

Adverse reactions

All suspected adverse drug reactions, no matter how minor, should be reported in children under 18 years (even if the black triangle symbol has been removed), using the Yellow Card reporting scheme (www.mhra.gov.uk/yellowcard)[14].

As with most vaccines, the most common side-effect is mild-to-moderate swelling, redness and pain at the site where the injection is given[15]. Other mild side-effects (eg, slightly raised temperature, sickness, dizziness, diarrhoea and muscle aches) have been reported.

Very rarely, as with most vaccines, some people have an allergic reaction or anaphylaxis soon after immunisation.

There have been a few case reports of primary ovarian failure following vaccination, thought to be due to the vaccine triggering an autoimmune condition[16]. Systematic reviews and meta-analyses of the vaccine so far, however, suggest the incidence of serious adverse reactions is insignificant[17].

Individuals with immunosuppression or with HIV infection should be considered for HPV vaccines. However, individuals who are immunosuppressed may not develop a full antibody response. Three-dose schedules are advised in this group. Re-immunisation should be considered after treatment is finished and/or recovery has occurred. Specialist advice may be required.

Further reading & references

- **Human papillomavirus (HPV): the green book, chapter 18a**: Public Health England (June 2014)
- **Stanley M, O'Mahony C, Barton S**: HPV vaccination. BMJ. 2014 Jul 29;349:g4783. doi: 10.1136/bmj.g4783.
- **HPV vaccine to be given to boys in England**: Govuk (July 24th 2018)
- **British National Formulary**

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