Department of Health

The 'Green Book' chapter on Human papillomavirus (HPV)

18a

Human papillomavirus (HPV)

The disease

Human papillomavirus (HPV) is a double stranded DNA virus, that 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 (McCance, 2004). Although most infections are asymptomatic and self-limiting, genital infection by HPV is associated with genital warts and anogenital cancers in both men and women. 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, primarily through sexual intercourse. The risk therefore, is related to the number of sexual partners, the introduction of a new sexual partner, and the sexual history of any partner. Studies of incident HPV infection, based on HPV DNA detection, demonstrate that acquisition of at least one type of HPV infection often occurs soon after sexual debut with almost 40% of women being infected within two years (Winer *et al*., 2003; Winer *et al*., 2008).

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.

Persistent infection by high-risk HPV types is detectable in more than 99% of cervical cancers (Walboomers *et al*., 1999). Of these high-risk types, HPV16 is responsible for almost 60% and HPV18 for more than 15%, of all cervical cancers in Europe (Smith *et al*., 2007). A further 11 high-risk types have been described (WHO IARC, 2007)[1]. In addition to cervical cancer, HPV is causally associated with other less common cancers, including

[1] Including types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66

cancer of the vulva, vagina, penis and anus, and some cancers of the head and neck (Parkin *et al*., 2006; Stanley, 2007). Infection by multiple types is common (Cusheri *et al*, 2004).

The majority of HPV infections are transient and cause no clinical problems. Around 70% of new infections will clear within one year and approximately 90% will clear within two years (Ho *et al*., 1998; Franco *et al*., 1999). The median duration of a new infection is eight months. 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 is more common for infections by HPV types 16 and 18 than for other high-risk types. The time span between infection by HPV and the development of CIN3 or cervical cancer varies from one to ten years (Moscicki *et al*., 2006).

Although high-risk HPV infection is a risk factor for the development of vaginal or vulval lesions, unlike cervical cancer, only approximately 40% are associated with HPV infection (Munoz *et al*., 2006). The natural history of vaginal and vulval cancers is not completely understood. HPV infection is associated with 80-90% of all anal squamous cell cancers and HPV types 16 and 18 are found in the majority of HPV-related anal cancers (Munoz *et al*., 2006). Around 40% of cases of penile cancer are attributable to HPV infection (Rubin *et al*., 2001). For all sites, the evidence for a causal association is greater for HPV types 16 and 18, than for other HPV types, and the majority of HPV related cancers are associated with types 16 and 18.

Low-risk HPV types are responsible for genital warts, which is the most commonly diagnosed viral sexually transmitted infection in the UK (Fenton *et al*., 2004), (HPA, 2012). HPV types 6 and 11 cause the majority of all genital warts (Lacey *et al*., 2006; Garland *et al*., 2007). Genital warts appear from three weeks to eight months after primary infection (most commonly two to three months) (Oriel, 1971). In the absence of treatment, up to 30% of individuals clear the infection in the short term (Tyring *et al*., 1998; Edwards *et al*., 1998). The rate of spontaneous regression in the long term is not known. Treatments focus on removal of the warts, but do not necessarily eliminate infection, which may persist sub-clinically, and be a source of recurrence and continuing viral transmission. Genital warts are not life threatening, but they can cause significant morbidity.

HPV infection has been associated with cancerous and non-cancerous lesions outside the ano-genital area including laryngeal papillomas, (Stamataki *et al*., 2007) and some head and neck cancers (Psyrri *et al*., 2008).

History and epidemiology of the disease

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. Among 10- to 29-year-old women, 11%, 3%, 12% and 5% have evidence of ever having been infected by HPV types 6, 11, 16 or 18 respectively (Jit *et al*., 2007).

Information on the prevalence of high-risk HPV infection is available from a large cross-sectional study of women having routine cervical screening in England (Howell-Jones *et al*., 2010). This study found evidence of current high-risk HPV infection (indicated by the presence of HPV DNA) in 29% of women aged 25 to 29 years, with prevalence declining with increasing age after 30 years. Prevalence of any HPV type, and particularly of HPV 16 or 18, was higher in women who had abnormal cytology.

Information on incidence of genital warts comes primarily from people attending genitourinary medicine (GUM) clinics. Over 90,000 new cases of genital warts were diagnosed in GUM clinics throughout the UK in 2009 (HPA, 2012). Rates of diagnoses are highest in young men and women under 24 years.

Cervical cancer is the second commonest cancer of women worldwide, with approximately 500,000 new cases and 270,000 deaths annually (Munoz *et al*., 2006; Parkin *et al*., 2006).

The introduction of a national cervical screening programme in the UK has made a major contribution to the fall in the incidence and death rate from cervical cancer. Due to cervical screening in the UK, mortality rates fell approximately 60% between 1974 and 2004 (Peto *et al*., 2004).

The national HPV immunisation programme was introduced in September 2008 with all girls in school year 8 (aged 12 to 13 years) offered vaccine against HPV infection, with a 'catch-up' campaign for girls aged from 14 years to less than 18 years.

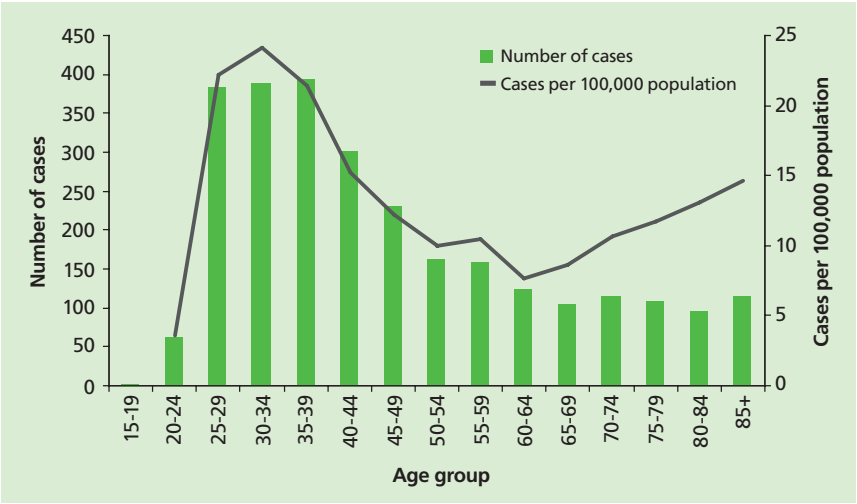

Figure 1 Number of cases of newly diagnosed cervical cancer in England, 2009 (source: National Statistics, 2011).

A total of 2747 new cases of invasive cervical cancer were diagnosed in England in 2009 (National Statistics, 2011). The peak incidence occurred in women in their 30s with a second smaller peak in women in their 70s-80s (i.e. women less likely to have benefited from cervical screening during their lifetimes; Figure 1). In the UK, the lifetime risk of developing cervical cancer is estimated as 1 in 116 (National Statistics, 2004). In the UK, approximately one third of women die within five years of the diagnosis of invasive cervical cancer (National Statistics, 2011).

There are certain groups of women reported to have low cervical screening rates, e.g. ethnic minority groups and women born in foreign countries (Webb *et al*., 2004; Thomas *et al*., 2005). There has also been a downward trend in the number of young women taking up invitations for cervical screening since the mid-1990s (Department of Health, 2007, NHS Cervical Screening Review, 2011).

In addition to cervical cancer, HPV is also associated with other anogenital cancers. In the UK, anal cancer is rare, with around 850 cases diagnosed annually (National Statistics, 2011). Overall, anal cancer is more common in women than in men, but relatively high rates are found among men who have sex with men. In the UK, there are around 1200 cases of vulval and vaginal cancers per year.

The HPV vaccination

HPV vaccines are sub-unit vaccines made from the major protein of the viral-coat or capsid of HPV. Virus-like particles (VLPs) are prepared from recombinant proteins grown in either yeast or baculovirus infected insect cells (the latter derive from a type of moth). VLPs mimic the structure of the native virus but do not contain any viral DNA. There are currently two different HPV vaccine products. Cervarix® contains VLPs for two HPV types (16 and 18 – bivalent vaccine) and Gardasil® contains VLPs for four HPV types (6, 11, 16 and 18 – quadrivalent vaccine). The VLPs used in Cervarix® are adjuvanted by AS04 containing 3-O-desacyl-4'- monophosphoryl lipid A (MPL) adsorbed on aluminium hydroxide. The VLPs used in Gardasil® are adsorbed on amorphous aluminium hydroxyphosphate sulphate adjuvant.

The above vaccines do not contain thiomersal. They do not contain live organisms and cannot cause the diseases against which they protect.

HPV vaccines are highly effective at preventing the infection of susceptible women with the HPV types covered by the vaccine. In clinical trials in young women with no evidence of previous infection, both vaccines are over 99% effective at preventing pre-cancerous lesions associated with HPV types 16 or 18 (Harper *et al*., 2006; Ault *et al*., 2007; Lu *et al*., 2011). Current studies suggest that protection is maintained for at least seven years. Based on the immune responses, it is expected that protection will be extended further; long-term follow-up studies are in place. Some other high-risk HPV types are closely related to those contained in the vaccines, and vaccination has been shown to provide some cross-protection against infection by these types (Brown *et al*., 2009; Lehtinen *et al*., 2012). Gardasil® is also 99% effective at preventing genital warts associated with vaccine types in young women (Barr *et al*., 2007).

Cervarix® was the HPV vaccine offered from September 2008 to August 2012 with Gardasil® being offered from September 2012 (Department of Health, 2011).

Storage

Vaccines should be stored in the original packaging at +2°C to +8°C (ideally aim for 5°C) and protected from light. All vaccines are sensitive to some extent to heat or cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. Freezing

may cause increased reactogenicity and loss of potency for some vaccines. It can also cause hairline cracks in the container, leading to contamination of the contents.

Presentation

HPV vaccines are all supplied as suspensions of VLPs in pre-filled syringes. During storage, a white precipitate may develop and the vaccines should be shaken before use to form a white cloudy liquid.

Dosage and schedule

The two vaccine products are not routinely interchangeable and, ideally, one vaccine product should be used for the entire course (see below). Following the introduction of Gardasil® as the vaccine for the national immunisation programme, there will continue to be a supply of Cervarix® available for a further six months to allow girls who started the schedule with Cervarix® but missed vaccinations to complete the course.

The Summaries of Product Characteristics for Cervarix® and Gardasil® allow flexibility in their administration.

Schedule for Cervarix® (containing HPV types 16,18)

- First dose of 0.5ml of Cervarix® HPV vaccine.
- Second dose of 0.5ml, one to two and a half months after the first dose.
- A third dose of 0.5ml at least five months after the first dose.

Schedule for Gardasil® (containing HPV types 6,11,16,18)

- First dose of 0.5ml of Gardasil® HPV vaccine.
- Second dose of 0.5ml at least one month after the first dose.
- A third dose of 0.5ml at least three months after the second dose.

For planning purposes, a vaccination schedule of 0, 1, 4-6 months is appropriate for both vaccines. All three doses should be ideally given within a 12-month period. If the course is interrupted, it should be resumed (using the same vaccine) but not repeated, ideally allowing the appropriate interval between the remaining doses.

Minimum interval for the third dose of HPV vaccine

There is no clinical data on whether the interval between doses two and three can be reduced below three months. Where the second dose is given late and there is a high likelihood that the individual will not return for a third dose after three months or if, for practical reasons, it is not possible to schedule a third dose within this time-frame, then a third dose can be given at least one month after the second dose. This applies to both Cervarix® and Gardasil®.

Whenever possible, immunisations for all individuals should follow the recommended 0, 1, 4-6 month schedule.

Previous incomplete vaccination with Cervarix® – advice for girls and young women covered by the national HPV vaccination programme

The advice below applies to those girls and young women who are eligible to receive HPV vaccination as part of the national HPV immunisation programme as described in the guidance issued by the Department of Health (PL/CMO/2008/4).

If an individual has started a course of Cervarix®, then this course should, where possible, be completed with Cervarix®. In instances where this is not possible or where the make of the initial vaccination is not known, then the vaccination course can be completed with Gardasil® to three doses in total. The course should be completed according to a vaccination schedule of 0, 1, 4-6 months. As there is no evidence on the interchangeability of the two HPV vaccine products, this advice is based on expert judgement of the data from partial courses of each vaccine.

It is not advisable to implement a three-dose course of Gardasil® following a partial or complete course of Cervarix® as there are no safety data on individuals who receive mixed courses of vaccines involving four or more HPV vaccine doses.

The primary purpose of the national immunisation programme is to protect against cervical cancer. It would not be appropriate, therefore, as part of the NHS programme, to offer Gardasil® to those who have had a full course of Cervarix® with the aim of providing additional protection against genital warts.

Administration

Vaccines are routinely given intramuscularly into the upper arm or anterolateral thigh. This is to reduce the risk of localised reactions, which are more common when vaccines are given subcutaneously (Mark *et al*., 1999; Zuckerman, 2000; Diggle *et al*., 2000). However, for individuals who have a bleeding disorder, vaccines should be given by deep subcutaneous injection to reduce the risk of bleeding.

HPV vaccines can be given at the same time as other vaccines such as Td/IPV, MMR and hepatitis B. A trend of lower anti-HPV titres has been observed when Gardasil® is administered concomitantly with dTaP, dT/IPV and dTaP/IPV vaccines, though the clinical significance of this observation is unclear. The vaccines should be given at a separate site, preferably in a different limb. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2006). The site at which each vaccine was given should be noted in the individual's records.

Disposal

Equipment used for vaccination, including used vials, ampoules, or partially discharged vaccines should be disposed of at the end of a session by sealing in a proper, puncture-resistant 'sharps' box according to local authority regulations and guidance in the technical memorandum 07-01 (Department of Health, 2006).

Recommendations for the use of the vaccine

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 puts them at subsequent risk of cervical cancer.

Prevention of HPV infection in those eligible for vaccination and in others outside of the routine programme should include advice on safer sex. All women, whether vaccinated or not, should be strongly encouraged to attend routine cervical screening at the scheduled age.

National HPV vaccination programme cohorts

The cohorts included in the national HPV vaccination programme were detailed in the Department of Health CMO letter dated 2 May 2008 (PL/CMO/2008/4). http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_084546.pdf.

Table 1 Routine and catch-up cohorts 2008/09 – 2011/12, dates of birth and academic year vaccination should have been undertaken*

HPV vaccination cohorts 2008/09 – 2011/12

Dates of birth	Cohort type	Academic year vaccination scheduled
1 Sep 1990 to 31 Aug 1991	Catch-up	2008/09
1 Sep 1991 to 31 Aug 1992	Catch-up	2009/10
1 Sep 1992 to 31 Aug 1993	Catch-up	2009/10
1 Sep 1993 to 31 Aug 1994	Catch-up	2010/11
1 Sep 1994 to 31 Aug 1995	Catch-up	2010/11
1 Sep 1995 to 31 Aug 1996	Routine	2008/09
1 Sep 1996 to 31 Aug 1997	Routine	2009/10
1 Sep 1997 to 31 Aug 1998	Routine	2010/11
1 Sep 1998 to 31 Aug 1999	Routine	2011/12

*As set out in the 2 May 2008 CMO letter. In many areas the catch-up campaign was accelerated as described in the CMO letter of 30 January 2009: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_094026.pdf

Females aged nine to 12 years

Cervarix® and Gardasil® are licensed for individuals from nine years old. Vaccination of girls of this age is not covered by the national HPV vaccination programme.

Females aged 12 to 13 years

From September 2008, HPV vaccination was routinely recommended for all girls at 12 to 13 years of age (school year 8 or S2 in Scotland or school year 9 in Northern Ireland). The course of HPV vaccination should be administered

according to the guidance given in the dosage and schedule section. If the course is interrupted then it should be resumed but not repeated, ideally allowing the appropriate interval between the remaining doses.

Females aged 13 to under 18 years

Girls aged 13 years to under 18 years, who are in or have completed school year 9 (S3 in Scotland or school year 10 in Northern Ireland), should have been offered HPV vaccine as part of the routine programme, or catch-up programmes run in 2008/09, 2009/10 and 2010/11. For girls with unknown or incomplete immunisation status see below.

Females aged 18 or over

Vaccination for females over the age of 18 years is not covered by the national HPV vaccination programme. However, for girls who commenced, but did not complete vaccination in the catch-up programmes (born after 1 September 1990), it is reasonable to complete their HPV vaccination course after the age of 18 years.

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 she has had. A female who has started but did not complete the schedule before reaching the age of 18 years, should complete the vaccination course at the minimum interval (see above) where possible. The course of HPV vaccination should be administered according to the guidance given in the dosage and schedule section. If the course is interrupted then it should be resumed but not repeated, ideally allowing the appropriate interval between the remaining doses. Females coming to the UK from overseas and registered with a GP practice may not have been offered protection against HPV in their country of origin and should be offered vaccination if they are aged under 18 years. If they are aged 18 years or over, and commenced, but did not complete vaccination, it is reasonable to complete their HPV vaccination course.

http://www.who.int/vaccines/globalsummary/immunization/scheduleselect.cfm

Vaccination of boys and young men

Males of any age are not covered by the national HPV vaccination programme.

Contraindications

There are very few individuals who cannot receive HPV vaccine. Where there is doubt, appropriate advice should be sought from an immunisation coordinator or consultant in health protection rather than withholding vaccination.

The vaccine should not be given to those who have had:

- a confirmed anaphylactic reaction to a previous dose of HPV vaccine, or
- a confirmed anaphylactic reaction to any components of the vaccine.

Yeast allergy is not a contraindication to the HPV vaccine. Even though Gardasil® is grown in yeast cells, the final vaccine product does not contain any yeast (DiMiceli *et al*., 2006).

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation may be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any signs or symptoms to any possible adverse effects of the vaccine.

Pregnancy and breast-feeding

There is no known risk associated with giving inactivated, recombinant viral or bacterial vaccines or toxoids during pregnancy or whilst breast-feeding (Atkinson *et al*., 2008). Since inactivated vaccines cannot replicate they cannot cause infection in either the mother or the foetus. However, on a precautionary basis, HPV vaccine is not advised in pregnancy. If a woman finds out she is pregnant after she has started a course of HPV vaccine, she should complete her pregnancy before finishing the three-dose schedule. This precaution is not due to any known risk associated with giving HPV vaccine during pregnancy, but due to absence of data. Limited data are available because pregnant women were specifically excluded from clinical trials of HPV vaccine. However, despite these exclusion criteria some women were inadvertently immunised whilst pregnant or shortly before becoming pregnant (many pregnant women have also now been vaccinated following the introduction of HPV vaccination programmes). No specific safety concerns have been identified in the women who have been given

HPV vaccine, either for the outcome of pregnancy or fetal development, when compared with women who received a placebo or control vaccine. Routine questioning about last menstrual period and/or pregnancy testing is not required before offering HPV vaccine.

Girls aged under 18 years in the target cohort who are known to be sexually active, including those who are or who have been pregnant, may still be susceptible to high-risk HPV infection and could therefore benefit from vaccination according to the UK schedule. If pregnant, they should be offered vaccine as soon as possible after pregnancy. If high-risk sexual activity continues during pregnancy, and the opportunity for vaccination after pregnancy is uncertain, the benefit of vaccination during pregnancy is likely to outweigh any potential risk.

Termination of pregnancy following inadvertent immunisation should not be recommended. The available evidence on the use of HPV vaccine in pregnancy should be discussed with the prospective parents.

Due to the relatively limited experience of HPV vaccine in pregnant women to date, it is important to record and follow up such cases of inadvertent administration during pregnancy to provide further data on the outcome. Surveillance of vaccination in pregnancy is being conducted by the Immunisation Department at HPA Colindale, to whom such cases in England and Wales should be reported via the website (http://www. hpa.org.uk) or by telephone (01788 540298 or 0208 327 7471). Cases in Scotland should be reported to Health Protection Scotland on 0141 300 1100, Immunisation Department. Cases in Northern Ireland should be reported to the Public Health Agency Duty Room (028 9055 3997).

Immunosuppression and HIV infection

Individuals with immunosuppression or with HIV infection (regardless of CD4 count) should be considered for HPV vaccines in accordance with the recommendations above. However, individuals who are immunosuppressed may not develop a full antibody response. Clinical trials to study the effectiveness of HPV vaccination in immunosuppressed individuals are in progress. Re-immunisation should be considered after treatment is finished and/or recovery has occurred. Specialist advice may be required.

Adverse reactions

As with all vaccines and medicines, healthcare professionals and parents/carers are encouraged to report suspected adverse reactions to the Medicines and Healthcare products Regulatory Agency (MHRA) using the Yellow Card reporting scheme (www.mhra.gov.uk/yellowcard).

The most common adverse reaction observed after HPV vaccine administration is mild to moderate short-lasting pain at the injection site. An immediate localised stinging sensation has also been reported. Redness has also been reported at the injection site.

Other reactions commonly reported are headache, myalgia, fatigue, and low grade fever.

A detailed list of adverse reactions associated with Cervarix® and Gardasil® is available in the Summary of Product Characteristics (SPC) for each vaccine, which are available from the European Medicines Agency website http://www.ema.europa.eu.

Syncope (vasovagal reaction), or fainting, can occur during any vaccination, most commonly amongst adolescents. Some individuals may also experience panic attacks before vaccination. The clinical features of fainting and panic attacks are described in detail in Chapter 8 of the Green Book. Fainting and panic attacks occurring before or very shortly after vaccination are not usually direct side effects (adverse reactions) of the vaccine but events associated with the injection process itself.

Only reactions suspected to be related to the vaccine (and not those associated with the injection process) should be reported via the Yellow Card Scheme.

Reporting anaphylaxis and other allergic reactions

Anaphylaxis is a very rare, recognised side effect of most vaccines and suspected cases should be reported via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard). Chapter 8 of the Green Book gives detailed guidance on distinguishing between faints, panic attacks and the signs and symptoms of anaphylaxis. If a case of suspected anaphylaxis meets the clinical features described in Chapter 8, this should be reported via the Yellow Card Scheme as a case of 'anaphylaxis' (or if appropriate 'anaphylactoid reaction'). Cases

of less severe allergic reactions (i.e. not including the aforementioned clinical features for anaphylaxis) should not be reported as anaphylaxis but as 'allergic reaction'.

Supplies

- Cervarix® – manufactured by GlaxoSmithKline.
- Gardasil® – manufactured by Sanofi Pasteur MSD.

HPV vaccine is supplied by Movianto UK Ltd (Tel: 0870 8711890) as part of the national childhood immunisation programme.

In Scotland, supplies should be obtained from local childhood vaccine-holding centres. Details of these are available from Scottish Healthcare Supplies (Tel: 0131 275 6154).

In Northern Ireland, supplies can be obtained from local childhood vaccine holding centres. Details of these are available from the Regional Pharmaceutical Procurement Service (Tel: 028 90552386).

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