18a

Human papillomavirus (HPV)

NOTIFIABLE

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). Infection by multiple types is common (Cuschieri *et al.*, 2004).

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.

HPV is recognised as a necessary cause of cervical cancer and persistent infection by high-risk HPV types is detectable in more than 99% of cervical cancers (Walboomers *et al*., 1999; Bouvard *et al*., 2009; WHO IARC, 2007)[1]. 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 less common cancers at other sites, including cancer of the vulva, vagina, penis and anus, and some cancers of the head and neck (Parkin., 2011; Stanley., 2007; Psyrri *et al.*, 2008; WHO IARC, 2012; Giuliano *et al*., 2015) .

1 Including types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68

Human papillomavirus (HPV)

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; Winer *et al* 2011). 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 pre-cancerous lesions varies from one to ten years, and longer for the development of invasive cancer (Moscicki *et al*., 2006).

The natural history of HPV-related cancers at other sites is less well understood. 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). 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 50% of cases of penile cancer are attributable to HPV infection (de Martel., 2017). HPV is also known to be a cause of oropharyngeal cancers though estimates of the attributable fraction vary widely and range from 6% to 71% (Stein *et al*., 2015). The wide range is likely to be explained by 1) the accuracy in the distinction of cancer of the oropharynx and tonsil from other subsites; 2) the competing effect of smoking or chewing tobacco; and 3) the quality of tissue biopsies and HPV-testing protocols used (WHO IARC, 2012 ; Plumber *et al*., 2016). The prevalence of HPV type 16/18 associated oropharyngeal cancer is lower in women than in men. A systematic review of HPV prevalence studies estimated that overall 47% of oropharyngeal cancer cases were HPV related (men and women all ages combined) (Kreimer *et al*., 2005) but the prevalence of HPV types16/18 has been reported as 66% and 53% in North America in men and women respectively (Steinau *et al*., 2014). In the UK, a recent study estimated the attributable fraction for oropharyngeal carcinoma to be 52% (Schache *et al*., 2016). For all sites, the evidence for a causal association is greatest for HPV type 16 than for other HPV types, and the majority of HPV related cancers are associated with type 16.

Low-risk HPV types are responsible for genital warts, which is the most commonly diagnosed viral sexually transmitted infection in the UK (Public Health England (PHE), 2017). HPV types 6 and 11 cause approximately 90% of all genital warts (Lacey *et al*., 2006; Garland *et al*., 2007; Hawkins *et al*., 2013). 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 types 6 and 11 infection also causes laryngeal papillomas, (Stamataki *et al*., 2007) an infection of the upper respiratory tract.

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 infections were extremely infrequent in girls aged under 14 years but rose sharply from the mid-teens. Among 10- to 29-year-old women, 11%, 3%, 12% and 5% had serological evidence of 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 large cross-sectional studies. A study of women having routine cervical screening in 2007-9 found evidence of current high-risk HPV infection (indicated by the presence of HPV DNA) in 29% of women aged 25 to 29 years undergoing cervical screening, 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 (Howell-Jones *et al*., 2010).

Cervical cancer is the fourth commonest cancer of women worldwide, with approximately 500,000 new cases and 270,000 deaths annually (Ferlay *et al*., 2012). While HPV vaccination prevents against infection and subsequent disease, the secondary prevention of cervical cancer is achieved through the early detection of cervical abnormalities by cervical screening. The introduction of an organised, call and recall, national cervical screening programme in the UK has been responsible for a major fall in the incidence and death rate from cervical cancer. It has been estimated that mortality rates fell approximately 60% between 1974 and 2004 in the UK due to cervical screening (Peto *et al*., 2004).

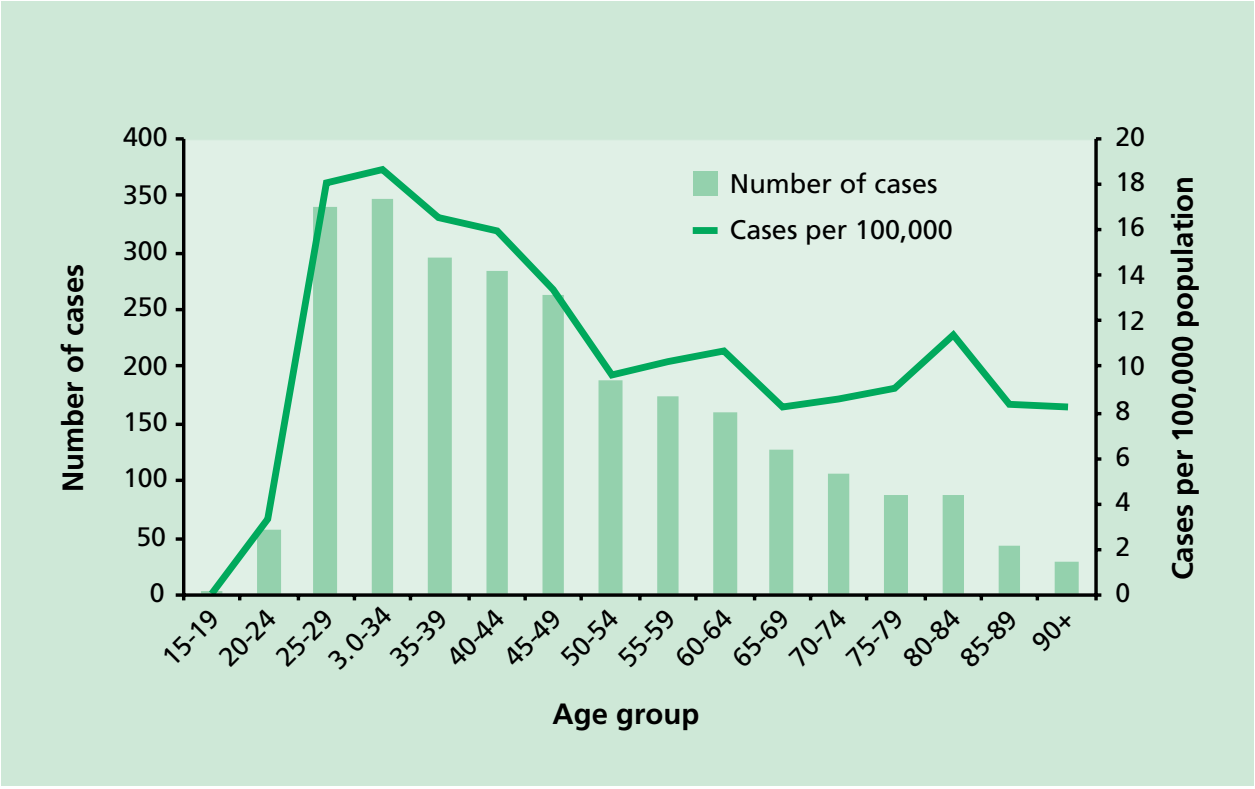

Figure 1 Number of cases of newly diagnosed cervical cancer in England, 2016 (source: National Statistics, 2018)

A total of 2594 new cases of invasive cervical cancer were diagnosed in England in 2016 (National Statistics, 2018). The peak incidence of cervical cancer occurs in women aged 25-29, A second smaller peak occurs in women in their 80s (i.e. women less likely to have benefited from cervical screening during their lifetimes; Figure 18a.1). Older women remain at risk with more than 50% of new cases diagnosed in women over the age of 40 and more than 15% in women over 65 years of age. 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).

The national policy for cervical screening is that women are offered screening every three or five years depending on their age. Women aged 25-49 are invited every 3 years, whereas those aged 50-64 are invited every 5 years. There are certain groups of women reported to have low cervical screening rates, e.g. some ethnic minority groups and women born in foreign countries (Webb *et al*., 2004; Thomas *et al*., 2005; Marlow *et al* 2015). There continues to be a downward trend in the number of young women taking up invitations for cervical screening (NHS Cervical Screening Report, 2017-18).

In England, anal cancer is rarer, with around 833 cases diagnosed in women and 421 cases diagnosed in men in 2016 (National Statistics, 2018). Although anal cancer is more common in women than in men, the risk of anal cancer among men who have sex with men is higher than among women (Frisch *et al.*, 2003; Wilkinson *et al*, 2014) and especially those who are HIV positive (Machalek *et al*., 2012). Men who have sex with men (MSM) are more likely to be infected with HPV and bear a significantly increased burden of HPV related disease and adverse outcomes compared with heterosexual men (Nyitray *et al*, 2011; Anic *et al.*, 2012). In England, there are around 1200 cases of vulval and vaginal cancers and 512 penile cancers per year. The number of oropharyngeal cancers[1] diagnosed in men and women in England in 2016 were 4689 and 1749 respectively. Rates of HPV associated oropharyngeal cancer have risen significantly in the last twenty years in both genders but more so in men. The rate of HPV negative oropharyngeal cancer has also increased significantly.

Information on diagnoses of genital warts comes primarily from people attending sexual health services in England. Over 60,000 new cases of genital warts were diagnosed in sexual health service throughout England in 2016 (PHE, 2017). Rates of diagnoses are highest in young men and women under 24 years. A cross-sectional study of MSM aged 18–40 attending a London sexual health clinic indicated a quarter (25.1%) had evidence of infection with one HPV type that the quadrivalent vaccine protects against (HPV16,18, 6 & 11), 7.4% had two or three types and none had all four types. The prevalence of the high risk HPV vaccines types 16 and 18 (used in the bivalent vaccine) was 17% (King *et al*., 2015).

In 2008, following a detailed review of the impact and cost-effectiveness of a routine HPV vaccination programme in adolescents aimed at reducing the burden of HPV-associated cervical cancer, JCVI recommended a universal programme of HPV vaccination in girls aged 12-13 years in schools, along with a catch up programme for girls aged from 13 to under 18 years (JCVI, 2008). The national HPV immunisation programme was introduced in September 2008 with all girls in school year 8 in England (aged 12 to 13 years offered vaccine against HPV infection, with a 'catch-up' campaign for girls aged up to 18 years. The bivalent vaccine Cervarix® was the HPV vaccine offered from September 2008 to

1 ICD codes C01, C08, C10, C02, C06 and C32

August 2012 with the quadrivalent vaccine Gardasil® being offered from September 2012 (Department of Health, 2011), both as three dose courses. In February 2014, JCVI concluded that a two dose schedule in adolescents could be recommended up to (and including) 14 years of age for both Cervarix and Gardasil. A two dose schedule of Gardasil® was implemented in the national programme for the routine vaccination cohort of females aged 11 to 13 years old (academic year 8 in England and Wales) from September 2014.

A cross-sectional study of MSM aged 18–40 attending a London sexual health clinic indicated that most MSM, even among this high-risk population attending a sexual health clinic are not currently infected with vaccine-type HPV. This data suggested that a targeted vaccination strategy for MSM could have substantial benefits (King *et al*., 2015), as this group were unlikely to benefit from the herd immunity generated by the existing girls programme. These findings were used to inform an impact and cost effectiveness assessment for the JCVI (Lin *et al*., 2016). In November 2015, the JCVI advised that a targeted HPV immunisation programme should be introduced for MSM up to and including the age of 45 years who attend specialist sexual health services (SSHS) and HIV clinics (JCVI, 2015). From June 2016, a pilot was commenced in England which offered the HPV vaccine opportunistically to MSM up to and including the age of 45, attending selected SSHS and HIV clinics. Following a positive evaluation of the pilot (Edelstein *et al*, 2018), the programme was rolled out across England from April 1st 2018. The aim of the programme is to extend protection against HPV infection, HPV associated cancers and genital warts to the MSM population attending SSHS and HIV clinics.

In July 2018, the Joint Committee on Vaccination and Immunisation (JCVI) advised that the existing HPV vaccination programme for girls could be extended to adolescent boys as well (JCVI. 2018). As a result of JCVI's advice, the Government announced in July 2018 that the national HPV immunisation programme would be extended to include adolescent boys. As well as providing individual protection to males from anogenital warts and non-cervical HPV associated cancers this should add resilience to the UK programme, accelerate the control of cervical cancer in women and offers the potential for the elimination of HPV vaccine types in the UK. In addition, this programme will eventually generate herd protection in the MSM population.

Early evidence on the impact of the national HPV immunisation programme showing reduction in HPV type 16/18 infection, genital warts and pre-cancerous lesions among vaccinated cohorts and herd protection among unvaccinated groups is now emerging globally including in the UK (Drolet *et al.,* 2015;2019).

An ongoing cross-sectional study of young 16-24 year old women attending for chlamydia screening across England has shown reductions in the prevalence of HPV vaccine types since the introduction of the national programme. Among 16-18 year old females where vaccine coverage was highest, HPV 16/18 prevalence decreased from 8.2% in 2010/11 to 1.6% in 2016. Reductions were also seen in 19–21 year old females with lower estimated vaccination coverage (from 14.0% HPV type 16/18 prevalence in 2010/11, to 1.6% in 2016 (Mesher *et al*., 2018). In Scotland, a 7 year cross-sectional study showed reductions in HPV type 16/18 prevalence from 28.9% in 2009 to 4.8% in 2015 (Kavanagh K *et al*., 2017).

In 2016, the rate of first episode genital warts diagnoses among females aged 15 to 17 years attending sexual health clinics, most of whom would have been offered the

quadrivalent HPV vaccine (protecting against HPV types 16,18, 6 & 11) when aged 12-13 years old, was 72% lower compared to 2009 (121.5 vs 436.5 per 100,000 population). A decline of 62% (31.4 vs 83.4 per 100,000) was seen in heterosexual males of the same age over this time period, suggesting substantial herd protection (PHE, 2017).

The full impact of the national HPV immunisation programme on cervical cancer is yet to be fully realised as girls in the catch-up cohorts are only just beginning to enter cervical screening and the first cohort of routinely vaccinated adolescent girls will became eligible for cervical screening in England in September 2020. In Wales the age at which screening commences was changed in 2013 (from 20 years to 25 years). In time it is expected that the HPV vaccine will save hundreds of lives every year in the UK.

In Scotland the age at which screening commences was changed in 2016 (from 20 years to 25 years) meaning women from the catch-up cohorts have been screened since 2010 and women from the routinely immunized cohorts have been screened since 2015. A recent study in Scotland has shown 89% reduction (95% CI 81% to 94%) in prevalent cervical intraepithelial neoplasia (CIN) grade 3 or worse in the first cohort of women (born in 1995/6) vaccinated at age 12-13 years with the bivalent vaccine through the national immunisation programme, compared with unvaccinated women born in 1988 (Palmer *et al.*, 2019). Population studies in other settings have also shown a major impact of the quadrivalent vaccine on precancerous lesions (McClung *et al.*, 2019; Herweijer *et al.*, 2016; Gertig *et al.*, 2013)

The HPV vaccination

HPV vaccines have been available since 2006. Currently available 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 three different HPV vaccine products. Cervarix® contains VLPs for two HPV types (16 and 18 – bivalent vaccine), Gardasil® contains VLPs for four HPV types (6, 11, 16 and 18 – quadrivalent vaccine) and Gardasil®9 contains VLPs for nine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58 – nine valent 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® and Gardasil®9 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 ten years (Kjaer *et al.,* 2018). Based on the immune responses, it is expected that protection will be extended further and may be lifelong; long-term follow-up studies are in place.

As high efficacy had been demonstrated in young women through clinical trials, immunological studies which show equivalent response in terms of immunogenicity have become an acceptable "bridge" to infer efficacy and duration of protection in 9-15 year old girls (see the Summary of Product Characteristics (SPC) for Gardasil, Cervarix). Direct

evidence on the efficacy/effectiveness of HPV vaccination in males is limited but the available evidence indicates that the vaccine is safe and efficacious against genital HPV infection and high-grade anal intraepithelial lesions especially in HPV naive individuals (Harder *et al*., 2018; Giuliano *et al*., 2011). The licensing indication for Gardasil is based on the demonstration of efficacy of Gardasil in females 16 to 45 years of age and in males 16 to 26 years of age and on the demonstration of immunogenicity of Gardasil in 9 to 15 year old children and adolescents. For Cervarix immunogenicity in males has been demonstrated to be non-inferior compared with young girls and women to infer efficacy. Adolescents vaccinated using a two dose schedule administered as a prime and boost (separated by a minimum of 6 months) have equivalent responses to the three dose schedule in older women (including Dobson *et al*., 2013; Safaeian *et al*., 2013). In 2013/14, both Gardasil and Cervarix received licensing approval from the European Medicines Agency (EMA) for a two dose schedule in adolescent girls (SPC Gardasil, Cervarix). A 3-dose schedule remains necessary for the HPV vaccines if immunisation is initiated after the 15th birthday (WHO, 2014).

For the nine valent vaccine the indication is based on non- inferiority with the 4 vaccine types in the quadrivalent vaccine for girls, women and men; demonstration of efficacy against HPV Types 31, 33, 45, 52 and 58 in girls and women and; demonstration of non-inferior immunogenicity against the Gardasil 9 HPV types in boys and girls aged 9 to 15 years and men aged 16 to 26 years, compared to girls and women aged 16 to 26 years. Gardasil 9 received licensing approval from the European Medicines Agency (EMA) for a two dose schedule in adolescent girls in April 2016 and is licensed for individuals aged 9 up to and including 14 years of age (SPC, Gardasil9). The WHO's Strategic Advisory Group of Experts (SAGE) on immunisation also recommended a 2-dose schedule for girls, if vaccination is initiated prior to 15 years of age.

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; Brotherton., 2017). A systematic review and meta-analysis including data from seven studies demonstrating reductions in the high-risk HPV vaccine types (HPV16 and 18) among 13 to 19 year old females in countries with female vaccination coverage of at least 50% also showed evidence of a reduction in HPV types 31, 33 and 45, confirming some cross-protection. (Drolet *et al*., 2015). Gardasil® is also 99% effective at preventing genital warts associated with vaccine types in young women (Barr *et al*., 2007).

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.

HPV immunisation programme

Dosage and schedule for HPV vaccines licensed in the UK[1]

Two dose schedule (for children and adolescents aged between nine years old and below 15 years of age)

Schedule for Gardasil® (containing HPV types 6,11,16,18), Gardasil®9 (containing HPV types 6, 11, 16 18, 31, 33, 45, 52, 58) and Cervarix® (containing HPV types 16,18)

- first dose of 0.5ml of HPV vaccine
- second dose of 0.5ml six to 24 months after the first dose

For adolescents aged less than 15 years of age, JCVI recommends a schedule of 0, 6-24 months for all HPV vaccines. Any gap between doses of between six and 24 months is clinically acceptable. As long as the first dose was received before the age of 15 years the two-dose schedule can be followed. If the course is interrupted, it should be resumed (using the same vaccine) but not repeated, even if more than 24 months have elapsed since the first dose.

Whenever possible, immunisations for all individuals should follow the recommended 0, 6-24 months schedule, but there is some clinical data that the interval between the two doses can be reduced to five months for Cervarix. For Gardasil® the minimum interval between the two doses should be 6 months. For Gardasil®9 the minimum interval between the two doses can be 5 months.

Three dose schedule (for those aged 15 years and above)

Schedule for Gardasil® (containing HPV types 6,11,16,18) or Gardasil®9 (containing HPV types 6, 11, 16 18, 31, 33, 45, 52, 58)

- first dose of 0.5ml of 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

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

- first dose of 0.5ml of 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

A vaccination schedule of 0, 1, 4-6 months is appropriate for the HPV vaccine for those commencing the course at age 15 years and above. All three doses should ideally be 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.

There is no clinical data on whether the interval between doses two and three can be

1 Gardasil® is currently the only HPV vaccine supplied for the national HPV programme (for both adolescents and MSM).

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 all the currently licensed HPV vaccines.

For the MSM programme, owing to the opportunistic nature of delivery, a 24 month period for completion of the course is clinically acceptable. Due to the flexibility in the Gardasil® Summary of Product Characteristics (SPC), variable spacing options for the three doses are possible, providing the minimum interval between doses is respected where possible. This should enable the administration of subsequent doses to be aligned with recommended SSHS re-attendance in order to avoid the need for additional visits for vaccination only.

Previous incomplete HPV vaccination

Evidence is starting to emerge on the interchangeability of the HPV vaccines (JCVI, 2018). For individuals who may have started the schedule with an HPV vaccine that is no longer used in the UK programme but did not complete the vaccination course, the course can be completed in the UK with the vaccine currently in use in the UK programme. The course should be completed according to a vaccination schedule of 0, 1, 4-6 months or 0, 6-24 months, depending on the age of the individual when they received the first dose and whether 1 or 2 doses have already been given.

Two doses given less than 6 months apart should not be considered adequate to provide long term protection and a third dose should be given according to the guidance given in the dosage and schedule section.

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, Influenza, MenACWY 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 syringes, should be disposed of by placing them in a proper, puncture-resistant 'sharps' box according to local authority regulations and guidance in *Health Technical Memorandum 07-01: Safe management of healthcare waste* (Department of Health, 2013).

Recommendations for the use of the vaccine

National adolescent HPV vaccination programme

The objective of the HPV immunisation programme for adolescents is to provide two doses of HPV vaccine at least six months apart to boys and girls before they reach an age when the risk of HPV infection increases and puts them at subsequent risk of cervical and other HPV-related cancers.

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.

Children aged nine to 11 years

Cervarix® Gardasil® and Gardasil® 9 are licensed for individuals from nine years old Vaccination of girls and boys of this age is not covered by the national HPV vaccination programme.

Adolescents aged 11 to 14 years

HPV vaccination is routinely recommended for all girls and boys at 11 to 14 years of age with the first dose offered in school year 8 in England and Wales, S1 in Scotland, and school year 9 in Northern Ireland. The two dose schedule allows flexibility around the schedule with the interval between the first and second dose from 6 months to 24 months (0, 6-24 months) and covers girls and boys from 11 up to and including the age of 14 years. The second dose is therefore offered in school year 8 to 9 in England and Wales, S1 to S3 in Scotland or school year 9 to 10 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. For those 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.

Two doses less than 6 months apart should not be considered adequate to provide long term protection and a third dose should be given according to the guidance given in the dosage and schedule section.

Older adolescents and adults aged 15 to 25 years

Males and females in cohorts eligible for vaccination in the national programme remain so until their 25th birthday. Females and males in those cohorts who were eligible for the routine programme (i.e. for England, females born after 01/09/1991 and males born after 01/09/2006) 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 25 years. For Scotland, Wales and Northern Ireland dates of birth for eligible cohorts may vary due to the different ages at which the HPV vaccine is first offered. Contractual arrangements for these programmes should be checked with relevant commissioners. Those aged 15 years of age or above should start a three-dose schedule.

Where an older male or female in the target cohorts presents with an inadequate vaccination history, every effort should be made to clarify what doses they have had and when they received them. A male or female who has started but did not complete the schedule before

reaching the age of 25 years, should complete the vaccination course at the minimum interval (see above) where possible. If the course is interrupted then it should be resumed but not repeated, ideally allowing the appropriate interval between the remaining doses.

Two doses less than 6 months apart should not be considered adequate to provide long term protection and a third dose should be given according to the guidance given in the dosage and schedule section.

HPV vaccination programme for men who have sex with men (MSM)

The objective of the national programme for MSM is to extend protection to those in the MSM population who are considered at highest risk of HPV infection and subsequent disease by offering opportunistic vaccination at SSHS and HIV clinics. This programme is expected to continue after boys become eligible through the schools programme, as herd immunity in the MSM population is likely to take some years to accrue in this population.

For more information relating to the HPV programme for MSM, including detailed guidance, please see: https://www.gov.uk/government/collections/hpv-vaccination-for-men-who-have-sex-with-men-msm-programme#guidance

MSM aged up to and including 45 years

Gardasil® is the vaccine currently used for the MSM programme. All MSM aged up to and including 45 years old who attend SSHS or HIV services are eligible for vaccination, if they have not already previously been vaccinated.

MSM aged 46 years and over

Anyone eligible for the HPV vaccination programme for MSM that started, but did not complete the schedule before reaching the age of 46 years, should complete the vaccination course, providing the first dose was given as part of the pilot or national programme.

Transgender and other individuals

There may be considerable benefit in offering the HPV vaccine to individuals attending SSHS or HIV clinics who were not eligible for the routine HPV programme and are deemed to have a similar risk profile to that seen in the MSM population. This includes some transgender individuals, sex workers, and men and women living with HIV infection. Those whose risk of acquiring HPV is considered equivalent to the risk of MSM eligible for the HPV vaccine, should be offered vaccination. For those who have previously completed a course of HPV vaccination as part of the school HPV programme, no further doses need be given.

Contraindications

There are very few individuals who cannot receive HPV vaccine. Where there is doubt, rather than withholding vaccination, appropriate advice should be sought from the relevant specialist, or from the local immunisation or health protection team.

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 fetus.

As with most pharmaceutical products, specific clinical trials of HPV vaccine in pregnant women have not been carried out. During the clinical development programme, almost 4,000 women (Gardasil = 1,894 vs. comparator = 1,925) reported at least one pregnancy during follow-up. There were no significant differences in types of anomalies or proportion of pregnancies with an adverse outcome in each arm. Many pregnant women have also been exposed to HPV vaccine during the post-marketing period. A nationwide register-based cohort study involving all pregnant women in Denmark found no significant risk associated with the quadrivalent vaccine, compared with no vaccination, of spontaneous abortion, major birth defect, stillbirth, preterm birth, small size for gestational age, and low birth weight (Scheller *et al*., 2017).

Although the available data do not indicate any safety concern or harm to pregnancy, there is insufficient evidence to recommend use of Gardasil during pregnancy. Vaccination should be postponed until completion of 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 recommended schedule. Routine questioning about last menstrual period and/or pregnancy testing is not required before offering HPV vaccine.

Schoolgirls 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.

Immunosuppression and HIV infection

Eligible MSM with human immunodeficiency virus (HIV) infection should be offered the HPV vaccine regardless of CD4 count, antiretroviral therapy use or viral load.

The quadrivalent HPV vaccine is safe and highly immunogenic in HIV-infected adults (Wilkin *et al*., 2010; Kojic *et al* 2014). Although the immunogenicity and efficacy of HPV vaccines may be reduced in HIV infected females, they appear to be preserved (Toft *et al.*, 2014; McClymont., 2018).

Lower geometric mean titre antibody levels have been observed in HIV infected subjects compared to non-HIV infected subjects of the same age for both vaccines (SPC Gardasil, Cervarix). However, the clinical relevance of these observations is unknown.

Suboptimal immunogenicity of HPV vaccine in transplant patients has also been observed (Kumar *et al.*, 2013).

There is no data on fewer than 3 doses among HIV-infected or immunocompromised populations. Therefore a 3-dose schedule should be offered to individuals who are known to be HIV-infected, including those on antiretroviral therapy, or are known to be immunocompromised at the time of immunization. This recommendation is endorsed by WHO SAGE. Re-immunisation should be considered after treatment is finished and/or recovery has occurred. Specialist advice may be required.

Further guidance is provided by the Royal College of Paediatrics and Child Health (http://www.rcpch.ac.uk/), the British HIV Association (BHIVA) immunisation guidelines for HIV-infected adults (BHIVA, 2015; and the Children's HIV Association (CHIVA) immunisation guidelines (https://www.chiva.org.uk/guidelines/immunisation/).

Adverse reactions

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

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 EMA website http://www.ema.europa.eu.

Syncope (vasovagal reaction), or fainting, can occur during any vaccination, most commonly amongst adolescents and adults. 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.

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'.

Since 2008, a range of suspected serious adverse reactions have been reported in temporal association with HPV vaccines at global level. These relate to a wide range of illnesses, mostly chronic syndromes. Four population-based studies, from the UK, Norway, Finland and The Netherlands, have found no evidence that HPV vaccines may be a cause of chronic fatigue syndrome (Donegan *et al.*, 2013; Feiring *et al.*, 2017; Schurink-van't Klooster *et al.*, 2018). Numerous published epidemiological studies from independent academics have found no evidence of serious harm based a wide range of safety endpoints, including autoimmune disorders [Macartney., 2013 *et al*]. Reviews by national and international safety committees have concluded that these concerns are unfounded and have strongly supported the safety and use of the vaccine (WHO GACVS, 2015).

Any suspected adverse reactions should continue to be reported to the Yellow Card Scheme.

Supplies

- Cervarix® – manufactured by GlaxoSmithKline.
- Gardasil® – manufactured by MSD.
- Gardasil®9 – manufactured by MSD

HPV vaccines used in the National programme are distributed in the UK by Movianto UK Ltd (Tel: 01234 248631) as part of the national childhood immunisation programme.

Vaccine for the national programme are supplied centrally via ImmForm. There are separate order lines for the MSM and adolescent HPV programmes on Immform. The correct one must be used to order vaccine volumes for each programme, even where an ImmForm account holder is ordering for both.

Vaccines for use outside of the national programme recommendations should be ordered from the manufacturers or pharmaceutical wholesaler.

In Scotland, supplies should be obtained from local childhood vaccine holding centres. Details of these are available from Procurement, Commissioning & Facilities of NHS National Services Scotland (Tel: 0131 275 6725).

In Northern Ireland, supplies should be obtained from local childhood vaccine holding centres. Details of these are available from the Regional Pharmaceutical Procurement Service (Tel: 028 9442 4346).

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