Public Health England

Protecting and improving the nation's health

HPV vaccination

Information for healthcare practitioners

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Executive summary

In July 2018, it was announced that the HPV vaccination programme will be extended to boys aged 12 to 13 years in England. It is intended that this expanded programme will commence from 1st September 2019.

Persistant infection by high risk Human Papillomavirus (HPV) types is detectable in more than 99% of all cervical cancers[1]. There is also evidence of an association between HPV infection and cancers at other sites, including anogenital and oropharyngeal cancers, although the proportion of cancers which are caused by HPV vary by cancer site.

Females from 12 years of age (school year 8), and men who have sex with men (MSM) aged 45 years and under, who attend Specialist Sexual Health Services (SSHS) and/or HIV clinics, have been eligible to receive the HPV vaccine since 2008 (females) and 2018 (MSM).

Since the introduction of the girls programme, the number of diagnoses of genital warts in England has fallen sharply in both girls and boys and there has been a reduction in the prevalence of the types of HPV that the vaccine protects against. This suggests that boys are already benefiting significantly from the indirect protection (herd protection) that has built up from ten years of the girls programme.

The Joint Committee on Vaccination and Immunisation (JCVI) discussed this[2] and felt that that there were relatively few additional benefits to be gained in vaccinating boys when there is high vaccine coverage in girls. For this reason, a catch-up programme for older boys will not be offered.

Extending the HPV vaccination programme to include boys from 12 years of age, will help prevent more cases of HPV-related cancers in both males and females, such as head, neck and ano-genital cancers, and will also strengthen herd protection.

This guidance document provides information for healthcare practitioners about HPV programme eligibility, scheduling and vaccine administration for the adolescent programme. Other documents relating to the universal human

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[1] Munoz N, Castellsague X, de Gonzalez AB *et al*. (2006) Chapter 1: HPV in the etiology of human cancer. *Vaccine* **24S3** S1-S10

[2] Minutes of the HPV Sub-Committee of the Joint Committee on Vaccination and Immunisation, 18 May 2018 Available at: https://app.box.com/s/600veu6zr6s3gjvx8mkt/file/305789906344 [Accessed on 24/05/2019]

papilloma virus vaccination programme can be found on the Gov.UK website in the HPV vaccination programme collection

Further information and resources for the MSM HPV vaccination programme is available at https://www.gov.uk/government/collections/hpv-vaccination-for-men-who-have-sex-with-men-msm-programme

From September 1st 2019, the HPV vaccine programme will be for:

- all adolescents in school year 8 (aged 12 and 13 years)
- MSM up to and including 45 years of age, attending participating sexual health or HIV clinics

Humanpapilloma virus (HPV)

HPV is a double-stranded DNA virus that infects the surface of the skin and mucosae of the upper respiratory and anogenital tracts.

There are over 100 types of HPV viruses of which about 40 infect the genital tract. They are classified as being either high risk or low risk depending upon their association with the development of cancer. [3] Types 16 and 18 are high risk and types 6 and 11 are low risk.

Types 16 and 18 account for around 80% of all cervical cancers, the remaining 20% are due to 11 other high-risk HPV types.The proportion of cancers of the anus, penis, mouth & throat, vagina and vulva which are related to a high-risk HPV infection (and which are caused by types 16 and 18) vary by cancer site.

The majority of HPV infections do not cause any symptoms and infection is usually cleared by the body's own immune system without the need for other treatment.

- 70% of new high risk infections will clear within a year
- 90% of new infections clear within 2 years

Persistent infection with high risk HPV types such as types 16 and 18 can cause cell changes leading to lesions, warts or ano-genital cancers. These include cancer

[3] Immunisation against infectious disease (the Green book), Chapter 18a (HPV), Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/317821/Green_Book_Chapter_18a.pdf [Accessed 19th December 2018]

of the cervix, vulva or vagina in women, cancer of the penis in men and some cancers of the head, neck, throat or anus in either sex. Other types of HPV such as 6 and 11 cause genital warts which is the most commonly-diagnosed viral sexually-transmitted infection in the UK.

Transmission of HPV

HPV infections are spread primarily by sexual contact with an infected partner, particularly through sexual intercourse but also by non-penetrative genital contact, including oral sex.

HPV is one of the most commonly transmitted sexually-transmitted infections in the UK and anyone who is sexually active can contract it. The risk of acquiring infection increases with the number of previous sexual partners, the introduction of a new sexual partner, and the sexual history of partners.[3]

Infection commonly occurs soon after sexual debut and almost 40% of women are infected within two years.

Background to the HPV vaccination programme

On the advice of the Joint Committee on Vaccination and Immunisation (JCVI), a HPV national vaccination programme was introduced in 2008 to protect secondary school year 8 girls (aged 12-13 years old) against cervical cancer. At that time, a catch-up programme also took place to vaccinate girls aged 13 to18 years old.[4]

The recommendation for a three dose schedule of HPV vaccine in the vaccination programme for adolescent girls was reviewed by JCVI in May 2014. Following this,

[4] The Joint Committee on Vaccination and Immunisation (JCVI) statement on human papillomavirus vaccines to protect against cervical cancer July 2008 Available at https://webarchive.nationalarchives.gov.uk/20120907151322/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_094739.pdf Accessed 29th May 2019]

a two-dose schedule was recommended as antibody response to two doses in adolescent girls is as good as a three dose course[5].

Emerging evidence from evaluations of the programme has shown that the number of young women with pre-cancerous cervical disease is falling (Scotland data), and that the number of infections of HPV types 16 and 18, the main cancer-causing types, has reduced by 86% in 16-21 year old women in England.[6] Current indications are that this protection will last for many years.

In June 2012, the JCVI asked the Health Protection Agency (now PHE), to undertake modelling studies to assess the impact and cost effectiveness of HPV vaccination of men who have sex with men (MSM), as this group were expected to receive very little indirect protection or benefit from the HPV vaccination programme offered to adolescent females.[7]

In 2015, JCVI advised that all MSM up to and including 45 years who attend sexual health and HIV services should be offered the vaccine. [8]

In 2016, a successful PHE-led pilot was set up which offered vaccine to MSM through existing appointments at selected local sexual health services in England.[9] In April 2018, the vaccination programme was extended to include MSM up to and including 45 years attending all sexual health and HIV services.[10]

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[5] PHE, DH, NHS England tripartite letter, PHE Publications Gateway Number: 2014057 Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/310958/HPV_Joint_Letter_14_May.pdf [Accessed 29th May 2019]

[6] Saliba V, PHE Blog, Ten years on since the start of the HPV vaccine programme – what impact is it having? Available at https://publichealthmatters.blog.gov.uk/2018/06/18/ten-years-on-since-the-start-of-the-hpv-vaccine-programme-what-impact-is-it-having/ [Accessed 29th May 2019]

[7] The Joint Committee on Vaccination and Immunisation (JCVI), Minute of the meeting on Wednesday 13 June 2012, Available at https://webarchive.nationalarchives.gov.uk/20120907100504/http://transparency.dh.gov.uk/2012/07/25/jcvi-meeting-june-2012/ [Accessed 29th May 2019]

[8] JCVI statement on HPV vaccination of men who have sex with men, November 2015 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/477954/JCVI_HPV.pdf [Accessed 29th May 2019]

[9] Operational guidance for HPV MSM pilot https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/694370/Withdrawn_clinical_and_operational_guidance_for_HPV_MSM_pilot.pdf [Withdrawn April 2018, accessed 14th February 2019]

[10] HPV for MSM: Clinical and operational guidance, 2018 Available at https://www.gov.uk/government/publications/hpv-vaccination-for-msm-guidance-for-health-professionals [Accessed 29th May 2019]

Extending the HPV programme for boys in school year 8

In 2017 JCVI considered evidence for extending the HPV vaccination programme to boys. At that time extending the programme to boys was not considered cost-effective and JCVI was unable to recommend extension.

Following stakeholder responses to this interim advice additional analyses were conducted which adjusted for the long natural history of HPV associated disease. This analysis found extension of HPV vaccination to boys to be cost effective and It is anticipated that ongoing reduction in the incidence of cervical cancer, other cancers in both men and women and genital warts will substantially reduce the burden of HPV-related diseases .[11]

Vaccinating adolescent males will provide clear health benefits, including:

- direct protection for vaccinated boys against HPV infection and associated disease such as anogenital warts, anal, penile and oropharyngeal cancers
- protection against HPV for MSM by offering them vaccination before their sexual debut
- indirect protection for non-vaccinated males and females.

A clinical trial of the HPV vaccine Gardasil in healthy boys and men (3463 reported being heterosexual and 602 reported sexual contact with a male partner in the previous year), showed that the vaccine can prevent development of external genital lesions caused by persistent infection with HPV type 6, 11, 16, or 18 in boys and men 16 to 26 years of age.[12]

Extending the HPV vaccination programme to boys aged 12 to 13 will offer them direct protection against the main cancer-causing types of HPV, [13] reduce the

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[11] JCVI Statement on HPV vaccination, July 2018, Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/726319/JCVI_Statement_on_HPV_vaccination_2018.pdf [Accessed 25th May 2019]

[12] Giuliano A, Palefsky J, Goldstone S et al Efficacy of Quadrivalent HPV Vaccine against HPV Infection and Disease in Males 2011The new England journal of medicine 364:401-411 Available at https://www.nejm.org/doi/full/10.1056/nejmoa0909537 [Accessed 14 February 2019]

[13] Department of Health and Social Care Equity analysis Human Papilloma Virus (HPV), November 2018 Available at:

overall burden of these cancers sooner than a girls only programme would do, and add resilience to the UK vaccination programme against any short term fluctuations in vaccine uptake in females.

HPV schedule for boys

As a nationally-recommended vaccination programme for adolescents, the HPV vaccination programme for boys should be delivered as a two-dose programme, with a minimum interval of at least six months between doses, in the same way as the current programme for girls in school year 8.

The first dose of HPV vaccine can be given at any time during school year 8 (usually when students are 12 to 13 years old). The second dose should be given during school year 8 or school year 9. Those receiving the first dose will remain eligible to complete the schedule until they reach their 25th birthday.

Local areas may choose to schedule the second dose from 6 months to 24 months after the first.

Boys aged 13 to 25 years

Boys in the eligible cohort (born after 01/09/2006) remain eligible to receive the vaccine until their 25th birthday. Older boys (born before 01/09/2006) will not be offered the vaccine as they are already benefitting greatly from the indirect protection.

When the girls' programme was introduced in 2008, there was no population protection from HPV. So, although the programme was aimed at girls aged 12 to 13, a catch-up programme for older girls was introduced to try and accelerate the protection the programme would provide.

The situation is very different now and the high uptake of HPV vaccine among girls over the last ten years has reduced the prevalence of the types of HPV that the vaccine protects against. This means that the risk of unvaccinated boys and girls coming into contact with HPV viruses, and passing them on, is far lower than before the programme started in 2008.

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https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/758777/HPV_Boys_Equality_Assessment.pdf [Accessed 29th May 2019]

In addition, the number of diagnoses of genital warts in England has also fallen sharply in both males and females since the vaccination programme started. [14]

Impact of the female HPV vaccination programme

Surveillance conducted among young women attending for chlamydia screening in England has already demonstrated dramatic declines in HPV infection since the introduction of the girls' vaccination programme. The prevalence of HPV16/18 infection among 16-18 year old women who were eligible to receive the HPV vaccine reduced by over 80%, from 8.2% in 2010 to 1.6% in 2016[15]. There is also evidence of some cross-protection with clear reductions in the prevalence of HPV31, 33 and 45 (closely related types which aren't included in the HPV vaccine) from 6.5% in 2010 to 0.6% in 2016. These results suggest very high vaccine effectiveness as well as some herd protection among unvaccinated women.

Since the introduction of the quadrivalent vaccine in England, there has been evidence of a decline in the number of new diagnoses at sexual health clinics of anogenital warts (AGW) which have declined by 72% among 15-17 year olds between 2009, when no women would have been vaccinated, and 2016 when almost all 15-17 year old females would have been eligible for the quadrivalent HPV vaccine.[16] There was also a decline in the number of AGW diagnoses among heterosexual men (62% lower in 2016 compared to 2009) suggesting a substantial herd protection effect.

The impact of the vaccination programme on cervical disease and cancer is yet to be fully realised as the first cohort of routinely vaccinated girls only became eligible for cervical screening in England in 2016. However, there is emerging global evidence that vaccination is strongly associated with a reduction in both low and high grade cervical abnormalities (CIN of grade 1 or worse) in young women.

In Scotland, girls vaccinated as part of the catch up programme have been

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[14] Health Protection Report, Sexually transmitted infections and screening for chlamydia in England, 2017, Volume 12 Number 20, June 2018 Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/713944/hpr2018_AA-STIs_v5.pdf [Accessed 29th May 2019]

[15] Mesher D, Panwar K, Thomas SL et al. The Impact of the National HPV Vaccination Program in England Using the Bivalent HPV Vaccine: Surveillance of Type-Specific HPV in Young Females, 2010-2016. J Infect Dis **2018;** 218:911-21

[16] Health Protection Report, Sexually transmitted infections and screening for chlamydia in England, 2017, Volume 12 Number 20, June 2018: Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/713944/hpr2018_AA-STIs_v5.pdf [Accessed 14th January 2018]

entering the cervical screening programme since 2011 as screening there was recommended from age 20. The vaccine is associated with an 88% reduction in CIN2 and an 89% reduction in CIN 3+ or worse at population level.[17]

Vaccine effectiveness against CIN 2 and 3 lesions was greater in those women from the most deprived backgrounds. [18]

Attitudes to immunisation

National vaccination programmes in England have been supported and informed by a series of surveys exploring attitudes of parents towards infant immunisation since 1991. In 2017, the first annual survey of young people and their parents was undertaken to explore their attitudes to, and experience of, the adolescent vaccination programme. The 2018 survey was carried out between July and September. Face-to-face interviews were conducted with 1000 parents and 1000 young people aged 13-15 years in their homes.

- over 90% parents reported that their teenagers had all the vaccines they were offered. Only 2% had refused at least one vaccination
- less than 1% of young people had seen or heard anything that would cause them to be concerned about having the HPV vaccine
- genital cancers and cancers of the head and neck were perceived as equally serious as cervical cancer and meningitis
- over 90% of parents and young people rated all the vaccines offered as being completely safe or just a slight risk
- only 5% of young people believe that any vaccinations are worse for them than the disease. No specific vaccine was mentioned as being worse than the disease by more than 2% of young people

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[17] Palmer T, Wallace L, Pollock K, Cuschieri K, Robertson C, Kavanagh K et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study BMJ 2019; 365 :l1161 Available at https://www.bmj.com/content/365/bmj.l1161 [Accessed 29th May 2019]

[18] Cameron RL, Kavanagh K, Cameron Watt D, et al The impact of bivalent HPV vaccine on cervical intraepithelial neoplasia by deprivation in Scotland: reducing the gap, J Epidemiol Community Health 2017;71:954-960. Available at https://jech.bmj.com/content/71/10/954 [Accessed 29th May 2019]

- 95% of teenagers reported that it was important to be vaccinated; of these 69% thought it was ‘very important’ increasing to 77% where the young person had been taught about immunisation in school

- parents (91%) and young people (92%) had a high level of trust in advice given by health professionals. Parents and young people generally had very similar views.

Confidence in the adolescent vaccination programme is high. Being taught about immunisation in school and trust in health professionals are important in influencing positive attitudes to immunisation in young people. Recommendations include providing accessible information through schools and providing appropriate training to ensure health professionals are confident when providing immunisation information.

HPV vaccine recommendations

From September 1st 2019, the HPV vaccine recommendations will be as follows:

- all adolescents in school year 8, (usually aged 12 – 13 years)
- MSM up to and including 45 years of age, attending participating sexual health or HIV clinics, regardless of risk, sexual behaviour or disease status.

Although the universal adolescent HPV programme will be delivered as a school-based programme, eligible individuals who are home-schooled, or schooled outside of mainstream schooling should also be offered the vaccine.

Individuals with a similar risk profile to MSM

JCVI considers that there may be considerable benefit in offering the HPV vaccine to other individuals who have a similar risk profile to that seen in the sexual health and HIV clinic attending MSM population, including some MSM over 45, sex workers, HIV+ve women, and HIV+ve men. Clinicians are able to offer vaccinations outside of the national programme using individual clinical judgement, and HPV vaccination could therefore be considered for such individuals on a case-by-case basis. [3]

In these instances, vaccine should be purchased directly from the manufacturer. Vaccine stock centrally-procured for the schools-based or the MSM programme should not be used for this purpose.

Vaccination of individuals not eligible to receive HPV vaccine as part of an NHS approved vaccination programme

For these indivduals, if, following a clinical assessment, HPV vaccine is clinically indicated, the vaccine can be prescribed but must be sought separately from the national immunisation stock and there will be no reimbursement as part of the national programme.

Some parents may opt to make alternative arrangements to have their child immunised with the HPV vaccine if their child does not meet the eligibility criteria for the routine programme. Parents should be informed that if the vaccine is not clinically indicated and a private arrangement is made for vaccination, the provider may charge for the service as this arrangement is outside of the national programme.

Individuals moving from abroad

If an individual moves into school from overseas and meets the eligibility criteria for HPV vaccine, they should be offered it at the next scheduled or mop up session planned for that school.

If these students request the vaccine from their GP, it can be provided but this service is currently subject to negotiations and is not expected to be covered by the GP contract until 2021.

Individuals that have not had their first HPV vaccine dose by the age of 15 years

Individuals who have not had their first dose of HPV vaccine by the time they are 15 years old should be offered the three-dose schedule at 0, 1, 4-6 months (see Green book chapter 18a (HPV)

Eligible individuals with a history of receiving an incomplete course of HPV vaccine

Where an individual in the eligible cohort (i.e. females born after 01/09/1991 and males born after 01/09/2006) presents with an incomplete vaccination history, every effort should be made to clarify what doses they have had and when they were administered.

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 the first dose was administered and whether one or two doses have already been given. If the course is interrupted, it should be resumed but not repeated.

Eligible adolescents who commenced a three-dose schedule after their 15 birthday and who have received two doses of vaccine less than 6 months apart should complete the three-dose schedule as originally planned.

Eligible individuals who commenced a three-dose schedule before the age of 15 years and who received the first two doses of vaccine at least 6 months apart do not require a third dose and should be considered to have completed the full course.

The HPV vaccine

Recommended vaccine

Gardasil is the currently recommended vaccine for the universal HPV vaccination programme. It is the only market-authorized quadrivalent HPV vaccine in the UK, it is approved for use in males and females from 9 years of age and it is the vaccine that has been used in the existing girls programme since 2012.

Gardasil provides protection against four HPV strains: HPV16 and HPV18, two high risk HPV types that can lead to cancer; and HPV6 and HPV11, the two HPV types that cause approximately 90% of all anogenital warts in males and females.

The vaccine is made from the proteins that make up the outer coat of the virus types. These proteins assemble into small spheres that are called virus-like particles (VLPs). VLPs are not infectious and cannot cause HPV-associated cancers or genital warts as they do not contain the virus's DNA. However, VLPs are very immunogenic, which means that they induce high levels of antibody production by the body. Following vaccination with HPV vaccine, the immune system should mount a response against the VLPs. Upon subsequent expsosure to to the live virus, the immune system reacts quickly to prevent infection.

The WHO vaccine-preventable diseases monitoring system 2018 global summary[19] listed 121 countries using HPV vaccine around the world. Over 10.5 million doses have been given in the UK since 2008,[6] and more than 80 million people have been vaccinated worldwide.

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[19] World Health Organisation vaccine-preventable diseases: monitoring system. 2018 global summary Available at http://apps.who.int/immunization_monitoring/globalsummary/schedules [Accessed 29th May 2019]

HPV vaccine excipients

Gardasil does not contain thiomersal or porcine gelatin. For a full list of excipients (other substances contained in the vaccine besides the HPV antigens), healthcare professionals should read the: manufacturer's Summary of Product Characteristics (SPC).

Vaccine efficacy

Gardasil has been shown to be highly effective in preventing the types of HPV infection for which it is indicated. Evidence from clinical trials has shown that protection is maintained for at least ten years but is expected to last much longer and may be lifelong.

In clinical trials in young women with no previous history of HPV infection, the vaccine was 99% effective at preventing pre-cancerous lesions associated with HPV types 16 and 18. [6,7,8.] Gardasil is also 99% effective at preventing genital warts associated with vaccine types in young women.[9]

Although Miltz et al concluded that there was no evidence that HPV vaccines are effective in preventing vaccine-type HPV associated pre-cancer in women with evidence of prior HPV exposure,[20] it has been suggested that they may be an effective post-treatment adjuvant form of therapy by boosting immunity, reducing recurrences or preventing re-infection in people with a history of previously treated high-grade anal intraepithelial neoplasia (HGAIN).[21]

However, prior infection with an HPV type does not diminish the efficacy of the vaccine against other HPV types included in the vaccine. To get the best protection, it is important that the full course of vaccination is received.

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Miltz A, Price H, Shahmanesh M, Copas A, Gilson R. Systematic review and meta-analysis of L1-VLP-based human papillomavirus vaccine efficacy against anogenitalpre-cancer in women with evidence of prior HPV exposure. Available at https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0090348#abstract0 [Accessed 29th May 2019]

[21] Swedish KA, Factor SH, Goldstone SE. Prevention of recurrent high-grade analneoplasia with quadrivalent human papillomavirus vaccination of men who have sexwith men: a nonconcurrent cohort study. Clin Infect Dis. 2012;54:891-8.Available at https://www.ncbi.nlm.nih.gov/pubmed/22291111 [Accessed on 29th May 2019]

Differences between JCVI recommendations and information included in the Summary of Product Characteristics (SPC) for Gardasil

In 2014, Gardasil received licensing approval from the European Medicines Agency (EMA) for a two-dose schedule in adolescents. The two-dose schedule for Gardasil is licensed for individuals aged from age nine, up to and including, 13 years of age. JCVI recommended a two-dose schedule up to (and including) 14 years of age for Gardasil.

The WHO's Strategic Advisory Group of Experts (SAGE) on immunisation also recently reviewed the evidence on HPV immunisation schedules. Upon review of the evidence, SAGE also recommended a two-dose schedule before the age of 15 years.[22]

A three-dose schedule remains necessary if immunisation is initiated after the 15th birthday.

Individuals under 15 years of age

Gardasil can be administered as a two-dose schedule of 0.5ml given six months apart (0 and 6-24 months is clinically acceptable).

Any gap between doses of between 6 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. For example, if first dose given aged 14 years but patient does not re-present in clinic until aged 17 years, only one further dose need be given.

Individuals 15 years of age and older

Gardasil should be administered as a 3-dose schedule of 0.5 ml.

Due to the flexibility in the Gardasil SPC, variable spacing options for the three doses are possible.

For guidance, in a 3-dose schedule, the second dose should be administered at least 1 month after the first dose and the third dose should be administered at least

[22] WHO Strategic Advisory Group of Experts on immunization Working group on Human Papilloma (HPV) Immunization report to SAGE, September 2018 Available at https://www.who.int/immunization/sage/meetings/2018/october/3_SAGE2018_WG_recommendation_FINAL.pdf?ua=1 [Accessed on 29th may 2019]

3 months after the second dose. All three doses should ideally be given within one year, however a 24 month period is clinically acceptable.

Duration of protection

Current studies suggest that protection is maintained for at least 10 years although protection is expected to last longer and may be lifelong. Long term follow up studies are currently in place to evaluate this and will determine the need for any subsequent boosters.

Vaccine safety

The safety of Gardasil vaccine has been established through rigorous testing in clinical trials, followed by use of many millions of doses across the world. As with any medicinal product, some people may experience a side effect (see adverse reactions below), but these are generally mild, of short duration and are far outweighed by the expected benefits of the vaccine.

The UK Medicines and Healthcare products Regulatory Agency (MHRA) have published extensive reviews of HPV vaccine safety (www.mhra.gov.uk/HPVvaccine)

The US health authorities have also posted very clear advice on their website supporting the safety of HPV vaccine (http://www.cdc.gov/vaccinesafety/Vaccines/HPV/index.html)

Postural Orthostatic Tachycardia Syndrome (POTS)

POTS is 4 times more common in females and has peak onset in adolescence. Given the number of girls vaccinated over this time, a large number of diagnoses of POTS around the age the vaccine is given would be expected, regardless of any association with the vaccine.

In previous years, concerns regarding the safety of the HPV vaccine have been raised in the UK and other European countries, with some parents and pressure groups linking the vaccine to POTS. In June 2015, the JCVI carried out a routine review of HPV vaccine safety and concluded that it had no concerns about the safety of the HPV vaccine. The European Medicines Agency (EMA) has also conducted an independent review and, in line with findings from the UK's MHRA, concluded that available evidence does not support that HPV vaccines cause complex regional pain syndrome (CPRS) or POTS.

Although the Japanese authorities have currently suspended the proactive promotion of the HPV vaccine programme, the HPV vaccine is still available in Japan for any eligible person that wants it. No causal link between the vaccine and the illnesses reported in Japan has been confirmed, no other health authorities have taken similar action, and the World Health Organisation continues to endorse the HPV vaccine.[23]

Various worldwide independent health bodies and authorities have also reviewed the safety of HPV vaccine and all have concluded that evidence does not support a link between HPV vaccine and the development of a range of chronic illnesses.

HPV vaccine storage

Gardasil should be stored in its original packaging between +2˚C and +8˚C (ideally aim for 5°C) and protected from light. Gardasil should not be frozen.

Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. Those responsible for the ordering, storage and use of vaccines should be familiar with the recommendations in chapter 3 of the green book. Vaccines should not be over-ordered or stockpiled.

Data from stability studies demonstrate that the Gardasil vaccine components are stable for 72 hours when stored at temperatures from 8°C to 42°C. At the end of this period Gardasil vaccine should be used or discarded. This information is provided in case of cold chain breach only. Every effort should be made to ensure that the vaccine is stored between +2˚C and +8˚C.

[23] Sayaka Ikeda, Yutaka Ueda, Asami Yagi, Shinya Matsuzaki, Eiji Kobayashi, Tadashi Kimura, Etsuko Miyagi, Masayuki Sekine, Takayuki Enomoto & Kazuya Kudoh (2019) HPV vaccination in Japan: what is happening in Japan?, Expert Review of Vaccines, 18:4, 323-325, Available at DOI: 10.1080/14760584.2019.1584040 [Accessed 07/06/2019]

Vaccine administration

Obtaining consent

The giving and obtaining of consent for immunisation should be seen as a process and not a one-off event, where doses of HPV vaccine are being given in school, it may be more practical to obtain written consent for both doses of HPV vaccine from parents once rather than separately for each dose. As the two HPV doses may be given across two different academic years (year 8 and year 9) in areas delivering a school-based programme, if written consent is sought from parents, this need only be done once for the full course.

Written consent: In the routine school-based immunisation programmes, an information leaflet and consent form is usually sent to the parent to complete and return as they are not present at the time of vaccination. Email or electronic forms of consent are increasingly being used. Consent forms should not act as a barrier to immunisation, they should be as simple to complete as possible. Any information being collected about the young person, such as their health and immunisation status, or medications being taken, should be relevant to the immunisation being offered.

Verbal consent: On the day of the immunisation session, some school nurses and school immunisation teams attempt to make contact with the parent /guardian of young people who are keen to be immunised but who have not returned a written consent form. This enables them to obtain consent over the phone which maximises uptake and reduces the need for additional catch-up sessions. This strategy also has the added benefit of reducing inequalities by including people who are unable to complete written consent forms due to language or literacy issues.

Self-consent: As is clearly outlined in the Green book Consent chapter, some young people can self-consent. If a parent cannot be reached on the phone at the time of the immunisation session, self-consent should be used, where appropriate, to ensure the child is protected:

- young people aged 16 and 17 are presumed, in law, to be able to consent to their own medical treatment

- younger children who understand fully what is involved in the proposed procedure (referred to as ‘Gillick competent’) can also give consent, although ideally their parents will be involved. Although there is no lower age for Gillick

competency, as this will vary from child to child, some immunisation teams choose to reserve this option for senior school children

- if a person aged 16 or 17 or a Gillick-competent child consents to treatment, a parent cannot override that consent
- if the health professional taking consent felt a child was not Gillick-competent then the consent of someone with parental responsibility would be sought
- if a person aged 16 or 17 or a Gillick-competent child refuses treatment that refusal should be accepted. It is unlikely that a person with parental responsibility could overrule such a refusal.

A number of local areas are already successfully using self-consent for young people aged 16-17 and Gillick-competent children in their schools-based programmes. Some teams advise parents in the information provided, that the young person will be offered the opportunity to self-consent if the completed consent form is not returned. Self-consent can also increase inclusion where parents have language or literacy issues and could also reduce the need for additional immunisation sessions at the school.

Administering HPV vaccine

Healthcare professionals are encouraged to read the manufacturer's Summary of Product Characteristics to ensure accurate delivery of the product.

Each Gardasil dose has a volume of 0.5ml and is supplied in a pre-filled syringe which should be shaken well before use to obtain a white, cloudy suspension.

The vaccine should then be administered by a single intramuscular injection into the upper arm (deltoid region). See section below for individuals taking anti-coagulants or who have a bleeding disorder.

Two needles of different lengths are provided in the pack. Healthcare professionals should choose the appropriate needle to ensure an intramuscular (IM) administration depending on the vaccinee’s size and weight.

A small air bubble may be visible in the prefilled syringe. This is not harmful and should not be removed prior to administration. This small bolus of air injected following administration of medication clears the needle and prevents a localised reaction from the vaccination. To try to expel it risks accidently expelling some of the vaccine and therefore not giving the patient the full dose.

Vaccination of individuals taking anticoagulants or with a bleeding disorder

There is a lack of evidence that the subcutaneous route of vaccination is any safer than the intramuscular route in people taking anticoagulants. The subcutaneous route can itself be associated with an increase in localised reactions.

Individuals on stable anticoagulation therapy, including individuals on warfarin who are up to date with their scheduled INR testing and whose latest INR was below the upper threshold of their therapeutic range, can receive intramuscular vaccination. A fine needle (equal to 23 gauge or finer calibre) should be used for the vaccination, followed by firm pressure applied to the site (without rubbing) for at least 2 minutes. If in any doubt, consult with the clinician responsible for prescribing or monitoring the individual's anticoagulant therapy.

Individuals with bleeding disorders may be vaccinated intramuscularly if, in the opinion of a doctor familiar with the individual's bleeding risk, vaccines or similar small volume intramuscular injections can be administered with reasonable safety by this route. If the individual receives medication/treatment to reduce bleeding, for example treatment for haemophilia, intramuscular vaccination can be scheduled shortly after such medication/treatment is administered. A fine needle (equal to 23 gauge or finer calibre) should be used for the vaccination, followed by firm pressure applied to the site (without rubbing) for at least 2 minutes[24]. The individual/parent/carer should be informed about the risk of haematoma from the injection.

Administering the HPV vaccine at the same time as other vaccines

Gardasil is an inactivated vaccine and will not be affected by, nor interfere with other inactivated or live vaccines given at the same time as, or at any interval from each other.

HPV vaccines can be given at the same time as other vaccines such as Td/IPV, MMR, Influenza, MenACWY and Hepatitis B. 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. The site at which each vaccine was given should be noted in the individual's records.

[24] Centers for Disease Control and Prevention. Vaccine recommendations and guidelines of the ACIP. Vaccinating Persons with Increased Bleeding Risk. Available at: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/special-situations.html

Contraindications for receiving Gardasil

There are very few individuals who cannot receive HPV vaccines. Where there is doubt, instead of withholding immunisation, appropriate advice should be sought from a consultant with immunisation expertise, a member of the screening and immunisation team or from the local health protection team.

Gardasil should not be administered to those who have had:

1. A confirmed anaphylaxis to a previous dose of the vaccine OR

2. A confirmed anaphylaxis to any constituent or excipient of the vaccine

For the composition and full list of excipients of the vaccine, please refer to the manufacturer's Summary of Product Characteristics (SPC).

Yeast allergy

Although Gardasil vaccine is grown in yeast cells, the final product does not contain any yeast. Individuals with a yeast allergy can receive Gardasil vaccine as this is not a contraindication.[25]

Adverse reactions following HPV vaccination

In clinical vaccine trials, the most common adverse reaction observed were injection-site reactions (77.1% of vaccinees within 5 days following any vaccination visit). These include mild to moderate short-lasting pain at the injection site, immediate localised stinging sensation and redness at the injection site.

Other reactions commonly reported are headache, myalgia, fatigue, and low grade fever. These adverse reactions are usually mild or moderate in intensity.

For a detailed list of adverse reactions associated with Gardasil please refer to the manufacturer's Summary of Product Characteristics (SPC) or the Patient Information Leaflet (PIL) that comes with each vaccine.

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[25] DiMiceli L, Pool V, Kelso JM et al. (2006) Vaccination of yeast sensitive individuals: review of safety data in US vaccine adverse event reporting system (VAERS). Vaccine 24(6): 703-7. Available at https://www.sciencedirect.com/science/article/pii/S0264410X05007486 [Accessed 14th February 2019]

Any suspected adverse reactions following administration should be reported to the Yellow Card Scheme https://yellowcard.mhra.gov.uk/.This is a voluntary scheme and its success depend upon early, complete and accurate reporting. A report should be submitted even if there is uncertainty about whether a vaccine caused a condition.

Vaccine administration errors

Interruption of the schedule or missed doses

If the vaccine course is interrupted, it should be resumed but not repeated, ideally allowing the appropriate interval between the remaining doses and using the vaccine currently in use in the UK programme.

Individuals should be advised that although they will ultimately be protected if they receive the vaccine over a longer period of time, they may remain susceptible to HPV infection prior to completing the course.

Vaccines administered at less than the recommended interval

Where vaccines have been given at less than the recommended interval, the dose should be repeated once the recommended time period has elapsed and at least four weeks from the last dose given. Individuals should be advised this may lead to an increased risk of local reaction.

If an individual following the two-dose schedule has received their vaccine doses at less than a six month interval, a third dose should be given according to the guidance on the 3-dose schedule. Although the number of days within a 6 month period can vary depending on what time of the year it covers, two doses of Gardasil given less than six months apart should not be considered adequate to provide long-term protection. As the Green book HPV chapter and HPV PGD recommend a minimum interval of 6 months between doses, vaccination sessions that are less than 6 months apart should not routinely be scheduled.

Administration of an incomplete dose

In the event that Gardasil vaccine is administered at less than the recommended 0.5 ml dose, the vaccination will need to be repeated because the dose that the individual received may not be sufficient to evoke a full immune response. Where possible, the dose should be repeated on the same day or as soon as possible after.

PGDs and patient information

Patient group directions (PGDs) and off-label use of Gardasil

Gardasil should only be administered using a:

- Prescription written manually or electronically by a registered medical practitioner or other authorised prescriber
- Patient Specific Direction (PSD)
- Patient Group Direction (PGD)

PHE have developed a national PGD template which should be reviewed and authorised locally before use. Off-label use of licensed products can be permitted under a PGD if that use is included within the PGD.

Patient information leaflets (PILs)

The manufacturer of Gardasil has updated their Patient Information Leaflet (PIL) following licensing approval from the EMA for a two-dose schedule.

Individuals with underlying medical conditions

Immunosuppression

There is no data for two-dose schedules for immunocompromised individuals. For this reason, a three-dose schedule should be offered to individuals who are are known to be immunocompromised at the time of immunisation. Re-immunisation should be considered after treatment is finished and/or recovery has occurred. Specialist advice may be required (see Green Book chapters 7 and 18a).

HIV positive individuals

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

Evidence suggests individuals with HIV infection are at increased risk of acquiring HPV and persistent infection, as well as frequent carriage of multiple HPV types and increased risk of HPV-related rapidly progressive malignancies.[13]

There are limited data on 3-dose schedules in HIV-infected individuals; however HPV vaccines are known to be safe and immunogenic when given to individuals infected with HIV with no adverse impact on CD4 cell counts or viral load observed.

There is no data to support giving fewer than 3 doses among HIV-infected individuals, therefore only a 3-dose schedule should be offered to individuals in the eligible cohort who are known to be HIV-infected. The immune response to this vaccination and its effectiveness may be less than that observed among those who are non-HIV infected.

COVER data

Vaccine coverage data for the HPV programme

Vaccine coverage data will continue to be collected via ImmForm but future collections will provide separate estimates of coverage for males and females. Vaccine coverage data for the HPV programme is available at https://www.gov.uk/government/collections/vaccine-uptake#hpv-vaccine-uptake.

Further information about the HPV ImmForm vaccine coverage data collection is available in Annex B1 of the NHS England/PHE letter ‘Introduction of a universal HPV immunisation programme’ available on the PHE HPV webpage.

Useful Links

Gardasil Summary of Product Characteristics. Available at the electronic Medicines Compendium (eMC) https://www.medicines.org.uk/emc/medicine/19016

Gardasil Patient Information Leaflet. Available at the electronics Medicines Compendium (eMC) GARDASIL - Patient Information Leaflet (PIL) - (eMC)

Public Health England Resources for the HPV vaccination programme including guidance and promotional material and documents relating to the universal human papilloma virus (HPV) vaccination programme for girls and boys can be found on the Gov.UK website

This page includes the following resources:

- HPV universal vaccination: leaflet
- HPV universal vaccination: poster
- HPV universal vaccination: record card
- HPV universal vaccination: factsheet for health professionals
- HPV universal vaccination: consent form

HPV resources available to order from the health and Social Care Publications Orderline can be downloaded and/or ordered as printed publications.

www.orderline.dh.gov.uk/ecom_dh/public/home.jsf
Telephone: 0300 123 1002