JCVI Joint Committee on Vaccination and Immunisation

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

JCVI Interim Statement on Extending HPV Vaccination to Adolescent Boys

Introduction

1. 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. At this time JCVI agreed that the evidence indicated that vaccinating boys was unlikely to be cost-effective, as high coverage in girls would provide substantial herd protection for boys.
2. JCVI keeps the eligibility criteria of all vaccination programmes under review, and in October 2013 JCVI began consideration of a number of questions regarding HPV vaccination, including a move to a two dose schedule for adolescent girls; the vaccination of men who have sex with men (MSM), and potential extension of the programme to include adolescent boys. The latter was under review because of strengthening evidence on the association of HPV vaccine types with non-cervical cancers. During the review process, considerations regarding vaccination of MSM were prioritised, as MSM were known to have a relatively high burden of HPV-associated disease but were expected to receive little indirect benefit from the girls programme.
3. Work on the impact and cost effectiveness of a targeted programme for MSM was considered by JCVI between September 2014[1] and October 2015.[2] On the basis of the evidence considered, JCVI advised that a targeted HPV vaccination programme with a course of three doses for MSM aged up to 45 who attend GUM and HIV clinics should be undertaken, subject to procurement of the vaccine and delivery of the programme at a cost-effective price.[3] As a result a pilot to evaluate a service providing HPV vaccination to MSM up to and including 45 years of age who attend GUM and HIV clinics is being undertaken in selected clinics across England
4. In January 2014 JCVI requested that Public Health England (PHE) develop a new model and review all available evidence regarding the costs and benefits of extending the HPV programme to adolescent boys. The individual based model (IBM) developed by PHE is a highly sophisticated model, which takes into account cervical cancer screening and uses the latest UK data to model sexual behaviour. The modelling work also takes into account the vaccination of MSM.
5. The Department of Health (DH) commissioned the University of Warwick to separately conduct an independent modelling assessment on vaccinating adolescent boys. Warwick University are funded by DH to conduct second opinion

[1] Minute of the JCVI HPV Subcommittee held on Sept 22 2014
[2] Minute of the JCVI meeting held on 7 October 2015
[3] JCVI statement on HPV vaccination of men who have sex with men

modelling for assurance purposes on major JCVI decisions that are likely to have significant financial implications or that are of a highly complex nature.

6. A key part of JCVI's consideration of a vaccination programme for adolescent boys has been the impact and cost effectiveness modelling study conducted and coordinated by PHE. The findings of the PHE modelling are supported by a number of other evidence sources, these include modelling undertaken by the University of Warwick, an HPV modelling meta-analysis of 16 published models, undertaken by Marc Brisson, (a world leading expert in the modelling of infectious diseases) and the original modelling work developed in 2008 by PHE (then the Health Protection Agency). The modelling has been considered alongside published and unpublished literature on the HPV vaccine and the contribution of HPV infection to a wide range of cancers. The latest evidence on the impact of HPV vaccination in the UK and globally has also been included as part of the evidence considered by the committee.
7. The evidence considered clearly indicates that HPV is associated with a number of cancers which affect both sexes. The evidence also indicates that HPV vaccination would provide direct protection against many of these cancers.
8. The analyses considered consistently show that when there is high uptake of HPV vaccine in adolescent girls, considerable herd protection is provided to the male population. While there are some additional population level health benefits to both males and females by extending the programme to boys, impact and cost-effectiveness modelling indicates that adding boys is highly unlikely to be cost-effective in the UK, where uptake in adolescent girls is consistently high (over 85%).
9. This statement sets out the key evidence and describes the considerations and interim position of the JCVI. The JCVI is consulting on its interim findings to ensure that the most appropriate and up-to-date evidence has been used, and that reasonable assumptions have been made where evidence is limited or unavailable. Once the consultation is completed, the JCVI will develop and publish its final advice.

Background

Previous deliberations on HPV

10. JCVI began consideration of HPV vaccination in 2006. JCVI examined all available evidence before making a recommendation for the introduction of an HPV vaccination programme in the UK, including:

    • vaccine efficacy studies;

    • burden of disease resulting from HPV infection (epidemiology);

    • the expected health benefits of introducing an HPV vaccination programme;

    • whether the programme would be cost-effective;

    • attitudinal work; and

    • the suitability of a routine immunisation programme.

11. At the October 2007 meeting JCVI concluded that a universal HPV vaccination programme for girls aged 12 to 13 years would be cost effective. In addition to this, the Committee also recommended a time-limited 'catch up' vaccination campaign for girls aged 13 to less than 18 years. In July 2008 a full statement on HPV vaccination was issued[4].

12. JCVI did not recommend vaccinating boys at this time as it was considered unlikely to be cost-effective. The Committee considered that high coverage in girls would provide herd protection to boys, and that vaccination of boys would generate little additional benefit to the prevention of cervical cancer, which was the main aim of the programme. Additionally, JCVI agreed that there was insufficient evidence on the protective effects of the vaccine against cancers affecting males such as anal, head and neck cancers. JCVI agreed that when more data became available, high-risk groups such as MSM would be considered.

HPV vaccination for MSM

13. Work on the impact and cost effectiveness of a targeted programme for MSM was considered by JCVI between September 2014 and October 2015[5]. On the basis of the evidence considered, JCVI advised that a targeted HPV vaccination programme with a course of three doses for MSM aged up to 45 who attend GUM and HIV clinics should be undertaken, subject to procurement of the vaccine and delivery of the programme at a cost-effective price. JCVI recognised the complexities associated with commissioning and delivery of a programme involving GUM and HIV services in England. As a result a pilot to evaluate a service providing HPV vaccination to MSM up to and including 45 years of age who attend GUM and HIV clinics is being undertaken in selected clinics across England: https://www.gov.uk/government/publications/hpv-vaccination-pilot-for-men-who-have-sex-with-men-msm.

[4] JCVI statement on human papillomavirus vaccines to protect against cervical cancer
[5] JCVI statement on HPV vaccination of men who have sex with men

Review of the existing programme - extending HPV vaccination to adolescent boys

14. JCVI keeps the eligibility criteria of all vaccination programmes under review and in October 2013 JCVI recommended a HPV sub-committee be formed to consider a range of issues; a two dose HPV vaccination schedule; the impact of the current HPV programme; HPV immunisation of MSM; the impact of HPV immunisation on a wider range of HPV-related diseases; the potential impact of higher valent vaccines; and the potential extension of the programme to include adolescent boys. This was considered important as more evidence was becoming available on the association between HPV infection and non-cervical cancers, and the effectiveness of HPV vaccine in protecting males from HPV infections.

15. In October 2013 JCVI received a presentation from PHE which indicated provisional timelines for development of mathematical modelling for each of the key issues to be addressed. Modelling work on vaccinating MSM was already underway as this was considered a priority as this is a group with a high burden of HPV associated diseases that is expected to receive relatively little indirect benefit from the girls programme. JCVI noted that the development of an 'individual based model' would improve proper assessment of an adolescent boys vaccination programme. Individual based models are very complex mathematical models simulating the impact of an intervention on individuals within a population over time, and take a considerable amount of time and expert resource to develop.

16. An individual based model was already in development to assess the impact of using HPV testing as the primary screen in cervical cancer screening (as opposed to cytological screening as the primary screening tool). PHE therefore suggested that the HPV vaccination model could be developed by extending the HPV screening model, thereby creating an integrated screening and vaccination model. PHE is of the view that an integrated individual based model will be of great benefit in assessing the synergies which come from coordinated screening and immunisation practices. Such a model will also be important in understanding the impact and cost-effectiveness of higher valent vaccines and for informing future tendering exercises for HPV vaccine for the routine adolescent girls programme.

17. The Committee was advised that the HPV cervical screening model would likely be completed in April 2014, and work to revise the model for vaccination would require between 12 and 24 months depending on available resource. This led to the conclusion that results would not be available until the end of 2015 at the earliest.

18. At the January 2014 meeting the Subcommittee was informed by the Department of Health that a parallel stream of HPV modelling to look at the issue of extending vaccination to boys was being conducted by Warwick University as part of the second opinion work that DH commissions, and this would also take between 18 and 24 months.

19. At the October 2014 JCVI meeting the Committee noted that the screening model was now not due to be completed until early 2015. Although disappointed that modelling work on the cost-effectiveness of HPV vaccination of adolescent boys by PHE would not begin until early 2015 the Committee agreed that it would not be

advisable to take any shortcuts in order to expedite the work, which could undermine the validity of the outputs. In October 2014 JCVI was also informed that the work by Warwick was underway.

20. At the February 2015 JCVI meeting the Chair informed the Committee that the view from PHE was that incorporation of vaccination into the yet to be completed individual based cervical screening model (which had been delayed until early 2015), set the completion date of the PHE HPV vaccination model as early 2017 at the earliest.

21. The first results of the Warwick study were presented in June 2015 to the HPV Subcommittee. At the June 2015 JCVI meeting the Committee agreed that the University of Warwick work would be used to help inform and contribute to this process and challenge the assumptions in the main (PHE) model. This process would ensure that the Committee's conclusions would be as robust as possible. The Committee agreed that it would be important to follow the agreed process.

22. At the February 2016 HPV Subcommittee meeting the latest results of the Warwick modelling study were considered by the Committee. The results indicated a boys' programme was highly unlikely to be cost-effective under a two dose schedule. The HPV Subcommittee also noted that the PHE model, which was still in development, was the main model that would be used for the consideration of gender neutral vaccination and this was expected in early 2017.

23. At the January 2017 HPV Subcommittee the first results of the PHE impact and cost-effectiveness assessment were presented to the Committee. The Committee agreed that more work was needed to give more certainty to the results. PHE was asked to focus on the most important changes to answer with a higher degree of certainty whether it would be cost effective or not to extend vaccination to adolescent boys in the context of high coverage in girls as consistently achieved in the UK. PHE estimated that the necessary work would take approximately 4 months and the results could be presented to the HPV Subcommittee in early June and the outcome of this reported at the June JCVI meeting. At the January 2017 JCVI sub-committee meeting after further reviewing the work of the Warwick modelling study the Committee agreed that this work should undergo independent peer review.

24. At the June 2017 HPV sub-committee and main JCVI meetings the latest results of the PHE study, and the results of the peer review of the work by the University of Warwick, were considered which are outlined below together with the considerations of the Committee.

Evidence considered by JCVI

Epidemiology

Much of this information has been drawn from the call for evidence that JCVI requested in 2012.

Human papillomavirus (HPV) infects both males and females, and in males can progress to cause anal, penile, oropharyngeal, and oral cavity cancers as well as

anogenital warts. The high risk HPV types 16 and 18 are strongly implicated in anal/genital cancers (penis, vagina and vulva, anus) although the prevalence of these cancers in the general population is low. HPV-associated cancers in all males are relatively rare compared with cancer of the cervix (and other sites) in all females, even where effective cervical screening programmes are run. Research and prevention strategies have therefore more often targeted females and cervical disease. Parkin (2011)[6] estimated the UK attributable fraction for the number of HPV associated cervical cancers and non-cervical cancers in females to be 2691 and 1367 respectively, compared to 1030 cases of non-cervical cancer in males. Table 1a and Table 1b give the breakdown of cancer registrations associated with HPV infection newly diagnosed in 2014 in England for males and females

Table 1a Office for National Statistics (ONS) reported registrations of newly diagnosed cases of cancer in Females 2014 England, with attributable fraction associated with high risk HPV types

cancer site (females)	ICD10 codes	newly diagnosed cases	Rate* per 100,000 population	deaths	High-risk HPV type (attribution fraction†)
Cervix	C53	2,590	9.5	726	HPV16/18/31/33/45/52/58/other (35/39/51/56/59/68) (95.1%)
Vulva	C51	1,054	3.9	359	HPV16/18/33 (12.7%)
Vagina	C52	199	0.7	84	HPV16 (53.7%)
Anus	C21	725	2.7	166	HPV16/18/33 (77.0%)
Oropharynx	C01, C09 & C10	562	2.2	114	HPV16 (24.7%)
Oral cavity	C02 to C06	1,280	4.9	401	HPV16/18 (1.1%)
Larynx	C32	303	1.2	117	HPV16/18 (1.9%)

*Directly age-standardised and age-specific rates

†Attributable fraction for high risk HPV types associated with cancer as modelled by PHE and based on IARC reviews

Source Office for National Statistics and Public Health England

[6] Parkin DM. Cancers attributable to infection in the UK in 2010. British Journal of Cancer (2011) 105, S49 – S56

Table 1b Office for National Statistics (ONS) reported registrations of newly diagnosed cases of cancer in males 2014 England, with attributable fraction associated with high risk HPV types

cancer site (males)	ICD10 codes	newly diagnosed cases	Rate* per 100,000 population	deaths	High-risk HPV type (attribution fraction†)
Anus	C21	356	1.5	115	HPV16/18/33 (77.0%)
Penis	C60	513	2.2	103	HPV16/18 (28.6%)
Oropharynx	C01, C09 & C10	1,818	7.5	365	HPV16 (12.8%)
Oral cavity	C02 to C06	1,731	7.3	641	HPV16/18 (1.4%)
Larynx	C32	1,519	6.7	539	HPV16/18 (0.6%)

*Directly age-standardised and age-specific rates

†Attributable fraction for high risk HPV types associated with cancer as modelled by PHE and based on IARC reviews

Source Office for National Statistics and Public Health England

Despite fewer studies of HPV epidemiology in males, the risk factors for infection (i.e. sexual behaviours, young age), the prevalence of genital HPV infection and the rates of genital warts diagnoses are understood to be broadly comparable between males and females. It is also known that infection rates are higher (and continue to be higher into older age groups) in MSM than in heterosexual males, as are rates of HPV-associated disease, particularly for anal cancer. HIV infection is associated with much higher incidence of HPV-associated disease, which further increases the risk amongst MSM. More than 80% of anal cancers are caused by high risk HPV types.

The prevalence or burden of anal infection is higher in women than men and possibly increasing proportionately with high risk sexual behaviours. Most anal HPV infections, however, are cleared within a year. MSM are disproportionately affected compared to heterosexual men and women. The incidence of anal cancer is highest in HIV positive MSM and rates of anal cancer in MSM are increasing. Infection with HIV appears to greatly increase the risk of anal cancers. Anal cancer incidence has been estimated at 1, 5 and 46/100 000 person years in all men, HIV-negative MSM and HIV-positive MSM, respectively (Frisch et al, 2003; Wilkinson et al, 2014): this

compares to ~9.5 cervical cancer cases /100,000 females in England (CRUK: data for 2014).

Evidence is accumulating for a strong HPV association with head and neck cancers in particular oropharyngeal (base of tongue, tonsil, oropharynx, and larynx). Globally, estimates of the proportion of oropharyngeal cancers with HPV infection vary widely from 18% to as high as 93%. HPV 16 has been consistently found to be the most prevalent type (approx. > 90% of infections) followed by HPV 18. Oropharyngeal squamous cell carcinoma (OSCC) has been increasing worldwide, including the UK, particularly among men and younger age groups. In Scotland the rate of OSCC has increased more than any other cancer.

In western countries, including the UK, the proportion of HPV +ve OSCC diagnosed is increasing over HPV-ve OSCC. This may indicate an epidemiological shift from smoking related risk factors to sexual practice related risk factors for OSCC although alcohol is also an important risk factor. HPV positive OSCC individuals have a better prognosis in terms of progression to disease and survival compared to HPV –ve OSCC individuals. The majority of oropharyngeal cancers are in males who also have higher mortality rates than women. The prevalence of oral HPV infection appears to be higher in MSM than in heterosexual men.

It is expected that the bivalent and quadrivalent HPV vaccines will protect against HPV 16/18-related non-cervical pre-cancers and cancers while the quadrivalent vaccine has proven efficacy against genital warts. Efficacy has already been demonstrated against vagina, vulva and anal HPV infections and precancerous lesions and against oral HPV 16/18 infection (Herrero *et al*., 2013). No data are available for either vaccine on efficacy against head and neck cancers.

Cervical cancer is a disease of the young and is the most common cancer among women under the age of 35. According to latest UK figures around 3100 women are diagnosed with cervical cancer and around 900 women die from cervical cancer each year. Human papillomaviruses cause more than 99% of all cervical cancers. The HPV vaccine currently used in the UK programme protects against the two HPV types (HPV 16 and 18) that cause most cases (over 70%) of cervical cancer. In addition the vaccine currently used in the UK also provides protection against genital warts, the most common viral sexually transmitted infection in the UK.

Impact of girls programme

Surveillance data already suggest that the programme is achieving its aims thanks to high vaccination coverage. The vaccine has contributed to a significant decrease in rates of infection with the two main cancer-causing human papillomaviruses in women.[7] [8] This is consistent with very high vaccine effectiveness among those

[7] Mesher D, Panwar K, Thomas SL, et al Continuing reductions in HPV 16/18 in a population with high coverage of bivalent HPV vaccination in England: an ongoing cross-sectional study BMJ Open 2016;6:e009915. doi: 10.1136/bmjopen-2015-009915

[8] Cameron RL, Kavanagh K, Pan J, et al. Human Papillomavirus Prevalence and Herd Immunity after Introduction of Vaccination Program, Scotland, 2009–2013. *Emerging Infectious Diseases*. 2016;22(1):56-64. doi:10.3201/eid2201.150736.

vaccinated and also suggests that herd-protection is also lowering prevalence among females who are not vaccinated. Herd protection from the girls programme has also been observed in males with a 62% reduction in the rate of first episode genital warts in young men in England since 2009 compared with a 72% decrease in young women[9].

The UK programme is expected to eventually prevent hundreds of deaths from cervical cancer every year. In the original modelling work by PHE (Choi et al, 2009; Jit et al, 2008) it was estimated that in the long term, use of the quadrivalent vaccine (the vaccine currently used in the UK) may prevent around 630 - 1100 (median 700) cervical cancer cases a year and 380 - 950 cases of anal, vulva and vaginal cancer a year. If the additional protection against HPV 16/18 related penile and oropharyngeal cancers is taken into account, the number of non-cervical cancers prevented could be 560 – 1000 cases a year. These are cases prevented in addition to those prevented by the cervical screening programme. The quadrivalent vaccine is also expected to eventually prevent up to 95% of vaccine related anogenital warts a year in males and females.

Safety

JCVI keeps the safety of all vaccines under review and receives regular reports from the Medicines and Healthcare products Regulatory Agency (MHRA) on the post marketing surveillance of the safety of vaccines as well as any specific investigations and research findings. JCVI carried out routine reviews of HPV vaccine safety in 2015 and concluded that it had no concerns about the safety of the HPV vaccine.

Extensive reviews of HPV vaccine safety have also been undertaken by various independent health bodies and authorities worldwide. These have concluded that evidence does not support a link between HPV vaccine and the development of a range of chronic illnesses. Notably, in December 2015, the World Health Organization's Global Advisory Committee on Vaccine Safety advised it had not found any safety issues to date that would alter its recommendation to use the vaccine. Thorough reviews undertaken by the European Medicines Agency, US Centre for Disease Control and Prevention and Health Canada have arrived at similar conclusions.

Data presented to the HPV Subcommittee on the safety profile of the 9 valent vaccine shows that this is similar to that of the quadrivalent vaccine and shows that it is well tolerated in both girls and boys; men (including MSM) and women.[10;11]. A similar situation has been seen for Cervarix with no serious safety concerns. JCVI

[9] Sexually Transmitted Infections and Chlamydia Screening in England, 2016 Health Protection Report Volume 11 Number 20

[10] Van Damme P, Meijer CJ, Kieninger D *et al*. A phase III clinical study to compare the immunogenicity and safety of the 9-valent and quadrivalent HPV vaccines in men. Vaccine. 2016 Jul 29;34(35):4205-12. doi: 10.1016/j.vaccine.2016.06.056. Epub 2016 Jun 25.

[11] Castellsagué X, Giuliano AR, Goldstone S
et al. Immunogenicity and safety of the 9-valent HPV vaccine in men.

has no concerns about the safety of any of the available HPV vaccines in both sexes.

Immunogenicity

Data presented to JCVI by the manufacturer on the 9 valent vaccine shows that the immunogenicity seen in boys and men is non-inferior to that seen in girls and women for the HPV high risk cancer causing vaccine types HPV16 and 18 and HPV11 and 6 which cause warts[12]. The immunogenicity of the 9 valent vaccine is lower in MSM than in heterosexual men but follows the same trend as for the quadrivalent vaccine. Data on the bivalent vaccine also shows comparable immunogenicity in males and females.

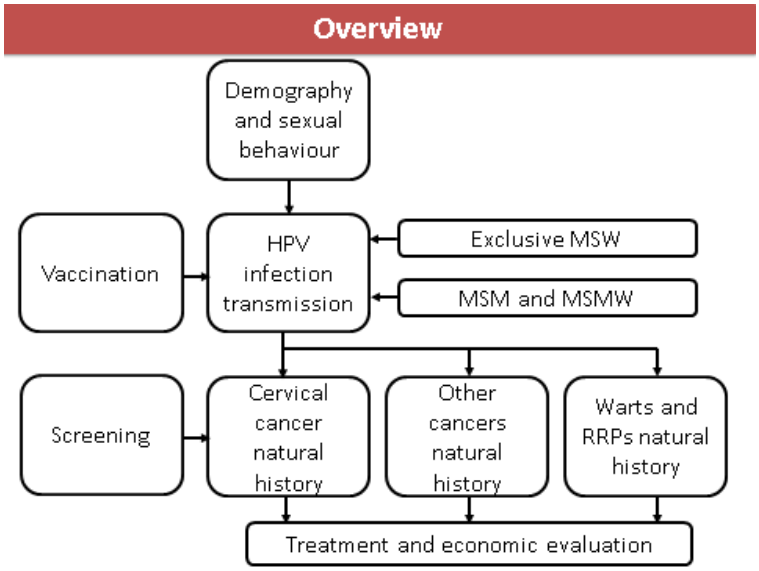
PHE Impact and cost effectiveness study

A key part of JCVI's consideration of a vaccination programme for adolescent boys was its assessment of a modelling and cost-effectiveness study conducted and coordinated by Public Health England. The PHE impact and cost-effectiveness study model is the main study intended to inform the Committee's final deliberation on whether to extend HPV vaccination to adolescent boys. As much detail as possible has been provided on the PHE model without compromising the academic confidentiality that is required for the intended future publication of this work.

Fig 1 provides an overview of the PHE model.

The PHE model is an individual-based model (IBM), which models sex acts within a partnership over the duration of the partnership. The IBM models exclusively heterosexual partnerships and estimates the average probability of transmission per sex act within a discordant heterosexual partnership. Same-sex partnerships are modelled separately based on the previous PHE model used to inform the MSM-targeted vaccination programme. In the IBM a single partnership lasts for a certain length of time, consists of a number of sex acts, and can occur concurrently with a different partnership involving common partners.

[12] Summary of Product Characteristics Gardasil 9



Data sources

Sexual behaviour

PHE used the most recently cleaned dataset from the third National Survey of Sexual Attitudes and Lifestyles 2010 (Natsal-3) to parameterise the sexual demography in the IBM.

Based on the available data, the model assigns individuals in the population with an age of sexual debut, rate of new partner acquisition, age preference between partners, duration of partnership, concurrency of partnerships, and frequency of sexual contacts within each partnership. Individuals in the model were stratified into four risk groups from high to low based on the average number of partners they had in the previous five years.

Concurrency (overlapping partnerships) was taken into account; however, because of difficulties in generating partnerships that reflect all reported Natsal data two scenarios were run:

- the model parameterised using duration of partnerships based on Natsal data - which does not fit the concurrency data in Natsal.
- the model parameterised using the shortest duration of partnership - which fits the concurrency data in Natsal but means there are many individuals not in partnerships.

HPV transmission

Parameters governing HPV transmission within sexual partnerships were inferred using female HPV prevalence data (HPV prevalence data are not available for a representative male population of the United Kingdom) as well as male and female seroprevalence data from England.

The IBM was used to model sexual behaviour and transmission and infection with HPV with the high risk HPV types 18 and 16 responsible for approximately 80 % of

cervical cancers attributable to HPV in the UK. The model also included other high risk types and the low risk HPV types responsible for the majority of anogenital warts i.e. HPV 11 and 6. The high risk HPV types covered by Gardasil 9 were also modelled individually: 31, 33, 45, 52, and 58.

Disease progression was modelled for cancer of the: cervix, vulva, vagina, penis, anus, oral cavity, oropharynx (includes tonsil and base of tongue) and larynx.

The attributable fractions for HPV types for each cancer type were estimated using the International Agency for Research on Cancer (IARC) monograph 100B-11 human papillomavirus for evidence on HPV subtype attribution in HPV-related cancers. (See table 1a and 1b in previous epidemiology section for the estimates of the attributable fractions for the HR HPV types modelled for each cancer type in males and females)

A recent analysis of the global burden of cancers attributable to infections in 2012, by Plummer et al. (2016) was used to identify the latest published evidence on HPV attribution fraction to the various cancers considered in the PHE models.

The most recent incidence of non-cervical cancers had also been taken into account although no prediction was made about future trends in cancer incidence.

Disease progression

A hybrid approach was taken for modelling disease progression with the most common cancer i.e. squamous cell cervical cancer modelled using the IBM while progression to the rarer squamous cell cancers was modelled using a compartmental model.

Vaccination scenario

The model simulates the HPV immunisation programme from its introduction in 2008 for adolescent girls including catch up cohorts in older girls, the change from Cervarix to Gardasil in 2012 and the start of the MSM programme in 2016 and looked at the impact of extending the programme to boys from 2017/18. For the base case the duration of protection was assumed to be life-long and a two dose course used for adolescents under the age of 15 years. Sensitivity analyses were performed for 20 years duration of protection.

Cost-effectiveness

The incremental cost effectiveness of extending the programme to adolescent boys was measured against the cost-effectiveness of the current adolescent girls programme and the targeted MSM programme.

The net monetary benefit per vaccinated person was calculated, representing the maximum cost-effective price that could be paid to fully vaccinate one person. This was the value under the assumption of a two dose course of vaccine including the administration cost of delivering the two doses.

Parameters

Results were calculated using the current National Institute for Health and Care Excellence (NICE) discounting rate for costs and benefits of 3.5% to estimate the net monetary benefit at £20,000 per Quality Adjusted Life Year (QALY). Uncertainty was estimated by calculating the net monetary benefit at the threshold of £30,000 per QALY. Sensitivity analyses were performed using 1.5% discounting.

Costs

PHE conducted a systematic review of published evidence on cost and disutility associated with HPV-related diseases. As a result many of these have been revised since the model in 2011. The systematic review will be published in due course.

Results

These results were reported at the June HPV Subcommittee and JCVI meetings.

At the standard discounting rate of 3.5% the net monetary benefit per vaccinated person (males) for extending HPV vaccination to boys was only marginally positive. This willingness to pay price per dose of vaccine is below a realistic threshold price after adjusting for a two dose schedule with associated administrative costs (i.e. dividing the net monetary benefit per vaccinated person by two and subtracting the likely administration cost of around £10). The price per dose of vaccine was also below a realistic threshold price for 90% of the simulations at the £30,000 per QALY threshold in the uncertainty analyses. In the sensitivity analysis using a 1.5% discounting rate for costs and benefits the willingness to pay price per dose of vaccine is also below a realistic threshold price after adjusting for a two dose schedule with associated administrative costs.

The Committee's view

The Committee has noted that the changes made to the PHE model since January 2017 have enabled a much better fit to the data under the base case assumption of life time protection. Using the standard economic rules that JCVI is required to follow for assessing cost effectiveness the result does not meet the current economic cost-effectiveness criteria for the introduction of a new vaccine.

As per standard practice for major JCVI decisions PHE also conducted an uncertainty analysis that is designed to mitigate the risk that a programme will not do harm to the net health benefit of the NHS budget. This showed that in only a very small proportion of simulations was a willingness to pay price of less than £5 per dose achievable, which is regarded as a very unlikely outcome.

The results of the base case analysis and uncertainty analysis means that extending immunisation to adolescent boys is highly unlikely to be cost effective in the UK.

Both the Subcommittee and JCVI are in agreement that the parameters used in the PHE assessment are the most plausible based on the available evidence. The Committee acknowledges, however, that there is still work being done on the model. For example the sensitivity analysis for 20 years duration of protection requires further simulations in order to provide a robust cost effectiveness estimate. The

results, however, are sufficiently robust to draw a conclusion on whether or not to extend vaccination to adolescent boys particularly when considered together with the totality of evidence from other models.

Impact and cost-effectiveness analysis from the University of Warwick

The modelling and cost effectiveness study by Warwick was considered by the Committee between June 2015 and June 2017.

The model is an SIRS (Susceptible, Infectious, Recovered, Susceptible) individual based model that used the latest data from the 3rd national survey of the National Survey of Sexual Attitudes and Lifestyles (Natsal-3) along with data from NATSAL-2 to model sexual behaviour and the rate of partnerships for different ages, sex and sexual orientation.

To fit the transmission model to HPV prevalence before vaccination programmes were introduced, a range of data (15 datasets using either serological or DNA detection), across a variety of countries, was used. The model assumes individual transmission and recovery rates for each of the 9 strains of HPV in the 9 valent vaccine with different probabilities of transmission for all nine strains, with a limited period of immunity before the individual becomes susceptible once more. Cross protection of the bivalent vaccine against warts was modelled in sensitivity analyses. By default, vaccine waning was assumed to occur after 20 years.

The model takes into account the HPV immunisation programme from its introduction in 2008 for adolescent girls including catch up cohorts in older girls, the change from the bivalent to the quadrivalent vaccine and then switching to a range of scenarios in 2015 including the introduction of gender neutral vaccination using either the bivalent, quadrivalent or nonovalent vaccines. In the baseline analysis the uptake for adolescent girls and boys was assumed to be 90% and 67%, respectively.

For each scenario modelled the threshold price was then calculated at which the price (willingness to pay) of the vaccine would be cost effective at £20,000 per Quality Adjusted Life Year (QALY) using 3.5% discounting for costs and benefits.

The main findings of the study reported to JCVI in June 2016 were that extending vaccination to boys was highly unlikely to be cost effective since more than 90% of simulations for extending vaccination to boys incrementally on the girls programme gave a threshold price that does not meet the current economic cost-effectiveness criteria for the introduction of a new vaccine.

Peer review

In February 2017 JCVI agreed that the work by Warwick should undergo independent peer review. The results of the independent peer review were reported at the June HPV Subcommittee and main JCVI meetings. Suggested changes included using data from Scotland as the study covered the UK; changing the time modelled for the introduction of the boys programme to 2017; giving more detailed breakdown on the QALY and healthcare costs of the different health conditions, changing the assumption about the uptake in boys so that it is closer to that of girls, considering an uptake of 80% in girls rather than 90% in the baseline assessment;

taking into account comments received from the Natsal investigators on the use of the Natsal survey data in the model.

After reviewing the peer reviewer's comments and the response from Warwick the Committee agreed that the Warwick team should take into account these issues before publishing but that the changes are unlikely to affect the main outcome of the findings.

A systematic review and meta-analysis by Brisson *et al*

Professor Marc Brisson presented the findings of a meta analyses to the HPV Subcommittee in January and the JCVI in February 2017. Included among the 16 published models used in the meta-analysis was the original model developed by PHE for the decision in 2008 to advise an adolescent girls programme. Base-case vaccine characteristics were 100% efficacy and lifetime protection. Some of the key findings highlighted from the meta-analyses were that in the context of high coverage in girls (80%) there is very little additional benefit to be had by vaccinating boys; using the same number of doses to achieve 80% coverage in girls only, would have more impact than using the same number of doses to achieve 40% coverage in girls and boys; vaccinating boys would only give substantial impact when coverage in girls is much lower than in the UK (40%); the advantage in vaccinating boys when HPV vaccination is first introduced is that there is a more rapid impact in the decline of HPV vaccine type infections. Gender-neutral vaccination also allows the possibility of achieving complete elimination of HPV circulation; however the possibility of elimination also depends on the heterogeneity of sexual behaviour in the population.

Work presented to the committee by Dr Hans Berkhof

As part of its considerations the committee has also considered work presented by Dr Hans Berkhof, from VU University Amsterdam, to the HPV Subcommittee in June 2015.[13] .

Dr Berkhof's research group estimated that to prevent one HPV associated cancer in males you would need to vaccinate 795 boys when uptake is 60% in girls and 1735 boys when uptake is 90% in girls. In comparison vaccinating 200 girls is enough to prevent one case of cervical cancer. Therefore vaccinating girls is approximately 4 times more effective in preventing cervical cancer than vaccinating a boy to prevent an HPV associated cancer[14].

Dr Berkhof concluded that there is benefit in vaccinating boys and all the models are likely to show this but the outcome of cost effectiveness for HPV is strongly influenced by the rules used for discounting and cost-effectiveness. This is because the costs (of vaccinating) occur in the present but the benefits of cancer prevention is not realised until approximately 50 years later. Vaccinating boys as well as girls is unfavourable in term of cost-effectiveness because the benefits, which are smaller in

[13] Minute of the JCVI HPV Subcommittee held on June 8 2015

[14] Bogaards JA, Wallinga J, Brakenhoff R, *et al.* Direct benefit of vaccinating boys along with girls against oncogenic human papillomavirus: bayesian evidence synthesis. *BMJ* 2015;350:h2016 doi: 10.1136/bmj.h2016.

boys than in girls, are discounted. Furthermore, most of the benefit in boys can be achieved through achieving high uptake in a girl's only vaccination programme.

Key stakeholder concerns

In forming its advice the Committee has also noted the points raised by HPV Action (http://www.hpvaction.org/) on the University of Warwick model, which was shared in confidence in September 2016, as well as the other concerns raised in general on the question of extending vaccination to adolescent boys.

Sex with unvaccinated women (either at home or abroad)

Analyses on the issue of boys having sexual encounters with unvaccinated women were presented to the sub-committee and JCVI by both PHE and Warwick (Feb 2016). Partnerships abroad were shown to have a negligible effect on the cost effectiveness of a boys programme in the Warwick model.

Data derived by NATSAL indicated that most men (approximately 86%) under the age of 24 were not having sex abroad. Of those males (13% of 16-24 year olds and 15% of 25-34 year olds) that did have sexual encounters with women from abroad a large proportion of these were with women from countries with established HPV programmes. A similar pattern was observed for UK males who have had partnerships with women from abroad whilst in the UK with the majority of males never having had such partnerships

It was noted that if this work were to be incorporated into the PHE model it would add 8 months to the timeline for completion of the model. It was also agreed that if contact with females from abroad was incorporated in the PHE model the effect on the cost effectiveness for a boys programme would likely be very small and that this issue did not need to be included in the modelling work by PHE.

Moreover, in areas of the country where the uptake in girls is lower than the national average the evidence from the published modelling meta-analysis (Brisson et al) indicates that it would be better to concentrate on improving uptake in girls rather than extending vaccination to boys.

The risk of a fall in uptake in girls due to vaccine hesitancy

The Committee notes that while some other countries (Japan, Denmark, Eire) have experienced a drop in uptake over unfounded claims about the safety of the HPV vaccine, coverage has not changed in the UK. The Committee has previously reviewed the safety of the HPV vaccine (as have the EMA and WHO) and concluded that it had no concerns over the safety of the HPV vaccine. The Committee continues to keep the safety of the HPV vaccine under review (as it does for all vaccines used in the UK).

The programme for adolescent girls began in 2008, and included a catch up for all girls born after September 1991. Therefore, by now, all women under the age of 25 should have been offered the HPV vaccine. Furthermore, the uptake in the routine programme has been consistently high since its introduction and above 85% in the last five years. The sustained high uptake in the girls programme together with the

length of time it has been running adds considerable resilience to the programme in the event of a temporary fall in coverage.

MSM are not protected by the girls programme

In November 2015 the Committee recommended a targeted programme for MSM attending GUM and HIV clinics. As a result the HPV MSM pilot was started in June 2016 to evaluate whether it is operationally possible and cost effective to deliver such a programme through GUM and HIV clinics. The Committee notes that the pilot has been very well received and informal early feedback indicates that the programme is proving a success both within the clinical community and among MSM themselves.

The Modelling work by PHE and Warwick has also taken into account the impact on the MSM community of extending the HPV programme to adolescent boys. The Committee notes that not all cancer outcomes or anogenital warts would be eliminated in MSM under the scenario of a girls programme plus a targeted MSM programme. PHE estimates that of the additional benefit that would be gained by extending vaccination to adolescent boys, approximately 30-40% of this would be attributable to the impact in MSM with the remaining 60-70% of the additional benefit attributable to girls and boys (non MSM).

Sex with unvaccinated women

On the issue of sexual behaviour and males having sex with unvaccinated women whether at home or abroad both PHE and Warwick have shown that this will have little effect on the conclusions of their analyses (see above). While there is no explicit tracking of commercial sex in the PHE model, paid sexual activity is included in the total number of partners recorded in Natsal-3 data and hence this should be captured in the PHE model. The frequency of unprotected sex is also included in the PHE model since the probability of transmission is a weighted average of probabilities for both protected and unprotected sex.

Definition of MSM and concurrency

The PHE model also incorporates a definition of MSM based on past sexual activity and uses the outputs of the MSM model that informed the JCVI decision for a targeted programme in GUM and HIV clinics. The PHE model uses the Natsal definition of what constitutes MSM which is not based on a self-definition but on whether the reporter has had same sex sexual activity in the last five years. Therefore the model should also capture recent single or occasional same sex partnerships by non-self-defined MSM. Concurrency or overlapping partnerships has not been included in many of the published models but the Committee notes that the PHE model, which is one of the most complex model developed to date with regards to sexual behaviour, includes concurrency.

Population growth, ethnicity and trends in oropharyngeal cancer rates

On the influence of population growth which has been not included in any of the published models, the Committee agreed with PHE's view that although this is likely to be important, population projections beyond a few decades are extremely

uncertain. Similarly the most recent ONS rates of oropharyngeal cancer were used rather than speculating what the future trends of this may be. Ethnicity was also not factored in by the PHE model though the view is that this should not affect aggregate results significantly unless an ethnically-based vaccination strategy is proposed. Findings from the London School of Hygiene and Tropical Medicine (in press) looking at ethnic disparities in vaccine and cervical screening uptake indicate that women from ethnic minorities have a disproportionate share of cervical disease. These disparities, however, are predicted to be reduced by the overall impact of the current programme through herd protection.

Considerations of the Committee

Benefits of HPV immunisation

The full impact of the HPV vaccination programme on cervical cancer is yet to be fully realised as the programme started in 2008 and in England the first cohort of routinely vaccinated adolescent girls has yet to reach the eligible age for cervical screening which is when cervical cancer cases are most commonly detected.

Evidence on the impact of national HPV vaccination campaigns showing reduction in HPV 16/18 infection, cross protective types HPV 31,33 and 45, genital warts and all grades of cervical pre-cancerous lesions among vaccinated cohorts and herd protection among unvaccinated groups is now emerging globally including in the United Kingdom,[15] and anticipates a large future impact on cancer.

Evidence considered by the Committee shows that the HPV vaccine is both safe to use in boys and generates comparable immunogenicity to that seen in girls and is therefore likely to be as effective in preventing HPV associated non-cervical cancers and anogenital warts in boys and men. Vaccinating boys as well as girls indicates that additional cases of cervical and non-cervical cancer will be prevented in women and additional cases of non-cervical cancer will be prevented in males especially in MSM. The benefits of vaccinating boys may be greatest for prevention of HPV associated cancers in women.

Data on one dose and mixed schedules

At the HPV Subcommittee meeting in February 2017 published data from clinical trials on the efficacy of one dose of the bivalent and quadrivalent vaccine against HPV vaccine-type infection were considered. These findings show potential for the consideration of one dose schedules in the future but longer term studies on the antibody responses and evidence of longer duration of efficacy are needed. At that time the Committee agreed that the cost effectiveness of a one dose programme for girls and boys should be looked at once the cost effectiveness work has finished looking at a programme under two doses for girls and boys. The Committee is aware that there are a number of planned/ongoing randomised control trials involving one

[15] Drolet M et al. Population-level impact and herd effects following human papillomavirus vaccination: a systematic review and meta-analysis. Lancet Infect Dis. 2015 May; 15(5):565-80

dose schedules and will be reviewing this evidence as it emerges. This also means that the issue of extending immunisation to adolescent boys will be kept under review in the light of the potential for the use of one dose schedules in the HPV vaccination programme.

The Committee has also highlighted that research into mixed schedules should be prioritised to see if the available HPV vaccines are interchangeable while maintaining protection that is non-inferior to single vaccine schedules. The Committee will be reviewing this evidence as it emerges and will also consider the potential impact of such schedules in the context of extending immunisation to adolescent boys.

Equality

The Committee is mindful that the argument for gender equality has been put forward to justify the need for a gender neutral programme. On this issue the Committee has considered the following:

- JCVI is tasked to provide scientific advice based on the best available evidence and impact and cost-effectiveness modelling;
- JCVI, and its sub-committees are expert scientific advisory committees, and by design are not equipped to fully consider equality issues in detail;
- JCVI should however show due regard to equality by identifying potential issues for further consideration;
- DH is equipped to fully consider issues of equality when developing policy based on the advice of JCVI, and produced an equality impact assessment on HPV vaccination in 2008;
- the primary objective of the programme to date has been to reduce the burden of cervical cancer, although it is now recognised the vaccine would also provide direct protection to boys/men from a number of HPV associated cancers, and provide direct protection against genital warts;
- modelling (and operational evidence) shows strong herd effects from a girls programme, which will indirectly provide significant protection to boys from HPV associated cancers and genital warts (at the uptake rates seen in the UK);
- all modelling considered to date has indicated that extending vaccination to boys would provide little additional health benefits, with the majority of that additional benefit being seen in girls;
- the MSM programme will provide access to HPV vaccine for MSM; and
- modelling indicates that improving uptake in girls would have a greater health impact than vaccination of boys (e.g. where there is geographic variability in uptake).

Ultimately JCVI's role is to consider the scientific, clinical and economic evidence when formulating its advice. Much of this indicates that while there is a disparity

between males and females in terms of protection from HPV, the strong herd effects of the programme provide substantial benefit to males. The Committee has also recognised that MSM are disproportionately affected by HPV infection and disease compared to other men and as a result has advised a targeted programme for MSM which is already being piloted.

Conclusions and advice

The Committee has considered the best available scientific evidence in forming its advice. When the programme was first introduced the primary objective was to prevent cervical cancer in women. Since that time evidence has emerged linking HPV to other cancers many of which affect men as well as women and the Committee recognises the importance of preventing these cancers. The Committee has considered arguments put forward throughout their deliberations on the merits of extending the HPV vaccination programme beyond the current routine programme in adolescent girls. JCVI reviewed evidence showing that there could be additional improvement to the health of the UK population by vaccinating boys. Furthermore, the Committee recognises that there are strongly held views that the HPV vaccination programme should be extended to adolescent males, with many comments focussing on issues around equality of access, and the individual level protection such a programme would afford vaccinated boys.

JCVI is an expert scientific advisory committee which advises the Department of Health on matters relating to vaccination and immunisation. In advising on the public health benefits of national vaccination programmes the Committee is bound to consider the population level impact of changes to the national programme, and consider the cost-effectiveness of using finite NHS resources to support such programmes. It is important that the finite resources of the health service are used to maximise the health of the population, and this is the key driver behind consideration of cost-effectiveness.

The two specially commissioned mathematical models undertaken by PHE and the University of Warwick, and a systematic review and meta-analysis of a further 16 mathematical models, have all reached the same conclusion**.** There are aspects in both of the models that continue to be developed, however the Committee is of the view that the results are sufficiently robust to form advice on this issue, and the changes to be made are unlikely to affect the conclusions drawn from the analyses.

Each analysis concludes that with the high uptake levels consistently seen in the UK HPV vaccination programme there will be a substantial effect on HPV related disease, not just in the female population, but also indirectly in the male population. Modelling does predict some additional population health benefits from extending the programme to adolescent boys, with most of these benefits being seen in unvaccinated girls, and MSM.

Clearly there is benefit in vaccinating boys and the data considered by the Committee shows that the HPV vaccine is both safe to use in boys and generates comparable immunogenicity to that seen in girls. While it is clear that a programme

to vaccinate adolescent males would provide those vaccinated with direct protection against HPV infection, and associated disease, all the evidence suggests that the risk of infection in males has already been dramatically reduced by the girls programme and that these herd effects will continue to have a substantial impact. Therefore, most of the benefit in boys can be achieved through achieving high uptake in a girl's only vaccination programme

The additional benefits gained from extending the programme to adolescent boys therefore, would be small, relative to the impact of the girls programme. The findings of both cost-effectiveness analyses provided specifically to the committee predict that extending the HPV programme to adolescent boys would not be a cost-effective use of health service resources in the UK setting. These findings are also supported by the meta-analysis of 16 published models. Taking the evidence as a whole the Committee therefore is unable to recommend extension of the national HPV programme to adolescent boys according to the most robust cost-effectiveness analyses undertaken.

Due regard to issues of equality

The Committee recognises arguments made by stakeholders on the issue of equality of access and that there are additional clinical benefits that could be achieved in males with a gender neutral programme. The Committee therefore wishes to refer the issue of equality of access to the Department of Health for consideration,.

Invitation to stakeholders

As with all significant decisions, the JCVI is issuing its interim findings for consultation to ensure that the most appropriate and up-to-date evidence has been used, and that reasonable assumptions have been made where evidence is limited or unavailable. The consultation is open for six weeks until the end of August 2017. All responses should be sent to:

jcvi-consultation@phe.gov.uk

or by post to

JCVI Secretariat

Immunisation Department

Public health England,

Wellington House,

133-155 Waterloo Road

London SE1 8UG

Once the consultation is completed, the JCVI will develop its final advice to the Secretary of State for Health.

The Joint Committee on Vaccination and Immunisation

July 2017