

Statement on HPV vaccination

Joint Committee on Vaccination and
Immunisation

July 2018

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Statement on HPV vaccination

Joint Committee on Vaccination and
Immunisation

**Prepared by the Joint Committee on Vaccination and Immunisation Scientific
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Introduction

1. The Joint Committee on Vaccination and Immunisation (JCVI) is an expert scientific advisory committee which advises the UK Government on matters relating to vaccination and immunisation.
2. 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.
3. At that time 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.
4. JCVI keeps the eligibility criteria of all vaccination programmes under review and has been considering whether the HPV programme should be gender-neutral, because of strengthening evidence on the efficacy of HPV vaccination in preventing a number of non-cervical cancers.
5. JCVI has been reviewing the evidence for vaccinating boys since 2013. The Committee issued an interim statement for consultation on 19 July 2017. The consultation ran for six weeks. The JCVI Interim Statement on Extending HPV Vaccination to Adolescent Boys can be found at: <https://www.gov.uk/government/publications/jcvi-statement-extending-the-hpv-vaccination-programme>
6. At that time the findings of cost-effectiveness analyses provided to the Committee predicted that extending the HPV programme to adolescent boys would not be a cost-effective use of health service resources in the UK setting. JCVI's interim advice was that taking the evidence as a whole it was unable to recommend extension of the national HPV programme to adolescent boys.
7. JCVI met on the 4 October 2017 to discuss the responses from stakeholders to its consultation together with updated results on the impact and cost-effectiveness of vaccinating boys.
8. In February 2018 JCVI agreed that it needed to see additional analyses before concluding its advice.
9. The HPV sub-committee met on 18 May 2018 and reported its findings at the June 2018 JCVI meeting. JCVI considers it is now in a position to conclude its advice and this statement sets out the key aspects and final conclusions of the Committee.

Evidence reviewed

10. 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 incidence of these cancers in the general population is low. HPV-associated cancers in males are relatively rare compared with cancer of the cervix (and other sites) in females, even where effective cervical screening programmes are run. Research and prevention strategies have therefore more often been targeted at females and cervical disease. Parkinⁱ (2011) estimated the number of cervical and non-cervical cancers in women in the UK (2010) that could be attributed to HPV, and those numbers were 2691 and 1367 respectively, compared with 1030 cases of HPV attributable non-cervical cancer in males.
11. It is predicted that by vaccinating boys as well as girls, additional cases of HPV attributable cervical and non-cervical cancer will be prevented in women and additional cases of HPV attributable non-cervical cancer will be prevented in males especially in men who have sex with men (MSM). The impact of gender neutral vaccination in numbers of cases and proportion by each sex will depend on the parameters and assumptions used and the specific vaccine modelled
12. A key part of JCVI's consideration has been impact and cost effectiveness modelling. This includes modelling undertaken by the University of Warwick, an HPV modelling meta-analysis of 16 published models (Brisson *et al*ⁱⁱ), and modelling work undertaken by PHE. The modelling has been considered alongside evidence on the HPV vaccines and the contribution of HPV infection to a wide range of cancers. The latest information on the impact of HPV vaccination in the UK and globally has also been included as part of the evidence considered by the Committee.
13. Models from both PHE and the University of Warwick were reviewed. JCVI noted considerable further delays were anticipated to fully review the PHE model. The two models are in overall agreement and give similar findings and conclusions when examined, and are also in line with published evidence including the meta-analysis of published models (Brisson *et al*). JCVI therefore agreed that the robust modelling undertaken by the University of Warwick was sufficient for it to finalise its advice.
14. JCVI considered evidence on single dose vaccination, and although the evidence was promising it was insufficient to recommend a one dose course, and was not considered further. More information on the discussion concerning the potential for using one dose schedules in the HPV programme can be found in the HPV sub-committee May 2018 and June 2018 JCVI minutes. Dosing regimens will be revisited by the Committee as new data emerge.

Considerations

15. When the programme was introduced the primary objective was to prevent cervical cancer in women. Since that time evidence has strengthened on the association of HPV with non-cervical cancers, which affect men as well as women, and that vaccination is efficacious in preventing these other HPV related cancers. The Committee recognises the importance of preventing these cancers, and has considered arguments put forward on the merits of gender-neutral vaccination.
16. There would clearly be an improvement to the health of the UK population from gender-neutral vaccination. The key question for JCVI has been whether the additional benefits gained from extension of the programme represent a good use of NHS resources. 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. JCVI uses NICE HTA methodology according to its terms of reference in its consideration of cost-effectiveness.
17. Detailed background to the considerations made by JCVI on extending HPV vaccination to adolescent boys is available in the interim statement at: <https://www.gov.uk/government/publications/jcvi-statement-extending-the-hpv-vaccination-programme>

Vaccination in boys

18. There are clear health benefits in vaccinating boys. The data considered by the Committee show that the HPV vaccine is both safe to use in boys and generates comparable immunogenicity to that seen in girls. It is clear that a programme to vaccinate adolescent males would provide those vaccinated with direct protection against HPV infection, and associated disease including anogenital warts, anal, penile and oropharyngeal cancers. A gender-neutral programme would potentially provide optimal protection to men who have sex with men (MSM), by offering vaccination before the age of sexual debut.

Indirect protection

19. With the high uptake levels consistently seen in the UK HPV vaccination programme for girls there will be a substantial effect on HPV related disease, not just in the female population, but also indirectly in the male population. Modelling predicts some additional population health benefits from extending the programme to adolescent boys, with many of these benefits being seen in unvaccinated girls and MSM.
20. High uptake in girls reduces the cost-effectiveness of a gender neutral programme but a substantial drop in the uptake of a girls' programme, as seen in some countries, would make a boys' programme more cost-effective. The Committee recognises that despite the high uptake in girls there is an argument for a gender neutral programme in

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terms of providing some short-term resilience to the programme. A gender-neutral programme is likely to be more robust with respect to potential short-term fluctuations in uptake, and may reduce the overall burden of HPV related malignancy sooner than a girls'-only programme.

HPV and oropharyngeal cancer

21. JCVI has considered evidence on the number of cancers which are associated with HPV infection, and the proportion of those cancers which are directly attributable to infection. While HPV infection is seen as a necessary cause of cervical cancer, the contribution or attributable fraction of HPV to oropharyngeal cancer is not so clear cut and varies from study to study and country to country. The consumption of alcohol and/or smoking are also known risk factors strongly associated with oropharyngeal cancers. In the Warwick model the initial assumption of 28.2%, for the proportion of oropharyngeal cancers that were attributable to HPV infection, was increased to 31% following consideration of data from Europe (Anatharanan et alⁱⁱⁱ). Data from elsewhere including the US and defined regions of Scotland have indicated that a higher proportion, between 50% and 60%, of oropharyngeal cancers may be attributable to HPV infection. Sensitivity analyses presented to JCVI by Warwick University at the June 2018 meeting show that under the standard rules JCVI follows, increasing the attributable fraction, to the maximum rates reported (i.e. from 31% to 60%) improves the cost-effectiveness of adding a programme for adolescent boys, taking the threshold price from a negative value to a very low and yet unrealistic threshold vaccine price. Data from elsewhere in the UK suggest that the attributable fraction lies somewhere within the range above^{iv}. The sensitivity analysis on oropharyngeal cancer rates does not change the previous advice of the Committee.

Timing of benefits

22. HPV infection may take many years to manifest as disease and so the potential benefits of vaccination against HPV in terms of cancer prevention will not be realised until a long time into the future. While infection with strains associated with genital warts can manifest in a short time frame, cancers associated with HPV infection can occur decades after infection. The peak incidence of cervical cancer in the UK occurs in women aged 25-29 years, however, older women remain at risk with more than 50% of new cases diagnosed in women over the age of 40 years and more than 15% in women over 65 years of age. As the cancer can affect women at a relatively young age, those who die from cervical cancer may lose a large number of life years. For non-cervical HPV-associated cancers, the peak incidence of cases occurs later in life than for cervical cancer. The latter suggests that, for non-cervical disease, there is a longer delay between the infection and the onset of disease and therefore potentially fewer years of life are lost from non-cervical cancer compared with cervical cancer.

Equality

23. The Committee recognises the views that have been expressed, that for reasons of equality, boys should receive the HPV vaccine, and the arguments regarding the individual level protection such a programme would afford.
24. As an expert scientific advisory committee, JCVI is not tasked with providing advice on equality issues. Such issues should be considered by the Department for Health and Social Care (DHSC) in the development of Government policy. However, the Committee has considered an analysis using an alternative comparator, in case this is helpful in those considerations (see below).

Cost-effectiveness

JCVI Code of Practice

25. The JCVI code of Practice states that: *“In order to assess whether a national NHS-provided vaccination programme can be considered cost effective (or not), JCVI uses the methodology and criteria of the National Institute for Health and Clinical Excellence (NICE).”*
26. The assessment of cost-effectiveness in the case of gender-neutral HPV vaccination is, however, complex. The existing HPV vaccination programme in girls will provide substantial herd protection to adolescent boys. The time from infection to disease is long, and many life years may be lost, per patient, from HPV associated cancers. Vaccinating in early adolescence optimises protection against HPV infection and potential disease, meaning that the time from intervention to benefit is also long. This makes the assessment of benefits highly sensitive to the rate of discounting applied.
27. Under the standard NICE Health Technology Assessment methodology (£20k/QALY, 3.5% discount rate, incremental on a girls’ programme), the baseline analysis considered consistently indicated a willingness to pay threshold price of around zero pounds per dose of vaccine, and failed the uncertainty criteria used by JCVI. This means that under the standard rules, gender-neutral vaccination is highly unlikely to be cost-effective at a realistic price.

Discount rate sensitivity

28. A lower discount rate gives more value to benefits in the future. Reducing the discount rate to 1.5% can be considered under NICE guidelines where the impact of a lifesaving intervention is sustained over a period of at least 30 years: *“A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved”* (NICE guide to the methods of technology appraisal 2013). JCVI agreed that this guidance could be interpreted to apply to HPV vaccination. JCVI agreed that a reduced discount rate could be appropriate in the case of HPV where the cancer occurrence can be decades after initial infection, and optimal benefit is achieved with vaccination prior to infection. Furthermore, given the ages affected by HPV related cancers, more than 30 life years will be lost in some cases. As such the benefits of a programme would be seen over an extended period of time. Reducing the discount rate makes gender-neutral vaccination highly likely to be cost-effective at what may be a realistic price per dose.

Equality

29. Equality has been put forward as a strong argument from stakeholders for gender neutral vaccination. JCVI has not been tasked with considering equality (DHSC will

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complete the equality analysis following JCVI's advice), and consideration of equality is not within the terms of reference of the Committee. However, for completeness we have considered an alternative approach. The standard methodology is to consider 'viable' interventions incrementally on each other. Cost-effectiveness analyses undertaken so far have assumed that the vaccination of girls should be the comparator against which a boys' programme is measured. However, changing the comparator to vaccination of both girls and boys together, incrementally on no programme, would make gender-neutral vaccination highly cost-effective at what is likely to be a realistic vaccine price.

Conclusions

30. The findings from modelling undertaken by the University of Warwick, taken together with the results from PHE and other published evidence, have provided sufficient evidence for JCVI to conclude its advice.
31. The consideration of HPV vaccination in boys is a complex issue and JCVI have had to take into account the wider issues of health economic methodology and be aware of the arguments made on equality issues. There is evidence of benefit in vaccinating boys and a gender neutral programme would provide resilience against short-term fluctuations in uptake as well as offer the prospect of better control of the main cancer causing types of HPV. There may be additional future savings in the cervical screening programme, and gender-neutral vaccination would also provide optimal protection in MSM in the long term.
32. Under the standard economic methodology, the findings of the modelling work by Warwick University predict that extending the HPV programme to adolescent boys would not be a cost-effective use of health service resources in the UK setting. Increasing the attributable fraction of HPV for oropharyngeal cancer does not alter this conclusion. On consideration of these results JCVI is not able to advise extension of the programme to adolescent boys.
33. Because of the long natural history of HPV associated disease it can be reasonably argued that a 1.5% discount rate would be more appropriate. This lower discount rate would better take into account the longer term impact of HPV vaccination in cancer prevention, and the life years lost to cancer. JCVI is therefore supportive of taking this approach. Using a 1.5% discount rate it is likely that a gender neutral programme would be cost-effective, and on the basis of these findings JCVI would advise extending immunisation to adolescent boys.
34. If considering a cost-effectiveness analysis where a combined girls' and boys' programme is compared to no vaccination, gender-neutral HPV vaccination is highly likely to be cost-effective.

Global context

35. Whilst primarily focused on providing advice for the UK, JCVI is mindful of the wider potential impact that its advice may have globally. JCVI strongly supports WHO's position in prioritising the vaccination of girls in countries where there is no HPV vaccination programme and often little or no cervical screening, since this is the most efficient approach to reduce the cancer burden in a population, and thus the best use of scarce resources. The Committee urges vaccine manufacturers to continue to support Gavi, the Vaccine Alliance, in making the HPV vaccine accessible to low income countries who would otherwise not be able to afford such a programme.

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

ⁱⁱ Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. Brisson, M et al. *Lancet Public Health*, Vol1, Issue 1, e8 - e17

ⁱⁱⁱ Anantharaman D et al. Geographic heterogeneity in the prevalence of human papillomavirus in head and neck cancer. *Int J Cancer*. 2017 May 1;140(9):1968-1975

^{iv} Schache A, Powell NG, Cuschieri KS, Robinson M, Leary S, Mehanna H.....Evans M, Jones TJ. HPV-Related Oropharynx Cancer in the United Kingdom: An Evolution in the Understanding of Disease Etiology. *Cancer Research* 2016;76(22):6598-6606.