

# An update on HPV and the vaccination

BY HANNAH ROSALIE FOX AND VINIDH PALERI

In recent years, the role of HPV in the development of oropharyngeal cancers has become apparent. **Hannah Fox** and **Vin Paleri** contend that while we may not always be able to cure oropharyngeal cancers, vaccination offers our best hope for prevention.

Professor Harold zur Hausen discovered the link between the human papilloma virus (HPV) and cervical cancer in the 1970s. His team developed an HPV vaccine in 2006 and Hausen was subsequently awarded the 2008 Nobel Prize for his work on HPV. Hausen's work led to our understanding that patients infected with high risk HPV types 16 and 18 are at increased risk of developing cancer of the cervix, vagina, vulva, penis, anus, and oropharynx. Those infected with types 6 and 11 are at increased risk of genital warts and recurrent respiratory laryngeal papillomatosis. The cost to the United Kingdom's NHS for treatment of genital warts and laryngeal papillomatosis is significant at over £50,000,000 every year [1].

## HPV and oropharyngeal cancer

In the early 1980s it was suggested that HPV might play a role in the development of oral and oropharyngeal squamous cell carcinoma (OPSCC). Brandsma and Abramson were the first to report the presence of HPV-16 DNA in two of seven tonsillar SCCs using Southern blot hybridisation in 1989 [2]. In the USA, a retrospective analysis of clinical trial material demonstrated that 64% of OPSCC were HPV-associated. It is now clear that the incidence of OPSCC has increased dramatically in recent decades in many developed countries, especially in younger men (<60 years). This has been shown in absolute numbers of OPSCC in countries including Australia, Canada, Japan, UK and USA. Retrospective archival material shows HPV prevalence rates of OPSCC ranging from 36% to >80%, although rates vary

with geographical location and anatomical subsites [3,4].

The UK has seen a doubling of incidence between 1990 and 2006, with a further doubling between 2006 and 2010. The projected figures for OPSCC in the UK indicate that by 2025, HPV will account for over one third of head and neck cancers diagnoses, with over half of the projected cases being in people under the age of 60. It is likely that population-specific incidence rates of HPV-positive OPSCC are influenced by the prevalence of the genital HPV infection, sexual behaviour, and consumption of alcohol and tobacco. The UK National Clinical Guidance and the Database of the Royal College of Pathologists recommends that assessment of the HPV status should be performed in quality assured laboratories. Currently p16 immunohistochemistry is recommended as a minimum test, preferably followed on by in situ hybridisation to confirm high-risk HPV DNA.

## HPV vaccination

There are currently two types of HPV vaccination licensed in the UK: Cervarix® (GlaxoSmithKline) and Gardasil® (Merck). Cervarix® protects against HPV types 16 and 18, whereas Gardasil® offers protection against the four highest risk strains: HPV 6, 11, 16 and 18. Between 2008 and 2012, Cervarix® was used to vaccinate girls aged 13-17 years of age. Since September 2012, Gardasil® is being used for girls aged 12-13 years old in schools, along with a catch up programme for girls aged 13 to under 18 years. The use of quadrivalent vaccine used in the UK is aimed at the prevention of premalignant

genital lesions and cancers of the cervix and anus related to HPV types 16 and 18, and genital warts related to HPV types 6 and 11.

The vaccination programme currently achieves >85% coverage of the target population. It has reduced the prevalence of HPV 16 and 18 in young, sexually active women (6.5% compared to 19.1% prior to vaccination). However, around a third of cervical cancers are caused by types of HPV other than HPV-16 and HPV-18 and will not be prevented by current vaccines. As the current programme includes follow-up for only five years, there is no knowledge as to how long immunity from vaccination lasts.

Although vaccination does reduce the prevalence of oral HPV infection, there is currently no direct evidence that vaccination will prevent OPSCC. Nevertheless, it is reasonable to anticipate that reduced prevalence of anogenital HPV in women and herd immunity will ultimately be reflected in reduced incidence of OPSCC. It is not expected that this will benefit men who have sex with men (MSM) or heterosexual men who have sex with women from unvaccinated populations. Thus, strong arguments exist to extend the vaccination programme to include boys.

In 2015, ENT UK joined HPV Action (HPVA), a collaborative partnership of 44 patient and professional organisations that are working to reduce the health burden of HPV. HPVA are delivering an advocacy campaign that aims to achieve gender-neutral HPV vaccination. This means that all boys and girls will be routinely offered vaccination against

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HPV at the age of 12 to 13. HPVA believes that boys should now be included in the programme for the following reasons:

- To ensure the maximum possible protection of women against cervical cancer.
- To protect both men and women from other HPV-related cancers (anal, penile, oropharyngeal, vaginal, vulval).
- To protect both men and women from genital warts and also children and adults from recurrent respiratory papillomatosis (RRP) [www.hpvaction.org/about-hpv-action.html].

The Joint Committee on Vaccination and Immunisation's (JCVI) is considering expanding the UK vaccination programme to include both MSM and adolescent boys. In 2015 they released a statement on HPV vaccination of MSM supporting "a targeted HPV vaccination programme for MSM aged up to 45 who attend genitourinary and HIV clinics"[5]. A pilot study by Public Health England is planned in the near future.

The JCVI is considering an additional vaccine - Gardasil 9 - a 9-valent vaccine offering additional protection against HPV types 31, 33, 45, 52 and 58. Gardasil 9 was initially granted a licence for a three dose schedule in June 2015 (likely to be cost-prohibitive in the UK). However, its use under a two dose schedule in adolescent girls has been shown to be safe and effective. A one dose schedule is being assessed in current epidemiological and modelling studies, particularly addressing whether it will offer long-term protection which would be cost-effective and safe. The JCVI have noted that "modellers at the University of Warwick had estimated that the 9-valent vaccine could eventually prevent an additional 300 cervical cancer cases a year if the programme switched to using this vaccine. These cases would be in addition to the cases of cervical cancer predicted to be eventually prevented by the programme using the quadrivalent vaccine" [6]. The 9-valent vaccine is likely to be the preferred option by the JCVI, given the additional protection offered.

The JCVI is awaiting the results from ongoing work that will assess the impact of the HPV vaccination of adolescent

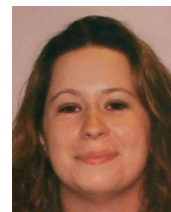
boys. Modelling by the University of Warwick has suggested that vaccination of adolescent boys under a two dose schedule would be highly unlikely to be cost-effective if a gender neutral programme was introduced in the near future. The results showed that the threshold price for the vaccine (willingness to pay) at which a boy's programme would be cost effective was close to zero with confidence intervals that included zero. Warwick had also conducted an uncertainty test which showed that it was highly unlikely that extending vaccination to boys would be cost-effective. The JCVI plans to complete the work on a two dose gender neutral vaccination programme prior to consideration of a one dose programme. Also, the vaccine patent is due to expire in the near future. It is anticipated that cheaper alternative vaccines from Asia will likely become increasingly available following this.

In summary, it is widely believed that vaccination (and expansion of the current vaccination programme) is currently the best option for prevention of HPV-positive OPSCC, and for reducing the health burden from benign HPV-related pathology. With regards to it being a long-term intervention, however, its effects on incidence of HPV-positive OPSCC will not be seen for 20 to 30 years. Hence, in the short-term, there is an urgent need for improved treatments for the increasing numbers of HPV-positive OPSCC patients.

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