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**Can a single dose of the human papilloma virus (HPV) vaccine prevent oropharyngeal cancer?**

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The incidence of human papillomavirus (HPV)-related head and neck squamous cell carcinomas has been rising[1,2]. Clinicians treating patients with oropharyngeal cancer strongly support the Joint Committee on Vaccination and Immunisation recommendation[3] on gender-neutral vaccination to prevent anal, cervical, oropharyngeal and penile cancer. However, although the HPV vaccines were initially tested and approved in triple-dose regimens[4], there is evidence to support a single-dose vaccination schedule to optimise population uptake and provide some coverage.

Since September 2019, the HPV vaccine has been recommended for all adolescents from school year 8 (usually aged 12–13 years) and for 'men who have sex with men' up to and including age 45 years who attend sexual health or HIV clinics, regardless of risk, sexual behaviour, or disease status. The persistence of this latter category has proved controversial because it is at odds with evidence that the increasing incidence of oropharyngeal cancer is in no way specific to this group. Although the universal adolescent HPV programme is being delivered as a school-based programme, eligible individuals who are home-schooled, or schooled outside of mainstream settings should also be offered the vaccine. In July 2018, Public Health England announced that the HPV vaccination programme was to be extended to include boys aged 12–13 years in England[3,5].

Since the HPV vaccination programme was introduced for girls, the incidence of genital warts has fallen sharply in both girls and boys. There has also been a reduction in the prevalence of the types of HPV that the vaccine protects against in England. This indicates that high levels of vaccine uptake in females can provide herd immunity for most males, and this has been taken into account by the British government when making policy decisions, such as opting not to add a catch-up programme for older boys[3]. Unfortunately, this approach fails to account for the fact that uptake of the HPV vaccine is dropping worldwide[6], with a recent review indicating that levels were suboptimal[7]. This alone renders the herd protection argument invalid, but we must also consider that depending on the future relationship agreed between the EU and UK, free-movement within Europe may continue to add to the problem.

Regarding HPV vaccination, parents are typically motivated to protect their children and prevent disease[8]. However, clinicians have a duty to provide unambiguous information in a timely manner and to be in a position to address parental concerns regarding vaccine safety. Given that safety data are available for the HPV vaccines, safety concerns cannot be used as a valid argument against their use. Data collected since introducing HPV vaccines ( the bivalent vaccine, which targets HPV types 16 and 18, and the quadrivalent vaccine, which also targets

HPV types 6 and 11) indicate that they are both safe and highly immunogenic[9]. A recent systematic review and meta-analysis, which included data for 60 million people up to 8 years after vaccination, provided compelling evidence of the effect of HPV vaccination on infection among girls and women, and on anogenital wart diagnoses among girls, women, boys and men. Several papers also provide credible data about the low HPV vaccine uptake, the relatively low proportion of the population that have completed the full course, and the relatively low proportion of the population vaccinated altogether. One study estimated that, by 2014, only 1.1% of girls aged 10–20 years in 84 low-income and lower to middle-income countries had been vaccinated with one or more doses of the HPV vaccine[10]. The same study showed that more than two-thirds (70%) of all cases of cervical cancer occurred in countries without a national HPV vaccination program[10]. Within countries, the coverage achieved by national programmes has been highly variable[11].

For the reasons stated, clinicians may therefore need to redirect the focus and desired outcomes of vaccination programmes abroad and in the UK. The current focus on attaining 100% coverage may be unrealistic and unnecessary in most societies, especially given that we now have evidence that we can alter the disease epidemiology with coverage as low as 40% or even less[12]. There are over 100 HPV types, of which about 40 are known to infect the genital tract[3,5,9]. They are classified as being either high-risk or low risk depending on their association with cancer. Of note, HPV types 16 and 18 are considered high-risk and HPV types 6 and 11 are considered low risk. Types 16 and 18 account for around 80% of all cervical cancers, with the remaining 20% due to 11 other high-risk HPV types. Cancers due to high-risk HPV types that affect the anus, penis, mouth and throat, and vagina and vulva vary in proportion by site. In a UK study of 1200 respondents (54.1% female), it was somewhat concerning to discover that public awareness of HPV-associated disease was quite low: 172 (38.7%; 34.3%–43.3%) recognised HPV as a risk factor for oropharyngeal squamous cell cancer and 283 (63.7%; 59.2%–68.1%) knew that a preventive vaccine existed[13].

A way forward that may allow some protection against HPV-related disease in a larger proportion of the population may be to consider single-dose vaccination. At present, it is fair to say that we are lacking evidence relating to oropharyngeal cancer in particular. The strongest evidence for the efficacy of single-dose vaccination is expected to come at some point after 2023 from the ongoing ESCUDDO population-based randomised trial[14], in which one or two doses of either 2-valent or 9-valent HPV vaccines will be compared. In the UK, there is currently no catch-up vaccination for older boys or older women or men, in unvaccinated parts

of the population. The administration of three doses of the HPV vaccine is also a challenge, and if we could prove that one dose was as effective as two or three doses, then it may be possible to increase vaccine uptake greatly and to reduce costs.

To support the argument for a single-dose vaccination strategy, we may consider the evidence presented by Sankaranarayanan et al. (2015)[15]. In a multicentre prospective cohort study, they looked at immunogenicity and HPV infection after a single dose of 4-valent HPV vaccine given to girls in India. During a median follow-up of 4.7 years (IQR 4.2–5.1), they showed that one and two doses of a 4-valent vaccine were sufficient to prevent incident and persistent cervical infection with HPV types 6, 11, 16 and 18, similar to the protection afforded by a three-dose schedule[15]. Kreimer et al. (2018)[16] have also published data showing that a single dose of the HPV vaccine offered continued protection against HPV infection, with documented stability of antibody levels and avidity up to 7 years after vaccination. The findings of a national cohort analysis from Australia further support the hypothesis that a single-dose vaccination may be a viable strategy when working towards the global elimination of cervical cancer[17].

The research outlined in this article may have implications for the prevention of oropharyngeal cancer. If single-dose HPV vaccination is proven to be an effective and viable strategy, it will benefit from important cost and logistical advantages, and may even help to reach people who may otherwise miss out. A single-dose strategy could increase vaccine uptake and help to reduce preventable disease burden due to cancer. In future trials of head and neck surgery, we should consider including single-dose and catch-up arms in appropriate groups.

There is no doubt that HPV infection causes oropharyngeal cancer. As clinicians, we must reflect on the lesson learned from the COVID-19 pandemic, where an effective vaccine is not currently available. In this author's opinion, single-dose HPV vaccination may well represent a landmark in the achievement of global access to a cancer-preventing vaccine.

**Conflict of interest:** The author has no conflicts of interest to declare.

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