Community Dental Health (2022) **39,** 14–21
Received 10 March 2021; Accepted 17 May 2021
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doi:10.1922/CDH_00072Kaczmarczyk08

The impact of HPV vaccination on the prevention of oropharyngeal cancer: A scoping review

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Introduction: HPV-associated oropharyngeal cancer (OPC) has one of the most rapidly rising incidences of any cancer in high-income countries. HPV vaccination is being tested to prevent HPV-associated OPC. ***Objective***: To determine the effect of Human Papilloma Virus (HPV) vaccination on the prevention of OPC in adults worldwide. ***Basic research design***: Scoping review conducted using PRISMA-ScR Checklist. ***Method***: An electronic literature search identified relevant records. Titles and abstracts were screened to assess eligibility by two researchers, and data from relevant full-text articles were extracted and synthesised. ***Results***: Three-hundred-and-forty-three studies were identified, with eleven articles meeting the inclusion criteria. The most common study design was cross-sectional (n = 7), the most common location was the US (n = 6) and data collection periods spanned 2004 to 2020. One article found unvaccinated participants had a 19 times increased risk of developing OPC compared with those who had been vaccinated against HPV. The remaining papers showed that prevalence of HPV-vaccine-type oral infection was significantly lower in vaccinated participants than unvaccinated participants, with a reduction of oral HPV detection ranging from 72% to 93%. This reduction varied by sex. ***Conclusions***: There is evidence to suggest that HPV vaccination reduces oral HPV infection and decreases the incidence of HPV-associated OPC. There is substantial need for further research which directly examines the relationship between HPV vaccination status and subsequent OPC development.

Keywords*: Prevention, review, vaccination, alphapapillomavirus, oropharyngeal neoplasms*

Introduction

HPV is one of the most common sexually transmitted infections globally, with over 290 million women infected worldwide (World Health Organisation, 2018). Low-risk types (HPV-6 and -11) are responsible for causing 90% of genital warts, the second most commonly diagnosed sexually transmitted infection in the UK. High-risk types (HPV-16 and -18) are associated with increased risk of oropharyngeal and cervical cancer (Suijkerbuijink *et al*., 2016).

HPV-associated oropharyngeal cancer (OPC) has one of the most rapidly rising incidences of any cancer in high-income countries, mainly affecting men (Lechner *et al*., 2019). Its incidence varies between developed and developing countries. Epidemiological studies have demonstrated that those with HPV-associated OPC are more likely to be younger (median age of 54 years) and from a higher socioeconomic background. HPV-associated OPC is less likely to be related to tobacco and alcohol exposure and is more common among white populations (Sedrak and Rizzolo, 2009; Benard *et al*., 2008). OPC sites include the base of tongue, soft palate, tonsils and related tissues. The oropharynx is the only subsite of the head and neck with increasing incidence of squamous cell carcinoma, with a concomitant increase in HPV-16 infection rates implicated in this rise (Elrefaey *et al*., 2014). There are challenges in early detection of OPC, but opportunistic screening for those at high risk or symptomatic individuals has been recommended (Holmes *et al*., 2003). OPC has significant impacts including morbidity experienced by the patient and the economic burden on the healthcare system (Keeping *et al*., 2017).

Cervical cancer is the most frequent HPV-associated disease. Globally, it is the fourth most common cancer among women. Prevention of cervical cancer includes HPV vaccination and screening and treatment of pre-cancerous lesions. However, due to limited access to HPV vaccinations, more than 85% of deaths occur in low- and middle-income countries, highlighting health inequalities (WHO, 2020). HPV vaccination has been shown to be highly effective in inducing antibody-mediated immunity against HPV thus reducing rates of HPV-associated cervical cancer (Drolet *et al*., 2019; Takes *et al*., 2015).

The economic impact of vaccination programmes is vital to inform an accurate cost-benefit analysis (Suijkerbuijk *et al*., 2016). In the UK, the cost of treating HPV infection-related complications costs over £86.5 million annually (Prue *et al*., 2018). Head and neck cancer attributed to HPV infection cost over £117 million from 2006 to 2011, with males accounting for nearly 75% of costs (Keeping *et al*., 2017). Vaccinating UK males against HPV has been estimated to cost £20-22 million annually, an investment which would be expected to have considerable impact on reducing disease burden and associated costs (Prue *et al*., 2018).

The first HPV vaccine was licensed in the US and Canada in 2006, with over 100 countries now approving it for vaccination programmes (WHO, 2019a). The first government-funded HPV vaccination programme began in Australia in 2007; other countries also offering vaccination

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include New Zealand, Japan, Mexico, Panama and Trinidad (Takes *et al*., 2015). The UK HPV vaccination programme began in 2008. Initially, bivalent vaccine Cervarix was used, which offers protection against HPV-16 and HPV-18, moving to quadrivalent vaccine Gardasil in 2012, which protects against HPV-6, -11, -16 and -18. School-based vaccination programmes target boys and girls aged 12 and 13 in the UK. Men who have sex with men and trans women under 45 are also eligible for the vaccine (NHS, 2019).

Considering the worldwide impact of cervical cancer a public health issue, the WHO launched a call in 2018 to tackle and eradicate it. HPV vaccination programmes have been one of the most disrupted by the pandemic worldwide for multiple reasons. Schools are commonly used as the vaccination sites and have been mainly closed for many months, and healthcare staff have been redeployed to different areas (UNICEF, 2020).

Whilst many studies have looked at associations between HPV and OPC, there is no comprehensive review of the effect of HPV vaccination on HPV-associated OPC incidence or prevalence. This is especially important presently, with the questions surrounding licensing of the vaccine for prevention of OPC, male eligibility and current disruption of vaccination programmes. Therefore, a scoping review of the literature investigated the research question: *what is the effect of Human Papilloma Virus vaccination on the prevention of oropharyngeal cancer in adults worldwide?* The aims were: (1) to determine the effect of HPV vaccination on oropharyngeal cancer prevalence worldwide and (2) to identify areas where further research is indicated.

Methods

The initial literature search did not find any comprehensive reviews with a similar research question and robust methods, and the existing evidence base appeared limited, so a scoping review was deemed the most appropriate method. The Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist was used to develop a priori (Tricco *et al*., 2018).

Identifying the research question

The research question was formulated using the PICO framework where participants were adults worldwide, the intervention was HPV vaccination, the comparison was no vaccination and the outcome was oropharyngeal cancer incidence or prevalence.

Information sources and search strategy

A literature search was conducted by a librarian from the British Dental Association with the MESH terms, covering the 15 years up to 08 April 2021, which covered two databases: Medline and PubMed. MESH terms derived from the research question included: human papillomavirus vaccine / gardasil / cervarix; wart virus vaccine / HPV vaccine; oropharynx / oropharyngeal / tonsil / tongue / oral / mouth / throat cancer / carcinoma / neoplasm; incidence / epidemiology / risk / prevalence (see full strategy at https://qmro.qmul.ac.uk/xmlui/handle/123456789/72721).

Eligibility criteria and selection of sources of evidence

The search did not have any restrictions on language. Papers were excluded if they were published before 2005, as the first HPV vaccination was only made available in 2006. As this is a scoping review in a novel area, there were no other exclusion criteria, ensuring all relevant papers could be identified. Length of follow-up, for example, was not an exclusion criterion as follow-up periods currently would be expected to be limited.

The titles and abstracts of papers were screened manually twice by two researchers (KK and HY) to identify eligibility for inclusion. Studies were included if they mentioned HPV vaccination alongside a measurable impact on oropharyngeal cancer incidence. Due to the lack of articles that answered the research question, the inclusion criteria were widened to include any paper that assessed the impact of HPV vaccination on the presence of HPV in the oral cavity or oropharynx. This was as a proxy for OPC, assuming that a decrease in oral HPV infection would lead to a decrease in HPV-associated OPC.

Further screening assessed full-text articles for eligibility. Articles were excluded if they did not include oropharyngeal cancer incidence or HPV infection following HPV vaccination. For example, articles were excluded if they examined induction of anti-HPV antibodies after vaccination rather than measuring infection incidence or if they focused on economic evaluations or prediction modelling, evaluated the tumoricidal effect of vaccination, only recorded baseline HPV and OPC incidence before vaccination, evaluated incidence of OPC associated with HPV vaccine types or evaluated knowledge of healthcare professionals on the subject. Articles were also excluded if they recommended research in the area but did not provide current evidence. The reference lists of included papers were screened to ensure all relevant papers had been identified.

Data charting process and synthesis

One researcher (KK) designed the data collection proforma based on the articles identified by the initial search and data were then extracted. A pilot study was not conducted on a sample of articles but rather on all the articles. Data collection categories were widened after the first assessment and each article was then reassessed. Data were extracted from each paper by KK and HY on study design, country, period of data collection, sample and gender split, variables included, findings and any additional discussion points. Differences in extracted data were discussed and agreement made. The data were then synthesised and presented descriptively.

Results

Three-hundred-and-forty-four studies were identified (Figure 1), resulting in 314 records (titles and abstracts) being screened against the initial exclusion criteria. Forty-nine full-text articles were then assessed.

Eleven met the inclusion criteria and were considered valuable to analyse (Table 1). Of these 7 reported cross-sectional studies (Katz 2020; Castillo *et al*., 2019; Mehanna *et al*., 2019; Chaturvedi *et al*., 2018; Gillison *et al*., 2017; Hirth *et al*., 2017; Gillison *et al*., 2012), two were review articles (Du et al., 2021; Takes et al., 2015),

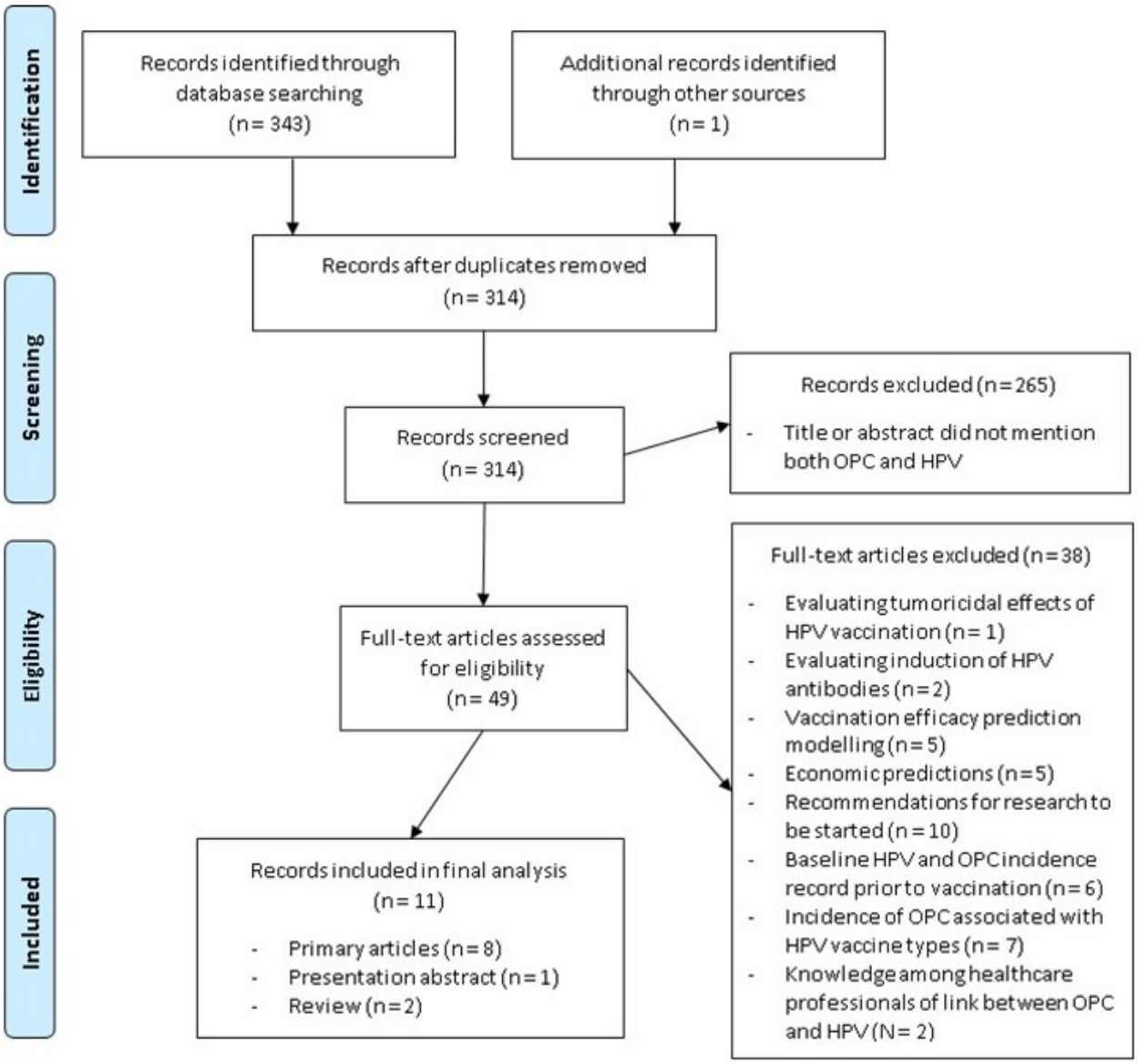

Figure 1. PRISMA Flow diagram for literature identified during search.

one described a cohort study (Schlecht *et al*., 2019) and one was a double-blind randomised control trial (Herrero *et al*., 2013). Data collection periods spanned 2004 – 2020 and articles were published from 2012 – 2021. Locations specified included the US (6 articles: Katz 2020; Schlecht *et al*., 2019; Chaturvedi *et al*., 2018; Gillison *et al*., 2017; Hirth *et al*., 2017; Gillison *et al*., 2012) and one each from the United Kingdom (Mehanna *et al*., 2019), Sweden (Du *et al*., 2021), Costa Rica (Herrero *et al*., 2013) and Colombia (Castillo *et al*., 2019).

Oropharyngeal cancer and HPV vaccination status

Only one article was deemed explicitly relevant to the research question (Katz, 2020). The author was from the US and the design was a cross-sectional study analysing data collected by a separate repository from June 2011 until April 2020. There were 1,310,334 participants, of which two thirds were female and 1.76% had been vaccinated. The key variables assessed were vaccination status and OPC development. Unvaccinated participants had a 19 times increased risk of developing OPC compared with those who had been vaccinated against HPV (RR 19.7, 95% CI 7.2-51.6, $P = 0.0001$). Protection varied by sex. Non-vaccinated males were at 23 times increased risk of developing OPC (RR 23.8, 95% CI 3.4-169.2, $P = 0.0015$) and non-vaccinated females at 9 times increased risk compared to those who had been vaccinated against HPV (RR 9.3, 95% CI 3.0-29.0, $P = 0.0001$).

Oral/oropharyngeal HPV infection and HPV vaccination status

One review speculated on the impact of HPV vaccination to prevent oropharyngeal carcinoma (Takes *et al*., 2015). This article did not describe its methods for retrieval of relevant papers or define itself as a particular type of review. The paper briefly considered 2 studies examining the relationship between HPV vaccination and oral HPV infection, concluding that more data are required regarding this link but that initial studies seem promising. One of these studies was also identified during the present literature search and is discussed below (Herrero *et al*., 2013). The other study was cross-sectional and used

Table 1: Relevant record synthesis

Author, date	*Publication format*	*Study design*	*Location*	*Data collection period*	*Sample (M = male, F = female)*	*Data collection*	*Vaccine types included and vaccine given if known*	*Infection detection*	*Results*
Katz 2020	Primary article	Cross-sectional	US	June 2011 – April 2020	23174 (33% M, 66% F) aged 0-84 Vaccinated: 23 174 Unvaccinated: 1 287 160	Vaccination status OPC development	Bivalent, quadrivalent, nonavalent	n/a	19xs higher risk if not vaccinated 0.017% vaccinated participants developed OPC. Non-vaccinated Ms at 23xs increased risk of developing OPC, non-vaccinated Fs at 9xs increased risk
Takes et al., 2015	Primary article	Review	n/a	n/a	n/a	n/a	n/a	n/a	No primary results presented
Gillison et al., 2012	Primary article	Cross-sectional	US	2009 - 2010	5579 (M and F) Fs: vaccinated 1985 Fs: unvaccinated 290 Fs aged 14-59	Oral HPV infection Vaccination status as a demographic characteristic	Not recorded	Oral rinse and gargle specimen	Prevalence of oral HPV infection was 0% in vaccinated women compared to 0.5% (95% CI 0.2–1.7) in unvaccinated women
Gillison et al., 2017	Presentation abstract	Cross-sectional	US	2011 - 2014	2627 M and F aged 18-33	Vaccination status Oral HPV detection	6, 11, 16, 18	Not specified	Prevalence of oral HPV16/18/6/11 infections lower in vaccinated vs. unvaccinated participants (0.11% vs. 1.61%; P= 0.008), estimated 88.2% (95%CI = 5.7%-98.5%) reduction. Oral HPV 16/18/6/11 prevalence lower in vaccinated vs. unvaccinated men (0.0% vs. 2.13%; P= 0.007).
Chaturvedi et al., 2018	Primary article (presented in part in paper above)	Cross-sectional	US	2011 – 2014	2627 M and F aged 18-33	HPV vaccination status Oral HPV vaccine types infection	6, 11, 16, 18	Oral rinse and gargle specimen	As above
Hirth et al., 2017	Primary article	Cross-sectional	US	2009 – 2014	3040 Aged 18-30	Vaccination status Vaccinated (type) HPV infection in oral rinse	6, 11, 16, 18	Oral rinse	Vaccinated adults had a lower prevalence of oral HPV (types 6, 11, 16, 18) compared to unvaccinated. Ms had higher prevalence of any HPV types.
Mehanna et al., 2019	Primary article	Cross-sectional	UK	2013 - 2015	600 Fs undergoing voluntary tonsillectomy for non-malignant conditions Aged 12-24 340 Ms – unclear on ages	Vaccination status Tonsillar tissue HPV infection HPV infection in oral exfoliated cells	Cervarix 16, 18	Oral exfoliated cells and tonsillar tissue	Oropharyngeal HPV-16 prevalence lower in vaccinated vs. unvaccinated Fs (0.5% vs 5.6%, P = 0.04). Oropharyngeal HPV-16 prevalence in unvaccinated males was similar to vaccinated females (0% vs 0.5%, P > 0.99), lower than unvaccinated females (0% vs 5.6%, P = .08).

Table 1 continued overleaf...

Table 1: Relevant record synthesis continued

Herrero et al., 2013	Primary article	Double-blind randomised control trial	Costa Rica	2004-2009 Followed subjects over 4 years	Final cohort 5840 Fs aged 18-25 2910 vaccinated 2924 control (hep A vaccine)	Vaccination status Oral HPV16/18 infection	16, 18	Oral specimen (rinse and gargle)	Oral HPV16/18 prevalence 4 years after vaccination lower among HPV-vaccinated Fs compared to control-arm Fs.
Castillo et al., 2019	Primary article	Cross-sectional	Colombia	Unspecified	1784 aged 14-17 HPV Vaccinated 944 Fs Unvaccinated 95 Fs, 745 Ms	Vaccination status Number of doses received Gender Oral HPV16 detection	Gardasil 4 16	Oral specimen (rinse and gargle)	Odds ratio of detection of HPV-16 in vaccinated versus unvaccinated students was 0.28 (95% CI: 0.07–0.88), 72% reduction in HPV-16 detection. Odds of detection of HPV-16 in unvaccinated Ms 3.6 xs those of vaccinated Fs (OR=3.6, 95% CI: 1.21–12.81).
Schlecht et al., 2019	Primary article	Cohort	US	2007 - 2017	1259 Fs aged 13-21 at entry, followed up to age 25 Vaccinated 1067 Unvaccinated 192	Vaccination status Oral HPV6/ 11 /16 / 18 detection	Quadrivalent vaccine 6, 11, 16, 18	Oral specimen (rinse and gargle)	Detection of HPV lower among those who had received at least 1 dose of the quadrivalent HPV vaccine vs. unvaccinated (odds ratio, 0.20; 95% CI, 0.04-0.998).
Du et al., 2021	Review	2 cohorts (youth clinic, high school)	Sweden	2009 - 2018	Final cohorts: 1200 at youth clinic and 627 at high school Aged 15-23	Vaccination status Oral HPV detection	Gardasil 6, 11, 16, 18	Oral specimen (gargle)	Oral HPV prevalence was ~ 10% in unvaccinated youth at the youth clinic, but after 2013 it dropped to < 2% at youth clinic and high schools

US National Health and Nutrition Examination Survey (NHANES) data collected between 2009 and 2010. The study found that oral HPV prevalence in women aged 14-59 was 0.5% amongst unvaccinated women (n = 1985, 95% CI 0.2-1.7) compared with 0% amongst vaccinated women (n = 290) (Gillison *et al*., 2012). No studies mentioned in that article provided direct evidence with regards to this paper's research question.

Eight further papers were identified, which were deemed valuable to analyse (Gu *et al*., 2021; Mehanna *et al*., 2019; Schlecht *et al*., 2019; Castillo *et al*., 2019; Chaturvedi *et al*., 2018; Gillison *et al*., 2017; Hirth *et al*., 2017; Herrero *et al*., 2013). These papers considered the impact of HPV vaccination on HPV infection in the oral cavity and/or oropharynx. Three studies used overlapping NHANES data (Chaturvedi *et al*., 2018; Gillison *et al*., 2017; Hirth *et al*., 2017). Overall, the reviewed studies showed that prevalence of HPV vaccine type oral infection was appreciably lower in vaccinated than unvaccinated participants, with a reduction of oral HPV detection ranging from 72% (Castillo *et al*., 2019) to 93% (Herrero *et al*., 2013). This reduction varied by sex (Chaturvedi *et al*., 2018; Gillison *et al*., 2017; Hirth *et al*., 2017). Several studies also noted significant differences in the odds of detection of oral HPV in unvaccinated males versus unvaccinated and vaccinated females (Castillo *et al*., 2019; Mehanna *et al*., 2019).

Discussion

This scoping review aimed to determine the effect of HPV vaccination on the incidence of OPC worldwide. We found one study conducted in the US to support a link between HPV vaccination and prevention of HPV-associated OPC. However, direct evidence is currently very limited. Nevertheless, the paucity of available evidence does not mean that there is no value in evaluating this relationship further. Of relevance, nine studies found a significant link between HPV vaccination and reduction in oral HPV infection (a necessary precursor to HPV-associated OPC). Most of this evidence is from cross-sectional studies conducted in the United States. This review also identified gaps in the literature: there is substantial need for further research directly examining the relationship between HPV vaccination status and subsequent OPC development.

This study highlighted the lack of research available in this area, although promisingly, further research has been conducted since a previous review (Takes *et al*., 2015). There was also little homogeneity between study methods, which leads to difficulty synthesising results, hence a scoping review was most appropriate here. This demonstrates the requirements for standardisation in the methods used to assess oral HPV infection and also the point at which a participant is considered 'vaccinated'. Most studies counted one dose of a vaccination as 'vaccinated' even though the full vaccine regimen requires more than one. However, there is emerging evidence that a single-dose may be effective in preventing HPV infection (Single-Dose HPV Vaccine Evaluation Consortium, 2020), which could simplify synthesising results across studies. Both oral HPV infection and OPC are relatively rare conditions: in a study with over 1.3 million participants,

only 0.3% of the sample developed OPC (Katz *et al*., 2020); thus there is difficulty assessing vaccine efficacy with small samples.

Another issue with estimating the efficacy of HPV vaccination in preventing HPV-associated OPC is the absence of an objective screening method for pre-malignant disease, unlike the availability of the Papanicolaou cervical cancer screening test. The lack of intermediate endpoints is recognised as a difficulty (Takes *et al*., 2015; Suijkerbuijk *et al*., 2016), and the US National Cancer Institute has now accepted that prevention of persistent oral HPV infection is an acceptable endpoint for trials (Lowry *et al*., 2015). This also will help to alleviate the issue of small samples with regards to OPC development.

There are many possible reasons for why little research is available to answer the research question. Implementation of HPV vaccination programmes is a relatively recent initiative in clinical research terms, considering the average recommended age of vaccination (age 12-13; NHS, 2019) compared with the average age of HPV-associated OPC diagnosis (age 61-63; Viens *et al*., 2016), so it is reasonable to expect a time delay in assessing vaccine efficacy. Promisingly, several studies across multiple countries including Australia, Germany, Norway, the US and Argentina have looked at measuring baseline HPV infections and OPC rates before vaccination to enable effectiveness monitoring in the future (Rudolph and Katalinic, 2019; Borracci *et al*., 2018; Hansen *et al*., 2018; Jamieson *et al*., 2018; Buttmann-Schweiger *et al*., 2017; Steinau *et al*., 2014; Hocking *et al*., 2011). It is important to note that the focus of HPV vaccination programmes has been to reduce the incidence of cervical cancer. However, HPV infection is associated with other cancers, including OPC, which impact on oral health related quality of life and cause significant morbidity and mortality.

We aimed to identify the impact of HPV vaccination on OPC development worldwide. Although studies were identified across four countries, most were conducted in the US. This leads to issues with generalisability, especially considering that the initial vaccination programmes began in high income countries. This will lead to a lag in data collection and publication of studies in low- and middle-income countries. However, all studies drew similar conclusions, supporting reliability. Some studies only included participants to age 25, however HPV-associated OPC is most prevalent amongst 30-34 year olds and 60-64 year olds (Guo *et al*., 2016). Two studies only recruited women (Schelct *et al*., 2019, Herrero *et al*., 2013) although over 80% of OPCs are in men (Guo *et al*., 2016). Excluding these groups could bias effect estimates. However, the relatively recent introduction of vaccination programmes and the exclusion of males from programmes in many countries may make this unavoidable.

A further limitation was the lack of research into any direct association of HPV vaccination on OPC development. Here, papers retrieved on HPV vaccination and oral HPV infection were analysed, regarding oral HPV infection as a proxy as a necessary precursor to HPV-associated OPC. This is not necessarily transferable, as there are other variables to consider such as tobacco and alcohol use. Nevertheless, a significant body of research confirms that oral HPV infection can lead to HPV-associated OPC development (Suijkerbuijink *et al*., 2016), so these studies were considered relevant to the research question. Further searches specifically examining at the association between HPV vaccination and oral HPV infection may have retrieved further papers, however this was not possible due to resource constraints and scanning of reference lists of included papers did not retrieve further papers. HPV surveillance is complex due to there being a high proportion of asymptomatic infections. There is also variable presentation according to viral type and a prolonged period between infection and disease.

Very few studies adjusted for confounding variables such as tobacco and alcohol. Interestingly, the three papers that considered tobacco and alcohol use found an inverse relationship between these factors and HPV vaccination status (Schlecht *et al*., 2019; Chaturvedi *et al*., 2018; Hirth *et al*., 2017). This may amplify the size of the relationship between HPV vaccination status and OPC development. However, one paper did adjust results according to cigarette use and found no relationship with HPV infection status (Schlecht *et al*., 2019).

Implications and recommendations

There is a clear need for further research into the relationship between HPV vaccination and OPC development. Ideally, this will be conducted with large cohort studies across a lifetime, with data collected on whether HPV vaccination is related to survival after subsequently developing OPC and also whether prior HPV vaccination has an impact on quality of life for those who later develop OPC. There is also need for a comprehensive systematic review to consider the cost-effectiveness of HPV vaccination for prevention of OPC. To maximise impacts and cost effectiveness, the vaccination of both boys and girls is recommended to reduce the risk of OPC and cervical cancers. In the UK, the Joint Committee on Vaccination and Immunisation has confirmed this would be a good return on investment (JCVI, 2018). Unfortunately, the WHO has called for countries to stop vaccinating boys as there is currently insufficient production of vaccines (WHO, 2019b). The gap in vaccination delivery during the COVID-19 pandemic (UNICEF, 2020) may also impact on data collection.

In conclusion, there is evidence, although limited, to suggest that HPV vaccination decreases the incidence of HPV-associated OPC. There is a larger body of evidence that demonstrates a correlation between HPV vaccination and a reduction in oral HPV infection. This review also identified the substantial need for further research which directly examines the relationship between HPV vaccination status and subsequent OPC development, which will require the collection of baseline data and subsequent cohort monitoring.

Conflict of interest

None.

Acknowledgements

British Dental Association Library Services.

Funding

No sources to declare.

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