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Prophylactic human papilloma virus vaccination in head and neck: indications and future perspectives

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Purpose of review
To gain the evidence-based knowledge concerning the efficacy of HPV vaccination for oropharyngeal sites and to highlight the trials and strategies for vaccine administration in HPV-dependent head and neck diseases.

Recent findings
Vaccination can be provided in two injections. There is increasing anecdotal evidence that therapeutic vaccination is effective in treatment of recurrent respiratory papillomatosis.

Summary
The availability and broadening spectrum of HPV vaccines make possible the prevention of cervical and other HPV-dependent diseases. Vaccination is now included in the national immunization programs of most industrial countries and will be used, it is hoped, in developing countries within the next few years. In developing countries, few women are screened for cervical precancerous lesions, making immunization even more important. In affluent countries and matured societies, with high coverage of cervical screening, the focus of interest will shift to other HPV-related diseases. The HPV vaccination is effective in preventing oral infection with types targeted by the vaccines.

Keywords
human papilloma virus, oropharyngeal cancer, precancerous lesions, prophylactic vaccination, recurrent respiratory papillomatosis, therapeutic vaccination

INTRODUCTION

Vaccination is a main public health approach for controlling infections and its value has been widely documented. Currently, vaccination also plays an increasing role in the prevention of hepatocellular and HPV-related cancers. HPV vaccination programs for the prevention of cervical cancer are being implemented worldwide. Routine vaccination has proved to be a successful policy, and recommended for preventing HPV-associated cervical and other anogenital cancers. Nowadays, HPV is causing a growing proportion of HPV-related noncervical cancers (penile, anal, vaginal, vulvar, and oropharyngeal) that together may within a decade exceed the incidence of cervical cancer in industrial countries, where cervical screening is effective. However, little is known about the epidemiology, natural history, or risk factors for oral HPV infection and derived diseases. Although some studies indicate that HPV vaccination lowers the risk of oral infections associated with types targeted by the vaccines [1–3], an effect on the impact on oral lesions has not yet been established. What's more, the risk factors for oral HPV infection differ in mucosal sites as to the incidence, clearance, and impact of co-factors, such as cigarette smoking, marijuana use, and anogenital sex. Taking into consideration all these variables makes it difficult to estimate the effect of vaccination in oropharyngeal and laryngeal sites.

The main goal of this article is to gain the evidence-based knowledge concerning the efficacy of HPV vaccination for oropharyngeal sites and to highlight the trials and strategies for vaccine administration in HPV-dependent head and neck diseases. We address the following issues:

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KEY POINTS

- The rapidly growing burden of HPV-positive oropharyngeal cancers (OPC) has important healthcare implications.
- Evidence-based knowledge concerning the efficacy of HPV vaccination for oropharyngeal sites is poorly documented, but there are epidemiological premises that emphasize the role of population vaccinations programs for HPV oral prevalence.
- Those premises support the importance of prophylactic HPV vaccination for both sexes.
- Efficacy of vaccination on treatment of recurrent respiratory papillomatosis still remains not fully predictable.

(1) the tools to prevent HPV infection;
(2) the association between HPV vaccination and oral HPV infection based on clinical observations;
(3) efficacy of various HPV vaccines against oral HPV in experimental trials;
(4) prophylactic vaccination and effect for oral/oropharyngeal premalignant and malignant lesions;
(5) effectiveness of vaccination in recurrent respiratory papillomatosis (RRP).

THE TOOLS TO PREVENT HUMAN PAPILLOMA VIRUS INFECTION

The vaccines use virus-like particles for the designated HPV types and trigger high titers of type-specific antibodies, which provide protection against vaccine-related HPV types [4,5]. Three prophylactic vaccines are currently approved for control of several high-risk HPV types and two of them are also approved for control of two low-risk types. These are Cervarix (HPV16, 18), Gardasil (HPV6, 11, 16, 18), and Gardasil9, which is a second-generation vaccine providing protection against HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58 [6]. Though the phenomenon of cross-protection of Cervarix against vaccine-related types has been observed [7], L2-based vaccines are now being considered to be more broadly cross-protective [8–10]. Beyond the HPV types covered in the first-generation vaccines, oncogenic HPV types 31, 33, 45, 52 and 58 account for nearly additional 20% of the cervical cancers worldwide.

All vaccine types are well tolerated. Initially they were administered as a three-dose series of intramuscular injections over a 6-month period for the female population aged 11–12 years, but vaccination can start at 9 years of age [11]. Depending on age and country, most vaccination schemes have been reduced to two. Boys are advised to receive the quadrivalent (4v) [12] or the nonavalent (9v) HPV vaccine [13,14] at the same age interval as girls. HPV vaccines can be administered regardless of a history of anogenital warts and precancerous lesions or abnormal Pap/HPV tests [13,14], in men or women not older than 26 years [11]).

In February 2015, the Advisory Committee on Immunization Practice (ACIP) included the 9v HPV vaccine in its recommendation for routine HPV vaccination of preadolescents aged 11 or 12 years, women aged 13–26 years and men aged 13–21 years who had not previously received 2v HPV or 4v HPV vaccination, including MSM, immune-compromised persons, and those with HIV infection through the age of 26 years [15]. The latest recommendations for the 9vHPV vaccination schedule (i.e. two doses for boys and girls aged 9–14 years) by the Food and Drug Administration were followed by the European Medicine Agency and the ACIP. Institutions approved the two-dose regimen of the 9vHPV vaccine for young adolescents at the age of 9–14 years and recommended that the second dose should be followed within months 6–12 after the first dose [16▪].

THE ASSOCIATION BETWEEN HUMAN PAPILLOMA VIRUS VACCINATION AND ORAL HUMAN PAPILLOMA VIRUS INFECTION BASED ON CLINICAL OBSERVATIONS

Oral HPV prevalence and incidence have been investigated rarely in relation to HPV vaccination. Randomized clinical trials demonstrate more than 90% vaccine efficacy in the prevention of clinical anogenital HPV infections and precancerous lesions. Apart from that, significant reduction in genital HPV prevalence was proved [17,18]. In contrast, few studies have evaluated the population-level effect of HPV vaccination on oral HPV infections [19,20,21▪]. These studies support the idea that the immunization programs would have an impact on infection and disease beyond those recently demonstrated for the anogenital tract [22].

The first lesson was learned from epidemiological studies, where the rates of oral HPV16 are higher in men than in women. A national US study on oral HPV infection in 14–69-year-old individuals demonstrated that the prevalence of oral HPV was approximately three-fold higher in men than women and the prevalence of HPV16 was more than five-fold higher in men than women [23]. None of the men who were fully vaccinated were positive for at least one vaccine-type HPV, versus 6.3% of men who were not vaccinated [24].

As HPV infections can also induce cancers of the anus, penis, and oral cavity, male vaccination has been advocated for more than a decade, but systematic reviews on efficacy and safety in males are lacking [25–27,28▪,29▪]. Incident oral infections with high-risk HPV types and vaccine effectiveness of 91% were observed by Giuliano *et al.* [30,31].

The proof-of-principle study demonstrating the prevention potential of HPV vaccination against oral HPV infection was shown by Herrero *et al.* in 2013 in Costa Rica [19]. Similarly, a study performed on Swedish students proved a substantial decrease in oral HPV prevalence. Following the introduction of HPV vaccination between 2007 and 2014, prevalence went down from 9.3% in 2009–2011 to 1.4% in 2013–2014 [32]. In a Scottish population, the feasibility of measuring prevalence, incidence, and determinants of oral HPV infection in dental settings in the HOPSKOTCH study was investigated. Feasibility was demonstrated indicating that the incidence of oral HPV can be studied in Scotland, the National HPV Immunisation Programme of which is showing sustained high levels of coverage (>90%) [33].

HPV vaccination was associated with a reduction in vaccine-type oral HPV prevalence among young US adults [34]. However, because of low-vaccine uptake, the population-level effect was modest overall and particularly low in men [35].

EFFICACY OF VARIOUS HUMAN PAPILLOMA VIRUS VACCINES AGAINST ORAL HUMAN PAPILLOMA VIRUS IN EXPERIMENTAL TRIALS

It is a well known phenomenon that vaccines accelerate clearance of vaccine-matched HPV types in cervix. However, still it is not sufficiently documented if vaccination against a restricted set of HPV types leads to replacement with vaccine-unrelated HPV types [5]. Similarly, there is a scarce knowledge concerning prevention of oral infections. To address these questions, Ahn *et al.* [36] assessed the efficacy of various HPV vaccines against oral HPV infection in mice in 2017. The results showed that oral HPV16 pseudovirus (PsV) infection was completely prevented with four different methods of prophylactic HPV immunization. These methods were Gardasil (Merck, Kenilworth, New Jersey, USA), a candidate pan-HPV L2 vaccine with alum adjuvant and with passive transfer of either Gardasil (Merck) human antisera or nonimmunized sera (100 μl intraperitoneal injection). These findings provide preliminary evidence that human vaccines induce robust protection against oral HPV infection [36].

Pinto *et al.* [37] in 2016, whose original purpose was to confirm that oral samples might be a useful resource for the detection of HPV16 and HPV18-specific antibodies in saliva following vaccination, presented the first human study. In this intentionally designed study, the authors confirmed three main findings: that HPV antibody response was detected in oral secretions after vaccination in a very high percentage of patients (93.2% of mouthwash, 95.7% of sponge specimens), oral antibody levels correlate closely with the serum levels obtained after vaccination, and the normalized IgG levels are not substantially different than serum levels. These findings were confirmed later on by Parker *et al.* in 2018 [38]. The immunogenicity of HPV vaccines showed that all vaccine recipients had detectable serum antibodies against HPV16 and HPV18 and reproducible antibody titers in mouthwashes, but levels were several logs lower than those in serum.

PROPHYLACTIC VACCINATION AND EFFECT FOR ORAL/OROPHARYNGEAL PREMALIGNANT AND MALIGNANT LESIONS

The rapidly growing burden of HPV-positive oropharyngeal cancers (OPC) has important public health and clinical implications. The overall rise in OPC incidence in the United States during 1984 to 2004 was univocally associated with the increasing incidence of HPV-positive cancers; HPV prevalence increased from 16.3% during the 1980s to 72.7% during the 2000s [39]. Data from Europe are not available. By 2020, the number of HPV-positive OPSCs is expected to surpass the number of cervical cancers [39]. That indicated a significance of the prophylactic HPV vaccination on both sexes, with stress to the males.

Significant challenges remain in the subject of persistent HPV infections and associated OPCs. The knowledge of viral nature, keratinocyte physiology, and HPV tissue tropism, the role of host innate immunity, tumor–host restriction factors, DNA damage response mechanisms have been explained [40,41]. Nevertheless, the impact of the current prophylactic vaccines on a selected HPV types and the impact for successful mucosal cleaning has still to be learned.

EFFECTIVENESS OF VACCINATION IN RECURRENT RESPIRATORY PAPILLOMATOSIS

Recurrent respiratory papillomatosis (RRP) is a disease with exophytic epithelial lesions primarily caused by HPV. RRP is having trimodal age distribution affecting

as well young children (below 5 years), young adults (around 35 years of age), and seniors (approximately 64 years old) [42]. A vast majority of cases was found in larynx, where it causes dysphonia, audible as hoarseness, and voice change, potentially including cough. Deterioration of voice may be also a result of frequent surgical interventions. Altogether quality of life appears to be lower than in controls and the value of psychosocial care was proved in a Dutch/Finnish study [43].

RRP is a rare disease. Recent estimation ranges from one to four cases per 100 000. Taking separately pediatric and adult population, the numbers in USA are 4.4 versus 1.8 [44]. Although pathological background of RRP is still not sufficiently established, a vast majority of RRP cases is associated with HPV6 and HPV11, both known as low-risk subtypes in relation to oncogenic potential. HPV11 seems to be responsible for more severe manifestation of RRP [45,46]. HPV11 was found more frequently in African-Americans than in Caucasians. Another contributory factor of the disease is immunodeficiency. On the contrary, ethnicity did not influence HPV type distribution when the results of an Iranian study group were compared with the literature data [47,48].

Treatment of RRP extends from surgery to antiviral drugs jointly or separately. Because of a tendency to reoccur, RRP could be recognized as an incurable disease. Such opinion was derived from long-lasting combined treatment (surgery, adjuvant therapy) of 86 Korean patients. Twenty-nine patients required three operations for complete remission for 2 years [49]. In any case, the bad experience is not exceptional. Hermann *et al.* [50] attempted vaccination in the group of nine children aging 9–17 years who had been already treated by surgery from 2 to more than 50 times.

Current RRP treatment procedures include cold steel, microdebrider, or laser surgery for debulking the papillomatous lesion and vaccination [51]. The latter attracts more and more attention. The point, however, is that the recommended age of vaccine application,11–12 years, is recognized sufficiently preventive for HPV-associated cancer, but cannot be effective for RRP prophylaxis, as the disease often starts earlier. On the other hand, vaccines seem to improve combined treatment of RRP patients. It has been shown that as well mouse as humans receiving Gardasil-induced production of HPV antibodies with therapeutic potential [37,38,52]. Another study performed on Costa Rican female subjects treated with bivalent vaccine has shown 4-year efficacy against HPV16 and HPV18 infections [53]. Further, an applicability of oral fluid as a marker HPV antibody response was tested in woman receiving prophylactic HPV6/11/16/18 quadrivalent vaccination. It was established that sensitivity of oral fluid equaled to 100% [54]. It is worth to note that education programs and anxiety related to a fear of HPV-related diseases including HIV have caused a relatively high coverage of vaccination against HPV: 57.3% adolescent girls and 34.6% adolescent boys were HPV-vaccinated in USA in 2013 [11]. The results could be extended for other industrial countries.

In the literature, there are few reports concerning RRP treatment outcome following application of HPV vaccines. Moreover, the results coming from various clinics are quite divergent. Katsutta *et al.* [55] have treated a 2-year-old boy with RRP four times by microlaryngoscopic surgical interventions that was followed by quadrivalent vaccination. Within the next year, direct laryngoscopy did not confirm therapeutic effect. Papaioannou *et al.* compared treatment outcomes in 27 juvenile and 79 adult RRP patients [56]. Children had more surgical interventions than adults in the observation time. Only a minority of the study group had decided to undertake HPV vaccination. A statistically significant lower number of surgeries per year was achieved after vaccination [56]. Another German group reported a study performed on 24 RRP patients consisting of 4 children and 20 adults. Thirteen patients were HPV-vaccinated. Mean time of disease recurrence was considerably longer in nonvaccinated group than in HPV-vaccinated (54.9 versus 12.3 months). The important point was that only 2/13 vaccinated patients developed recurrence within the observation time [57]. A British retrospective case–control analysis of the efficacy of Gardasil vaccination in 28 patients with recurrent respiratory papillomatosis of the larynx compared two cohorts: 12 HPV-vaccinated (Gardasil) against 16 nonvaccinated patients. Taking into account, the number of necessary surgical procedures, and the time interval between procedure and complete remission, the authors concluded that vaccination does not appear to have any effect on RRP burden [58]. Yiu *et al.* [59] found similarly contradicting results.

To sum up, efficacy of RRP treatment still remains not fully predictable. It seems to be connected with heterogeneity of immune system. Further, a growing coverage of anti-HPV vaccination prevents vertical HPV transmission to newborns [60]. Novakovic *et al.* [61▪▪] demonstrated the beneficial effect for Australia of increased vaccination rates.

CONCLUSION

The availability and broadening the spectrum of HPV vaccines is the success to prevent cervical and other HPV-dependent diseases. Vaccination is now included in the national immunization

programs of most industrial countries and will be used, it is hoped, in developing countries within the next few years. In developing countries, few women are screened for cervical precancerous lesions, making immunization even more important. In affluent countries and matured societies, with high coverage of cervical screening, the focus of interest will shift to other HPV-related diseases. The HPV vaccination is effective in preventing oral infection with types targeted by the vaccines.

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Conflicts of interest

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