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Increasing HPV vaccination coverage to prevent oropharyngeal cancer: A cost-effectiveness analysis

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ABSTRACT

The incidence of oropharyngeal cancer (OPC) has been rising, especially among middle-aged men. While Human Papillomavirus (HPV) has been irrevocably implicated in the pathogenesis of oropharyngeal cancer (OPC), the current HPV vaccination uptake rate remains low in the US. The aim of our study was to evaluate the impact of increased HPV vaccination coverage on HPV-associated OPC incidence and costs. A decision analytic model was constructed for hypothetical cohorts of 9-year-old boys and girls. Two strategies were compared: 1) Maintaining the current vaccination uptake rates; 2) Increasing HPV vaccination uptake rates to the Healthy People 2030 target (80%) for both sexes. Increasing HPV vaccination coverage rates to 80% would be expected to prevent 5,339 OPC cases at a cost of $0.57 billion USD. Increased HPV vaccination coverage would result in 7,430 quality-adjusted life year (QALY) gains in the overall population, and it is estimated to be cost-effective for males with an incremental cost-effectiveness ratio of $86,940 per QALY gained under certain conditions. Expanding HPV vaccination rates would likely provide a cost-effective way to reduce the OPC incidence, particularly among males.

1. Introduction

Oropharyngeal cancer (OPC) incidence has been on the rise, especially among middle-aged men [1], and persistent Human Papillomavirus (HPV) infection (mostly HPV-16 and -18) is the most significant risk factor of OPC in the US, attributable to 60–70% of OPC cases [2–4]. The rates of OPCs have increased by 2.7% per year among men [5], and by 0.8% per year among women between 1999 and 2015; this trend contrasts dramatically with cervical cancer, which decreased by 1.6% per year during this period. OPC is now the most common HPV-associated cancer in the US with incidence rates of 8.5 and 1.7 per 100,000 people among males and females respectively [5,6]. Most OPCs are diagnosed later in life around the median age of 60, requiring intensive therapy that leads to significant long-term morbidity and mortality [7]. This is evidenced by the higher incidence rates of 23.7 and 35.1 per 100,000 among males in age groups of 50–59 and 60–69, respectively [5,6]. By 2030, the OPC projected incidence is projected to increase to 13.3 and 6.8 per 100,000 males and females, respectively [8].

HPV infection plays a pivotal role in the pathogenesis of a range of other cancers including virtually all cervical cancers, nearly 90% of anal cancers, and 75% of vaginal cancers in the US [4]. HPV vaccination has been advocated and practiced as a prevention strategy since 2006, primarily for the prevention of cervical, anal, and vaginal and vulvar cancers [9–11], and it had been recommended for routine vaccination of adolescents at ages 11–12 years in the US. Recently updated guideline recommends vaccination as early as 9 years old, and catch up vaccination through age 26 years for all persons while it was previously recommended males through age 21 years and certain special populations through age 26 years [12]. Moreover, U.S. Food and Drug Administration (FDA) has recently approved HPV vaccination to prevent head-and-neck cancers, including OPC [13]. Despite compelling data

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and practice guidelines, compliance of the US at risk population with HPV immunization remains low: 53.7% among females and 48.7% among males as of 2018, well below the 80% target from the Healthy People 2030 goal [14].

The aim of this study was to evaluate the potential health and economic benefits associated with increasing HPV vaccination coverage rates to the Healthy People 2030 goal level by potentially reducing the OPC incidence in the US.

2. Materials and methods

2.1. Model design

Markov cohort simulation models were constructed by generating hypothetical cohorts of US 9-year-old girls and boys separately, that were simulated and followed until age 85 or death. The model was comprised of nine mutually exclusive health states that represent the true underlying health states of the population: Well/Healthy (with or without vaccine), Infection (with or without vaccine), Local/regional cancer, Distant cancer, Survival (from local/regional cancer or from distant cancer), and Death (Figure S1). Individuals were able to transition between states annually; every year the simulated individuals could stay in the same state, progress to the next state, or die from any cause or due to cancer. The model incorporated possible causes of death: all-cause mortality, accounting for age-specific life expectancy [15], and cancer-specific mortality [16].

Two scenarios were simulated and compared for each sex: 1) maintaining the status quo (current HPV vaccination uptake rates of 53.7% for females and 48.7% for males) [17], and 2) increasing HPV vaccination uptake rate to 80% for both sexes. In both scenarios, simulated individuals were vaccinated at any age following the observed trends of the vaccination uptake, and the vaccination targets were modeled to reach by age 26 (Figure S2). A decision analytic Markov state transition model was constructed in TreeAge Pro (TreeAge, Williamstown, MA).

2.2. Data and modeling assumptions

Data required for the study included prevalence of HPV infection, age- and sex-specific HPV-positive OPC incidence and prevalence, and cancer-specific mortality, disease-specific quality of life, and average costs to cancer cases and vaccination. Model parameters were estimated from the literature and publicly available national survey/registry data (Table 1).

To ensure the validity, we calibrated our model against 1) oral HPV prevalence (HPV 16 and 18), 2) HPV-positive OPC incidence, and 3) HPV-positive OPC prevalence. Calibration and optimization tool available in TreeAge were used to minimize sum of square differences, performing Nelder-Mead search from random starting sets of inputs to the calibration targets prior to HPV vaccine introduction (2003–2006 data) one at a time [18]. Progression rates to HPV infection were calibrated to the national oral HPV prevalence statistics available from National Health and Nutrition Examination Survey (NHANES) (Figure S3), accounting for sex- and age-specific clearance rates (Table S1) [19]. Progression rates from HPV infection to OPC were calibrated to HPV-positive OPC incidence rates available from the Surveillance, Epidemiology, and End Results (SEER) [20,21], incorporating percentages of all OPC cases that are attributable to HPV infection (Figure S4) [4]. Progression from infection to OPC was assumed to result in local/regional cancer with subsequent likelihood of developing distant metastases (progression to distant cancer) [22,23]. Recurrence rates after treatment were obtained using a published study on recurrence patterns for radiotherapy and chemoradiotherapy treatments for OPC [24]. Progression and recurrence rates to OPC were further used to calibrate to the HPV-positive OPC prevalence available from SEER (Figure S5), accounting for the survival and recurrence rates. OPC-specific mortality rates were obtained from SEER data and published literature on the effectiveness of cancer therapies [16,25,26]. 86% of patients receiving chemoradiotherapy and 51% of those receiving radiotherapy only experienced complications from cancer therapy [27], and patients with complications were modeled to either stay in the corresponding cancer state with no recovery or die from complications [28]. Herd immunity effects were incorporated as a function of the vaccinated proportions of the opposite sex and vaccine efficacy for both scenarios to assess the potential impact of herd

Table 1
Model parameters and sources.

Parameters	Estimate, Base Case	Range	Source
Costs (2020 US$)			
Having OPC	$18,424	($17,206, $25,154)	[29]
Local/regional OPC treatment	$81,557	($56,197, $99,570)	[29]
Distant OPC treatment	$117,242	($77,230, $135,266)	[29]
Complication from local/regional OPC	$7,940	($6,593, $23,079)	[27,50–52]
Complication from distant OPC	$20,190	($7,284, $34,922)	[27,50–52]
Survival from local/regional OPC	$4,018		[30]
Survival from distant OPC	$5,452		[30]
Vaccine (2 doses)	$430	($380, $500)	[53]
Efficacy			
Vaccine efficacy	0.9	(0.775, 1)	[54,55]
Disease risk			
Baseline oral HPV 16 and 18 infection	Calibrated	(0.02, 0.2)	NHANES
Baseline OPC incidence and prevalence	Calibrated	(0.001, 0.006)	SEER
HPV Infection clearance rate	Table S1		[19]
Receiving OPC treatment within one year of onset	0.9		[56,57]
Complication from local/regional OPC	0.51	(0.1, 0.9)	[27]
Complication from distant OPC	0.86	(0.1, 0.9)	[27]
Recurrences from local/regional and distant OPC	Calibrated		[24]
Progression of local/regional OPC to distant OPC	0.17		[22,23]
Mortality of local/regional OPC	0.023		[16]
Mortality of distant OPC	0.14		[16]
Mortality with local/regional OPC treatment	0.019		[25]
Mortality with distant OPC treatment	0.026		[26]
Mortality of complication from local/regional OPC	0.009		[28]
Mortality of complication from distant OPC	0.009	(0.005, 0.015)	[28]
All-Cause mortality			CDC
Utilities			
Well	1		[30,36,38,58–60]
HPV infection	1		[30,36,38,58–60]
OPC	0.597		[30]
Local/regional OPC treatment	−0.06		[61]
Distant OPC treatment	- 0.09		[61]
Complication from local/regional OPC	- 0.15		[62]
Complication from distant OPC	−0.15	(-0.1, −0.3)	[62]
OPC survival state	0.769		[30]

Abbreviation: OPC=Oropharyngeal Cancer, NHANES = National Health and Nutritional Examination Survey, SEER = Surveillance, Epidemiology, and End Results, CDC = Centers for Disease Prevention and Control.

immunity on lowering the risk of HPV infection among unvaccinated individuals (Text S1).

The annual costs of having OPC and undergoing treatment were obtained from average estimates and ranges of costs for radiation therapy and chemoradiation therapy [29]. Direct costs of survivorship in local/regional and distant OPC were estimated using the relative values of the two costs from a prior cost-effectiveness study on HPV vaccination [30]. A measure for quality-adjusted life years (QALY) was used to account for the health status during a period of living, as QALY accounts for both the quality and the quantity of life lived, weighted by the utility score for each of the nine health states. Utility scores, weights that incorporate the prognoses and likelihood of successful treatments, were assigned; 0.60 for having OPC, and 0.77 for survival from OPC state [30]. Local/regional and distant cancer treatment utilities were estimated by deducting the utility weights associated with radiation therapy and chemoradiation respectively [31]. All cost estimates were converted to 2020 year USD using the Consumer Price Index (United States Bureau of Labor Statistics) [32], and costs and expected life years were discounted at an annual rate of 3% to adjust for the relative values of present dollars or a present year of life [33].

2.3. Outcomes

The primary outcome of the analysis was the incremental cost-effectiveness ratio (ICER), incremental costs per QALY gained, between the two competing scenarios. A willingness-to-pay (WTP) of less than $150,000/QALY was used as a threshold to determine whether the scenario was cost-effective or not [34]. The cost-effectiveness analysis was conducted from a healthcare perspective. Other assessed outcomes included costs of additional vaccination, cost saved per dollar spent on vaccination, and cumulative reduction in OPC cases. The results except ICER, such as reduction in cancer cases and saved costs were estimated from a population perspective for this closed cohort, using the 2018 US census data at age 9 for males (2,068,473) and females (1,986,805), and represent the gains from a total time period of simulation (until age 85).

2.4. Sensitivity and uncertainly analyses

Overall progression rates to OPC states were varied from 50% to 200% of the base-case values (lowest to highest possible OPC incidence rates) [30]. The impact of a range of vaccination coverages rates, from 60% to 100%, were assessed. Additional one-way sensitivity analyses were performed to investigate the changes in the estimated outcomes across a wide range of values of various model parameters, including complication rates from cancer treatment, annual costs of local/regional and distant OPC, efficacy of HPV vaccine, and utility score and mortality rate from distant OPC complications. The ranges of parameter vales were based on published data (Table 1).

Probabilistic sensitivity analysis was performed, where the probability distributions for specific model parameters were assigned and varied simultaneously, rather than using discrete values as in our base-case analysis. 1000 iterations were performed to reduce the variability in our estimates and gain further insight into the optimal strategy under uncertain conditions within our defined WTP threshold (Table S2).

3. Results

3.1. Model calibration

Using the calibrated parameters, the model projected oral HPV infection prevalence matched the current data available from NHANES data by age and sex within <5% absolute error (Figure S3). The model-projected HPV-positive OPC incidence and prevalence were also consistent with the SEER data by age and sex (Figures S4-S5).

3.2. Base-case results

The base-case analyses are presented in Table 2. If the current vaccination coverage rates remained the same (status quo), overall spending on HPV vaccination and treating OPC was projected to be 1.86 billion and 0.63 billion USD for males and females, with 58.71 million and 57.79 million QALYs, respectively among the studied cohort. If HPV vaccination uptake rate increased to 80% by the age of 26, the total QALY gains would be 6,493 and 939 for males and females, respectively, translating into 5,339 total averted cases of OPC over the course of life (Fig. 1).

In terms of cost-effectiveness analysis, increasing HPV vaccination coverage to 80% was cost-effective for males by saving 6,493 QALYS at $0.57 billion USD, an ICER of $86,940 per QALY gained (Table 2). For females, increasing the vaccination coverage saved 939 QALYS at $0.30 billion USD, an ICER of $322,728, which was not cost-effective.

3.3. Sensitivity analyses

The results of one-way sensitivity analyses are summarized in Table 2 and Fig. 2. None of the sensitivity analyses substantially changed our fundamental finding of QALY gains from increasing HPV vaccination coverage rates. When the HPV vaccination coverage rates were varied from 60% to 100%, the total QALY gains ranged from 2,625 to 10,453 for males, and from 231 to 1,632 for females (Table 2). For males, it was cost-effective as long as the coverage rate remained to be greater than 70%, the ICERs were expected to be below $100k per QALY. For females, increasing vaccination coverage was never cost-effective at all levels of coverage rates.

When the overall progression rates to OPC were varied from the lowest to highest values (50%–200% of the base-case progression rates), increasing vaccination coverage was cost-effective when progression rates remained the same or greater for males. For females, increasing the coverage from that in status quo was only cost-effective at the fastest progression rate (Table 2).

The variable that affected the outcome the most was complication rates from local/regional OPC treatment followed by local/regional cancer treatment cost for males and vaccine efficacy for females (Fig. 2). ICERs ranged from $54,596 to $110,472 per QALY gained among males, and from $259,200 to $368,711 per QALY gained among females when the treatment complication probability was varied from 0.1 to 0.9. When local/regional OPC treatment cost was varied, increasing vaccination coverage to 80% was not cost-effective for males at its maximum evaluated cost with an ICER of $112,223 per QALY gained.

Probabilistic sensitivity analyses found that for males, increasing the vaccination coverage was preferred when the WTP was greater than $37,500 per QALY, increasing the coverage was preferred and remained optimal in 96.1% of the iterations at the WTP of $150,000 per QALY. Maintaining the status quo was preferred in 91.4%–98.8% of iterations for females within the WTP thresholds between $0 and $150,000 per QALY (Figure S6).

4. Discussion

Increasing HPV vaccination uptake rate to the Healthy People 2030 target of 80% is expected to have meaningful public health benefits from preventing OPC in males based on our simulation results. Increasing HPV vaccination uptake rate was estimated to be cost-effective for males with substantial reductions in morbidity and mortality by reducing OPC cases by 50% over the course of life in the base-case. From probabilistic sensitivity analysis, increasing vaccination coverage was preferred for males in 58.0%–96.1% of iterations when the WTP was greater than $37,500 using conventional WTP in the U.S. ($50,000 - $150,000 per QALY).

There have been a number of studies suggesting the potential impact of HPV vaccination on preventing oral HPV infection and HPV-

Table 2
Base-case and sensitivity analyses results by sex (vs. status quo).

Progression Rates	Cost of vaccination (USD 100 million)	Reduction in cancer cases (thousands)	Incremental Cost (USD 100 million)	Incremental QALYs (thousands)	ICER (USD per QALY gained)
Male					
Vaccine Coverage and Progression rates					
60% Coverage					
50%	1.01	0.72	2.60	1.45	179,330
Base-case		1.85	2.95	2.62	112,250
200%		10.31	22.94	21.11	108,671
70% Coverage					
50%	1.89	1.31	4.90	2.67	183,481
Base-case		3.36	4.74	4.78	99,217
200%		19.11	34.80	39.34	88,478
80% Coverage					
50%	2.78	1.80	6.59	3.67	179,419
Base-case		4.57	5.65	6.49	86,940
200%		26.53	32.90	54.8	60,037
90% Coverage					
50%	3.67	2.41	8.63	4.95	174,356
Base-case		6.02	6.35	8.56	74,204
200%		36.29	19.46	75.33	25,834
100% Coverage					
50%	4.56	3.32	8.47	7.22	117,336
Base-case		7.35	6.81	10.45	65,150
200%		54.17	−66.11	118.86	−55,620
Female					
Vaccine Coverage and Progression rates					
60% Coverage					
50%	0.54	0.08	0.63	0.13	468,246
Base-case		0.19	0.81	0.23	351,209
200%		2.00	2.66	3.24	81,945
70% Coverage					
50%	1.39	0.18	1.38	0.29	470,530
Base-case		0.42	1.74	0.51	343,539
200%		4.39	5.00	7.19	69,555
80% Coverage					
50%	2.25	0.34	2.45	0.55	443,766
Base-case		0.77	3.03	0.94	322,728
200%		8.35	7.80	13.81	56,443
90% Coverage					
50%	3.10	0.46	3.31	0.77	430,644
Base-case		1.05	4.00	1.28	311,458
200%		11.79	8.70	19.69	44,183
100% Coverage					
50%	3.96	0.63	4.47	1.11	402,441
Base-case		1.33	5.25	1.63	310,679
200%		17.22	8.13	30.48	26,669

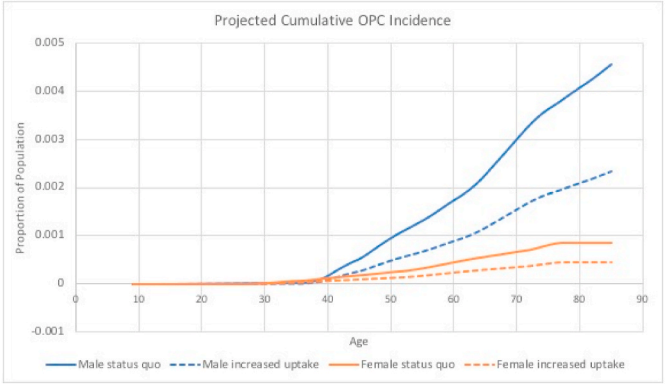

Fig. 1. Projected cumulative incidence of HPV-positive oropharyngeal cancer.

associated cancers, including more recent data indicating a decline in oral HPV prevalence [35]. Prior studies have suggested the health and economic implications of HPV vaccination through its cumulative influence in preventing HPV-associated cancers, such as vaginal, anal, and vulvar caners, including various head and neck cancers [36–39]. While these studies have demonstrated the benefits of HPV vaccine in an aggregated form, or mainly towards cervical cancer, a study on potentially reducing OPC, in specific, has been lacking. Moreover, many of prior cost-effectiveness studies in the US evaluated the effectiveness of various HPV vaccination coverage levels for female-only and gender-neutral cohorts, but not for a male-only cohort [40,41]. Because OPC incidence has been increasing constantly among males in the US with a relative lower vaccination coverage compared to females, our analysis adds values to the literature by evaluating the value of increasing the vaccination coverage levels through age 26, reflecting the recent trends of OPC, thus, establishing a strong evidence for the significance of HPV vaccination in preventing OPC among males.

Our study evaluates the impact of widespread coverage of HPV vaccination on preventing OPC among a single-age cohort in the US, however, the potential benefit from increasing HPV vaccination coverage is expected to be larger by averting other HPV-associated cancers. Because our findings are based on evaluating the vaccination benefit on OPC, our model results are likely to be conservative due to not incorporating vaccination benefit on other HPV-associated cancers. For example, in females, cervical cancer incidence rates are higher than OPC incidence rates and the benefits in QALY gains and healthcare cost saved would be expected to be significantly higher than our results. Since prevalence of other HPV-associated cancers lie in different ranges, and are more commonplace in women relative to men, it would be difficult

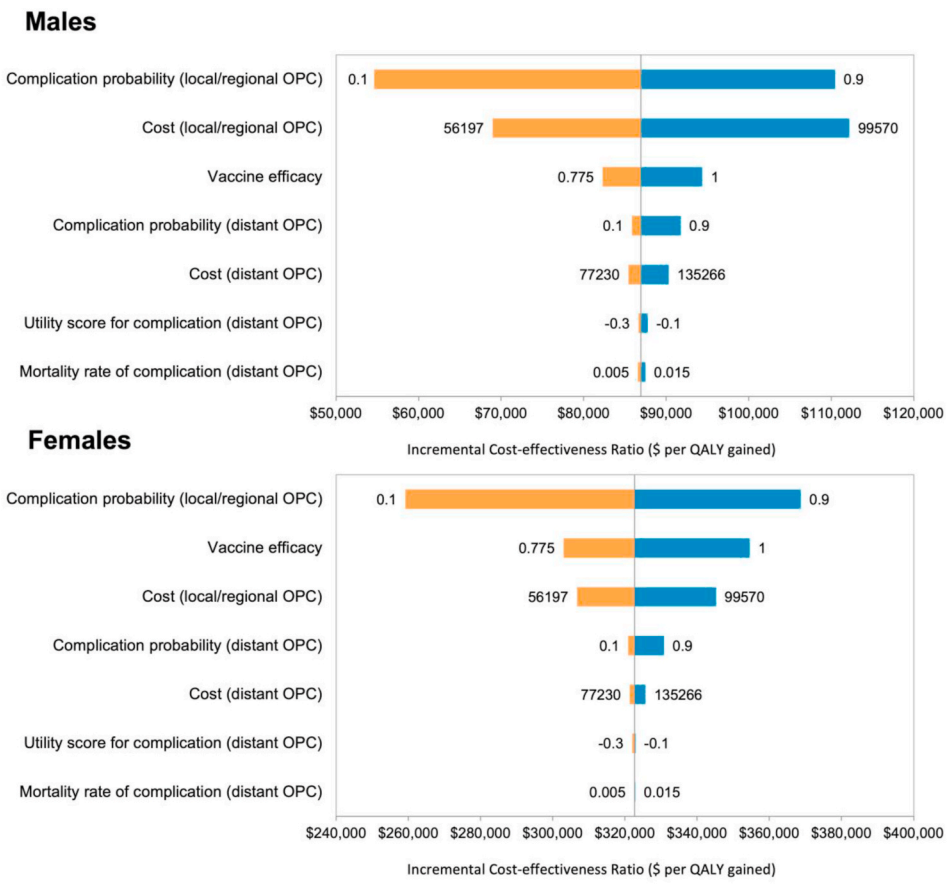

Fig. 2. Tornado diagrams for one-way sensitivity analyses.

to comment with certainty on the overall gains of an increased vaccination uptake program that is sex-indiscriminate.

Our study has limitations inherent to modeling based on secondary data sources. First, only the sex and age dependence were considered without incorporating other potential factors affecting vaccination uptake rates, risk of oral HPV infection and OPC, such as socioeconomic or demographic factors. The examination of health benefits in each subpopulation, however, is more nuanced due to differences in HPV infection, vaccination initiation and completion, and OPC incidence rates, [42] and the likelihood of catching infection and adherence till recommended doses also vary by economic status, education, and general willingness and outlook towards vaccination [43]. A thorough incorporation of important determinants and individualized simulations remains an area for future research. Also, the expected cost of HPV vaccination promotion efforts was not incorporated in our model, thus, our results of cost-effectiveness analysis, particularly for males, would be dependent on the cost needed to increase the coverage rate. The results of our analysis could be used as a guideline to support a decision on budget allocation for the HPV vaccination promotion strategies. Another major limitation is that because Markov-cohort model was used in this analysis, individual-level transmission, which is common in infections disease models, was not specifically modeled. Thus, our calibrated infection and progression rates were assumed to be constant by age and sex, and only serve as proxy for more detailed individual level transmissions. Moreover, all HPV types were not separately modeled, however, because more than 70% OPC cases are caused by HPV16, our results would not be substantially affected by this simplified approach. Next, the model parameters were calibrated to the targets one at a time rather than simultaneously using a multi-dimensional process. Because the order in which these parameters were calibrated may result at different model inputs, our calibration procedures may generate additional source of model uncertainty. Finally, though a relationship between HPV vaccination uptake and OPC is evidenced, a large longitudinal randomized control trial would provide a more robust relationship between the vaccination and incidence of OPC.

One of the most effective means to increase vaccination rates is provider recommendation [44]. Efforts should be directed towards educating patients on the importance of HPV vaccination as a cancer prevention tool and in promoting HPV immunization programs. Ease of access for preventive vaccinations to include pharmacies and nurse-staffed walk-in clinics has proved to be an effective strategy to increase immunization compliance for a range of diseases including influenza, pneumonia and herpes zoster [45,46]. 84.6% of children aged 2–17 years visited dental providers in 2016 [47]. Given these rather frequent encounters of dentists with young patients, raising awareness about the importance of HPV vaccination and encouraging referrals by dental providers may have favorable outcomes [48,49].

Expanding HPV vaccination coverage would be expected to lower the risk of oral HPV infection and potentially OPC in the US, and would be cost-effective for males under certain conditions. Encouraging male children and their parents to receive HPV vaccination would improve health outcomes and still be cost-effective.

Author contributions

SE.C.: Conceptualization, data curation, methodology, formal analysis, drafting of the manuscript, critical revision of the manuscript; **A.C.:** formal analysis, drafting of the manuscript, critical revision of the manuscript; **J.H.:** formal analysis, drafting of the manuscript; **S.S., AR. G.**: critical revision of the manuscript; **A.V.**: study conception and design, drafting of the manuscript, critical revision of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tvr.2021.200234.

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