Long-term impact of HPV vaccination and COVID-19 pandemic on oropharyngeal cancer incidence and burden among men in the USA: A modeling study

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Summary

Background Oropharyngeal cancer (OPC) incidence is rising rapidly among men in the United States of America (USA). We aimed to project the impact of maintaining the current HPV vaccination uptake and achieving 80% national (Healthy People) goal on OPC incidence and burden.

Methods We developed an open-cohort micro-simulation model of OPC natural history among contemporary and future birth cohorts of men, accounting for sexual behaviors, population growth, aging, and herd immunity. We used data from nationally representative databases, cancer registries from all 50 states, large clinical trials, and literature. We evaluated the status quo scenario (the current HPV vaccination uptake remained stable) and alternative scenarios of improvements in uptake rates in adolescents (aged 9-17 years) and young adults (aged 18-26 years) by 2025 to achieve and maintain the 80% goal. The primary outcome was to project OPC incidence and burden from 2009 to 2100. We also assessed the impact of disruption in HPV vaccine uptake during the COVID-19 pandemic.

Findings OPC incidence is projected to rise until the mid-2030s, reaching the age-standardized incidence rate of 9.8 (95% uncertainty interval [UI] 9.5-10.1) per 100,000 men, with the peak annual burden of 23,850 (UI, 23,200-24,500) cases. Under the status quo scenario, HPV vaccination could prevent 124,000 (UI, 117,000-131,000) by 2060, 400,000 (UI, 384,000-416,000) by 2080, and 792,000 (UI, 763,000-821,000) by 2100 OPC cases among men. Achievement and maintenance of 80% coverage among adolescent girls only, adolescent girls and boys, and adolescents plus young adults could prevent an additional number of 100,000 (UI, 95,000-105,000), 118,000 (UI, 113,000-123,000), and 142,000 (UI, 136,000-148,000) male OPC cases by 2100. Delayed recovery of the HPV vaccine uptake during the COVID-19 pandemic could lead to 600 (UI, 580-620) to 6200 (UI, 5940-6460) additional male OPC cases by 2100, conditional on the decline in the extent of the national HPV vaccination coverage and potential delay in rebounding.

Interpretation Oropharyngeal cancer burden is projected to rise among men in the USA. Nationwide efforts to achieve the HPV vaccination goal of 80% coverage should be a public health priority. Rapid recovery of the declined HPV vaccination uptake during the COVID-19 pandemic is also crucial to prevent future excess OPC burden.

Funding National Cancer Institute and National Institute on Minority Health and Health Disparities of the USA.

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Keywords: Oral HPV infection; Oropharyngeal cancer; HPV vaccination; Covid-19 pandemic; Long-term impact; Simulation modeling; Natural history modeling; Micro-simulation; Mathematical modeling

Abbreviations: HPV, human papillomavirus; OPC, oropharyngeal cancer; COVID-19, Coronavirus Disease

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Research in context

Evidence before this study

Human papillomavirus (HPV) associated oropharyngeal cancer (OPC) incidence is rising rapidly in several high-income countries, including Australia, Canada, Denmark, the Netherlands, Norway, Sweden, the United Kingdom, and the United States of America (USA). In the USA, OPC incidence and burden (annual number of cases) among men surpassed cervical cancer, making OPC the most common HPV-associated cancer. The USA Advisory Committee on Immunization Practices recommends routine HPV vaccination at ages 11-12 years and catch-up vaccination through age 26 years. The Healthy People program (nationwide health promotion and disease prevention program) of the USA Department of Health and Human Services had set a target to achieve 80% HPV vaccination coverage among adolescents by 2020. However, in 2019, only 54% of adolescents and 21% of young adults were up-to-date on their HPV vaccine schedule. Recent studies have indicated no improvements in HPV vaccination coverage among adolescents, growing HPV vaccine hesitancy among parents, increase in safety concerns, and a further decline in the HPV vaccine uptake during the COVID-19 pandemic. HPV vaccination could translate into OPC prevention in future years. Yet, the potential long-term impact of maintaining the current HPV vaccination uptake and improvements in coverage on OPC incidence and burden remains unclear.

We searched Pubmed for studies published in English from January 1, 2007 to June 1, 2021 with search terms “oropharyngeal cancer” OR “oropharynx cancer” AND “HPV vaccine” AND “impact” AND “simulation” AND “modeling”. Our search found no prior mathematical modeling studies that comprehensively evaluated the long-term impact of the current (status quo scenario) and potentially scaling-up the HPV vaccination coverage on OPC prevention among men in the USA. Furthermore, the long-term impact of reduced HPV vaccination uptake during the COVID-19 pandemic on future OPC burden remains unknown.

Added value of this study

Our study is the first to develop and validate a comprehensive mathematical modeling framework of the natural history of oral HPV infection and its progression to OPC. Our objective was to quantify the impact of maintaining the current HPV vaccination uptake and achieving the 80% national HPV vaccination goal on OPC incidence and burden (annual number of new diagnoses) among men in the USA. We found that OPC incidence will continue to rise among men until the mid-2030s, reaching the peak age-standardized incidence of 9.8 (95% uncertainty interval [UI] 9.5-10.1) per 100 000 men in 2037, causing nearly 24 000 new cases diagnosed during 2036 to 2042. Maintaining the status quo HPV vaccination uptake could prevent a cumulative male OPC burden of 124 000, 400 000, and 792 000 by 2060, 2080, and 2100. Alternative scale-up scenarios of achieving 80% coverage by 2025 among adolescent (up to age 17 years) girls only, adolescent boys and girls, and young adults (up to age 26 years) could prevent nearly 892 000, 910 000, and 934 000 cumulative number of male OPC cases by 2100. The decline in uptake during the COVID-19 pandemic and potential delays in rebounding could lead to a cumulative excess burden of 600 to 6200 male OPC cases over the 21st century.

Implications of all the available evidence

The findings of this study suggest that maintaining the current HPV vaccination uptake could translate into the prevention of 792 000 male OPC cases over the 21st century. Rapid improvements in the HPV vaccination uptake rate leading to the achievement of 80% coverage among adolescents and adolescents plus young adults can prevent an additional 118 000 and 142 000 male OPC cases, respectively. Rigorous national efforts to improve HPV vaccination coverage are needed to curb the rising OPC burden among men in the USA.

Introduction

Oropharyngeal cancer (OPC) incidence has increased in several economically developed countries over recent decades. In the USA, OPC is now the leading human papillomavirus (HPV) associated malignancy. Of 15 450 OPC cases diagnosed annually from 2012 to 2016 among men in the USA, 73% were caused by HPV infection, with HPV type 16 responsible for over 90% of diagnoses. Due to the current inability to detect HPV-induced precancer and inadequate diagnostic technology to identify localized-stage cancer, screening for OPC is not possible. Therefore, OPC control planning solely relies on primary prevention through HPV vaccination.

The HPV vaccine is efficacious against oral HPV infections and emerging evidence indicates possible herd protection among unvaccinated individuals. In 2006, the USA Food and Drug Administration approved the vaccine for anogenital HPV infection and associated cancer prevention and recently (in June 2020) extended the approval for OPC prevention. The vaccine has been recommended for routine use since 2006 in females and 2011 in males. However, 54% of adolescents and only 21% of young adults received the recommended doses in 2019, which is substantially lower than the national (The Healthy People program of the USA) goal of 80% attainment. Unfortunately, from 2015 to 2018, no improvement in HPV vaccination coverage was observed among adolescent boys while uptake declined among adolescent girls. Furthermore, a recent nationwide study reported high HPV vaccine hesitancy in 2017-2018, with nearly 60% of parents of unvaccinated adolescents had no intention to initiate vaccination.
the HPV vaccine series primarily due to safety concerns, lack of provider recommendation, and lack of knowledge.\textsuperscript{12} The Coronavirus Disease 2019 (COVID-19) pandemic dramatically disrupted the HPV vaccine delivery in the USA (up to a 77% drop in the uptake rate was reported in 2020), posing additional challenges in getting HPV vaccination coverage back on track.\textsuperscript{33–35}

A comprehensive assessment of the long-term impact of HPV vaccination under alternative scenarios could inform and support national immunization planning. We developed a comprehensive mathematical modeling framework of the natural history of oral HPV infection and its progression to OPC, accounting for sexual behaviors, aging, population growth, and herd immunity. Our objective was to evaluate the impact of maintaining the current HPV vaccination uptake and achieving the 80% national HPV vaccination goal on oral HPV infections, OPC incidence, and OPC burden among men from 2009 to 2100. We also assessed the impact of the decline in HPV vaccination uptake during the COVID-19 pandemic and potential recovery duration on future OPC burden.

Methods

Study design and data sources

We developed an open cohort micro-simulation model that simulated OPC carcinogenesis among a nationally representative population of men in the USA from 2009 to 2100. Micro-simulation signifies that each individual within the simulation has a unique set of characteristics and trajectory, which allows consideration towards the stochastic variation in disease progression as well as variation due to individual characteristics.\textsuperscript{16,17} Individual characteristics were defined to reflect age, HPV infection (i.e., specific genotype), HPV vaccination status (unvaccinated or received the recommended doses of the 4-valent/9-valent vaccine) (Appendix Figure 1). The model tracks age-structured birth cohorts of men who transition through a series of health states representative of the duration of genotype-specific HPV infection persistence, leading to a likelihood of invasion and progression to OPC. The model was parameterized using data from the National Health and Nutrition Examination Survey (NHANES), HPV infection in Men Study (HIM study), and other published studies. The unobservable progression probabilities were calibrated to reproduce the observed squamous cell OPC incidence trends and the annual number of cases estimated using the National Program of Cancer Registries (NPCR) and Surveillance Epidemiology and End Results (SEER) data (data providing 100% population coverage for all 50 states and the District of Columbia [DC]). We used data from the census bureau of the USA to assign population age distribution, new births, life expectancies, and obtain a projected population of men through 2100.\textsuperscript{36,37} The model considered the efficacy of HPV vaccination for oral HPV infection prevention based on a post hoc analysis of a randomized controlled trial and a US-representative surveillance study.\textsuperscript{38–40} The model also considered HPV vaccination coverage and herd protection through female vaccination. A detailed description of the model structure, data sources, parameter estimation, and other technical aspects are available in Appendix 1, Table 1. The model was developed in Matlab R2020b (Mathworks; Natick, MA).

Simulation pathways and OPC natural history

The model comprised of two main components (1) initial population characteristics (age, number of sex partners in the past 12 months, HPV vaccination status, and oral HPV infection status) (2) health states reflective of OPC natural history [incidence, clearance, and persistence]. At baseline (i.e., in 2009), the population was structured to reflect age-specific oral HPV infection prevalence, specific HPV types, and duration of HPV infection (Appendix 2, Appendix Figure 2 and 3). We grouped oncogenic oral HPV types as HPV16, HPV18, HPV31/33/45/52/58 (i.e., oncogenic HPV types covered by the 9-valent HPV vaccine), and HPV35/39/51/56/59/68 (i.e., oncogenic types not covered by the 9-valent vaccine).

At any given time, persons occupying one health state could transition to another state based on the progression rates. Based on age and HPV vaccination status, individuals may have a prevalent oncogenic oral HPV infection. Each year, persons were at risk of acquiring oral HPV infection. Genotype-specific oral HPV clearance rates were a function of age and duration of HPV infection. We used three-time thresholds (0–6 months, 7–18 months, and longer than 18 months) for modeling the duration of HPV infection. Age-specific incidence of HPV infection and the likelihood of clearance of incident or prevalent infection was based on HIM and other published high-quality studies (Appendix 3, Appendix Figures 4–8).\textsuperscript{41–43} Age- and genotype-specific progression to OPC among individuals with persistent oncogenic HPV infection was systematically calibrated. The detailed calibration process is described in Appendix 4 and Appendix Figures 9 and 10. Briefly, based on available data, the model was calibrated such that clearance among older age groups was less likely than younger age groups, HPV16 infections were less likely to clear than other oncogenic HPV types, and time to clearance was more rapid for incident HPV infections than prevalent infections.\textsuperscript{3,41,42} Persons with persistent oncogenic HPV infection, based on age, carcinogenicity, and duration of infection, were at risk of progressing to OPC. To project HPV-negative OPC incidence and burden, we used an incidence-based modeling approach that considered an age-specific fraction of OPC cases that are HPV negative (Appendix 3).
HPV vaccine efficacy and coverage

For base case analysis, we assumed that HPV vaccination results in a 90% reduction in the acquisition of vaccine-type oral HPV infections among vaccinated men (Appendix 5). We modeled herd effects, assuming a linear inverse relationship between HPV acquisition and female vaccine coverage. We considered age-mixing patterns to calculate age-specific herd protection through female vaccination (Appendix 6). We reproduce the current national HPV vaccination coverage for adolescents (9-17 years) and young adults (18-26 years) estimated using the NHANES data and validated against the National Immunization Survey-Teen (NIS-Teen) and National Health Information Survey (NHIS) data (Appendix Figures 11 and 12).

Simulation scenarios: status quo, healthy people goal of 80% coverage achieved by 2025, optimistic scenario, impact of the COVID-19 pandemic

The status quo scenario assumed that the uptake rates in 2019 would continue. Alternative scenarios considered steady improvements in uptake rates such that the Healthy People goal of 80% coverage is achieved among girls only (80% female only scenario) and girls plus boys (80% gender-neutral scenario) by 2025, and maintained thereafter. We also simulated an optimistic scenario of achieving 100% coverage by 2025. Given the differences in HPV vaccination coverage by age groups (adolescents versus young adults), we evaluated alternative scenarios of achieving 80% coverage among young adults plus adolescents. We also simulated COVID-19 scenarios where we dropped the vaccine uptake by 20% to 70% among adolescents in 2020 and assumed that the rebound would occur over the duration of 1-3 years. For the COVID-19 scenarios, the decline in uptake was considered among 2003-2011 birth cohorts. A detailed description of the scenarios is in Appendix 5.

Model outcomes

For each scenario, we projected oral HPV infection prevalence, age-standardized (to 2000 USA population) OPC incidence, and OPC burden through 2100. These outcomes were determined according to age at cancer diagnosis and fractions of cases attributable to HPV16, HPV18, HPV31/33/45/52/58, HPV35/39/51/56/59/68, and no HPV infection. Finally, we determined the cumulative number of OPC cases prevented under different scenarios.

Sensitivity analysis

We performed a probabilistic sensitivity analysis to determine the confidence in our model projections in each scenario given the joint uncertainty of model parameters. Using 100 model outputs from the probabilistic sensitivity analysis, we generated the 95% uncertainty intervals (UIs) of model outcomes. We also evaluated the effect of potential variation in the HPV vaccine efficacy in terms of the degree of protection and duration of protection. Furthermore, we also conducted deterministic sensitivity analyses varying HPV incidence/clearance and progression to evaluate the impact of potential variation in the natural history parameters on study outcomes.

Role of the funding source

We acknowledge funding from the US National Cancer Institute (R01CA238888) and the National Institute on Minority Health and Health Disparities (K01MD016440). The funder had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the US National Cancer Institute and the National Institute on Minority Health and Health Disparities.

GMC is a staff member of IARC. The external funder (NCI and NIMHD of the USA) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Model validation

We performed extensive model validation to ensure that model-predicted outcomes corresponded with the observed data. First, we compared the model-predicted age-specific oral HPV infection prevalence (HPV16/18 and all oncogenic HPV types) against data from the NHANES 2013-2016 cycles (Figure 1A and B). Second, to validate the direct and potential herd protection, we compared the prevalence of vaccine-type oral HPV infection and oral HPV16/18 infection among vaccinated (Figure 1C) and unvaccinated (Figure 1D) men, respectively, against the NHANES data (also see previous publications). Third, we compared the model-predicted age-specific OPC incidence among men against the estimates from the NPCR and SEER data (Figure 1E). Finally, we compared the model-predicted OPC burden from 2009 to 2016 against estimates from the USA cancer registry data (Figure 1F).

Status quo adolescent vaccination scenario

Under the status quo scenario, the model predicted that the decline in vaccine-type infection prevalence (HPV16, HPV18, HPV31/33/45/52/58) would continue in future years (Appendix Figure 13A). In contrast, the prevalence of high-risk genotypes not covered by the HPV vaccine (HPV35/39/51/56/59/68) will remain...
unchanged. The burden of vaccine-type infections will remain stable until the mid-2030s (Appendix Figure 13B). The number of persons with 9-valent vaccine type infections will decrease from approximately 3.8 million in 2010 to 1.8 million in 2100.

OPC incidence rates from 2009 to 2100 under no vaccination, status quo scenario considering herd protection, and alternative scenario without herd protection are presented in Appendix Figure 14. OPC incidence peak (9.8; 95% UI, 9.5-10.1 per 100,000 men) will be observed in the early 2030s. When stratified by age, consistent with estimates from the NPCR and SEER data (Appendix Figure 15 and Appendix Table 6), OPC incidence has begun to decline among <45-year-old men and stabilized among those aged 45-54 and 55-64 years (Figure 2A). The decline among 45-54-year-old men
and those aged 55-64 years would not be seen until the mid-2020s and early 2040s, respectively. OPC burden will shift towards men aged ≥65 years in future years (from nearly 25% of all cases in 2009 to over 70% in 2050) (Figure 2B). Notably, the HPV-related OPC fraction will continue to increase with the increasing proportion of cases attributable to HPV16 (Figure 2C). For instance, at its peak burden of nearly 24 000 annual OPC cases during the years 2036-2042, approximately 82% of cases will be attributable to oncogenic HPV and 74% will be attributable to HPV16.

Improvements in adolescent and young adult HPV vaccination coverage scenarios

Compared to no vaccination, status quo, 80% female-only, and 80% gender-neutral scenarios will result in nearly 226 million (UI, 219-233 million), 249 million (UI, 241-257 million), and 257 million (UI, 249-265 million) cumulative number of 9-valent oral HPV infections prevented (Appendix Figure 16). Under these scenarios, the cumulative number of HPV-16 infections prevented will be 156 million (UI, 151-161 million), 171 million (UI, 166-176 million), and 176 million (UI, 171-181 million), respectively.

Of note, under all vaccination scenarios, the overall OPC incidence (Figure 3A) and burden (Figure 3B) will continue to rise and a decline will not be seen until the mid-2030s. Compared to the no vaccination scenario, under the status quo, female-only, and gender-neutral vaccination scenarios, approximately 792 000 (UI, 763 000-821 000), 892 000 (UI, 859 000-925 000), and 910 000 (UI, 876 000-944 000) male OPC cases would be prevented over the 21st century (Figure 3C). The impact of alternative HPV vaccination scenarios on OPC incidence trajectories among specific age groups is presented in Appendix Figure 17A–17E.

The results of the young adult vaccination scenario are presented in Figure 4 and Appendix Figure 18. Compared to the status quo scenario, achieving 80% coverage among 18-26-year-old females only and 18-26-year-old males and females by 2025 could translate into an additional 106 000 (UI, 102 000-110 000) and 142 000 (UI, 137 000-147 000) cumulative number of OPC cases prevented.

COVID-19 pandemic scenario

As a result of the COVID-19 pandemic, a drop in vaccination uptake among adolescents during 2020 and a delay in rebounding can contribute to the rise in OPC burden (Figure 5). For instance, a 20% national drop in uptake rate with a one-year to three-year rebound can lead to approximately 600 (UI, 580-620) to 1700 (UI, 1640-1760) additional OPC cases over the 21st century. With a further drop in coverage and/or longer rebounding time, the implications on future OPC burden will be severe, e.g., a drop rate of 70% with a 3-year rebound can lead to approximately 6200 (UI, 5940-6460) additional cases.

Sensitivity analysis

Our findings were sensitive to the variations in HPV vaccine effectiveness measures and natural history parameters. Variation in vaccine efficacy could drive future changes in OPC incidence trends and burden. For instance, every 10% drop in vaccine efficacy could lead to approximately 70 000 cumulative OPC cases over the 21st century (Figure 6A, B). Vaccine duration of protection of at least 30 years will be required to see a meaningful impact on OPC incidence trends (Figure 6C, D). Potential changes in HPV acquisition/clearance and progression could have an impact on the projected OPC incidence trajectory (Appendix Figs. 19A–19D).

Discussion

Our study is the first to our knowledge to project the long-term impact of maintaining the current HPV vaccination uptake and potential improvements in coverage on oral HPV infections and OPC incidence and burden among men in the USA, taking into account OPC natural history, sexual behaviors, and herd immunity. Our findings indicate that the overall rising trend in OPC incidence will continue to persist over the next 15 to 20 years. Achieving and maintaining the national goal of 80% gender-neutral adolescent HPV vaccination coverage could translate into the prevention of nearly 910 000 OPC cases among men over the 21st century. Further improvements in coverage among young adults could cumulatively lead to the prevention of nearly 934 000 OPC cases. Our study also indicates the importance of the rapid recovery of HPV vaccination uptake hampered during the COVID-19 pandemic. Collectively, our findings underscore an urgent need to achieve and maintain the national HPV vaccination goal to reduce the worsening OPC burden among men in the USA.

If herd protection translates into cancer prevention, the impact of HPV vaccination on OPC incidence could be seen as early as the mid-2030s. Notably, the impact will be first observed among young age groups, followed by the mid-adult and elderly populations. Our projected decline among the young (<45 years) age group is consistent with the observed HPV-associated OPC trends and projected stabilization among mid-adult men is consistent with a study by Tota et al that predicted stabilization of HPV-associated OPC incidence beginning from the early 2020s among 45-54-year-old men.14 These patterns may not be attributable to HPV vaccination given the long latency between infection and cancer; recent moderation in high-risk sexual behaviors and reduction in smoking in recent years may explain these trends.25
Figure 2. Oropharyngeal cancer incidence and burden under the status quo scenario of HPV vaccination coverage in the US, 2009-2100. (A) Age-specific incidence trend for age groups <45, 45-54, 55-64, 65-74, and ≥75 years. (B) Annual OPC burden stratified by age at diagnosis of <45, 45-54, 55-64, and ≥75 years. (C) Annual OPC burden stratified by cancer-causing infection type (HPV16, HPV18, HPV31/33/45/52/58, HPV-35/39/51/56/59/68, HPV-negative).

Acronyms: HPV, human papillomavirus; OPC, oropharyngeal cancer.
Figure 3. Oropharyngeal cancer incidence and burden under alternative scale-up scenarios among adolescent (aged 9-17 years), 2009-2100. The figure illustrates how oral HPV infection prevalence, oropharyngeal cancer incidence, and oropharyngeal cancer burden will change under no vaccination, status quo, and potential improvements in HPV vaccination coverage scenarios of achievement and maintenance of 80% vaccination coverage among females only and males and females by 2025, and achievement of 100% HPV vaccination coverage among males and females by 2025. (A) OPC incidence trends considering different scenarios. (B) OPC burden considering different scenarios. (C) Number of OPC cases prevented under different scenarios.

Acronyms: HPV, human papillomavirus; OPC, oropharyngeal cancer.
monitoring is needed to understand the reasons for these age-specific patterns.

Our sensitivity analysis indicates that the long-term benefits of HPV vaccination will be dependent on the duration of protection of the HPV vaccine. Most women acquire oncogenic cervical HPV infection before age 30 and the peak age at cervical cancer incidence is around 30-40 years in the USA. In contrast, oncogenic oral HPV infection incidence is higher among mid-adult men and oral HPV clearance decreases with increasing age. Furthermore, OPC incidence peak occurs around age 60-70 years among men, implying that despite high vaccine efficacy, longer (at least 30 years) duration of protection will be needed to realize a meaningful population-wide impact of HPV vaccination on OPC incidence. These natural history differences also imply that age at “causal” oral HPV infection is likely greater among men and catch-up vaccination may have greater benefits for OPC prevention. Future studies are needed to determine age at causal oral HPV infection and the impact and cost-effectiveness of the mid-adult vaccination program.

The projected two-fold increase in HPV-positive OPC burden will be largely attributable to the growing population size of elderly men and the continued marked rise in OPC incidence among men aged 65 years and older. The rising burden of HPV-positive individuals who were never age-eligible for the HPV vaccines implies an urgent need to identify effective and cost-effective screening strategies for OPC prevention or early detection. In terms of implications for treatment, de-intensification strategies (i.e., reducing toxicity while maintaining similar outcomes) are being investigated for young HPV-positive patients due to their superior prognosis compared to patients with HPV-negative tumors. While de-intensification protocols may appear appealing for elderly patients given the poor cause-specific survival and higher comorbidities, their use among elderly patients remains unclear. Our finding of the potential rise in HPV-positive elderly OPC burden adds to the growing body of knowledge, highlighting the need for future studies evaluating treatment harms and benefits for elderly HPV-positive patients.

**Figure 4.** Additional number of oropharyngeal cancer cases prevented by achieving 80% young adult (aged 18-26 years) HPV vaccination coverage. The figure illustrates how improvement and maintenance (i.e., the achievement of 80% coverage among females only, the achievement of 80% coverage among the female and male population) of HPV vaccination coverage among the young adult age group could translate into an additional number of OPC cases prevented compared to the status quo scenario.

Acronyms: HPV, human papillomavirus; OPC, oropharyngeal cancer.
patients. Finally, our projections also indicate the need to improve OPC treatment infrastructure and prepare the health care workforce to serve the rising OPC burden among the elderly in future decades.

Three recent studies that estimated the cost-effectiveness of mid-adult HPV vaccination program projected future OPC burden (either alone or as part of non-cervical HPV-associated cancers) under current recommendations. Chesson and colleagues projected that the current vaccination program could prevent 381,492 OPC cases over 100 years. Daniels and colleagues estimated that the cumulative OPC burden attributable to 9-valent HPV infection types over the 100-year time horizon will be 509,557. Laprise and colleagues also reported that current HPV vaccine recommendations could prevent 769,000 non-cervical HPV-associated cancers in men and women. Compared with these studies, the unique aspects of our study include the use of a comprehensive natural history modeling framework that accounts for age- and time-dependency and attention to nationwide and contemporary calendar trends in oral HPv infection and OPC incidence. In addition, we also considered population dynamics (such as aging, population growth, and herd immunity). As a result, we were able to project trends in oral HPV infection prevalence, overall and age-specific HPV-positive and HPV-negative OPC burden, and OPC cases attributable to specific HPV genotypes. Consideration of age-specific natural history also allowed us to estimate the impact of improvements in HPV vaccination uptake among young adults aged 18-26 years.

**Figure 5.** Impact of COVID-19 pandemic resulting in rapid decline and potential rebounds in HPV vaccination coverage on the oropharyngeal cancer burden in the US, 2010-2100. The figure illustrates a combination of scenarios, where a drop in HPV vaccination coverage in the range of 20% to 70% occurred during 2020 and was rebounded over the duration of 1 to 3 years. For each combination of scenarios, the bars illustrate the additional number of OPC cases that could occur over the 21st century.

Acronyms: OPC, oropharyngeal cancer.
Another important strength of our modeling framework is its capability to evaluate how potential uncertainties (e.g., vaccine efficacy, vaccine durability, infection patterns) might impact the future OPC burden.

In the USA, only a few states and regions (Massachusetts, Rhode Island, North Dakota, and DC) are on the path (coverage in 2019 was above 70%) to achieve the national HPV vaccination goal. In many states in the Midwest (e.g., Indiana, Ohio, Kansas) and Southeast (e.g., Mississippi, Alabama, Georgia) regions that collectively contribute to over 50% of the national OPC burden, HPV vaccination coverage is overwhelmingly low (less than 50%).

Notably, over a 100% rise in safety concerns in these states was observed in recent years, leading to vaccine refusal among parents of adolescents. While our findings highlight the impact of potential improvement in HPV vaccination coverage at the national level, extensive efforts will be needed in states with low HPV vaccination coverage and high vaccine hesitancy.

The COVID-19 pandemic has derailed the national progress making the trajectory and timeline for achieving 80% national goal uncertain. Given the current circumstances, a key takeaway from our findings is that the pace of recovery would determine avoidable excess OPC burden in future years. A recent analysis of vaccine administration data from 10 jurisdictions in the USA showed that HPV doses administered declined a median of 63.6% and 71.3%, respectively, during March-May 2020 compared with doses administered during the same period in 2018 and 2019. Furthermore, the recovery was not fully achieved during June-September 2020 (declines of 12.2% and 28.1%). Another recent study of healthcare claims data showed that reduced uptake persisted until August 2020 and further reported that an estimated additional 2882 to 6447 cervical cancer cases could occur based on the pace of recovery. The rapid emergence and spread of the highly transmissible delta and Omicron variants added further uncertainty to recovery efforts, particularly in the context of potential prioritization of adolescent COVID vaccination and likely exacerbation of vaccine hesitancy. Collectively, these data highlight the need of aggressive and coordinated efforts at local and national levels to mitigate the translation of reduced HPV vaccination uptake into excess OPC burden in future years.

Our analysis had a few limitations. First, our outcomes projected for nearly 100 years are based on known data specific to contemporary birth cohorts. Potential changes in sexual behaviors, technological advancements (e.g., availability of screening), and

![Figure 6](https://www.thelancet.com/)

Figure 6. Sensitivity analysis evaluating the impact of vaccine degree and duration of protection on oropharyngeal cancer incidence trends and cumulative OPC burden. The Figure illustrates the impact of potential variation in HPV vaccine efficacy on (A) oropharyngeal cancer incidence (B) oropharyngeal cancer burden. The impact of potential variation in vaccine duration of protection on (C) oropharyngeal cancer incidence and (D) burden is also described.
unforeseen demographic changes may affect future OPC patterns. Second, our model captures herd immunity benefits using a systematic approach that considers female vaccination coverage. We validated our findings by comparing them with other transmission-based simulation models and oral HPV infection prevalence trends among unvaccinated men in the USA. However, future modeling advancements can consider HPV transmission dynamics. Third, HPV vaccine efficacy data are based on a posthoc analysis of a randomized controlled trial and a surveillance study. Further evidence from an ongoing randomized controlled trial (NCT04199689) is needed.

Fourth, due to data unavailability, we could not evaluate the impact of the COVID-19 pandemic on changes in sexual behaviors among the sexually active young adult population. Therefore, we limited the COVID-19 scenario evaluation to only specific birth cohorts. For the COVID-19 scenario, we assumed that the HPV vaccination uptake is unlikely among adolescents who transition to the young adult age groups given the low historic uptake among young adults. Because young adults will still be eligible for catch-up vaccination, our findings should be interpreted within the context of this limitation. Finally, OPC risk factors such as smoking and alcohol use were not considered due to a lack of clarity regarding the contribution of these risk factors to HPV-positive OPC carcinogenesis. Although we estimated future projections of HPV-negative OPC cases, which are largely attributable to smoking, our approach may have overestimated future HPV-negative OPC burden given the decreasing prevalence of tobacco use in the USA. Furthermore, the estimated projections of HPV-negative OPC will not affect the future impact of HPV vaccination. Despite these limitations, consideration towards the duration of HPV infection and the use of the best available data allowed us to generate nationally representative and robust outcomes that closely matched empirical data.

In summary, OPC incidence and burden will continue to rise over the next two decades among men in the USA. Maintaining the progress achieved by the HPV vaccination program in the USA will substantially reduce the future HPV-associated OPC burden. Our study also underscores the need for rigorous national efforts to reach and maintain the national goal of 80% HPV vaccination coverage despite the challenges posed by the COVID-19 pandemic.

Declaration of interests
JC reported Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Bayer and is a partner of Value Analytics Lab. ARG is a member of several Merck & Co, scientific and global advisory boards and her institution receives grants for research from Merck & Co, Inc. All other authors declare no competing interests.

Acknowledgments
The authors alone are responsible for the views expressed in this paper and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated. Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jana.2021.100143.

Contributors
HD and AAD conceptualized the study. Formal analysis was done by HD. HD and AAD wrote the first draft of the manuscript and are responsible for methodology and data validation. All authors were responsible for the investigation, visualization, and manuscript review & editing. All authors have approved the final manuscript and had final responsibility for the decision to submit for publication.

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