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Upper age limits for US male human papillomavirus vaccination for oropharyngeal cancer prevention: a microsimulation-based modeling study

Rebecca Landy (iD), PhD,[1]* Gregory Haber, PhD,[2] Barry I. Graubard, PhD,[1] Nicole G. Campos, PhD,[3] Stephen Sy, MS,[3] Jane J. Kim, PhD,[3] Emily A. Burger (iD), PhD,[3,4] Li C. Cheung, PhD,[1] Hormuzd A. Katki (iD), PhD,[1] Maura L. Gillison, MD, PhD,[5] Anil K. Chaturvedi, PhD[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA
[2]Information Technology Laboratory, National Institute of Standards and Technology, Gaithersburg, MD, USA
[3]Center for Health Decision Science, Harvard T. H. Chan School of Public Health, Boston, MA, USA
[4]Department of Health Management and Health Economics, University of Oslo, Norway
[5]Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX, USA

*Correspondence to: Rebecca Landy, PhD, Clinical Epidemiology Unit, Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Rm. 6E554, Rockville, MD, USA (e-mail: rebecca.landy@nih.gov).

Abstract

Background: Human papillomavirus (HVP)–positive oropharyngeal cancer is the most common HPV-associated cancer in the United States. The age at acquisition of oral HPV infections that cause oropharyngeal cancer (causal infections) is unknown; consequently, the benefit of vaccination of US men aged 27-45 years remains uncertain.

Methods: We developed a microsimulation-based, individual-level, state-transition model of oral HPV16 and HPV16-positive oropharyngeal cancer among heterosexual US men aged 15-84 years, calibrated to population-level data. We estimated the benefit of vaccination of men aged 27-45 years for prevention of oropharyngeal cancer, accounting for direct- and indirect effects (ie, herd effects) of male and female vaccination.

Results: In the absence of vaccination, most (70%) causal oral HPV16 infections are acquired by age 26 years, and 29% are acquired between ages 27 and 45 years. Among men aged 15-45 years in 2021 (1976-2006 birth cohorts), status quo vaccination of men through age 26 years is estimated to prevent 95% of 153 450 vaccine-preventable cancers. Assuming 100% vaccination in 2021, extending the upper age limit to 30, 35, 40, or 45 years for men aged 27-45 years (1976-1994 cohorts) is estimated to yield small benefits (3.0%, 4.2%, 5.1%, and 5.6% additional cancers prevented, respectively). Importantly, status quo vaccination of men through age 26 years is predicted to result in notable declines in HPV16-positive oropharyngeal cancer incidence in young men by 2035 (51% and 24% declines at ages 40-44 years and 45-49 years, respectively) and noticeable declines (12%) overall by 2045.

Conclusion: Most causal oral HPV16 infections in US men are acquired by age 26 years, underscoring limited benefit from vaccination of men aged 27-45 years for prevention of HPV16-positive oropharyngeal cancers.

Prophylactic human papillomavirus (HPV) vaccines are highly (>95%) efficacious in preventing infections at the cervix, vagina, vulva, penis, anus, and oral cavity and oropharynx; anogenital warts; anogenital precancers; and cervical cancers (1-9) and have led to population-level declines in many of these outcomes in several countries (10-17). HPV vaccination was introduced for US females and males in 2006 and 2011, respectively. For both sexes, routine vaccination is recommended for ages 9-12 years and catch-up vaccination for ages 13-26 years and through shared decision making for ages 27-45 years (8).

A key question is the value of HPV vaccination at ages 27-45 years. This question is particularly important for US men. First, HPV-positive oropharyngeal cancer incidence has increased more than 200% since the 1990s in US men (18,19). Today, more than 70% of oropharyngeal cancers are caused by HPV, primarily HPV16 (approximately 90%) (18,20). HPV-positive oropharyngeal cancer is the most common HPV-associated cancer in the United

States, accounting for approximately 77% of the burden of HPV-associated cancers in men (20). Second, current recommendations for US men aged 27-45 years are based on microsimulation models that consider HPV infection at the person level rather than the anatomic site level (21). This is notable because the natural history of HPV infections differs across sites (22). Third, vaccination is the only prevention tool for HPV-positive oropharyngeal cancers because there are no screening methods (23). Fourth, a low proportion (<5%) of US men aged 27-45 years in 2021 have been vaccinated.

We developed a microsimulation-based natural history model for oral HPV16 acquisition and progression to HPV16-positive oropharyngeal cancer for US men to estimate the ages at acquisition of causal oral HPV16 infections in the absence of vaccination. Then, across vaccination scenarios, we evaluated the benefit of vaccination of US men aged 27-45 years for prevention of oropharyngeal cancers.

Methods

Overview of methodology

We constructed a microsimulation-based, individual-level, state-transition model for current birth cohorts of heterosexual US men aged 15-84 years in 2021 (1937-2006 cohorts; closed population). The model was calibrated to population-level data on oral HPV16 prevalence and HPV16-positive oropharyngeal cancer incidence. We used the model in the absence of vaccination (ie, natural history) to estimate the age at acquisition of causal oral HPV16 infections. We then incorporated direct and indirect (ie, herd immunity) effects from 14 female and male vaccination scenarios to estimate the number of HPV16-positive oropharyngeal cancers prevented and thereby determine the benefit of different upper age limits for vaccination of US men.

Herein, we provide a brief overview of the methodology. Specific details are provided in Supplement 1, including data sources (Supplementary Table 1, available online). HPV-FRAME guidelines were followed (Supplementary Table 2, available online) (24).

Microsimulation model

The dynamic model included 3 health states: susceptible to oral HPV16, oral HPV16-infected, and HPV16-positive oropharyngeal cancer, with annual state transitions (events assumed to occur at mid-year; Supplementary Figure 1, available online). To incorporate known heterogeneity in oral sexual behaviors, oral HPV16 prevalence, and HPV16-positive oropharyngeal cancer incidence (18,25,26), we stratified the US male population into 32 subcohorts defined by race and ethnicity, smoking, and age-specific quartiles of lifetime oral sex partners. Each subcohort included 100 000 participants and had a stratum-specific weight derived from 4 National Health and Nutrition Examination Survey (NHANES) cycles (2009-2016) (Supplementary Methods 1, available online) (27). Thus, our model reflects the size and structure of the US male population.

The model estimates natural history from acquisition of oral HPV16 infection to HPV16-positive oropharyngeal cancer in the absence of vaccination. Each individual's follow-up began at age 15 years and ended at the earliest of death (from background causes), oropharyngeal cancer, or age 85 years. Primary analyses assumed no birth cohort effects in sexual behaviors. Sexual mixing was semi-assortative based on sexual behaviors, and partnership formation and dissolution were instantaneous.

Acquisition of oral HPV16

Cervical HPV16 was the presumed reservoir for oral HPV16 in heterosexual men. For each age, using observed and self-reported data from NHANES 2009-2016 (27), we modeled the probability of contact with a new sex partner over the past 12 months (ie, recent); number of recent female oral sex (performed) partners; age of each recent female partner; age-specific prevaccine era genital HPV16 status of each partner; and probability of transmission given contact with infected partner(s) (Supplementary Methods 2.1, Supplementary Figures 2 and 3, available online).

Persistence and clearance of oral HPV16

The only determinant of oral HPV16 persistence and clearance was the accrued duration and persistence of infection (Supplementary Methods 2.2, Supplementary Figure 4, Supplementary Table 3, available online). Because there are no long-term studies of oral HPV16 natural history, we estimated the relationship of accrued duration with persistence/clearance using data on incident cervical HPV16 infections, with follow-up through 12 years. The natural histories of cervical and oral HPV infections are expected to differ; thus, we used a wide range (+/-75% of the parameter values) around the cervical clearance curve's Weibull parameters to accommodate anatomic-site variability. We assumed no natural immunity from prior oral HPV16 infections in men (28).

Although we used the cervical HPV clearance curve parameters (with a wide range) as the distributions from which the oral HPV clearance curve parameters were drawn, we underscore that no assumptions are made regarding similar natural histories between oral and cervical HPV16 infections.

Methodologic considerations vis-à-vis existing studies

There are a few studies of natural history of oral HPV infections, albeit short-term [eg, the HPV Infection in Men (HIM) study (29) and the Persistent Oral Papillomavirus Study (POPS)] (30). We elected not to utilize these studies as parameter sources or as calibration targets owing to the following reasons. First, neither HIM nor POPS is representative of the US male population aged 15-84 years; specifically, HIM was conducted across the United States, Mexico, and Brazil, and POPS included HIV-infected and high-risk HIV-negative men and women from Baltimore, Maryland. Thus, the sexual behaviors, sexual networking patterns, and genital HPV infection status of female (and male) partners (all key predictors of oral HPV acquisition) would be expected to differ from the general US heterosexual male population. Second, HIM (31) and POPS (30) included few incident oral HPV16 infections (n = 13 and 49, respectively) and the clearance estimates represent an admixture of incident and prevalent infections, without additional stratification by country in HIM or HIV-status, sex and sexual orientation in POPS.

Progression to HPV16-positive oropharyngeal cancer

The key determinant of annual progression from prevalent oral HPV16 to oropharyngeal cancer was accrued duration and persistence of an infection (Supplementary Methods 2.3, Supplementary Table 4, available online). Because there are no available progression estimates, we based calculations on the Armitage and Doll multistage carcinogenesis model for the log-log relationship of cancer incidence with age (32). As with the Armitage and Doll lung carcinogenesis model (which assumed age as a surrogate for smoking duration) (32), we assumed age as a surrogate for accrued duration and persistence of oral HPV16 infection.

Model calibration

We ran 500 000 simulations to select the 50 best-fitting parameter sets, through calibration with US population-level data for age-specific oral HPV16 prevalence (NHANES 2009-2016; Supplementary Table 5, available online) and HPV16-positive oropharyngeal cancer incidence (Surveillance, Epidemiology, and End Results 2009-2016, with HPV16-positive assumptions; Supplementary Table 6, available online). Although our group has previously shown in NHANES 2009-2010 that the prevalence of oral HPV infections follows a bimodal age pattern (26), such bimodality (potentially a reflection of cohort effects) has dissipated across successive NHANES cycles (through 2015-2016), as would be expected from cohort effects. Best-fitting simulations were selected through χ^2 statistics (Supplementary Methods 3.1 and 3.2, available online) (18,27).

Vaccination effects

We incorporated both direct effects from male vaccination (assuming 95% lifelong efficacy against oral HPV16 acquisition) and indirect herd immunity from male and female vaccination (Supplementary Methods 4.1, Supplementary Figure 5, Supplementary Tables 7-9, available online). Herd effects were estimated using the Harvard-HPV model (an agent-based dynamic transmission model) (33) and expressed as birth cohort-, age-, and male and female vaccination level–specific reductions in cervical HPV16 prevalence relative to the prevaccine era (NHANES 2005-2006).

Vaccination scenarios

We evaluated 3 broad vaccination scenarios (Supplementary Methods 4.2, Supplementary Table 10, available online): 1) status quo vaccination in men (24.9% by age 12 years, 9.7% per year ages 12-18 years, and 1.9% per year thereafter) (21) through ages 26, 30, 35, 40, or 45 years—this scenario provides the impact of current vaccine uptake; 2) vaccination of 100% of men in 2021 through ages 26, 30, 35, 40, or 45 years, although unrealistic, this scenario provides the maximum possible impact of vaccination; and 3) a birth cohort–specific approach, with 100% vaccination of men from the 1976-1994 birth cohorts (aged 27-45 years in 2021) through ages 30, 35, 40, or 45 years and status quo vaccination for men from the 1995-2006 birth cohorts through age 26 years—this scenario provides the impact of an optimized vaccination approach for birth cohorts that did not achieve high uptake through 2021. In each scenario, female vaccination was assumed at status quo uptake through age 45 years.

Evaluation of upper age limits for vaccination

For each birth cohort of men aged 15-84 years (1937-2006 cohorts) in 2021, we ran the microsimulation model retrospectively from age 15 years to attained age in 2021 and incorporated estimated direct and indirect vaccination effects. Then, starting with the accrued birth cohort- and age-specific vaccination levels in men and women in 2021, we prospectively applied hypothetical vaccination scenarios to estimate the number of HPV16-positive oropharyngeal cancers through age 85 years. We did not consider alternative vaccination scenarios before 2021, as these vaccinations (and potentially prevented cancers) have already occurred. Analyses accounted for the size of each birth cohort in 2021 and future attrition from oropharyngeal cancer incidence and age-, race-, and smoking-specific all-cause mortality (Supplementary Methods 5, Supplementary Table 11, available online). Metrics for comparisons across scenarios were the number of HPV16-positive oropharyngeal cancers prevented and the number needed to vaccinate to prevent 1 oropharyngeal cancer (relative to status quo vaccination through age 26 years).

Sensitivity analyses

We evaluated robustness of our results (model calibration and ages at acquisition of causal infections) to assumptions regarding cohort effects in sexual behaviors, impact of smoking on oral HPV16 clearance, and acquisition of natural immunity in men (Supplementary Methods 6.1-6.4, Supplementary Tables 12 and 13, available online). We also conducted sensitivity analyses with different herd-immunity assumptions (Supplement S6.5, available online).

Results

The 50 best-fitting parameter sets were well calibrated to US population-level data for oral HPV16 prevalence (Figure 1, A) and HPV16-positive oropharyngeal cancer incidence (Figure 1, B).

Acquisition and persistence of oral HPV16

In the absence of vaccination, the estimated incidence of oral HPV16 infection in men peaked around age 25 years (range across 50 best-fitting parameter sets = 3.6-6.0 per 1000 men) and declined thereafter through age 84 years (range = 0.3-0.5 per 1000) (Figure 2, A). The estimated median lifetime probability of acquisition of at least 1 oral HPV16 infection from ages 15 through 84 years was 10.4% (interquartile range [IQR] = 10.0%-11.2%). Incident oral HPV16 infections in men cleared rapidly initially (median clearance at 2.5 years = 71%; range = 68%-77%; at 5.5 years = 76%; range = 73%-82%) (Figure 2, B), but clearance was progressively slower in infections that persisted beyond 5 years. Consequently, accrued persistence of prevalent oral HPV16 infections increased substantially with increasing age (Figure 2, C).

Progression to HPV16-positive oropharyngeal cancer

Oral HPV16 infections that persisted for no more than 15 years seldom progressed to cancer. Thereafter, annual progression increased with increasing accrued duration and persistence and peaked around 50 years of persistence (median = 2.2%; range = 2.0%-2.6%) (Figure 3, A). Median latency from acquisition of oral HPV16 infection to progression to HPV16-positive oropharyngeal cancer diagnosis was 39 (IQR = 32-47) years (Figure 3, B). In the absence of vaccination, an estimated 70% of causal oral HPV16 infections is acquired by age 26 years, 29% acquired during ages 27 to 45 years, and almost none after age 45 years (Figure 3, C).

Sensitivity analyses

Our key results were similar in sensitivity analyses (Supplementary Methods 6, Supplementary Figures 6, A-F, 7, A-C, 8, A-C, 9, 10, 11, available online). Importantly, the proportion of causal oral HPV16 infections acquired by age 26 years changed minimally after accounting for birth cohort effects in oral sexual behaviors (70% vs 71% accounting for cohort effects).

Upper age limits for vaccination

In the absence of vaccination, an estimated 435 704 HPV16-positive oropharyngeal cancers would occur among US men aged 15-84 years (1937-2006 birth cohorts), starting in 2021 through age 85 years. Of these cancers, 64% (n = 280 800) would not be preventable under any vaccination scenario because the causal infections have already been acquired (Figure 4, A). Of the 154 904 preventable cancers, nearly all would occur in individuals aged 45 years and younger in 2021 (ie, cohorts born after 1975), including 58 869 preventable cancers in 1976-1994 cohorts and 94 581 in 1995-2006 cohorts (Figure 4, A). Of note, the numbers of preventable cancers represent the estimated maximum under the assumption of 100% vaccination up to age 45 years in 2021.

Among the 1976-2006 cohorts (ages 15-45 years in 2021) through age 85 years, status quo vaccination to age 26 years would prevent an estimated 145 357 (95%) of the 153 450 preventable HPV16-positive oropharyngeal cancers (Figure 4, B). Extending the upper age limit at status quo uptake from 26 years to ages 30, 35, 40, or 45 years would provide minimal increases in prevented cancers (relative increases = 0.1%, 0.3%, 0.5%, and 0.6%, respectively) (Figure 4, B). Vaccination of 100% of all eligible
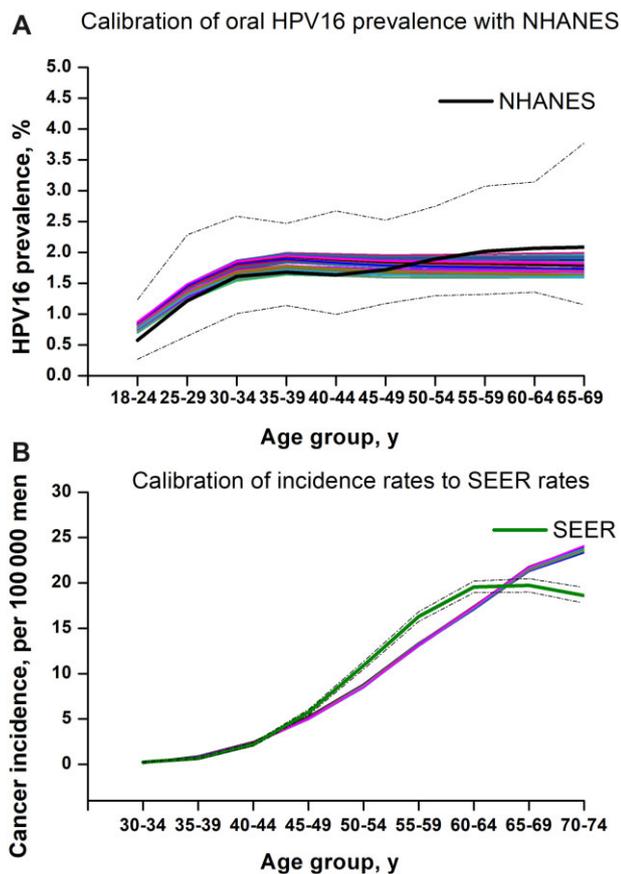
Figure 1. Model calibration to US population-level data on oral HPV16 prevalence and HPV16-positive oropharyngeal cancer incidence in US men. Model calibration to US population data: **panel (A)** shows model fit of estimated HPV16 prevalence from the 50 best-fitting parameter sets vs male oral HPV16 prevalence from NHANES 2009-2016; **panel (B)** shows model fit of estimated HPV16-positive oropharyngeal cancer incidence from the 50 best-fitting parameter sets vs male oropharyngeal cancer incidence from SEER-18 2009-2016, adjusted for the proportion estimated to be HPV16-positive. In both panels, the **dotted lines** show the 95% confidence intervals. HPV = human papillomavirus; NHANES = National Health and Nutrition Examination Survey; SEER = Surveillance, Epidemiology, and End Results.

Figure 2. Natural history (absence of vaccination) of oral HPV16 infections in US men, ages 15-84 years. Estimated oral HPV16 incidence, clearance, and duration in US men aged 15-84 years. Results are shown from the 50 best-fitting model parameter sets. **Panel (A)** shows the estimated oral HPV16 incidence in US men by age; **panel (B)** shows the estimated clearance of incident oral HPV16 infections in US men, by duration of infection (minimum, 25th percentile, mean, 75th percentile and maximum); and **panel (C)** shows the estimated duration of prevalent oral HPV16 infections in US men by age (medians and interquartile ranges). HPV = human papillomavirus.

birth cohorts in 2021 through ages 26, 30, 35, 40, or 45 years would prevent (relative to status quo vaccination to 26) an additional 1.9%, 3.0%, 4.2%, 5.1%, and 5.6%, respectively, of preventable HPV16-positive oropharyngeal cancers (Figure 4, B). However, such incremental prevention would occur with steeper number needed to vaccinate increases. Cumulatively, 100% vaccination in 2021 of all eligible birth cohorts (1976-2006) through age 45 years would prevent 8093 additional cancers when compared with status quo vaccination to age 26 years.

A birth cohort–specific approach of status quo vaccination through age 26 years for the 1995-2006 cohorts and 100% vaccination through ages 30, 35, 40, or 45 years for the 1976-1994 cohorts would prevent an additional 1.4%, 2.9%, 3.9%, and 4.4% of HPV16-positive oropharyngeal cancers, respectively, relative to status quo vaccination to age 26 years for all cohorts (1976-2006) (Figure 4, C).

Projected cancer burden

Under status quo vaccination of men to age 26 years, notable declines in the incidence of HPV16-positive oropharyngeal cancers would emerge around 20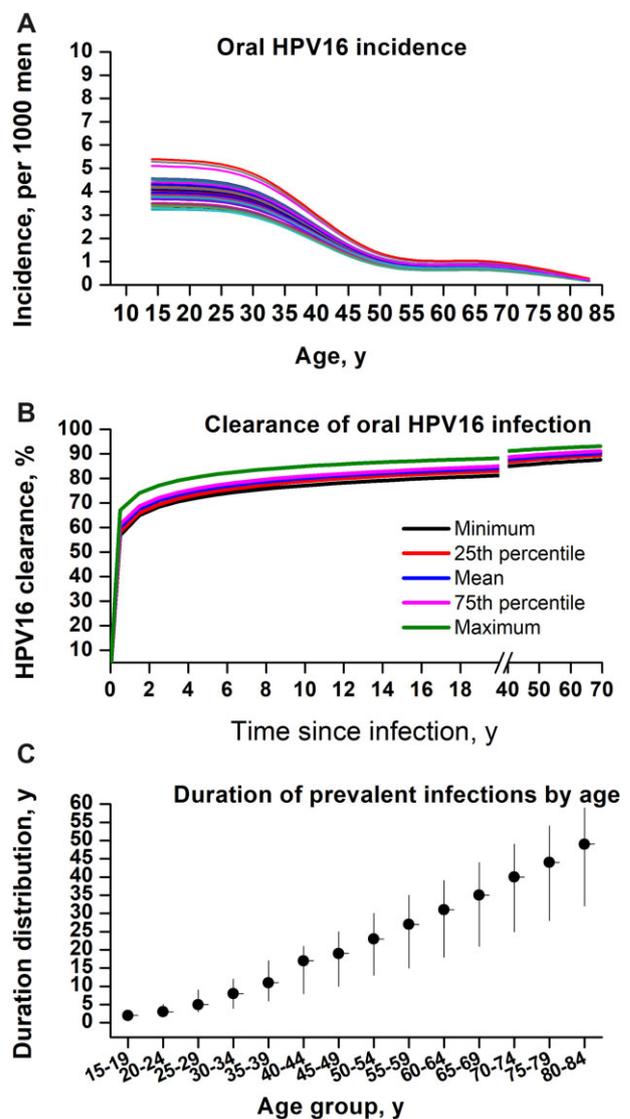35 in young men (declines of 51% and 24% at ages 40-44 and 45-49 years, respectively, vs 2021) and noticeable declines overall around 2045 (12% decline vs 2021) (Figure 5; Supplementary Methods 7, Supplementary Tables 14 and 15, Supplementary Figure 12, available online).

Discussion

Our microsimulation-based modeling study in current birth cohorts of US men aged 15-85 years (in year 2021) provides 3 key inferences. First, in the absence of vaccination, 70% of causal oral HPV16 infections are estimated to be acquired by age 26 years, 29% during ages 27-45 years, and almost none beyond age 45 years. Second, extension of the upper age limit for vaccination beyond 26 years to any age up to 45 years for current birth
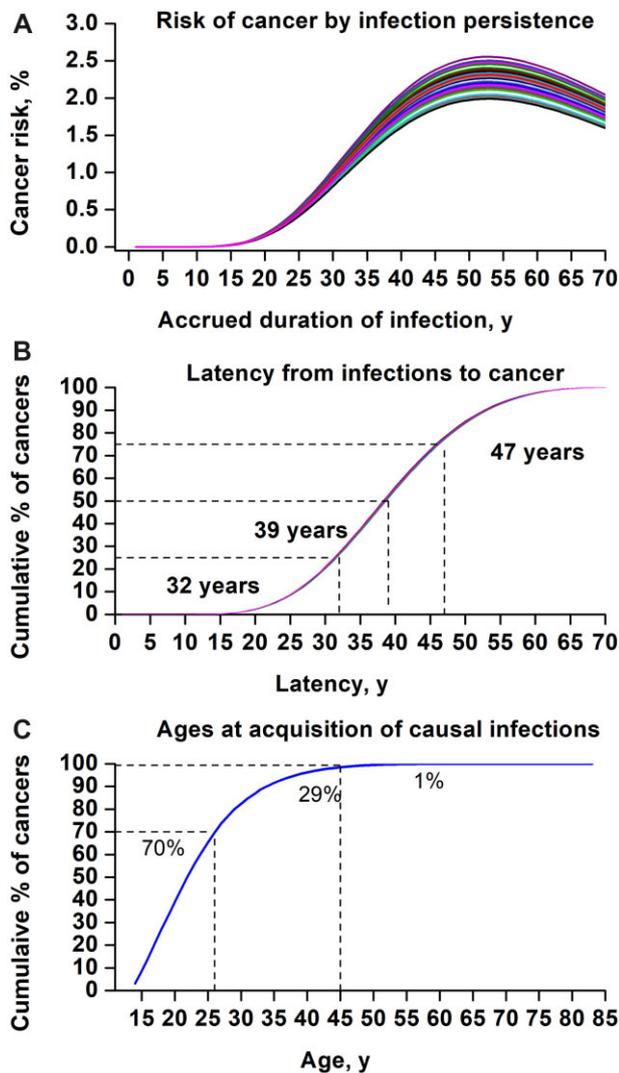
Figure 3. Natural history (absence of vaccination) of progression from oral HPV16 infections to oropharyngeal cancer in US men, ages 15-84 years. Estimated progression from oral HPV16 infection to cancer, latency from infection acquisition to cancer, and age at acquisition of causal infections in US men aged 15-84 years. Results are shown from the 50 best-fitting model parameter sets. **Panel (A)** shows the estimated 1-year progression risk from oral HPV16 infection to HPV16-positive oropharyngeal cancer in US men, by duration of infection; **panel (B)** shows the estimated latency from acquisition of oral HPV16 infection to HPV16-positive oropharyngeal cancer in US men; and **panel (C)** shows the estimated ages at acquisition of causal oral HPV16 infections in US men. HPV = human papillomavirus.

Figure 4. Estimated burden of oral HPV16-positive oropharyngeal cancer in US men under scenarios of no vaccination and different vaccination approaches. The estimated impact of HPV vaccination on the number of cases of HPV16-positive oropharyngeal cancer diagnosed in US men aged 15-84 years in 2021, with follow-up through an attained age of 85 years. Results represent mean estimates across the 50 best-fitting simulations. **Panel (A)** shows the estimated number of vaccine-preventable and not-preventable HPV16-positive oropharyngeal cancers among US men of all birth cohorts (1937-2006) aged 15-84 years in 2021 and stratified by birth cohort (1937-1975, 1976-1994 and 1995-2006). **Panel (B)** shows for US men aged 15-45 years in 2021 (1976-2006 birth cohorts) the number of cancers in the absence of vaccination; the number of cancers prevented by status quo vaccination up to age 26, 30, 35, 40 or 45 years ("preventable [status quo]"); and the additional number of cancers prevented through 100% vaccination in 2021 of men up to age 26, 30, 35, 40, or 45 years ("additional preventable [100% vaccination]," relative to status quo vaccination to each age). Also shown for each vaccination scenario are the additional percentages of cancers prevented under 100% vaccination through ages 26, 30, 35, 40, and 45 years relative to status quo vaccination up to age 26 years ("gain in preventable cancers [vs status quo (SQ) 26]") as well as the NNV to prevent 1 HPV16-positive oropharyngeal cancer under 100% vaccination through ages 26, 30, 35, 40, and 45 years relative to status quo vaccination up to age 26 years (ie,

cohorts of US men is estimated to have very low population-level benefit for prevention of HPV16-positive oropharyngeal cancers, even under scenarios of 100% vaccination. Third, even under status quo vaccination uptake through age 26 years in US men, HPV16-positive oropharyngeal cancer incidence is predicted to noticeably decrease around the year 2035 in US men aged younger than 50 years. Nonetheless, because incidence remains low at ages younger than 50 years, overall declines would start to emerge around 2045.

Our observation of low utility of HPV vaccination beyond 26 years among US men for prevention of HPV16-positive oropharyngeal cancers is consistent with 3 primarily cervix-oriented microsimulation models (21,34). These studies did not explicitly model the natural history of oral HPV or oropharyngeal cancer.
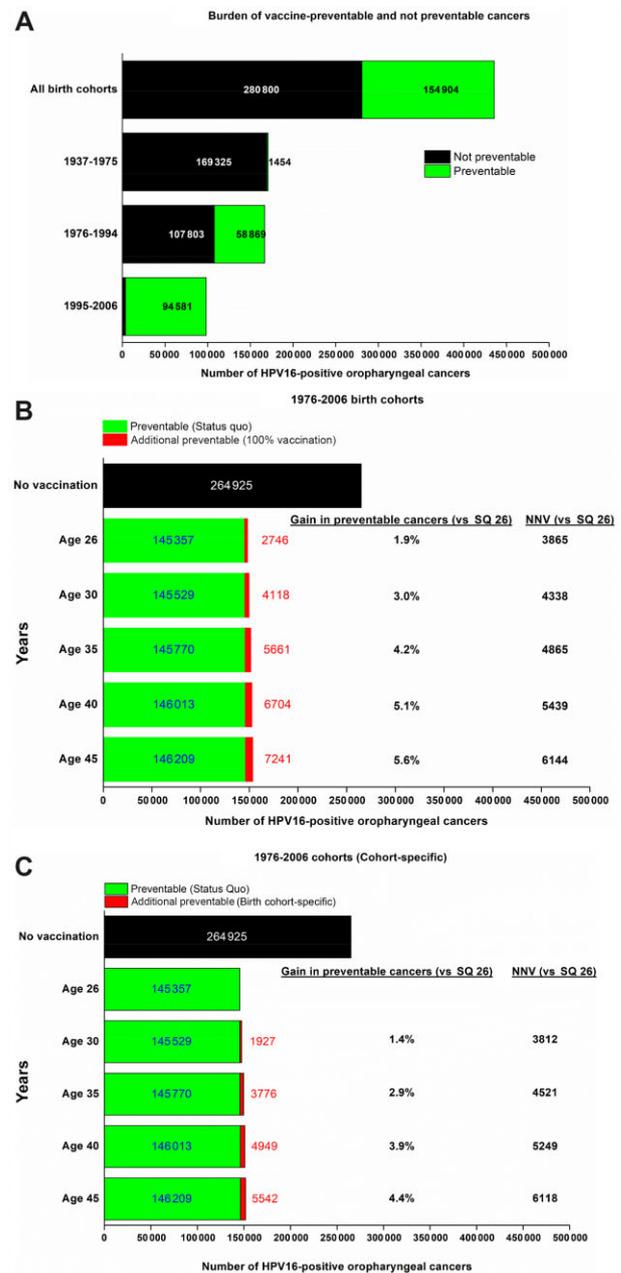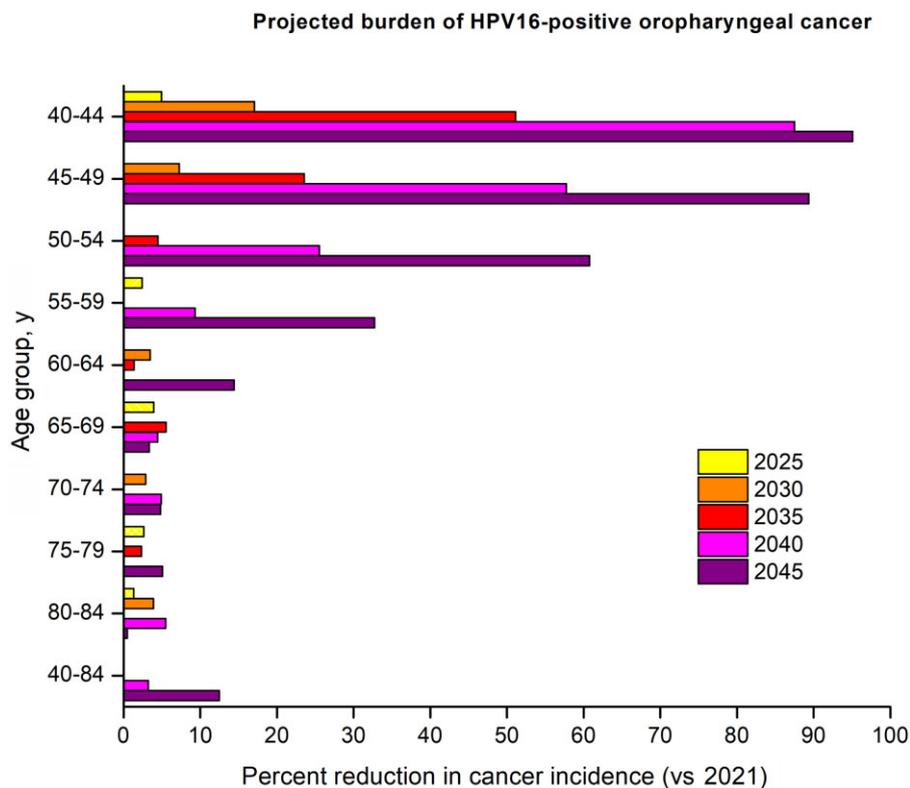
Figure 5. Projected relative burden of HPV16-positive oropharyngeal cancer in US men under status quo vaccination of men to age 26 years. Projected relative burden of HPV16-positive oropharyngeal cancers in US men aged 40-84 years, with follow-up through attained age of 85 years. Shown are mean percent reductions in cancer incidence (relative to incidence in 2021) that would be achieved through status quo vaccination of US men to age 26 years. Results are shown stratified by calendar year and attained age. HPV = human papillomavirus.

Because oropharyngeal cancer accounts for a majority of the male HPV-associated cancer burden, we undertook to specifically model the natural history of oral HPV16 and HPV16-positive oropharyngeal cancer in US men.

The low utility of extending the upper age limit arises from 3 birth cohort–specific effects. Men aged older than 45 years in 2021 (born prior to 1976) have already acquired nearly all causal oral HPV16 infections; thus, almost none of the oropharyngeal cancers in these birth cohorts are vaccine preventable. By contrast, men aged 15-26 years in 2021 (1995-2006 birth cohorts) have already achieved considerable vaccination themselves (52% in men) and also benefit substantially from herd immunity. Among men aged 27-45 years in 2021 (1976-1994 cohorts), a majority (approximately 67%) of causal infections have already

occurred, and herd effects are estimated to prevent a large proportion of vaccine-preventable cancers. Collectively, status quo vaccination to age 26 years in US men is estimated to prevent 98% of the approximately 94 500 preventable cancers in the 1995-2006 birth cohorts and 90% of the approximately 59 000 preventable cancers in the 1976-1994 cohorts.

Our observations that vaccination to age 26 years in US men at status quo uptake would prevent a substantial proportion of vaccine-preventable HPV16-positive oropharyngeal cancers and that the incidence of these cancers would decline noticeably in young men around 2035 and overall around 2045 are similar to a recent modeling study (35) but differ from another study (36). Differences in modeling methodologies could explain the contrasting results. For example, the study by Zhang et al. (36) did not account for herd effects. Of note, we show that herd effects play a major role in reducing the burden of HPV16-positive oropharyngeal cancers in US men in coming years.

Our sensitivity analyses under an extreme assumption of 25% lower herd immunity than estimated by the Harvard-HPV model indicated that vaccination of men older than 26 years may be more beneficial. However, we note 2 key considerations pertaining to vaccination of older US men. First, the ongoing HPV vaccine shortage is expected to last for approximately 5 years, underscoring the need to prioritize female vaccination globally (37). Second, the cost-effectiveness of vaccinating men aged 27-45 years would need to be considered. We refrained from such analyses because cost-effectiveness is best addressed at the person level with consideration of all HPV-associated diseases (in both sexes) rather than the anatomic site level.

Figure 4. Continued
the additional number of men vaccinated divided by the additional number of cancers prevented). **Panel (C)** shows for US men aged 15-45 years in 2021 (1976-2006 birth cohorts) the number of cancers in the absence of vaccination; the number of cancers prevented by status quo vaccination up to age 26, 30, 35, 40, or 45 years ("preventable [status quo]"); and the additional number of cancers prevented through 100% vaccination in 2021 of men from the 1976-1994 birth cohorts to each age ("additional preventable [birth cohort–specific]," relative to status quo vaccination to each age). Also shown for each vaccination scenario are the additional percentage of cancers prevented under birth cohort–specific vaccination up to ages 30, 35, 40, and 45 years relative to status quo vaccination up to age 26 years, as well as the NNV to prevent one HPV16-positive oropharyngeal cancer under birth cohort–specific vaccination up to ages 30, 35, 40, and 45 years relative to status quo vaccination up to age 26 years. HPV = human papillomavirus; NNV = number needed to vaccinate.

We note several limitations inherent to microsimulation modeling studies. In the absence of observed data on each state transition, such studies do not provide unique solutions (eg, across combinations of incidence and clearance rates) (38). Our best-fitting simulations predominantly favored low incidence–low clearance combinations, in part, because our incidence model was constrained (being based primarily on observed and reported data on probability of contact with female partners with or without genital HPV16). Our model was restricted to oral HPV16 infections and heterosexual men; however, a vast majority of the US burden of HPV-associated oropharyngeal cancers are caused by HPV16 (approximately 90%) and occurs among heterosexual men (approximately 80% of total burden in both sexes) (18,25). Strengths of our study include relevance to current US male cohorts, incorporation of the full extent of direct and herd effects from male and female vaccination, and evaluation of several key modeling assumptions. Importantly, our sensitivity analyses also examined birth cohort effects in oral sexual behaviors, the primary driver of rising HPV-positive oropharyngeal cancer incidence in US men.

Our results have public health implications. Our results underscore low benefit from extension of the upper age limit beyond 26 years for HPV vaccination among current birth cohorts of US men for the prevention of HPV16-positive oropharyngeal cancers.

Funding

Notes

Data availability

Data availability: Code and links to the datasets used in this manuscript are available from https://github.com/rebeccalandy/oral_HPV16_microsimulation.

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