Technical Appendix

Cost-effectiveness of HPV vaccination for adults through age 45 years in the United States: Estimates from a simplified transmission model

(2019 model version)

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This technical appendix was adapted from a previous version [Chesson HW, Markowitz LE, Hariri S, Ekwueme DU, and Saraiya M, "Technical Appendix: A model of the impact and cost-effectiveness of nonavalent HPV vaccination in the United States (2018 update)"] which accompanied an analysis of nonavalent HPV vaccination among young adult males [Chesson HW, Meites E, Ekwueme DU, Saraiya M, Markowitz LE. "Cost-effectiveness of nonavalent HPV vaccination among males aged 22 through 26 years in the United States." Vaccine 2018; 36: 4362–4368]. Although this version of the technical appendix has been modified to describe the incorporation of recent data and other modifications to the model, most sections of this technical appendix are similar or identical to the analogous sections of the previous version.

Contents

1 Overview of Model History and Summary of Updates to Current Version

Our deterministic and dynamic population-based model is an updated version of a model that has been used previously to examine a range of HPV vaccination strategies in the United States.[1-3]

1.1 Summary of previous model versions

In this section, we provide a brief overview of the history of the model.

1.1.1 2008 version of model

The first version of the model was published in 2008 and focused on quadrivalent HPV vaccination of young girls.[1] The original model version was static and did not account for HPV transmission dynamics. However, the published results did include some scenarios in which "herd effects" were incorporated by simple assumptions about the degree of the effect of herd immunity. Specifically, the "herd effects" scenarios were calculated by assuming an additional impact of the vaccine on non-vaccinated persons, rather than modeling HPV transmission dynamics. The analysis incorporated the effects of female vaccination on genital warts in males, but cancers in males were not included.

1.1.2 2011 version of model

The second version of the model was expanded to include HPV transmission dynamics, and was used in 2011 to examine quadrivalent HPV vaccination of males.[2] Another important change to the model was the inclusion of additional health outcomes, most importantly HPV-associated cancers in males (anal, penile, and oropharyngeal). The model was also expanded to include the potential for HPV vaccination to prevent juvenile-onset recurrent respiratory papillomatosis (RRP) in the children of vaccinated mothers.

1.1.3 2016 version of model

The third version of the model was expanded to include the additional HPV types in the nonavalent HPV vaccine, and was used in 2016 to examine the cost-effectiveness of nonavalent HPV vaccination vs. quadrivalent HPV vaccination in the US.[3] This third version of the model was also applied (along with a much more complex individual-based model referred to as "HPV ADVISE") in a 2016 study of the cost-effectiveness of providing nonavalent HPV vaccine to females who had previously received the quadrivalent vaccine.[4]

1.1.4 2018 version of the model

In 2018, the model was applied to estimate the incremental cost-effectiveness of HPV vaccination of males aged 22–26 years.[5] In this 2018 application, the model had the same structure as the 2016 version, but included updated values for certain parameters: vaccine cost, vaccination coverage, and medical treatment costs, which were updated for inflation. Also, the methods for the sensitivity analyses were modified. Specifically, we applied more realistic distributions of the parameter values in the multivariate sensitivity analyses (e.g., we used the lognormal distribution for cost parameters rather than a uniform distribution, as described in Section 4).

1.2 2019 version of the model

For the 2019 application of the model, we made four key changes. First, we modified the manner in which HPV acquisition probabilities were applied in the model so that the model can more closely approximate scenarios in which there is re-infection with HPV (see Section 1.2.1). Second, we updated vaccine cost assumptions and medical treatment cost assumptions as described below in Sections 1.2.2 and 1.2.3. Of note, the cancer treatment cost estimates we

applied in the 2019 version were notably higher than in previous model versions, owing to the incorporation of recent, higher cancer treatment cost estimates from studies identified in a systematic literature review.[6] We also modified the cost assumptions for genital warts as described in Section 1.2.3.2. Third, we added an additional HPV-associated health outcome to the model: adult-onset recurrent respiratory papillomatosis (AORRP) as noted in Section 1.2.4. Thus, the 2019 version of the model includes AORRP and juvenile-onset RRP (JORRP), whereas previous versions included JORRP. Fourth, we modified the incidence rates of CIN as described in Section 3.4.1. The new values are slightly higher than before and more consistent with data published since our previous model application. However, other than these four main changes, the model has the same structure as the 2018 version and the 2016 version.

1.2.1 Modifying the application of annual HPV acquisition probabilities

As described in more detail in our full description of the model (Section 2), one of the key simplifications of the model is that the natural history of HPV is not explicitly modeled. Instead, the model approximates the relative reduction in HPV disease due to vaccination based on the relative reduction in cumulative HPV 16 acquisition due to vaccination (we will call this "Approximation 1"). We have described the model in the past as assuming 100% natural immunity, but perhaps a better description would be that "Approximation 1" is most accurate when there is 100% natural immunity but becomes less precise in scenarios without 100% natural immunity as re-infection increases.

To reduce the potential bias of "Approximation 1", we modified how the model applies the annual probabilities of acquiring HPV. Because the model approximates the effects of vaccination based on relative, not absolute, changes in cumulative HPV acquisition, we can apply lower absolute values for the annual HPV acquisition probabilities without changing the

relative age distribution of the annual HPV acquisition probabilities. Specifically, in this revised version of the model, we now divide all the annual HPV acquisition probabilities by 1000 before applying them in the model. This division by 1000 does not change the age distribution of the probability of HPV acquisition for those not yet infected (Appendix Figure 1), but greatly reduces the cumulative lifetime incidence of each HPV type. In the example of HPV 16, cumulative lifetime incidence was about 50% using the original HPV 16 acquisition probabilities, but less than 1% when applying the modified (divided by 1000) values. Because the model approximates the effects of vaccination against HPV 16 based on relative not absolute changes in cumulative HPV 16 acquisition resulting from vaccination, the absolute value of cumulative HPV 16 acquisition is not particularly important. However, the benefit of the modified (divided by 1000) values is that because so few people are ever infected (cumulative lifetime incidence <1%), the bias created by not accounting for the possibility of re-infection is greatly reduced.

This reduction in potential bias is illustrated in Appendix Figure 2. For this illustration, we calculated cumulative lifetime HPV 16 acquisition acquired by age under the previous model assumptions (orange line) and when using the revised model in which the annual HPV acquisition probabilities were divided by 1000 (blue line). We also calculated the cumulative percentage of lifelong HPV 16 infections acquired by a given age when applying the HPV 16 acquisition probabilities as in the previous version of the model (that is, not divided by 1000), assuming that re-infection of HPV 16 is possible (such that HPV 16 acquisition is possible every year regardless of past HPV 16 acquisition), and assuming that 20% of HPV 16 infections are lifelong. This assumption of 20% was chosen for illustrative purposes, as when more realistic values of the percent of HPV 16 infections that are lifelong (such as 10%, 5%, 1%, or less) are

assumed, the black line and blue line in Appendix Figure 2 are practically indistinguishable from one another. Under these assumptions, cumulative acquisition of a lifelong HPV 16 infection by age a ($Lifelong_a$) was calculated as: $Lifelong_a = (0.2)\lambda_a(1-Lifelong_{a-1})+ Lifelong_{a-1}$, where λ_a is the annual probability of acquiring HPV 16 at age a, and $Lifelong_{12}$ was set to 0.

Relative reductions in HPV outcomes such as cervical cancer in our model are approximated based on relative reductions in cumulative HPV acquisition. Under the assumptions in this illustrative scenario, cumulative HPV 16 acquisition in the revised model (shown by the blue line in the figure) provides a close approximation of cumulative acquisition of lifelong HPV 16 acquisition in a scenario in which there is re-infection with HPV 16. Thus, this model adjustment is expected to substantially reduce the bias from "Approximation 1" in the estimation of the direct benefits of vaccination in reducing HPV-associated health outcomes.

1.2.2 Vaccine cost assumptions

For vaccination up to and including age 18 years, the base-case vaccine cost per 3-dose series, including administration costs, was $636 (range: $530–$742). We assumed the vaccine cost per dose was $168.10 (public) and $217.11 (private) based on the CDC pediatric vaccine price list (https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html) as of December 16, 2018. The cost of administration per dose was assumed to be $8.44 public and $30.09 private, based on estimates of the administrative costs for pneumococcal conjugate vaccine.[7] The base case value reflects an average of the public and private costs, and the range was calculated using the public costs (lower bound) and the private costs (the upper bound). The cost of a 2-dose series (for vaccination started through age 14 years) was two-thirds that of the 3-dose series.

For vaccination at age 19 years and older, the base-case vaccine cost per 3-dose series, including administration costs, was $714 (range: $530–$742). We assumed the vaccine cost per dose was $144.18 (public) and $217.11 (private) based on the CDC adult vaccine price (https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html) list as of December 16, 2018. The base case value was calculated assuming that the private costs are applicable in 90% of adult vaccinations, and we applied the same range of values ($530–$742) as for ages 18 years and under.

1.2.3 Updates of medical treatment cost estimates

All medical treatment costs were updated to third quarter 2018 U.S. dollars using the health care component of the Personal Consumption Expenditures price index (http://www.bea.gov).[8] The medical treatment cost estimates for cervical intraepithelial neoplasia (CIN), penile cancer, and JORRP were obtained from the 2018 version of the model,[3] updated for inflation. The medical treatment costs for other HPV-associated cancers, genital warts, and AORRP are described below. See Section 3.3 for additional information on the direct medical costs applied in the model.

1.2.3.1 Updated cancer cost estimates

We incorporated new data regarding the treatment costs of HPV-associated cancers from the publications identified in a recent literature review.[6] In that review, cost estimates based on commercially-insured populations were higher than the cost estimates based on Medicare data, a pattern that was also reported in a study of oral, oral pharyngeal, and salivary gland cancers.[9]

Our general approach to updating the cancer cost estimates was as follows. For cancer sites in which two cost estimates were available in the literature review (anal cancer and oropharyngeal cancer), we applied the lower of the two available estimates as the lower bound

value, the higher of the two available estimates as the upper bound value, and the average of the two available estimates (a weighted average in the case of oropharyngeal cancer) as the base case value. For cancer sites in which only one cost estimate was available in the literature review (cervical cancer, vaginal cancer, and vulvar cancer) the estimate from the literature review was combined with the base case estimate from our 2018 version of the model. Specifically, the previous base case estimate from the 2018 version of the model was applied as the new lower bound, and the cost estimate from the literature review was applied as the new upper bound. The new base case value was calculated as a weighted average of the previous base case estimate from the 2018 version of the model (25% weight) and the cost estimate from the literature review (75% weight). Details for the cost estimates we applied for each cancer are below.

1.2.3.1.1 Cervical cancer costs

We used our previous base case estimate from the 2018 version of the model ($43,500 in 3Q 2018 US dollars) as the new lower bound value. We applied the average cost estimate of $82,500 from the Lairson et al. (2017) study as the new upper bound value.[10] The new base case value of $72,800 was calculated as the weighted average of these two estimates: (0.25 x 43,500) + (0.75 x 82,500).

1.2.3.1.2 Oropharyngeal cancer costs

From the literature review of cancer costs, the estimated cost of oropharyngeal cancer was $146,900 in the study that used a commercially-insured population[11] and $65,400 in a study that used Medicare payment schedules.[12] We applied $65,400 as the new lower bound value and $146,900 as the new upper bound value. We applied $126,500 as the new base case value, which reflects a weighted average of the two source studies, with a 75% weight on the $146,900 estimate and a 25% weight on the $65,400 estimate. We applied the 75% weight to the higher

estimate ($146,900) because this estimate was more recent and included actual cost data (instead of cost calculations based on fee schedules).

1.2.3.1.3 Vaginal cancer costs

We used our previous base case estimate from the 2018 version of the model ($30,300 in 3Q 2018 US dollars) as the new lower bound value. We applied the average cost estimate of $145,200 from the Fu et al. (2018) study as the new upper bound value.[13] The new base case value of $116,500 was calculated as the weighted average of these two estimates: (0.25 x 30,300) + (0.75 x 145,200).

1.2.3.1.4 Vulvar cancer costs

We used our previous base case estimate from the 2018 version of the model ($26,400 in 3Q 2018 US dollars) as the new lower bound value. We applied the average cost estimate of $59,700 from the Fu et al. (2018) study as the new upper bound value.[13] The new base case value of $51,400 was calculated as the weighted average of these two estimates: (0.25 x 26,400) + (0.75 x 59,700).

1.2.3.1.5 Anal cancer costs

The estimated cost of anal cancer was $134,100 in the study of a commercially-insured population[11] and $53,000 in a study that used SEER-Medicare data.[12] We applied $53,000 as the new lower bound value and $134,100 as the new upper bound value. The new base case value of $93,600 was calculated as the average of $53,000 and $134,100.

1.2.3.1.6 Penile cancer costs

The systematic literature review yielded no recent studies on the cost of penile cancer in the United States.[6] We applied the same base case value and range that we applied in the 2018

version of the model. With the adjustment for inflation, the base case cost (range) for penile cancer was updated to $22,200 ($11,000–$43,500).

1.2.3.1.7 A note on the new base case cost estimates for cancers

For cervical cancer, vaginal cancer, and vulvar cancer, our base case cost estimate was a weighted average of our previous cost estimate (25%) and the higher, updated cost estimate from the literature review (75%). We opted not to use an unweighted average because we wanted to emphasize the more recent cost data. However, we opted not to use the updated cost estimate from the literature review as the base case value, because the updated cost estimate for each of these cancers was based on a commercially insured populations, which could over-estimate the costs in other populations.

For anal cancer, we applied an unweighted average of two updated cost studies from the literature review. We used an unweighted average because these two studies were both recent (2018) and each used a different population.

For oropharyngeal cancer, we applied a weighted average of two updated cost studies from the literature review. As noted previously, we applied the 75% weight to the higher estimate ($146,900) because this estimate was more recent and included actual cost data (instead of cost calculations based on fee schedules).

To supplement the average cost per case estimates from the recent cost studies for cervical, oropharyngeal, vaginal, and vulvar cancers,[10,13,14] we obtained median costs estimates from David Lairson (personal communication, 8/14/2018), one of the authors of these recent studies. The median two-year cost estimates (updated to 3Q 2018 US dollars) were as follows: $66,100 for cervical cancer; $113,100 for vaginal cancer; $42,100 for vulvar cancer, and $143,200 for oropharyngeal cancer. Because the median values are not influenced by the low

and high cost outliers (which might be reflective of limitations of medical claims data than of actual patient experiences), the median values might be a better representation of the cost of care to a typical patient.[15]

We note that the weighted averages we applied for the base case values for the cost of these cancers are generally consistent with these median cost estimates. Had we used unweighted averages for the base case values, the resulting base case values for vaginal cancer and oropharyngeal cancer would each be more than 20% lower than the median cost estimates noted above.

1.2.3.2 Updated genital warts costs

We updated the genital warts cost assumptions as follows. The new base case value was obtained from Hoy et al. (2009)[16] and updated for inflation. This is the same source as used in the previous model version, except that we no longer adjust the cost downward to account for the possibility that treatment is not sought.

The new lower bound value was calculated as 50% of the base case value, and is consistent with the cost reported in the Hoy et al. (2009) study for males up to age 19 years, the group with the lowest average cost per case.

The new upper bound value incorporates information from Dahlstrom et al. (2018), which estimated the cost per case of genital warts at $7,060.[17] We did not incorporate this new estimate in our base case value, but instead used it to inform our upper bound value. Our main reason for not including the Dahlstrom estimate as our base case value was that it was not based on the average patient with genital warts, but instead was based on a subset of patients with recurring genital warts. That is, the inclusion criteria for the Dahlstrom study, which included

"two outpatient claims (at least 30 days apart) with a primary or secondary diagnosis as genital warts," could bias the cost estimate upward by censoring those with only 1 visit.

We calculated the new upper bound value for the cost of genital warts as follows. In the Hoy et al. (2009) study, the average number of visits per episode of care was 1.5 for females and 1.9 for males, suggesting that many patients will have less than 2 visits. If half of patients incur the $860 base case cost and half incur the $7,060 cost suggested by the Dahlstrom study, the average cost per case would be $3,960. In the Hoy et al. (2009) study, however, the cost per case was $1,620 among females aged 60–64 years, the group with the highest average cost per case, suggesting $1,620 as a reasonable upper bound value. We applied $2,790 as the new upper bound value, calculated as the average of $3,960 and $1,620.

1.2.4 Incorporation of adult-onset recurrent respiratory papillomatosis

In this application of the model, we add adult-onset recurrent respiratory papillomatosis (AORRP) as one of the possible adverse health outcomes that can be prevented by HPV vaccination.

1.2.4.1 Cost of adult-onset recurrent respiratory papillomatosis (AORRP)

We could find no published estimates of the lifetime cost of AORRP. Typically, JORRP follows a more aggressive course than AORRP.[18] One study of 32 patients found that the average number of procedures needed per patient was 4.5 for those with age of onset of 20 years or later compared to 16 for those younger than age 20 years at onset.[19] Based on this study, the relative burden of procedures needed for AORRP to that of JORRP was about 28% (4.5 divided by 16). In another study, the percentage of cases classified as aggressive (vs. non-aggressive) was 74% for JORRP vs. 29% for AORRP, suggesting that AORRP was about 40% as likely as JORRP to be classified as aggressive.[20] Based on these two studies of the AORRP burden relative to

JORRP, we assumed that the cost and quality of life impact of AORRP would be 40% that of JORRP.

So, we applied a base case lifetime cost of AORRP equal to 40% of the estimated base case lifetime cost of JORRP. We used an analogous approach to generate a lower bound estimate for the cost of AORRP. In order to capture the uncertainty in our 40% adjustment factor, we allowed for an upper bound scenario in which the lifetime cost of AORRP was the same as the lifetime cost of JORRP, and applied the same upper bound value for AORRP as we applied for JORRP. The resulting base case value (range) for the lifetime cost of AORRP was $47,100 ($22,600–$433,700). Of note, to replicate this result, the corresponding values presented for JORRP (base case $149,300, range: $71,700–$385,300) must be multiplied by $(1.03)^4$, because the JORRP values as reported in this Technical Appendix have been discounted (at 3% annually) for the 4-year period from birth to onset of JORRP.

1.2.4.2 Quality of life impacts of AORRP

As noted in our description of cost assumptions for AORRP, we assumed that on average AORRP would be about 40% as severe as JORRP. We thus assumed the base case number of QALYs lost per case of AORRP was 40% that of JORRP. We used an analogous approach to estimate the lower bound value for the number of QALYs lost per case of AORRP. In order to capture the uncertainty in our 40% adjustment factor, we allowed for an upper bound scenario in which the lifetime number of QALYs lost per case of AORRP was the same as for JORRP. The resulting base case value for the lifetime number of QALYs lost per case of AORRP was 0.47 (range: 0.15–3.43). Of note, to replicate this result, the corresponding values presented for JORRP (base case 1.05, range: 0.33–3.05) must be multiplied by $(1.03)^4$, because the JORRP

values as reported in this Technical Appendix have been discounted (at 3% annually) for the 4-year period from birth to onset of JORRP.

1.2.4.3 Incidence or AORRP in the absence of HPV vaccination

A 1995 study estimated RRP incidence rates per 100,000 of 4.3 among children and 1.8 among adults.[21] However, this 1995 study used extrapolation methods that might have resulted in an overestimation of RRP incidence rates.[22] To calculate AORRP incidence rates, we used the relative rate of AORRP incidence (vs. JORRP incidence). That is, we calculated that the rate of AORRP would be about 40% of the rate of JORRP (calculated as 1.8 divided by 4.3). Thus, the incidence rates we applied for AORRP were calculated by multiplying the incidence rates for JORRP by 40%. Of note, it is coincidence that our assumption of the relative severity of AORRP to JORRP (40%) matches our assumption of the relative frequency of AORRP to JORRP (40%); these two assumptions were based on different data sources as described above.

1.2.4.4 Percentage of AORRP attributable to HPV 6/11

As with our assumptions for JORRP, we assumed that 90% of AORRP was attributable to HPV 6/11.

1.2.5 Revised assumptions regarding CIN incidence

The fourth main change in the 2019 version of the model is that the CIN incidence rates we applied were modified as described in Section 3.4.1. Further, in previous model versions, we assumed that vaccine-attributable reductions in CIN 1 and CIN 2/3 were not possible until at least 1 and 2 years, respectively, following vaccine-attributable reductions in HPV incidence (see Section 2.4.2). In this application of the model, we did not impose this restriction, as studies

have demonstrated that progression from infection to CIN 1 or CIN 2/3 is possible within one year.[23]

2 Model Description

Our model is a deterministic, dynamic population-based model. All results presented in the manuscript and in this appendix were calculated using Excel 2016 (Microsoft Corporation).

2.1 Perspective, time frame, and model population

2.1.1 Perspective

We used a health care system perspective and included costs and benefits of vaccination without regard to who incurs the costs or who receives the benefits. The costs and benefits we included were limited to the direct costs of vaccination, the direct medical costs averted by vaccination, and the QALYs saved by vaccination. Other potential costs and benefits (e.g., productivity costs, patient time and transportation costs) were not included in this analysis.

2.1.2 Time horizon and analytic horizon

We examined the first 100 years of an HPV vaccination program (time horizon). The benefits of HPV-associated disease cases averted during the first 100 years of the vaccination program were allowed to accrue over the lifetime of the affected people (analytic horizon). The time horizon and analytic horizon are illustrated in Appendix Figure 3.

2.1.3 Discounting and base year of costs

All future costs and benefits were discounted at 3% annually, consistent with US cost-effectiveness recommendations[24] and with previous studies of the cost-effectiveness of HPV

vaccination.[2,25,26] For additional details regarding the discounting of future costs and benefits, see Sections 3.3.1 and 3.6.1. All costs are presented in 3Q US dollars.

2.1.4 Model population

We modeled 191 birth cohorts, including the 92 cohorts between the ages of 8 years and 99 years (inclusive) in year one of the vaccine program and the subsequent 99 cohorts of incoming 8-year-olds in years 2 through 100 of the vaccine program. In each year, we focused on those aged 8 through 99 years in the given year; benefits of vaccination to those under age 8 years or over age 99 years in the given year were not included in calculations for the given year. Each cohort of 8-year-olds consisted of 2 million boys and 2 million girls, such that the population aged 8–99 years in our model was 285,524,128 when applying the annual mortality rates in Appendix Table 36.

2.2 Overview of three main simplifying features of the model

Compared to other published models on the impact and cost-effectiveness of HPV vaccination strategies,[25-29] our model is relatively simple and requires fewer parameter values. Our approach uses three main simplifying features in approximating the impact of HPV vaccination: not explicitly modeling the natural history of HPV; not explicitly modeling cervical cancer screening; and using a simple approximation of HPV transmission dynamics. These simplifying features are explained in more detail below.

2.2.1 Approximating the impact of HPV vaccination

In estimating the impact of HPV vaccination, we did not explicitly model the natural history of HPV (e.g., the transition from HPV acquisition to HPV-associated health outcomes). Instead, the number of disease cases averted by vaccination for a given age cohort in a given year

was approximated based on the percentage reduction in cumulative lifetime exposure to HPV in the given year for the given age cohort (described in more detail in Section 2.4).

2.2.2 Cervical cancer screening not explicitly modeled

Our approach does not explicitly model cervical cancer screening activities. Instead, we assume that the observed rates of cervical intraepithelial neoplasia (CIN) and cervical cancer applied in the model (those that have occurred in the context of current and historical cervical cancer screening practices in the US) would remain constant over time in the absence of HPV vaccination. Because we did not explicitly incorporate cervical cancer screening in our model, we cannot assess the impact of changing cervical cancer screening strategies. Thus, our model provides an assessment of the potential impact and cost-effectiveness of HPV vaccination in a scenario in which the probability of detection through screening remains constant over the duration of the HPV vaccine program.

2.2.3 Simplified transmission model

We used a relatively simple approach to depict the indirect effects ("herd effects") of vaccination. For example, we employed a discrete-time approach in which the impact of vaccination was modeled as a sequence of 1-year transitions among four mutually exclusive classes as described in Section 2.3. That is, we used a one-year time step. As another example, we did not classify the population according to sexual activity level (e.g., rate of sex partner change). Instead, we assumed that in each year all people were subject to a sex- and age-specific probability of acquiring a specific HPV type. As described in Section 2.3.2.1, these sex- and age-specific HPV acquisition probabilities were adjusted each year in accordance with sex- and age-specific reductions in HPV in the population.

2.3 Description of the model

The model is described below in detail for HPV 16. The benefits of vaccination against other HPV vaccine types (18, 31, 33, 45, 52, 58, and 6/11) were calculated in an analogous manner as summarized in Section 2.4.3.

2.3.1 Model classes

Each age cohort was divided into four classes, based on vaccination status ("vaccinated" and "not vaccinated") and HPV 16 exposure status ("never infected" and "ever infected") as illustrated in Appendix Figure 4. The four possible classes are: (1) Not vaccinated; never acquired HPV 16, denoted as class X; (2) Vaccinated, never acquired HPV 16, denoted as class V; (3) Not vaccinated, acquired HPV 16 (ever), denoted as class Y; and (4) Vaccinated, acquired HPV 16 (ever), denoted as class Z. Movement occurs between the classes according to age-specific probabilities of acquiring HPV 16 and probabilities of being vaccinated. Vaccination reduces the probability of acquiring HPV 16 according to the vaccine efficacy assumptions.

Those in the "not vaccinated, acquired HPV 16" class cannot move to the "not vaccinated, never acquired HPV 16" class, and those in the "vaccinated, acquired HPV 16" class cannot move to the "vaccinated, never acquired HPV 16" class. The model does not keep track of HPV 16 prevalence. Instead, for each sex-specific birth cohort, the model keeps track of the percentage that have every acquired HPV 16. That is, the model keeps track of susceptible and "ever infected" without regard to whether or not the "ever infected" can recover, and if so, whether or not they can be susceptible again.

2.3.2 Model equations

Each year, a cohort of 2 million 8-year-old boys and 2 million 8-year-old girls enters the model in the "not vaccinated, never acquired HPV 16" class and the cohort of 99-year-old men

and women turns 100 and exits the model. Under the mortality rates described in Appendix Table 36, the resulting size of the population aged 8–99 years is 285,524,128, or a total population of about 318 million when including cohorts younger than age 8 years of roughly the same size as the 8-year-old cohort. For each year t of the 100 years of the vaccination program, the model tracks cumulative HPV 16 exposure through year t for each age cohort (8–99 years) by sex. In each year, cumulative HPV 16 exposure for each age cohort in the scenario of HPV vaccination is compared to what it would have been in the absence of a vaccination program. Age-specific HPV 16 acquisition probabilities in year t+1 are adjusted proportionately according to reductions in cumulative HPV 16 exposure in year t in the opposite sex, to reflect changes in HPV prevalence in sex partners as a result of HPV vaccination.

These calculations are described in the equations below, in which k denotes sex (1 = female, 2 = male), a denotes age (in years, from ages 8–99), and t denotes year of vaccination program (year 0 through 100). For year 0 (the year before onset of the vaccination program in year 1), the percentage of each age cohort in the "Not vaccinated; never acquired HPV 16" class and the "Not vaccinated, acquired HPV 16 (ever)" class was calculated based on the cumulative probability of acquiring HPV 16 for sex k by age a in the absence of vaccination. The distribution of each age cohort into the four classes (X, Y, V, and Z as defined above and in Appendix Figure 4) was calculated as follows:

$$X_{k,a,t} = X_{k,a-1,t-1}(1-\theta_{k,a,t})(1-\lambda_{k,a,t})$$

$$Y_{k,a,t} = X_{k,a-1,t-1}(1-\theta_{k,a,t})\lambda_{k,a,t} + Y_{k,a-1,t-1}(1-\theta_{k,a,t})$$

$$V_{k,a,t} = X_{k,a-1,t-1}(\theta_{k,a,t})(1-\lambda_{k,a,t}(1-E_k)) + V_{k,a-1,t-1}(1-\lambda_{k,a,t}(1-E_k))$$

$$Z_{k,a,t} = Z_{k,a-1,t-1} + V_{k,a-1,t-1}(\lambda_{k,a,t})(1-E_k) + Y_{k,a-1,t-1}(\theta_{k,a,t}) + X_{k,a-1,t-1}(\theta_{k,a,t})\lambda_{k,a,t}(1-E_k),$$

and $X_{k,7,t} = 1$, $Y_{k,7,t} = 0$, $V_{k,7,t} = 0$, $Z_{k,7,t} = 0$,

where $\theta_{k,a,t}$ is the annual probability of receiving HPV vaccination for sex k at age a in year t, E_k is vaccine efficacy against HPV 16 acquisition for sex k, and $\lambda_{k,a,t}$ is the annual probability of acquiring HPV 16 for sex k at age a in year t. The probability of acquiring HPV 16 ($\lambda_{k,a,t}$) was calculated as $\lambda_{k,a,t} = P_{k,a,}(1 - A_{k,a,t})$, where $P_{k,a}$ is the sex- and age-specific annual HPV 16 acquisition probability in the absence of vaccination (Appendix Table 34), and $A_{k,a,t}$ is an adjustment term to account for population-level changes in HPV prevalence as described in Section 2.3.2.1.

2.3.2.1 Adjustment term (A)

The adjustment term $A_{k,a,t}$ accounts for changes in HPV prevalence in the population due to HPV vaccination and was calculated based on changes in cumulative exposure to HPV 16 in the population, where we defined cumulative exposure to HPV 16 at a given age to be the probability of having acquired HPV at or before the given age. The reduction in cumulative exposure for sex k at age a in year t ($C_{k,a,t}$) was calculated as $C_{k,a,t} = 1 -(\bar{e}_{k,a,t}/e_{k,a,t})$, where $e_{k,a,t}$ is the cumulative exposure to HPV 16 for sex k at age a years in the absence of an HPV vaccination program, and $\bar{e}_{k,a,t}$ is the cumulative exposure to HPV 16 for sex k at age a years in year t of the vaccination program.

The adjustment term was calculated as $A_{k,a,t} = (1-\varepsilon)\dot{C}_{k',a,t-1} + \varepsilon\hat{C}_{k',a,t-1}$, where $\dot{C}_{k',a,t-1}$ is the average of $C_{k',a-5,t-1}$ through $C_{k',a+5,t-1,}$(that is, the average value of C for those of sex k' within 5 years of age a, excluding those younger than age 8 years or older than age 99 years), $\hat{C}_{k',a,t-1}$ is the average of $C_{k',a,t-1}$ for ages 8 years through 99 years (i.e., the average of $C_{k',8,t-1}$ through $C_{k',99,t-1}$), and k' refers to the opposite sex from k. The term ε was used to reflect sexual mixing across age groups, where ε = 1 corresponds to random mixing by age group and ε = 0 corresponds to assortative mixing by age group such that all of a person's sex partners are within

5 years of age of that person. We used $\varepsilon = 0.1$ to reflect the fact that mixing by age group tends to be assortative.[25,30,31] We did not specifically vary ε in the sensitivity analyses presented in the main manuscript, but the estimated impact of vaccination was varied in the probabilistic sensitivity analyses to reflect uncertainty in a range of factors, including ε.

2.4 Description of calculations of vaccine impact

2.4.1 Deaths from other causes

For simplicity, the same age- and sex-specific death rates were applied to all classes (X, Y, V, and Z), such that the number of people in each cohort decreased from year to year due to death, but death did not influence the age and year-specific percentage of the population in each class. We made this simplifying assumption because HPV-attributable mortality is a very small fraction of overall mortality. The death rates we applied are listed in Appendix Table 36.[32]

2.4.2 Reduction in HPV 16 related health outcomes

Reductions in HPV 16-associated cervical cancer, for women of age a in year t of the vaccination program, were calculated as $R_a\ (POP_{a,t}/100{,}000)(ATTRIB_{16})C_{1,a\text{-}lag,t\text{-}lag}$ where R_a is the rate of cervical cancer (per 100,000) in age group a in the absence of vaccination, $POP_{a,t}$ is the number of females in age group a at time t, $ATTRIB_{16}$ is the percentage of cervical cancer attributable to HPV 16, $C_{1,a,t}$ is the reduction in cumulative infection with HPV 16 due to vaccination as described above, and *lag* is a disease-specific lag term. This lag term was included to establish a minimum time between vaccination and the prevention of a given health outcome. Although protection against the HPV vaccine types was assumed to begin after completion of the vaccine series, we applied the lag term so that the adverse health outcomes averted by vaccination would accrue over a plausible time frame. For cervical and other cancers (including cancers in males), we used a minimum lag time of 5 years such that reductions in

cancer for a given age cohort would not be observed in the first 5 years in which members of that cohort were vaccinated.

The number of cases of other HPV 16-related health outcomes (other cancers, CIN 1, CIN 2/3) averted by vaccination were estimated in a manner analogous to that for cervical cancer. However, the lag term we applied was 0 for CIN 1, CIN 2/3, adult-onset RRP, and genital warts.

2.4.3 Reductions in health outcomes attributable to other HPV types

The reduction in the number of cases of health outcomes attributable to other high-risk HPV types (18, 31, 33, 45, 52, and 58) was estimated in a manner analogous to that of HPV 16-related health outcomes. Similarly, the reduction in the number of cases of HPV 6- and HPV 11-related health outcomes attributable to vaccination was estimated in the same fashion, except that HPV 6 and HPV 11 were treated as if they were a single HPV type ("HPV 6/11"). To clarify, we estimated eight versions of the model described above, in order to estimate reductions in health outcomes attributable to (1) HPV 16, (2) HPV 18, (3) HPV 31, (4) HPV 33, (5) HPV 45, (6) HPV 52, (7) HPV 58, and (8) HPV 6/11. These eight reductions in health outcomes were combined to estimate the impact and cost-effectiveness of HPV vaccination, according to the efficacy assumptions against each type for the given HPV vaccine.

2.4.4 Benefits of preventing JORRP

We assumed HPV vaccination would reduce juvenile-onset RRP (JORRP) in children of vaccinated mothers, and these potential benefits of preventing JORRP were approximated as described elsewhere.[33] Briefly, we applied the following age-specific birth rates (per 1000 women): 10- 14 years, 0.4; 15–17 years, 14.1; 18–19 years, 51.4; 20–24 years, 83.1; 25–29 years, 106.5; 30–34 years, 97.3; 35–39 years, 48.3; 40–44 years, 10.4.[34] Base case values related

to the cost and quality-of-life impact of JORRP are described elsewhere in this appendix but are summarized here for convenience. We applied a base case value 0.735 per 100,000 (range: 0.12–2.13 per 100,000) for the annual incidence rate of JORRP (per child per year from birth through age 18) in the absence of HPV vaccination.[22,33,35] For simplicity, the cumulative lifetime probability (per birth) of a case of JORRP through age 18 years was calculated by multiplying the annual probability of JORRP by 18. Although JORRP could occur in our model over the first 18 years of life, for simplicity we assumed that all cases occurred at age four years. The JORRP cost per case, discounted to birth assuming an average age of onset of JORRP of four years and updated to 3Q 2018 US dollars, was $149,300 (range: $71,700–$385,300).[36] We assumed 1.05 QALYs (range: 0.33–3.05) would be lost per case of JORRP (discounted to birth).[33] We assumed a one-year value of the lag term (described earlier) when estimating the benefits of reductions in the probability of RRP in children born to vaccinated mothers.

3 Model Parameters

This section describes the parameter values applied in the model of HPV vaccine cost effectiveness. Many parameter values are unchanged from the 2018 version of the model; however, this section includes a description and documentation of all model assumptions so that interested readers will not have to look elsewhere for this information.

3.1 Vaccination coverage

3.1.1 Base case vaccination coverage of females

Vaccination coverage assumptions are summarized in Appendix Table 2 and Appendix Table 3. We estimated the annual probability of HPV vaccination based on reported HPV coverage rates from National Immunization Survey-Teen (NIS-Teen).[37,38] We assumed the

probability of HPV vaccination for females through age 12 years was 29.5%, so that girls turning 13 in our model would have the same 3-dose coverage rates as reported for 13-year-olds in 2015.[37]

Estimates of the probability of vaccination for females aged 13–18 were based on changes in vaccination coverage from 2014 to 2015 as follows. In 2014, 3-dose HPV vaccination coverage among females was 26.2% among 13-year-olds, 35.9% among 14-year-olds, 41.2% among 15-year-olds, and 43.8% among 16-year-olds.[38] In 2015, 3-dose HPV vaccination coverage among females was 37.3% among 14-year-olds, 44.1% among 15-year-olds, 44.2% among 16-year-olds, and 54.4% among 17-year-olds.[37]

For HPV vaccination coverage rates among females to increase from 26.2% among 13-year-olds in 2014 to 37.3% among 14-year-olds in 2015, the average annual probability of vaccination in this age interval would have to be about 15.0%. For HPV vaccination coverage rates among females to increase from 35.9% among 14-year-olds in 2014 to 44.1% among 15-year-olds in 2015, the average annual probability of vaccination in this age interval would have to be about 12.8%. For HPV vaccination coverage rates among females to increase from 41.2% among 15-year-olds in 2014 to 44.2% among 16-year-olds in 2015, the average annual probability of vaccination in this age interval would have to be about 5.1%. For HPV vaccination coverage rates among females to increase from 43.8% among 16-year-olds in 2014 to 54.4% among 17-year-olds in 2015, the average annual probability of vaccination in this age interval would have to be about 18.9%. We used 12.9% (the average of 15.0%, 12.8%, 5.1%, and 18.9%) as the average annual probability of vaccination for females aged 13–18 years.

We assumed the annual probability of vaccination for females aged 19–26 was 20% the annual probability for those aged 13–18 years, as HPV vaccine uptake rates in adults are

relatively low.[39] The 20% adjustment was applied so that the resulting probability of vaccination for those aged 19–26 years would be consistent with available data. With a 2.6% annual probability of vaccination, average 3-dose coverage among females aged 19–26 years who were not vaccinated prior to age 19 years will be 11.0%, which is consistent with estimated 1-dose coverage of 11.8% among females aged 19–26 years who were not vaccinated prior to age 19 years.[39] For mid-adult vaccination strategies in which the catch-up age was extended to women beyond age 26 years, we applied the same annual probability of vaccination as for women aged 19–26 years.

3.1.2 Base case vaccination coverage of males

We estimated the annual probability of HPV vaccination among males in the same manner as for females. We assumed the probability of HPV vaccination for males at age 12 years was 24.9%, so that boys turning 13 in our model would have the same 3-dose coverage rates as reported for 13-year-olds in 2015.

Estimates of the probability of vaccination for males aged 13–18 years were based on changes in vaccination coverage in males from 2014 to 2015, as follows. In 2014, 3-dose HPV vaccination coverage among males was 16.2% among 13-year-olds, 20.9% among 14-year-olds, 24.9% among 15-year-olds, and 22.9% in 16-year-olds.[38] In 2015, 3-dose HPV vaccination coverage among males was 27.7% among 14-year-olds, 28.6% among 15-year-olds, 30.6% among 16-year-olds, and 28.8% among 17-year-olds.[37]

For HPV vaccination coverage rates among males to increase from 16.2% among 13-year-olds in 2014 to 27.7% among 14-year-olds in 2015, the average annual probability of vaccination in this age interval would have to be about 13.7%. For HPV vaccination coverage rates among males to increase from 20.9% among 14-year-olds in 2014 to 28.6% among 15-

year-olds in 2015, the average annual probability of vaccination in this age interval would have to be about 9.7%. For HPV vaccination coverage rates among males to increase from 24.9% among 15-year-olds in 2014 to 30.6% among 16-year-olds in 2015, the average annual probability of vaccination in this age interval would have to be about 7.6%. For HPV vaccination coverage rates among males to increase from 22.9% among 16-year-olds in 2014 to 28.8% among 17-year-olds in 2015, the average annual probability of vaccination in this age interval would have to be about 7.7%. We used 9.7% (the average of 13.7%, 9.7%, 7.6%, and 7.7%) as the average annual probability of vaccination for males aged 13–18 years.

We assumed the probability of receiving HPV vaccine for males aged 19–26 years was 20% the annual probability for males aged 13–18 years, based on the assumptions applied for females as described above. For mid-adult vaccination strategies in which the catch-up age was extended to men beyond age 26 years, we applied the same annual probability of vaccination as for men aged 19–26 years.

3.1.3 Lower and higher coverage scenarios

We also examined a lower and higher coverage scenario. For the lower coverage scenario, we reduced the base case probability of vaccination for those aged 13–18 years by 40% for females and 82% for males, so that the implied coverage among the 13–17 year age group was consistent with reported 3-dose coverage rates for this age group in 2015 (41.9% for females and 28.1% for males).[37] Whereas our base case probabilities reflect "vaccination incidence" rates extrapolated from NIS-Teen data, our lower bound probabilities were calculated to yield "vaccination prevalence" rates among 13- to 17-year-olds consistent with NIS-Teen data.

For the higher coverage assumption, we followed the same approach used for the base case except that we examined annual changes in 1-dose coverage from 2014 to 2015 instead of annual changes in 3-dose coverage. The higher coverage scenario thus reflects 1-dose vaccine uptake rates instead of 3-dose vaccine uptake rates.

3.2 Vaccine efficacy and cost

For females and males, vaccine efficacy was assumed to be 95% (range: 85%–100%) for protection against infection with each of the HPV vaccine types.[40] As described in Section 1.2.2, the base-case vaccine cost per 3-dose series, including administration costs, was $714 (range: $530–$742) for those 19 years old and older, and $636 (range: $530–$742) for those under age 19 years.

3.3 Costs of HPV-associated health outcomes

Appendix Table 4 provides the lifetime, discounted, direct medical treatment costs we applied per health outcome. As noted in Section 1.2.3, costs for HPV-associated outcomes other than cancers, genital warts, and AORRP were obtained from the 2018 version of the model[3] (which reported costs in 2016 US dollars) and were updated to third quarter 2018 US dollars using the health care component of the Personal Consumption Expenditures price index (http://www.bea.gov).[8] Changes in the medical treatment cost assumptions from the 2018 version of the model are described above in Section 1.2.3.1 (cancers), Section 1.2.3.2 (genital warts), and Section 1.2.4.1 (AORRP).

3.3.1 A note on discounting of averted medical costs

We multiplied the number of outcomes averted in year t of the vaccination program by the estimate of the discounted lifetime medical cost of the outcome. This yielded the lifetime

medical costs saved by the outcomes averted in year t, discounted to year t. In order to discount these averted medical costs to the onset of the vaccination program, we discounted these averted medical costs by an additional t-1 years. Of note, some of the cancer treatment cost estimates we applied were for the first two years after diagnosis, which we applied as an approximation of the lifetime cost per case.

3.4 Disease incidence rates

The age-specific incidence rates of CIN, genital warts, and cervical and other cancers we applied in the model are listed in Appendix Table 5 through Appendix Table 16. These incidence rates were applied in our model as those that would be expected in the absence of HPV vaccination, and we calculated the reductions in these outcomes after onset of vaccination as described in Section 2.

3.4.1 Incidence of CIN

Incidence rates for CIN 1 and CIN 2/3 (Appendix Table 5 and Appendix Table 6) were based on data from a 2010 study by Henk and colleagues using medical claims[41] and on data from a 2004 study by Insinga and colleagues using health plan administrative and laboratory data.[42]

For CIN 1, base case values were based on the Henk study through age 59 years and the Insinga study for those aged 60–79 years. The Henk study provided confidence intervals for ages 20–29 years and for ages 30–39 years. For ages 40–59 years, we approximated confidence intervals based on the confidence intervals for ages 30–39 years (relative to the base case value for ages 30–39 years). For ages 15–19 years, and for ages 60 years and over, the lower bound value was set to 0 and the upper bound value was set to twice the base case value.

For CIN 2/3, in our 2018 version of the model, base case values were based on the Henk study through age 69 years and the Insinga study for ages 70 years and older. In this application of the model, base case values for ages 20 through 49 years were based on the Insinga study rather than the Henk study. The reason for this change is that the CIN 2/3 rates reported by the Insinga study among young adults are more consistent with data from the HPV Vaccine Impact Monitoring Project (HPV-IMPACT) for the 2008 time period (the time period closest to the pre-vaccine era).[43] The HPV-IMPACT project reported annual rates of CIN 2+ per 100,000 women of 584.6 among ages 21–24 years, 505.8 for ages 25–29 years, 367.0 for ages 30–34 years, and 221.8 for ages 35–39 years.[43] For each age group, lower and upper bound values were created by assuming the same ratio to the base case value as in our 2018 model. For example, in our 2018 model, for ages 20–24 years, the upper bound value of 0.00441 was 1.361 times the base case value of 0.00324. In the 2019 model, the upper bound value for ages 20–24 years was calculated as the base case value (0.0045) multiplied by 1.361, or 0.006125.

In previous applications of the model, we reduced the CIN rates by 10% to account for potential lower utilization of cervical cancer screening services in the general US population as compared to women in the Henk and Insinga studies.[42] However, in this application of the model, we no longer make this adjustment, as the CIN 2+ rates reported by HPV-IMPACT do not suggest a systematic overestimation bias in the CIN 2/3 rates reported by the Henk and Insinga studies.

3.4.2 Incidence of genital warts

Incidence rates for genital warts (Appendix Table 7 and Appendix Table 8) were based on reported incidence rates among a commercially-insured population.[16] To obtain lower bound values, we estimated 95% confidence intervals based on the age-specific incidence rates in that

study and our conservative approximation of the age-specific sample sizes in that study.[16] The upper bound values we applied are estimates of genital warts prevalence (rather than incidence) rates among members of a privately insured population.[44]

3.4.3 Incidence of cervical and other HPV-associated cancers

Cancer incidence rates (Appendix Table 9 through Appendix Table 16) were obtained from population-based cancer registries that participate in the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program.[45,46] The annual incidence rates we applied reflect the average annual rate over the period 2006–2010. Incidence rates and cancer case counts are suppressed if there are fewer than 16 cases. In such instances, we assumed a rate of 0. The International Classification of Diseases for Oncology (ICD-O- 3) codes that were used for the various cancer sites are listed in Appendix Table 17, along with other details of the cancer registry data.

3.4.4 Incidence of recurrent respiratory papillomatosis (RRP)

We assumed an annual incidence rate (per 100,000) of JORRP of 0.735 (range: 0.12–2.13) for children through age 18 years.[22,33,35] Although we calculated the probability that a child would have RRP at any time from birth to age 18, for simplicity the costs of JORRP and quality of life impact of JORRP were calculated assuming that all cases of JORRP occurred at age 4 years, as was assumed in one of the source studies for our JORRP cost and quality of life estimates.[33] See Section 2.4.4 for additional details of our assessment of vaccine impact on JORRP.

As described in Section 1.2.4.3, we assumed AORRP incidence would be 40% that of JORRP incidence. Specifically, we assumed an annual incidence rate (per 100,000) of AORRP of 0.294 (range: 0.048–0.852) for ages 19 years and older.

3.5 Percentages of health outcomes attributable to HPV vaccine types

3.5.1 Percent of CIN 1 and CIN 2/3 attributable to HPV vaccine types

Appendix Table 18 provides the estimated percentages of CIN 1 and CIN 2/3 attributable to the nonavalent HPV vaccine types. Base case values and ranges for CIN 1 were obtained from a systematic review of the prevalence and attribution of HPV types in cervical precancers and cancers in the US.[47] The ranges reflect the 95% confidence intervals reported in that study. Estimates for CIN 2/3 were based on data from the HPV vaccine impact monitoring project (HPV-IMPACT).[48] The ranges we applied for CIN 2/3 represent the extreme values across four 5-year age groups (20–24, 25–29, 30–34, and 35–39 years). These ranges are notably greater than the 95% confidence intervals suggested by the HPV-IMPACT study and allow more uncertainty in the percent of CIN 2/3 attributable to each HPV type.

3.5.2 Percent of genital warts and RRP attributable to HPV 6 and 11

Appendix Table 19 provides the assumptions regarding the percentage of genital warts and JORRP attributable to HPV 6 and 11. We assumed that HPV 6 and 11 account for 90% of genital warts (range: 70%–100%)[49,50] and 90% of JORRP (range: 70%–100%). The values we applied for JORRP were the same as for genital warts, based on evidence that a maternal history of genital warts in pregnancy is the strongest reported risk factor for RRP in the child.[51] We applied the same attributable percentages for AORRP as for JORRP.

3.5.3 Percent of cancers attributable to high-risk nonavalent HPV types

The percent of cancers attributable to the nonavalent HPV types (Appendix Table 20 and Appendix Table 21) was based on a study of HPV typing of cancers in the US, which included data from seven cancer registries (Kentucky, Michigan, Louisiana, Florida, Hawaii, Iowa, and Los Angeles).[52] In these data HPV was detected in 91% of cases of cervical cancer.[52] This study provides grouped results for HPV 31,33,45,52, and 58. For these types, the base case values and confidence intervals from this study were provided by Trevor Thompson (personal communication, April 21, 2014). As described in Section 4, in the sensitivity analyses we modified the upper bound values when necessary so that the sum of the attributable percentages for each vaccine type was capped at 100%.

3.6 QALYs lost per HPV-related health outcome

Estimates of the age-specific, expected number of discounted lifetime quality-adjusted life years (QALYs) lost per HPV-related health outcome (discounted to year of onset of the health outcome except as noted for JORRP, which for simplicity of calculation is discounted to birth) are presented in Appendix Table 22 through Appendix Table 30. When estimating the quality of life impact of HPV-associated health outcomes, we took into account the quality of life in the absence of these HPV-associated health outcomes (Appendix Table 31).[53] The methods we used to develop these QALY estimates are described below.

3.6.1 Discounting of QALYs lost per health outcome

We multiplied the number of outcomes averted in year t of the vaccination program by the appropriate age- and sex-specific estimate of the discounted lifetime number of QALYs lost per health outcome. This yielded the number of QALYs saved by the outcomes averted in year t,

discounted to year t. In order to discount these QALYs saved to the onset of the vaccination program, we discounted these QALYs by an additional t - 1 years.

3.6.2 QALYs lost per case of genital warts

The number of QALYs lost per case of genital warts was calculated based on an average of two published studies. Drolet et al. (2011) provide estimates of the number of QALYs lost per case of genital warts, based on a study of 272 Canadian patients with genital warts.[54] Drolet et al. assessed quality of life impacts using the EuroQol EQ- 5D, a visual analog scale (VAS) and the Short-Form (SF)- 12 and estimated the loss in QALYs per episode of genital warts to be 0.017 to 0.041.[54] Woodhall et al. (2011) applied the EQ- 5D questionnaire to a sample of 370 patients with genital warts in England and Northern Ireland and found the loss in QALYs per episode of genital warts to be 0.018 (range: 0.008–0.031).[55] Combined, these two studies suggest that each episode of genital warts impose an average loss of about 0.024 QALYs per episode, with a range of 0.008–0.041. This range is generally consistent with the range of 0.0014–0.039 estimated by Woodhall et al. (2009),[56] based on data on the average duration of genital warts among approximately 200 patients in the United Kingdom combined with previous estimates of the impact of genital warts on the disutility associated with genital warts by Woodhall et al. (2008).[57] To examine a wide range of plausible values for the quality of life loss to genital warts, we applied an upper bound value of the number of QALYs lost per case of genital warts of 0.10, which is consistent with assumptions of a relative loss in quality of life of 0.09 over a duration of about 1.1 years.[2,25] We did not use age-specific values for the number of QALYs lost per case of genital warts.

3.6.3 QALYS lost per case of CIN

The number of QALYs lost per case of CIN was based on two published studies. For our base case value, we used estimates from Drolet et al. (2012),[58] which assessed quality of life impacts of abnormal cervical smear results using the EuroQol EQ- 5D, a visual analog scale (VAS) and the Short-Form (SF)- 12. Their study included 952 Canadian women, of which 492 had an abnormal cervical screening result and 460 had a normal result. The loss in QALYs was about 0.007 per case of LSIL and 0.010 per case of HSIL. For our upper bound value, we used estimates from Insinga et al. (2007),[59] which combined information regarding the duration of various health states related to CIN with information on quality of life from an earlier patient preference study.[60] This approach suggested that 0.105 QALYs are lost per case of CIN 1 and 0.115 QALYs are lost per case of CIN 2/3. Owing to the considerable uncertainty in the impact of CIN on quality of life, we assigned a lower bound value of 0. We did not use age-specific values for the number of QALYs lost per case CIN.

3.6.4 QALYS lost per case of RRP

We assumed 1.05 QALYs (range: 0.33–3.05) would be lost per case of JORRP (discounted to birth), based on a study of how the inclusion of prevention of JORRP can affect the estimated cost-effectiveness of HPV vaccination.[33] As described in Section 1.2.4.2, we assumed a base case value for the lifetime number of QALYs lost per case of AORRP of 0.47 (range: 0.15–3.43), based on assumptions regarding the severity of AORRP relative to JORRP.

3.6.5 QALYs lost per case of HPV-associated cancer

For each HPV-associated cancer, the age-specific number of QALYs lost was calculated based on quality of life in the absence of cancer (Appendix Table 31), quality of life detriments as a result of cancer (Appendix Table 32), and cancer survival probabilities (Appendix Table 33).

Cancer survival probabilities were obtained for two age groups: those under age 50 years and those 50 years and older. In order to allow for a more gradual change with age in the probability of cancer survival, the probability of survival for those under age 45 was adjusted linearly through age 55 years, rather than being applied abruptly at age 50 years.

Quality of life detriments associated with HPV-associated cancers were obtained from Jit el al. (2011).[61] As described in more detail by Jit et al. (2011), the quality of life weights for cervical cancer treatment were obtained from a time-tradeoff study,[60] and were consistent with results obtained from applying the Health and Limitations Index (HALex) instrument to data from a nationally representative survey (National Health Interview Surveys [NHIS], 1987 to 1992).[53] Similarly, the quality of life weights used by Jit et al. (2011) for treatment of vulvar, vaginal, and anal cancers were based on the NHIS data and HALex instrument.[53] Jit et al. (2011) based their quality of life weights for oropharyngeal cancer treatment on a study that administered the EuroQol EQ- 5D survey by mail to oral and oropharyngeal cancer patients after primary surgery.[62] The quality of life weight for penile cancer treatment used by Jit et al. (2011) was based on expert opinion.[63] Jit et al. (2011) assumed a permanent, post-treatment reduction in quality of life of 0.0305 (range: 0–0.061) among cancer survivors, based on studies of cervical cancer survivors that used various health-related quality of life survey instruments.[64-66] We made the same assumption except that we applied an upper bound value of 0.15 rather than 0.061, based on 2010 NHIS data which suggested that cancer survivors were about 15 percentage points more likely to report poor physical health-related quality of life than adults without cancer.[67]

The number of QALYs lost per case of HPV-associated cancer was estimated by assuming that everyone with cancer would be subject to the treatment-related detriment to

quality of life for exactly two years. After these two years, survivors would be subject to the permanent reduction in quality of life, and non-survivors would lose all their remaining QALYs.

3.6.5.1 Example: QALYs lost due to cervical cancer at age x years

The discounted number of QALYs lost per case of cervical cancer for a women diagnosed at age x years was calculated as follows. First, we calculated the potential QALY loss over the first two years as $0.285*Q_x + (0.285*Q_{x+1}*[1-D_x])/(1+r)$, where Q_x is the number of QALYs for a woman at age x years in the absence of cervical cancer (Appendix Table 31), 0.285 is the detriment to quality of life during treatment for cervical cancer as described above and in Appendix Table 32, D_x is the annual all-cause probability of death at age x years as in Appendix Table 35, and r is the discount rate (3%). The term D_x is included to account for the probability of death due to background mortality at age x years, so that no QALY losses are attributed to cervical cancer beyond age x years for those who would have died at age x years due to causes unrelated to cervical cancer.

Second, we calculated the QALY loss over the remaining years of life according to the probability of survival. The QALY loss at age x + 2 years due to cancer at age x years was calculated as $(0.0305*Q_{x+2}*[1-D_x]*[1-D_{x+1}])/(1+r)^2$ for cancer survivors (for whom we assumed a residual loss in quality of life of 0.0305) and $(Q_{x+2}*[1-D_x]*[1-D_{x+1}])/(1+r)^2$ for cancer non-survivors. Similarly, the QALY loss at age x + 3 years due to cancer at age x years was calculated as $(0.0305*Q_{x+3}*[1-D_x]*[1-D_{x+1}]*[1-D_{x+2}])/(1+r)^3$ for cancer survivors and $(Q_{x+3}*[1-Dx]*[1-Dx+1]*[1-Dx+2])/(1+r)^3$ for cancer non-survivors. QALY losses in all remaining years (ages x + 4 years and beyond up to the maximum potential age of 99 years) were calculated in an analogous manner.

This example shows how we calculated the base-case, age-specific estimates of the number of QALYs lost per case of cervical cancer. Calculations for the other cancers were performed in an analogous manner.

3.6.5.2 Upper and lower bound values for QALY losses due to cancer

The lower bound values of the discounted number of QALYs lost due to cancer were calculated by applying the upper bound value of cancer survival (Appendix Table 33) and the lower bound values of the QALY detriments (Appendix Table 32). The upper bound values of the discounted number of QALYs lost due to cancer were calculated by applying the lower bound value of cancer survival and the upper bound values of the QALY detriments.

3.7 HPV incidence (annual HPV acquisition probabilities) in the absence of vaccination

Appendix Table 34 lists the type-specific annual probabilities of HPV acquisition by age that we applied in the model for ages 8- 60 years. These values represent the probability of acquisition of a given HPV type at a given age, provided no acquisition of that HPV type had occurred previously. The table provides values through age 60 years. We assumed the type-specific probability of HPV acquisition decreased by 10% in each year of age after age 60 years. As noted in our summary of updates to the 2019 version of the model in Section 1.2.1, when applying the annual probabilities of acquiring HPV, these probabilities (as listed in Appendix Table 34) were multiplied by 1/1000. For example, the probability of acquiring HPV 16 for a 22-year-old is listed in Table 34 as 0.0449, but was applied in the model as 0.0000449. The reason for this adjustment is that the estimated impact of HPV vaccination is calculated based on relative, not absolute, changes in cumulative HPV acquisition, and the use of these much lower

absolute values helps to mitigate the bias arising from not explicitly accounting for the possibility of re-infection (see Section 1.2.1).

3.7.1 Description of base case HPV incidence assumptions

The base case values for the probability of acquisition of each HPV type were calculated as follows. First, the age-specific probability of acquisition of any HPV type was estimated as the average of the probabilities in two previously published models by Myers et al. (2000)[68] and Canfell et al. (2004).[69] The youngest age at which acquisition probabilities were provided was 15 years by Myers et al. (2000) and 16 years by Canfell et al. (2004). To calculate HPV acquisition probabilities for these younger ages, we assumed that HPV acquisition was possible beginning at age 13 years, and assigned probabilities of HPV acquisition by assuming that the probability of acquiring HPV at age x-1 years was 0.25 that of age x years. That is, we calculated HPV acquisition probabilities for ages 13 and 14 years based on the probability provided by the Myers model for age 15 years, and we calculated HPV acquisition probabilities for ages 13–15 years based on the probability provided by the Canfell model for age 16 years.

Second, we smoothed the HPV acquisition probabilities noted above (which were provided by age group) to allow for gradual changes in the probability of HPV acquisition with age. In this smoothing process, the probability of HPV acquisition was held constant for age 12 years and age 60 years. For intermediate years, the smoothed probability of HPV acquisition at age x years, was set equal to the average of the unadjusted probability of HPV acquisition at age x-1 years, age x years, and age x+1 years.

Third, we estimated type-specific acquisition probabilities by multiplying by the all-type acquisition probabilities by type-specific adjustment term. The adjustment for a given HPV type was selected manually so that the resulting HPV acquisition probabilities for the given type

would be consistent with the observed prevalence of the given type in the US.[70] To do so, we calculated the age-specific HPV prevalence rates implied by our HPV acquisition rates under the following two assumptions: (1) the probability that an infection would be persistent was 8% for HPV 16 and 3.5% for other HPV types;[28] and (2) the average probability of clearance per year was 45% for high-risk HPV types and 75% for HPV 6/11.[71] These assumptions regarding persistence and clearance were applied only for the purposes of estimating annual HPV acquisition probabilities and were not otherwise applied in the HPV transmission model. As noted, a key simplification of our model is that HPV natural history (from infection to disease) is not explicitly modeled.

Our base case values of the age-specific HPV acquisition probabilities were based on models of HPV in females.[68,69] We assumed that males and females have the same age-specific HPV incidence rates, owing to a lack of data on type-specific HPV incidence and prevalence among males in the pre-vaccine era.

3.7.2 "Increased HPV incidence for ages 30 years and older" scenario

In order to conduct additional sensitivity analyses relevant to HPV vaccination of adults, we created an alternate HPV incidence scenario in which the type-specific annual probabilities of HPV acquisition remained constant from age 30 years through age 45 years and then declined by 25% from age 45 years to age 60 years, rather than declining by about 75% from age 30 years through age 45 years as in the base case. Further, in this alternate scenario, HPV incidence rates were assumed to decrease by 2.5% per year of age after age 60 years, rather than by 10% per year as in the base case. The HPV acquisition probabilities in this "increased HPV incidence for ages 30 years and older" scenario are listed in Appendix Table 35. As with the base case HPV acquisition probabilities, when applying the annual probabilities of acquiring HPV in the

"increased HPV incidence for ages 30 years and older" scenario, these probabilities (as listed in Appendix Table 35) are multiplied by 1/1000. For example, the probability of acquiring HPV 16 for a 22-year-old is listed in Appendix Table 35 as 0.0449, but is applied in the model as 0.0000449.

3.8 Issues regarding model fit, calibration and validation

In our model, we assess how HPV vaccination can reduce the burden of HPV-associated health outcomes, including cervical and other cancers, CIN, and genital warts. As described above, we did not specifically model the transition from HPV acquisition to HPV-associated diseases. A key simplification of our approach is that we estimated the percentage reduction in HPV-associated outcomes that can be achieved by vaccination, and then applied these percentage reductions to the existing burden of these HPV-associated outcomes in the absence of vaccination. The burden of HPV-associated outcomes in the absence of vaccination is based on the best data available: SEER/NPCR data for the incidence of HPV-associated cancers and medical claims data for the incidence of CIN and genital warts. Our model is constructed using age-specific disease incidence rates in the absence of HPV vaccination as listed in Appendix Table 5 to Appendix Table 16. Thus, it is of no use to show how well our model "fits" the disease incidence data in these tables, because in the absence of vaccination, our model would, by its simple design, predict exactly the same incidence rates as in Appendix Table 5 to Appendix Table 16.

4 Sensitivity Analyses

We conducted one-way and multi-way sensitivity analyses.

4.1 One-way sensitivity analyses

In the one-way sensitivity analyses, one parameter value (or set of parameter values, as explained below) was varied at a time, holding all other parameters at their base case values. Specifically, we calculated the cost-effectiveness of 9vHPV vaccination strategies would change when varying one of the follow parameter values at a time: HPV acquisition probabilities; vaccine price per series; vaccine efficacy; the medical cost per case of the HPV-associated health outcomes; the number of QALYs lost per case of each health outcome; the incidence rates of the health outcomes in the absence of vaccination; and the percentages of the health outcomes attributable to the HPV vaccine types.

When varying vaccine efficacy, all vaccine efficacy parameters (HPV 16 efficacy, HPV 18 efficacy, HPV 6/11 efficacy, HPV 31 efficacy, and so on) were treated as a set and varied in the same manner. That is, when varying vaccine efficacy values, all efficacy parameters were varied together such that all were set to their lower bound value or all were set to their upper bound value (e.g., we did not examine scenarios in which HPV 16 efficacy was set to its upper bound value while HPV 18 efficacy was set to its lower bound value). The same approach was used for the remaining parameter groups (cost of HPV health outcomes, number of QALYs lost per HPV health outcome, and the percent of each health outcome attributable to the HPV vaccine types). That is, when varying the cost of HPV health outcomes, all cost parameters were varied together such that all were set to their lower bound value or all were set to their upper bound value (e.g., we did not examine scenarios in which the cost per case of cervical cancer was set to its lower bound value while the cost per case of penile cancer was set to its upper bound value). Likewise, the number of QALYs lost per health outcome was varied as a group for all health outcomes, and the incidence rates of the health outcomes in the absence of vaccination were

varied as a group for all health outcomes. Likewise, the percentages of the health outcomes attributable to the HPV vaccine types were varied as a group (e.g., we did not examine scenarios in which the percent of cervical cancer attributable to HPV 16 was set to its lower bound while the percent of cervical cancer attributable to HPV 18 was set to its upper bound; and we did not examine scenarios in which the percent of cervical cancer attributable to HPV 16 was set to its lower bound while the percent of vaginal cancer attributable to HPV 16 was set to its upper bound). When setting the percentage of cancers attributable to each HPV type at its upper bound value, the total percentage of cancers attributable to the 9 HPV vaccine types exceeded 100% for vaginal cancer, anal cancer in women, and anal cancer in men (the sums were 126%, 119%, and 124%, respectively). We therefore capped these sums at 100%, by reducing each upper bound value in a proportional manner.

4.2 Multi-way sensitivity analyses

We conducted multi-way sensitivity analyses to examine how the cost-effectiveness of 9vHPV vaccination strategies would change when numerous parameter values (or set of parameter values, as explained above) were varied simultaneously. Specifically, we conducted a probabilistic sensitivity analysis consisting of 5,000 model simulations. In each simulation, four sets of parameter values were varied (treatment costs per case of each health outcome, number of QALYs lost per case of each health outcome, the incidence rates of the health outcomes in the absence of vaccination, and the percentages of the health outcomes attributable to the HPV vaccine types). Parameter values within each parameter set were varied as a group as described above for the one-way sensitivity analyses.

We used the lognormal distribution for cost parameters because this is a common practice in health economic studies. That is, the lognormal distribution is often used to capture

uncertainty in cost parameters, given that the cost estimates cannot be negative and cost estimates are typically right-skewed.[28,72] We used the lognormal distribution for the number of QALYs lost per case of each health outcome and for the incidence rates of the health outcomes, because these values are also constrained to be non-negative. For the percentage of each health outcome attributable to the HPV vaccine types, we assumed a uniform distribution between the lower and upper bound values.

We followed the methods of Elbasha and Dasbach (2010) to estimate the lognormal distribution parameters.[28] Specifically, we calculated the parameter μ as $\ln(\text{BASECASE}) - 0.5\ln[1+(SE^2/\text{BASECASE}^2)]$, where BASECASE is the base case value, ln indicates the natural log, and SE is the standard error (approximated as the upper bound minus the lower bound, divided by 2*1.96). We calculated the parameter σ as the square root of $\ln[1+(SE^2/\text{BASECASE}^2)]$.

The 5,000 simulations were done using the base case assumptions regarding vaccine efficacy, vaccination coverage, and vaccine price. Even when assuming fixed values for vaccine efficacy, coverage, and price, the model is subject to uncertainty beyond that which is reflected by the four parameter sets listed above (treatment costs per case of each health outcome, number of QALYs lost per case of each health outcome, the incidence rates of the health outcomes in the absence of vaccination, and the percentages of the health outcomes attributable to the HPV vaccine types). To account for additional uncertainty, we applied an adjustment factor to each simulation to account for uncertainty in the model predictions regarding the percentage reduction in each HPV-associated health outcome. Specifically, before calculating cost-effectiveness ratios in each simulation, the total number of QALYs gained and the costs averted by vaccination were both multiplied by an impact adjustment factor which ranged from 0.75 to 1.25 and was

assumed to follow a uniform distribution. This adjustment factor in effect allows for us to include scenarios in which the impact of vaccination (in terms of the percentage reduction in HPV-attributable health outcomes) is up to 25% less or 25% greater than suggested by the model, in addition to the effects of varying the percentage of health outcomes attributable to the HPV types, the incidence rates of the health outcomes included in the analysis, and assumptions regarding the cost and number of QALYs lost per case of disease.

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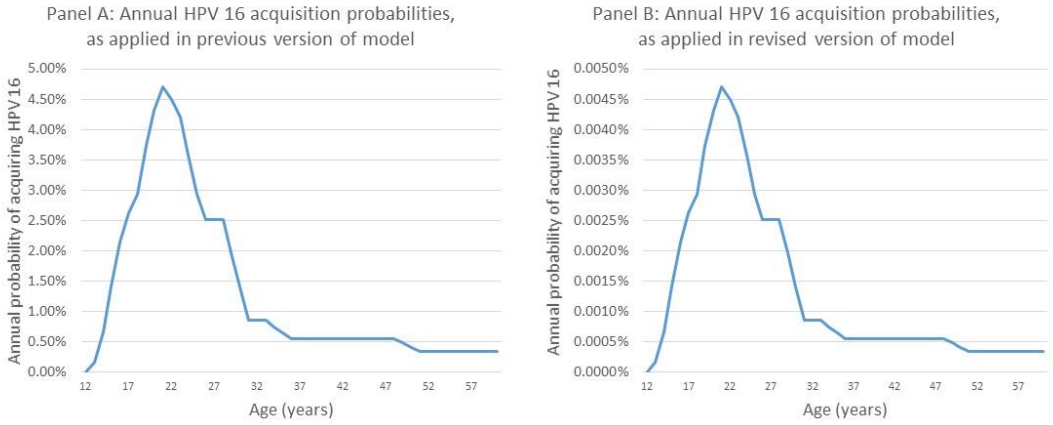
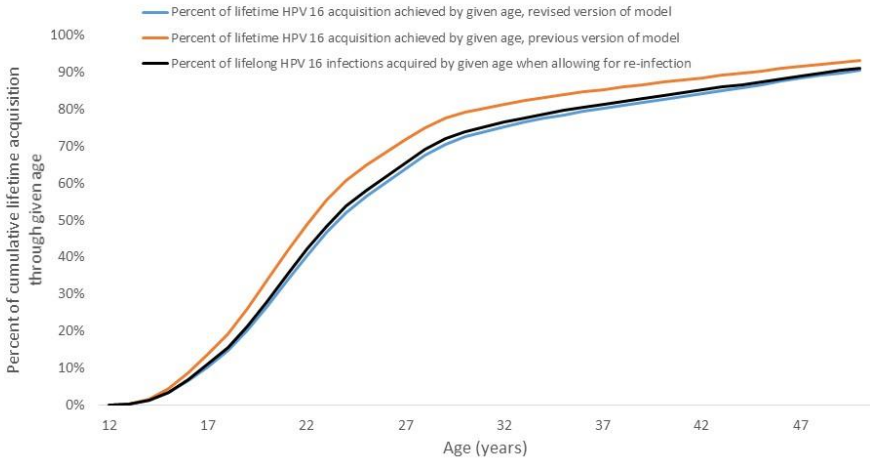
6 Figures

Appendix Figure 1: Illustration of application of annual HPV acquisition probabilities in revised version of model



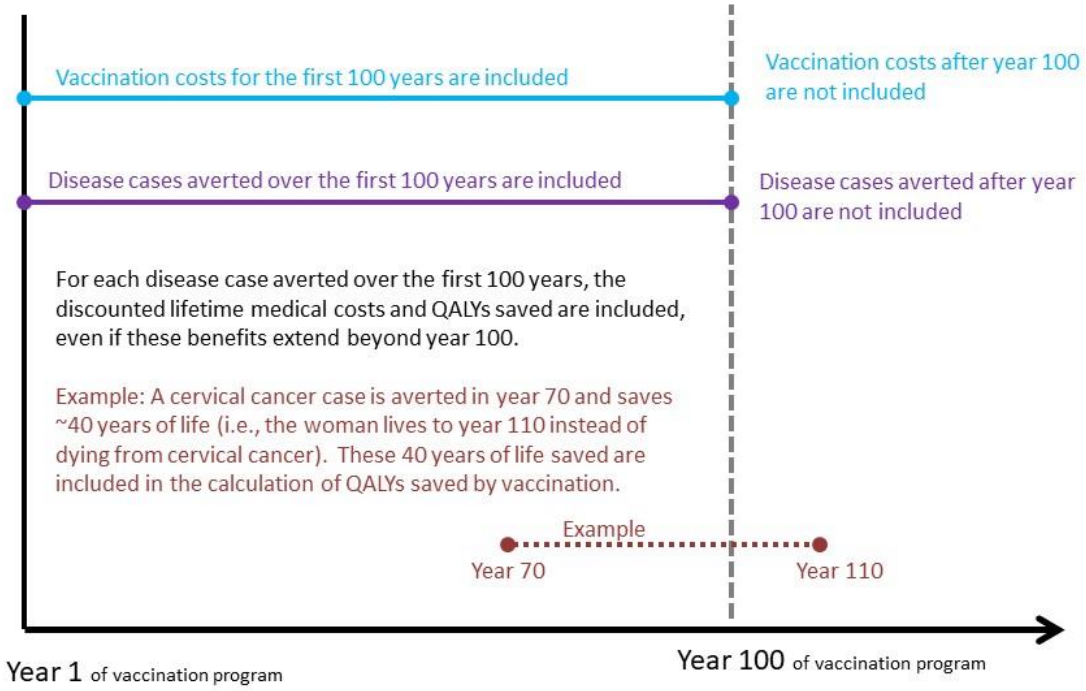
The annual HPV acquisition probabilities (Panel A) are divided by 1000 (Panel B) when applied in the revised version of the model. This division by 1000 maintains the relative probability of HPV acquisition by age, as shown by Panel A and Panel B. As described in the text of this Technical Appendix, dividing the HPV acquisition probabilities by 1000: (1) exploits a key model feature in which the effects of vaccination are approximated based on relative, not absolute, changes in cumulative HPV acquisition; and (2) reduces the bias created by not accounting for re-infection, because virtually everyone is at risk for initial HPV infection when using the lower absolute probabilities (cumulative lifetime incidence is about 50% when using the Panel A values, but less than 1% when using the Panel B values).

Appendix Figure 2: Illustration of how the application of the revised HPV 16 acquisition probabilities (Appendix Figure 1) help to approximate the potential effects of HPV vaccination when allowing for re-infection of HPV 16



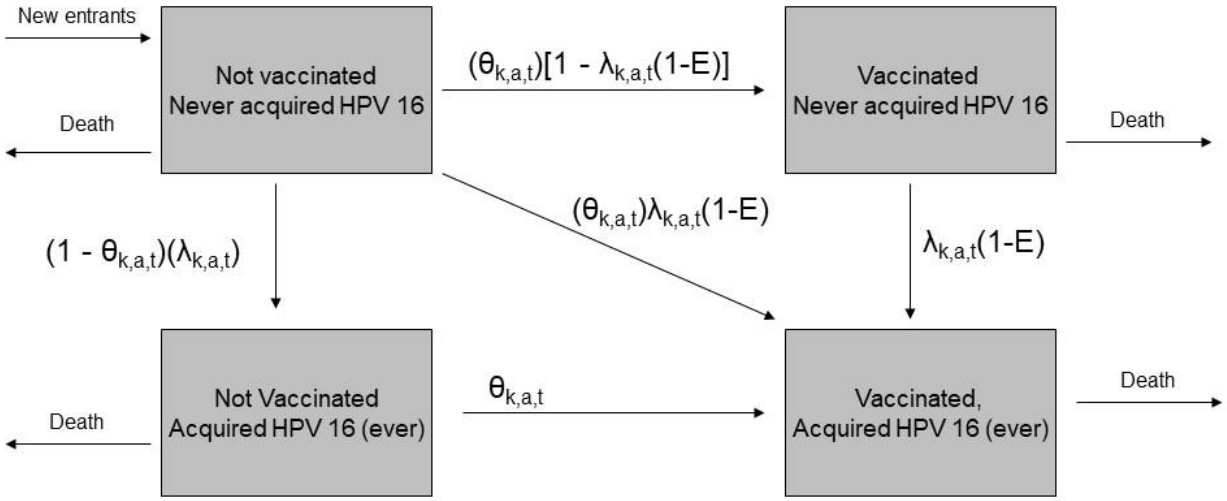
The orange line shows the cumulative percentage of lifetime HPV 16 acquisition acquired by a given age when applying the original HPV 16 acquisition probabilities (previous figure, Panel A); the blue line shows how this cumulative lifetime acquisition changes when the HPV 16 acquisition probabilities are divided by 1000 (previous figure, Panel B). The black line shows the cumulative percentage of lifelong HPV 16 infections acquired by a given age when applying the original HPV 16 acquisition probabilities (previous figure, Panel A) and when allowing for HPV 16 re-infection and when assuming that 20% of HPV 16 infections are lifelong. This assumption of 20% was chosen for illustrative purposes, as when more realistic values of the percent of HPV 16 infections that are lifelong (such as 10%, 5%, 1%, or less) are assumed, the black line and blue line are practically indistinguishable.

Appendix Figure 3: Illustration of time horizon and analytic horizon



This figure illustrates the time horizon and analytic horizon of our analysis. We examined the first 100 years of an HPV vaccination program (time horizon). The benefits of HPV-associated disease cases averted during the first 100 years of the vaccination program were accrued over the lifetimes of the affected people (analytic horizon).

Appendix Figure 4: Illustration of model of cumulative, lifetime probability of exposure to HPV 16



A cohort of susceptible 8-year-olds enters the population each year. In each year of the vaccine program (from year 1 to 100), there is a probability of death, a probability of acquiring HPV 16 (λ) for those never infected with HPV 16 previously, and a probability of receiving HPV vaccination (θ). Vaccine efficacy against infection with HPV 16 is given by E. The subscripts k, a, and t denote sex, age, and year of vaccine program, respectively. The age- and sex-specific probabilities of HPV 16 infection (λ) were adjusted for each year t to reflect changes in HPV exposure in sex partners as a result of HPV vaccination.

The reduction in HPV 16-related heath outcomes due to vaccination for a given age cohort in a given year was assumed to be proportional to the reduction in cumulative HPV 16 infection in that age cohort attributable to vaccination.

Reductions in health outcomes attributable to other HPV types were estimated in an analogous manner.

7 Tables

7.1 Tables of HPV-associated cancer costs

Appendix Table 1: Recent studies of average cost of HPV-associated cancers in United States settings as published in a 2019 literature review

Type of HPV-associated cancer	Study author (year of publication)	Treatment cost estimate
Anal	Deshmukh(2018)[12]	$53,000
Anal	Wu (2018)[11]	$134,100
Cervical	Lairson (2017)[10]	$82,500
Oropharyngeal	Lairson (2017)[14]	$146,900
Oropharyngeal	Sher (2016)[73]	$65,400
Vaginal	Fu (2018)[13]	$145,200
Vulvar	Fu (2018)[13]	$59,700

Costs are reported in 3Q 2018 dollars.

This table was obtained from a recent literature review of HPV-associated cancer costs.[6] See the review for more details. These costs were incorporated in the model as described in Section 1.2.3.1. See Appendix Table 4 for the actual base case cost estimates and ranges applied in the analysis.

7.2 Tables of vaccination coverage assumptions

Appendix Table 2: Probabilities of vaccination by age under three coverage scenarios

Age (years)	Lower coverage scenario		Base coverage scenario		Higher coverage scenario	
	Female	Male	Female	Male	Female	Male
12	0.295	0.249	0.295	0.249	0.564	0.487
13–18	0.077	0.017	0.129	0.097	0.143	0.142
19+	0.015	0.003	0.026	0.019	0.029	0.028

Appendix Table 3: Approximate cumulative vaccination coverage implied by vaccine probability assumptions

Age (years)	Lower coverage scenario		Base coverage scenario		Higher coverage scenario	
	Female	Male	Female	Male	Female	Male
13–17	41.9%	28.1%	49.0%	41.1%	69.6%	64.1%
17	52.9%	31.2%	64.7%	54.9%	79.8%	76.1%
26	61.6%	34.3%	75.0%	65.2%	86.3%	83.7%

7.3 Table of medical treatment costs applied in model

Appendix Table 4: Base case estimates and ranges of the cost per case of HPV-related health outcomes (3Q 2018 US dollars)

Health outcome	Base case value	Lower bound	Upper bound
CIN 1	$1,390	$960	$1,810
CIN 2/3	$2,560	$1,070	$4,150
Genital warts	$860	$430	$2,790
Cervical cancer	$72,800	$43,500	$82,500
Anal cancer	$93,600	$53,000	$134,100
Vaginal cancer	$116,500	$30,300	$145,200
Vulvar cancer	$51,400	$26,400	$59,700
Oropharyngeal cancer	$126,500	$65,400	$146,900
Penile cancer	$22,200	$11,000	$43,500
JORRP	$149,300	$71,700	$385,300
AORRP	$67,200	$32,300	$433,700

CIN: cervical intraepithelial neoplasia. JORRP: juvenile-onset recurrent respiratory papillomatosis. AORRP: adult-onset recurrent respiratory papillomatosis.

Cervical cancer screening costs were not included because we did not explicitly model cervical cancer screening, and these costs were assumed to be incurred regardless of HPV vaccination strategy.

All costs were updated to 3Q 2018 US dollars using the health care component of the Personal Consumption Expenditures price index (http://www.bea.gov).[8] The medical treatment costs for CIN and JORRP were obtained from the 2018 version of the model.[5] The treatment costs for HPV-associated cancers, genital warts, and AORRP were obtained as described in Section 1.2.3.

JORRP costs reflect the expected lifetime costs of JORRP discounted to birth, and the cost estimate shown here has been discounted by 4 years to reflect a 4-year average time from birth to onset of JORRP. The cost of AORRP was calculated based on the JORRP cost before discounting to birth (40% of the JORRP value for the lower bound and base case, and 100% of the JORRP value for the upper bound).

7.4 Tables of disease incidence rates

7.4.1 CIN incidence tables

Appendix Table 5: Annual CIN 1 incidence rates (per person)

Age (years)	Base case	Lower bound	Upper bound
0–14	0	0	0
15–19	0.0004	0	0.0008
20–24	0.0033	0.0021	0.0046
25–29	0.0033	0.0021	0.0046
30–34	0.0029	0.0016	0.0047
35–39	0.0029	0.0016	0.0047
40–44	0.0019	0.0011	0.0031
45–49	0.0019	0.0011	0.0031
50–54	0.0019	0.0011	0.0031
55–59	0.0019	0.0011	0.0031
60–64	0.0004	0	0.0008
65–69	0.0004	0	0.0008
70–74	0.0002	0	0.0004
75–79	0.0002	0	0.0004
80–84	0	0	0
85+	0	0	0

CIN: cervical intraepithelial neoplasia. See notes to Appendix Table 6.

Appendix Table 6: Annual CIN 2/3 incidence rates (per person)

Age (years)	Rate	Lower bound	Upper bound
0–14	0	0	0
15–19	0.0002	0	0.0004
20–24	0.0045	0.0030	0.0061
25–29	0.0079	0.0053	0.0108
30–34	0.0032	0.0017	0.0052
35–39	0.0032	0.0017	0.0052
40–44	0.0010	0.0005	0.0016
45–49	0.0010	0.0005	0.0016
50–54	0.0006	0.0003	0.0010
55–59	0.0006	0.0003	0.0010
60–64	0.0006	0.0003	0.0010
65–69	0.0006	0.0003	0.0010
70–74	0.0001	0	0.0002
75–79	0.0001	0	0.0002
80–84	0	0	0
85+	0	0	0

CIN: cervical intraepithelial neoplasia

Incidence rates for CIN 1 and CIN 2/3 were based on data from a 2010 study by Henk and colleagues using medical claims data[41] and a 2004 study by Insinga and colleagues using health plan administrative and laboratory data.[42]

7.4.2 Genital warts incidence tables

Appendix Table 7: Annual genital warts incidence rates, females (per person)

Age (years)	Rate	Lower bound	Upper bound
10–14	0.00013	0.00004	0.00043
15–19	0.00223	0.00176	0.00287
20–24	0.00459	0.00356	0.00620
25–29	0.00272	0.00195	0.00394
30–34	0.00150	0.00119	0.00265
35–39	0.00150	0.00119	0.00199
40–44	0.00108	0.00081	0.00139
45–49	0.00108	0.00081	0.00144
50–54	0.00073	0.00052	0.00092
55–59	0.00073	0.00052	0.00086
60–64	0.00062	0.00035	0.00076
65–69	0.00062	0.00029	0.00055
70–74	0.00045	0.00018	0.00055
75–79	0.00045	0.00018	0.00055
80–84	0.00016	0.00001	0.00055
85+	0.00016	0.00001	0.00055

See notes in the following table.

Appendix Table 8: Annual genital warts incidence rates, males (per person)

Age (years)	Rate	Lower bound	Upper bound
10–14	0.00011	0.00003	0.00041
15–19	0.00074	0.00051	0.00065
20–24	0.00236	0.00176	0.00293
25–29	0.00272	0.00207	0.00501
30–34	0.00223	0.00183	0.00388
35–39	0.00223	0.00183	0.00252
40–44	0.00118	0.00094	0.00189
45–49	0.00118	0.00094	0.00128
50–54	0.00092	0.00071	0.00118
55–59	0.00092	0.00071	0.00086
60–64	0.00048	0.00028	0.00100
65–69	0.00048	0.00024	0.00087
70–74	0.00043	0.00020	0.00087
75–79	0.00043	0.00020	0.00087
80–84	0.00024	0.00008	0.00087
85+	0.00024	0.00008	0.00087

Based on reported incidence rates among a commercially-insured population.[16] Lower bound values reflect approximate 95% confidence intervals and the upper bound values are estimates of genital warts prevalence rates.[44]

7.4.3 Cancer incidence tables

Appendix Table 9: Annual cervical cancer incidence rates (per 100,000)

Age (years)	Rate	Lower bound	Upper bound
10–14	0.0	0.0	0.0
15–19	0.1	0.1	0.2
20–24	1.2	1.1	1.3
25–29	5.2	5.0	5.4
30–34	10.3	10.0	10.6
35–39	14.1	13.8	14.4
40–44	14.8	14.4	15.1
45–49	13.6	13.3	13.9
50–54	12.2	11.9	12.5
55–59	12.2	11.9	12.5
60–64	12.0	11.7	12.4
65–69	12.0	11.7	12.5
70–74	11.2	10.7	11.6
75–79	9.6	9.1	10.0
80–84	9.0	8.6	9.5
85+	7.4	7.0	7.8

Base case values and 95% confidence intervals were obtained from population-based cancer registries that participate in the National Program of Cancer Registries (NPCR) and the Surveillance, Epidemiology, and End Results (SEER) Program, 2006- 2010.[45,46] Incidence rates and cancer case counts are suppressed if there are fewer than 16 cases. In such instances, we assumed a rate of 0.

Appendix Table 10: Annual vulvar cancer incidence rates (per 100,000)

Age (years)	Rate	Lower bound	Upper bound
10–14	0.0	0.0	0.0
15–19	0.0	0.0	0.0
20–24	0.0	0.0	0.1
25–29	0.1	0.1	0.2
30–34	0.4	0.3	0.5
35–39	0.9	0.8	1.0
40–44	1.6	1.5	1.8
45–49	2.5	2.4	2.7
50–54	2.9	2.8	3.1
55–59	3.3	3.1	3.4
60–64	3.9	3.7	4.1
65–69	4.7	4.4	4.9
70–74	6.4	6.1	6.8
75–79	8.4	8.0	8.8
80–84	10.6	10.1	11.1
85+	12.8	12.3	13.3

For more information, see Appendix Table 9 and Appendix Table 17.

Appendix Table 11: Annual vaginal cancer incidence rates (per 100,000)

Age (years)	Rate	Lower bound	Upper bound
10–14	0.0	0.0	0.0
15–19	0.0	0.0	0.0
20–24	0.0	0.0	0.0
25–29	0.0	0.0	0.0
30–34	0.1	0.0	0.1
35–39	0.1	0.1	0.2
40–44	0.3	0.2	0.3
45–49	0.4	0.4	0.5
50–54	0.6	0.6	0.7
55–59	0.8	0.7	0.9
60–64	1.0	0.9	1.2
65–69	1.3	1.2	1.4
70–74	1.7	1.6	1.9
75–79	2.1	1.9	2.3
80–84	2.5	2.3	2.8
85+	2.9	2.6	3.2

For more information, see Appendix Table 9 and Appendix Table 17.

Appendix Table 12: Annual penile cancer incidence rates (per 100,000)

Age (years)	Rate	Lower bound	Upper bound
10–14	0.0	0.0	0.0
15–19	0.0	0.0	0.0
20–24	0.0	0.0	0.0
25–29	0.0	0.0	0.1
30–34	0.1	0.1	0.2
35–39	0.2	0.2	0.2
40–44	0.4	0.3	0.5
45–49	0.5	0.5	0.6
50–54	0.8	0.7	0.9
55–59	1.2	1.1	1.3
60–64	1.8	1.6	1.9
65–69	2.6	2.4	2.8
70–74	3.5	3.3	3.8
75–79	4.4	4.1	4.8
80–84	5.1	4.7	5.5
85+	6.3	5.8	6.9

For more information, see Appendix Table 9 and Appendix Table 17.

Appendix Table 13: Annual anal cancer incidence rates, males (per 100,000)

Age (years)	Rate	Lower bound	Upper bound
10–14	0.0	0.0	0.0
15–19	0.0	0.0	0.0
20–24	0.0	0.0	0.0
25–29	0.1	0.1	0.1
30–34	0.2	0.2	0.2
35–39	0.6	0.5	0.7
40–44	1.5	1.4	1.6
45–49	2.1	2.0	2.2
50–54	2.4	2.3	2.5
55–59	2.5	2.4	2.7
60–64	2.6	2.4	2.8
65–69	2.9	2.7	3.2
70–74	2.8	2.5	3.0
75–79	2.8	2.5	3.0
80–84	2.9	2.6	3.3
85+	2.6	2.3	3.0

For more information, see Appendix Table 9 and Appendix Table 17.

Appendix Table 14: Annual anal cancer incidence rates, females (per 100,000)

Age (years)	Rate	Lower bound	Upper bound
10–14	0.0	0.0	0.0
15–19	0.0	0.0	0.0
20–24	0.0	0.0	0.0
25–29	0.0	0.0	0.0
30–34	0.2	0.1	0.2
35–39	0.5	0.4	0.6
40–44	1.3	1.2	1.4
45–49	2.8	2.6	2.9
50–54	4.3	4.1	4.5
55–59	4.9	4.7	5.1
60–64	4.9	4.7	5.1
65–69	4.9	4.7	5.2
70–74	5.3	5.0	5.6
75–79	5.1	4.8	5.4
80–84	5.1	4.8	5.5
85+	4.5	4.2	4.8

For more information, see Appendix Table 9 and Appendix Table 17.

Appendix Table 15: Annual oropharyngeal cancer incidence rates, males (per 100,000)

Age (years)	Rate	Lower bound	Upper bound
10–14	0.0	0.0	0.0
15–19	0.0	0.0	0.0
20–24	0.0	0.0	0.1
25–29	0.1	0.1	0.1
30–34	0.3	0.2	0.3
35–39	1.2	1.1	1.3
40–44	3.9	3.8	4.1
45–49	9.8	9.5	10.0
50–54	17.4	17.0	17.7
55–59	23.6	23.1	24.0
60–64	24.8	24.3	25.3
65–69	23.4	22.8	23.9
70–74	20.3	19.7	21.0
75–79	15.9	15.3	16.6
80–84	13.0	12.4	13.7
85+	8.5	7.9	9.2

For more information, see Appendix Table 9 and Appendix Table 17.

Appendix Table 16: Annual oropharyngeal cancer incidence rates, females (per 100,000)

Age (years)	Rate	Lower bound	Upper bound
10–14	0.0	0.0	0.0
15–19	0.0	0.0	0.0
20–24	0.0	0.0	0.1
25–29	0.1	0.0	0.1
30–34	0.2	0.1	0.2
35–39	0.4	0.4	0.5
40–44	0.9	0.8	1.0
45–49	1.9	1.8	2.0
50–54	3.2	3.0	3.3
55–59	4.1	3.9	4.3
60–64	4.8	4.6	5.0
65–69	5.3	5.1	5.6
70–74	5.3	5.0	5.6
75–79	5.0	4.7	5.3
80–84	4.2	3.9	4.5
85+	3.2	3.0	3.5

For more information, see Appendix Table 9 and Appendix Table 17.

Appendix Table 17: Details of cancer incidence data by cancer site

Cancer site	Site variable description	Histologic type ICD-O- 3	Site code	Diagnostic Confirmation
Cervix	"Cervix Uteri"	8010-8671,8940- 8941	C530-C539	Microscopically confirmed
Anus	"Rectum", "Anus, Anal Canal and Anorectum"	8050-8084,8120- 8131	C210-C212, C218, C209	Microscopically confirmed
Penis	"Penis"	8050-8084,8120- 8131	C600-C609	Microscopically confirmed
Vagina	"Vagina"	8050-8084,8120- 8131	C529	Microscopically confirmed
Vulva	"Vulva"	8050-8084,8120- 8131	C510-C519	Microscopically confirmed
Oropharynx	Primary Site=19,24,28,90-91,98- 99,102,108-109,140,142,148	8050-8084,8120- 8131	(as listed)	Microscopically confirmed

ICD-O-: International Classification of Diseases for Oncology. Cancer incidence rates were calculated for the United States by including all states meeting United States Cancer Statistics (USCS) publication criteria for all years 2006- 2010, which covers approximately 94.8% of the US population.
Source: Meg Watson, personal communication, May 4, 2015.

7.5 Tables of HPV type attribution

Appendix Table 18: Percent of cervical intraepithelial neoplasia (CIN) 1- 3 attributable to HPV types

HPV type	CIN 1	CIN 2/3
6/11	6.9 (2.7–17.0)	0
16	8.6 (5.3–13.7)	45.6 (32.4–50.4)
18	4.9 (2.5–9.2)	3.8 (1.6–8.3)
31	6.4 (3.6–11.1)	9.6 (7.0–15.0)
33	3.3 (1.5–7.1)	2.6 (1.3–5.5)
45	3.7 (1.7–7.6)	1.5 (0.4–3.4)
52	6.2 (3.5–10.8)	7.4 (4.9–12.9)
58	2.4 (1.0–6.0)	4.2 (2.0–5.5)

Values are in percent. Estimates for CIN 1 were obtained from a systematic review of the prevalence and attribution of HPV types among cervical precancers and cancers in the United States.[47] Estimates for CIN 2/3 were based on data from the HPV vaccine impact monitoring project (HPV-IMPACT).[48] The ranges we applied for CIN 2/3 represent the extreme values across four 5-year age groups (20- 24, 25- 29, 30- 34, and 35- 39 years).

Appendix Table 19: Percent of genital warts and recurrent respiratory papillomatosis (RRP) attributable to HPV 6 & 11

Health outcome	Base case	Lower bound	Upper bound
Genital warts	90.0	70.0	100
RRP	90.0	70.0	100

Values are in percent, and were based on several several sources[49-51] as described in Sections 3.5.1 and 3.5.2. The assumptions shown for RRP were applied to both juvenile-onset and adult-onset RRP.

Appendix Table 20: Percent of cervical, vulvar, vaginal, and penile cancers attributable to HPV types

HPV type	Cervical	Vulvar	Vaginal	Penile
16	50.1 (46.6–53.6)	48.1 (40.8–55.4)	53.4 (40.9–59.5)	45.2 (34.7–56.1)
18	16.1 (13.7–18.8)	0.6 (0.1–3.2)	1.7 (0.3–5.4)	2.7 (0.8–9.0)
31	2.1 (1.3–3.3)	1.1 (0.3–4.0)	0.0	0.0
33	3.5 (2.4–5.0)	9.3 (5.8–14.5)	11.6 (5.7–17.0)	5.1 (2.0–12.3)
45	5.5 (4.1–7.3)	0.6 (0.1–3.1)	3.3 (0.9–7.4)	2.7 (0.8–9.0)
52	1.8 (1.1–3.1)	2.7 (1.1–6.2)	1.7 (0.3–5.4)	1.3 (0.2–6.8)
58	1.8 (1.1–3.0)	0.6 (0.1–3.1)	1.7 (0.3–5.4)	0.0

Values are in percent. Values were obtained from a study of prevaccine type-specific prevalence of HPV–associated cancers in the United States.[52] This prevalence study provided grouped results for HPV 31,33,45,52, and 58. For these types, the base case values and confidence intervals from the study were provided by Trevor Thompson (personal communication, April 21, 2014). For vaginal cancer, anal cancer in females, and anal cancers in males, the sum of the upper bound percentage-attributable values exceed 100%. These were scaled down so that their sum was capped at 100%. The values shown here and in the subsequent table are the adjusted values.

Appendix Table 21: Percent of anal and oropharyngeal cancers attributable to HPV types

HPV	Anal		Oropharyngeal	
type	Male	Female	Male	Female
16	75.3 (62.3–79.3)	78.5 (69.1–80.9)	61.6 (56.9–66.0)	48.4 (40.6–56.4)
18	3.8 (1.1–7.5)	1.1 (0.2–2.7)	1.8 (0.9–3.6)	2.4 (0.9–6.2)
31	0.0	1.2 (0.2–2.8)	0.0 (0.0–0.9)	0.7 (0.1–3.7)
33	1.9 (0.3–5.2)	8.4 (4.3–10.9)	2.8 (1.6–4.8)	8.8 (5.3–14.5)
45	0.0	0.0	0.7 (0.2–2.0)	0.0
52	1.9 (0.3–5.2)	0.0	0.7 (0.2–2.0)	0.0
58	0.0 (0.0–2.8)	1.1 (0.2–2.7)	0.2 (0.0–1.3)	0.0

Values are in percent. See notes to previous table.

7.6 Tables of QALY losses per HPV-associated health outcome

Appendix Table 22: Number of QALYs lost per case of genital warts, cervical intraepithelial neoplasia (CIN), and recurrent respiratory papillomatosis (RRP)

Health outcome	Base case	Lower bound	Upper bound
Genital warts	0.024	0.008	0.100
CIN 1	0.007	0.0	0.105
CIN 2/3	0.01	0.0	0.115
JORRP	1.05	0.33	3.05
AORRP	0.47	0.15	3.43

For references and additional information, see Section 3.6: QALYs lost per HPV-related health outcome.
JORRP: juvenile-onset recurrent respiratory papillomatosis
AORRP: adult-onset recurrent respiratory papillomatosis

Appendix Table 23: Number of QALYs lost per case of cervical cancer

Age (years)	Base case	Lower bound	Upper bound
15–19	6.32	5.48	8.76
20–24	6.08	5.28	8.42
25–29	5.82	5.04	8.04
30–34	5.51	4.77	7.61
35–39	5.17	4.48	7.13
40–44	4.80	4.16	6.61
45–49	5.00	4.41	6.59
50–54	5.89	5.37	7.18
55–59	5.97	5.51	7.03
60–64	5.20	4.79	6.12
65–69	4.39	4.04	5.16
70–74	3.55	3.26	4.17
75–79	2.76	2.53	3.25
80–84	2.06	1.88	2.42
85–89	1.56	1.41	1.83
90–94	1.26	1.14	1.48
95 +	0.57	0.50	0.67

For references and additional information, see Section 3.6: QALYs lost per HPV-related health outcome.

Appendix Table 24: Number of QALYs lost per case of vaginal cancer

Age (years)	Base case	Lower bound	Upper bound
15–19	7.95	5.13	12.50
20–24	7.64	4.93	12.02
25–29	7.30	4.71	11.49
30–34	6.91	4.45	10.88
35–39	6.48	4.17	10.20
40–44	6.01	3.86	9.46
45–49	6.04	4.20	8.98
50–54	6.68	5.29	8.84
55–59	6.59	5.51	8.24
60–64	5.74	4.77	7.21
65–69	4.84	4.01	6.11
70–74	3.92	3.21	4.98
75–79	3.05	2.48	3.90
80–84	2.28	1.81	2.95
85–89	1.72	1.34	2.27
90–94	1.39	1.05	1.87
95 +	0.64	0.42	0.93

For references and additional information, see Section 3.6: QALYs lost per HPV-related health outcome.

Appendix Table 25: Number of QALYs lost per case of vulvar cancer

Age (years)	Base case	Lower bound	Upper bound
15–19	4.81	3.20	8.29
20–24	4.63	3.08	7.98
25–29	4.44	2.94	7.64
30–34	4.21	2.79	7.25
35–39	3.96	2.62	6.81
40–44	3.69	2.43	6.34
45–49	4.02	2.90	6.35
50–54	5.08	4.13	6.95
55–59	5.29	4.48	6.82
60–64	4.62	3.89	5.98
65–69	3.92	3.27	5.09
70–74	3.19	2.63	4.18
75–79	2.49	2.04	3.29
80–84	1.88	1.50	2.52
85–89	1.44	1.12	1.96
90–94	1.18	0.89	1.64
95 +	0.58	0.37	0.87

For references and additional information, see Section 3.6: QALYs lost per HPV-related health outcome.

Appendix Table 26: Number of QALYs lost per case of penile cancer

Age (years)	Base case	Lower bound	Upper bound
15–19	6.62	4.32	10.63
20–24	6.34	4.14	10.18
25–29	6.04	3.94	9.69
30–34	5.69	3.72	9.12
35–39	5.30	3.46	8.48
40–44	4.87	3.18	7.78
45–49	4.66	3.22	7.14
50–54	4.70	3.63	6.58
55–59	4.41	3.58	5.88
60–64	3.79	3.07	5.05
65–69	3.17	2.56	4.22
70–74	2.56	2.06	3.41
75–79	1.99	1.59	2.65
80–84	1.51	1.19	2.01
85–89	1.17	0.92	1.56
90–94	0.99	0.77	1.31
95 +	0.51	0.37	0.67

For references and additional information, see Section 3.6: QALYs lost per HPV-related health outcome.

Appendix Table 27: Number of QALYs lost per case of anal cancer, females

Age (years)	Base case	Lower bound	Upper bound
15–19	6.73	4.80	10.30
20–24	6.49	4.62	9.92
25–29	6.22	4.41	9.52
30–34	5.91	4.18	9.05
35–39	5.56	3.92	8.52
40–44	5.19	3.64	7.95
45–49	4.93	3.53	7.41
50–54	4.83	3.63	6.97
55–59	4.50	3.46	6.33
60–64	3.98	3.02	5.63
65–69	3.43	2.56	4.87
70–74	2.86	2.08	4.09
75–79	2.28	1.63	3.29
80–84	1.81	1.23	2.64
85–89	1.45	0.94	2.15
90–94	1.25	0.78	1.88
95 +	0.76	0.38	1.19

For references and additional information, see Section 3.6: QALYs lost per HPV-related health outcome.

Appendix Table 28: Number of QALYs lost per case of anal cancer, males

Age (years)	Base case	Lower bound	Upper bound
15–19	9.79	7.88	12.95
20–24	9.39	7.54	12.43
25–29	8.95	7.17	11.87
30–34	8.44	6.74	11.21
35–39	7.87	6.26	10.46
40–44	7.25	5.74	9.66
45–49	6.50	5.13	8.70
50–54	5.66	4.44	7.62
55–59	4.90	3.82	6.62
60–64	4.26	3.27	5.79
65–69	3.59	2.73	4.91
70–74	2.96	2.19	4.08
75–79	2.34	1.70	3.26
80–84	1.84	1.27	2.60
85–89	1.48	0.98	2.13
90–94	1.29	0.82	1.88
95 +	0.76	0.39	1.18

For references and additional information, see Section 3.6: QALYs lost per HPV-related health outcome.

Appendix Table 29: Number of QALYs lost per case of oropharyngeal cancer, female

Age (years)	Base case	Lower bound	Upper bound
15–19	9.42	7.74	12.34
20–24	9.05	7.44	11.86
25–29	8.64	7.10	11.31
30–34	8.16	6.71	10.69
35–39	7.64	6.28	10.00
40–44	7.07	5.81	9.25
45–49	6.68	5.60	8.58
50–54	6.51	5.72	7.99
55–59	6.05	5.43	7.24
60–64	5.26	4.72	6.29
65–69	4.43	3.97	5.30
70–74	3.57	3.19	4.27
75–79	2.77	2.47	3.31
80–84	2.05	1.82	2.46
85–89	1.54	1.36	1.84
90–94	1.23	1.08	1.48
95 +	0.54	0.46	0.64

For references and additional information, see Section 3.6: QALYs lost per HPV-related health outcome.

Appendix Table 30: Number of QALYs lost per case of oropharyngeal cancer, male

Age (years)	Base case	Lower bound	Upper bound
15–19	6.81	5.73	9.34
20–24	6.52	5.48	8.95
25–29	6.21	5.22	8.51
30–34	5.84	4.91	8.01
35–39	5.44	4.57	7.44
40–44	4.99	4.19	6.83
45–49	4.81	4.12	6.41
50–54	4.95	4.42	6.24
55–59	4.69	4.26	5.74
60–64	4.02	3.64	4.92
65–69	3.35	3.03	4.09
70–74	2.69	2.42	3.28
75–79	2.08	1.87	2.54
80–84	1.56	1.39	1.90
85–89	1.20	1.06	1.46
90–94	1.00	0.88	1.21
95 +	0.48	0.40	0.58

For references and additional information, see Section 3.6: QALYs lost per HPV-related health outcome.

7.6.1 Tables of inputs used to calculate QALY losses for cancer

Appendix Table 31: Quality of life weights for general population

Age (years)	Male	Female
17 and younger	0.93	0.93
18–24	0.92	0.91
25–34	0.92	0.91
35–44	0.90	0.89
45–54	0.87	0.86
55–64	0.81	0.80
65–74	0.76	0.78
75+	0.69	0.70

Obtained from Gold et al. (1998).[53]

Appendix Table 32: Quality of life detriments for treatment for HPV-associated cancers

	Base case	Lower bound	Upper bound
Cervical cancer	0.285	0.24	0.33
Vaginal cancer	0.32	0.16	0.52
Vulvar cancer	0.32	0.16	0.52
Penile cancer	0.29	0.20	0.38
Anal cancer	0.51	0.21	0.83
Oropharyngeal cancer	0.25	0.20	0.30

All values in the above table are the same as applied by Jit et al. (2011)[61] except the lower and upper bound values of 0.20 and 0.30 for oropharyngeal cancer, which we selected based on Jit et al.'s use of a normal distribution with a mean of 0.25 and a standard error of 0.02.

Appendix Table 33: Relative five-year cancer survival probabilities

	Age < 50 years			Age 50 years and over		
	Base case	Lower bound	Upper bound	Base case	Lower bound	Upper bound
Cervical	0.774	0.764	0.783	0.571	0.557	0.585
Vaginal	0.705	0.592	0.792	0.524	0.470	0.575
Vulvar	0.844	0.805	0.875	0.632	0.605	0.658
Penile	0.755	0.662	0.826	0.667	0.621	0.708
Anal, women	0.774	0.732	0.810	0.723	0.698	0.747
Anal, men	0.629	0.584	0.670	0.654	0.618	0.688
Oropharyngeal, women	0.634	0.580	0.683	0.560	0.533	0.586
Oropharyngeal, men	0.743	0.721	0.764	0.635	0.622	0.647

Obtained from Surveillance, Epidemiology, and End Results (SEER) Program data provided by Meg Watson and Jessica Blythe King, CDC (personal communication, April 18, 2014).

7.7 HPV acquisition probabilities and other data

Appendix Table 34: Base case values of annual probability of HPV acquisition

Age	HPV type							
(years)	6 & 11	16	18	31	33	45	52	58
12	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
13	0.0020	0.0016	0.0007	0.0009	0.0006	0.0008	0.0016	0.0005
14	0.0083	0.0067	0.0029	0.0037	0.0025	0.0034	0.0068	0.0022
15	0.0176	0.0142	0.0062	0.0079	0.0052	0.0071	0.0145	0.0047
16	0.0268	0.0215	0.0095	0.0120	0.0079	0.0108	0.0220	0.0072
17	0.0328	0.0263	0.0116	0.0146	0.0097	0.0133	0.0269	0.0088
18	0.0364	0.0293	0.0129	0.0163	0.0108	0.0147	0.0299	0.0098
19	0.0466	0.0374	0.0165	0.0208	0.0138	0.0189	0.0383	0.0125
20	0.0536	0.0431	0.0190	0.0239	0.0159	0.0217	0.0440	0.0144
21	0.0586	0.0470	0.0207	0.0261	0.0174	0.0237	0.0481	0.0157
22	0.0559	0.0449	0.0198	0.0250	0.0166	0.0226	0.0459	0.0150
23	0.0523	0.0420	0.0185	0.0233	0.0155	0.0212	0.0429	0.0140
24	0.0444	0.0357	0.0157	0.0198	0.0132	0.0180	0.0365	0.0119
25	0.0366	0.0294	0.0130	0.0163	0.0109	0.0148	0.0301	0.0098
26	0.0314	0.0252	0.0111	0.0140	0.0093	0.0127	0.0258	0.0084
27	0.0314	0.0252	0.0111	0.0140	0.0093	0.0127	0.0258	0.0084
28	0.0314	0.0252	0.0111	0.0140	0.0093	0.0127	0.0258	0.0084
29	0.0244	0.0196	0.0087	0.0109	0.0072	0.0099	0.0201	0.0065
30	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
31	0.0106	0.0085	0.0038	0.0047	0.0031	0.0043	0.0087	0.0028
32	0.0106	0.0085	0.0038	0.0047	0.0031	0.0043	0.0087	0.0028
33	0.0106	0.0085	0.0038	0.0047	0.0031	0.0043	0.0087	0.0028
34	0.0093	0.0075	0.0033	0.0042	0.0028	0.0038	0.0077	0.0025
35	0.0081	0.0065	0.0029	0.0036	0.0024	0.0033	0.0066	0.0022
36	0.0068	0.0055	0.0024	0.0030	0.0020	0.0027	0.0056	0.0018
37	0.0068	0.0055	0.0024	0.0030	0.0020	0.0027	0.0056	0.0018

Age	HPV type							
(years)	6 & 11	16	18	31	33	45	52	58
38	0.0068	0.0055	0.0024	0.0030	0.0020	0.0027	0.0056	0.0018
39	0.0068	0.0055	0.0024	0.0030	0.0020	0.0027	0.0056	0.0018
40	0.0068	0.0055	0.0024	0.0030	0.0020	0.0027	0.0056	0.0018
41	0.0068	0.0055	0.0024	0.0030	0.0020	0.0027	0.0056	0.0018
42	0.0068	0.0055	0.0024	0.0030	0.0020	0.0027	0.0056	0.0018
43	0.0068	0.0055	0.0024	0.0030	0.0020	0.0027	0.0056	0.0018
44	0.0068	0.0055	0.0024	0.0030	0.0020	0.0027	0.0056	0.0018
45	0.0068	0.0055	0.0024	0.0030	0.0020	0.0027	0.0056	0.0018
46	0.0068	0.0055	0.0024	0.0030	0.0020	0.0027	0.0056	0.0018
47	0.0068	0.0055	0.0024	0.0030	0.0020	0.0027	0.0056	0.0018
48	0.0068	0.0055	0.0024	0.0030	0.0020	0.0027	0.0056	0.0018
49	0.0059	0.0048	0.0021	0.0027	0.0018	0.0024	0.0049	0.0016
50	0.0051	0.0041	0.0018	0.0023	0.0015	0.0021	0.0042	0.0014
51	0.0043	0.0034	0.0015	0.0019	0.0013	0.0017	0.0035	0.0011
52	0.0043	0.0034	0.0015	0.0019	0.0013	0.0017	0.0035	0.0011
53	0.0043	0.0034	0.0015	0.0019	0.0013	0.0017	0.0035	0.0011
54	0.0043	0.0034	0.0015	0.0019	0.0013	0.0017	0.0035	0.0011
55	0.0043	0.0034	0.0015	0.0019	0.0013	0.0017	0.0035	0.0011
56	0.0043	0.0034	0.0015	0.0019	0.0013	0.0017	0.0035	0.0011
57	0.0043	0.0034	0.0015	0.0019	0.0013	0.0017	0.0035	0.0011
58	0.0043	0.0034	0.0015	0.0019	0.0013	0.0017	0.0035	0.0011
59	0.0043	0.0034	0.0015	0.0019	0.0013	0.0017	0.0035	0.0011
60	0.0043	0.0034	0.0015	0.0019	0.0013	0.0017	0.0035	0.0011

Based on estimates of overall HPV acquisition probability by age applied in cervical cancer screening models by Myers et al. (2000)[68] and Canfell et al. (2004)[69], scaled for each HPV type to be consistent with prevalence of HPV types observed in US [70] as described in Section 3.7. As described in Section 1.2.1, to better approximate scenarios in which HPV re-infection is possible, these probabilities are divided by 1000 when applied in the model equations. The estimated impact of HPV vaccination is calculated based on relative, not absolute, changes in HPV acquisition, and the use of lower absolute values helps mitigate the bias arising from not explicitly accounting for the possibility of re-infection.

Appendix Table 35: Alternate HPV incidence scenario: Annual probability of HPV acquisition in the "Increased HPV incidence for ages 30 years and older" scenario

Age	HPV type							
(years)	6 & 11	16	18	31	33	45	52	58
12	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
13	0.0020	0.0016	0.0007	0.0009	0.0006	0.0008	0.0016	0.0005
14	0.0083	0.0067	0.0029	0.0037	0.0025	0.0034	0.0068	0.0022
15	0.0176	0.0142	0.0062	0.0079	0.0052	0.0071	0.0145	0.0047
16	0.0268	0.0215	0.0095	0.0120	0.0079	0.0108	0.0220	0.0072
17	0.0328	0.0263	0.0116	0.0146	0.0097	0.0133	0.0269	0.0088
18	0.0364	0.0293	0.0129	0.0163	0.0108	0.0147	0.0299	0.0098
19	0.0466	0.0374	0.0165	0.0208	0.0138	0.0189	0.0383	0.0125
20	0.0536	0.0431	0.0190	0.0239	0.0159	0.0217	0.0440	0.0144
21	0.0586	0.0470	0.0207	0.0261	0.0174	0.0237	0.0481	0.0157
22	0.0559	0.0449	0.0198	0.0250	0.0166	0.0226	0.0459	0.0150
23	0.0523	0.0420	0.0185	0.0233	0.0155	0.0212	0.0429	0.0140
24	0.0444	0.0357	0.0157	0.0198	0.0132	0.0180	0.0365	0.0119
25	0.0366	0.0294	0.0130	0.0163	0.0109	0.0148	0.0301	0.0098
26	0.0314	0.0252	0.0111	0.0140	0.0093	0.0127	0.0258	0.0084
27	0.0314	0.0252	0.0111	0.0140	0.0093	0.0127	0.0258	0.0084
28	0.0314	0.0252	0.0111	0.0140	0.0093	0.0127	0.0258	0.0084
29	0.0244	0.0196	0.0087	0.0109	0.0072	0.0099	0.0201	0.0065
30	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
31	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
32	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
33	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
34	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
35	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
36	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
37	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
38	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047

Age	HPV type							
(years)	6 & 11	16	18	31	33	45	52	58
39	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
40	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
41	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
42	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
43	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
44	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
45	0.0175	0.0141	0.0062	0.0078	0.0052	0.0071	0.0144	0.0047
46	0.0172	0.0139	0.0061	0.0077	0.0051	0.0070	0.0142	0.0046
47	0.0169	0.0136	0.0060	0.0075	0.0050	0.0069	0.0139	0.0045
48	0.0166	0.0134	0.0059	0.0074	0.0049	0.0067	0.0137	0.0045
49	0.0163	0.0132	0.0058	0.0073	0.0049	0.0066	0.0134	0.0044
50	0.0160	0.0129	0.0057	0.0072	0.0048	0.0065	0.0132	0.0043
51	0.0158	0.0127	0.0056	0.0070	0.0047	0.0064	0.0130	0.0042
52	0.0155	0.0125	0.0055	0.0069	0.0046	0.0063	0.0127	0.0042
53	0.0152	0.0122	0.0054	0.0068	0.0045	0.0062	0.0125	0.0041
54	0.0149	0.0120	0.0053	0.0066	0.0044	0.0060	0.0122	0.0040
55	0.0146	0.0118	0.0052	0.0065	0.0043	0.0059	0.0120	0.0039
56	0.0143	0.0115	0.0051	0.0064	0.0042	0.0058	0.0118	0.0038
57	0.0140	0.0113	0.0050	0.0062	0.0042	0.0057	0.0115	0.0038
58	0.0137	0.0110	0.0049	0.0061	0.0041	0.0056	0.0113	0.0037
59	0.0134	0.0108	0.0048	0.0060	0.0040	0.0054	0.0110	0.0036
60	0.0131	0.0106	0.0047	0.0059	0.0039	0.0053	0.0108	0.0035

For ages 30 years and younger, the annual acquisition probabilities in this table are the same as in Appendix Table 34. As described in Section 1.2.1, to better approximate scenarios in which HPV re-infection is possible, these probabilities are divided by 1000 when applied in the model equations. The estimated impact of HPV vaccination is calculated based on relative, not absolute, changes in HPV acquisition, and the use of lower absolute values helps mitigate the bias arising from not explicitly accounting for the possibility of re-infection.

Appendix Table 36: Annual death rates (per 100,000) applied in model

Age (years)	Male	Female
8–9	12.8	10.1
10–14	16.3	12.1
15–19	69.6	28.1
20–24	126.4	44.8
25–29	135.7	55.7
30–34	147.7	72.6
35–39	175.4	102.6
40–44	248.4	154.3
45–49	401.0	248.9
50–54	613.5	374.5
55–59	911.2	524.5
60–64	1,269.2	781.7
65–69	1,871.3	1,222.0
70–74	2,831.9	1,926.9
75–79	4,493.7	3,151.9
80–84	7,358.2	5,319.8
85+	15,414.3	13,219.2

Source: National Vital Statistics Reports, Vol. 61, No. 4, May 8, 2013