Appendix:

The Estimated Lifetime Medical Cost of Diseases Attributable to Human Papillomavirus Infections Acquired in 2018

Harrell W. Chesson, PhD[1*]

Jean-François Laprise, PhD[2]

Marc Brisson, PhD[2,3,4]

Dave Martin, PhD[2]

Donatus U. Ekwueme, PhD[5]

Lauri E. Markowitz, MD[6]

[1]Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[2]Centre de recherche du CHU de Québec-Université Laval, Québec, Canada

[3]Département de médecine sociale et préventive, Université Laval, Québec, Canada

[4]Department of Infectious Disease Epidemiology, Imperial College, London, UK

[5]Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[6]Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

*Corresponding author: Harrell Chesson, Centers for Disease Control and Prevention, Mail-stop US12-3, 1600 Clifton Road, Atlanta, GA, 30329-4027. Phone: (404) 639-8182. Email: Hbc7@cdc.gov.

Work by Marc Brisson, Jean-François Laprise, and Dave Martin was supported by a contract from the Centers for Disease Control and Prevention (CDC; contract 00HCVGEB-2019-35238), a Fonds de recherche du Québec - Santé (FRQS) Research Scholars award (to MB), and a foundation scheme grant from the Canadian Institutes of Health Research (grant number FDN-143283).

HPV-ADVISE simulations were run on super computers managed by Compute Canada (www.computecanada.ca).

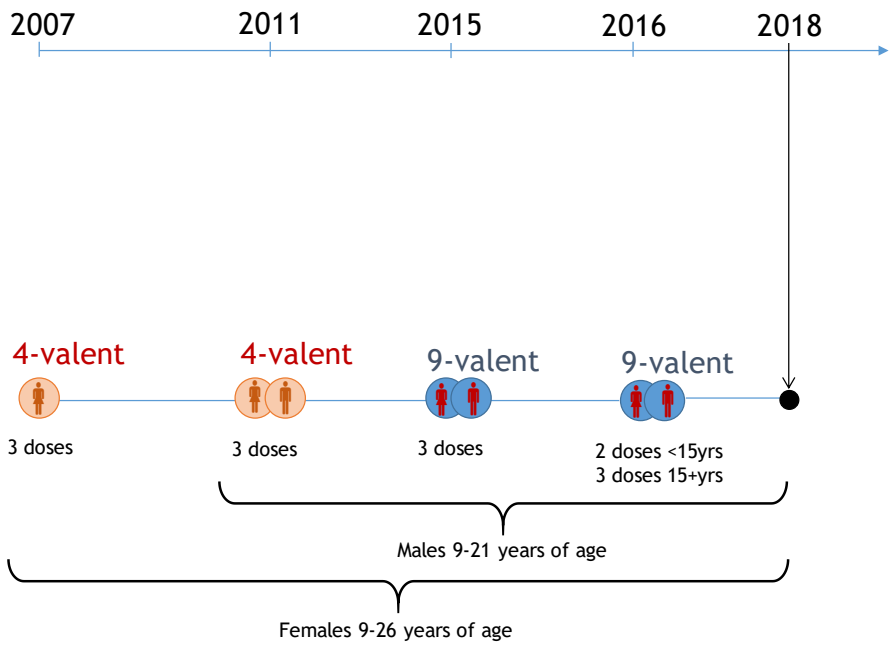
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Section 1: HPV vaccination program and coverage assumptions

HPV vaccination program

We estimated the lifetime number of health outcomes attributable to HPV infections acquired in 2018 in the context of the ongoing HPV vaccination program in the United States. To approximate the historical vaccination program, our model included the changes in HPV vaccination in the United States since 2007: introduction of 4-valent vaccination of girls in 2007 and of gender-neutral vaccination in 2011, and introduction of 9-valent vaccination in 2015. Appendix Figure 1 illustrates the historical changes in the HPV vaccination program. Of note, the change to a 2-dose schedule in 2016 for persons initiating vaccination before their 15th birthday is not relevant for this application of the model, as we assumed full efficacy after the 2nd dose.

Appendix Figure 1. Historical changes in United States HPV vaccination program.



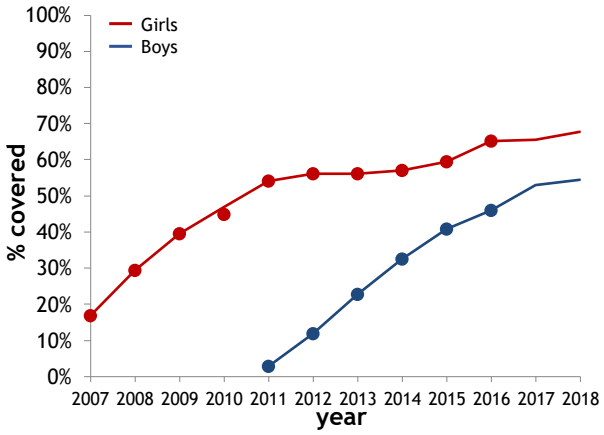
Vaccination efficacy and coverage assumptions

We assumed that there is 0% efficacy until the 2nd dose and that full efficacy is achieved with the 2nd dose, where full efficacy was defined as 95% effectiveness against infection with the HPV vaccine types.

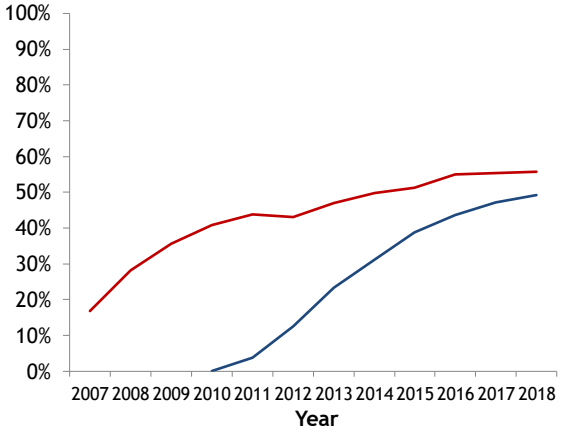
For simplicity, vaccination at age 13 years in our model incorporates vaccination series that occur from ages 9 through 13 years. For 13- to 17-year-olds we reproduced vaccination coverage for 2 doses and more from National Immunization Survey (NIS)-Teen from 2007 to 2016. We assumed uptake rates to be constant at 2016 values from 2017 onwards. We obtained NIS-Teen coverage data from various publications of *The Morbidity and Mortality Weekly Report (MMWR)* Series, such as Reagan-Steiner S. et al., MMWR Morb Mortal Wkly Rep. 2016;65(33):850-8.

Appendix Figure 2. Vaccination coverage. A) Example of model fit: percent covered with 2 doses or more at age 17 years for girls (in red) and boys (in blue) with solid lines representing model predictions and circles representing observed data. B) Average % covered with 2 doses or more in 13- to 17-year-old girls (in red) and boys (in blue).

A) Example of model fit: Percent covered with 2 doses or more at age 17 years for girls and boys



B) Average % covered with 2 doses or more in 13- to 17-year-old girls and boys



Section 2. Number of years that costs were discounted for each health outcome

Genital warts costs were discounted for 0.5 years, which is similar to the value of 0 years applied in the previous cost study (Owusu-Edusei et al., Sex Transm Dis 2013;40:197-201), and is consistent with a 5.0 month median interval from infection to detection of HPV-6-related genital warts in an analysis of young women enrolled in the placebo arm of 2 HPV vaccine trials (Garland et al., J Inf Dis 2009; 199:805-14). Costs for CIN1 and CIN 2/3 were discounted for 1 year and 3 years, respectively. These values are consistent with estimates of a median time from infection to cervical lesions of 12.7 months for CIN 1, 28.2 months for CIN 2, and 34.5 months for CIN 3 from a previous application of the HPV-ADVISE model (Laprise et al., Ann Intern Med 2020;172:22-29). These values are also consistent with estimates based on the placebo arm of an HPV vaccine trial which suggested that nearly all infections that progress to detectable CIN do so within 36 months (Insinga et al., Cancer Epidemiol Biomarkers Prev 2011;20;287–96). Costs for cervical cancer were discounted for 26 years, which is consistent with unpublished estimates of the median time from infection to detection of cervical cancer in the HPV-ADVISE model as well as published estimates from a Cancer Intervention and Surveillance Modeling Network (CISNET) comparative modeling analysis of the phases of cervical carcinogenesis (Burger et al., JNCI J Natl Cancer Inst 2020 112: 955-63). In that study, the median time from HPV acquisition to cervical cancer detection in the four CISNET models was 17.5 years, 25.0 years, 25.7 years, and 26.0 years. For the other cancers, costs were discounted based on the median age at diagnosis relative to the median age of cervical cancer diagnosis. Specifically, costs were discounted by the number of years suggested by the following expression: 26 + (M – 49), where M is the median age of diagnosis for the given cancer site, 26 represents the number of years we discounted cervical cancer costs, and 49 is the median age of cervical cancer diagnosis. The values we applied for the median age of diagnosis (in years) were: penile cancer: 69; vulvar and vaginal cancer: 67 (an average of 66 and 68, respectively); anal cancer: 62 in females and 59 in males; and oropharyngeal cancer: 63 in females and 61 in males. For example, penile cancer costs

were discounted for 46 years, calculated as 26 + (69 – 49). That is, penile cancer costs were discounted for 20 years longer than cervical cancer costs were discounted, because the median age at penile cancer diagnosis is about 20 years older than that of cervical cancer. The median age at cancer diagnosis was obtained from https://www.cdc.gov/cancer/hpv/statistics/age.htm, accessed 12/17/2020, which summarizes information from Viens and colleagues (MMWR 2016;65:661–6).

Section 3. Details of base case calculations of total lifetime cost of disease attributable to HPV infections acquired in 2018

In the base case calculations, we estimated the discounted lifetime cost of all HPV infections acquired in 2018 as $\sum_{i=1}^{7}(Discounted\ cost\ per\ case, females_i \times Number\ of\ cases, females_i) + \sum_{j=1}^{4}(Discounted\ cost\ per\ case, males_j \times Number\ of\ cases, males_j) + Cost\ of\ RRP,$ where *i* denotes the seven health outcomes in females included in the HPV-ADVISE model (genital warts; cervical intraepithelial neoplasia [CIN] grade1; CIN grade 2/3; cervical cancer; anal cancer; vaginal/vulvar cancer; and oropharyngeal cancer); *j* denotes the four health outcomes in males included in the HPV-ADVISE model (genital warts; penile cancer; anal cancer; and oropharyngeal cancer); *Discounted cost per case* reflects the average, lifetime direct medical cost per diagnosed case of the given health outcome, discounted from the year of diagnosis to the year of HPV infection (2018); *Number of cases* reflects the lifetime number of cases of the given health outcome *i* or *j* (in 2018 and beyond) attributable to HPV infections acquired in 2018; and *Cost of RRP* denotes the cost of recurrent respiratory papillomatosis (RRP), which included juvenile-onset RRP (JORRP) and adult-onset RRP (AORRP).

The cost per case estimates for each of these eight outcomes are listed in Table 1 of the main manuscript. The lifetime numbers of cases of the health outcomes attributable to HPV infections acquired in 2018 are listed in Table 2 of the main manuscript and are presented in more detail in

Appendix Table A1. The total cost of RRP was estimated separately and was simply assumed to be 0.6 that of the total cost of genital warts.

Section 4. Details of probabilistic sensitivity analyses

For the probabilistic sensitivity analysis, we calculated the estimated total lifetime medical cost of HPV 10,000 times. In each of the 10,000 calculations, we drew random values for each of the calculation inputs listed in Appendix Table A2, according to the distribution listed therein.

Lognormal distributions for cost per case estimates

For the cost per case estimates we applied lognormal distributions, following methods described elsewhere [Elbasha & Dasbach 2010, Vaccine 28: 6858-67; Wan et al. 2014, BMC Med Res Methodol 14:135] in which the standard error was approximated as the difference between the lower and upper bound values, divided by the term (2 x 1.96).

Custom distributions for estimated numbers of health outcomes

We applied custom distributions for the lifetime number of diagnosed cases of health outcomes attributable to HPV infections acquired in 2018. These custom distributions were designed to approximate the distribution of the 1000 runs of the HPV-ADVISE model. For each health outcome in the analysis (e.g., the number of genital warts cases in females attributable to HPV infections acquired in 2018), we obtained the 10^{th} percentile (P_{10}), 25^{th} percentile (P_{25}), mean, which we denote as P_{50} for simplicity, 75^{th} percentile (P_{75}), and 90^{th} percentile (P_{90}) of results from the HPV-ADVISE model. The minimum was calculated as $P_0 = P_{10} – (2/3)*(P_{25}-P_{10})$ and was set to 0 if this calculation yielded a negative number. The maximum was calculated as $P_{100} = P_{90} + (2/3)*(P_{90}-P_{75})$. As an example, values for the P_i terms for the number of cases of oropharyngeal cancer in males are provided in Appendix Table A3.

To use the custom distribution, we drew a random value q from a uniform distribution between 0 and 1, and then we assigned a value to the custom distribution according to the chart in Appendix

Table A4. For example, if q = 0.05, the value of the custom distribution would be halfway between P_0 and P_{10}. If q = 0.10, the value of the custom distribution would be P_{10}. If q = 0.80, the value of the custom distribution would be one-third of the way between P_{75} and P_{90}. To provide a more detailed example, the custom distribution for the number of cases of oropharyngeal cancer in males is described in Appendix Table A5.

Correlation of model inputs across simulations: Correlation of number of health outcomes

We assumed a 50% correlation across the health outcomes in the 10,000 calculations in our probabilistic sensitivity analysis (e.g., the lifetime number of cervical cancers had a 50% correlation with the lifetime number of penile cancers across the 10,000 calculations). To approximate a correlation of 50% across the number of health outcomes in the 10,000 calculations, in ~50% of the calculations, the same value of q was applied for all health outcomes in the given calculation. For example, in each calculation, there was a 50% probability that the same random value q would be applied to each of the health outcomes, and a 50% probability that each health outcome would be assigned its own random value q.

Correlation of model inputs across simulations: Correlation of cancer cost estimates

We also assumed 50% correlation of the cancer cost estimates. To do so, in 50% of the calculations, the relative deviation of the cost estimates was the same (e.g., if a given draw corresponds to the 48^{th} percentile, then the value chosen for the cost per case of cervical cancer corresponds to the 48^{th} percentile of the distribution defined for the cost of cervical cancer, the value chosen for the cost of penile cancer corresponds to the 48^{th} percentile of the distribution defined for the cost of penile cancer, and so on for the other cancer sites) and in 50% of the calculations the relative deviation was allowed to vary across each cancer site.

Additional results of probabilistic sensitivity analyses

Additional results from the probabilistic sensitivity analyses are shown in Appendix Table A6. In this table, the first column of results shows the same results as presented in the main manuscript for the scenario in which we assumed 50% correlation across the health outcomes and 50% correlation of the cancer cost estimates. The next columns show how the results changed when the correlation assumptions were varied to 0% and to 100%. The final column shows the results when we used a gamma distribution for the number of health outcomes attributable to HPV infections acquired in 2018, rather than the customized distributions. For the gamma distributions, the distribution parameters were estimated to yield results consistent with the mean, 25th percentile, and 75th percentile of the HPV-ADVISE modeling results.

Appendix Table A1: Estimated lifetime number of diagnosed cases of diseases attributable to HPV infections acquired in 2018: 10th, 25th, mean, 75th, and 90th percentiles of results from the HPV-ADVISE model

Panel A: Ages 15–59 years

Health outcome	Lifetime number of cases				
	10th percentile	25th percentile	Mean	75th percentile	90th percentile
Genital warts, females	15,621	18,629	25,442	33,662	35,484
Genital warts males	16,721	19,928	24,967	30,829	33,128
CIN1	11,572	39,538	162,974	270,980	393,451
CIN2/3	33,752	42,431	52,074	60,754	66,540
Cervical cancer	1,912	2,393	3,153	3,920	4,674
Vulvar/Vaginal cancer	559	657	849	1,003	1,300
Penile cancer	279	328	454	492	838
Anal cancer, females	524	596	780	917	1,218
Anal cancer, males	402	480	675	731	1,271
Oropharyngeal cancer, females	388	450	587	699	904
Oropharyngeal cancer, males	2,233	2,634	3,665	3,954	6,868

Appendix Table A1, continued: Estimated lifetime number of diagnosed cases of diseases attributable to HPV infections acquired in 2018: 10th, 25th, mean, 75th, and 90th percentiles of results from the HPV-ADVISE model

Panel B: Ages 15–24 years

Health outcome	Lifetime number of cases				
	10th percentile	25th percentile	Mean	75th percentile	90th percentile
Genital warts, females	4,632	5,213	6,310	7,374	8,531
Genital warts males	1,555	1,710	2,325	3,062	3,217
CIN1	6,953	23,808	103,660	154,225	275,583
CIN2/3	18,751	24,440	29,707	36,028	40,031
Cervical cancer	1,307	1,457	1,978	2,424	2,782
Vulvar/Vaginal cancer	381	450	550	663	751
Penile cancer	169	199	265	291	474
Anal cancer, females	320	359	441	529	593
Anal cancer, males	174	201	268	290	491
Oropharyngeal cancer, females	260	300	370	449	505
Oropharyngeal cancer, males	964	1,112	1,462	1,580	2,655

Appendix Table A2: Details of probabilistic sensitivity analyses: Calculation inputs that were varied and the distributions used

Calculation input	Distribution used in probabilistic sensitivity analyses
Undiscounted cost per case estimates[*]	
Cost per case of CIN 1	lognormal (7.24, 0.16)
Cost per case of CIN 2/3	lognormal (7.82, 0.30)
Cost per case of genital warts	lognormal (6.57, 0.63)
Cost per case of cervical cancer	lognormal (11.20, 0.14)
Cost per case of anal cancer	lognormal (11.44, 0.22)
Cost per case of vaginal/vulvar cancer	lognormal (11.33, 0.22)
Cost per case of oropharyngeal cancer	lognormal (11.75, 0.16)
Cost per case of penile cancer	lognormal (11.08, 0.22)
Number of cases attributable to HPV infections acquired in 2018	
Number of cases of CIN 1	Custom distribution (see Appendix text)
Number of cases of CIN 2/3	Custom distribution
Number of cases of genital warts (females)	Custom distribution
Number of cases of genital warts (males)	Custom distribution
Number of cases of cervical cancer	Custom distribution
Number of cases of anal cancer (females)	Custom distribution
Number of cases of anal cancer (males)	Custom distribution
Number of cases of vaginal/vulvar cancer	Custom distribution
Number of cases of oropharyngeal cancer (females)	Custom distribution
Number of cases of oropharyngeal cancer (males)	Custom distribution
Number of cases of penile cancer	Custom distribution
Ratio of RRP costs to genital warts costs	Uniform distribution between 0.2 and 1

[*]In the probabilistic sensitivity analysis, we drew a random value for the undiscounted cost per case estimate according to the distribution shown, and then discounted this value at a rate of 3% for the number of years listed in Table 1 of the main manuscript.

Appendix Table A3: Percentiles used to inform custom distribution: Example of lifetime number of oropharyngeal cancers in males attributable to HPV infections acquired in 2018

Percentile	Estimate from HPV-ADVISE model
0^{th} percentile (P_0)	1,964.6
10^{th} percentile (P_{10})	2,232.5
25^{th} percentile (P_{25})	2,634.4
Mean value (P_{50})	3,664.6
75^{th} percentile (P_{75})	3,953.8
90^{th} percentile (P_{90})	6,868.3
100^{th} percentile (P_{100})	8,811.4

Values for the 10^{th}, 25^{th}, 75^{th}, and 90^{th} percentiles and for the mean (denoted as P_{50}) were obtained from the HPV-ADVISE model and correspond to the rounded results presented in Appendix Table A1.

Appendix Table A4: Description of custom distribution used in probabilistic sensitivity analyses

Value of q (uniformly distributed between 0 and 1)	Value of customized distribution for the lifetime number of diagnosed cases of a given health outcome attributable to HPV infections acquired in 2018, for a given random value of q
If q ≤ 0.1	$P_0 + [\left(\frac{q}{0.1}\right)(P_{10} - P_0)]$
If 0.1 < q ≤ 0.25	$P_{10} + [\left(\frac{q - 0.1}{0.25 - 0.1}\right)(P_{25} - P_{10})]$
If 0.25 < q ≤ 0.5	$P_{25} + [\left(\frac{q - 0.25}{0.5 - 0.25}\right)(P_{50} - P_{25})]$
If 0.5 < q ≤ 0.75	$P_{50} + [\left(\frac{q - 0.5}{0.75 - 0.5}\right)(P_{75} - P_{50})]$
If 0.75 < q ≤ 0.9	$P_{75} + [\left(\frac{q - 0.75}{0.9 - 0.75}\right)(P_{90} - P_{75})]$
If q > 0.9	$P_{90} + [\left(\frac{q - 0.90}{0.1}\right)(P_{100} - P_{90})]$

P_i corresponds to the i^{th} percentile of results from the HPV-ADVISE model. For example, for cervical cancer, P_{10} corresponds to the 10^{th} percentile of the HPV-ADVISE model simulations for the number of diagnosed cases of cervical cancer attributable to HPV infections acquired in 2018. For P_{50}, we applied the mean value rather than the median value from the HPV model results.

Appendix Table A5: Custom distribution: Example of lifetime number of oropharyngeal cancers in males attributable to HPV infections acquired in 2018

Value of q	Value of custom distribution	Value of q	Value of custom distribution	Value of q	Value of custom distribution	Value of q	Value of custom distribution
0.00	1,964.63	0.25	3,676.32	0.5	5,388.00	0.75	7,099.68
0.01	1,991.42	0.26	2,675.56	0.51	3,676.19	0.76	4,148.08
0.02	2,018.21	0.27	2,716.77	0.52	3,687.76	0.77	4,342.39
0.03	2,045.00	0.28	2,757.98	0.53	3,699.33	0.78	4,536.69
0.04	2,071.79	0.29	2,799.20	0.54	3,710.89	0.79	4,730.99
0.05	2,098.58	0.3	2,840.41	0.55	3,722.46	0.8	4,925.30
0.06	2,125.37	0.31	2,881.62	0.56	3,734.02	0.81	5,119.60
0.07	2,152.15	0.32	2,922.83	0.57	3,745.59	0.82	5,313.90
0.08	2,178.94	0.33	2,964.04	0.58	3,757.16	0.83	5,508.21
0.09	2,205.73	0.34	3,005.25	0.59	3,768.72	0.84	5,702.51
0.1	2,232.52	0.35	3,046.46	0.6	3,780.29	0.85	5,896.81
0.11	2,259.31	0.36	3,087.67	0.61	3,791.85	0.86	6,091.12
0.12	2,286.10	0.37	3,128.88	0.62	3,803.42	0.87	6,285.42
0.13	2,312.89	0.38	3,170.09	0.63	3,814.99	0.88	6,479.73
0.14	2,339.68	0.39	3,211.31	0.64	3,826.55	0.89	6,674.03
0.15	2,366.46	0.4	3,252.52	0.65	3,838.12	0.9	6,868.33
0.16	2,393.25	0.41	3,293.73	0.66	3,849.69	0.91	7,062.64
0.17	2,420.04	0.42	3,334.94	0.67	3,861.25	0.92	7,256.94
0.18	2,446.83	0.43	3,376.15	0.68	3,872.82	0.93	7,451.24
0.19	2,473.62	0.44	3,417.36	0.69	3,884.38	0.94	7,645.55
0.2	2,500.41	0.45	3,458.57	0.7	3,895.95	0.95	7,839.85
0.21	2,527.20	0.46	3,499.78	0.71	3,907.52	0.96	8,034.15
0.22	2,553.98	0.47	3,540.99	0.72	3,919.08	0.97	8,228.46
0.23	2,580.77	0.48	3,582.20	0.73	3,930.65	0.98	8,422.76
0.24	2,607.56	0.49	3,623.42	0.74	3,942.21	0.99	8,617.06
0.25	3,676.32	0.5	5,388.00	0.75	7,099.68	1.00	8,811.37

Appendix Table A6. Results from probabilistic sensitivity analyses under different assumptions about correlation of model parameters and distribution of number of health outcomes: Estimated lifetime cost of HPV infections acquired in 2018 ($ billions)

Panel A: Ages 15–59 years

Percentile	Estimated lifetime cost of HPV infections acquired among population aged 15–59 years in 2018					
	Correlation of outcomes set to 0.5; correlation of cost estimates set to 0.5	Correlation of outcomes set to 0	Correlation of outcomes set to 1	Correlation of cost estimates set to 0	Correlation of cost estimates set to 1	Alternate (gamma) distribution of outcomes: Correlation of outcomes set to 0.5; correlation of cost estimates set to 0.5
2.5th percentile	0.31	0.41	0.29	0.32	0.31	0.30
10th percentile	0.41	0.49	0.36	0.42	0.41	0.41
25th percentile	0.55	0.60	0.47	0.56	0.55	0.53
Median	0.77	0.77	0.75	0.77	0.77	0.69
75th percentile	1.01	0.98	1.05	1.01	1.01	0.92
90th percentile	1.28	1.17	1.38	1.27	1.27	1.23
97.5th percentile	1.57	1.38	1.65	1.55	1.56	1.73

Appendix Table A6, continued. Results from probabilistic sensitivity analyses under different assumptions about correlation of model parameters and distribution of number of health outcomes: Estimated lifetime cost of HPV infections acquired in 2018 ($ billions)

Panel B: Ages 15–24 years

Percentile	Estimated lifetime cost of HPV infections acquired among population aged 15–24 years in 2018					
	Correlation of outcomes set to 0.5; correlation of cost estimates set to 0.5	Correlation of outcomes set to 0	Correlation of outcomes set to 1	Correlation of cost estimates set to 0	Correlation of cost estimates set to 1	Alternate (gamma) distribution of outcomes: Correlation of outcomes set to 0.5; correlation of cost estimates set to 0.5
2.5th percentile	0.16	0.20	0.15	0.17	0.16	0.15
10th percentile	0.21	0.24	0.18	0.21	0.21	0.21
25th percentile	0.27	0.30	0.24	0.28	0.28	0.27
Median	0.39	0.40	0.40	0.40	0.40	0.36
75th percentile	0.54	0.52	0.55	0.54	0.54	0.49
90th percentile	0.72	0.67	0.76	0.72	0.72	0.65
97.5th percentile	0.90	0.81	0.93	0.88	0.89	0.92

Appendix Table A7: Population estimates used to calculate lifetime number of diagnosed cases of disease attributable to HPV infections acquired in 2018

Age group	Population size		
	Total	Male	Female
Ages 15 to 59 years	193,236,367	96,802,234	96,434,133
Ages 15 to 24 years	43,163,455	22,094,421	21,069,034

From the 2018 American Community Survey 1-Year Estimates, Table S0201,using American FactFinder; http://factfinder.census.gov; obtained from Kristen Kreisel February 13, 2020.