**Supplementary materials for “****Updated estimate of the annual direct medical cost of screening and treatment for human papillomavirus associated disease in the United States”**

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**Section 1: Mean and confidence interval calculations for number of screenings and number of HPV-attributable disease cases**

* 1. Total number of cervical cancer screenings per year

Using the National Health Interview Survey (NHIS), we first estimated the number of women aged 21-65 years with no prior hysterectomy living in the United States in 2018. We then estimated the proportion of women in this category who received a cervical cancer screening in the past year as the average from four different sources (NHIS, New Mexico HPV Pap Registry (NMHPR), HPV Vaccine Impact Monitoring Project (HPV-IMPACT), and MarketScan). We multiplied the average proportion of women eligible for screening who are screened in a given year by the number of women eligible for screening to calculate the total number of screenings per year. See Table S1 for estimates of the number of women screened from each data source.

**NHIS:** NHIS is a nationally representative household survey [1]. We analyzed NHIS data directly rather than relying on published data. To estimate the proportion of women screened annually using NHIS, we took the weighted proportion of women between the ages of 21 and 65 years in 2018 with no history of hysterectomy that reported having had a cervical cancer screening or co-screening in the past year, and calculated Wilson confidence intervals. We then multiplied this number by 0.8 to account for overreporting. The adjustment factor of 0.8 falls within overreporting adjustment ranges based on previous comparisons of survey based and non-survey based data collection [2,3].

**NMHPR:** In the NMHPR, data on cervical cancer screenings were collected from all hospitals and clinics operating in New Mexico via the laboratories which process cervical screening tests [4]. Studies have reported the percentage of women in New Mexico screened every 1, 2, 3, 4, 5, or >5-7 years for women aged 25-29 years and 30-64 years [5]. We assume that the screening intervals of women aged 21-24 years are the same as the reported screening intervals for women aged 25-29 years. Census data shows that 22.8% of U.S. women between the ages of 20 and 64 years (an approximation of our age range of interest) fall between the ages of 20 and 29 years (based on 2019 data). Applying reported screening intervals for women aged 25-29 years to 22.8% of the U.S. female population aged 21-65 years without hysterectomies and applying reported screening intervals for women aged 30-64 years to the remainder of the population aged 21-65 years without hysterectomies, we estimated 37.6 million screenings. In doing so, we assumed that the probability of being screened in the past year was 100% for women screened every year, 50% for women screened every two years, 33% for women screened every three years, 25% for women screened every four years, 20% for women screened every five years, and 15% for the least frequently screened group (we assumed the women in the <5-7 years category were screened every 6.5 years).

We then adjusted this estimate for the fact that 67% of New Mexico’s population lives in a metropolitan statistical area (MSA), while 85% of the national population lives in an MSA, indicating that New Mexico has a higher proportion of residents living in rural areas than the United States as a whole. In New Mexico, an additional 3.1% of urban women aged 21-29 years are up to date on their screening compared to rural women, while an additional 1.2% of urban women aged 30-65 years are up to date on their screening compared to rural women [6] (defined as Pap test every 3 years for women aged 21-29 years and Pap test every 3 years or Pap test plus high-risk HPV testing every 5 years for women aged 30-65 years).

We make the simplifying assumptions that (1) the difference in percent of women following screening guidelines in rural vs. urban areas comes from the difference in the percent of women who follow screening guidelines exactly and the percent of women who are in the least frequent screening category, (2) that women over the age of 30 years who are screened every 4 or 5 years are also co-tested for HPV, and (3) that the age distribution of women living in rural and urban areas is the same. These assumptions allow us scale up the proportion of women screened annually in New Mexico to the national scale using the following procedure.

First, we assumed that 67% of the national population of women aged 21-65 years without hysterectomies were in urban areas and assumed that 33% of the population was in rural areas, as in New Mexico. We then adjusted screening intervals for each of these groups such that an increased number of urban women were up to date on their screenings, as described above. We then summed the expected numbers of annual screenings. We repeated this procedure, assuming that 86% of the population lived in urban areas, and 14% of the population lived in rural areas, matching 2020 Census Redistricting Data. Recalculating the expected number of annual screenings, we found an increase of 0.044%. Thus, to calculate the annual proportion of women nationally who are screened for cervical cancer, we multiplied the proportion of New Mexican women screened annually by 1.00044, giving a mean national estimate of 37.7 million screenings. Confidence intervals of total screenings were derived from confidence intervals of reported screening intervals [5].

**HPV-IMPACT:** HPV-IMPACT site data [7] includes the number of women who have been screened each year in 5 sentinel sites (4 counties and 1 metro area across the country). HPV-IMPACT sites incorporate MarketScan, Behavioral Risk Factor Surveillance System (BRFSS), and American Community Survey (ACS) data into estimates of the proportion of women in each sentinel site who were screened each year.

We used HPV-IMPACT data from 2016. Data only included estimates up to age 39 years. For ages 40-65 years, we assumed that screening rates are the same as for individuals ages 35-39 years as they are for individuals aged 40-65 years, and we assumed that the ratio of individuals aged 35-39 years to individuals ages 40-65 years is the same in each sentinel site as it is at the national level. From these sites, we collected the average proportion of women screened in a year and calculated confidence intervals using each site as a data point. HPV-IMPACT sites only collect data from MSAs, whereas only 85% of U.S. individuals live in MSAs. Thus, we adjusted our screening estimate using the data and methodology used to adjust for urbanicity in NMHPR.

**Marketscan:** We took published data from MartketScan which show the percentage of women in various age groups who received cervical screening tests alone, or in combination with high-risk HPV tests in 2019 [8]. We multiplied these numbers by the relative proportion of U.S. women in each age group from census data. We calculated the overall proportion of women who received cervical cancer screenings in 2019. Confidence intervals are not reported, and so we derived confidence intervals from the standard error of test use averaged across age groups.

* 1. Total number of high-risk HPV tests per year

The cost of testing for high-risk HPV types was not included in the 2012 study [9]. However, HPV tests are now part of the standard testing recommendation for women over the age of 29 years. Thus, we estimated the percent of women ages 21-65 years who are tested for HPV each year, using the average of NMHPR and MarketScan estimates, and multiplied this by the number of women nationally ages 21-65 years with no history of hysterectomy.

From NMHPR, 61,991 HPV tests were performed in 2019 [10]. This is 9.32% of the women in the 21-65 years age range in 2019 based on U.S. census data. When estimating the percentage of women who are screened for cervical cancer annually, we estimated that we needed to increase the estimate from New Mexico by 0.6%. Repeating this procedure, we find that 9.38% of women were tested annually for HPV. Confidence intervals were not reported for these data, so we used the same proportional confidence intervals for HPV testing percentages taken from the NMHPR as we estimated for our cervical cancer screening estimate from NMHPR.

* 1. Number of anogenital and oropharyngeal cancer cases

Estimates were taken directly from the CDC website [www.cdc.gov/cancer/hpv/statistics/cases.htm](http://www.cdc.gov/cancer/hpv/statistics/cases.htm). Confidence intervals are not reported. Following the 2012 estimate [9], we relied on confidence intervals of the proportion of anogenital and oropharyngeal cancer cases that contain HPV to calculate confidence intervals for the total number of anogenital and oropharyngeal cancer cases attributable to HPV.

* 1. Proportion of anogenital and oropharyngeal cancer cases attributable to HPV

The percentage of cancers containing HPV DNA (and therefore assumed to be attributable to HPV) by cancer location and patient sex were taken from a 2015 study [11]. Wilson 95% confidence intervals were obtained from unpublished results of the 2015 study.

* 1. Total number of CIN and genital warts cases

We applied estimates for the number of diagnosed CIN I, CIN II-III, and genital warts cases each year, based on an epidemiological model [11]. 80% confidence intervals are reported, which we adjusted to 95%. These estimates reflect the number of lifetime diagnosed cases attributable to HPV infections acquired in 2018. However, for the purposes of our current study, we assumed that these estimates reflect reasonable approximations of the average annual number of diagnosed cases attributable to HPV in recent years.

* 1. Total number of JORRP cases

We applied case estimates from a study conducted by the CDC that calculated the incidence of JORRP in 2 year blocks from 2004-2013 [13]. Trends show that JORPP incidence was significantly decreasing over time. Thus, JORPP incidence in 2022 is likely lower than in 2013. However, lacking more updated estimates, we applied the 2013 JORPP incidence estimate. We calculated Wilson 95% confidence intervals based on the number of cases and annual births reported in the 2013 estimate.

**Section 2: Mean and confidence interval calculations for cost per screening and cost of treating HPV-attributable diseases**

 In all cases below, costs were updated to 2020 dollars with the health services component of the personal consumption expenditures index (available at <https://apps.bea.gov/>).

* 1. Cost per cervical cancer screening

We applied one estimate for screening costs for underserved women tested through nationally funded programs (National Breast and Cervical Cancer Early Detection Program (NBCCEDP) data), and one estimate for privately insured women [14]. We used women tested through nationally funded programs as a proxy for individuals enrolled in Medicaid and calculated a weighted average of these values based on the proportion of individuals on Medicaid. Specifically, we assumed that 22.8 % of individuals are on Medicaid, based on November 2021 Medicaid Enrollment Data and the Census.gov estimated population size on November 1, 2021.

Cost data for individuals screened through nationally funded programs were based on a web-based cost assessment tool used by different grantees. We used the number of grantees as the sample size when converting reported standard deviations to 95% confidence intervals.

For privately insured women, cost data were collected at the individual scale. Thus, we used the number of women as the sample size to convert reported standard deviations to confidence intervals.

* 1. Cost per HPV screening

Almost all HPV testing occurs in the context of cervical cancer screening or during follow-up for abnormal screening [8]. Thus, we assumed that HPV co-testing imposed only that additional cost of lab tests for the HPV test, as the cost of the office visit was already considered in our estimate of the cost of cervical cancer screening. We used the HPV lab test cost from the 2020 Medicare fee schedule (available at https://cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched).

* 1. Cancer cost estimation methods and treatment costs for cervical cancer

We collected estimates for the cost of treating HPV-associated cancers from Chesson et al. 2019 [15] and from a literature search for cost papers published since Chesson et al. 2019 (search 4, below). Across studies and cancer types, we found estimates of the annual average cost of treatment, the cost of treatment for the two years post diagnosis, the cost per month to treat cancer during different stages of cancer, and the lifetime cost of cancer treatment. We then examined which of these types of cost estimates were available for each type of anogenital and oropharyngeal cancer.

* Sources for cervical cancer costs included annual average costs [16,17], 2-year costs [18–20], and monthly costs per treatment stage [21].
* Sources for vaginal and vulvar cancer costs only included 2-year costs [19,20,22].
* Sources for anal cancer costs included 2-year costs [19,23] as well as lifetime cost estimates for patients over the age of 66 [24].
* Sources for penile costs only included 2-year costs [25].
* Sources for oropharyngeal cancer costs included 2-year costs [19,26,27] and lifetime costs [28].

The average annual cost of treating HPV-attributable cancer in the United States can be approximated as the number of new cases diagnosed per year multiplied by the lifetime medical cost per case, assuming that cancer incidence and treatment costs do not change substantially from one year to the next. Thus, given that we applied annual cancer incidence estimates in our analysis, it would have been ideal for us also to have applied estimates of the lifetime cost per case of cancer. However, we applied 2-year cost estimates given that these estimates were available for all HPV associated cancer types. We assumed that these 2-year estimates reflect a reasonable approximation of the lifetime costs. This assumption is supported by the cost data for the two cancers (anal and oropharyngeal) for which 2-year cost estimates and lifetime cost estimates were available. Although the 2-year and lifetime cost estimates were not directly comparable, the 2-year cost estimates were actually greater than the lifetime cost estimates, suggesting that our use of 2-year cost-estimates instead of lifetime cost estimates did not cause substantial underestimation of the cost of HPV cancers (e.g. our total 2-year cost per case estimates of anal and oropharyngeal cancer were $129,000 and $141,000 respectively in 2020 dollars while published lifetime cost per case estimates were $55,014 and $114,447 respectively in 2020 dollars [24,28]). Further, our use of 2-year costs allowed us to be consistent across all the HPV cancers, thereby yielding more meaningful estimates for the proportion of the total cost attributable to each cancer.

If cancer treatment cost papers reported standard deviations, then we used sample size to convert the standard deviations of the cost estimates to confidence intervals via standard error. In cases where mean costs were reported for two years of data, but standard deviation was only reported for one year of data [18], we assumed that the standard deviation range for the first-year costs was the standard deviation range for the full 2-year costs, before converting to confidence intervals. In cases where the standard deviation was reported separately for first- and second-year costs, we calculated the combined 2-year cost standard deviation by converting standard deviations to variances, and then found the square root of the summed variances before converting to confidence intervals.

* 1. Treatment cost per cervical cancer case

For cervical cancer, we found cost estimates for privately insured individuals [18], Medicaid insured individuals [22], and nationally representative estimates [19]. We performed a weighted average of the estimated 2-year costs based on the percentage of individuals in the country with private or Medicaid insurance, and averaged the error estimates accordingly as well. In doing so, we assumed that 22.8 percent of individuals are on Medicaid, as noted above in the “cost of cervical cancer screening” section (Appendix Table S2). Each estimate was given a weight based on the portion of the population they represent; i.e., Medicaid estimates were given a weight of 0.228, private insurance estimates were given a weight of (1 - 0.228), and nationally representative estimates are given a weight of 1.

* 1. Treatment cost per vaginal or vulvar cancer case

We estimated 2-year costs per vaginal and vulvar case the same way we did for cervical cancer cases, given that we had estimates for privately insured individuals [20], Medicaid insured individuals [22], and nationally representative estimates [19] (Appendix Table S2).

* 1. Treatment cost per oropharyngeal cancer case

We estimated 2-year costs per oropharyngeal case the same way we did for cervical cancer cases, given that we had estimates for privately insured individuals [27], Medicaid insured individuals [26], and nationally representative estimates [19] (Appendix Table S2).

* 1. Treatment cost per anal cancer case

We found estimates of 2-year costs for anal cancer for privately insured individuals [23] and nationally representative estimates [19]. We calculated a theoretical cost of Medicaid insured individuals by looking at the average ratio of privately insured costs to Medicaid costs for cervical, vaginal, vulvar, and oropharyngeal cancers, and then dividing the privately insured anal cancer cost by this ratio. We then took a weighted average of the three estimates (Appendix Table S2).

2.8 Treatment cost per penile cancer case

For penile cancer, we only found cost estimates for privately insured individuals [25]. As with anal cancers, we used the average ratio of privately insured costs to Medicaid costs, and privately insured costs to nationally representative costs, to create theoretical Medicaid and national penile cancer costs. We then took a weighted average of the three estimates (Appendix Table S2).

* 1. Cost per screening follow-up: CIN treatment

We found no updated cost estimates for CIN treatment. CIN treatment costs were calculated and updated from our original source: administrative and laboratory records of the Kaiser Permanente Northwest health plan [2]. The CIN treatment costs we obtained reflected the costs of an “episode” of CIN, which included treatment of CIN and follow-up visits; the average duration of an episode was about 20 months.

* 1. Treatment cost per genital warts case

We applied estimates from a study [29] that published the number of medical visits per episode of care of privately insured individuals with genital warts in 2002, and also the cost per episode of care. The source study defined an episode of care as the period starting at initial diagnoses and continuing until one full year had passed without any wart-related medical claims. Thus, we interpreted the estimated cost per episode of care as being equivalent to a 2-year cost estimate, given that the average duration per episode of care was less than 120 days for men and 70 days for women.

Cost estimates per episode of care and standard deviations were stratified by age, with various sample sizes per age. Thus, we took the weighted average of the mean, and used the formula for averaging size varying standard deviations to find a new standard deviation, which we converted to confidence intervals using the summed samples sizes.

* 1. Treatment cost per JORRP case

We applied 2-year cost estimates for JORRP [30]. This paper estimates costs independently for privately insured and Medicaid insured patients. We used a weighted average of the two based on the proportion of people in the United States who are on Medicaid (22.8%).

**Section 3: Estimating total costs when case data are absent**

* 1. Total cost of follow-up of false-positive cervical cancer screening

For the follow-up costs of false-positive tests, we applied the estimate used in the 2012 study (0.4 billion dollars) and adjusted to 2020 dollars. We then decreased this estimate to account for changes in the total number of cervical cancer screenings, as we assumed that the probability of a false-positive result per screening has not changed.

* 1. Total cost of AORRP

The 2012 HPV cost study did not include sources for the estimates of the total number of AORRP cases or the cost per case. Instead, it was assumed that the total cost of AORRP was 0.39 that of JORRP. For our updated study, we did not assume that this ratio has held, given that HPV vaccination is expected to affect JORRP incidence at the population level more quickly that AORRP incidence. Thus, recent decreases in JORRP might not be reflective of trends in AORRP.

While we found costs per case of AORRP [30], we found no estimates for annual number of AORRP cases. Thus, we simply used the total cost due to AORRP in the previous study and adjusted for inflation. While this approach does not make use of any new data since the previous study, any bias from this approach is likely minimal given that AORRP makes up 0.6% of the total estimated cost of HPV.

**Section 4: Using incident cases and lifetime costs as inputs to approximate the annual cost of treatment of all prevalent cases**

For each health outcome, our general approach was to multiply the annual number of diagnosed cases attributable to HPV by the lifetime treatment cost per case; this approach approximates the annual cost burden of treatment of all diagnosed HPV-attributable cases, regardless of when the cases were first diagnosed. The annual cost of cancer in a given year includes all treatment costs of cancer in the given year, regardless of when the cancers were diagnosed. This would include first-year costs for those cancers diagnosed in the given year, second-year costs for cancers diagnosed in the previous year, third-year costs for cancers diagnosed two years ago, and so on. Unfortunately, data required to estimate annual cost in this manner is unavailable. However, we can estimate the annual cost burden by multiplying the number of new cases per year by the lifetime treatment cost. This approximates the annual cost burden, provided the annual number of cases and the cost per case do not change much from year to year.

Here we give an example with fictional cost estimates: Suppose each cancer case has a lifetime cost of $100, and that this lifetime cost per case of $100 is broken down to $50 in year 1, $40 in year 2, and $10 in year 3, and $0 in years 4 and beyond. Suppose 10 cancer cases are diagnosed per year. Each year, there will be 10 new cases incurring a first-year cost of $50 each ($500 total), 10 cases diagnosed the previous year incurring a second-year cost of $40 each ($400 total), and 10 cases diagnosed 2 years ago incurring a third-year cost of $10 each ($100 total). This works out to an annual treatment cost of all cancers of $1000. Alternatively, we can use the method employed in this manuscript, where we estimate the total annual cost burden of cancer cases as the number of new cases per year (10) multiplied by the lifetime cost per case ($100), which works out to the same annual burden of $1000. This approximation works out if cancer incidence and treatment costs are fairly steady from one year to the next.

**Section 5: Estimating total cost of annual vaccination in the United States**

We estimated annual cost of HPV vaccination as the cost per two-dose course of the GARDASIL® vaccine, multiplied by the number of individuals vaccinated annually.

The cost per dose of GARDASIL is listed as $208.05 (public) and $268.77 (private) according to the CDC Vaccine Price list as of February 3, 2023 (<https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html>). We assumed the public price would be applicable to half of recipients [31]. We assumed an average administration cost of $20 per dose, for a total average cost per dose of $258.41 ($238.41 + $20) [31].

We assume that most vaccinations occur in adolescents rather than adults, such that adult vaccination is a relatively minor percentage of the annual cost of HPV vaccination. NIS-Teen, a survey of adolescents in the United States using a random-digit-dialed telephone recruitment strategy estimated that 79% of 17-year-olds in the United States in 2020 had been vaccinated for HPV [32] with at least one dose, and 64.5% were up to date with the vaccine series (defined as those with ≥3 doses, and those with 2 doses when the first HPV vaccine dose was initiated before age 15 years and there was at least 5 months minus 4 days between the first and second dose). We assumed there would be an average of 2 doses per adolescent who initiates the HPV vaccine series. Although some adolescents might receive only one dose, this will be offset at least in part by those who receive three or more doses. The U.S. census estimates approximately 4,300,000 individuals aged 17 in the United States. While most of vaccinated 17-year-olds would be vaccinated at younger ages, we can still take the number of vaccinated 17-year-olds as the approximate number of individuals needing to be vaccinated a year to maintain 79% vaccination coverage for those leaving adolescence. Thus, multiplying the number of 17-year-olds by 79%, we estimate 3,400,000 annual vaccinations.

Multiplying this number by two doses at $258.41 per dose, we estimate that the annual cost of HPV vaccination in the U.S. is $1.8 billion.

**Section 6: All PubMed literature searches**

Search 1: Pap smear frequency

Title/Abstract: Pap OR Papanicolaou

AND

Title/Abstract: “National Health Interview Survey” OR “National Ambulatory Medical Care Survey” OR “National Hospital Ambulatory Medical Care Survey”

Dates: Jan 1, 2012 – April 1, 2022

Results: 52 papers

3 remaining after title and abstract review

Search 2: Pap smear frequency 2

Title/Abstract: "cervical cancer screening rate” OR "cervical cancer screening rates" OR "cervical cancer screening frequency" OR "Pap smear frequency"

Since 2012

Results: 163 papers

Search 3: Cost of Pap smears, CIN, false-positives

Title/Abstract: cost OR costs OR “economic burden” OR “economic impact”

AND

Title/Abstract: “cervical cancer screening” OR Pap OR Papanicolaou OR “cervical intraepithelial neoplasia”

Dates: Jan 1, 2012 – April 8, 2022

Results: 1135 papers

Search 4: cancer treatment costs

Title/Abstract: cancer OR cancers OR neoplasm OR neoplasms

AND

Title/Abstract: cervical OR vulvar OR vaginal OR penile OR anal OR oropharyngeal OR “oral pharyngeal” OR “head and neck”

AND

Title/Abstract: cost OR costs OR “economic impact” OR “economic burden”

Dates: Nov 29, 2018 – April 6, 2022

Results: 1126 papers.

Filtered out all papers that (a) did not contain primary cost data, (b) were set in another country, (c) estimates costs of specific treatments rather than total costs, (d) only estimated costs for a single year after diagnoses, (e) applied to specific sub-populations (e.g. veterans).

8 remaining after title and abstract review

Search 5: RRP Incidence

Title/Abstract: “recurrent respiratory papillomatosis”

AND

Title/Abstract: incidence OR trend

Since 2012

46 papers

Search 6: RRP cost

Title/Abstract: “recurrent respiratory papillomatosis”

AND

Title/Abstract: cost OR costs OR “economic impact” OR “economic burden”

Since 2012

28 papers

**CITATIONS**

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Table S1: Mean and 95% confidence intervals for the annual number of cervical cancer screenings from various sources.

|  |  |  |
| --- | --- | --- |
| **Source** | **Mean Estimate** | **95% Confidence Interval** |
| NHIS | 32.7 million | 31.7 – 33.6 million |
| NMHPR | 37.6 million | 36.8 – 38.5 million  |
| HPV-IMPACT | 24.1 million | 18.9 – 29.4 million |
| Marketscan | 24.0 million | 21.2 – 26.9 million |
| Combined | 29.6 million | 27.2 – 32.1 million |

Table S2: Cost in 2020 dollars of 2 years of treatment post diagnosis for HPV associated cancers.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cancer site** | **Private cost** | **Medicaid cost** | **Nationally representative cost** | **Weighted average** |
| Cervical | 95,800 | 28,000 | 93,300 | 86,800 |
| Vaginal | 113,000 | 29,600 | 141,000 | 117,000 |
| Vulvar | 43,700 | 10,300 | 81,700 | 58,900 |
| Oropharyngeal | 170,000 | 69,300 | 134,000 | 141,000 |
| Anal | 156,000 | 44,600\* | 128,000 | 129,000 |
| Penile | 93,200 | 26,700\* | 103,000\* | 90,400 |

\*Costs were extrapolated from private and nationally representative costs based on average ratios of between cost sources for cervical, vaginal, vulvar, and oropharyngeal cancers.