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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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Abstract

The annual direct medical cost attributable to human papillomavirus (HPV) in the United States over the period 2004–2007 was estimated at $9.36 billion in 2012 (updated to 2020 dollars). The purpose of this report was to update that estimate to account for the impact of HPV vaccination on HPV-attributable disease, reductions in the frequency of cervical cancer screening, and new data on the cost per case of treating HPV-attributable cancers. Based primarily on data from the literature, we estimated the annual direct medical cost burden as the sum of the costs of cervical cancer screening and follow-up and the cost of treating HPV-attributable cancers, anogenital warts, and recurrent respiratory papillomatosis (RRP). We estimated the total direct medical cost of HPV to be $9.01 billion annually over the period 2014–2018 (2020 U.S. dollars). Of this total cost, 55.0% was for routine cervical cancer screening and follow-up, 43.8% was for treatment of HPV-attributable cancer, and less than 2% was for treating anogenital warts and RRP. Although our updated estimate of the direct medical cost of HPV is slightly lower than the previous estimate, it would have been substantially lower had we not incorporated more recent, higher cancer treatment costs.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the National Cancer Institute.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.02.049.

Keywords

Human papillomavirus; Cost; Screening; Health economics; Cervical cancer; Intraepithelial neoplasia

1. Introduction

Human papillomavirus (HPV) causes the majority of anogenital and oropharyngeal cancers in the U.S., with an estimated 37,500 cancer cases annually [1]. Further, HPV causes anogenital warts and recurrent respiratory papillomatosis (RRP). In addition to reducing quality of life, HPV imposes a substantial direct economic cost burden annually. Screening and treatment of HPV-attributable disease cost the U.S. an estimated $9.36 billion annually over the period 2004–2007, updated to 2020 U.S. dollars [2].

The purpose of this study was to update the annual direct medical cost of screening for and treating HPV associated disease. This update is needed for three reasons. First, the implementation of HPV vaccination has lowered the prevalence of HPV types responsible for causing cervical intraepithelial neoplasia (CIN), anogenital warts, and RRP [3-7]. In turn, the incidence of these diseases has decreased [7-10]. Second, the costs of cervical cancer screening and follow-up have likely declined substantially, due not only to the decrease in CIN [11-14] but also to less detection due to reduced frequency of screening as a result of changes in screening recommendations [15-17]. Finally, updated estimates of the cost per case of treating HPV-attributable cancers are substantially higher than applied in the previous study [2]. For instance, the average 2-year cost of cervical cancer in 1998–2003 was $37,300 in 2020 dollars, while the cost was $93,200 in 2011–2017 [18,19]. Although the main purpose of our study was to quantify the current direct medical cost burden of HPV in the United States, our estimates can also be useful to illustrate the current and potential future impact of HPV vaccination on this burden and to inform cost-effectiveness analyses of HPV vaccination.

2. Methods

We estimated the total annual cost of screening for and treating HPV-attributable disease. Following the methods used for the previous cost study [2], we excluded the cost of HPV vaccination and focused on the cost of cervical cancer screening and follow-up and the cost of treating anogenital warts, RRP, and anogenital and oropharyngeal cancers caused by HPV. Thus, our estimate will represent costs that could be averted with continued HPV vaccination. 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; although this approach uses incident cases and lifetime costs as inputs, it approximates the annual cost of treatment of all prevalent cases (see supplement).

We conducted literature reviews to find updated incidence and cost-*per*-case estimates (see supplement for search term details). For inputs with no updates published since 2012, we re-analyzed sources that were used in the study published in 2012 [2], and updated accordingly. For each input we applied (e.g., incidence estimates, cost estimates), we provide detailed

descriptions of how we derived mean estimates and 95% confidence intervals from each source in the supplement. All costs were represented in 2020 dollars; costs originally reported in prior years were adjusted with the health services component of the personal consumption expenditures index (available at https://apps.bea.gov/).

2.1. Estimating number of screenings and cases of HPV-attributable disease

To estimate the number of women screened for cervical cancer in a given year, we multiplied the U.S. population of women aged 21–65 years with no history of hysterectomies (obtained from the National Health Interview Survey (NHIS) [20]) by the proportion of women who were screened in a given year, which we obtained independently from NHIS, Marketscan [21], the New Mexico HPV Pap Registry (NMHPR) [22], and the HPV Impact Monitoring Project [23]. Epidemiological data for these screening estimates were collected from 2013 to 2016 [23], 2013 to 2019 [21,22], and 2018 [20]. We then averaged the estimates from these four sources. We estimated the portion of these screenings which co-tested for HPV using data from Marketscan and NMHPR, collected from 2013 to 2019 [24], and then averaged these estimates as well. See Table S1 for the range of estimates from each source.

We applied estimates of the number of diagnosed cases of CIN1 – CIN3 and anogenital warts in 2018 from a recent epidemiologic model [25]. The most recent estimate for the annual number of juvenile onset RRP (JORRP) cases is based on data through 2013, and shows that JORRP cases are significantly decreasing over time after onset of HPV vaccination [6]. We used this 2013 estimate but note that JORRP cases have likely decreased further since 2013. Finally, using data from 2014 to 2018 from the CDC's National Program of Cancer Registries (NPCR) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, we used the average annual number of anogenital and oropharyngeal cancers diagnosed in the U.S. [26], and multiplied these numbers by the percentage of each cancer type in which HPV was detected [27] to find the annual number of HPV-attributable cancer cases.

2.2. Cost per screening/case estimates

We estimated costs per cervical cancer screening as a weighted average (based on the proportion of the population enrolled in Medicaid vs private insurance) of screening costs in nationally funded programs (data from the National Breast and Cervical Cancer Early Detection Program), and screening costs for privately insured individuals [28]. HPV tests, when done, are generally in the context of cervical cancer screening for patients aged 30–65 years. However, our estimates for screening costs were collected from 2000 to 2004, before co-testing became common [24]. Thus, we estimated HPV testing costs separately. Given that almost all HPV testing occurs as part of cervical cancer screening or as part of the follow up for an abnormal screening test result [21] we assumed that office visit costs for HPV tests were already included in our cervical screening cost estimates. Thus, we calculated cost of HPV tests from the 2020 Medicare laboratory fee schedule (available at https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched).

For each HPV outcome, we aimed to apply estimates of the lifetime cost of treatment per case. Most of the updated estimates for the treatment cost per case only record treatment costs for the two years post-diagnosis. However, this timeframe likely captures the majority of lifetime treatment costs; for instance, cervical cancer treatment costs per month are more than four times higher in the six months after diagnosis than they are for any other portion of a patient's lifespan compared to non-cancer controls [29]. Thus, we used the available two-year treatment cost estimates as a proxy for lifetime treatment costs, ignoring costs in subsequent years, unless otherwise specified.

We found independent cancer cost estimates for privately insured individuals (from 2011 to 2014 records), individuals with Medicaid (from 2008 to 2012 records), and a national representative mix of people for most anogenital and oropharyngeal cancers (from 2011 to 2017 records) [18,30-36]. We took weighted means of these estimates based on the proportion of the U.S. population enrolled in Medicaid. For JORRP, we similarly took a weighted average of Medicaid and private costs derived from 2008 to 2012 data [37]. CIN treatment costs were calculated from administrative and laboratory records of the Kaiser Permanente Northwest health plan from 1997 to 2002 [38]. The treatment cost per case of anogenital warts was based on a study of the average cost per episode, defined in the source study as the period from the initial diagnoses until one full year had passed without any wart-related medical claims, derived from data collected from 2003 to 2004 [39].

2.3. Direct estimates of total cost for two health outcomes: false-positive screenings and adult-onset RRP

For two health outcomes, we directly estimated the total cost at the national scale, rather than multiplying the estimated number of outcomes by the average cost per outcome. We found no updated estimates for the cost of false-positive follow-ups for cervical cancer screening, so we used the estimate of 0.4 billion dollars annually [38] from the study published in 2012 [2] and adjusted for both inflation and the decreased number of cervical cancer screenings (29.6 vs 52 million screenings, see results as compared to the estimate published in 2012).

We found no updated case data for adult onset RRP (AORRP). Given that decreases in RRP due to vaccination would be expected to occur much sooner for JORRP than AORRP, we assumed AORRP incidence has not yet been substantially affected by HPV vaccination. Thus, we applied the estimate of the total annual cost of AORRP from our previous study [2] and updated it to 2020 dollars.

3. Results

From 2014 through 2018, an average of 46,200 cases of anogenital and oropharyngeal cancers were diagnosed annually. Approximately 79% of these cancers were attributable to HPV, of which 58.6% occurred in women (Table 1).

We estimated that the U.S. spends $9.01 billion annually in direct medical costs for screening and treatment of diseases caused by HPV (Table 2). Approximately 65.2% of this cost is related to cervical cancer: either for screening (including HPV co-testing, 47.1%),

screening follow-up (including the treatment of cervical pre-cancers, 8.0%), or treatment (10.2%). About 43.8% of the total direct medical cost is for treatment of cancers (including cervical), with oropharyngeal cancer accounting for the largest proportion of treatment costs, at 21.1% of the total direct cost of HPV. Anogenital warts and RRP account for 1.2% of the total cost.

Our updated estimate for the annual direct medical cost of HPV is 3.7% lower than in the 2012 study ($9.36 billion vs $9.01 billion in 2020 dollars, Table 3) [2]. However, this minor overall difference masks larger changes in individual cost component estimates. Our updated estimated cost of cervical cancer screening and follow-up is 35% lower than in the 2012 study ($7.70 billion vs $4.96 billion). This difference is largely due to decreases in estimated annual screenings (52 million vs 29.6 million screenings), but reductions in the total cost of follow-up also contributed ($1.43 billion vs $0.717 billion). Our updated estimated cost of anogenital warts and RRP is 81% lower than in the 2012 study ($0.537 billion vs $0.104 billion) due to decreased wart and JORRP cases. However, our estimated cost of treating HPV-attributable cancers is more than 3 times the estimate in the 2012 study ($1.12 billion vs $3.95 billion). This difference is due both to a 45% increase in the estimated annual number of HPV-attributable cancers (from 25,100 to 36,500) and to a 144% increase in the weighted average cost per cancer case (from $44,300 to $108,000).

4. Discussion

We estimated that the United States spends $9.01 billion in direct medical costs annually on screening and treatment for HPV-attributable diseases. Our estimate of the annual medical cost burden is similar to that of a previous study for 2004–2007 when updated for inflation [2], because reductions in the estimated number of screenings for cervical cancer and cases of anogenital warts and JORRP have largely been balanced by increases in the estimated cost of treating HPV associated oropharyngeal and anogenital cancers.

Decreases in the annual number of cervical cancer screenings are likely due to changes in screening recommendations. In 2012, major medical organizations recommended delaying an initial screening to age 21 years, and screening at longer intervals for women aged 30–65 years: co-testing every 5 years or cytology alone every 3 years [17]. In 2018, the US Preventive Services Task Force recommended screening for cervical cancer every 3 years with cervical cytology alone in women aged 21 to 29 years; every 3 years with cervical cytology alone, every 5 years with HPV testing alone, or every 5 years with HPV co-testing for women aged 30–65 years [15]. However, many women are being screened more frequently than is recommended [22]. Thus, the annual economic burden of HPV may decrease further if adherence to screening guidelines increases. Alternatively, this study did not include race or ethnicity, or the related screening disparities. Increases in screening adherence in groups that historically have not had access to screening might increase screening costs, but also might reduce cancer treatment costs.

It has long been predicted that HPV vaccination would lead to discernable reductions in outcomes such as CIN and anogenital warts decades before such reductions in HPV-attributable cancers [40,41]. Recent epidemiological evidence has confirmed these

predictions, showing notable reductions in HPV prevalence, anogenital warts, CIN, and RRP following the onset of HPV vaccination in the United States [7-13]. Our updated cost estimates reflect these decreases as well. Specifically, the estimates we applied for the annual number of anogenital warts cases and JORRP cases are substantially lower than applied in the 2012 study, and the total cost for CIN that we estimated is lower than estimated in the 2012 study. In contrast, the increases in the estimated annual number of HPV-attributable cancers over the past ten years are more likely due to pre-vaccine than post-vaccine HPV dynamics. For example, increases in oral sex have been suggested as an important reason for increasing trends in HPV-attributable oropharyngeal cancers [27,42]. We expect that in the future the incidence of HPV-attributable cancers will decline, along with the overall cost of cancer treatment. Thus, the $3.95 billion current annual cost of cancer treatment represents a substantial potential economic benefit of the ongoing HPV vaccination program.

Cost-effectiveness analyses have indicated that routine HPV vaccination of adolescents can be cost-saving [43]; that is, vaccination could pay for itself in terms of averted medical costs. Although our results cannot be interpreted as direct evidence of vaccine impact, our results illustrate the potential for reductions in the estimated annual medical cost burden of HPV to exceed the annual cost of HPV vaccination. This potential is demonstrated by the estimated annual cost of treating HPV-attributable diseases ($4.05 billion, Table 2) being more than twice the estimated annual cost of HPV vaccination ($1.8 billion, supplementary materials).

In our analysis, due to the availability of data, the “lifetime” cost estimates we applied for HPV disease reflect the medical costs incurred over the first two years post-diagnosis. Therefore, we likely underestimated the overall cost of treating HPV-attributable cancers. However, the first two years of treatment capture the most cost-intensive time periods [29]. Further, even though the cost per case estimates we applied only reflected costs over the first two years, we found a 144% increase in the estimated cost per cancer case (from $44,300 to $108,000), even controlling for inflation. Some of the increase in the estimated cost per case of cancer can be attributed to changes in the standard of care over time, including the incorporation of new technologies such as intensity-modulated radiotherapy (IMRT) for treatment of oropharyngeal cancers [32,34,44]. Some of the increase in the estimated cost of cancer treatment might be attributed to changes in the methodology of the cost studies. The earlier cost studies typically used a “micro-costing” approach, in which the lifetime cost estimate was calculated based on estimates of the number and cost of each healthcare resource consumed by the average cancer patient. In contrast, many of the more recent studies were based on analyses of medical claims data that compared the costs of enrollees with cancer to the costs of control enrollees without cancer [44]. Studies of medical claims data that compare cancer cases to controls might be able to identify additional cancer-attributable costs that might be overlooked when using a “micro-costing” framework. Conversely, comparisons of cancer cases to controls might overestimate the cost of cancer treatment if there are unobserved or unmeasurable differences between the cancer patients and the control patients [44]. Our use of the “two-year” costs from the recent cancer cost studies as an approximation of the lifetime cost per case helps to guard against this possible overestimation of costs.

Our $9.01 billion estimate of the annual medical cost burden of screening for and treating HPV disease is notably higher than the recent estimate of $794 million for the annual lifetime medical cost of diseases attributable to HPV infections acquired in 2018 (updated to 2020 dollars) [25]. However, these two estimates are not directly comparable, because (1) our $9.01 billion estimate includes cervical cancer screening costs whereas the $794 million estimate does not, and (2) the $9.01 billion estimate reflects the annual cost of HPV disease regardless of when the causal HPV infection was acquired, whereas the $794 million estimate reflects lifetime costs of disease attributable to HPV infections acquired in 2018, and these future costs were discounted to present value at 3% annually.

One limitation of our study is that we did not include screening costs for non-cervical cancer. Individuals living with HIV, and in particular gay, bisexual, and other men who have sex with men living with HIV have a higher incidence of HPV-attributable anal cancer than other populations, and therefore may undergo screening for anal pre-cancers [45]. We did not include additional costs of cervical cancer screening for individuals living with HIV, nor the cost burden of non-cervical precancers. We excluded these costs so that our total cost could be compared to the estimate from our study published in 2012 [2], which also excluded these costs. However, the treatment of cancers in these populations with a high incidence of HPV associated disease is included in our cost estimates.

Another limitation of our study is that the epidemiologic data (e.g., number of cancer cases, number of cervical cancer screenings) and cost data (e.g., cost per case of cervical cancer) we applied were from a wide range of years; thus we cannot state a specific calendar year to which our annual cost estimates apply. The most recent incidence estimates of HPV cancers and other outcomes were generally based on data from 2018 or before. Thus, the annual cost estimates presented here might be most applicable to the 2014–2018 timeframe and may be different than current annual costs. Still, our annual cost estimate can be reasonably interpreted as an approximation of the average annual cost over the past decade. Despite these limitations, the estimated annual costs we present here reflect an updated estimate of the current medical cost burden of HPV and can be used to show the potential economic benefits of continued HPV vaccination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

All data analyzed for the article comes from previously published data sources.

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Table 1

Estimated HPV associated cancers by sex, based on data from 2014 to 2018 [26,27].

Anatomic area	Average annual number of cases	Estimated percent of cases in which HPV is present		Estimated annual number of HPV-attributable cases	
		Mean	95% CI	Mean	95 % CI
Female					
Cervix	12,200	90.6%	88.3–92.5%	11,100	10,800–11,300
Vulva	4,190	68.8%	61.6–75.1%	2,880	2,580–3,150
Anus	4,910	92.5%	85.3–96.3%	4,540	4,190–4,730
Oropharynx	3,560	63.3%	55.4–70.6%	2,250	1,970–2,510
Vagina	863	75.0%	62.8–84.2%	647	542–727
Total	25,700			21,400	
Male					
Oropharynx	16,700	72.4%	68.0–76.4%	12,100	11,300–12,700
Anus	2,380	88.7%	77.4–94.7%	2,110	1,840–2,250
Penis	1,370	63.3%	52.3–73.1%	864	714–1,000
Total	20,500			15,100	
Total	46,200	79.0%		36,500	35,600–37,300

HPV: human papillomavirus.

CI: confidence interval.

Table 2

Estimates of the annual direct medical costs of screening for and treating HPV-attributable disease from 2014 to 2018, in 2020 U.S. dollars.

Cost component	Annual number of tests or cases		Cost applied per test or case (U.S. dollars)*		Annual cost (millions, U.S. dollars)		Percent of cost burden
	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Routine screening total**					4,240	3,930–4,560	47.1
Cervical cancer screening	29.6 million	27.2–32.1 million	127	126–128	3,760	3,500–4,020	41.7
HPV co-testing	13.8 million	7.65–20.0 million	35.10	NA	484	268–701	5.3
Follow-up total***					717	483–957	8.0
False positive follow-up	NA	NA	NA	NA	279	262–296	3.1
CIN 1	163,000	0–705,000	1,540	1,290–1,790	251	40.0–468	2.8
CIN 2/3	52,100	24,100–74,200	3,580	2,380–4,750	187	93.6–293	2.1
Screening and follow-up total					**4,960**	**4,570–5,350**	**55.0**
Cancer treatment total					3,950	3,800–4,080	43.8
Cervical cancer	11,100	10,800–11,300	82,600	76,700–88,400	917	855–971	10.2
Oropharyngeal cancer	14,300	13,700–15,000	133,000	126,000–137,000	1,900	1,790–2,020	21.1
Anal cancer	6,700	6,280–7,020	122,000	114,000–131,000	817	753–871	9.1
Vulvar cancer	2,880	2,580–3,150	57,000	49,900–64,000	164	142–187	1.8
Vaginal cancer	647	542–727	113,000	99,100–126,000	73.1	60.9–85.9	0.8
Penile cancer	864	714–1,010	86,200	69,500–103,000	74.5	58.7–91.3	0.8
Non-cancer treatment total					104	53.5–154	1.2
Anogenital warts	50,400	22,800–78,200	916	804–1,030	46.2	24.7–68.2	0.5
Juvenile onset RRP	18	13–25	68,500	52,400–84,400	1.23	0.873–1.63	less than 0.1
Adult onset RRP	NA	NA	NA	NA	56.2	2.34–276	0.6
Treatment total					**4,050**	**3,900–4,200**	**45.0**
Total burden					**9,010**	**8,590–9,430**	**100%**

HPV: human papillomavirus.

CIN: cervical intraepithelial neoplasia.

RRP: recurrent respiratory papillomatosis.

CI: Confidence interval.

NA: not applicable.

*Cost applied per case of cancer reflects the total costs over the first two years after diagnosis, as explained in methods and supplementary materials.

**'Routine screening total' includes the cost of routine cervical cancer screening and the cost of HPV co-testing.

***'Follow-up total' includes the cost of false-positive follow-ups and CIN treatment.

Table 3

Comparisons of estimates of the direct medical costs of screening and treatment for HPV-attributable disease: Current study vs prior study (Chesson et al., 2012).*

	Mean annual number of tests or cases		Mean cost applied per test or case (U.S. dollars)**		Mean annual cost (millions, U.S. dollars)	
	Prior Study (2004–2007)	**Current Study (2014–2018***)**	**Prior Study (2004–2007)**	**Current Study (2014–2018)**	**Prior Study (2004–2007)**	**Current Study (2014–2018)**
Routine screening total					6,270	4,240
Cervical cancer screening	52 million	29.6 million	121	127	6,270	3,760
HPV co-testing	NA	13.8 million	NA	35.10	NA	484
Follow-up total	NA	NA	NA	NA	1,430	717
Screening and follow-up total					**7,700**	**4,960**
Cancer treatment total					1,120	3,950
Cervical cancer	11,370	11,100	45,400	82,600	516	917
Oropharyngeal cancer	7080	14,300	50,500	133,000	358	1,900
Anal cancer	4270	6,700	42,400	122,000	181	817
Vulvar cancer	1560	2,880	27,600	57,000	43.3	164
Vaginal cancer	460	647	31,700	113,000	14.0	73.1
Penile cancer	360	864	23,200	86,200	8.19	74.5
Non-cancer treatment total					537	104
Anogenital warts	355,000	50,400	948	916	337	46.2
Juvenile onset RRP	820	18	175,500	68,500	144	1.23
Adult onset RRP	NA	NA	NA	NA	56.2	56.2
Treatment total					**1,660**	**4,050**
Total burden					**9,360**	**9,010**

HPV: human papillomavirus.

RRP: recurrent respiratory papillomatosis.

NA: not applicable.

*Chesson et al., 2012 combined estimates for false-positive follow-up costs and CIN treatment into a single category of “Screening Follow-up”, so we have combined these categories here for direct comparison. Chesson et al. 2012 did not estimate costs of HPV testing, as co-testing for HPV and cervical cancer screening was not recommended over the period of prior analysis.

**Cost is in 2020 dollars.

*** As described in the text, the annual cost estimate of $9.01 billion in the current study can be interpreted as an approximate average annual cost over the past decade and is likely most applicable to 2014–2018.