Supplemental Appendix of Results

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

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1. Detailed intermediate results from base case cost-effectiveness analysis

Supplement Table 1: Discounted number of disease cases averted and discounted number vaccinated, for comparison strategy and mid-adult vaccination through age 45 years.

	Comparison strategy	Mid-adult vaccination	Difference
CIN 1	1,323,558	1,332,328	8,770
CIN 2/3	2,946,179	2,956,668	10,489
Cancer total	209,551	214,223	4,672
Female cancers			
Total	146,013	148,632	2,619
Cervical	96,900	98,151	1,252
Total (non-cervical)	49,113	50,480	1,367
Anal	19,626	20,146	520
Vaginal	3,737	3,855	117
Vulvar	14,474	14,891	418
Oropharyngeal	11,277	11,589	312
Male cancers	63,538	65,592	2,053
Anal	10,022	10,304	282
Oropharyngeal	49,465	51,075	1,610
Penile	4,052	4,213	161
Genital warts total	4,590,912	4,620,738	29,826
Female	2,641,087	2,653,063	11,976
Male	1,949,826	1,967,675	17,849
JORRP	8,212	8,225	13
AORRP	6,663	6,758	96
Number vaccinated	85,271,029	103,976,707	18,705,678

The comparison strategy column shows the impact of routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through age 26 years for females and 21 years for males (versus no vaccination). The mid-adult column shows the impact of routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through age 45 years for females and males (versus no vaccination).
CIN: cervical intraepithelial neoplasia.
AORRP: adult-onset recurrent respiratory papillomatosis.
JORRP: juvenile-onset recurrent respiratory papillomatosis.

Supplement Table 2: Number of disease cases averted and number vaccinated, for comparison strategy and mid-adult vaccination through age 45 years, NOT DISCOUNTED

	Comparison strategy	Mid-adult vaccination	Difference
CIN 1	6,231,118	6,258,287	27,169
CIN 2/3	12,863,980	12,897,451	33,471
Cancer total	1,447,552	1,468,486	20,934
Female cancers			
Total	957,776	969,345	11,568
Cervical	579,118	584,259	5,141
Total (non-cervical)	378,658	385,085	6,427
Anal	147,661	149,972	2,311
Vaginal	30,573	31,172	599
Vulvar	114,314	116,438	2,124
Oropharyngeal	86,111	87,504	1,393
Male cancers	489,776	499,142	9,366
Anal	73,360	74,651	1,291
Oropharyngeal	381,492	388,693	7,200
Penile	34,924	35,798	875
Genital warts total	20,897,424	21,000,114	102,691
Female	11,503,494	11,545,216	41,722
Male	9,393,930	9,454,898	60,968
JORRP	34,199	34,239	40
AORRP	36,657	37,038	381
Number vaccinated	269,580,167	324,768,314	55,188,147

The comparison strategy column shows the impact of routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through age 26 years for females and 21 years for males (versus no vaccination). The mid-adult column shows the impact of routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through age 45 years for females and males (versus no vaccination).
CIN: cervical intraepithelial neoplasia.
AORRP: adult-onset recurrent respiratory papillomatosis.
JORRP: juvenile-onset recurrent respiratory papillomatosis.

Supplement Table 3: Detailed cost-effectiveness results, comparison strategy versus no vaccination

	Discounted costs averted	Discounted QALYs gained
CIN 1 due to HPV 16, 18, 31, 33, 45, 52, 58	$1,540,361,623	7,757
CIN 1 due to HPV 6, 11	$299,383,740	1,508
CIN 2/3	$7,542,217,633	29,462
AORRP (women)	$237,042,753	1,658
Cervical cancer	$7,054,290,213	497,441
Genital warts (female)	$2,271,334,557	63,386
Anal cancer (women)	$1,836,991,688	80,584
Vaginal cancer	$435,367,119	18,301
Vulvar cancer	$743,942,023	54,058
Oropharyngeal cancer (women)	$1,426,519,641	60,314
JORRP	$1,226,104,982	8,623
Warts (male)	$1,676,850,012	46,796
Anal cancer (men)	$938,044,656	53,913
Oropharyngeal cancer (men)	$6,257,288,487	207,357
Penile cancer	$89,950,559	13,624
AORRP (men)	$210,682,693	1,474
Number of females vaccinated (discounted)	Discounted number vaccinated	
Ages 12 to 14 years	28,371,862	
Ages 15 to 18 years	16,741,890	
Ages 19+ years	5,594,515	
Number of males vaccinated (discounted)	Discounted number vaccinated	
Ages 12 to 14 years	21,067,226	
Ages 15 to 18 years	11,978,586	
Ages 19+ years	1,516,950	
	Discounted cost	
Vaccination costs female	$26,671,995,164	
Vaccination costs male	$17,633,986,990	
Total vaccination costs	$44,305,982,154	

This table shows the costs and number of QALYs gained by the comparison strategy (routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through age 26 years for females and 21 years for males) versus no vaccination. The costs averted and QALYs saved by preventing JORRP include all children and are not stratified by sex.

CIN: cervical intraepithelial neoplasia.
AORRP: adult-onset recurrent respiratory papillomatosis.
JORRP: juvenile-onset recurrent respiratory papillomatosis.
QALY: quality-adjusted life year.

Supplement Table 4: Detailed cost-effectiveness results, mid-adult vaccination versus no vaccination

	Discounted costs averted	Discounted QALYs gained
CIN 1 due to HPV 16, 18, 31, 33, 45, 52, 58	$1,550,563,922	7,809
CIN 1 due to HPV 6, 11	$301,371,338	1,518
CIN 2/3	$7,569,070,423	29,567
AORRP (women)	$240,068,060	1,679
Cervical cancer	$7,145,427,387	503,230
Genital warts (female)	$2,281,634,106	63,674
Anal cancer (women)	$1,885,629,704	82,419
Vaginal cancer	$449,050,800	18,781
Vulvar cancer	$765,407,357	55,416
Oropharyngeal cancer (women)	$1,465,987,704	61,728
JORRP	$1,227,991,106	8,636
Warts (male)	$1,692,200,485	47,224
Anal cancer (men)	$964,461,632	55,136
Oropharyngeal cancer (men)	$6,460,962,799	213,512
Penile cancer	$93,526,350	14,075
AORRP (men)	$214,101,097	1,497
Number of females vaccinated (discounted)	Discounted number vaccinated	
Ages 12 to 14 years	28,371,862	
Ages 15 to 18 years	16,741,890	
Ages 19+ years	13,792,966	
Number of males vaccinated (discounted)	Discounted number vaccinated	
Ages 12 to 14 years	21,067,226	
Ages 15 to 18 years	11,978,586	
Ages 19+ years	12,024,176	
	Discounted cost	
Vaccination costs female	$32,525,689,698	
Vaccination costs male	$25,136,146,226	
Total vaccination costs	$57,661,835,924	

This table shows the costs and number of QALYs gained by the mid-adult vaccination strategy (routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through age 45 years for females and males) versus no vaccination. The costs averted and QALYs saved by preventing JORRP include all children and are not stratified by sex.

CIN: cervical intraepithelial neoplasia.
AORRP: adult-onset recurrent respiratory papillomatosis.
JORRP: juvenile-onset recurrent respiratory papillomatosis.
QALY: quality-adjusted life year.

2. Effects of model changes and updates

As described in the Technical Appendix, this 2019 application of the model incorporates four main changes and updates from the 2018 application: (1) updated vaccine cost assumptions and medical treatment costs assumptions; (2) modifying the model to more closely approximate scenarios in which there is re-infection with HPV; (3) adding adult-onset recurrent respiratory papillomatosis (AORRP) as a potential outcome prevented by HPV vaccination; and (4) applied modified (and generally higher) incidence rates of cervical intraepithelial neoplasia (CIN).

In this section, we show how these adjustments affect the estimated cost-effectiveness of mid-adult vaccination. To illustrate the effects of these model adjustments more clearly, we separated the effects of the vaccine cost change and the medical treatment cost updates.

Supplement Table 5: Cost per quality-adjusted life year (QALY) gained by mid-adult vaccination strategies when applying 2018 model and when sequentially applying the main adjustments to the 2018 model.

Strategy	(1) 2018 model without any changes	(2) 2018 model, plus updated vaccine costs	(3) 2018 model, plus updated vaccine costs and treatment costs	(4) 2018 model, plus updated vaccine costs and treatment costs, plus modification for re-infection	(5) 2018 model, plus updated vaccine costs and treatment costs, plus modification for re-infection, plus AORRP	(6) 2019 model [2018 model plus updated vaccine costs and treatment costs, plus modification for re-infection, plus AORRP, plus CIN incidence adjustment]
Comparison strategy (vs. no vaccination)	$16,400	$24,100	$14,100	$12,600	$12,100	$9,200
Age 30 (vs. comparison strategy)	$417,600	$575,800	$562,500	$592,600	$590,700	$587,600
Age 45 (vs. comparison strategy)	$545,000	$750,000	$736,500	$657,500	$655,700	$653,300

The comparison strategy is routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through age 26 years for females and 21 years for males. The mid-adult vaccination strategies include routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through the given age (30, 35, 40, or 45 years) for females and males. For example, the "Age 30 (vs. comparison strategy)" row shows the incremental cost effectiveness of expanding vaccination to include mid-adults through age 30 years. In this example, the mid-adult strategy through age 30 years is routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through age 30 years for females and males, and the comparison strategy is routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through age 26 years for females and 21 years for males.
CIN: cervical intraepithelial neoplasia
AORRP: adult-onset recurrent respiratory papillomatosis

3. Influence of herd effects on model results

As described in the Technical Appendix, we use a relatively simple approach to approximate HPV transmission dynamics after the onset of HPV vaccination. To examine the potential effects of our simplified model approximations of transmission dynamics, we conducted a supplemental analysis in which we assumed HPV vaccination would not have any effect on HPV transmission dynamics. In this scenario, the only benefits of HPV vaccination were the direct benefits to those vaccinated. The idea behind this supplemental analysis is that (1) the indirect benefits to mid-adults and others through HPV vaccination in the comparison strategy likely far outweighs the marginal indirect benefits to mid-adults and others when expanding vaccination to include mid-adults. By removing the indirect effects from the model, we examine a scenario that is likely more favorable towards mid-adult vaccination. So, if our simple approach to HPV transmission dynamics is biased against mid-adult vaccination, this approach provides us with a reasonable bound of the potential effect of this bias on the estimated cost-effectiveness of mid-adult vaccination.

Supplement Table 6: Cost per quality-adjusted life year (QALY) gained by mid-adult vaccination strategies when excluding indirect effects*

Vaccination strategy	**Cost per QALY gained**
Comparison strategy (vs. no vaccination)	$25,800
Mid-adult vaccination through age 30 years (vs. comparison strategy)	$204,800
Mid-adult vaccination through age 45 years (vs. comparison strategy)	$463,300

*In this scenario, there are no “herd effects,” therefore in the vaccination scenarios, unvaccinated people have the same annual probability of acquiring HPV as they do in the “no vaccination” scenario.

The comparison strategy is routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through age 26 years for females and 21 years for males. The mid-adult vaccination strategies include routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through the given age (30, 35, 40, or 45 years) for females and males.

4. Maximum cost and quality of life impact scenarios

In this scenario, we apply the medical treatment cost assumptions and quality of life impact assumptions most favorable to vaccination. That is, we apply the upper bound values for the medical treatment costs per case of each HPV health outcome. Simultaneously, we apply the upper bound values for the number of quality-adjusted life years (QALYs) lost per HPV health outcome.

We first examine the maximum cost and quality of life assumptions when keeping all other parameter values at their base case values. We then examine the maximum cost and quality of life assumptions under the "Increased HPV incidence for ages 30 years and older" scenario as described in the manuscript and Technical Appendix. In the "Increased HPV incidence for ages 30 years and older" scenario, HPV incidence rates do not decline from age 30 years through age 45 years and decline by 25% from age 45 years to age 60 years. For example, in the base case, the annual probability of acquiring HPV 16 in the absence of vaccination is 1.41% at age 30 years, 0.55% at age 40 years, 0.41% at age 50 years, and 0.34% at age 60 years. In the scenario of increased incidence for ages 30 years and older, the annual probability of acquiring HPV 16 in the absence of vaccination is 1.41% at age 30 years, 1.41% at age 40 years, 1.29% at age 50 years, and 1.06% at age 60 years.

Supplement Table 7: Cost per quality-adjusted life year (QALY) gained by mid-adult vaccination strategies when applying upper bound values for the medical treatment costs per case and the number of QALYs lost per case

Vaccination strategy	**Cost per QALY gained**	
	Base case HPV incidence	Increased HPV incidence for ages 30 years and older
Comparison strategy (vs. no vaccination)	< 0 (cost-saving)	< 0 (cost-saving)
Mid-adult vaccination through age 30 years (vs. comparison strategy)	$362,900	$251,100
Mid-adult vaccination through age 45 years (vs. comparison strategy)	$431,400	$213,500

In the "Base case HPV incidence" column, all model parameters are set to their base case values except the medical treatment costs per case and the number of QALYs lost per case. In the "Increased HPV incidence for ages 30 years and older" column, all model parameters are set to their base case values except the medical treatment costs per case, the number of QALYs lost per case, and the annual probabilities of HPV acquisition.