Supplementary Material*

Laprise JF, Chesson HW, Markowitz LE, Drolet M, Martin D, Bénard É, Brisson M. Effectiveness and Cost-Effectiveness of Human Papillomavirus Vaccination Through Age 45 Years in the United States. Ann Intern Med. 10 December 2019 [Epub ahead of print]. doi:10.7326/M19-1182

Supplement. **Supplemental Appendix**

* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

Appendix

Laprise JF, Chesson HW, Markowitz LE, *et al*. Effectiveness and cost-effectiveness of HPV vaccination through age 45 years in the United States

Appendix Table 1. Parameters used for model predictions (costs in 2018 US dollars)

		Sensitivity analysis	
	Base case	Minimum	Maximum
Mid-adult vaccination coverage*			
- Uptake rates† in women	2.6%		12.9%
- Uptake rates in men	1.9%		9.7%
Historical vaccination coverage			
- Uptake rates	Observed	75% of base case uptake rates	
Vaccine efficacy (against PI with vaccine types)	95%	85%	
Vaccine cost per dose‡ ($/dose)			
- Age ≤18 years	205	176	235
- Age ≥19 years	225	176	235
Health care costs ($)			
Anogenital warts§	680	340	770
Screening & treatment‖			
Cytology	129	85	164
Colposcopy/biopsy	583	358	862
CIN 2/3 treatment	3,095	1,876	4,872
Cancers§			
Cervical cancer (SCC & ADC)	64,800	43,300	81,000
Vulvar cancer	41,300	26,300	58,700
Vaginal cancer	111,400	30,200	142,400
Anal cancer	52,600	40,400	78,300
Oropharyngeal cancer	141,800	82,000	166,600
Penile cancer	22,100	10,900	43,300
Natural history of HPV¶	Include all 50 parameter sets	22/50 parameter sets that have the lowest female natural immunity & fastest progression to CIN1/2/3 lesions	28/50 parameter sets that have a higher female natural immunity & slower progression to CIN1/2/3 lesions

PI=Persistent Infections; SCC=Squamous Cell Carcinoma; ADC=Adenocarcinoma; CIN=Cervical Intraepithelial Neoplasia.

*: Based on Chesson et al. 2018(1)
†: Uptake rates: Annual probability of vaccination among unvaccinated individuals
‡: Vaccination costs were based on the CDC vaccine price list as of August 1, 2018 (https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html) and include the cost of vaccine administration.
§: Medical treatment costs for anogenital warts and HPV-associated cancers were obtained from a range of sources(1-6). In addition to using the average cost estimates reported in recent studies of the cost of cervical, oropharyngeal, vaginal, and vulvar cancers(2, 3, 5), we also incorporated median cost estimates (obtained from David Lairson via personal communication with Harrell Chesson (hbc7@cdc.gov) on 8/14/2018).
||: Medical costs for cervical cancer screening and treatment of HPV-associated cervical lesions were obtained from a range of sources (7-12), see Brisson et al.(13) for details. Screening and treatment costs were inflated to 2018 US dollars using the medical care component of the United States consumer price index (14).
¶: We separated the 50 parameter sets into the parameter sets that have lower probability of natural immunity following clearance in females (≤40% vs >40%) and faster progression to CIN1/2/3 (e.g., average median time from infection to CIN1 of 10 vs 15 months, and average median time from infection to CIN3 of 32 vs 36 months) (22/50 parameter sets) and those that have a higher natural immunity and slower progression (28/50 parameter sets).

Appendix Table 2. Predicted median times from infection to cervical lesions

	Probability of developing Natural immunity (%)	Median times from infection to cervical lesions (months)		
		CIN 1	CIN 2	CIN 3
All parameter sets (50)	37.6	12.7	28.2	34.5
Lower immunity & faster progression* (n=22)	27.6	10.1	27.5	32.0
Higher immunity & slower progression* (n=28)	45.4	14.7	28.8	36.4

CIN=Cervical Intraepithelial Neoplasia;
*: We separated the 50 parameter sets into the parameter sets that have lower probability of natural immunity following clearance in women (≤40% vs >40%, based on Beachler et al.(15)) and faster progression to CIN1/2/3 (22/50 parameter sets) and those that have a higher natural immunity and slower progression (28/50 parameter sets).

Appendix Table 3. Impact inventory for the health care sector perspective*

Sector	Type of Impact	Included in this analysis from … perspective? Health care sector	Notes on sources of Evidence
Formal health care sector			
Health	Health outcomes (effects)		
	Longevity effects	✓	See Technical appendix**
	Health-related quality-of-life effects	✓	See Technical appendix**
	Other health effects (eg, adverse events and secondary transmissions of infections)	✓	See Technical appendix**
	Medical costs		
	Paid for by third-party payers	✓	See Appendix Table 1
	Paid for by patients out-of-pocket	✓	See Appendix Table 1
	Future related medical costs (payers and patients)	✓	See Appendix Table 1
	Future unrelated medical costs (payers and patients)	×	
Informal Health Care Sector			
Health	Patient-time costs	×	
	Unpaid caregiver-time costs	×	
	Transportation costs	×	
Non−Health Care Sectors (with examples of possible items)			
Productivity	Labor market earnings lost	×	
	Cost of unpaid lost productivity due to illness	×	
	Cost of uncompensated household production	×	
Consumption	Future consumption unrelated to health	×	
Social Services	Cost of social services as part of intervention	×	
Legal or Criminal Justice	Number of crimes related to intervention	×	
	Cost of crimes related to intervention	×	
Education	Impact of intervention on educational achievement of population	×	
Housing	Cost of intervention on home improvements (eg, removing lead paint)	×	
Environment	Production of toxic waste pollution by intervention	×	
Other (specify)	Other impacts	×	

*. Source: Sanders et al.

**. The analysis included longevity effects and health-related quality of life effects of the following HPV-associated diseases: cervical, vulvar, vaginal, anal, penile, and oropharyngeal cancers, and anogenital warts. HPV-ADVISE (the individual-based transmission-dynamic model of HPV infection and associated diseases that we applied) included herd effects (i.e., prevention of secondary transmission of HPV, or reductions in HPV-associated outcomes in unvaccinated mid-adult women and men).

Appendix Table 4. Health outcomes prevented over 100 years

	Health outcomes prevented							
	AGW* diagnoses		Diagnosed CIN2/3		Cervical cancer		Non cervical HPV-associated cancers†	
	Cases	(%‡)	Cases	(%‡)	Cases	(%‡)	Cases	(%‡)
Current recommendation vs No vaccination	31,620,000	(82.5)	12,790,000	(79.6)	653,100	(59.0)	768,800	(39.2)
Mid-adult vaccination vs current recommendation								
Women & men ≤26 years	40,000	(0.1)	12,800	(0.1)	100	(0.1)	900	(0.03)
Women & men ≤30 years	49,600	(0.2)	31,900	(0.2)	1,100	(0.1)	1,900	(0.1)
Women & men ≤40 years	107,000	(0.4)	51,900	(0.3)	2,100	(0.2)	3,300	(0.1)
Women & men ≤45 years	123,700	(0.4)	55,800	(0.4)	2,900	(0.2)	3,600	(0.2)

AGW=Anogenital Warts; CIN=Cervical Intraepithelial Neoplasia. Base case: 100-year time horizon, United States population. Model predictions are represented as the median estimate of the 50 best fitting parameter sets.

*: We assume 90% AGW are positive for HPV-6/11.

†: Includes HPV-negative cancers.

‡: Percent reduction in cumulative incidence; Additional reductions are in percentage points and represent the median value from the 50 best fitting parameter sets. The values cannot be estimated directly from the table.

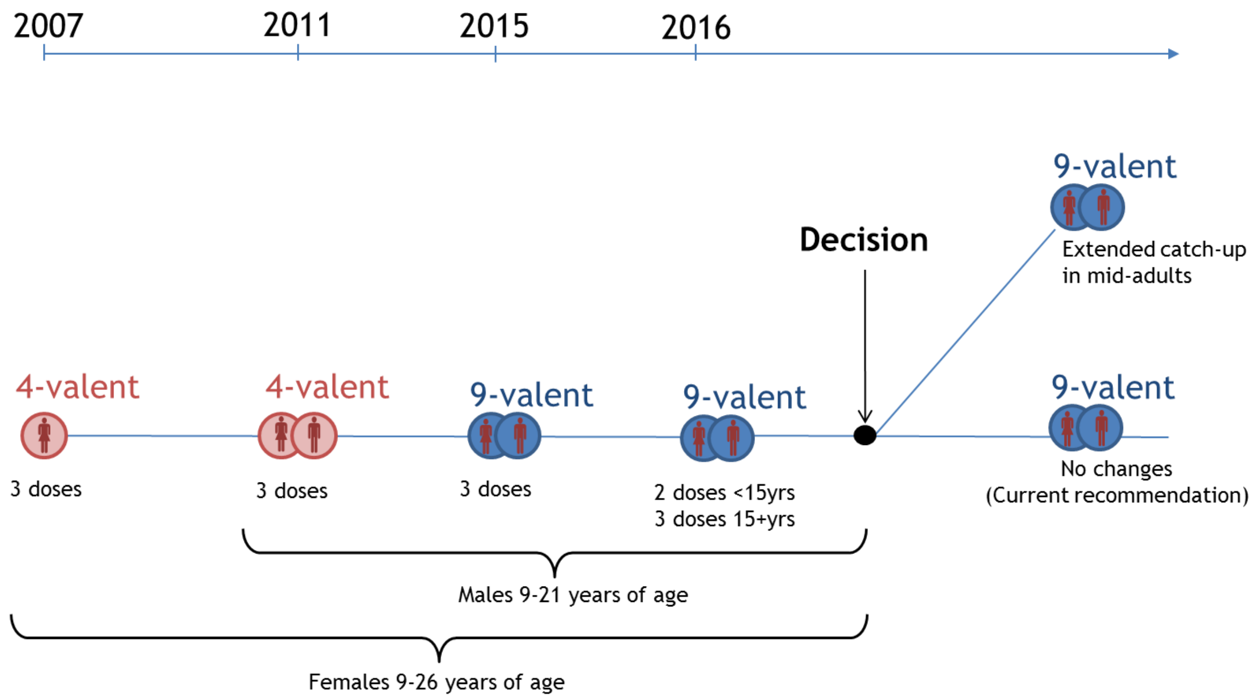
Appendix Table 5. Sensitivity analysis: Cost-effectiveness of maximum benefit scenarios.
Routine vaccination of 30- or 40-year-old Women & men*

		Cost-effectiveness ratio ($/QALY gained)	
		Median	**(90% UI)**
100% vaccination coverage			
Vaccination at age 30 years	vs no vacc.	200,000	(157,000; 261,000)
Vaccination at age 40 years	vs no vacc.	781,000	(484,000; 1,530,000)
80% vaccination coverage			
Vaccination at age 30 years	vs no vacc.	184,000	(149,000; 246,000)
Vaccination at age 40 years	vs no vacc.	748,000	(465,000; 1,650,000)

QALY=Quality-Adjusted Life-Year. Discount rate=3%; Time horizon=100 years; 9-valent cost/dose=$225; Vaccine efficacy=95%. Model predictions are represented as the median estimate generated by the 50 best fitting parameter sets; 90% UI=90% Uncertainty intervals represented by the 5th and 95th percentiles of model predictions generated by the 50 best fitting parameter sets.

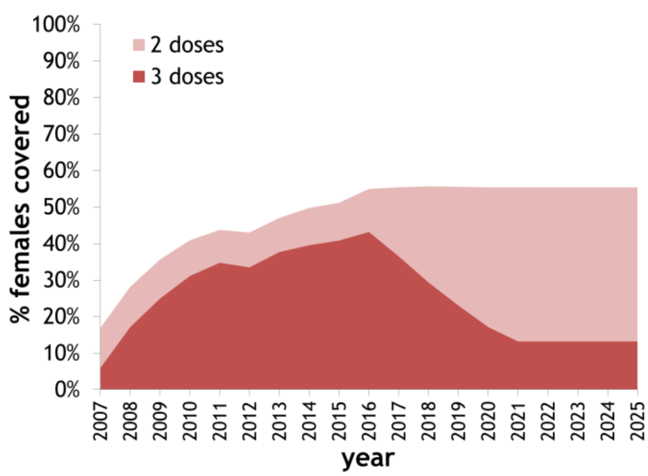
*: Only herd effects are from the routine 30- or 40-year-old program; No vaccination outside these age groups

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

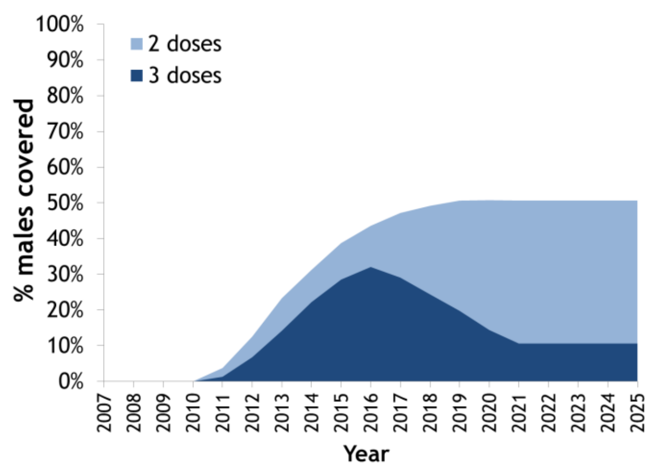


Appendix Figure 2. Vaccination coverage in 13- to 17-year-olds. Average % covered in 13- to 17-year-old A) females and B) males. For 13- to 17-year-olds we reproduced 2 and 3 dose vaccination coverage from National Immunization Survey (NIS)-Teen from 2007 to 2016(16-19). We assume uptake rates to be constant at 2016 values from 2017 onwards and that 2 doses are given under 15 years of age after 2016.

A) Females of age 13-17 years

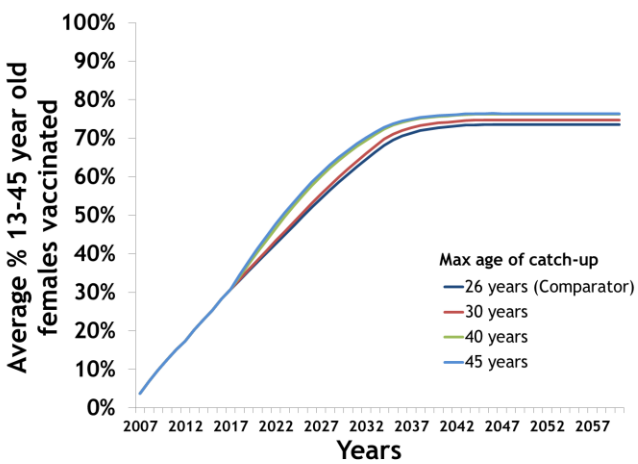


B) Males of age 13-17 years

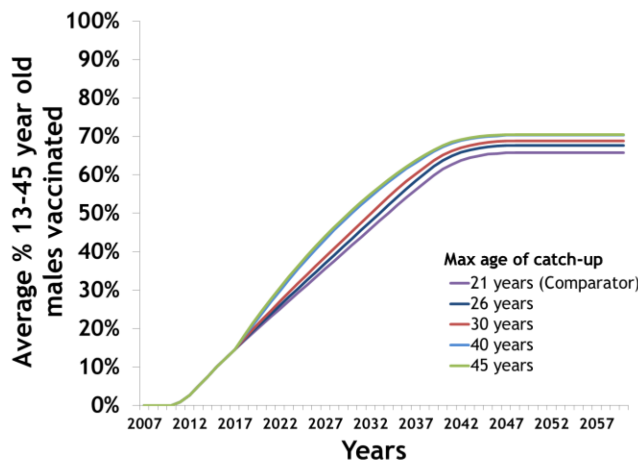


Appendix Figure 3. Vaccination coverage scenarios. Average % of 13- to 45-year-olds vaccinated for A) females and B) males in the base case coverage scenarios (we assumed uptake rates of 2.6% and 1.9% for mid-adult women and men, respectively), C) females and D) males in the high mid-adult coverage scenarios (we assumed uptake rates of 12.9% and 9.7% for mid-adult women and men, respectively).

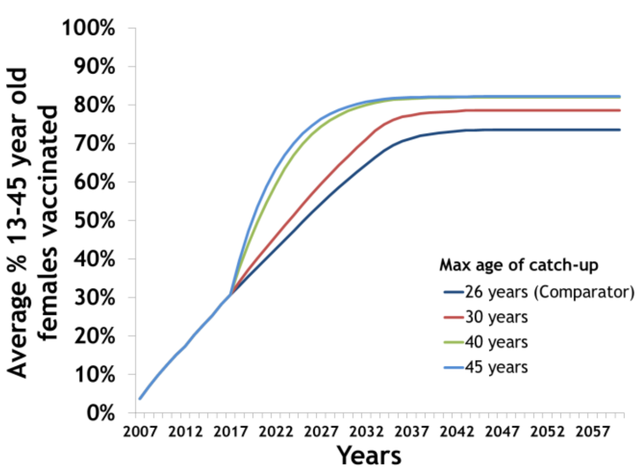
A) Females, base case coverage



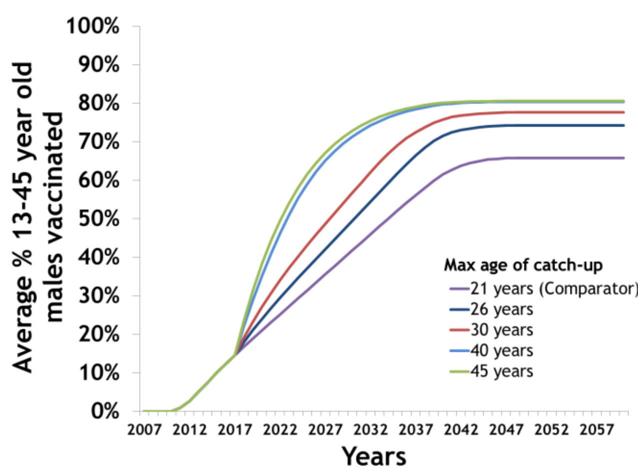
B) Males, base case coverage



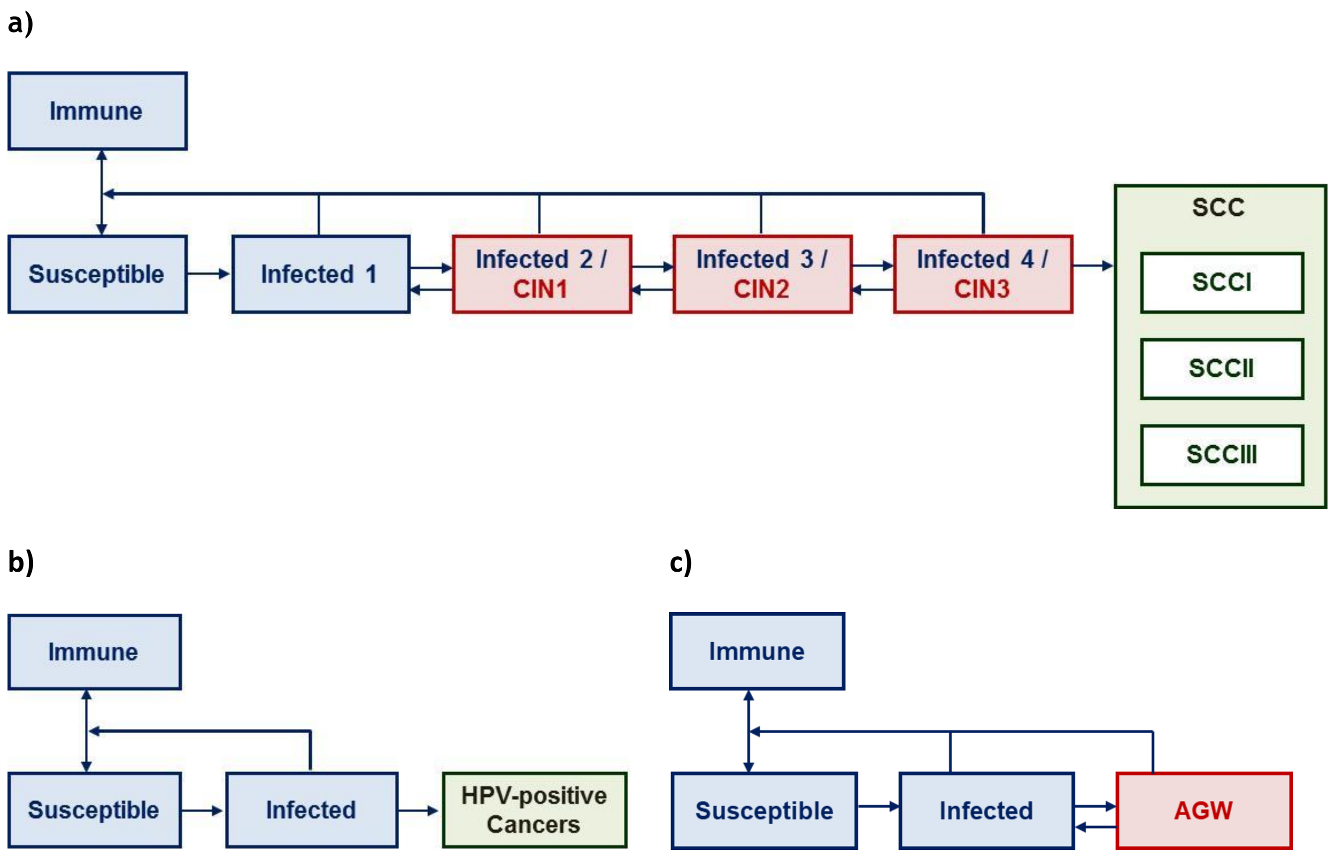
C) Females, high mid-adult coverage



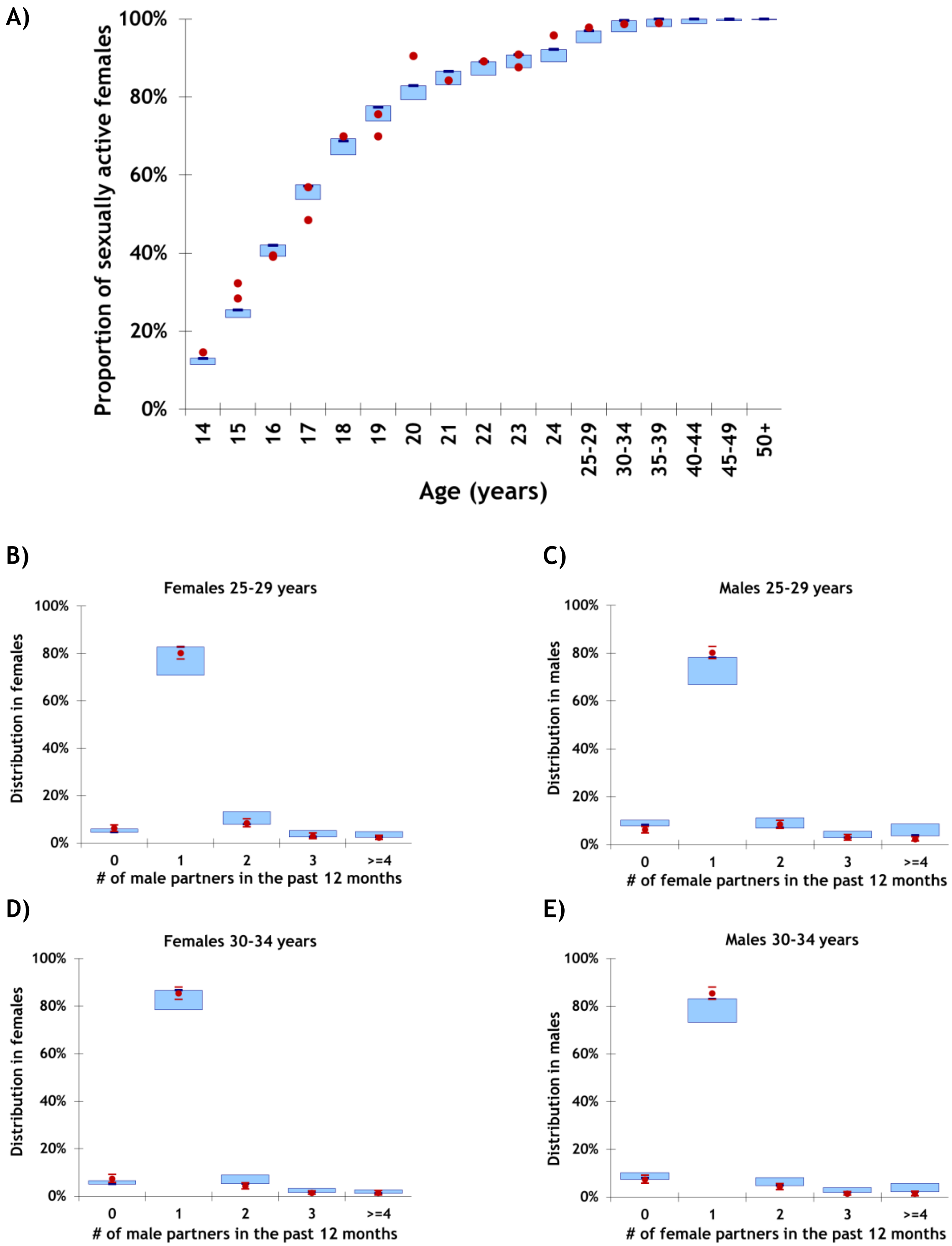
D) Males, high mid-adult coverage



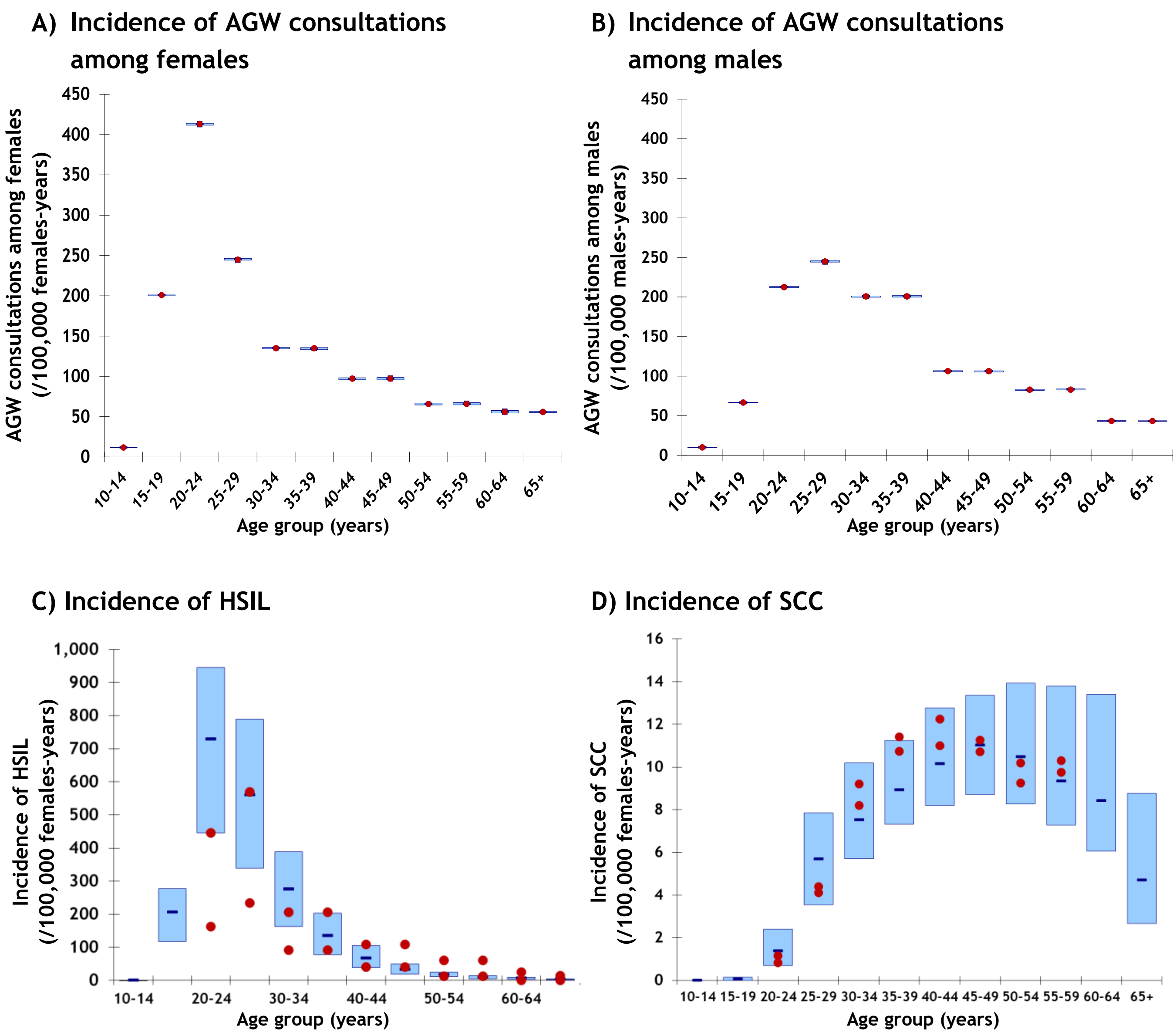
Appendix Figure 4. Visual representation of the modeled natural history: A) squamous cell carcinoma (SCC) in absence of screening; b) other HPV-related cancers (cervical adenocarcinoma, and cancers of the anus, oropharynx, vulva, vagina, and penis); and c) anogenital warts (AGW). The mutually exclusive compartments represent the different HPV epidemiological states. Arrows represent the possible HPV-type, age, and gender specific transitions between these states for each individual. CIN=Cervical Intraepithelial Neoplasia; SCC=Squamous Cell Carcinoma.



Appendix Figure 5. Examples of model fit to sexual behavior: A) proportion of sexually active females by age; B-E) number of partners in the past 12 months among mid-adult women and men. Box plots represent the median, minimum and maximum values of the model predictions generated by the 50 best fitting parameter sets. Dots represent empirical data from the United States(20-22). See Technical appendix(23) for details on model calibration and more examples of model fit to sexual behavior data.

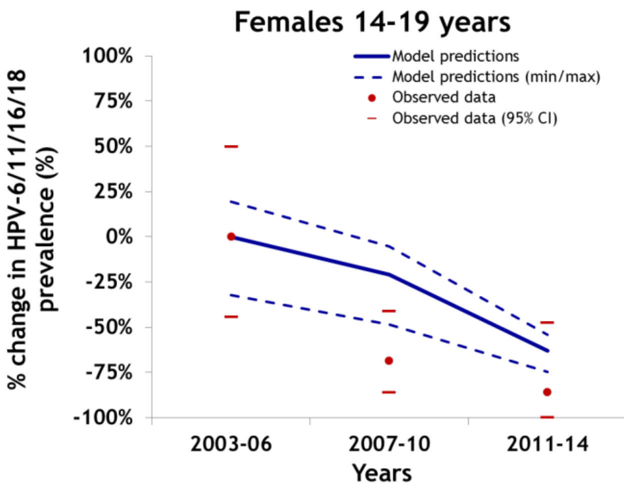


Appendix Figure 6. Examples of model fit to HPV-associated disease outcomes: anogenital wart (AGW) consultations among A) females, and B) males, C) incidence of cervical high grade intraepithelial lesion (HSIL), and D) incidence of diagnosed squamous cell carcinoma (SCC). Box plots represent median, minimum and maximum values of model predictions generated with the 50 best fitting parameter sets. The dots represent observed data from the pre-vaccination era (AGW: Hoy et al.(24); Incidence of HSIL: Insinga et al.(25); Incidence of SCC: SEER(26)). See Technical appendix(23) for details on model calibration and more examples of model fit to pre-vaccination HPV-associated disease outcomes data.

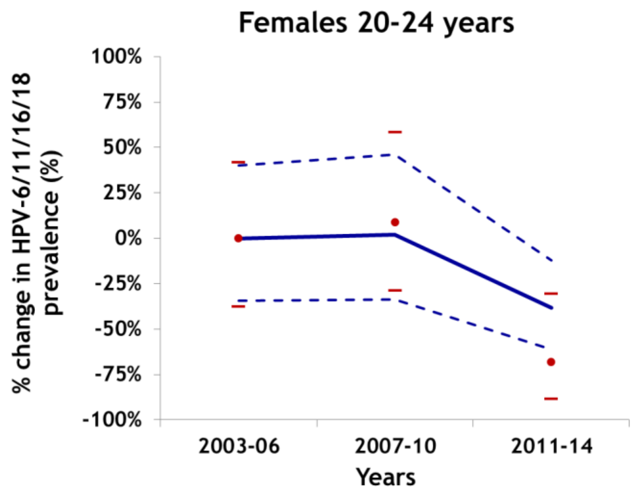


Appendix Figure 7. Comparison of model predictions to post-vaccination United States data: HPV-6/11/16/11 prevalence in females aged A) 14-19 years, B) 20-24 years, and C) 25-29 years. Change in prevalence over time is shown as % change versus pre-vaccination values (2003-2006). Solid and dotted blue lines represent the average, minimum and maximum values of HPV-ADVISE predictions generated by the 50 best fitting parameter sets. Red dots and bars represent the observed data for HPV-6/11/16/18 prevalence from NHANES(21).

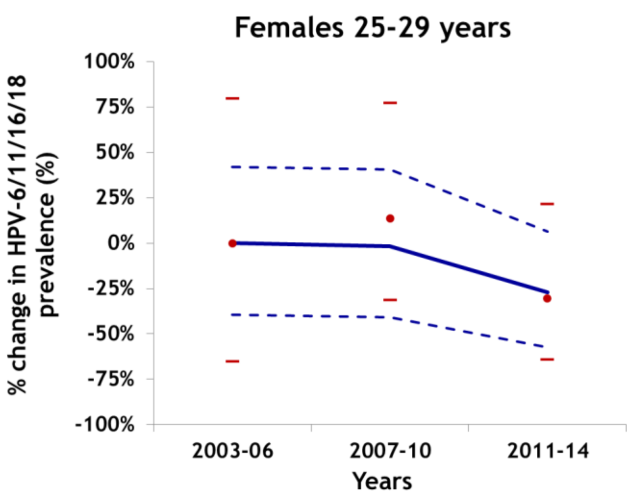
A)



B)

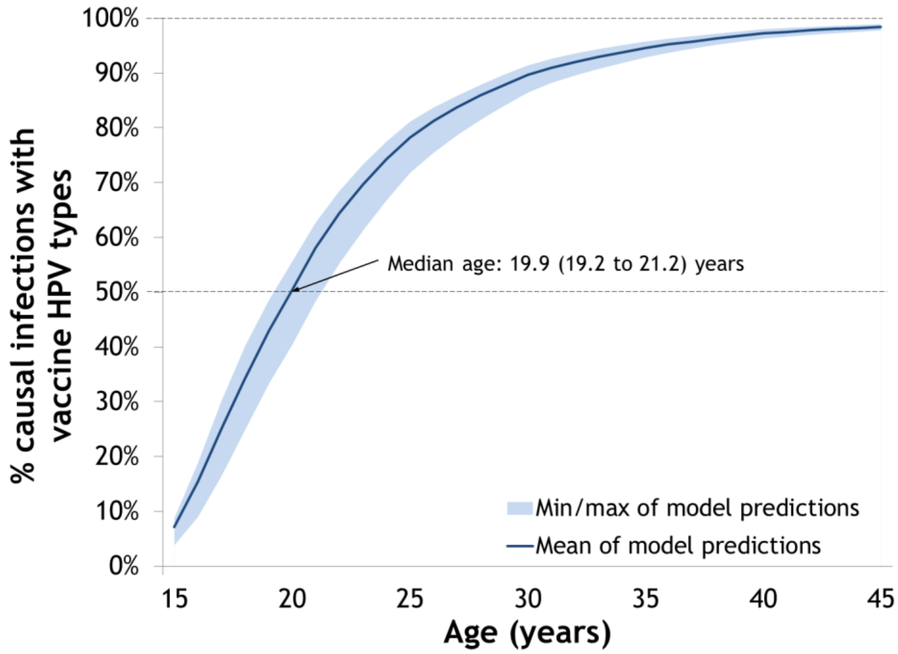


C)

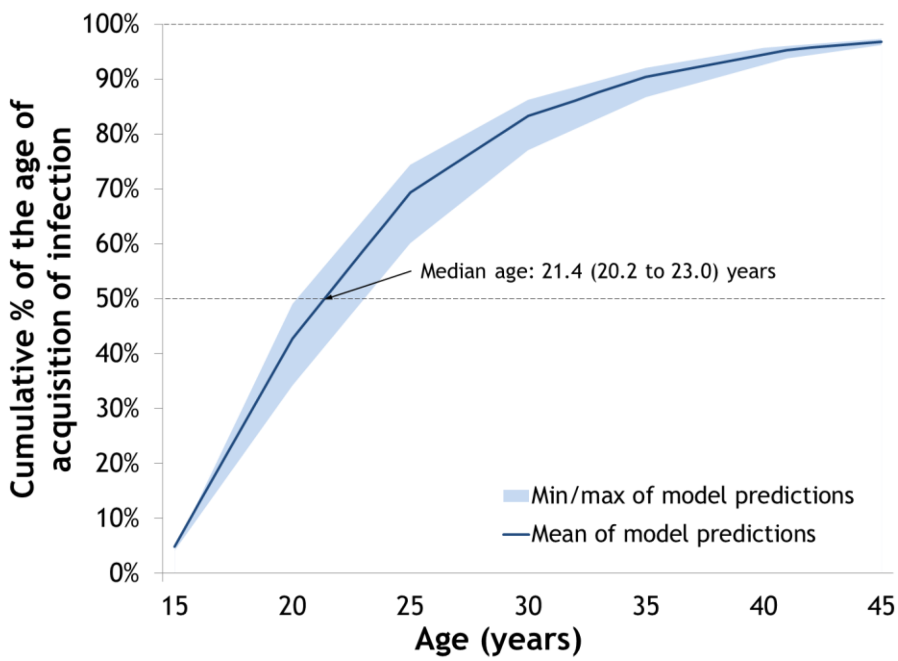


Appendix Figure 8. Predicted cumulative proportion of age at acquisition of HPV infection among females in the pre-vaccination era: A) cumulative proportion of the age of acquisition of *causal* HPV-16/18/31/33/45/52/58 infection (no vaccination or screening), and B) cumulative proportion of the age of acquisition of HPV-16/18/31/33/45/52/58 infection (no vaccination). Solid line and shaded area represent the average, minimum and maximum values of model predictions generated by the 50 best fitting parameter sets.

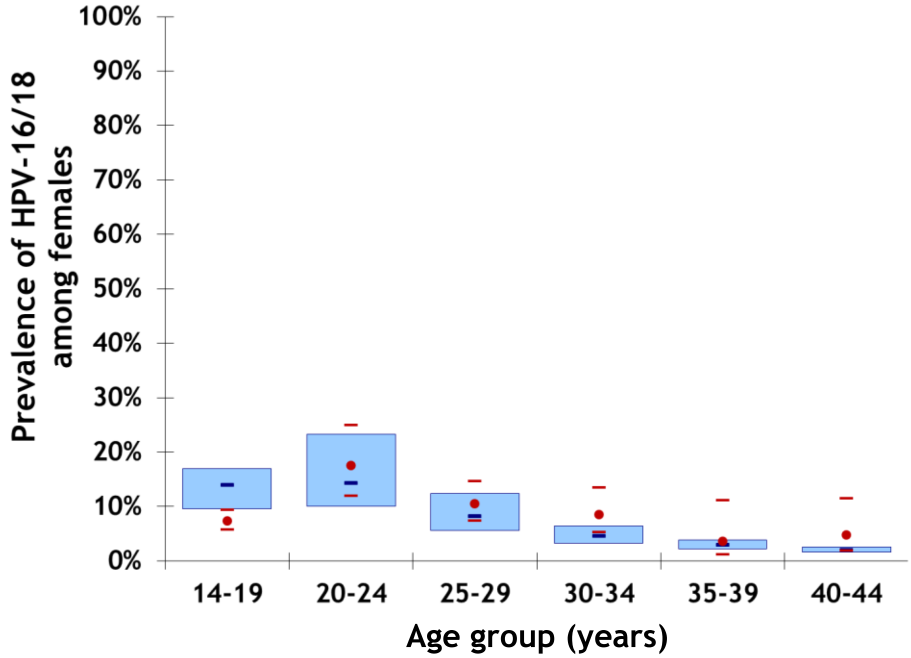
A) Cumulative proportion of the age at acquisition of causal infection (HPV-16/18/31/33/45/52/58 infection that caused cervical cancer)



B) Cumulative proportion of the age at infection (HPV-16/18/31/33/45/52/58; includes re-infections**)**

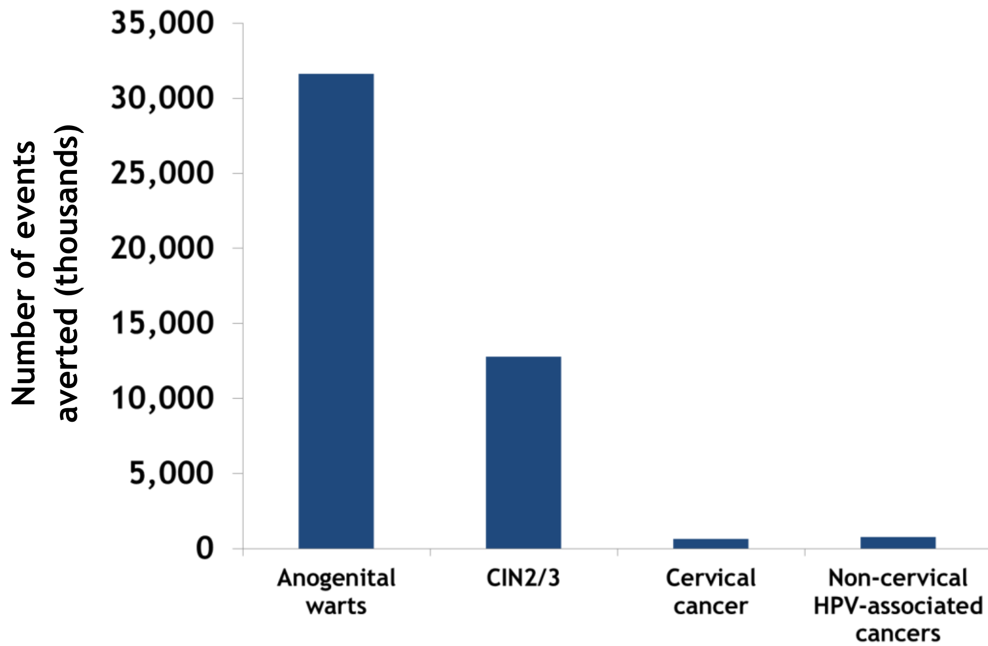


Appendix Figure 9. Model validation to pre-vaccination HPV prevalence: HPV-16/18 prevalence in females by age. Box plots represent median, minimum and maximum values of model predictions generated with the 50 best fitting parameter sets. The dots represent observed data from the pre-vaccination era from NHANES(21).

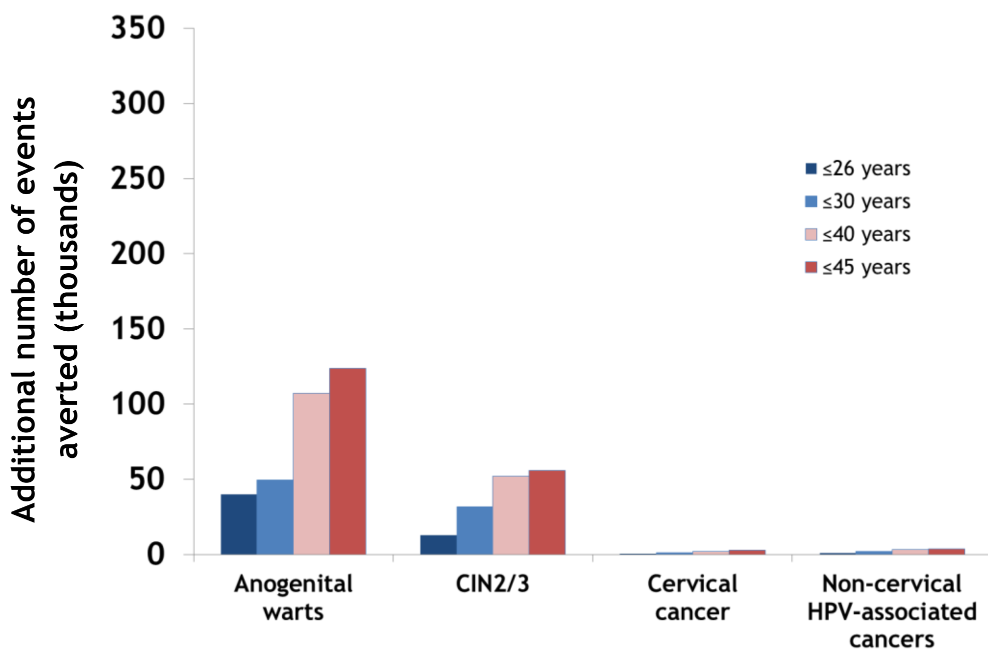


Appendix Figure 10. Health outcomes prevented: A) current recommendation vs no vaccination, and B) mid-adult vaccination scenarios vs current recommendation. Assuming base case historical coverage. 100-year time horizon and United States population. Model predictions are represented as the median estimate generated by the 50 best fitting parameter sets. Definitions: CIN=Cervical Intraepithelial Neoplasia.

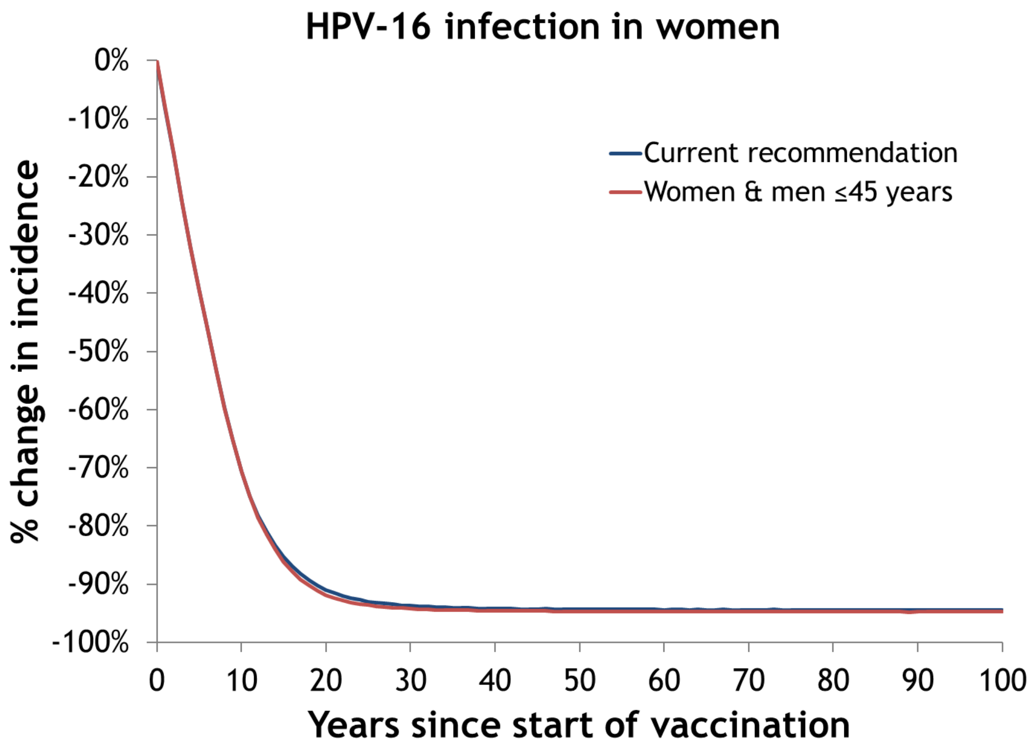
A)



B)

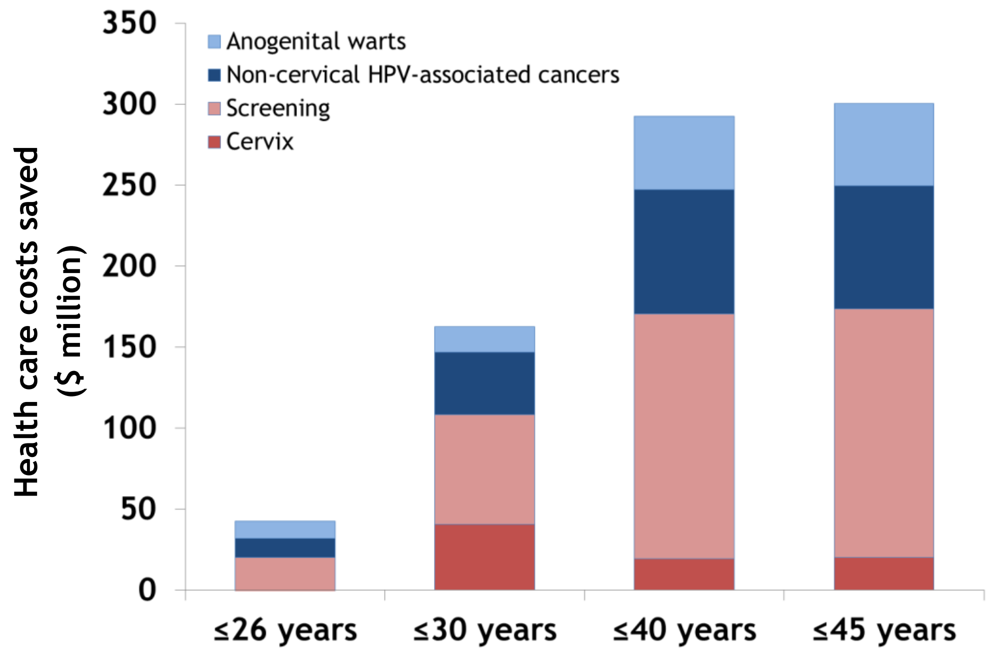


Appendix Figure 11. Percent reduction in incidence of HPV-16 infection in women over time: Under the current United States HPV vaccine recommendation and extended vaccination of women and men up to age 45 years.

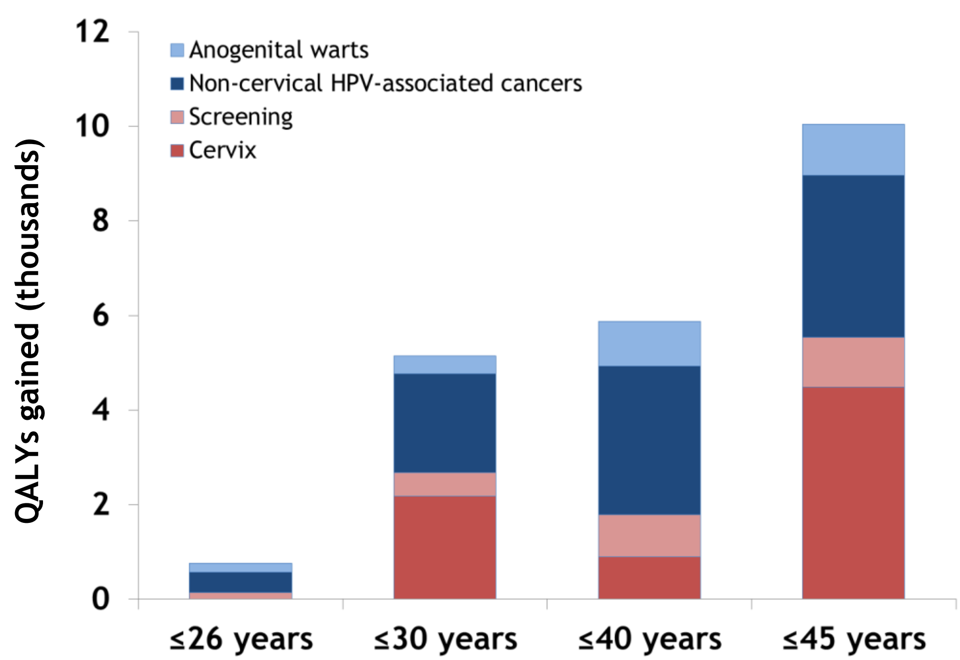


Appendix Figure 12. Cost offsets and benefits: A) additional health care costs saved and B) additional QALYs gained. Base case assumptions (9-valent cost/dose=$205 in ≤18-year-olds; $225 in 19- to 45-year-olds), 100-year time horizon, 3% discount rate for costs and benefits, and United States population. Model predictions are represented as the median estimate generated by the 50 best fitting parameter sets.

A) Health care costs saved



B) QALYs gained



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