Supplementary Material

Brisson M, Laprise JF, Chesson HW, et al. Health and economic impact of switching from a 4-valent to a 9-valent HPV vaccination program in the United States

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplementary Table 1. Economic parameters

Parameters	Base-case*	Sensitivity analysis		References
		Minimum	Maximum	
Case-fatality[†]				
Cervical cancer (stage 1; 2-3; 4)	9%; 42%; 82%			
Vulvar/vaginal	33%	31%	39%	(16)
Anal	31%	30%	32%	(16)
Oropharyngeal	39%	39%	40%	(16)
Penile	32%	29%	35%	(16)
% AGW attributed to HPV-6/11[‡]	90%	66%	100%	(17-20)
AGW consultations per episode				
Women	1.15	1.12	1.23	(21)
Men	1.21	1.15	1.33	(21)
QALYs-lost				
QALYs-lost per episode				
AGW	0.02	0.01	0.04	(22,23)
CIN1 or LSIL	0.006	0.006	0.008	(24)
CIN2/3 or HSIL	0.01	0.009	0.012	(24)
Disutility				
Cervical cancer (stage 1; 2-3; 4)	28%;39%;45%	19%;29%;29%	51%;58%;64%	(25-27)
Vulvar/vaginal	32%			
Anal	51%			
Oropharyngeal	25%			
Penile	29%			
Costs ($US)				
AGW episode				
Women	605	496	661	(5,28,29)
Men	791	496	933	(5,28,29)
Normal cytology	103	68	131	(30-32)
Colposcopy/biopsy	467	287	690	(31,33)
CIN2/3 treatment[§]	2,478	1,502	3,901	(33-35)
Cervical cancer (stage 1; 2-3; 4)	31,368; 33,586; 53,796	14,058; 17,476; 18,871	32,687; 43,325; 121,460	(31,33)
Relative costs vs. Cervical cancer (stage 1)				
Vulvar/vaginal	81%	67%	95%	(30)
Anal	115%	96%	135%	(30)
Oropharyngeal	138%	114%	161%	(30)
Penile	63%	52%	74%	(30)

* Base-case values are the median from the literature. Abbreviations: AGW: Anogenital warts; CIN: Cervical intraepithelial neoplasia; LSIL: Low-grade squamous intraepithelial lesion; HSIL: High-grade squamous intraepithelial lesion; QALY: Quality-adjusted life-years

[†] (Case fatality) = 100% – (5-year survival [%])

[‡] Proportion of HPV-6 and 11 among HPV positive anogenital warts

[§] Treatment costs excluding the initial Pap and colposcopy/biopsy

All costs are $US 2010.

Supplementary Table 2. Description of calibration data

Outcomes	Stratification	Reference	Targets Points
Sexual Behavior			
Percent that ever had sexual intercourse	Age (15, … 24, [25-29], …, [40-44]yrs); Gender ($g \in \{1, 2\}$)	(1-3)	56
Distribution of the number of partners in past 12 months	Age ([15-19], …, [30-34], [35-44]yrs); Gender ($g \in \{1, 2\}$) † Number of partners (0, 1, 2, 3, ≥4)	(1,2)	98
Average number of partners in past 12 months by level of sexual activity	Age ([15-19], …, [30-34], [35-44]yrs); Gender ($g \in \{1, 2\}$); Sexual Activity Level ($l \in \{0, 1, 2, 3\}$)	(1,2)	78
Natural history			
Prevalence of HPV-16*	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	(3)	12
Prevalence of HPV-18*	Age ([20-24] & [25-29]yrs); Sexual Activity Level ($l = 2$)	(3)	2
Prevalence of HPV-16/18*	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	(3)	12
Prevalence of HPV-6*	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	(3)	12
Prevalence of HPV-11*	Age ([20-24] & [25-29]yrs); Sexual Activity Level ($l = 2$)	(3)	2
Prevalence of HPV-6/11*	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	(3)	12
Prevalence of HPV-HR*	Age ([15-19], …, [45-49]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	(3,4)	42
Prevalence of HPV-HRC*	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	(3)	12
Prevalence of HPV-HRNC*	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	(3)	12

Outcomes	Stratification	Reference	Targets Points
Rate of genital warts consultations	Age ([15-19], …[65+]yrs); Gender ($g \in \{1, 2\}$)	(5)	24
Positivity of HPV types in CIN2/3	HPV-16,18,6,11,HRC,HRNC	(6,7)	12
Positivity of HPV types in SCC	HPV-16,18,HRC,HRNC	(8-11)	8
Incidence of SCC	Age ([20-24], …, [50-54]yrs)	(12)	14
Proportion of cervical adenocarcinoma	Age ([20-24], [25-29], …, [60-64]yrs) HPV-16, 18, 31, 33, 45 ,52, 58	(13)	63
Incidence of anal cancer	Age ([25-29], [30-34], …, [60-64]yrs) Gender ($g \in \{1, 2\}$) HPV-16, 18, 31, 33	(12)	64
Incidence of oropharyngeal cancer	Age ([20-24], [25-29], …, [60-64]yrs) Gender ($g \in \{1, 2\}$) HPV-16, 18, 33	(12)	54
Incidence of vulvar cancer	Age ([20-24], [25-29], …, [60-64]yrs) HPV-16, 18, 31, 33, 45	(12)	45
Incidence of vaginal cancer	Age ([30-34], [35-39], …, [60-64]yrs) HPV-16, 18, 31, 33, 45, 52, 58	(12)	49
Incidence of penile cancer	Age ([20-24], [25-29], [60-64]yrs) HPV-16, 18, 31, 33, 45	(12)	45
Screening			
Proportion of women ever screened	Age ([15-19], [20-24], [25-29], [30-34]yrs)	(14)	8
Incidence of ASC-US/LSIL	Age ([20-24], ..., [60-64], [65+]yrs)	(15)	20
Incidence of HSIL	Age ([20-24], ..., [60-64], [65+]yrs)	(15)	20
Total number of data points			**776**

***** Among sexually active individuals. Prevalence estimates were adjusted to take into account misclassification in number of lifetime partners and false positives due to test specificity. Abbreviations: HR=High oncogenic risk types; HRC=HR cross-protective types: 31, 33, 45, 52, 58; HRNC= HR non cross-protective types: 35, 39, 51, 56, 59, 66, 68, 73, 82

† We were unable to fit the % of boys with less than 1 partner in the last year in the 15-19 age group (mainly because of age-specific mixing where females are more likely to choose male partners older than them).

Supplementary Table 3. Vaccine efficacy parameters*

	Base case		
	VE persistent infection (%)		
HPV-type	**4-valent (No cross-protection)**	**4-valent (With cross-protection)**	**9-valent**
16/18	95.0	95.0	95.0
6/11	95.0	95.0	95.0
31	0.0	46.2	95.0
33	0.0	28.7	95.0
45	0.0	7.8	95.0
52	0.0	18.4	95.0
58	0.0	5.5	95.0
Other HR-types	0.0	0.0	0.0

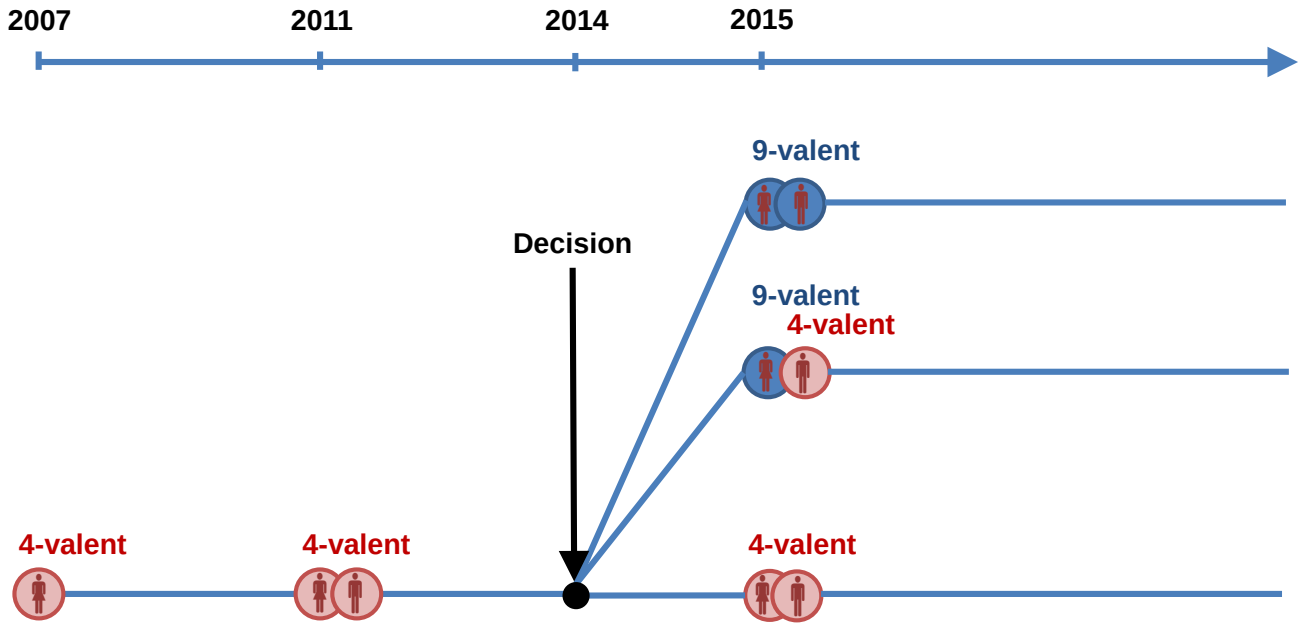
*Abbreviations: VE: Vaccine Efficacy; HR: High risk

Supplementary Table 4. Percentage point reduction in incidence 70 years post-vaccination*

Vaccination Scenarios	Comparison Scenarios	Mean change in percentage points (80% UI)							
		Anogenital warts		CIN2/3		Cervical cancer		Other HPV-related cancers	
<u>No Cross-protection for 4-valent</u>									
(1) 4-valent gender-neutral	1 vs. No Vaccination	80	(75, 87)	61	(57, 66)	65	(60, 69)	76	(74, 76)
(2) 9-valent Girls 4-valent Boys	2 vs. 1	0	(-2, 1)	17	(12, 21)	13	(9, 18)	6	(5, 6)
(3) 9-valent gender-neutral	3 vs. 2	0	(-1, 2)	2	(0, 3)	1	(-2, 5)	1	(0, 1)
	3 vs.1	0	(-2, 2)	18	(14, 22)	14	(9, 19)	7	(6, 7)
<u>With Cross-protection for 4-valent</u>									
(1) 4-valent gender-neutral	1 vs. No Vaccination	80	(74, 88)	68	(62, 72)	69	(65, 73)	79	(78, 81)
(2) 9-valent Girls 4-valent Boys	2 vs. 1	0	(-2,2)	11	(8, 13)	9	(4, 13)	3	(2, 3)
(3) 9-valent gender-neutral	3 vs. 2	0	(-2, 2)	1	(0, 2)	1	(-2, 5)	0	(0, 1)
	3 vs.1	0	(-2, 1)	12	(10, 14)	10	(6, 13)	3	(3, 4)

*BASE-CASE: Vaccine-type efficacy=95%, cross-protective vaccine efficacy presented in Supplementary Table 3, duration=Lifelong.
PREDICTIONS: Mean estimate generated by the 50 best fitting parameter sets. Each parameter set run 20 times. Uncertainty intervals: 10th and 90th percentiles of model results based on the 50 best fitting parameter sets, reflects uncertainty in the natural history parameters. Abbreviations: CIN: Cervical Intraepithelial Neoplasia; UI: Uncertainty intervals
Mean pre-vaccination incidence rate of diagnosed CIN2/3 and Cervical cancers are 123 and 8 per 100,000 women-years, respectively. Mean pre-vaccination incidence rate of anogenital warts consultations and Other HPV-attributable cancers are 153 and 7 per 100,000 person-years, respectively.

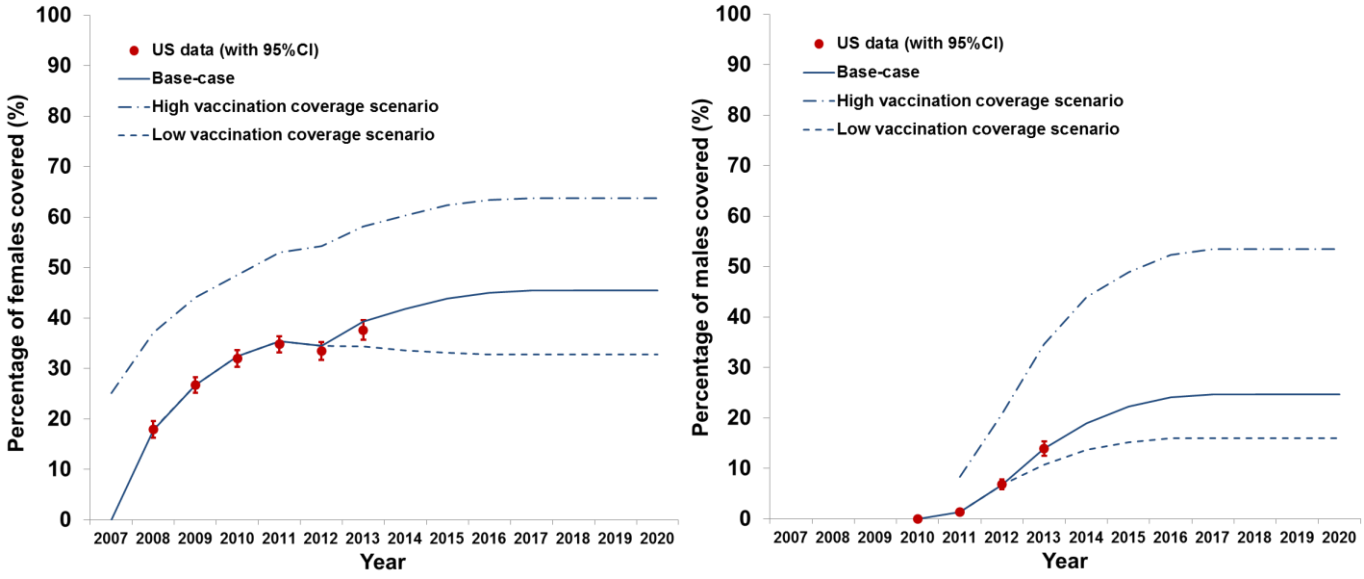
Supplementary Figure 1. Vaccination scenarios examined



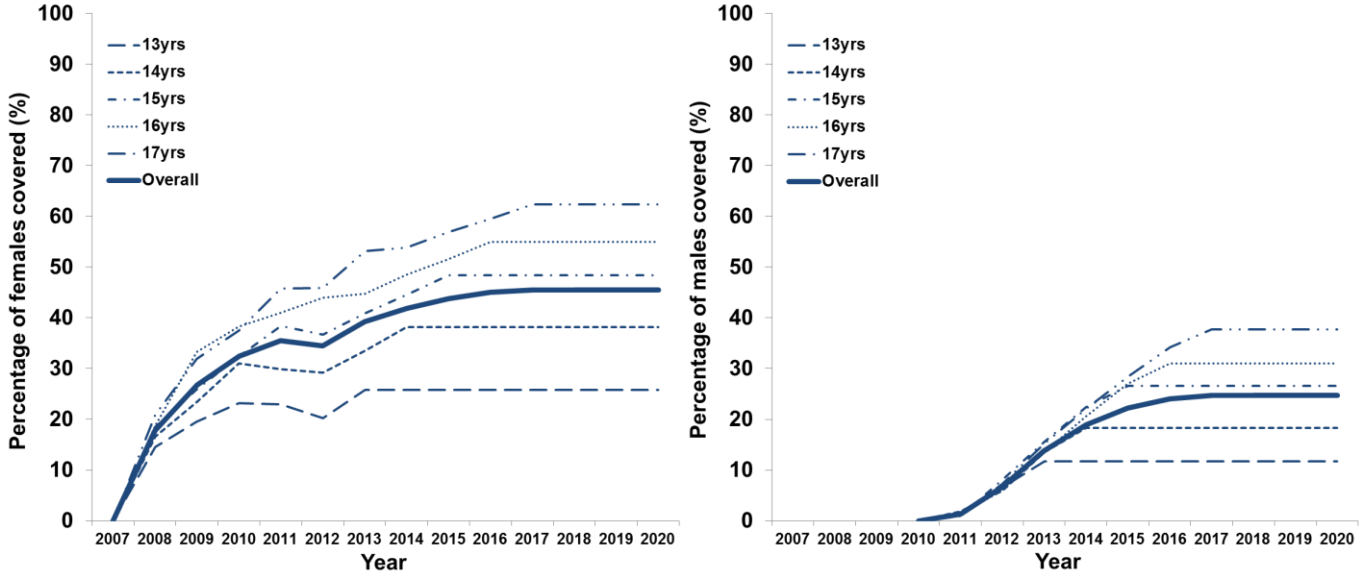
Four vaccination scenarios were examined: 0) no vaccination, 1) the current 4-valent gender-neutral (females/males) HPV vaccination program, 2) switching to a 9-valent for females but maintaining the 4-valent for males, or 3) switching to a 9-valent gender-neutral program. For scenarios 1 to 3, we modeled the changes in HPV vaccination in the United States from 2007 up to 2014 (i.e., introduction of gender-neutral vaccination in 2011). All changes to the current HPV vaccination strategy (scenarios 2 and 3) were modeled to occur at the beginning of 2015.

Supplementary Figure 2. Vaccination coverage 13-17 year-olds

A) Vaccination coverage of females 13-17 years old B) Vaccination coverage of males 13-17 years old



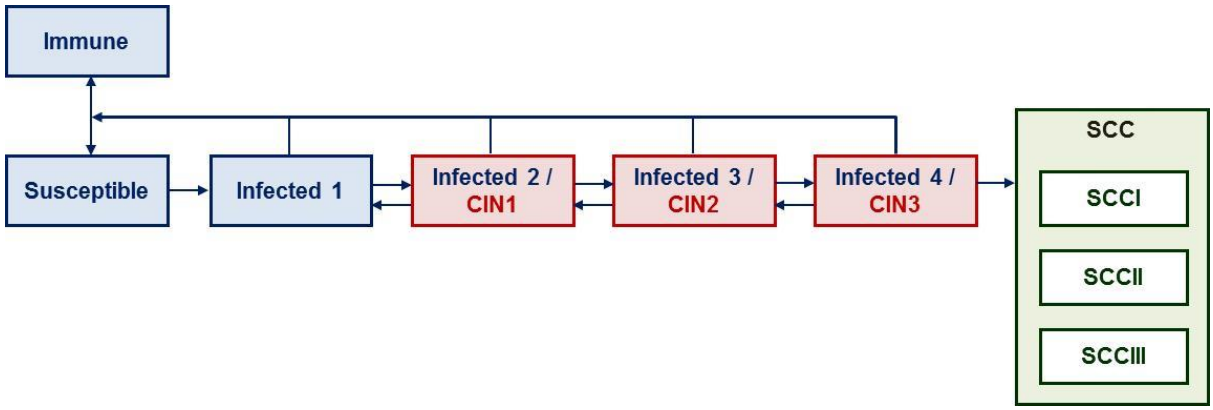
C) Vaccination coverage of females by age D) Vaccination coverage of males by age



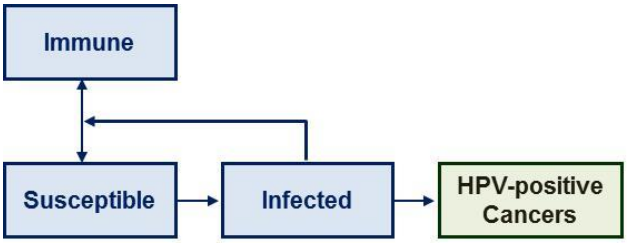
A-B) Overall vaccination coverage in 13-17 year-olds. The blue lines represent the model predictions and the red dots and bars the United States (U.S.) data with 95% CI (National Immunization Survey). BASE-CASE: Vaccine uptake rates were modeled by age and derived from the observed vaccination coverage by age in the U.S. (National Immunization Survey) for years 2007 to 2013; we assume constant vaccine uptake rates at 2013 levels from 2014 onward. The overall vaccination coverage increases until 2017, the time it takes for the 2013 cohort of 13-year-olds to reach 17 years of age. HIGH VACCINATION COVERAGE SCENARIO: We use 1-dose U.S. estimates and assume vaccine protection after 1 dose. LOW VACCINATION COVERAGE SCENARIO: We assume that the 3-dose coverage remains constant at 2012 levels from 2013 onwards (2012 was the lowest estimated uptake rate between 2010-2013). **C-D)** Base-case vaccination coverage by age (thin blue lines) and overall vaccination coverage in 13-17 year-olds (thick blue line). **Definitions:** CI: Confidence Interval. VACCINE UPTAKE RATE: Probability for unvaccinated females or males to be vaccinated in a given year. VACCINATION COVERAGE: Percentage of females or males that are vaccinated.

Supplementary Figure 3. Natural history flow diagrams

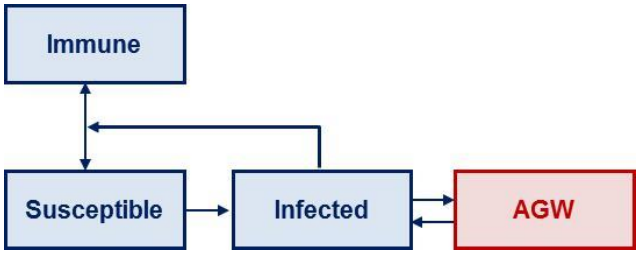
A) Cervical intraepithelial neoplasia (CIN) and squamous cell carcinoma (SCC) in the absence of screening



B) Other HPV-attributable cancers (cervical adenocarcinomas, cancers of the vulva, vagina, penis, anus and oropharynx)



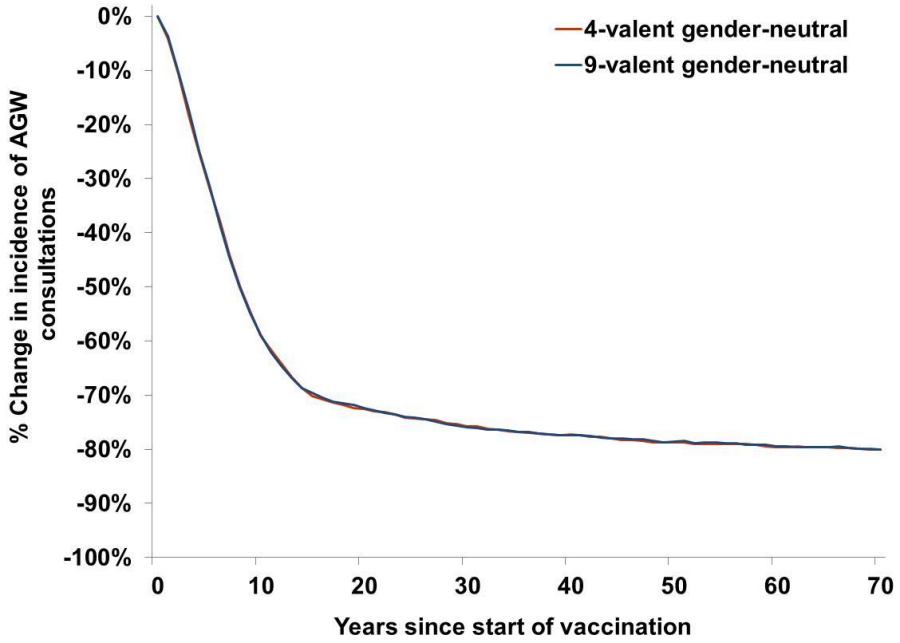
C) Anogenital warts (AGW)



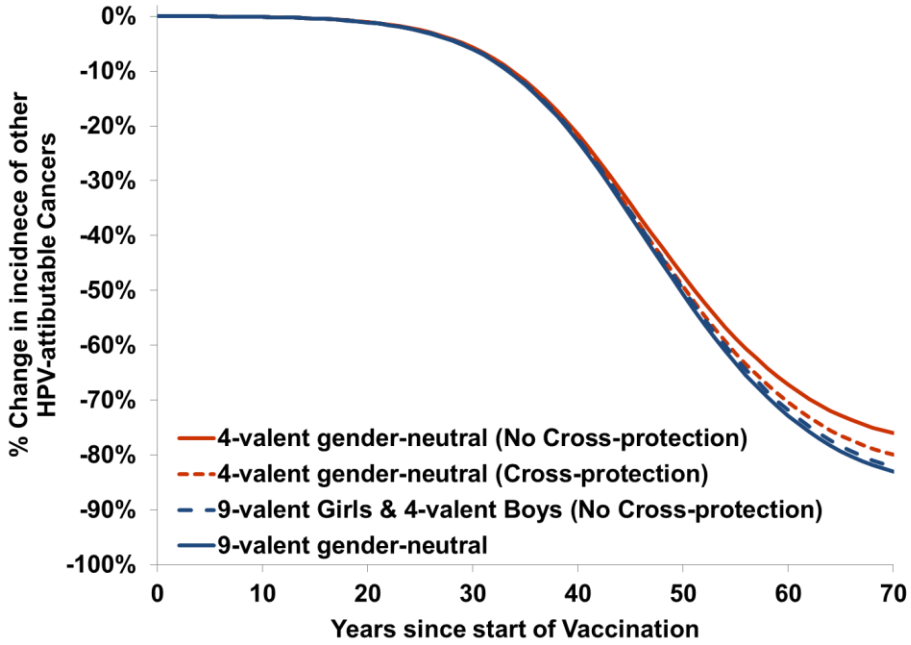
The mutually exclusive compartments represent the different HPV epidemiological states. Arrows represent the possible HPV-type specific transitions between these states for each individual. Arrows represent the possible HPV-type, age, and gender specific transitions between these states for each individual. **A) SCC:** Our model reproduces progression/clearance through different clinical cytological classifications (e.g, CIN1 to CIN3), and the course of underlying HPV infection progression/clearance to CIN3 based on duration of infection and HPV-type. The infection status (susceptible, infected, and immune) of each individual is type-specific and, therefore, an individual can be infected with multiple genotypes at the same time. Infected women can either clear the infection and return to immune/susceptible status or remain infected (Infected 1-4) and progress in the model to more severe stages of cervical intraepithelial lesions of grade 1 (CIN1), 2 (CIN2) or 3 (CIN3), and invasive squamous cervical cancer (SCC) of stage 1 (localized), stage 2 (regional) or stage 3 (distant). Women with CIN may also regress to a less severe stage or clear the infection and directly return to susceptible/immune status. **B) Other HPV-attributable cancers**: Simulated infected individuals have a gender- and type-specific probability of progressing towards cervical adenocarcinoma, and cancers of the anus, oropharynx, vulva, vagina, and penis, and a gender- and type-specific time of progression from persistent infection to cancer. **C) AGW**: Simulated individuals have a joint probability of developing and being diagnosed with anogenital warts (AGW) or clearing their infection. Individuals can experience multiple episodes of AGW through recurrence of a persistent infection, re-infection with a previously cleared HPV-type or infection with a new HPV-type.

Supplementary Figure 4. Estimated percentage change following vaccination

A) Incidence of anogenital warts (AGW) consultations among women and men*



B) Incidence of other HPV-attributable cancers†



BASE-CASE: Vaccine-type efficacy=95%, cross-protective vaccine efficacy presented in Supplementary Table 3, duration of protection=Lifelong.
PREDICTIONS: Mean estimate generated by the 50 best fitting parameter sets. Each parameter set run 20 times.
* Mean pre-vaccination incidence rate of anogenital warts consultations=153 per 100,000 person-years,
† Mean pre-vaccination incidence of other HPV-attributable cancers=7 per 100,000 women-years.

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