Incremental Cost-Effectiveness of the 9-valent vs. the 4-valent HPV vaccine in the U.S.

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October, 2014

Modeling Team

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Disclaimer

- The findings and conclusions expressed are those of the author and do not necessarily represent the official views of the Centers for Disease Control and Prevention (CDC) or the Department of Health and Human Services (DHHS)

Peer reviewed

- Follows *Guidelines for economic analyses to be presented to the ACIP*

Conflicts of interest statements

- Brisson (past 3 years): Unrestricted grant from Merck Frosst (Zoster vaccine, none ongoing)
- Drolet (past 3 years): Consulted for GSK (Zoster vaccine)
- Boily, Laprise, Chesson & Markowitz
  - No known conflicts of interest

Funding

Canada Research Chairs
Chaires de recherche du Canada

Canada

Public Health Agency of Canada
Agence de santé publique du Canada

Santé et Services sociaux Québec

CDC

Université Laval

IRSC CIHR
Instituts de recherche en santé du Canada
Canadian Institutes of Health Research

Imperial College London

Study Question

- From the societal perspective, what is the additional impact and cost-effectiveness of the 9-valent compared to 4-valent (quadrivalent) HPV vaccine in the context of an established 4-valent HPV vaccine program in the U.S.?

Objective

- To evaluate the:
  - additional population-level effectiveness, and
  - incremental cost-effectiveness

  of switching from the 4-valent to the 9-valent HPV vaccine in the U.S.

Methods

Model Overview – HPV-ADVISE

- **Model type**: Individual-based transmission-dynamic model[&]
- **Components**: Demographic
  Sexual behaviour & HPV transmission
  Natural history of disease
  Vaccination
  Screening & Treatment
  Economic
- **Population**: Open-Stable, 10 to 100 years of age
- **HPV infections**: 18 genotypes, including 6/11/16/18/31/33/45/52/58
- **Diseases**: Anogenital warts
  Cervical cancer (SCC & adenocarcinoma)
  Cancers of the anus, oropharynx, penis, vagina & vulva

&: Van de Velde et al. JNCI 2012 104(22):1712-23; Description of model components in extra slides

Parameter overview

Fitting process

Step 1: Uniform prior distributions are defined for each model parameter

- min-max values for each parameter derived from the literature

Step 2: Hundreds of thousands of different combinations of parameter values are drawn from the prior distributions

Step 3: Multiple parameter sets are identified, which fit U.S. data:

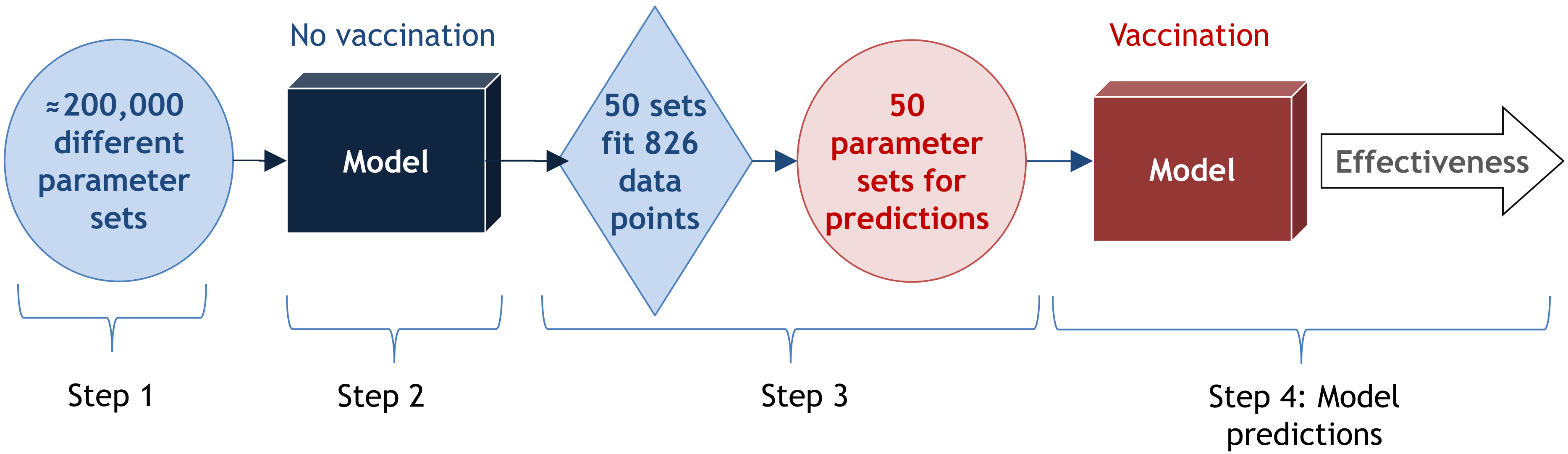
- Sexual & screening behaviour (stratified by gender and age)
- HPV prevalence (stratified by HPV type, gender, age and sexual activity)
- Incidence of AGW, cervical lesions, cervical cancer and other HPV-related cancers (stratified by HPV type, gender, and age)[&]
- Total of 826 data points fitted

&: Description of data used for fit and references available in extra slides

Model Fit Results

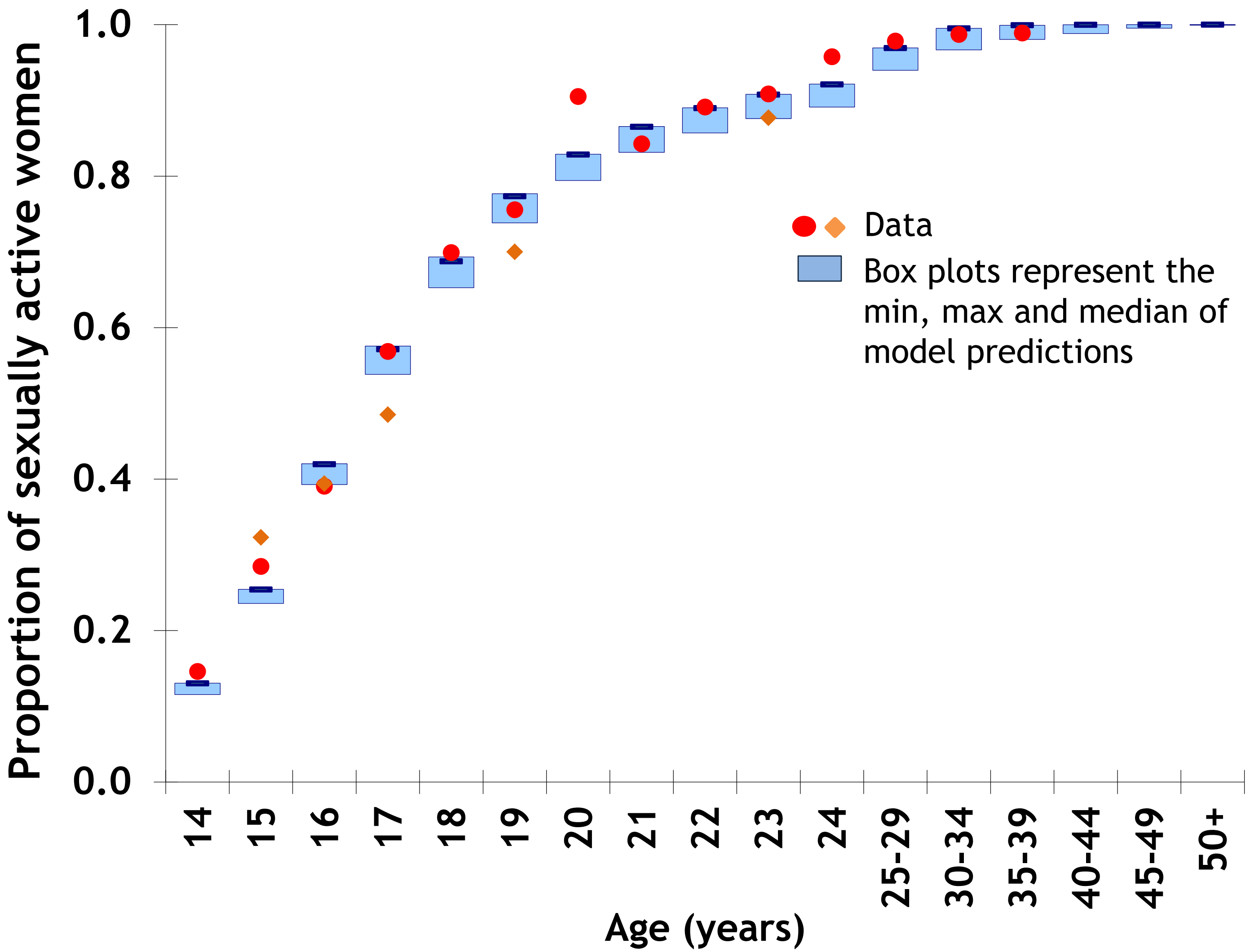
- ≈ 200,000 different combinations of parameters sampled from the prior parameter distributions

- 50 parameter sets produced acceptable fit to the 826 pre-specified data target points



Model Fit – sexual behaviour

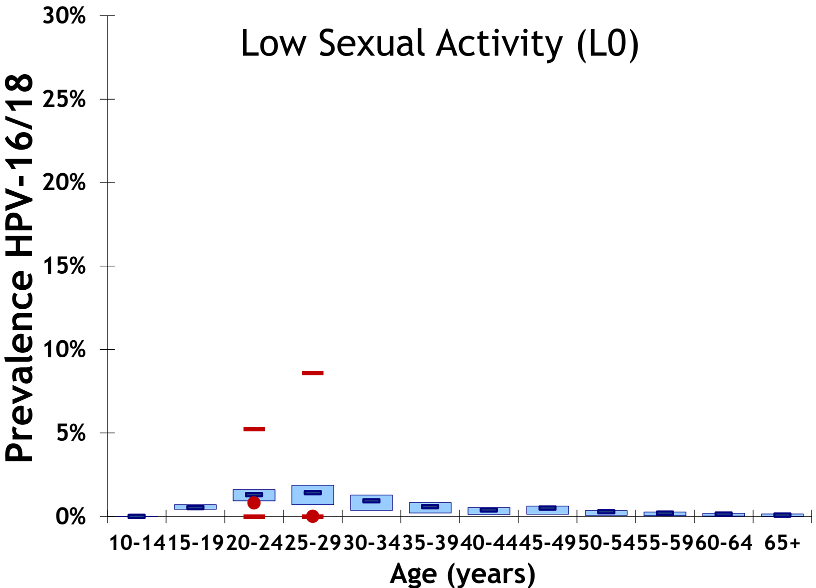
Ex: Proportion sexually active women

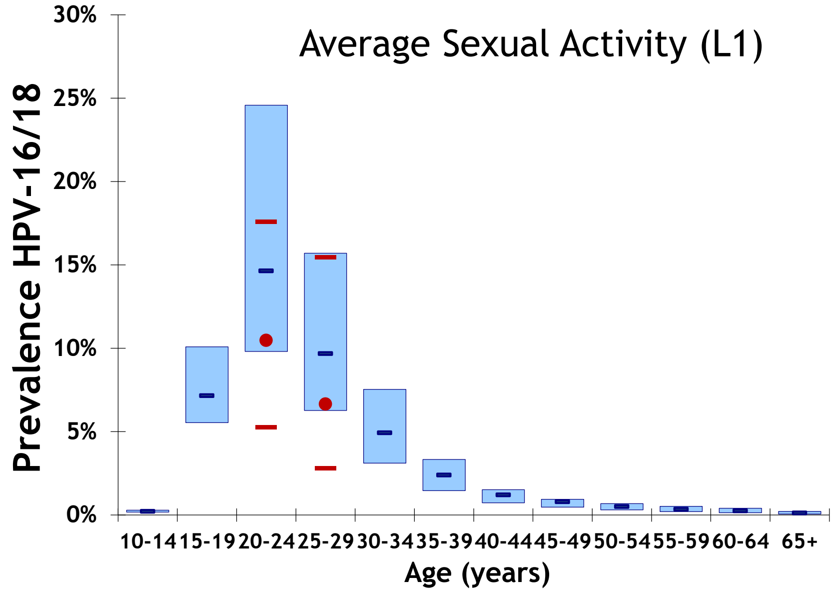


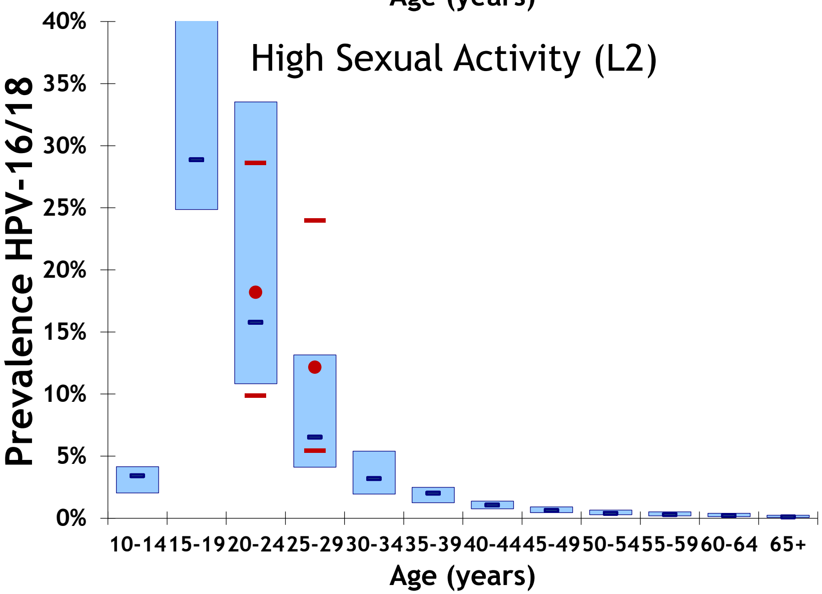
&: Other examples of model fit in extra slides; Data: NHANES

Model Fit – HPV Prevalence in women

Ex: HPV-16/18 prevalence by age and level of sexual activity







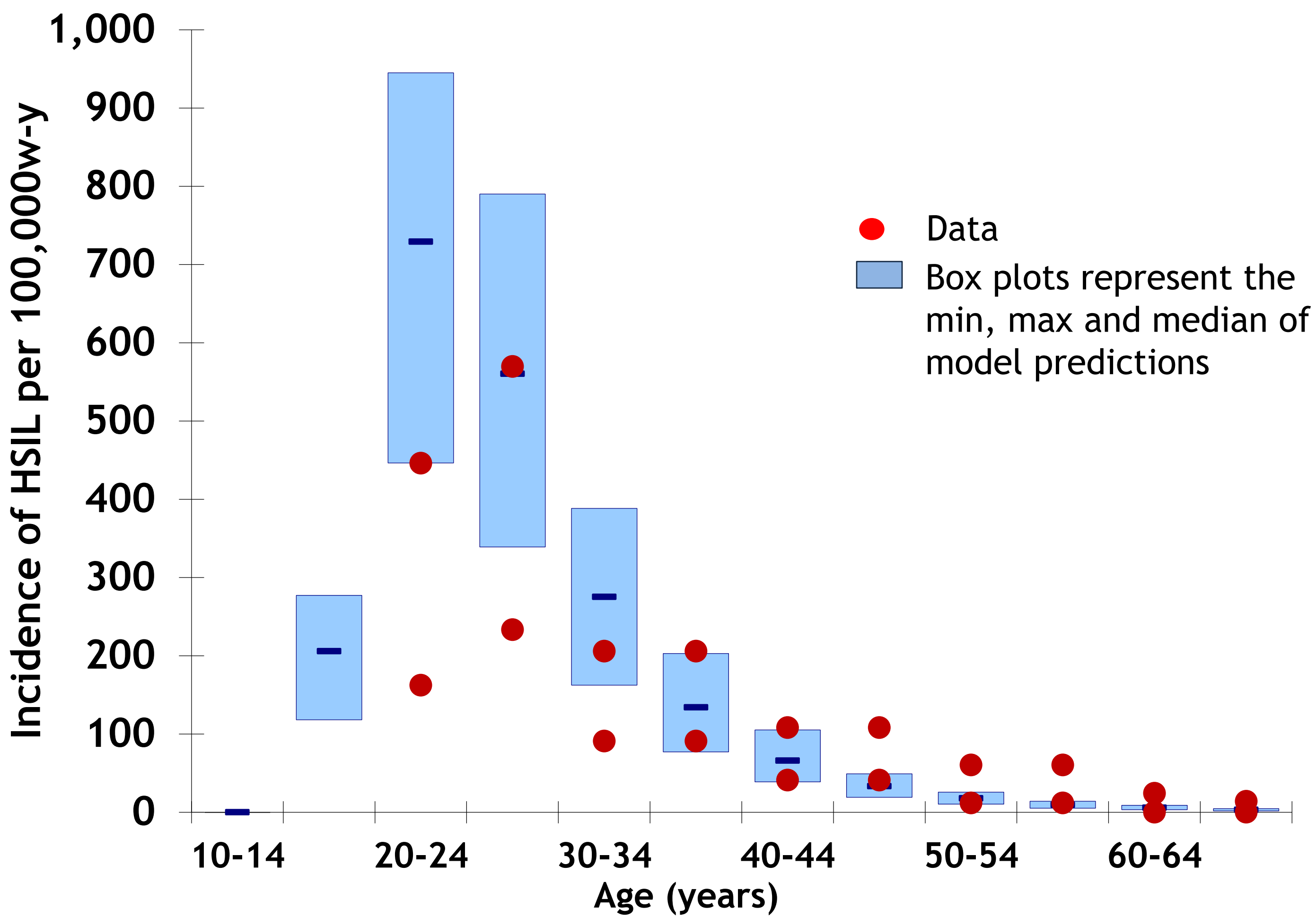
Data — 95%CI

Box plots represent the min, max and median of model predictions

&: Other examples of model fit in extra slides; Data: NHANES

Model Fit – Screening

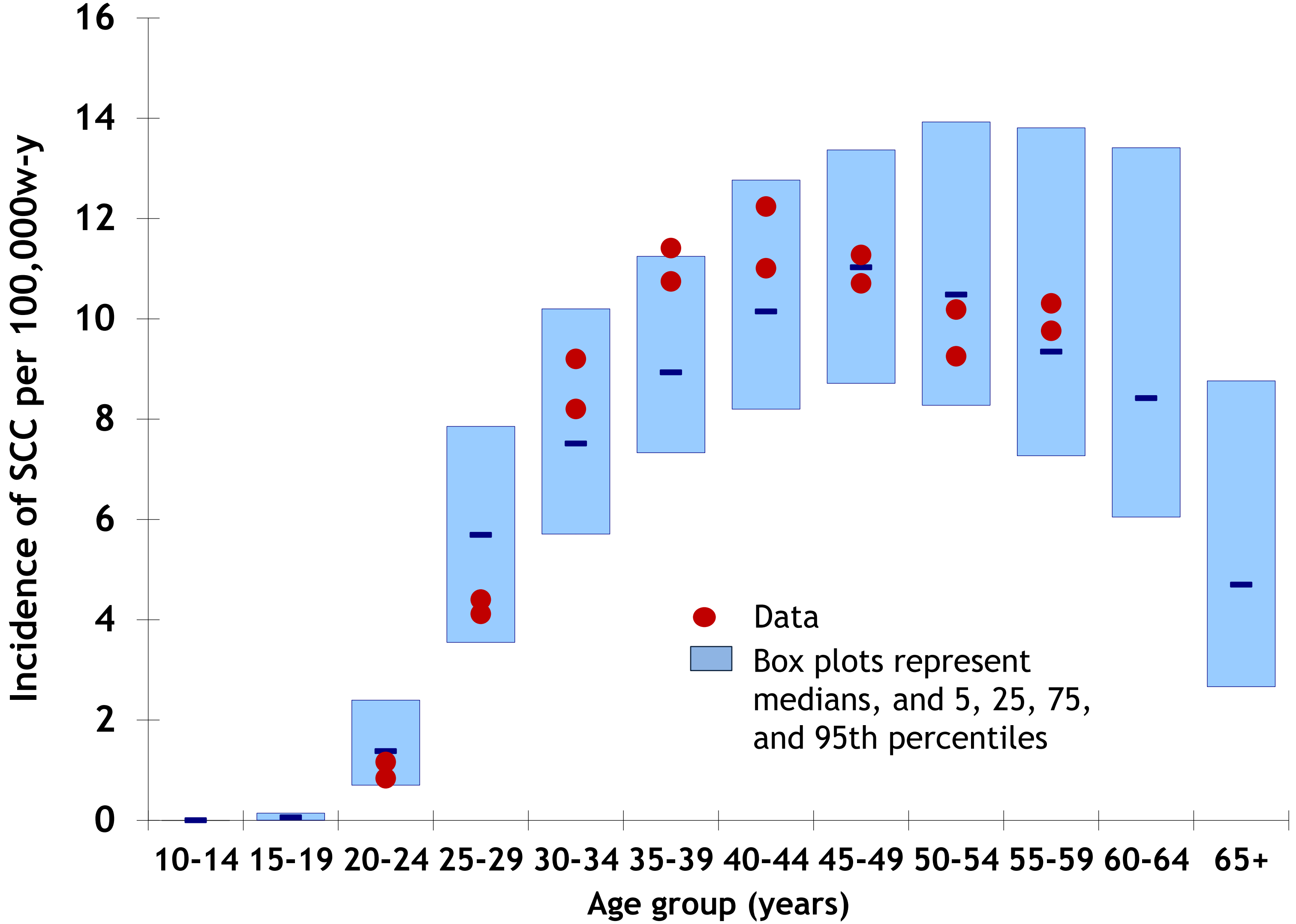
Ex: Incidence of HSIL



&: Other examples of model fit in extra slides; Data: Insinga 2004

Model Fit – Squamous cell carcinoma (SCC)

Ex: Incidence of SCC



&: Other examples of model fit in extra slides; Data: US Cancer Statistics (NPCR/SEER)

Vaccine efficacy (VE) parameters

VE among susceptible females & males

	Base case		
	VE persistent infection (%)		
HPV-type	4-valent (no cross protection)	4-valent[&] (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

&: Malagón, *Lancet Infectious Disease* 2012

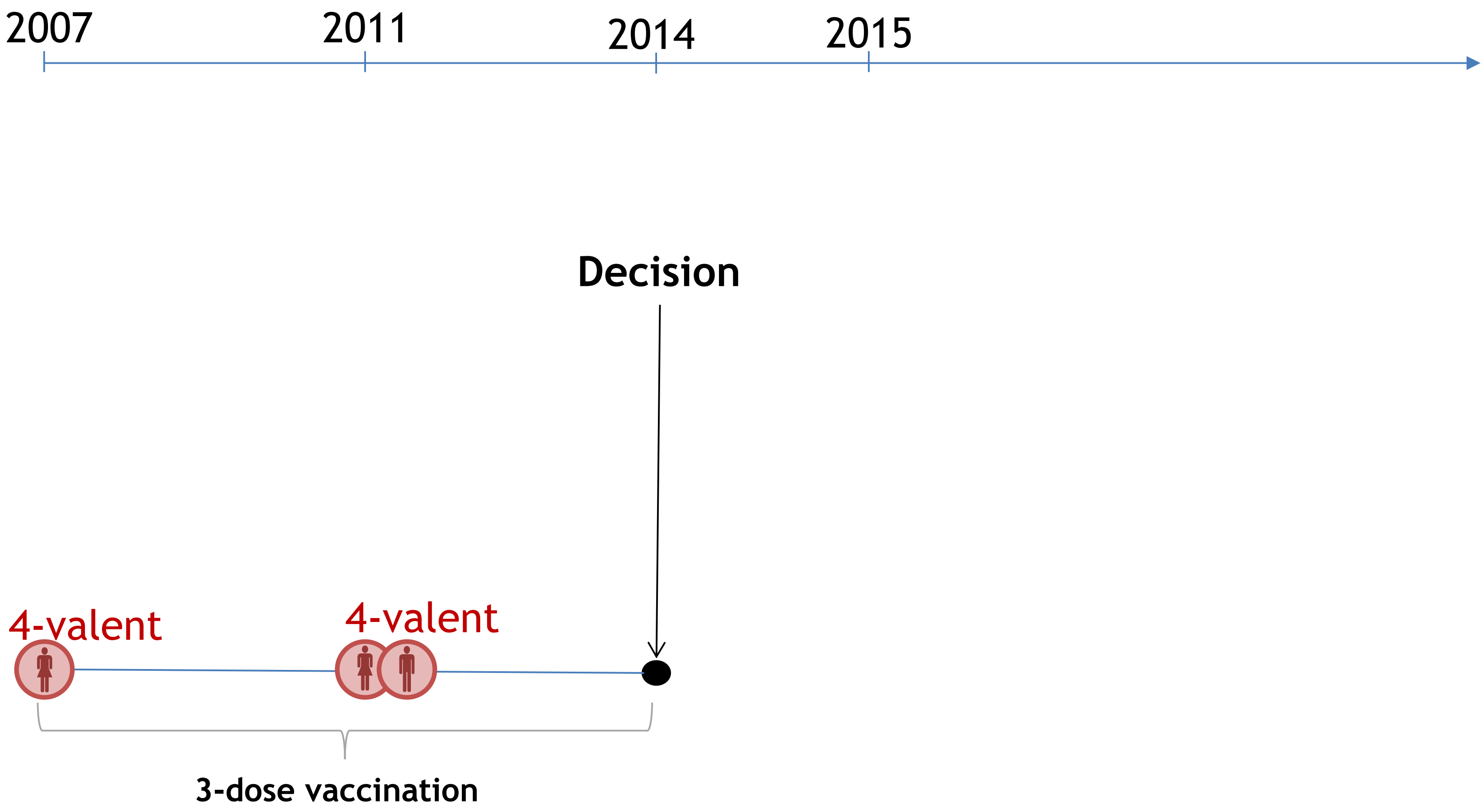
£: We assume that VE against HPV-16/18 is equal for the 4- and 9-valent vaccines (based on immunogenicity presented at Eurogin 2013)

Economic analysis

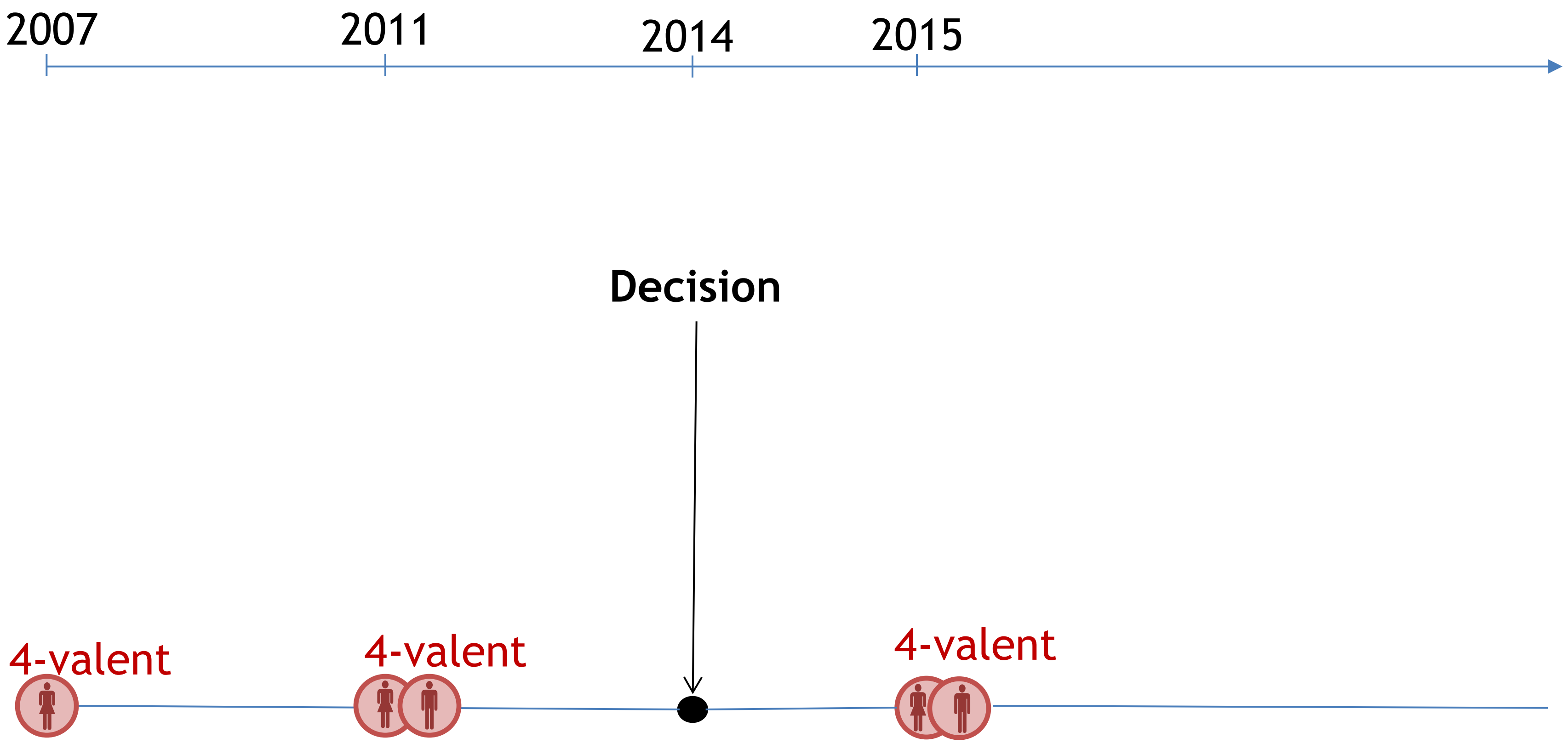
• Perspective:	Societal
• Costs:	All direct medical costs[&]
• Outcome Measure:	Cost per QALY gained[&]
• Discounting:	3% for costs and benefits
• Time Horizon:	70 years
• Vaccine Cost[†]: (with administration)	4-valent: $145/dose 9-valent: $158/dose

QALY=quality-adjusted life-year
&: Description of parameters and references available in extra slides
†: Cost from Merck presentation at the 29th International Papillomavirus Conference, 2014

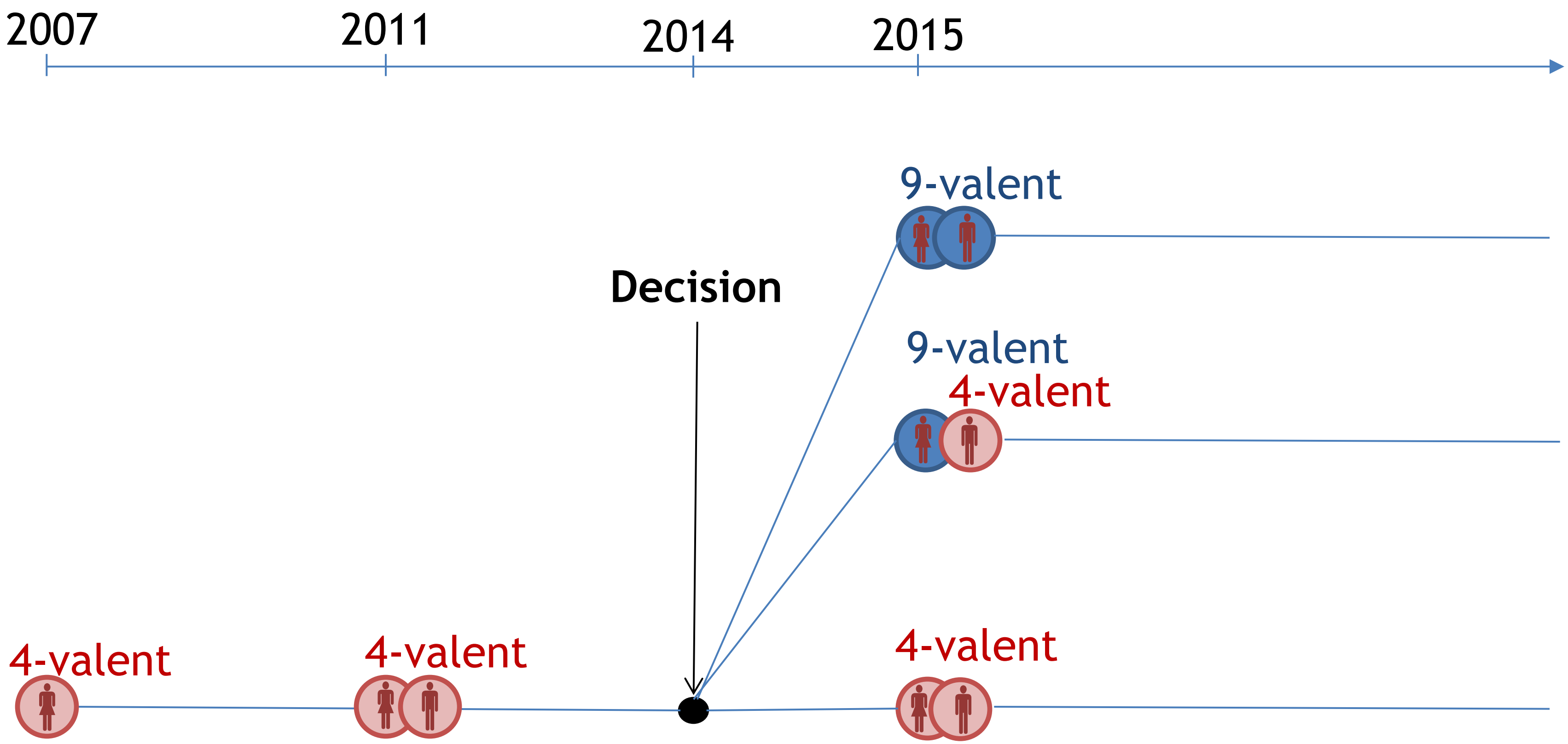
Intervention HPV vaccination 2007-2014



Intervention HPV vaccination 2015+



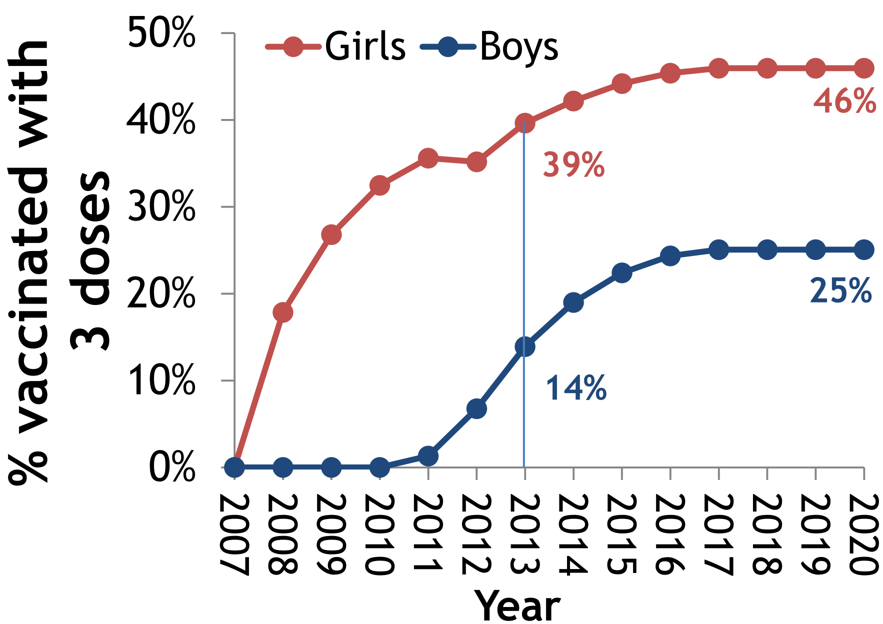
Intervention HPV vaccination 2015+



3-dose Vaccination Coverage

- Data: National Immunization Survey
- Used age-specific 3-dose uptake rates:
  - Annual % vaccinated with 3rd dose among those who had not previously received a 3rd dose
- 2007-13: Observed uptake rates
- 2014+: Assumed uptake rates constant at 2013 levels
- Overall vaccination coverage increases until 2017 due to age and time cohort effects

Coverage 13-17 year olds



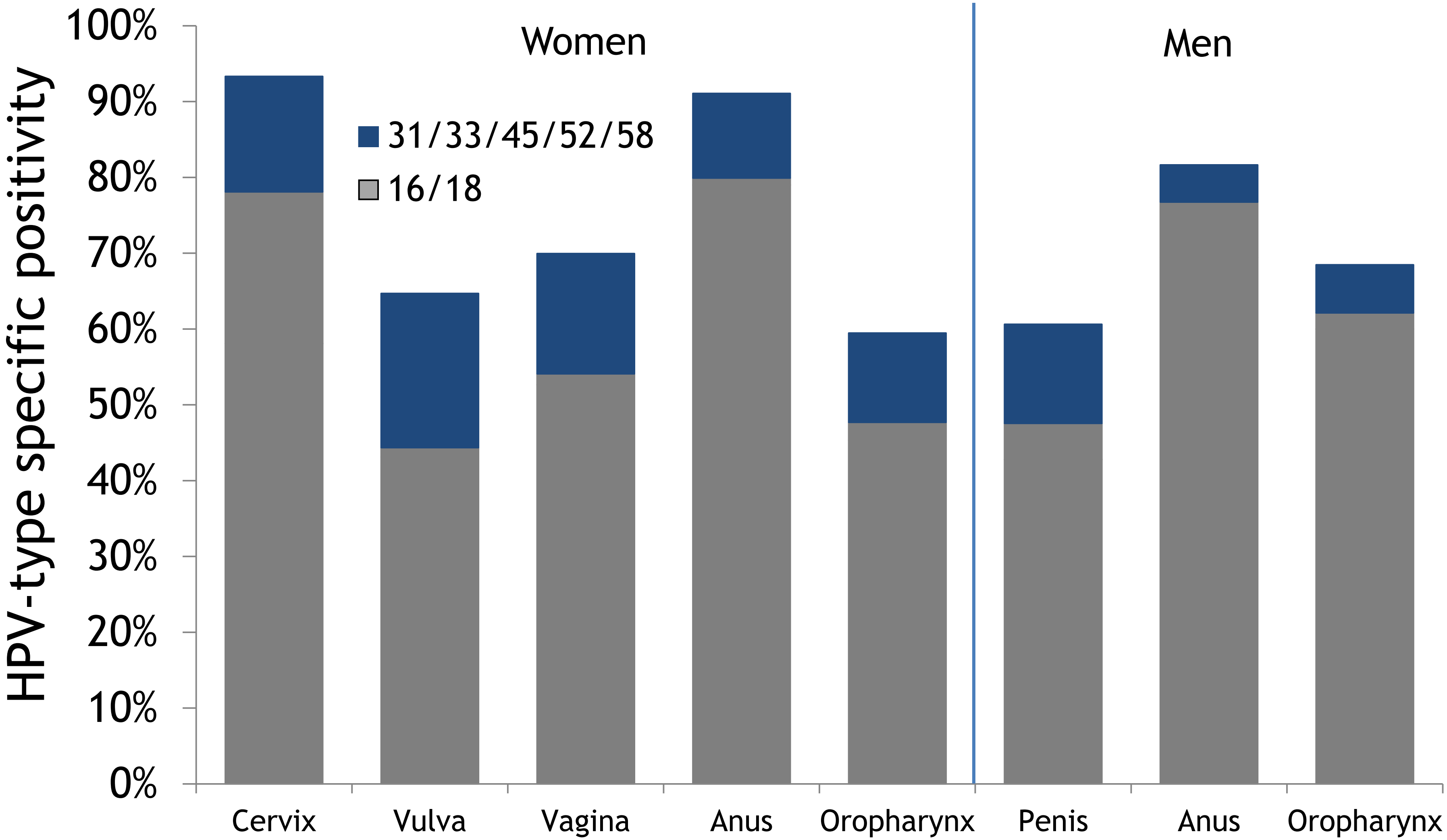
Coverage 2017+

Age (yrs)	Girls	Boys
13	26%	12%
14	38%	18%
15	48%	27%
16	55%	31%
17	62%	38%
13 to 17	46%	25%

Results: Health Outcomes

9-valent HPV vaccine

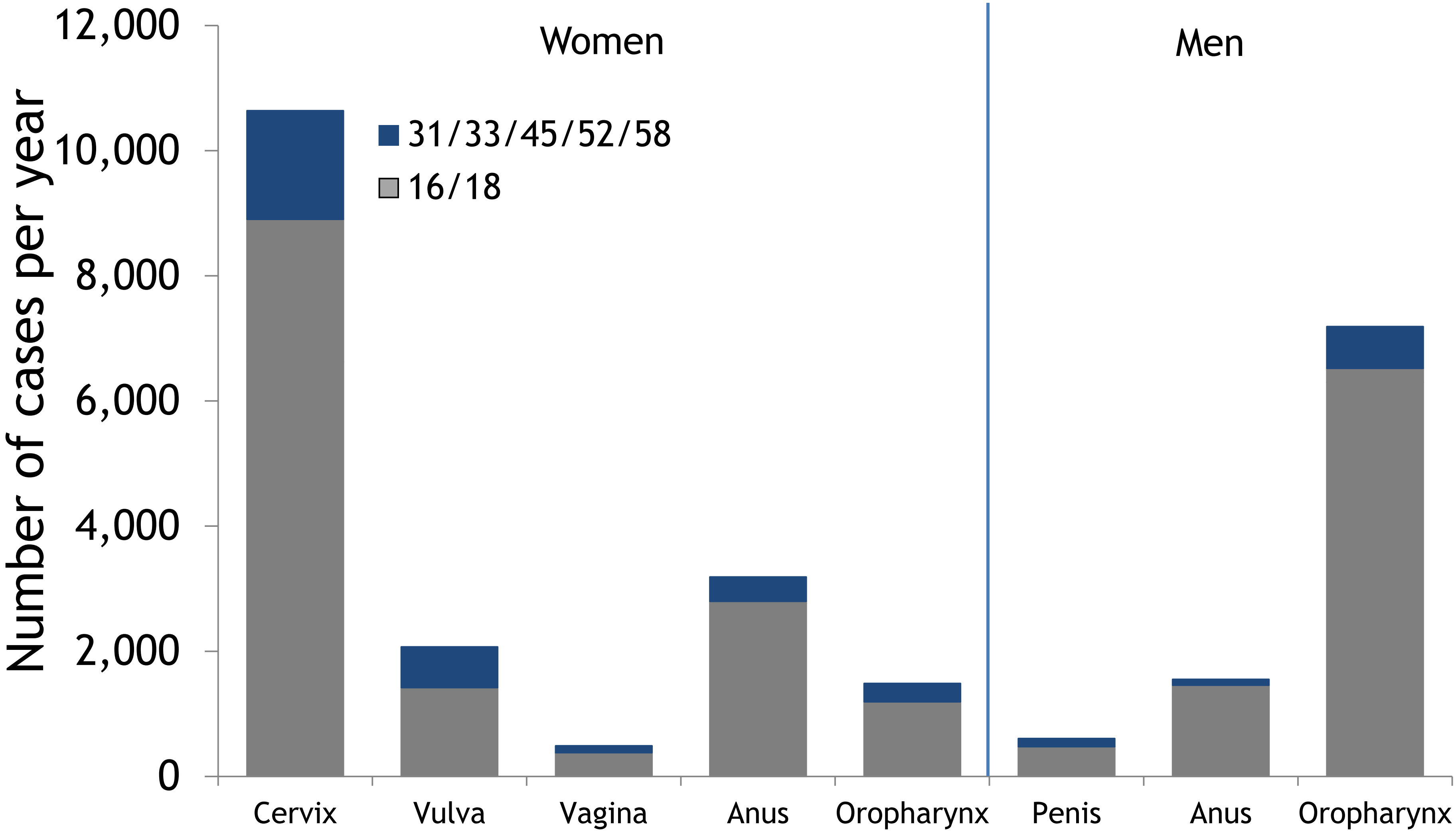
Potential for additional cancer prevention



&: 1) Saraiya, JNCI (under review)

9-valent HPV vaccine

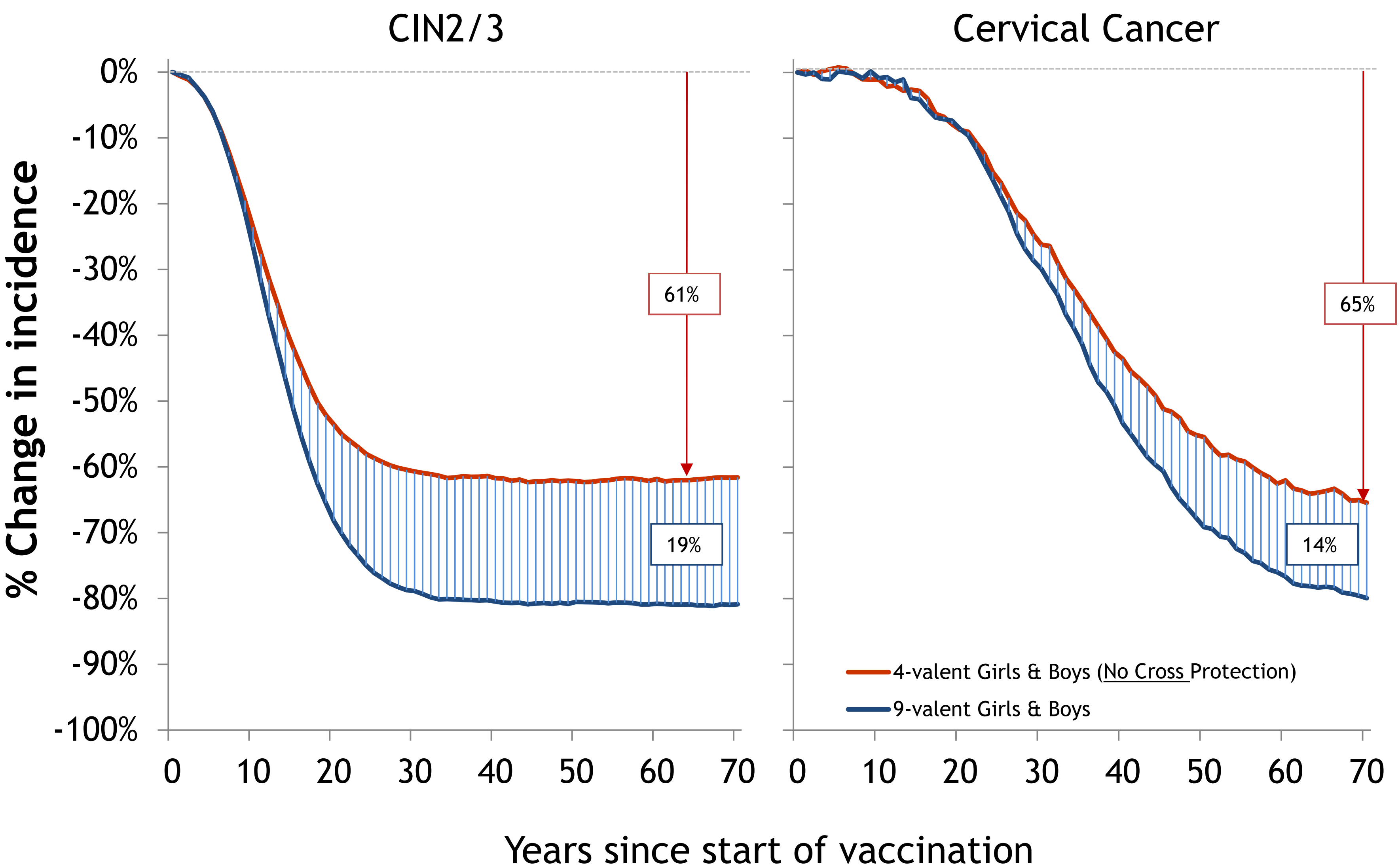
Potential for additional cancer prevention in the U.S.



Ref: 1) Jemal JNCI 2013; 2) Saraiya, JNCI (under review)

Effectiveness 4-valent vs. 9-valent Girls & Boys

Base case, No Cross Protection for 4-valent

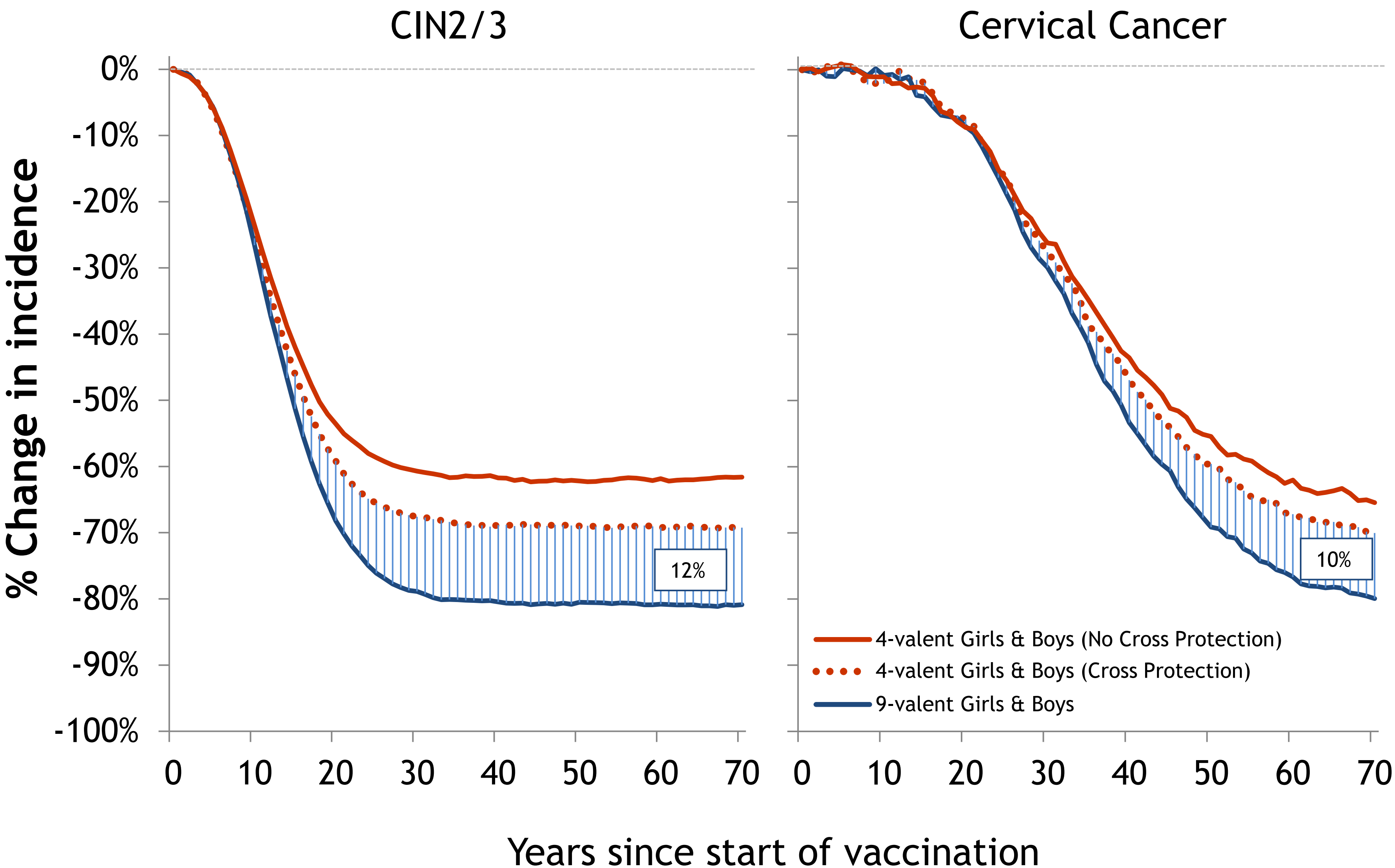


Base case: vaccine-type efficacy=95%, duration=Lifelong

Predictions: Mean estimate generated by the 50 best fitting parameter sets

Effectiveness 4-valent vs. 9-valent Girls & Boys

Base case, with & without Cross Protection for 4-valent

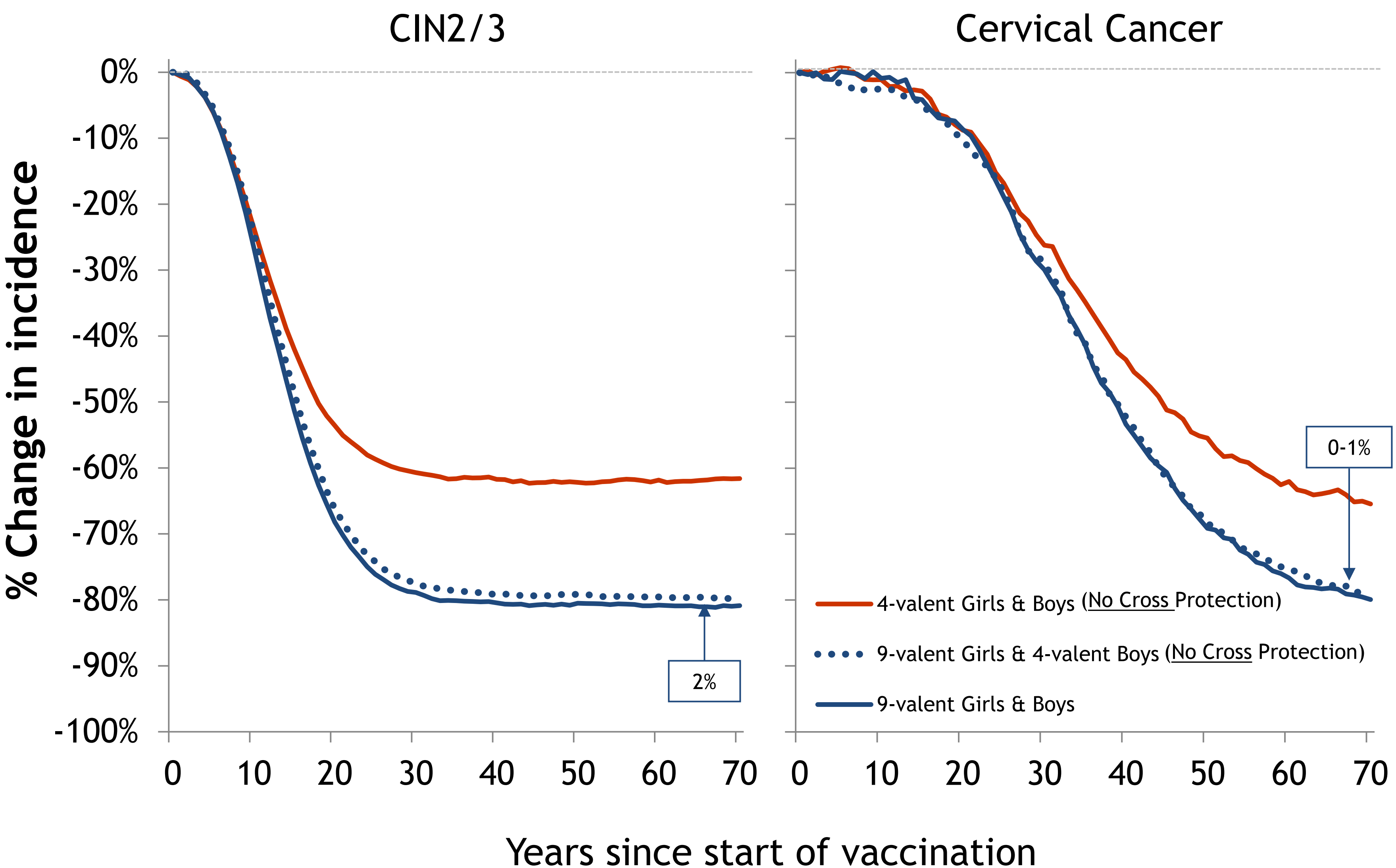


Base case: vaccine-type efficacy=95%, duration=Lifelong

Predictions: Mean estimate generated by the 50 best fitting parameter sets

Effectiveness 9-valent Girls & Boys vs. 9-valent Girls & 4-valent Boys

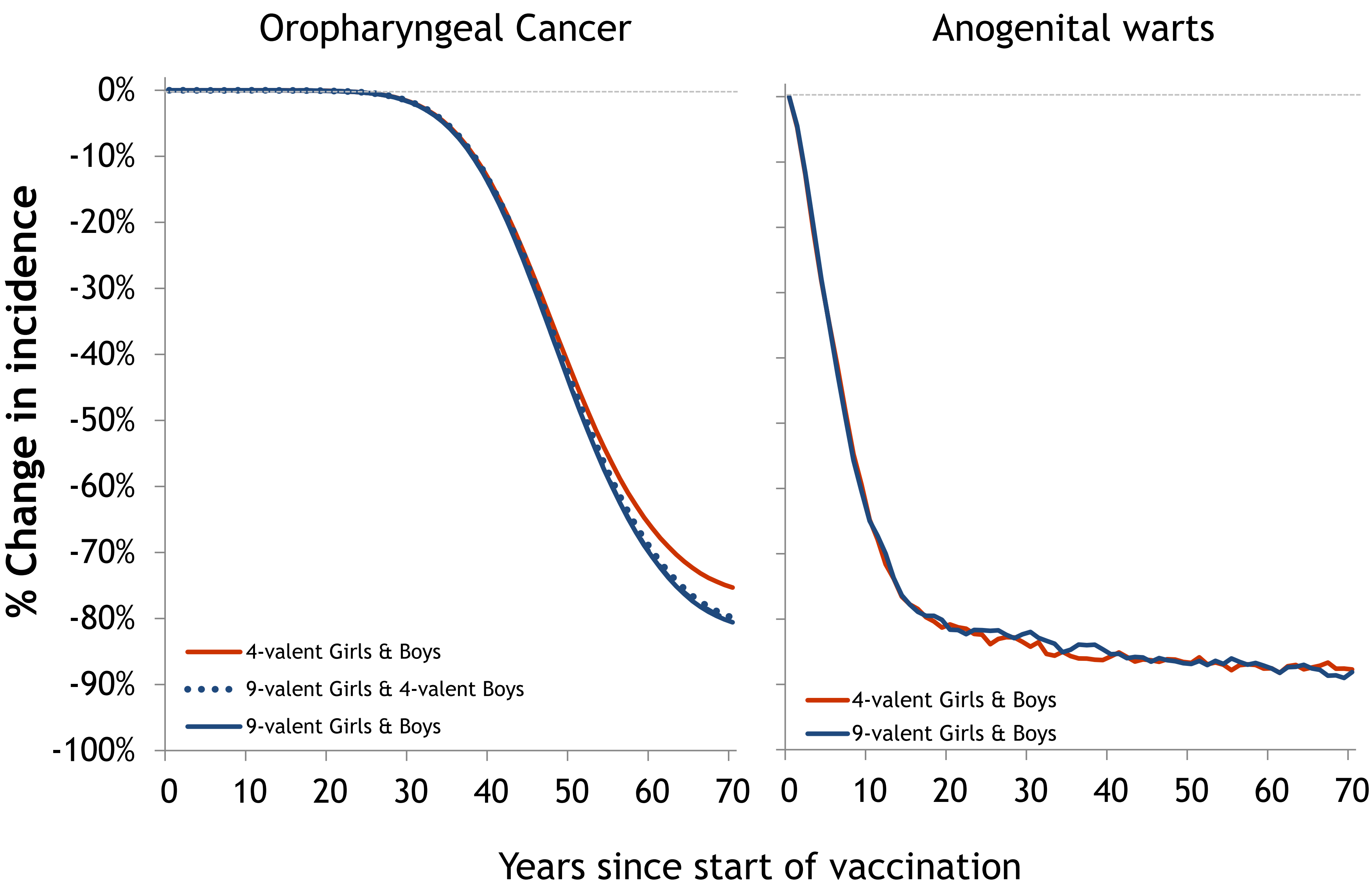
Base case, No Cross Protection for 4-valent



Base case: vaccine-type efficacy=95%, duration=Lifelong

Predictions: Mean estimate generated by the 50 best fitting parameter sets

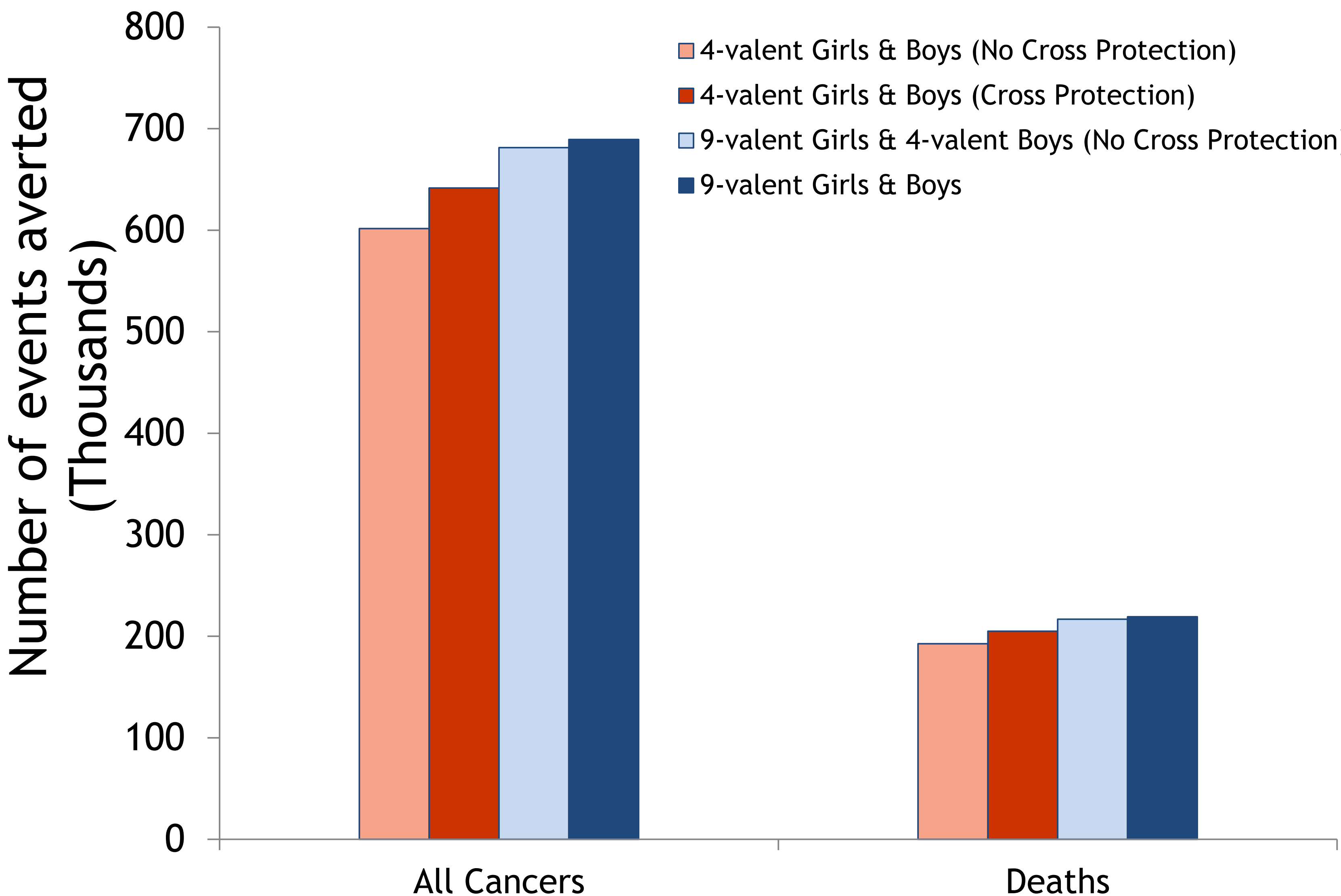
Effectiveness Base case, No Cross Protection for 4-valent



Base case: vaccine-type efficacy=95%, duration=Lifelong
Predictions: Mean estimate generated by the 50 best fitting parameter sets

Health Outcomes Prevented over 70 years

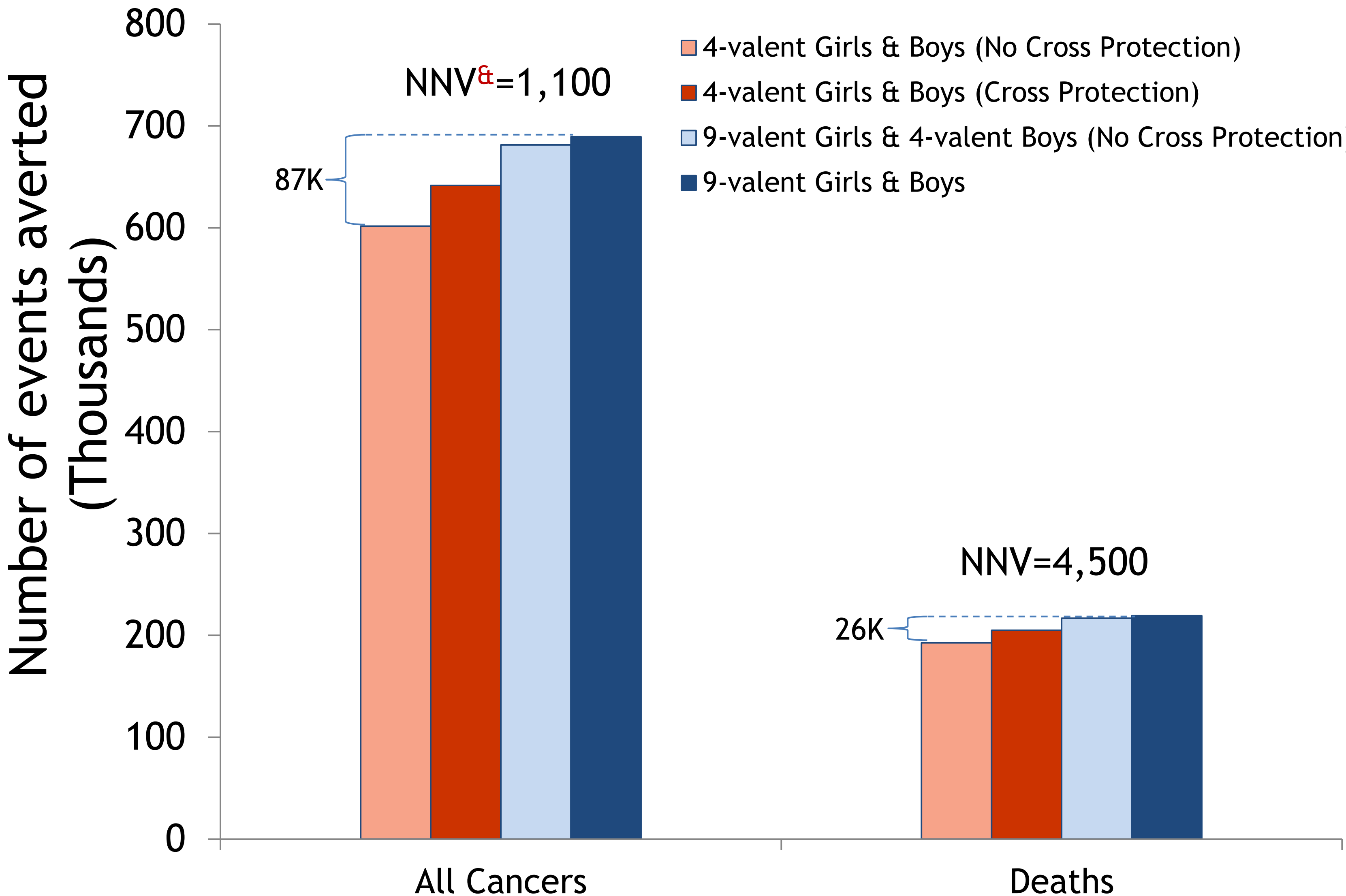
Base case



Base case: vaccine-type efficacy=95%, duration=Lifelong
Predictions: Mean estimate generated by the 50 best fitting parameter sets

Health Outcomes Prevented over 70 years

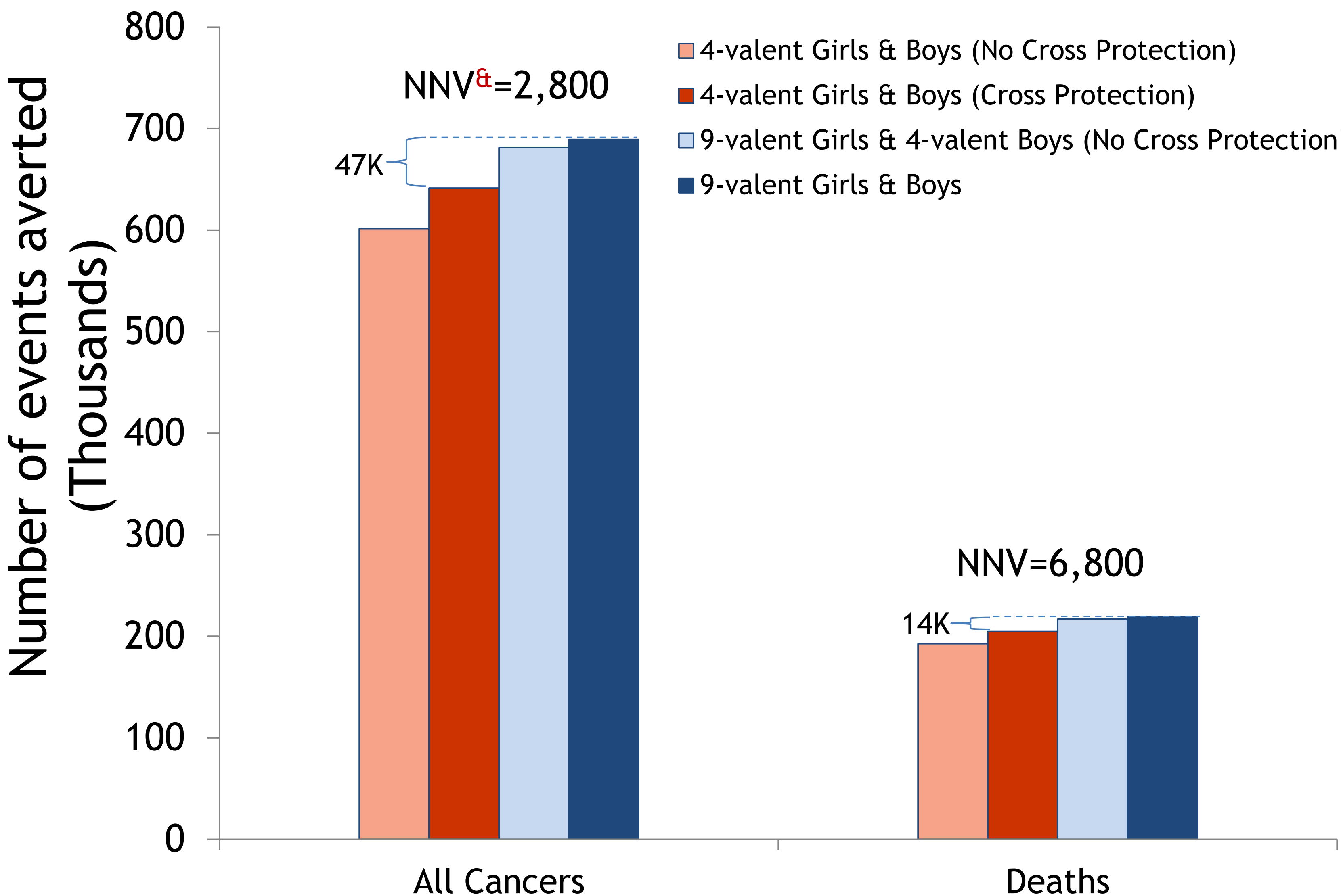
Base case, <u>No Cross</u> Protection for 4-valent



&: NNV=(# females vaccinated with 9-valent)÷(Additional events prevented by vaccinating females with 9-valent); Base case: vaccine-type efficacy=95%, duration=Lifelong; Predictions: Mean estimate generated by the 50 best fitting parameter sets

Health Outcomes Prevented over 70 years

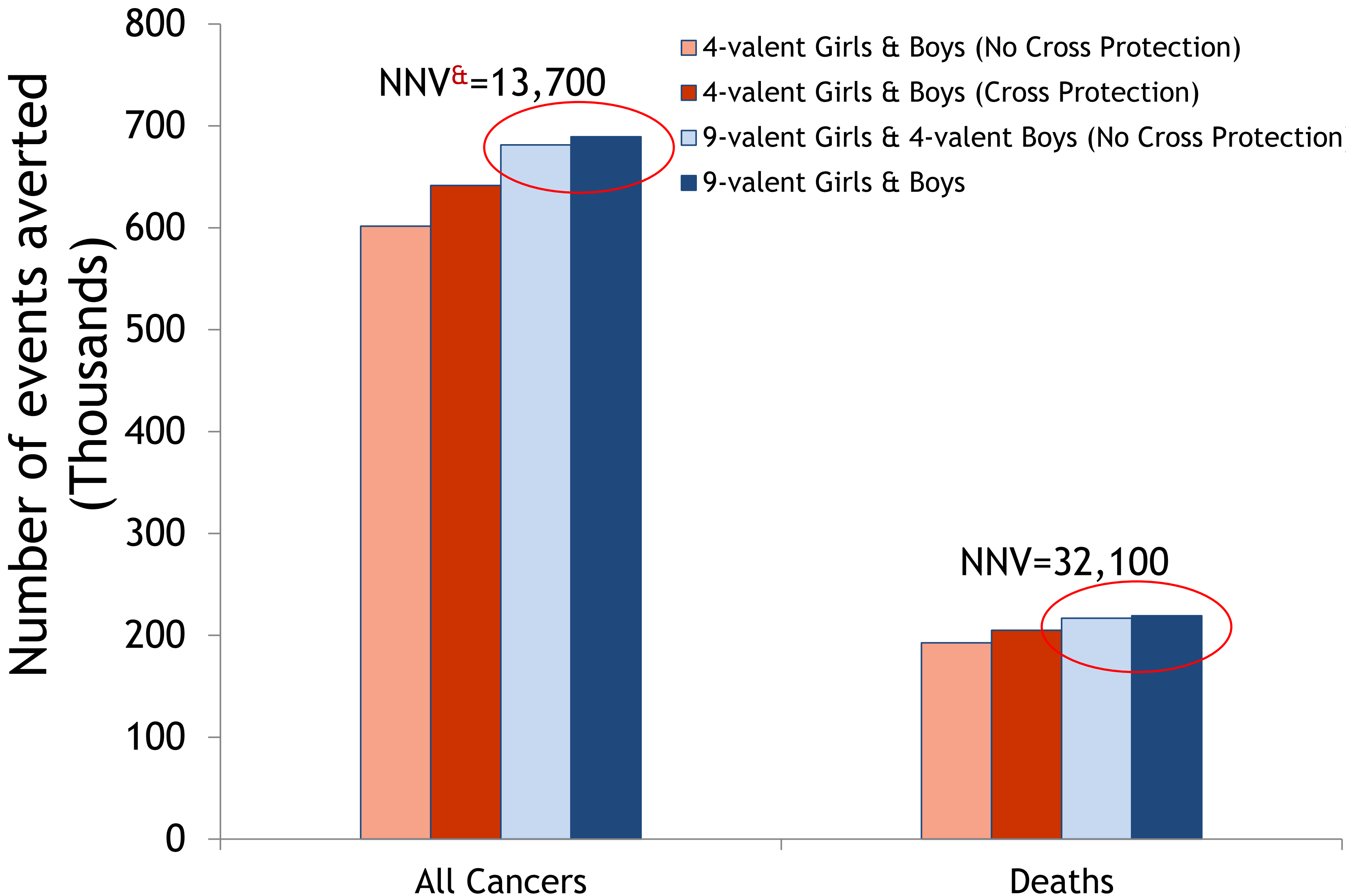
Base case, with Cross Protection for 4-valent



&: NNV=(# females vaccinated with 9-valent)÷(Additional events prevented by vaccinating females with 9-valent); Base case: vaccine-type efficacy=95%, duration=Lifelong; Predictions: Mean estimate generated by the 50 best fitting parameter sets

Health Outcomes Prevented over 70 years

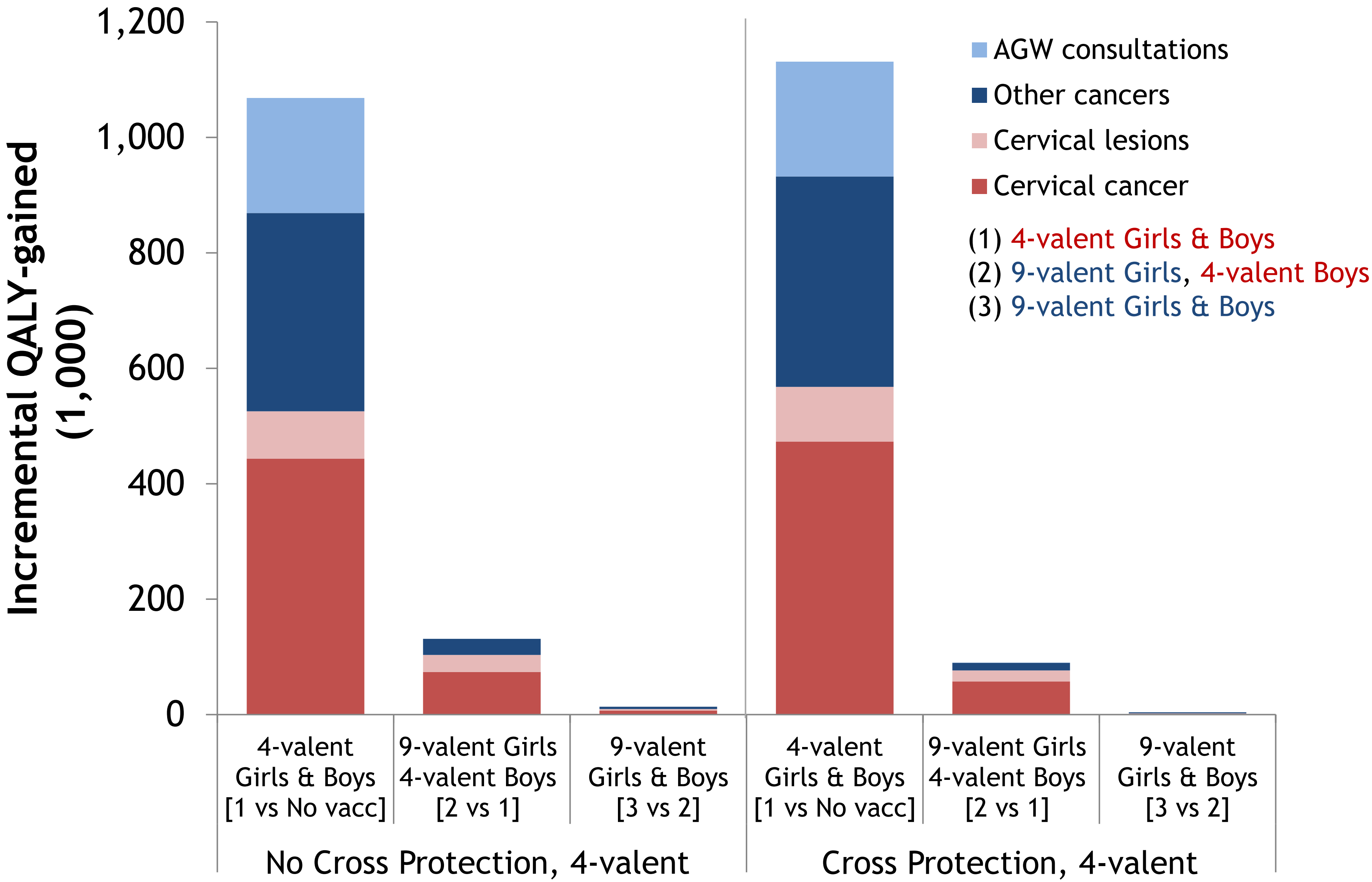
Base case, 9-valent Girls & Boys vs. 9-valent Girls & 4-valent Boys



&: NNV=(# boys vaccinated with 9-valent)÷(Additional events prevented by vaccinating boys with 9-valent); Base case: vaccine-type efficacy=95%, duration=Lifelong; Predictions: Mean estimate generated by the 50 best fitting parameter sets

Results: Cost-effectiveness

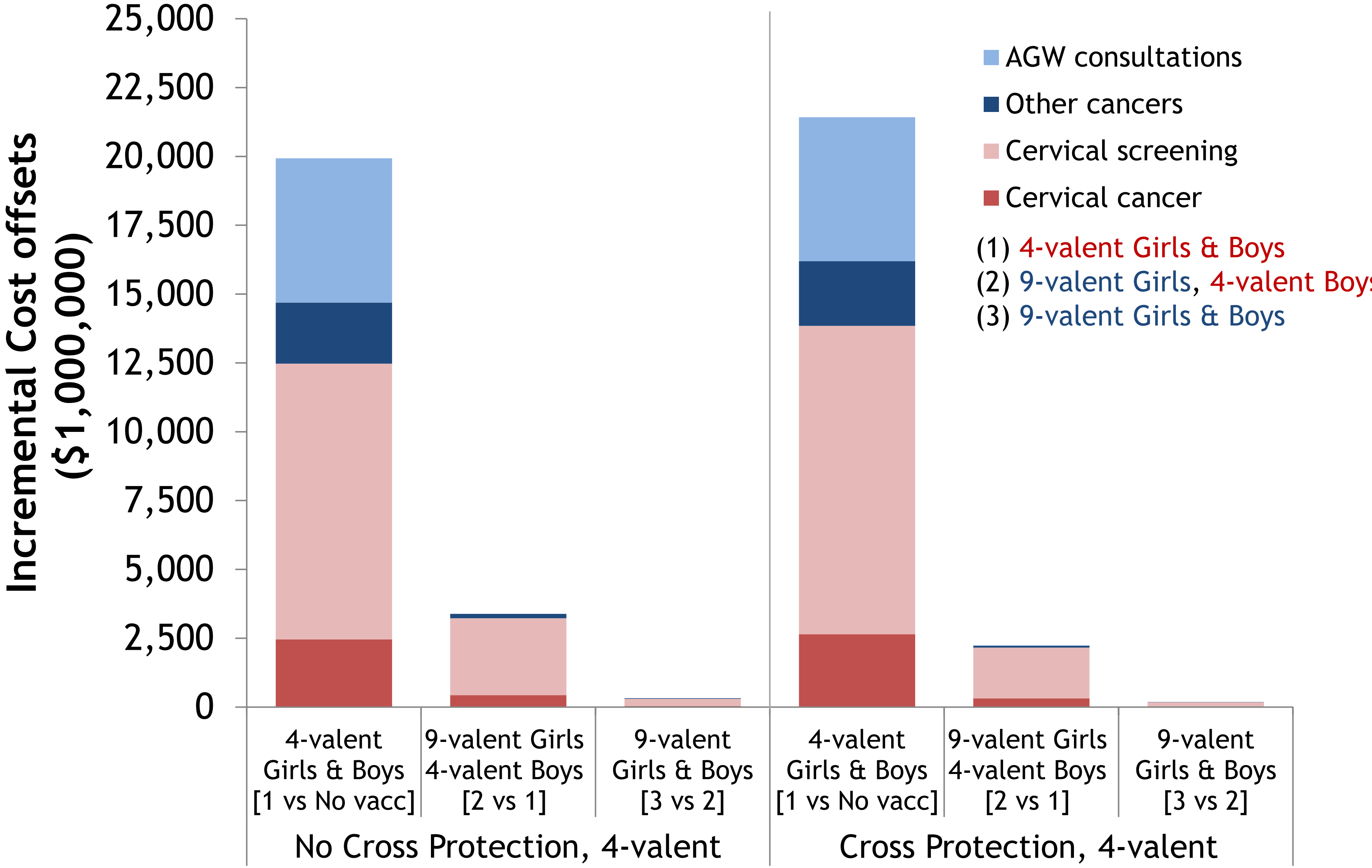
Incremental QALYs-gained Discounted over 70 years



Base case: vaccine-type efficacy=95%, duration=Lifelong
Predictions: Mean estimate generated by the 50 best fitting parameter sets

Incremental Healthcare costs saved

Discounted over 70 years



Base case: vaccine-type efficacy=95%, duration=Lifelong; 4-valent cost/dose=$145; 9-valent cost/dose=$158

Predictions: Mean estimate generated by the 50 best fitting parameter sets

Cost-effectiveness

Base Case, No Cross Protection for 4-valent

		Change in costs ($ million)	Change in QALY-gained (1,000 QALY)	ICER ($/QALY-gained)
(0) No Vaccination		-	-	-
(1) 4-valent Girls & Boys	1 vs. 0	6,866	1,068	6,400 [3,500; 10,100]
(2) 9-valent Girls 4-valent Boys	2 vs. 1	-2,149	131	Cost saving [CS; CS]
(3) 9-valent Girls & Boys	3 vs. 2	421	13	31,200 [1,900; >1million]
	3 vs. 1	-2,209	145	Cost saving [CS; CS]

ICER: Incremental Cost-Effectiveness Ratio; QALY=quality-adjusted life-year
Base case: Vaccine-type efficacy=95%, duration=Lifelong; 4-valent cost/dose=$145; 9-valent cost/dose=$158
Predictions: Mean result of the 50 best fitting parameter sets (25 runs per parameter set)
Uncertainty intervals: 10th and 90th percentiles of model results based on the 50 best fitting parameter sets, reflects uncertainty in the natural history parameters

Cost-effectiveness

Base Case, with Cross Protection for 4-valent

		Change in costs ($ million)	Change in QALY-gained (1,000 QALY)	ICER ($/QALY-gained)
(0) No Vaccination		-	-	-
(1) 4-valent Girls & Boys	1 vs. 0	5,379	1,131	4,800 [1,600; 8,600]
(2) 9-valent Girls 4-valent Boys	2 vs. 1	-1,009	90	Cost saving [CS; CS]
(3) 9-valent Girls & Boys	3 vs. 2	575	4	151,400 [4,000;>1million]
	3 vs. 1	-434	94	Cost saving [CS; 10,400]

ICER: Incremental Cost-Effectiveness Ratio; QALY=quality-adjusted life-year
Base case: Vaccine-type efficacy=95%, duration=Lifelong; 4-valent cost/dose=$145; 9-valent cost/dose=$158
Predictions: Mean result of the 50 best fitting parameter sets (25 runs per parameter set)
Uncertainty intervals: 10^{th} and 90^{th} percentiles of model results based on the 50 best fitting parameter sets, reflects uncertainty in the natural history parameters

Results: Sensitivity Analysis Influential Variables

Sensitivity Analysis Incremental cost-effectiveness ($/QALY-gained), No Cross Protection for 4-valent

	4-valent (Girls & Boys) vs. No vaccination	9-valent (Girls & Boys) vs 4-valent (Girls & Boys)
Base case	6,400	Cost saving
Duration of Protection=20yrs	8,300	Cost saving
Vaccine Coverage • All doses at 13 yrs of age • Girls=75%, Boys=69%	8,000 12,000	Cost saving Cost saving
Min Health Care Costs	13,300	Cost saving
Min Burden of Disease	10,500	Cost saving
Cervical screening - Co-testing	-	Cost saving

ICER: Incremental Cost-Effectiveness Ratio; QALY=quality-adjusted life-year
Base case: Vaccine-type efficacy=95%, duration of protection =Lifelong; 4-valent cost/dose=$145; 9-valent cost/dose=$158
Min: Minimum estimates from the U.S. literature; All doses given at 13 yrs of age: Vaccination coverage Girls=62%, Boys=38%;
HPV Co-testing: HPV co-testing every 5 years (30-65 year old women)
Predictions: Mean result of the 50 best fitting parameter sets (20 runs per parameter set)

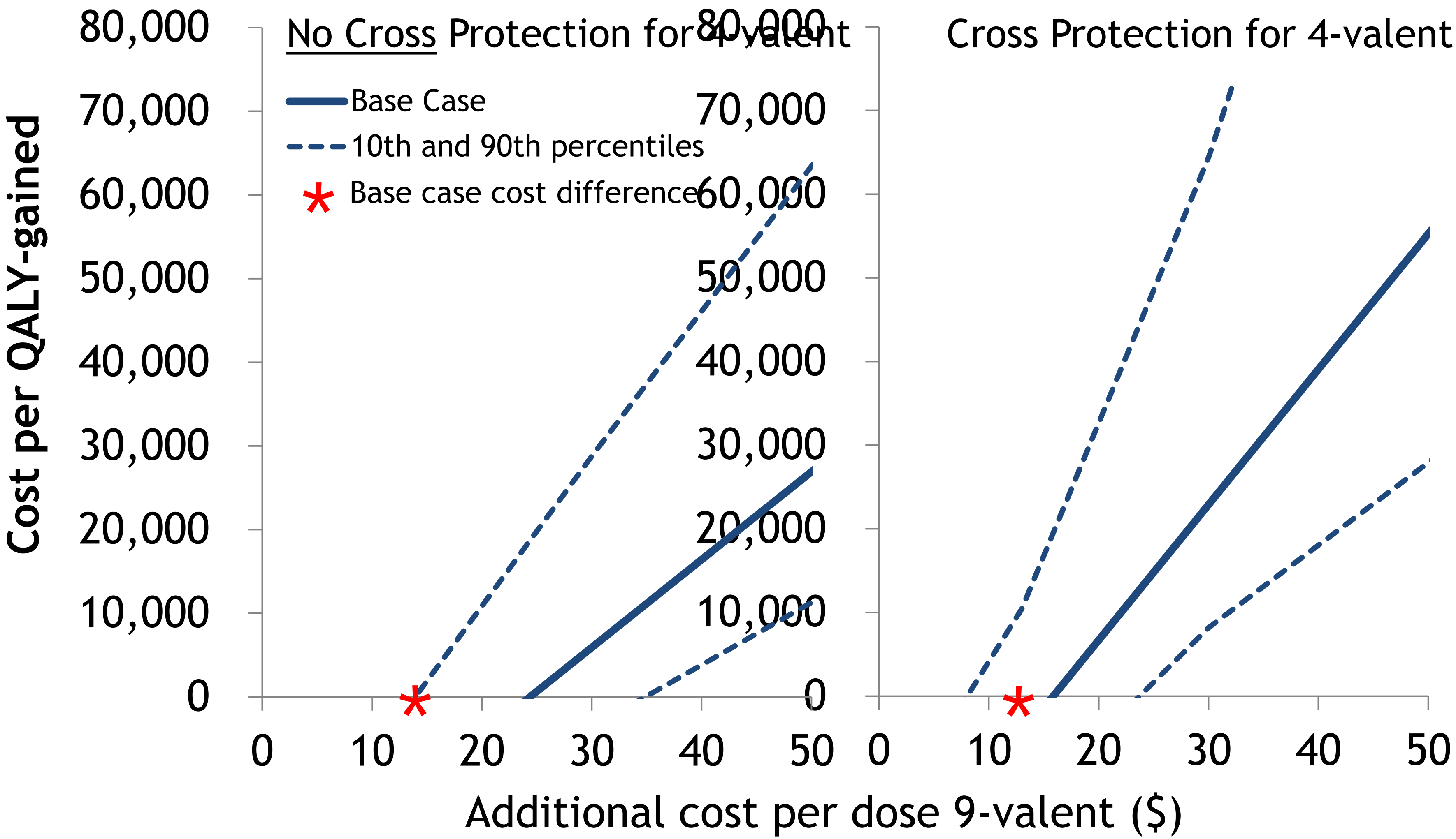
Sensitivity Analysis Incremental cost-effectiveness ($/QALY-gained), with Cross Protection for 4-valent

	4-valent (Girls & Boys) vs. No vaccination	9-valent (Girls & Boys) vs 4-valent (Girls & Boys)
Base case	4,800	Cost saving
Duration of Protection • 9- & 4-valent=20yrs • Cross-protection=20yrs	 6,500 4,900	 Cost saving Cost saving
Vaccination Coverage • All doses at 13 yrs of age • Girls=75%, Boys=69%	 6,700 9,900	 Cost saving 3,500
Min Health Care Costs	11,700	4,500
Min Burden of Disease	8,000	Cost saving

ICER: Incremental Cost-Effectiveness Ratio; QALY=quality-adjusted life-year
Base case: Vaccine-type efficacy=95%, duration of protection =Lifelong; 4-valent cost/dose=$145; 9-valent cost/dose=$158
Min: Minimum estimates from the U.S. literature; All doses given at 13 yrs of age: Vaccination coverage Girls=62%, Boys=32%;
Predictions: Mean result of the 50 best fitting parameter sets (20 runs per parameter set)

Sensitivity Analysis

Additional Cost/dose of the 9-valent (vs. 4-valent)



QALY=quality-adjusted life-year;
Base case: Vaccine-type efficacy=95%, duration of protection=Lifelong; 4-valent cost/dose=$145; 9-valent cost/dose=$158
Predictions: Mean, and 10th and 90th percentile of model results based on the 50 best fitting parameter sets (20 runs per parameter set). 10th and 90th percentiles reflect the uncertainty in the natural history parameters

Discussion: Limitations

Limitations

- Duration of 4- and 9-valent vaccine efficacy and future vaccination coverage remains unknown:
  - Varied duration of protection and vaccination coverage
  - Duration of protection and coverage had no impact on conclusions
- Modeled both cytology-based screening and HPV co-testing:
  - Screening may change in the coming years
  - If the changes to screening result in less costly and/or more effective cervical cancer prevention the 9-valent may be less cost-effective
- Did not present cost-effectiveness 9-valent vs 2-valent
  - In Canada, the 2-valent vaccine was less cost-effective than the 9- and 4-valent

Summary

Summary Population-level effectiveness predictions

- Current U.S. 4-valent Girls & Boys strategy is expected to substantially reduce HPV-related diseases
  - 61% and 65% reduction in CIN2/3 and Cervical cancer, respectively, after 70 years (assuming no cross protection)
  - 1 HPV-related cancer would be prevented for every 250 vaccinated individuals
- Switching to a 9-valent Girls & Boys is expected to further reduce precancerous lesions and cervical cancer, with less impact on other HPV-related outcomes
  - 19% and 14% additional reduction in CIN2/3 and Cervical cancer, respectively, after 70 years (assuming no cross protection)
  - 1 additional HPV-related cancer prevented for every 1,000 vaccinated individuals with the 9-valent instead of the 4-valent
- Vaccinating girls with the 9-valent provides the great majority of benefits of a 9-valent Girls & Boys program

Summary Cost-effectiveness predictions

- Current U.S. 4-valent Girls & Boys HPV vaccination program is highly cost-effective

- Switching to a 9-valent Girls & Boys program is likely cost-effective (and cost saving)
  - Vaccinating girls with the 9-valent provides the majority of cost savings and QALYs-gained of a 9-valent Girls & Boys program

- Results are robust across a range of plausible assumptions
  - with or without cross protection
  - price, duration of protection, health care costs, burden of illness

Thank you!