Population-level effectiveness & cost-effectiveness of the 9-valent HPV vaccine

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PCC2015

February 21st, 2015

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

IRSC CIHR

Instituts de recherche en santé du Canada

Canadian Institutes of Health Research

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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)

Context

- Recent results from a large clinical trial have shown that a 9-valent HPV vaccine is highly effective[1]
  - Published Feb 19th in the New England Journal of Medicine[1]
  - 9-valent includes types HPV-6/11/16/18/31/33/45/52/58
  - HPV types that cause about 90% of cervical cancers worldwide[2]
- 9-valent HPV vaccine (Gardasil®9) was approved by:
  - U.S. FDA (December 10th, 2014)
  - Health Canada (February 5th, 2015)
- Thursday (Feb 26th), the Advisory Committee on Immunization Practices (ACIP) will vote on whether to recommend 9-valent HPV vaccination in the U.S.

REF: 1) Joura, NEJM 2015; 2) de Sanjose, *Lancet Oncol* 2010

9-valent HPV vaccine efficacy

Phase III study

- 9-valent (n=7,099) vs Quadrivalent (n=7,105)
- Population at enrollment: 16-26-year old females, not infected

Results – outcomes with HPV types 31, 33, 45, 52, 58

- 97% efficacy (95%CI:81-100) against incidence of high-grade cervical/vulvar/vaginal disease caused by HPV types 31, 33, 45, 52, 58
- 97% efficacy (95%CI:92-99) against incidence of any grade
- 96% efficacy (95%CI:94-97) against six-month persistent HPV infection

What we don't know

- Added benefit in the context of potential cross-protection

REF: Joura, *NEJM* 2015

Main criteria considered when making recommendations for new vaccines

- Safety & Efficacy
- Preventable burden of illness
- Effectiveness & Cost-effectiveness
- Affordability & Programmatic feasibility
- Equity
- Public preferences & Politics

Objectives

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

  of switching from the 4-valent to the 9-valent HPV vaccine, using the U.S. as an example

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

Model fit

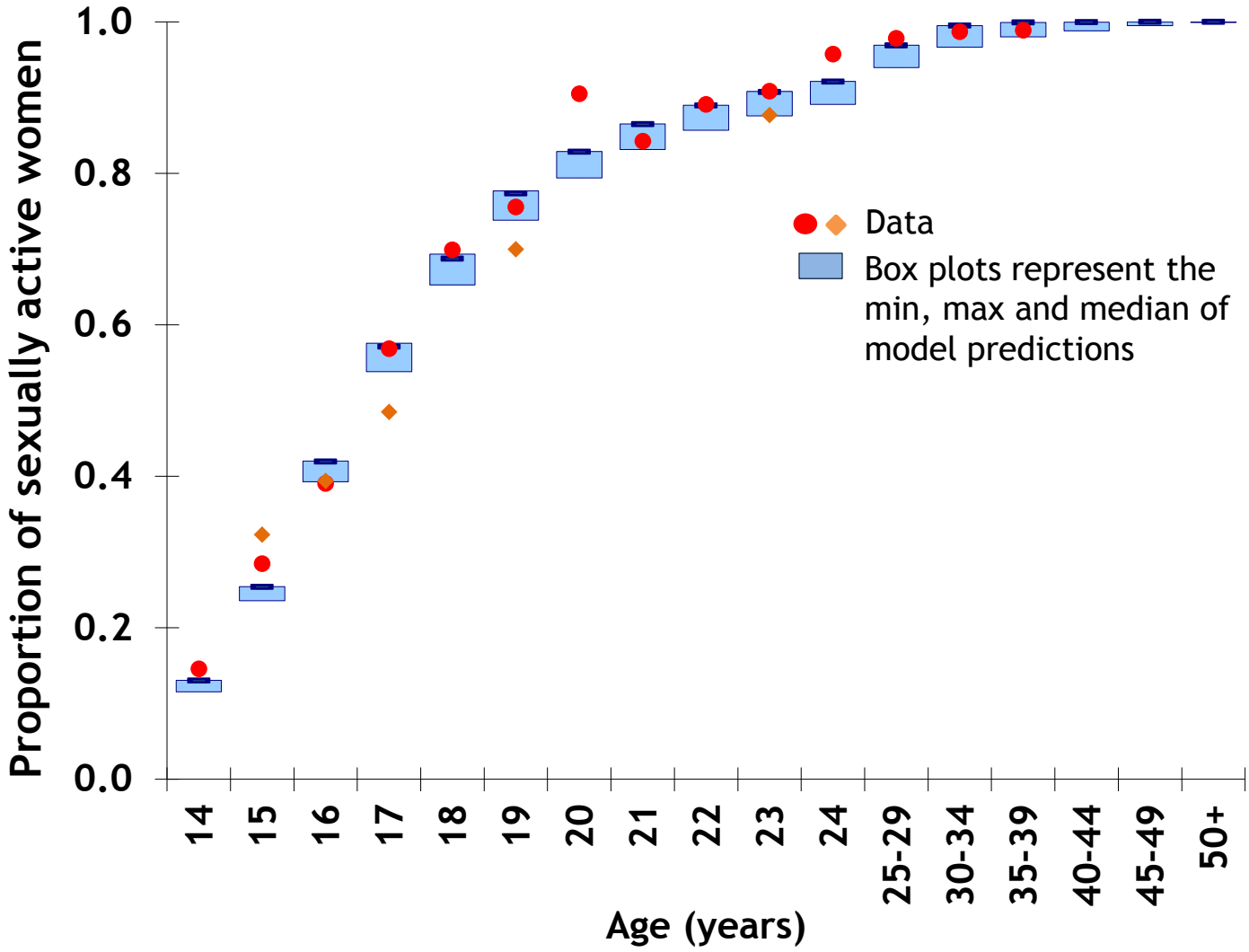
Results

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

- 50 parameter sets produced model results within the 826 pre-specified data targets

Model Fit – sexual behaviour

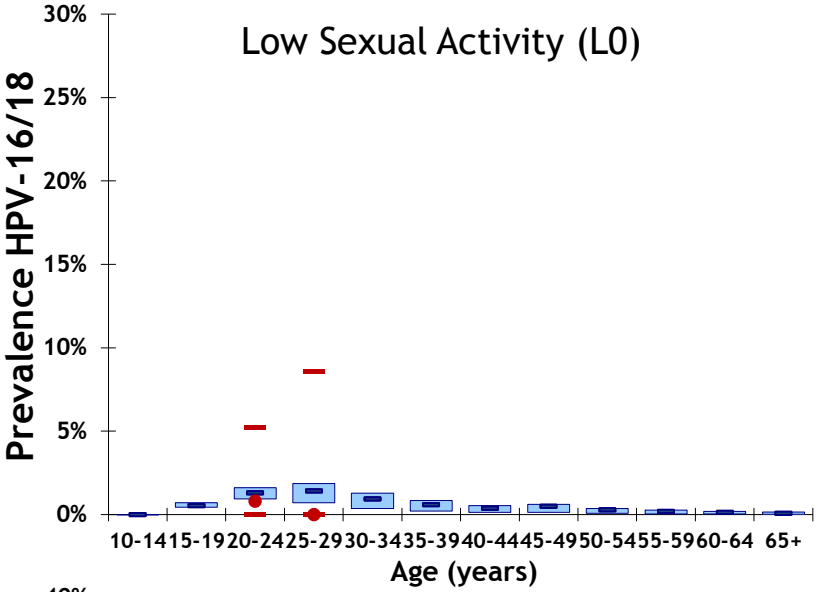
Ex: Proportion sexually active women

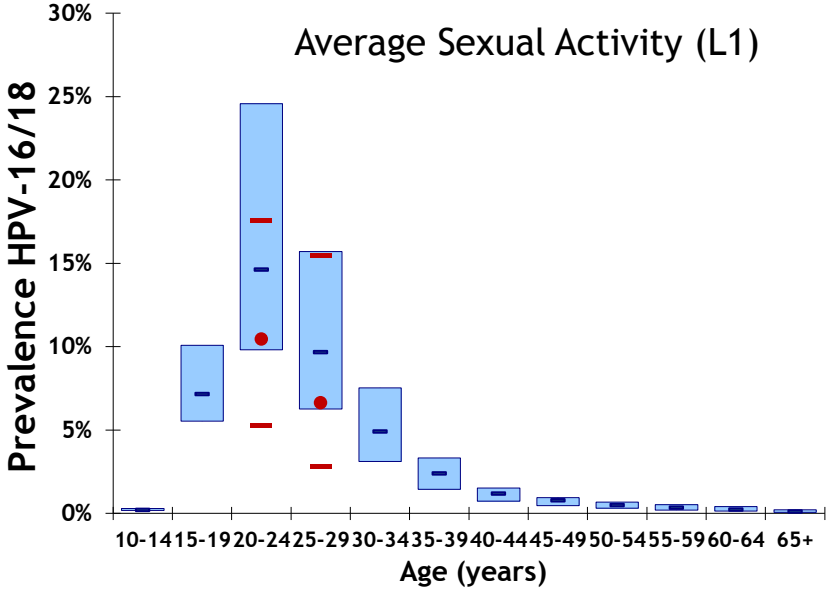


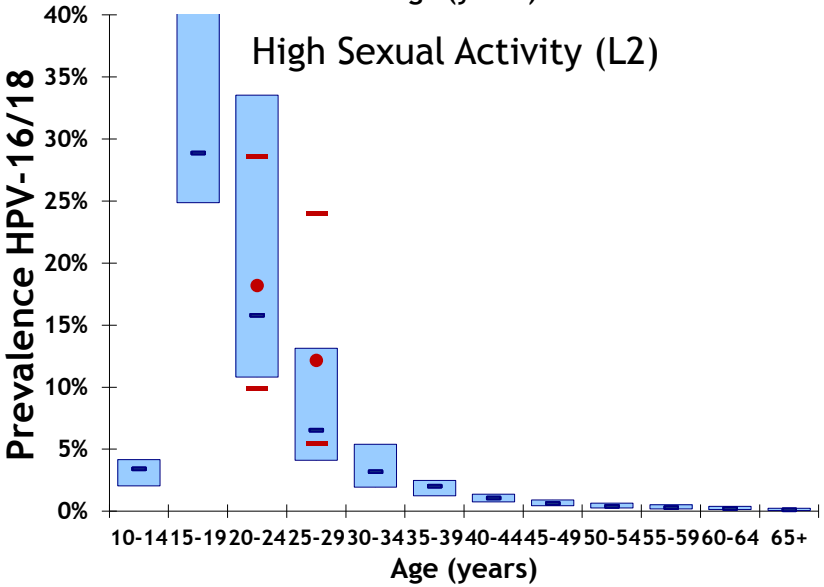
&: Other examples of model fit in extra slides; Data: NHANES

Model Fit – HPV Prevalence in women

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







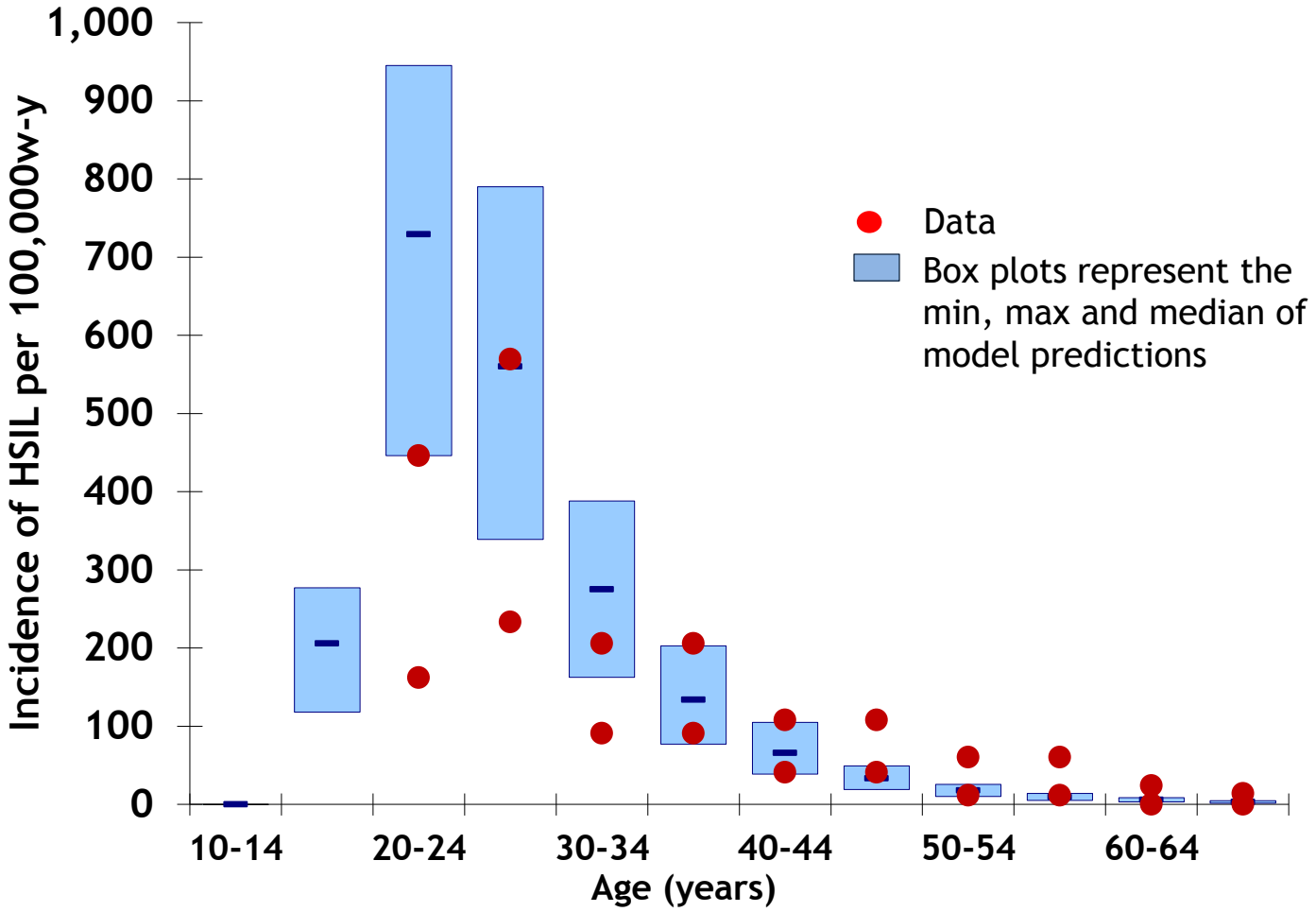
Data — 95%CI

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

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

Model Fit – Screening

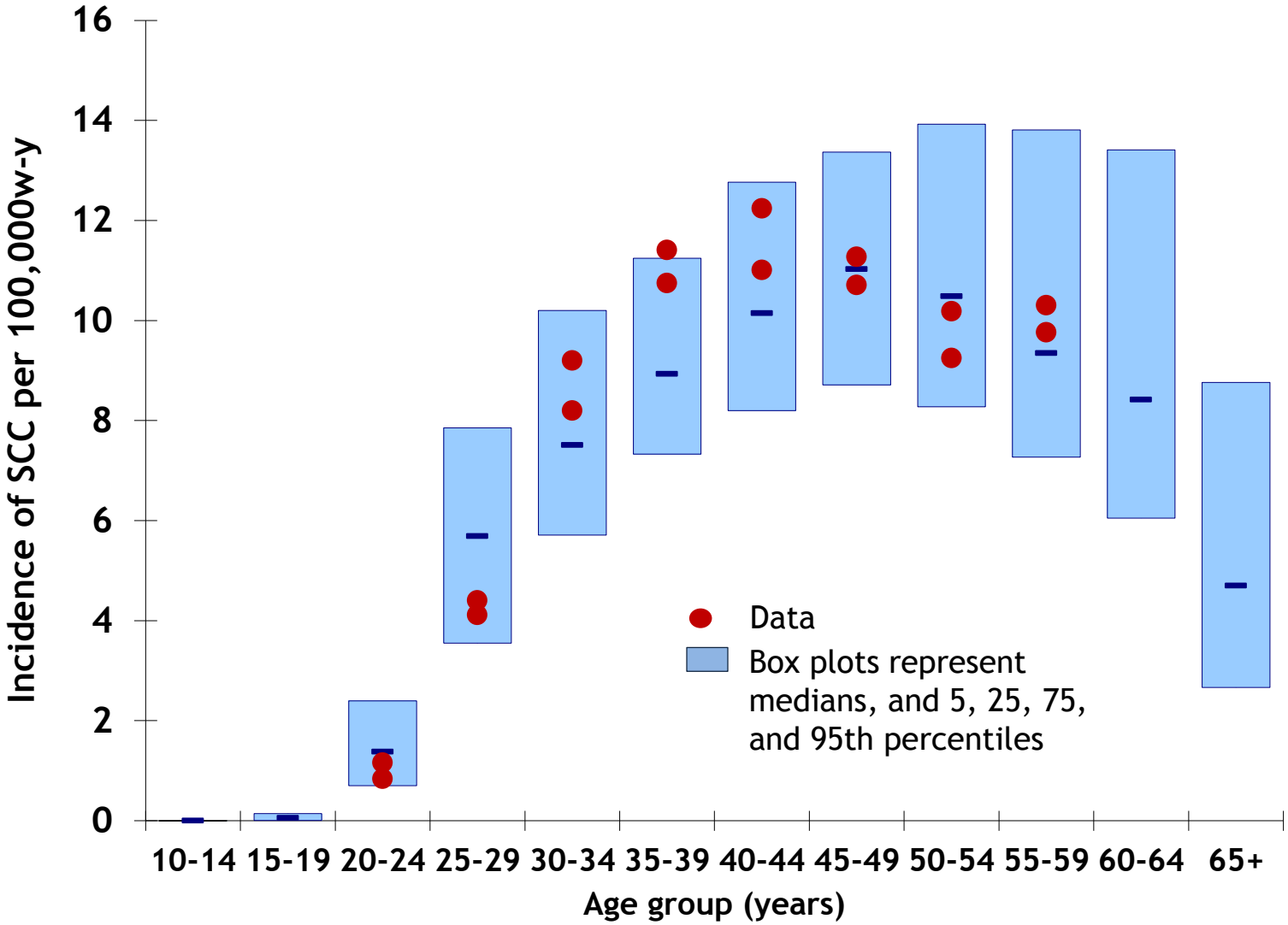
Ex: Incidence of HSIL



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

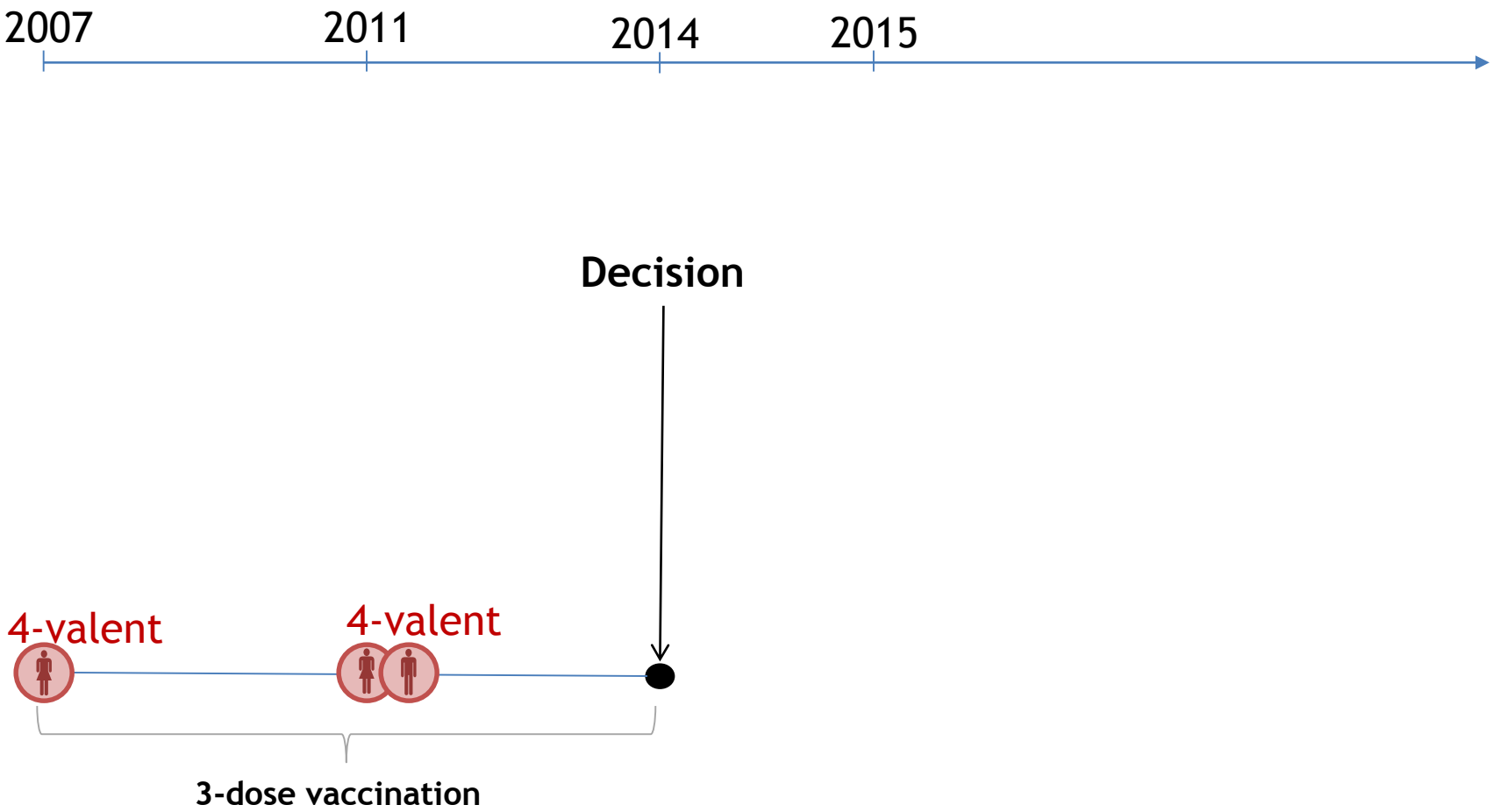
VE among susceptible females & males

	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

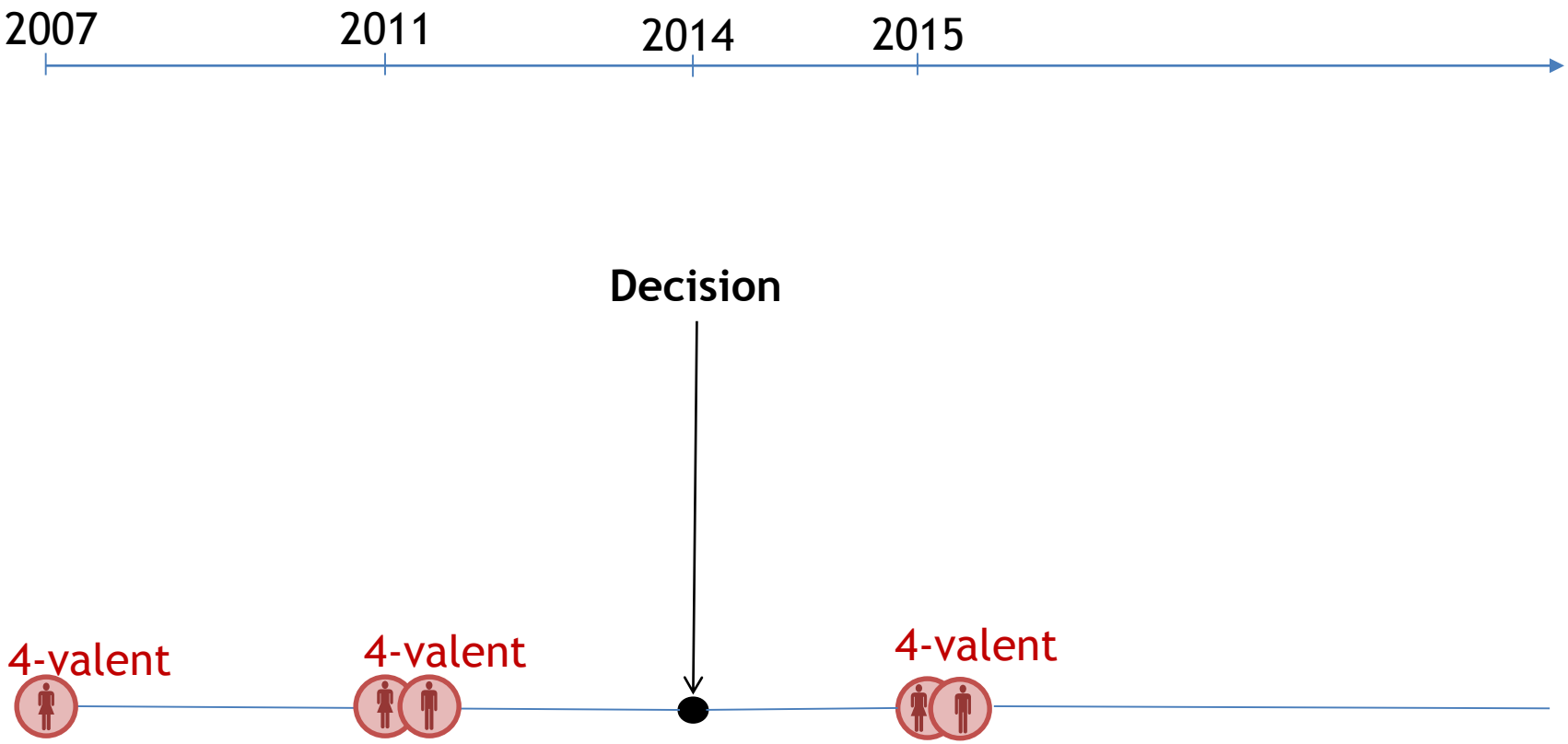
&: Malagón, *Lancet Infectious Disease* 2012

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

Intervention HPV vaccination 2007-2014



Intervention HPV vaccination 2015+



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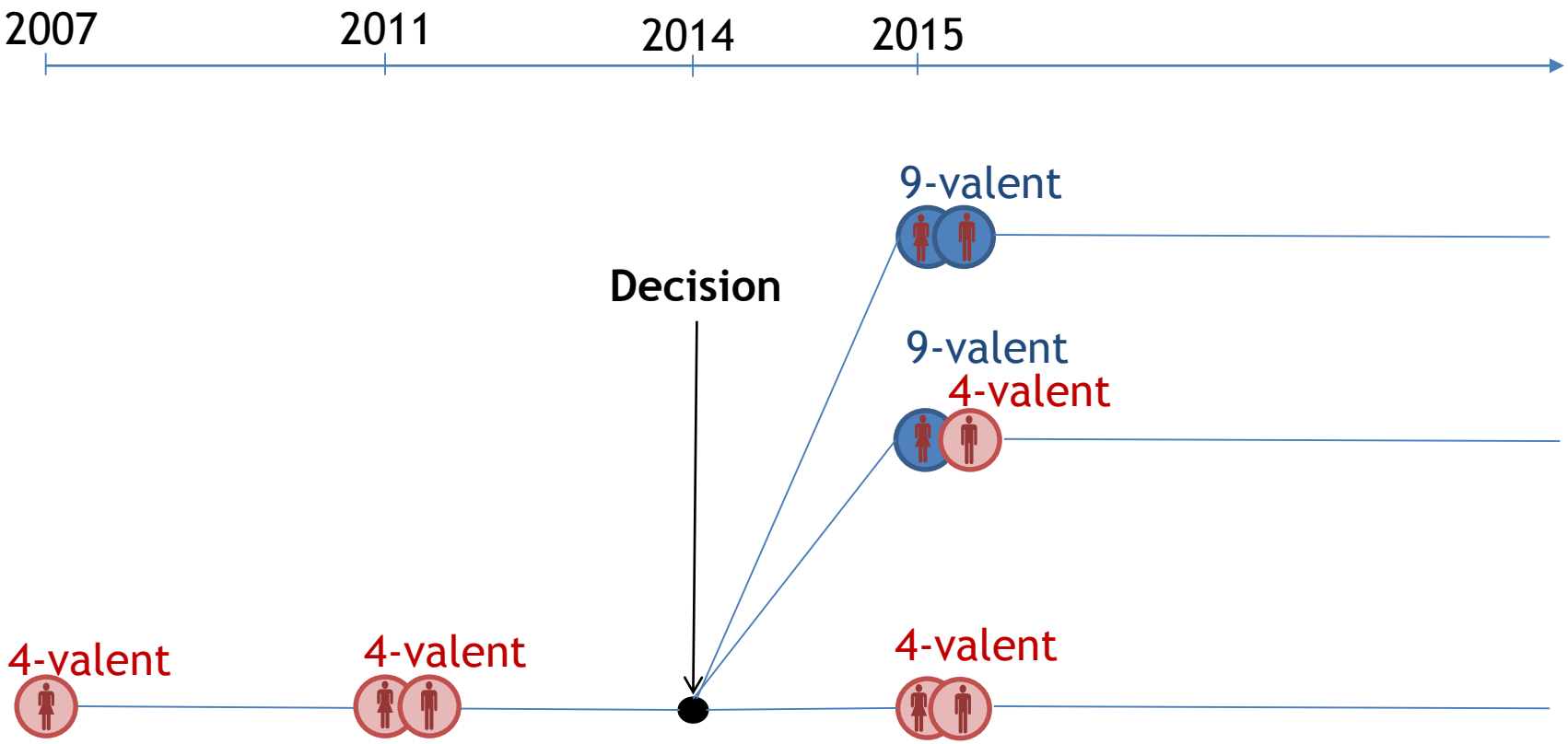
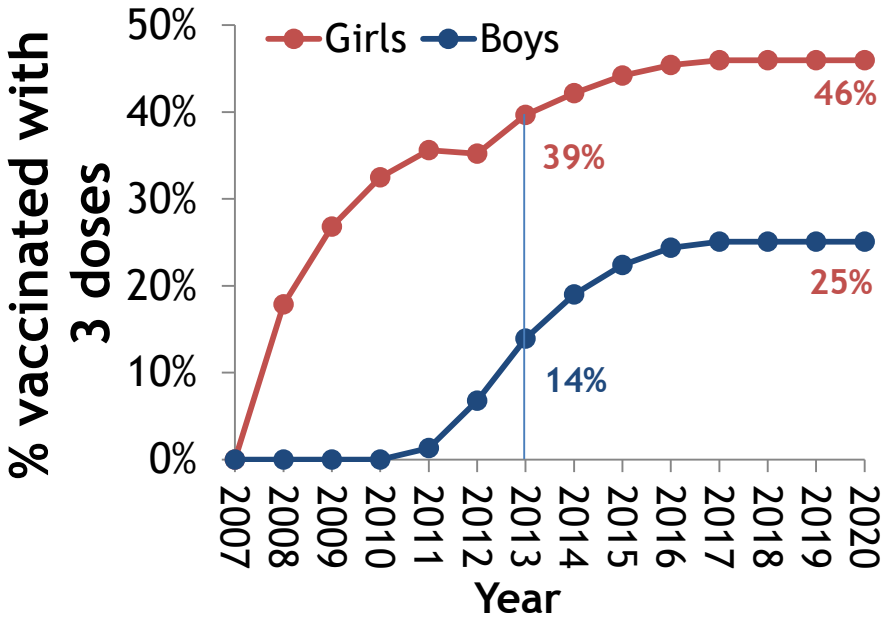


3-dose Vaccination Coverage

- 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



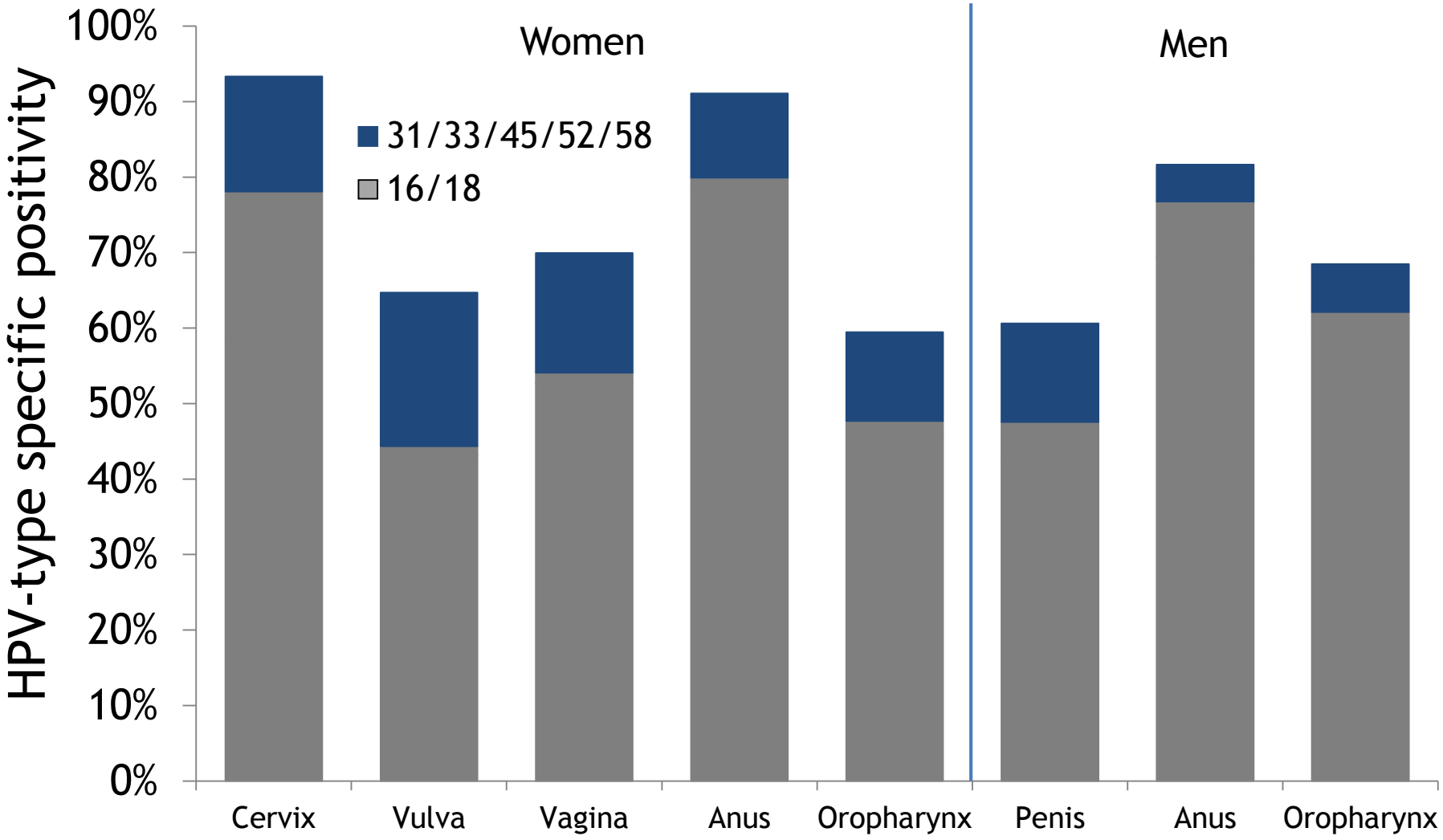
Coverage 2017+

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

Population-level effectiveness

9-valent HPV vaccine

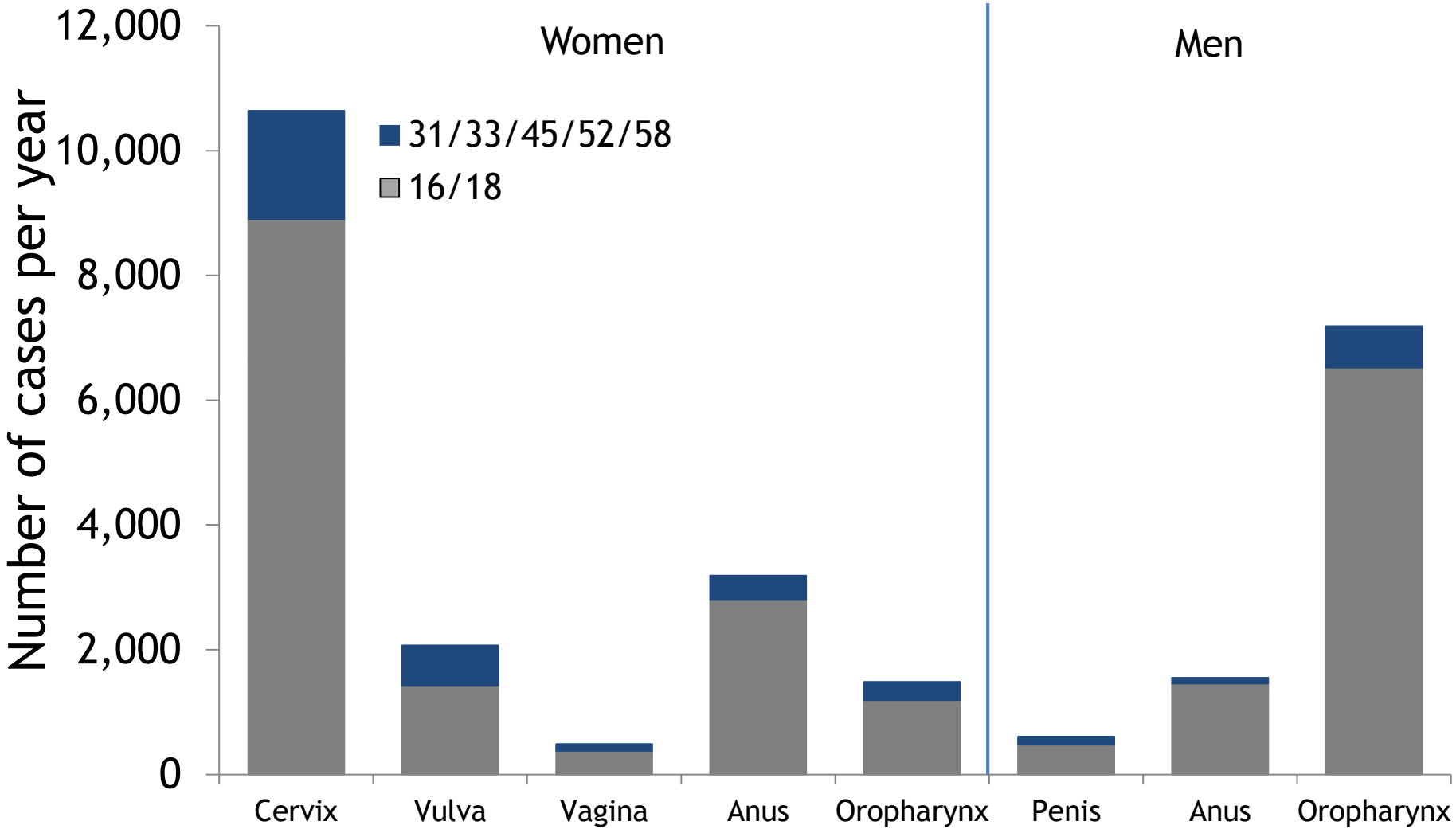
Potential for additional cancer prevention



&: 1) Saraiya, JNCI (under review)

9-valent HPV vaccine

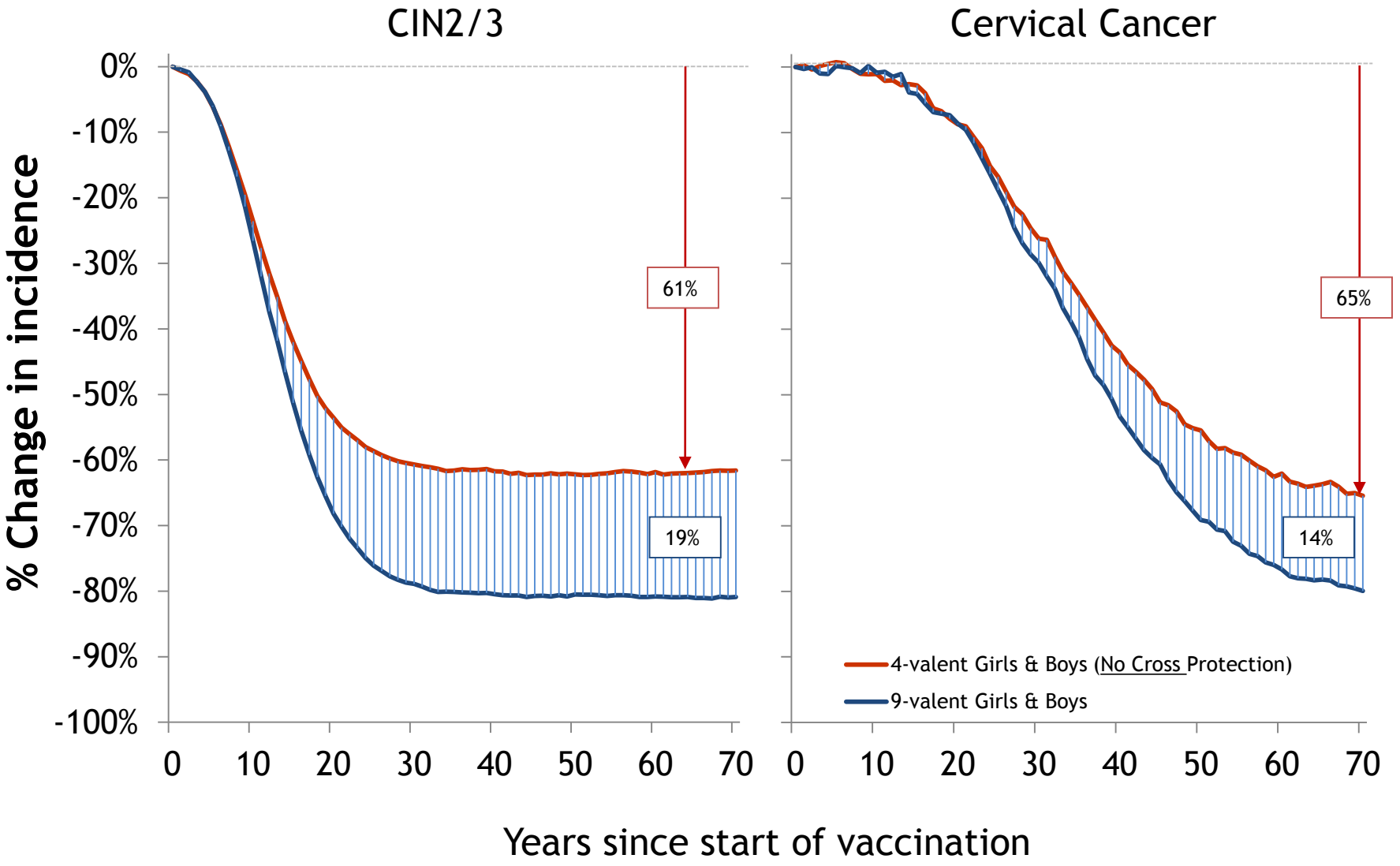
Potential for additional cancer prevention in the U.S.



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

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

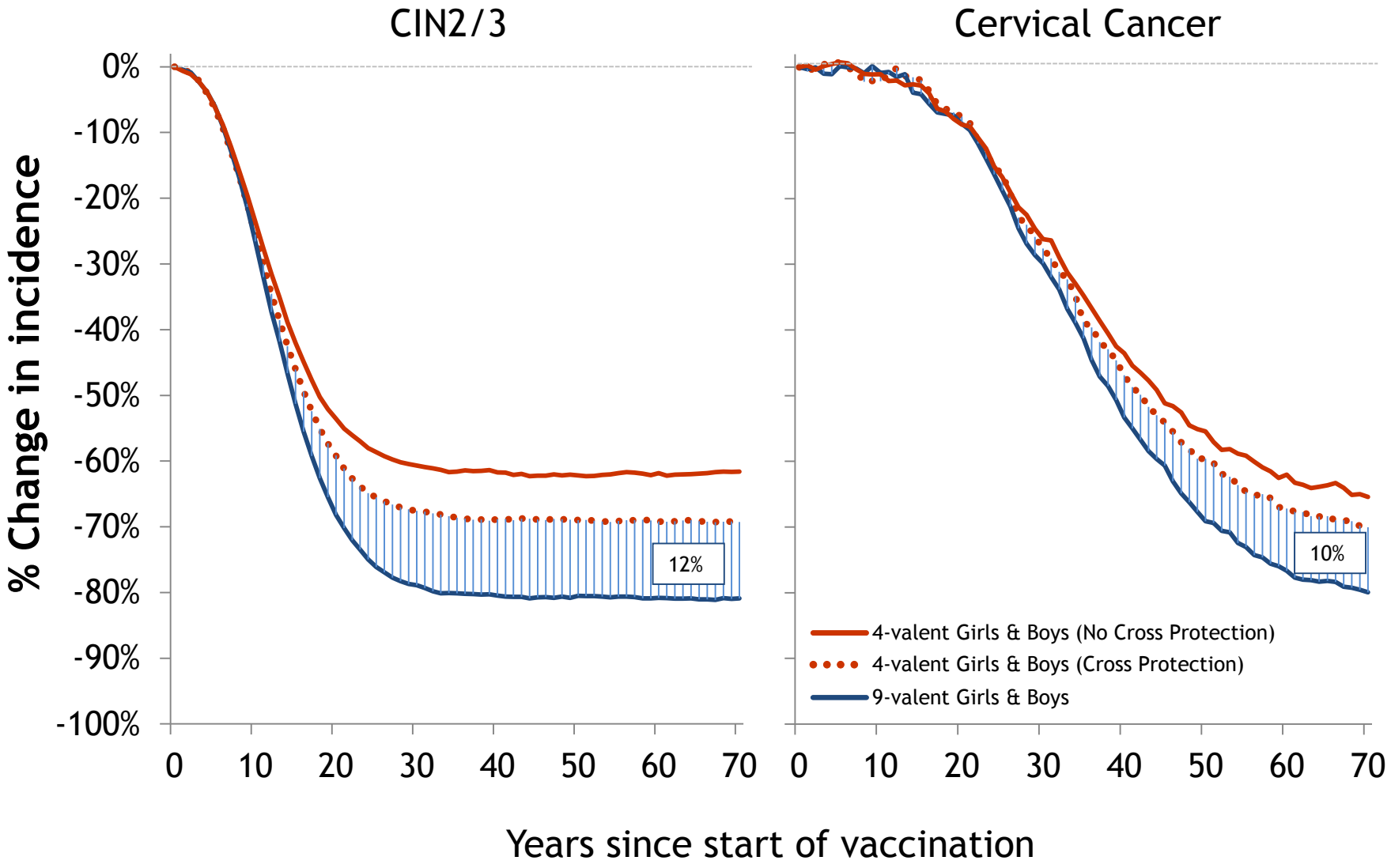
Base case, No Cross Protection for 4-valent



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

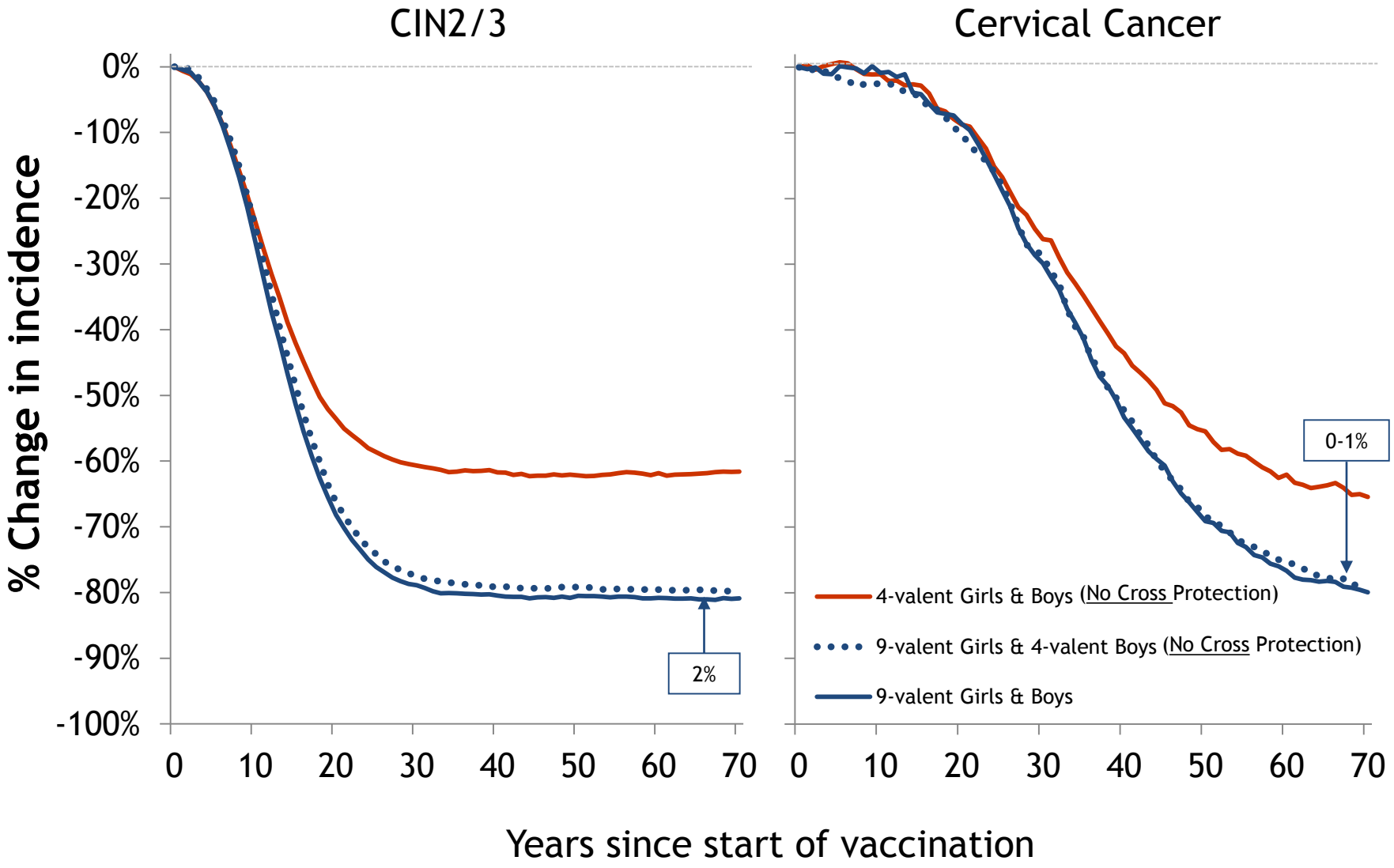
Base case, with & without Cross Protection for 4-valent



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



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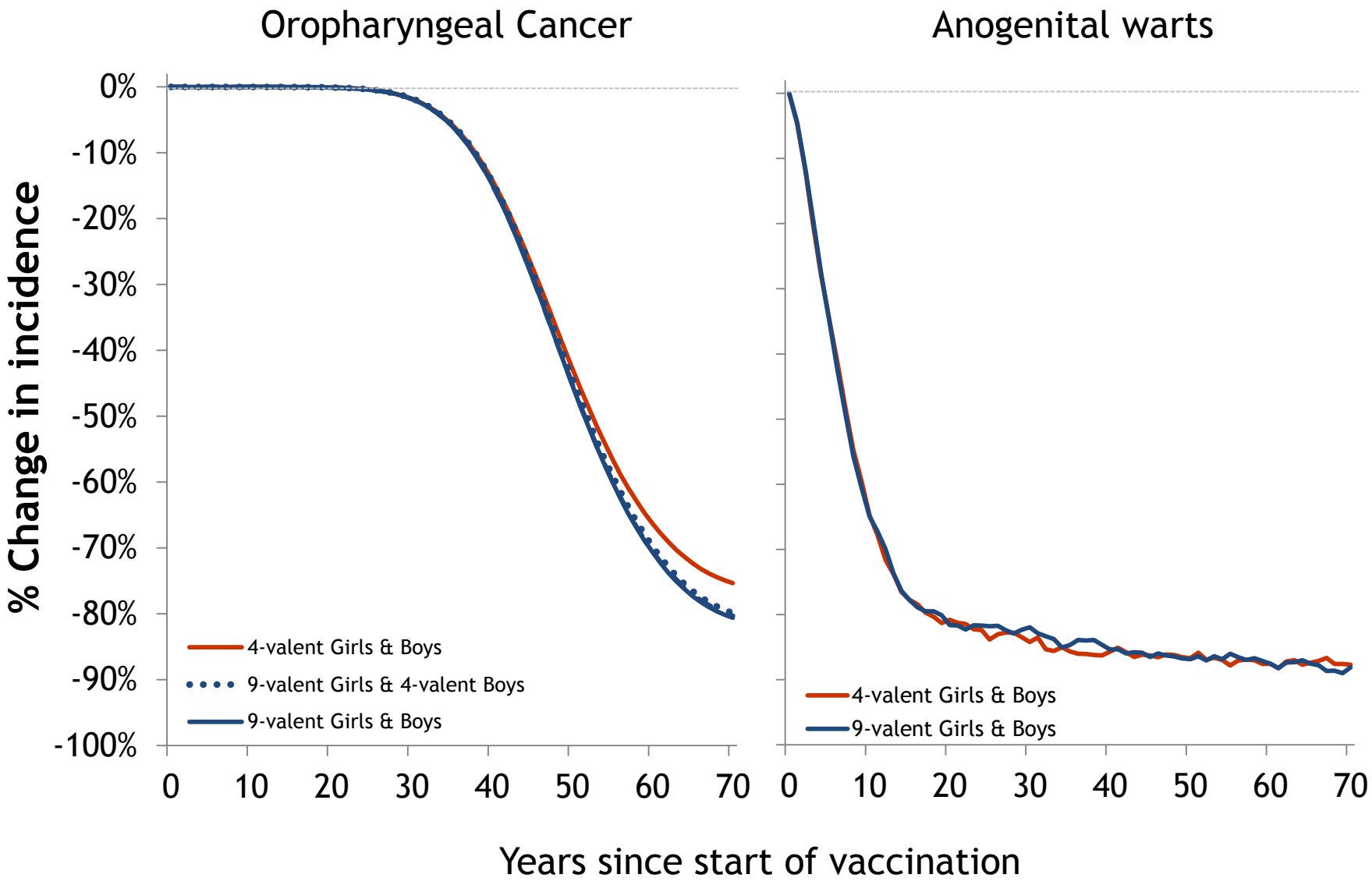
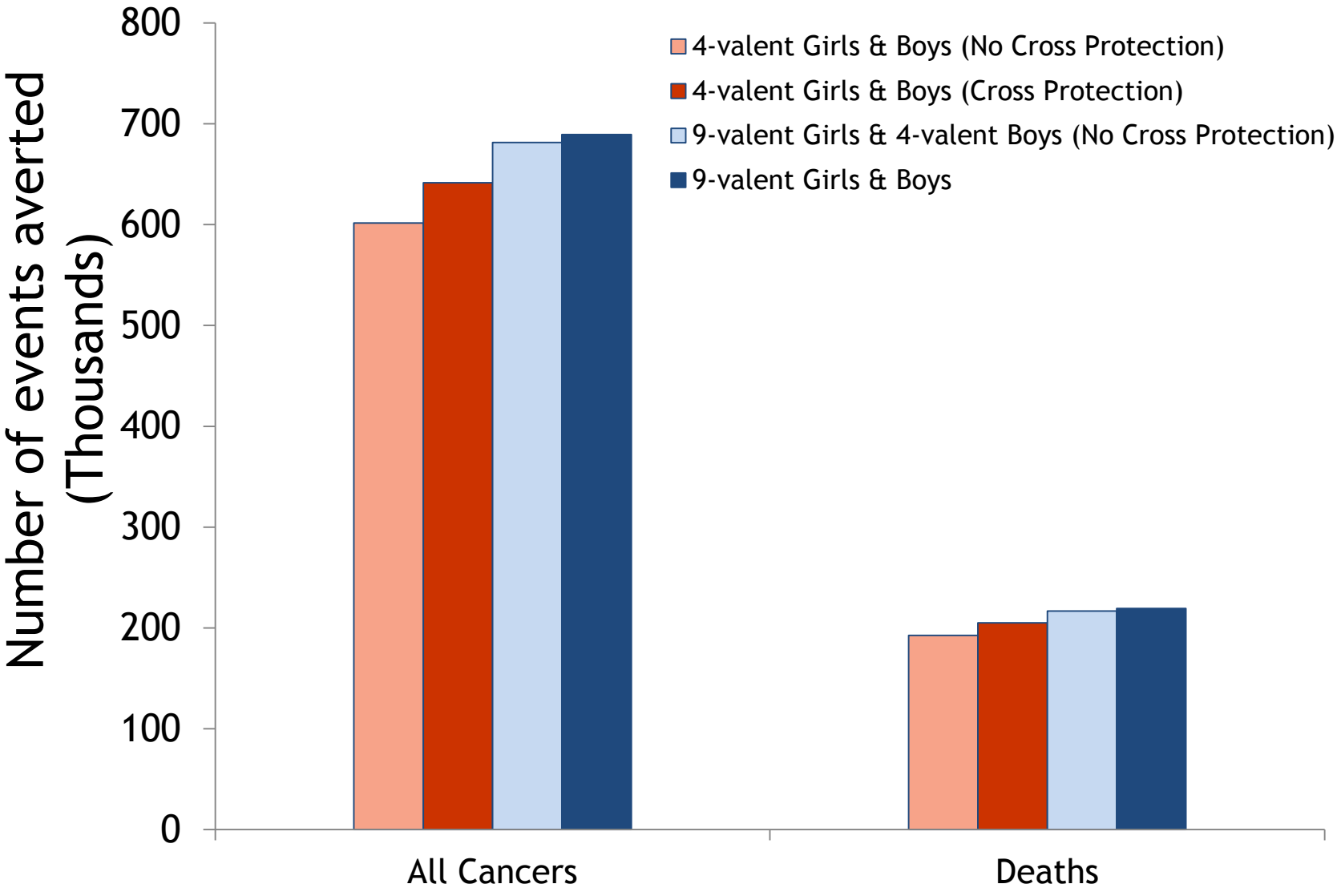
Effectiveness Base case, No Cross Protection for 4-valent



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



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Health Outcomes Prevented over 70 years

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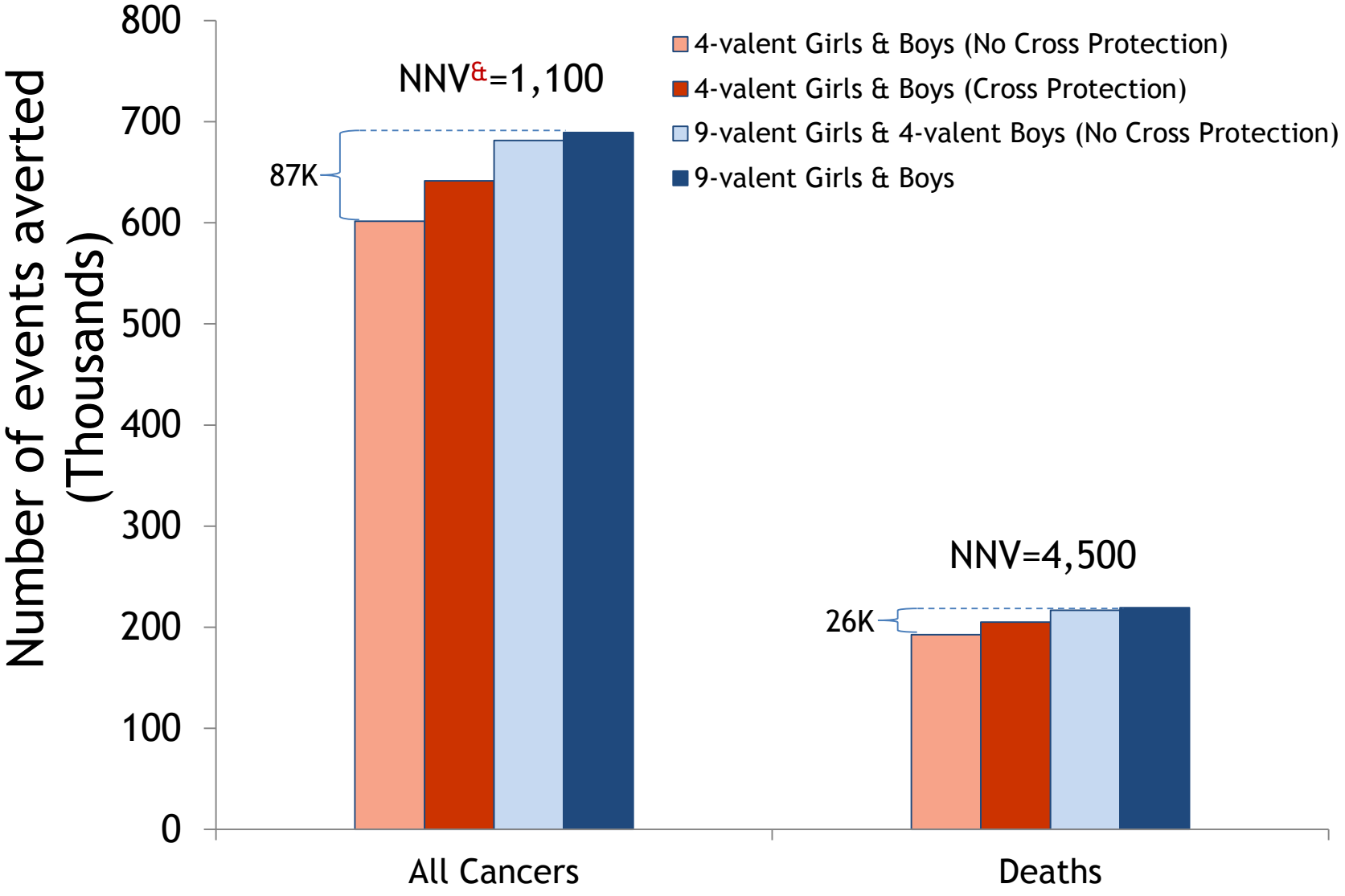
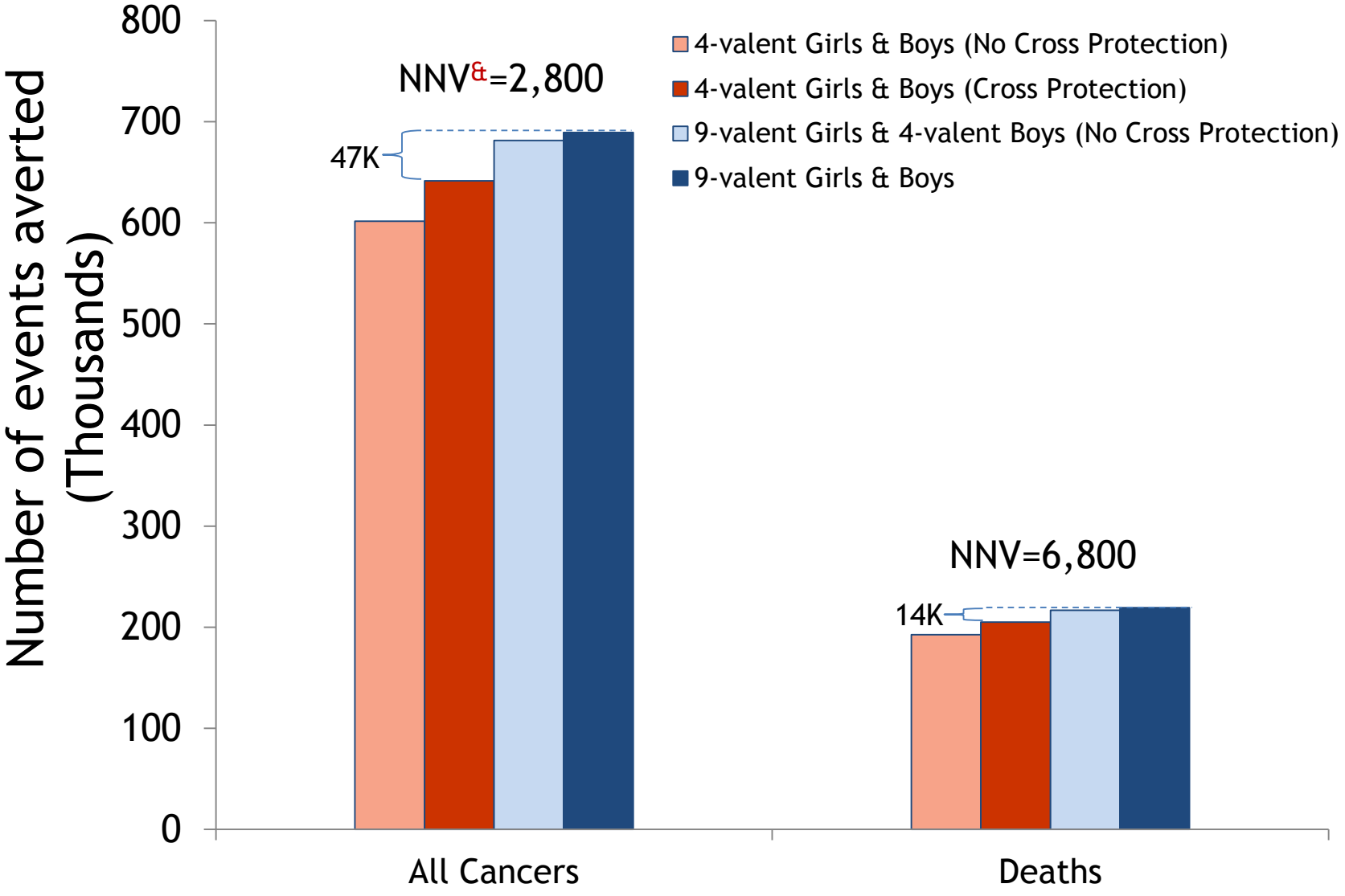


&: NNV=(# females vaccinated with 9-valent)÷(Additional events prevented by vaccinating females with 9-valent); Base case: vaccine-type efficacy=95%, duration=Lifelong; Predictions: Mean estimate generated by the 50 best fitting parameter sets

Health Outcomes Prevented over 70 years

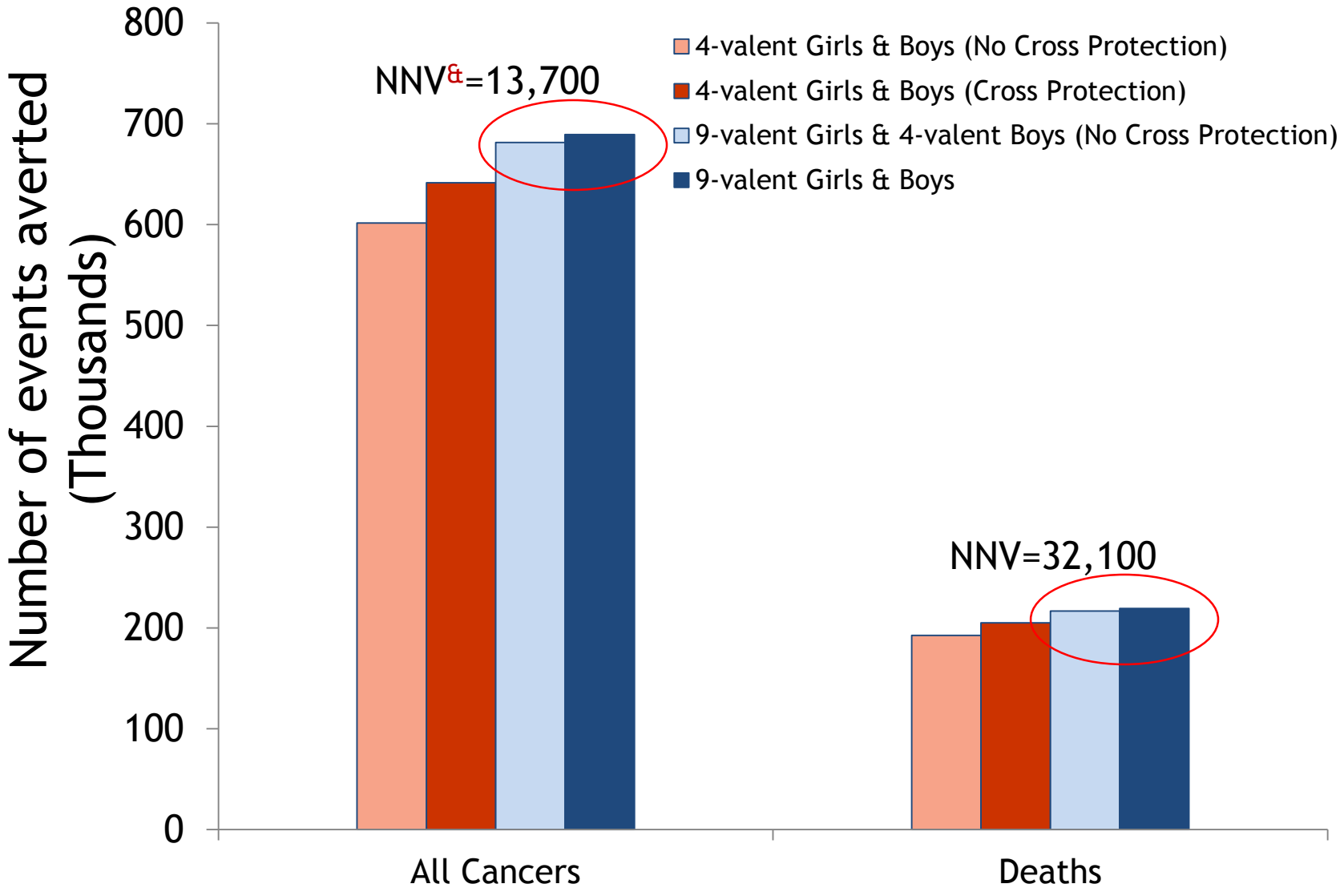
Base case, with Cross Protection for 4-valent



&: 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

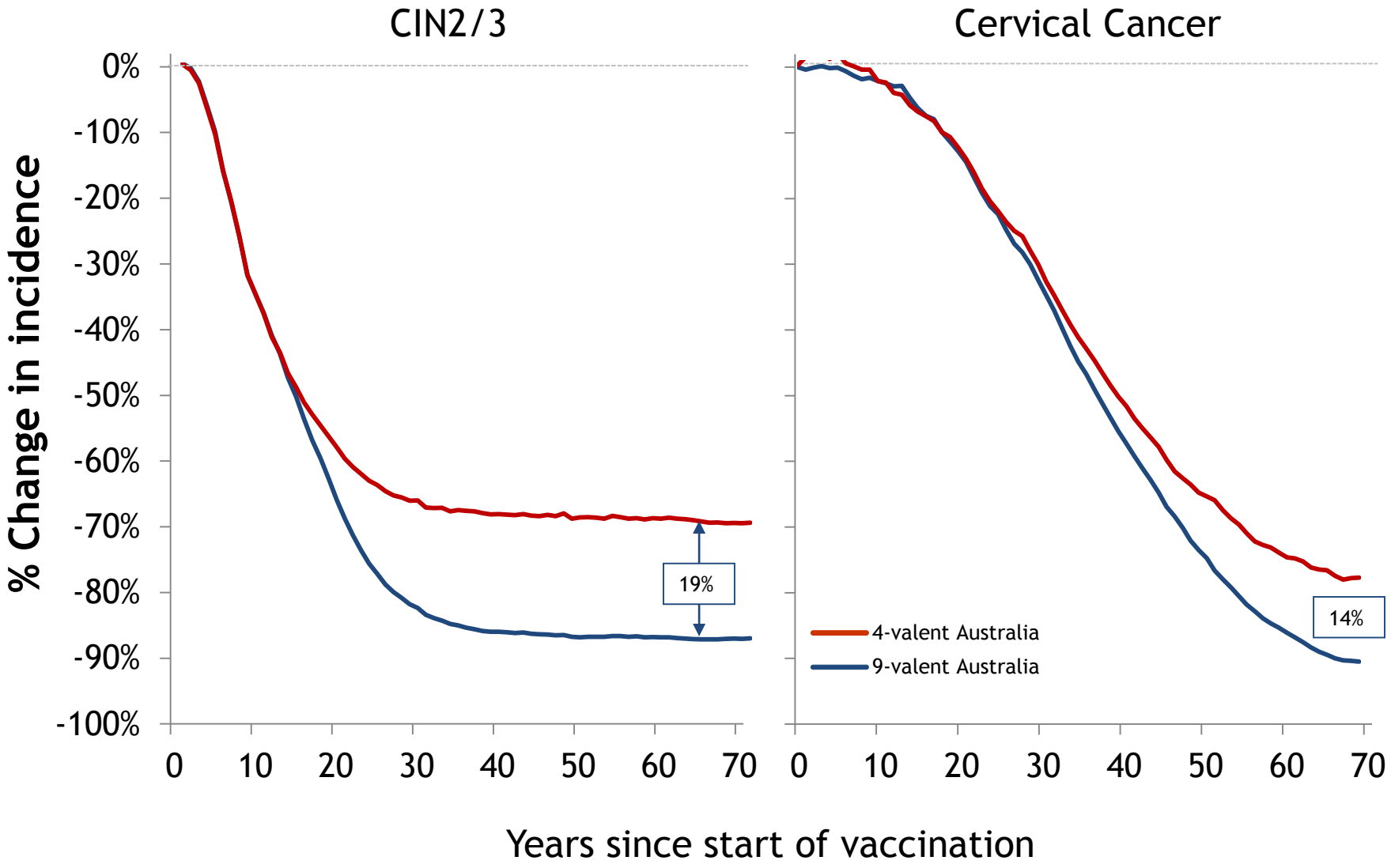
Base case, 9-valent Girls & Boys vs. 9-valent Girls & 4-valent Boys



&: 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

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

Australia (switch to 9-valent in 2015, Cross Protection)



Base case: vaccine-type efficacy=95%, duration=Lifelong
Predictions: Mean estimate generated by the 10 best fitting parameter sets

Summary Population-level effectiveness predictions

- Current 4-valent vaccination strategies are expected to substantially reduce HPV-related diseases
- Switching to a 9-valent strategy is expected to further reduce precancerous lesions and cervical cancer, with less impact on other HPV-related outcomes
- Vaccinating girls with the 9-valent provides the great majority of benefits of a 9-valent Girls & Boys program

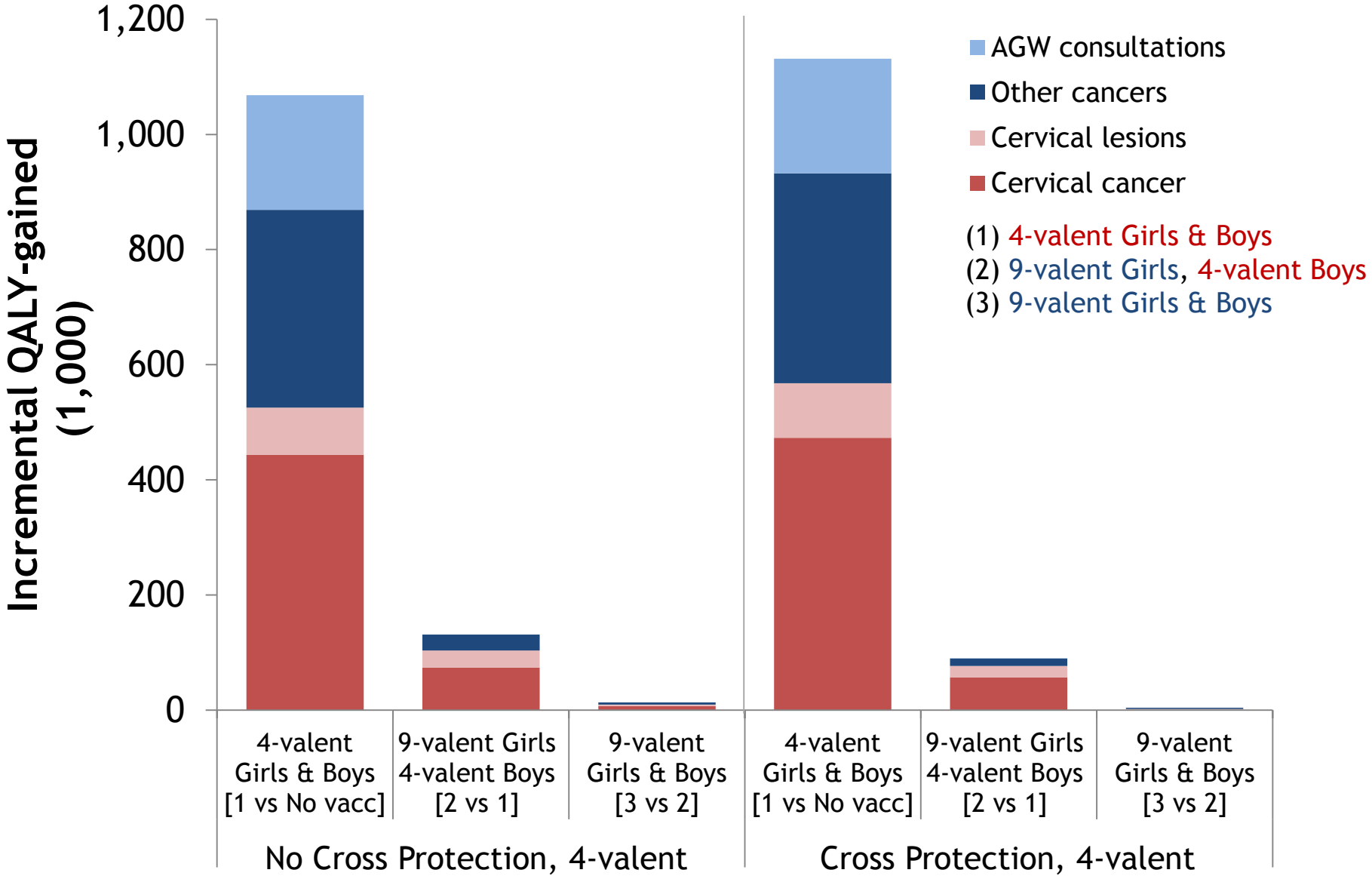
Cost-effectiveness

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

Incremental QALYs-gained Discounted over 70 years



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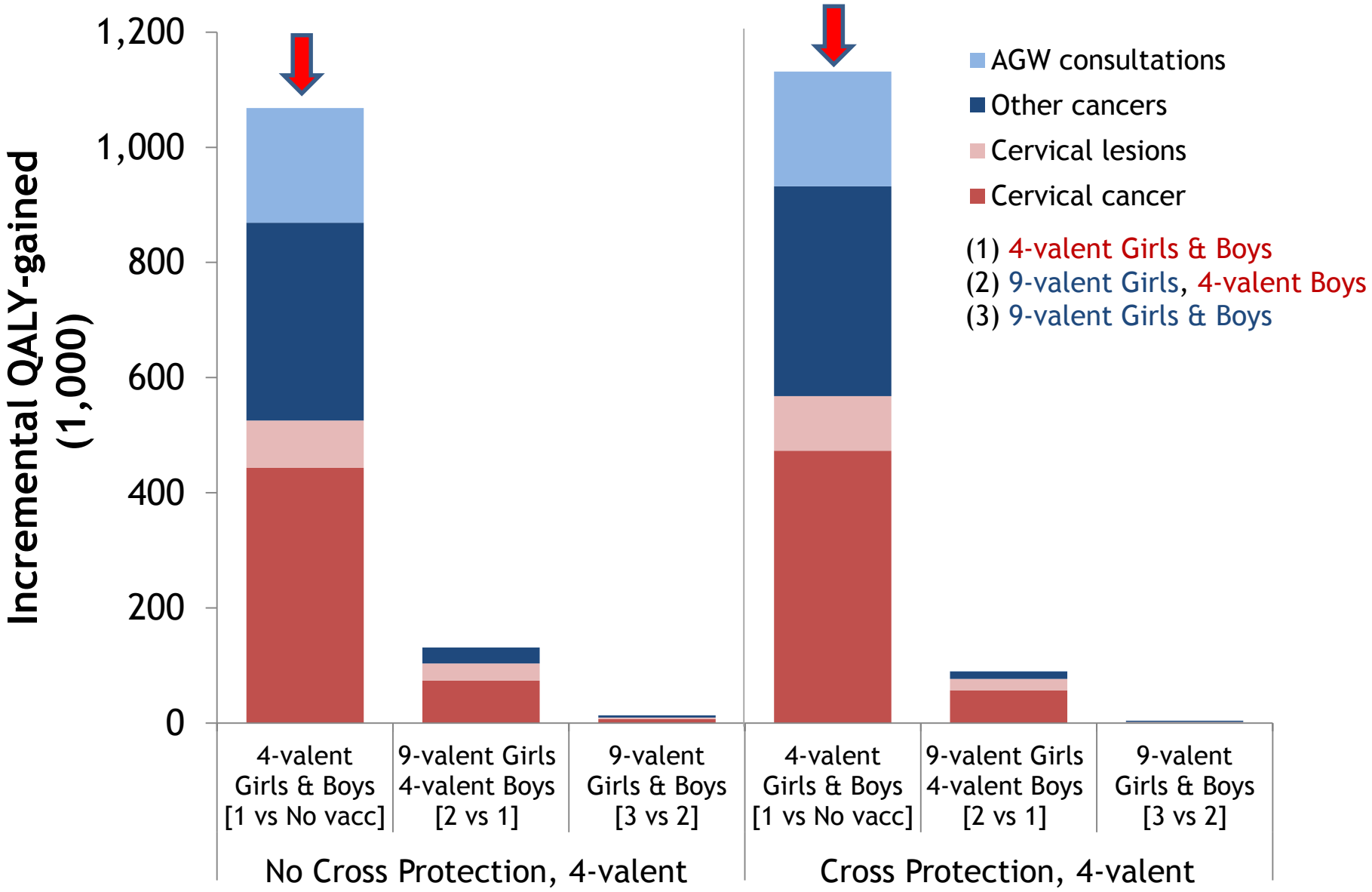

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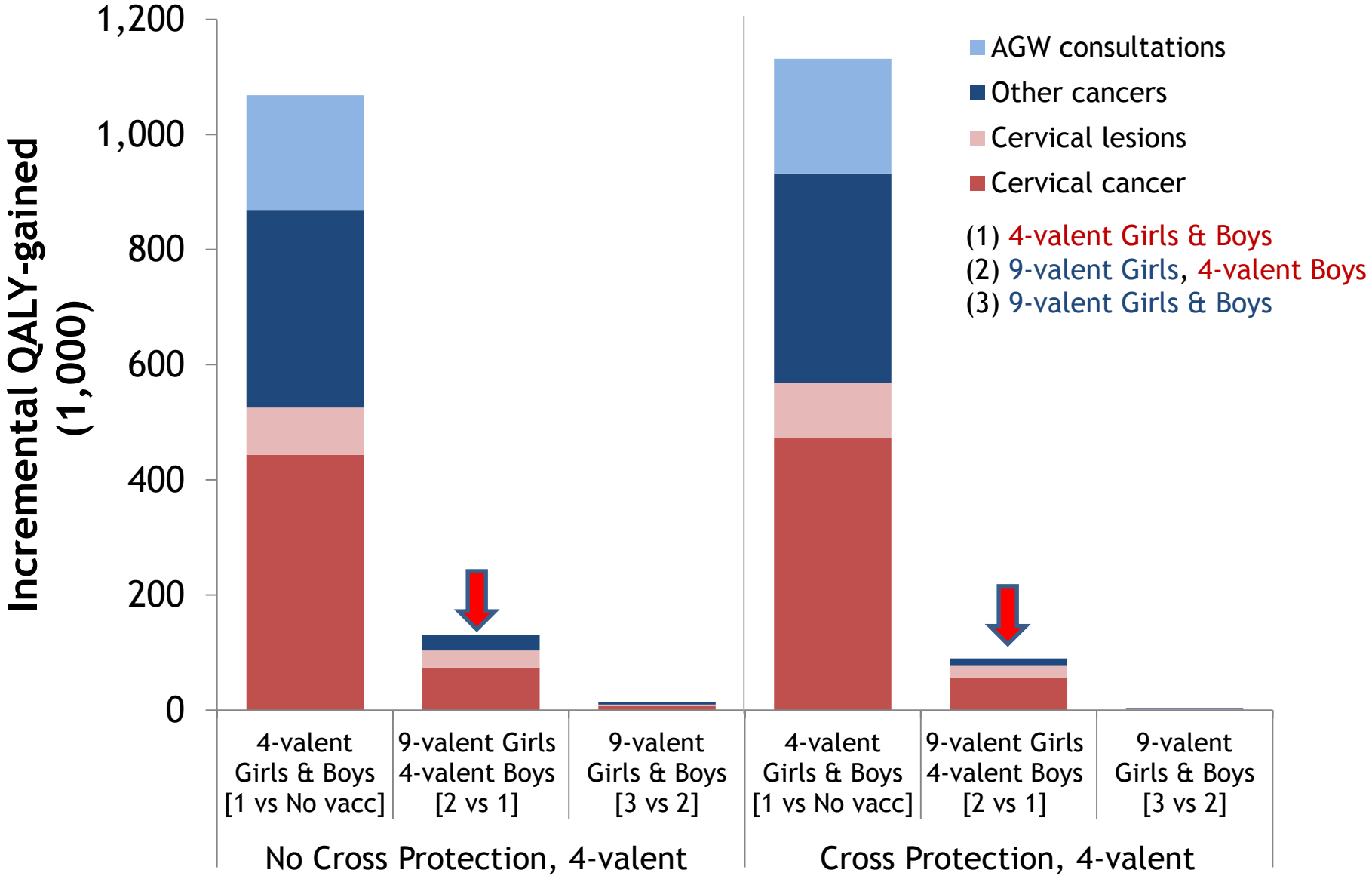

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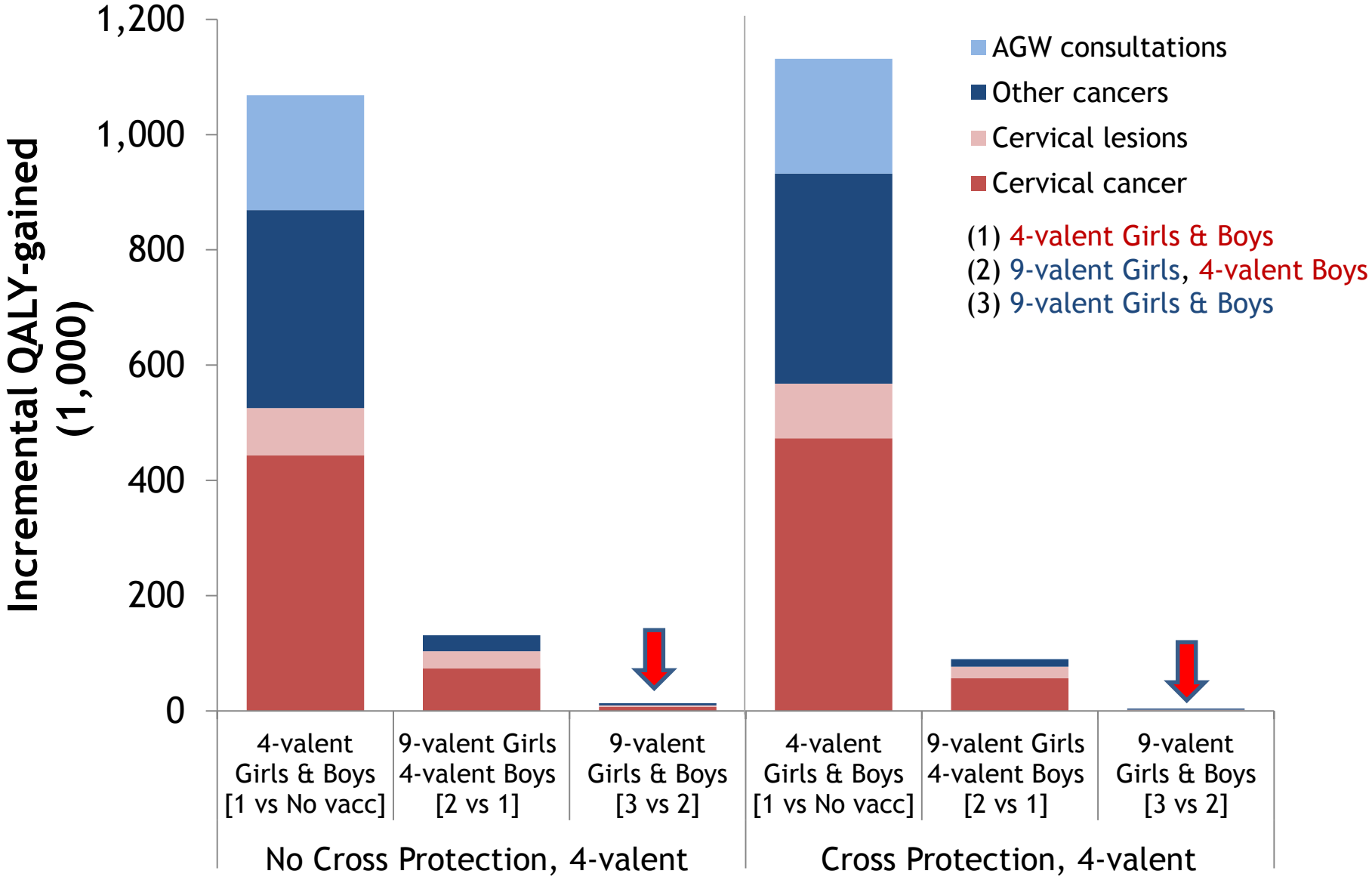
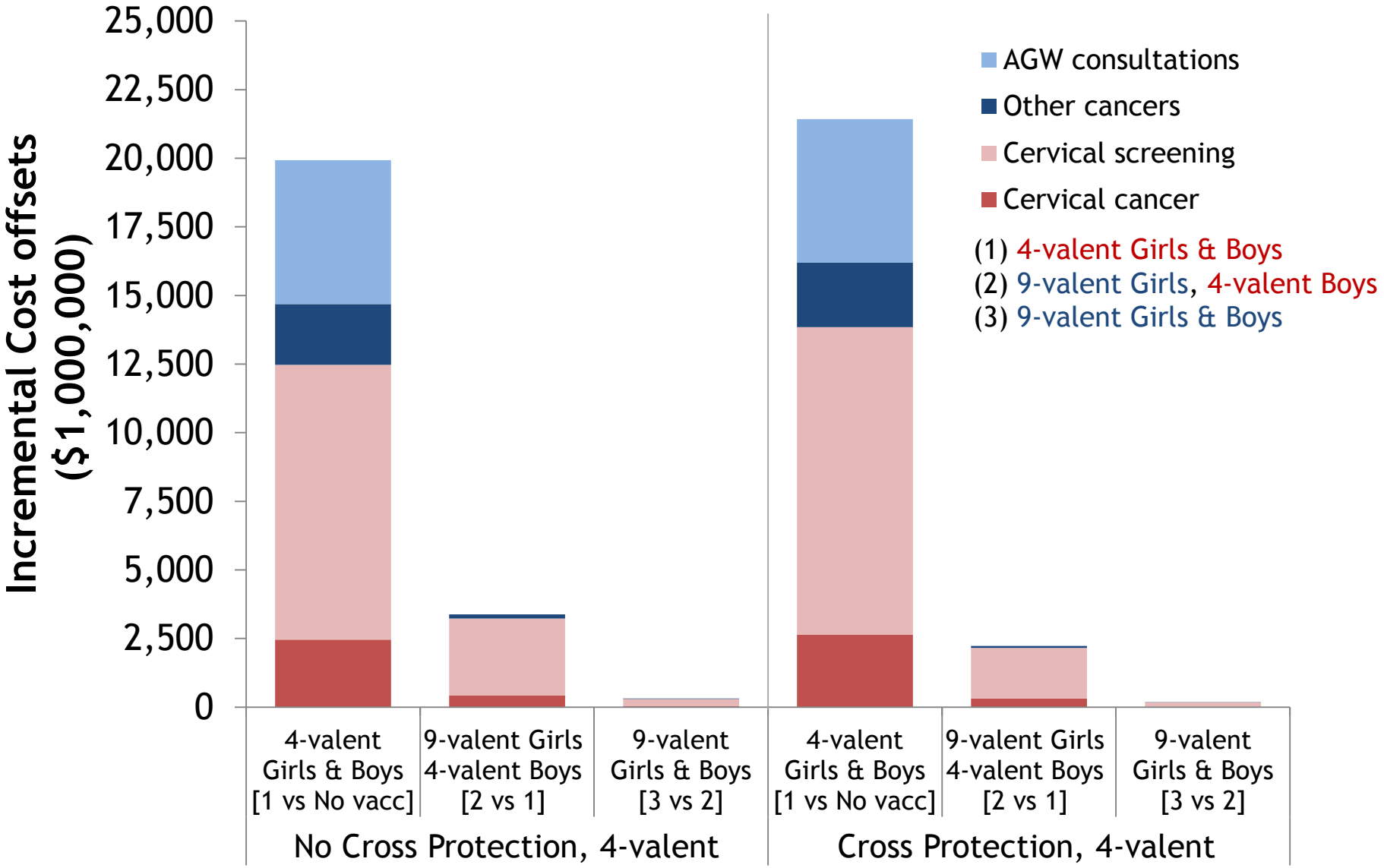


Base case: vaccine-type efficacy=95%, duration=Lifelong
Predictions: Mean estimate generated by the 50 best fitting parameter sets

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

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Incremental Healthcare costs saved

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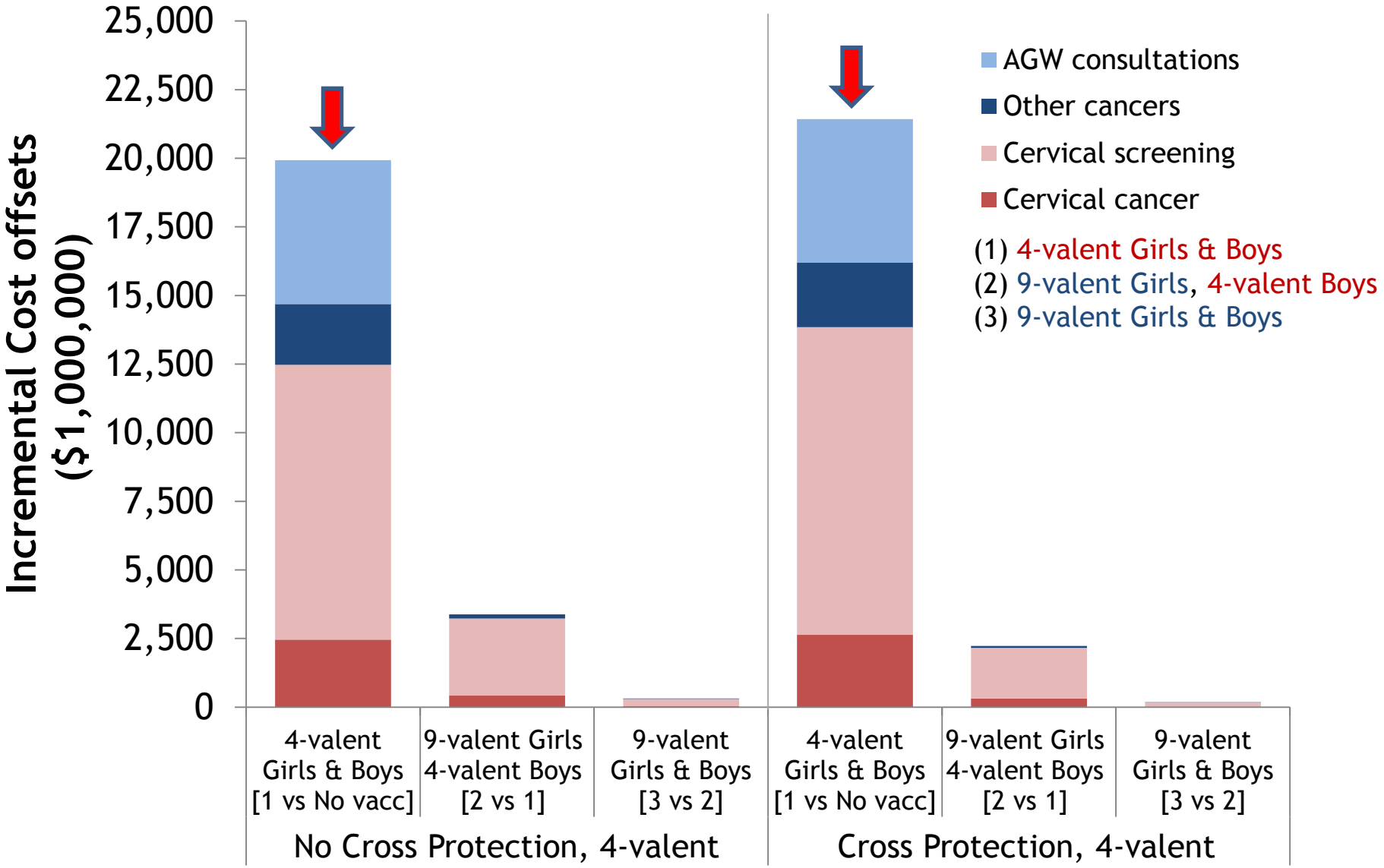

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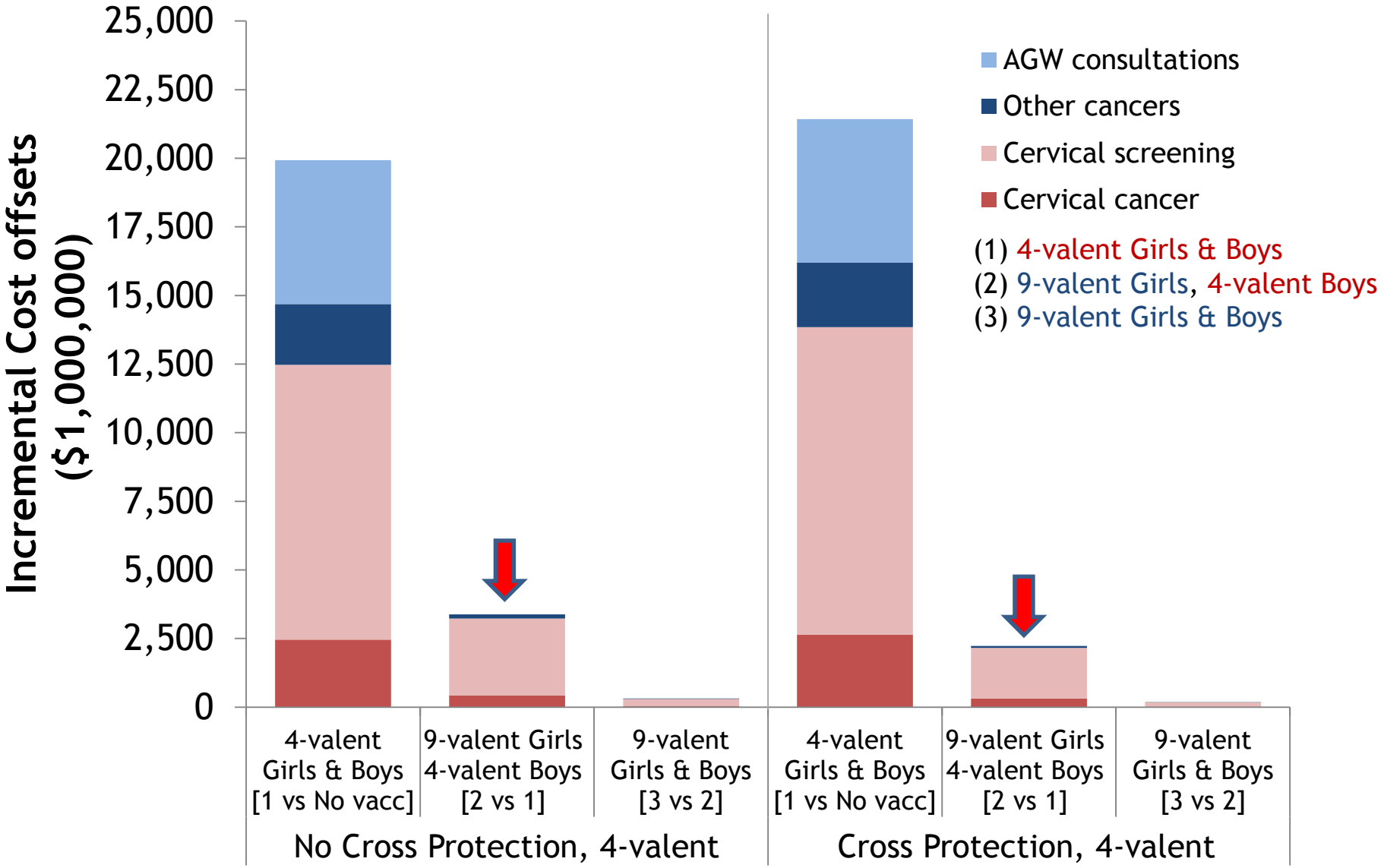

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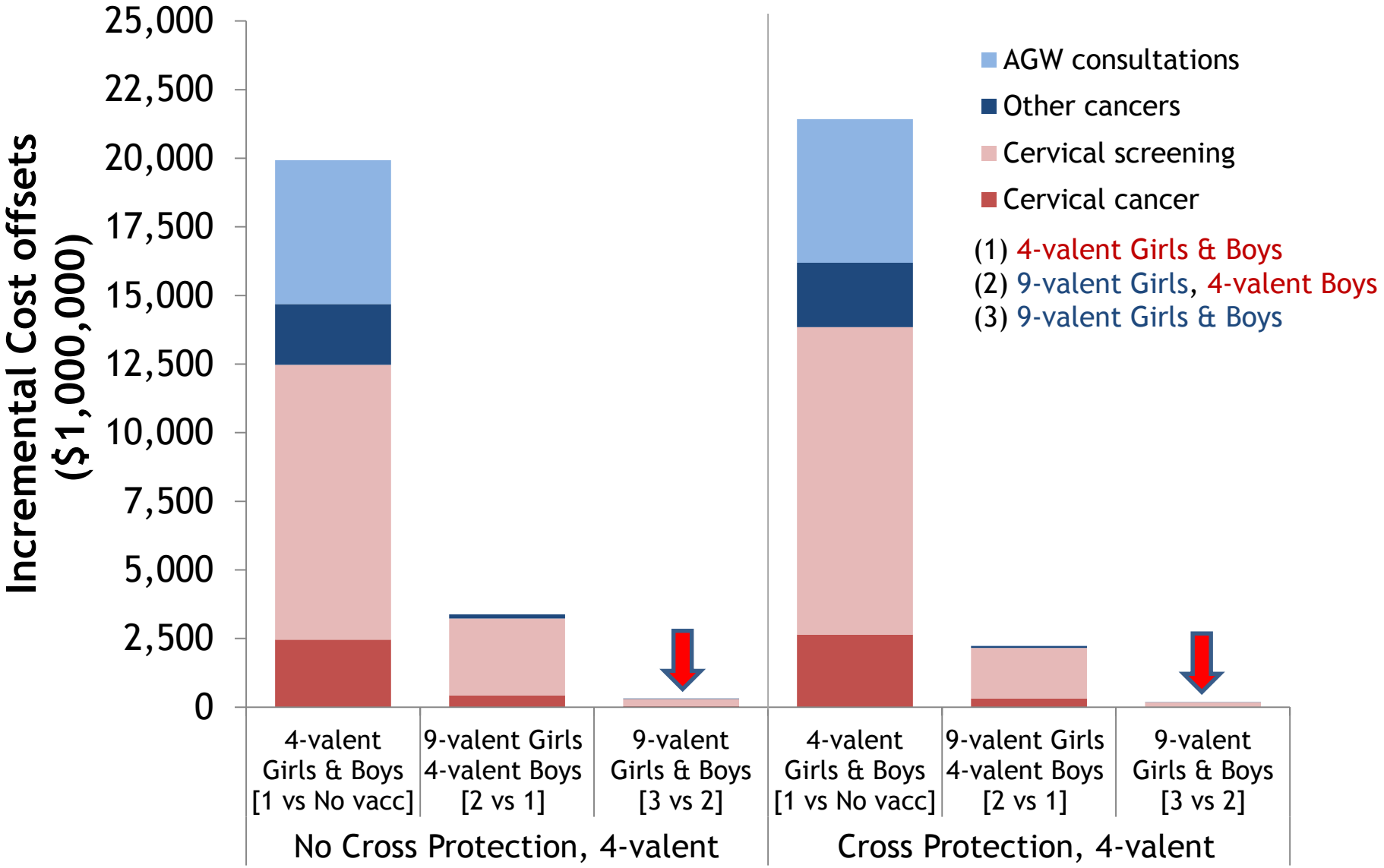

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Cost-effectiveness

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

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(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)
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Results: Sensitivity Analysis
Influential Variables

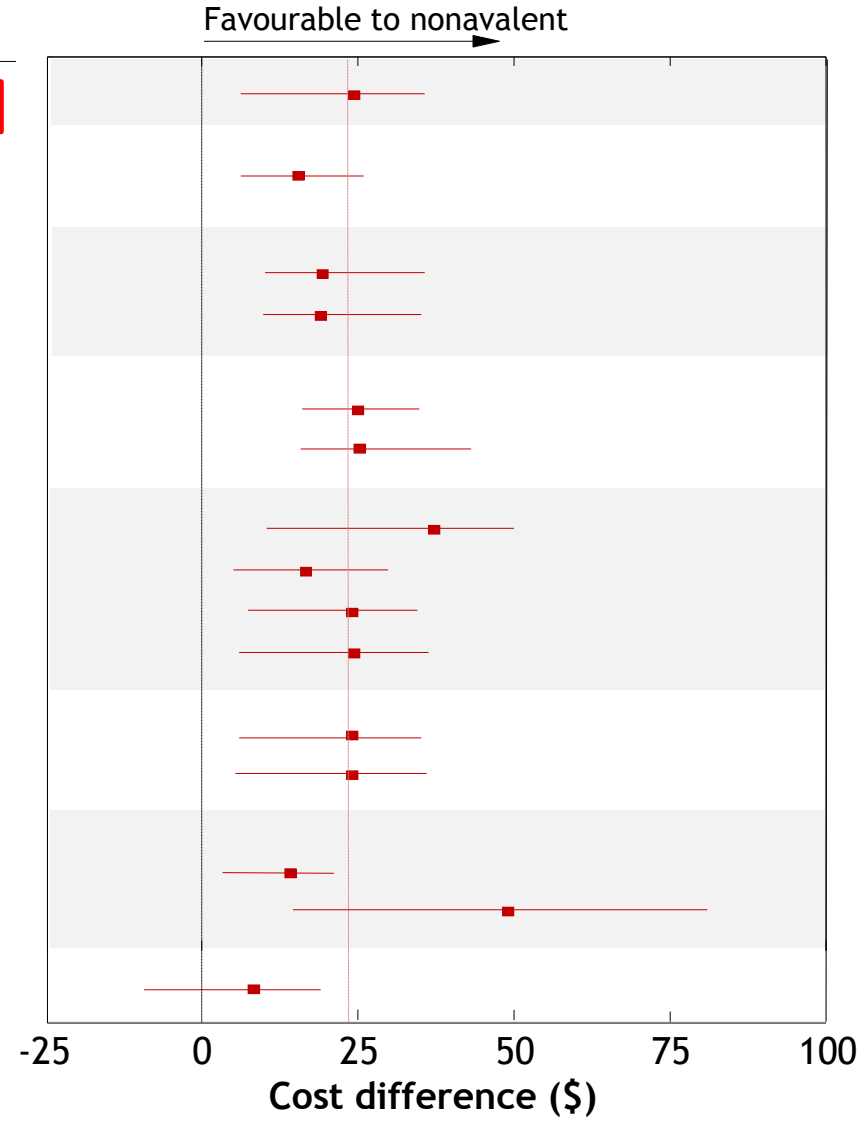
Sensitivity Analysis Incremental cost-effectiveness ($/QALY-gained), with Cross Protection for 4-valent

	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
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=32%;
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)

Max. additional cost/dose for the 9-valent to be cost-effective vs. Quadrivalent in Canada (at $40,000/QALY-gained) Girls-only, Coverage=80%, VE=95%, Quadrivalent X-protection

Description	Cost diff.
BASE CASE	24(6;36)
Vaccine duration (VD)	
VD=Life	16(6;26)
Lower nonavalent vaccine efficacy (VE)	
Nona VE=90%	19(10;36)
Nona VE=85%	19(10;35)
Vaccination coverage (VC)	
VC=70%	25(16;35)
VC=50%	25(16;43)
Disease Burden	
Max. cancer burden	37(10;50)
Min. cancer burden	16(5;30)
Max. AGW burden	24(7;34)
Min. AGW burden	24(6;36)
Disease endpoints	
Cervical cancer and AGW	24(6;35)
Cervical cancer only	24(5;36)
Cost-effectiveness threshold	
$20,000	14(4;21)
$100,000	49(13;81)
Most favourable scenario for quadrivalent	
Quad: VE=95%, VD=Life; Nona: VE=85%, VD=20yrs	8(-9;19)



REF: Drolet, *International Journal Cancer* 2013

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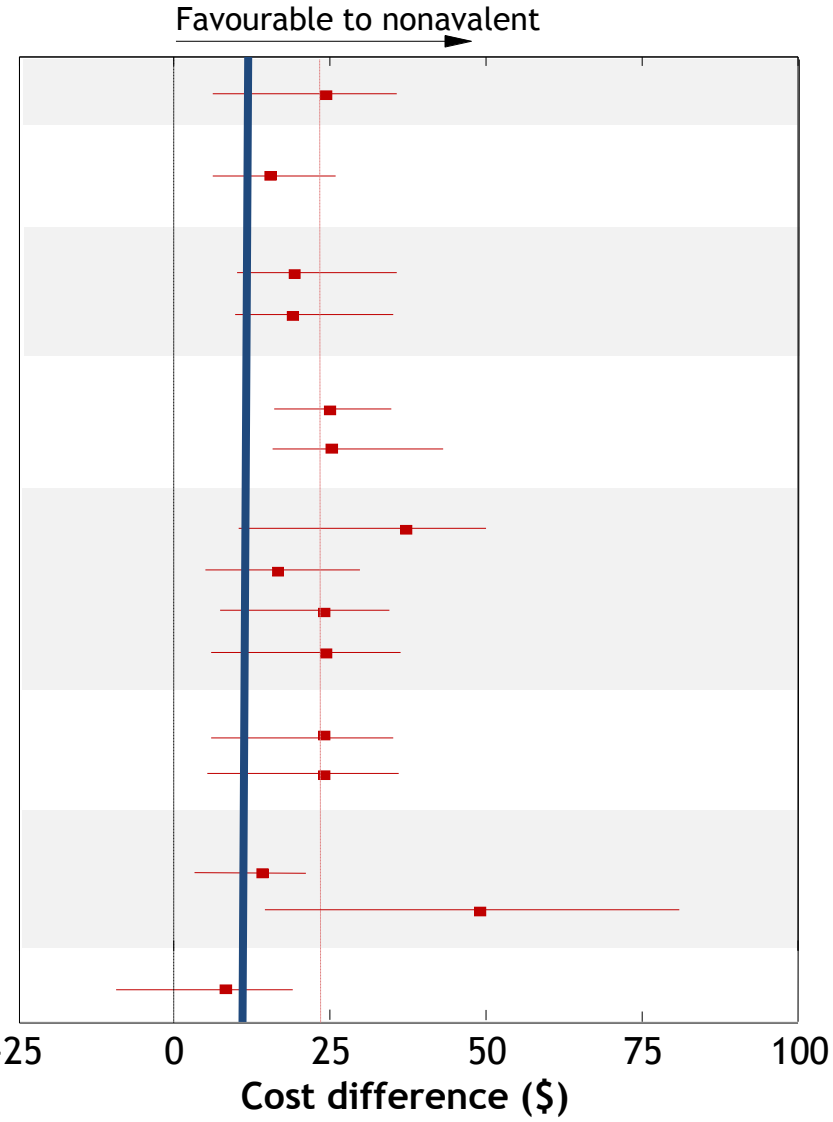

REF: Drolet, *International Journal Cancer* 2013

Summary

Summary Cost-effectiveness predictions

- Current 4-valent HPV vaccination programs are highly cost-effective
- Switching to a 9-valent program is likely cost-effective (and cost saving in the U.S.)
  - 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
  - vaccination coverage, price, duration of protection, health care costs, burden of illness

Thank you!