

Overview of Health Economic Models for HPV Vaccination of Mid-Adults in the United States

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HPV VACCINATION OF ADULTS

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Need for cost-effectiveness analyses of mid-adult HPV vaccination in US

- HPV vaccines originally licensed through age 26 years in the United States
- In April 2018, Merck submitted a supplemental application to FDA to expand age indication for 9-valent HPV vaccine through age 45 years
- FDA approved application in October 2018
- Advisory Committee on Immunization Practices (ACIP) reviews data and makes policy for licensed vaccines and indications for the US population

New cost-effectiveness question

- What is the cost-effectiveness of “mid-adult” vaccination?
- Specifically, what is the cost-effectiveness of extending the upper recommended catch-up age of HPV vaccination up to 45 years for males and females?

Outline

- Overview of five available models for United States
- Results that informed policy considerations of the Advisory Committee on Immunization Practices (ACIP)
 - Vaccination of adults older than age 26 years
- Reasons for differences in model results
- Summary

Five models to inform adult HPV vaccination policy decisions in the United States

- HPV-ADVISE model (Laval University / CDC)
 - Brisson, Boily, Laprise, Drolet, B nard, Martin, Chesson, Markowitz
- Simplified model (CDC)
 - Chesson, Markowitz, Meites, Ekwueme, Saraiya
- Merck model
 - Daniels, Prabhu, Pillsbury, Kothari, Elbasha
- Two CISNET models
 - Harvard
 - Policy1-Cervix (Cancer Council New South Wales)
 - Kim, Simms, Killen, Smith, Burger, Sy, Regan, Dowling, Canfell

Key similarities across HPV vaccination models

All five models:

- Include a wide range of health outcomes
 - Cervical precancers and cancer
 - Other HPV-associated cancers
 - Anal, vaginal, vulvar, penile, oropharyngeal
 - Anogenital warts
- Account for “herd effects”
 - Models account for herd effects on mid-adults from the existing vaccination program
- Examine a long time horizon (~100 years)

Key differences in HPV vaccination models

Models differ in:

- Structure
- Calibration (how the models were fit to data)
- Cervical cancer screening assumptions
- Vaccine uptake assumptions for mid-adults
- Natural history of HPV parameters
 - For example, natural immunity after HPV acquisition and clearance
- HPV transmission dynamics
 - For example, rate of acquisition of new sex partners by age
- Cost and quality of life assumptions

Models differ in structure and calibration

Model	Structure*	Calibration
HPV-ADVISE	Individual-based	50 best-fitting parameter sets used for analysis
Simplified	Compartmental	Not applicable
Merck	Compartmental	Single best-fitting parameter set used for analysis
CISNET (Harvard)	Individual-based	Single best-fitting parameter set used for analysis
CISNET (Policy1-Cervix)	Individual-based	Single best-fitting parameter set used for analysis

*Models with a compartmental (or aggregate) structure track groups in a population, those with an individual-based structure track individuals in the population (van Kleef et al., 2013, BMC Infect Dis).

Health economic comparisons to inform policy considerations

- Vaccination of adults older than age 26 years
 - Vaccination through age 30 years vs. current program
 - Vaccination through age 45 years vs. current program
- Focus of this presentation is adults older than age 26 years
 - Models also examined harmonization of catch-up vaccination through age 26 years
 - Vaccination through age 26 years for all persons vs. current program

Current program: routine vaccination at ages 11–12 years and catch-up vaccination through age 26 years for females and 21 years for males.

Vaccination through age 26 years for all persons: routine vaccination at ages 11–12 years and catch-up vaccination through age 26 years.

Vaccination through age 30 years: routine vaccination at ages 11–12 years and catch-up vaccination through age 30 years.

Vaccination through age 45 years: routine vaccination at ages 11–12 years and catch-up vaccination through age 45 years.

The exact specifications of vaccination strategies varied across models, but all models examined strategies similar to those listed here.

Cost-effectiveness of current HPV vaccination program

Cost per quality-adjusted life year (QALY) gained by current program vs. no vaccination

Vaccination strategy	Model				
	HPV-ADVISE	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1-Cervix)
Current program	Cost-saving	\$9,200	\$500	\$34,600	\$3,300

The current program is generally modeled as routine vaccination at ages 11 or 12 years, with catch-up vaccination through age 26 years for females and age 21 years for males; exact specifications differ slightly across models.

Number needed to vaccinate to prevent one case of disease

HPV-ADVISE model

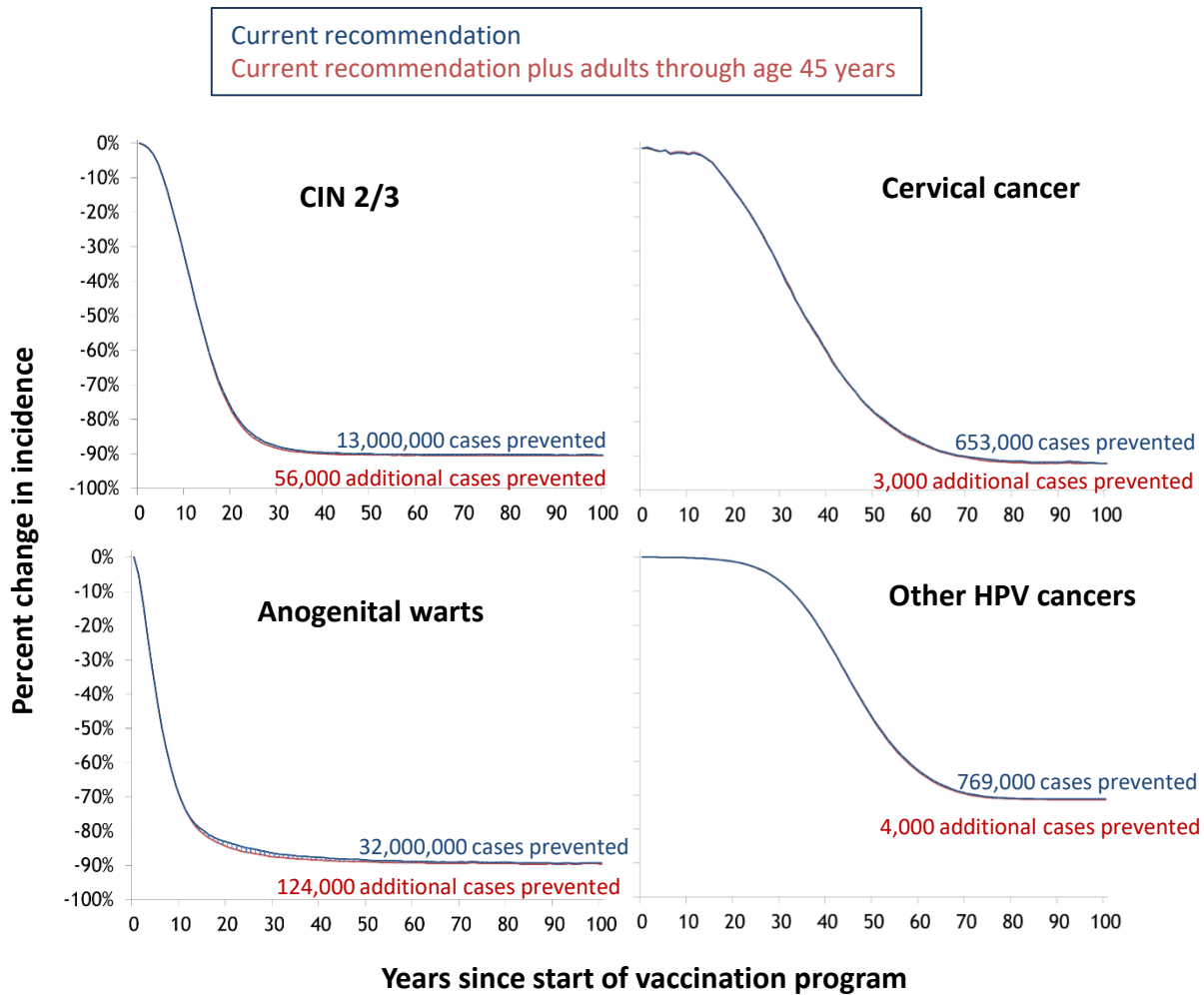
Scenario examined	Number needed to vaccinate to prevent one case of disease		
	Anogenital warts	CIN 2/3	Cancer
Current program vs. no vaccination	9	22	202
Vaccination of adults through age 45 years vs. current program			
All 50 parameter sets	390	860	7,690
22 sets w/ faster progression, lower natural immunity	120	800	6,500
28 sets w/ slower progression, higher natural immunity	870	880	8,580

CIN 2/3: Cervical intraepithelial neoplasia grade 2/3.

Results shown are the median values across the applicable parameter sets.

Estimated impact of HPV vaccination

HPV-ADVISE results (Brisson February 2019 ACIP)



CIN, cervical intraepithelial neoplasia; Median estimates generated by 50 best fitting parameter sets

Cost-effectiveness of vaccination of adults older than age 26 years

Cost per quality-adjusted life year (QALY) gained

Adult vaccination strategy	Model				
	HPV-ADVISE	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1-Cervix)
Through age 30 years (vs. current program)	\$830,000	\$587,600	\$81,200	\$627,700	\$341,100
Through age 45 years (vs. current program)	\$1,471,000	\$653,300	\$117,500	\$440,600	\$315,700

Current program: routine vaccination at ages 11–12 years and catch-up vaccination through age 26 years for females and 21 years for males.

“Through age 30 years”: routine vaccination at ages 11–12 years and catch-up vaccination through age 30 years.

“Through age 45 years”: routine vaccination at ages 11–12 years and catch-up vaccination through age 45 years.

Cost-effectiveness of vaccination of adults older than age 26 years

Cost per quality-adjusted life year (QALY) gained

Adult vaccination strategy	Model				
	HPV-ADVISE	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1-Cervix)
Through age 30 years (vs. current program)	\$830,000 \$404,000	\$587,600	\$81,200	\$627,700	\$341,100
Through age 45 years (vs. current program)	\$1,471,000 \$1,047,000	\$653,300	\$117,500	\$440,600	\$315,700

- HPV-ADVISE results reflect the median across 50 parameter sets
 - When using 22 parameter sets with faster progression, lower natural immunity
 - \$404,000 per QALY through age 30 years, \$1,047,000 per QALY through age 45 years

Cost-effectiveness of vaccination of adults older than age 26 years

Cost per quality-adjusted life year (QALY) gained

Adult vaccination strategy	Model				
	HPV-ADVISE	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1-Cervix)
Through age 30 years (vs. current program)	\$830,000 \$404,000 \$2,308,000	\$587,600	\$81,200	\$627,700	\$341,100
Through age 45 years (vs. current program)	\$1,471,000 \$1,047,000 \$1,592,000	\$653,300	\$117,500	\$440,600	\$315,700

- HPV-ADVISE results reflect the median across 50 parameter sets
 - When using 22 parameter sets with faster progression, lower natural immunity
 - \$404,000 per QALY through age 30 years, \$1,047,000 per QALY through age 45 years
 - When using 28 parameter sets with slower progression, higher natural immunity
 - \$2,308,000 per QALY through age 30 years, \$1,592,000 per QALY through age 45 years

Factors that may account for differences in model results

- Uncertainties about HPV natural history
 - Natural immunity following clearance of infections
 - Burden of disease caused by new HPV infections after age 26 years
- Degree of herd protection from existing HPV vaccination program
- Cervical cancer screening assumptions
- Health economic assumptions
- Deaths from undiagnosed cancer

Factors that may account for differences in model results

- Uncertainties about HPV natural history
 - Natural immunity following clearance of infections
 - Burden of disease caused by new HPV infections after age 26 years
 - Impact of natural history is illustrated by wide range of results in HPV-ADVISE when parameter sets are grouped by progression and natural immunity assumptions
 - \$830,000 per QALY for mid-adult vaccination through age 30 years
 - \$404,000 per QALY when using 22 parameter sets with faster progression, lower natural immunity
 - \$2,308,000 per QALY when using 28 parameter sets with slower progression, higher natural immunity
- Degree of herd protection from existing HPV vaccination program
- Cervical cancer screening assumptions
- Health economic assumptions
- Deaths from undiagnosed cancer

Factors that may account for differences in model results

- Uncertainties about HPV natural history
 - Natural immunity following clearance of infections
 - Burden of disease caused by new HPV infections after age 26 years
- Degree of herd protection from existing HPV vaccination program
 - Vaccination of adults older than age 26 years is more cost-effective when assuming lower or no historical vaccination coverage
- Cervical cancer screening assumptions
- Health economic assumptions
- Deaths from undiagnosed cancer

Cost per quality-adjusted life year (QALY) gained by mid-adult vaccination through age 30 years

Results when assuming no historical vaccination coverage shown in red

Vaccination strategy	Model				
	HPV-ADVISE	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1-Cervix)
Mid-adult vaccination through age 30 years	\$830,000 \$399,000	\$587,600 \$265,200	\$81,200	\$627,700	\$341,100

Factors that may account for differences in model results

- Uncertainties about HPV natural history
 - Natural immunity following clearance of infections
 - Burden of disease caused by new HPV infections after age 26 years
- Degree of herd protection from existing HPV vaccination program
- Cervical cancer screening assumptions
 - CISNET models assume perfect compliance in base case
 - Vaccination of adults older than age 26 years more cost-effective when assuming “real world” screening than when assuming perfect compliance to screening recommendations
- Health economic assumptions
- Deaths from undiagnosed cancer

Cost-effectiveness of vaccination of adults through age 45 years

Cost per quality-adjusted life year (QALY) gained

Values when assuming “real-world” screening are shown in red

Vaccination through age 45 years (vs. current program)	Model	
	CISNET (Harvard)	CISNET (Policy1-Cervix)
Base case results (perfect screening compliance)	\$440,600	\$315,700
Results when assuming “real-world” screening	\$363,800	\$199,300

Factors that may account for differences in model results

- Uncertainties about HPV natural history
 - Natural immunity following clearance of infections
 - Burden of disease caused by new HPV infections after age 26 years
- Degree of herd protection from existing HPV vaccination program
- Cervical cancer screening assumptions
- Health economic assumptions
 - ACIP reviewers asked modelers to include a set of results when using a standardized list of health economic parameters
 - Medical treatment costs, quality of life assumptions
- Deaths from undiagnosed cancer

Cost-effectiveness of vaccination of adults through age 45 years

Cost per quality-adjusted life year (QALY) gained

Vaccination through age 45 years (vs. current program)	Model				
	HPV-ADVISE	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1-Cervix)
Base case results	\$1,471,000	\$653,300	\$117,500	\$440,600	\$315,700
Results when using standardized health economic parameters	~1,471,000*	\$685,200	\$172,000	\$462,000	\$352,500

*This result, that the HPV-ADVISE results are virtually unchanged in the standardized scenario, is based on results in other scenarios (mid-adult vaccination to age 30 years, and mid-adult vaccination through age 40 years) in which the HPV-ADVISE results using the standardized health economic parameters differed by less than 0.3% from the base case results.

Factors that may account for differences in model results

- Uncertainties about HPV natural history
 - Natural immunity following clearance of infections
 - Burden of disease caused by new HPV infections after age 26 years
- Degree of herd protection from existing HPV vaccination program
- Cervical cancer screening assumptions
- Health economic assumptions
- Deaths from undiagnosed cancer

Deaths from undiagnosed cancer in absence of HPV vaccination

- Merck model
 - 9,860 deaths due to diagnosed HPV cancer each year
 - 24,424 deaths due to undiagnosed HPV cancer each year
 - 71% of HPV cancer deaths are due to undiagnosed cancer

Table of results across all models

Model	Percent of HPV cancer deaths attributable to undiagnosed cancers
Merck	71%*
CISNET (Harvard)	16% (cervical cancer)* 0% (other HPV cancers)**
HPV-ADVISE	0%**
Simplified	0%**
CISNET (Policy1-Cervix)	0%**

* These results are model outputs, not model assumptions.

** Values of 0% resulted from model assumption that no undiagnosed cancer deaths occur (for CISNET-Harvard, this assumption applied only to non-cervical cancers).

Cost-effectiveness of vaccination of adults through age 45 years

Cost per quality-adjusted life year (QALY) gained

Vaccination through age 45 years (vs. current program)	Merck model result
Base case	\$117,500
Excluding deaths due to undiagnosed cancer	\$202,200
Excluding deaths due to undiagnosed cancer, and applying standardized health economic parameters	\$428,900

- Undiagnosed cancer deaths have a notable effect on results
- However, undiagnosed cancer deaths do not account for all of the differences across the models
 - For example, results shown are from Merck model version that excludes potential benefits of preventing vaginal, vulvar, oropharyngeal and penile cancers caused by HPV 31/33/45/52/58
 - Estimated cost per QALY gained is lower when these benefits are included

Summary of health economics results

- Cost per QALY gained by current vaccination program < \$35,000
 - Cost-saving in HPV-ADVISE model
- Adult vaccination is much less cost-effective than current program
 - Notable differences in cost-effectiveness estimates across models
 - Uncertainties in HPV natural history and transmission dynamics preclude a precise estimate of the cost-effectiveness of vaccination of adults
 - Results more consistent when standardizing health economic assumptions and assumptions regarding deaths due to undiagnosed cancer
- In context of existing program, vaccinating adults over age 26 years would produce relatively small additional health benefits
 - Number needed to vaccinate to prevent one case of disease is ~40 times higher for adults through age 45 years than current program
 - For anogenital warts, CIN 2/3, and cancer

Summary of cost-effectiveness estimates

Vaccination of adults older than age 26 years

- Cost per QALY gained by adult vaccination through age 30 years
 - Exceeds \$300,000 in four of five available models
 - Exceeds \$800,000 in median of 50 parameter sets in HPV-ADVISE
- Cost per QALY gained by adult vaccination through age 45 years
 - Exceeds \$400,000 in three of five available models
 - Exceeds \$1,400,000 in median of 50 parameter sets in HPV-ADVISE

Acknowledgements

- Modeling team members
 - HPV-ADVISE model
 - Marc Brisson, Jean-François Laprise, Marie-Claude Boily, Mélanie Drolet, Élodie Bénard, Dave Martin, Harrell Chesson, Lauri Markowitz
 - Simplified model
 - Harrell Chesson, Lauri Markowitz, Elissa Meites, Donatus Ekwueme, Mona Saraiya
 - Merck model
 - Vince Daniels, Vimalanand Prabhu, Matthew Pillsbury, Smita Kothari, and Elamin Elbasha
 - CISNET models
 - Jane Kim, Kate Simms, James Killen, Megan Smith, Emily Burger, Stephen Sy, Catherine Regan, Emily Dowling, Karen Canfell

Cost-effectiveness of mid-adult vaccination

ADDITIONAL RESULTS

RESULTS:
**HARMONIZATION OF CATCH-UP
VACCINATION THROUGH AGE 26 YEARS**

Number needed to vaccinate to prevent one case of disease

HPV-ADVISE model

Scenario examined	Number needed to vaccinate to prevent one case of disease		
	Anogenital warts	CIN 2/3	Cancer
Current program vs. no vaccination	9	22	202
Harmonization of catch-up vaccination through age 26 years vs. current program			
All 50 parameter sets	140	430	7,590
22 sets w/ faster progression, lower natural immunity	40	450	3,260
28 sets w/ slower progression, higher natural immunity	840	340	8,200

CIN 2/3: Cervical intraepithelial neoplasia grade 2/3.

Results shown are the median values across the applicable parameter sets. For the “current program vs. no vaccination” comparison, results shown are for all 50 parameter sets. Results for this comparison did not change under the parameter subsets, except that the number needed to vaccinate to prevent one case of CIN 2/3 was 19 (instead of 22) when limited to the 28 parameter sets with slower progression and higher natural immunity.

Current program: routine vaccination at ages 11–12 years and catch-up vaccination through age 26 years for females and 21 years for males.

Harmonization of catch-up vaccination through age 26 years: routine vaccination at ages 11–12 years and catch-up vaccination through age 26 years.

Cost-effectiveness of harmonization of HPV vaccination

HPV-ADVISE model: Cost per quality-adjusted life year (QALY) gained

Vaccination strategy	Faster progression and lower natural immunity scenario (22 parameter sets)	Slower progression and higher natural immunity scenario (28 parameter sets)
Current program vs. no vaccination	Cost-saving	Cost-saving
Harmonization of catch-up vaccination through age 26 years vs. current program	\$178,000	*
Harmonization of catch-up vaccination through age 30 years vs. current program	\$404,000	\$2,308,000

*Not calculated, because no significant gains in QALYs could be measured

Cost-effectiveness of harmonization of HPV vaccination

HPV-ADVISE model: Cost per quality-adjusted life year (QALY) gained

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Cost-effectiveness of harmonization of HPV vaccination

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Vaccination strategy	Faster progression and lower natural immunity scenario (22 parameter sets)	Slower progression and higher natural immunity scenario (28 parameter sets)
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Harmonization of catch-up vaccination through age 30 years vs. current program	\$404,000	\$2,308,000

*Not calculated, because no significant gains in QALYs could be measured

- Estimated impact on cost of HPV vaccine program
 - Harmonization at age 26 years would increase total vaccination costs by < 5% under vaccine uptake assumptions**

**In a published version of Simplified model which did not account for historic vaccination coverage, harmonization at age 26 years cost \$228,800 per QALY gained and increased the total, discounted long-term costs of HPV vaccination by about 4% (Chesson et al. 2018 Vaccine). When accounting for historic vaccination coverage, the Simplified model (current version) estimates a cost per QALY gained of \$647,100 for harmonization at age 26 years (unpublished result). In the Merck model, harmonization at age 26 years cost \$86,600 per QALY gained vs. current program.

Summary of cost-effectiveness estimates

Harmonization of catch-up vaccination through age 26 years

- Cost per QALY gained by harmonization of catch-up vaccination through age 26 years (vs. current program) in HPV-ADVISE
 - \$178,000 using faster progression, lower natural immunity assumptions
 - No significant gain in QALYs using slower progression, higher natural immunity assumptions
- Results are not so favorable or unfavorable as to make a strong economic case for or against harmonization through age 26 years

Cost-effectiveness of mid-adult vaccination

BACKUP SLIDES

Models differ in natural immunity assumptions

- Models vary in percent with natural immunity after clearance of infection
- Models vary in degree and duration of protection of natural immunity

Model	Percent with natural immunity		Degree of protection for those with natural immunity		Duration of natural immunity
	Females	Males	Females	Males	
HPV-ADVISE	~10%–50%	~0%–20%	100%	100%	Lifelong
Merck	41%–75%	0%–75%	24%–50%	~0%–33%	Lifelong
CISNET (Harvard)	100%	100%	36%–50%	1%–10%	Lifelong
CISNET (Policy1-Cervix)	100%	100%	100%	100%	Not lifelong

For HPV-ADVISE, the ranges reflect differences across parameter sets and across HPV types. For the Merck model, the percent with natural immunity and the degree of protection are both type- and site-specific. For CISNET (Harvard), the ranges reflect differences across HPV types. In the Simplified model, natural immunity is not explicitly modeled.

Models differ in cost and quality-of-life assumptions

Example: Lifetime detriment in quality of life for cancer survivors

Model	Disutility for cancer survivors	Interpretation: Impact of cancer on quality of life in remaining years
HPV-ADVISE	0.00	No detriment to quality of life
Simplified	0.03	Slight lifelong detriment to quality of life
CISNET models	0.03	Slight lifelong detriment to quality of life
Merck	0.27	Notable lifelong detriment to quality of life

Differences in models

Models differ in vaccine uptake assumptions for mid-adults

Model	Annual probability that unvaccinated adults will be vaccinated	Allows for incomplete vaccine series
HPV-ADVISE Simplified CISNET (Harvard) CISNET (Policy1-Cervix)	2.6% women 1.9% men	No; all those vaccinated receive complete series
Merck	3.5% women 2.8% men (complete series uptake 2.3% women and 1.6% men)	Yes, uptake rates shown are for 1+ doses*

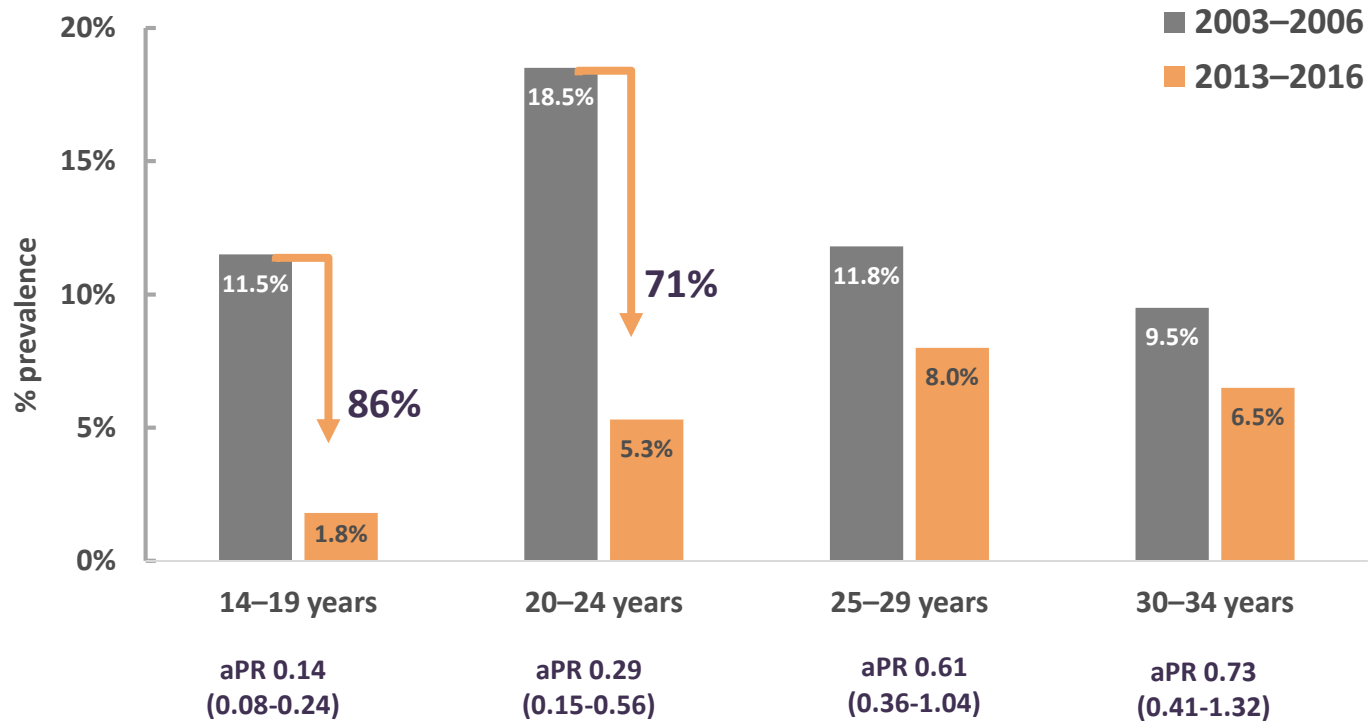
*In Merck model: 84% of women (78% of men) get second dose after first dose; 78% of women (72% of men) get third dose after second dose; 1-dose efficacy was 65% relative to 3 doses; 2-dose efficacy was 73% relative to 3 doses.

HPV vaccination coverage assumptions (Simplified model)

Sex and age group	Annual probability of HPV vaccination (if not already vaccinated)		
	Lower bound	Base case	Upper bound
Females, 12 years	29.5%	29.5%	56.4%
Females, 13–18 years	7.7%	12.9%	14.3%
Females, 19 years and older	1.5%	2.6%	2.9%
Males, 12 years	24.9%	24.9%	48.7%
Males, 13–18 years	1.7%	9.7%	14.2%
Males, 19 years and older	0.3%	1.9%	2.8%

Vaccine type prevalence (HPV 6,11,16,18), NHANES

2013–2016 compared to pre-vaccine era, females



Quality of life in long-term cervical cancer survivors

Lari Wenzel^{a,*}, Israel DeAlba^a, Rana Habbal^b, Brenda Coffey Kluhsman^c, Diane Fairclough^d,
Linda U. Krebs^c, Hoda Anton-Culver^b, Ross Berkowitz^{f,g}, Noreen Aziz^h

Objectives. To describe the quality of life (QOL) and long-term psychosocial sequelae of women of childbearing age diagnosed with cervical cancer 5–10 years earlier.

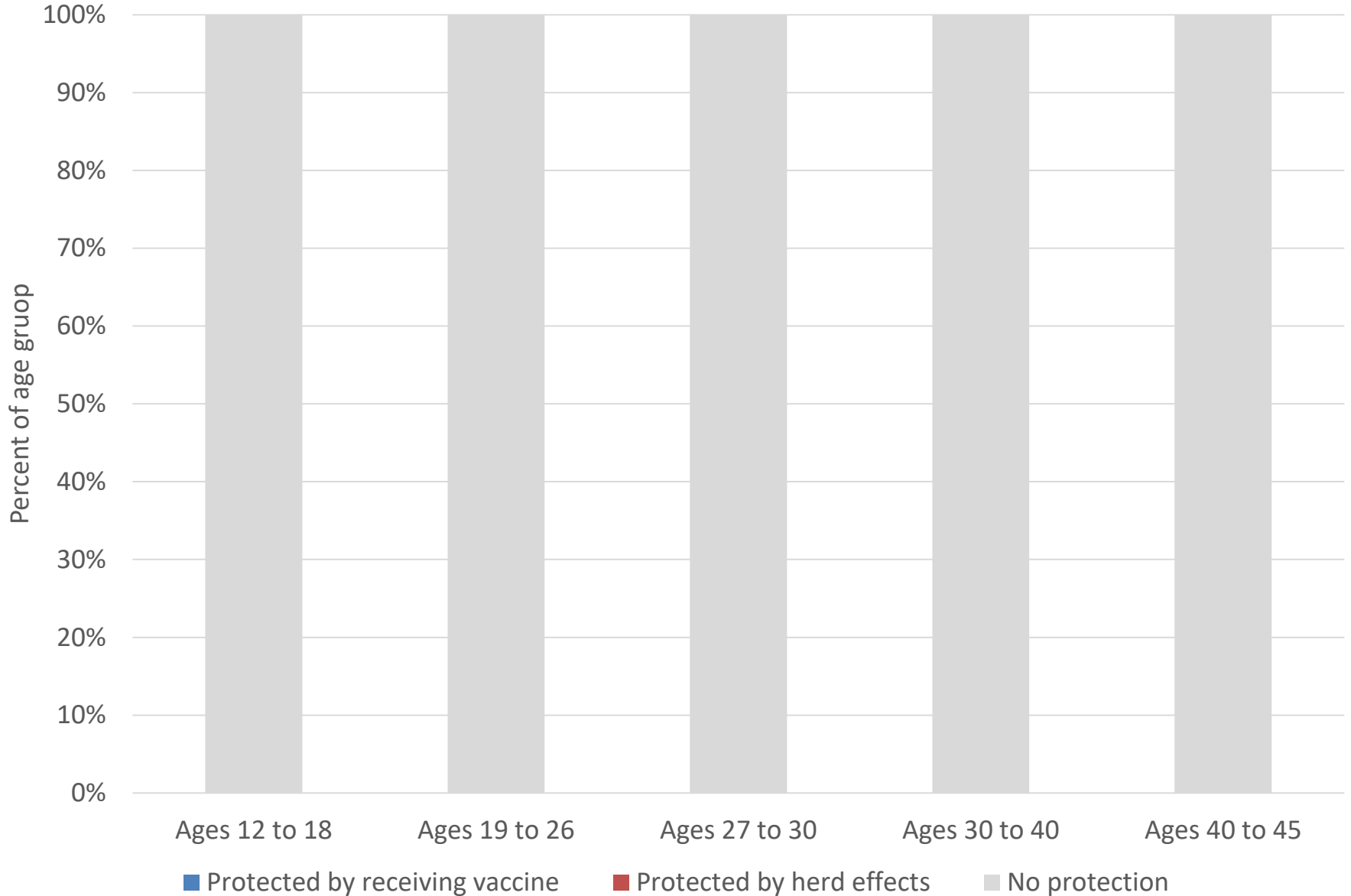
Methods. Utilizing a cross-sectional descriptive design, 51 cervical cancer survivors and 50 age-matched controls completed a comprehensive QOL interview.

Results. Participants were predominantly married, non-Hispanic White, with a mean age at diagnosis of 37 years and a mean age at interview of 45 years. This disease-free sample enjoys a good QOL, with physical, social, and emotional functioning comparable to or better than comparative norms. However, certain psychological survivorship sequelae and reproductive concerns persist. Participants reporting good QOL were less likely to report ongoing coping efforts related to having had this illness and were more likely to report greater social support, greater sexual pleasure, and less cervical cancer-specific distress. In a multiple-regression model, cancer-specific distress, spiritual well-being, maladaptive coping, and reproductive concerns accounted for 72% of the variance in QOL scores. Fifty-nine percent of respondents expressed that they would likely participate in a counseling program today to discuss psychosocial issues raised by having had cervical cancer, and 69% stated that they would have attended a support group program during the initial treatment if it had been offered.

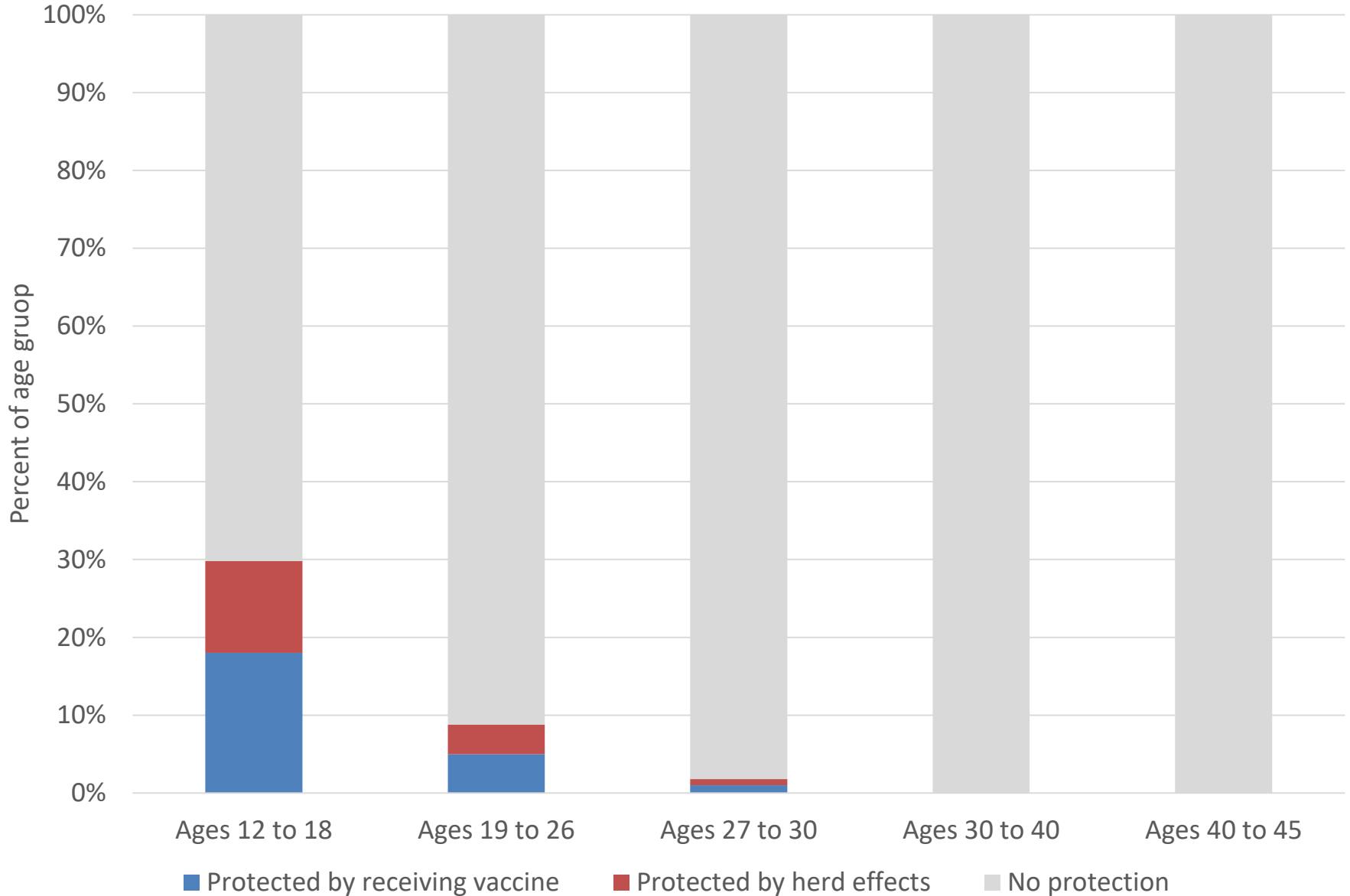
Conclusions. This information provides insight into the complex survivorship relationships between QOL and sequelae of cervical cancer for women diagnosed during childbearing years. Therefore, it is important for health care professionals to recognize that aspects of cancer survivorship continue to require attention and possible follow-up care.

“This disease-free sample enjoys a good QOL [quality of life], with physical, social, and emotional functioning comparable to or better than comparative norms.”

2005 (before vaccination)

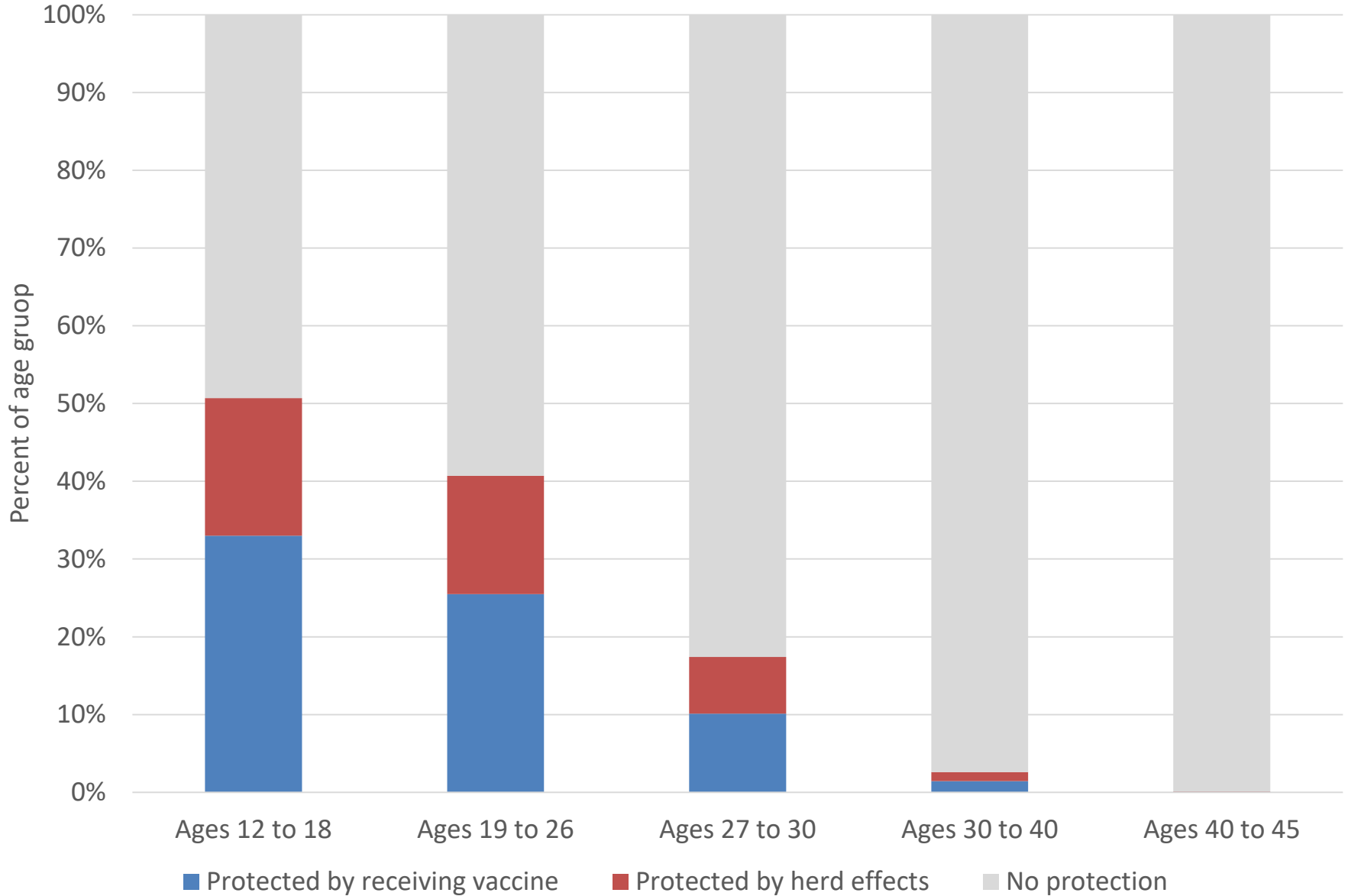


2008



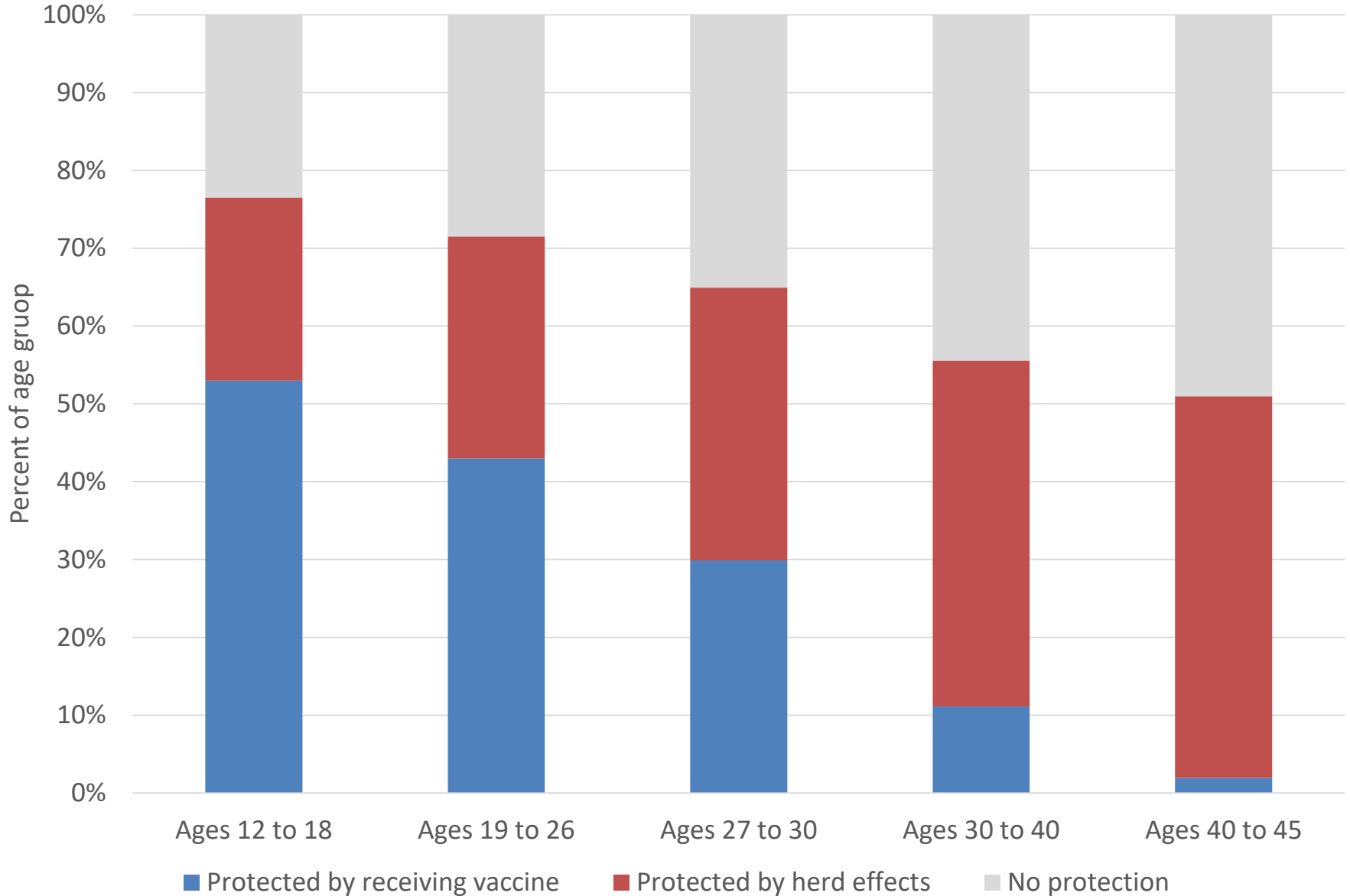
The magnitudes of the blue and red bars were created arbitrarily for illustrative purposes only and are not results from any of the HPV models.

2012



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2018



The magnitudes of the blue and red bars were created arbitrarily for illustrative purposes only and are not results from any of the HPV models.