Overview of Health Economic Models for HPV Vaccination of Mid-Adults

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History of health economics analyses of mid-adult HPV vaccination for ACIP

- October 2018 ACIP
  - Summary presentation of results from 3 models
    - HPV-ADVISE, Simplified, Merck
  - Differences in results across models
    - Post-meeting request to CISNET modeling group

- February 2019 ACIP
  - Two health economics presentations
    - HPV-ADVISE presentation (Brisson)
    - Summary presentation of results from 5 models (3 from October, plus 2 CISNET)

- Since February 2019 meeting
  - All models completed CDC economic review
    - In accordance with *ACIP Guidance for Health Economic Studies*
      - Completion of economic review does not confer any explicit or implied approval of the model reviewed
  - Better understanding of differences in model results

HPV-ADVISE: **A**gent-based **D**ynamic Model for **V**acc**I**nation and **S**creening **E**valuation
CISNET: **C**ancer **I**ntervention and **S**urveillance Modeling **Net**work

Outline

- Overview of five available models
- Results to inform both policy considerations
  - Harmonization of catch-up vaccination through age 26 years
  - 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)

- Simplified model (CDC)

- Merck model

- Two CISNET models
  - Harvard
  - Policy1-Cervix (Cancer Council New South Wales)

Modelling teams and conflict of interest statements

- ## HPV-ADVISE model
  - Brisson, Boily, Laprise, Drolet, Bénard, Martin, Chesson, Markowitz: <u>No conflicts</u>
- ## Simplified model
  - Chesson, Markowitz, Meites, Ekwueme, Saraiya: <u>No conflicts</u>
- ## Merck model
  - Daniels, Prabhu, Pillsbury, Kothari, Elbasha
  - Conflicts of interest statement: <u>All authors are employees of Merck & Co, Inc.</u>
- ## CISNET models
  - Kim, Simms, Killen, Smith, Burger, Sy, Regan, Dowling, Canfell: <u>No conflicts</u>

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
- Incorporate current medical cost estimates for HPV-associated cancers
- Account for "herd effects"
  - Models account for herd effects on mid-adults from the existing vaccination program
- Examine a long time horizon (~100 years or more)
- Exclude productivity costs

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

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).

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.

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.

Health economic comparisons
to inform both policy considerations

- Harmonization of catch-up vaccination through age 26 years
  - Vaccination through age 26 years for all persons vs. current program

- Vaccination of adults older than age 26 years
  - Vaccination through age 30 years vs. current program
  - Vaccination through age 45 years 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.

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

- 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.

RESULTS: VACCINATION OF ADULTS OLDER THAN AGE 26 YEARS

Number needed to vaccinate to prevent one case of disease
HPV-ADVISE model

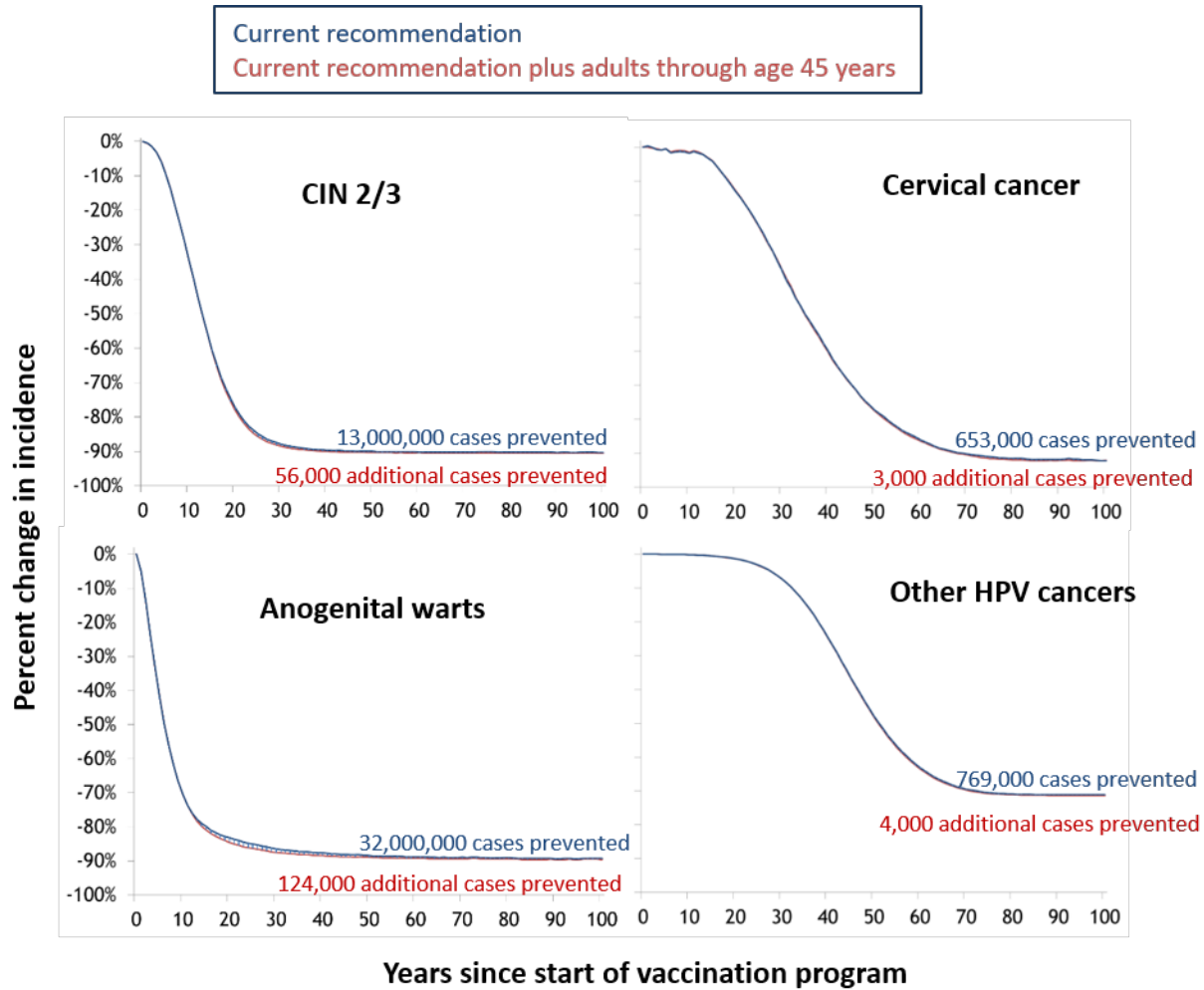| Scenario examined	Number needed to vaccinate to prevent one case of disease		
	Anogenital warts	CIN 2/3	Cancer
Current program vs. no vaccination	9	22	202
Vaccination of adults through age 45 years vs. current program			
All 50 parameter sets	390	860	7,690
22 sets w/ faster progression, lower natural 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.

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 of adults through age 45 years: routine vaccination at ages 11—12 years and catch-up vaccination through age 45 years.

Estimated impact of HPV vaccination
HPV-ADVISE results (Brisson February 2019 ACIP)

Current recommendation
Current recommendation plus adults through age 45 years

CIN 2/3
13,000,000 cases prevented
56,000 additional cases prevented

Cervical cancer
653,000 cases prevented
3,000 additional cases prevented

Anogenital warts
32,000,000 cases prevented
124,000 additional cases prevented

Other HPV cancers
769,000 cases prevented
4,000 additional cases prevented

Percent change in incidence

Years since start of vaccination program

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

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

- In CISNET models, cost per QALY is lower for vaccination through age 45 years than through age 30 years, likely due to herd effects
  - Cost per QALY higher for vaccination through age 45 years than through age 30 years in other models

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 was $265,200	$81,200	$627,700	$341,100
Through age 45 years (vs. current program)	$1,471,000	$653,300 was $417,200	$117,500	$440,600	$315,700

- Simplified model results are now higher than presented at February 2019 ACIP
    - Revised results reflect incorporation of ongoing vaccination program
    - Magnitude of this change consistent with expectations based on what the other models have shown about the importance of taking the ongoing vaccination program into account

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 was $105,100	$627,700	$341,100
Through age 45 years (vs. current program)	$1,471,000	$653,300	$117,500 was $149,100	$440,600	$315,700

- Merck model results are now lower than presented at February 2019 ACIP
  - Revised results reflect combination of minor changes to model*

*Changes to model were reported by Merck modelers to ACIP reviewers as a revision of anal cancer QALY calculations, update of certain parameter values, "improved model fit of pre-vaccine vaginal HPV 16 prevalence to available data, better accounting of historical coverage by 4vHPV and timing of 9vHPV launch," and "adoption of a new assumption that historical vaccination of <15-year-old persons with two doses confers the same level of protection as three doses." The parameters updated in Merck model were reported as: natural protection, fraction seroconverted, CIN and PIN vaccine protection, anal disease progression rates, and vulvar disease clearance rates.

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
- 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
  - Results using standardized list not available for February ACIP
- 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%[**]

"After years of analyzing completeness of case ascertainment, CDC has determined that NPCR registries consistently deliver high-quality, complete data."

-CDC's United States Cancer Statistics (USCS) website: https://www.cdc.gov/cancer/uscs/technical_notes/criteria/index.htm

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

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 <u>and</u> 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

QALY: quality-adjusted life year. CIN 2/3: Cervical intraepithelial neoplasia grade 2/3
Number needed to vaccinate based on HPV-ADVISE model, all 50 parameter sets, calculated when comparing vaccination of adults through age 45 years to the 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

QALY: quality-adjusted life year

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

QALY: quality-adjusted life year

Cost-effectiveness of mid-adult vaccination

COMMENTS FROM MODELING GROUPS IN ATTENDANCE

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  - 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