

# **Overview of Health Economic Results from Four Modeling Groups**

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# Notice of ongoing ACIP health economics review

- ACIP review process is ongoing for four of the five health economics models presented today
  - ACIP review completed for HPV-ADVISE model (Brisson)
    - Completion of the economic review does not confer any explicit or implied approval of the model
- A temporary waiver of the ACIP review policy was granted for this update to ACIP on ongoing modeling
  - Results of models under ACIP review should be considered preliminary

# Conflict of interest statements

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

\*HPV-ADVISE was originally developed in Canada. The United States version of HPV-ADVISE was calibrated to U.S. data. All references to HPV-ADVISE in this presentation are for the U.S. version of the model.

# Background

- October 2018 ACIP meeting
  - Review of 3 available models of 9vHPV for mid-adults
    - HPV-ADVISE, Simplified, Merck
  - Notable differences in cost-effectiveness estimates across models
- Since the October 2018 meeting
  - HPV-ADVISE estimates finalized
  - Simplified model adjusted to better approximate re-infection
  - Merck model
    - Recalibrated to fit pre-vaccine era HPV prevalence data
    - Now uses NIS-Teen data for historical vaccine coverage, as other models\*
  - Results from two CISNET models now available
  - Better understanding of differences across models

\*In results presented at October 2018 ACIP meeting, the Merck model used National Health and Nutrition Examination Survey (NHANES) data for historical coverage (i.e., coverage from 2006 to present). Now, all models use NIS-Teen for historical coverage assumptions (except the Simplified model, which does not include historical coverage).

Cost-effectiveness of mid-adult vaccination

# **OVERVIEW OF MODELS**

# Five models of 9vHPV through age 45 years 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, CCNSW)

# All five 9vHPV models

- Are dynamic (include “herd effects”)
- Include a wide range of health outcomes
  - Cervical precancers and cancer
  - Other HPV-associated cancers
    - Anal, vaginal, vulvar, penile, oropharyngeal
  - Genital warts
- Apply updated, higher direct medical costs estimates for HPV-associated cancers
- Exclude productivity costs
- Examine a long time horizon (~100 years or more)

## Selected model attributes

<b>Model</b>	<b>Structure*</b>	<b>Includes historical vaccine coverage**</b>	<b>Model calibration (Calibrated models were fit to U.S. data)</b>
<b>HPV-ADVISE</b>	Individual-based	Yes	50 best-fitting parameter sets used for analysis
<b>Simplified</b>	Compartmental	No	Not applicable
<b>Merck</b>	Compartmental	Yes	Single best-fitting parameter set used for analysis
<b>CISNET (Harvard)</b>	Individual-based	Yes	Single best-fitting parameter set used for analysis
<b>CISNET (Policy1-Cervix)</b>	Individual-based	Yes	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).

\*\*The model includes effect of historical vaccination (~2007-2018) and the strategies being compared start after the historical period (~2019 onwards).



## Selected model attributes, continued

<b>Model</b>	<b>Vaccine assumed to protect against re-infection</b> (for those vaccinated after clearance)	<b>Cervical cancer screening</b>
<b>HPV-ADVISE</b>	Yes	Approximates real-world screening
<b>Simplified</b>	No	Not explicitly modeled
<b>Merck</b>	Yes	Approximates real-world screening
<b>CISNET (Harvard)</b>	Yes	Assumes perfect compliance (real-world screening also considered)
<b>CISNET (Policy1-Cervix)</b>	Yes	Assumes perfect compliance (real-world screening also considered)

## Selected model attributes, continued (2)

<b>Model</b>	<b>Annual probability that unvaccinated adults will be vaccinated</b>	<b>Allows for incomplete vaccine series</b>
<b>HPV-ADVISE</b> <b>Simplified</b> <b>CISNET (Harvard)</b> <b>CISNET (Policy1-Cervix)</b>	2.6% women 1.9% men	No; all those vaccinated receive complete series
<b>Merck</b>	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.

## Selected model attributes, continued (3)

<b>Model</b>	<b>Natural immunity parameter values (Determined through model calibration in all models except Simplified)</b>
<b>HPV-ADVISE</b>	Following clearance, ~10% to 50% of women and 0% to 20% of men develop lifelong immunity
<b>Simplified</b>	Not explicitly modeled; model has been adjusted to more closely approximate scenarios with < 100% natural immunity
<b>Merck</b>	HPV 16 example: Following clearance, 74% of males and 50% of females seroconvert; of these, degree of protection ~7% for males and 24% for females and is lifelong
<b>CISNET (Harvard)</b>	Following clearance, 36% to 50% of women and 1% to 10% of men develop lifelong immunity (variable by genotype)
<b>CISNET (Policy1-Cervix)</b>	Following clearance, all individuals have a period of complete natural immunity, but this is not lifelong (1-20% lose natural immunity each year)

Cost-effectiveness of mid-adult vaccination

# **COMPARISON OF RESULTS ACROSS MODELS**

# Median age of first acquisition with at least one high risk 9vHPV type (16/18/31/33/45/52/58)

Among women who will ever acquire at least one high risk type

Model	HPV-ADVISE	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1-Cervix)
Median age in years	21.6* (20.2 to 23.0)	20.3	25-26	NA	NA

- From NHANES seroprevalence data presented earlier today (Markowitz)
  - By age 20–21 years an estimated >50% of females already had evidence of infection with >1 high risk 9vHPV type
  - Assuming 60% of females develop antibody after infection

\*The value shown for HPV-ADVISE is not the median age of first acquisition, but instead the age by which 50% of all infections, including re-infections, are acquired. The range shown in parentheses reflects the different predictions across the 50 parameter sets of HPV-ADVISE.

# Cost-effectiveness of current HPV vaccination strategy

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

<b>Model</b>	<b>HPV-ADVISE</b>	<b>Simplified</b>	<b>Merck</b>	<b>CISNET (Harvard)</b>	<b>CISNET (Policy1-Cervix)</b>
<b>Current program</b>	Cost-saving	\$9,800	\$200	NA	NA

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 vary across models.

NA: not available at time of presentation

It is only in recent years that HPV vaccination in the U.S. has been described as cost-saving across a range of published models. The more favorable estimates in current models are due primarily to the 2-dose schedule for those vaccinated through age 14 years, and to the additional benefits of 9vHPV (vs. 4-valent HPV vaccine). Although the current vaccine program was not cost-saving in the Simplified model, the model found vaccination of 12-year-olds to be cost-saving vs. no vaccination.

# Mid-adult vaccination strategies examined

- Two cost-effectiveness comparisons in this summary
  - Mid-adult vaccination through age 30 years vs. current program
  - Mid-adult vaccination through age 45 years vs. current program
- Though not presented today, modelers have examined numerous other mid-adult vaccination strategies
  - Such as extending current program to include mid-adults up to
    - Age 35 years
    - Age 40 years
  - Incremental cost-effectiveness analyses have been conducted
    - For example, what is the cost-effectiveness of a mid-adult vaccination program through age 35 years vs. age 30 years?

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

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

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

# Cost-effectiveness of mid-adult HPV vaccination through age 30 years

Cost per QALY gained by mid-adult vaccination vs. current program

Model	HPV-ADVISE	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1-Cervix)
Mid-adult vaccination through age 30 years	\$830,000	\$265,200	\$105,700	\$627,700	\$341,100

Current program: routine vaccination at ages 11–12 years and catch-up vaccination through age 26 years for females and 21 years for males.  
 Mid-adult vaccination through age 30 years: routine vaccination at ages 11–12 years and catch-up vaccination through age 30 years.



# Cost-effectiveness of mid-adult HPV vaccination through age 45 years

Cost per QALY gained by mid-adult vaccination vs. current program

Model	HPV-ADVISE	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1-Cervix)
Mid-adult vaccination through age 45 years	\$1,471,000	\$417,200	\$149,100	\$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.  
 Mid-adult vaccination through age 45 years: routine vaccination at ages 11–12 years and catch-up vaccination through age 45 years.

# Distinctive feature of CISNET results across two vaccination strategies

Model	HPV-ADVISE	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1-Cervix)
Through age 30 years (vs. current program)	\$830,000	\$265,200	\$105,700	\$627,700	\$341,100
Through age 45 years (vs. current program)	\$1,471,000	\$417,200	\$149,100	\$440,600	\$315,700

- In CISNET models, mid-adult vaccination through age 45 years had a lower cost per QALY than through age 30 years, likely due to
  - Herd effects\*, interaction with screening
    - Vaccination through age 45 years also had a lower cost per QALY than vaccination through age 35 years and through age 40 years (not shown)

\*For example, the herd effects of the current program are likely more pronounced among those  $\leq 30$  years than those  $> 30$  years, leaving greater potential benefits of mid-adult vaccination among those  $> 30$  years. HPV-ADVISE also finds similar results in some scenarios (not shown).

# What can account for differences across models?

## Selected factors

- Health economic parameters
  - Vaccination costs, medical treatment costs, quality of life assumptions
  - ACIP reviewers asked modelers to include a set of results when using a standardized list of health economic parameters
- Historical and future vaccination coverage assumptions
  - Historical coverage refers to vaccine uptake from 2006 to present
    - Before potential expansion of vaccination program to include mid-adults
- Model structure and assumptions regarding
  - Sexual behavior and HPV transmission dynamics
  - Natural history of HPV infection
  - Cervical cancer screening, diagnosis, treatment

# Can differences in results be explained by differences in health economic assumptions?

Vaccination costs  
Medical treatment costs  
Quality of life impacts

Answer: We do not know yet. Analyses are not yet complete.

# Do historical vaccination coverage assumptions matter?

All models include historical vaccination coverage, except the Simplified model which was unable to do so.

Does this matter?

Answer: Yes, this matters.

Assuming lower historical vaccination coverage reduces the cost per QALY gained by mid-adult vaccination.

With lower historical vaccination coverage, there are less herd effects of current vaccination program on mid-adults, and thus more potential benefits of mid-adult vaccination.

# 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

Model	HPV-ADVISE	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1-Cervix)
Mid-adult vaccination through age 30 years	\$830,000 \$399,000	\$265,200 \$265,200	\$105,700 \$59,900	\$627,700	\$341,100

The Simplified model is unable to incorporate historical vaccination coverage, and thus the base case result of \$265,200 reflects a scenario of no historical vaccination coverage.

For the HPV-ADVISE and Merck models, similar trends were found when examining scenarios in which historical vaccination coverage was lower than base case assumptions.

# What do we learn by exploring multiple parameter sets?

HPV-ADVISE examines the 50 best-fitting parameter sets.

Merck and CISNET models use single best-fitting parameter set.

Answer: Using multiple parameter sets helps to understand how sensitive the results are to key assumptions, such as

Natural history of HPV infection

HPV transmission dynamics (sexual behavior, transmission, etc.)

These assumptions are subject to considerable uncertainty.

# Cost per quality-adjusted life year (QALY) gained by mid-adult vaccination through age 45 years

90% uncertainty interval across 50 parameter sets shown in red

Model	HPV-ADVISE	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1-Cervix)
Mid-adult vaccination through age 45 years	\$1,471,000 Range: \$360,000 to undefined	\$417,200	\$149,100	\$440,600	\$315,700



# What is the effect of assuming perfect screening compliance?

CISNET models assume perfect cervical cancer screening compliance in their base case analysis (and “real-world” screening in a sensitivity analysis).

HPV-ADVISE and Merck model simulate “real-world” screening.

**Answer:** CISNET estimates of the cost per QALY gained by mid-adult vaccination are lower when “real-world” screening is assumed.

With “real-world” screening instead of perfect screening, more potential for vaccine to prevent cervical cancer.

# Cost per quality-adjusted life year (QALY) gained by mid-adult vaccination through age 45 years—“real world”

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

Model	HPV-ADVISE	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1-Cervix)
Mid-adult vaccination through age 45 years	\$1,471,000	\$417,200	\$149,100	\$440,600 \$363,800	\$315,700 \$199,300

HPV-ADVISE and Merck model simulate “real-world” cervical cancer screening in base case. Simplified model does not explicitly model cervical cancer screening.

Cost-effectiveness of mid-adult vaccination

# **SUMMARY AND NEXT STEPS**

# Cost-effectiveness of mid-adult vaccination through age 30 years

Is the estimated cost per QALY\* below the following values:  
\$100K, \$150K, \$200K, \$300K, \$400K and \$500K?

Model	HPV-ADVISE: Median	HPV-ADVISE: Lower bound (90% UI)	Simplified	Merck	CISNET (Harvard)	CISNET (Policy1- Cervix)
< \$100,000	No	No	No	No	No	No
< \$150,000	No	Yes	No	Yes	No	No
< \$200,000	No	Yes	No	Yes	No	No
< \$300,000	No	Yes	Yes	Yes	No	No
< \$400,000	No	Yes	Yes	Yes	No	Yes
< \$500,000	No	Yes	Yes	Yes	No	Yes

UI: Uncertainty interval (based on results across 50 parameter sets)

QALY: quality-adjusted life year

\*Cost per QALY gained by mid-adult vaccination through age 30 years compared to current program

# Cost-effectiveness of mid-adult vaccination through age 45 years

Is the estimated cost per QALY below the following values:  
\$100K, \$150K, \$200K, \$300K, \$400K and \$500K?

<b>Model</b>	<b>HPV-ADVISE: Median</b>	<b>HPV-ADVISE: Lower bound (90% UI)</b>	<b>Simplified</b>	<b>Merck</b>	<b>CISNET (Harvard)</b>	<b>CISNET (Policy1- Cervix)</b>
< \$100,000	No	No	No	No	No	No
<\$150,000	No	No	No	Yes	No	No
< \$200,000	No	No	No	Yes	No	No
< \$300,000	No	No	No	Yes	No	No
< \$400,000	No	Yes	No	Yes	No	Yes
< \$500,000	No	Yes	Yes	Yes	Yes	Yes

UI: Uncertainty interval (based on results across 50 parameter sets)

QALY: quality-adjusted life year

Cost per QALY gained by mid-adult vaccination through age 45 years compared to current program.

# Summary of cost-effectiveness estimates

- Current U.S. HPV vaccination program has a favorable cost-effectiveness profile
  - Cost-saving or <\$10,000 per QALY gained
- All models find that mid-adult vaccination is much less cost-effective than current program
- Uncertainties in HPV natural history and transmission dynamics preclude a precise estimate of the cost-effectiveness of mid-adult vaccination

# Summary of cost-effectiveness estimates, continued

- Mid-adult vaccination through age 30 years
  - Cost per QALY vs. current program
    - Exceeds \$200,000 in three of five available models
    - Exceeds \$300,000 in three of four models with historic vaccination coverage
    - Exceeds \$800,000 in median of 50 parameter sets in HPV-ADVISE
      - 90% uncertainty interval: \$104,000 to  $\infty$
- Mid-adult vaccination through age 45 years
  - Cost per QALY vs. current program
    - Exceeds \$300,000 in four of five available models
    - Exceeds \$400,000 in three of five available models
    - Exceeds \$1.4 million in median of 50 parameter sets in HPV-ADVISE
      - 90% uncertainty interval: \$360,000 to  $\infty$

# Next steps

- ACIP review ongoing for 4 of 5 models
  - HPV-ADVISE review complete
  - Other model results should be considered preliminary
- Modelers will continue collaboration
  - To understand the important differences in model structures and assumptions that drive the results
    - Completion of “standardized health economic assumptions” scenario
  - To finalize ACIP economics review process
  - To provide more details to the HPV Work Group
- Prepare for June 2019 ACIP meeting



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
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