

Cost-Effectiveness of extending HPV vaccination above age 26 years in the U.S.

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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, Laprise, Drolet, Martin, Bénard, Boily, Chesson & Markowitz
 - No known conflicts of interest

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Study Question

- From the health care sector perspective, what is the additional impact and cost-effectiveness of extending the established HPV vaccine program in the U.S. to females aged 27-45 years and males aged 22-45 years?

Objective

- To evaluate the:
 - additional population-level effectiveness, and
 - incremental cost-effectivenessof vaccinating females and males up to 45 years of age in the U.S. against HPV (vs current recommendation)

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 (AGW)
 - Cervical cancer (squamous cell carcinoma (SCC) & adenocarcinoma)
 - Cancers of the anus, oropharynx, penis, vagina & vulva

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

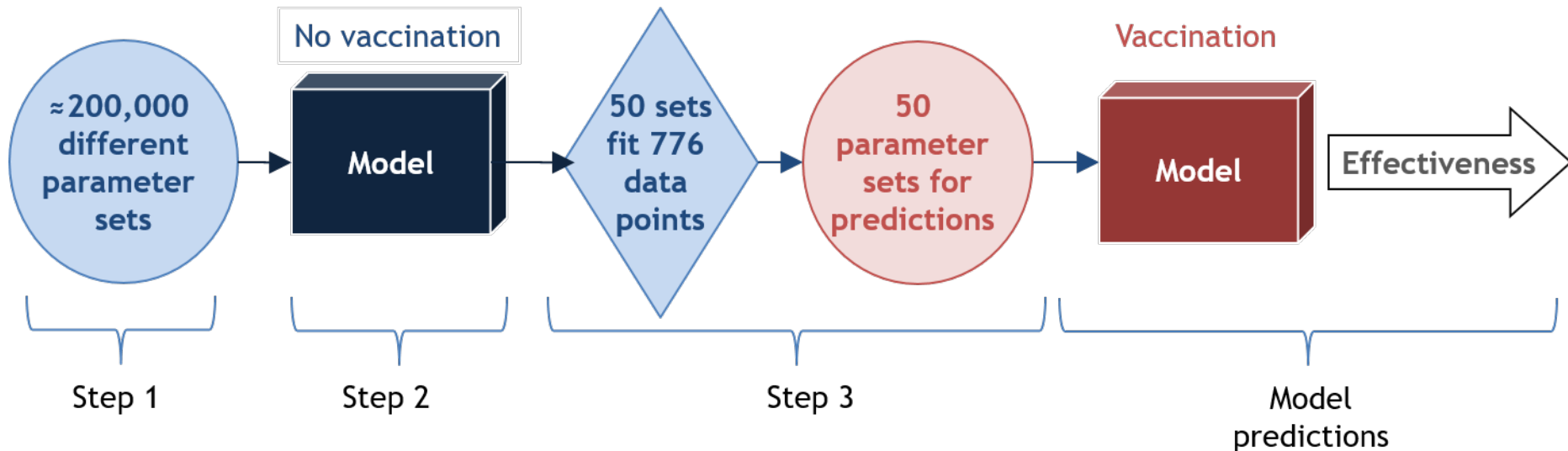
Step 3: Multiple parameter sets are identified, which fit U.S. data:

- Sexual & screening behaviour (stratified by gender and age)
- HPV prevalence (stratified by HPV type, gender, age and sexual activity)
- Incidence of anogenital warts, cervical lesions, cervical cancer and other HPV-related cancers (stratified by HPV type, gender, and age)[&]
- Total of 776 data points fitted

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

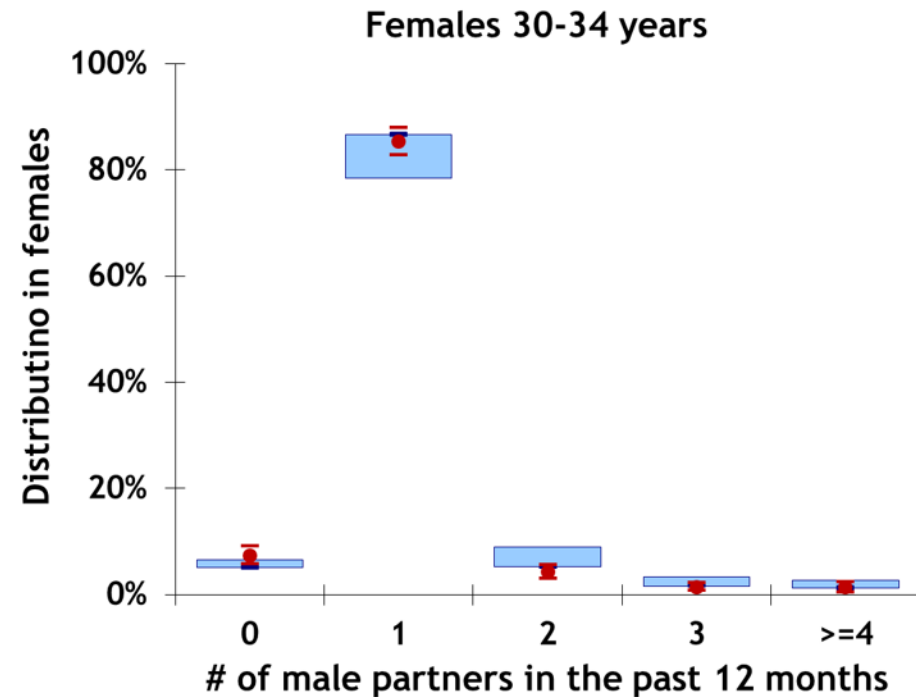
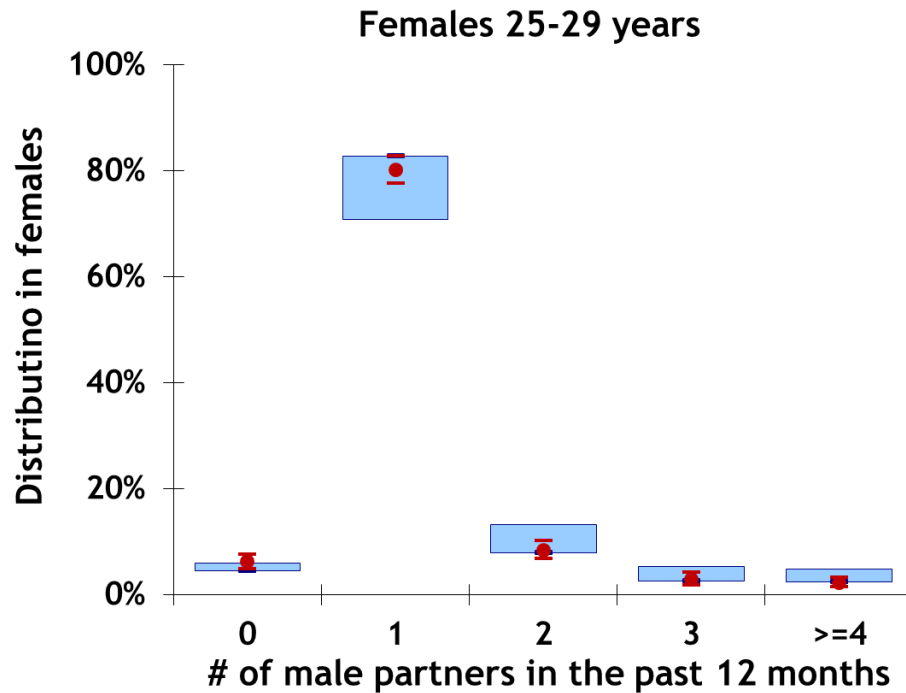
Model Fit

- $\approx 200,000$ different combinations of parameters sampled from the prior parameter distributions
- 50 parameter sets produced acceptable fit to the 776 pre-specified data target points



Model Fit - sexual behaviour

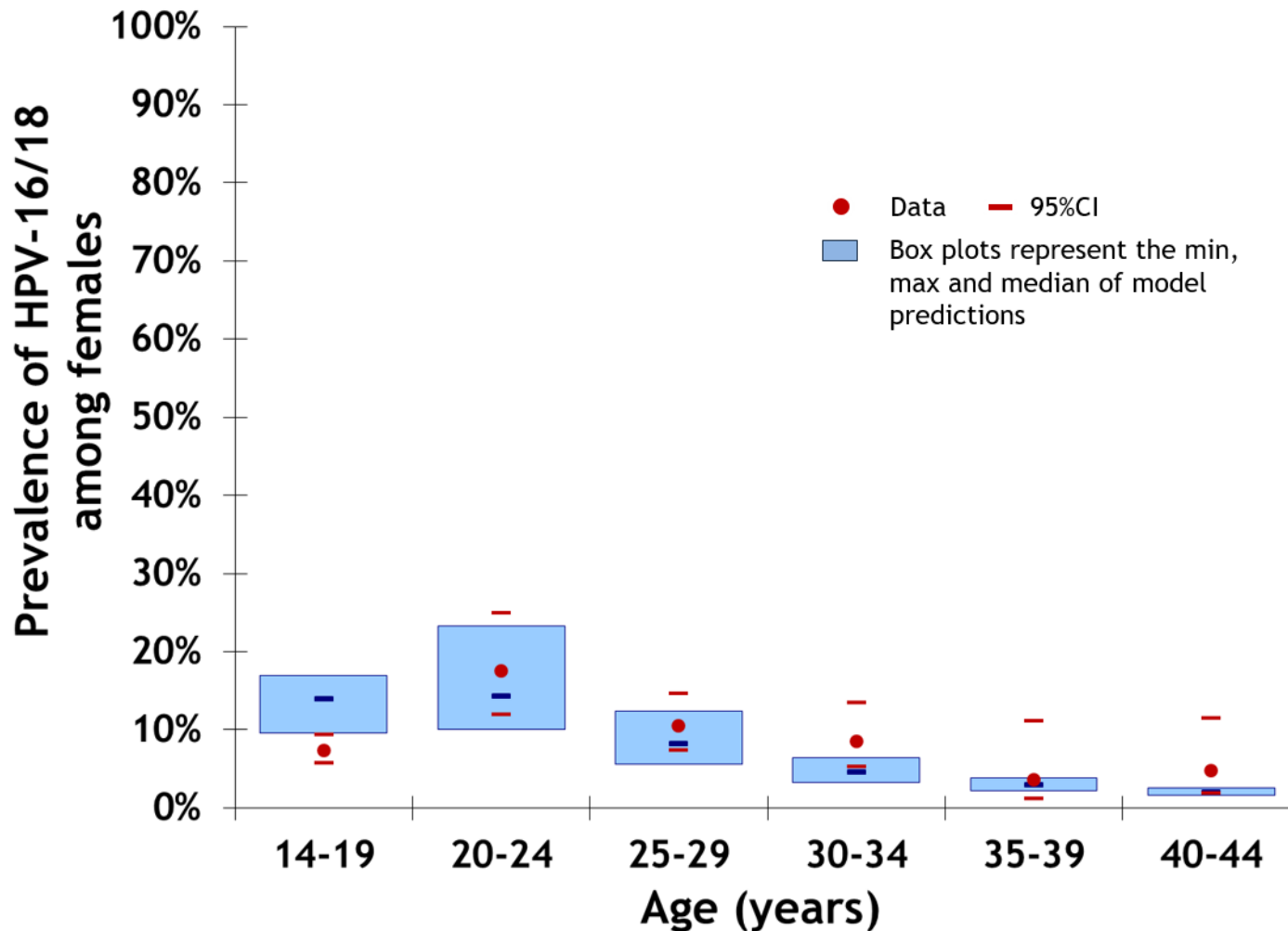
Ex: Number of partners in the past 12 months in women



- Data
- 95%CI
- Box plots represent the min, max and median of model predictions

Model Fit - HPV prevalence in women

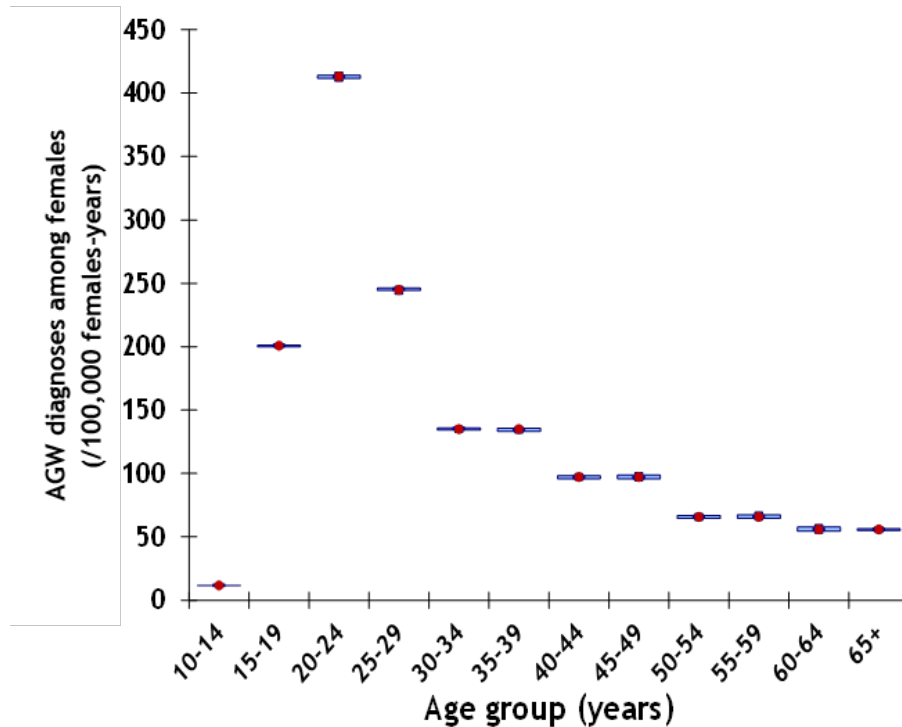
Ex: HPV-16/18 prevalence by age



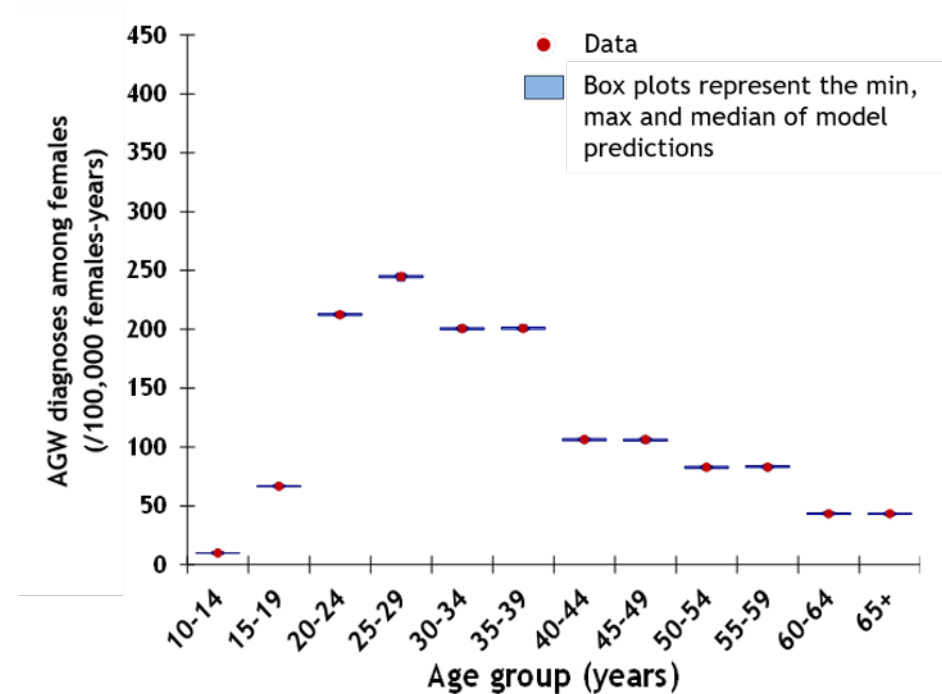
Model Fit - anogenital warts (AGW)

Ex: Incidence of AGW diagnoses

Incidence of AGW diagnoses among females



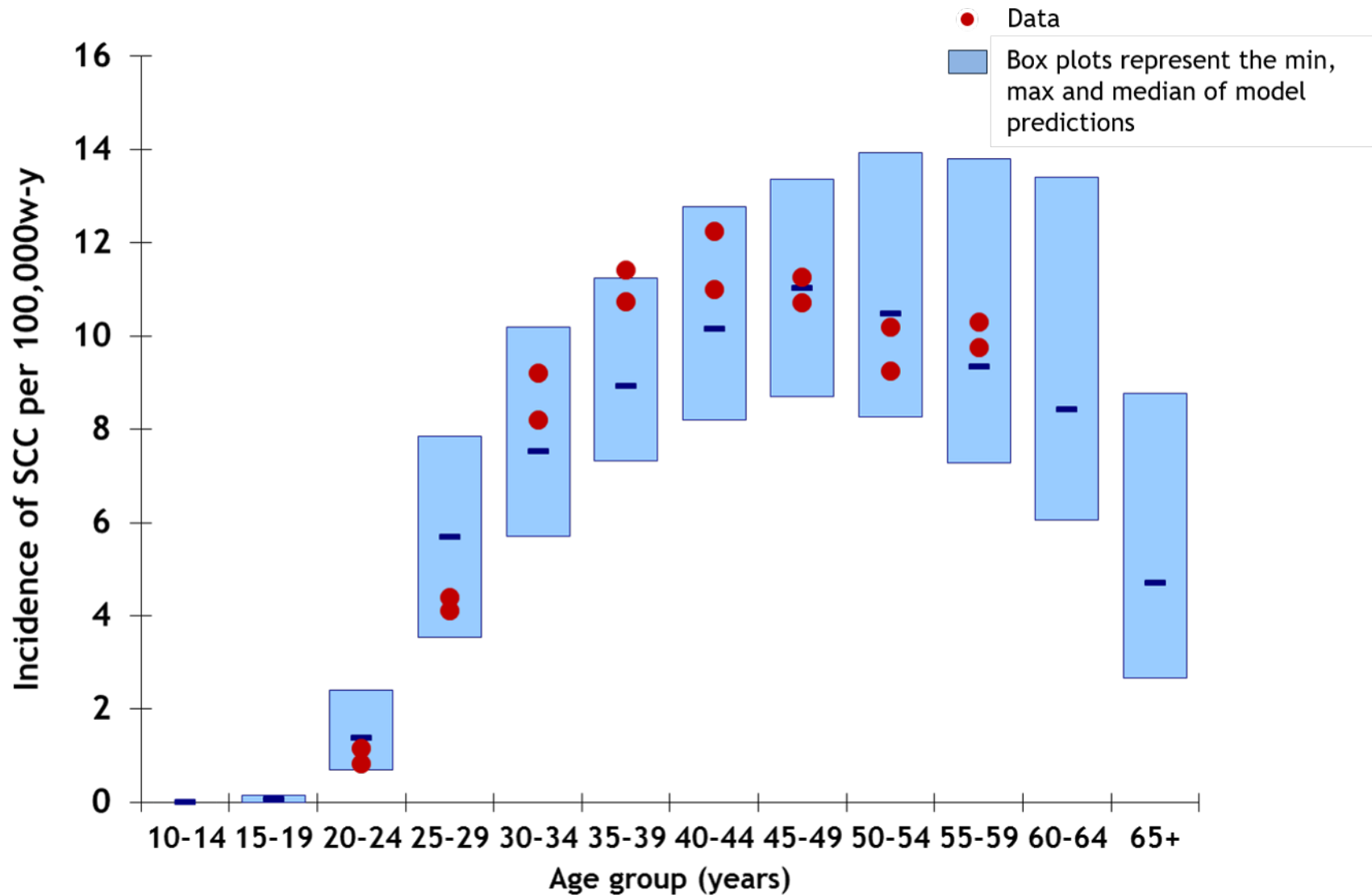
Incidence of AGW diagnoses among males



Data: Hoy Curr Med Res Opin 2009; Data adjusted to account for the % of AGW caused by HPV-6/11

Model Fit - squamous cell carcinoma (SCC)

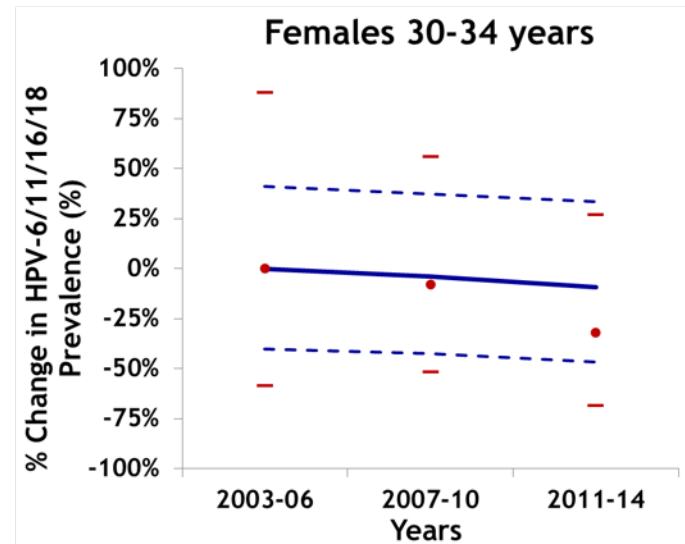
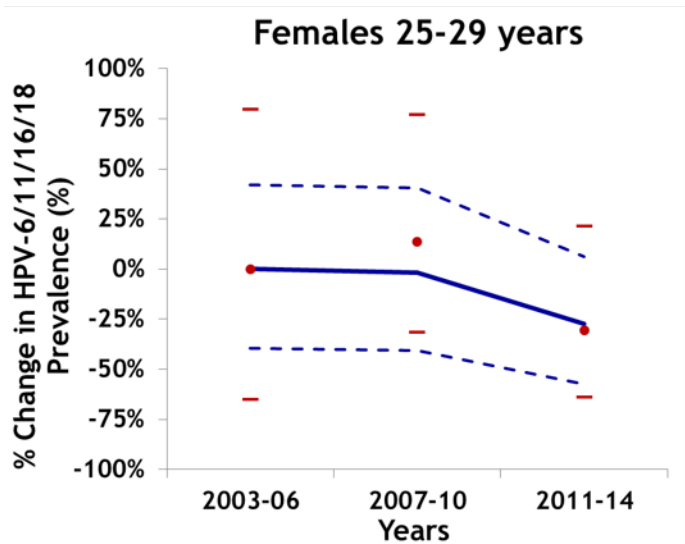
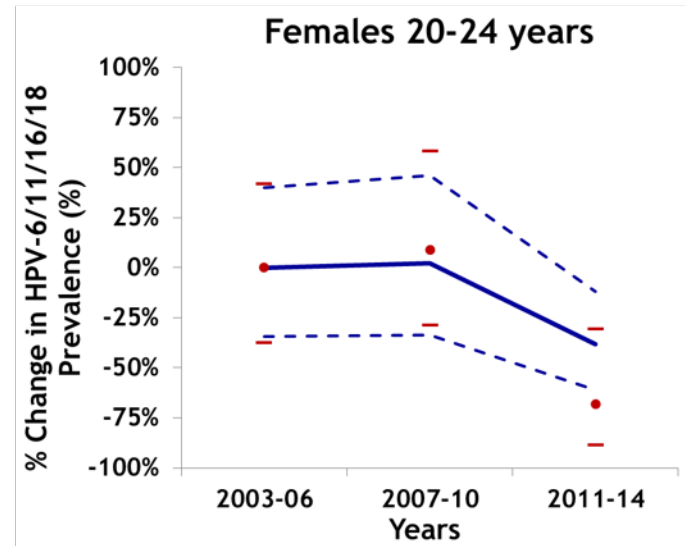
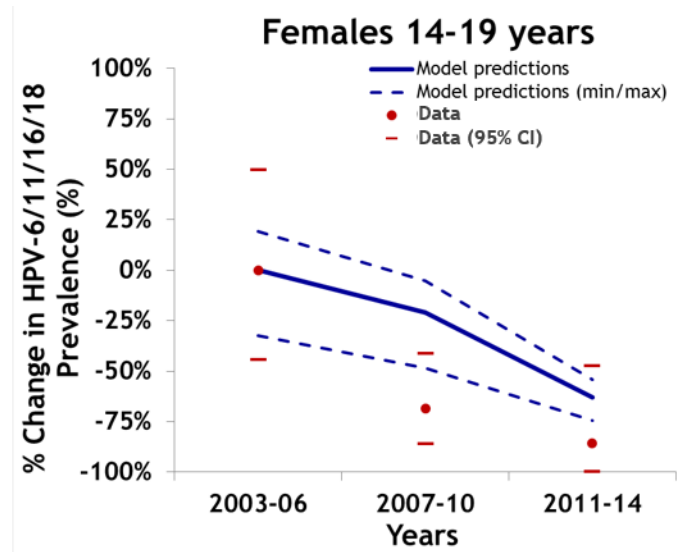
Ex: Incidence of SCC



Data: US Cancer Statistics (minimum & maximum estimates from NPCR/SEER 2004-2008)

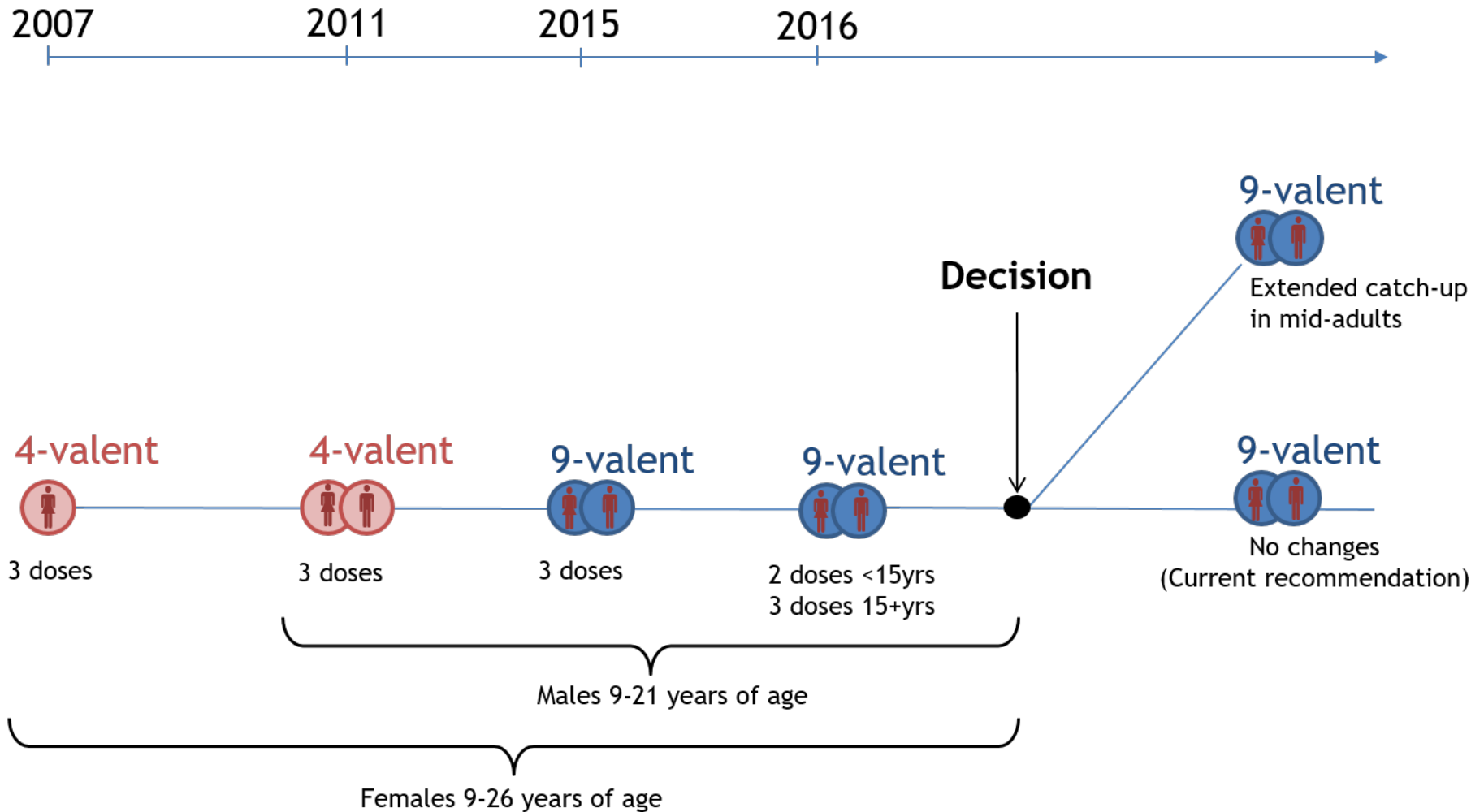
Model validation

Model predictions vs. Post-vaccination U.S. data



Change in prevalence over time is shown as % change versus pre-vaccination values (2003-2006). Predictions: Mean & min/max of HPV-ADVISE predictions; Data: NHANES

Intervention HPV vaccination



Vaccination coverage - Current recommendation

Base case

Girls & Boys age 18 years or less

- Data from National Immunization Survey-Teen (age 13-17 years)
- 2007-16: Observed uptake rates
 - 18 year-olds: Assume same uptake rates as 17 year-olds
- 2017+: Assume uptake rates constant at 2016 levels

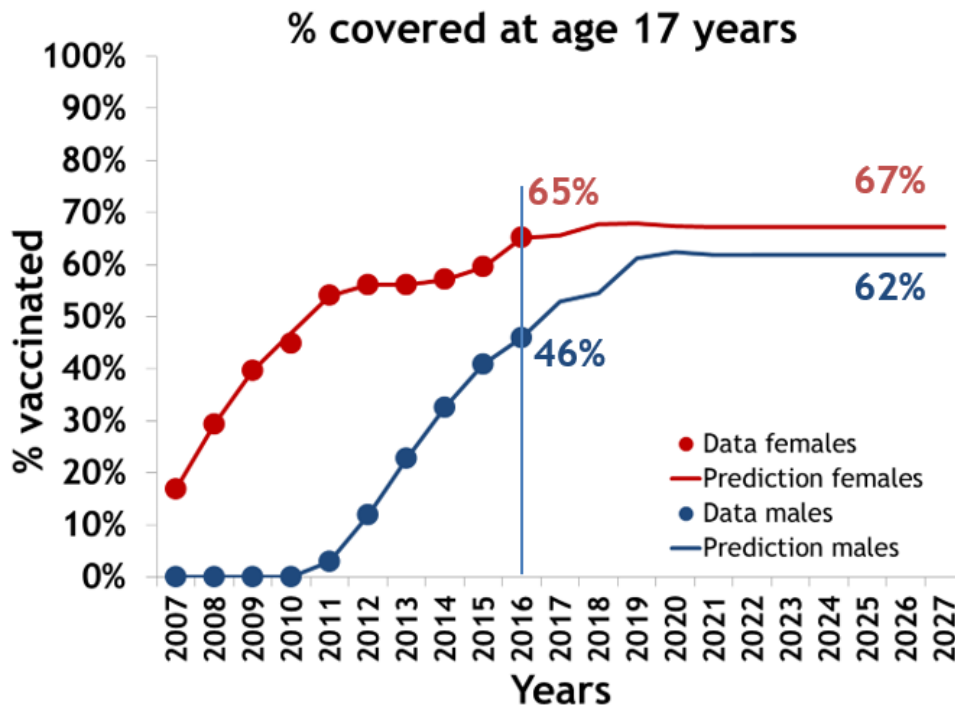
Women & Men above 18 years of age

- Uptake rates based on Chesson et al. *Vaccine* 2018
 - Females 19-26 years: 2.6% per year
 - Males 19-21 years: 1.9% per year

Vaccination coverage - Current recommendation

Base case, Fit to data

- Model reproduces data from National Immunization Survey-Teen



Coverage 2021+

Age (yrs)	Girls	Boys
13 ^{&}	43%	38%
14	49%	45%
15	57%	52%
16	61%	56%
17	67%	62%
13 to 17	55%	51%

[&]: For simplicity, vaccination at age 13 years in our model incorporates vaccination series that occur from ages 9 through 13 years. Vaccination coverage increases until 2021 due to age and time cohort effects.

Base case vaccination scenarios

- Mid-adult vaccination scenarios - Females and Males
 - ≤ 26 years of age (harmonization)
 - ≤ 30 years
 - ≤ 40 years
 - ≤ 45 years
- Vaccination uptake
 - Females: 2.6% per year
 - Males: 1.9% per year

Economic analysis

- Perspective: Health care sector
- Costs: All direct medical costs[&]
- Outcome Measure: Cost per QALY gained[&]
- Discounting: 3% for costs and benefits
- Time Horizon: 100 years (from onset of program)
- 9-valent vaccination cost/dose (min-max)[£]:
 - ≤18 years, \$205 (176-235)
 - ≥19 years, \$225 (176-235)

QALY=Quality-Adjusted Life-Year

[&]: Description of parameters and references available in extra slides

[£]: Cost per dose, *personal communication Harrell Chesson*

Economic analysis

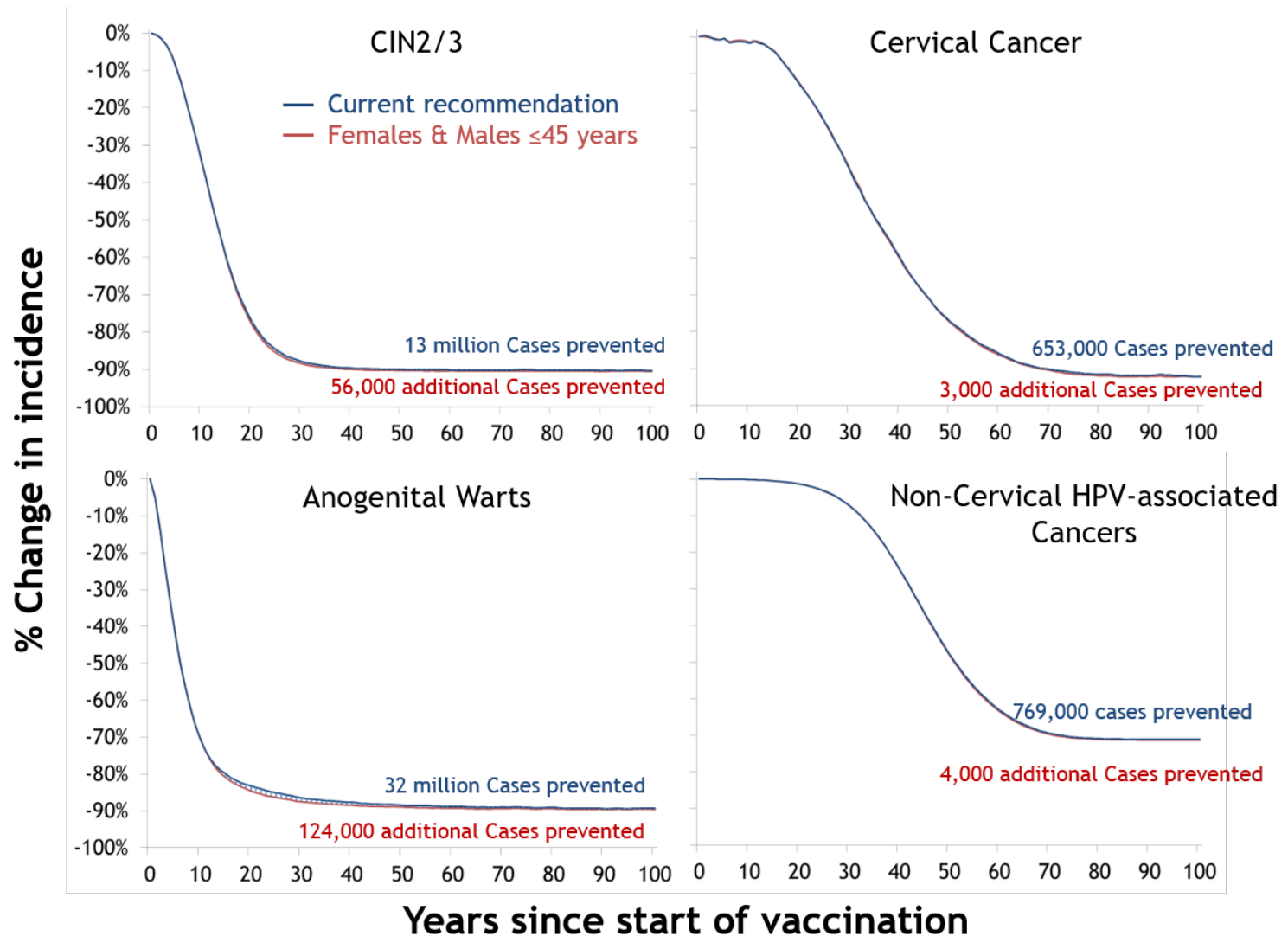
Health care costs (2018 USD)

Disease/Procedure	Base case	Maximum Cost	Standardized Cost ^{&}
Genital warts ^[1]	680	770	860
<u>Screening & treatment</u> ^[2]			
Routine test	129	164	129
Colposcopy/biopsy	583	862	583
CIN 2/3 treatment	3,095	4,872	3,095
<u>Cancers</u> ^[1]			
Cervical	64,800	81,000	72,800
Vulvar	41,300	58,700	51,400
Vaginal	111,400	142,400	116,500
Anal	52,600	78,300	93,600
Oropharyngeal	141,800	166,600	126,500
Penile	22,100	43,300	22,200

Results: Effectiveness

Effectiveness Extended to 45 years vs. Current recommendation

Base case



Why is Mid-adult vaccination predicted to produce small additional reductions in burden?

Number of people vaccinated:

- Number of additional people vaccinated by extending vaccination to mid-adults is small compared to the current program

Herd effects:

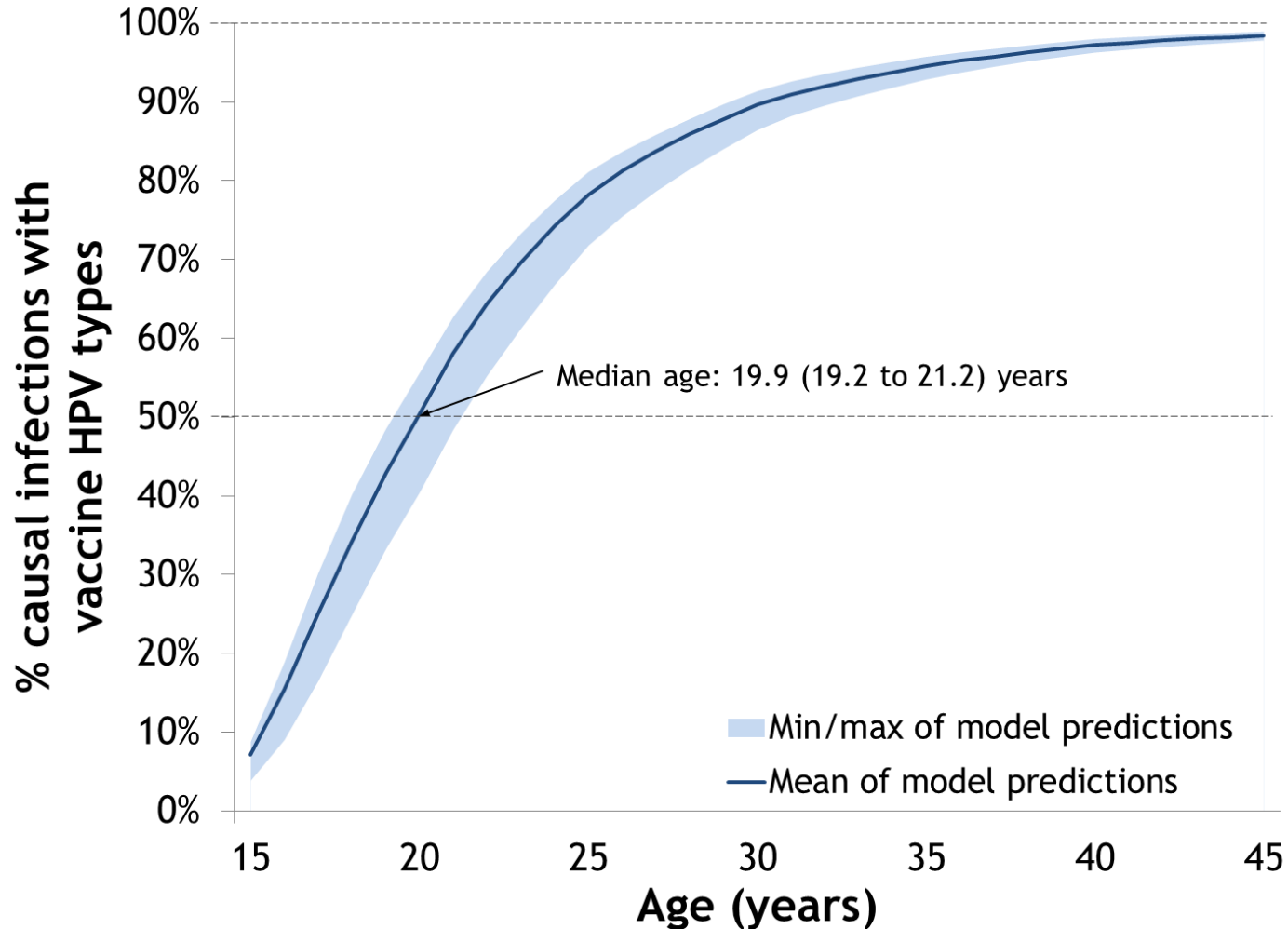
- Current vaccination program is predicted to provide substantial herd effects among unvaccinated adults older than 26 years
 - Incidence of infection and cancer among unvaccinated adults 26-45 years old will decline substantially (due to herd effects)

Age of causal infection:

- Large proportion of cervical cancers are predicted to be caused by an HPV infection acquired before 26 years of age

Cumulative proportion of the age of acquisition of HPV infection that causes cervical cancer

No Vaccination or Screening, HPV-16/18/31/33/45/52/58



Predictions: The solid blue line represents the mean and the shaded area the minimum and maximum of model predictions generated by the 50 best fitting parameter sets

&: Burger (*CID* 2017) predict a median age of 20 years

Results: Cost-effectiveness

Cost-effectiveness Mid-adult vs. Current recommendation

Base case

Scenario	Scenario Comparison	Cost-effectiveness ratio - Median (\$/QALY-gained)	Cost-effectiveness ratio - 90% UI (\$/QALY-gained)
(0) No vaccination			
(1) Current recommendation	1 vs. 0	CS	(CS; 5,000)
(2) Females & Males ≤26 yrs	2 vs. 1	-*	(40,000; -)
(3) Females & Males ≤30 yrs	3 vs. 1	830,000	(104,000; -)
(4) Females & Males ≤40 yrs	4 vs. 1	1,843,000	(339,000; -)
(5) Females & Males ≤45 yrs [¶]	5 vs. 1	1,471,000	(360,000; -)

QALY=Quality-Adjusted Life-Year; UI=Uncertainty Interval; CS=Cost Saving; **Predictions**: Median, and 5th to 95th percentiles (90% UI) of predictions generated with the 50 best fitting parameter sets; **Base case**: 9-valent cost/dose=\$205 in ≤18 year-olds and \$225 in 19-45 year-olds

*: A dash '-' means that no significant gains in QALY could be measured

¶: Dominance of scenario (5) over scenario (4) is likely due to the much greater herd effects of the current vaccination strategy among individuals aged 30-40 years compared to those aged >40 years. Lower herd effects among older mid-adults result in greater potential for benefits.

Cost-effectiveness Mid-adult vs. Current recommendation

Base case - Stratified by natural history parameters

Scenario	Scenario Comparison	All parameter sets (N=50) (\$/QALY-gained)	Faster progression & lower natural immunity ^{&} (n=22) (\$/QALY-gained)	Slower progression & higher natural immunity (n=28) (\$/QALY-gained)
(0) No vaccination				
(1) Current recommendation	1 vs. 0	CS	CS	CS
(2) Females & Males ≤26 yrs	2 vs. 1	-*	178,000	-
(3) Females & Males ≤30 yrs	3 vs. 1	830,000	404,000	2,308,000
(4) Females & Males ≤40 yrs	4 vs. 1	1,843,000	973,000	2,909,000
(5) Females & Males ≤45 yrs	5 vs. 1	1,471,000	1,047,000	1,592,000

CE=cost-effectiveness; QALY=Quality-Adjusted Life-Year; **Predictions**: Median of predictions; **Base case**: 9-valent cost/dose=\$205 in ≤18 year-olds and \$225 in 19-45 year-olds

[&]: Parameter sets that have lower probability of natural immunity following clearance in females (≤ 35% vs > 35%) and faster progression to CIN2/3 (26 months vs 30 months)

*: A dash '-' means no significant gains in QALY could be measured

Sensitivity Analysis Cost-effectiveness through age 30 years

Mid-adult vs. Current recommendation - Vaccination parameters

Scenario	All parameter sets (N=50) (\$/QALY-gained)	Fast progression & low natural immunity ^{&} (n=22) (\$/QALY-gained)	Slower progression & higher natural immunity (n=28) (\$/QALY-gained)
Base case	830,000	404,000	2,308,000
High catch-up coverage	747,000	507,000	1,487,000
Low historical vaccination coverage [£]	336,000	318,000	410,000
Stopping mid-adult catch-up after 40 years	616,000	296,000	1,697,000
Low vaccine efficacy [¶]	481,000	366,000	835,000

QALY=Quality-Adjusted Life-Year; **Predictions**: Median result; **Base case**: 9-valent cost/dose=\$225 in 19-45 year-olds; **&**: Parameter sets that have lower probability of natural immunity following clearance in females and faster progression to CIN1/2/3; **£**: 75% of base case vaccination uptake rates for historical coverage; **¶**: Vaccine efficacy is assumed to be 85% against persistent infections for all HPV types included in the vaccine. Lower vaccine efficacy produces lower cost-effectiveness ratios for mid-adult vaccination (vs current recommendations) because it results in fewer benefits and less herd effects under the current recommendations, thus allowing for greater mid-adult vaccination benefits.

Sensitivity Analysis Cost-effectiveness

through age 30 years

Mid-adult vs. Current recommendation - Economic parameters

Scenario	All parameter sets (N=50) (\$/QALY-gained)	Faster progression & lower natural immunity ^{&} (n=22) (\$/QALY-gained)	Slower progression & higher natural immunity (n=28) (\$/QALY-gained)
Base case	830,000	404,000	2,308,000
Vaccine cost/dose			
• \$176	644,000	310,000	1,775,000
• \$235	867,000	423,000	2,417,000
Max health care costs [§]	821,000	395,000	2,253,000
Max Burden of disease [§]	753,000	317,000	1,211,000
Disutility in cervical cancer survivors [*]	499,000	276,000	658,000
Standardized economic parameters	829,000	402,000	2,302,000

QALY=Quality-Adjusted Life-Year; **Predictions**: Median result; **Base case**: 9-valent cost/dose=\$225 in 19-45 year-olds;

[&]: Parameter sets that have lower probability of natural immunity following clearance in females and faster progression to CIN1/2/3

[§]: Maximum estimates from the US literature

^{*}: We assume a permanent 0.24 yearly disutility for cervical cancer survivors in this scenario (0 disutility after 5 yrs in the base case)

Discussion: Strengths & Limitations

Strengths

- HPV-ADVISE calibrated to highly stratified U.S. data
 - HPV-ADVISE is calibrated to represent country-specific sexual behaviour, HPV epidemiology, health care resource use and cervical cancer screening
- HPV-ADVISE validated with post-vaccination U.S. data
 - Predictions are consistent with age-specific post-vaccination HPV infection and Anogenital warts diagnosis prevalence data from the U.S.^[1]
 - HPV-ADVISE has also been validated to post-vaccination data in Australia^[2]
- Predictions are made using 50 parameter sets
 - Captures uncertainty in the natural history of HPV infection and related diseases, and variability in sexual behaviour data
 - Results in wide uncertainty intervals, reflecting that results are highly sensitive to natural history assumptions and lack of data among mid-adults
- Sensitivity analyses were performed on key parameters

Limitations of examining mid-adult vaccination

- Long term herd effects of vaccinating younger age cohorts on mid-adult women and men remain uncertain
 - If HPV-ADVISE overestimates herd effects of current program, our results may overestimate the cost-effectiveness ratios of vaccinating mid-adult men and women
 - However, our model reproduces short term post-vaccination herd effects
- Time to lesions & level of natural immunity after infection remains uncertain
 - Model predictions are very sensitive to these natural history parameters
- Relative progression of a re-infection or new infection in mid-adults (vs younger adults) is unknown
 - HPV-ADVISE assumes that progression is independent of age
 - However, it has been suggested that a proportion of re-detection is due to deposition^[1], and that new infections later in life have a smaller risk of progressing to cervical cancer^[2,3]
 - If this is the case, mid-adult vaccination would produce lower benefits and higher cost-effectiveness ratios
- Screening recommendations are changing in the U.S.
 - If changes to screening result in more effective cervical cancer prevention, mid-adult vaccination would produce lower benefits and higher cost-effectiveness ratios

Summary Effectiveness & Cost-effectiveness predictions

- Current HPV vaccination program:
 - Predicted to reduce the HPV-burden of disease substantially
 - E.g., 82% reduction in anogenital wart diagnoses and 59% of cervical cancer cases over 100 years
 - Likely cost-saving (vs. no vaccination)
- Extending vaccination to 45 year old females and males:
 - Predicted to produce small additional reductions in HPV burden of disease
 - E.g., additional 0.2-0.4 percentage point reduction in anogenital warts diagnoses and cervical cancer cases
 - Results in cost-effectiveness ratios \geq \$360,000 per QALY-gained in 95% of model simulations under base case assumptions (median=\$1.5 million)&
- The cost-effectiveness of mid-adult vaccination is highly sensitive to:
 - Level of natural immunity after infection & rate of progression to cervical lesions
 - Historical vaccination coverage

&: median cost per QALY-gained of extending vaccination to 30 year olds = \$830,000; 95% of simulations \geq \$104,000 per QALY-gained

Thank you!