

# Population-level effectiveness & cost-effectiveness of 2 vs 3 doses of HPV vaccine

Marc Brisson

Canadian Research Chair Modeling Infectious Diseases  
Associate Professor, Université Laval



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# Modeling Team

## Université Laval

- Jean-François Laprise
- Mélanie Drolet
- Talia Malagon
- Philippe Lemieux-Mellouki

## McGill University

- Eduardo Franco

## Québec Public Health

- Chantal Sauvageau

## Imperial College

- Marie-Claude Boily

## Public Health England

- Mark Jit

# HPV vaccines

- Bivalent (Cervarix®)
  - Protects against HPV-16/18 infection and associated lesions
  - Potential cross-protection against non-vaccine HPV-types (31/33/45/52/58)<sup>1-3</sup>
- Quadrivalent (Gardasil®)
  - Protects against HPV-6/11/16/18 infection and associated lesions
  - Evidence of lower cross-protection than the bivalent<sup>1-3</sup>

# Context

- Most high-income countries are using the quadrivalent HPV vaccine
- All HPV vaccination programs target pre-adolescent girls
  - A few countries include boys (e.g., US, Australia & Switzerland)
- Recently, many countries have switched from a 3-dose to a 2-dose vaccine schedule
  - Switzerland, Netherlands, Mexico, UK & Canada provinces
  - WHO has recommended a 2-dose schedule for girls aged 9-14 years<sup>1</sup>

# 2-dose HPV vaccine efficacy

## What we know

- 2 doses of bivalent vaccine as protective as 3 doses against persistent HPV-16/18 infection in the 1<sup>st</sup> year after vaccination
  - post-hoc, non-randomised, analysis<sup>1</sup>
- 2 doses of quadrivalent vaccine in 9-13 year olds as immunogenic as 3 doses in 16-26 year olds after 36 months<sup>2</sup>
- 2 doses of bivalent vaccine in 9-14 year olds is as immunogenic as 3 doses in 15-25 year olds after 24 months<sup>3</sup>

## What we don't know

- Long-term protection is unknown
- Cross-protection is unknown
  - Cross-neutralising antibody titres after 3 doses are found at much lower levels in the serum and cervicovaginal secretions than vaccine-type titres

# Main criteria considered when making immunization recommendations

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

# Objectives

Use mathematical modeling to examine the potential population-level impact and cost-effectiveness of:

- Reduced HPV vaccine dose schedules

# Model Overview - HPV-ADVISE

- **Model type:** Individual-based transmission-dynamic model<sup>&</sup>
- **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



# 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 data:

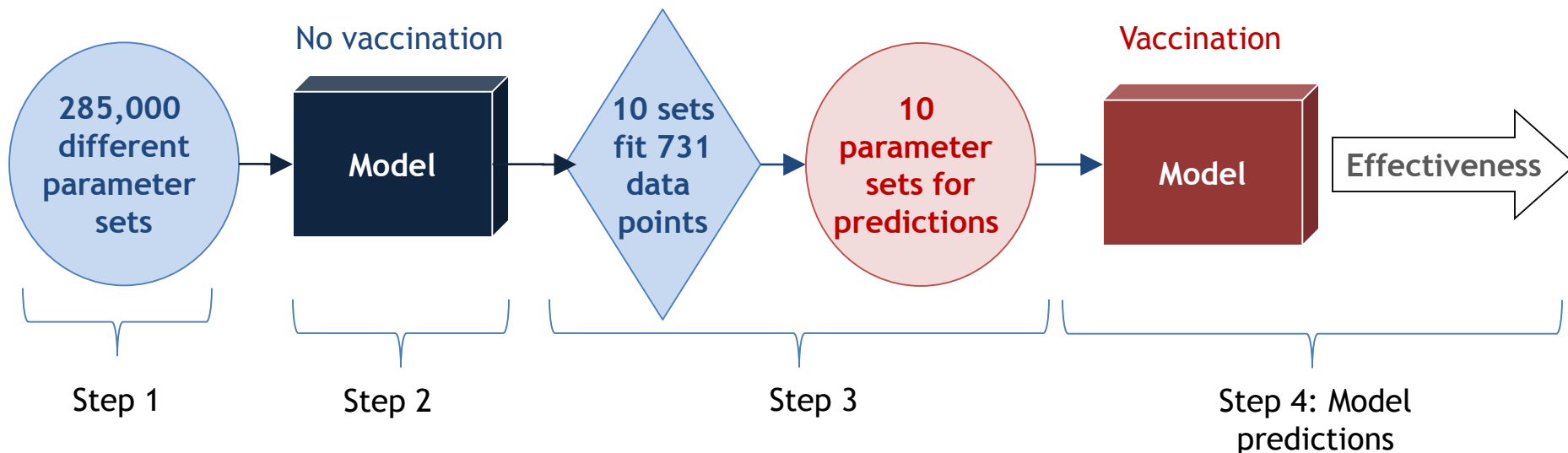
- Sexual & screening behaviour (stratified by gender and age)
- HPV prevalence (stratified by HPV type, gender, age and sexual activity)
- Incidence of AGW, cervical lesions, cervical cancer and other HPV-related cancers (stratified by HPV type, gender, and age)<sup>&</sup>
- Total of 731 data points fitted

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

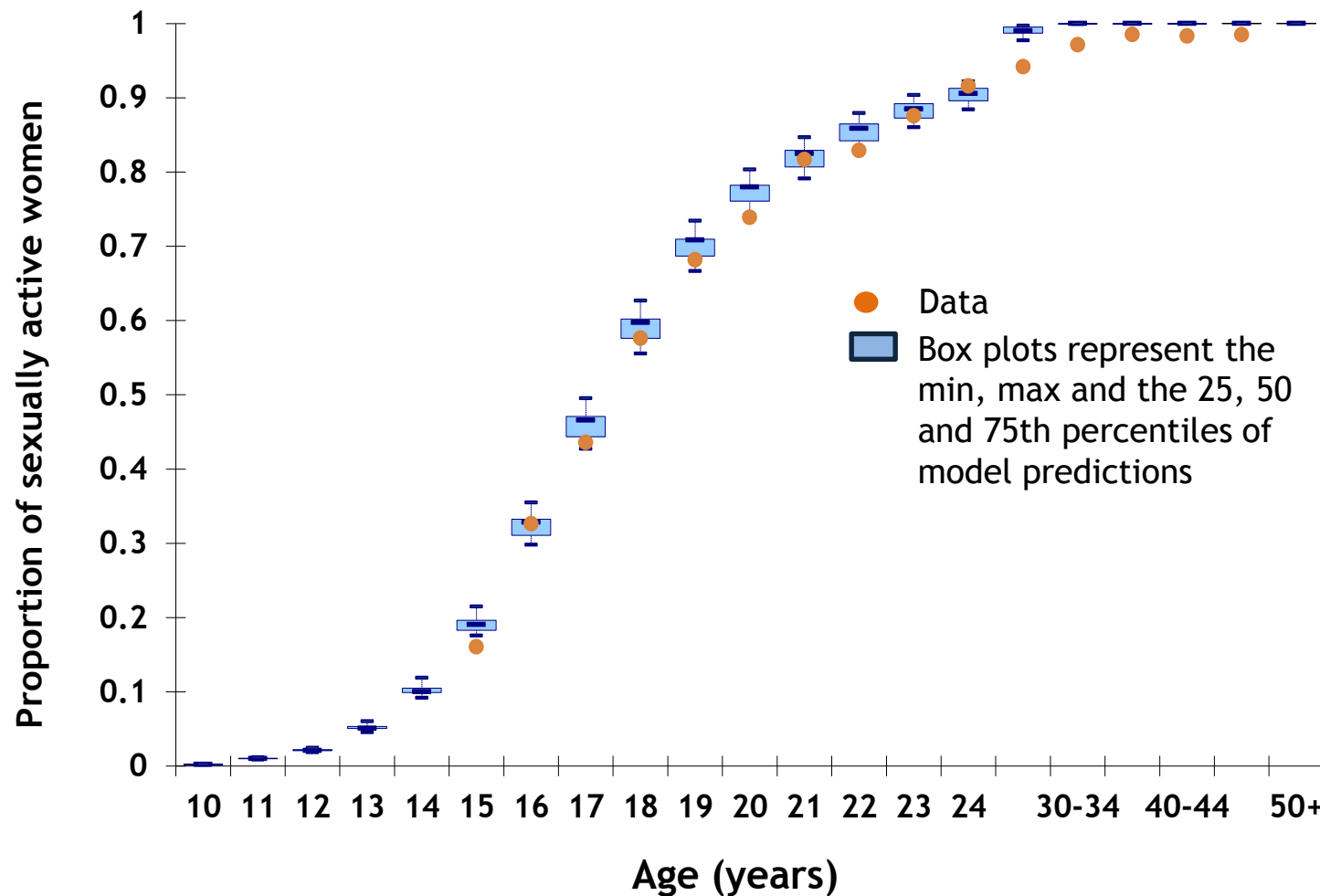
# Model Fit Results

- 285,000 different combinations of parameters sampled from the prior parameter distributions
- 10 parameter sets produced model results within the 731 pre-specified data targets



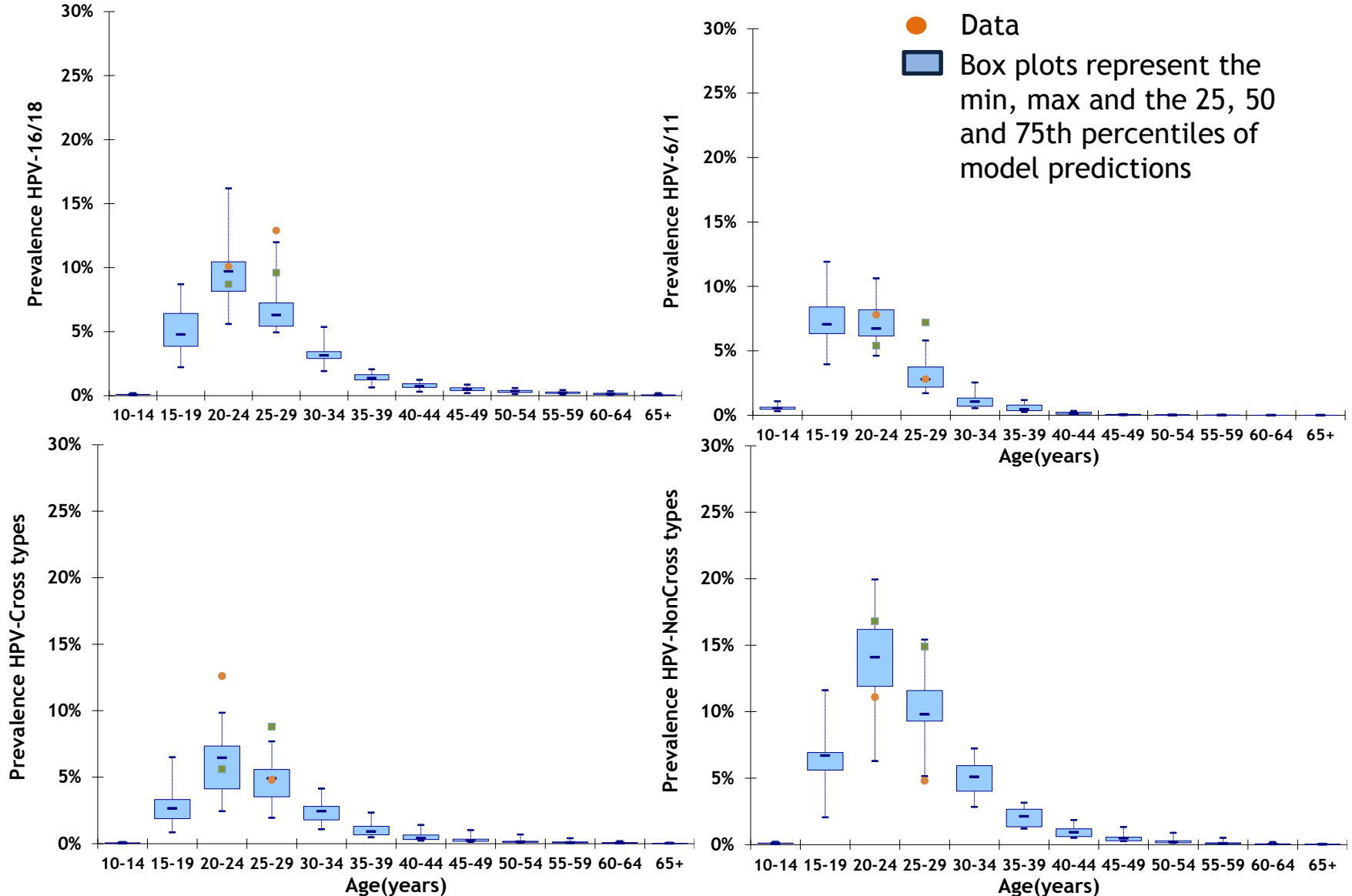
# Model fit - Sexual behaviour

Example: Proportion sexually active women



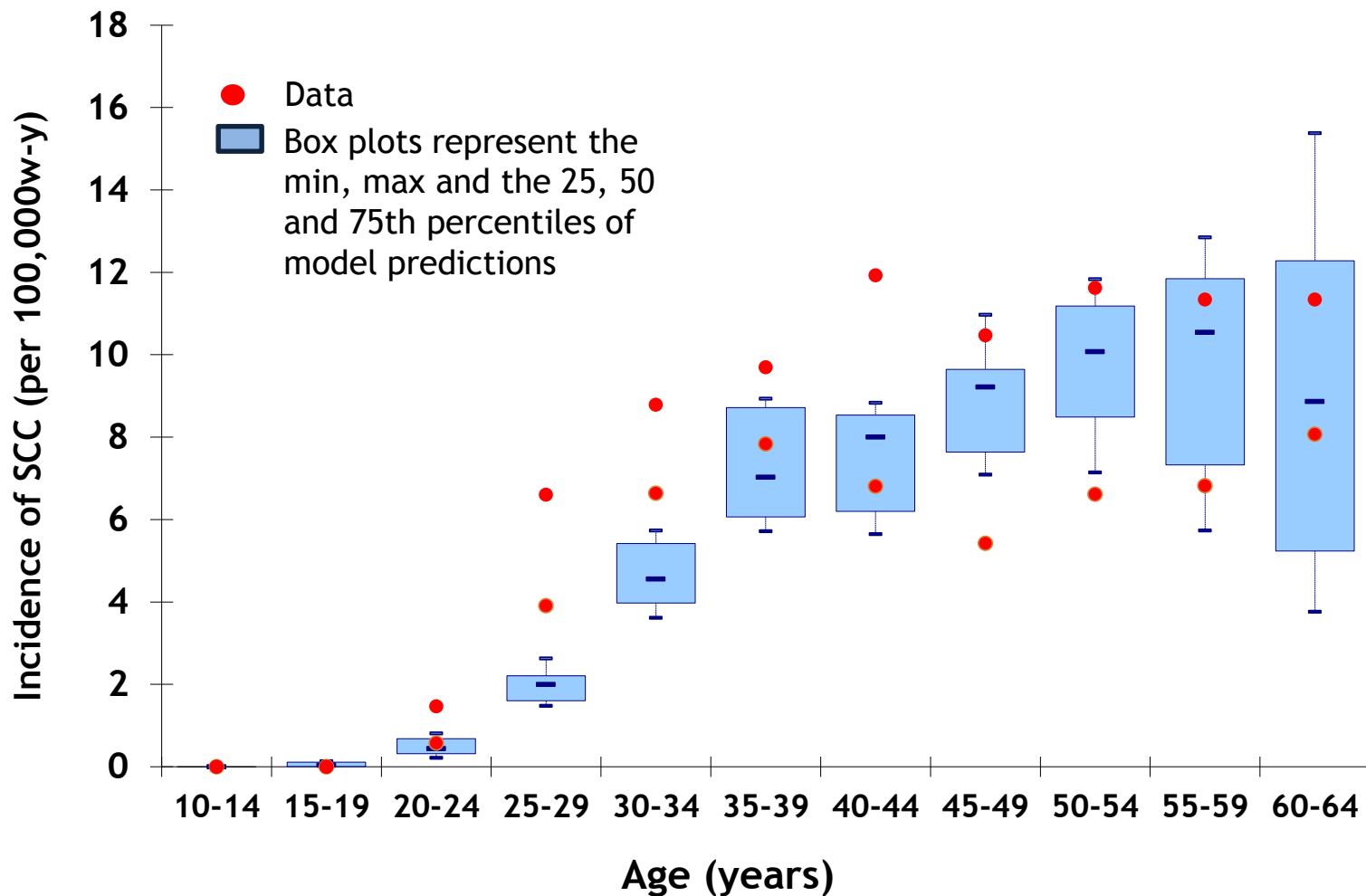
# Model fit - HPV prevalence in women

Example: Prevalence for sexual activity level 1 by age and type

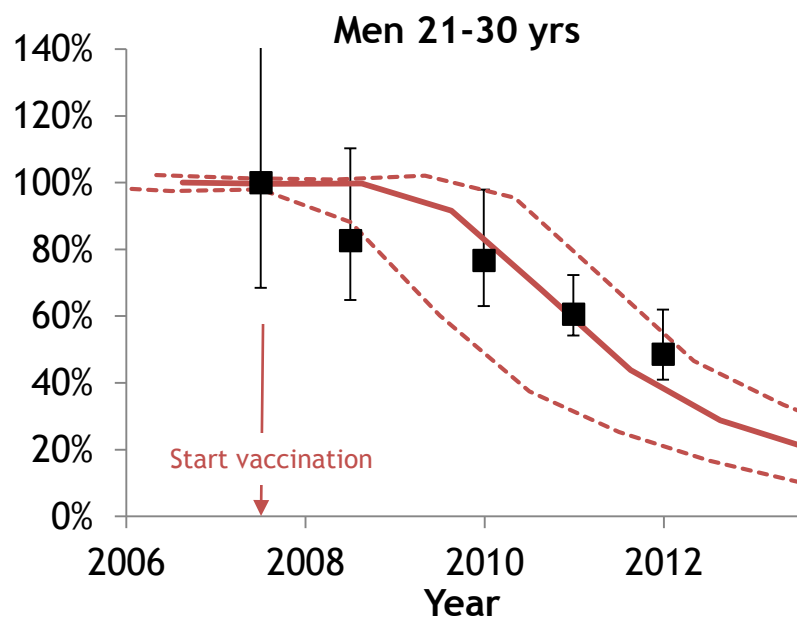
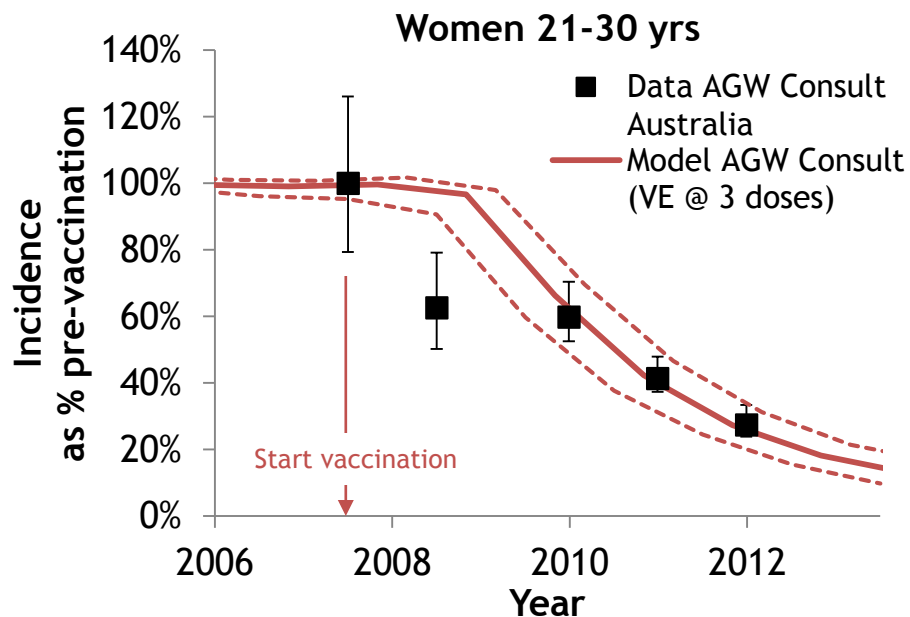
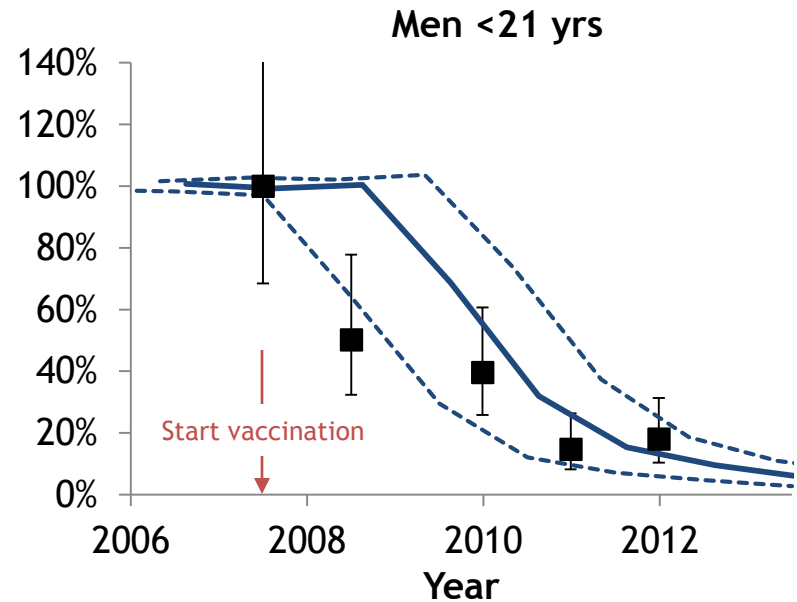
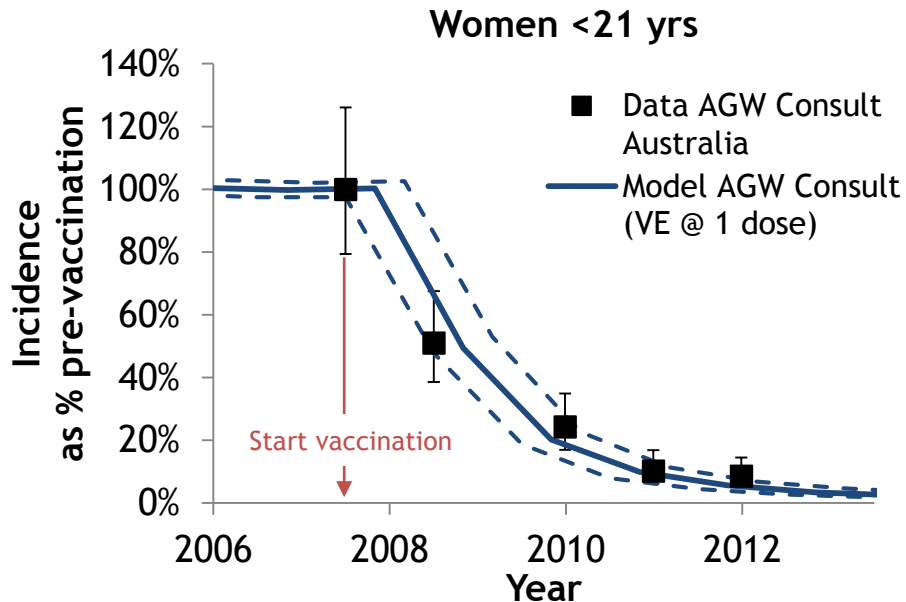


# Model fit - Squamous cell carcinoma (SCC)

## Example: Incidence of SCC



# HPV-ADVISE External/predictive validation - Australia



# REDUCED HPV VACCINE DOSES

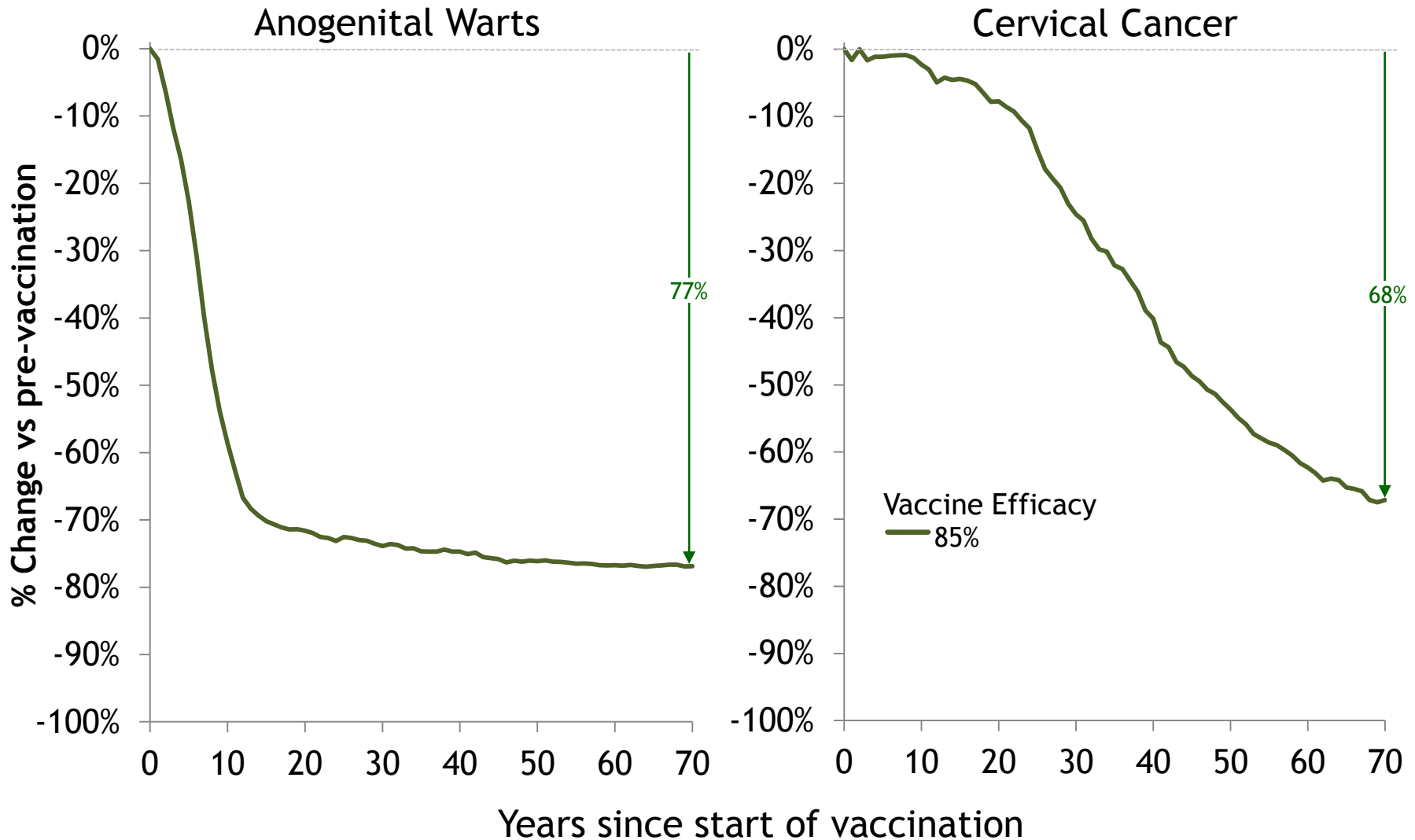
## EFFECTIVENESS

Key questions:

What vaccine characteristics are most important when considering reducing doses?

# Effectiveness Impact of vaccine efficacy

Girls-only, Quadrivalent, Coverage=80%<sup>&</sup>, Vaccine duration=Lifelong, Cross-protection

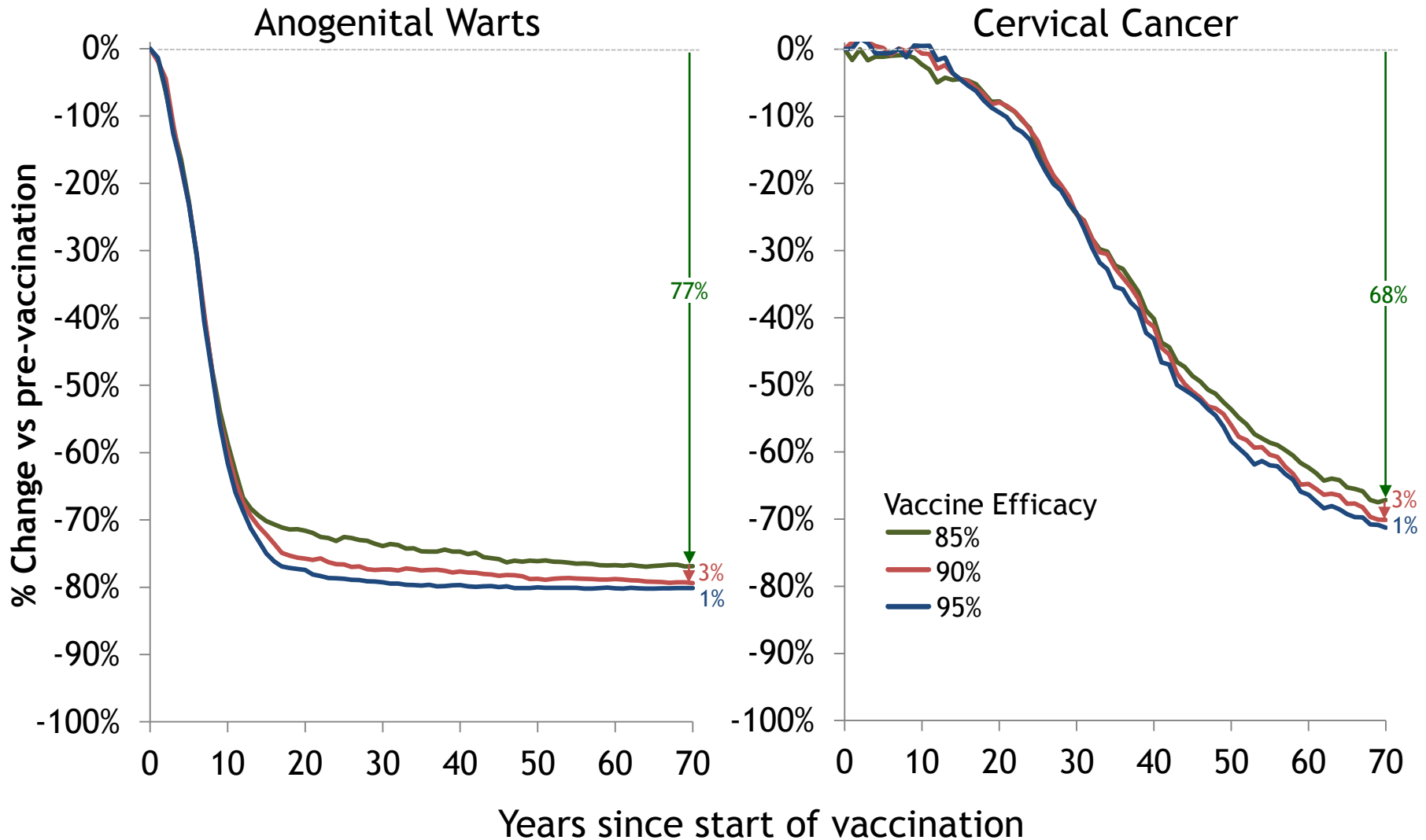


<sup>&</sup>. Population-level effectiveness is relatively insensitive to vaccine efficacy between 85-100%, when vaccination coverage > 50% (Van de Velde, *JNCI* 2012)



# Effectiveness Impact of vaccine efficacy

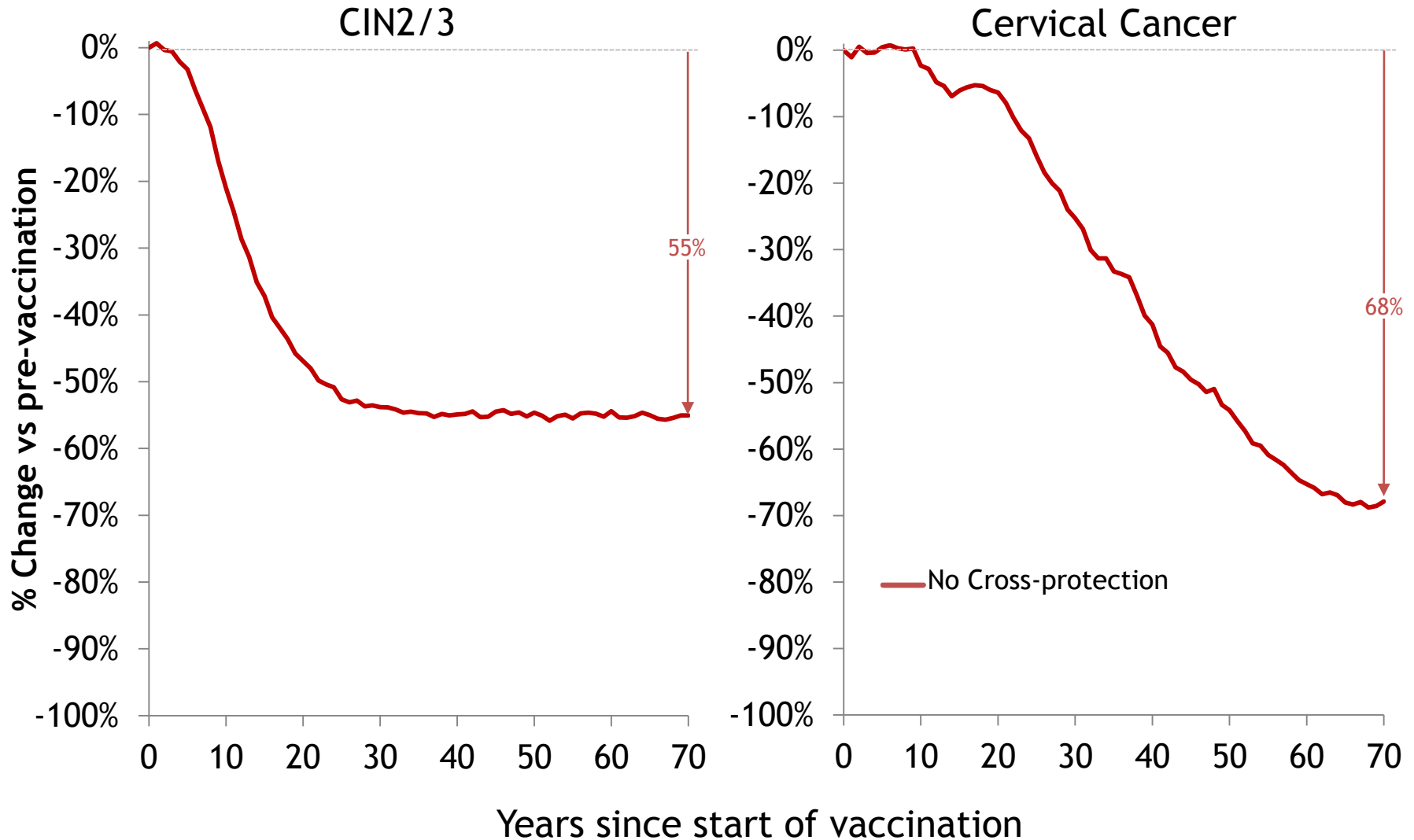
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# Effectiveness **Impact of cross-protection**

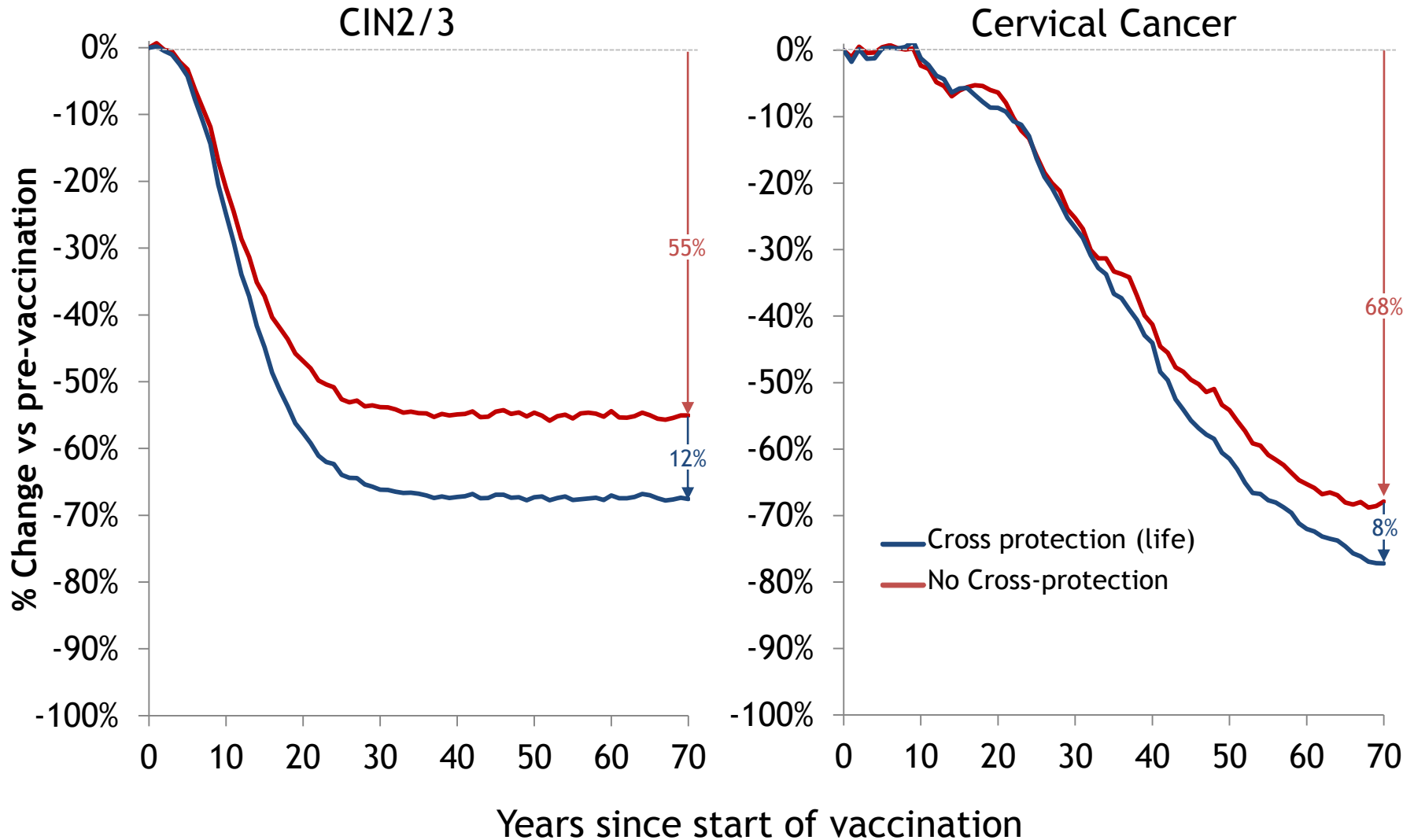
Girls-only, Quadrivalent, Coverage=80%, Vaccine duration=Lifelong, VE=95%, Cross-protection=persistent infection<sup>‡</sup>



<sup>‡</sup>. Malagon, *Lancet Infect Dis* 2012

# Effectiveness Impact of cross-protection

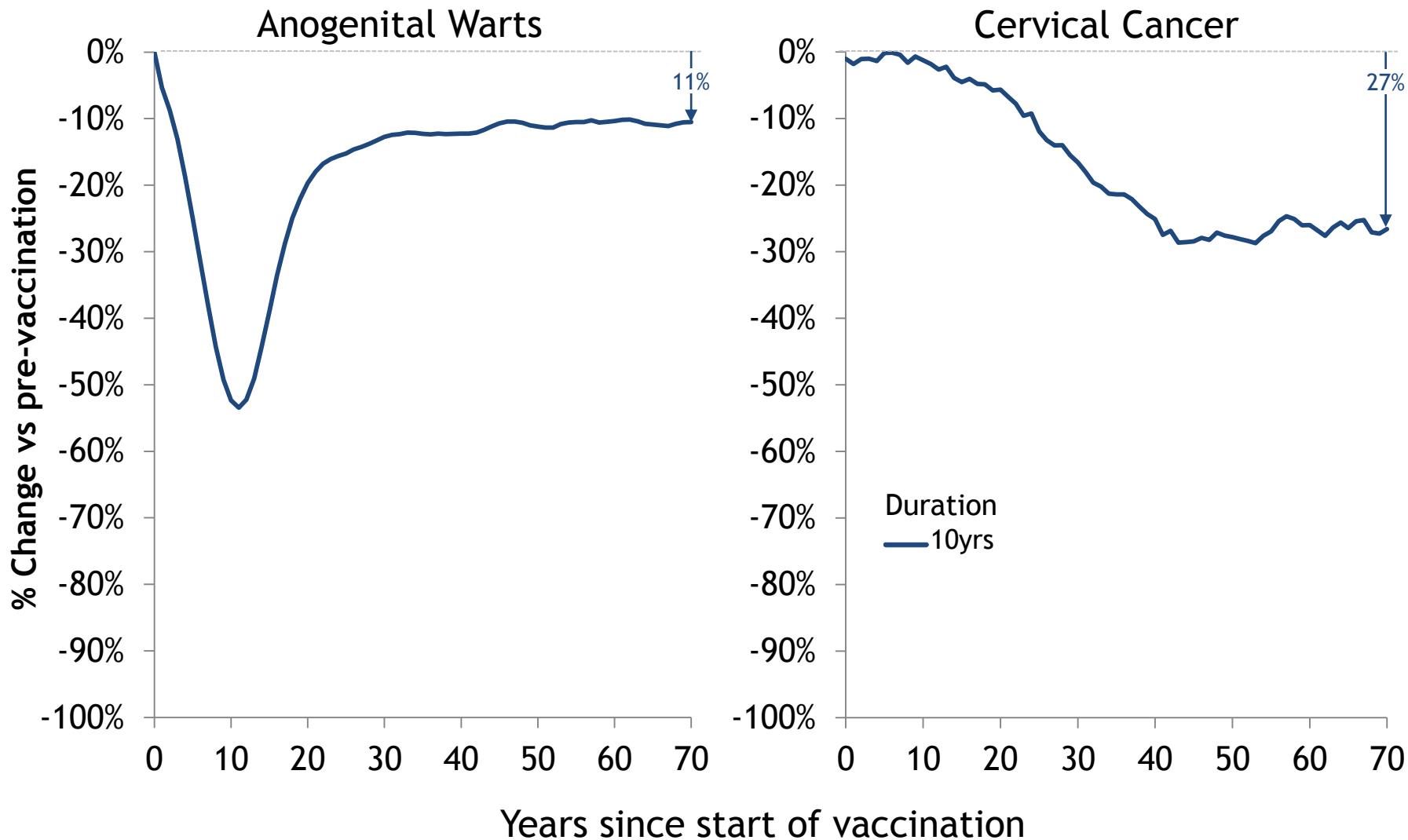
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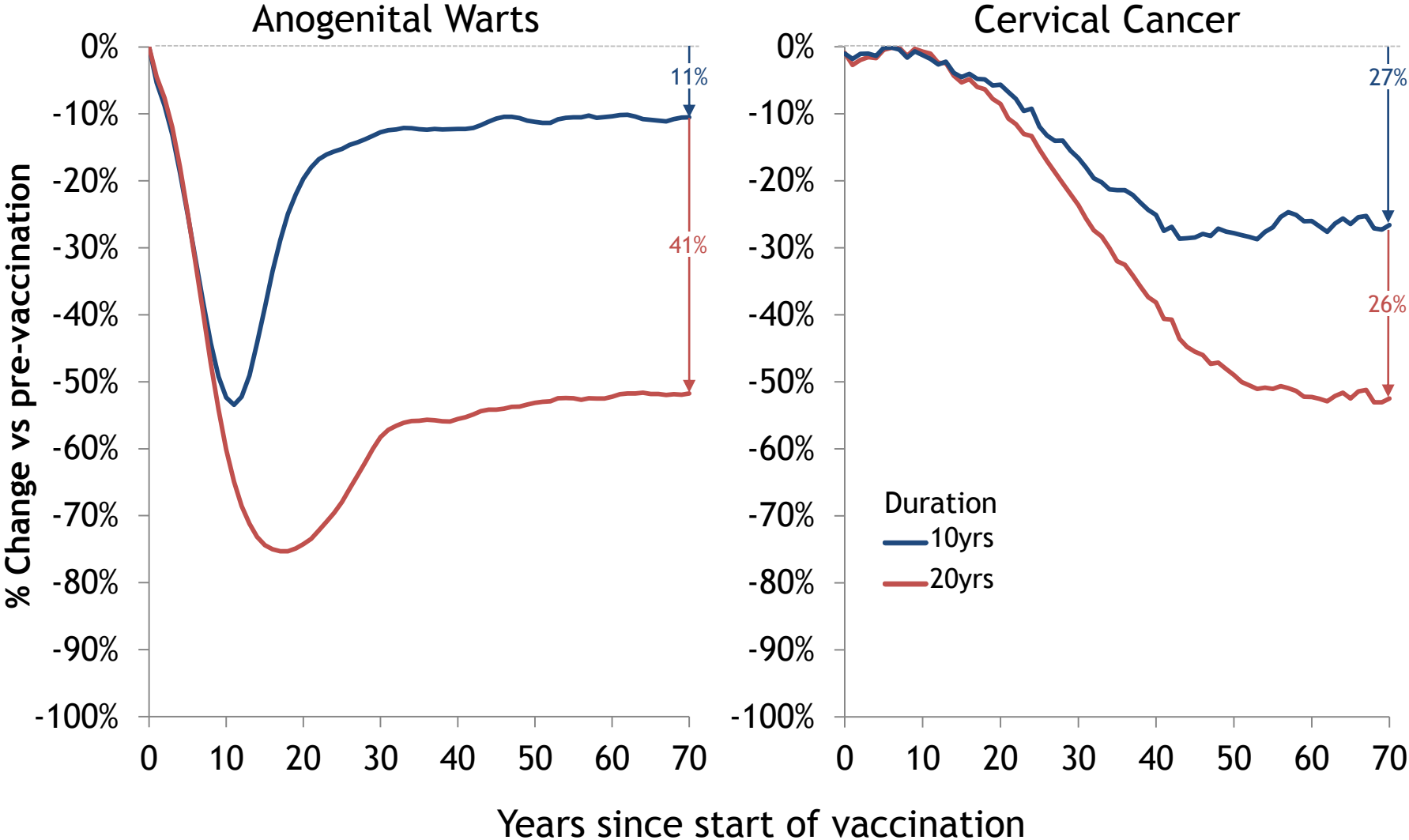
# Effectiveness **Impact of duration**

Girls-only, Quadrivalent, Coverage=80%, VE=95%, Cross-protection



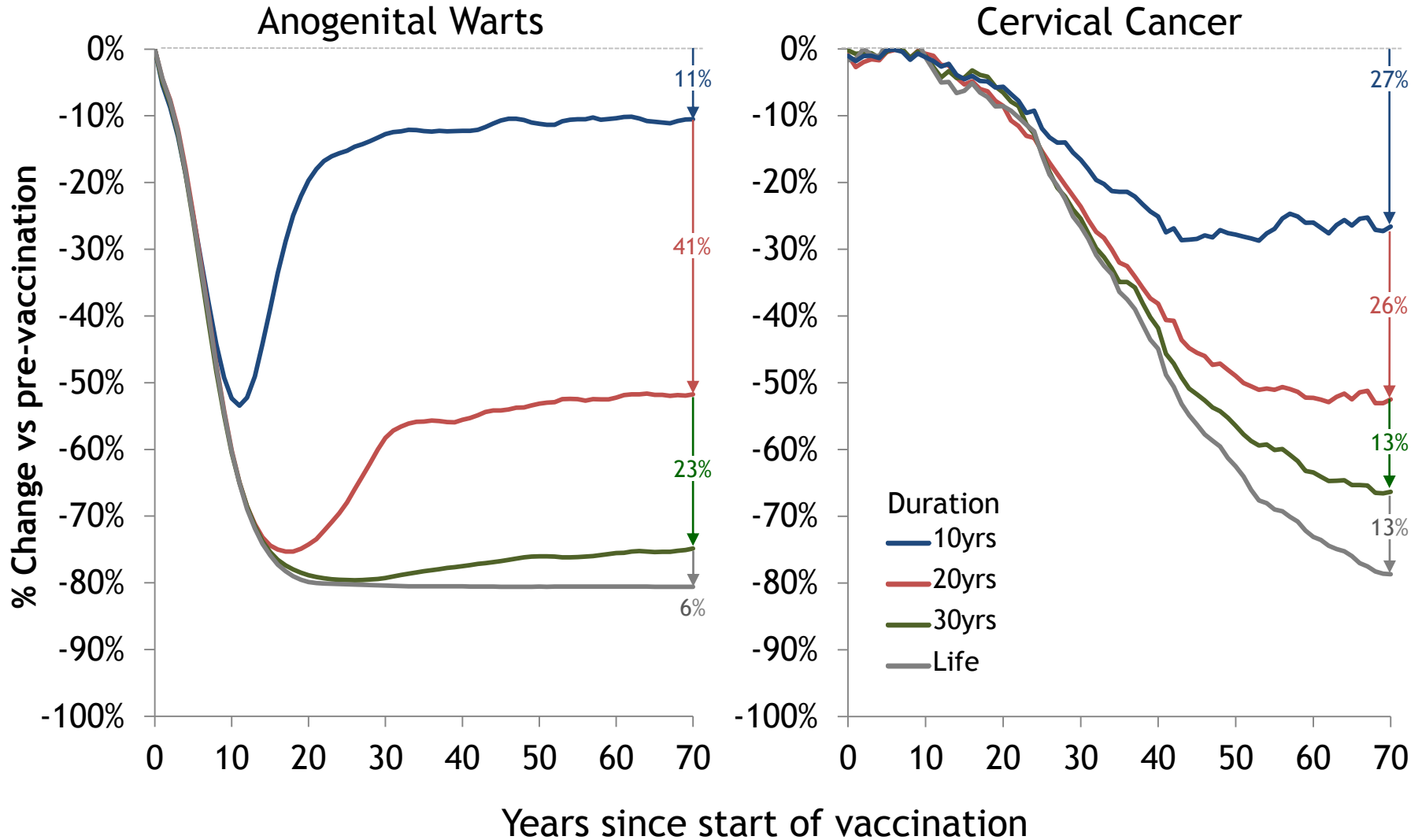
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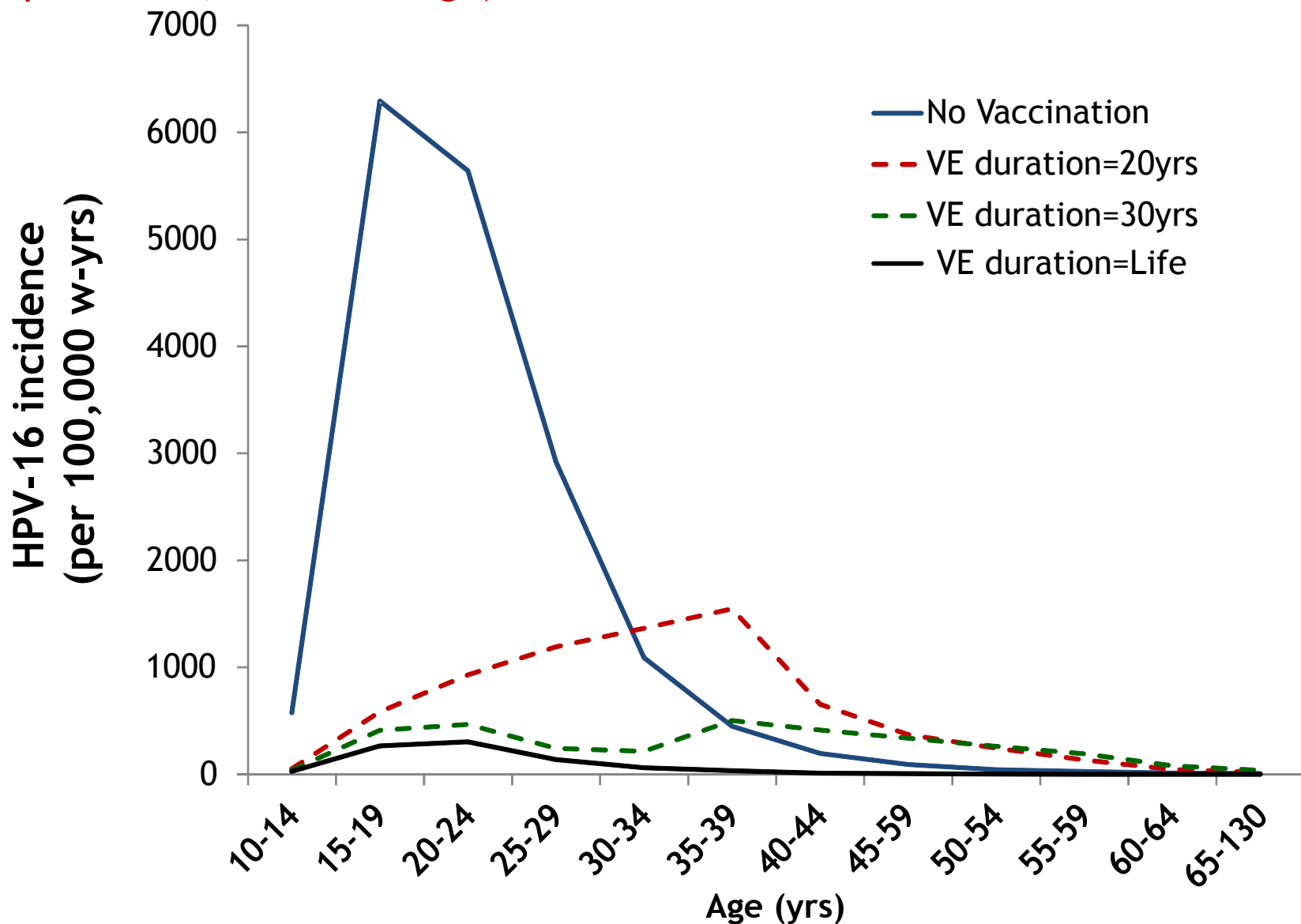
# Effectiveness **Impact of duration**

Girls-only, Quadrivalent, Coverage=80%, VE=95%, Cross-protection



# Impact of duration of protection

HPV-16 incidence rate by age and duration of protection (post-vaccination equilibrium, 80% coverage)



# Summary - Effectiveness

- **Reduced dose schedules can substantially decrease HPV-burden if they provide > 20 yrs protection**
  - Protection must be maintained during peak years of sex activity
  - Conclusions consistent between HPV-ADVISE and UK model<sup>1</sup>
  - Results likely generalizable to Australia due to similar sexual behavior<sup>2</sup>, HPV epidemiology and high vaccine coverage<sup>3</sup>
- **Effectiveness relatively insensitive to vaccine efficacy**
  - Results suggest similar vaccine efficacy for 2 & 3 doses<sup>4,5</sup>
  - Herd effects likely to mitigate any differences in efficacy



# REDUCED HPV VACCINE DOSES

## COST-EFFECTIVENESS

Key questions:

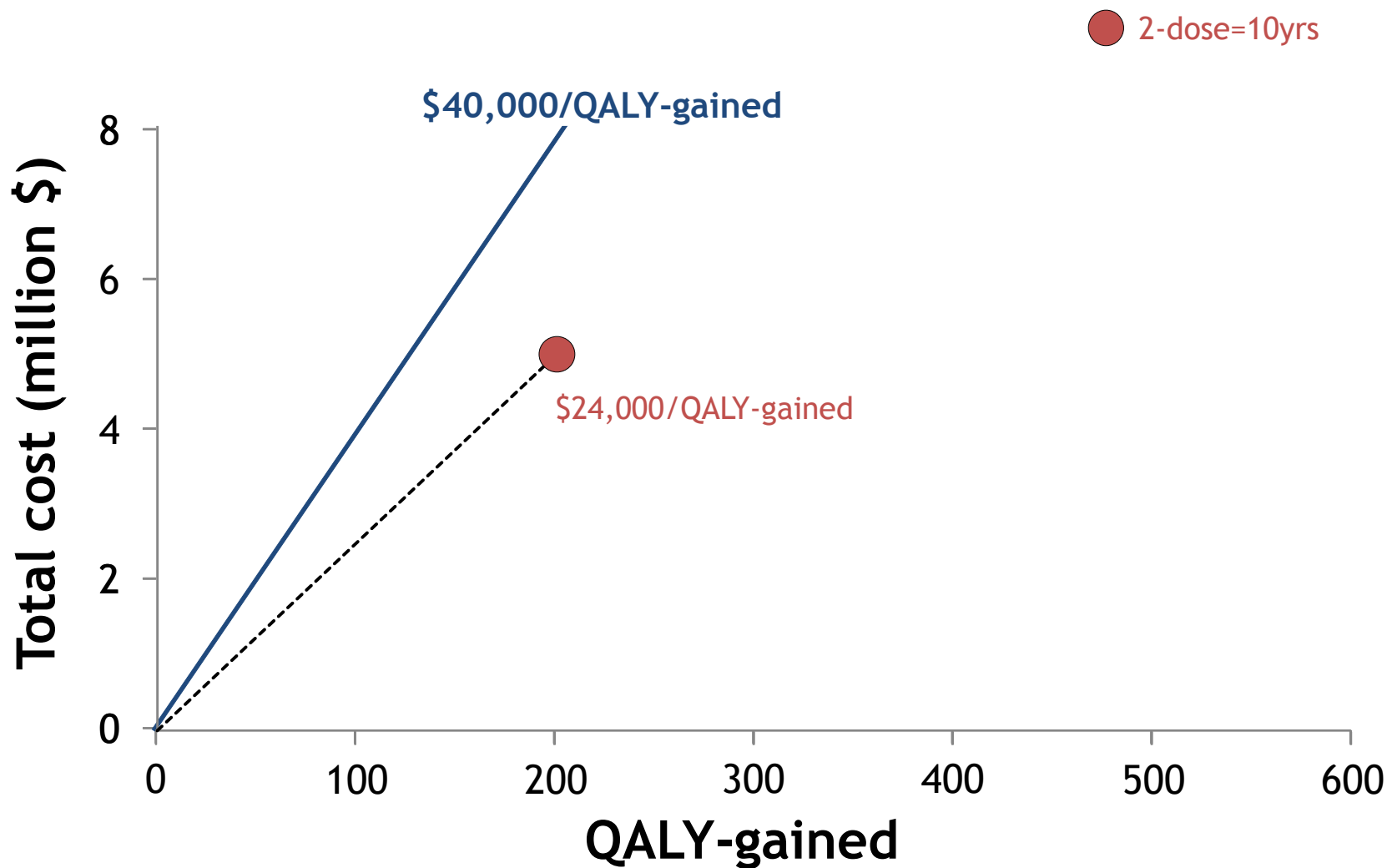
How long does 2-dose protection have to be to make the 3<sup>rd</sup> dose cost-ineffective ?

# Economic Analysis

- Perspective: Health care provider
- Outcome Measure: Cost per QALY gained
- Discounting: 3% for costs and benefits
- Time Horizon: 70 years  
(life expectancy of 1<sup>st</sup> cohort vaccinated)
- Vaccine Cost/dose: \$85
- Cost-effectiveness: \$40,000 per QALY-gained  
threshold

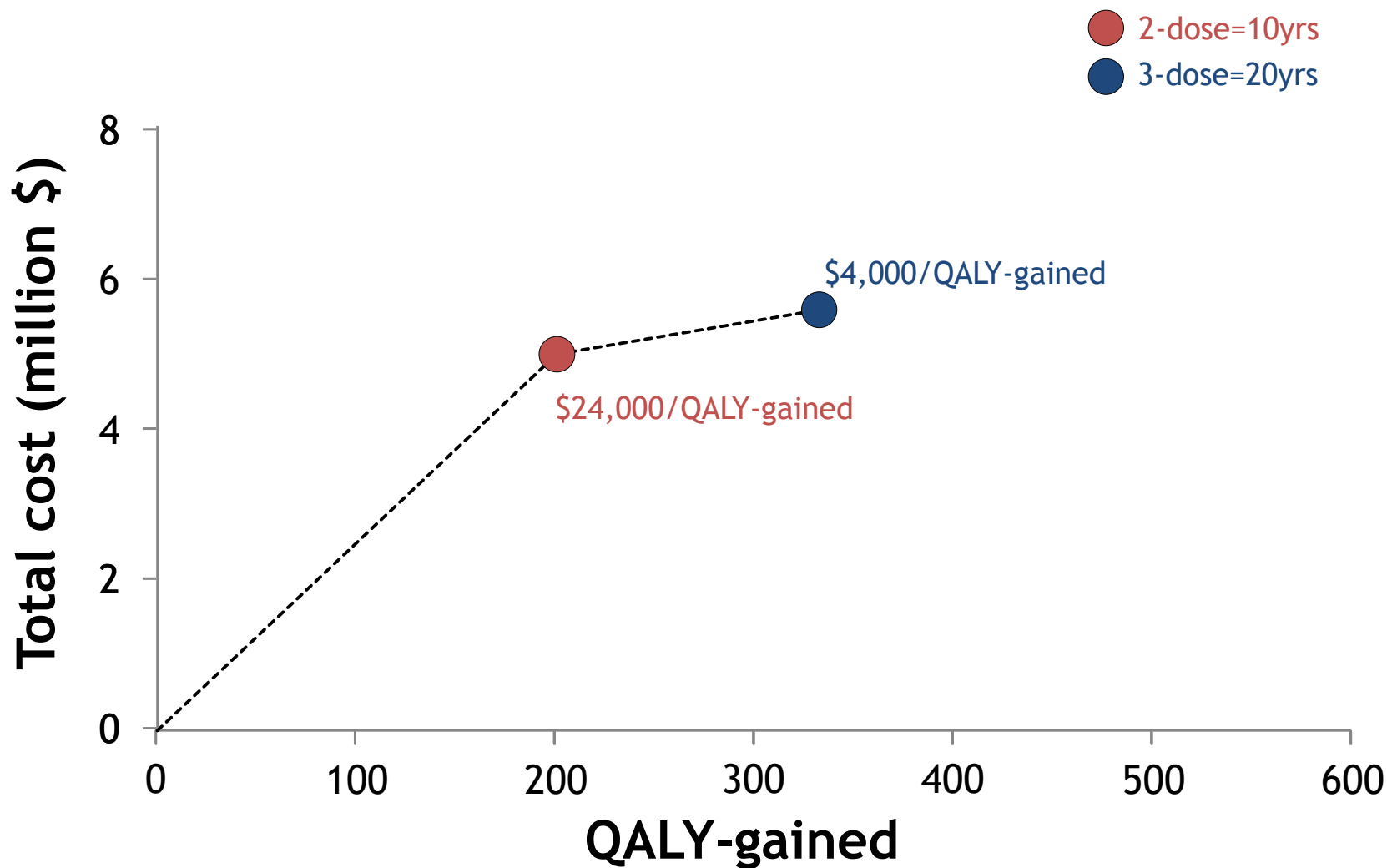
# Cost-effectiveness 2-dose duration=10yrs

Girls-only, Quadrivalent, Coverage=80%, VE=95%, Cross-protection Cost/dose=\$85



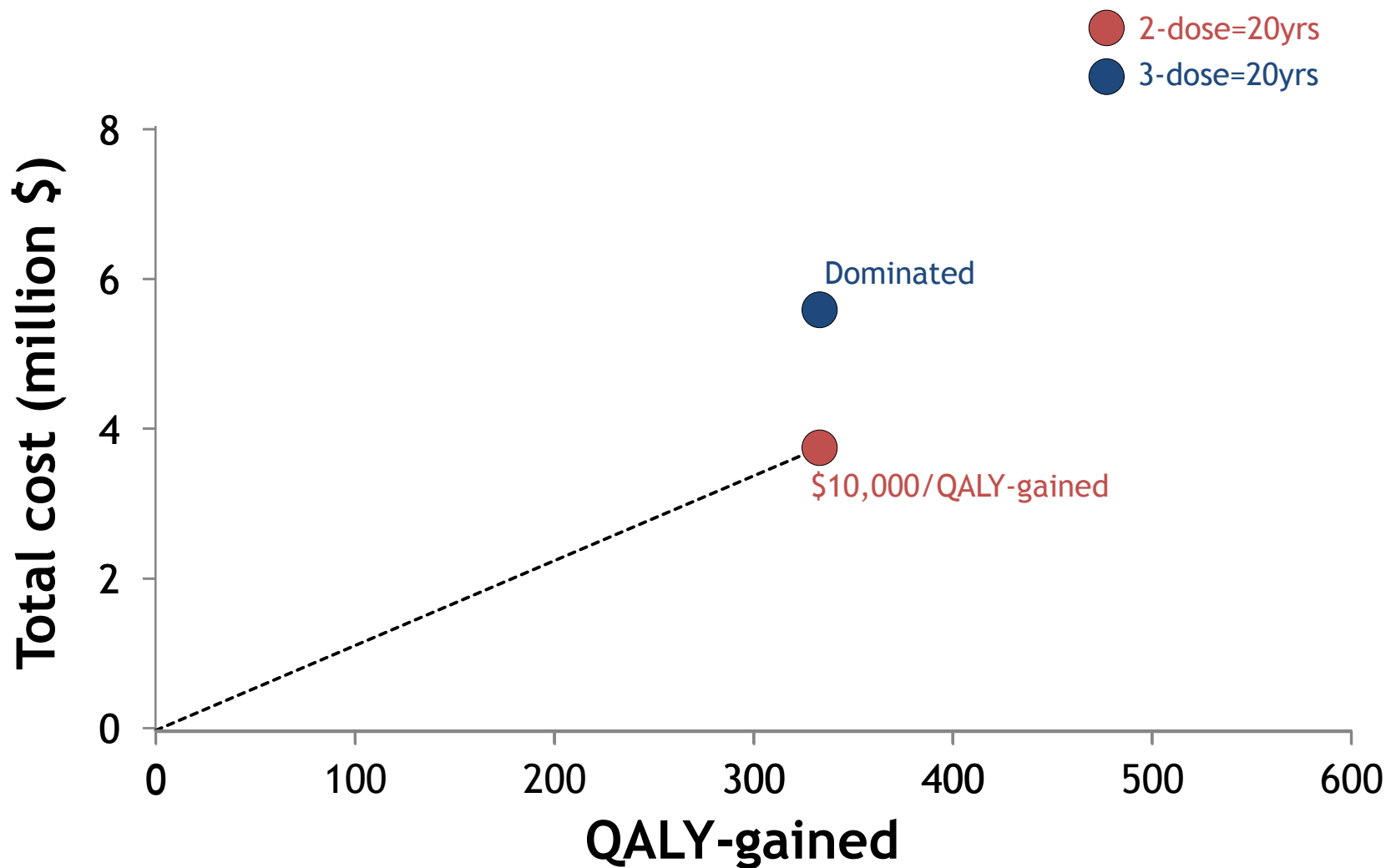
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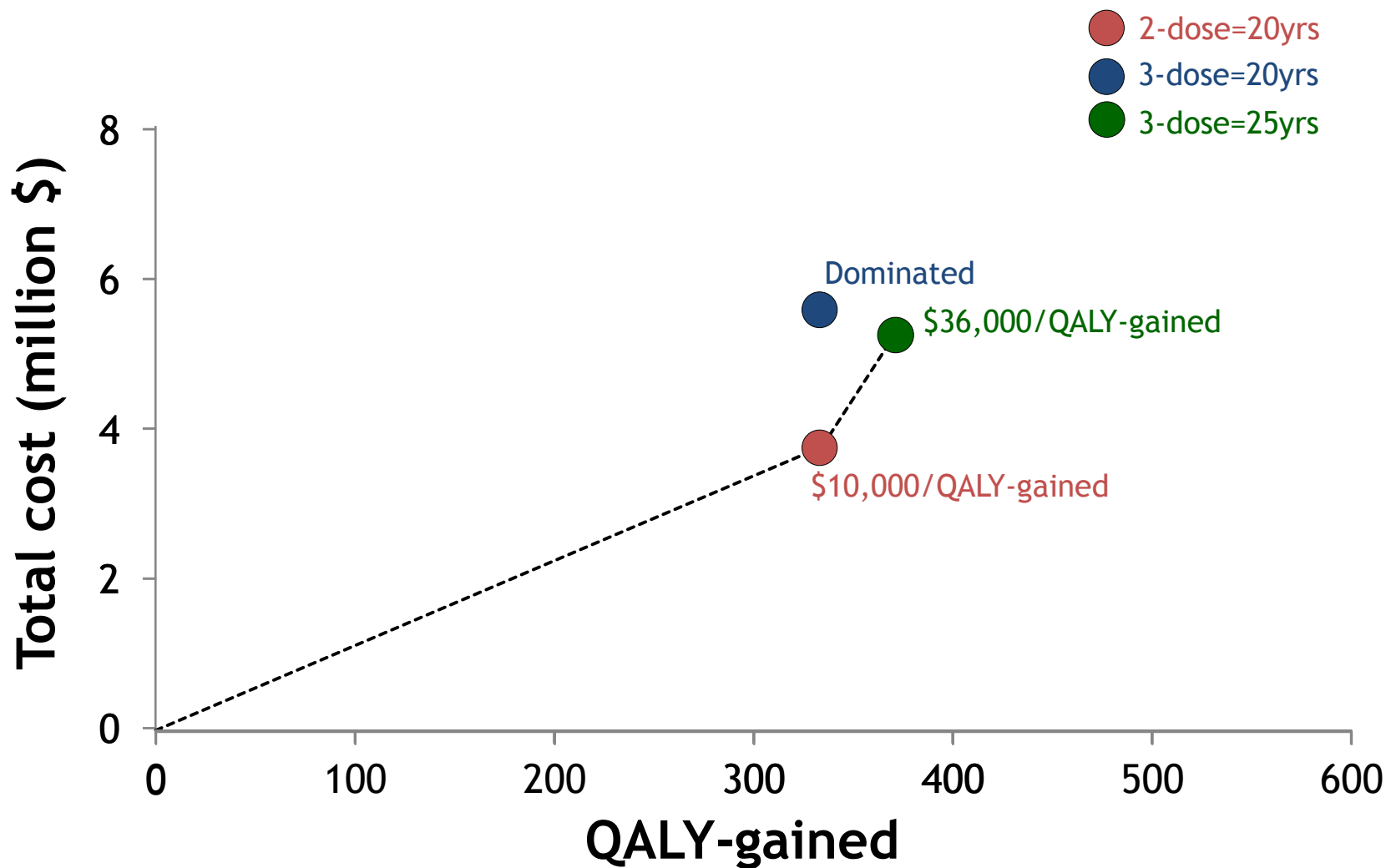
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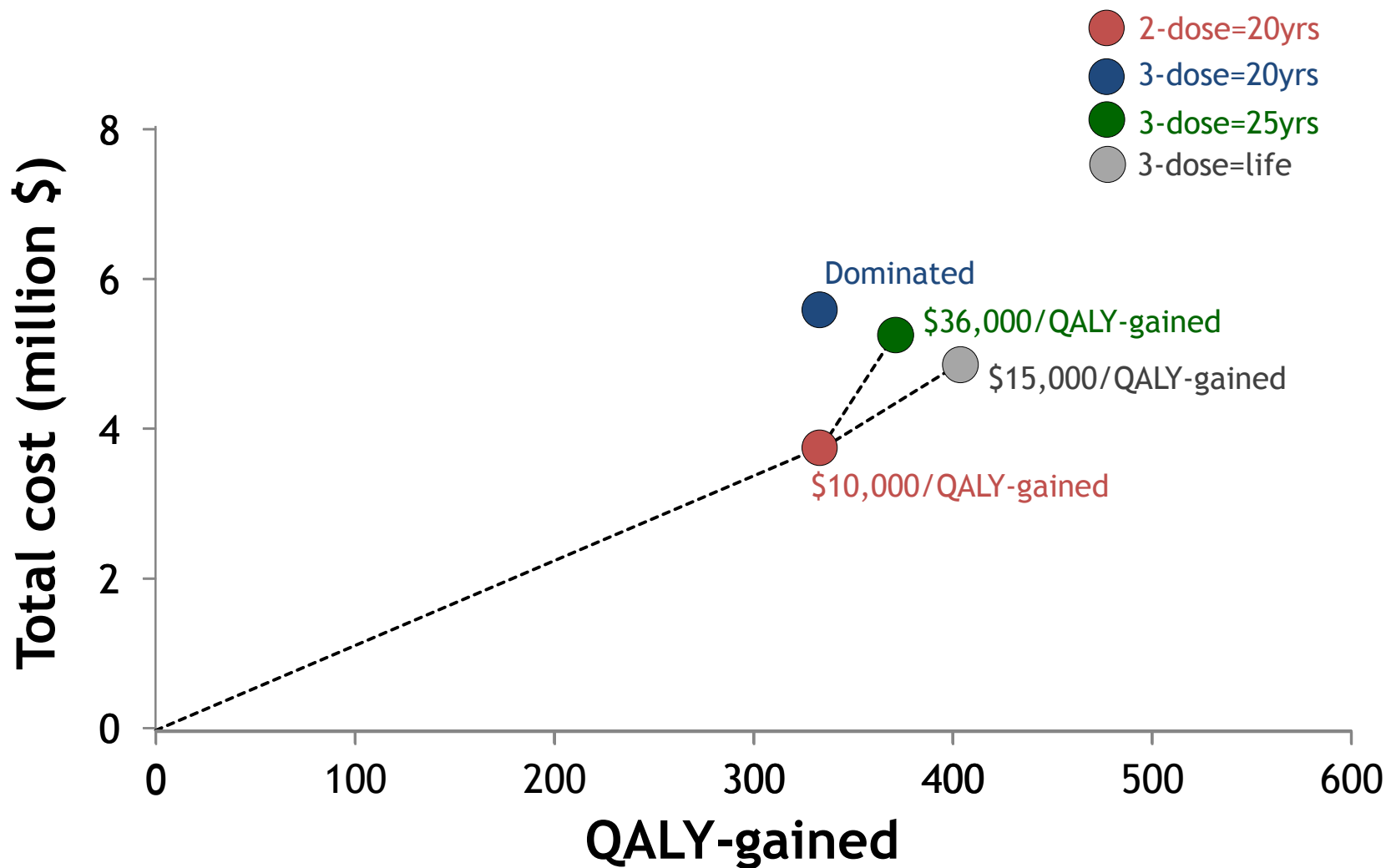
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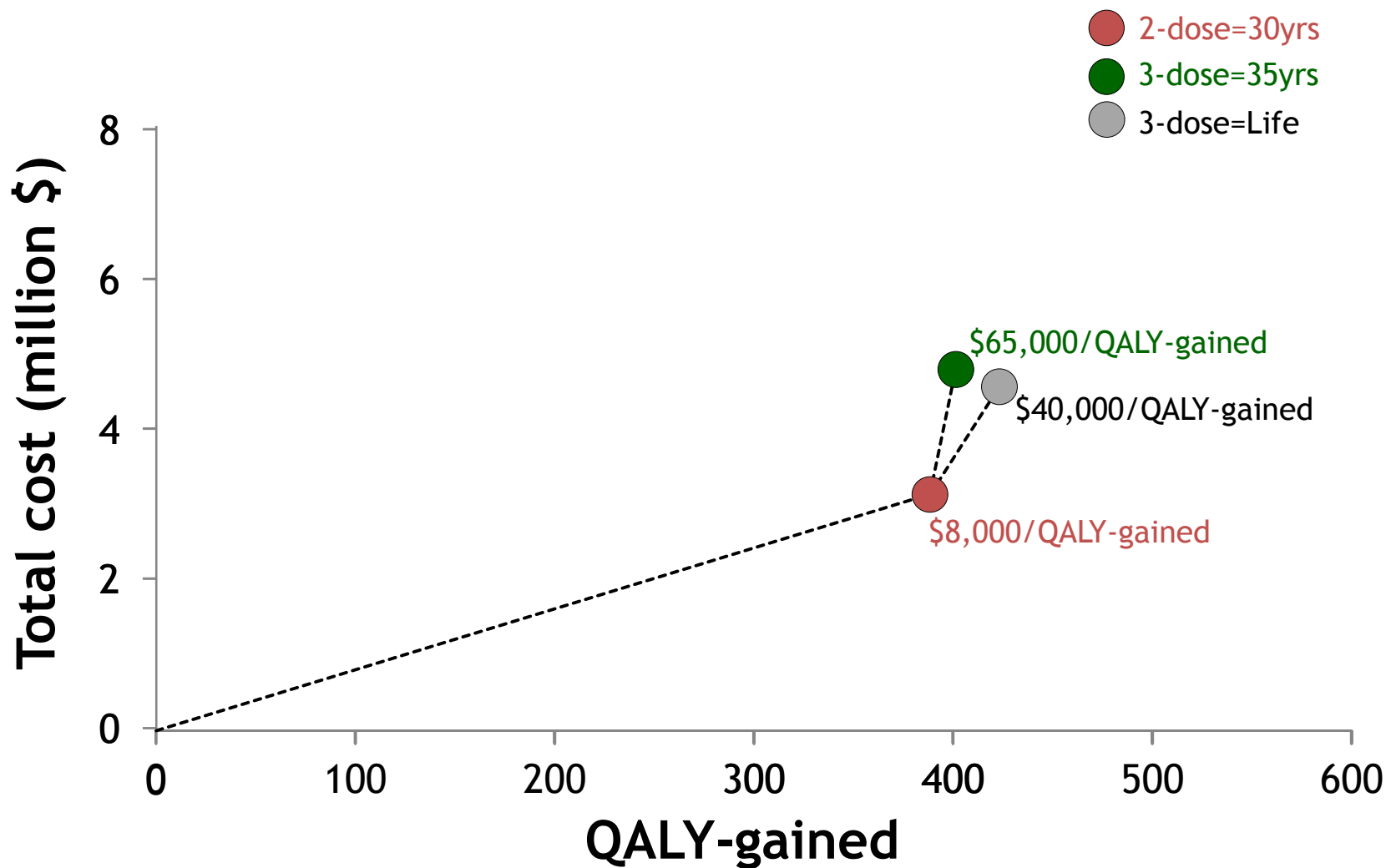
# Cost-effectiveness 2-dose duration=20yrs

Girls-only, Quadrivalent, Coverage=80%, VE=95%, Cross-protection Cost/dose=\$85



# Cost-effectiveness 2-dose duration=30yrs

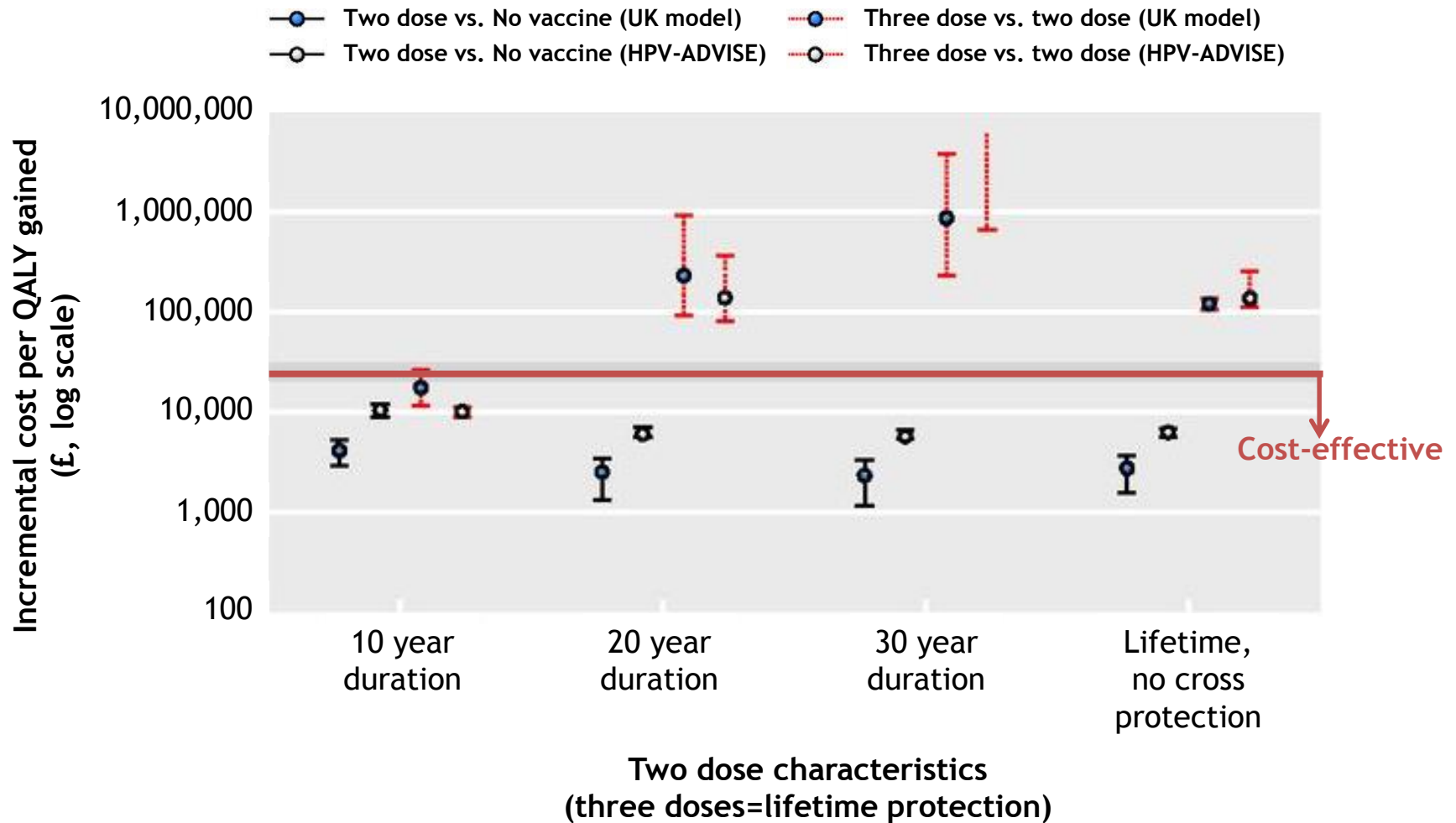
Girls-only, Quadrivalent, Coverage=80%, VE=95%, Cross-protection Cost/dose=\$85





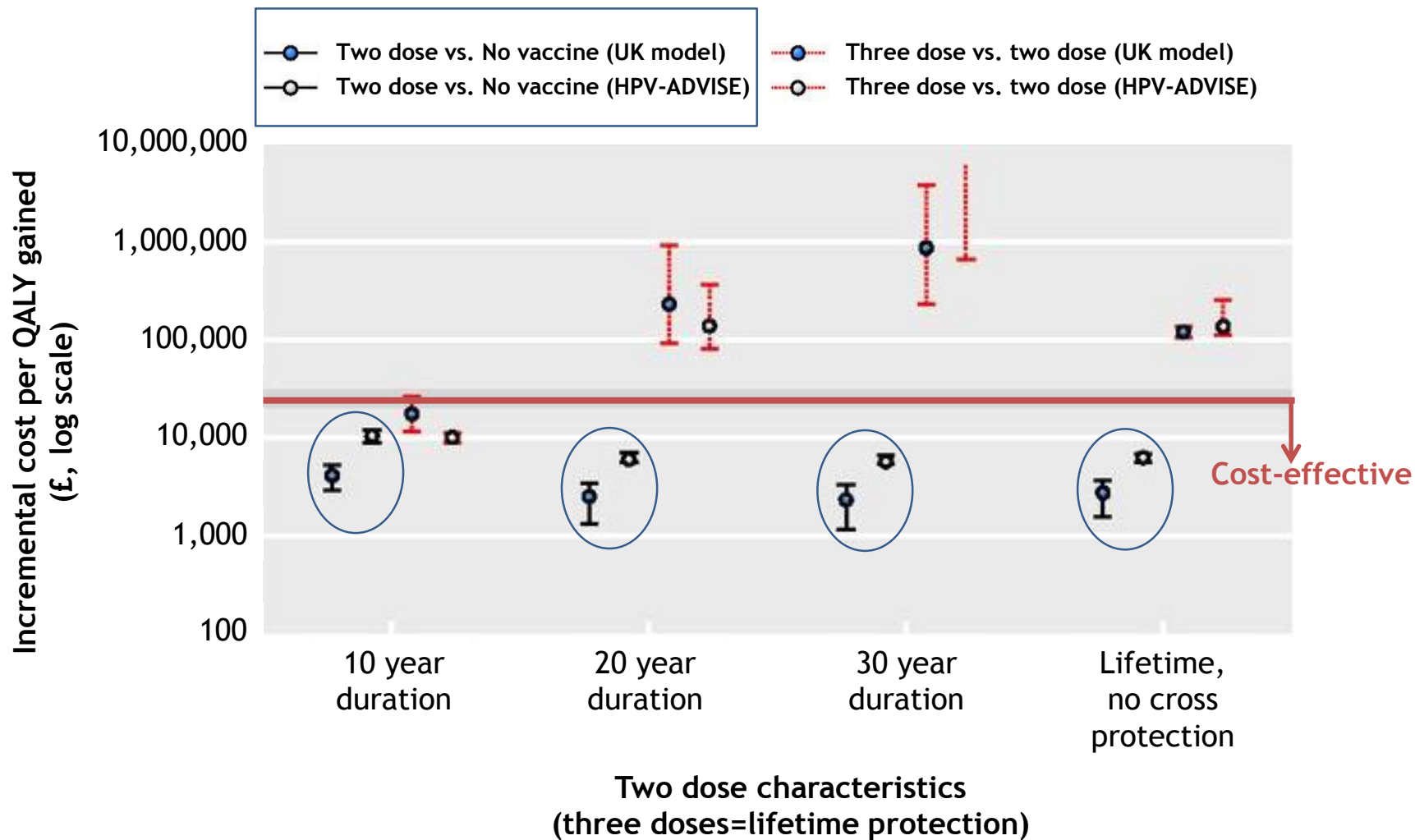
# Cost-effectiveness, England

Girls-only, Quadrivalent, Coverage=80%, Discount=3.5%



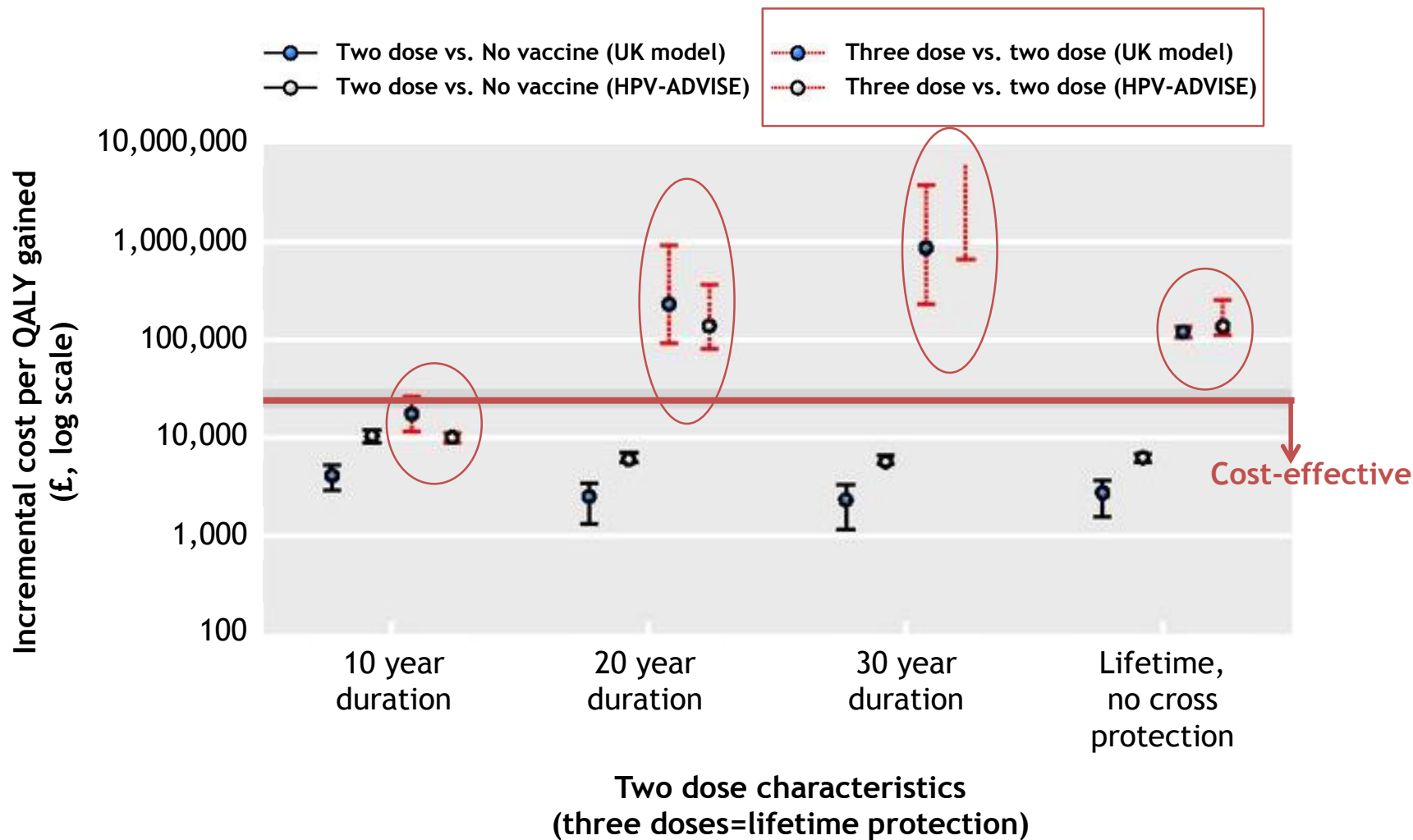
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Girls-only, Quadrivalent, Coverage=80%, Discount=3.5%



# Cost-effectiveness, England

Girls-only, Quadrivalent, Coverage=80%, Discount=3.5%



# Summary - Cost-effectiveness

- **Girls-only 2-dose vaccination**
  - Reduces HPV-burden of disease substantially, if duration of protection > 20yrs
  - Produces best (smallest) incremental cost-effectiveness ratios, if duration of protection >10 yrs
- **Girls-only 3-dose vaccination** is estimated to be cost-effective if it:
  - Provides longer duration of protection than 2-dose
  - 2-dose < 30yrs protection
- **Key issues**
  - What evidence is required by policymakers to reduce doses?
    - Data on Duration more important than short-term vaccine efficacy
    - Should we wait for evidence on duration of protection? Proxies for duration?

# Funding



Canada Research  
Chairs

Chaires de recherche  
du Canada

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Agency of Canada

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**Thanks!**