Observed and Modeled impact of different HPV immunization schedules and strategies

Brisson M[1,2,3], Drolet M[2], Jit M[4,5], Laprise JF[2], Boily MC[3], Alary M[1,2], Baussano I[6], Franceschi S[6], Martin D[2], Bénard É[2]

1.Université Laval, 2. Centre de recherche du CHU de Québec, 3. Imperial College, 4. London School of Hygiene & Tropical Medicine, 5. Public Health England, 6. International Agency for Research on Cancer (IARC)

Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)
October 20, 2016
Geneva

Objective

- Summarize existing evidence about the population-level effectiveness and cost-effectiveness of HPV immunization of different schedules and strategies, using:
  - Observational post-vaccination data
  - Predictions from Mathematical Models

Schedules/strategies

- Girls-only HPV immunization (2- or 4- vs 9-valent)
- Gender-neutral HPV immunization (vs Girls-only)
- Multiple age cohort HPV immunization (vs single age cohort)

Observed population-level effectiveness

Systematic review & meta-analysis

Methods

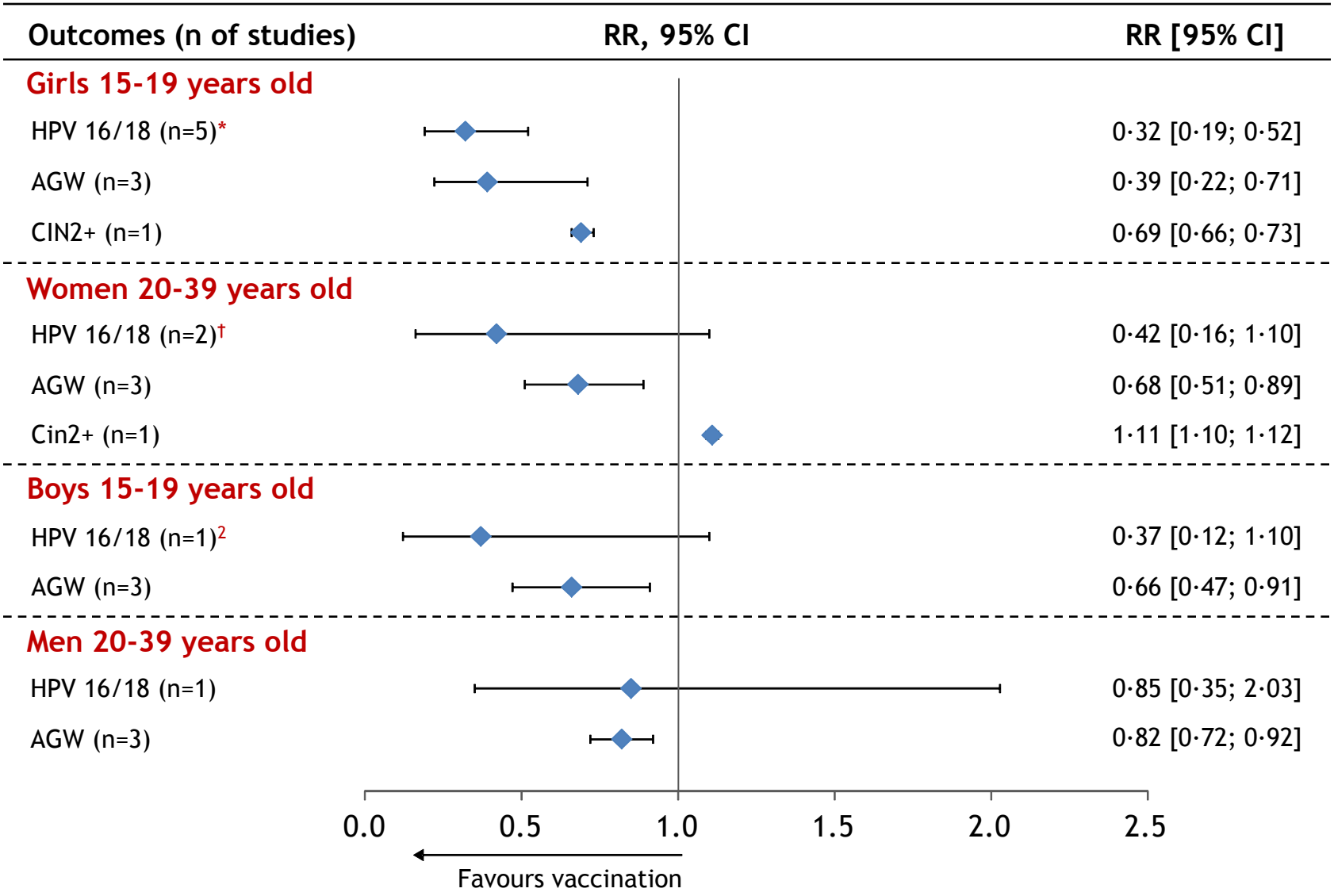
Systematic reviews - Population-level effectiveness & herd effects

- We conducted two systematic reviews
  - Initial review: Studies published between Jan 2007 & Feb 2014[1]
  - Updated review: Studies published between Feb 2014 & July 2016
  - Used same methodology
- Search strategy
  - Medline and Embase, and main HPV conference abstracts
- Eligibility
  - Comparisons between pre- and post-vaccination periods
  - Incidence/prevalence of HPV infection, anogenital warts, or CIN2+
- Analysis (initial review only)
  - Stratified by age & sex
  - Pooled relative risk (RR) derived from random-effects models

REF: 1. Drolet, *Lancet ID* 2015

Results of review[1] Girls-only immunization

High Income Countries with **≥ 50% vaccination coverage** of girls

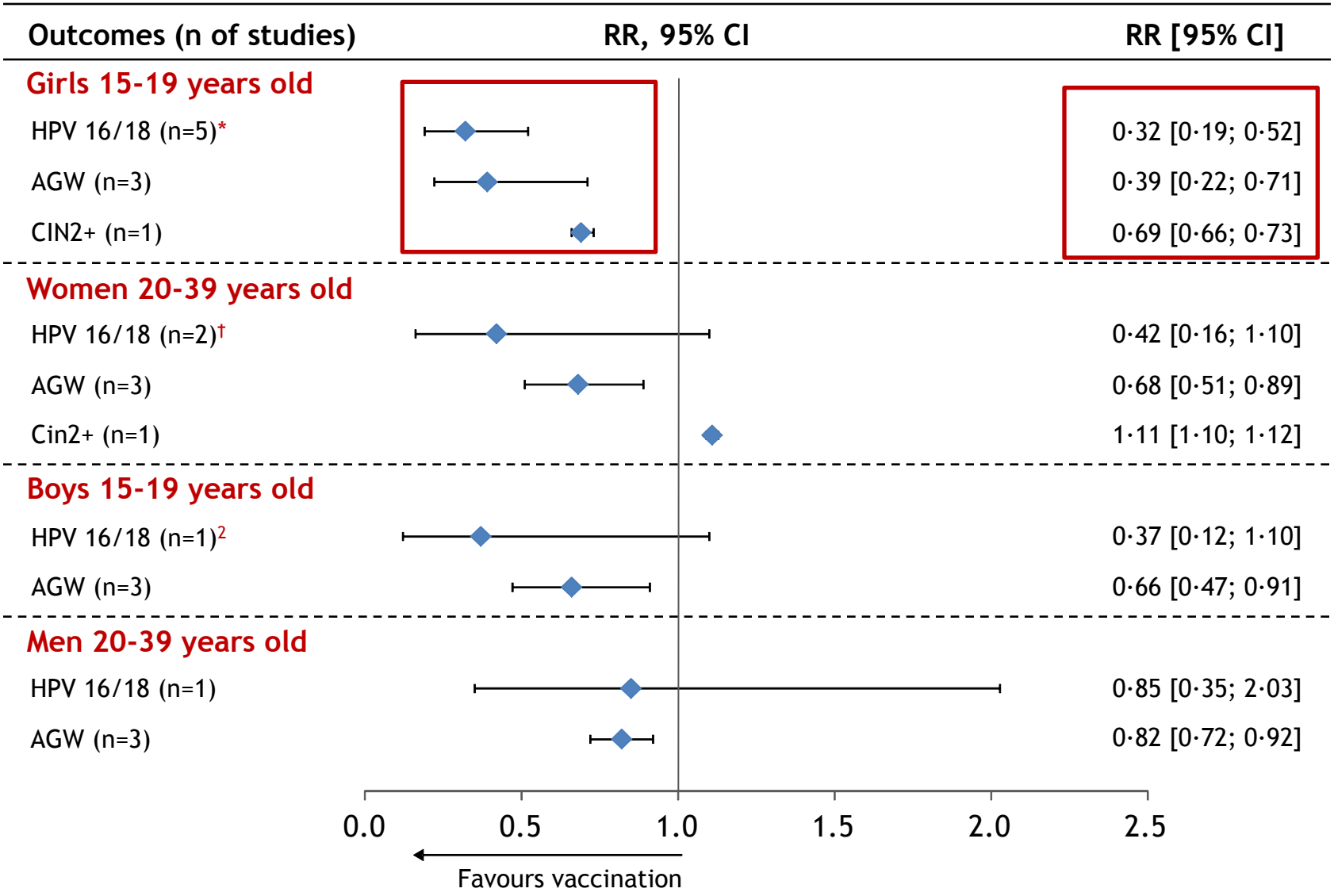


RR=prevalence ratio (post-vaccination÷pre-vaccination prevalence); * 13-19 year age group; † 20-24 years age group

REF: 1. Drolet, *Lancet ID* 2015; 2. Chow, *Lancet ID* 2016

Results of review[1] Girls-only immunization

High Income Countries with **≥ 50% vaccination coverage** of girls

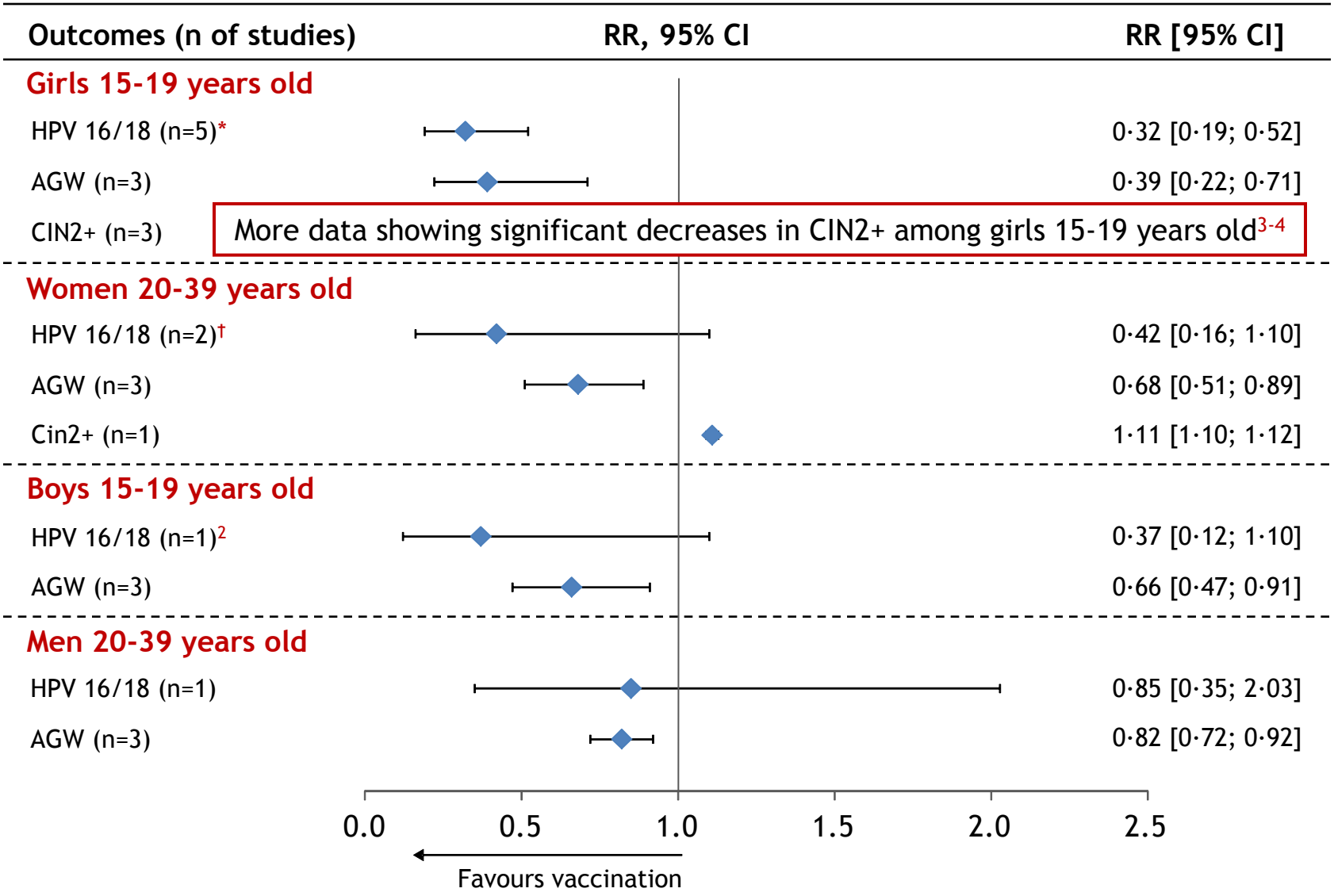


RR=prevalence ratio (post-vaccination÷pre-vaccination prevalence); * 13-19 year age group; † 20-24 years age group

REF: 1. Drolet, *Lancet ID* 2015; 2. Chow, *Lancet ID* 2016

Results of review[1] Girls-only immunization

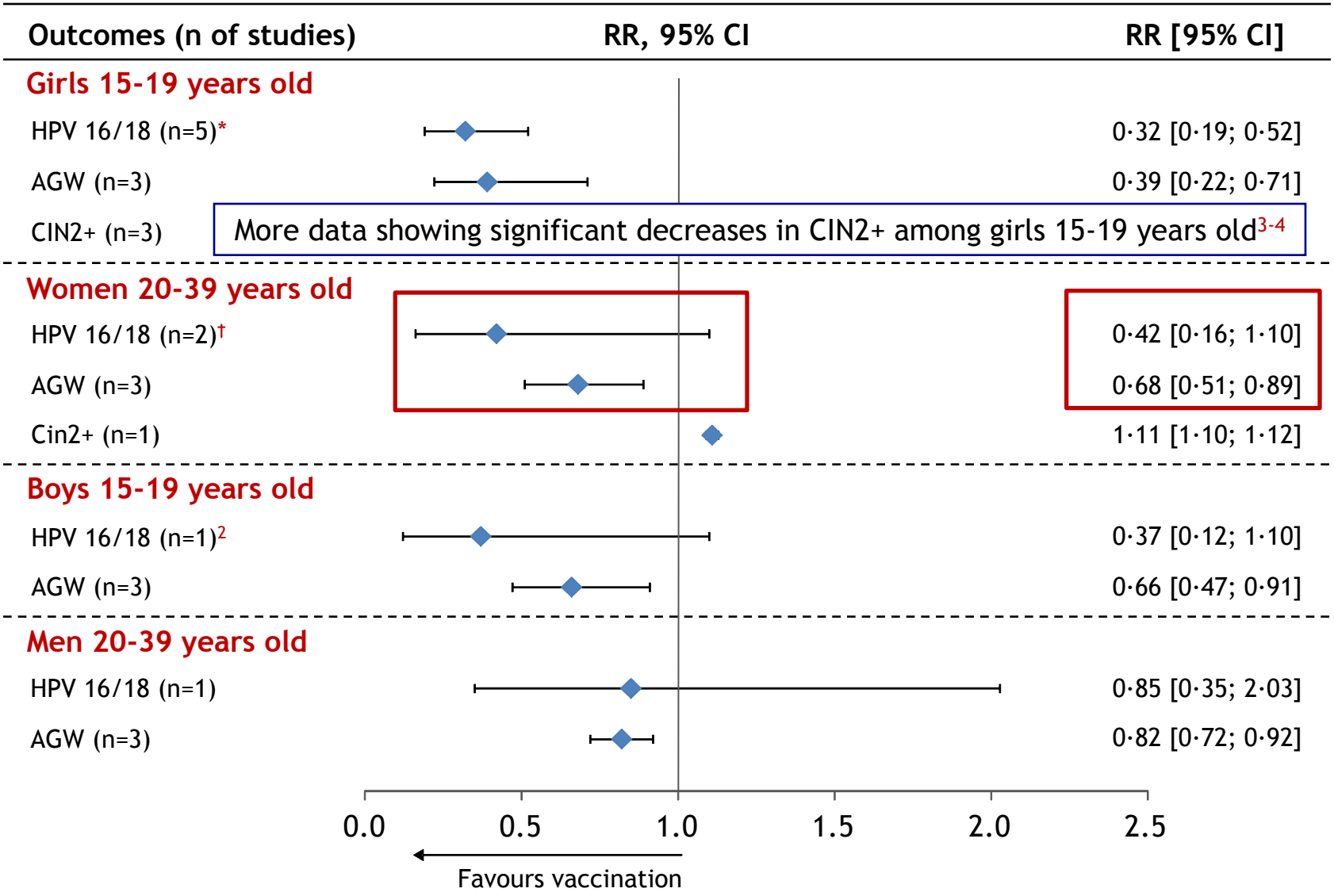
High Income Countries with **≥ 50% vaccination coverage** of girls



RR=prevalence ratio (post-vaccination÷pre-vaccination prevalence); * 13-19 year age group; † 20-24 years age group; REF: 1. Drolet, *Lancet ID* 2015; 2. Chow, *Lancet ID* 2016; 3. Baldur-Felskov, Cancer Causes Control 2014; 4. Ogilvie, IJC 2015

Results of review[1] Girls-only immunization

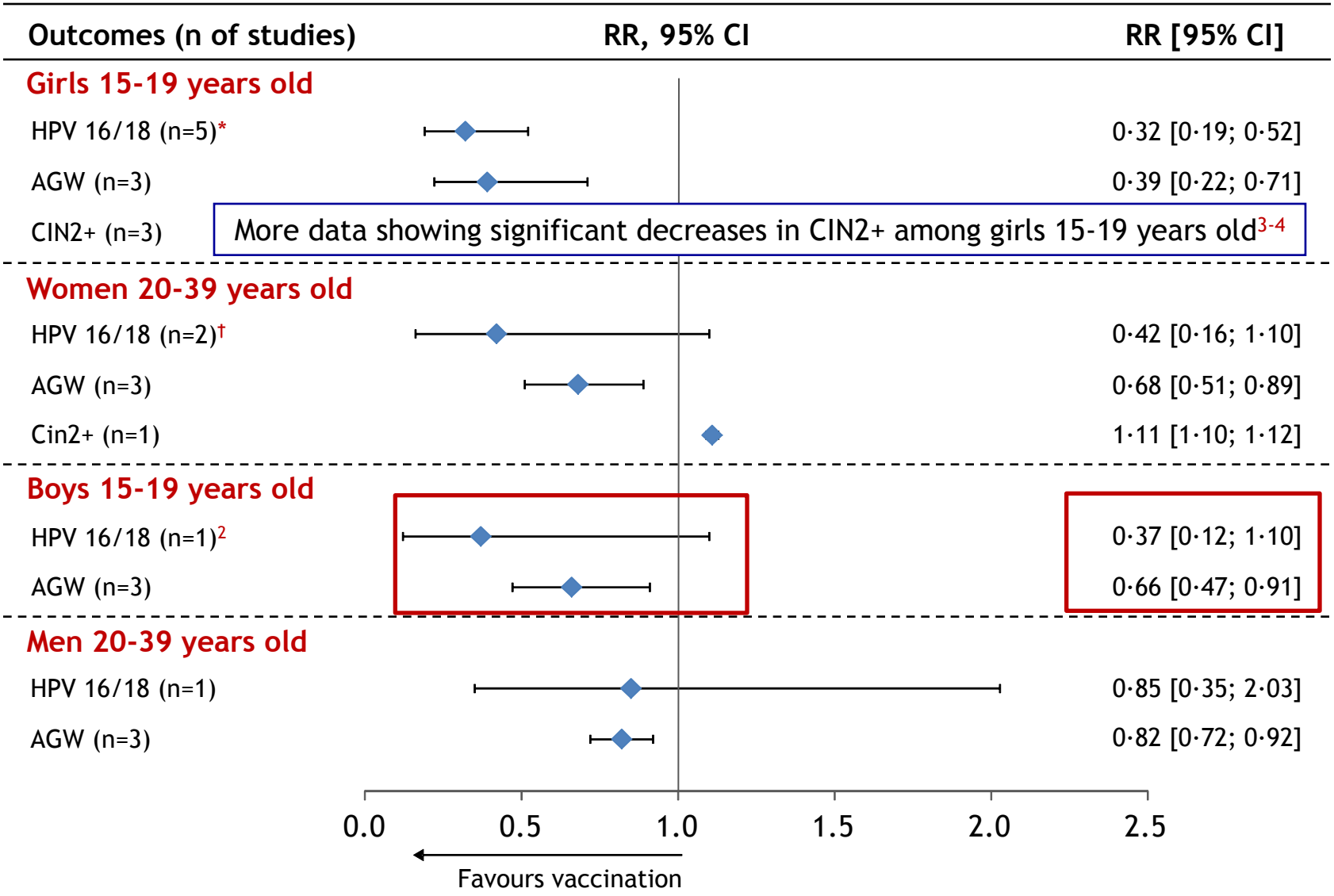
High Income Countries with **≥ 50% vaccination coverage** of girls



RR=prevalence ratio (post-vaccination÷pre-vaccination prevalence); * 13-19 year age group; † 20-24 years age group; REF: 1. Drolet, *Lancet ID* 2015; 2. Chow, *Lancet ID* 2016; 3. Baldur-Felskov, Cancer Causes Control 2014; 4. Ogilvie, IJC 2015

Results of review[1] Girls-only immunization

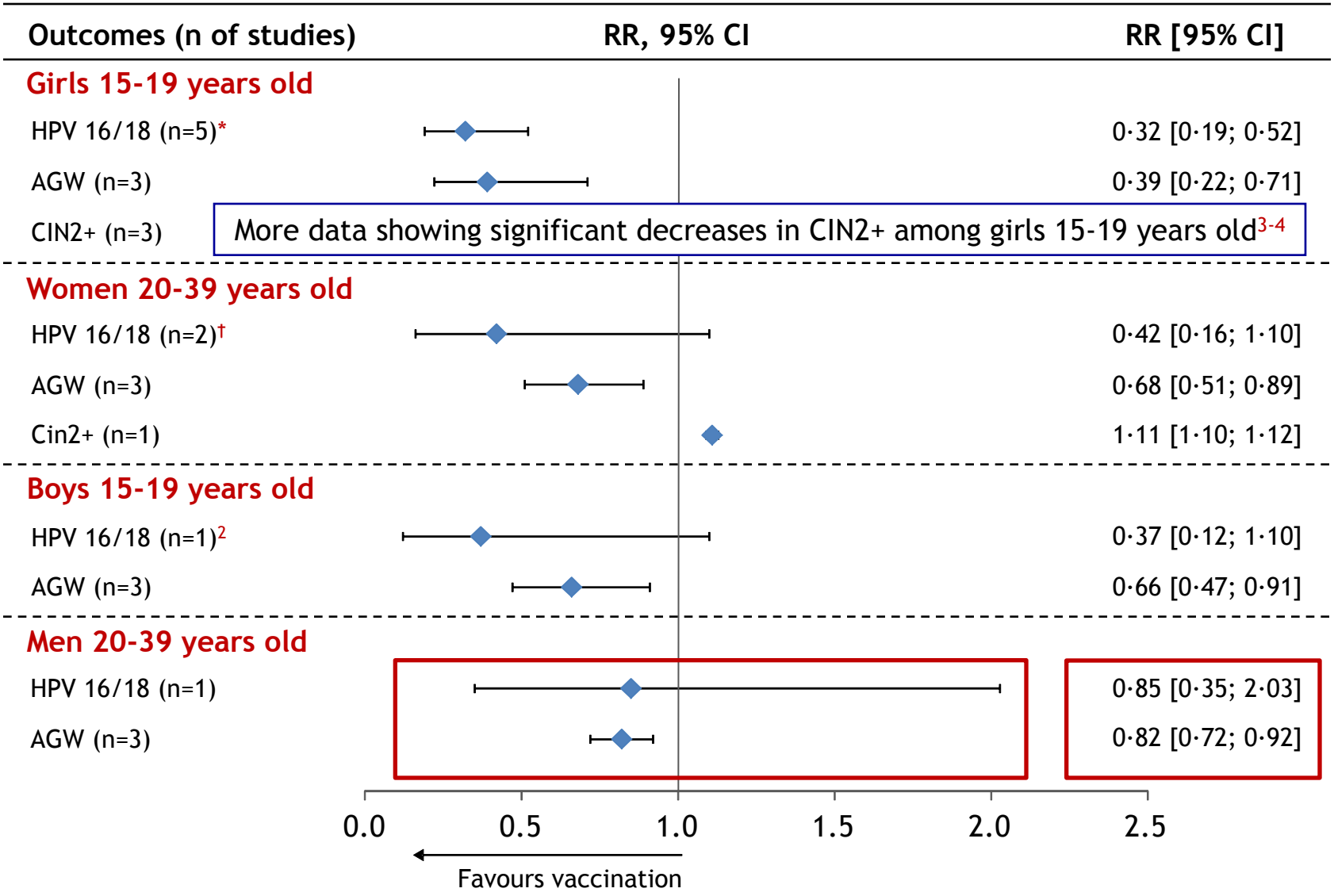
High Income Countries with **≥ 50% vaccination coverage** of girls



RR=prevalence ratio (post-vaccination÷pre-vaccination prevalence); * 13-19 year age group; † 20-24 years age group; REF: 1. Drolet, *Lancet ID* 2015; 2. Chow, *Lancet ID* 2016; 3. Baldur-Felskov, Cancer Causes Control 2014; 4. Ogilvie, IJC 2015

Results of review[1] Girls-only immunization

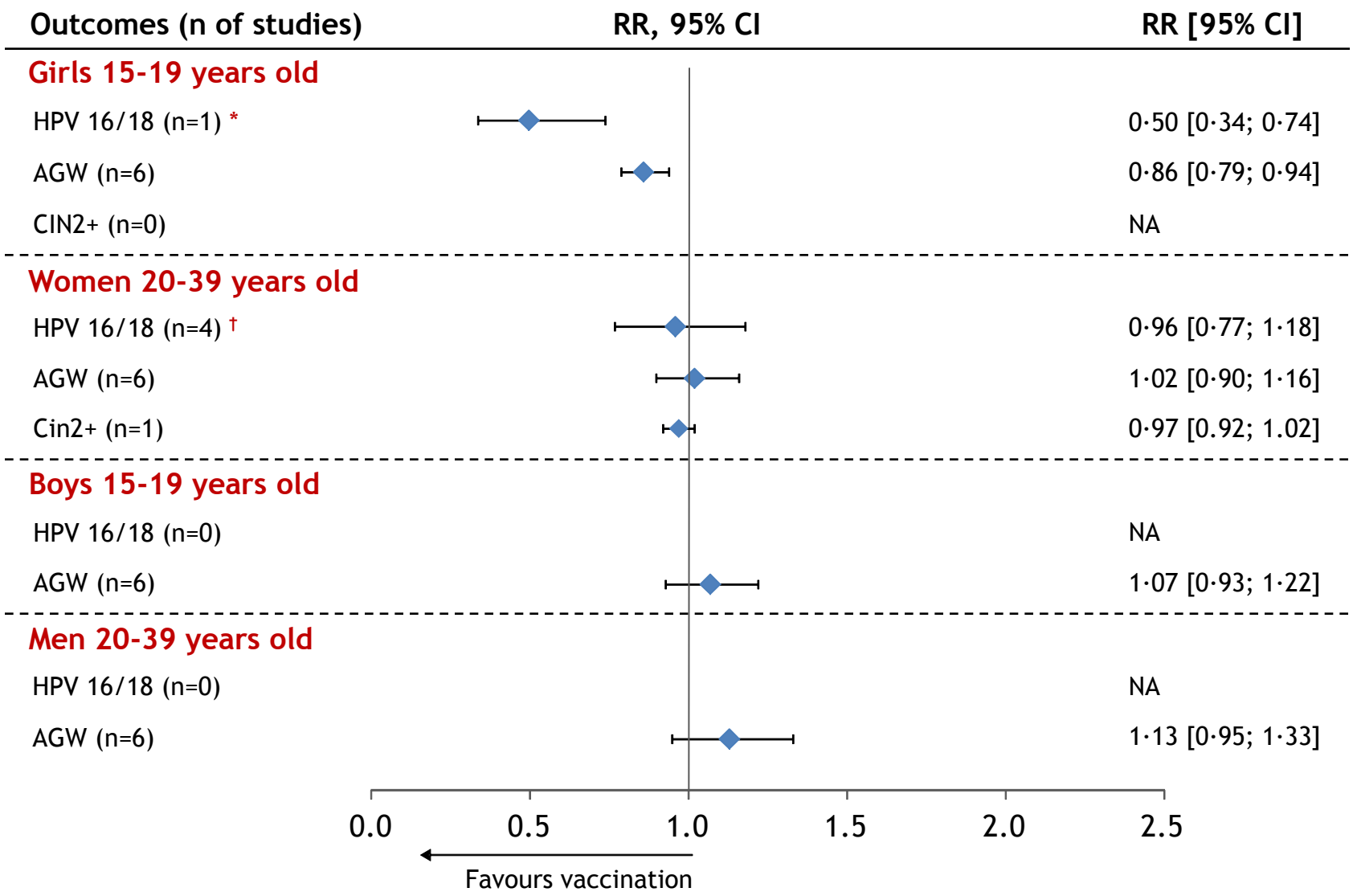
High Income Countries with **≥ 50% vaccination coverage** of girls



RR=prevalence ratio (post-vaccination÷pre-vaccination prevalence); * 13-19 year age group; † 20-24 years age group; REF: 1. Drolet, *Lancet ID* 2015; 2. Chow, *Lancet ID* 2016; 3. Baldur-Felskov, Cancer Causes Control 2014; 4. Ogilvie, IJC 2015

Results of review[1] Girls-only immunization

High Income Countries with **< 50% vaccination coverage** of girls

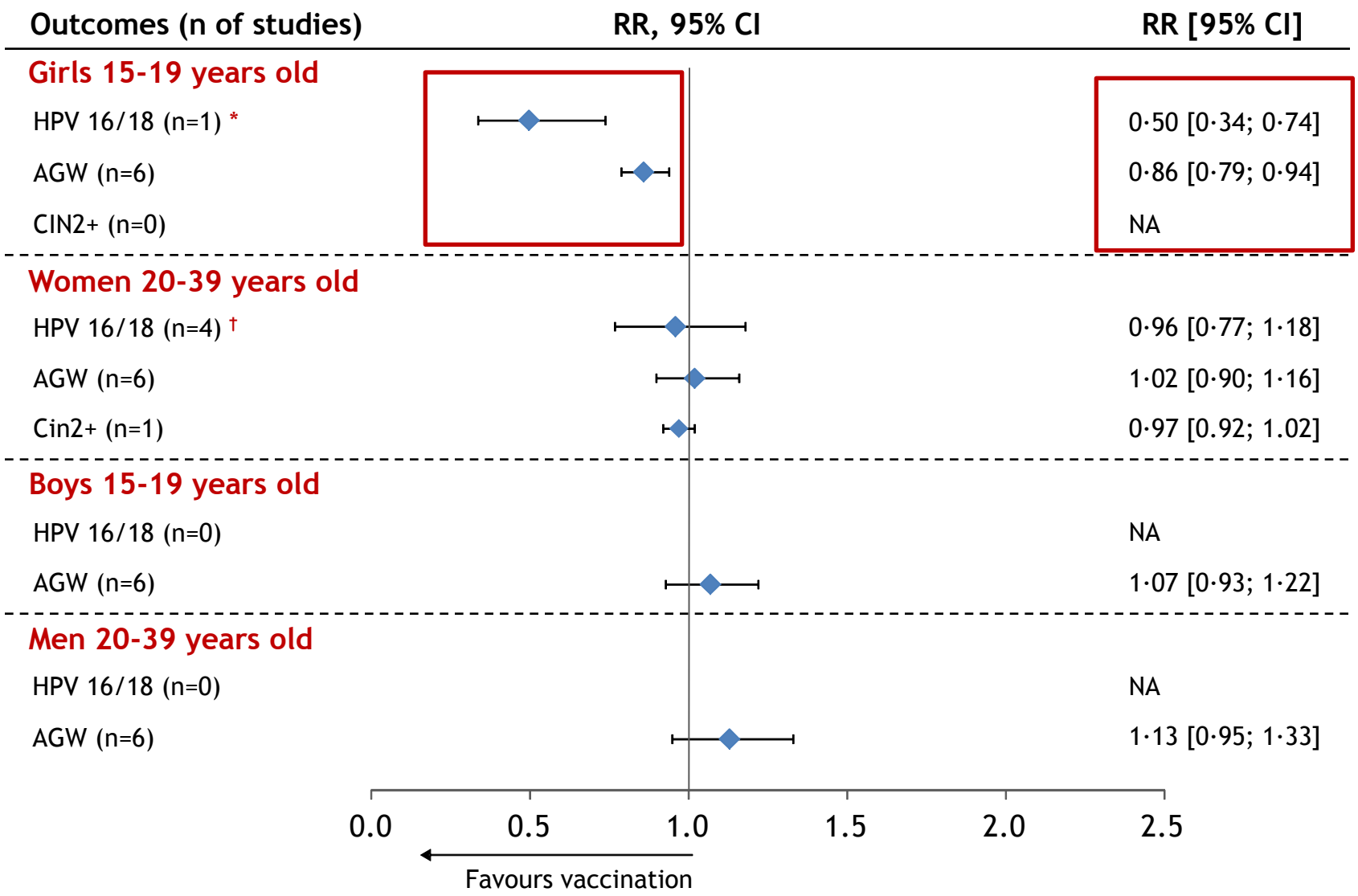


RR=prevalence ratio (post-vaccination÷pre-vaccination prevalence); * 13-19 year age group; † 20-24 years age group

REF: 1. Drolet, *Lancet ID* 2015

Results of review[1] Girls-only immunization

High Income Countries with **< 50% vaccination coverage** of girls

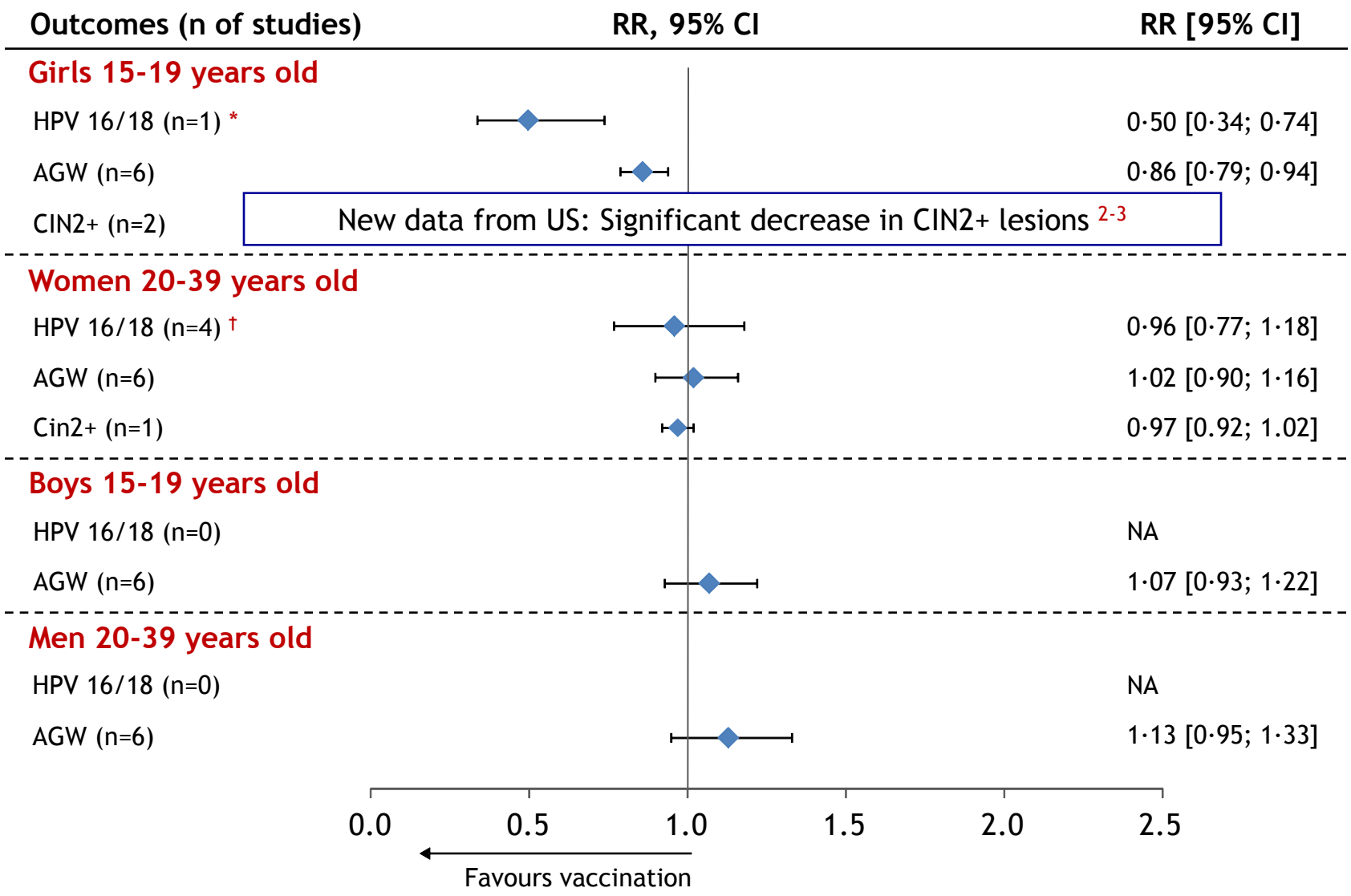


RR=prevalence ratio (post-vaccination÷pre-vaccination prevalence); * 13-19 year age group; † 20-24 years age group

REF: 1. Drolet, *Lancet ID* 2015

Results of review[1] Girls-only immunization

High Income Countries with **< 50% vaccination coverage** of girls

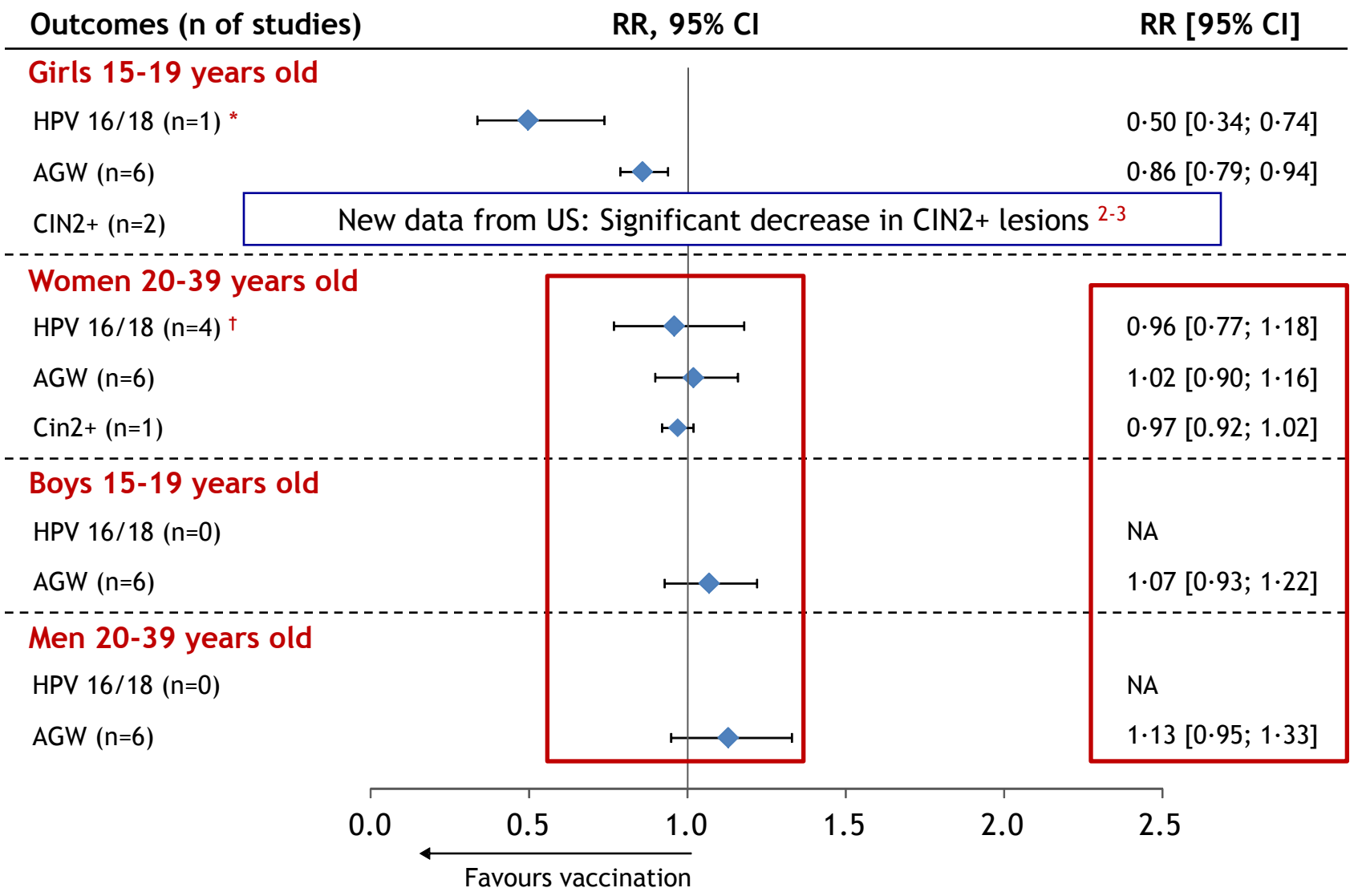


RR=prevalence ratio (post-vaccination÷pre-vaccination prevalence); * 13-19 year age group; † 20-24 years age group

REF: 1. Drolet, *Lancet ID* 2015; 2. Flagg, *STI* 2015; 3. Hariri, *Cancer* 2015

Results of review[1] Girls-only immunization

High Income Countries with **< 50% vaccination coverage** of girls



RR=prevalence ratio (post-vaccination÷pre-vaccination prevalence); * 13-19 year age group; † 20-24 years age group

REF: 1. Drolet, *Lancet ID* 2015; 2. Flagg, *STI* 2015; 3. Hariri, *Cancer* 2015

Results Gender-neutral & multiple age cohort immunization

- Gender-neutral immunization
  - 2 countries with population-level data after Gender-neutral immunization (Australia, the USA)[1-6]
  - Too early to measure the additional impact of Gender-neutral vaccination
    - Max follow-up available is 1-2 years after the switch from girls-only to gender-neutral vaccination
- Multiple age cohort immunization
  - Many countries vaccinated many age cohorts (Australia, Canada, Denmark, Greece, New-Zealand, Norway, Sweden, the UK and the US)
  - Too few countries without Multiple age cohort immunization to isolate the additional population-level impact of this strategy (vs a single cohort)

REF: 1. Drolet, *Lancet ID* 2015, 2. Chow, *Lancet* 2015; 3. Chow, STI 2015; 4. Chow, *Lancet ID* 2016; 5. Markowitz, *Pediatrics* 2016; 6. Dunne, *JID* 2015

Need for mathematical models

- Compelling population-level evidence suggest that Girls-only HPV immunization programs:
  - Reduce HPV-16/18 infection, anogenital warts and CIN2+ lesions
  - Provide herd effects
  - Magnitude of impact strongly depend on vaccination coverage

- Remaining questions: What will be the long term-population level effectiveness, and expected cost-effectiveness of:
  - Girls-only HPV immunization with 2- or 4-valent vs 9-valent
  - Gender-neutral vs Girls-only HPV immunization
  - Multiple vs single age cohort HPV immunization

- Mathematical models provide a formal framework to examine these questions

Predicted population-level effectiveness, herd effects & cost-effectiveness

Model-based analysis

Methods

Modeling - Population-level effectiveness & herd effects

HPV-ADVISE (Agent-based Dynamic model for VaccInation & Screening Evaluation)[1]

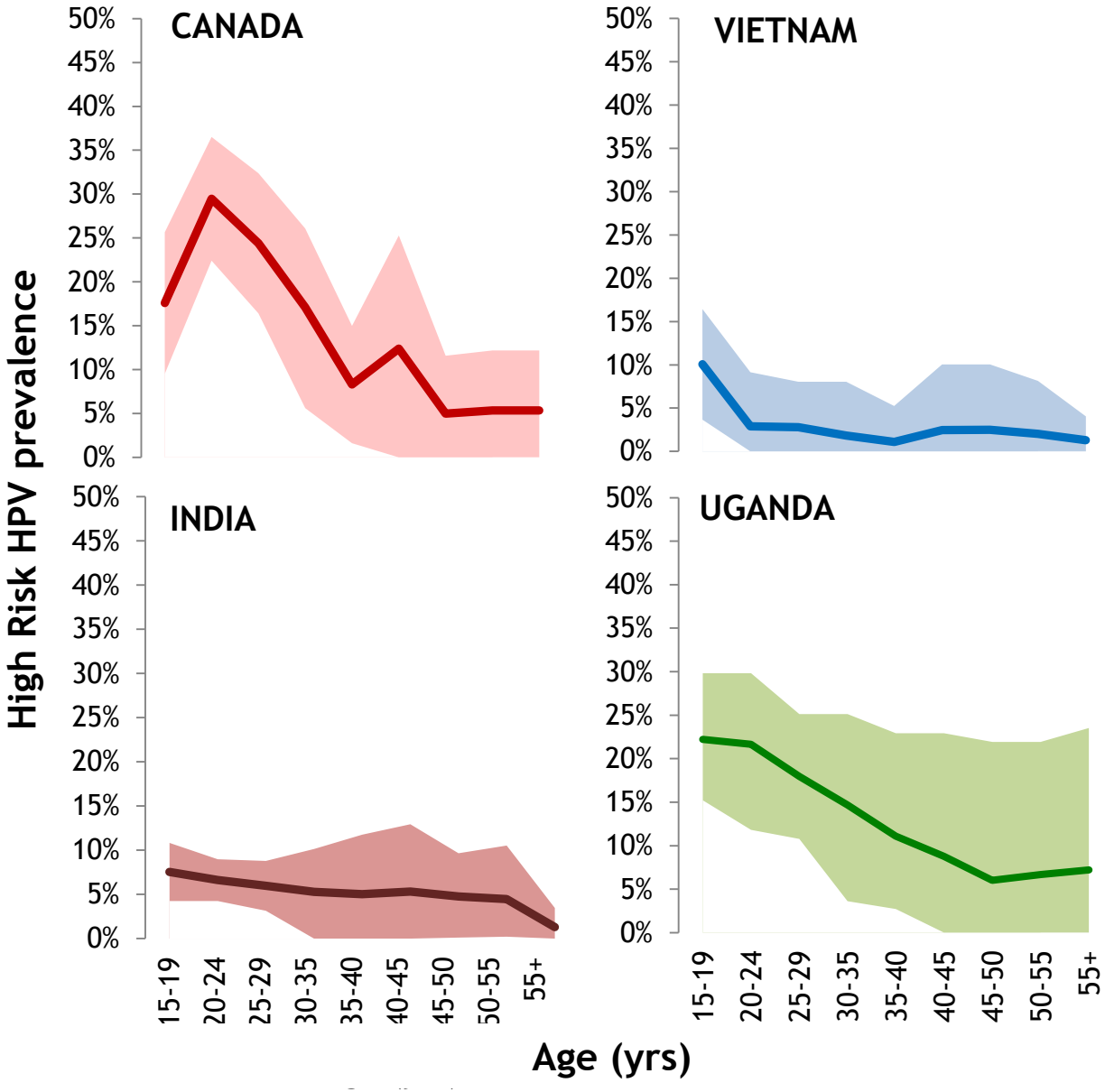
- Transmission-dynamic model of HPV infection and disease (includes herd immunity)

- Models 18 HPV types:
  - Types included in the 9-valent vaccine (HPV-6/11/16/18/31/33/45/52/58)
  - 9 other high risk types

- Fit HPV-ADVISE to Canada, India, Vietnam, and Uganda[&]
  - Demographic and sexual behaviour
  - HPV prevalence and cervical cancer incidence (age and type-specific)
  - Data from international databases and original studies[&]

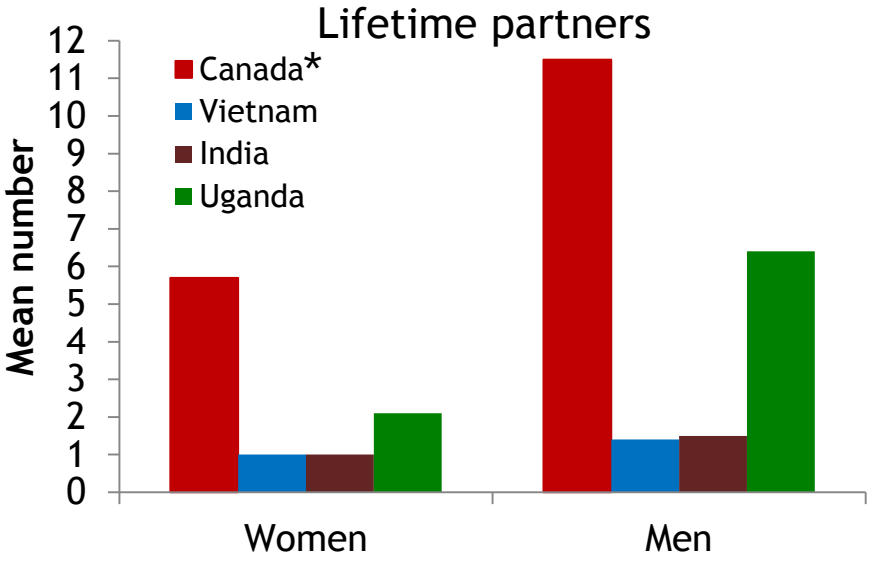
REF: 1. Brisson, *JNCI* 2015; &: Demographic and Health Surveys, Multiple Indicator Survey, ICO information Centre on HPV and Cancer, United Nations Statistics Division, HIV and AIDS HUB for Asia Pacific-Evidence to action, WHO Global Health Observatory data repository, literature reviews, and original studies from IARC and Dr. M Alary (see back-up slides for references & model fit)

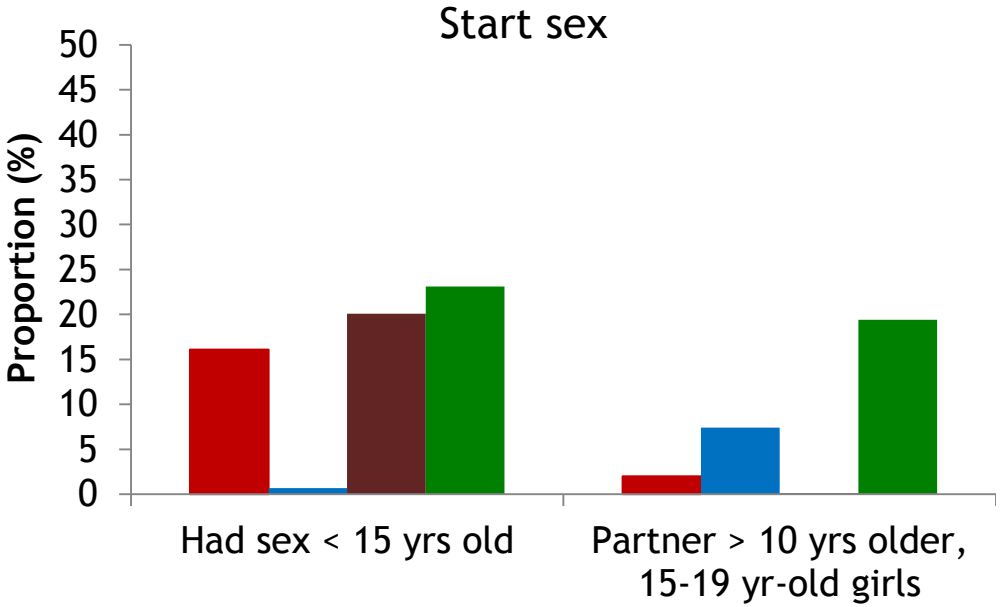
High risk HPV prevalence, women data for model fit

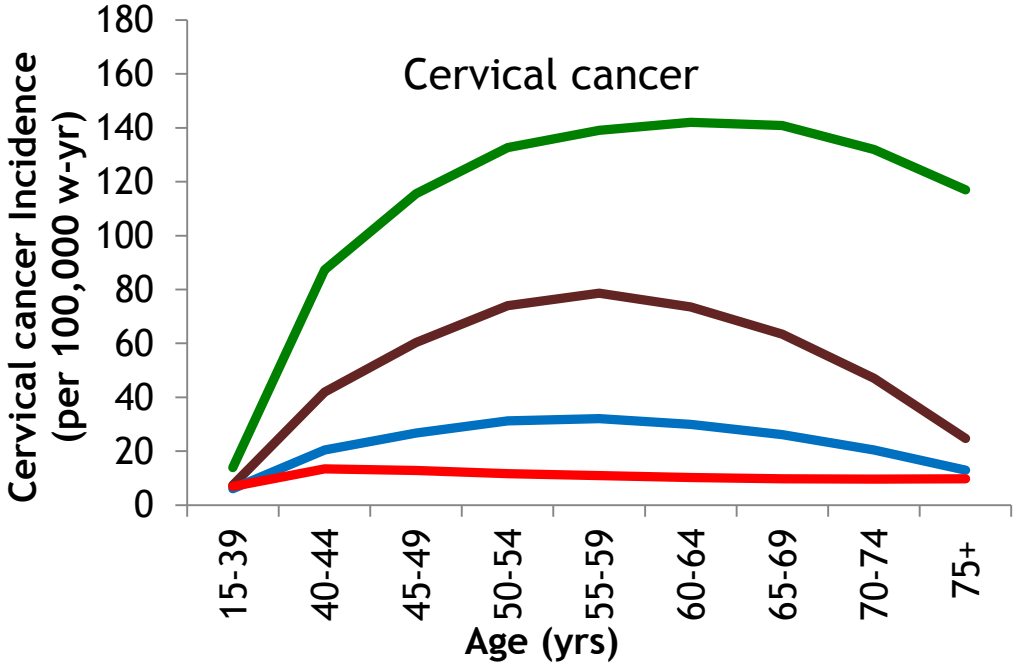


REF: Literature review (see back-up slides)

Sexual behavior & Cervical cancer data for model fit







REF: Sexual activity:
Demographic and Health Surveys, Multiple Indicator Survey, HIV and AIDS HUB for Asia Pacific-Evidence to action, National Health and Nutrition Examination Survey, National Survey of Family Growth

Cervical cancer:
GLOBOCAN 2012 (extrapolated from cervical cancer incidence by age)

* Canada Lifetime partners estimated from USA data

Methods

Modeling – Cost-effectiveness

Systematic Review[1]:

- Cost-effectiveness studies published up to July 2016

PRIME (Papillomavirus Rapid Interface for Modelling and Economics)[2]

- Developed by scientists from U Laval and London School of Hygiene and Tropical Medicine, in collaboration with WHO (www.PRIMEtool.org)

- Static model (no herd effects)

- Reproduces country-specific cervical cancer incidence and mortality, % of cervical cancer due to the vaccine types, vaccine costs

- Model predictions for 179 countries

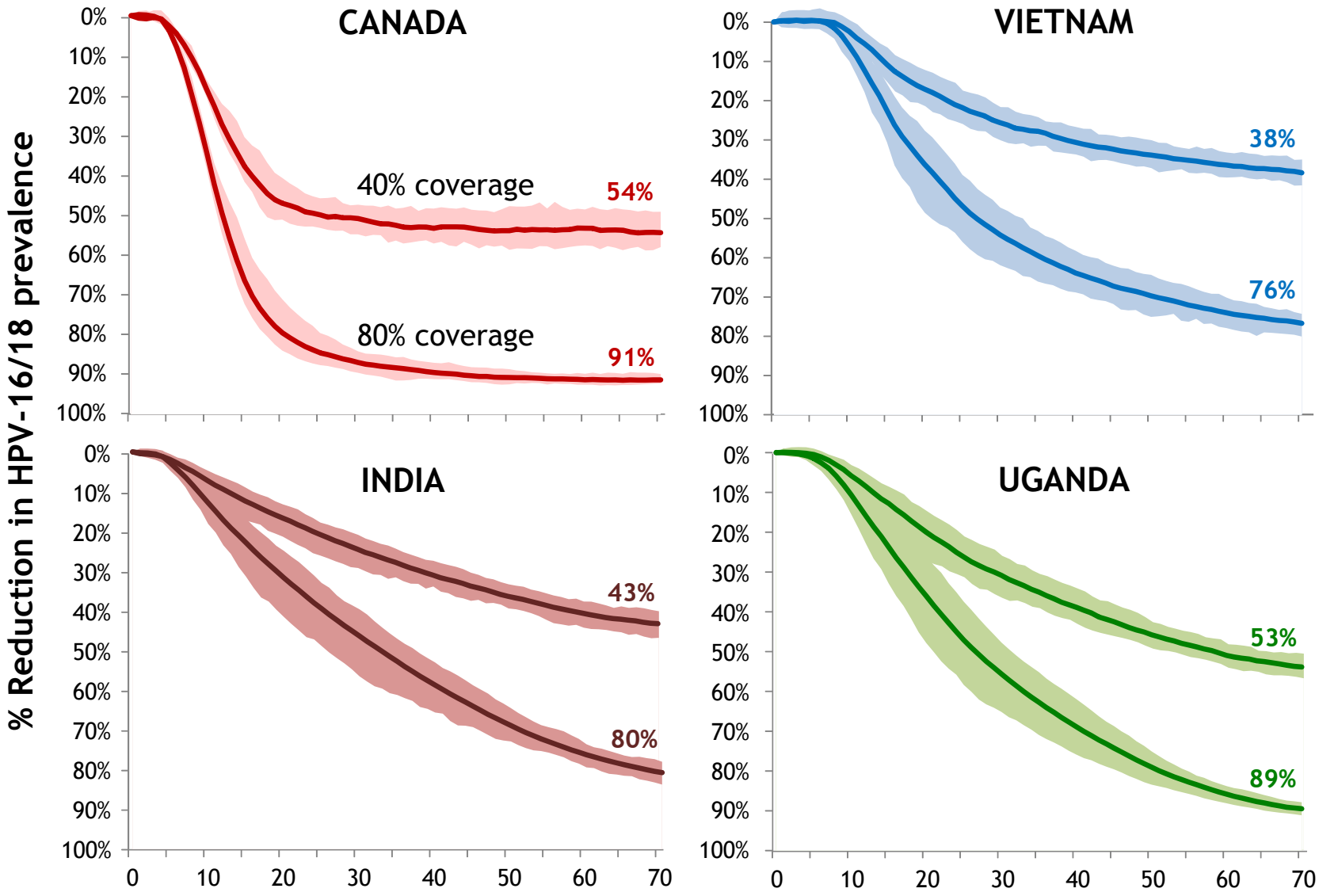
REF: 1. Chaiyakunapruk (SAGE background documents); 2. Jit, *Lancet Global Health* 2014 (see back-up slides for PRIME description)

Vaccinating Girls-only
(vs no vaccination)

Model predictions
Effectiveness & Cost-effectiveness

Effectiveness: Women HPV-16/18

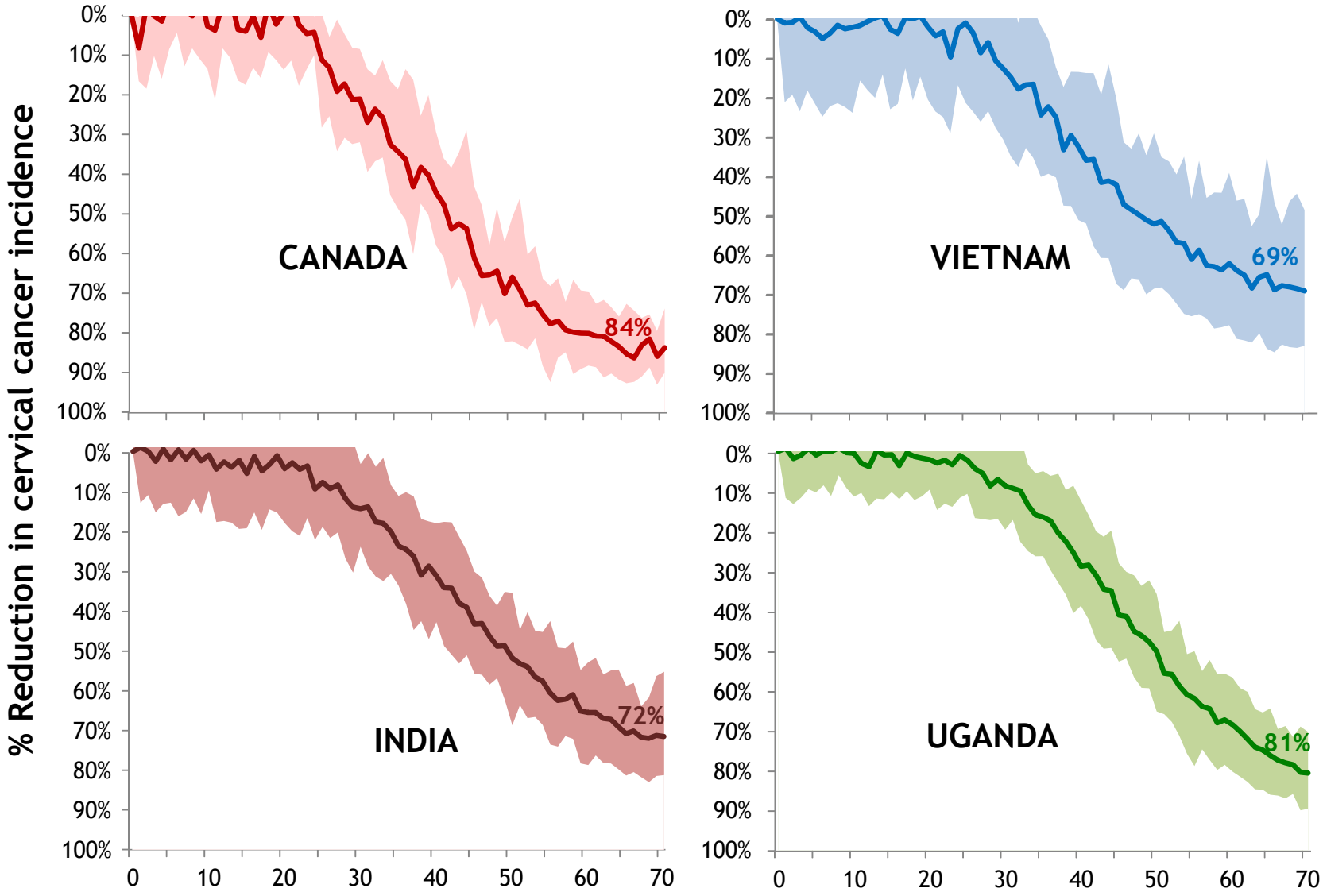
Girls-only vaccination (age=10yrs old), Vaccine duration=Lifelong, Vaccine Efficacy=95%



&: HPV-ADVISE, Median (line), and 10 and 90th percentiles (area) of the model predictions

Effectiveness: Cervical cancer

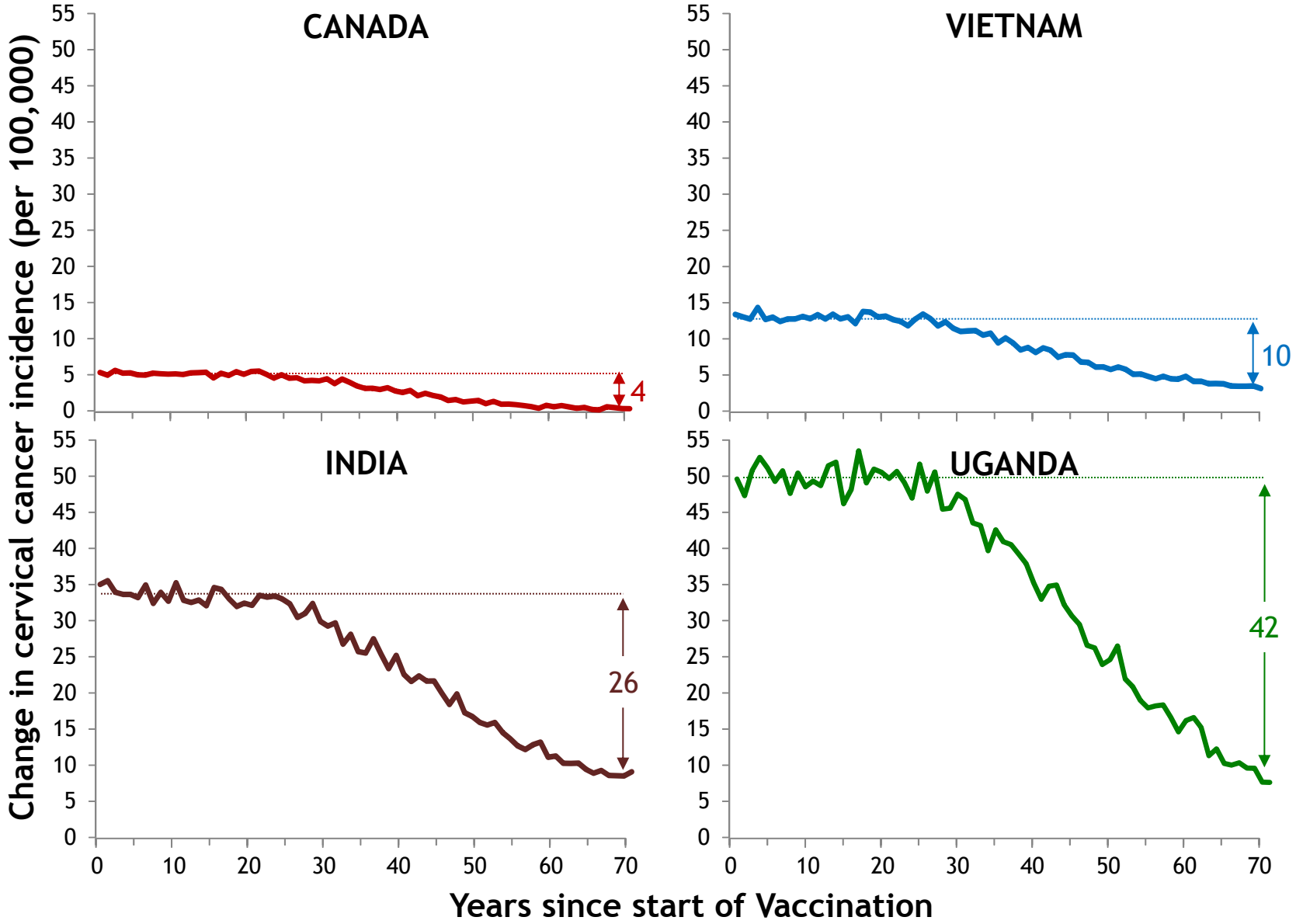
Girls-only & 9-valent (age=10yrs), Coverage=80%, Vacc duration=Lifelong, Vacc efficacy=95%



&: HPV-ADVISE, Median (line), and 10th and 90th percentiles (area) of the model predictions

Absolute reduction in Cervical cancer

Girls-only & 9-valent (age=10yrs), Coverage=80%, Vacc duration=Lifelong, Vacc efficacy=95%



&: HPV-ADVISE, Median of the model predictions; Incidence of squamous cell carcinoma

Cost-effectiveness: Girls-only vaccination

- Models from HIC[1-4] & LMIC[5] produce consistent conclusions

- Girls-only immunization is cost-effective (vs no vaccination)[1,3,4]
  - at current prices of the 2- and 4-valent vaccines
  - irrespective of the vaccine used
  - even when assuming no cross-protection or herd effects

- For example, Girls-only immunization is cost-effective in 173/179 countries in a global analysis using PRIME[5]
  - including only the direct impact on vaccinated women
  - including only cervical cancer as an outcome
  - using different cost-effectiveness thresholds

- Main driver: Prevention of HPV-16/18 related cervical cancer

REF: 1. Chaiyakunapruk (SAGE background documents); 2. Brisson, *Lancet Public Health* 2016;3. Brisson, *Public Health Genomics* 2009; 4. Canfell, *Vaccine* 2012; 5. Jit, *Lancet Global Health* 2015.

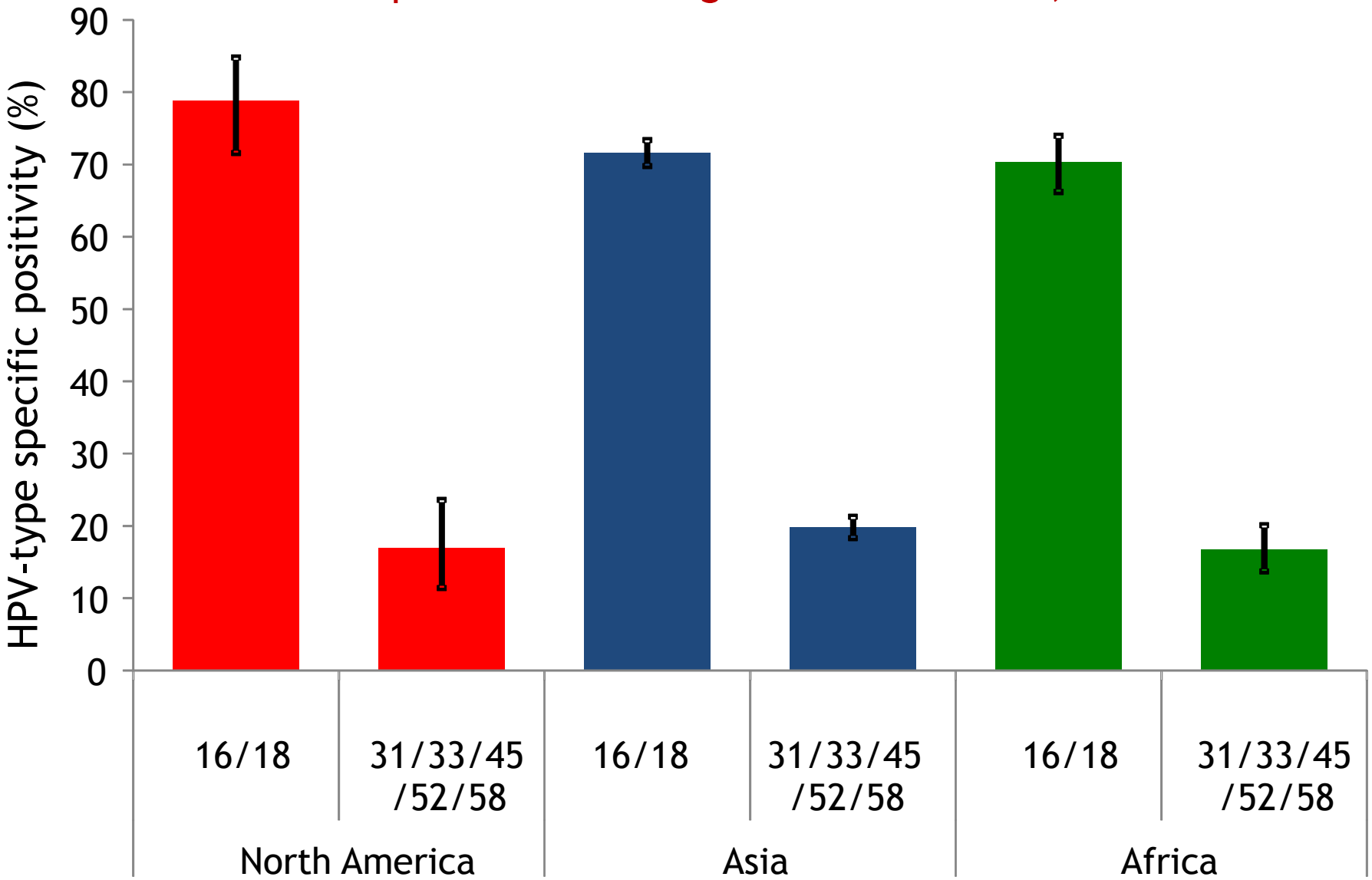
Vaccinating Girls-only

9-valent vaccine (vs 2/4-valent)

Model predictions
Effectiveness & Cost-effectiveness

Contribution of HPV-types to cervical cancer

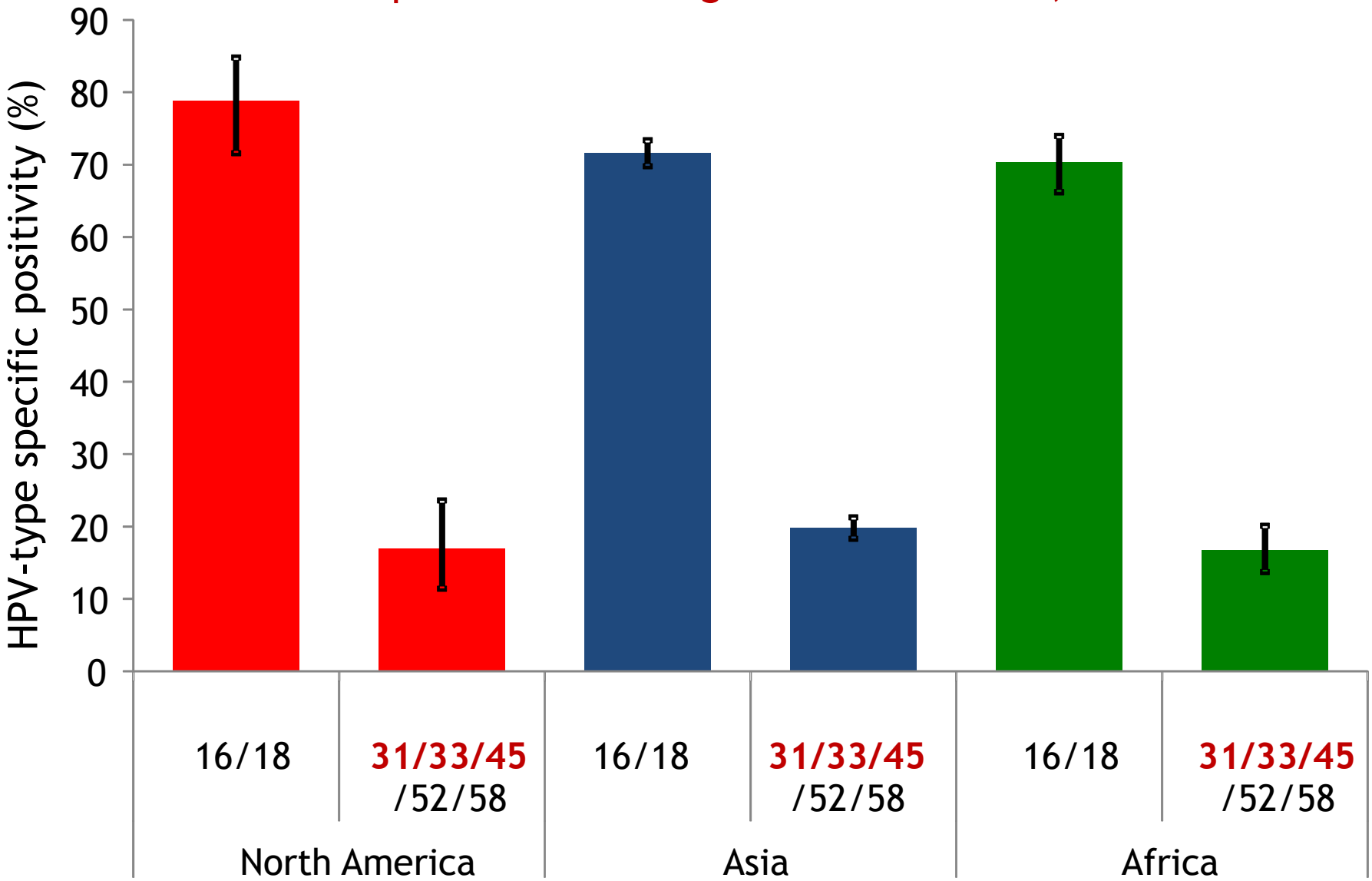
Potential for cancer prevention through HPV vaccination, data for model fit



REF: 1. Serrano, *Infectious Agents and Cancer* 2012

Contribution of HPV-types to cervical cancer

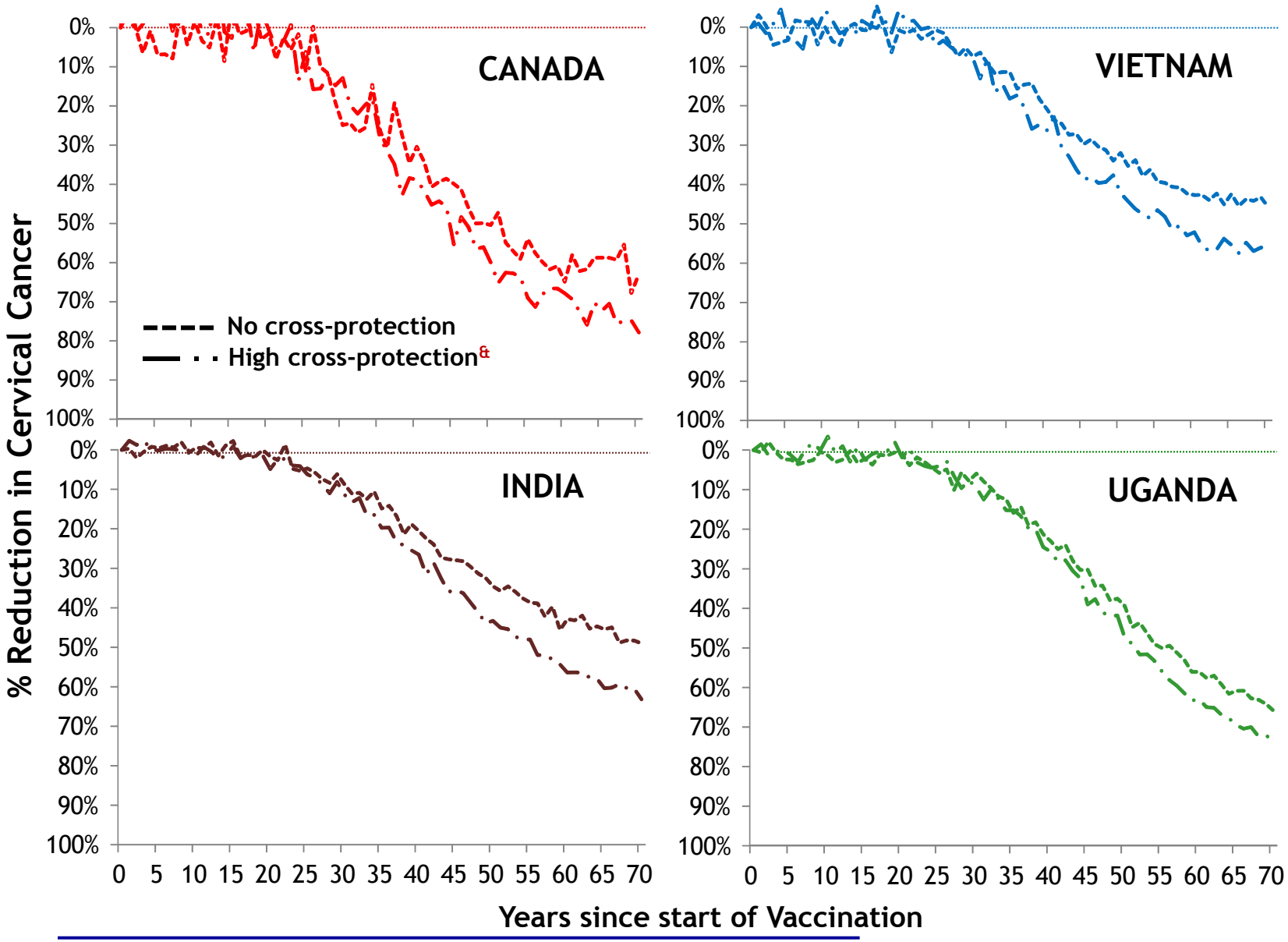
Potential for cancer prevention through HPV vaccination, data for model fit



REF: 1. Serrano, *Infectious Agents and Cancer* 2012

2- or 4-valent vaccine: Cervical cancer

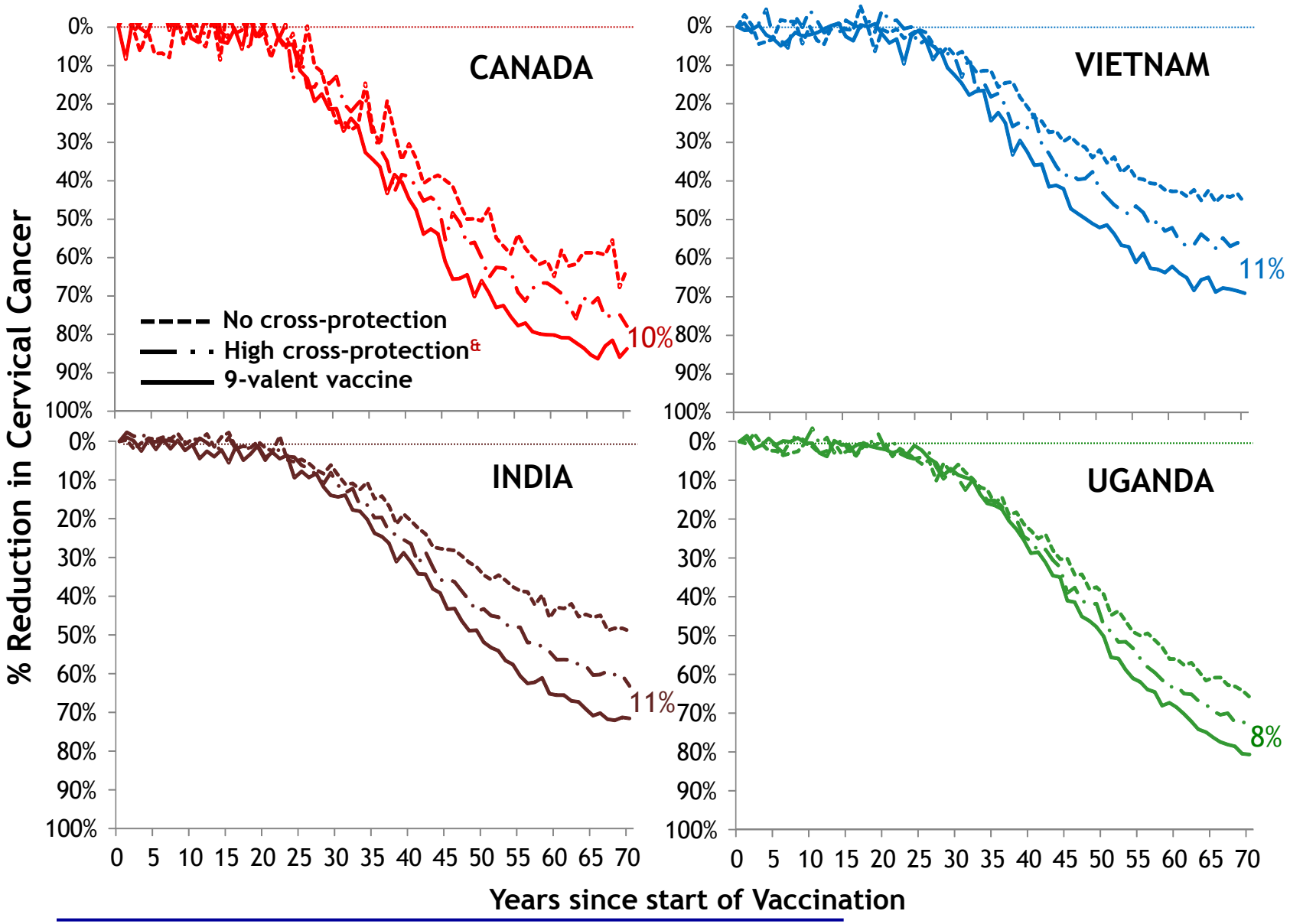
Girls-only (age=10 yrs), Coverage=80%, Vacc duration=Lifelong, Vacc Efficacy=95%



&: HPV-ADVISE, Median (line) of model predictions, High Cross protection 2-valent (CP)=Max CP in Malagon *LID* 2013

9-valent vs 2- or 4-valent vaccine: Cervical cancer

Girls-only (age=10 yrs), Coverage=80%, Vacc duration=Lifelong, Vacc Efficacy=95%



&: HPV-ADVISE, Median (line) of model predictions, High Cross protection 2-valent (CP)=Max CP in Malagon *LID* 2013

Cost-effectiveness: 9-valent vaccine

vs 2-valent or 4-valent vaccine

- HIC: 9-valent immunization is cost-effective in Canada, Austria, and cost saving in the US[1-6]
  - when additional cost/dose of the 9-valent was 10-15% greater than the 4-valent

- LMIC: Girls-only 9-valent immunization is cost-effective in LMIC, in a global analysis using PRIME[7]
  - assuming 2-dose vaccination & cost/dose of the 9-valent in the same range as the 2- and 4-valent vaccines
  - 9-valent was not cost-effective (vs 2-valent), under assumptions of maximum cross-protection for the 2-valent vaccine

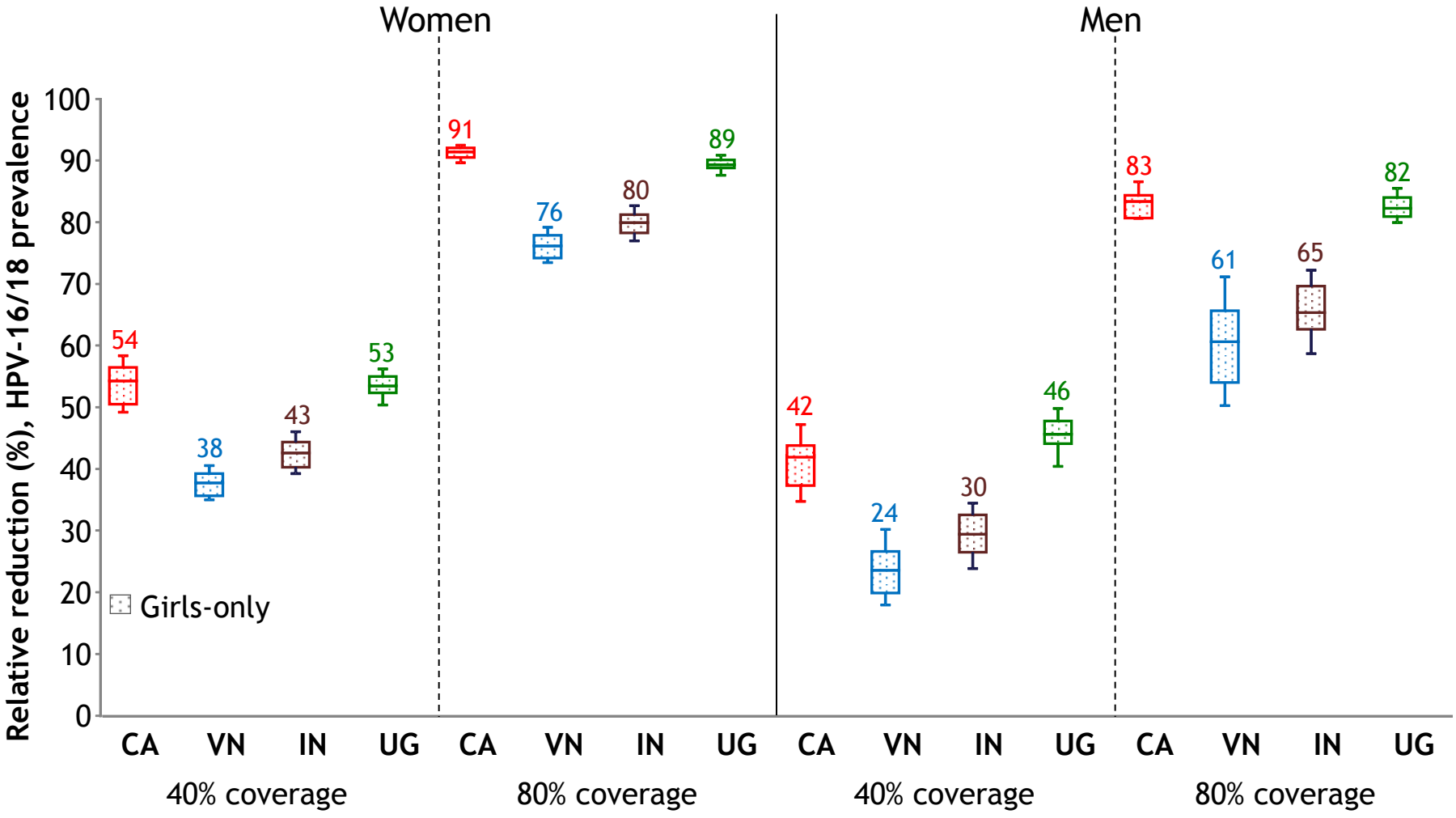
REF: 1. Chaiyakunapruk (SAGE background documents); 2. Brisson, *JNCI* 2016; 3. Chesson, *JID* 2016; 4. Drolet, *Int J Cancer* 2014; 5. Weiss, *IPV* 2014; 6. Boiron, *BMC Infect Dis* 2016; 7. Jit, *presentation at WHO Sept* 2016 (manuscript in preparation)

Gender-neutral vaccination

Model predictions
Effectiveness & Cost-effectiveness

Long term effectiveness: HPV-16/18

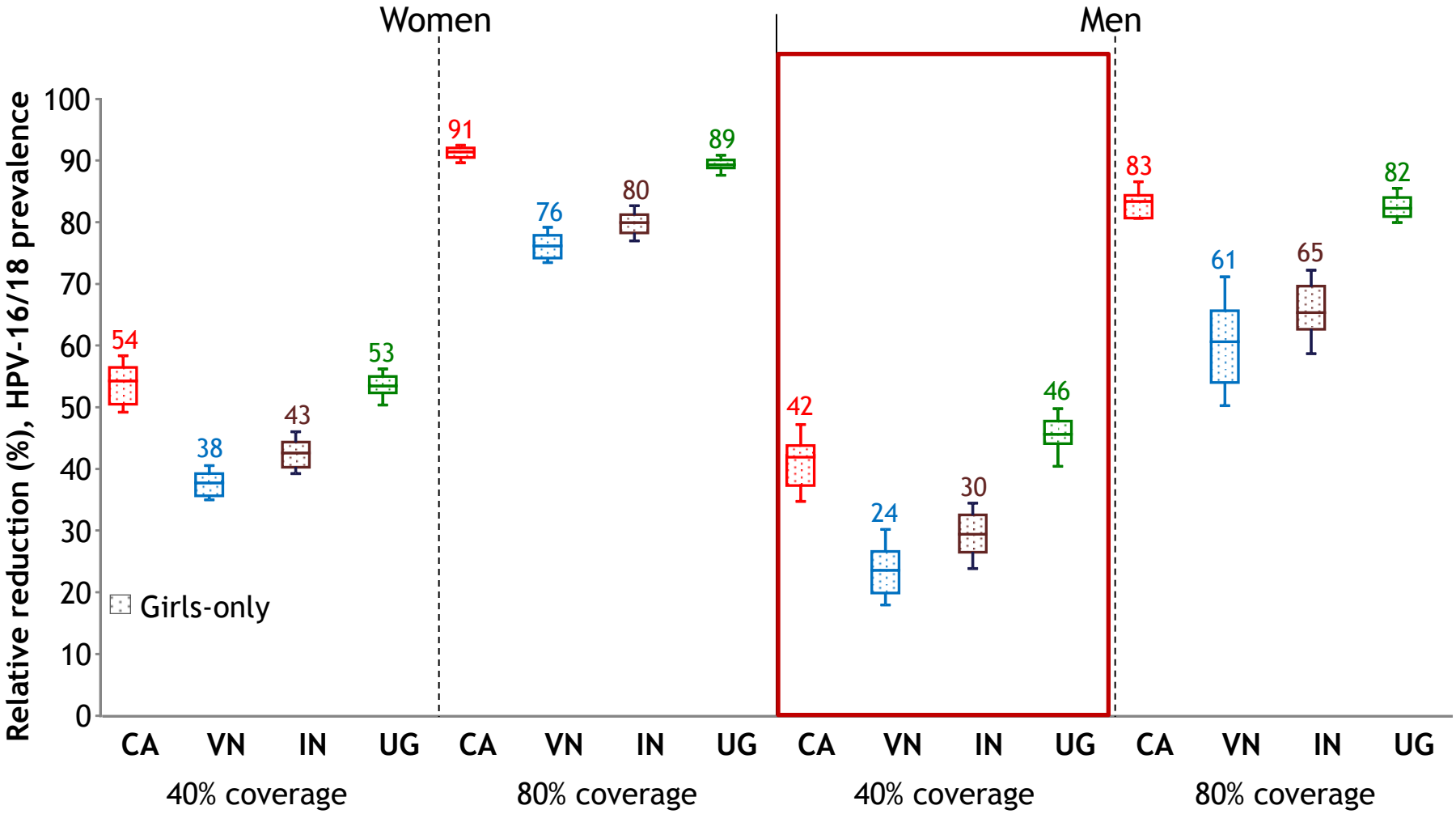
Girls-only vaccination (age=10yrs old), Vaccine duration=Lifelong, Vaccine efficacy=95%



&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; NOTE: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda

Long term effectiveness: Men/Herd Immunity

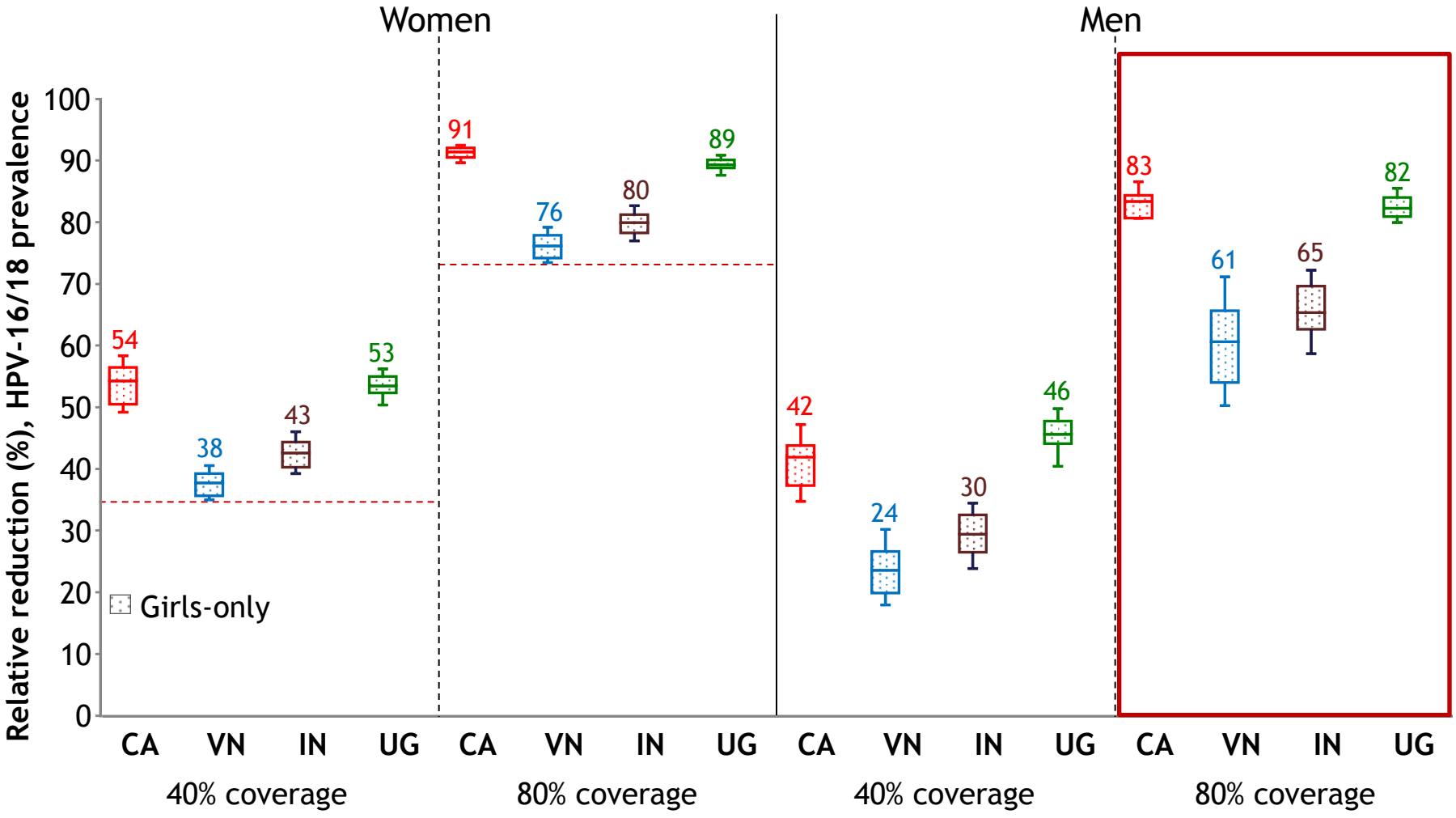
Girls-only vaccination (age=10yrs old), Vaccine duration=Lifelong, Vaccine efficacy=95%



&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; NOTE: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda

Long term effectiveness: Men/Herd Immunity

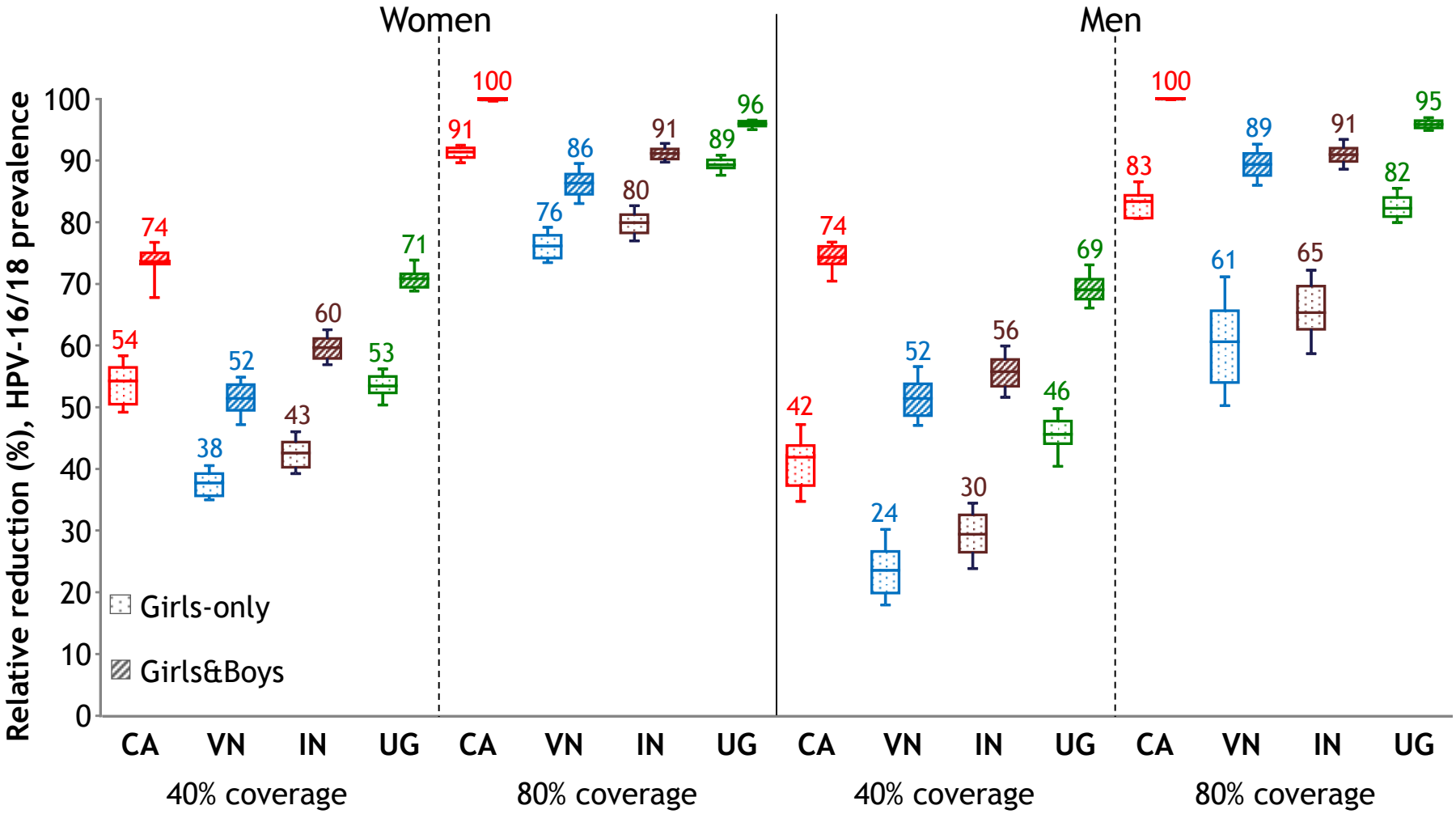
Girls-only vaccination (age=10yrs old), Vaccine duration=Lifelong, Vaccine efficacy=95%



&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; NOTE: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda

Long term effectiveness: HPV-16/18

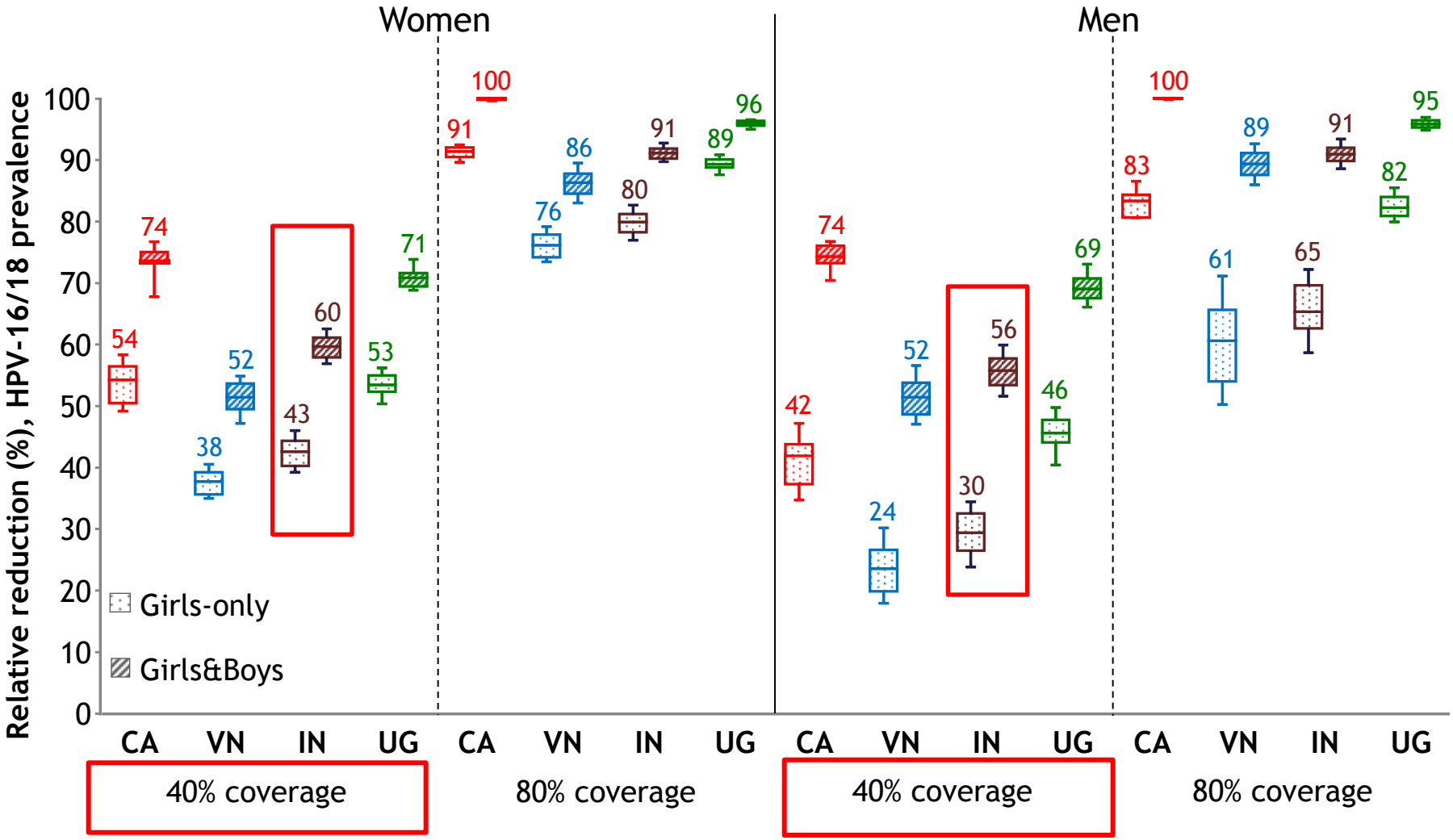
Girls-only & Girls&Boys vaccination, Vaccine duration=Lifelong, Vaccine efficacy=95%



&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; NOTE: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda

Long term effectiveness: HPV-16/18

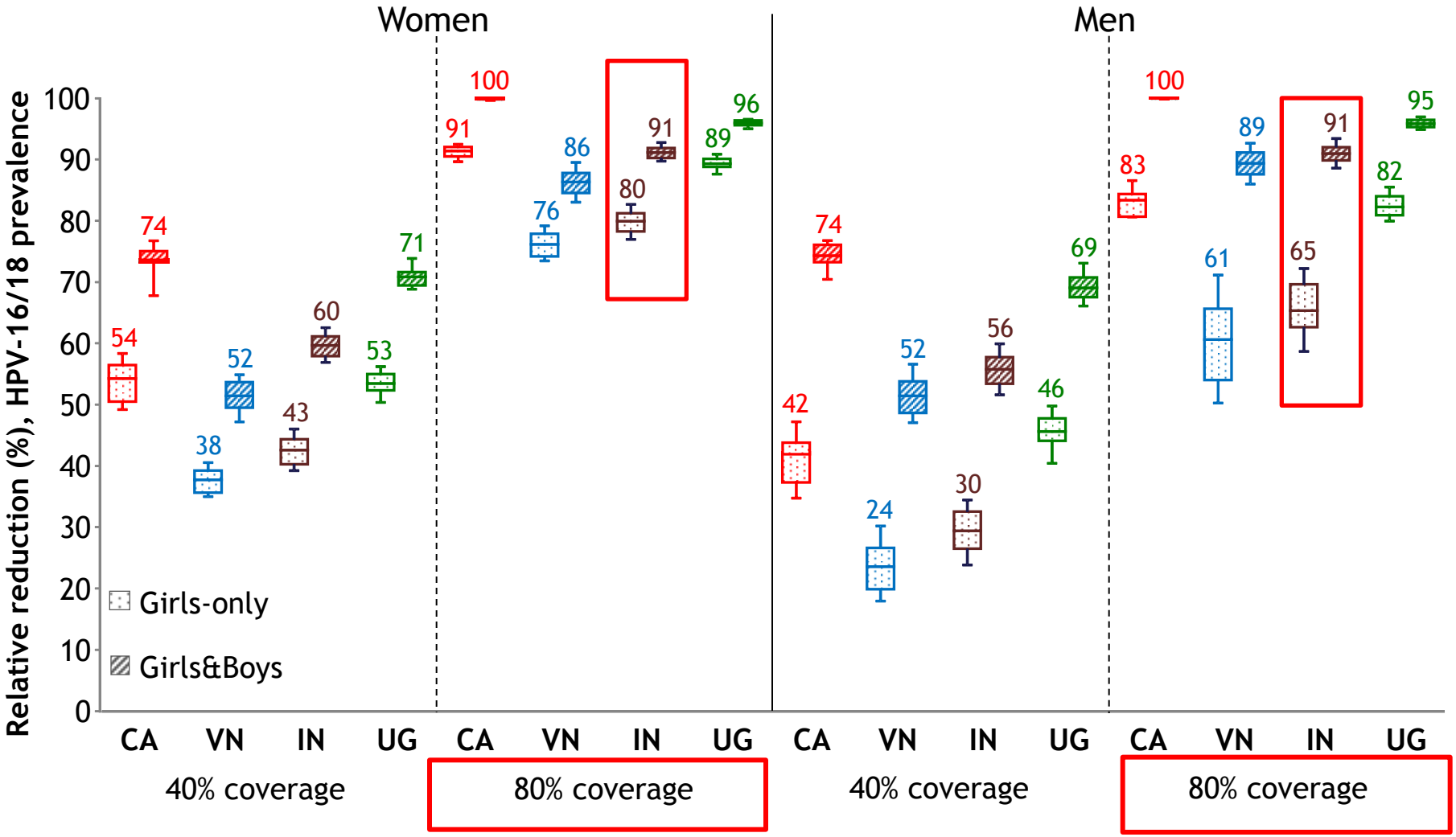
Girls-only & Girls&Boys vaccination, Vaccine duration=Lifelong, Vaccine efficacy=95%



&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; NOTE: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda

Long term effectiveness: HPV-16/18

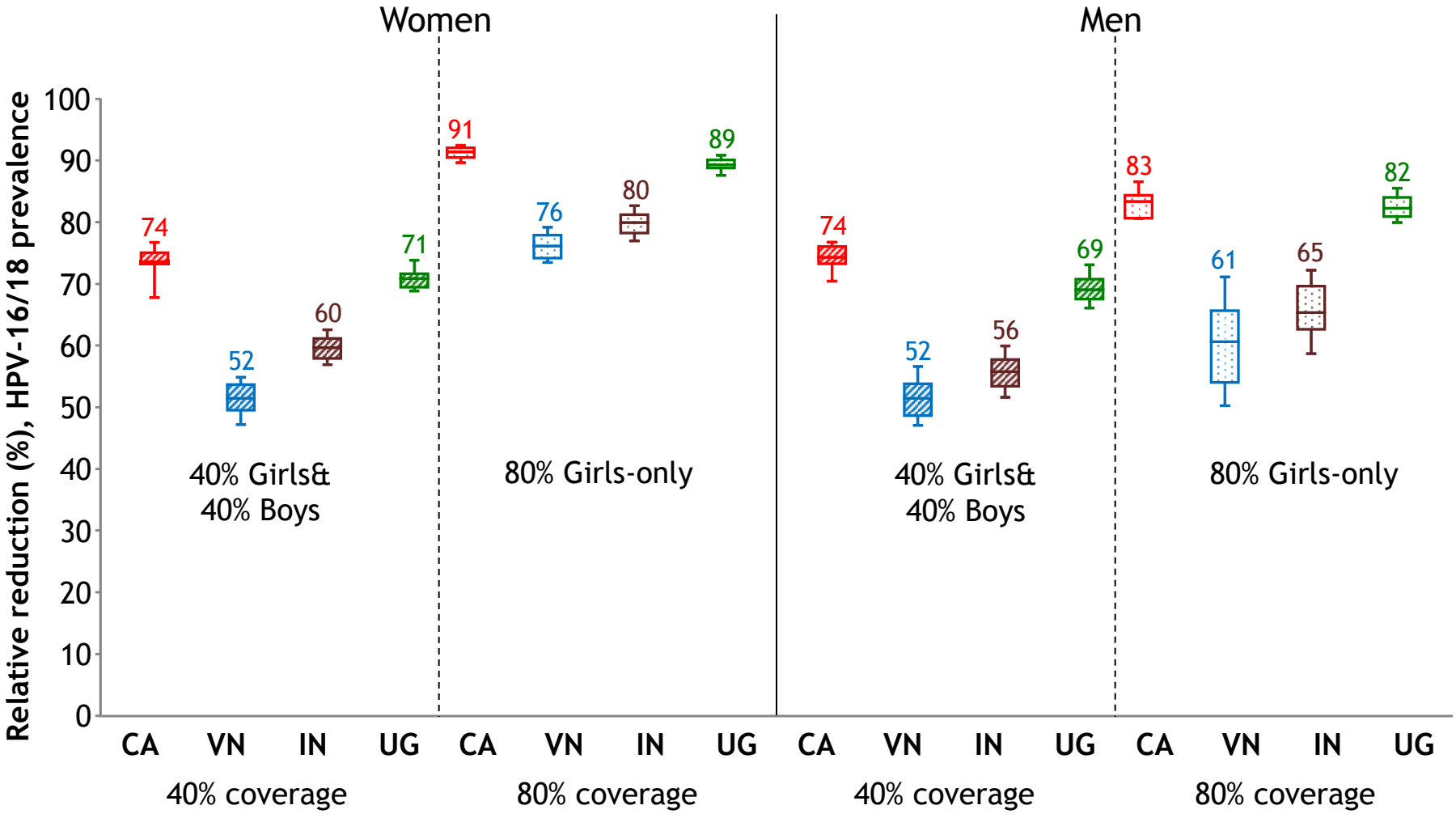
Girls-only & Girls&Boys vaccination, Vaccine duration=Lifelong, Vaccine efficacy=95%



&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; NOTE: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda

Effectiveness: Increasing coverage in Girls or Boys?

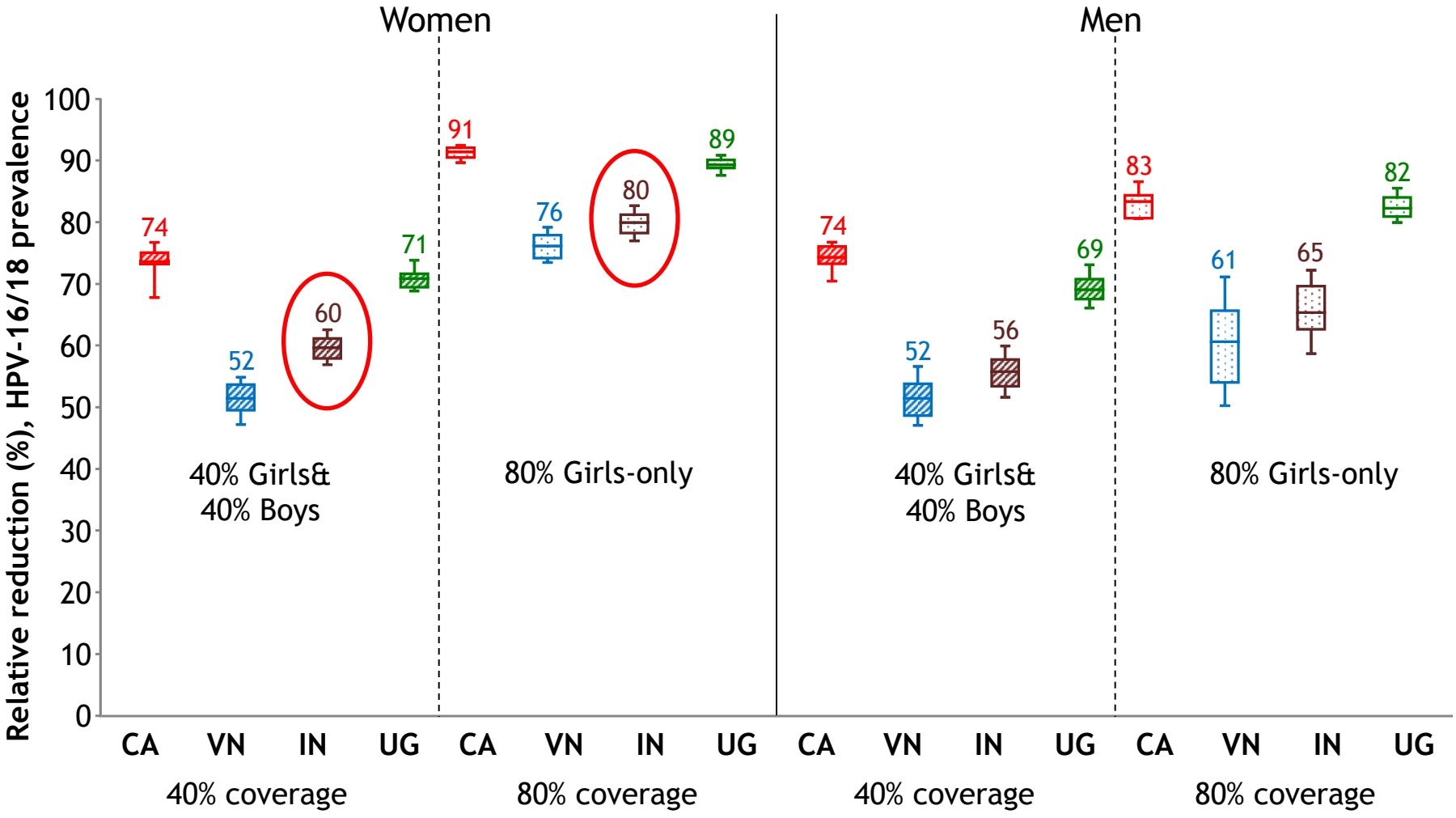
Girls-only & **Girls&Boys vaccination**, Vaccine duration=Lifelong, Vaccine efficacy=95%



&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; NOTE: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda

Effectiveness: Increasing coverage in Girls or Boys?

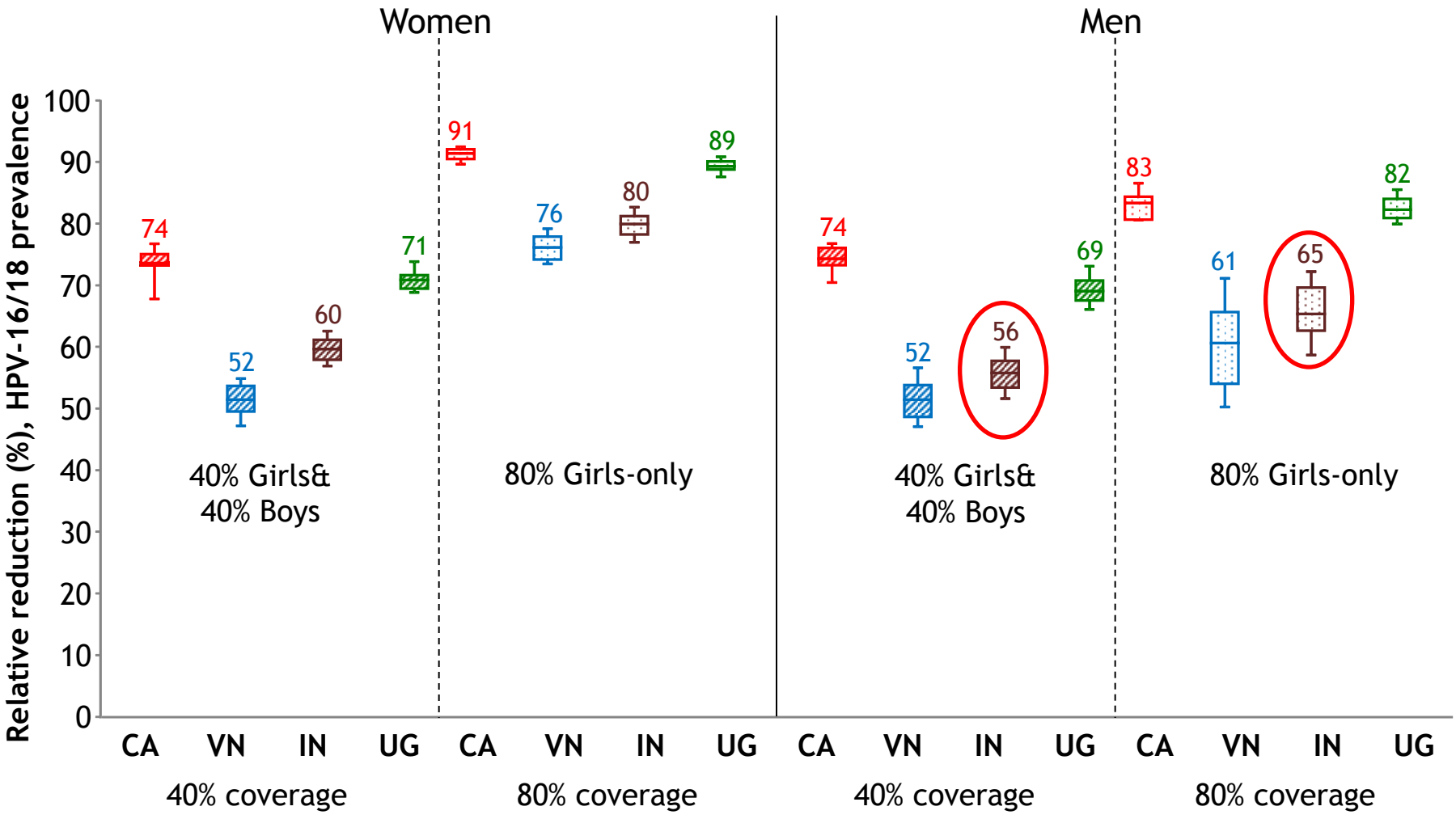
Girls-only & **Girls&Boys vaccination**, Vaccine duration=Lifelong, Vaccine efficacy=95%



&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; NOTE: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda

Effectiveness: Increasing coverage in Girls or Boys?

Girls-only & **Girls&Boys vaccination**, Vaccine duration=Lifelong, Vaccine efficacy=95%



&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; NOTE: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda

Cost-effectiveness: Gender-neutral vaccination

- Strong evidence suggests that Girls-only vaccination will provide substantial herd protection to boys/men[1,2]
  - Added benefit of vaccinating boys is predicted to be limited[1]
- Increasing coverage in girls provides greater impact than including boys
- HIC: Gender-neutral immunization (vs Girls-only) is:
  - Unlikely cost-effective IF vaccine coverage is high in girls[3]
  - May be cost-effective IF vaccine coverage is less than 50% in girls[3]
- LMIC: Cost-effectiveness studies of Gender-neutral immunization are largely lacking[3]
- Considerations about Gender-neutral immunization should focus on:
  - Feasibility of increasing coverage in girls vs vaccinating boys[1]
  - Equity for men who have sex with men
  - Vaccine price

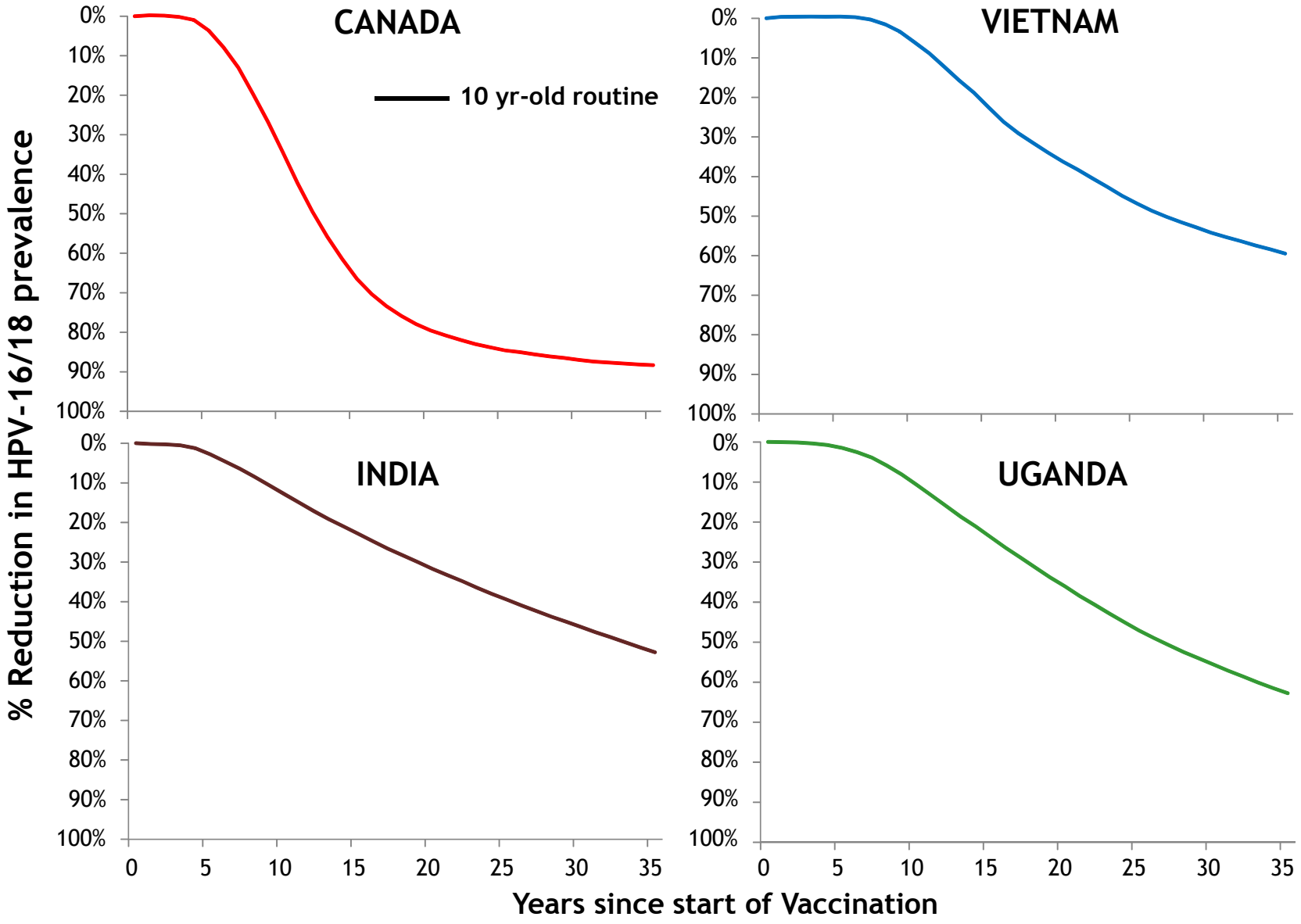
REF: 1. Brisson, *Lancet Public Health* 2016; 2. Drolet *Lancet Infect Dis* 2012; 3. Chaiyakunapruk (SAGE background documents).

Multiple age cohort HPV immunization

Model predictions
Effectiveness & Cost-effectiveness

Multiple age cohort immunization: HPV-16/18[&]

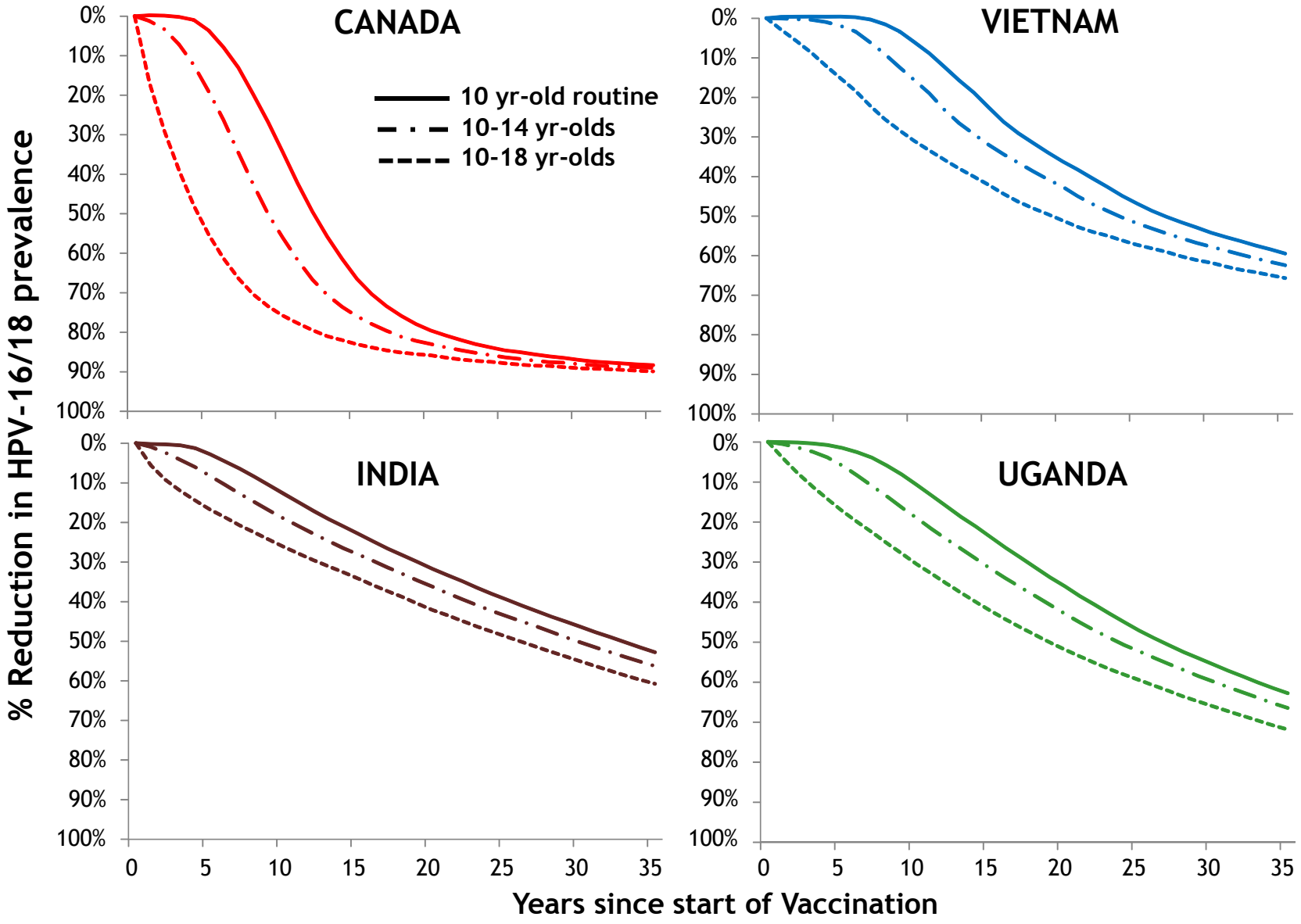
Girls-only vaccination, Coverage=80%, Vaccine duration=Lifelong, Vaccine Efficacy=95%



&: HPV-ADVISE, Median (line) of model predictions

Multiple age cohort immunization: HPV-16/18[&]

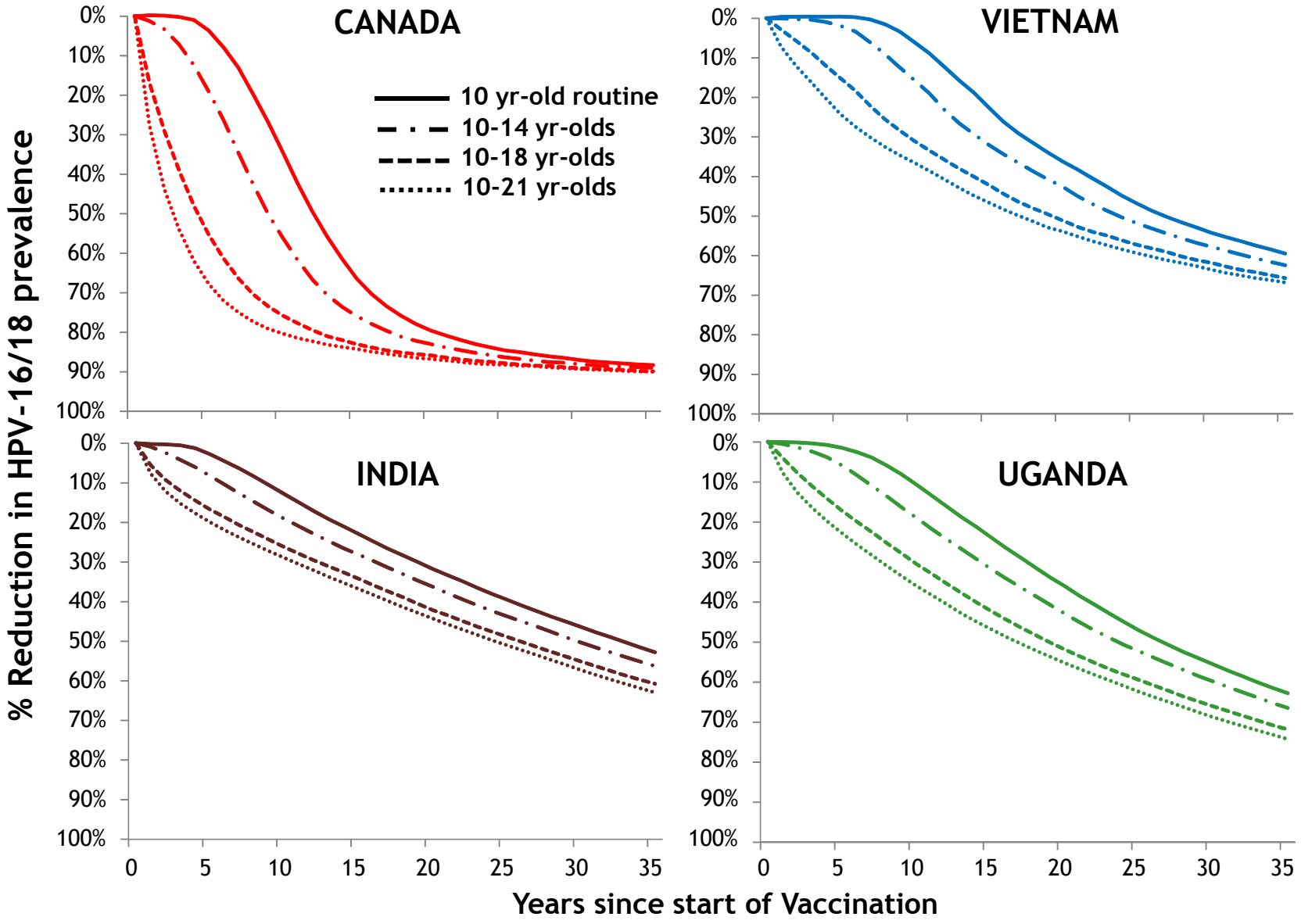
Girls-only vaccination, Coverage=80%, Vaccine duration=Lifelong, Vaccine Efficacy=95%



&: HPV-ADVISE, Median (line) of model predictions

Multiple age cohort immunization: HPV-16/18[&]

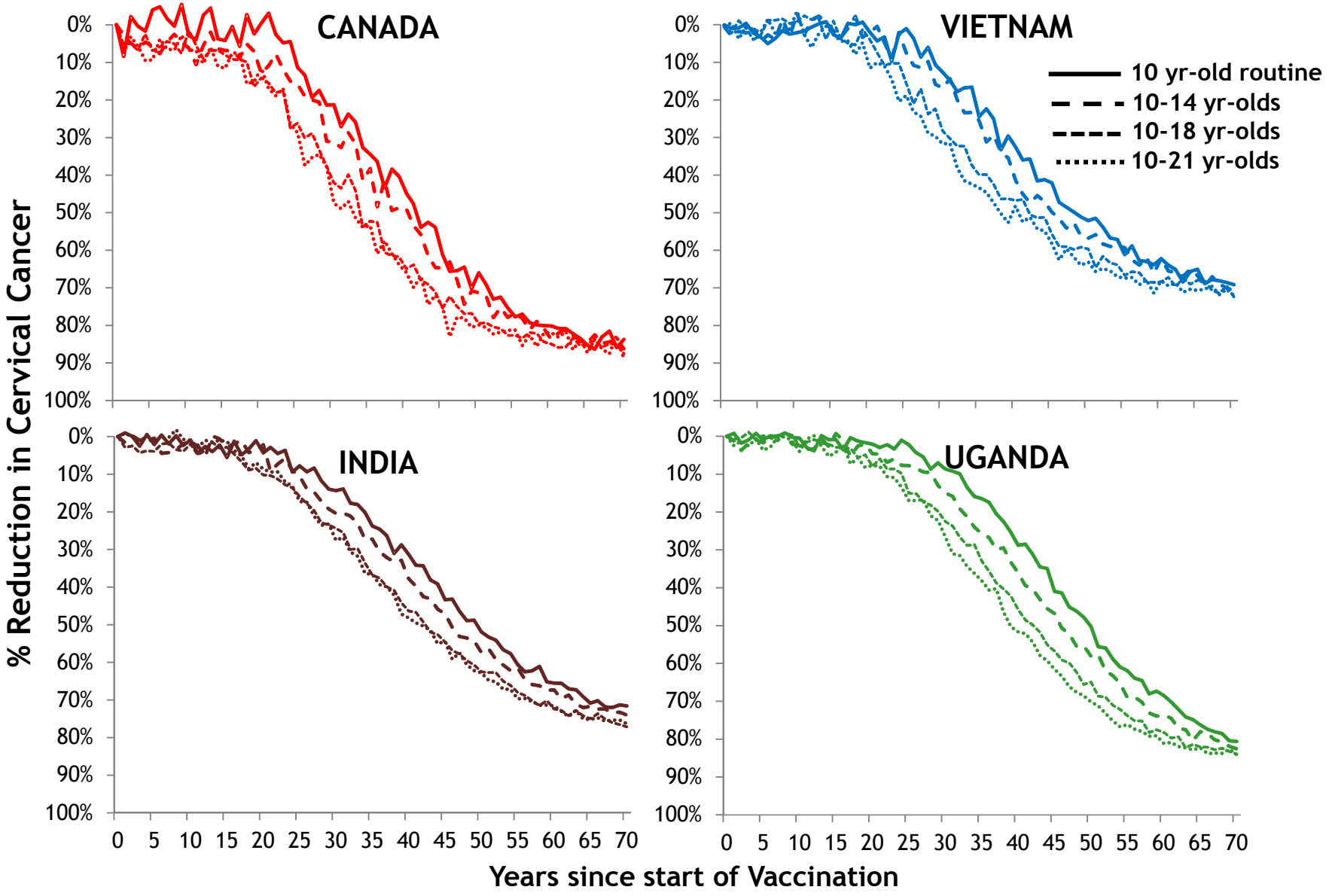
Girls-only vaccination, Coverage=80%, Vaccine duration=Lifelong, Vaccine Efficacy=95%



&: HPV-ADVISE, Median (line) of model predictions

Multiple age cohort immunization: Cervical cancer&

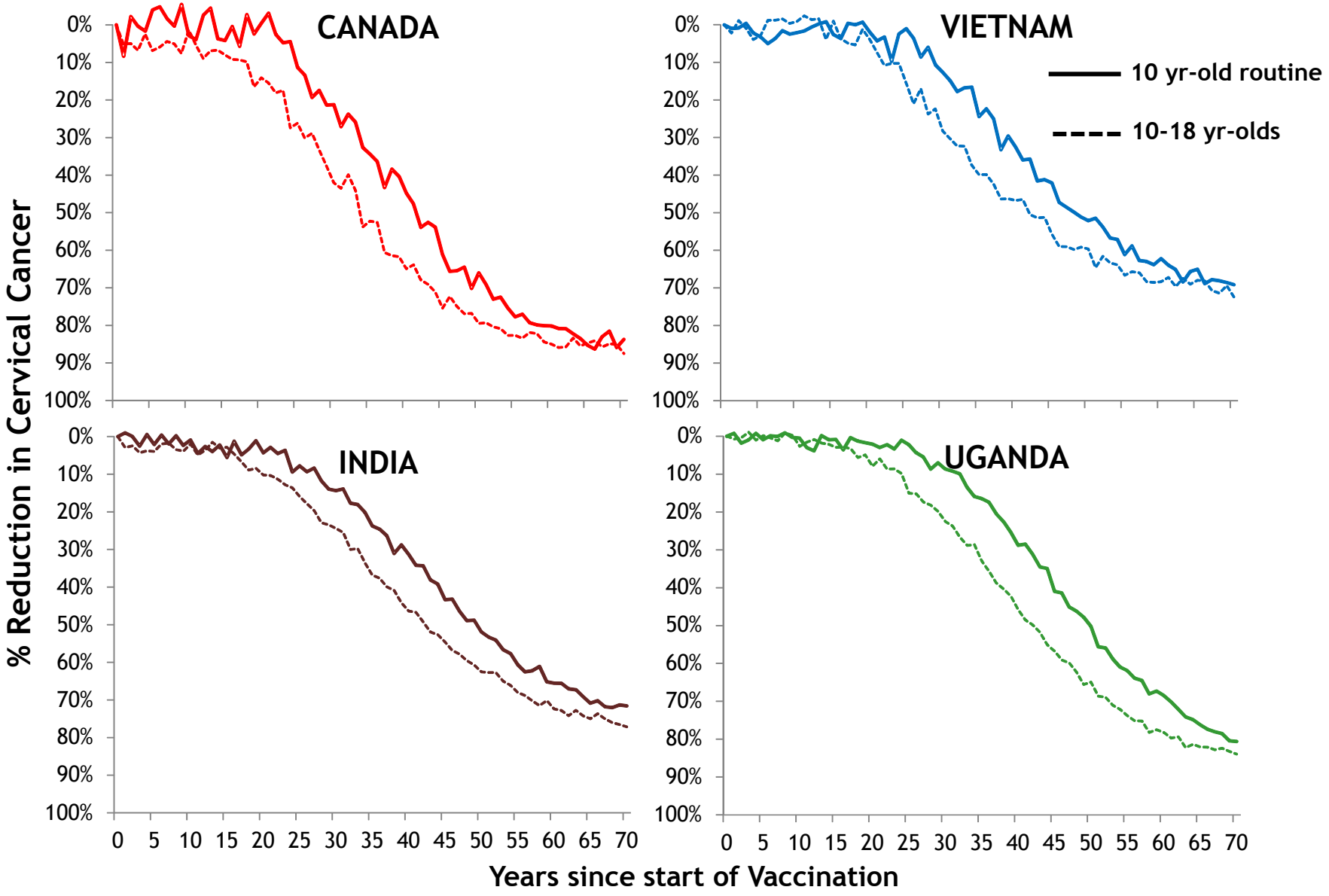
Girls-only & 9-valent, Coverage=80%, Vaccine duration=Lifelong, Vaccine Efficacy=95%



&: HPV-ADVISE, Median (line) of model predictions

Multiple age cohort immunization: Cervical cancer&

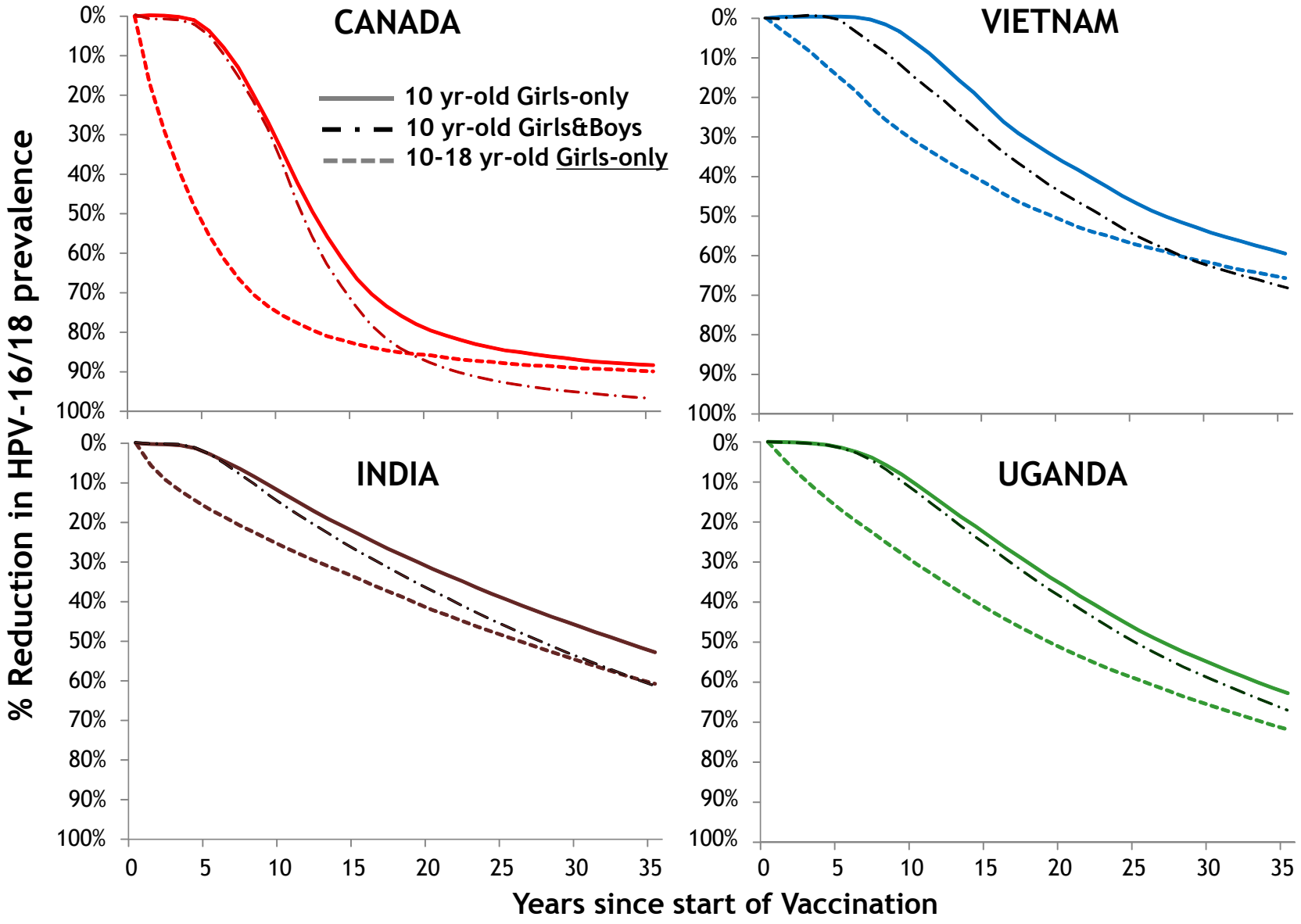
Girls-only & 9-valent, Coverage=80%, Vaccine duration=Lifelong, Vaccine Efficacy=95%



&: HPV-ADVISE, Median (line) of model predictions

Multiple age cohort vs Gender-Neutral: HPV16/18[&]

Coverage=80%, Vaccine duration=Lifelong, Vaccine Efficacy=95%



&: HPV-ADVISE, Median (line) of model predictions

Cost-effectiveness: Vaccinating multiple age cohorts

vs single age cohort vaccination

- Vaccinating multiple age cohorts predicted to produce faster population-level impact
  - substantial impact in all countries modeled with HPV-ADVISE
  - magnitude of impact depends on country-specific distribution of age at sexual debut and remaining lifetime risk of infection

- HIC: multiple age cohort vaccination of girls/women[1]
  - likely to be cost-effective between 9-18 yrs
  - unlikely to be cost-effective between 19-24 yrs vs 9-18 yrs

- LMIC: In a global analysis using PRIME[2-3], vaccinating multiple age cohorts
  - girls 9–14 yrs old: cost-effective using 2 dose schedules
  - cohorts older than 15 yrs old: reduced incremental cost-effectiveness
    - requires 3-dose schedule
    - more girls/women will already have been infected

REF: 1. Chaiyakunapruk (SAGE background documents); 2. Jit, *Lancet Global Health* 2014; 3. Jit, *presentation at WHO* Sept 2016 (manuscript in preparation)

Question

- What is the incremental effectiveness and cost-effectiveness for cervical cancer prevention of different HPV vaccines based on Girls-only immunization?

Key modeling results

- Girls-only HPV vaccination (vs no vaccination)
  - High population-level effectiveness & strong herd effects
  - Highly cost-effective, irrespective of vaccine used
  - Main driver: Prevention of HPV-16/18 related cervical cancer
    - Cost-effective even when excluding herd immunity, cross-protection & benefit from reducing non-cervical diseases
- 9-valent Girls-only vaccination (vs 2- or 4-valent)
  - Further reduction of cervical cancer, little impact on non-cervical cancers
  - Likely cost-effective (vs 2 and 4-valent) in HIC & LMIC unless
    - very strong cross-protection from 2- or 4-valent is expected
    - 9-valent priced too high
  - Main drivers: Cross-protection from 2/4-valent / vaccine price

Question

- What is the incremental effectiveness and cost-effectiveness of adolescent Gender-neutral HPV immunization compared to Girls-only HPV immunization?

Key modeling results

Incremental effectiveness

- Strong herd effects from girls-only vaccination
- Added benefit of vaccinating boys is predicted to be limited
- Increasing coverage in girls provides greater impact than including boys

Cost-effectiveness of vaccinating girls & boys (vs girls-only)

- HIC: Unlikely cost-effective IF vaccine coverage is high in girls
- LMIC: Studies are largely lacking; Results will vary between countries depending on predicted herd effects

Main drivers

- Magnitude of herd effects by Girls-only vaccination / Burden of anogenital warts and HPV-related cancers

Question

- What is the incremental effectiveness and cost-effectiveness of multiple age cohort HPV immunization of females compared to single age cohort immunization of girls-only aged 9–13 years?

Key modeling results

Incremental effectiveness of multiple age cohort vaccination

- Rapid impact with stronger herd effects
- More cervical cancer cases averted over time

Cost-effectiveness of multiple age cohorts (vs single age cohort immunization)

- Catch-up up to age 14 years predicted to be at least as cost-effective as routine vaccination
- Catch-up after 15 years of age less cost-effective

Main drivers of incremental effectiveness & cost-effectiveness

- Timing of benefits & enhanced herd effects
- Age of start of sexual activity (age-specific proportion susceptible)
- 3 dose recommendation for 15+ year olds

Thank you!

Conflicts of interest statements

- Brisson: Past 3 years, Unrestricted grant, Merck (Zoster burden)
- Drolet: Consultation, GSK (Zoster vaccine)
- Jit, Laprise, Boily, Baussano, Franceschi, Alary, Martin, Bénard : no potential conflicts to declare

HPV related funding

Canada Research Chairs

Chaires de recherche du Canada

Canada