Modelling cervical cancer inequalities worldwide with and without enhanced HPV vaccination and screening efforts

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HPV Board - Antwerp
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Modelling Team

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Conflicts of interest statements

- None to declare

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IRSC CIHR
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Canadian Institutes of Health Research

World Health Organization

Single-Dose HPV Vaccine
EVALUATION CONSORTIUM

Background

Optimization goals & outcomes when making vaccination decisions

What is the policy question to model?

Optimization issue	Reduction of Cervical cancer/ Elimination	Vaccine Supply constraints	Budget constraints
Goal	Maximise health benefits	Maximise health benefits for Minimal number of doses	Maximise health benefits for Minimal cost
Analysis	Population-level impact	Efficiency	Cost-effectiveness
Outcome	Absolute reduction in cervical cancer incidence over time	Number needed to vaccinate to prevent 1 cervical cancer (NNV)	Cost per DALY

To prioritize, it is important to understand what is to be optimized?
Prioritization will depend on the stated goals and outcomes of HPV vaccination.
Ranking of strategies will depend on the optimization goal.

HPV-ADVISE - Global analysis (67 LMICs)

Vaccination strategies ranked from lowest to the highest NNV

NNV=Number of doses needed to prevent 1 cervical cancer; Vaccination coverage=80%

Non-inferior 1-dose

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With non-inferior 1-dose (vs 2 doses):

1-dose routine vaccination of 9-year-old girls is the most efficient strategy

- Note: 2 doses is dominated by 1 dose (the 2nd dose is redundant)

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SCENARIO: 1-dose routine and MAC vaccination up to 20 year old; 2-dose MAC vaccination >20 years old. 1-dose VE=100% and VD=lifelong.

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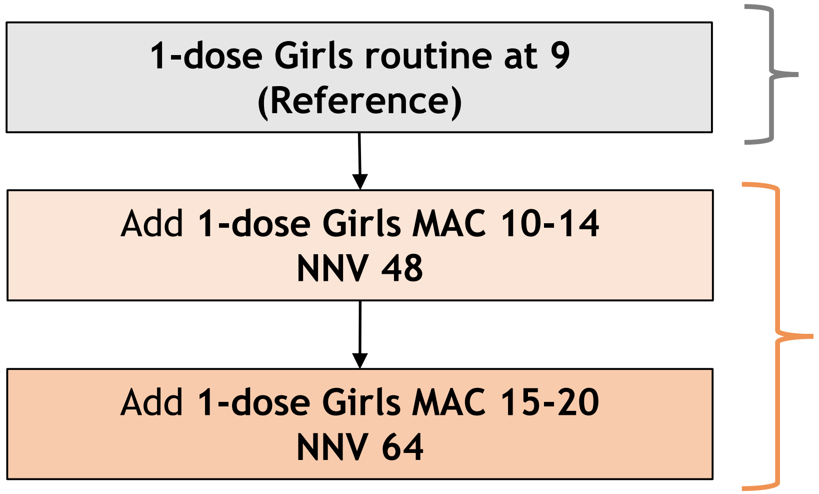

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Global inequalities & cervical cancer elimination

- About 85% of cervical cancers worldwide occur in LMICs[1]
  - driving factor for these current inequalities is disparity in access to screening
  - 26% of women ever screened in LMICs vs 83% in HICs[2]

- To reduce worldwide inequalities, the WHO announced a global call for action to eliminate cervical cancer
  - reduce cervical cancer incidence below 4/100,000 women-years in all countries
  - WHO target: vaccinate 90% of girls, screen 70% of women, and treat 90% of pre-cancers/cancers[3]

- Large inequities in HPV vaccine distribution remain between LMICs and HICs
  - 28% of girls vaccinated in LMICs vs 66% in HICs (2020)[4]
  - about 50% of LMICs vs >90% of HICs have vaccination programs for girls[5]
  - despite mathematical models consistently showing the high projected population-level impact, efficiency and cost-effectiveness of vaccinating girls and young women[6-9]

- Inequalities in cervical cancer are set to increase due to unequitable vaccine distribution

1. Globocan; 2. Bruni et al. Lancet Global Health 2022; 3. Brisson, Kim, Canfell et al. Lancet 2020; 4. Bruni (personal communication), 5. HPV Dashboard (2022); 6. Jit et al. Vaccine 2014; 7. Drolet, Laprise et al. Lancet Infec Dis 2021; 8. Bénard et al. Lancet Public Health 2023; 9. Bénard POSTER 200 IPVC 2024

Objective

Using mathematical modelling, to project and compare the trends in cervical cancer incidence in Low- and Lower-Middle Income (LMICs) vs High-Income Countries (HICs):

- assuming the status quo in HPV vaccination and screening coverage, and
- under various enhanced prevention strategies for LMICs

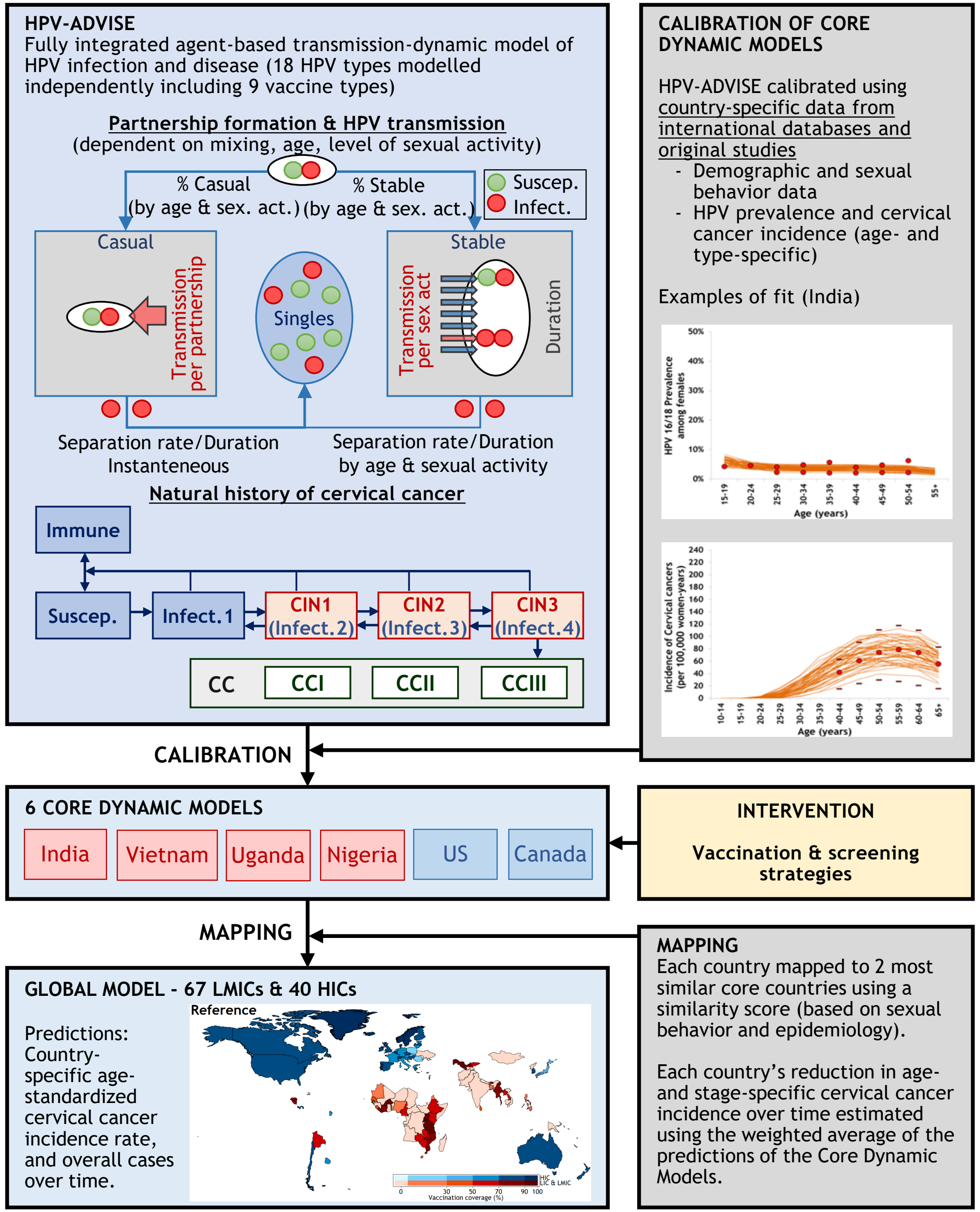
- To examine the following questions:
  - Are we currently on the path to cervical cancer elimination?
  - What is the potential evolution of inequalities in cervical cancer worldwide under current screening and vaccination coverage?
  - What would be the potential impact of enhanced prevention strategies on inequalities and elimination?

Methods

Methods HPV-ADVISE overview

Model Structure, Core Modelled Countries & Mapping

- HPV-ADVISE[1]
- Agent-based transmission-dynamic model of HPV infection & cancer
  - Stratified by sex, age, level of sexual activity & screening behaviour
- 18 HPV types modelled individually:
  - 9-valent vaccine types + 9 other high-risk types
- Fit HPV-ADVISE to 6 core countries (India, Vietnam, Nigeria, Uganda, US and Canada)
  - Demographic and sexual behaviour
  - HPV prevalence and cervical cancer incidence (age & type-specific)
  - Data from international databases and original studies[&]
- Mapped the results from the 6 modelled core countries
  - Using previously developed mapping algorithm
  - Each 67 LMIC & 40 HIC was mapped to the 2 most similar core countries based on sexual activity and epidemiology[2]

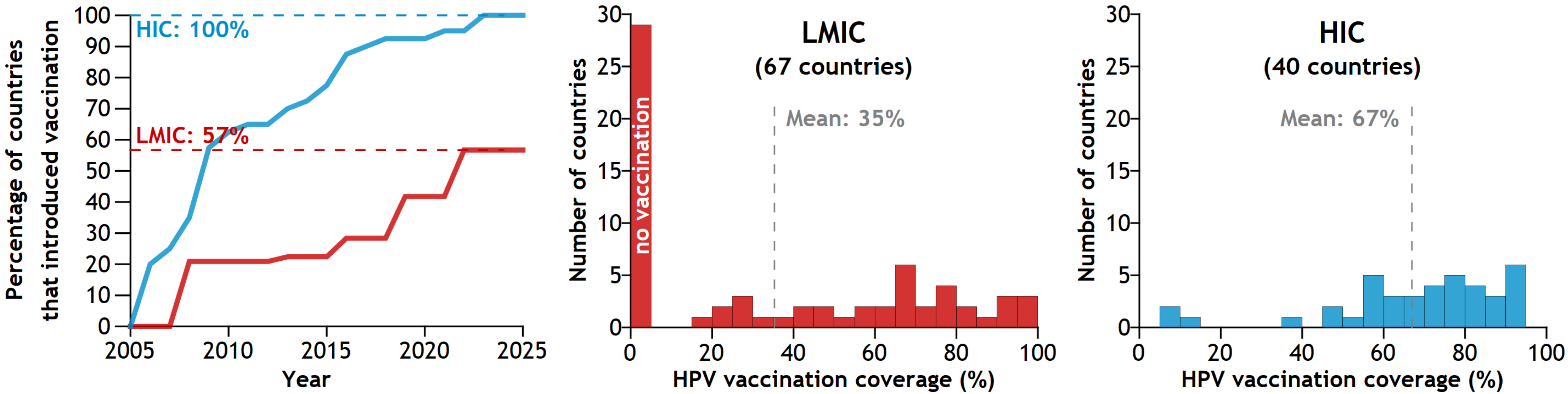


REF: 1. Drolet, Laprise et al., Lancet ID 2021; 2. Brisson, Kim & Canfell et al, The Lancet (2020); &: Demographic and Health Surveys, Multiple Indicator Survey, ICO information Centre on HPV and Cancer, United Nations Statistics Division, HIV and AIDS HUB for Asia Pacific-Evidence to action, WHO Global Health Observatory data repository, original studies from Dr Alary and IARC

Methods Status quo

Vaccination strategies & coverage

- Modelled the vaccination strategy for 67 LMICs and 40 HICs
  - vaccine used (2/4-valent, 9-valent)
  - year of start of vaccination
  - vaccination coverage
  - vaccination strategy (girls-only, girls & boys)



REF: HPV dashboard 2025 (2023 data); Note: only 1 of 67 LMIC has gender-neutral vaccination

Methods Status quo

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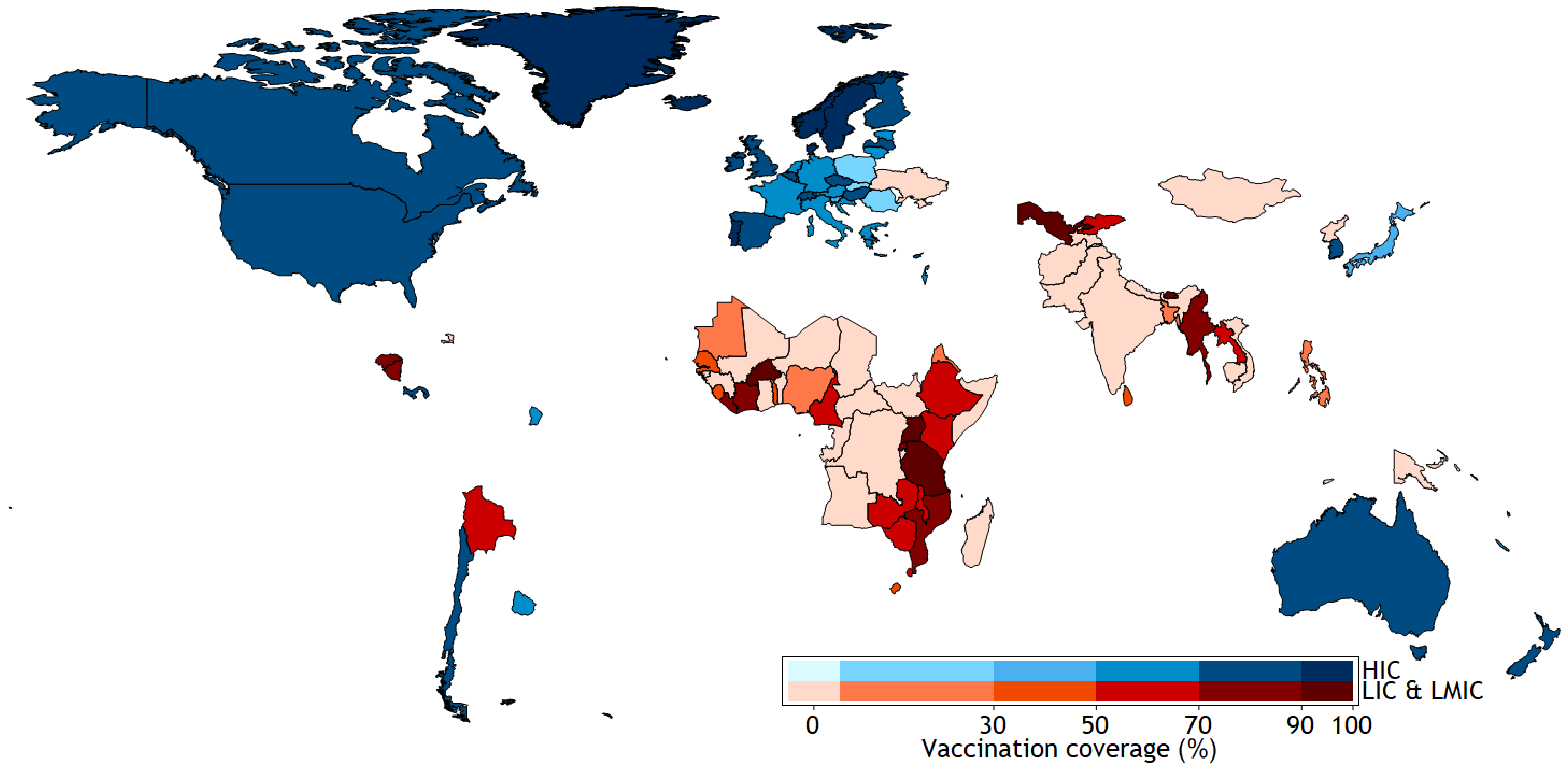

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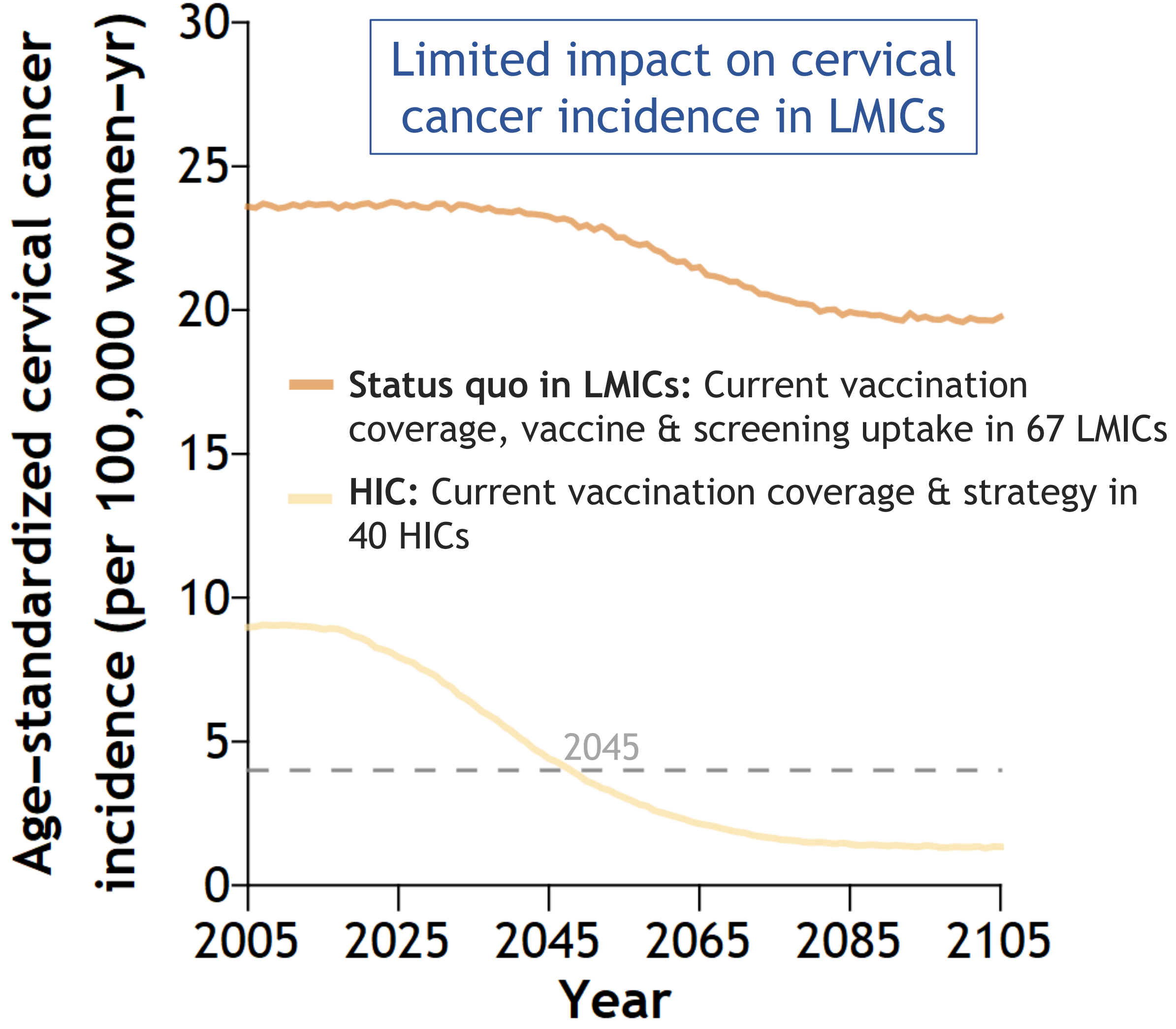
Methods Enhanced strategies

- Enhanced strategies for the 67 LMICs
  1. **9-valent:** All countries use the 9-valent
  2. **Girls-only:** 90% vaccination coverage for 9-year-old girls
  3. **Gender-neutral & MACs:** 90% coverage for 9-year-old girls and boys & multi-age-cohort (MAC) vaccination to age 25 years for women and 20 years for men
  4. **WHO targets:** 90% vaccination coverage & 70% screening coverage (twice lifetime) elimination targets
  5. **WHO targets + Gender-neutral & MACs:** 90% vaccination coverage & 70% screening coverage (twice lifetime) elimination targets + gender-neutral & MAC vaccination strategy

- Assumptions:
  - 100% vaccine efficacy & lifelong duration of protection
  - Maximum HPV vaccination coverage is reached in 2025
  - 9-valent vaccination is used in all scenarios except the status quo

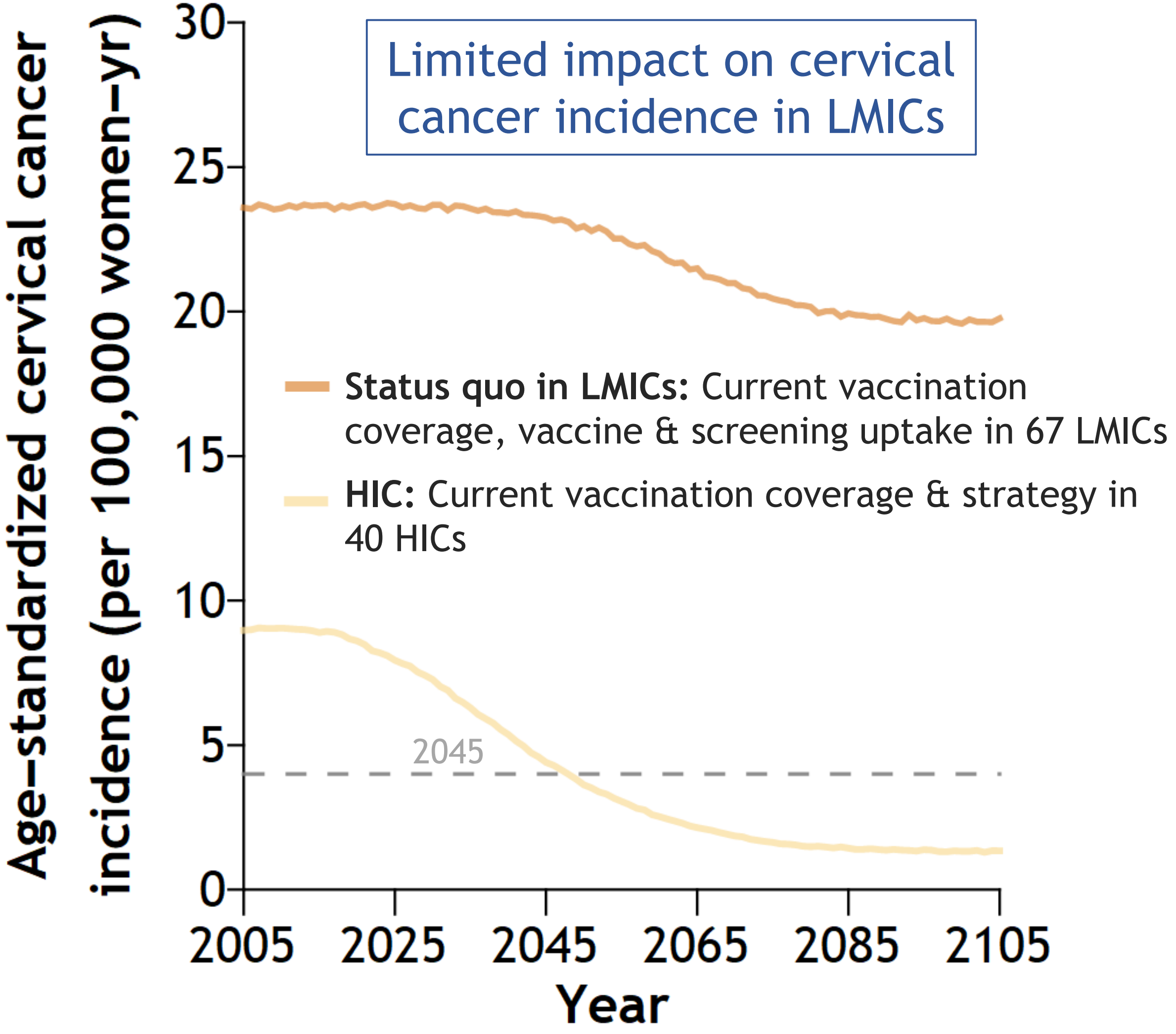
Results

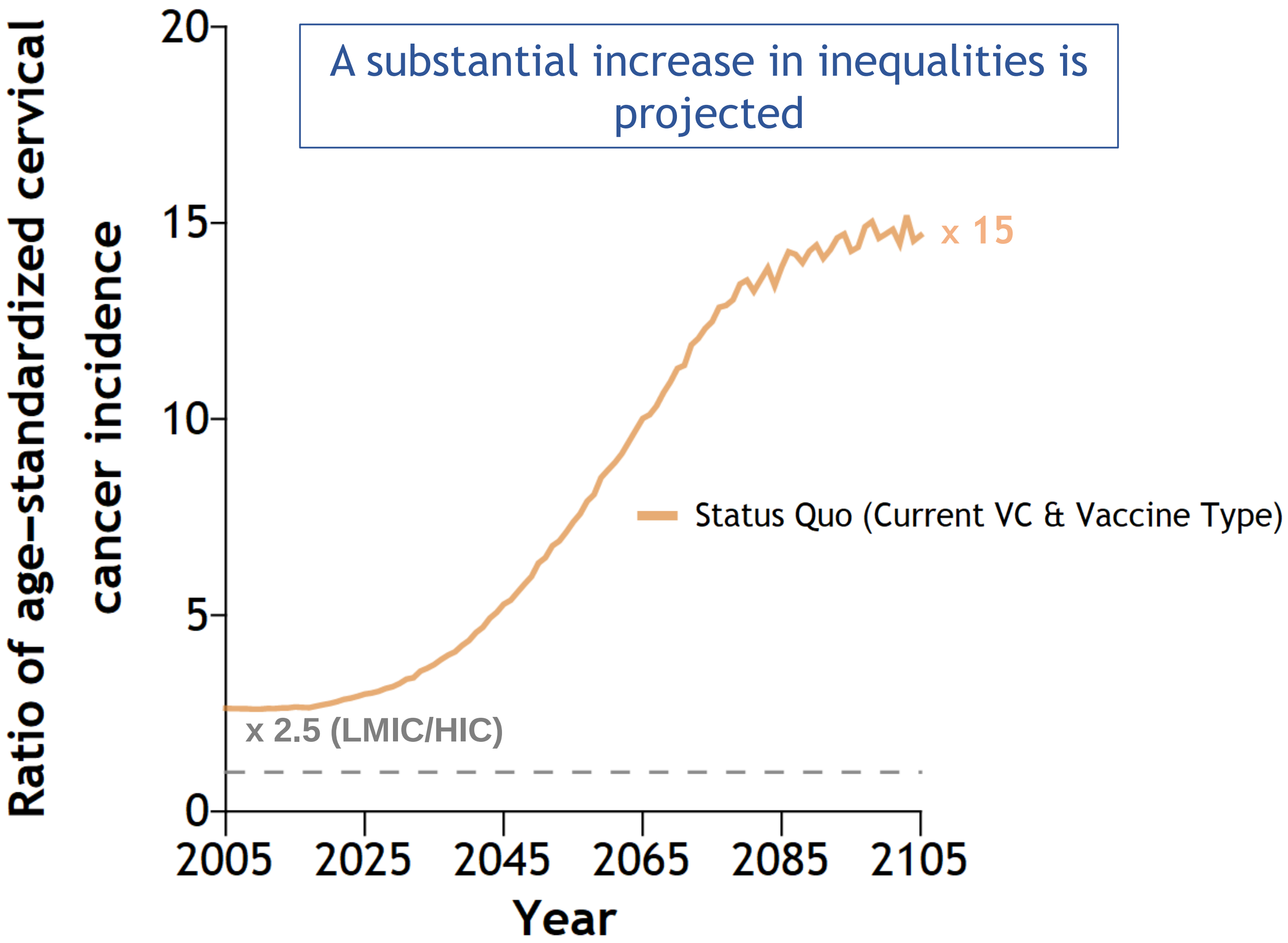
Cervical cancer elimination & Global Inequalities



HPV-ADVISE projections

Cervical cancer elimination & Global Inequalities





HPV-ADVISE projections; Ratio = age-standardized incidence in LMICs vs HIC

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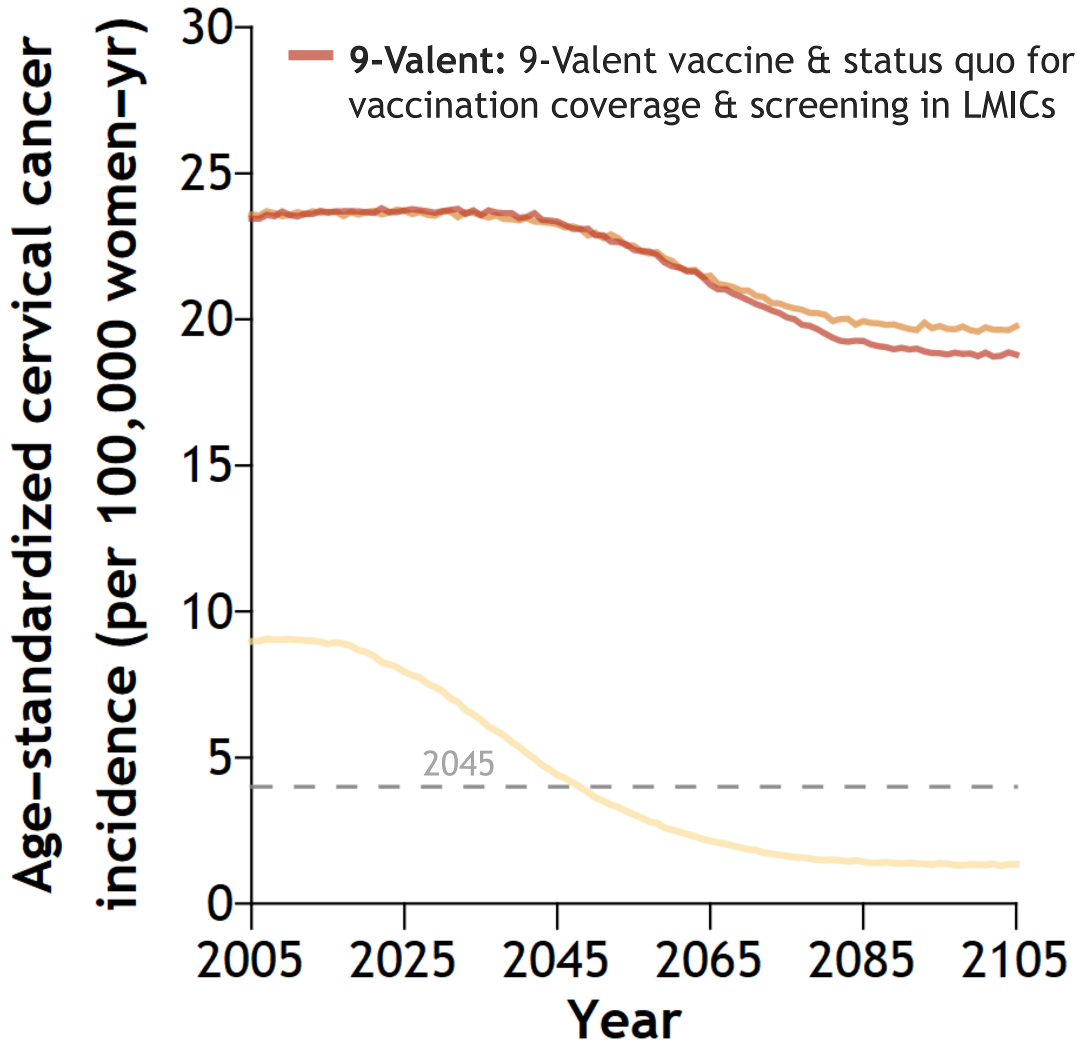

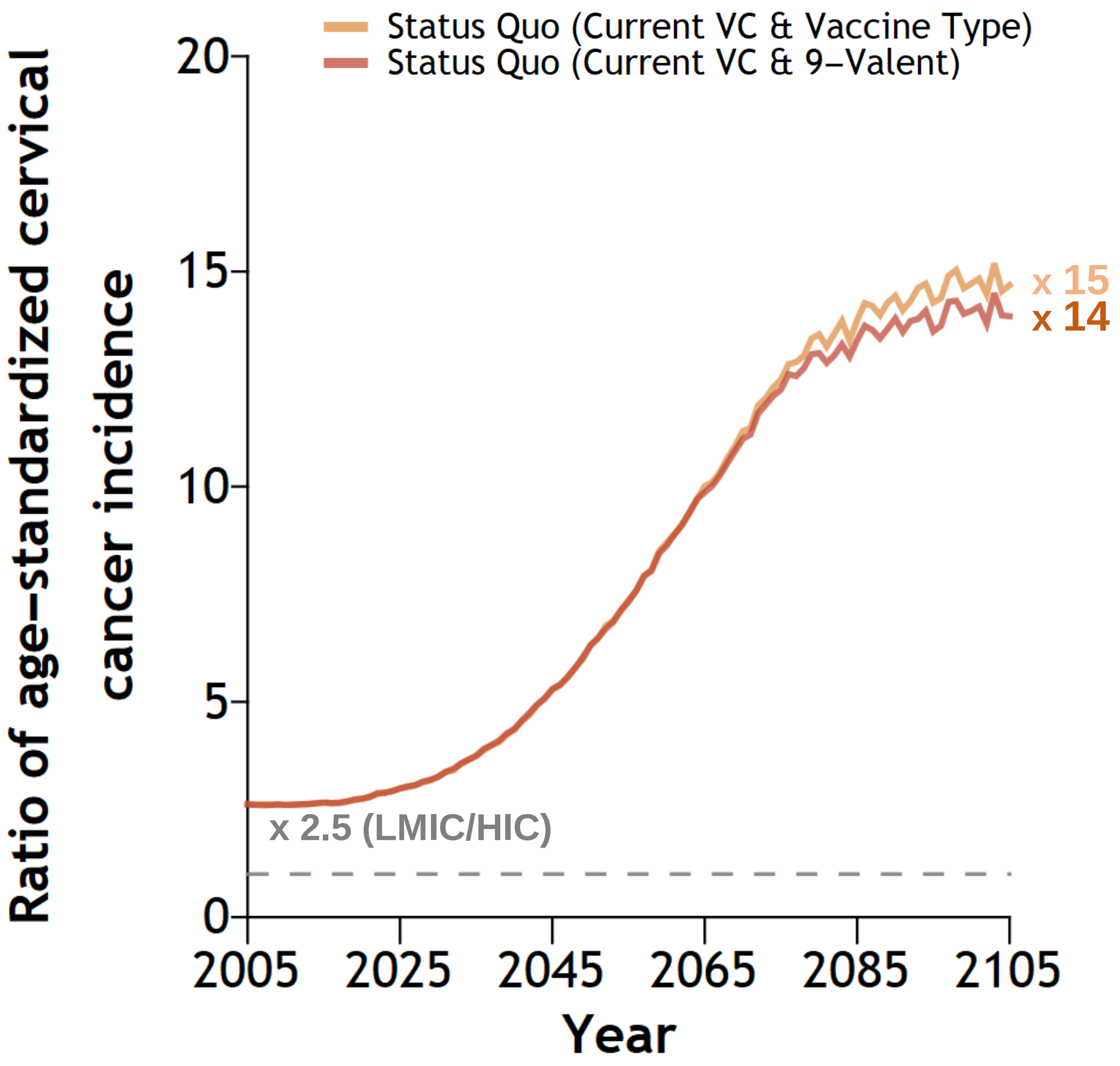

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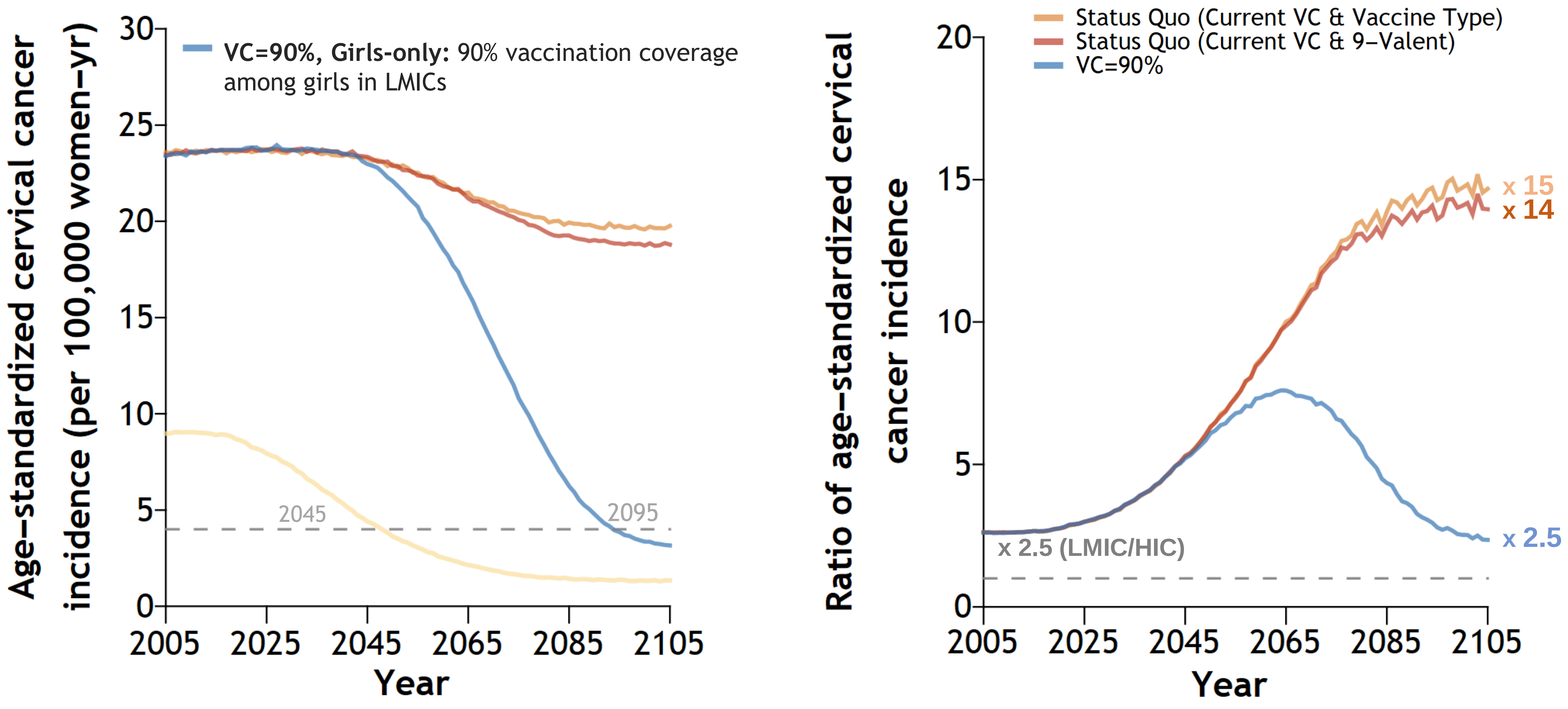

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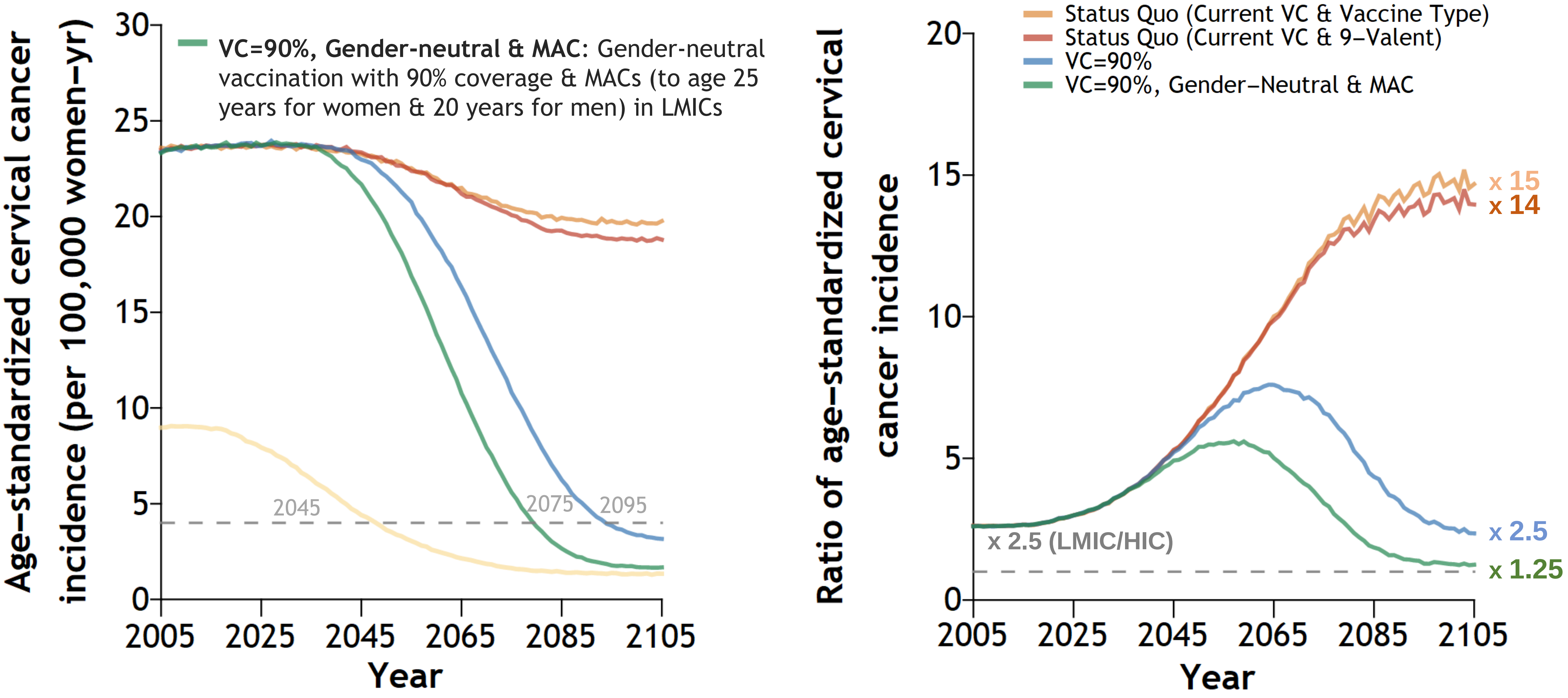

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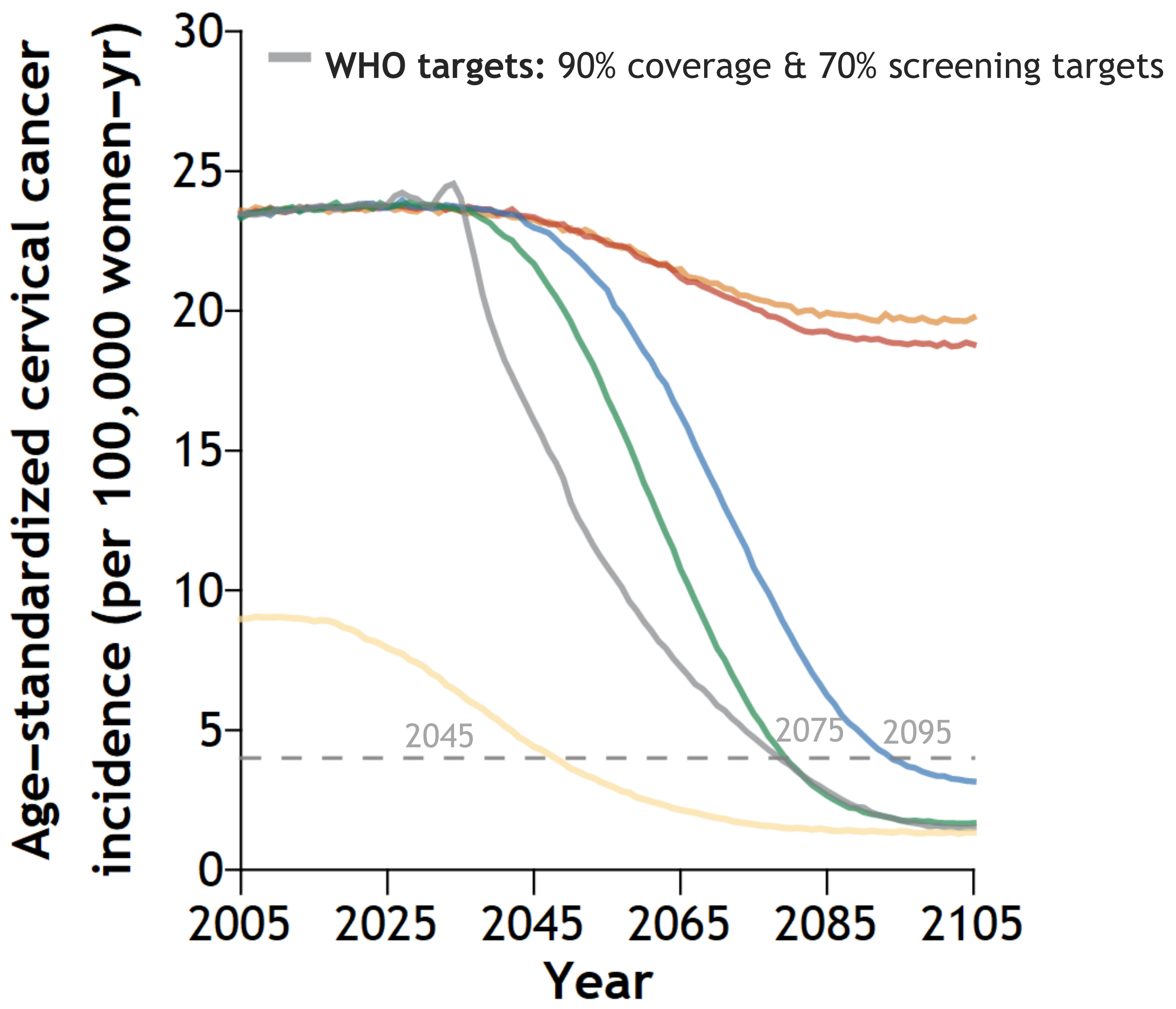

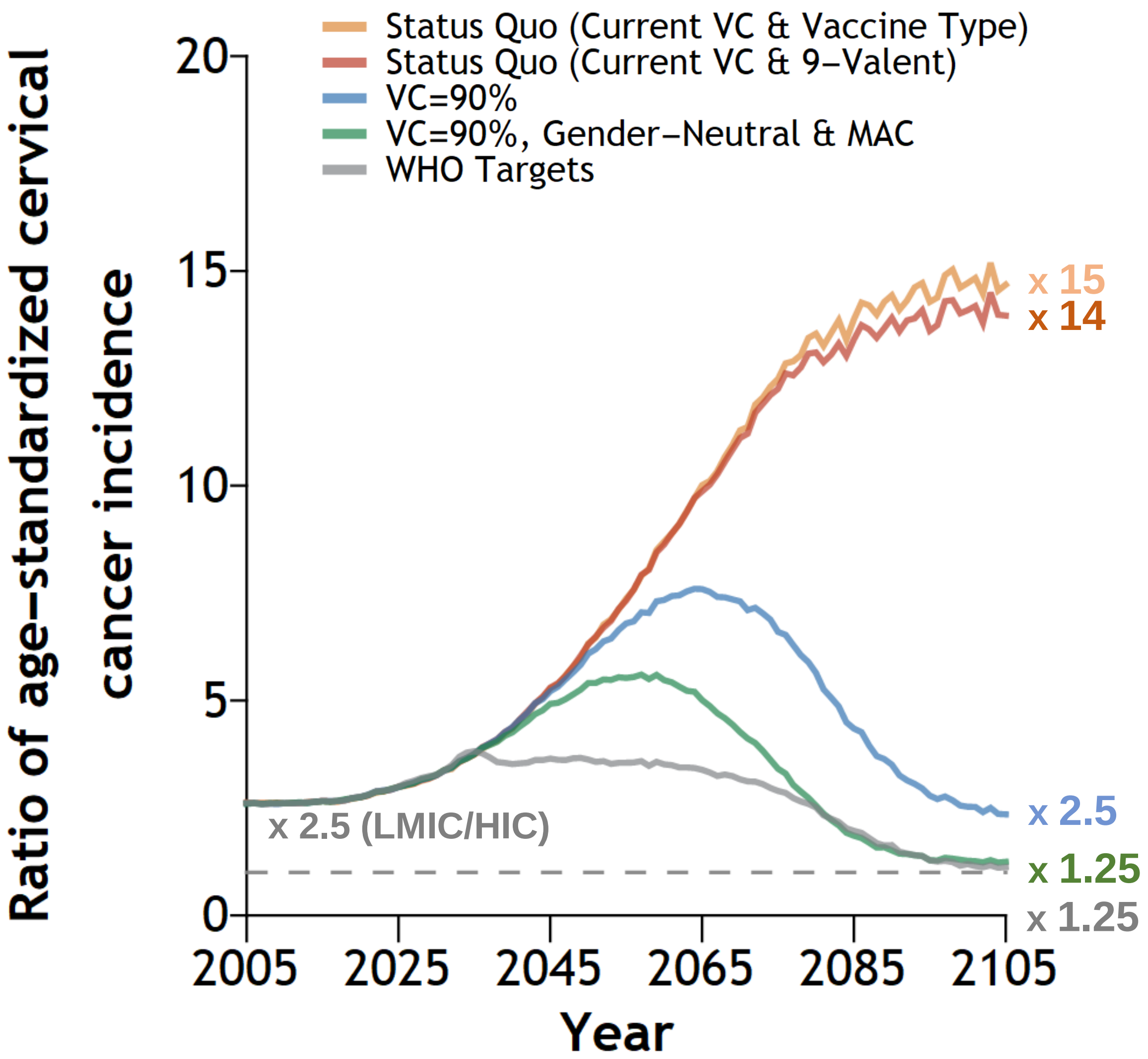

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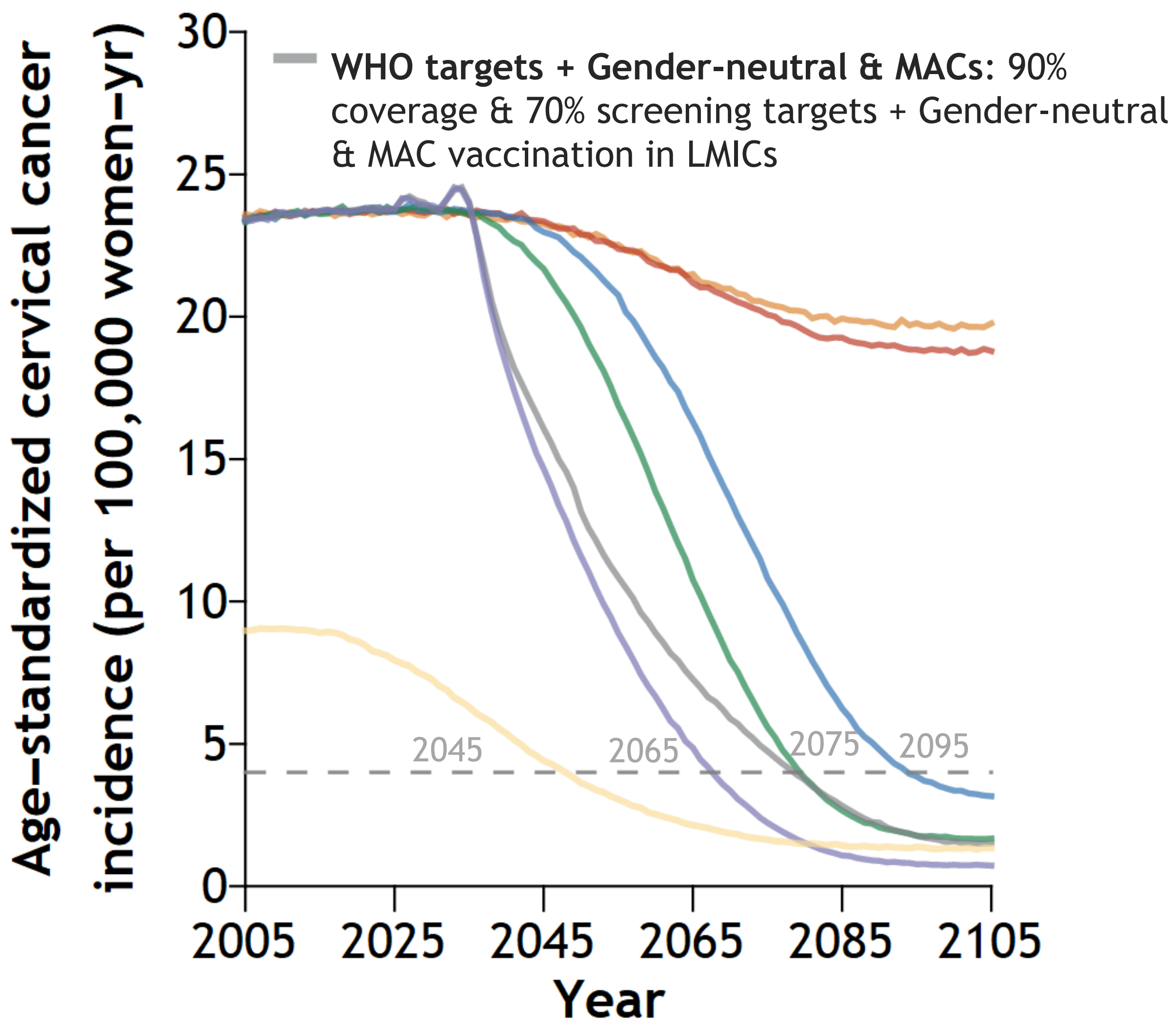

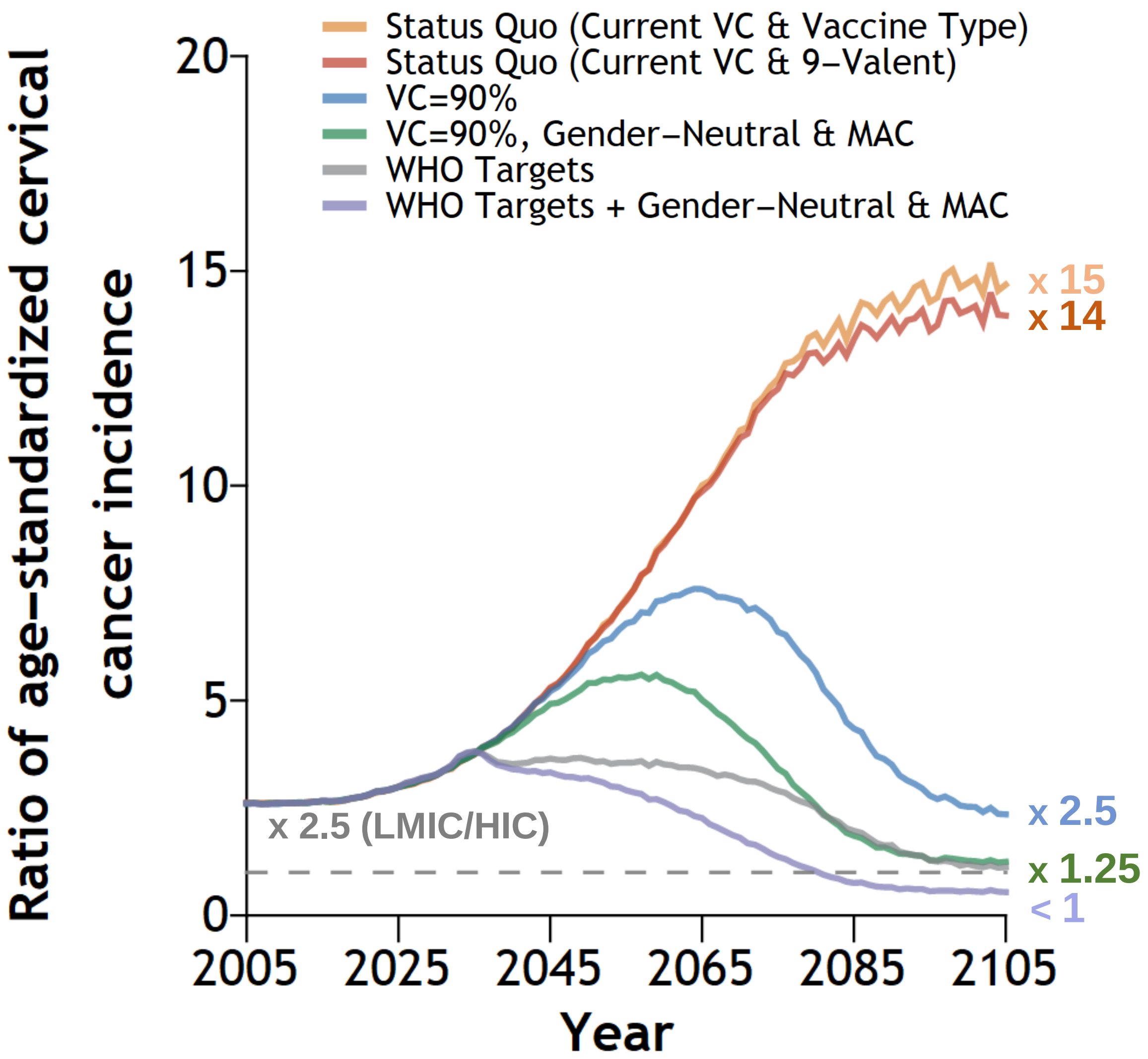

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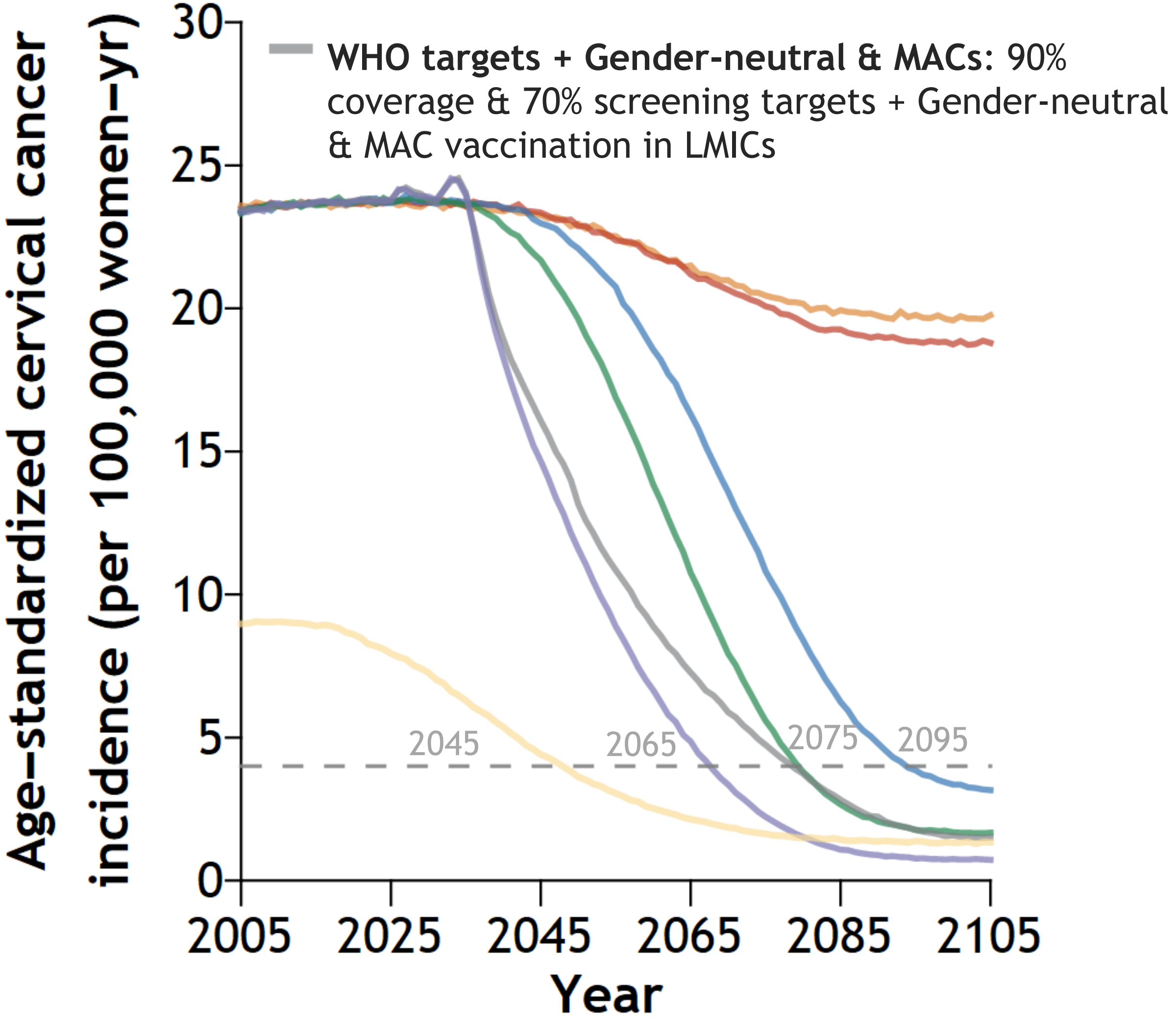
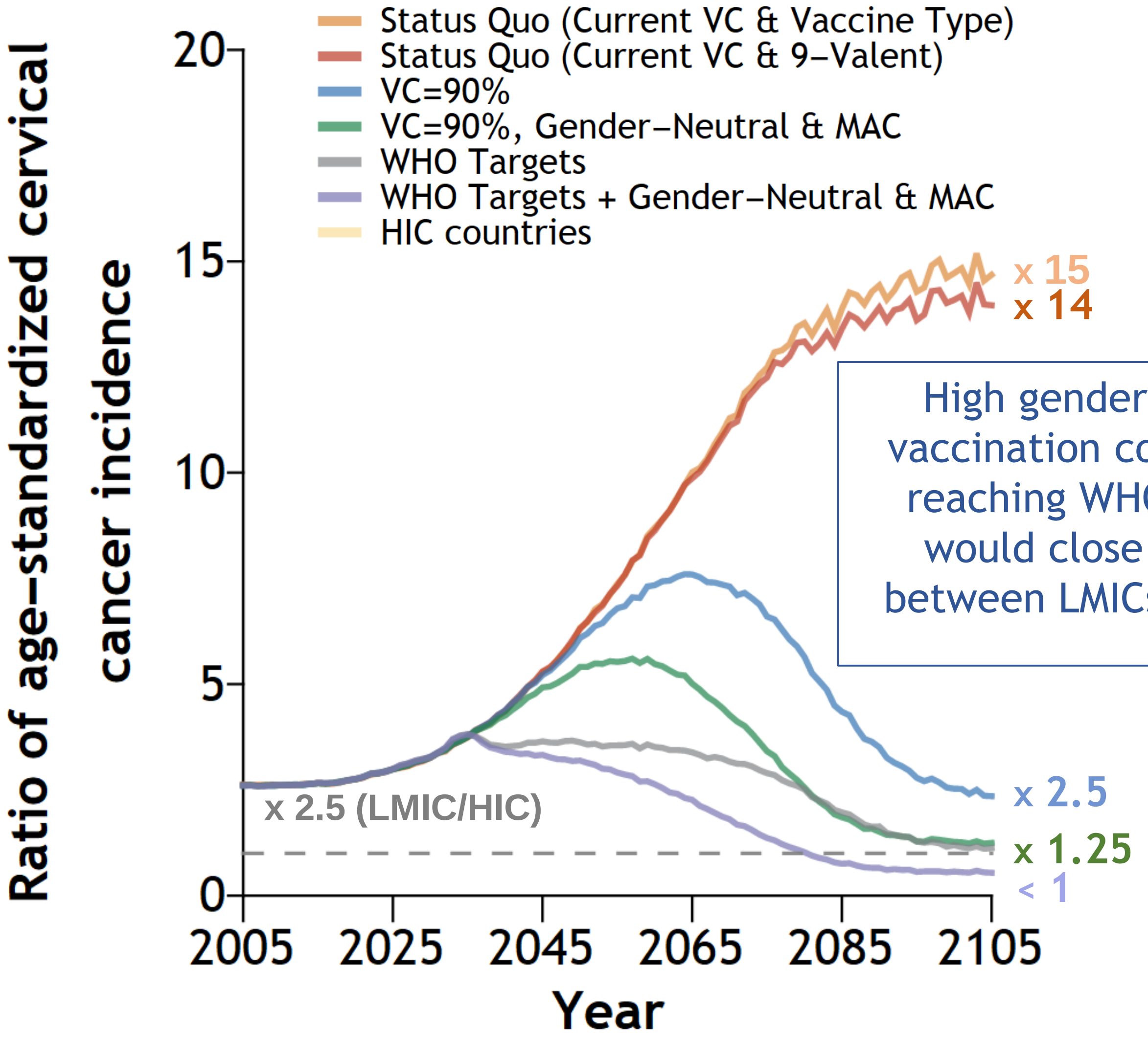


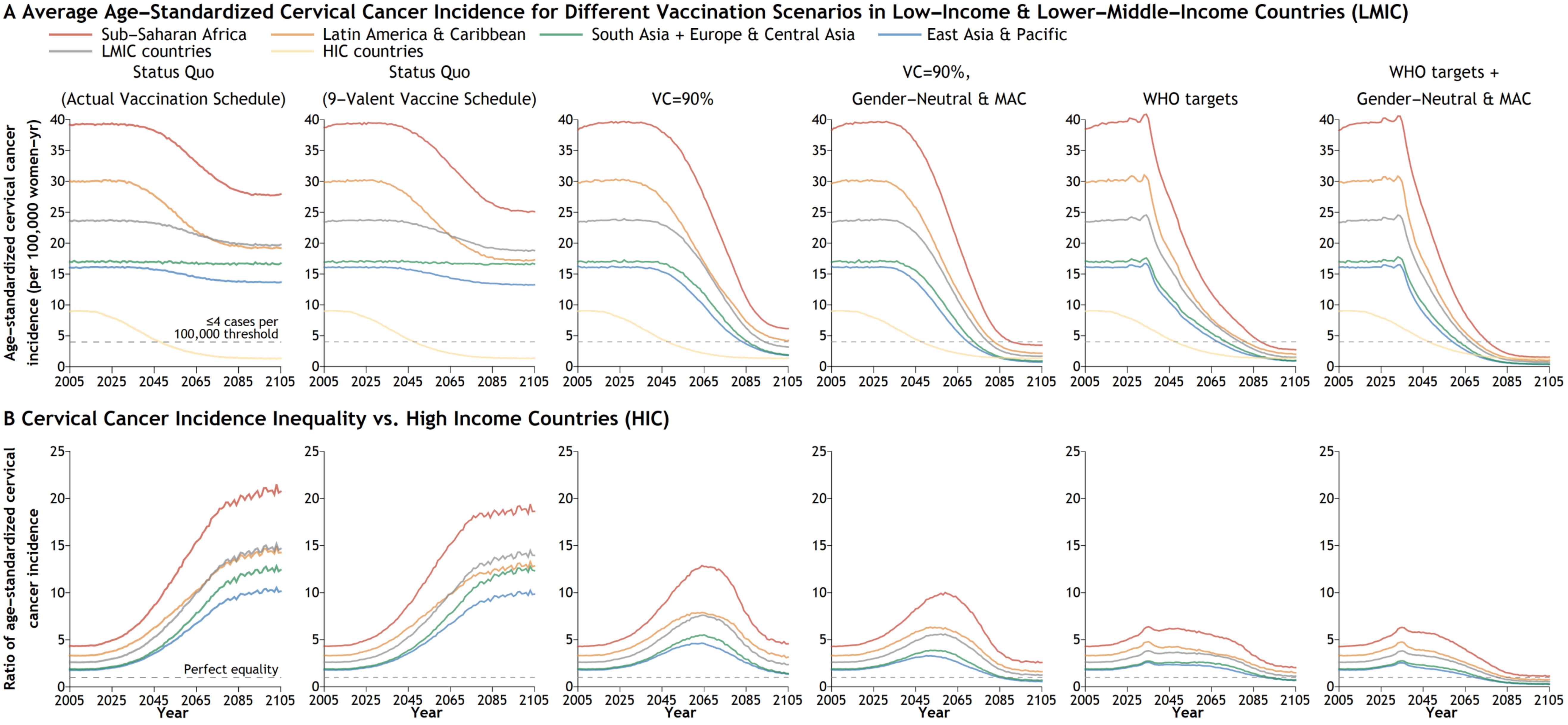


High gender-neutral vaccination coverage or reaching WHO targets would close the gap between LMICs and HICs

HPV-ADVISE projections; Ratio = age-standardized incidence in LMICs vs HIC

Differential inequalities by region

Cervical cancer elimination & Global Inequalities by region



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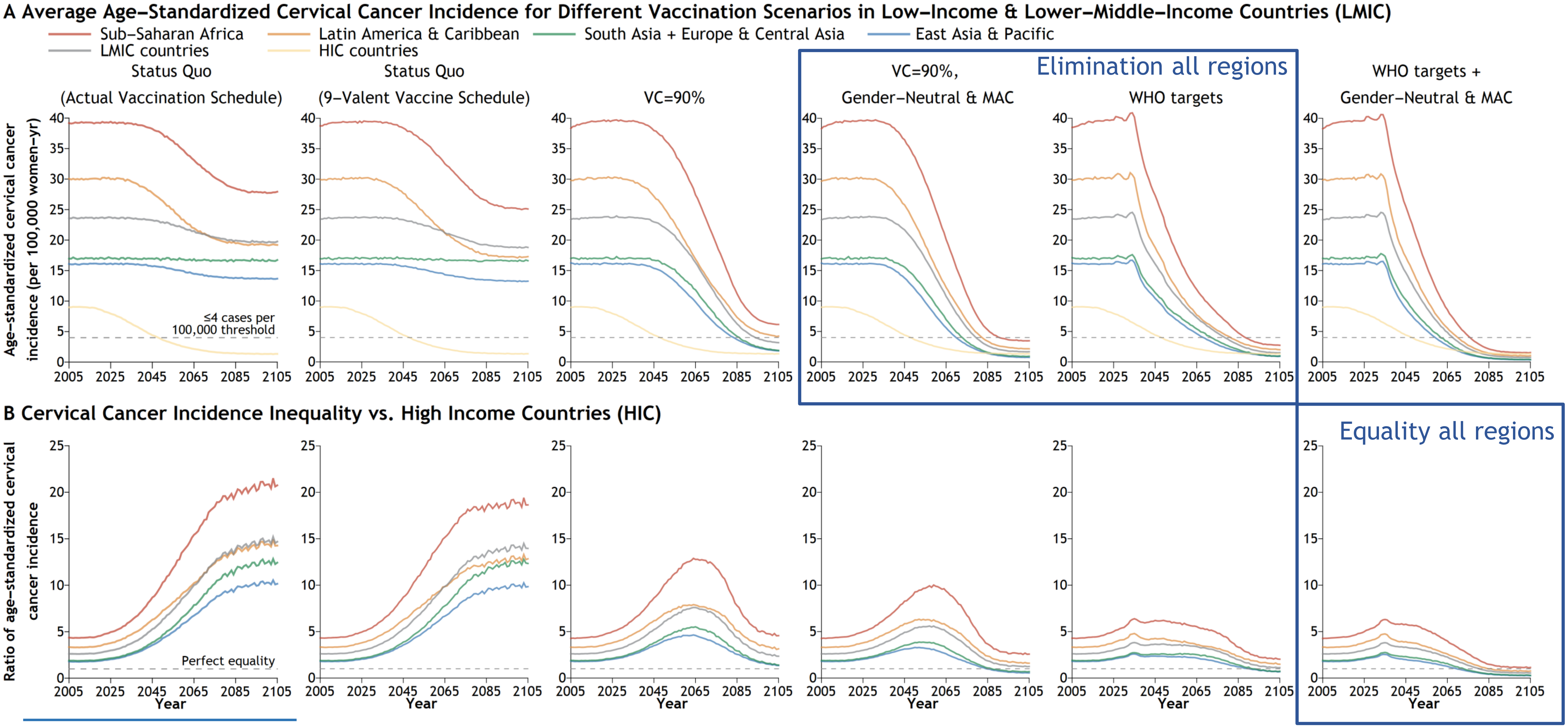

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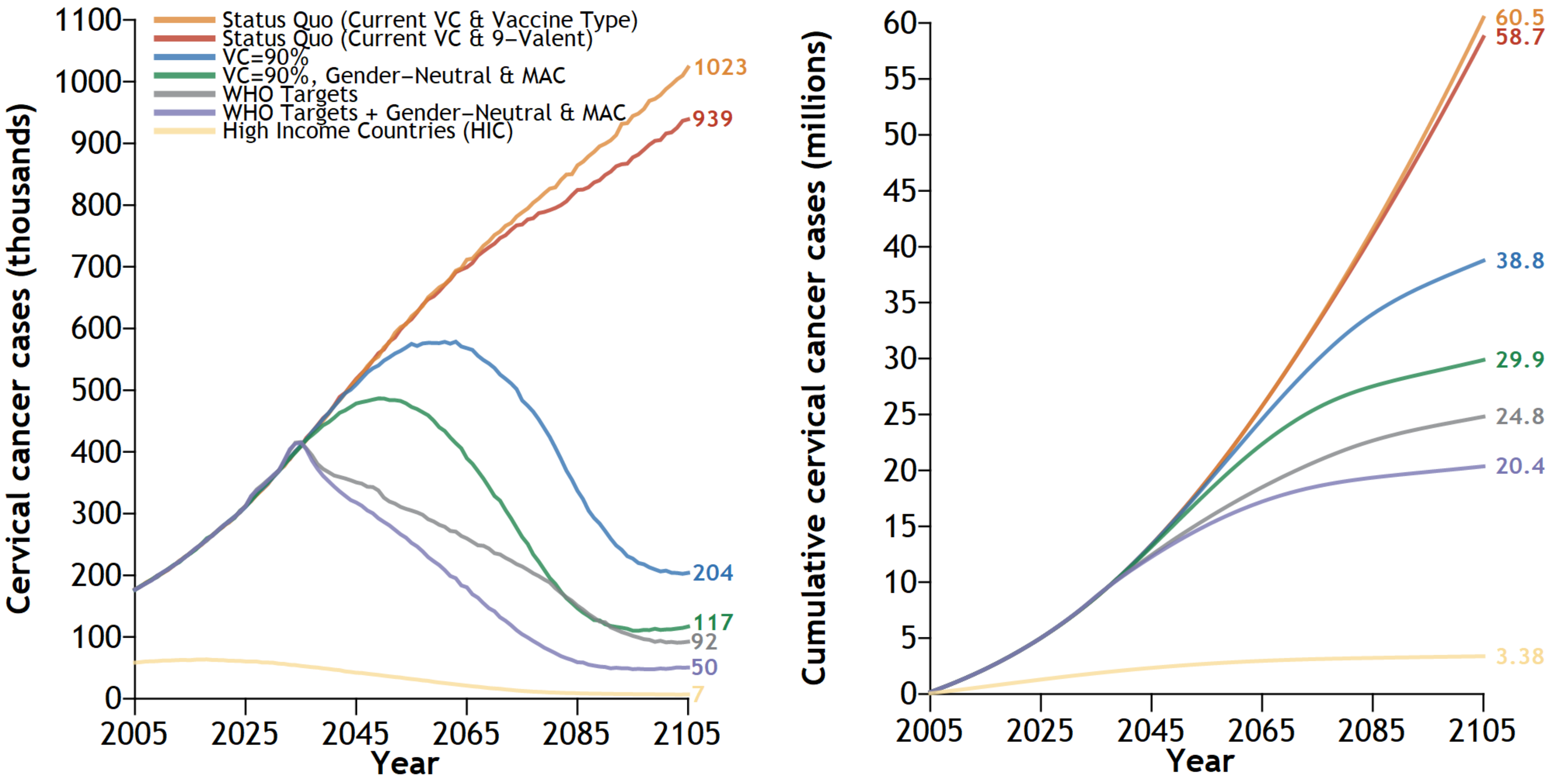
A different perspective – cases prevented

Global Inequalities – Cases prevented in LMICs



Cancers prevented (vs status quo)

0.8 million

21.7 million

30.9 million

35.7 million

40.1 million

HPV-ADVISE projections; Ratio = age-standardized incidence in LMICs vs HIC

Summary

- Mathematical models have consistently shown the high projected population-level impact, efficiency and cost-effectiveness of vaccinating girls and young women

- However, large inequities in HPV vaccine distribution remain between LMICs and HICs
  - partly due to restrained resources, competing health problems, delays due to past vaccine supply constraints & COVID-19
  - NNV to vaccinate girls/young women in LMICs = 45-65[1] vs NNV for the 2nd dose in HICs > 12,000[2]

- Substantial increases in cervical cancer inequalities are projected without significantly enhanced vaccination and screening efforts
  - only high gender-neutral vaccination coverage or high screening uptake would close the gap between LMICs and HICs
  - without such efforts Global elimination of cervical cancer will not be reached

- What can be done?
  - 1-dose vaccination, less expensive vaccines and increased supply can help reduce current inequalities in vaccination coverage

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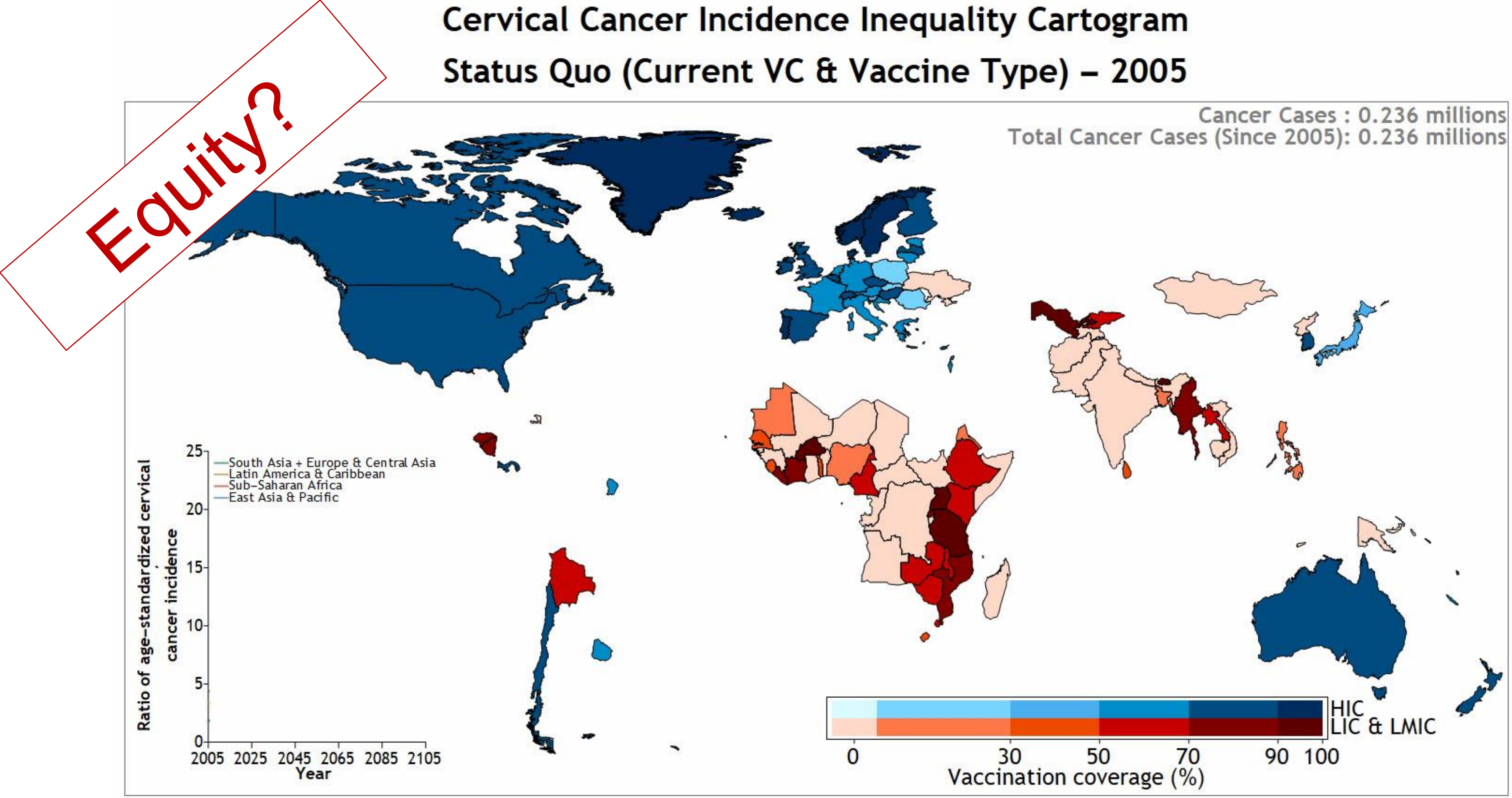
1. Bénard et al. IPVc 2025 POSTER 200; 2. Drolet et al. CMAJ 2024

Cervical Cancer Incidence Inequality Cartogram

Status Quo (Current VC & Vaccine Type) – 2005



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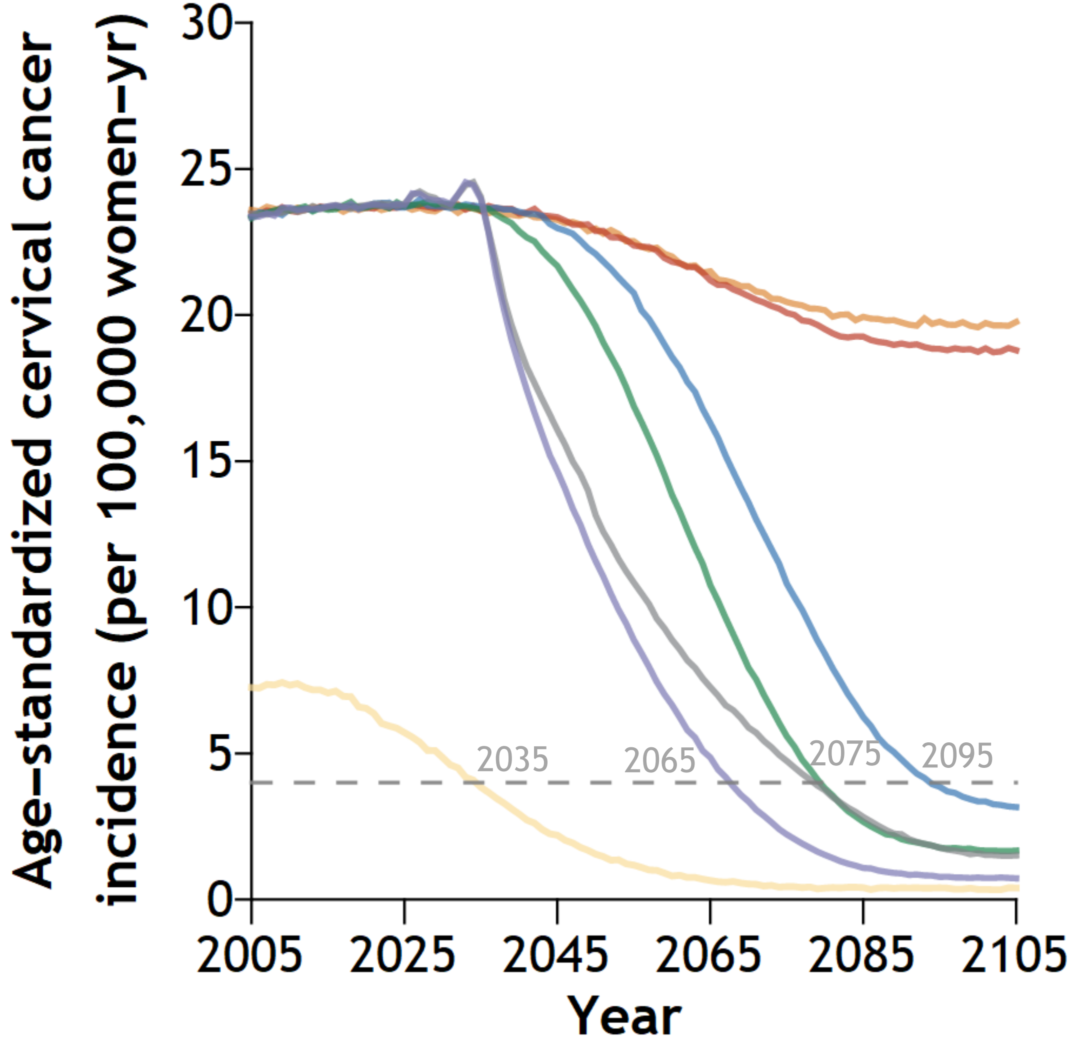
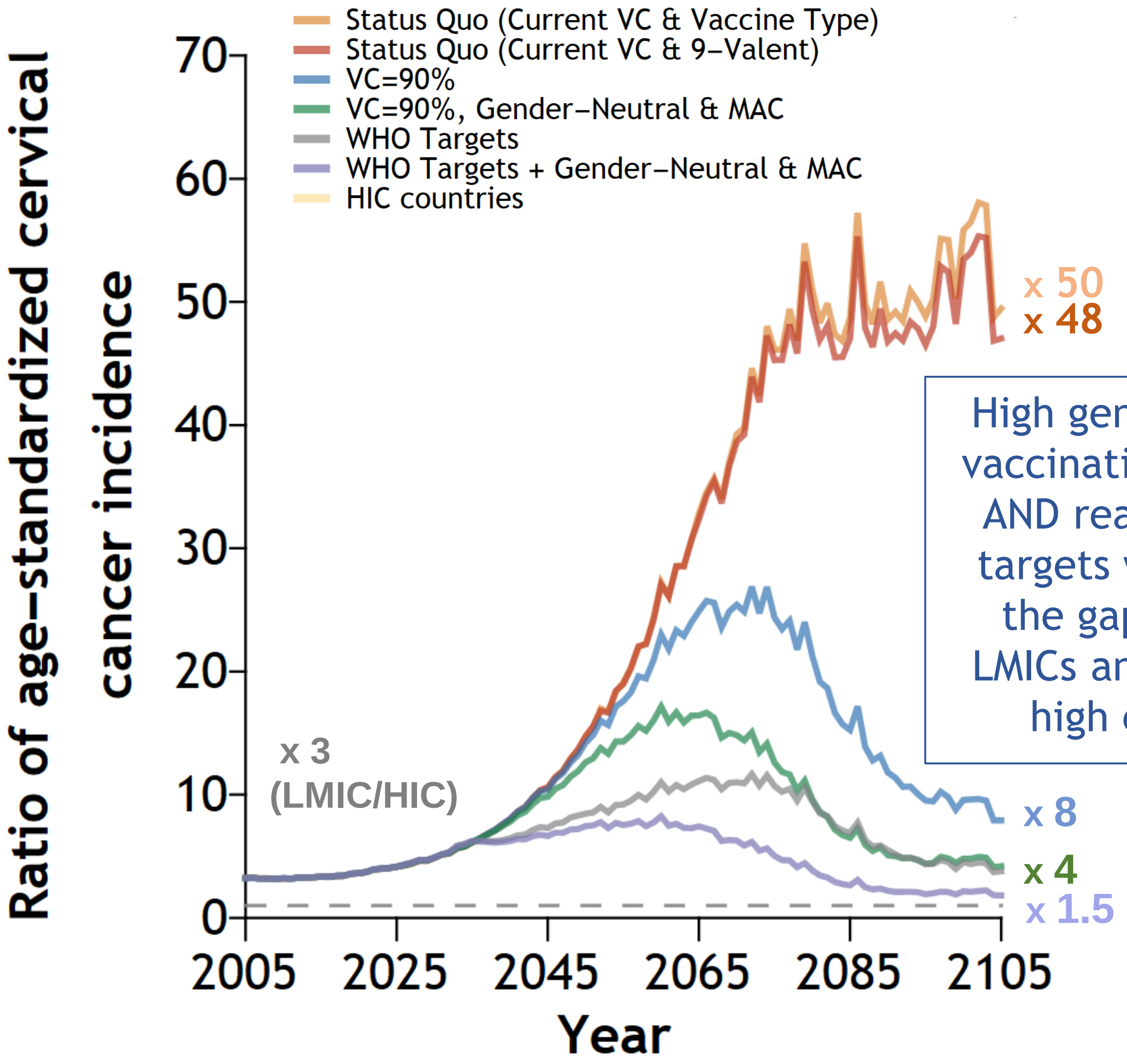
Inequalities vs HICs with high gender-neutral coverage

Cervical cancer elimination & Global Inequalities vs US & Canada





High gender-neutral vaccination coverage AND reaching WHO targets would close the gap between LMICs and HICs with high coverage

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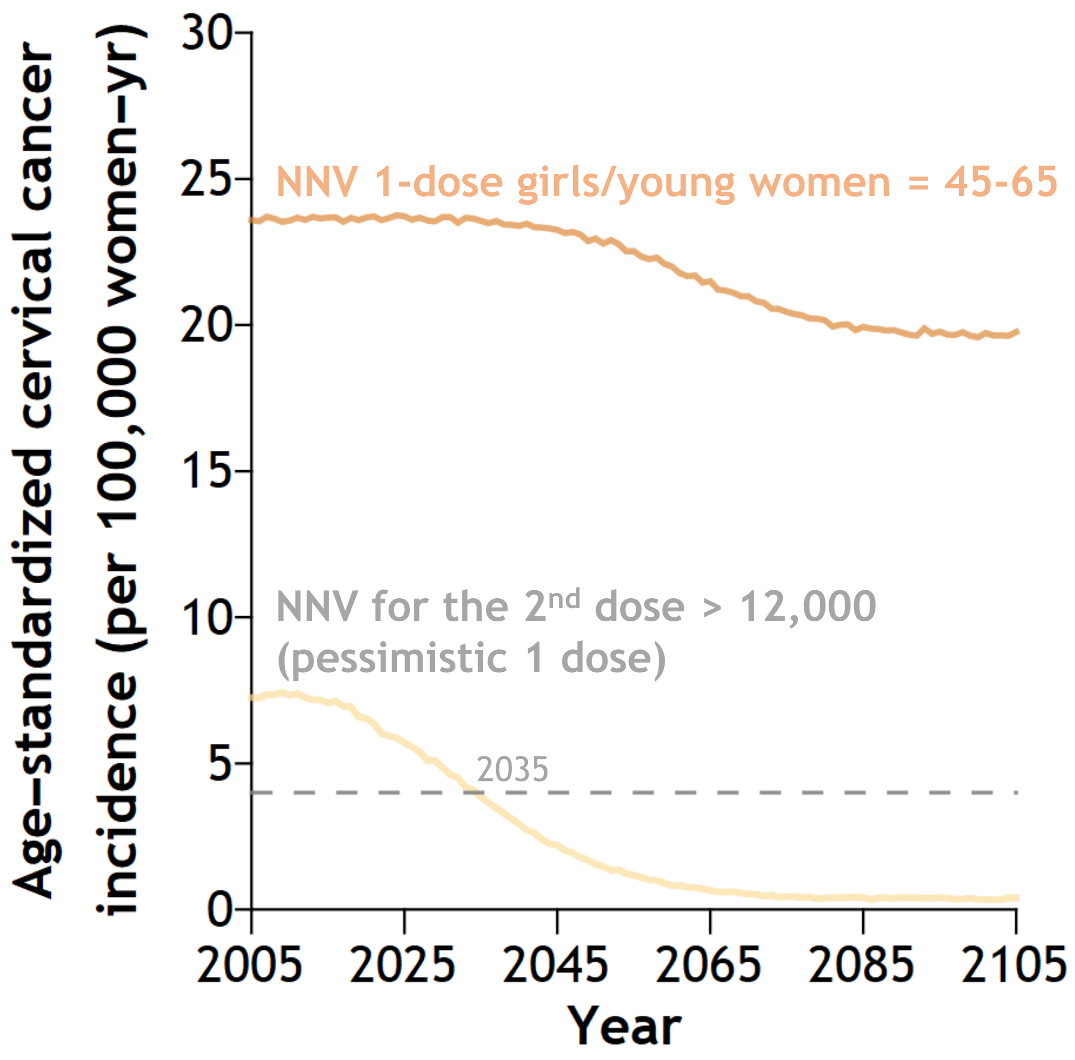

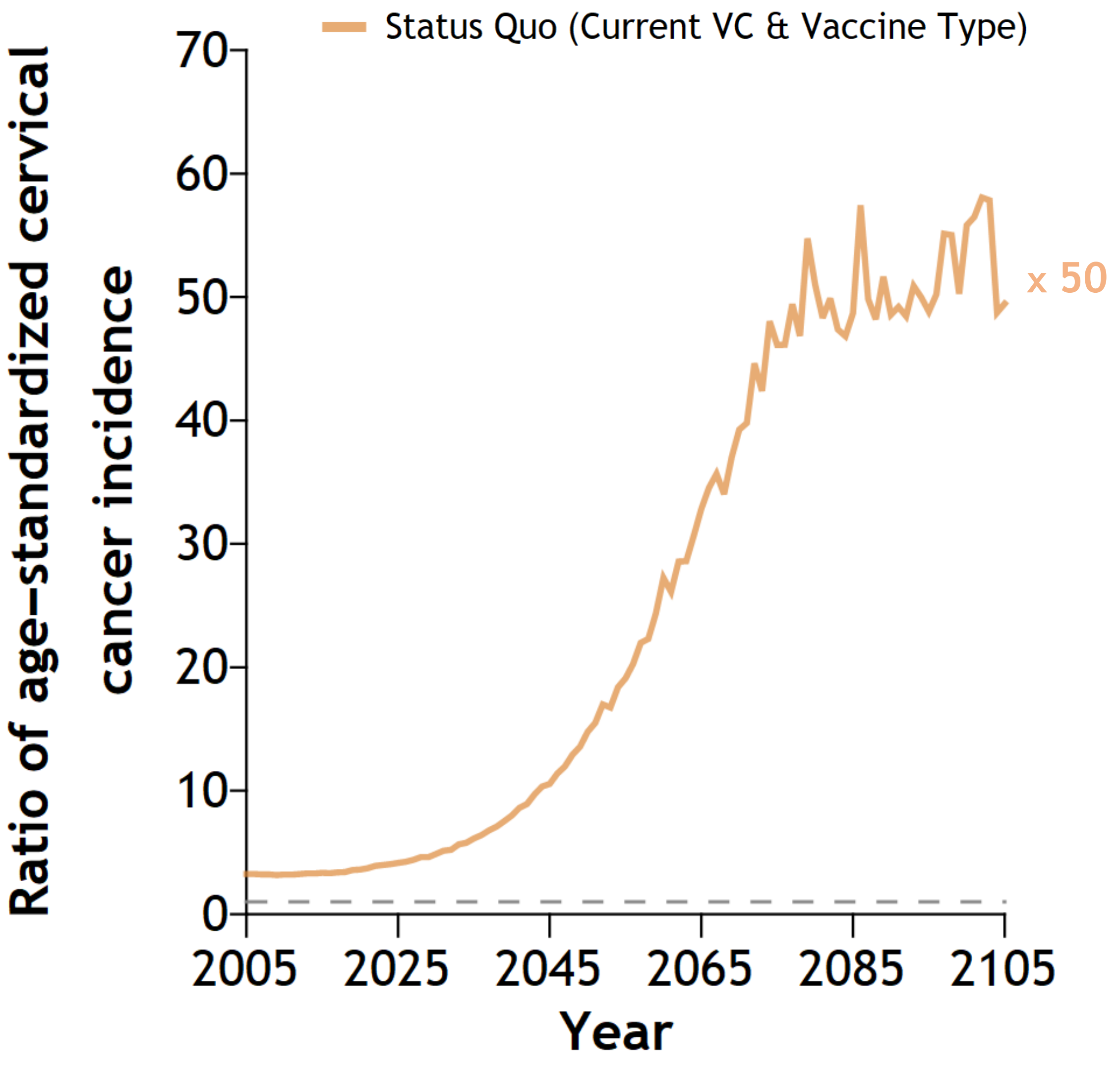

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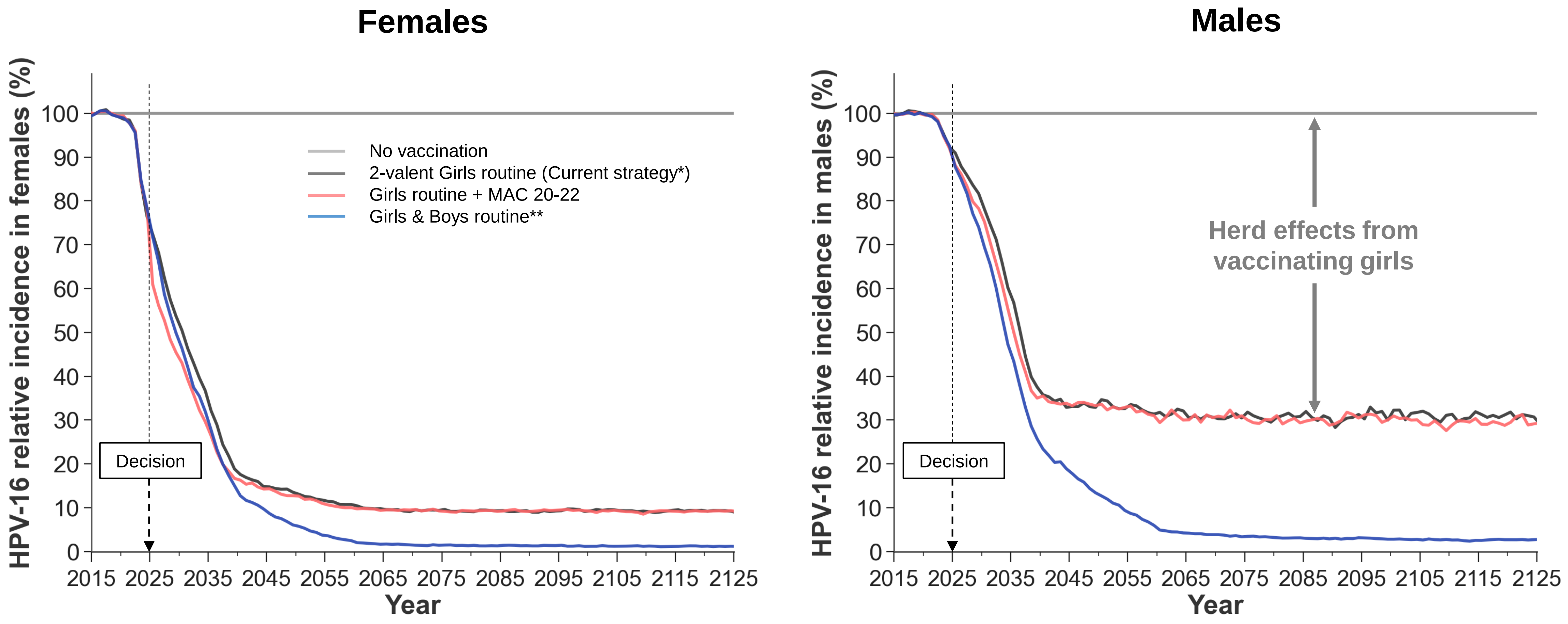
Herd immunity

Population-level impact HPV-16 incidence

2-valent or 9-valent (Duration=Life, vaccination coverage=90%)



Why adding boys does not produce greater gains? Herd effect

*. Current strategy: Historical vaccination coverage & 2-dose 2-valent Girls vaccination; ICER=Incremental Cost-Effectiveness Ratio; NNV=Number Needed to Vaccinate

Population-level impact HPV-16 incidence

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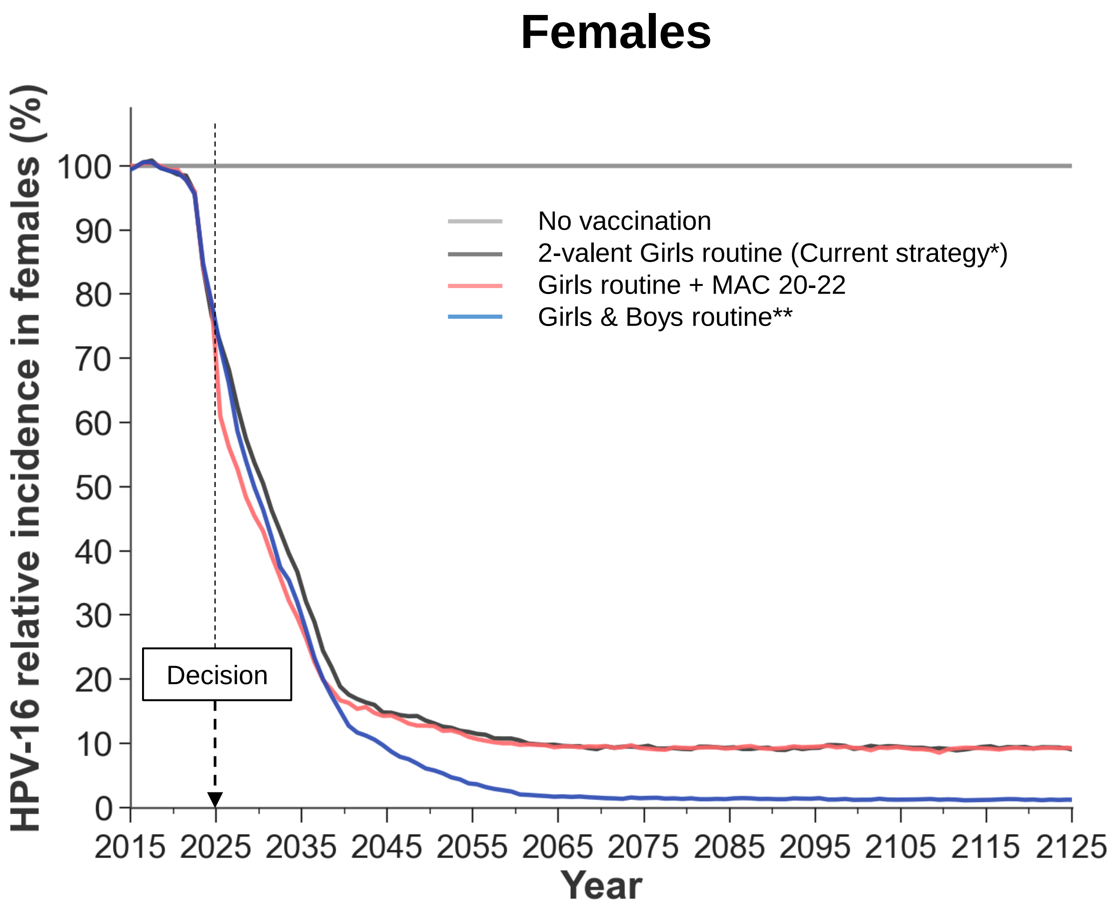

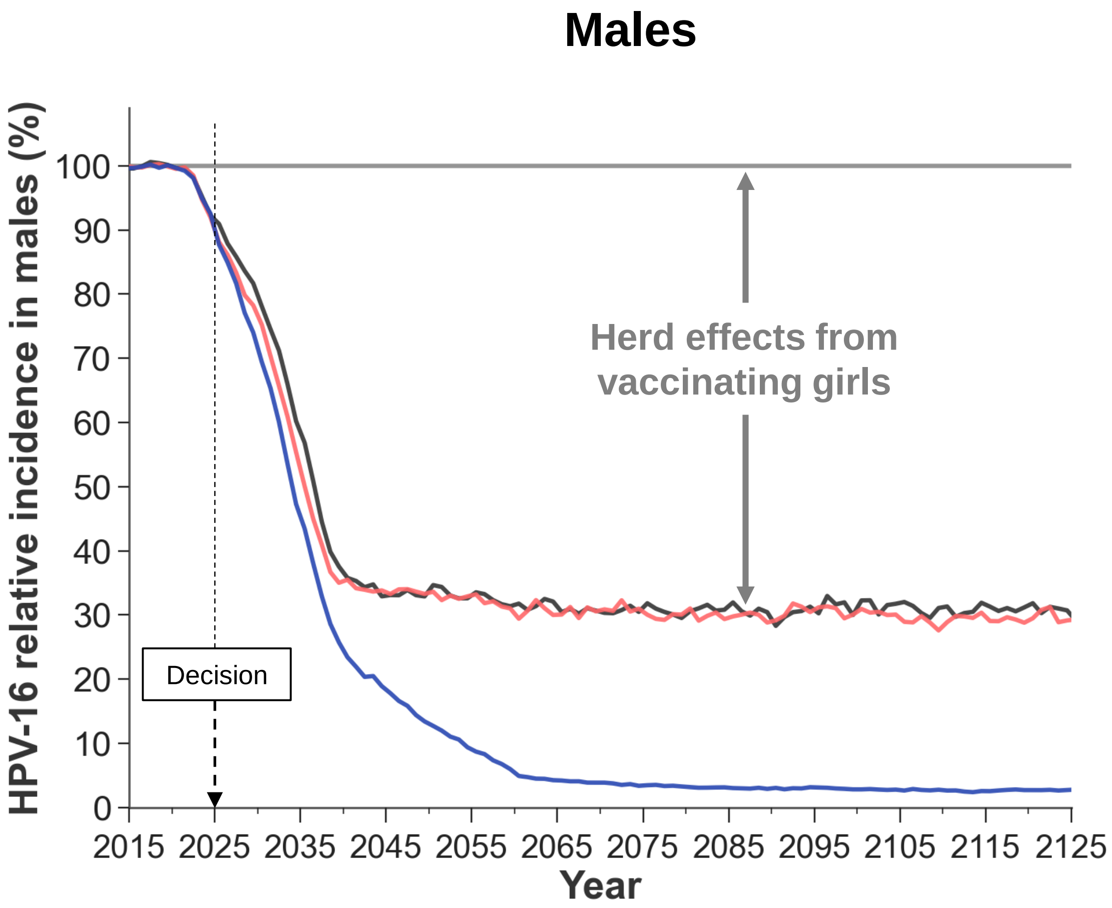

Why adding boys does not produce greater gains? Herd effect

- Vaccinating girls with high vaccination coverage of 90% reduced HPV infection in boys by 70%

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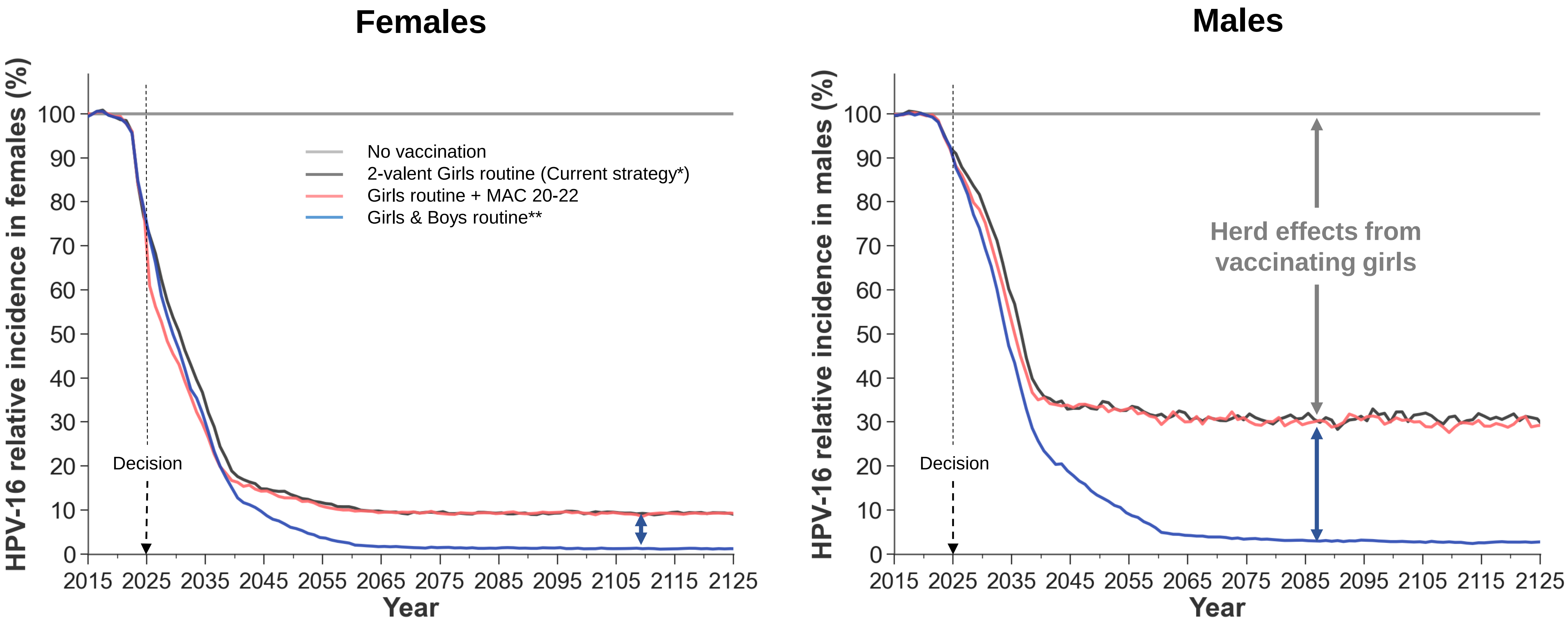
Population-level impact HPV-16 incidence

2-valent or 9-valent (Duration=Life, vaccination coverage=90%)



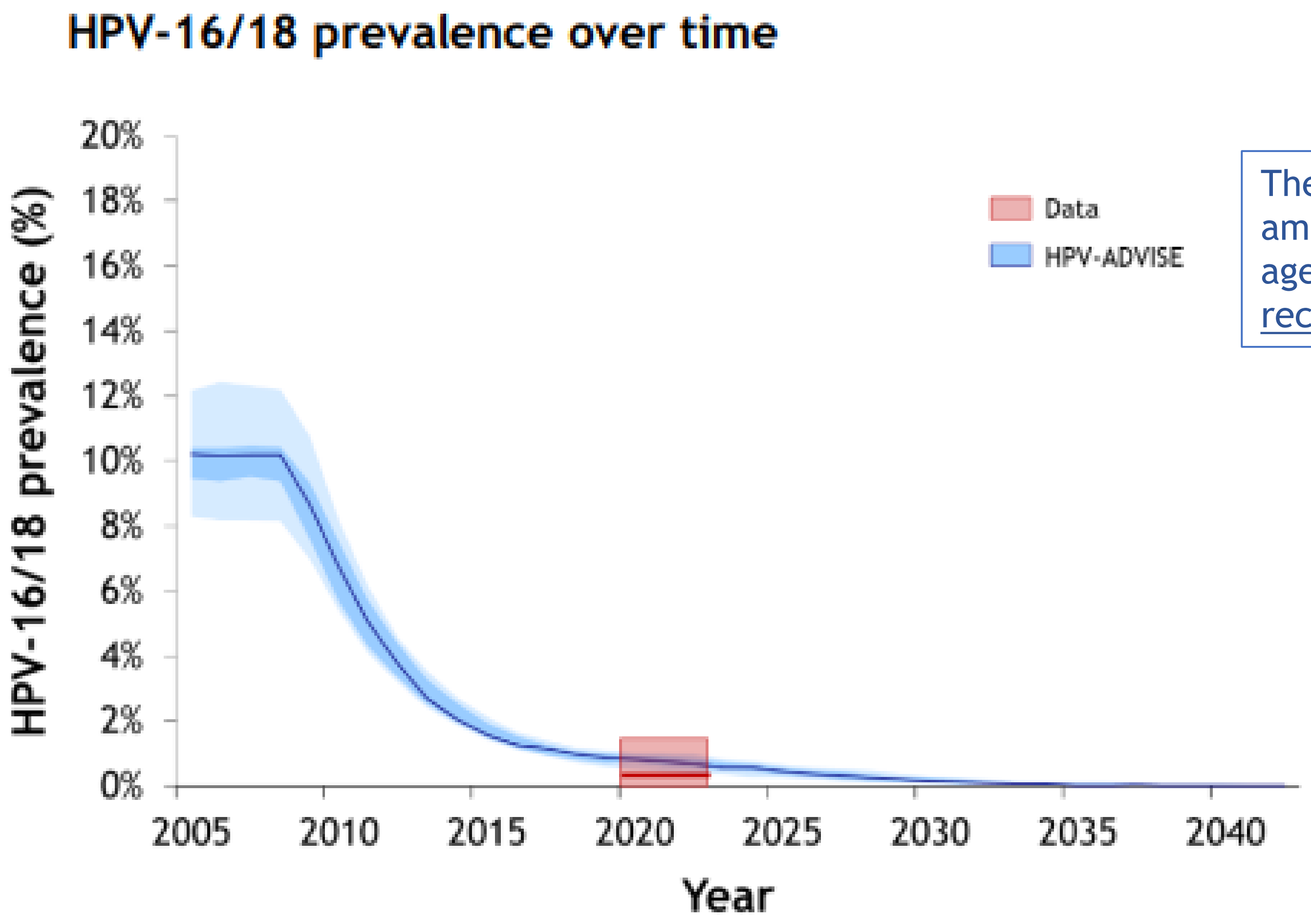
Why adding boys does not produce greater gains? Herd effect

- Vaccinating girls with high vaccination coverage of 90% reduced HPV infection in boys by 70%
- Hence, there are small incremental gains from vaccinating boys (considering the doses and costs are doubled)

*. Current strategy: Historical vaccination coverage & 2-dose 2-valent Girls vaccination; ICER=Incremental Cost-Effectiveness Ratio; NNV=Number Needed to Vaccinate

HPV-ADVISE Example of model reproducing post-vaccination data

Post-vaccination data among unvaccinated cohorts of males in Québec, Canada



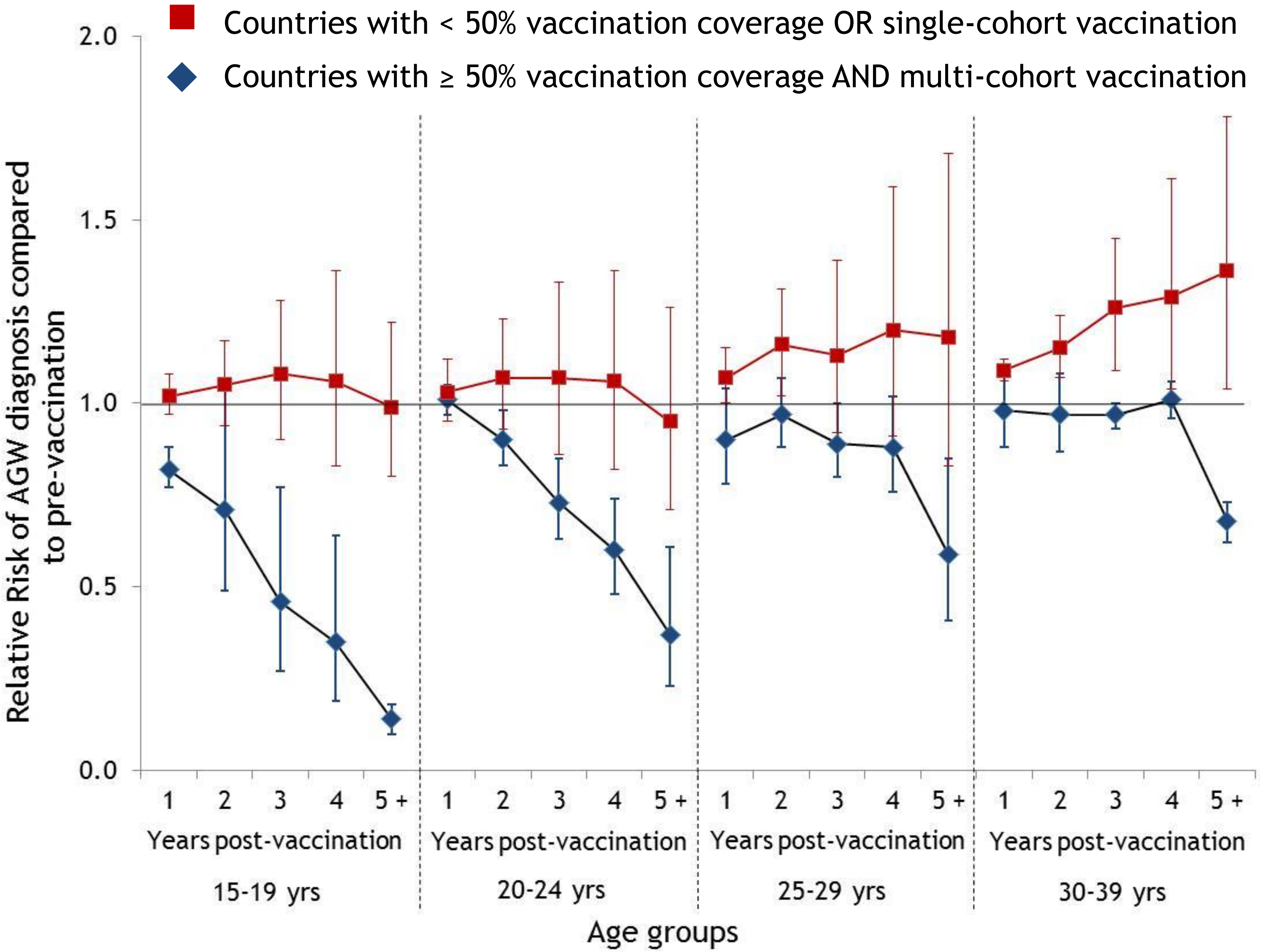
The model reproduces herd effects among unvaccinated cohorts of males aged 16 to 20 years in Québec, without recalibration to post-vaccination data

Data (red dots and 95% CI): **Collected in 2020-2022 among unvaccinated cohorts of males aged 16 to 20 years in Québec, Canada**. 16-to-20-year-old females were vaccinated with the quadrivalent vaccine, males of that age group were not vaccinated. The change in HPV prevalence represent herd effect from females-only vaccination.

HPV-ADVISE (blue boxplots and shaded areas): Boxplots and shaded areas represent the 10th, 25th, 75th and 90th percentiles of HPV-ADVISE projections using the best fit 50 parameter sets. The dark lines represent the median of projections. Note: The best fits were determined using pre-vaccination data.

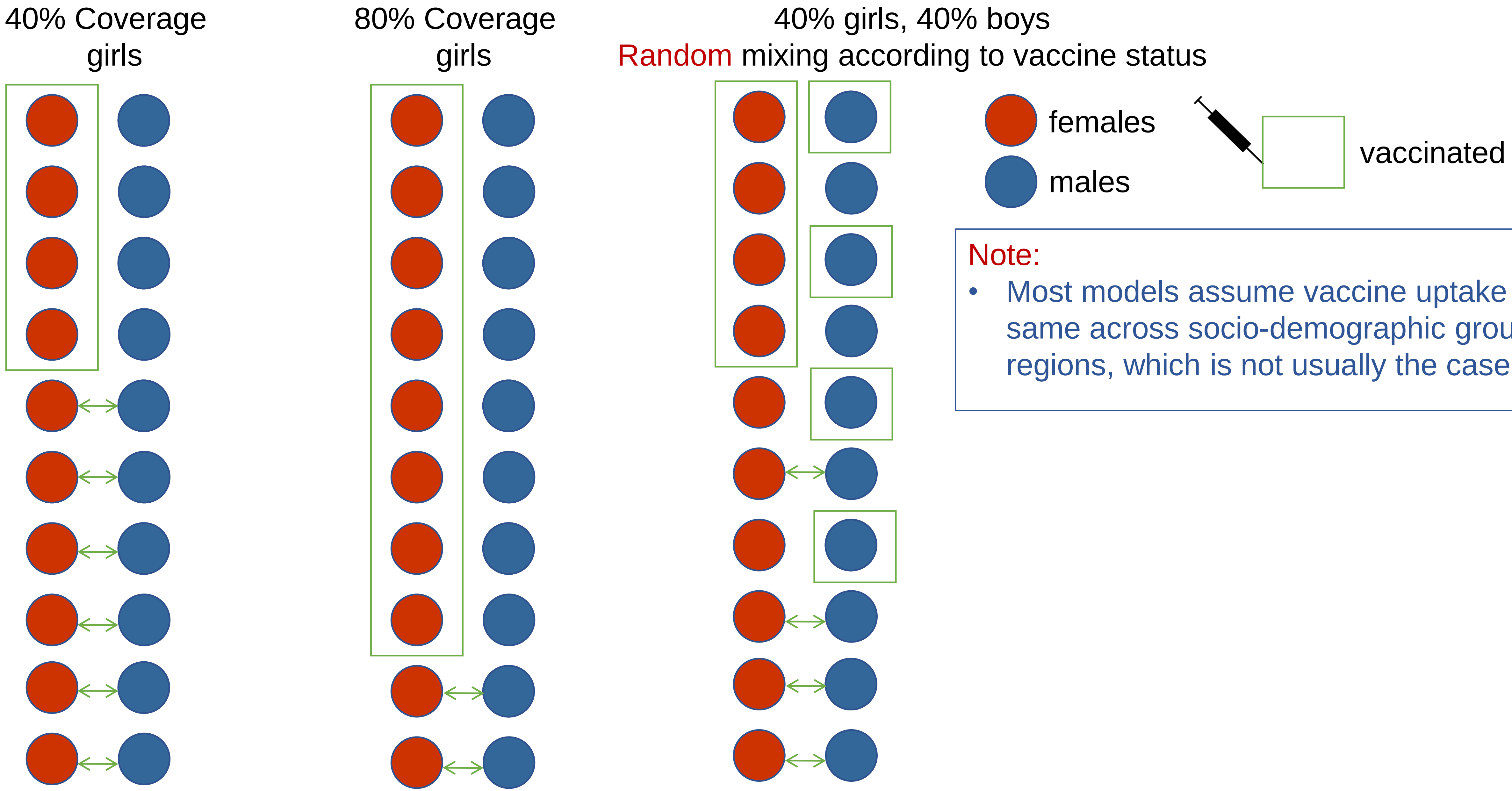
Herd immunity impact of female-only coverage

Anogenital warts – boys/men – Meta Analysis of population-level data[&]



&. Drolet et al. Lancet 2019

Why is it more efficient to increase coverage in girls than including boys?



Note:

- Most models assume vaccine uptake is the same across socio-demographic groups and regions, which is not usually the case

Proportion of cost in each types of cancers & economic burden

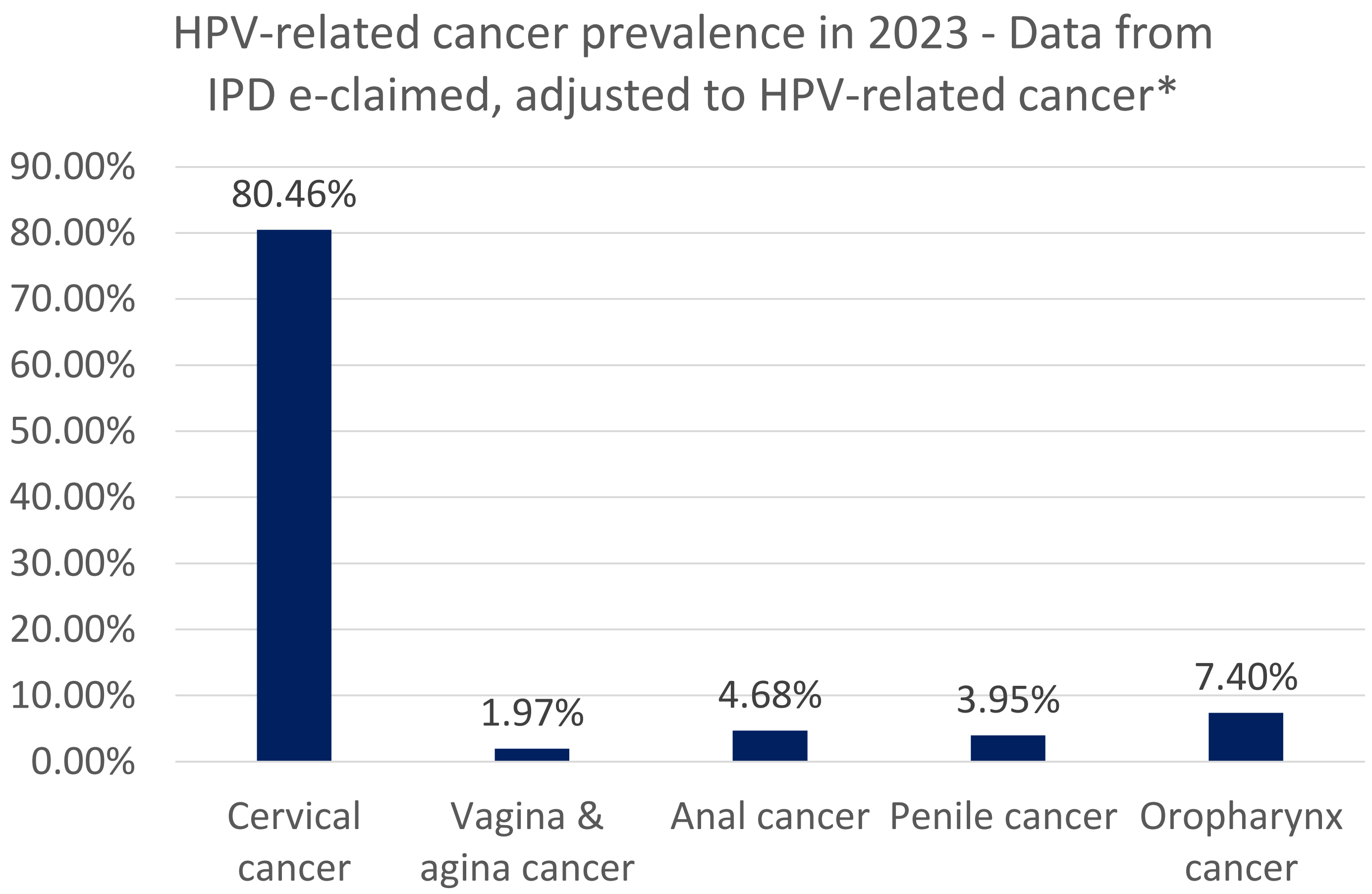


Table: Estimated Cost and Proportional Burden of HPV-Related Diseases with 2023's prevalence**

Disease	Total Cost of treatment	% Burden
Cervical cancer	2,716,738,886.52	89.09%
Non-cervical cancer	327,423,377.48	10.74%
Anogenital wart**	5,392,209.00	0.18%

*Adjust by Attribution factor from IARC, 2017
** Total Anogenital warts cost is from the total reimbursement in 2023, OPD individual (NHSO)

Studies included

65 articles from 14 High-income countries
Data from 60 million individuals
Up to 8 years after the introduction of <u>girls-only vaccination</u>

North America

Canada
USA

Europe

Belgium
Denmark
England
Germany
Italy
Netherlands
Norway
Scotland
Spain
Sweden

Australia

Australia
New Zealand

Single age cohort vaccination
(vaccinating 1 age group every year)

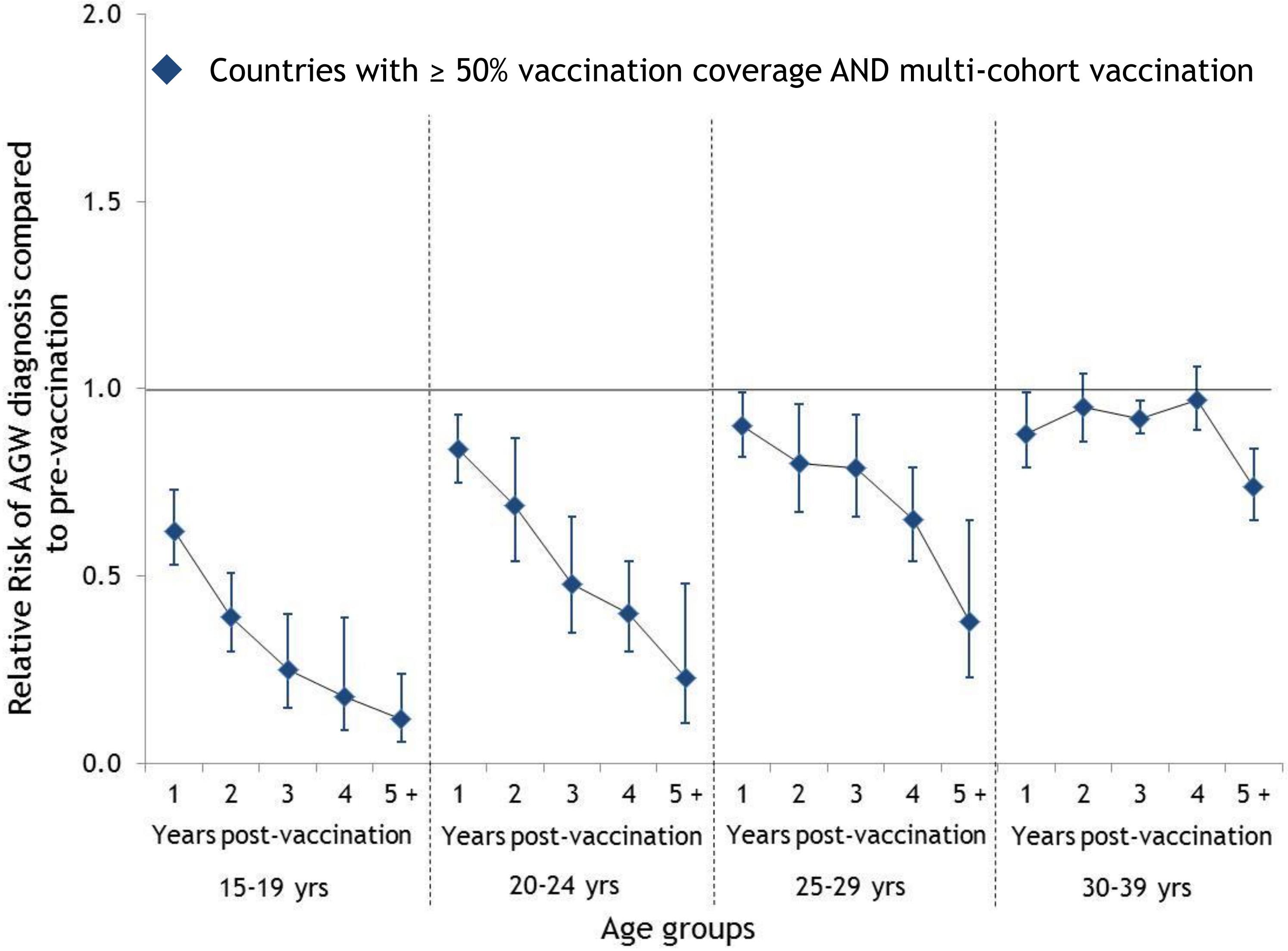
Canada (Manitoba, Ontario), Belgium, Norway, Italy, Spain

Multiple age cohort vaccination
(vaccinating multiple age groups during the first years of the program)

Canada (Quebec), USA, UK, Denmark, Sweden, Germany, The Netherlands, Australia

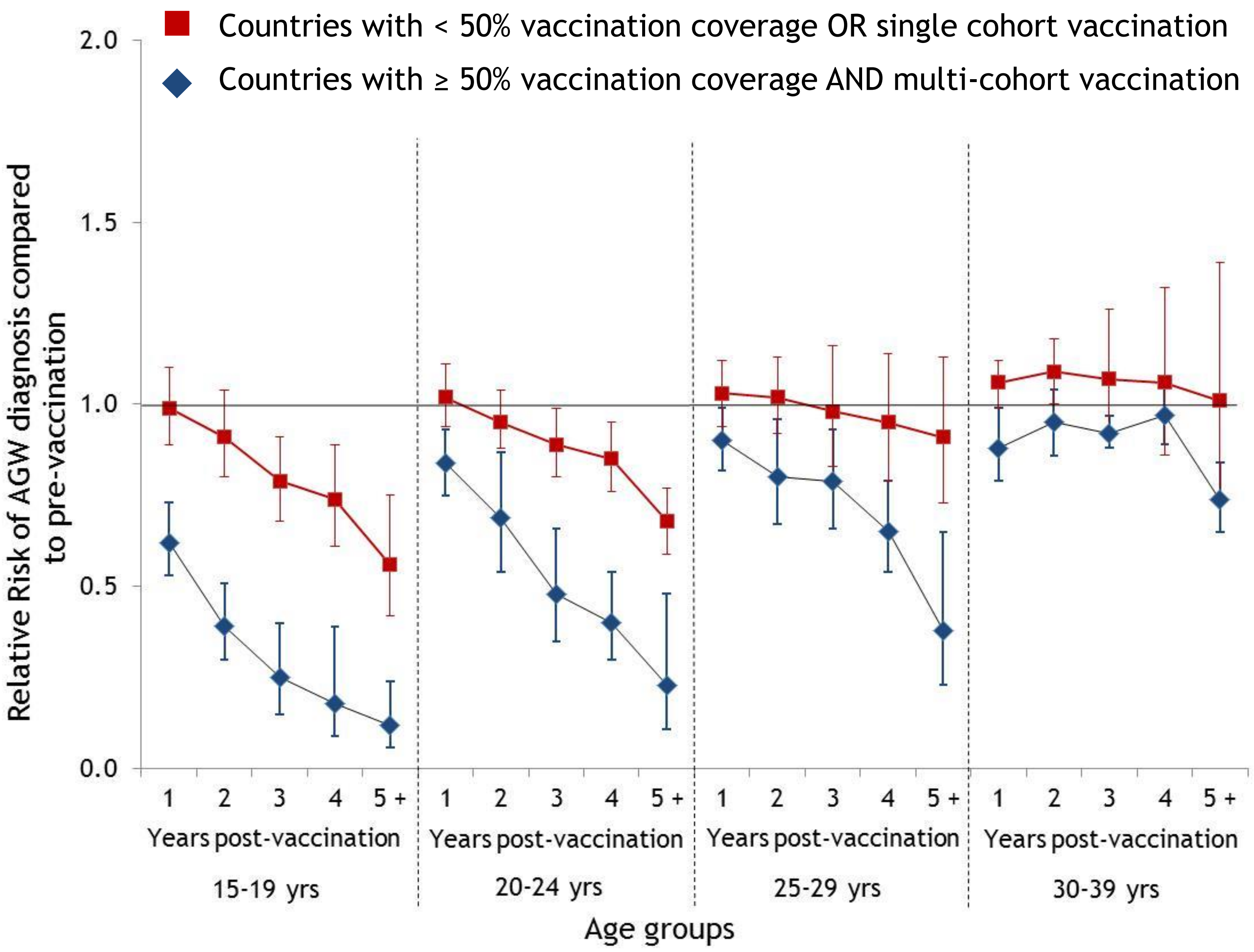
High coverage & multiple age cohort vaccination

Anogenital warts – girls/women



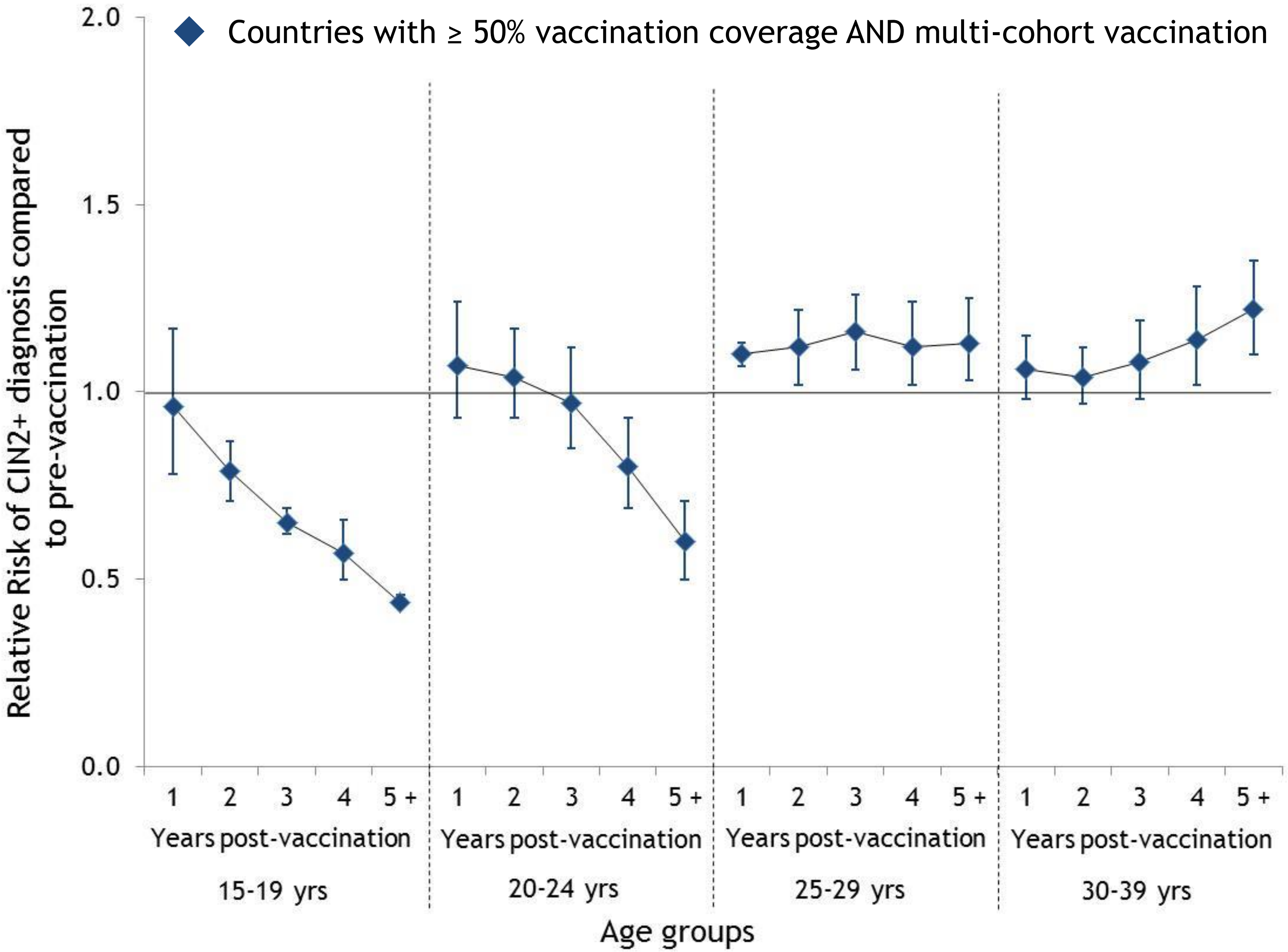
Impact of coverage & multiple age cohort vaccination

Anogenital warts – girls/women



High coverage & multiple age cohort vaccination

CIN2+ girls/women

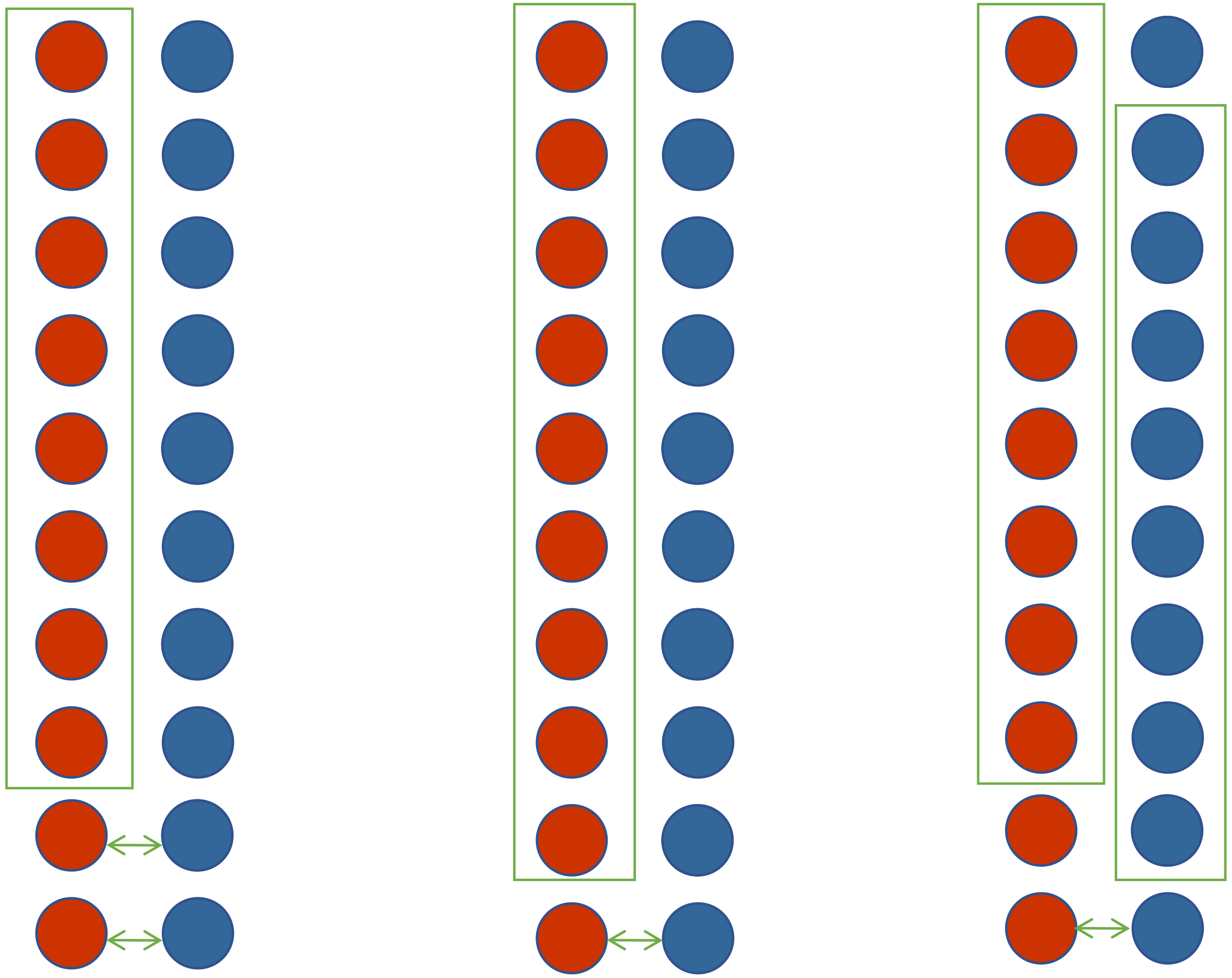


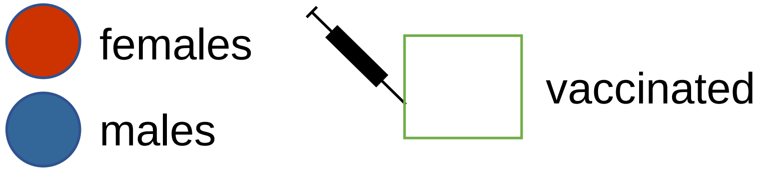
More efficient to increase coverage in girls than including boys

80% Coverage girls

+10% Coverage girls

+80% Coverage boys (+100% increase doses)
Random mixing according to vaccine status





Note:
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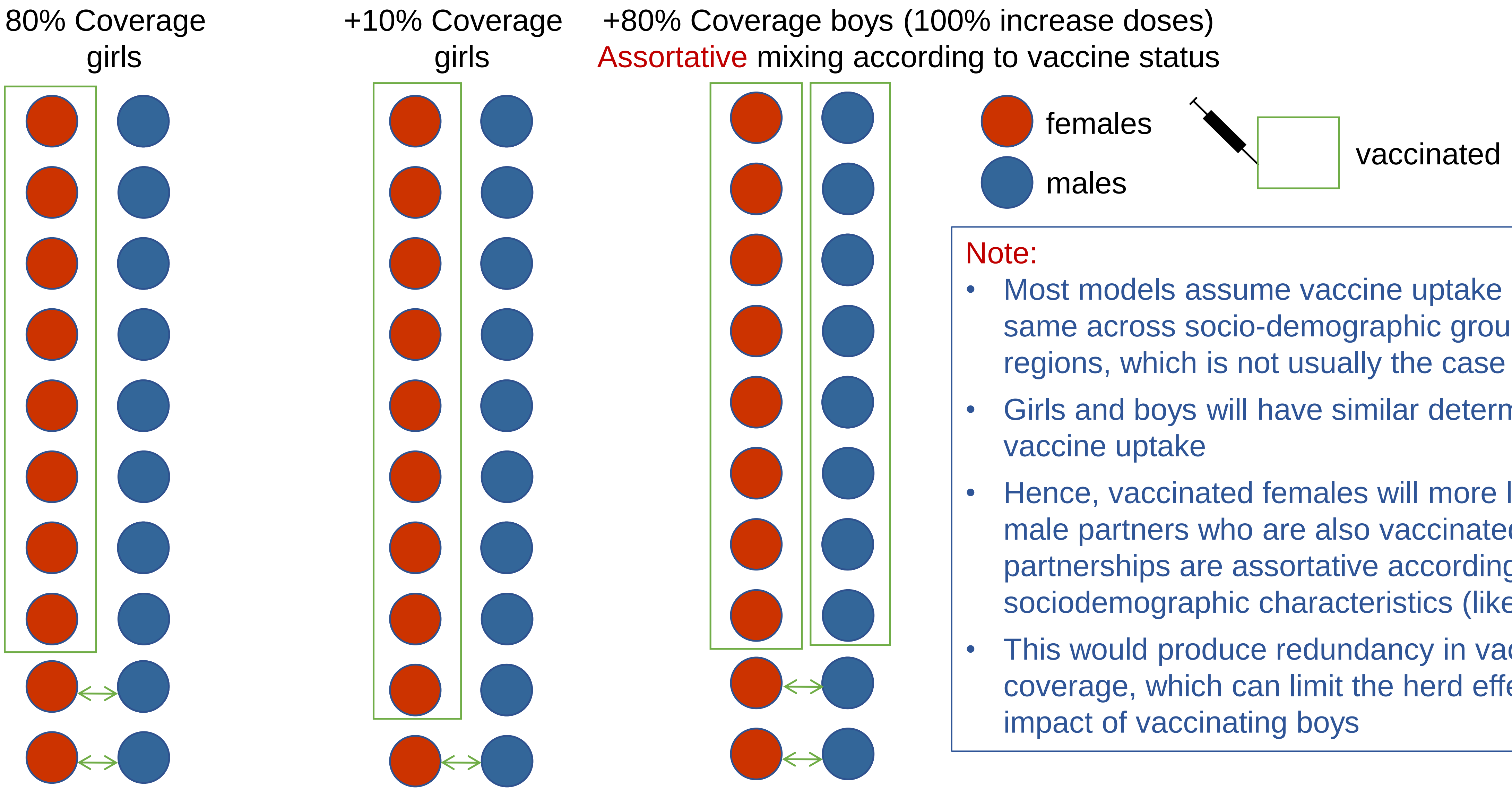
More efficient to increase coverage in girls than including boys



Note:

- Most models assume vaccine uptake is the same across socio-demographic groups and regions, which is not usually the case
- Girls and boys will have similar determinants of vaccine uptake
- Hence, vaccinated females will more likely have male partners who are also vaccinated, as partnerships are assortative according to sociodemographic characteristics (like-with-like)
- This would produce redundancy in vaccination coverage, which can limit the herd effects and impact of vaccinating boys

What is the policy question to model? What is the optimization?

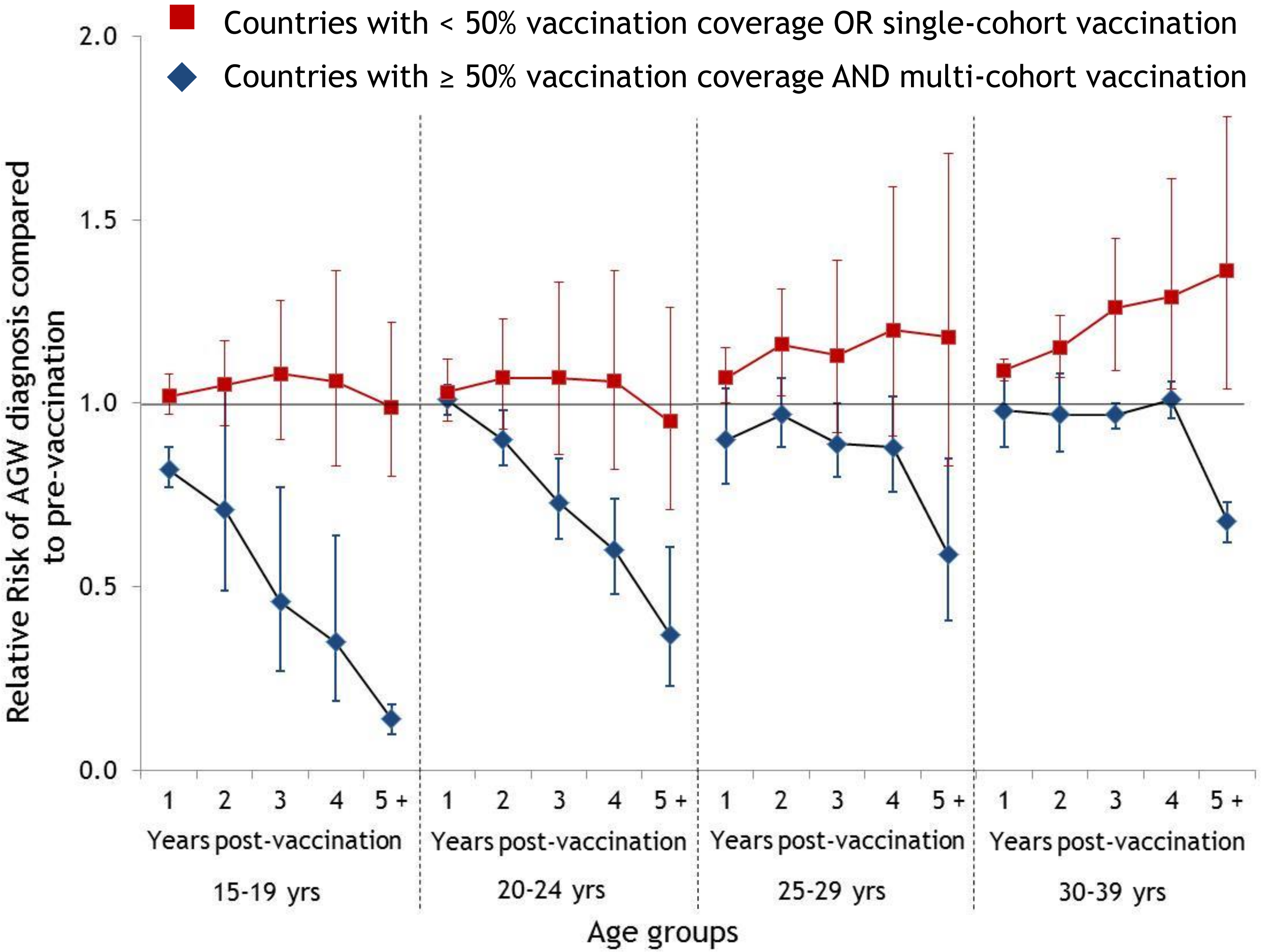
Optimization issue	Reduction of Cervical cancer/ Elimination	Vaccine Supply constraints	Budget constraints
Goal	Maximise health benefits	Maximise health benefits for Minimal number of doses	Maximise health benefits for Minimal cost
Analysis	Population-level impact	Efficiency	Cost-effectiveness
Outcome	Absolute reduction in cervical cancer incidence over time	Number needed to vaccinate to prevent 1 cervical cancer (NNV)	Cost per DALY

To prioritize, it is important to understand what is to be optimized?
Prioritization will depend on the stated goals and outcomes of HPV vaccination.
Ranking of strategies will depend on the optimization goal.

Supplementary information

Herd immunity impact of female-only coverage

Anogenital warts – boys/men – Meta Analysis of population-level data[&]

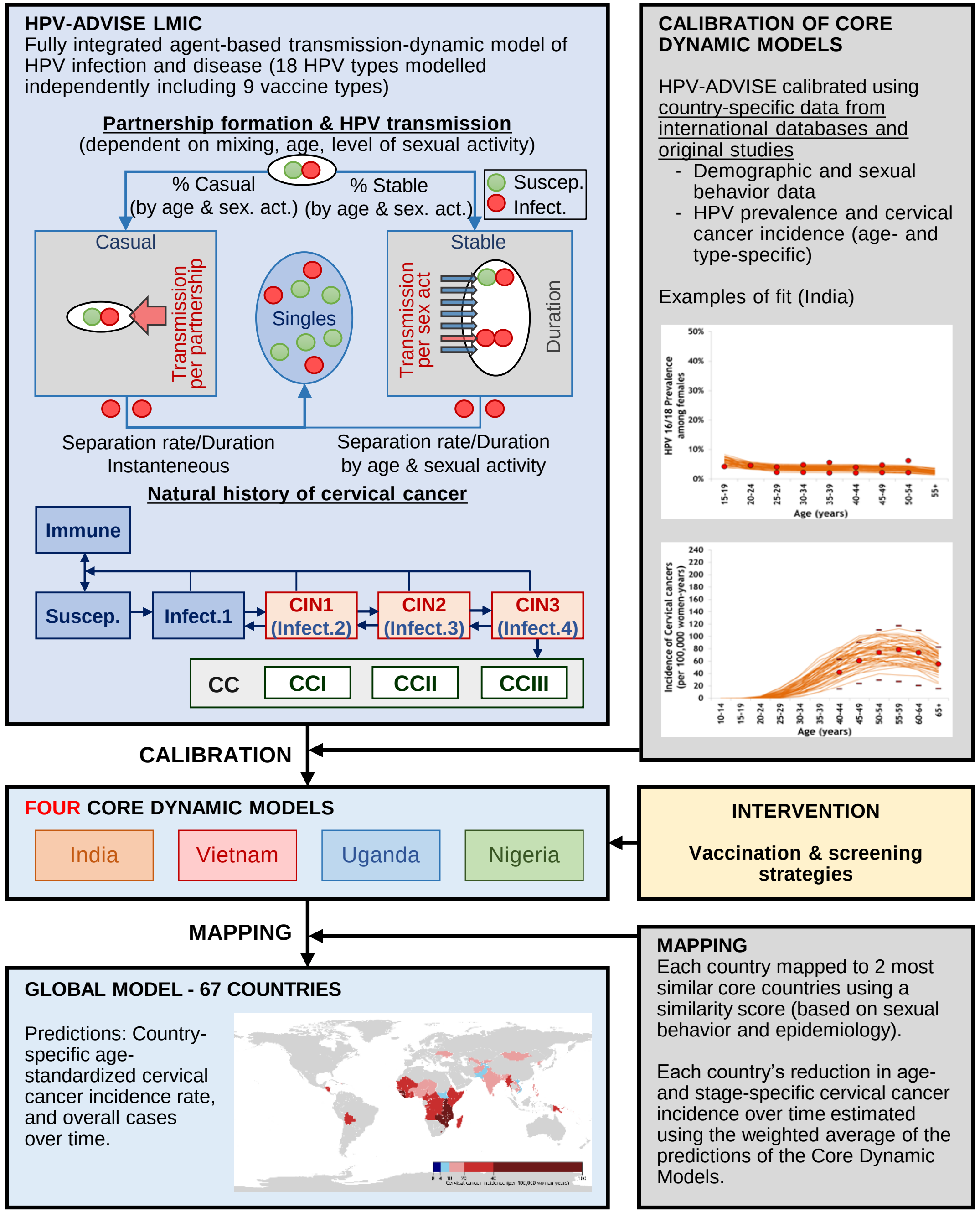


&. Drolet et al. Lancet 2019

Methods HPV-ADVISE overview

Model Structure, Core Modelled Countries & Mapping

- HPV-ADVISE LMIC[1]
- Agent-based transmission-dynamic model of HPV infection & cancer
  - Stratified by sex, age, level of sexual activity & screening behaviour
- 18 HPV types modelled individually:
  - 9-valent vaccine types + 9 other high-risk types
- Fit HPV-ADVISE to 4 core LMICs (India, Vietnam, Nigeria & Uganda)
  - Demographic and sexual behaviour
  - HPV prevalence and cervical cancer incidence (age & type-specific)
  - Data from international databases and original studies[&]
- Mapped 67 LMICs to the results obtained from the core countries
  - Using previously developed mapping algorithm
  - LMIC was mapped to the 2 most similar core LMICs based on sexual activity and epidemiology[2]



REF: 1. Drolet, Laprise et al., Lancet ID 2021; 2. Brisson, Kim & Canfell et al, The Lancet (2020); &: 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, original studies from Dr Alary and IARC

Methods Efficiency frontier

What are the optimal (most efficient) strategies?

- We modelled 162 vaccination strategies varying target populations, age at vaccination, number of doses (1 or 2 doses for girls/boys up to 20 years old; 2 doses for individuals >20 years old)

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  - NNV = Number of doses given / Number of cervical cancers (CC) averted over 100 years
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- Efficiency outcome : Number of doses needed to prevent one cervical cancer (NNV)
  - NNV = Number of doses given / Number of cervical cancers (CC) averted over 100 years
  - Lower NNV indicates a more efficient strategy
- Efficiency frontier – ranked all strategies from the lowest to the highest incremental NNV:
  - Initial strategy: Girls-only routine vaccination at 9 years old
  - Estimated the incremental NNVs of all strategies vs the initial strategy
  - Kept the strategy with the lowest incremental NNV (vs the initial strategy); this strategy became the new comparator
  - Estimated incremental NNVs of all strategies vs this new comparator to identify the next most efficient strategy
  - Repeated this process to identify the efficiency frontier

Note: We calculated the incremental NNVs of all vaccination scenarios versus the reference scenario, for each of the 50 parameter sets. The algorithm identified the vaccination scenario with the lowest incremental NNV for each of the 50 parameter sets. The scenario that was identified most often as producing the lowest incremental NNV over the 50 parameter sets was chosen as the most efficient scenario.

Methods Countries - Global analysis

Table: List of countries included in the global analysis

Country (n=67)			
Afghanistan	Eswatini	Mali	Sierra Leone
Angola	Ethiopia	Mauritania	Solomon Islands
Bangladesh	Gambia	Mongolia	Somalia
Benin	Ghana	Mozambique	South Soudan
Bhutan	Guinea	Myanmar	Sri Lanka
Bolivia	Guinea-Bissau	Nepal	Tajikistan
Burkina Faso	Haiti	Nicaragua	Tanzania
Burundi	Honduras	Niger	Timor-Leste
Cambodia	India	Nigeria	Togo
Cameroon	Ivory Coast	Pakistan	Uganda
Cape Verde	Kenya	Papua New Papua	Ukraine
Central African Republic	Kyrgyz Republic	Philippines	Uzbekistan
Chad	Lao PDR	Republic of the Congo	Vanuatu
Comoros	Lesotho	Rwanda	Vietnam
Democratic People's Republic of Korea	Liberia	Samoa	Zambia
Democratic Republic of the Congo	Madagascar	Sao Tome and Principe	Zimbabwe
Eritrea	Malawi	Senegal	

Methods Country grouping – Cervical cancer burden*

Table: List of countries included in the country grouping by cervical cancer burden*

	Country				
Very high burden setting (incidence* > 40/100,000 women-year, n=18)	Burundi	Gambia	Liberia	Mozambique	Zambia
	Bolivia	Guinea	Madagascar	Senegal	Zimbabwe
	Comoros	Guinea-Bissau	Malawi	Tanzania	
	Eswatini	Lesotho	Mali	Uganda	
High burden setting (incidence 20-40/100,000 women-year, n=25)	Angola	Ghana	Mongolia	Republic of the Congo	Togo
	Cameroon	Honduras	Myanmar	Rwanda	
	Central African Republic	India	Nepal	Sierra Leone	
	Chad	Ivory Coast	Nicaragua	Solomon Islands	
	Democratic Republic of the Congo	Kenya	Nigeria	Somalia	
	Ethiopia	Mauritania	Papua New Guinea	South Soudan	
Moderate burden setting (incidence 10-20/100,000 women-year, n=21)	Afghanistan	Cambodia	Kyrgyz Republic	Sao Tome and Principe	Vanuatu
	Bangladesh	Cape Verde	Lao PDR	Sri Lanka	
	Benin	Democratic People's Republic of Korea	Niger	Timor-Leste	
	Bhutan	Eritrea	Philippines	Ukraine	
	Burkina Faso	Haiti	Samoa	Uzbekistan	
Low burden setting (incidence < 10/100,000 women-year, n=3)	Pakistan	Tajikistan	Vietnam		

*Age-standardized cervical cancer incidence calculated using country- and age-specific cervical cancer incidence from Globocan 2020 and the 2015 world standard population (from the United Nations World Population Prospect, 2017 revision).

Methods Global analysis and country groupings

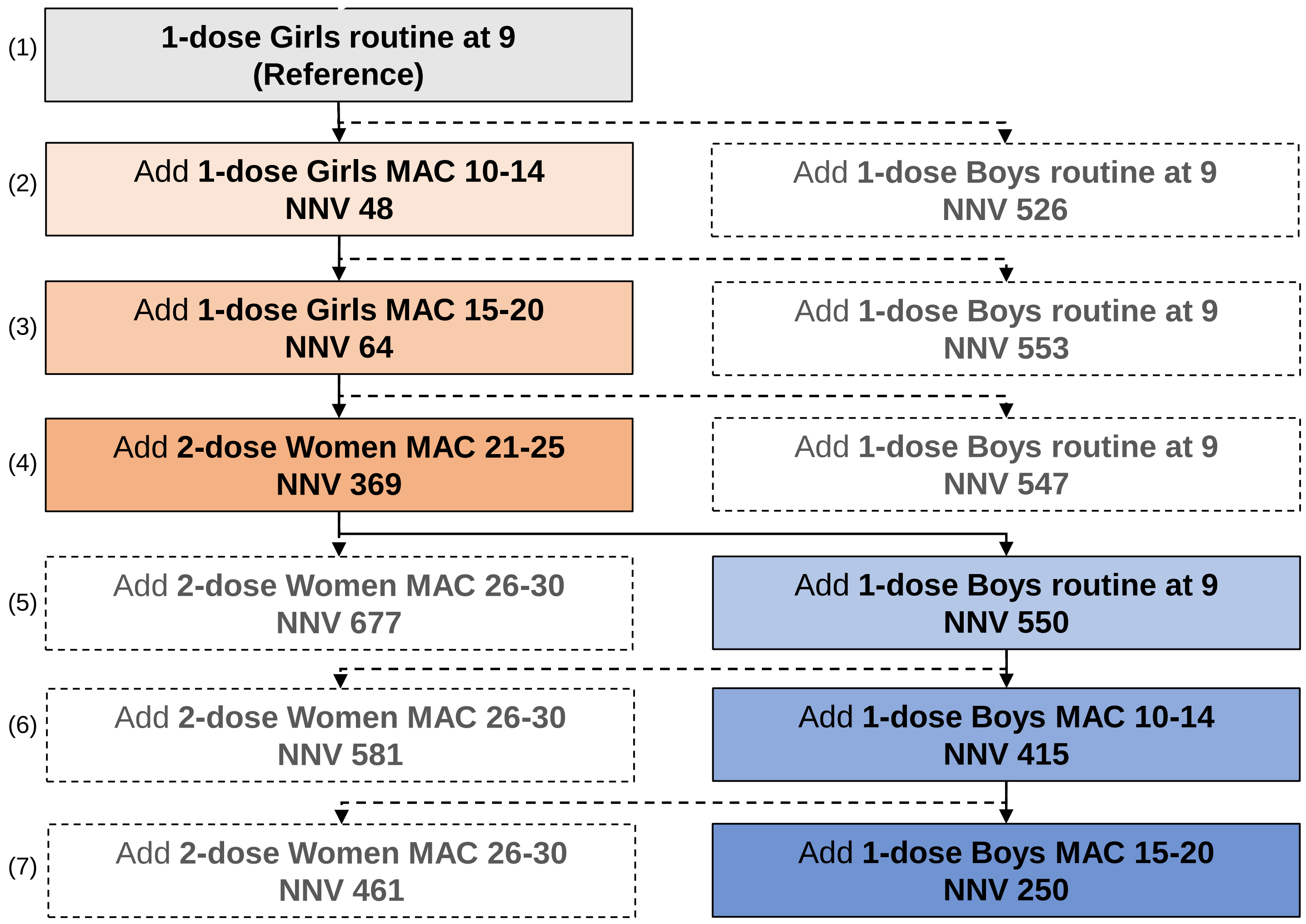
Table: Characteristics by country groupings

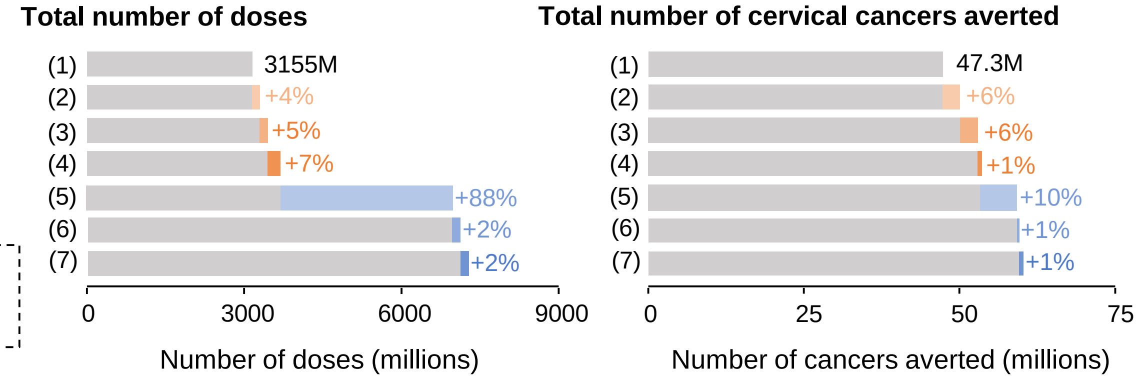
	Cervical cancer incidence per 100,000 women-year*	HPV prevalence among women (any type)[1]	Lifetime number of sexual partners, women[2]	First sexual intercourse by exact age 15 (%), women[2]
	Median (25th – 75th percentile)	Median (25th – 75th percentile)	Median (25th – 75th percentile)	Median (25th – 75th percentile)
Cervical cancer burden (incidence per 100,000 women-year*)				
Very high burden setting (>40)	57.2 (45.2 – 69.0)	26.6 (19.6 – 33.6)	2.1 (1.6 – 2.4)	13.6 (9.0 – 19.6)
High burden setting (20-40)	26.6 (23.2 – 31.5)	19.6 (16.8 – 24.0)	1.7 (1.4 – 2.3)	18.2 (10.7 – 24.0)¥
Moderate burden setting (10-20)	15.4 (12.5 – 17.7)	14.0 (9.4 – 19.6)	1.7 (1.4 – 2.1)	11.1 (1.5 – 14.4)
Low burden setting (<10)	7.6 (7.3 – 8.5)	9.4 (8.3 – 11.7)	1.3 (1.2 – 1.7)	0.7 (0.5 – 3.5)
Income level (World Bank, 2022 classification)				
Low income	28.1 (21.9 – 45.3)	24.0 (19.6 – 33.6)	2.0 (1.5 – 2.3)	19.9 (11.3 – 24.4)
Lower-middle income	21.5 (15.6 – 38.1)	17.4 (12.4 – 22.1)	1.7 (1.4 – 2.3)	10.4 (5.9 – 16.6)

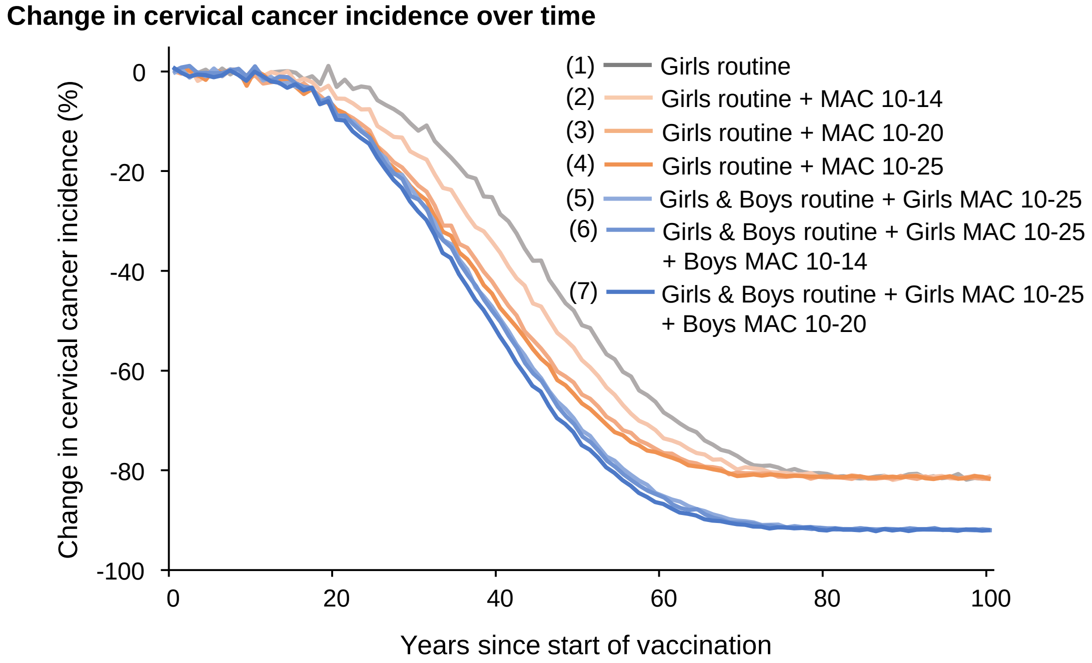
REF: 1. Bruni et al, JID 2010, 2. Demographic and Health Surveys (DHS). **NOTE:** *Age-standardized cervical cancer incidence calculated using country- and age-specific cervical cancer incidence from Globocan 2020 and the 2015 world standard population (from the United Nations World Population Prospect, 2017 revision). ¥In the high incidence group, the proportion of women who had their first sexual intercourse by exact age 15 varied noticeably depending on the main religion of the country.

Global analysis – Decision tree

Non-inferior 1-dose; Vaccination coverage=80%







All NNVs are incremental.

SCENARIO: 1-dose routine and MAC vaccination up to 20 year old; 2-dose MAC vaccination >20 years old. 1-dose VE=100% and VD=lifelong.

What are the most efficient strategies in countries with lower (40%, 70%) or higher (90%) vaccination coverage (assuming non-inferior 1 dose)?

Global analysis – 40% coverage

Non-inferior 1-dose

80% vaccination coverage

1-dose Girls routine at 9 (Reference)

↓

Add **1-dose Girls MAC 10-14**
NNV* 48

↓

Add **1-dose Girls MAC 15-20**
NNV 64

↓

Add **2-dose Women MAC 21-25**
NNV 369

↓

Add **1-dose Boys routine + MAC 10-20**
NNV 511

40% vaccination coverage

1-dose Girls routine at 9 (Reference)

↓

Add **1-dose Girls MAC 10-14**
NNV 45

↓

Add **1-dose Girls MAC 15-20**
NNV 66

↓

Increase VC to 80% of Girls 9-20
NNV 68

With 40% routine vaccination coverage:

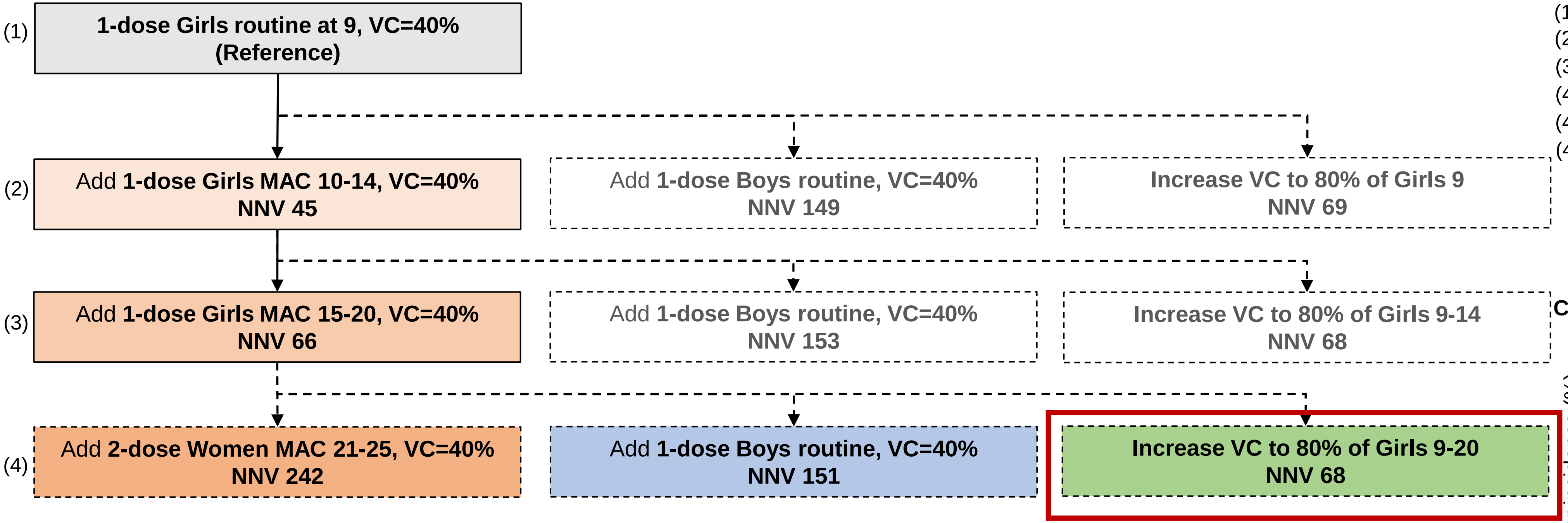
- once girls are vaccinated up to 20 years old, the next most efficient strategy is to **increase 1-dose vaccination coverage among girls in these age groups**

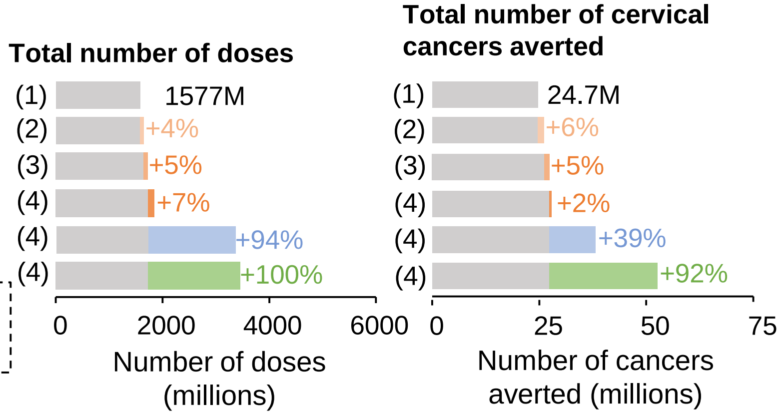
All NNVs are incremental.

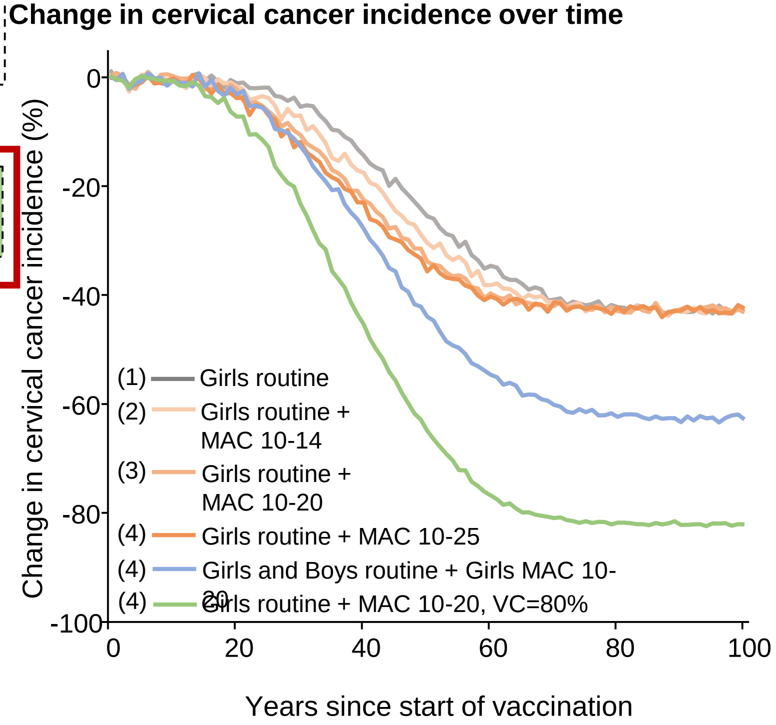
SCENARIO: 1-dose routine and MAC vaccination up to 20 year old; 2-dose MAC vaccination >20 years old. 1-dose VE=100% and VD=lifelong.

Global Analysis – Decision tree, 40% coverage

Non-inferior 1-dose







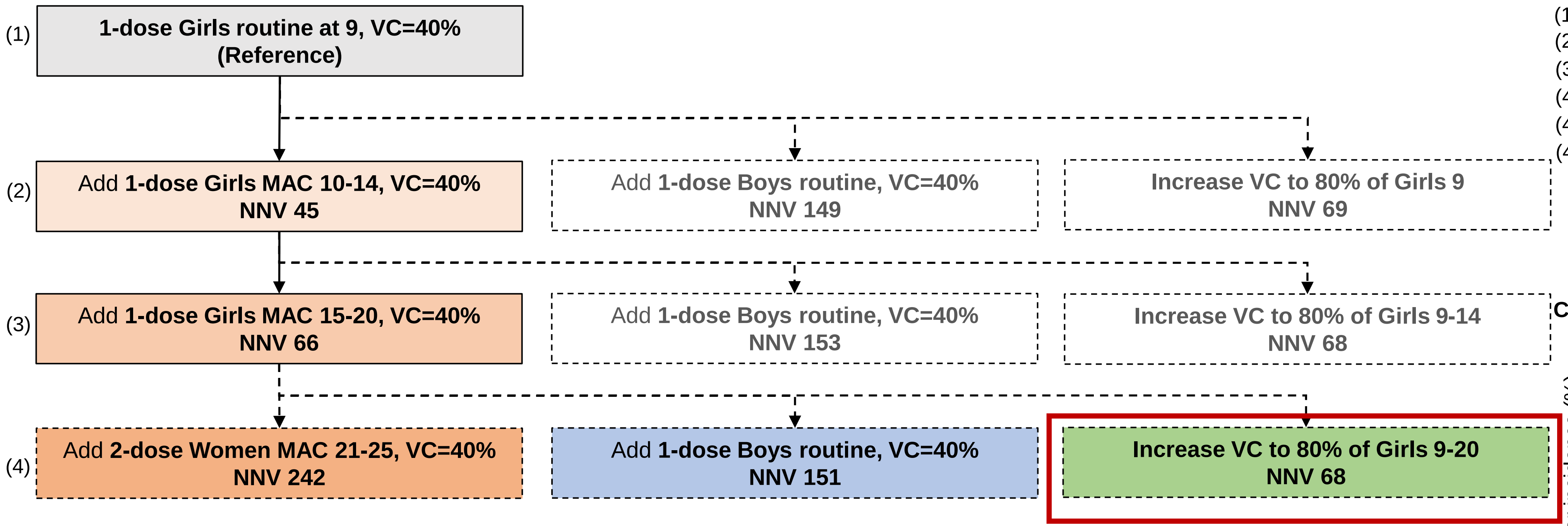
- Increasing vaccination coverage of girls leads to the lowest NNV

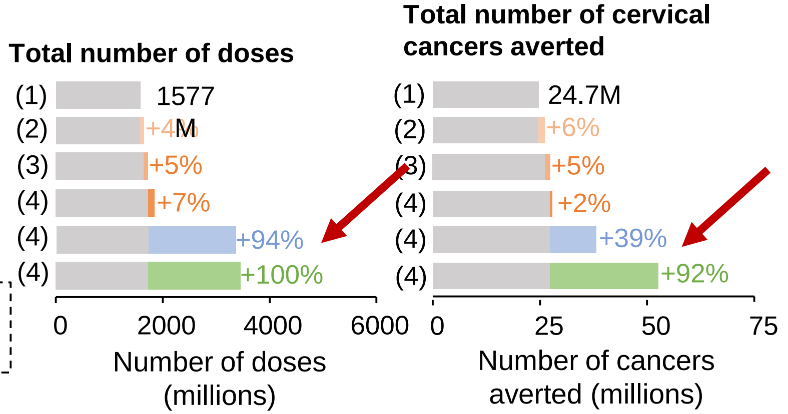
All NNVs are incremental.

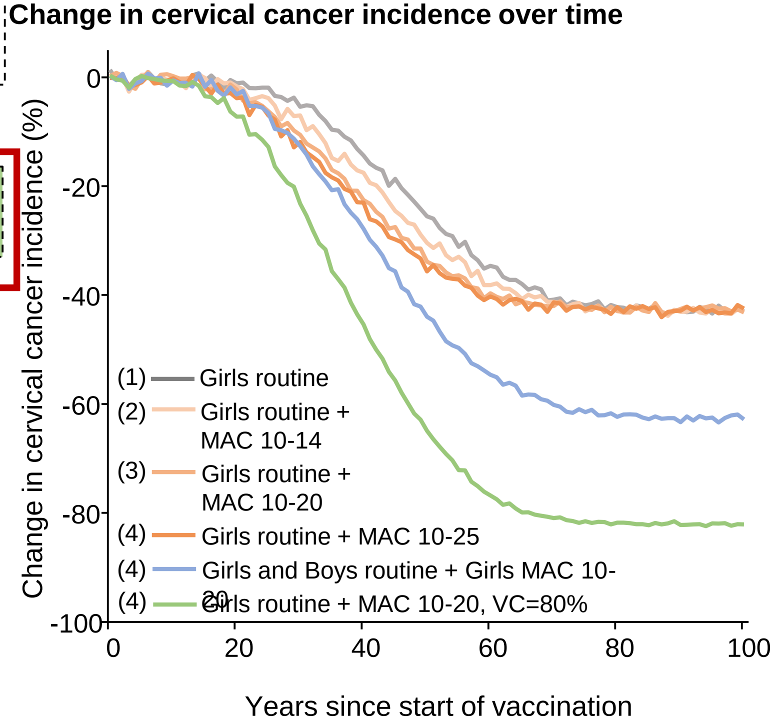
SCENARIO: 1-dose routine and MAC vaccination up to 20 year old; 2-dose MAC vaccination >20 years old. 1-dose VE=100% and VD=lifelong.

Global Analysis – Decision tree, 40% coverage

Non-inferior 1-dose







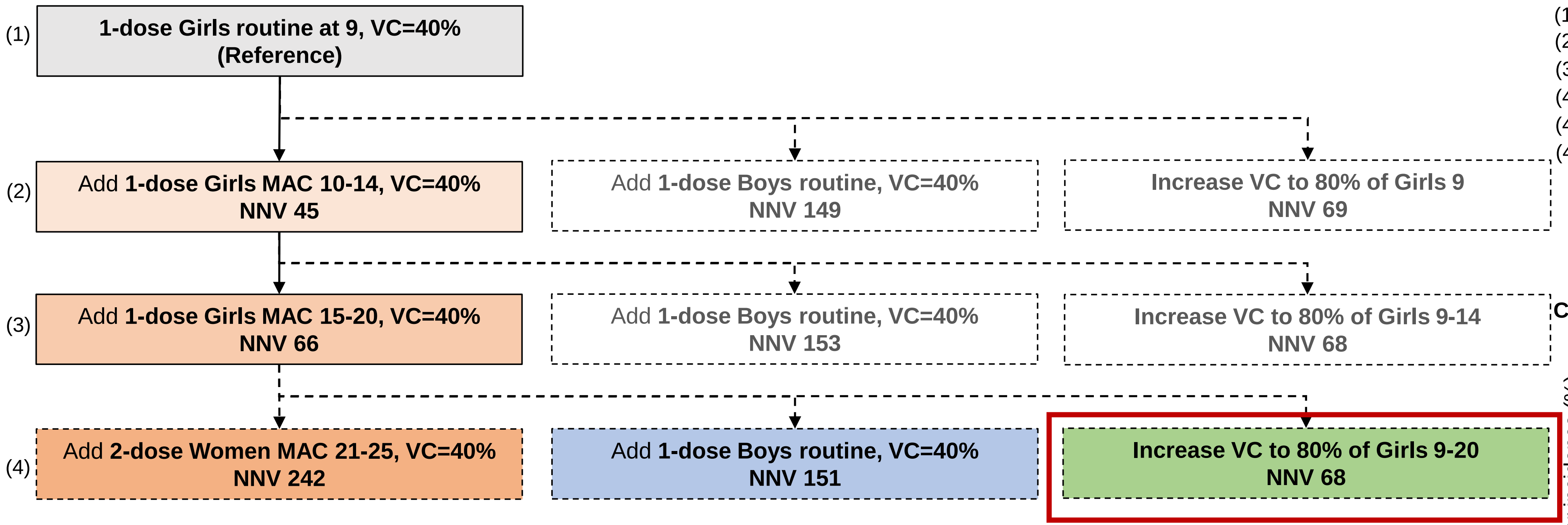
- Increasing vaccination coverage of girls leads to the lowest NNV
- For the same number of additional doses, doubling the coverage of girls (from 40% to 80%) leads to 3 times more CC averted than vaccinating boys (40% coverage)

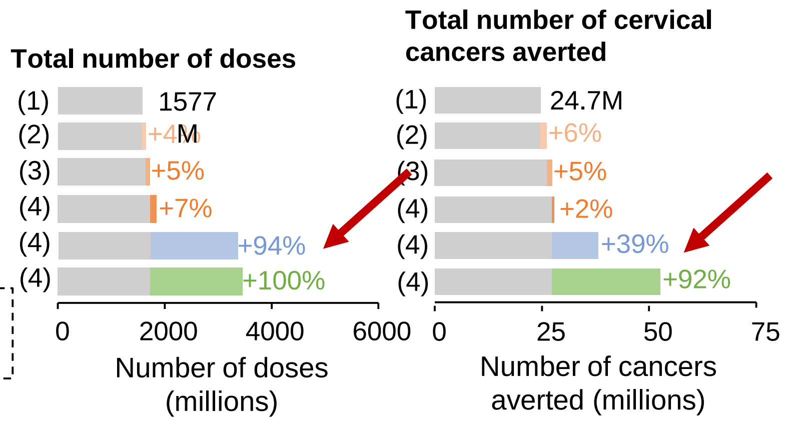
All NNVs are incremental.

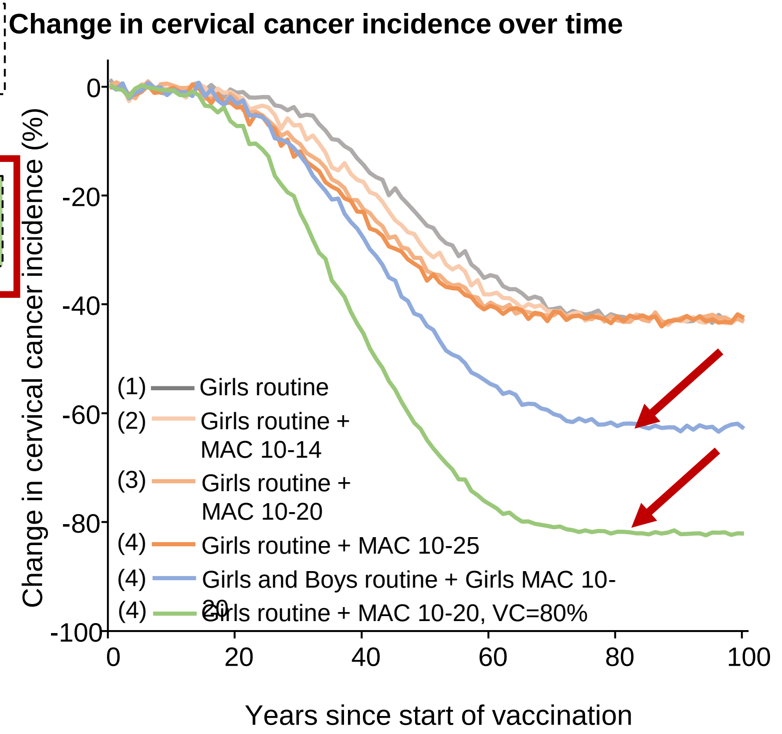
SCENARIO: 1-dose routine and MAC vaccination up to 20 year old; 2-dose MAC vaccination >20 years old. 1-dose VE=100% and VD=lifelong.

Global Analysis – Decision tree, 40% coverage

Non-inferior 1-dose





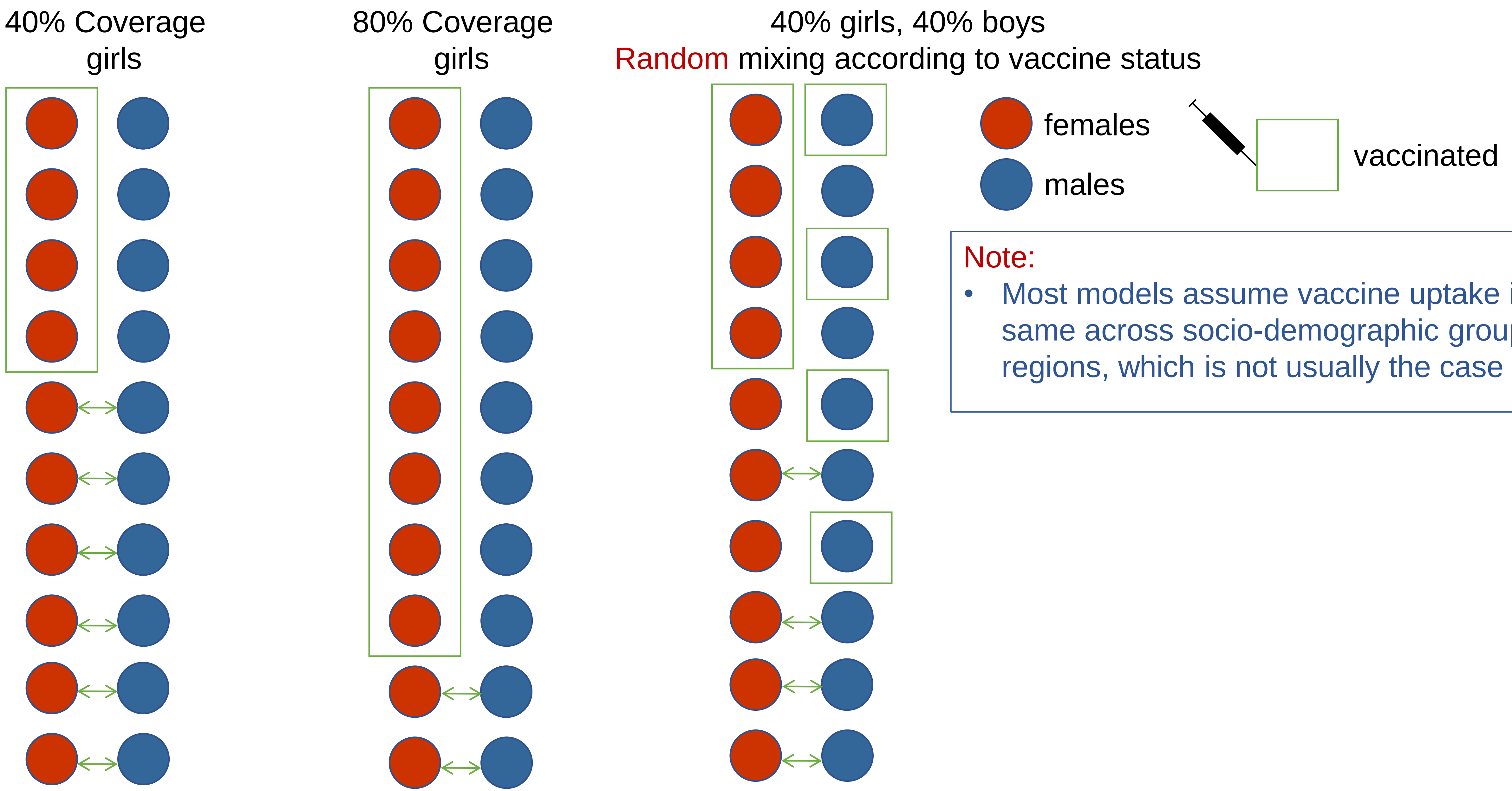


- Increasing vaccination coverage of girls leads to the lowest NNV
- For the same number of additional doses, doubling the coverage of girls (from 40% to 80%) leads to 3 times more CC averted than vaccinating boys (40% coverage)
- The impact on CC reduction is much more important when increasing coverage of girls compared to adding the vaccination of boys

All NNVs are incremental.

SCENARIO: 1-dose routine and MAC vaccination up to 20 year old; 2-dose MAC vaccination >20 years old. 1-dose VE=100% and VD=lifelong.

More efficient to increase coverage in girls than including boys

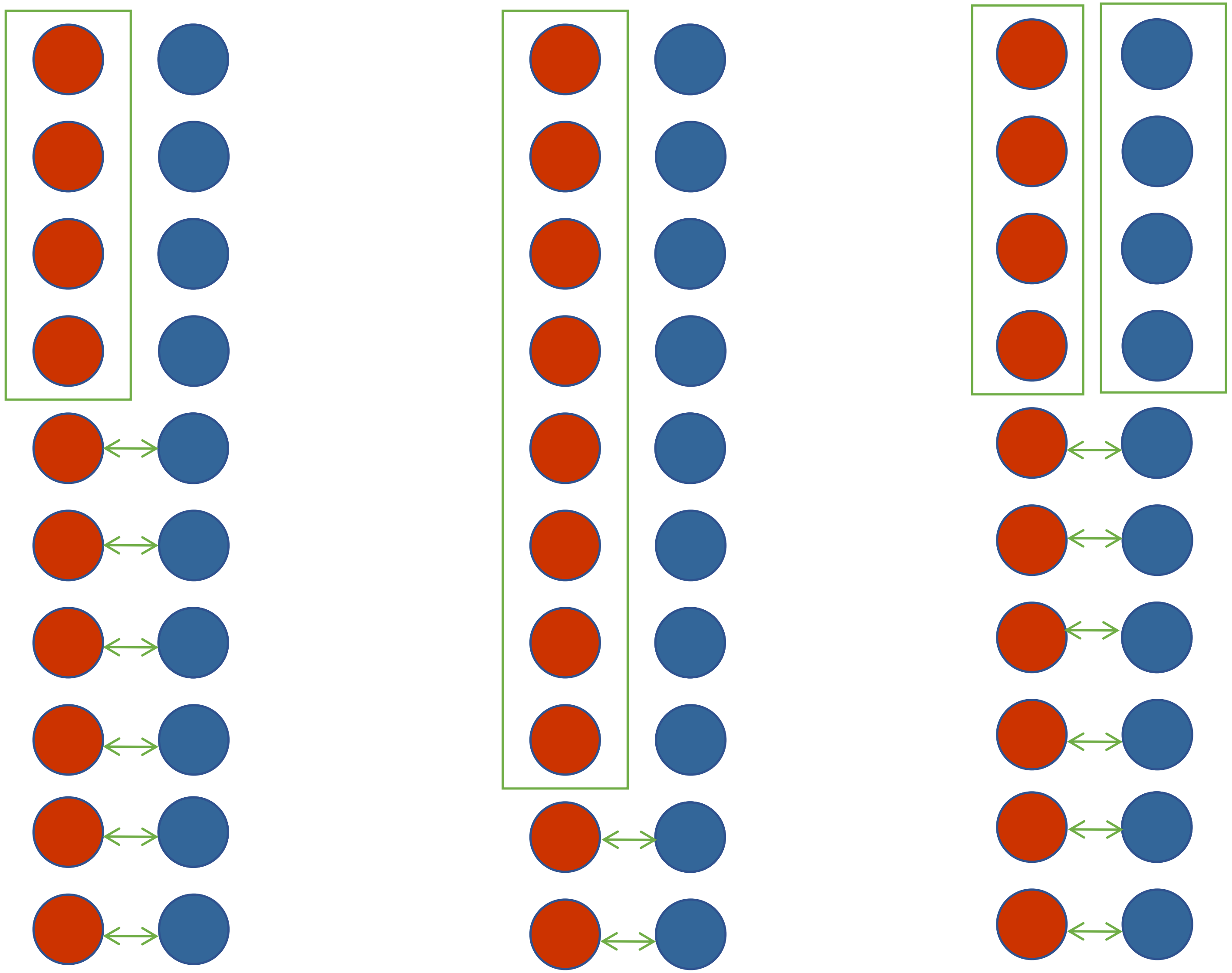


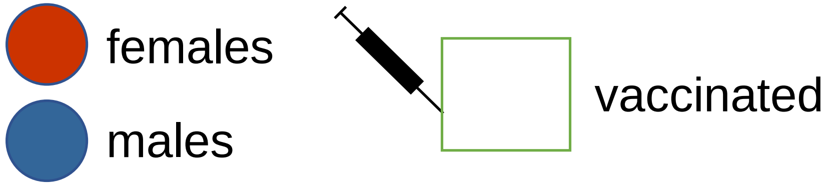
Note:

- Most models assume vaccine uptake is the same across socio-demographic groups and regions, which is not usually the case

More efficient to increase coverage in girls than including boys

40% Coverage girls | 80% Coverage girls | 40% girls, 40% boys
Assortative mixing according to vaccine status





Note:

- Most models assume vaccine uptake is the same across socio-demographic groups and regions, which is not usually the case
- Girls and boys will have similar determinants of vaccine uptake
- Hence, vaccinated females will more likely have male partners who are also vaccinated, as partnerships are assortative according to sociodemographic characteristics (like-with-like)
- This would produce redundancy in vaccination coverage, which can limit the herd effects and impact of vaccinating boys

Global analysis If feasible to increase vaccination coverage of girls

Non-inferior 1-dose

40% vaccination coverage	70% vaccination coverage	80% vaccination coverage	90% vaccination
1-dose Girls routine at 9 (Reference)	**1-dose Girls routine at 9 (Reference)**	**1-dose Girls routine at 9 (Reference)**	**1-dose Girls routine at 9 (Reference)**
Add **1-dose Girls MAC 10-14** **NNV 45**	Add **1-dose Girls MAC 10-14** **NNV 55**	Add **1-dose Girls MAC 10-14** **NNV 48**	Add **1-dose Girls MAC 10-14** **NNV 52**
Add **1-dose Girls MAC 15-20** **NNV 66**	Add **1-dose Girls MAC 15-20** **NNV 69**	Add **1-dose Girls MAC 15-20** **NNV 64**	Add **1-dose Girls MAC 15-20** **NNV 58**
Increase VC to 70% of Girls 9-20 **NNV 67**	**Increase VC to 80% of Girls 9-20** **NNV 70**	**Increase VC to 90% of Girls 9-20** **NNV 76**	Add **2-dose Women MAC 21-25** **NNV 403**
Increase VC to 80% of Girls 9-20 **NNV 70**	**Increase VC to 90% of Girls 9-20** **NNV 76**		Add **2-dose Women MAC 26-30** **NNV 634**
Increase VC to 90% of Girls 9-20 **NNV 76**			

If feasible to increase coverage, vaccinating more girls aged <20 years is the most efficient compared vs vaccination of boys or older girls/women

All NNVs are incremental.

SCENARIO: 1-dose routine and MAC vaccination up to 20 year old; 2-dose MAC vaccination >20 years old. 1-dose VE=100% and VD=lifelong.

Global analysis If unfeasible to increase vaccination coverage of girls

Non-inferior 1-dose

40% vaccination coverage	70% vaccination coverage	80% vaccination coverage	90% vaccination
1-dose Girls routine at 9 (Reference)	**1-dose Girls routine at 9 (Reference)**	**1-dose Girls routine at 9 (Reference)**	**1-dose Girls routine at 9 (Reference)**
Add **1-dose Girls MAC 10-14** **NNV 45**	Add **1-dose Girls MAC 10-14** **NNV 47**	Add **1-dose Girls MAC 10-14** **NNV 48**	Add **1-dose Girls MAC 10-14** **NNV 52**
Add **1-dose Girls MAC 15-20** **NNV 66**	Add **1-dose Girls MAC 15-20** **NNV 59**	Add **1-dose Girls MAC 15-20** **NNV 64**	Add **1-dose Girls MAC 15-20** **NNV 58**
Add **1-dose Boys routine+MAC 10-20** **NNV 142**	Add **1-dose Boys routine+MAC 10-20** **NNV 295**	Add **2-dose Women MAC 21-25** **NNV 369**	Add **2-dose Women MAC 21-25** **NNV 403**
Add **2-dose Women only MAC 21-25** **NNV 229**	Add **2-dose Women MAC 21-25** **NNV 322**	Add **1-dose Boys routine+MAC 10-20** **NNV 511**	Add **2-dose Women MAC 26-30** **NNV 634**

If vaccination coverage is lower than 90% among girls aged < 20 years and it is unfeasible to increase coverage, vaccinating boys can be an efficient use of HPV vaccines (can increase protection of girls through herd-immunity, assuming limited redundancy in vaccine distribution by sociodemographic characteristics)

All NNVs are incremental.

SCENARIO: 1-dose routine and MAC vaccination up to 20 year old; 2-dose MAC vaccination >20 years old. 1-dose VE=100% and VD=lifelong.

Are the most efficient strategies the same if the mean duration of protection of 1 dose is 30 years (pessimistic 1-dose scenario) ?

Global analysis – Shorter duration on protection 1-dose, Efficiency frontier

Vaccination coverage=80%

Non-inferior 1-dose	Pessimistic 1-dose duration (VD=30 yrs)
1-dose Girls routine at 9 (Reference)	**1-dose Girls routine at 9 (Reference)**
Add **1-dose Girls MAC 10-14 NNV* 48**	Add **1-dose Girls MAC 10-14 NNV 59**
Add **1-dose Girls MAC 15-20 NNV 64**	Add **1-dose Girls MAC 15-20 NNV 71**
Add **2-dose Women MAC 21-25 NNV 369**	Add **2-dose Women MAC 21-25 NNV 314**
Add **1-dose Boys routine + MAC 10-20 NNV 511**	Add **1-dose Boys routine + MAC 10-20 NNV 450**

With an average 30-year duration of protection for 1 dose:

- **same results as non-inferior 1 dose**
- girls/women are protected during the peak ages of sexual activity

All NNVs are incremental.

SCENARIO: Vaccination coverage=80%; 1-dose routine and MAC vaccination up to 20 year old; 2-dose MAC vaccination >20 years old.

Global analysis – Shorter duration on protection 1-dose, Efficiency frontier

Vaccination coverage=80%

Non-inferior 1-dose

1-dose Girls routine at 9 (Reference)

↓

Add **1-dose Girls MAC 10-14**
NNV* 48

↓

Add **1-dose Girls MAC 15-20**
NNV 64

↓

Add **2-dose Women MAC 21-25**
NNV 369

↓

Add **1-dose Boys routine + MAC 10-20**
NNV 511

Pessimistic 1-dose duration (VD=30 yrs)

1-dose Girls routine at 9 (Reference)

↓

Add **1-dose Girls MAC 10-14**
NNV 59

↓

Add **1-dose Girls MAC 15-20**
NNV 71

↓

Add **2-dose Women MAC 21-25**
NNV 314

↓

Add **1-dose Boys routine + MAC 10-20**
NNV 450

With an average 30-year duration of protection for 1 dose:

- **same results as non-inferior 1 dose**
- girls/women are protected during the peak ages of sexual activity

All NNVs are incremental.

SCENARIO: Vaccination coverage=80%; 1-dose routine and MAC vaccination up to 20 year old; 2-dose MAC vaccination >20 years old.

Are the most efficient strategies the same in countries with different levels of cervical cancer burden ?

Very high: >40 cervical cancers/100,000 w-yrs
High: 20-40 cervical cancers/100,000 w-yrs
Moderate: 10-19 cervical cancers/100,000 w-yrs
Low: <10 cervical cancers/100,000 w-yrs

Global analysis Efficiency frontier by cervical cancer burden

Non-inferior 1-dose

Very high burden setting	High burden setting	Moderate burden setting	Low burden setting
1-dose Girls routine at 9 (Reference)	**1-dose Girls routine at 9 (Reference)**	**1-dose Girls routine at 9 (Reference)**	**1-dose Girls routine at 9 (Reference)**
Add **1-dose Girls MAC 10-14** **NNV 21**	Add **1-dose Girls MAC 10-14** **NNV 50**	Add **1-dose Girls MAC 10-14** **NNV 78**	Add **1-dose Girls MAC 10-14** **NNV 144**
Add **1-dose Girls MAC 15-20** **NNV 26**	Add **1-dose Girls MAC 15-20** **NNV 68**	Add **1-dose Girls MAC 15-20** **NNV 110**	Add **1-dose Girls MAC 15-20** **NNV 193**
Add **2-dose Women MAC 21-25** **NNV 199**	Add **2-dose Women MAC 21-25** **NNV 370**	Add **1-dose Women MAC 21-25** **NNV 555**	Add **2-dose Women MAC 21-25** **NNV 1101**
Add **1-dose Boys routine+MAC 10-20** **NNV 239**	Add **1-dose Boys routine+MAC 10-20** **NNV 545**	Add **1-dose Boys routine+MAC 10-20** **NNV 965**	

Results are similar for LMICs with a moderate to very high burden.
For low burden settings, it is more efficient to vaccinate older women than boys, given the smaller potential of additional benefits from vaccinating boys.

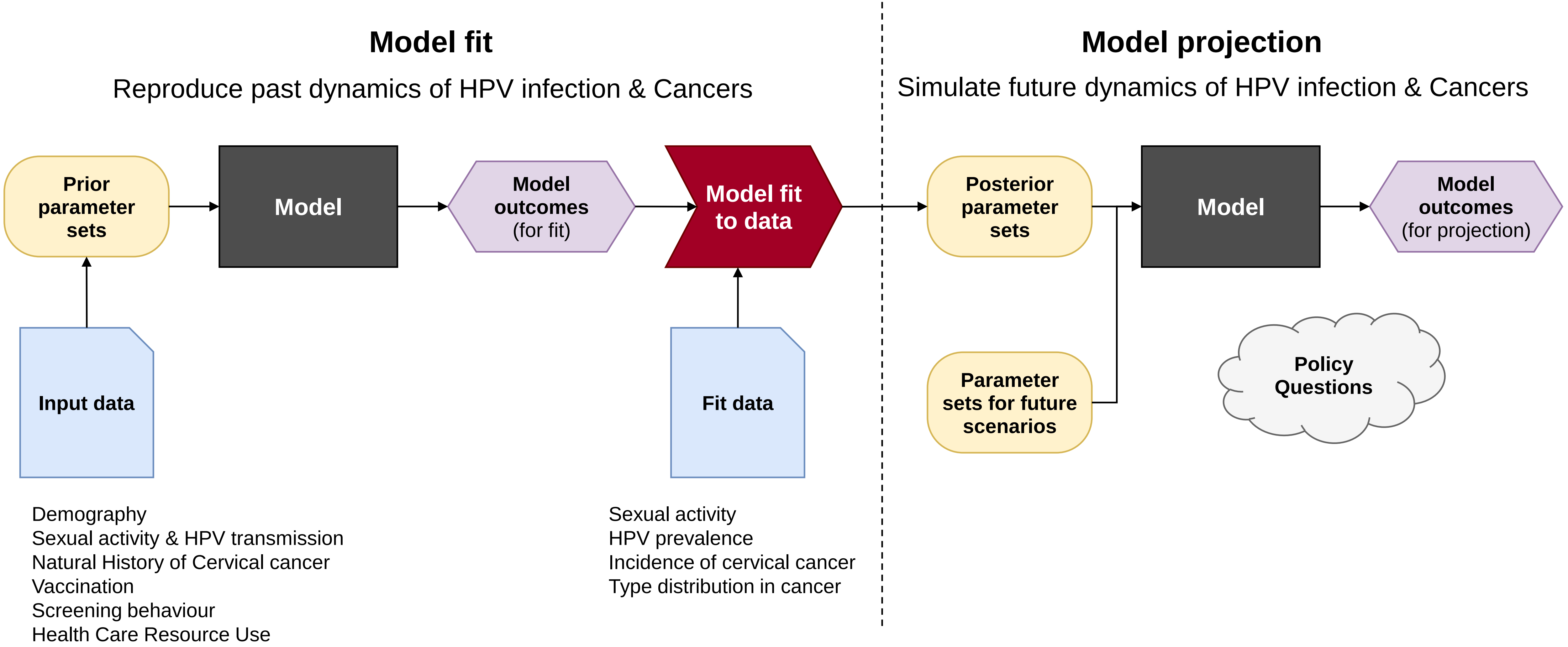
***All NNVs are incremental. SCENARIO**: Vaccination coverage=80%. 1-dose routine and MAC vaccination up to 20 years-old, and 2-dose MAC vaccination above 20 years-old. 1-dose vaccine efficacy=100% and duration of protection=lifelong. Routine vaccination at 9 years-old.

In summary – Optimal HPV vaccination strategies in LMICs

- Our model projects that, the most efficient HPV vaccination strategies are to:
  1) vaccinate girls/women up to 25 years old (1 dose up to 20 yrs old; 2 doses 21-25 yrs old)
  2) vaccinate boys up to 20 years old with 1 dose
- Conclusions are generally consistent across different 1-dose duration assumptions, vaccination coverages, and LMIC cervical cancer burden
- The priority is to adequately protect girls and young women to reduce cervical cancer
  - 85% of HPV-related cancers are cervical cancer among women in LMIC

HPV-ADVISE Conceptual framework of analysis

Model calibration (fitting process) & projections



HPV-ADVISE Overview

- **Model type:** Individual-based transmission-dynamic model of HPV infection & diseases
- **6 Components:** Demographic
  Sexual behaviour & HPV transmission
  Natural history of disease
  Screening, diagnosis & Treatment
  Vaccination
  Economic
- **Diseases:** Cervical cancer and Cancers of the anus, oropharynx, penis, vagina & vulva
  Anogenital warts

HPV-ADVISE Demographic component

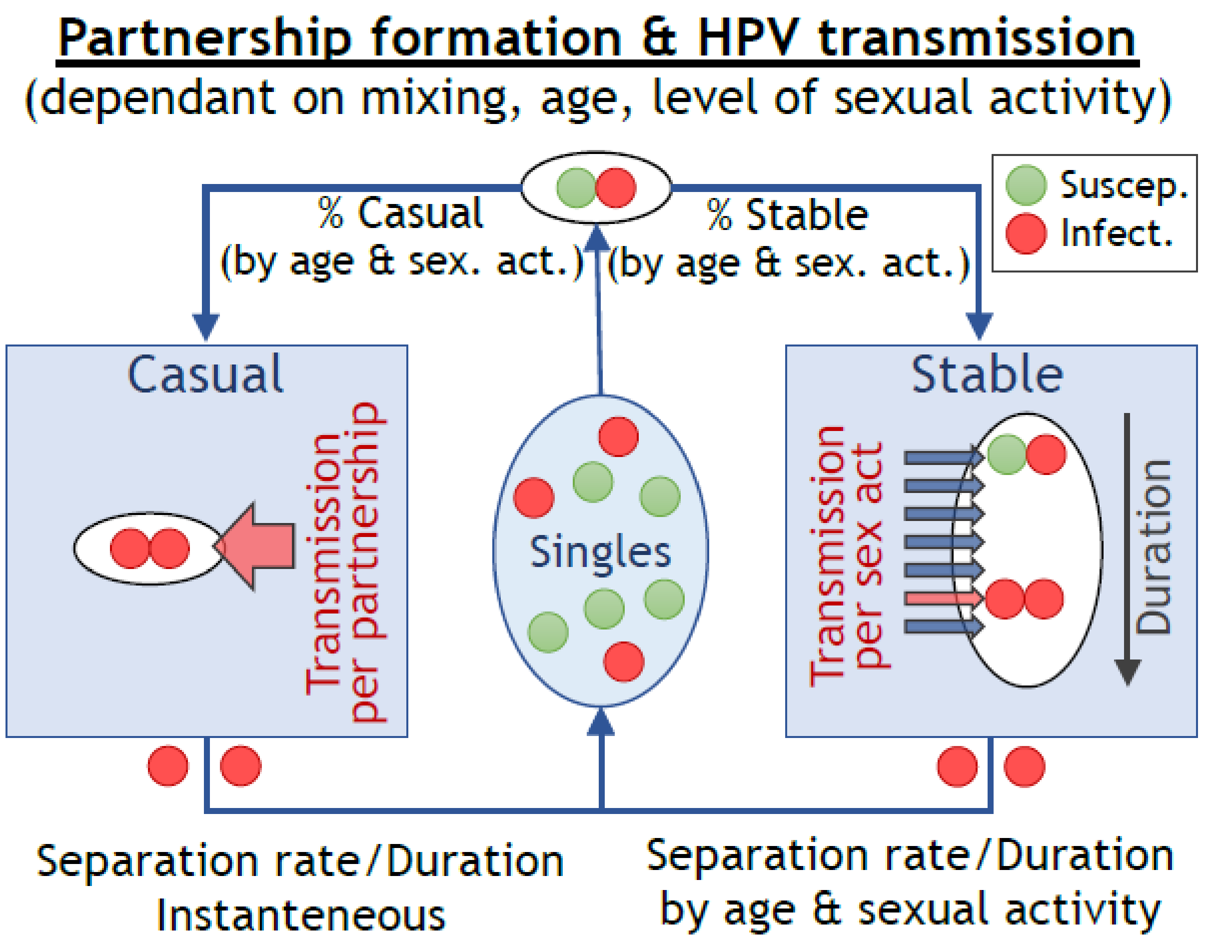
- **Open & stable population**
  - Age-specific death rates=crude birth rate
  - Capacity to include changes in birth and death rates over time

- **Individuals enter the population before sexual debut**

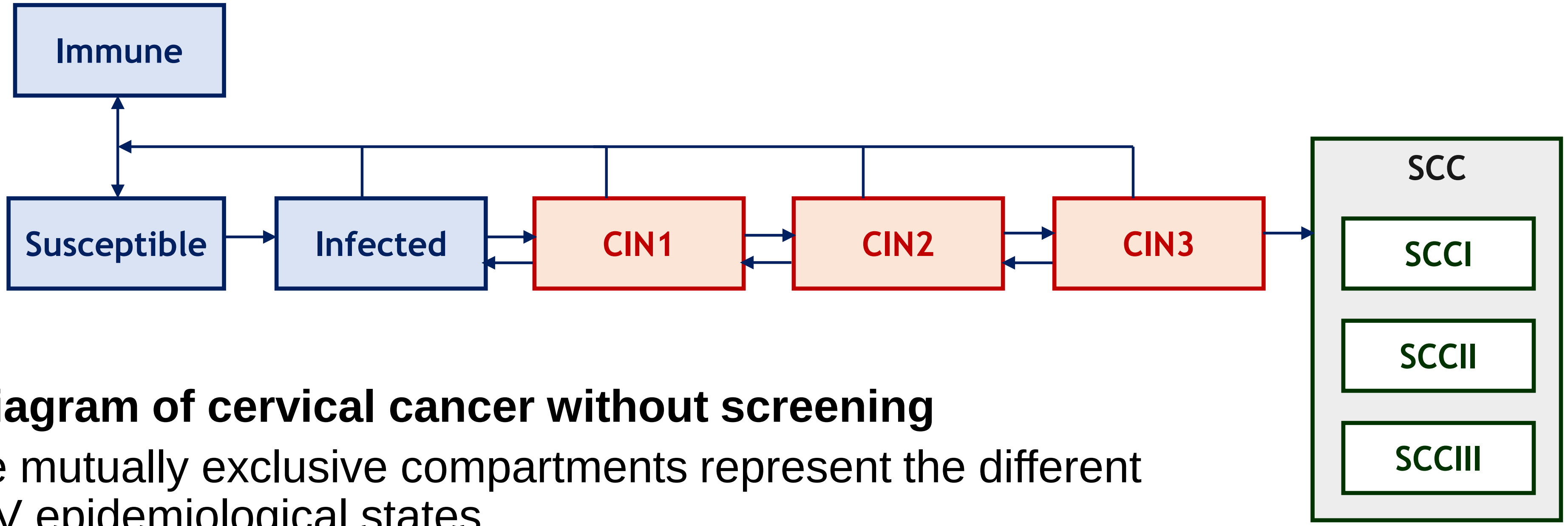
- **Risk factors for HPV infection and/or disease:**
  - Age (10 to 100 years old)
  - Sex (female, male)
  - Level of sexual activity (from low=0 to high=3)
  - Screening behaviour (from never=0 to frequently screened=4)

HPV-ADVISE Sexual behaviour & transmission component

- **Stable and casual partnerships**
- **Casual sexual partnerships between Female Sex Workers and men in stable partnerships**
- **Parameters are sex-, age- and sexual activity-specific**
  - Onset of sexual activity
  - Partner acquisition and separation rates
  - Sexual mixing patterns



HPV-ADVISE Natural history of disease component (Cervical Cancer)



- **Flow diagram of cervical cancer without screening**
  - The mutually exclusive compartments represent the different HPV epidemiological states
  - Arrows represent the possible transitions between states for each individual

- **Transition rates are age- and type- specific**

- **Natural history of other HPV-related cancers and anogenital warts can also be modeled**

HPV-ADVISE Vaccination component

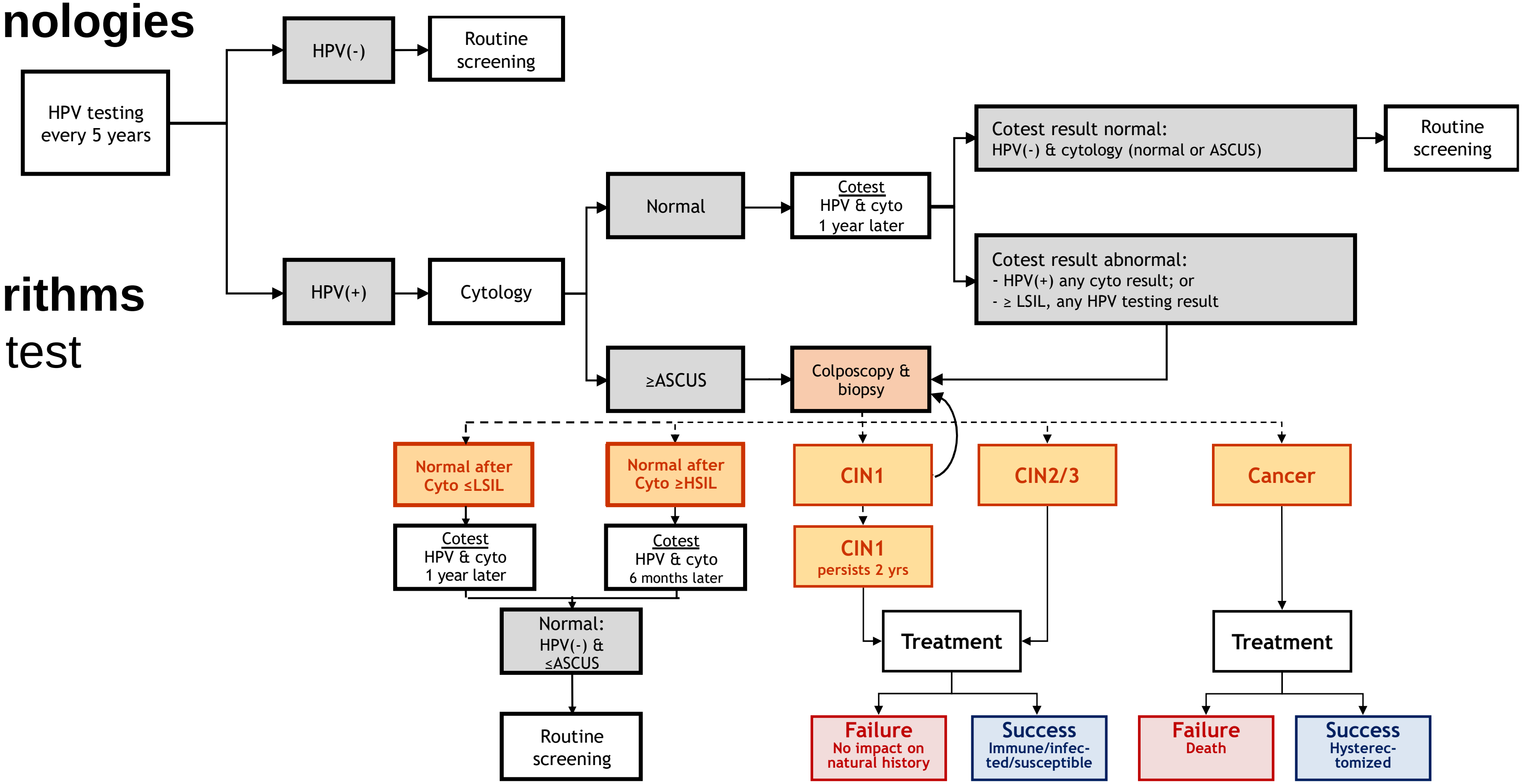
- **Vaccination can be efficacious against up to 18 HPV types (vaccine efficacy is type-specific)**
  - 2-valent: HPV-16/18
  - 4-valent: HPV-16/18/6/11
  - 9-valent: HPV-16/18/6/11/31/33/45/52/58
  - Can model cross-protection to types not included in the vaccine

- **Vaccine efficacy is modeled as a function of:**
  - Take (probability of developing immune protection)
  - Waning protection
  - Reduction in susceptibility to infection per sex act

- **Vaccination coverage can vary by:**
  - Time
  - Age
  - Sex
  - Sexual activity level
  - Screening behaviour

HPV-ADVISE Screening component

- **Women can be categorized into 5 lifetime levels of screening behaviour**
  - From short intervals between tests, to infrequently screened, and to never screened
- **Different screening technologies**
  - HPV testing
  - Cytology
  - Colposcopy
- **Different screening algorithms**
  - Pap test as a primary test
  - HPV triage
- **Coverage can vary by:**
  - Age
  - Sexual activity level
  - Vaccination status



HPV-ADVISE Economic component

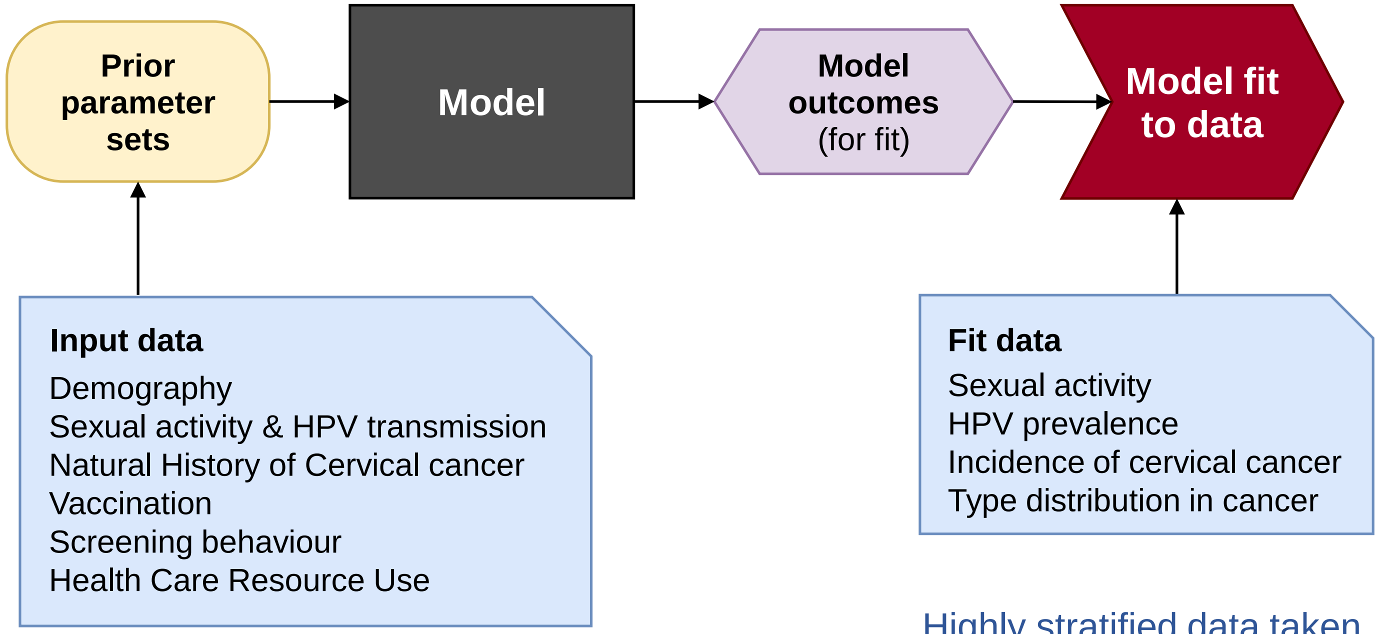
- **Health care resource use and Direct / Indirect medical costs**
  - Vaccination & Screening costs
  - Medical visits & Hospitalisation
- **QALYs or DALYs can be attributed to health outcomes over time**
  - CIN, HPV-related cancers, anogenital warts
- **Cost-effectiveness and budget impact can be estimated**

HPV-ADVISE Model calibration – Fitting process

Most important & complicated part of the analysis so the model represents Thailand

Model fit

Reproduce past dynamics of HPV infection & Cancers



Prior ranges & parameter values based on data taken from the literature and population-based datasets

Highly stratified data taken from the literature and population-based datasets (by age, HPV-type)

Uniform prior distributions are defined for each model parameter

min-max values for each parameter are derived from the literature

>100,000 of different **combinations of parameter values are drawn from the prior distributions**

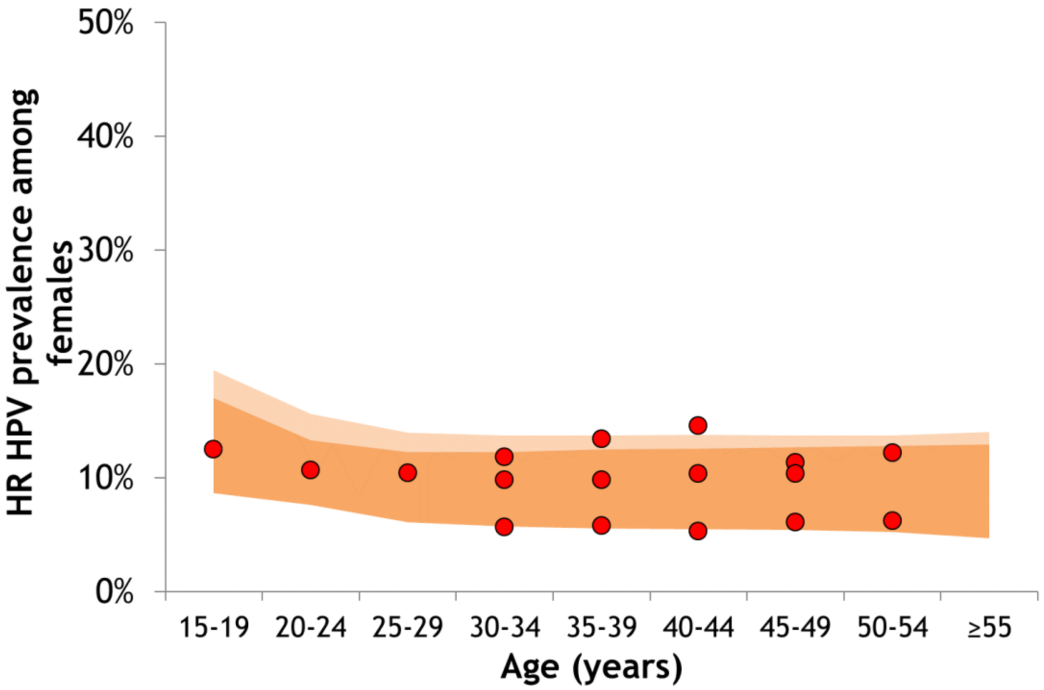
Parameter sets are qualified as producing a **“good fit” if the associated model predictions fall simultaneously within pre-specified targets (ranges)** of sexual behaviour and epidemiological data

HPV-ADVISE

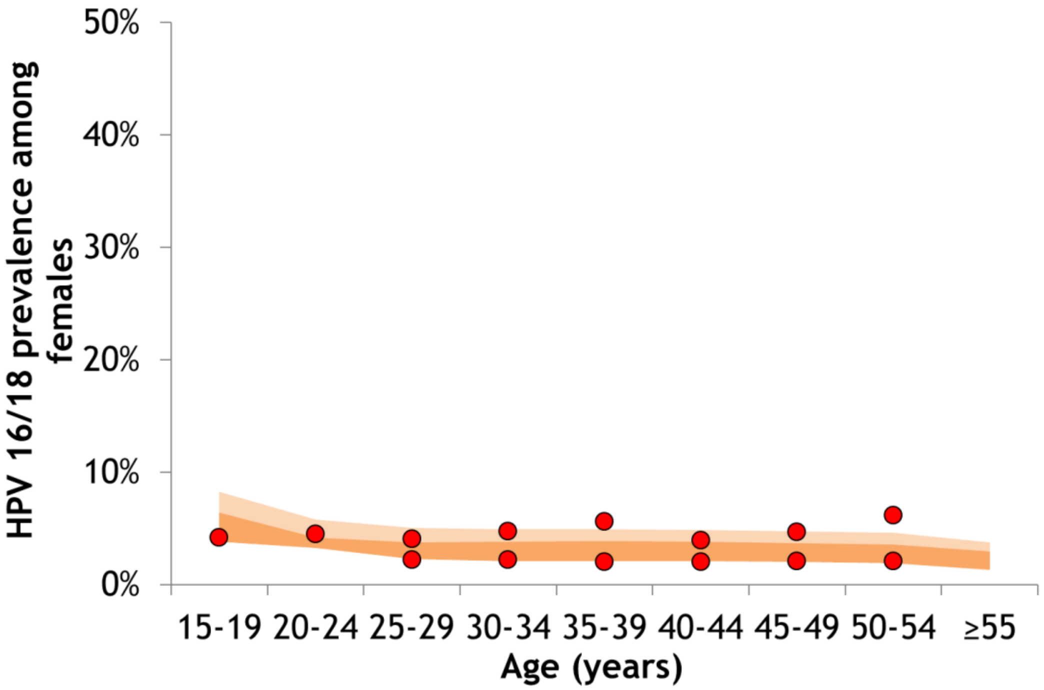
Example of fit to epidemiology - INDIA

Fit to HPV prevalence among sexually active females

High-Risk HPV prevalence



HPV-16/18 prevalence



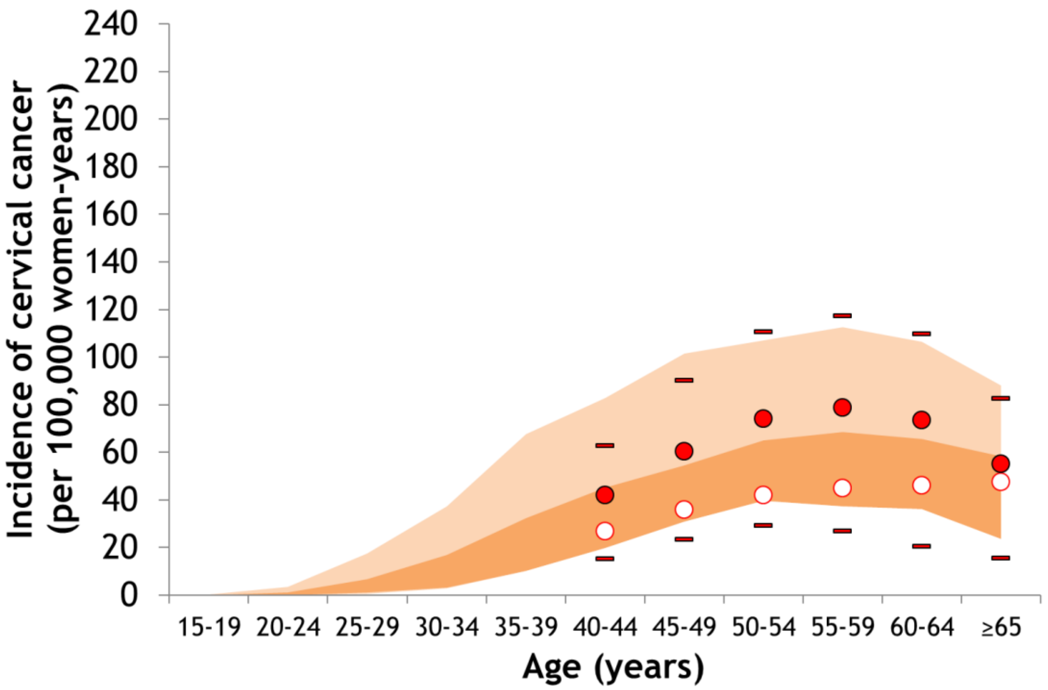
Shaded areas represent the min/max of model predictions generated by the 50 posterior parameter sets. Darker shaded areas represent min/max of 10 best fit parameter sets to Globocan 2020 cervical cancer incidence. For model predictions, we assumed a specificity of 99.7% for the HPV-test (in a HPV negative population, HPV-testing for 13 types with a specificity of 99.7% would result in an overall HPV-prevalence of 3.8%). Red dots represent the observed prevalence data. (Data sources: Dutta 2012, Sauvaget 2011, Basu 2013, and IARC prevalence data)

HPV-ADVISE

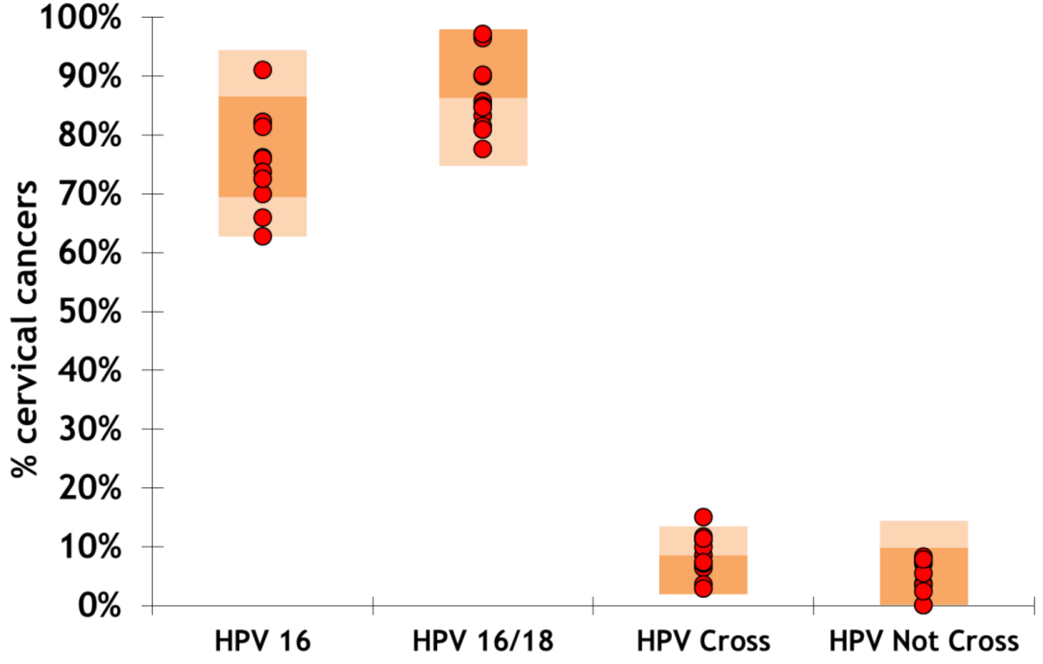
Example of fit to epidemiology - INDIA

Cervical cancer

Incidence of cervical cancer



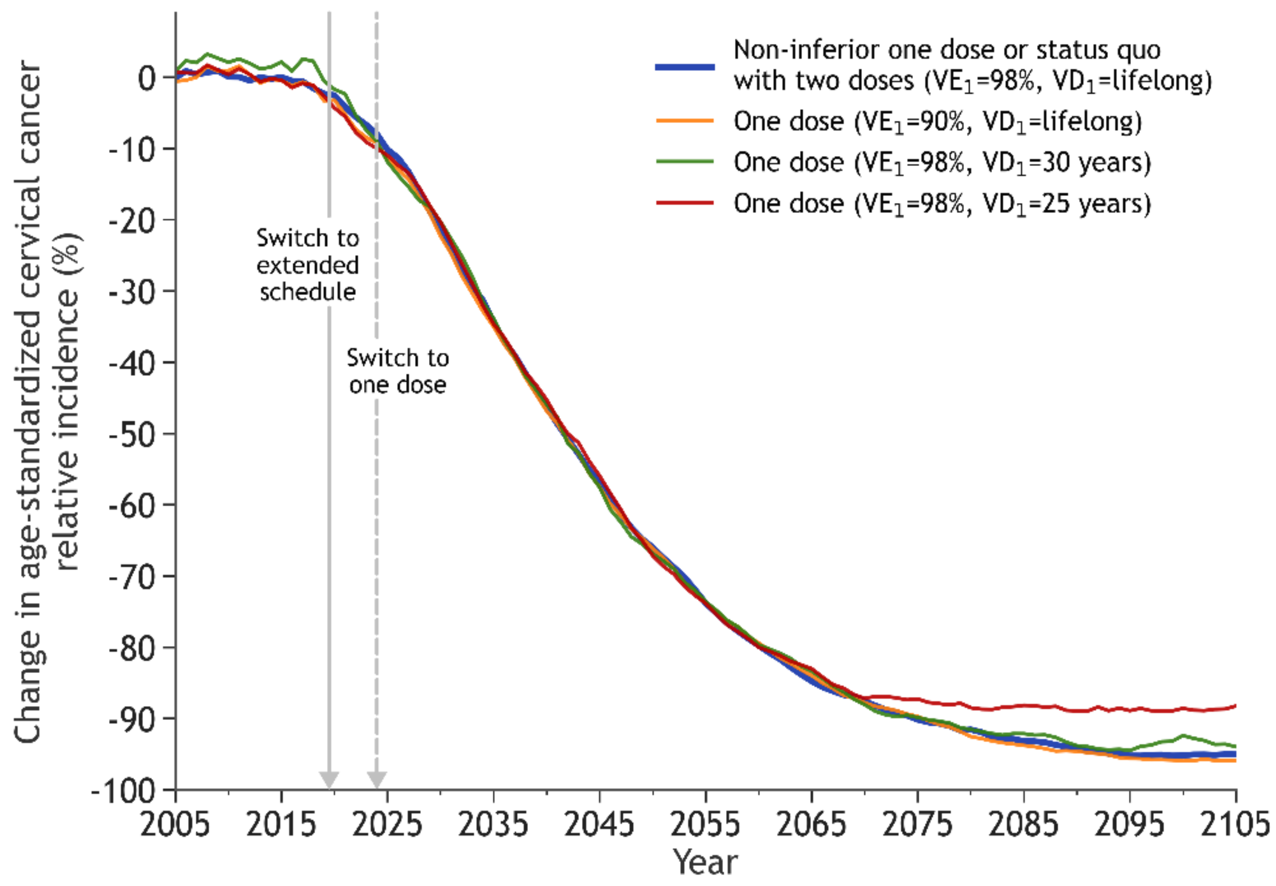
HPV type distribution in cervical cancer



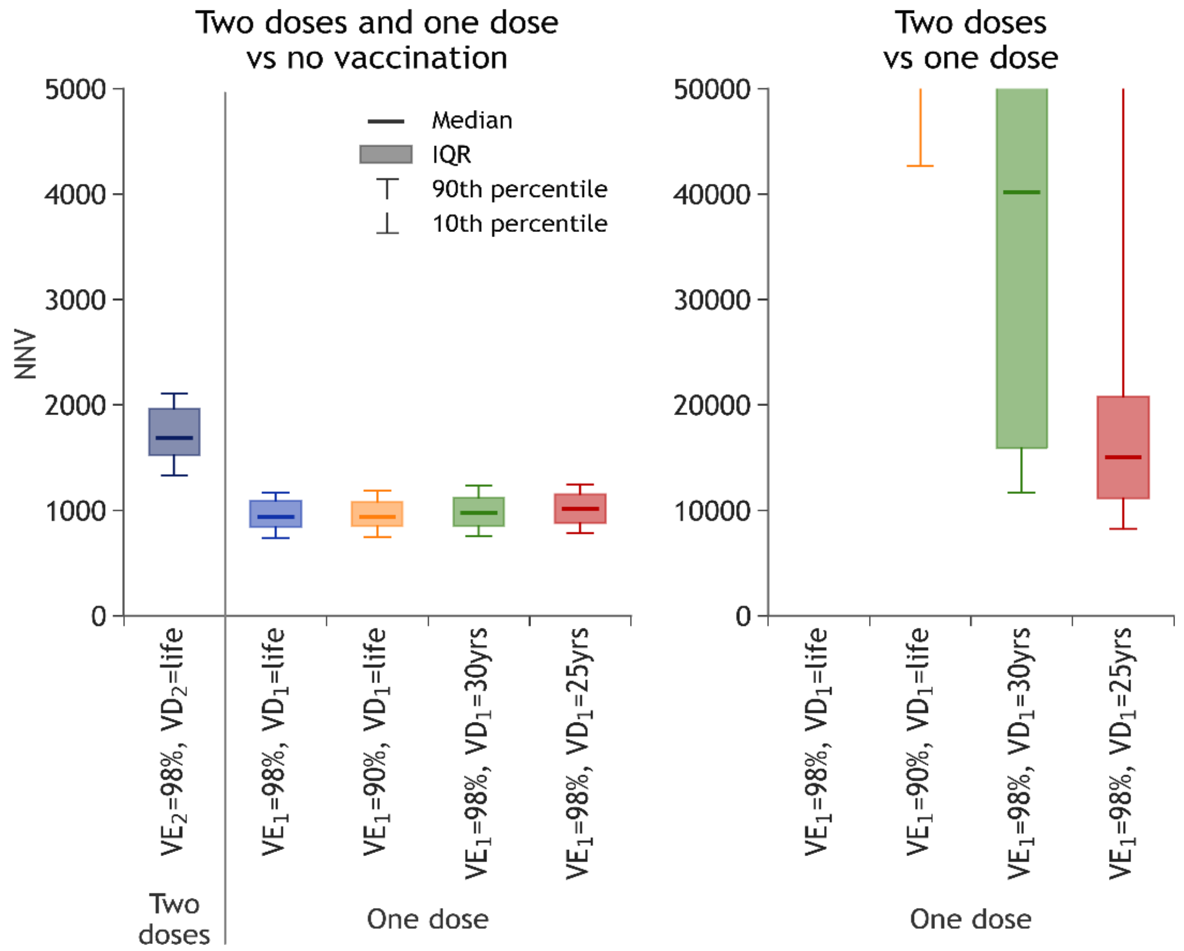
Shaded areas represent the min/max of model predictions generated by the 50 posterior parameter sets. Darker shaded areas represent min/max of 10 best fit parameter sets to Globocan 2020 cervical cancer incidence. Dots represent the observed data. For **Incidence of Cervical cancer**, red and white dots represent the observed data from Globocan 2012 and 2020, respectively; the bars represent the variability of cervical cancer observed incidence within the country. (Data sources: Cervical cancer incidence: Globocan 2012, Globocan 2020, Parkin 2002; HPV type distribution: Serrano 2012, Franceschi 2003, Munirajan 1998, Sowjanya 2005, Pillai 2010, Deodhar 2012, Srivastava 2014.)

1- and 2-dose vaccination in Canada
Impact and efficiency

Population-level impact



Efficiency - NNV



All NNVs are incremental.

SCENARIO Gender-neutral vaccination, Switch to 1-done in 2024; Vaccination coverage=80%

1-dose modeling: Bénard et al. results

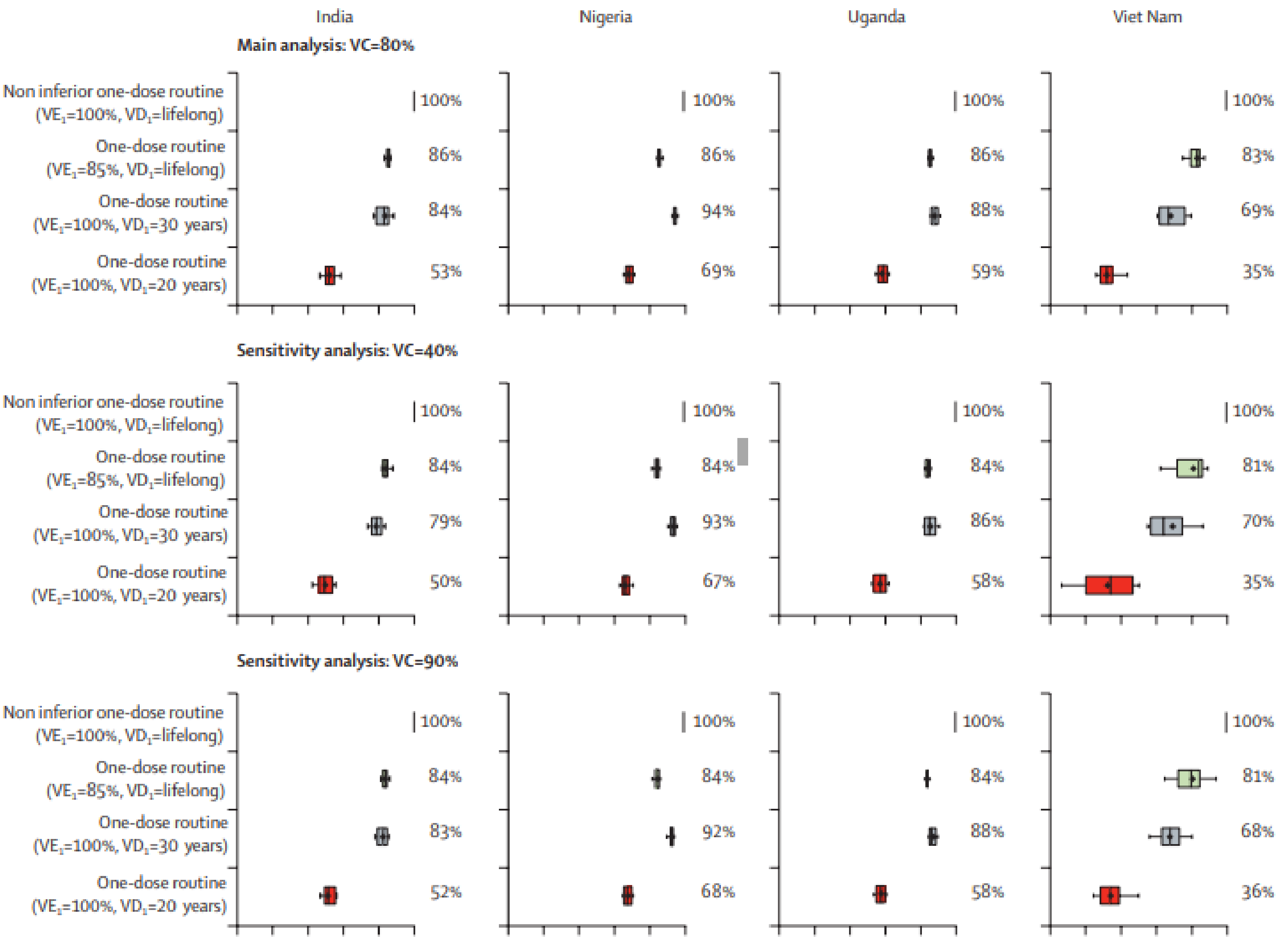


Figure 2: Projected percentage of averted cervical cancers with one-dose versus two-dose routine vaccination of girls aged 9 years, for different vaccination programme assumptions

REF: Bénard, Lancet Public Health 2023

1-dose modeling: Prem et al. results

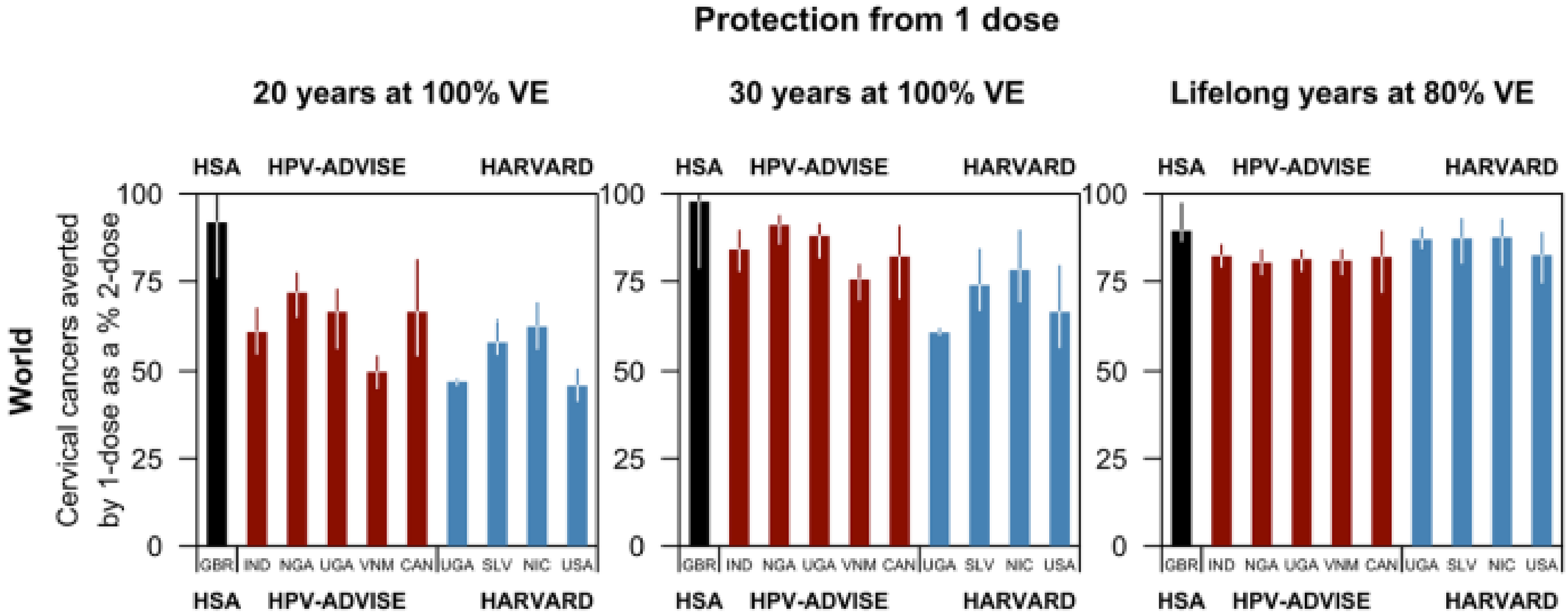


Fig. 3 Cervical cancers averted by routine one-dose HPV vaccination as a proportion of cervical cancers averted by routine HPV vaccination programmes conferring lifelong protection at 100% vaccine efficacy. The median percentage (intervals: 10–90th percentile) of cancers averted by a one-dose schedule compared to a two-dose programme of the 10 model-country settings: the HSA model in black, HPV-ADVISE model-country pairs in red, and the Harvard model-country pairs in blue. Health outcomes were discounted at 0%. Only cervical cancers caused by HPV 16, 18, 31, 33, 45, 52, and 58, which could be averted by the 9-valent HPV vaccine, were considered

REF: Prem, BMC Med 2023

Timeline of SAGE / WHO recommendations informed by modelling

- **2013** — **<u>Change from 3 to 2 dose vaccination for girls</u>**[1]
  - SAGE (Strategic Advisory Group of Experts on Immunization (SAGE)), WHO
- **2016** — **<u>Conduct Multi-Age-Cohort vaccination for girls</u>**: Primary target = 9-14 yr-olds[2]
  - SAGE, WHO
- **2018** — **<u>WHO cervical cancer elimination targets</u>**: 90% of girls vaccinated, 70% of women screened (twice lifetime), 90% of detected pre-cancers/cancers treated[3,4]
  - SAGE, WHO & World Health Assembly
- **2022** — **<u>1-dose vaccination can be considered instead of 2 doses</u>**[5]
  - SAGE, WHO
- **2024** — **<u>WHO prioritization framework</u>** : Girls 9-14 yrs-old -> Girls 15-20 yrs-old -> Women 21-25 yrs-old -> Boys/Men 9-20 yrs-old[6]
  - WHO prioritization (work in progress)

1. Jit et al. Vaccine 2014. 2. Drolet, Laprise et al. Lancet Infec Dis 2021; 3. Brisson, Kim, Canfell et al. Cervical cancer elimination. Lancet 2020; 4. Canfell, Kim, Brisson et al.. Lancet 2020; 5. Bénard et al. Lancet Public Health 2023; 6. Drolet et al. Eurogin 2024 & Poster 200

Recommendations: www.who.int/groups/strategic-advisory-group-of-experts-on-immunization