IMPACT OF HPV IMMUNIZATION STRATEGIES IN THE CONTEXT OF SUPPLY CONSTRAINT

Marc Brisson

Full Professor
Université Laval, Canada

SAGE meeting
October 9, 2019
Geneva

Optimal HPV immunization strategies in the context of limited resources & vaccine supply

Brisson M[1,2], Jit M[3,4], Bénard É[2], Martin D[2], Drolet M[2], Laprise JF[2], Boily MC[5], Alary M[1,2], Gingras G[2], Pérez N[2], Hutubessy R[7]

1. Université Laval, 2. Centre de recherche du CHU de Québec, 3. London School of Hygiene & Tropical Medicine, 4. Public Health England, 5. Imperial College,
6. International Agency for Research on Cancer (IARC), 7. World Health Organization (WHO)

UNIVERSITÉ LAVAL

Imperial College London

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

International Agency for Research on Cancer

World Health Organization

Specific objectives

Using mathematical models:

- To estimate the population-level effectiveness and cost-effectiveness of various HPV vaccination strategies targeting 9 to 14 year old girls
- To identify optimal HPV vaccination strategies that maximize the number of cervical cancers averted under vaccine supply constraints

Why focus on vaccination of 9 to 14 year old girls?

In previous analyses presented to SAGE[&], we showed that:

- Vaccinating girls between 9 & 14 years old was the most efficient and cost-effective strategy:
  - low Number Needed to Vaccinate (NNV) to prevent 1 cervical cancer case
  - very low incremental cost-effectiveness ratios

- Vaccinating boys & older women were much less efficient and cost-effective versus vaccinating girls between 9 & 14 years old

&: Brisson, SAGE (2017-2018); Brisson, SAGE Working Group Meeting (2019)

Population-level Effectiveness

What strategies maximize cancer prevention?

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 India, Vietnam, Nigeria 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

Vaccination Scenarios Investigated

Routine strategies without Multi-Age Cohort (MAC) or Catch-up vaccination

- **Routine 9 yrs old** (2 doses); No MAC **(S2)**
- **Routine 9 years old 5-year extended interval** (1+1 doses); No catch-up **(S5)**
- **Routine 14 years old** (2 doses); No MAC **(S8)**

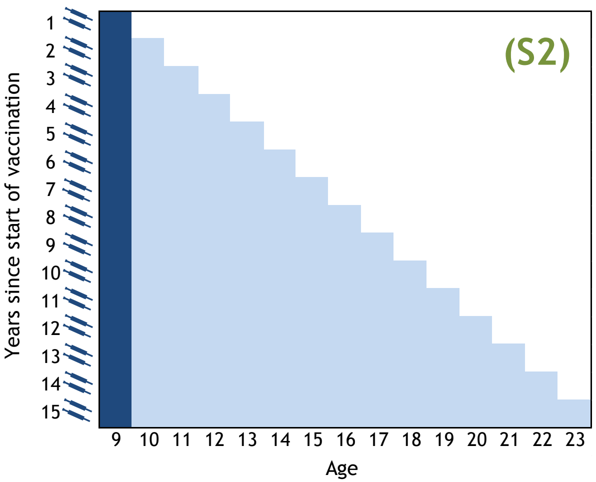
Routine strategies with MAC or Catch-up

- Routine 9 years old (2 doses); with **MAC 9-14 years old** **(S1)**
- Routine 9 years old **5-year extended interval** (1+1 doses); **Catch-up at 14 years old** **(S6)**
- Routine **14 years old** (2 doses); **Later switch to 9 years old** **(S7)**

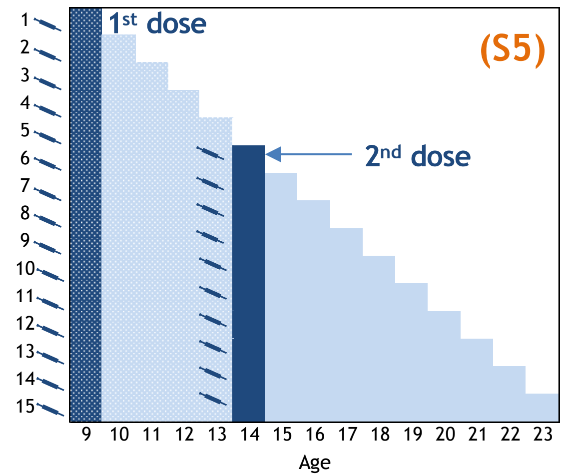
Vaccination Scenarios Investigated

Routine strategies without MAC or Catch-up vaccination

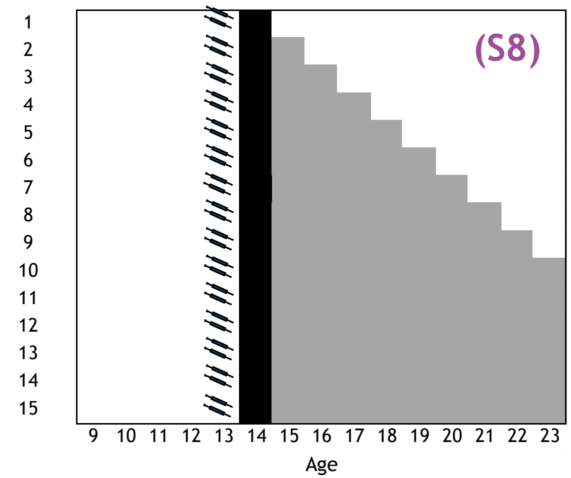
Routine 9 years old; No MACs



Routine 9 years old 5-year extended interval; No MACs

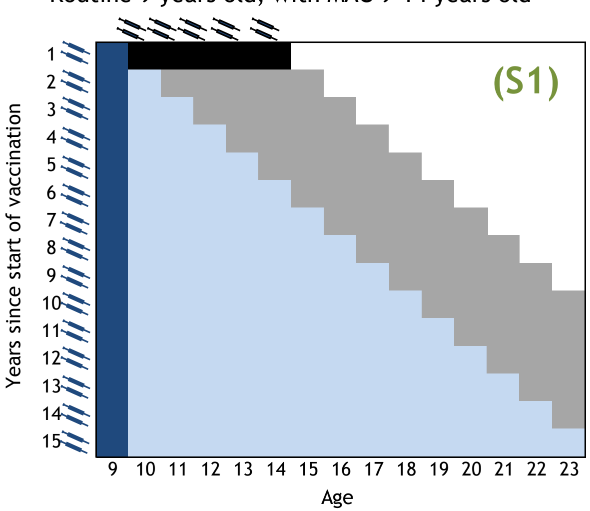


Routine 14 years old; No MACs

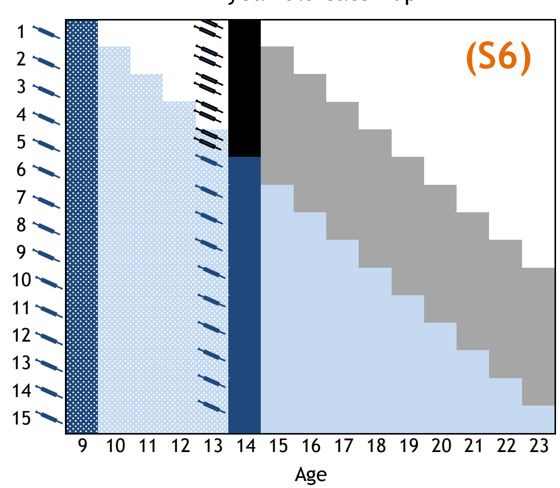


Routine strategies with MAC or Catch-up

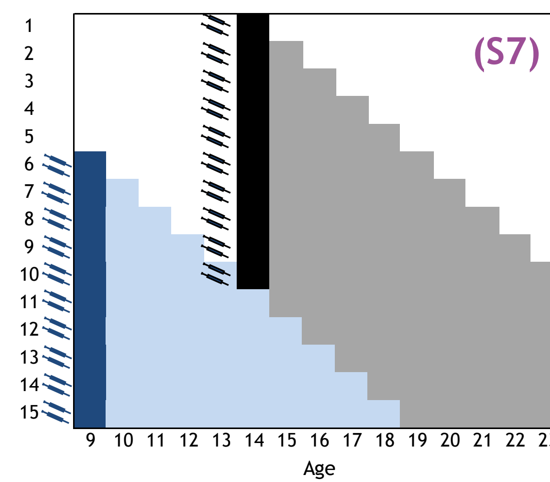
Routine 9 years old; with MAC 9-14 years old



Routine 9 years old 5-year extended interval; 14-year-old catch-up

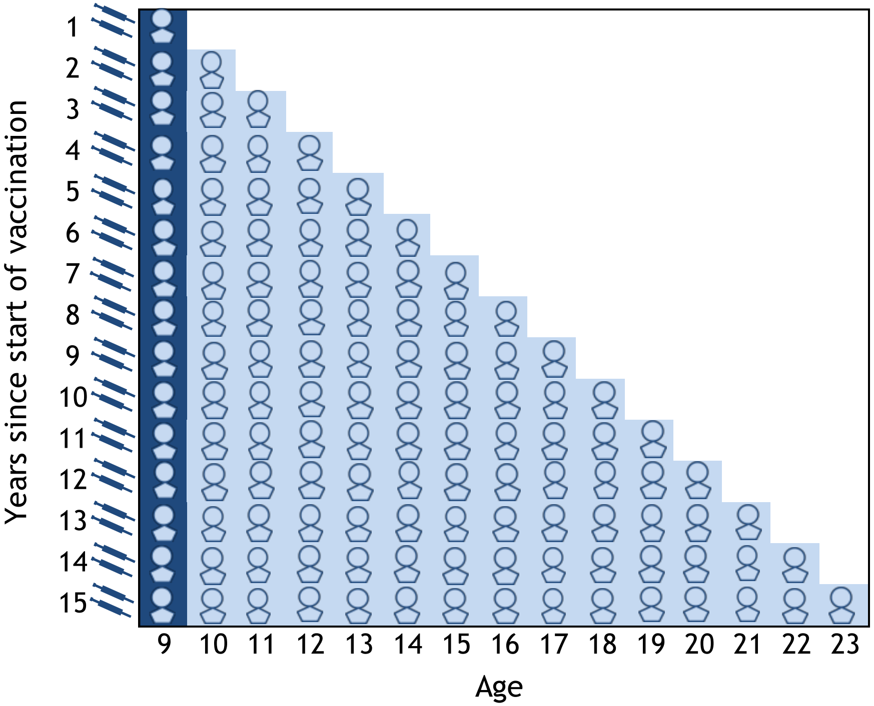


Routine 14 years old; Later switch to 9 years old



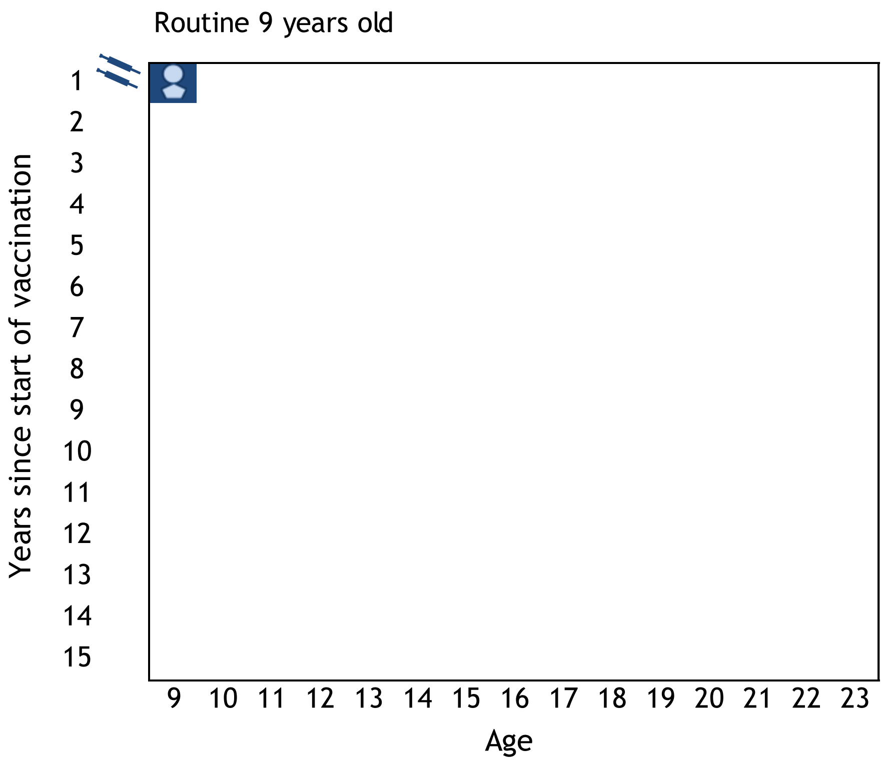
Example: Routine 9 years old (2 doses); No MAC

Strategy 2



Example: Routine 9 years old (2 doses); No MAC

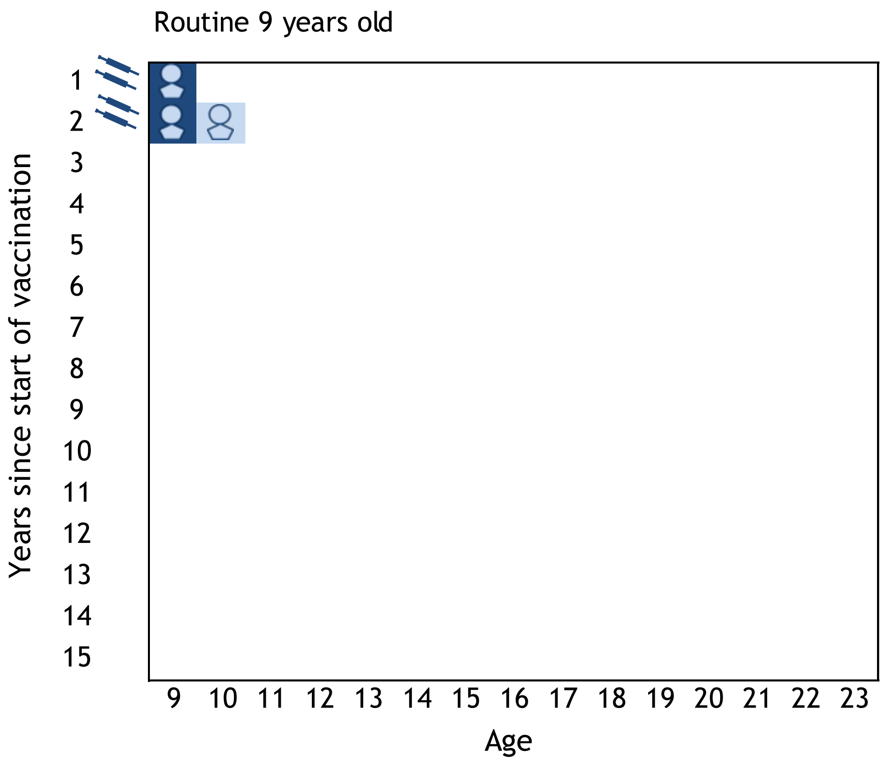
Strategy 2



Girls are vaccinated at 9 years old in the 1st year of the program

Example: Routine 9 years old (2 doses); No MAC

Strategy 2



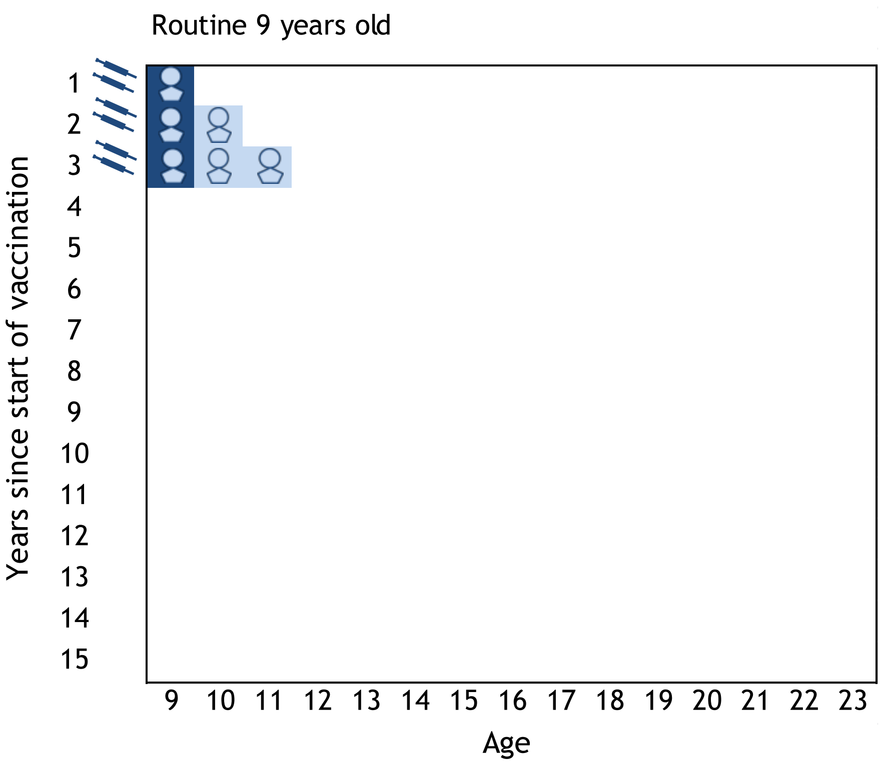
Girls vaccinated at **9 years old in the 1st year** of the program (dark blue)

are **10 years old in the 2nd year** of the program and they are protected (light blue)

A new cohort of 9-year-old girls are vaccinated in the **2nd year** of the program (dark blue)

Example: Routine 9 years old (2 doses); No MAC

Strategy 2



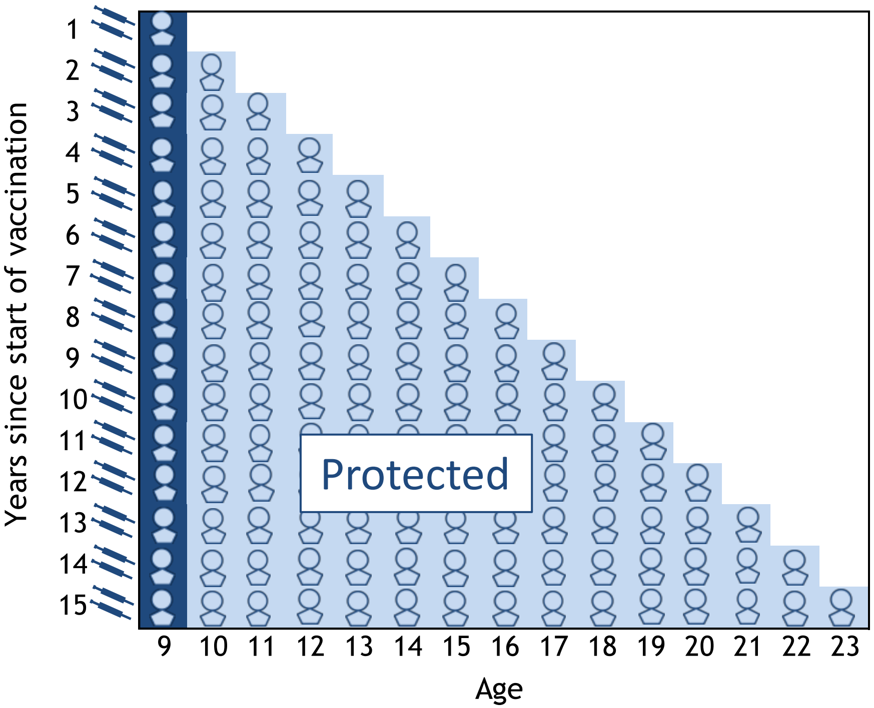
Girls vaccinated at **9 years old in the 1st and 2nd year** of the program (dark blue)

Are respectively **11 and 10 years old in the 3rd year** of the program and they are protected (light blue)

A new cohort of 9-year-old girls is vaccinated in the 3rd year of the program (dark blue)

Example: Routine 9 years old (2 doses); No MAC

Strategy 2

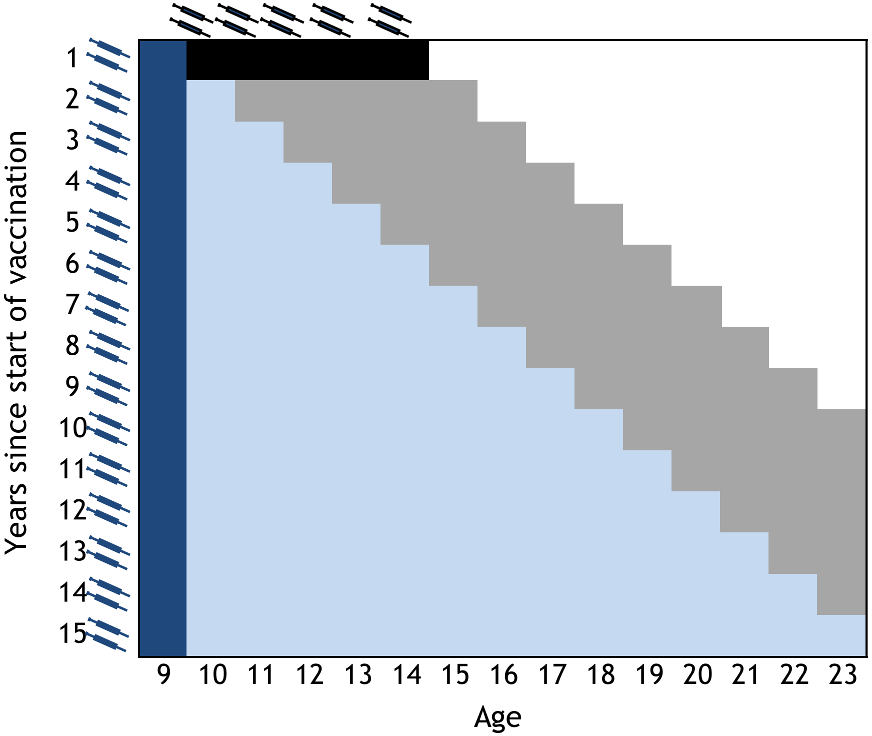


As the number of years of vaccination increases, the number of cohorts vaccinated and protected increases

Vaccinated Cohorts age protected (light blue)

Example: Routine 9 years old (2 doses); MAC 9-14 yrs

Strategy 1

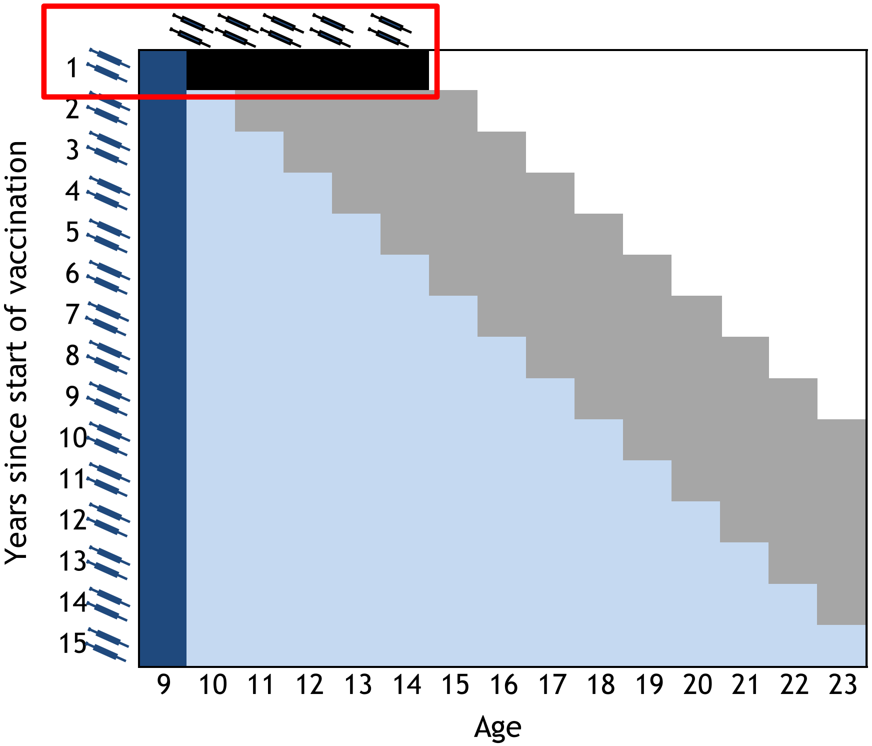


Adding Multi-Age Cohort vaccination:

Increases the number of vaccine doses 5-fold in the first year

Example: Routine 9 years old (2 doses); MAC 9-14 yrs

Strategy 1

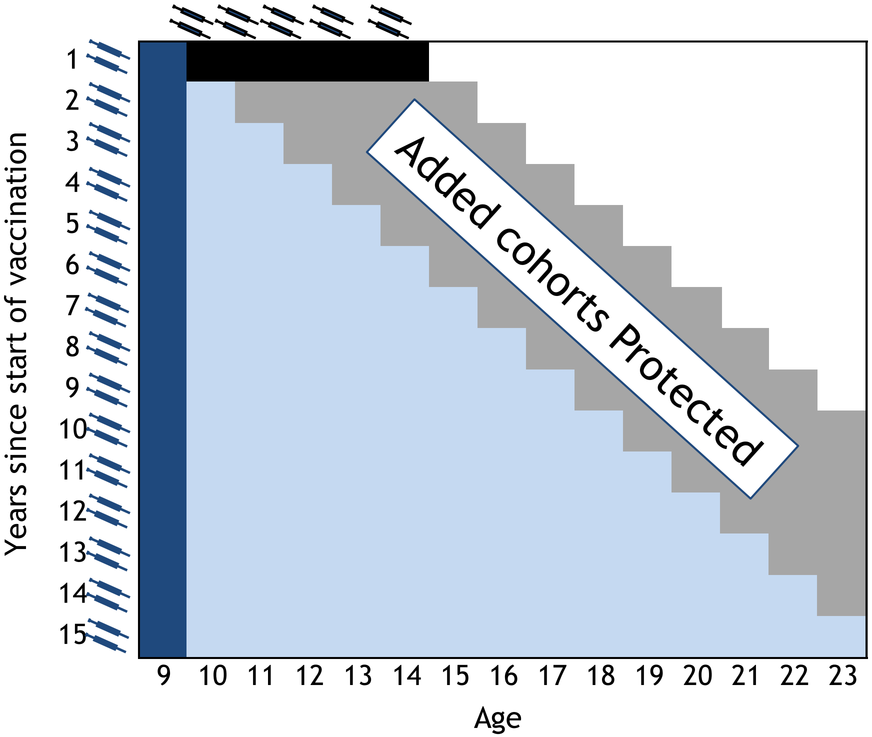


Adding Multi-Age Cohort vaccination:

Increases the number of vaccine doses 5-fold in the first year

Example: Routine 9 years old (2 doses); MAC 9-14 yrs

Strategy 1

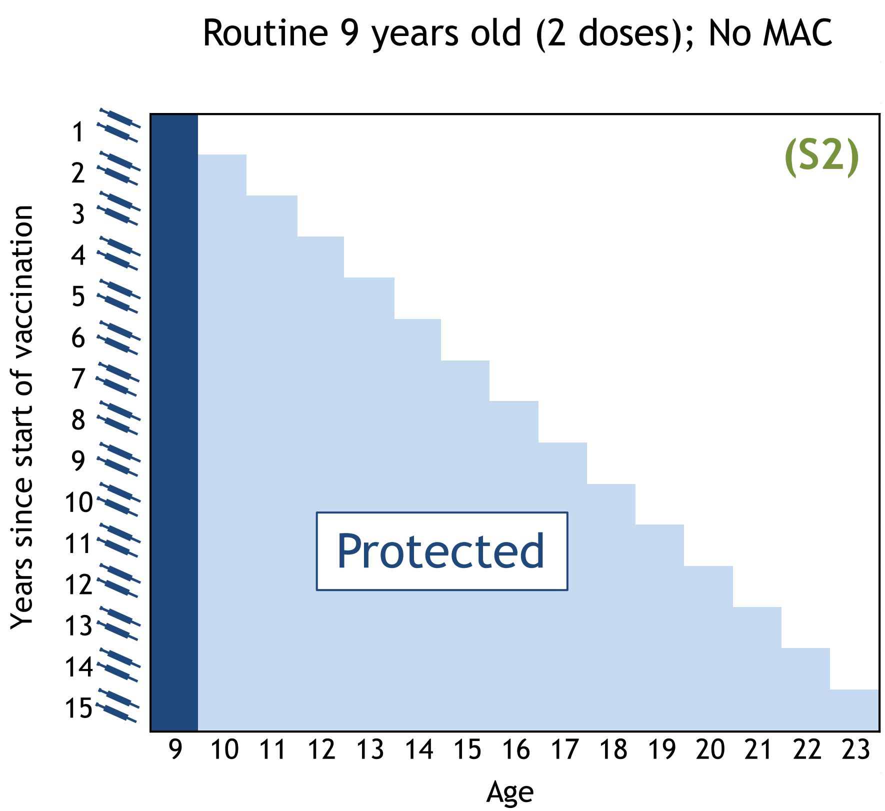


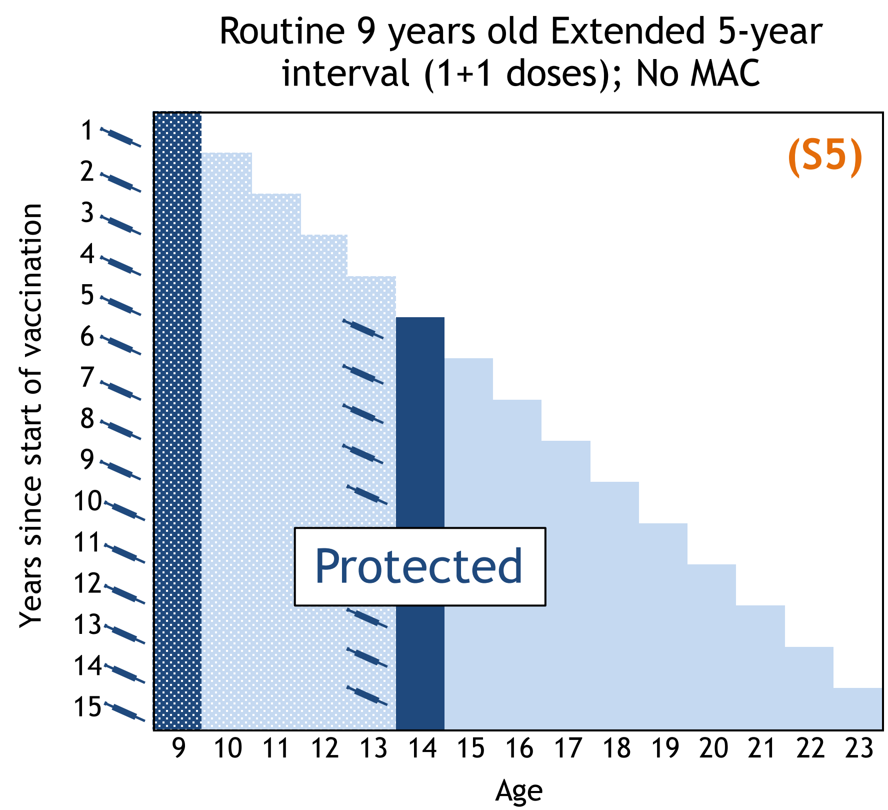
Impact of routine strategies

(no MAC or Catch-up)

Routine (2 doses) vs 5-year Extended interval (1+1 doses)

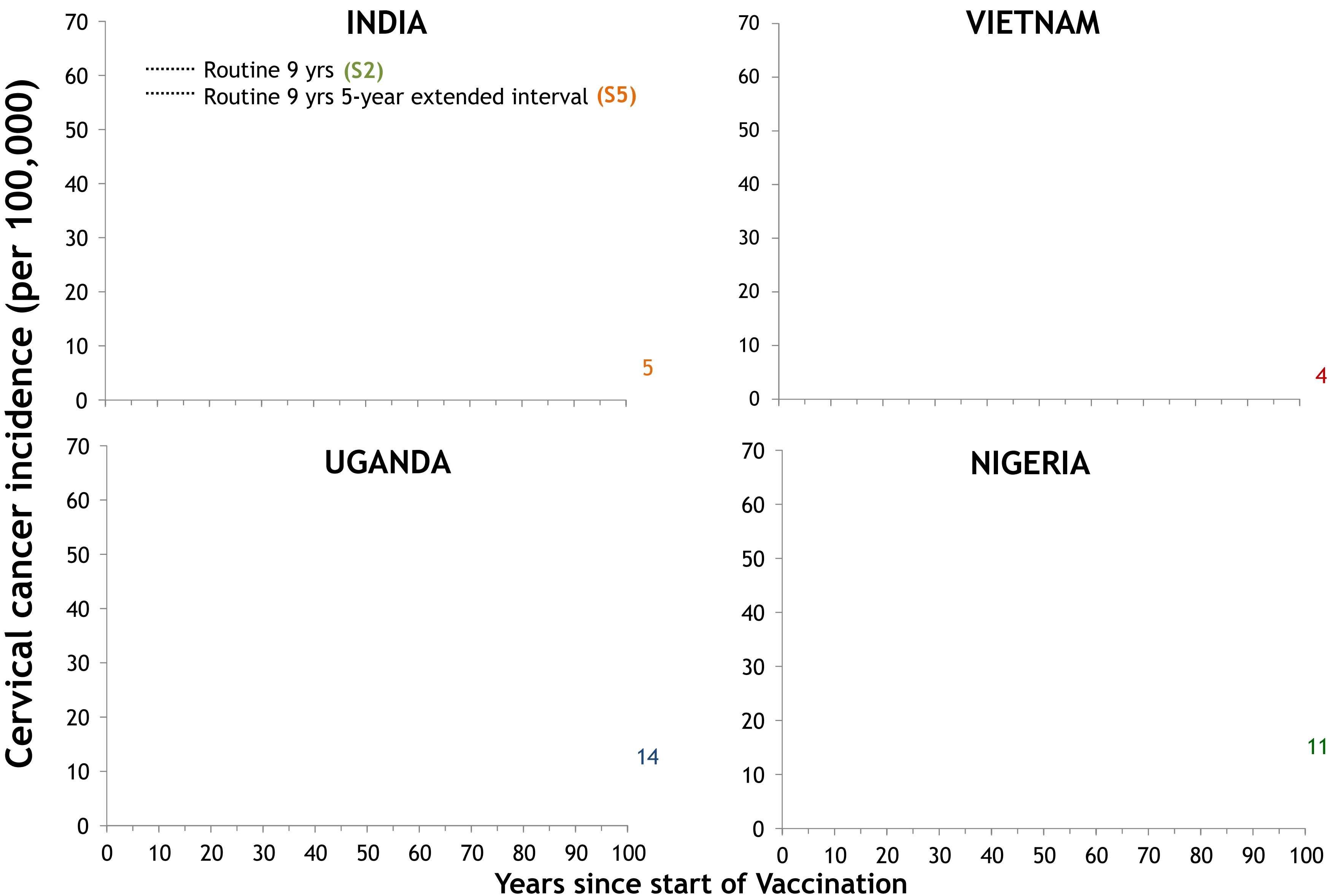
No MAC, 9 years old





Routine (2 doses) vs 5-year Extended interval (1+1 doses)

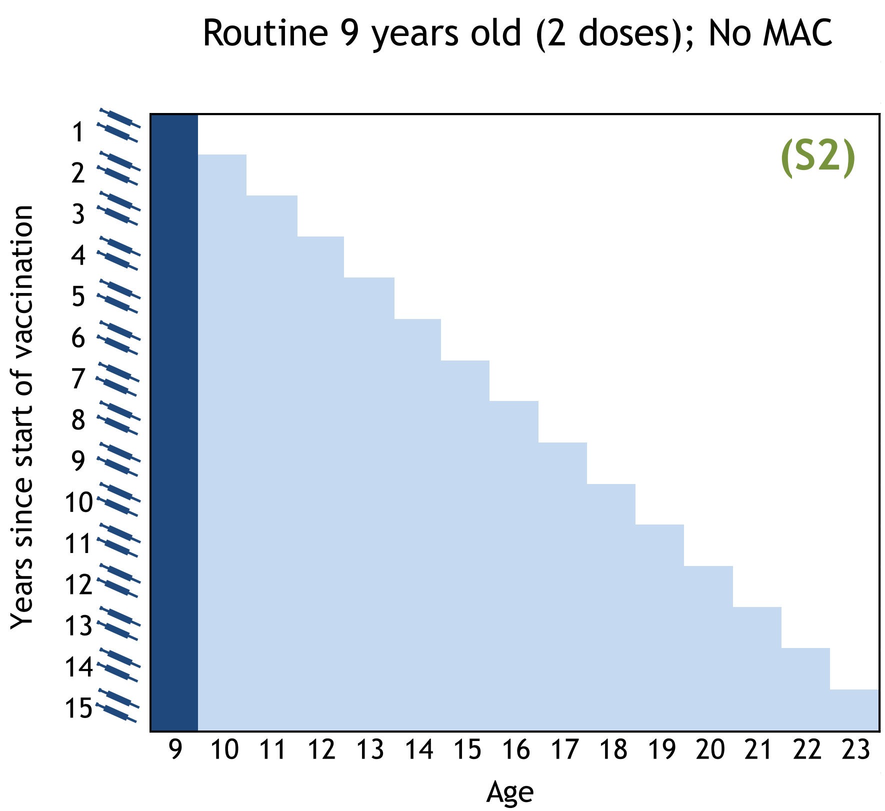
No MAC, 9 years old, Girls-only, 80% coverage

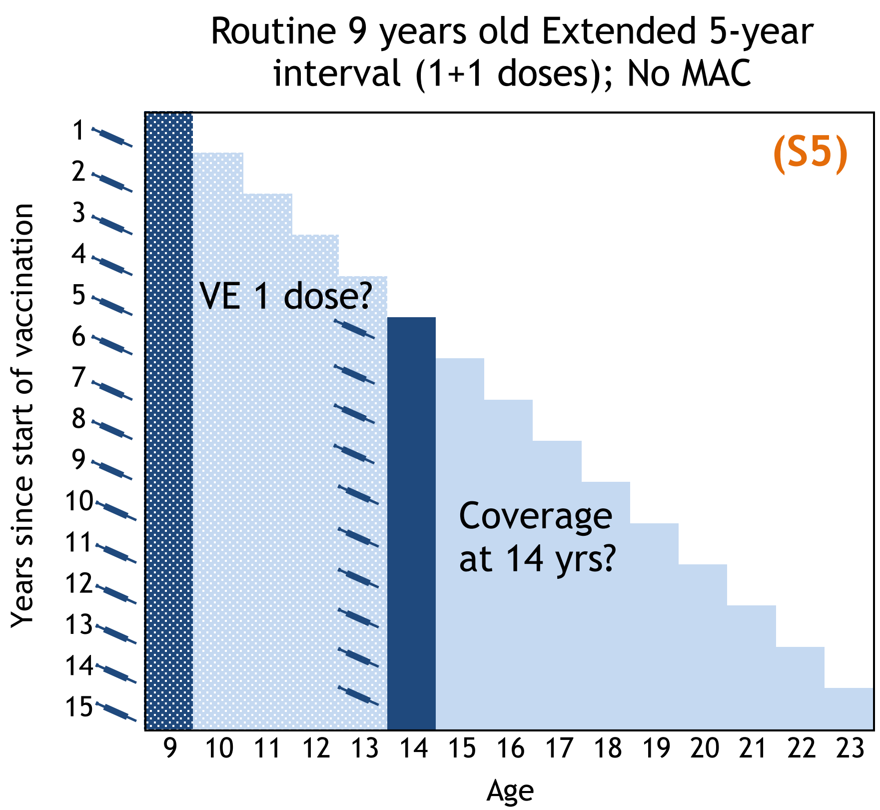


Mean of the model predictions; Base case: coverage=80%, 9valent, Efficacy=100%, Duration=Life

Routine (2 doses) vs 5-year Extended interval (1+1 doses)

No MAC, 9 years old



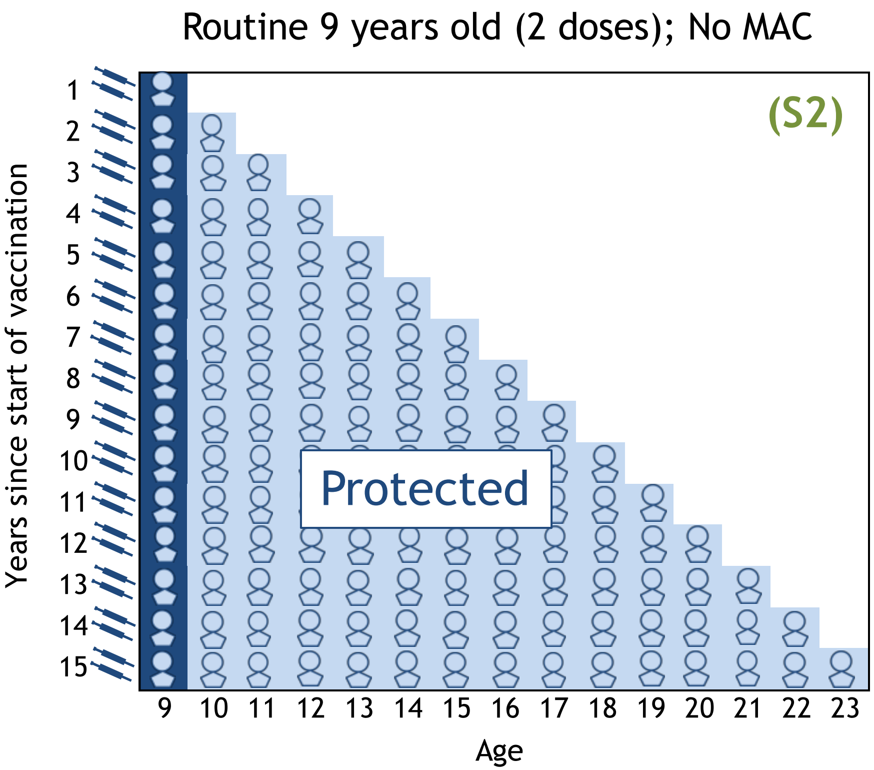


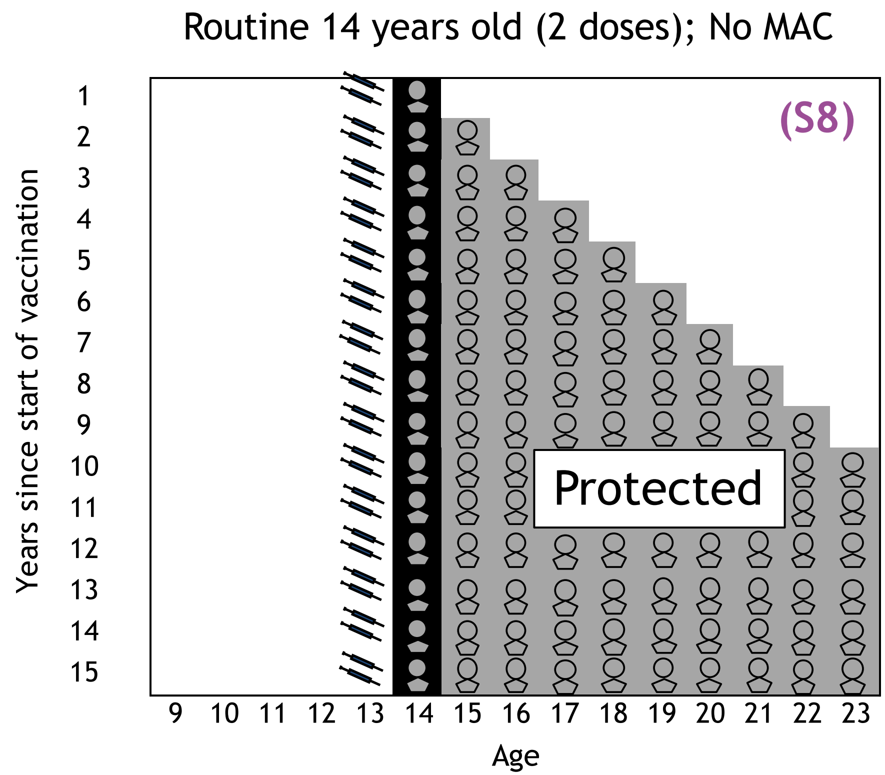
Extended (1+1 doses) = Routine (2 doses)

- If efficacy same for 1 and 2 doses OR
- If coverage same at 9 and 14 years old

Routine 9 years old vs Routine 14 years old, No MAC

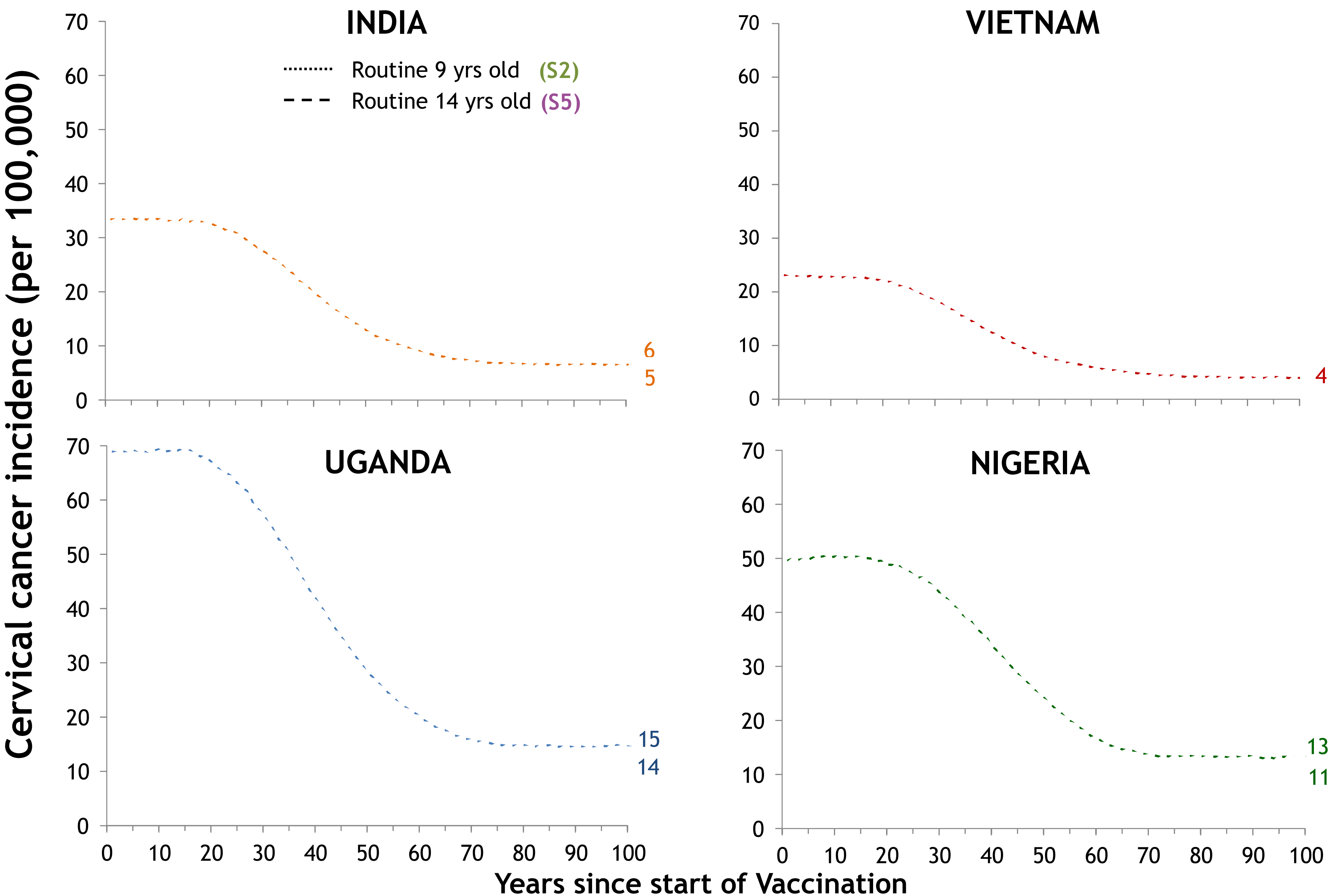
2 doses





Routine 9 years vs Routine 14 years old, No MAC

2 doses, Girls-only, assumes 80% coverage at 9 & 14 years old

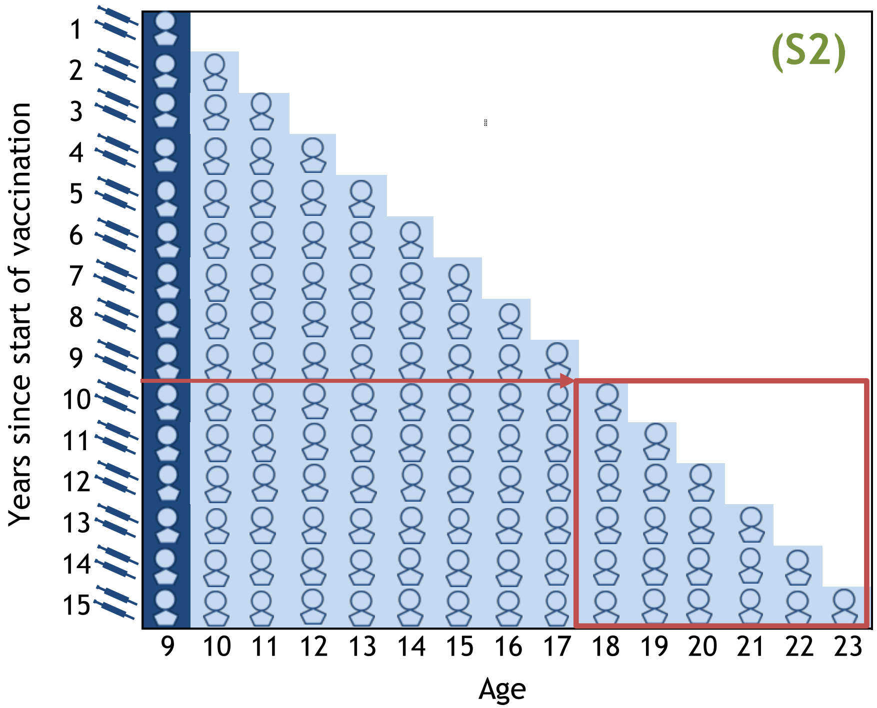


Mean of the model predictions; Base case: coverage=80%, 9valent, Efficacy=100%, Duration=Life

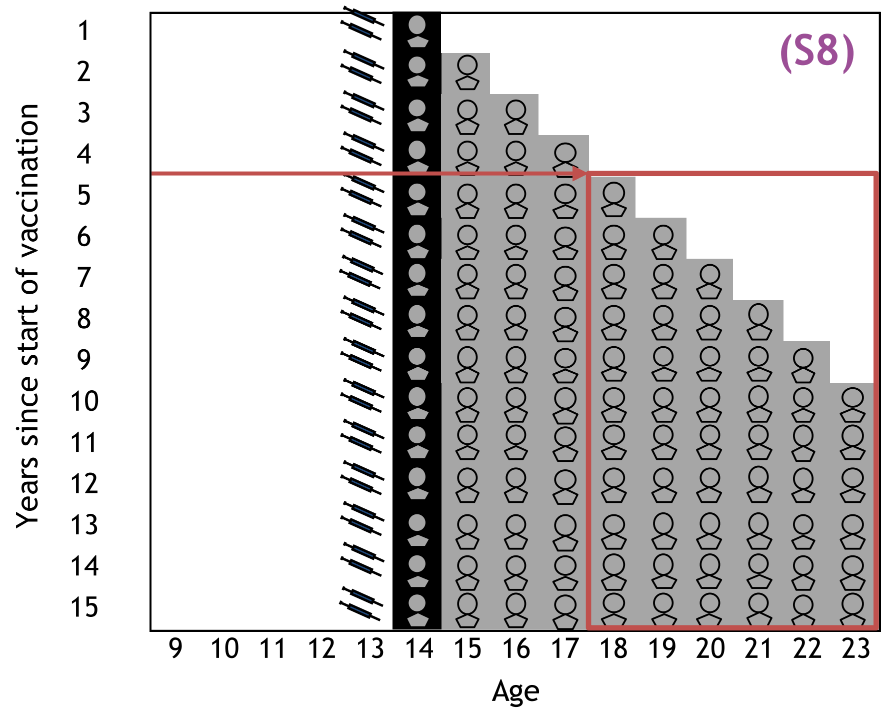
Routine 9 years old vs Routine 14 years old, No MAC

2 doses

Routine 9 years old (2 doses); No MAC



Routine 14 years old (2 doses); No MAC

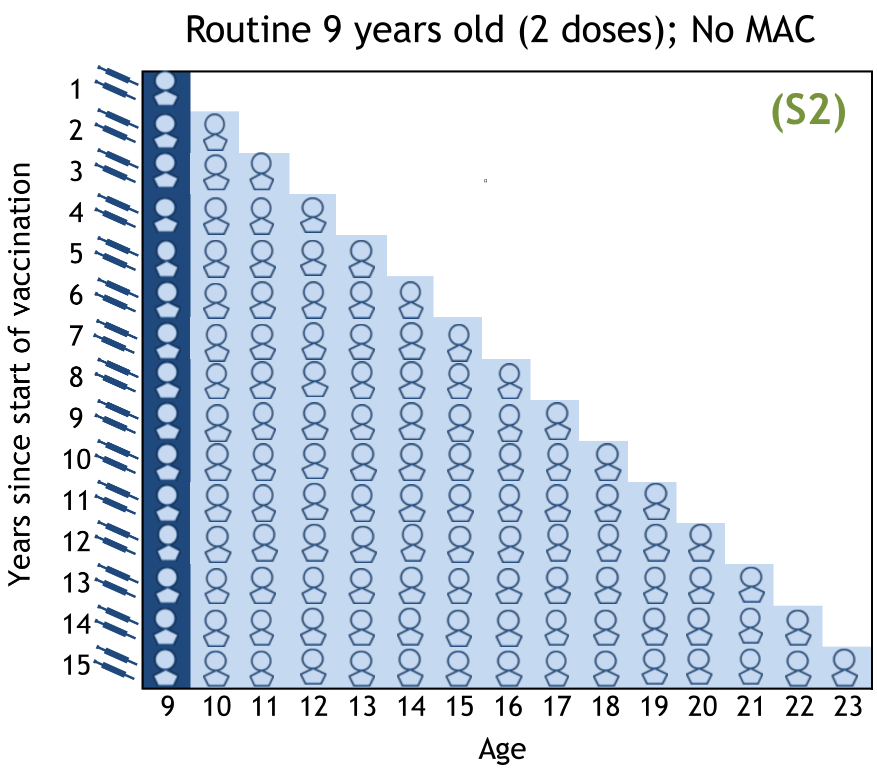


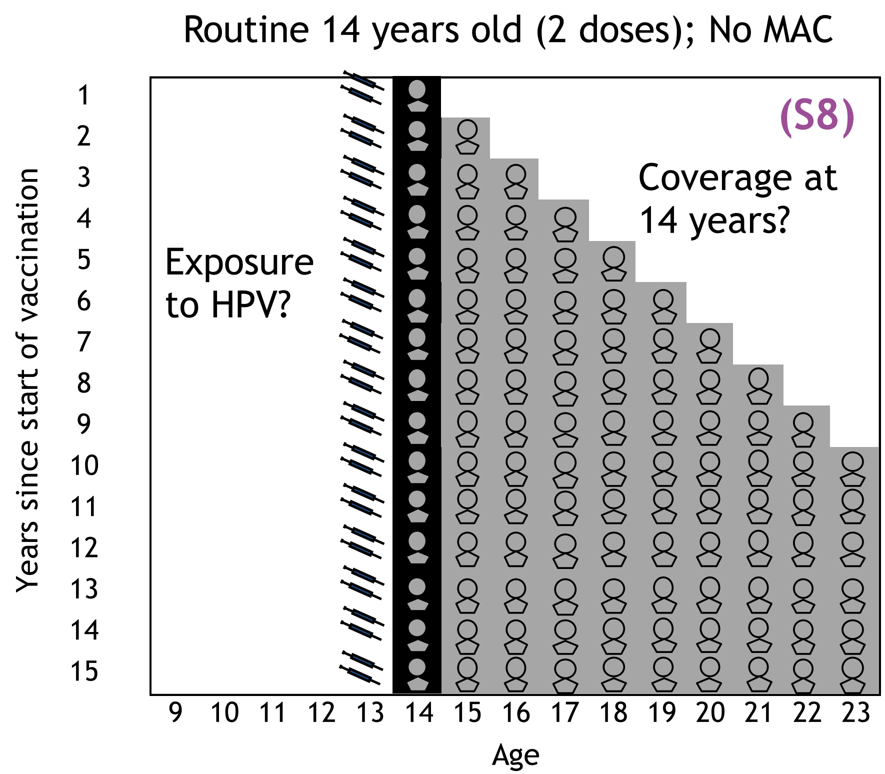
Routine at 14 years old

- Accelerates benefits

Routine 9 years old vs Routine 14 years old, No MAC

2 doses

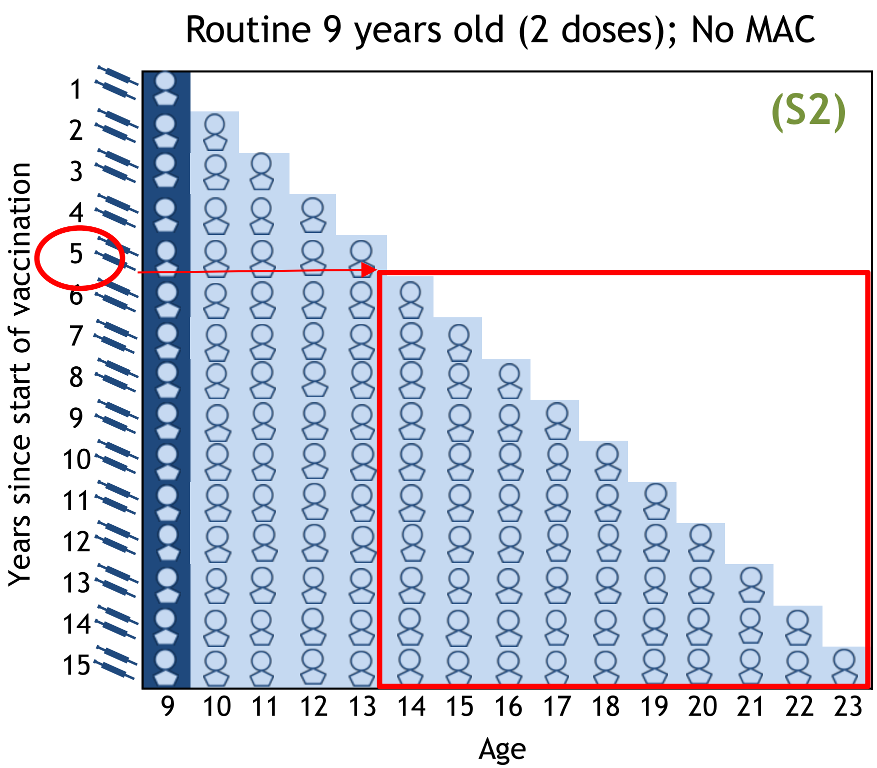


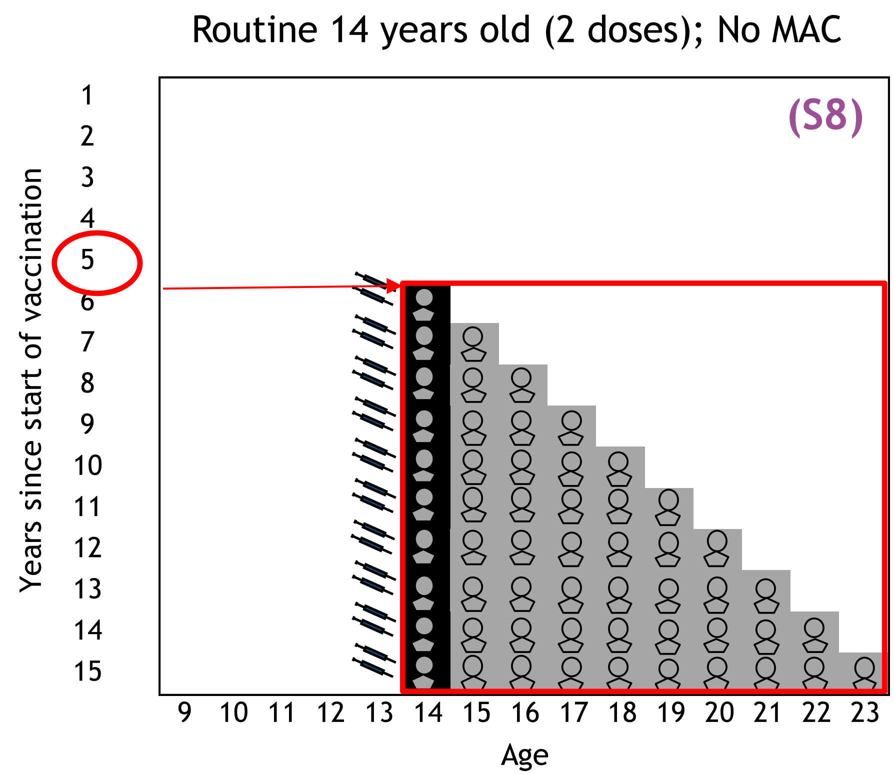


Routine at 14 years old
- Accelerates benefits
- Less benefits in long term if high risk girls start sex earlier than 14 years old
- Risk of lower effectiveness due to possible lower coverage

Routine 9 years old vs Routine 14 years old, No MAC

2 doses



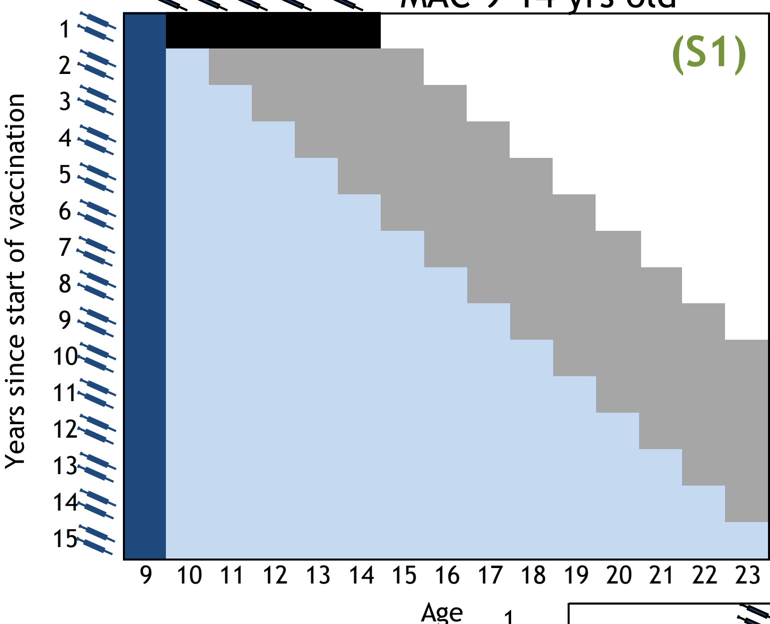


Routine 9 year old vaccination is similar to waiting 5 years before starting a routine 14 year old program
Assuming
- same coverage and
- low % of girls sexually active at 14 years old

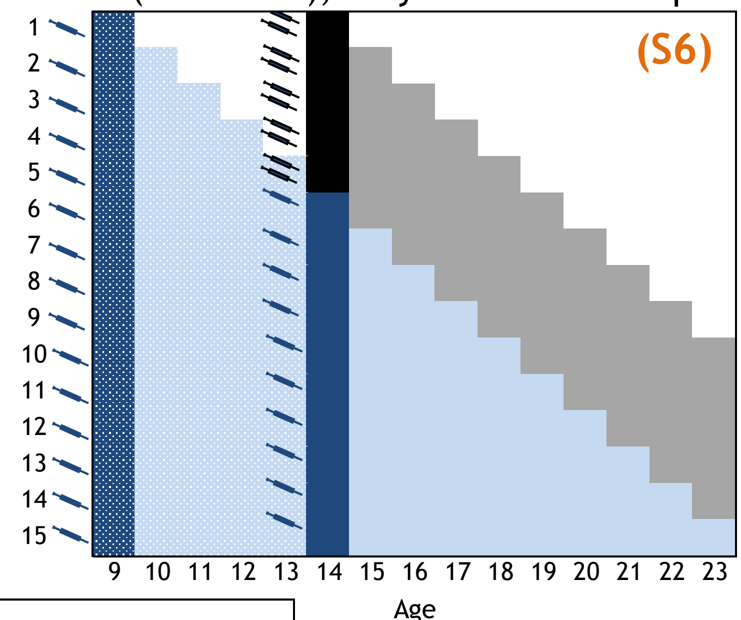
Impact of adding
MAC and Catch-up vaccination

Multiple age-cohort (MAC) & Catch-up Girls-only 2 doses

Routine 9 years old (2 doses);
MAC 9-14 yrs old

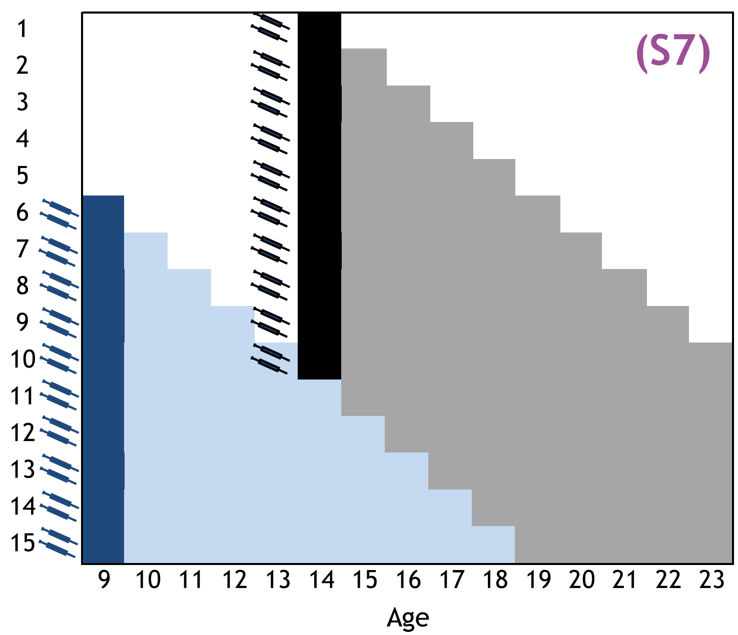


Routine 9 years old 5-year extended interval
(1+1 doses); 14-year-old catch-up



Routine 14 years old (2 doses), later switch to 9 years old

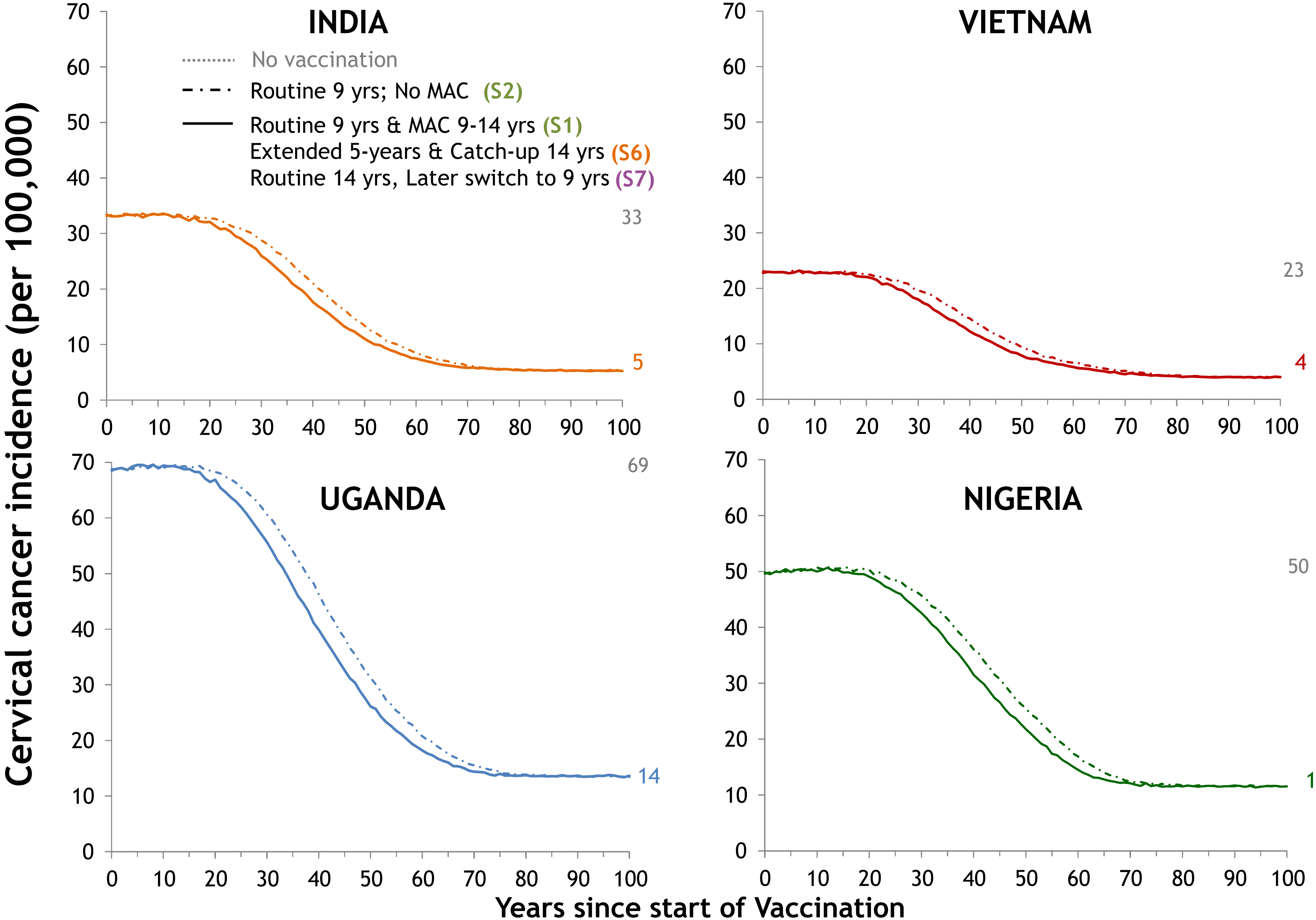
(reverse catch-up)



All 3 strategies vaccinate 14 year olds at the start
&
Have 9 year old vaccination in the long term

Impact of adding MAC or Catch-up vaccination

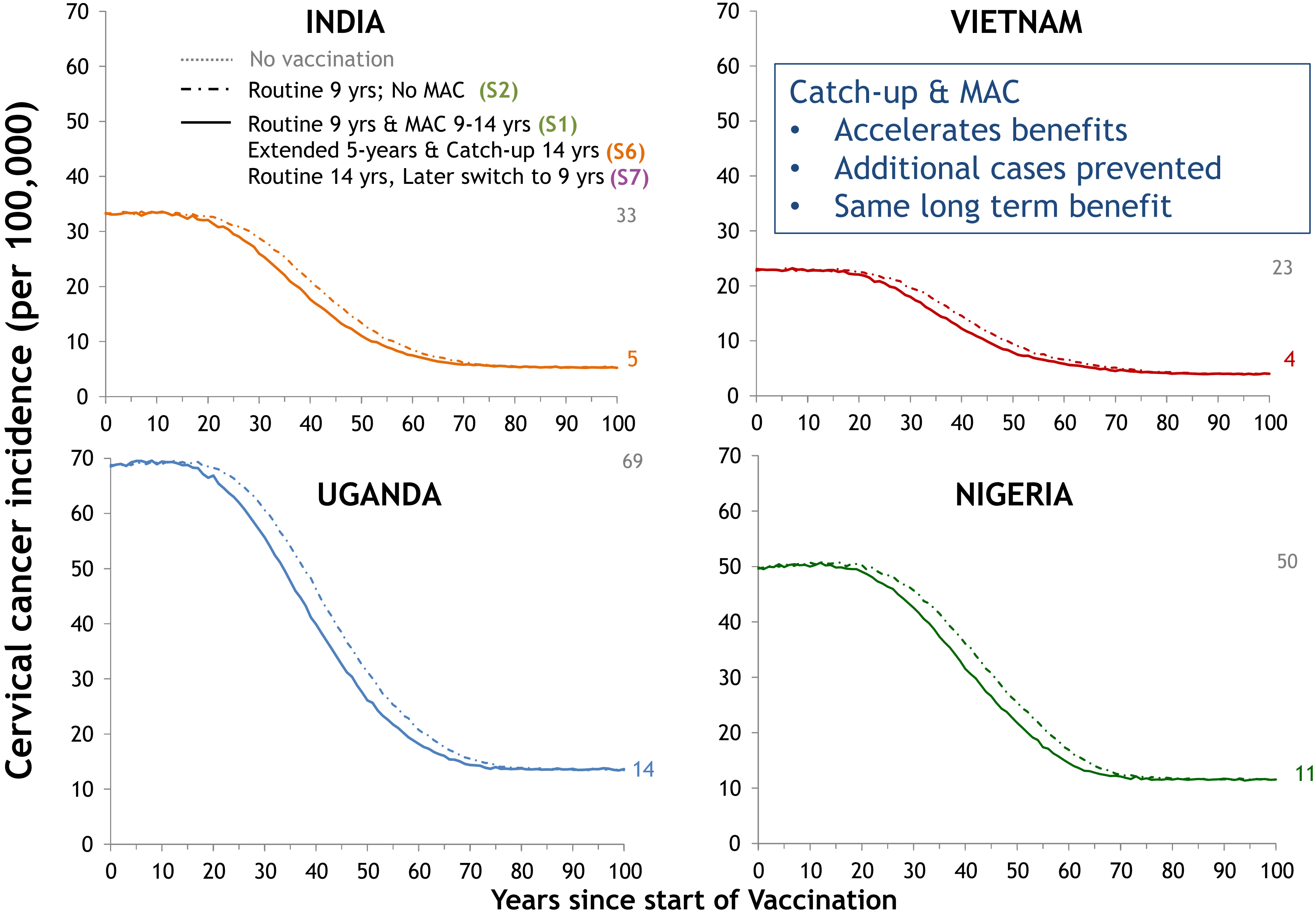
80% coverage



Mean of the model predictions; Base case: coverage=80%, 9valent, Efficacy=100%, Duration=Life

Impact of adding MAC or Catch-up vaccination

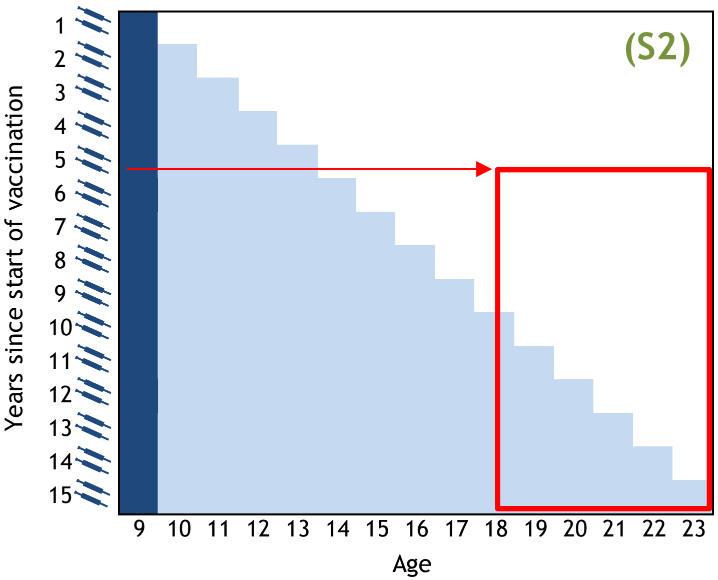
80% coverage



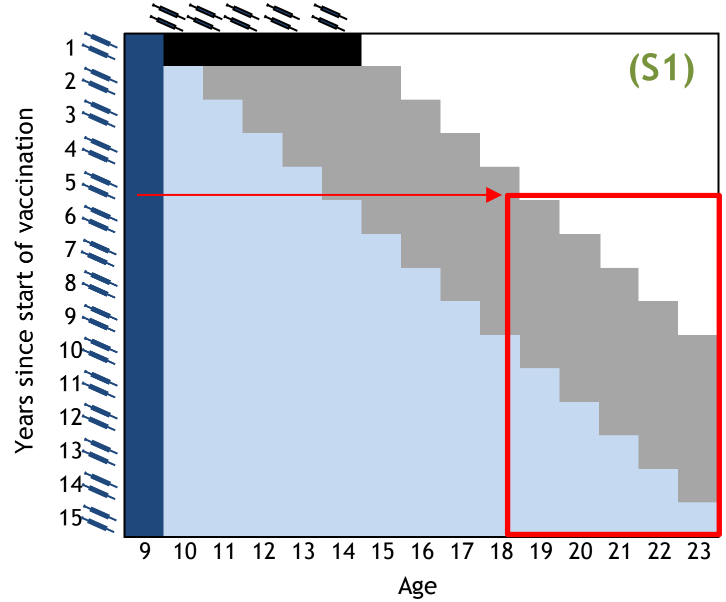
Mean of the model predictions; Base case: coverage=80%, 9valent, Efficacy=100%, Duration=Life

Routine only vs Routine with Catch-up or MAC

Routine 9 years old (2 doses); No MACs



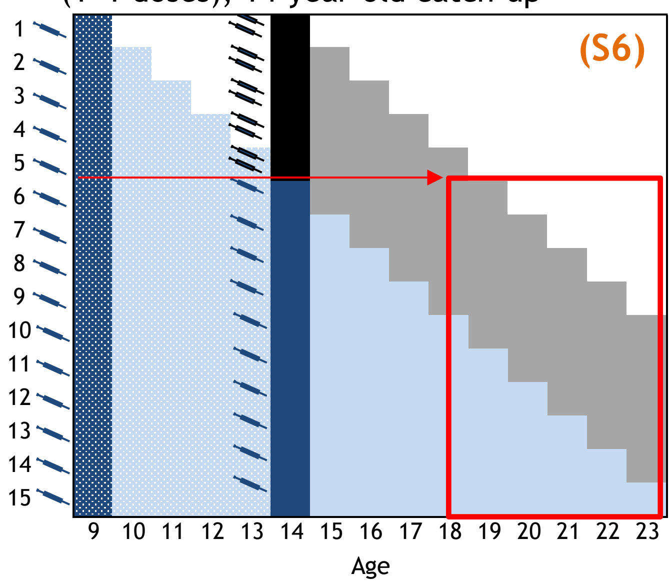
Routine 9 years old (2 doses); with MACs 9-14 years old



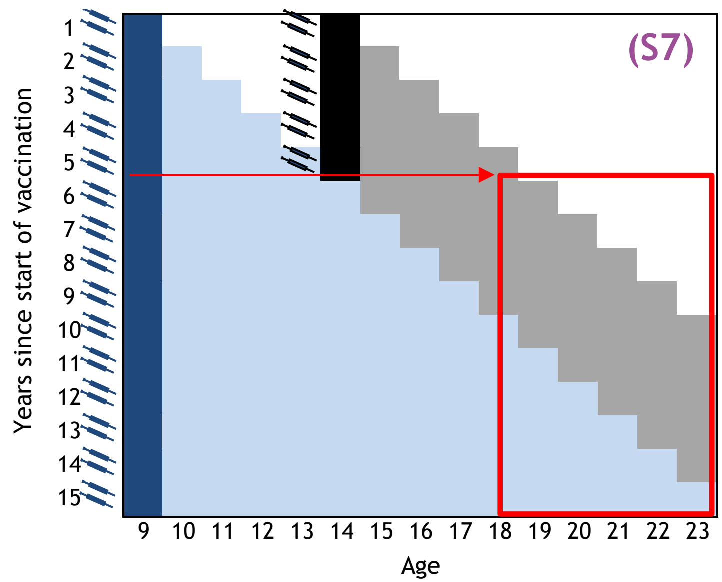
More cohorts protected (grey area)

Grey Area: Cohorts that would have been missed with routine only

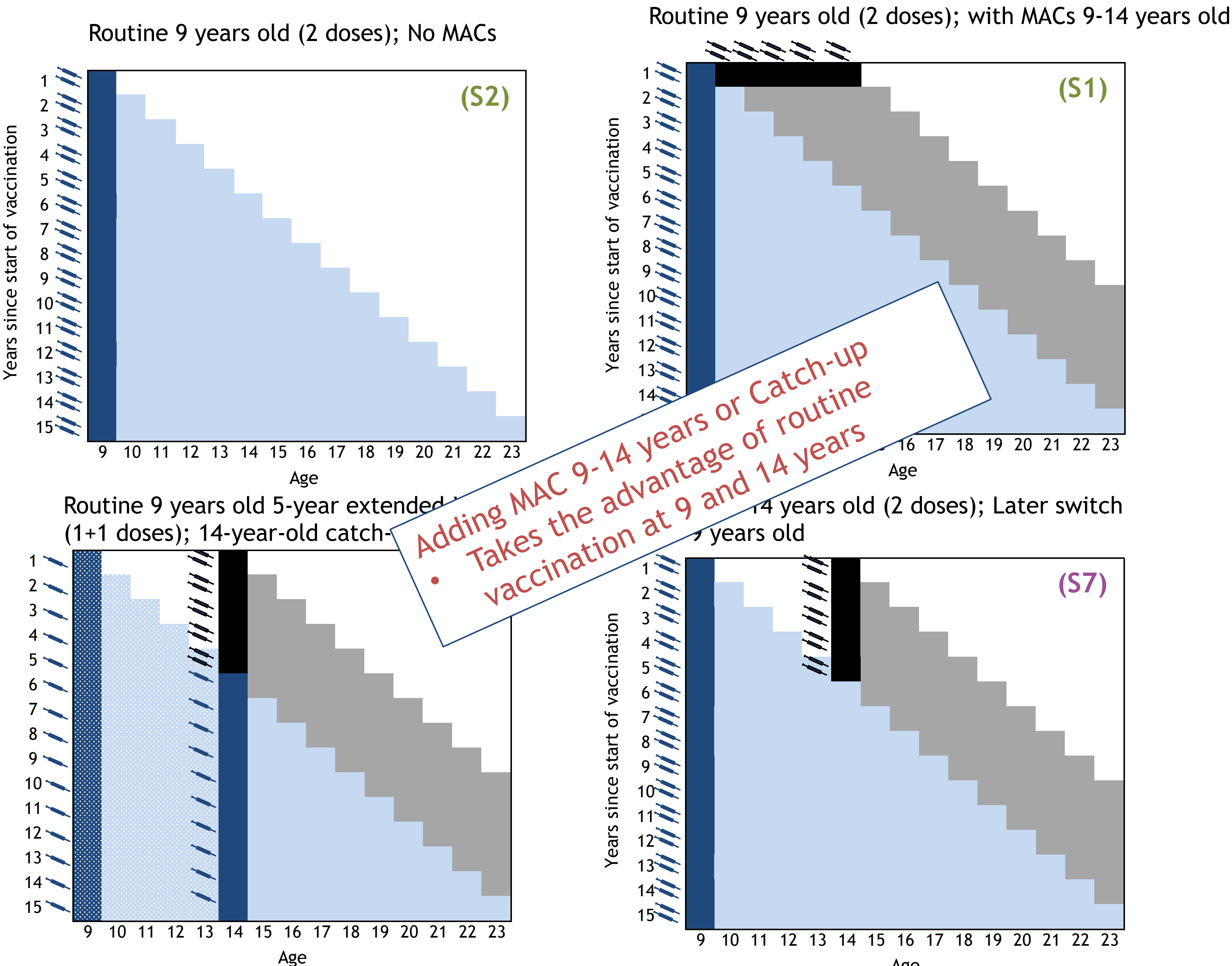
Routine 9 years old 5-year extended interval (1+1 doses); 14-year-old catch-up



Routine 14 years old (2 doses); Later switch to 9 years old



Routine only vs Routine with Catch-up or MAC



Summary Effectiveness

- Girls-only vaccination predicted to substantially reduce cervical cancer
- Age of routine vaccination:
  - Routine 9 years old: Lower long term incidence
    - If it allows Higher coverage
    - If high proportion of girls start sexual activity before 14 years old
  - Routine 14 years old: Accelerates decline in cervical cancer
    - Closer to sexual debut
- Adding MAC or CATCH-UP to routine vaccination
  - Benefits of both routine at 9 and 14 years old
  - Accelerates decline in cervical cancer

Number Needed to Vaccine (NNV) & Cost-effectiveness

What strategies are most efficient?

What are the strategies with the best return on investment?

Methods

Main outcomes

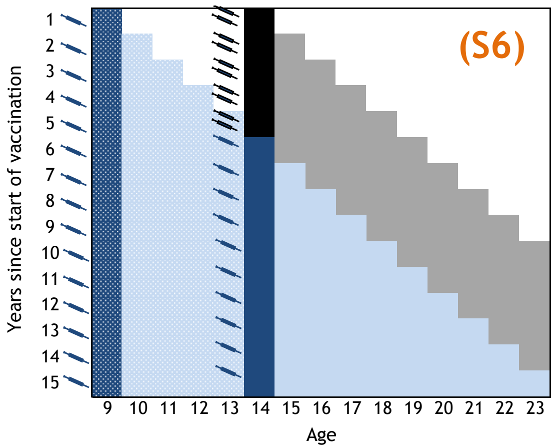
- Efficiency
  - Number needed to vaccinate (NNV) per dose
    - Number of cervical cancer prevented ÷ Number of doses given
- Cost-effectiveness
  - Cost/DALY averted

Efficiency (NNV) and cost-effectiveness (ICER)

9-14 year-old vaccination strategies, Girls-only

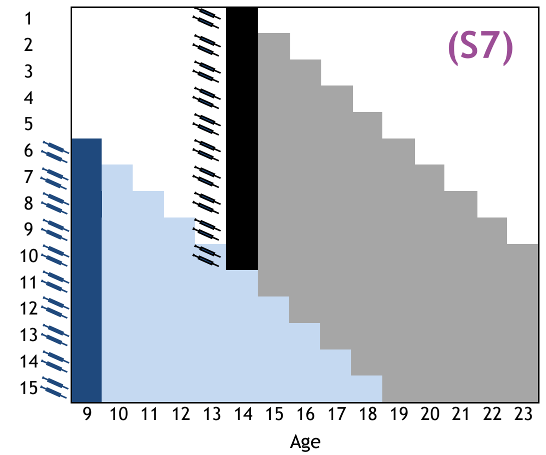
- The most efficient strategies in terms of NNV & cost-effectiveness are:

Routine 9 years old
5-year extended interval (1+1 doses);
14-year-old catch-up



	IN	VN	UG	NG
NNV	139	179	78	127
ICER	282	379	30	275

Routine 14 years old (2 doses);
later switch to routine 9 years old



	IN	VN	UG	NG
NNV	143	182	79	129
ICER	306	396	35	286

NNV: Number of doses needed to prevent 1 cervical cancer
ICER: Incremental cost-effectiveness ratio (Cost per DALY averted)
Base case: high-valency vaccine, VE=100%, duration=lifelong, coverage=80%; MAC: Multiple-age cohorts
[1] Vaccine cost per dose: $4.60;

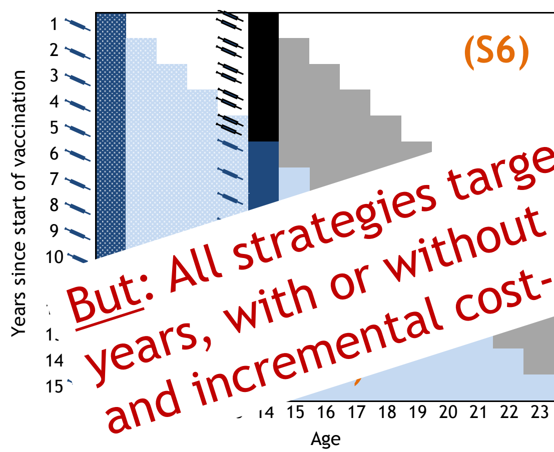
See extra slides for all NNV & ICER results

Efficiency (NNV) and cost-effectiveness (ICER)

9-14 year-old vaccination strategies, Girls-only

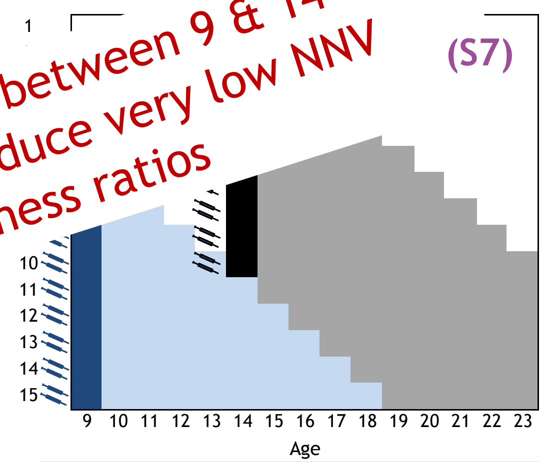
- The most efficient strategies in terms of NNV & cost-effectiveness are:

Routine 9 years old
5-year extended interval (1+1 doses);
14-year-old catch-up



	IN	VN	UG	NG
NNV	139	179	78	127
ICER	282	379	30	275

Routine 14 years old (2 doses);
later switch to routin… …ars old



	IN	VN	UG	NG
NNV	143	182	79	129
ICER	306	396	35	286

But: All strategies targeting girls between 9 & 14 years, with or without MAC, produce very low NNV and incremental cost-effectiveness ratios

NNV: Number of doses needed to prevent 1 cervical cancer
ICER: Incremental cost-effectiveness ratio (Cost per DALY averted)
Base case: high-valency vaccine, VE=100%, duration=lifelong, coverage=80%; MAC: Multiple-age cohorts
[1] Vaccine cost per dose: $4.60;

See extra slides for all NNV & ICER results

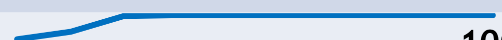
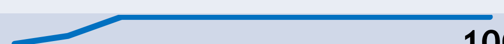
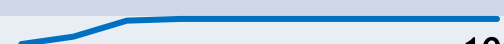
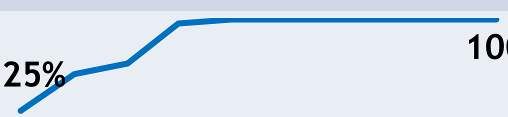
Optimal strategy in the context of limited vaccine supply

Methods

- Estimated the cumulative cervical cancer cases averted over 100 years:
  - For different vaccination strategies
  - for 92 LMIC, which have yet to introduce vaccination
  - using yearly vaccine supply scenarios provided by WHO
  - using HPV-ADVISE predictions

Maximizing cervical cancer cases prevented

Time horizon = 100 years, supply scenario = base case

		Cumulative number of countries (10 years) 1 2 3 4 5 6 7 8 9 10	Nb cases averted (Million)	Diff. cases averted (Million)
S7	Routine 14 yrs old (2 doses), later switch to 9 yrs old	 79% 100%	50.9	
S6	Routine 9 yrs old 5-yr extended interval (1+1 doses); with 14-yr-old catch-up	 49% 100%	50.6	-0.3
S1	Routine 9 yrs old (2 doses); MAC 9-14 yrs old	 21% 100%	49.7	-1.2
S8	Routine 14 yrs old (2 doses); No MACs	 79% 100%	49.3	-1.6
S5	Routine 9 yrs old 5-yr extended interval (1+1 doses); No MAC	 78% 100%	48.8	-2.1
S2	Routine 9 yrs old (2 doses); No MACs	 79% 100%	48.3	-2.6
S3	Routine 9 yrs old (1 dose); MACs 9-14 yrs old (Vaccine Efficacy=85%)	 21% 100%	43.4	-7.5
S3	Routine 9 yrs old (1 dose); MACs 9-14 yrs old (Vaccine Duration = 20yrs)	 25% 100%	29.6	-21.3

Maximizing cervical cancer cases prevented

Time horizon = 100 years, supply scenario = base case

		Cumulative number of countries (10 years) 1 2 3 4 5 6 7 8 9 10	Nb cases averted (Million)	Diff. cases averted (Million)
S7	Routine 14 yrs old (2 doses), later switch to 9 yrs old	79% 100%	50.9	
S6	Routine 9 yrs old 5-yr extended interval (1+1 doses); with 14-yr-old catch-up	49% 100%	50.6	-0.3
S1	Routine 9 yrs old (2 doses); MAC 9-14 yrs old	21% 100%	49.7	-1.2
S8	Routine 14 yrs old (2 doses); No MACs	79% 100%	49.3	-1.6
S5	Routine 9 yrs old 5-yr extended interval (1+1 doses); No MAC	78% 100%	48.8	-2.1
S2	Routine 9 yrs old (2 doses); No MACs	79% 100%	48.3	-2.6
S3	Routine 9 yrs old (1 dose); MACs 9-14 yrs old (Vaccine Efficacy=85%)	21% 100%	43.4	-7.5
S3	Routine 9 yrs old (1 dose); MACs 9-14 yrs old (Vaccine Duration = 20yrs)	25% 100%	29.6	-21.3

Maximizing cervical cancer cases prevented

Time horizon = 100 years, supply scenario = lower range

		Cumulative number of countries (10 years) 1 2 3 4 5 6 7 8 9 10		Nb cases averted (Million)	Diff. cases averted (Million)
S7	Routine 14 yrs old (2 doses), later switch to 9 yrs old	65%	100%	49.9	
S6	Routine 9 yrs old 5-yr extended interval (1+1 doses); with 14-yr-old catch-up	47%	100%	49.7	-0.2
S5	*Routine 9 yrs old 5-yr extended interval (1+1 doses); No MAC*	63%	100%	48.7	-1.2
S8	Routine 14 yrs old (2 doses); No MACs	66%	100%	48.6	-1.3
S1	*Routine 9 yrs old (2 doses); MAC 9-14 yrs old*	16%	99%	48.3	-1.6
S2	Routine 9 yrs old (2 doses); No MACs	65%	100%	47.6	-2.3
S3	Routine 9 yrs old (1 dose); MACs 9-14 yrs old (Vaccine Efficacy=85%)	25%	100%	43.0	-6.9
S3	Routine 9 yrs old (1 dose); MACs 9-14 yrs old (Vaccine Duration = 20yrs)	29%	100%	29.3	-20.6

Optimal strategy in the context of limited supply & projected demands

Kiesha Prem
Mark Jit

No conflicts of interest to declare

Contributors:
E Nickels, T Cernuschi,
S Malvolti, R Hutubessy,
M Brisson

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE
GLOBAL HEALTH CONSULTING
World Health Organization
linksbridge
UNIVERSITÉ LAVAL

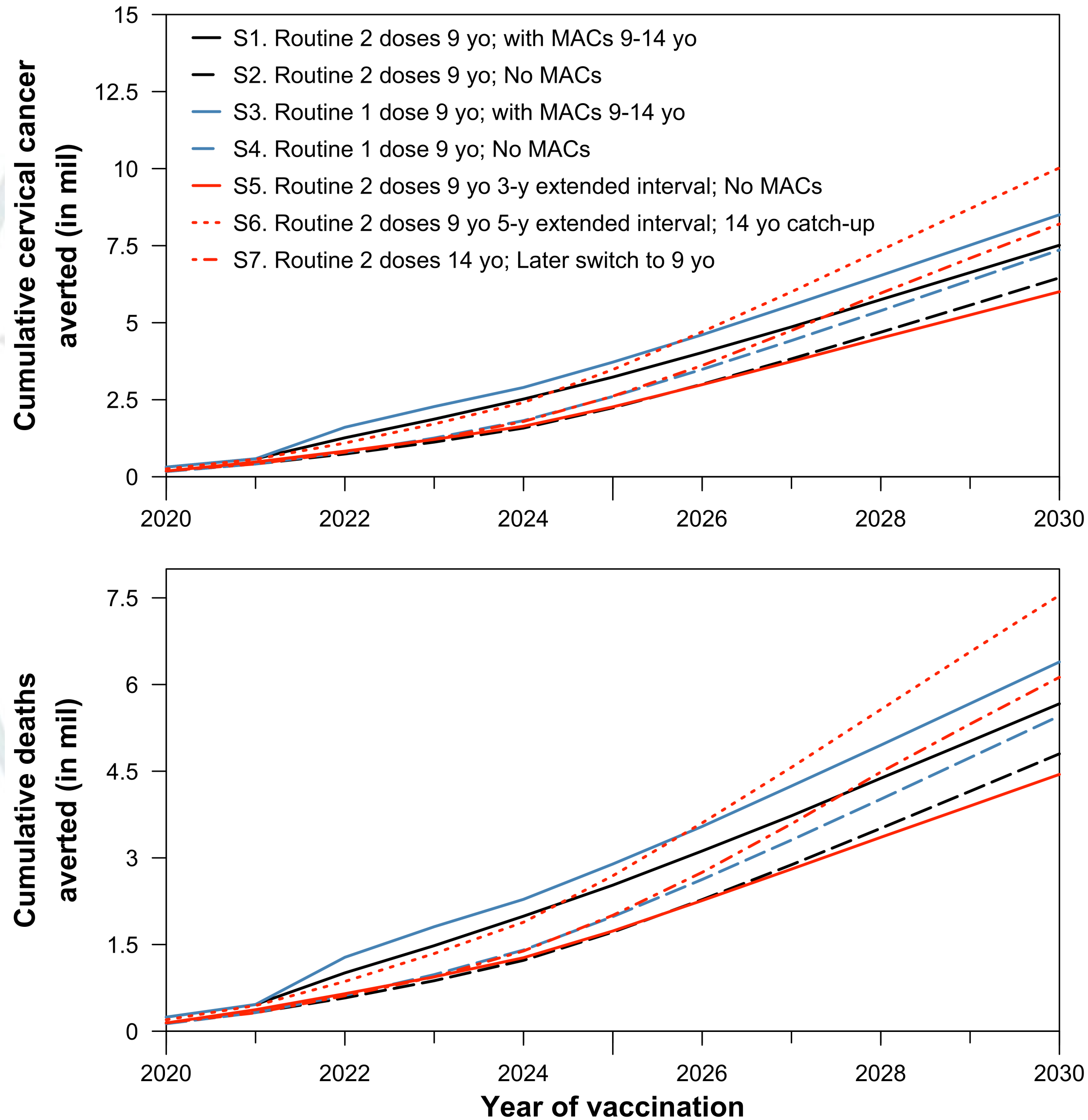
Methods

- Estimated the cumulative cervical cancer cases averted over 90 years:
  - for different vaccination strategies
  - using yearly vaccine supply scenarios & projected market dynamics provided by WHO[1]
  - using PRIME[2] predictions

[1] CERNUSHI presentation; [2]JIT. Lancet Glob Health 2014; 2: e406–14.

Impact of vaccination under 7 scenarios

Supply constrained environment & projected market dynamics



LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Optimal vaccination scenarios

Supply constrained environment & projected market dynamics

Top 3 Ranked Scenarios:

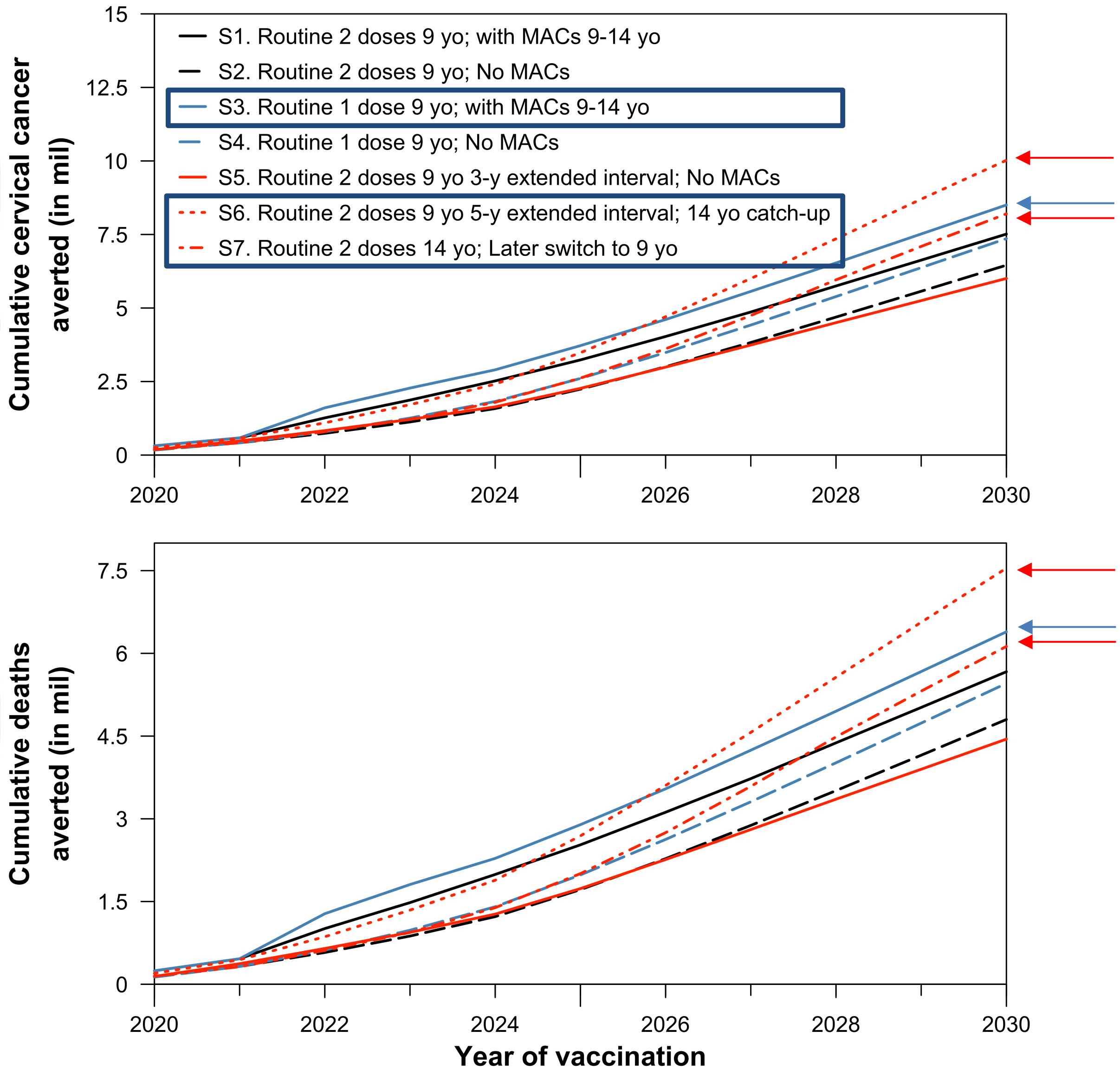
S6: Routine 2 doses **9 years old 5-year extended interval**; 14-year-old catch-up

S7: Routine 2 doses **14 years old; Later switch to 9 years old**

&

S3: **Routine 1 doses 9 years old**; MAC*

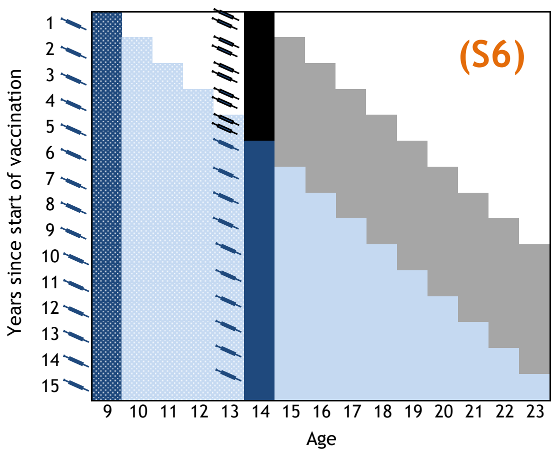
* Assumes 100% vaccine efficacy of 1 dose



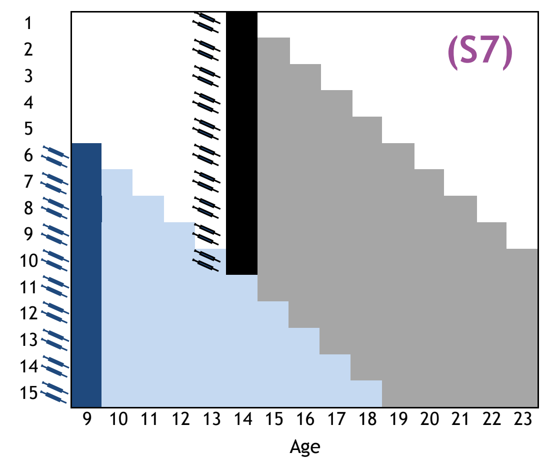
Summary Optimal strategies in context of supply constraints

- The strategies that optimized cervical cancer prevention were:

Routine 9 years old
5-year extended interval (1+1 doses);
14-year-old catch-up



Routine 14 years old (2 doses);
later switch to routine 9 years old

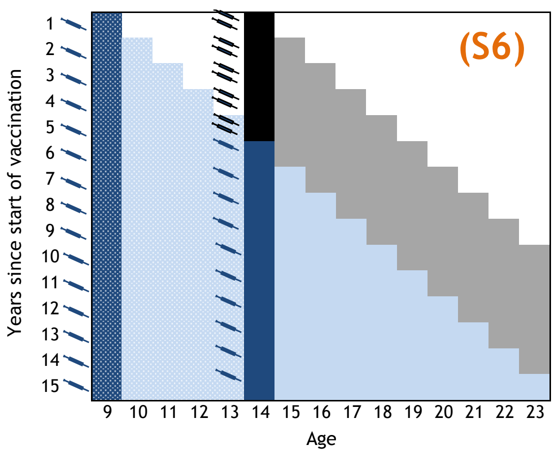


- Conclusions were robust to variations in supply constraints

Conclusion

- Two strategies are predicted to be optimal from the 3 different perspectives:
  - Efficiency – Cancer prevention per dose (NNV)
  - Return on investment - Cost-effectiveness (ICER)
  - Optimal vaccine distribution – Global cancer prevention

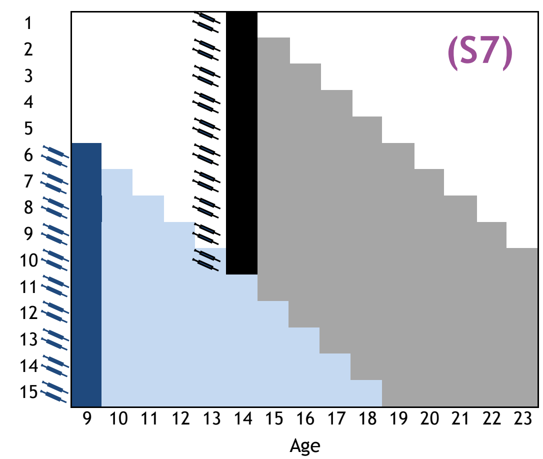
Routine 9 years old
5-year extended interval (1+1 doses);
14-year-old catch-up



	IN	VN	UG	NG
NNV	139	179	78	127
ICER	282	379	30	275

Cancers prevented 50.4M

Routine 14 years old (2 doses);
later switch to routine 9 years old



	IN	VN	UG	NG
NNV	143	182	79	129
ICER	306	396	35	286

Cancers prevented 50.9M

Thank you!