IMPACT OF HPV IMMUNIZATION STRATEGIES & POTENTIAL FOR CERVICAL CANCER ELIMINATION

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SAGE meeting
October 24, 2018
Geneva

UNIVERSITÉ LAVAL

Questions

A. What is the potential for Cervical Cancer elimination with HPV immunization?

B. What is the population-level effectiveness and cost-effectiveness of different HPV immunization schedules and strategies ?

POTENTIAL FOR CERVICAL CANCER ELIMINATION : A COMPARATIVE MODELING STUDY

M Brisson, J Kim, K Canfell,
C Gopalappa, E Burger, D Martin, E Benard, Kate Simms, M Drolet, S Sy, C Regan, A Keane, M Smith, C Pretorius, MC Boily, N Broutet & R Hutubessy

Université Laval, Canada; Harvard T.H. Chan School of Public Health, USA; Cancer Council NSW, Australia; University of Massachusetts Amherst, USA; CHU de Québec-Université Laval Research Center, Canada; Avenir Health, USA; Imperial College, UK; World Health Organization, Switzerland

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Call for action to eliminate cervical cancer

- In May, the WHO Director-General made a global call for action to eliminate cervical cancer as a public health problem[&]

- Elimination of cervical cancer as a public health problem is different to elimination of an infectious disease
  - Not reduction to 0 incidence
  - Control of cervical cancer at a low disease incidence
  - Requires clear well defined threshold
  - Previously used for other diseases by WHO
    - Neonatal Tetanus (NT): 1 NT per 1000 live births per yr
    - Congenital syphilis : Case rate of ≤50 per 100 000 live births

&: WHO Director-General Speech - http://www.who.int/reproductivehealth/DG_Call-to-Action.pdf

Call for action to eliminate cervical cancer

Key questions that must be addressed

- What is the definition of cervical cancer elimination as a public health problem?
  - What outcome? Cancer incidence? Mortality? % Reduction?
  - Same for every country?
  - Pragmatic? Optimistic?
- What combination of screening and vaccination strategies can lead to elimination (for different definitions)?
- When could elimination be reached, for different strategies and countries?
- What is the most efficient/cost-effective strategy to reach elimination?

Need for mathematical models

- Mathematical models provide a formal framework to examine key elimination questions
  - project long-term population-level effects (e.g., herd immunity)
  - evaluate multiple strategies under varying assumptions
- However, models require many simplifications & assumptions which leads to uncertainty in the validity of predictions
  - can create uncertainty for decision makers
- WHO initiated a model comparison to help provide guidance for cervical cancer elimination
  - the Cervical cancer elimination modeling consortium was created

Systematic comparative modeling approach

- Model Selection
  - Dynamic model
  - Model includes vaccination & screening
  - Independent model that has been peer reviewed/published

MARCH

- Policy 1 Model
  - Lead: Karen Canfell
  - Team: Kate Simms, Adam Keane, Megan Smith
  - Institution: Cancer Council NSW, Australia
- Harvard Model
  - Lead: Jane Kim
  - Team: Emily Burger, Stephen Sy, Catherine Regan
  - Institution: Harvard, USA
- HPV-ADVISE Model
  - Lead: Marc Brisson
  - Team: Mélanie Drolet, JF Laprise, Dave Martin, Élodie Bénard, Guillaume Gingras, Iacopo Baussano, Marie-Claude Boily, Mark Jit
  - Institution: U Laval, Canada; Imperial College, UK; LSHTM, UK; IARC, France
- Spectrum Model
  - Leads: Chaitra Gopalappa & Carel Pretorius
  - Institution: U Massachusetts & Avenir Health, USA

Global predictions

78 Low & Lower Middle Income Countries

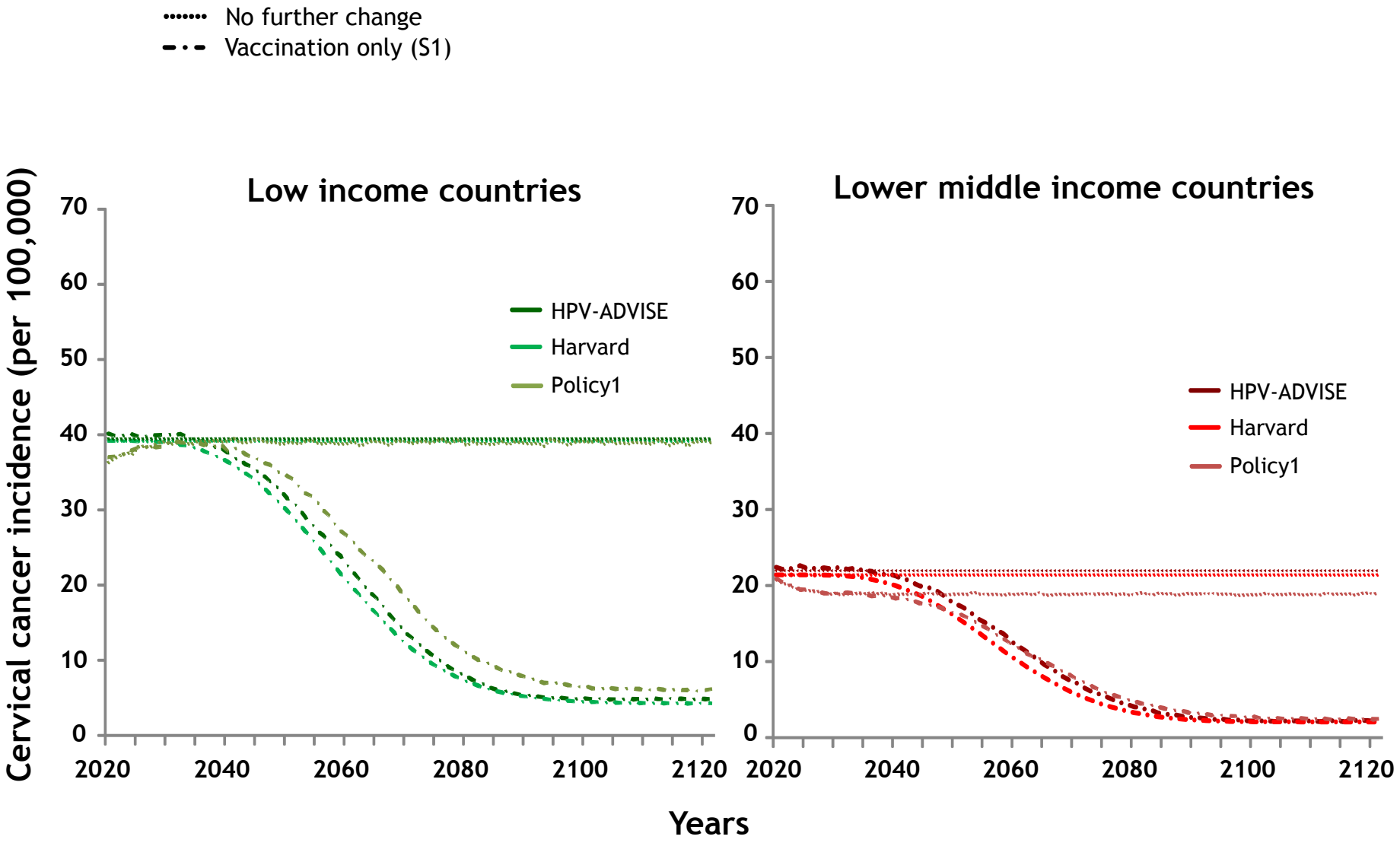
2 vaccination/screening scenarios

Vaccination & Screening scenarios

- S1 - Scenario 1:
  - Girls-only vaccination (90% coverage, 9-14 yr old)
  - No change in Screening
- S2 - Scenario 2:
  - Girls-only vaccination (90% coverage, 9-14 yr old)
  - 2 lifetime screens at 35 and 45 yrs old
  - High Screening ramp-up (45%, 70%, 90% in 2023, 2030, 2045, respectively)
- All scenarios:
  - Screening: HPV testing, 100% treatment efficacy, 10% Lost to follow-up
  - Vaccine: Lifelong duration, 100% efficacy, HPV16/18/31/33/45/52/58

Dynamics of elimination Consistency in model predictions

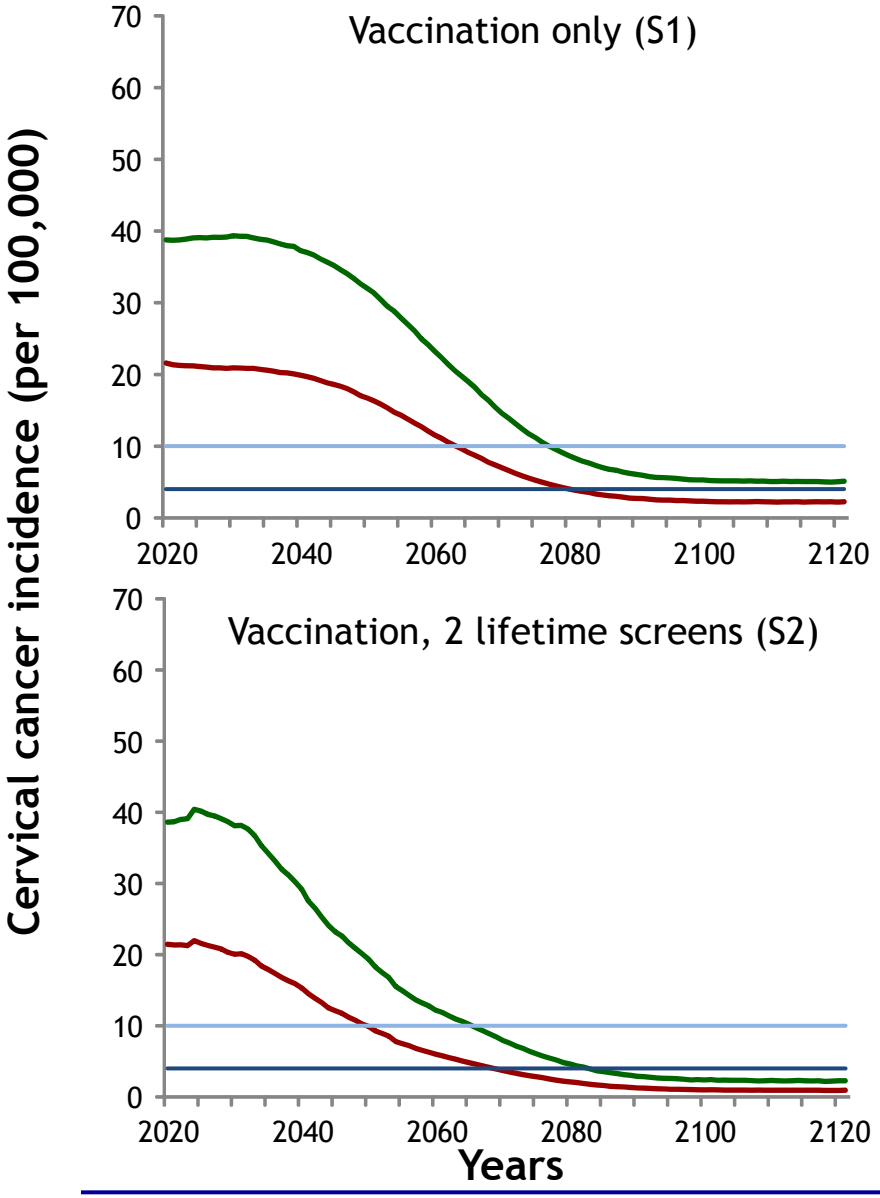
High vaccination coverage & Screening Ramp-up



Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58

Dynamics of elimination Impact over time

Low (LIC) & Lower Middle Income Countries (LMIC), High vaccination coverage & Screening Ramp-up

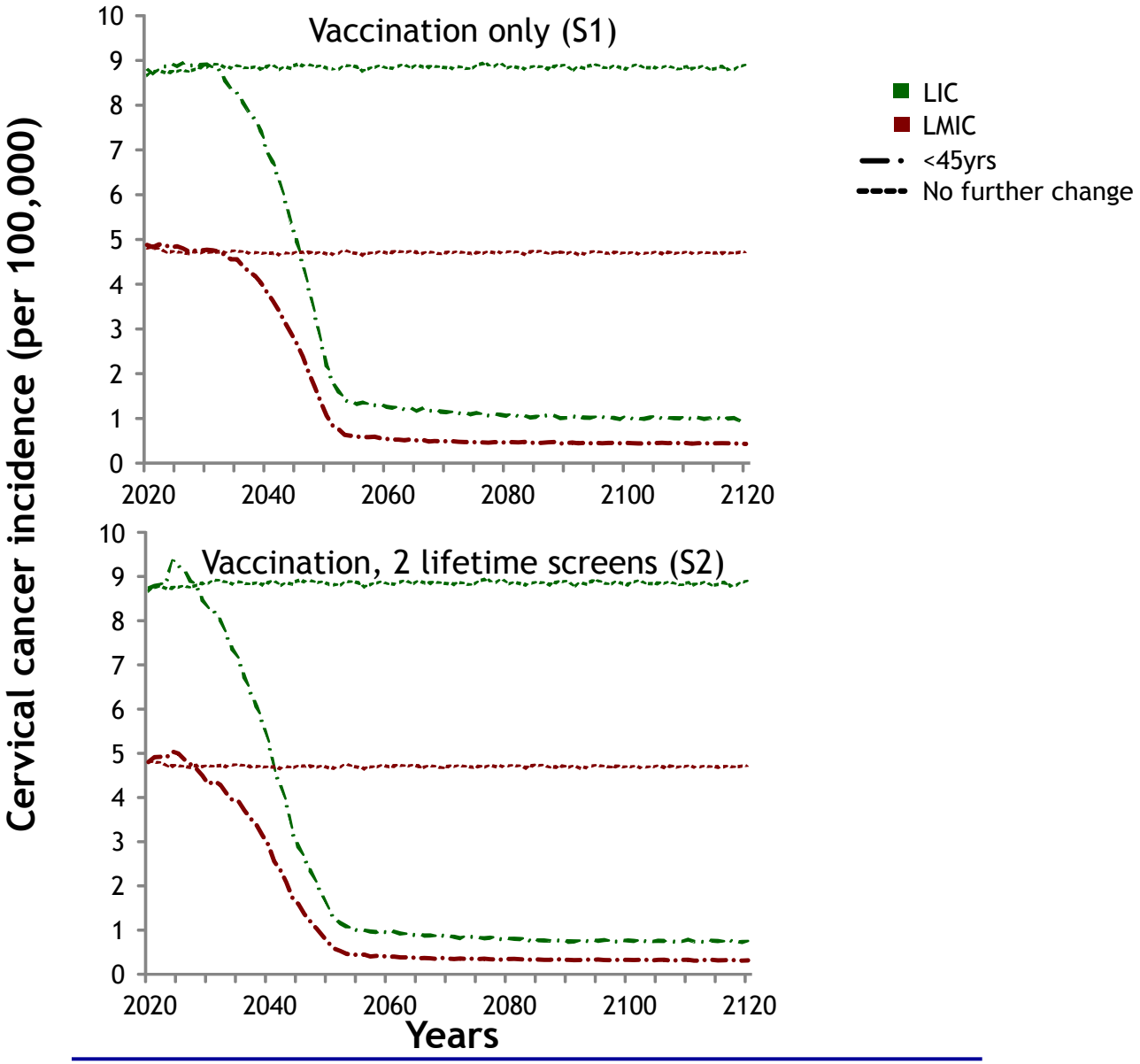


	Time to <10/100,000		Time to <4/100,000	
	LIC	LMIC	LIC	LMIC
S1	2078	2064	X	2081
S2	2066	2050	2083	2069

&. Mean predictions; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV testing

Dynamics of elimination Impact over time – under 45 year olds

Low (LIC) & Lower Middle Income Countries (LMIC), High vaccination coverage & Screening Ramp-up

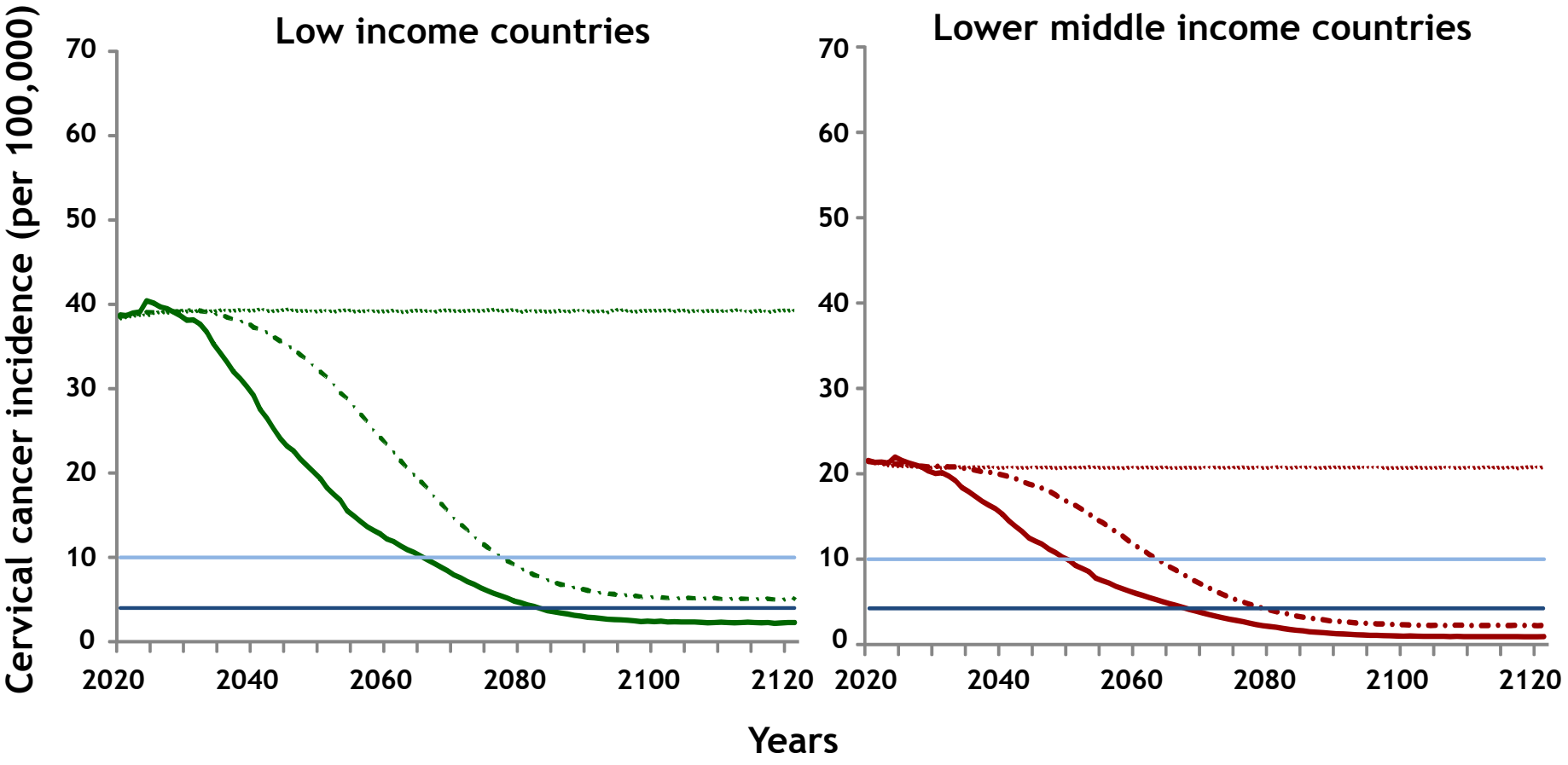


Mean prediction of models; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV testing

Dynamics of elimination Incremental benefits of strategies

High vaccination coverage & Screening Ramp-up

	Cases averted[&] (vs no change)		Incremental cases averted	
	LIC	LMIC	LIC	LMIC
No further change				
Vaccination only	3.5 M	11.5 M	3.5 M	11.5 M
Vaccination, 2 lifetime screens	4.3 M	14.2 M	0.8 M	2.7 M

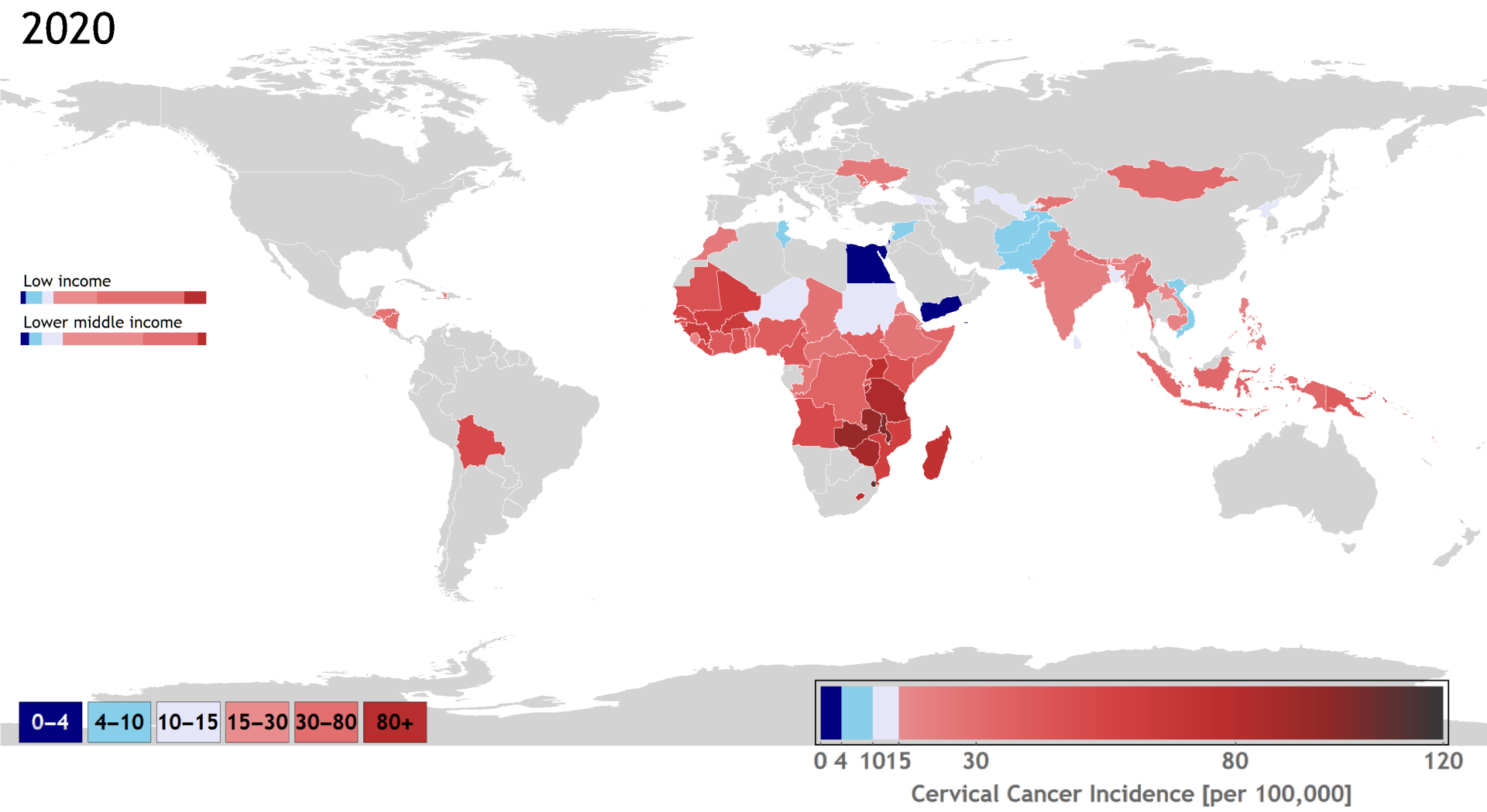


&. Mean prediction over 100 years; Adjusted cases averted for 2015 population; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV testing

Country specific predictions

Low income & Lower Middle income countries

Vaccination only (S1)

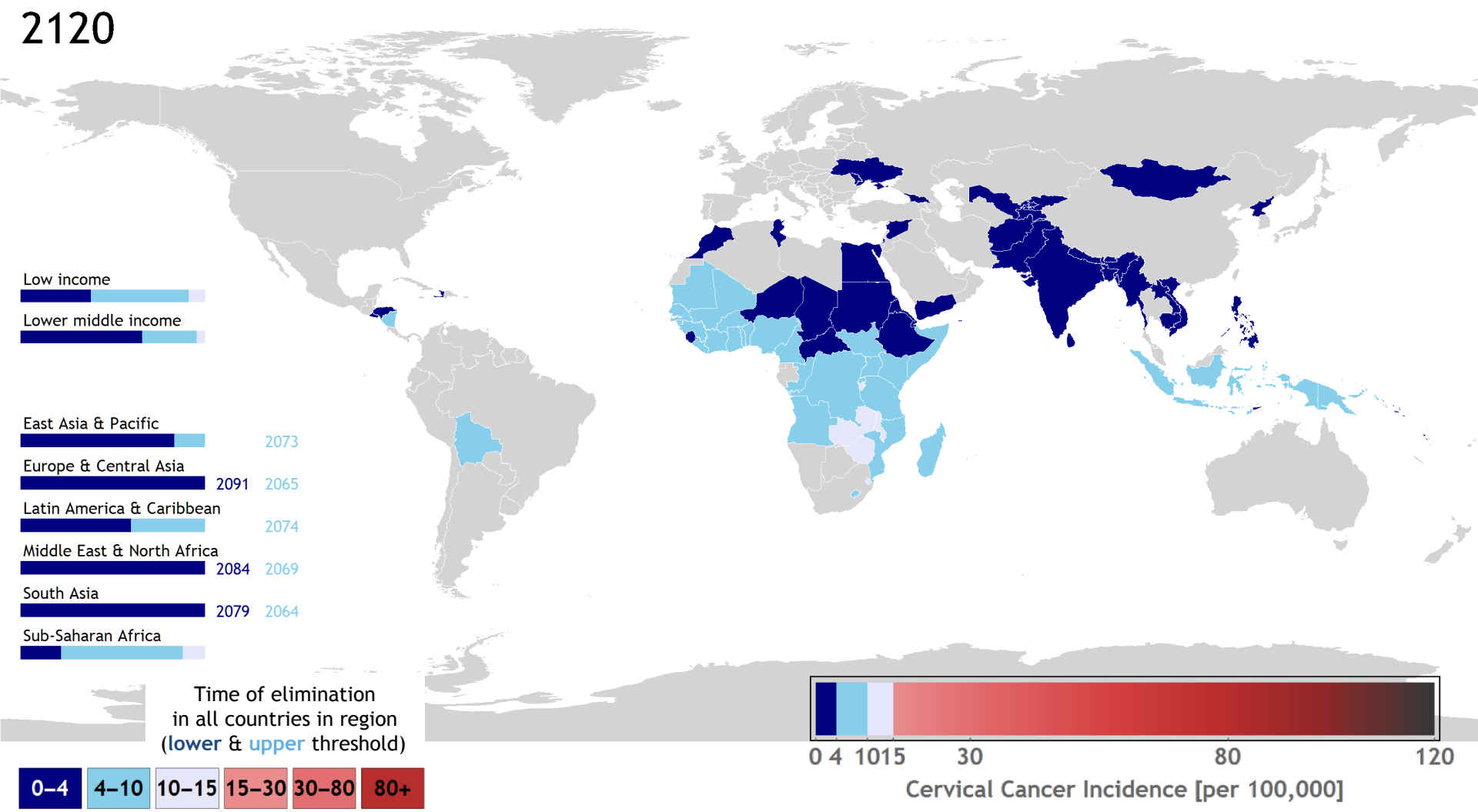


&. Median prediction; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58

Country specific predictions

Low income & Lower Middle income countries by region

Vaccination only (S1)

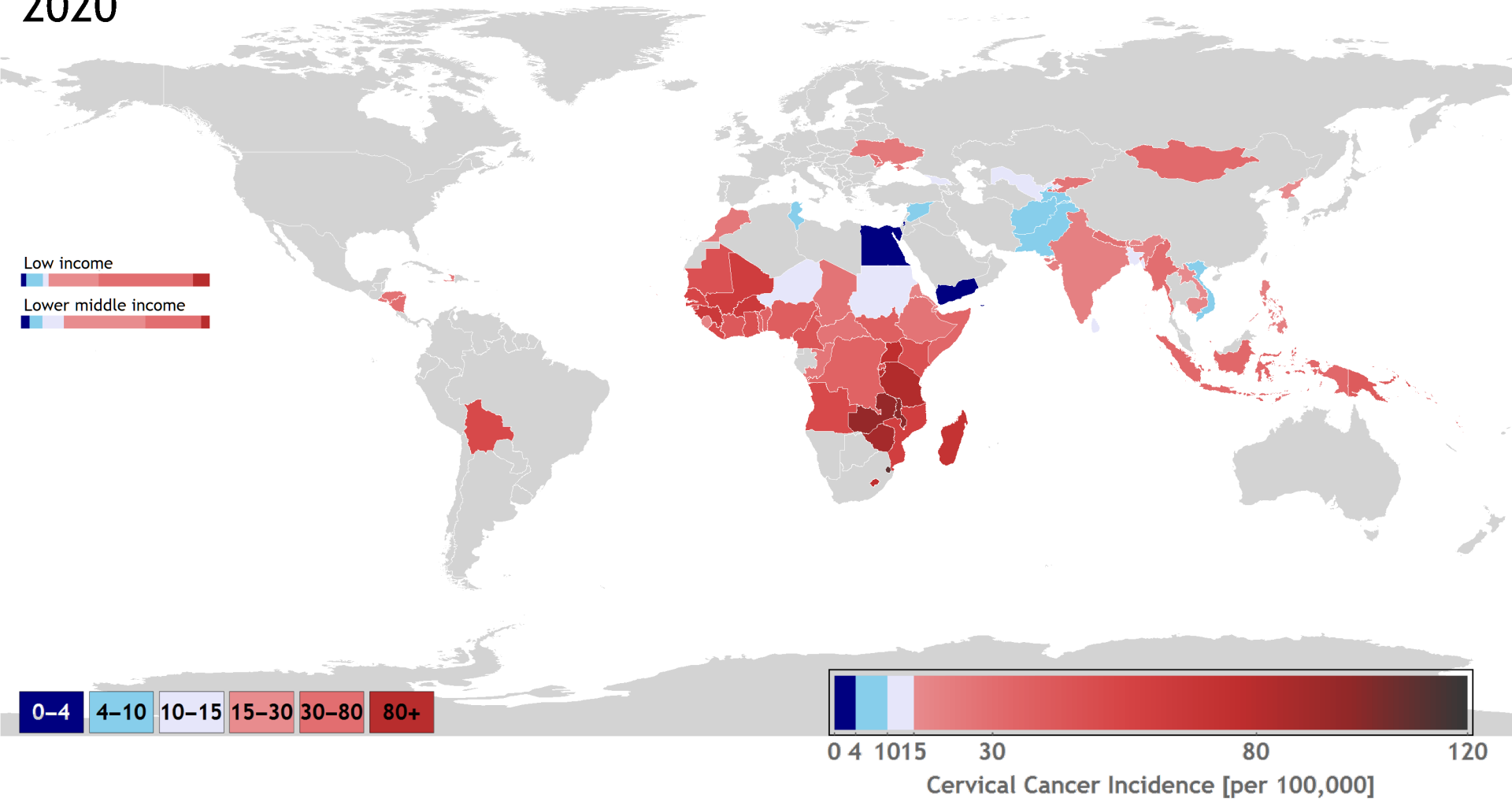


&. Median prediction; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58

Country specific predictions

Low income & Lower Middle income countries

Vaccination, 2 lifetime screens (S2)

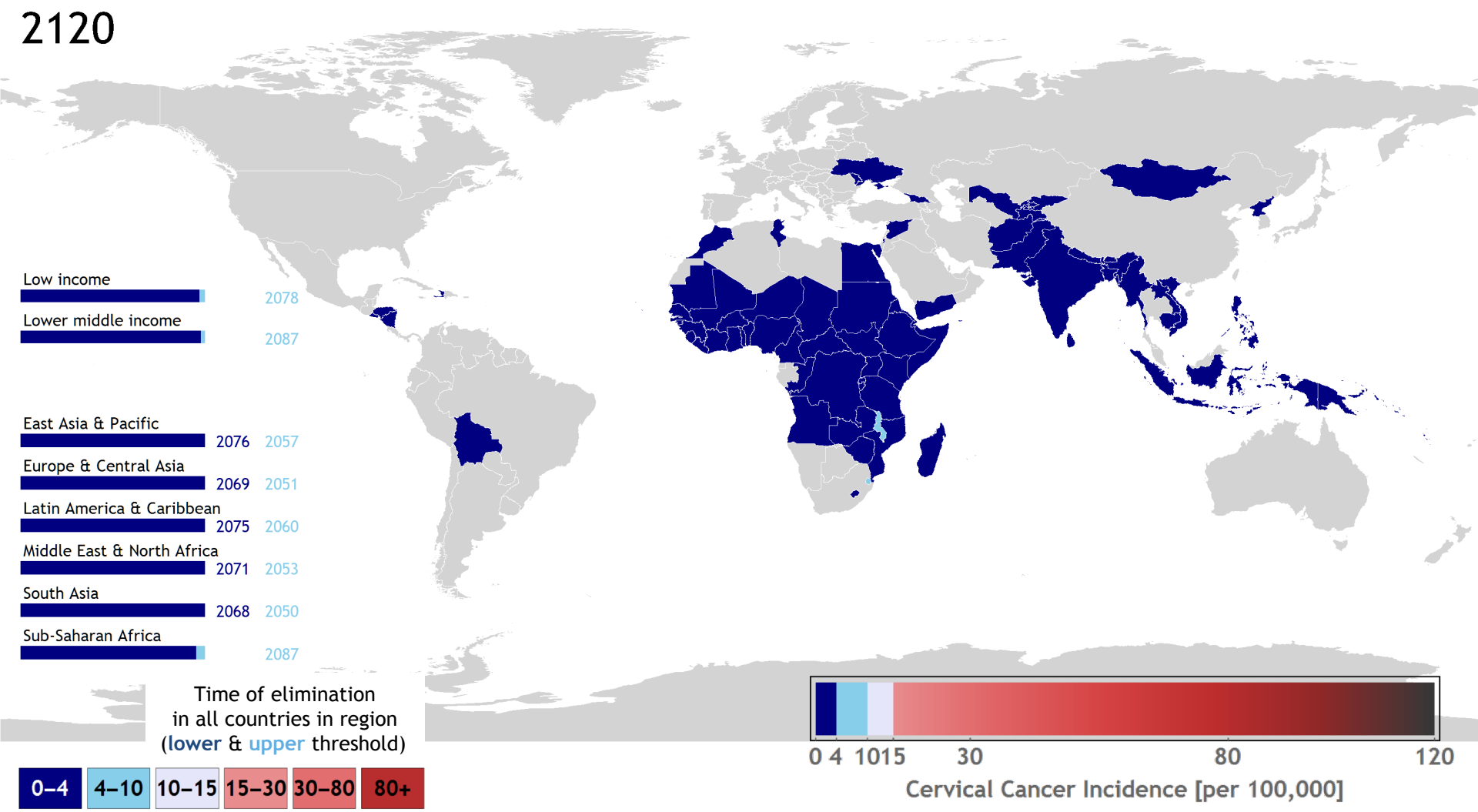


&. Median prediction; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV test

Country specific predictions

Low income & Lower Middle income countries by region

Vaccination, 2 lifetime screens (S2)

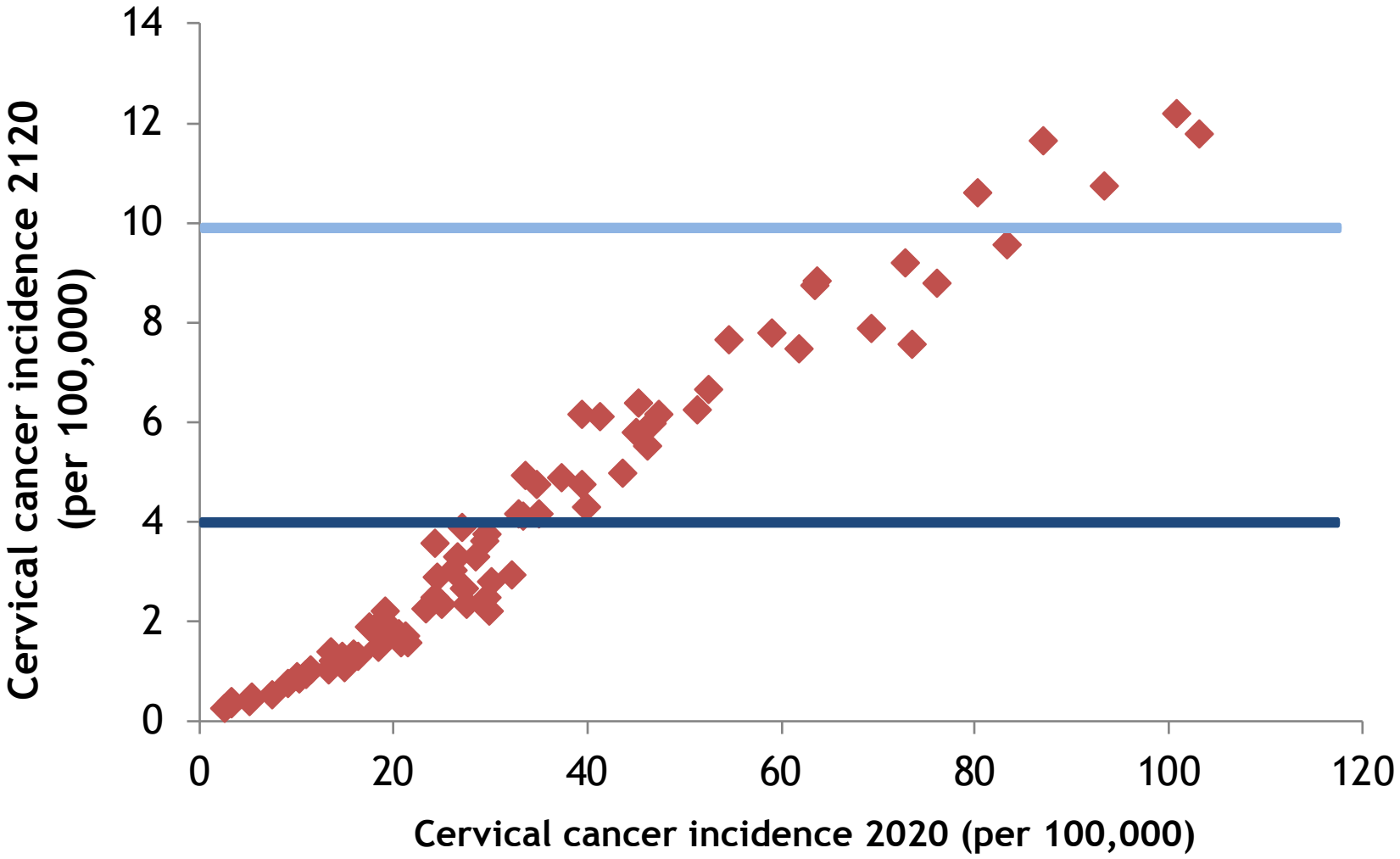


&. Median prediction; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV test

Country specific elimination predictions

Impact of starting cervical cancer (CC) incidence

Low & Lower middle income countries, Vaccination only (S1)

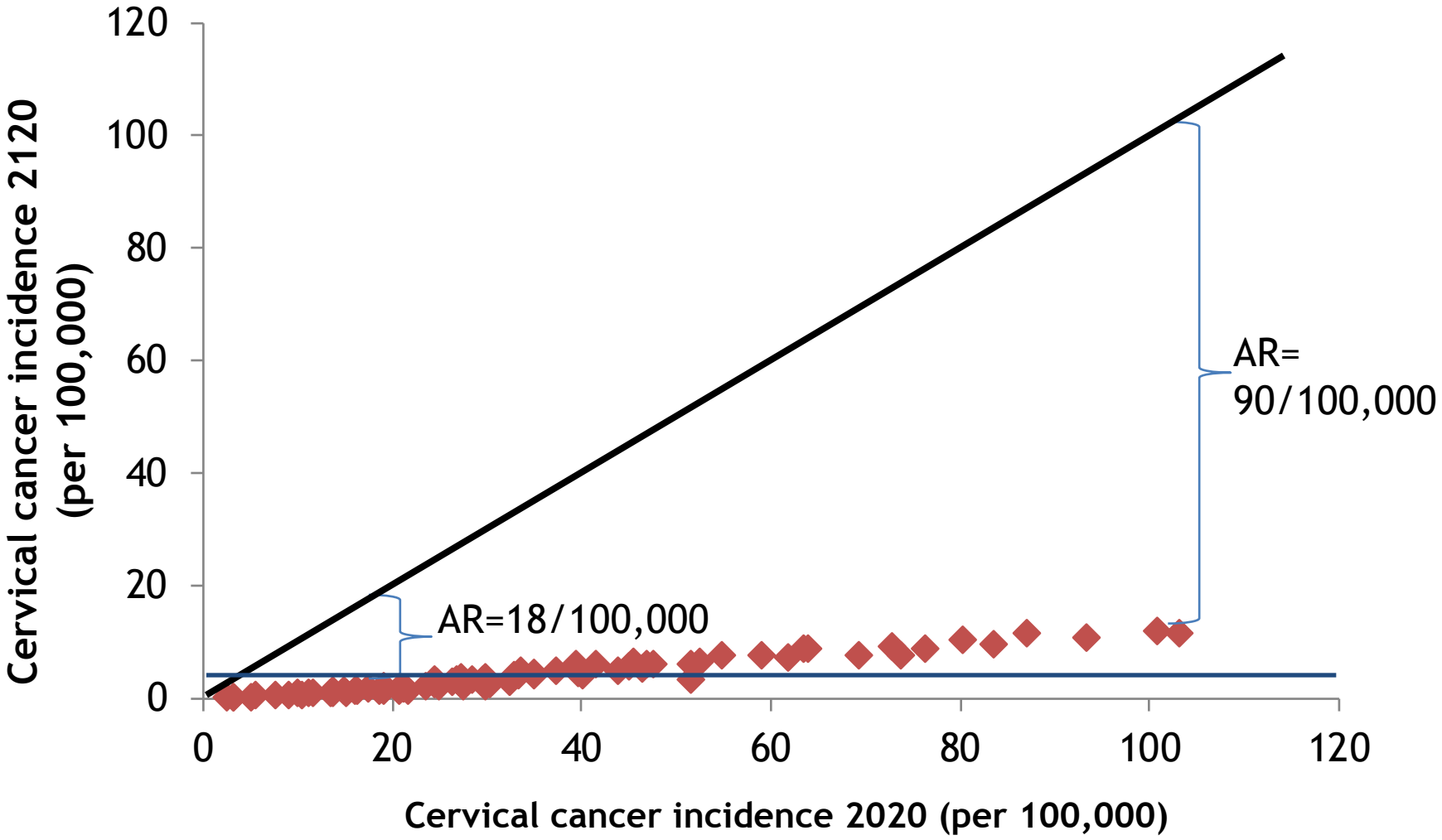


&. Harvard & HPV-ADVISE; High vaccination coverage and screening ramp-up, Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV test

Country specific predictions

Absolute Reductions (AR) in Cervical cancer (CC) & Elimination

Low & Lower middle income countries, Vaccination only (S1)



&. Harvard & HPV-ADVISE; High vaccination coverage and screening ramp-up, Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV test

Summary

Global analysis: 3 optimistic vaccination & screening coverage scenarios

What strategies lead to elimination?

- Girls-only vaccination leads to incidence <10/100,000 w-yrs without screening in most countries/regions
  - <15/100,000 w-yrs in Sub-Saharan Africa
- Girls-only vaccination & 2 lifetime screens leads to incidence <4/100,000 w-yrs in most countries/regions
  - <10/100,000 w-yrs in Sub-Saharan Africa

When does elimination occur?

- Average within LIC/LMIC: 2045-2060
  - UMIC/HIC: elimination occurs earlier
- 100% of countries: 2085-2105
- Depends on the strategy & threshold

&. Low (LIC), Lower Middle Income (LMIC), Upper Middle Income (LMIC), High Income Countries (HIC), Vaccine protection=HPV16/18/31/33/45/52/58, HPV test

Sensitivity Analysis

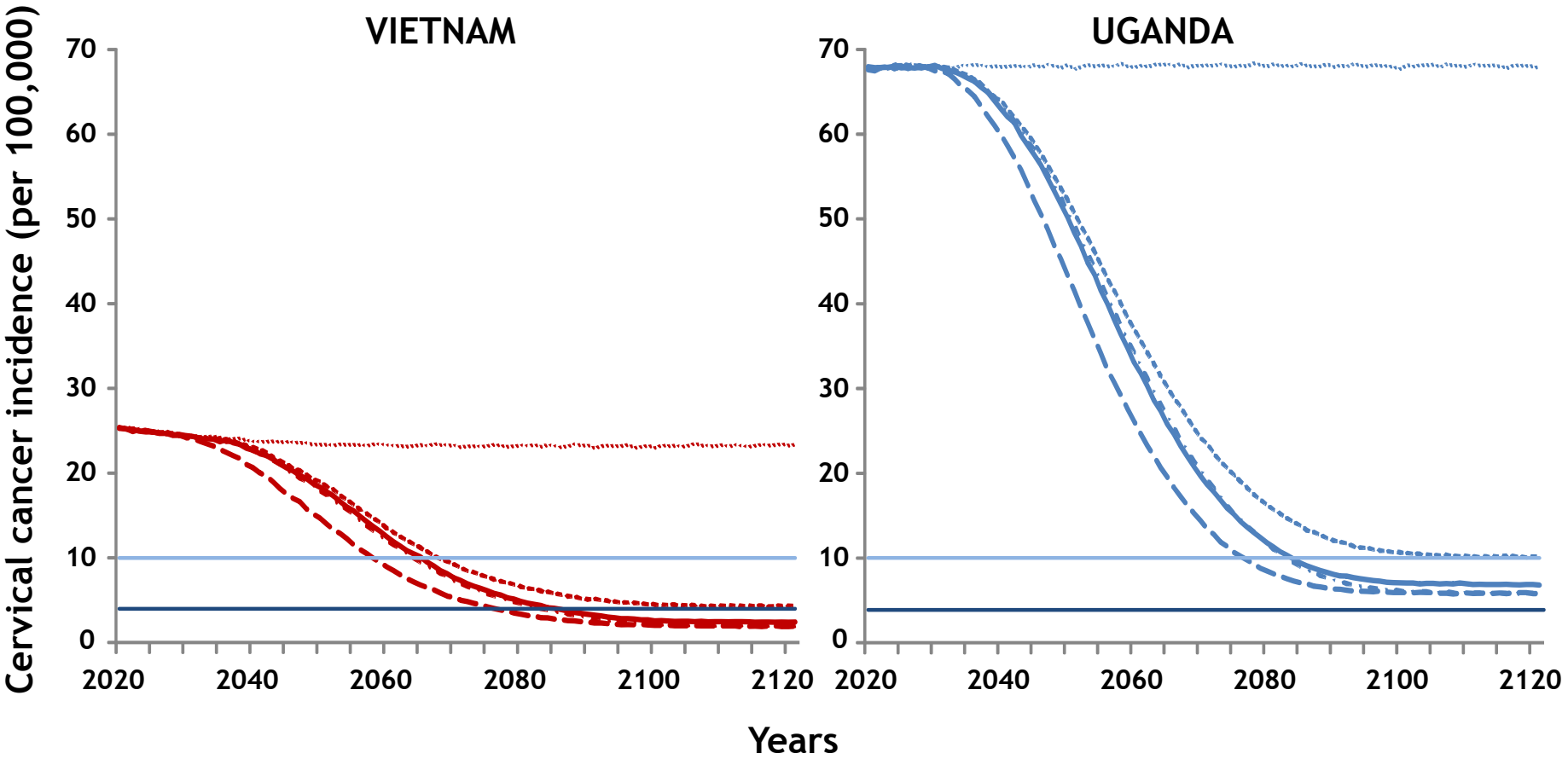
What is the impact of:

Vaccination Strategies & Coverage?
Number of Screens?
Vaccine characteristics?

Dynamics of elimination Impact of vaccination

No change in screening

	Time to <10/100,000		Time to <4/100,000	
	VN	UG	VN	UG
No further change	2066	2084	2086	X
90% Girls-only vaccination	2068	X	X	X
80% Girls-only vaccination	2064	2084	2084	X
80% Girls&Boys vaccination	2058	2077	2077	X
80% Girls&Boys vaccination, Catch-up				

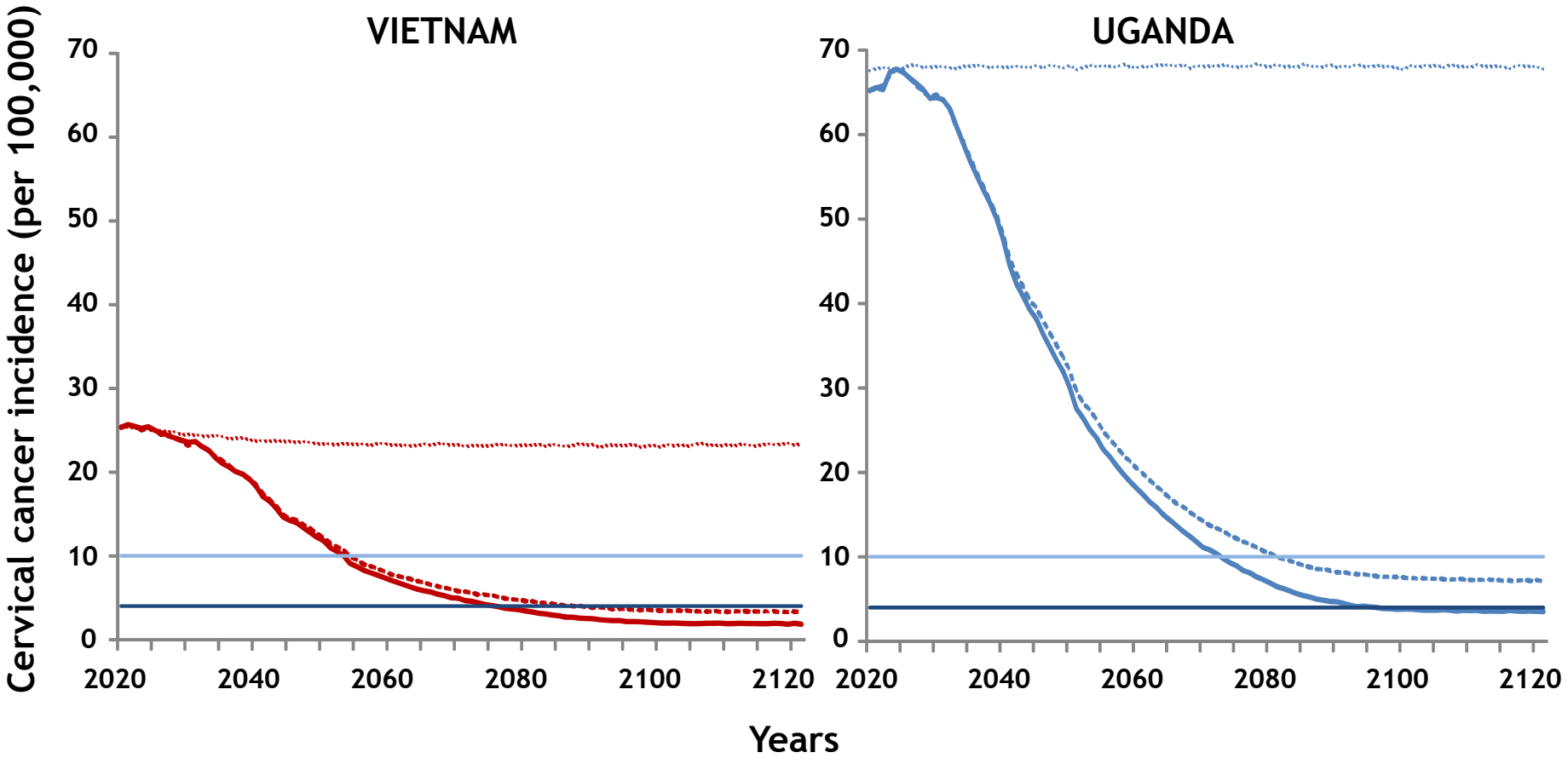


Mean predictions; Vietnam: Policy-1/HPV-ADVISE; Uganda: Harvard/HPV-ADVISE; Vaccine duration=lifelong; VE=100%

Dynamics of elimination Impact of number of HPV types protected

80% Girls-only vaccination, high screening ramp-up, 2 screens

	Time to <10/100,000		Time to <4/100,000	
	VN	UG	VN	UG
No further change	2054	2073	2077	2097
Efficacy against HPV16/18/31/33/45/52/58	2054	2082	2089	X
Efficacy against HPV16/18 only				

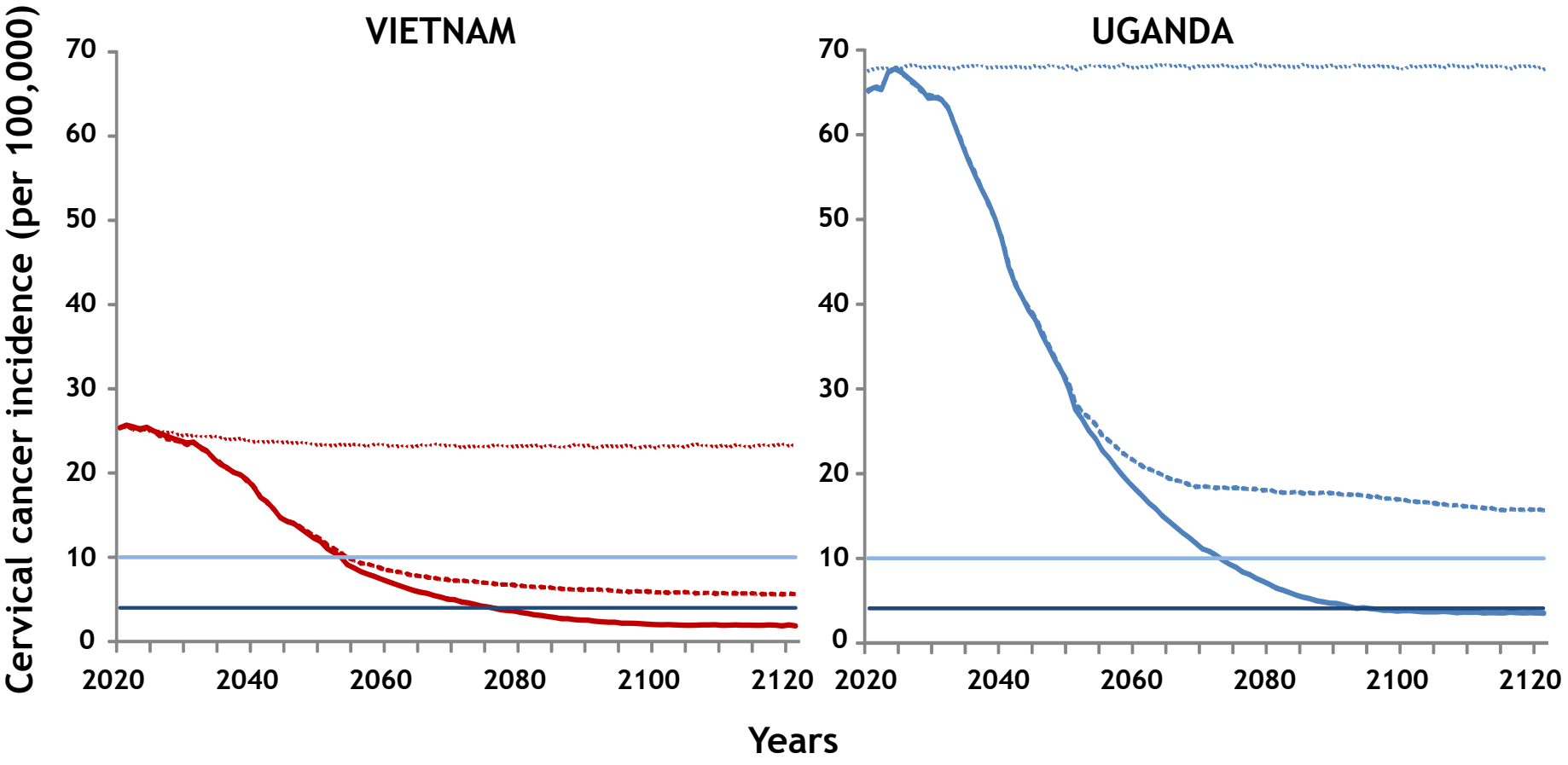


Mean predictions; Vietnam: Policy-1/HPV-ADVISE; Uganda: Harvard/HPV-ADVISE; Vaccine duration=lifelong; VE=100%

Dynamics of elimination Impact of duration of vaccine protected

80% Girls-only vaccination, high screening ramp-up, 2 screens

	Time to <10/100,000		Time to <4/100,000	
	VN	UG	VN	UG
No further change	2054	2073	2077	2097
Vaccine Duration = lifelong	2054	X	X	X
Vaccine Duration = 20 years				



Mean predictions; Vietnam: Policy-1/HPV-ADVISE; Uganda: Harvard/HPV-ADVISE; Vaccine duration=lifelong; VE=100%

Sensitivity analysis

40 scenarios, 12 countries

- Greatest additional benefits (cancers cases averted over time):
  - Vaccination of Girls-only with high coverage (vs no vaccination)
  - 2 lifetime screens (vs current screening)
  - Multi-cohort vaccination (vs single-cohort vaccination) – No impact on elimination
- Screening or multi-cohort vaccination accelerates elimination (5-15 yrs)
- Smallest additional impact
  - Vaccinating boys (vs Girls-only) if Girls-only coverage is high
- Long-term duration of vaccine protection is required for elimination

SUMMARY

- Models produced consistent findings
- Countries with cervical cancer incidence < 30/100,000 w-yrs
  - >80% Girls-only vaccination coverage could lead to elimination without changes to screening
- Countries with cervical cancer incidence ≥ 30/100,000 w-yrs
  - elimination is highly dependent on the threshold used
  - high screening & vaccination coverage, and a broad spectrum vaccine is required
  - hardest to eliminate but have greatest absolute reductions in incidence
  - countries with incidence ≥ 70/100,000 w-yrs may not reach elimination
- Long-term vaccine protection is needed (>20 years)
  - particularly for higher cervical cancer incidence countries

SUMMARY

- Greatest additional benefits:
  - Vaccination of Girls-only (vs no vaccination)
  - 2 lifetime screens (vs no screening)
  - Multi-cohort vaccination (vs single-cohort vaccination)
  - Screening at least once in a lifetime & multi-cohort vaccination accelerates elimination by about 10 years
- Results are most sensitive to:
  - Definition of elimination - Threshold
  - Starting cervical cancer incidence
- Future work:
  - Examine the cost and cost-effectiveness of elimination
  - Identify the most efficient strategies for elimination

IMPACT OF DIFFERENT HPV IMMUNIZATION SCHEDULES AND STRATEGIES

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], Baussano I[6], 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)

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Objective

- Examine the population-level effectiveness and cost-effectiveness of HPV immunization of different schedules and strategies in Low and Lower Middle Income Countries, using:
  - Predictions from Mathematical Models

Schedules/strategies

- Girls-only HPV immunization (HPV2 or HPV4 vs HPV9)
- Gender-neutral HPV immunization (vs Girls-only)
- Multiple age cohort HPV immunization (vs single age cohort)

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, Benin, 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 (see back-up slides for references & model fit)

Question: Girls-only immunization

- 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
- HPV9 vaccine Girls-only vaccination (vs HPV2 or HPV4)
  - Likely cost-effective (vs HPV2 or HPV4) in HIC & LMIC unless
    - very strong cross-protection from HPV2 or HPV4 is expected
    - HPV9 priced too high
  - Main drivers: Cross-protection from HPV2/4 and vaccine price

REF: HPV-ADVISE, *SAGE WG Meeting* 2018; Ng, *Vaccine* 2018; Jit, *Lancet Global Health* 2015; Fesenfeld, *Vaccine* 2013

Question: Gender-neutral immunization

- 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

- HIC: Small additional benefits of vaccinating boys (even at low coverage)
- LMIC: Greater added benefit of vaccinating boys than in HIC
- HIC & LMIC: 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: May be cost-effective even if coverage in girls is high
- LMIC: More cost-effective to increase coverage in girls when coverage is low

Main drivers

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

REF: HPV-ADVISE, *SAGE WG Meeting* 2018; Ng, *Vaccine* 2018; Brisson, *Lancet Public Health*

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Thank you!