

Towards Cervical cancer elimination: the context of HPV vaccination

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WHO IVB EPI

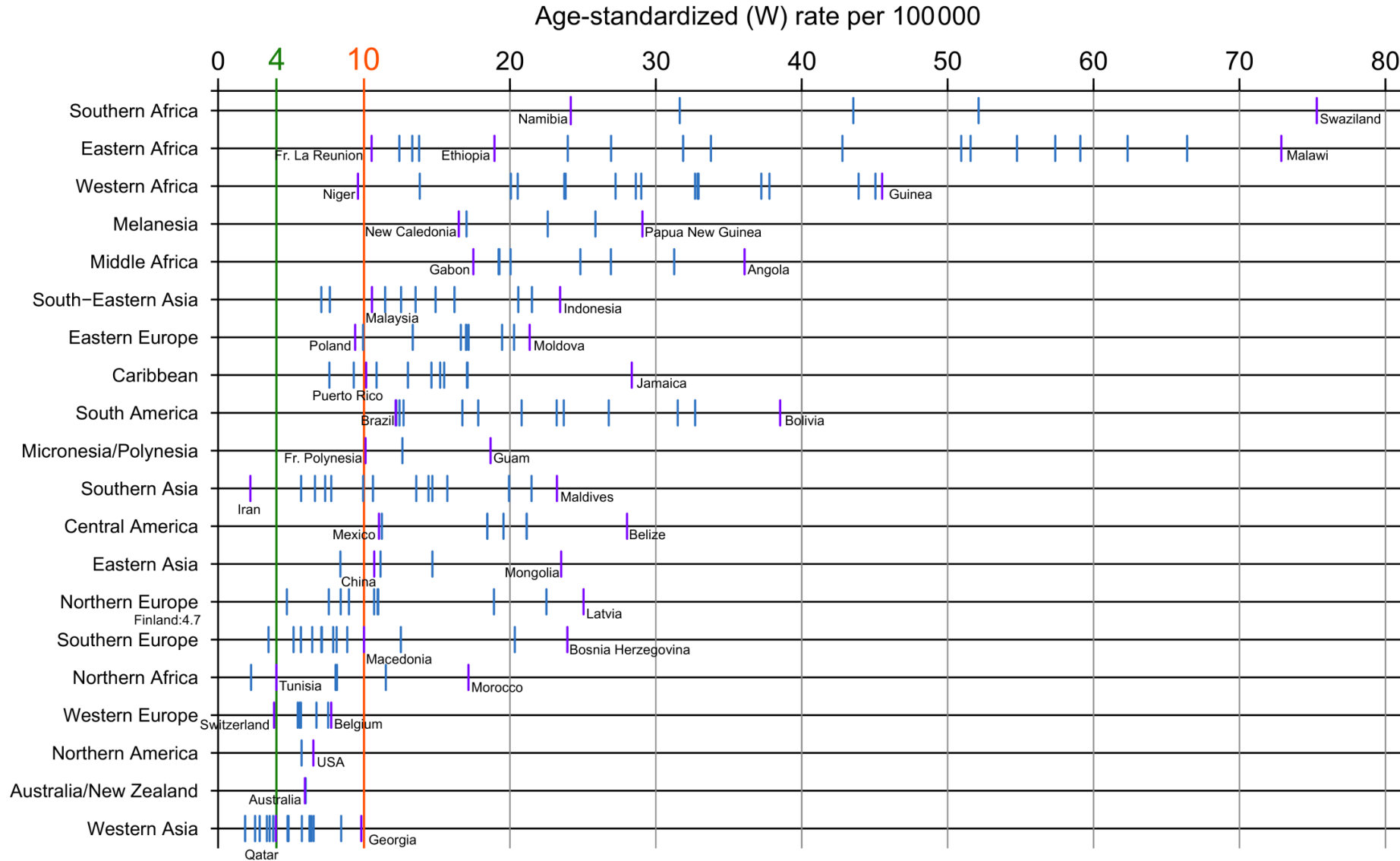
Antwerpen, 15 Nov 2019



Outline

- Cervical Cancer Elimination: HPV vaccine targets
- Global context of HPV vaccine introduction
- Performance of HPV programmes
- Global HPV vaccine supply situation
- SAGE recommendations to deal with supply constraints
- Key messages

Variability in Cervical Cancer Incidence Rates by World Region



Systematic Comparative Modeling Approach

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

MARCH 2018

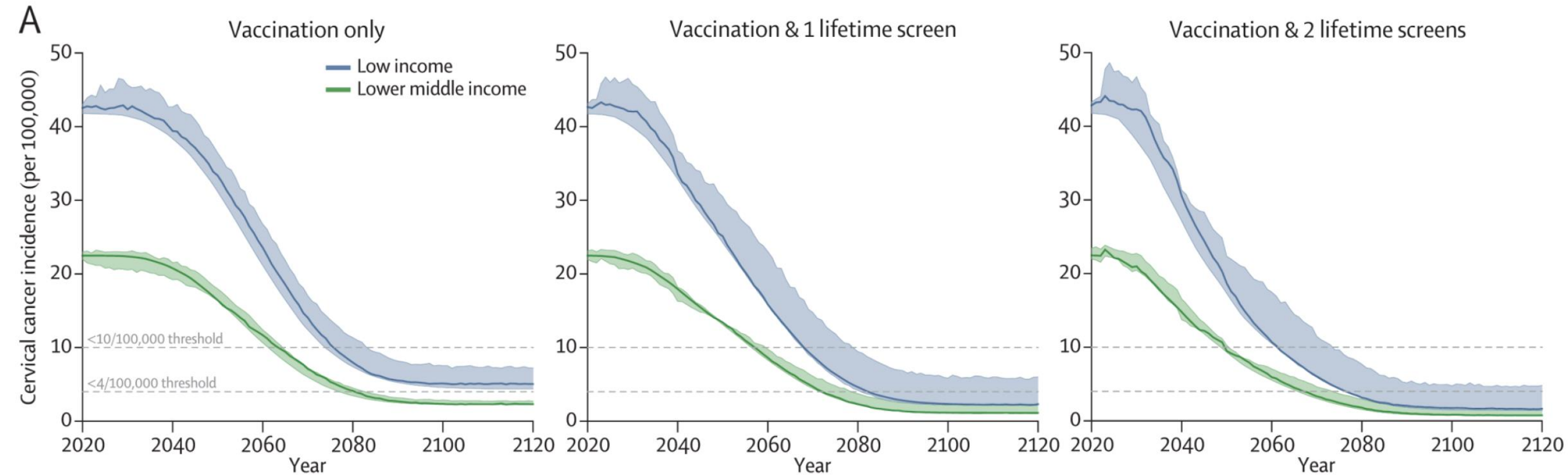
- **Policy 1 Model**
 - Lead: Karen Canfell
 - Team: Kate Simms, Adam Keane, Megan Smith
 - Institution: Cancer Council NSW, Australia
- **Harvard Model**
 - Lead: Jane Kim
 - Team: Emily Burger, Stephen Sy, Catherine Regan
 - Institution: Harvard, USA
- **HPV-ADVISE Model**
 - Lead: Marc Brisson
 - 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



Vaccination & Screening Scenarios

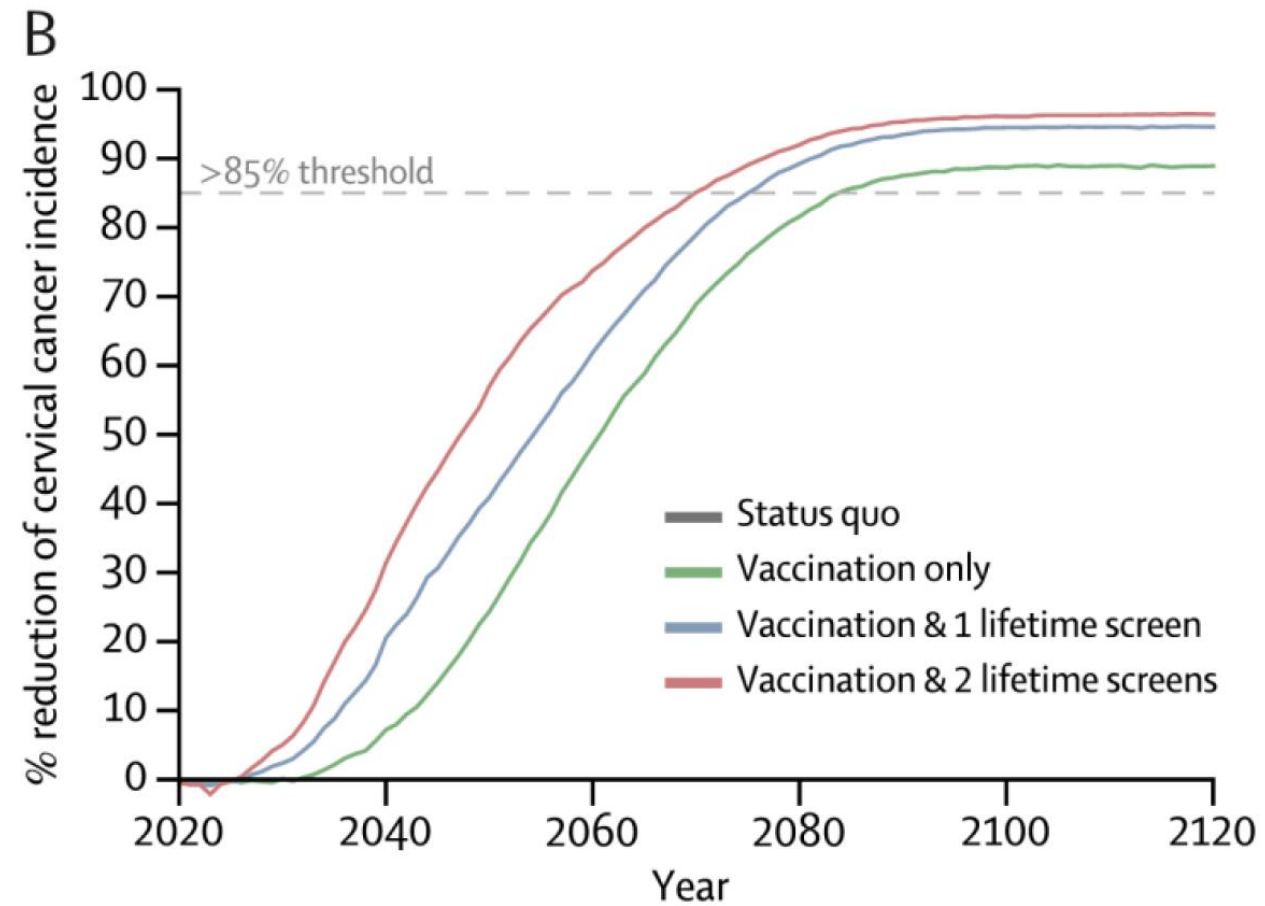
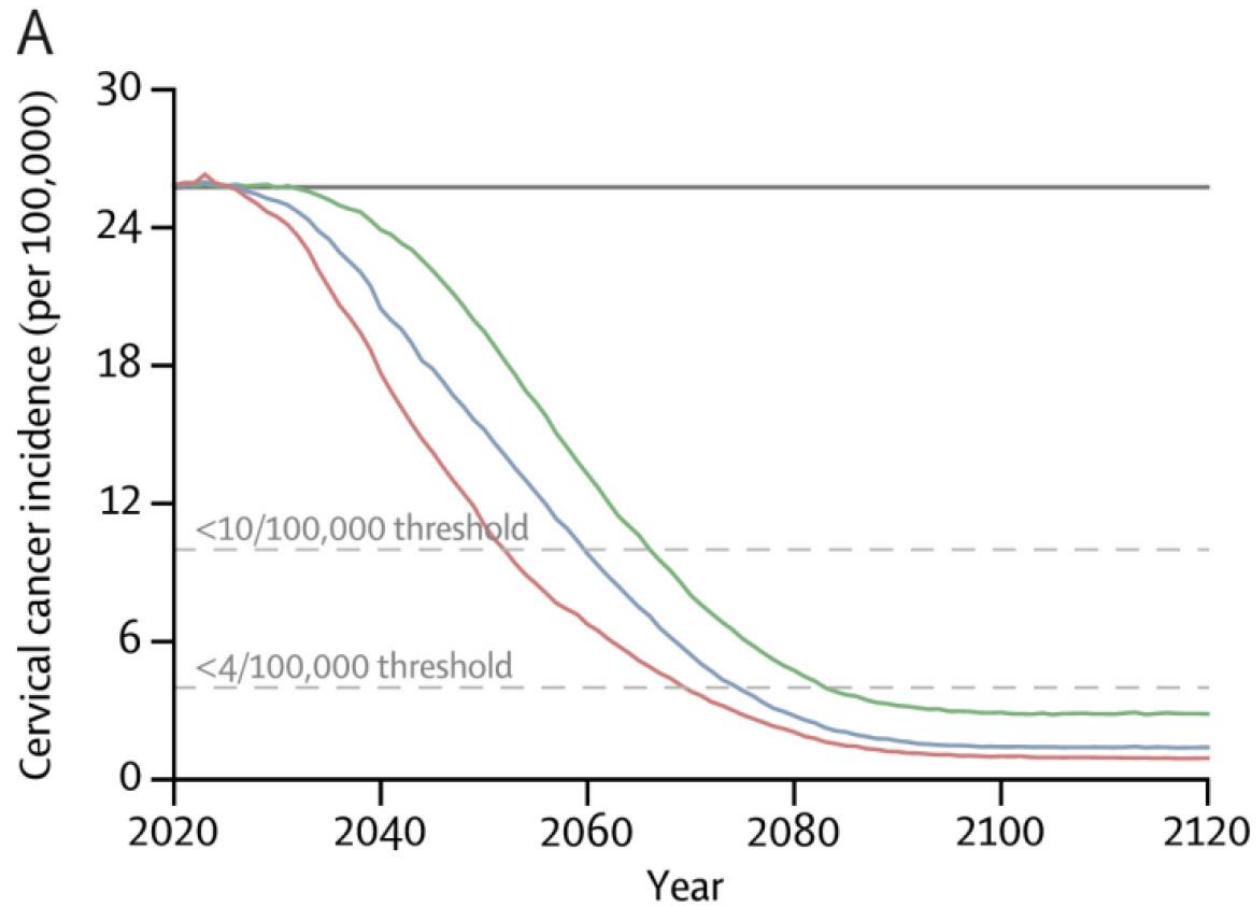
- **S1 - Scenario 1:**
 - Girls-only vaccination (90% coverage, 9-14 yr old)
 - No change in Screening
- **S2 - Scenario 2:**
 - Girls-only vaccination (90% coverage, 9-14 yr old)
 - 1 lifetime screen at 35 yrs old
 - High Screening ramp-up (45%, 70%, 90% in 2023, 2030, 2045, respectively)
- **S3 - Scenario 3:**
 - 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

Variability in Model Predictions of the Impact of HPV Vaccination and Screening Strategies - LIC vs LMIC



Source: M. Brisson, J. Kim & K. Canfell et al. In publication

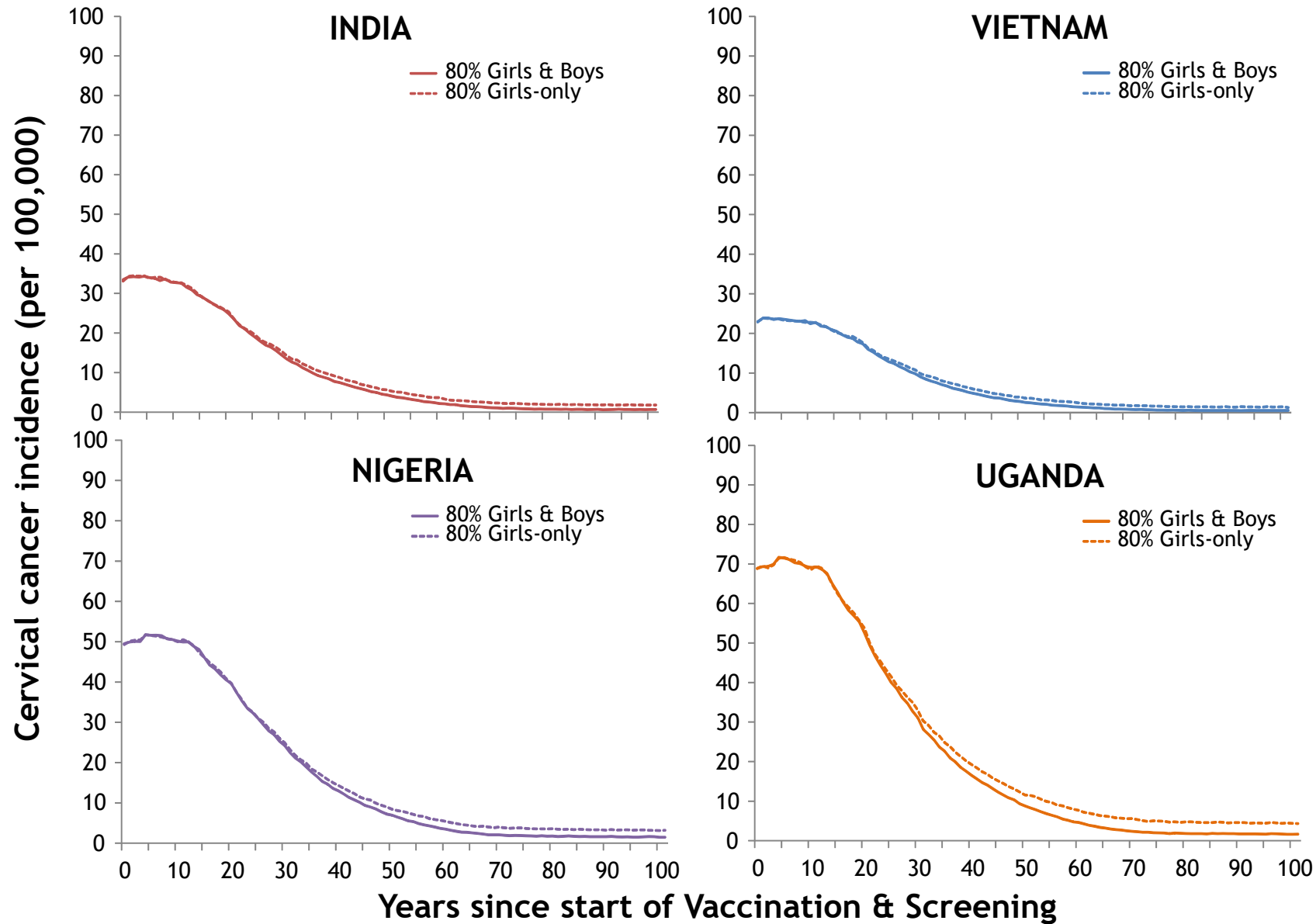
Dynamics of 78 LMICs Cervical Cancer Incidence After Vaccination and Screening



Source: M. Brisson, J. Kim & K. Canfell et al. In publication

Impact of Vaccinating boys

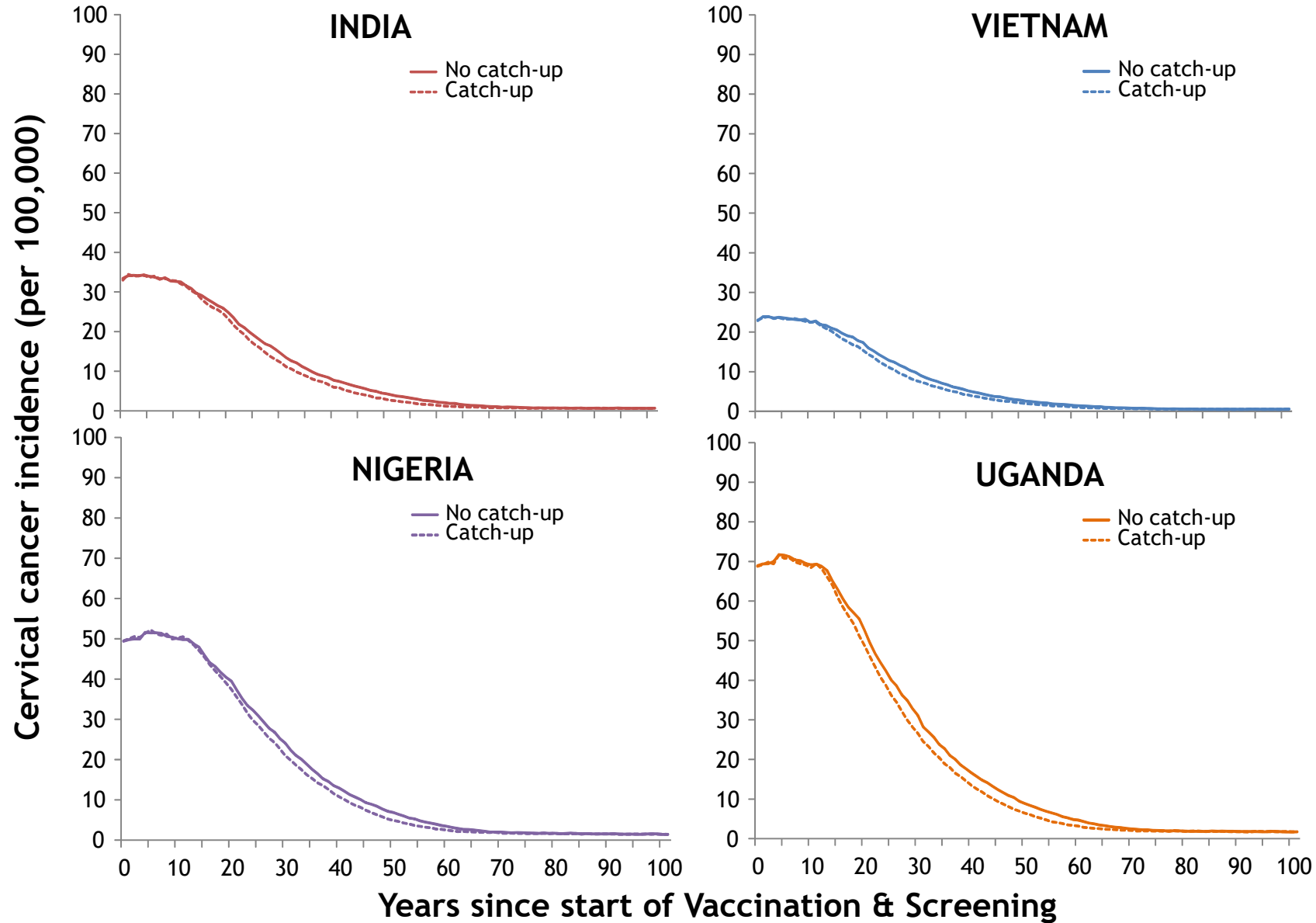
HPV9, 2 screens, High ramp-up, No catch-up



Ⓢ: HPV-ADVISE, Mean of the model predictions

Impact of Catch-up vaccination to 25 years old

80% Girls & Boys vaccination, HPV9



Ⓔ: HPV-ADVISE, Mean of the model predictions

Global Strategy towards the Elimination of Cervical Cancer

VISION: A world without cervical cancer

THRESHOLD: All countries to reach < 4 cases 100,000 women years

2030 CONTROL TARGETS

Timeline

Submitted to EB
2020 (Oct 2019)
for discussion at
WHA May 2020

90%

of girls fully
vaccinated with HPV
vaccine by 15 years
of age

70%

of women screened
with a high precision
test at 35 and 45 years
of age

90%

of women identified
with cervical disease
receive treatment and
care

SDG 2030: Target 3.4 – 30% reduction in mortality from cervical cancer

Factors affecting introductions and performance

Global Strategy towards the Elimination of Cervical Cancer



1. Supply: *Limited supply of the HPV vaccine*

2. Costs: *Vaccine price*
High delivery cost

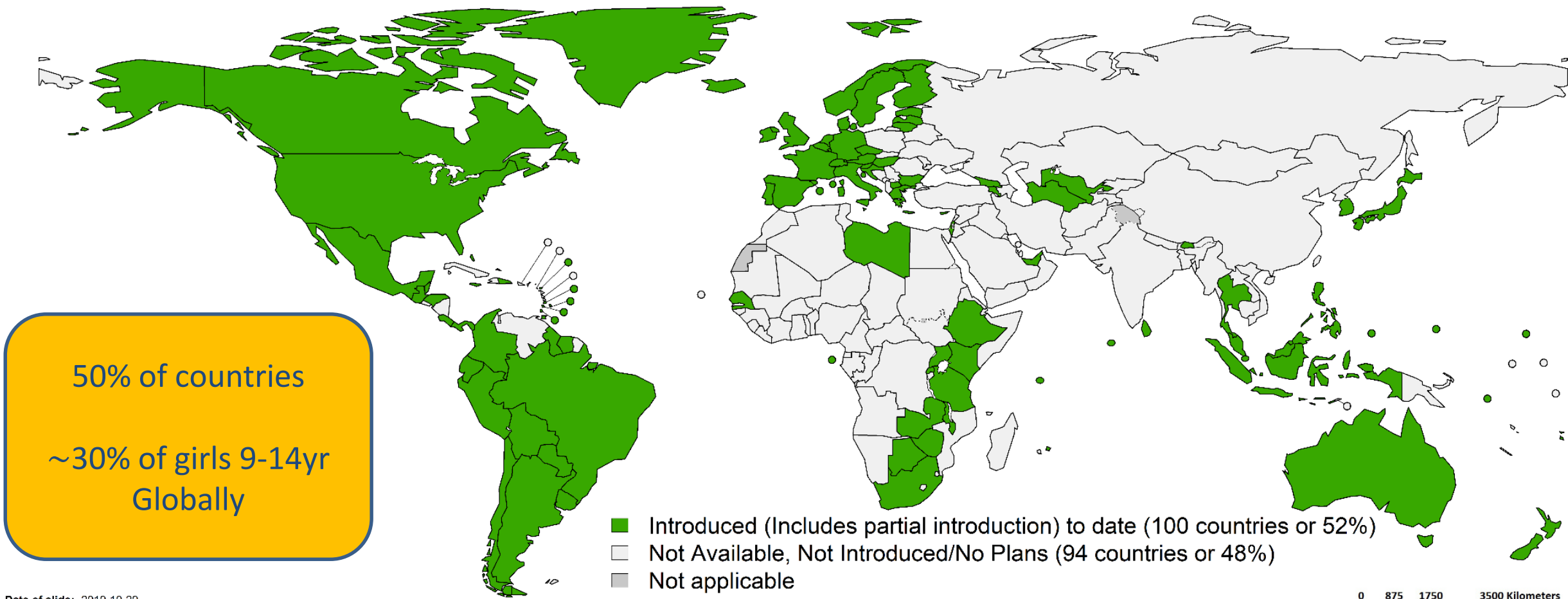
3. Quality of Introduction Planning and Management:

- *Choice and sustainability of delivery strategy*
- *Insufficient communication*
- *Addressing hesitancy related factors*

Vaccine
Introduction

High
Coverage

Countries with HPV vaccine in the National Immunization Programme



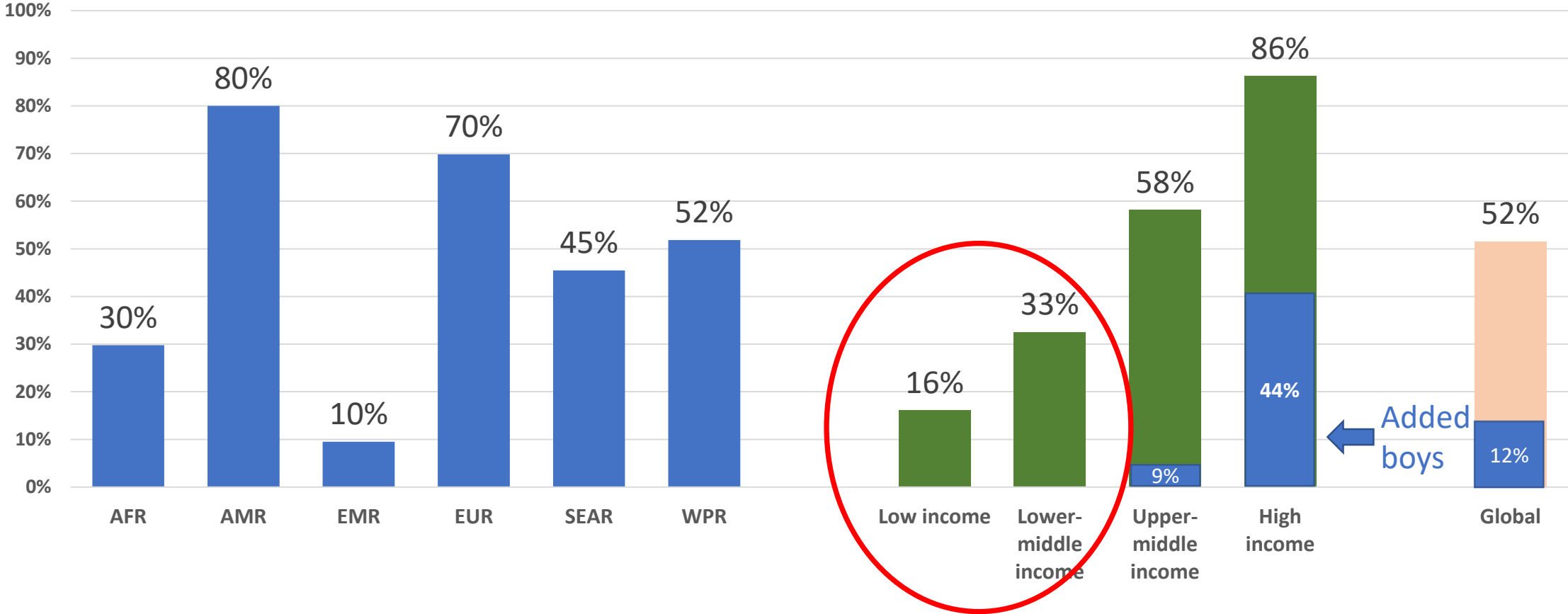
Date of slide: 2019-10-29
Map production: Immunization, Vaccines and Biologicals (IVB), World Health Organization(WHO)
Data source: IVB database as at 29th October 2019

Disclaimer:

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area nor of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
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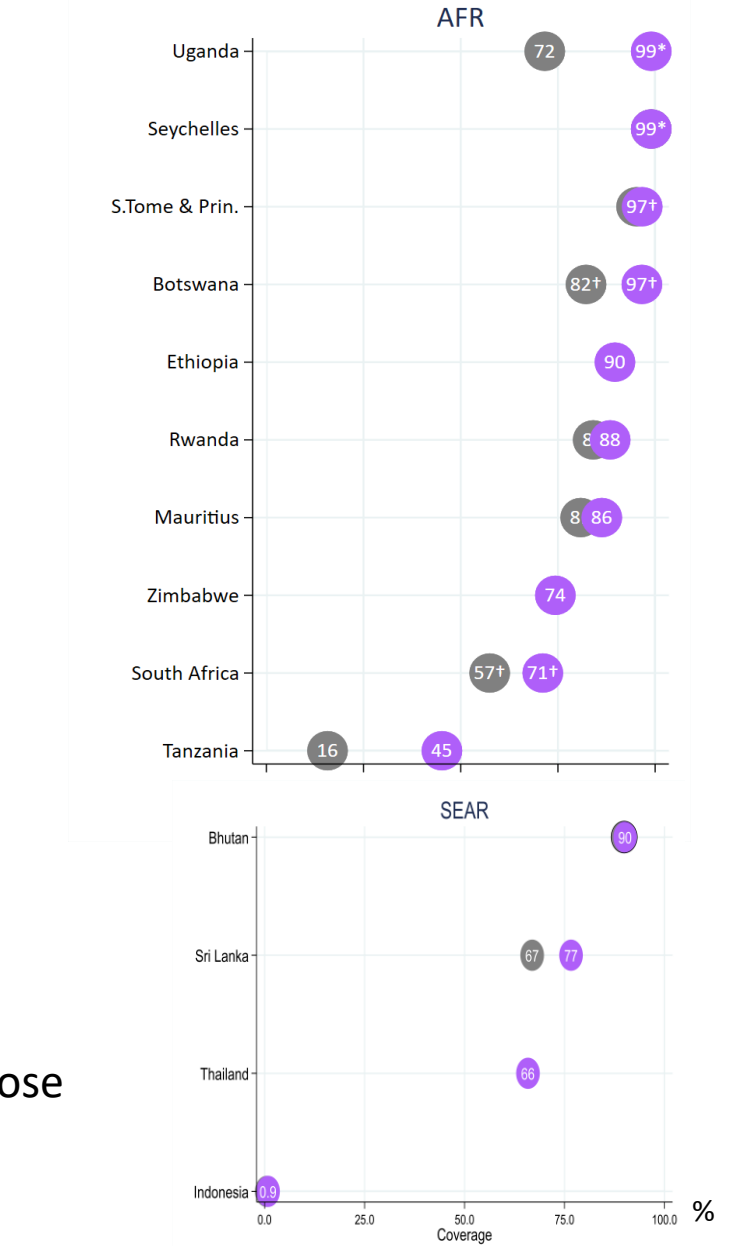
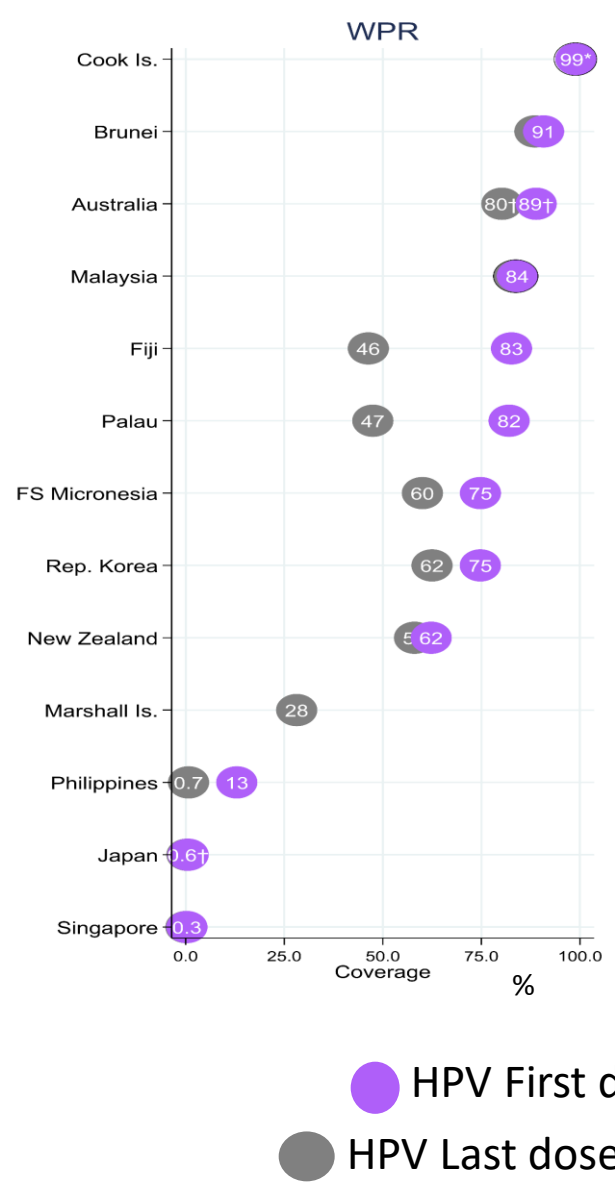
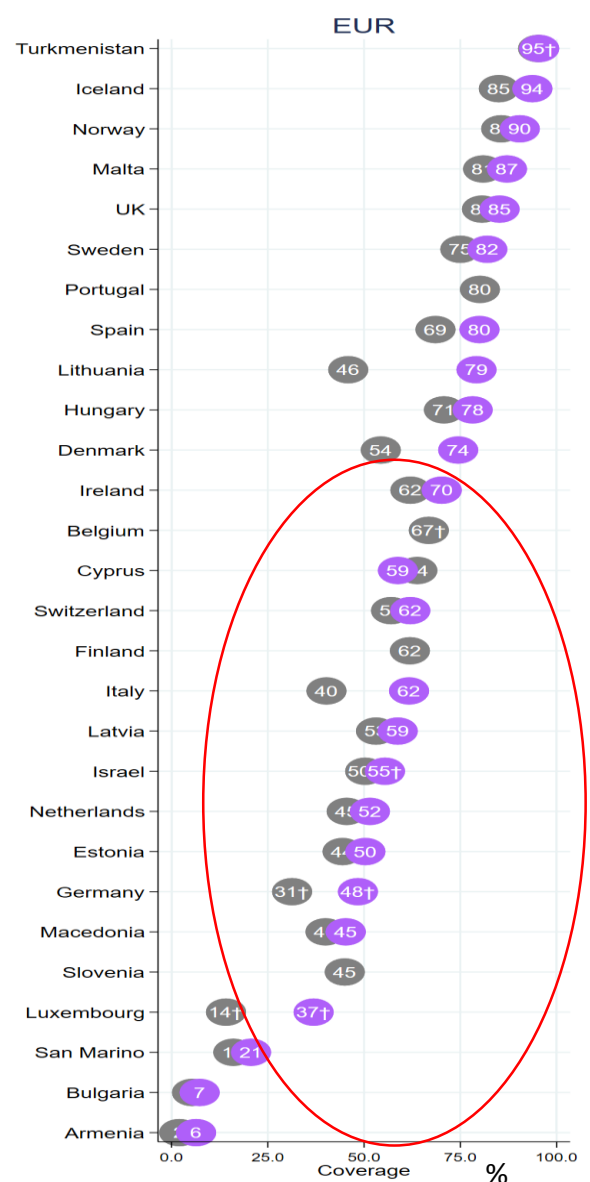
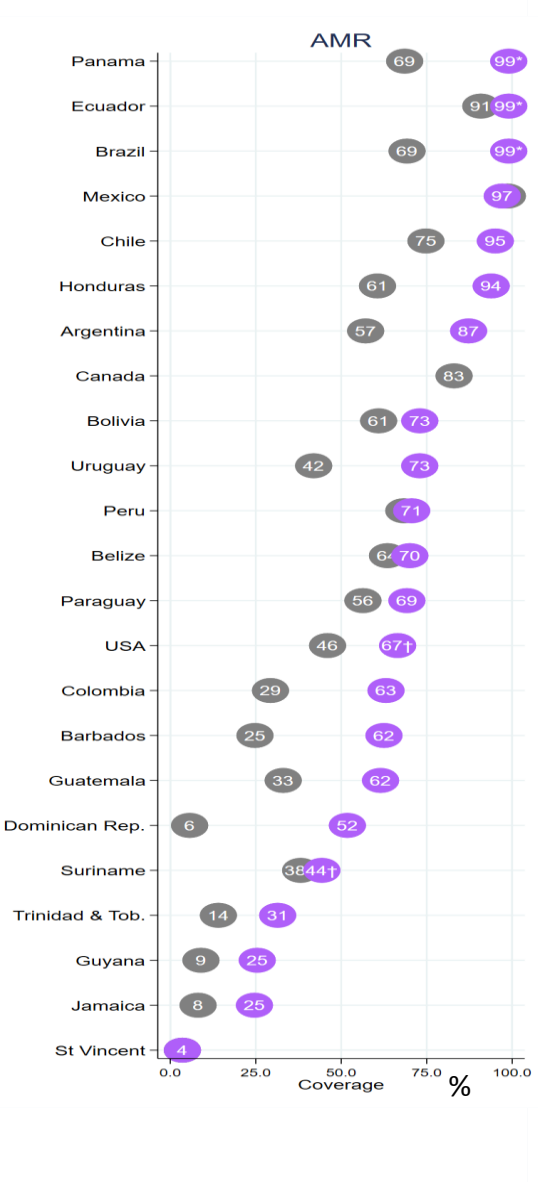


Proportion of Countries that have introduced HPV vaccine by *WHO region* and *WB Income level*



Source: IVB Database, 2 Oct 2019

ESTIMATES: HPV vaccine PROGRAM COVERAGE, FEMALES, 2018



Source: IVB Database, 15 July 2019

● HPV First dose
● HPV Last dose

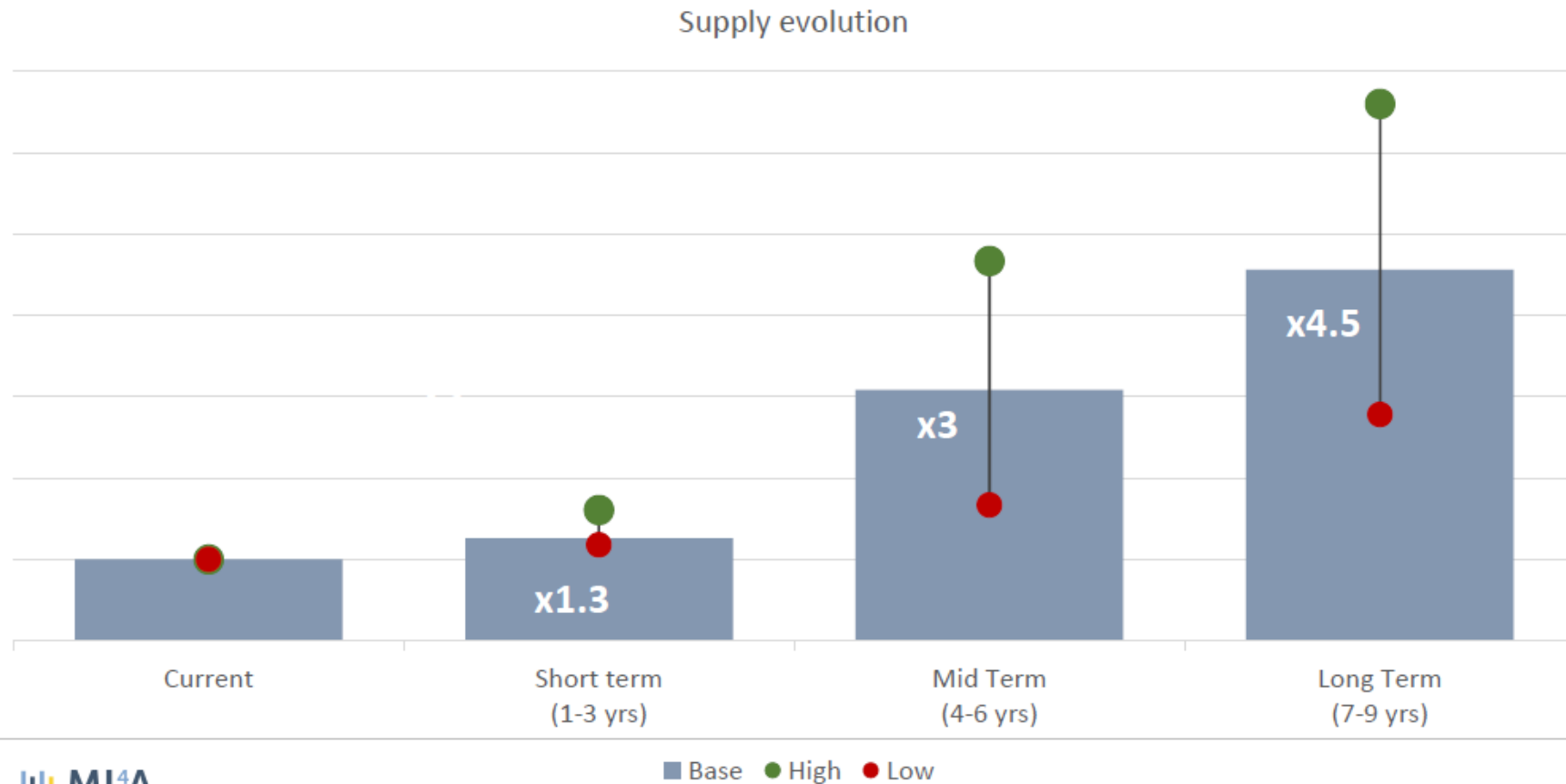
SUPPLY SHORTAGE

- Ongoing programmes generally receive vaccine supply they require - some stockouts, and supplier related challenges reported in PAHO
- Insufficient supply for overall GAVI countries demand - however all planned* 2019 GAVI supported HPV vaccine introductions are moving ahead with *routine cohorts* - Majority of planned Multi Age Cohort (MAC) postponed
 - * 11 countries planned, 10 received the final go-ahead for 2019, 4 of which with supply for MAC (smaller countries)
- 5 MICs have introduced in 2019 but at least one MIC has had to postpone introduction this year due to lack of supply

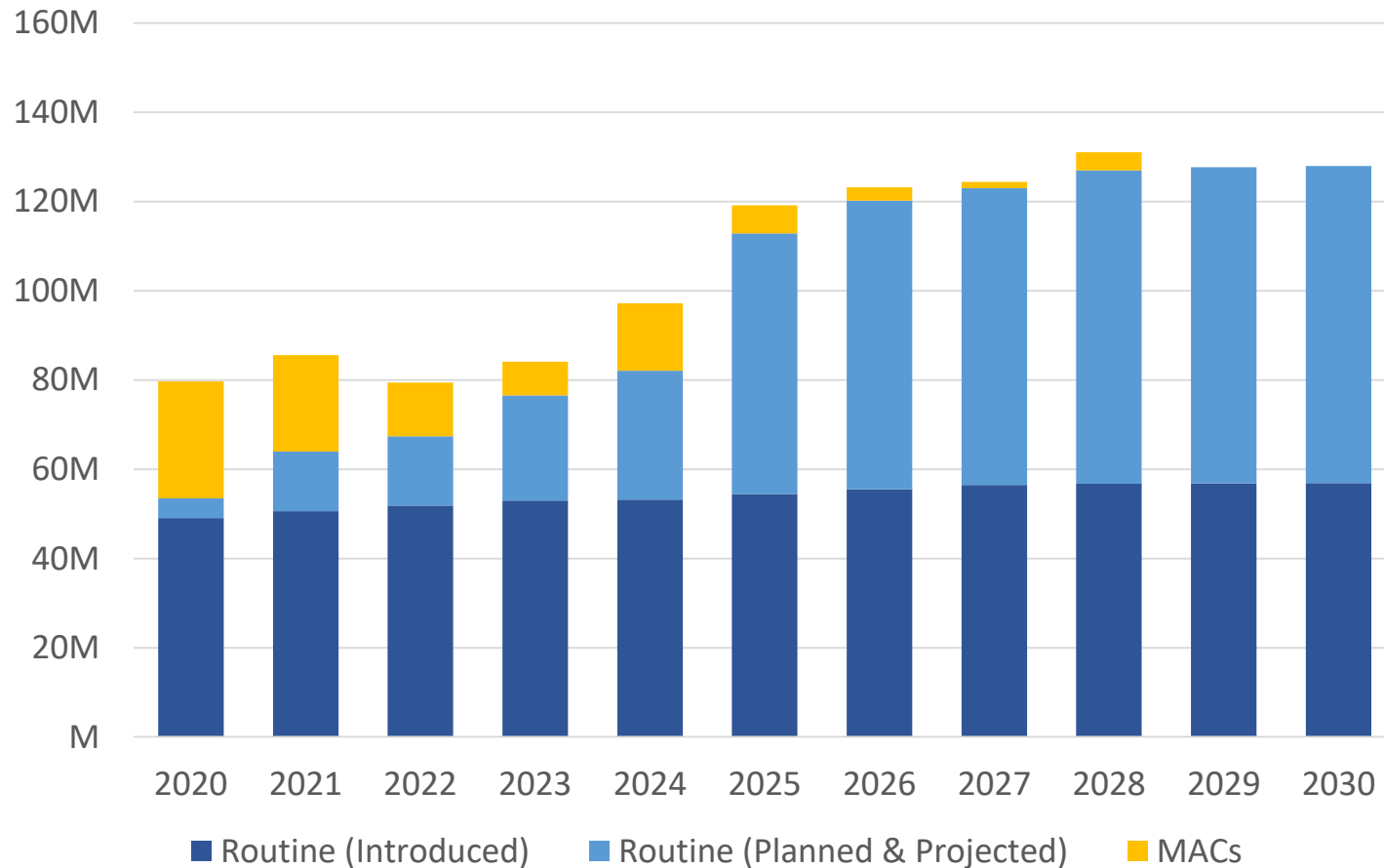


Supply to slowly grow in the short term, followed by steep ramp up from year 4-5

Available supply for commercialization may vary by +/-50% driven by manufacturers decisions and success in development/scale-up



Routine 2-dose scenarios (current recommendation)



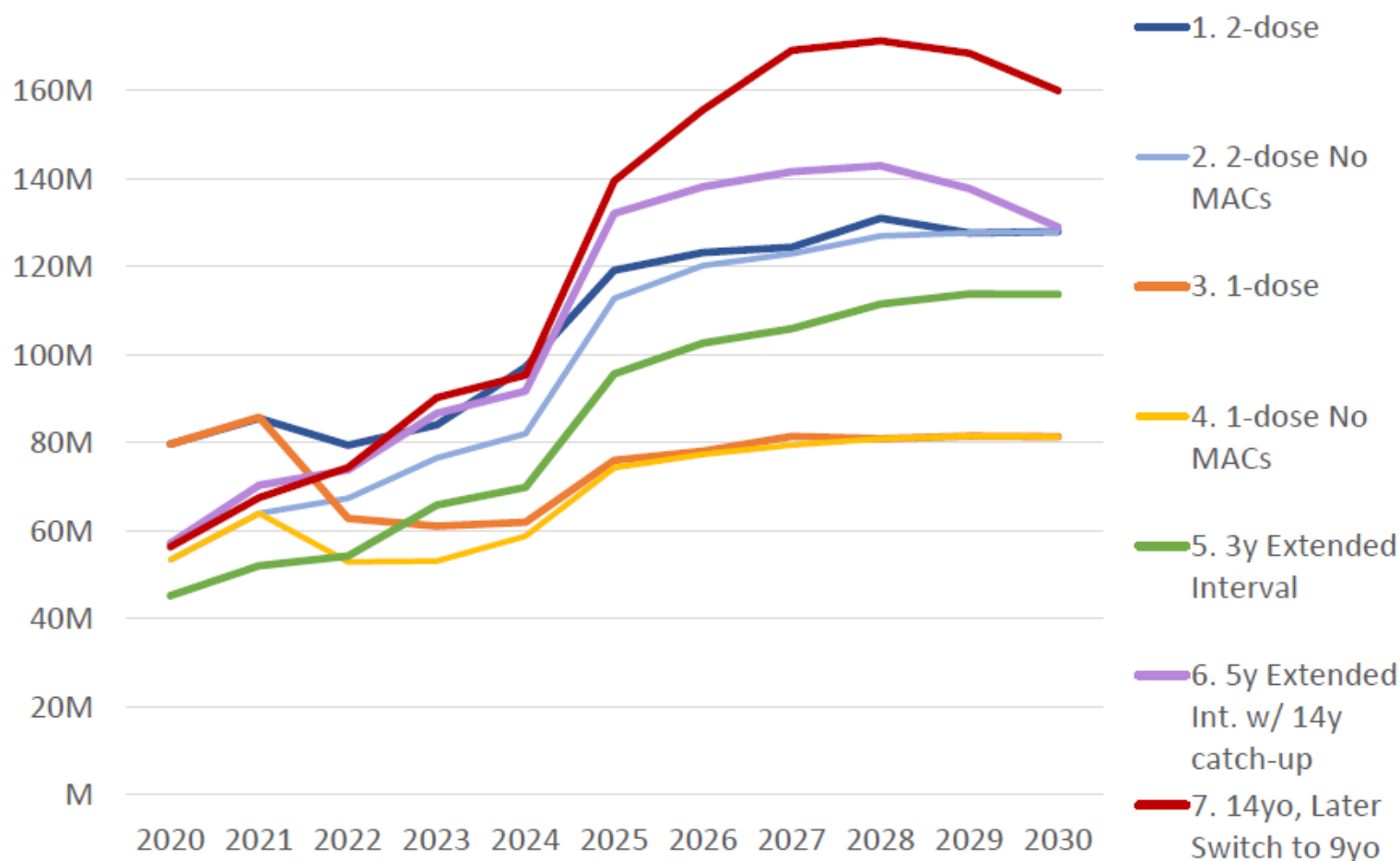
Assumptions:

- All countries introduce by 2029
- Gender neutral only in countries with existing recommendations
- *These apply to all scenarios, 1-7*

Results:

- Programmatic dose requirement reaches and stabilizes at ~120M doses in 2025
- MACs have been distributed across years, but remain an important contributor to dose requirement in the next 5 years

Comparing dose requirement across 7 scenarios



Results:

- Scenarios w/ MACs have the highest short-term programmatic dose requirement
- 3y extended interval results in lowest doses in the short-term
- One dose greatly reduces dose required in mid and long run
- 14yo with later switch to 9yo increases requirements considerably in the long run

Dynamic supply-demand balance

Demand Scenarios	Base Supply			Low Supply		
	Short-Term (1-3)	Mid-Term (4-6)	Long-Term (6-9)	Short-Term (1-3)	Mid-Term (4-6)	Long-Term (6-9)
#1 2-dose + MACs	Red	Green	Green	Red	Red	Red
#2 2-dose <u>No</u> MACs	Red	Green	Green	Red	Red	Yellow
#3 1-dose + MACs	Red	Green	Green	Red	Yellow	Green
#4 1-dose <u>No</u> MACs	Red	Green	Green	Red	Green	Green
#5 3y Extended Interval	Yellow	Green	Green	Yellow	Yellow	Yellow
#6 5y Ext. Int. + 14yo	Red	Green	Green	Red	Red	Red
#7 14yo, Later 9yo	Red	Green	Green	Red	Red	Red



As a result of persistent shortages in past years, demand has been influenced (e.g. MACs postponement, program delayed)



More extensive implementation of commercially attractive gender neutral and adult catch-up policies will influence balance



Refusal of specific products (based on valency or country of origin) constituting relevant share of supply would influence balance



Some countries delayed
Supply <1.1X Demand



No countries delayed
Supply <1.3X Demand



No countries delayed
Supply >1.3X Demand

Base Supply Detailed Results: Scenarios w/ MACs/catch-up

MACs and catch-up scenarios intensify supply constraints in the short term, with more introductions postponed

	Lives <u>Not</u> Saved due to supply constraints in specific countries not served		
	Short-Term (1-3)	Mid-Term (4-6)	Long-Term (6-9)
#1: 2-dose w/ MACs	143K (27 countries)		
#3: 1-dose w/ MACs	103K (23 countries)		
#6: 5y Ext. Int. + 14y catch-up	45K (10 countries)		
#7 14yo, Later Switch to 9yo	56K (21 countries)		

Of all alternative strategies, adoption of (#6) a 5 years extended interval between 1st and 2nd dose and (#7) intro in 14 yo with later switch to 9yo have the best outlook.



Base Supply Detailed Results: no MACs/catch up scenarios

Scenarios with no MACs/catch up contribute most to relieving supply constraints, allowing more countries to introduce sooner

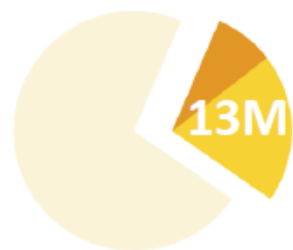
	Lives <u>Not</u> Saved due to supply constraints in specific countries not served		
	Short-Term (1-3)	Mid-Term (4-6)	Long-Term (6-9)
#2: 2-dose <u>No</u> MACs	20K (9 countries)		
#4: 1-dose <u>No</u> MACs	20K (9 countries)		
#5: 3y Extended Interval			

Adoption of a 3-years interval between 1st and 2nd doses from 2020 by all Gavi and PAHO RF countries further contributes to the improvement of the supply-demand balance freeing supply in the 2020-2021 critical period.

Impact of vaccinating boys for girls in low income/high burden settings



2019 demand for use in boys is **~9M** doses (18% of global demand)



Other HICs adding boys would require **additional ~4M** doses (1/3 Gavi demand)

Alternative use of doses: 9 low- and middle-income countries forecasted to have a delayed routine introductions in short term would be able to introduce

Implications: In short run, planned introductions would be delayed in **12** low- and middle-income countries.

Questions considered by the HPV vaccines SAGE Working Group

1. What is the current HPV vaccine uptake and what are the main barriers for access to HPV vaccines?
2. What does current evidence show on the immunogenicity and efficacy of a single dose of HPV vaccine; different intervals between the first and second doses of HPV vaccine and immunogenicity and efficacy of 2 vs 3 dose in 15-18 yr olds?
3. What are the potential demand scenarios and the supply of HPV vaccines (short and mid-term outlook) and what could one enhance HPV vaccine supply allocation?

How should HPV vaccination be prioritized with respect to **impact and feasibility**?



Summary one dose efficacy/effectiveness

Current evidence for most outcomes was of low to very low certainty due to limitations in study design and imprecision.

Evidence suggests that one dose results in higher GMTs than no vaccine, but lower than two or three doses.

There was inconclusive evidence for one dose on CIN 1, 2, and 3 compared to no vaccine, two doses, or three doses.

One dose may result in fewer HPV 16/18 infections than no vaccine, and little to no difference to two doses.

Removing sources of bias suggest there is little to no difference between one dose and two doses for the younger age groups (<16 years) for genital warts and CIN2+.

Study name (country)	Evidence type	Vaccine(s)	Brief description	2019	2020					2021				2022				2023				2024	2025
				Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4			
KEN SHE Kenya	Efficacy	HPV2 vs HPV9 vs MenACWY (delay HPV)	Girls 15-20 yo randomized to 1 dose of HPV2, HPV9, or MenACWY; n=750 each arm								★									★			
											18 months									Year 3			
ESCUDDO Costa Rica	Efficacy	HPV2 and HPV9	Girls 12-16 yo randomized to 1 or 2 doses of HPV2 or HPV9; n=5000 each arm																			★	
DoRIS Tanzania	Immunogenicity	HPV2 and HPV9	Girls 9-14 yo randomized to 1, 2, or 3 doses of HPV2 or HPV 9; n=155 each arm			★														★			
						24 months																	
Primavera Costa Rica	Immunogenicity	HPV2 and HPV4	Girls 10-13 yo 1-dose HPV2 immunobridge to women 18-25 yo 3-doses HPV4; n=520 each																	★		★	
																				24 months		36 months	
HANDS The Gambia	Immunogenicity	HPV9	Girls 4-8 yo and 9-14 yo randomized to 1 or 2 doses; girls 15-26 yo given 3 doses; n=344 each arm								★									★		★	
											24 months									36 months			
India IARC India	Efficacy	HPV4	Girls 10-18 yo received 1, 2, 3 doses of HPV4; n=17586, 1-dose n=4980	★					★													★	
				10 yr f/u					11 yr f/u													★	
																						★	
CVT Costa Rica	Efficacy / Immunogenicity	HPV2 vs control	Women 18-25 yo received 1, 2, or 3 doses of HPV2; n=3727, 1-dose n=196	★																		★	
				13 yr f/u																		15 yr f/u	
Thailand impact study Thailand	Effectiveness	HPV4	Girls in grade 8 given 1 or 2 doses; n=~8000 each arm prevalence surveys of girls grades 10, 12; n=2,400 each grade x 2 provinces																			★	
																						Year 2	
																						Year 4	
HOPE South Africa	Effectiveness	HPV2	Girls 17-18 yo serial prevalence surveys: unvaccinated (17-18 yo), 1-dose catch up (15-16 yo), and 2-dose routine (9 yo) cohorts; n≥3260																			★	
																						★	

RCTs
 Non-randomized RCTs
 Impact effectiveness studies

★ Interim results
 ★ Final results

SAGE recommendations on HPV (Oct 2019)

1. For the prevention of cervical cancer, the WG reaffirms the (2017) WHO recommendations for the use of HPV vaccines:

- Primary target: 9-14 years old girls, 2-dose schedule, Interval minimum 6 months, no maximum suggest 12-15m for programmatic reasons.
- HIV+ and females ≥ 15 years : 3-dose schedule

2. All three licensed HPV vaccines have excellent safety, efficacy, immunogenicity and effectiveness profiles, and are comparable for the prevention of cervical cancer.



SAGE recommendations on HPV (Oct 2019)

3. SAGE is deeply concerned that the current HPV vaccine shortage could result in failure to introduce or sustain HPV vaccine programmes in some countries, particularly those with a high burden of cervical cancer. In this context of limited supply of HPV vaccine, SAGE recommends the following additional strategies:

Countries should temporarily postpone implementation of gender-neutral, older age group (≥ 15 years) and multi-age cohort HPV vaccination strategies until all countries have access to HPV vaccine. This will significantly relieve supply constraints in the short term and enable allocation of doses to high-burden countries currently planning to introduce this vaccine.

NNV for any HPV-related cancer

Girls in Uganda = 78 <-> Girls Canada = 560

Boys Canada = 5,480

Middle age adults US = 8,500+

SAGE recommendations on HPV (Oct 2019)

4. Countries may, in consultation with their national immunization technical advisory groups (NITAGs), consider alternative strategies to ensure that girls receive two doses of HPV vaccine before the age of sexual activity, as appropriate to the individual national context

The [following alternative strategies](#), which require careful consideration of the programmatic challenges and clear, well-planned communication, are recommended:

- A To retain the accelerated impact of vaccinating multi-age cohorts (MACs), countries could [target an older cohort of girls \(e.g., 13 or 14 years old girls or in an equivalent school grade\)](#), who are close to initiating sexual activity and thus of high risk of exposure and in whom a high 2-dose coverage can be achieved.

Once the vaccine supply situation has improved, countries could then consider: (i) Continuing with this strategy (i.e., targeting older girls) if high 2-dose coverage is being achieved; or (ii) Shifting to a strategy of targeting younger girls (9 or 10 year old or lower school grade) if vaccinating older girls results in low coverage rates or high drop-out rates between doses 1 and 2 or if vaccination is occurring after the age of sexual activity.



SAGE recommendations on HPV (Oct 2019)

4. ...the following alternative strategies are recommended: *(Continued)*

- B. To temporarily reduce vaccine supply needs, countries could adopt a “1+1” schedule with an extended interval of 3-5 years between doses for younger girls (e.g., first dose provided at 9 or 10 years old or lower school grade) and taking measures to ensure that the girls receive two doses each. This strategy constitutes an *off-label use* of the vaccine.

This off-label use is justified considering evidence that:

- One dose is better than no vaccine. Some emerging evidence suggests likely protection after one dose.
 - A low risk of exposure between dose 1 and 2 is assumed in this young age group.
 - However, it requires careful consideration for programmatic challenges (capacity to trace girls later, registration, reminder systems) and risk considerations (age of onset of sexual activity)
5. SAGE calls upon WHO and its partners to urgently convene a dialogue on global access to HPV vaccine, engaging all relevant stakeholders including vaccine manufacturers.



Key Messages

- No change in WHO HPV Policy, 2-dose recommendation for all girls 9-14 yr old
- Urge to reach high coverage among girls and postpone or pause plans for vaccination males and adults (15+) until global supply has improved
- In case of supply challenges countries encourages to use 1+1 schedules or - in case of stock out - catch up any missed girls before reaching 15 yrs of age
- All countries that have not done so yet are encouraged to introduce HPV as soon as possible.
- Encourage programmes to monitor performance and intervene rapidly in case of decreases due to hesitancy & safety events.
- Low performing countries to develop *redesign* and HPV vaccine coverage improvement plans based on careful assessment



Thank You

HPV Vaccine Introduction Clearing House

Visit each area for related resources:



POLICY & DECISION-MAKING

Informing national decision-making for HPV vaccine introduction



PLANNING

Planning for HPV vaccine introduction



FINANCING

Budgeting and financing for HPV vaccine introduction



VACCINES & SAFETY

Characteristics, presentations and safety profiles of HPV vaccines



COMMUNICATION

Communicating effectively using research-based approaches



IMPLEMENTATION

Delivering HPV vaccination programmes



MONITORING & SURVEILLANCE

Monitoring the coverage and impact of HPV vaccine programmes



HPV PARTNERS

Links to HPV partners and resources