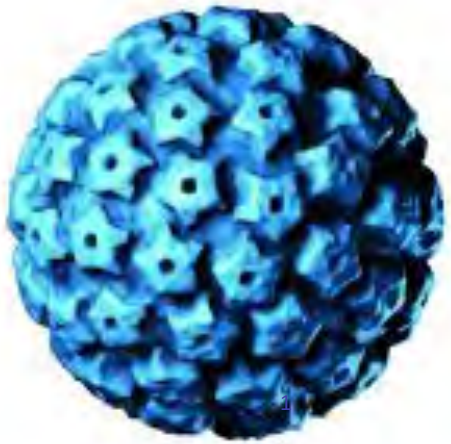
HPV vaccine

Session introduction and key questions

6 April 2022

Rakesh Aggarwal, SAGE Member
Chair, HPV Vaccine Working Group



WHO position on HPV vaccines (2017)

WHO recommends countries to implement HPV vaccination by vaccinating a routine targeted cohort of girls in the age range of 9-14 years and provide multi-age-cohort (MAC) vaccination at the introduction year (up to age 18)

- ❑ Target groups
  - Primary target group: Girls 9-14 years old
  - Secondary target group: Older girls (≥15 years), and males
- ❑ Vaccination schedule
  - Two doses Girls 9-14 years old
  - Three doses Girls ≥ 15 years, or immunocompromised

Human papillomavirus vaccines: WHO position paper. Wkly Epidemiol Rec 2017; 92: 241–68.

SAGE recommendations on HPV (Oct 2019)

- Countries should temporarily postpone implementation of boys, older age group (≥15 years) and MAC 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

Alternative strategies:

- To retain the disease impact of MACs, target an older cohort of girls (e.g. those who are 13 or 14 years old or in a higher school grade)
- To reduce vaccine supply needs, adopt a "1+1" schedule with an extended interval of 3-5 years between doses for younger girls (e.g. 9 or 10 years old or in a lower school grade)

Source: https://www.who.int/wer/2019/wer9447/en/

Evidence on single-dose HPV since 2019

- Since the SAGE meeting in 2019, evidence on single-dose HPV vaccine has been accumulating
- 2021: Publication of data from several studies implemented to definitively assess the potential for single-dose HPV vaccine as a routinely recommended schedule
- April 2021: Therefore, the SAGE HPV WG was reconvened to reassess the evidence on single-dose HPV vaccination strategy and to identify the remaining research needs

SAGE HPV WG composition: Members

- ***Rakesh Aggarwal*** (Chair) Jawaharlal Institute of Postgraduate Medical Education and Research, India
- **Punnee Pitisuttithum**(SAGE member), Mahidol University, Thailand
- **Neerja Bhatla**, All India Institute of Medical Sciences, India
- **Silvia Franceschi**, Centro di Riferimento Oncologico, Italy
- **Eduardo L. Franco**, McGill University, Canada
- **Suzanne Garland**, Murdoch Children's Research Institute, Australia
- **Lauri Markowitz**, Centers for Disease Control and Prevention, USA
- **Andrew J. Pollard**, University of Oxford, UK
- **You-Lin Qiao**, Peking Union Medical College, China
- **Helen Rees**, Wits Reproductive Health and HIV Institute , South Africa
- **John Schiller**, National Cancer Institute, USA
- **Margaret Stanley**, University of Cambridge, UK

SAGE HPV WG composition: Secretariat

• WHO (Immunization, Vaccines and Biologicals)	**Paul Bloem** (HPV vaccine lead) **Tracey Goodman** **Hiroki Akaba** **Christoff Steffen** **Joachim Hombach** **Tania Cernuschi** **Raymond Hutubessy**
• WHO (Reproductive Health and Research)	**Nathalie Broutet**
• WHO (HIV, Hepatitis and STIs)	**Shona Dalal**
• WHO contractor	**Julia Brotherton**

Questions considered by the Working Group

1. What evidence gaps exist and what research is recommended to enable SAGE to make a universal one-dose HPV schedule recommendation?

2. Should an off-label, permissive one-dose HPV vaccine schedule be recommended for use
    - In multi-age cohort (MAC) catch-up?
    - In routine cohorts?

Today's Agenda

Agenda	Presenter	Estimated time (min)
Session introduction and key questions	Rakesh Aggarwal, SAGE member	5
Update on progress of HPV vaccine introduction and coverage	Paul Bloem, WHO	8
Global market study on HPV vaccines, 2022 update	Tania Cernuschi, WHO	10
Evidence from clinical trials to inform decision-making on reduced HPV vaccination schedules	Lauri Markovitz, WG member	12
Systematic review of evidence on single HPV vaccination	Nicholas Henschke, Cochrane Response	10
Modelling evidence on the impact of 1-dose strategies	Marc Brisson, Laval University	10
Discussion and Q&A on evidence		35
Conclusions and proposed recommendations of the SAGE Working Group	Rakesh Aggarwal, SAGE member	10
Discussion on recommendations		40

Progress in HPV vaccine introduction & reaching the 2030 target of 90% coverage

an update

SAGE meeting

April 6, 2022

Paul Bloem
HPV vaccine strategy lead
WHO IVB Geneva

World Health Organization

Global strategy to accelerate 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

HPV vaccination estimated to avert > 45M deaths over next 100 years

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

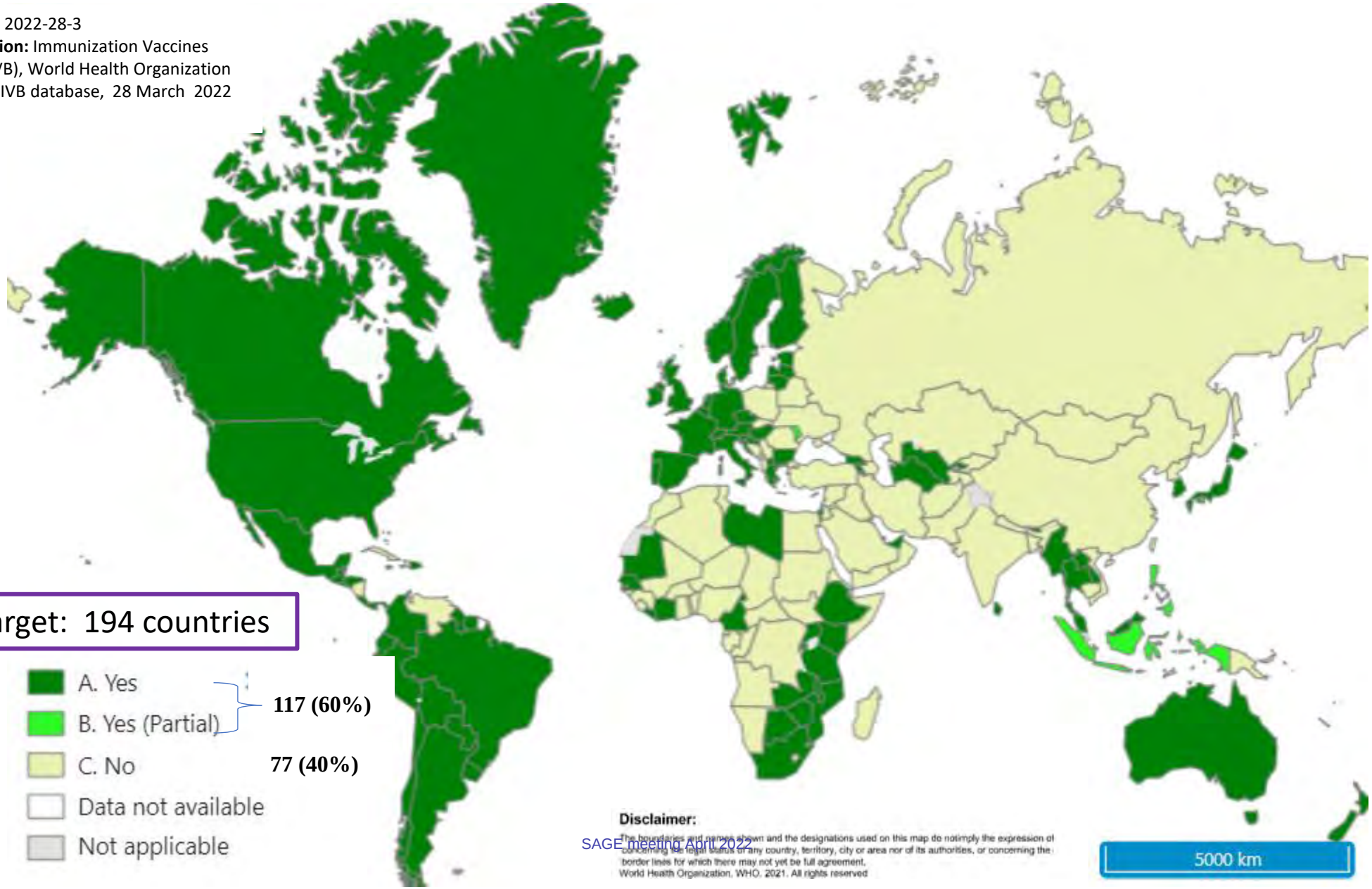
90%

of women identified with cervical disease receive treatment and care

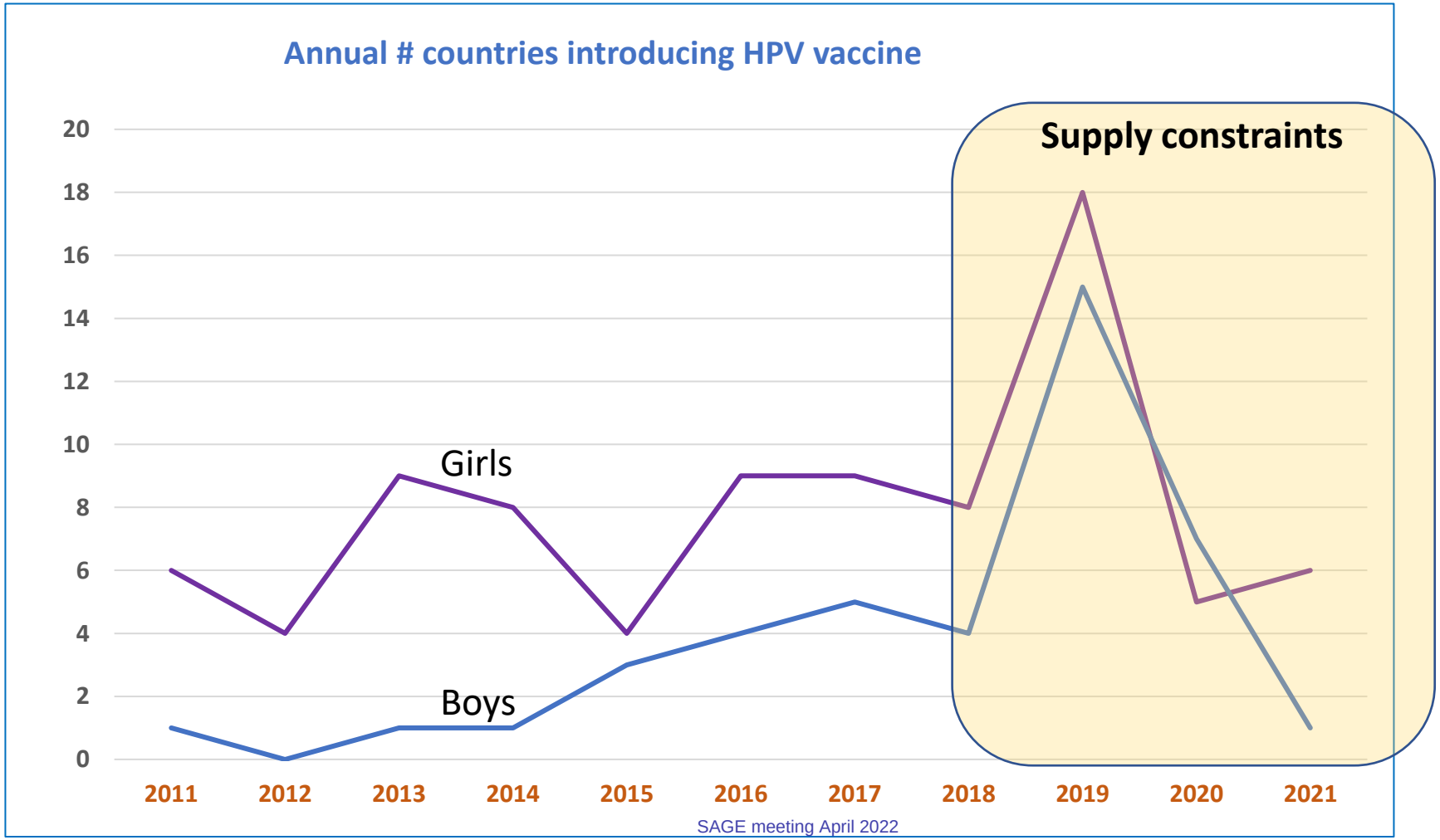
SDG 2030: Target 3.4 – 30% reduction in mortality from cervical cancer

Countries with HPV vaccine in the national immunization programme

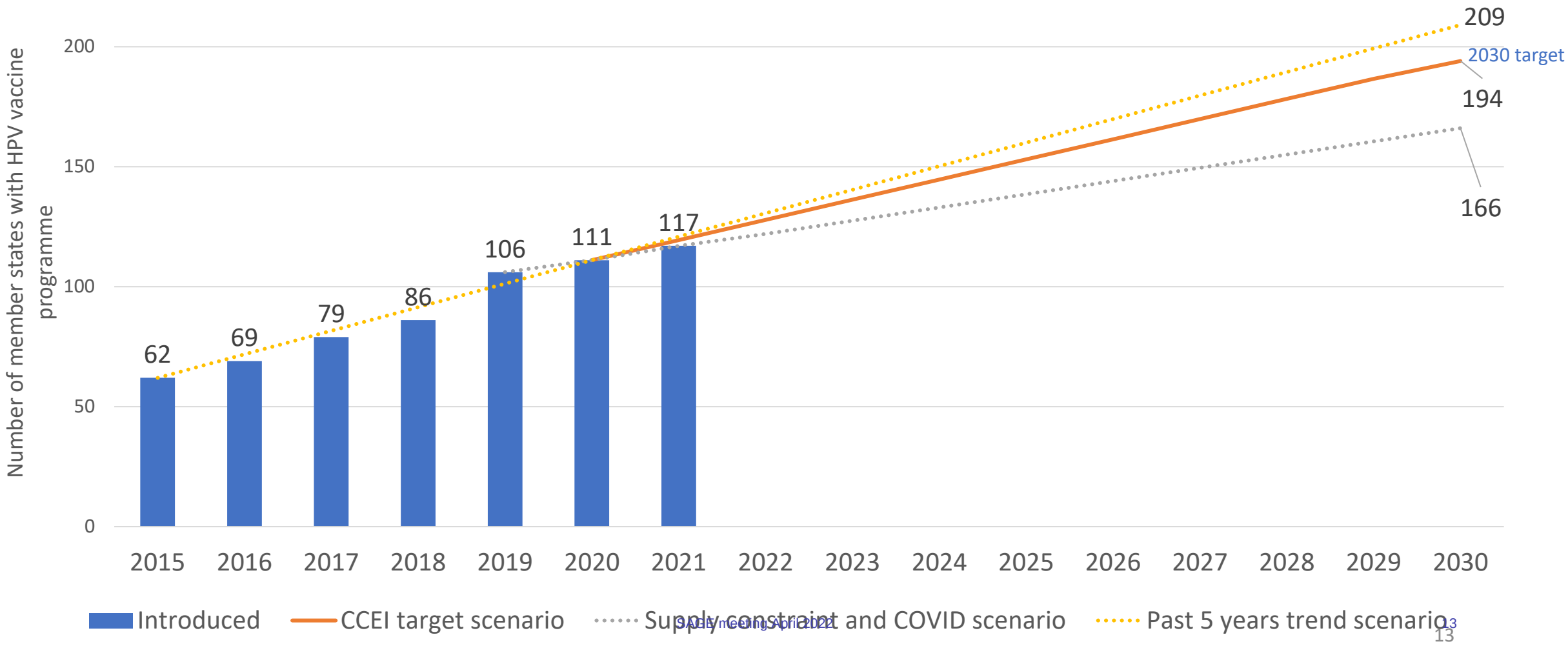
Date of slide: 2022-28-3
Map production: Immunization Vaccines Biologicals (IVB), World Health Organization
Data Source: IVB database, 28 March 2022



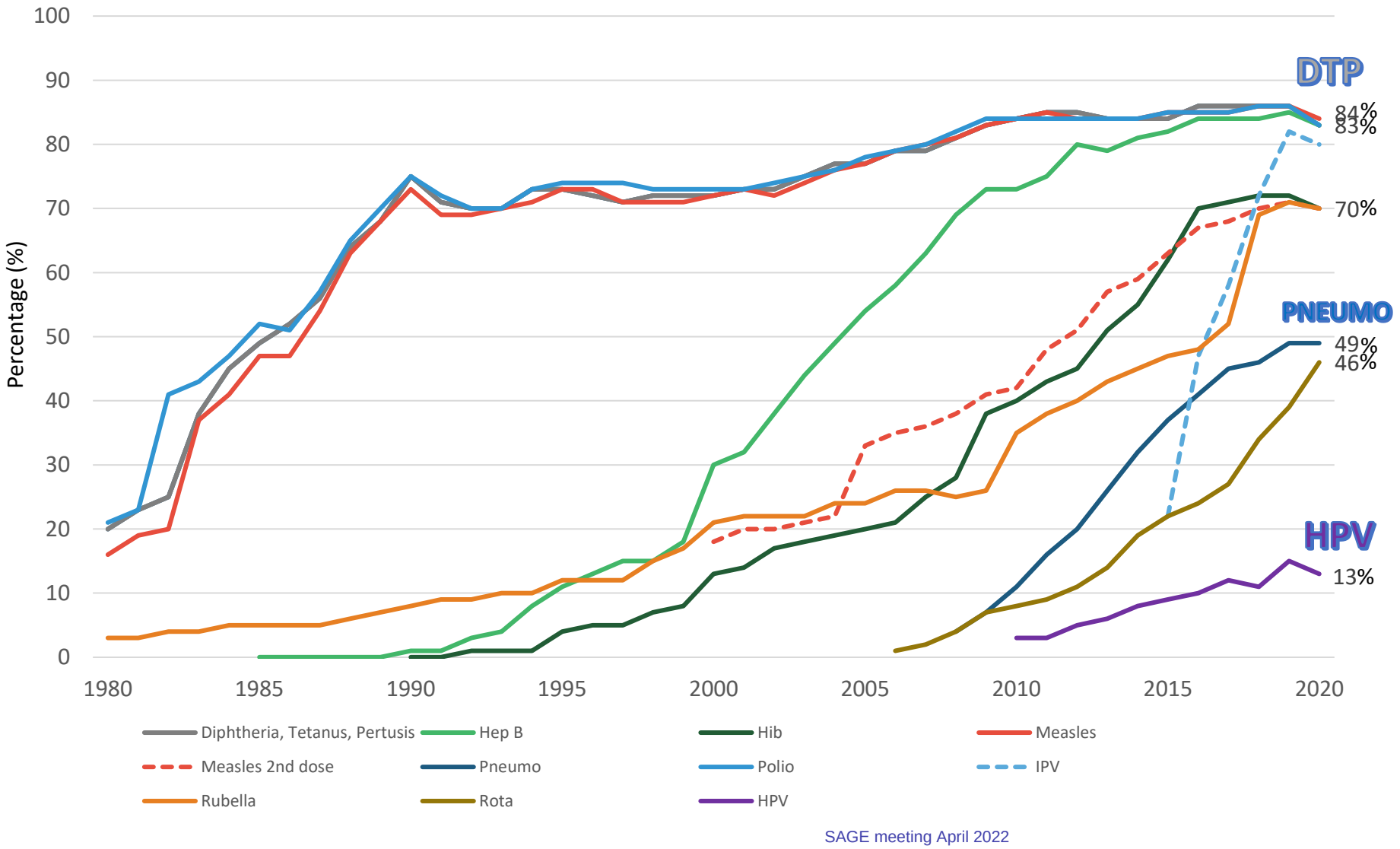
Trends in HPV vaccine introduction



Return to historic trend level needed to reach Global Cervical Cancer Elimination Strategy 2030 Target

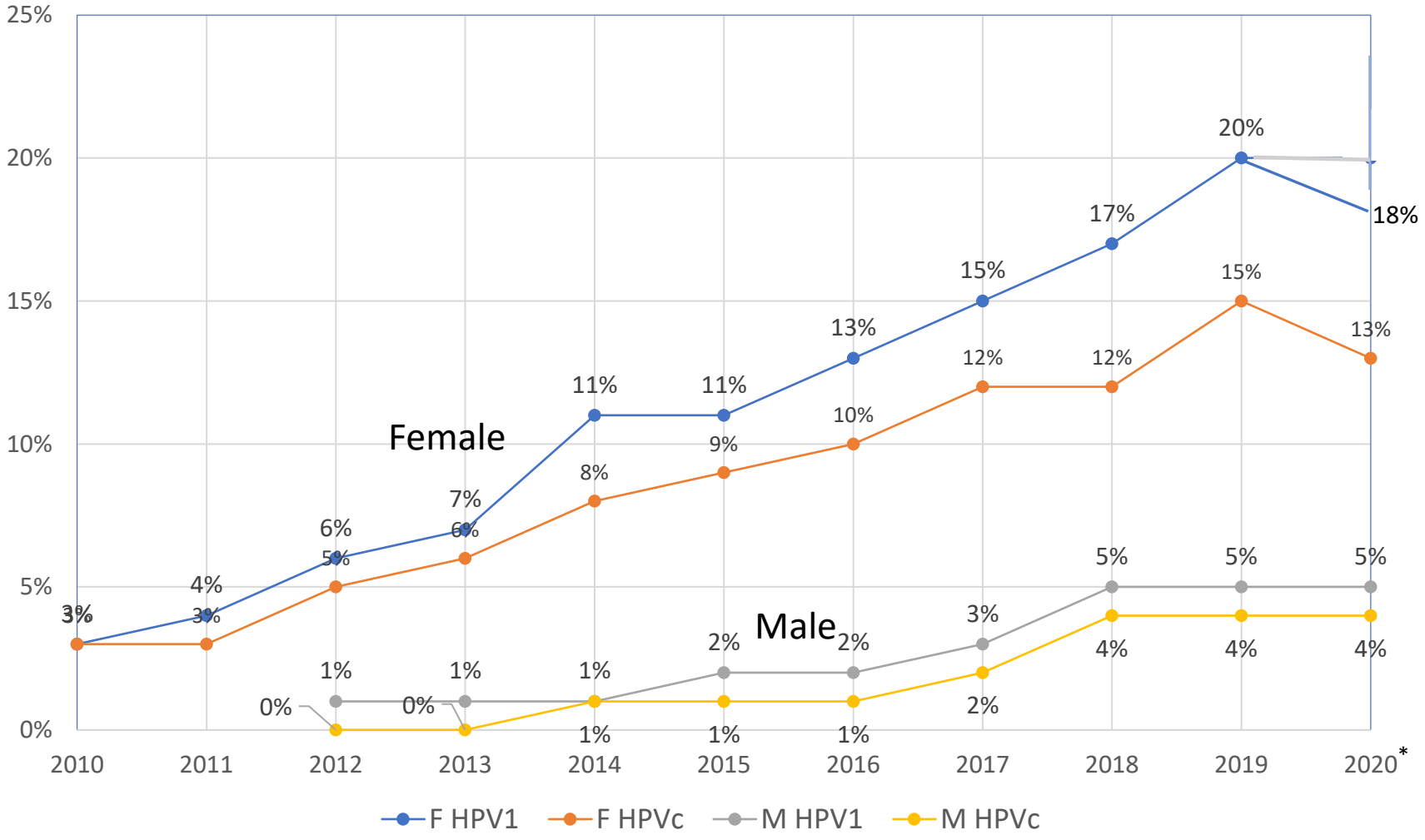


Global HPV Coverage remains low compared to childhood vaccines and other new vaccines



SAGE meeting April 2022

Global HPV vaccine coverage decreased - for the first time - in 2020



*2020 non reporting countries imputed using extrapolation from 2019 level with mean change by WHO region (15 July 2021)

HPV vaccine coverage was affected by COVID-19 pandemic and only 13% of girls are fully protected.

Currently less than third of the world's population of girls 9-14 years of age live in countries that provide the HPV vaccine.

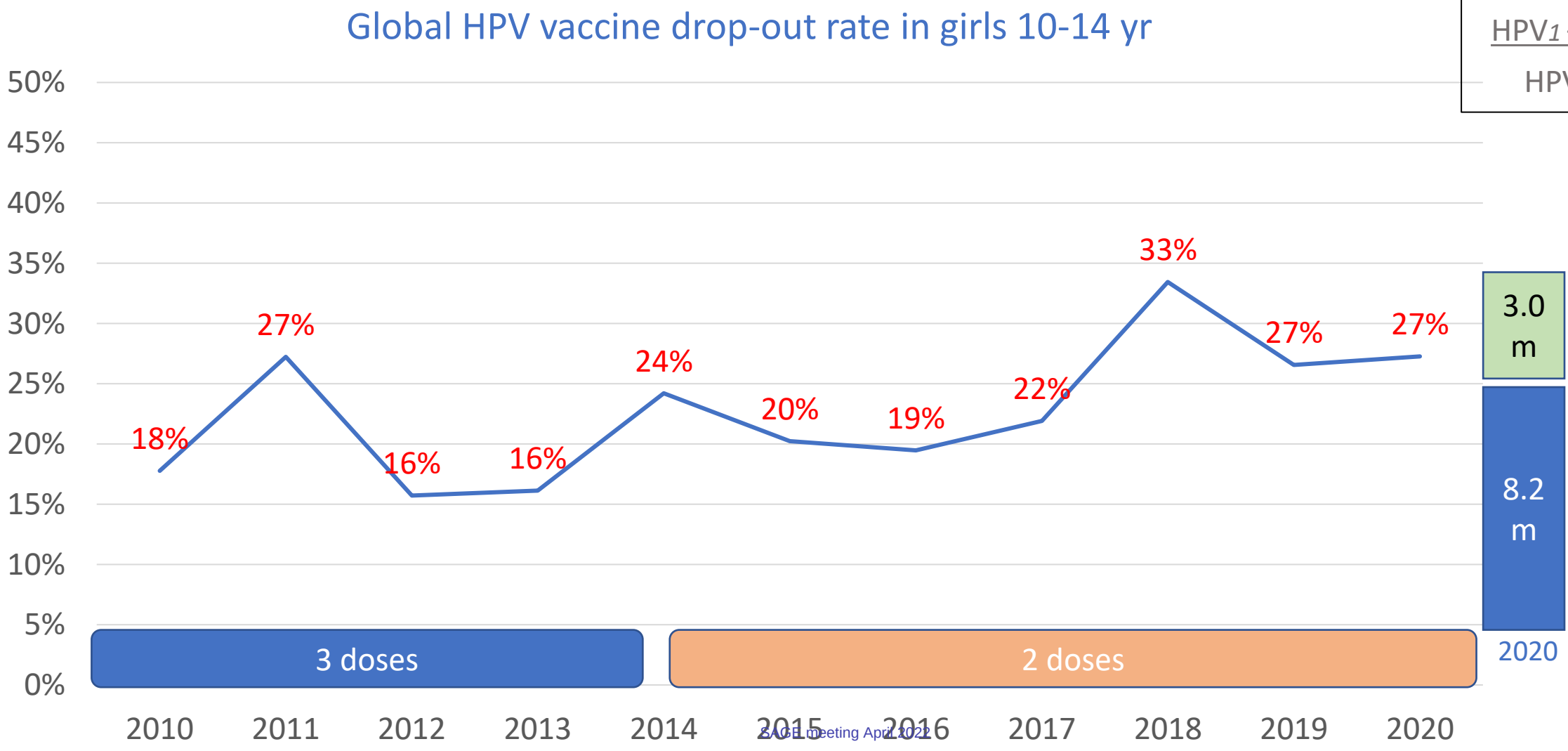
More countries now provide Male vaccination.
Over a third of all HPV programmes provide the vaccine to males.

unicef World Health Organization

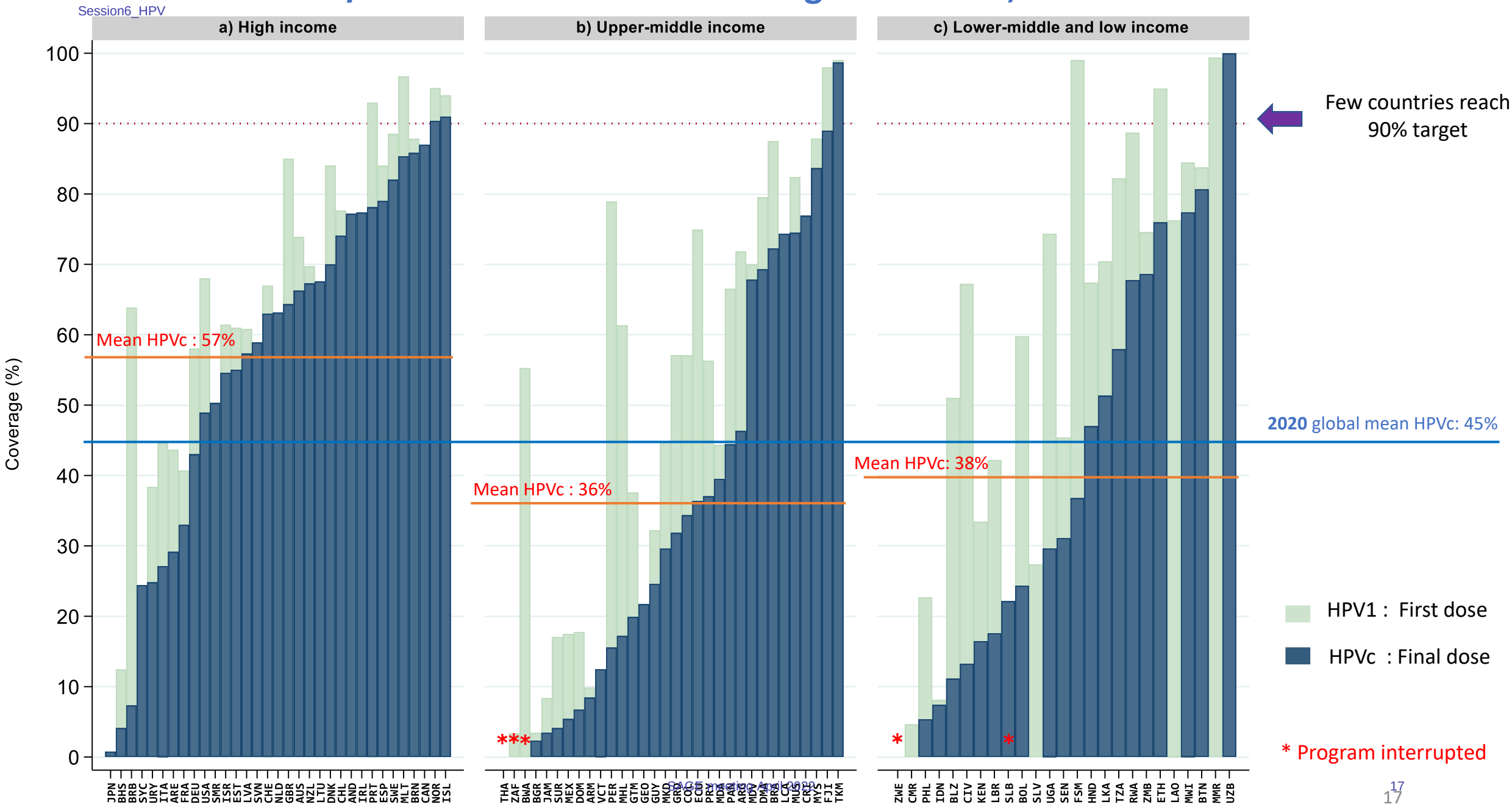
Historically, high drop out rates for HPV vaccine

Dropout rate =

$$\frac{\text{HPV}_1 - \text{HPV}_{final}}{\text{HPV}_1 \times 100}$$

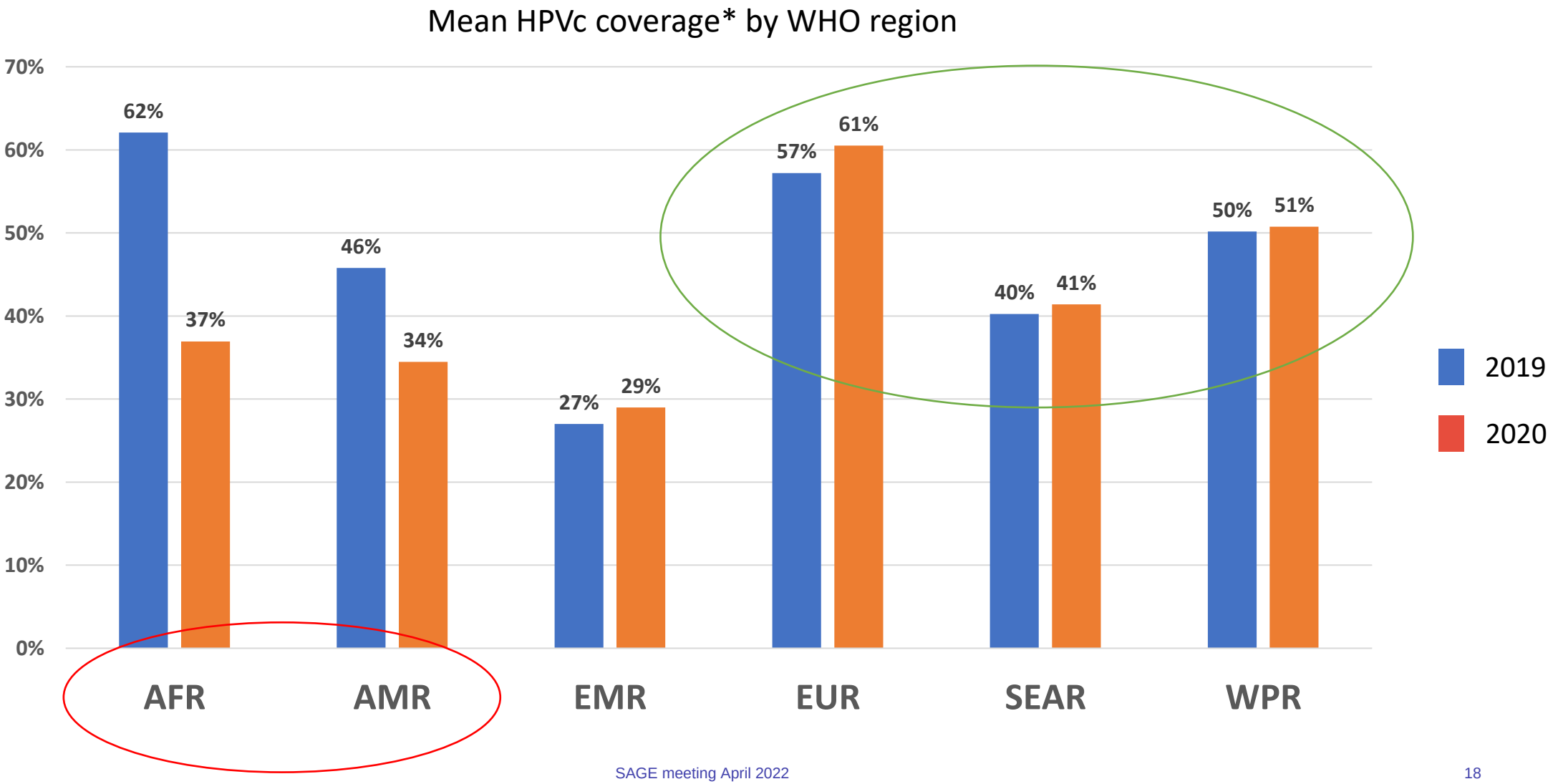


WHO/UNICEF HPV vaccine coverage estimates, 2020



Source: WHO/UNICEF (2021)

Africa and Americas regions most strongly affected by COVID



*Among countries with data for both years (Oct 2021)

Concluding observations

- HPV introduction rate slowed in recent years - affected by supply constraints & not on track for 2030 target.
- HPV vaccine coverage is suboptimal in most countries and high drop out indicate programmatic challenges.
- COVID affected programme coverage, particularly in UMIC &LMICs and recovery efforts urgently needed.
- COVID impact on L/MICs' capacity to introduce HPV in coming years uncertain.

HPv Global Vaccine Market Study 2022 update

WHO SAGE Meeting – 6 April 2022

Tania Cernuschi – WHO/UHC-LC/IVB

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Global Supply

Available Supply for Commercialization

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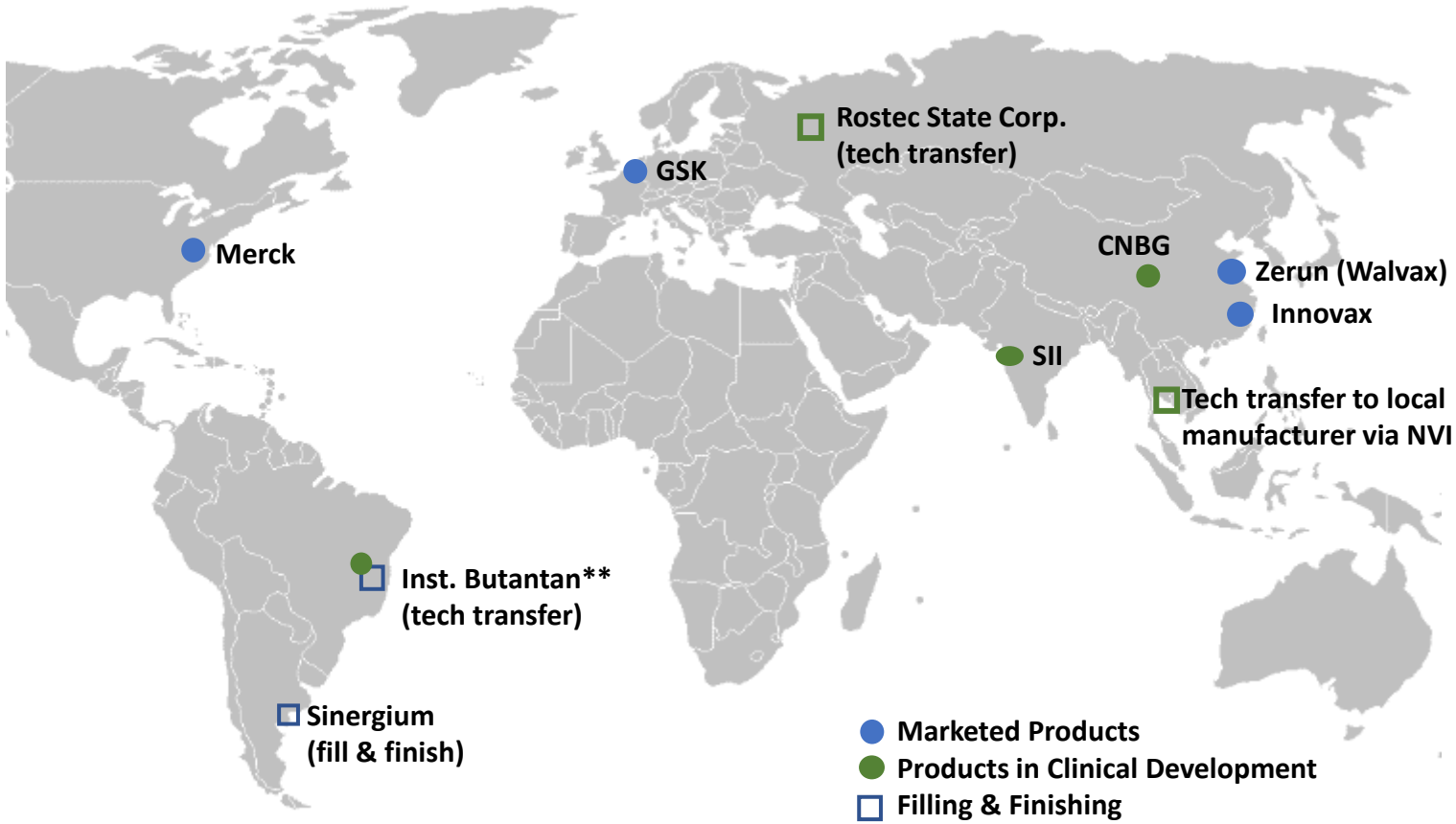
A supplier base in fast evolution



Merck Gardasil 4v & 9v	<u>Licensed globally / WHO prequalified</u> Adjuvant: Alum Sched.: 2 doses (9-14) or 3 doses (15+) Pres.: 1 dose vial (PQ) / PFS (non PQ)
GSK Cervarix 2v	<u>Licensed globally / WHO prequalified</u> Adjuvant: AS04 Sched.: 2 doses (9-14) or 3 doses (15+) Pres.: 1,2 dose vial (PQ)/ PFS (non PQ)
Innovax Cecolin 2v	<u>Licensed in China / WHO prequalified</u> Adjuvant: Alum Schedule: 2 doses (girls 9-14) or 3 doses (women 15-45) Presentation: 1 dose vial / PFS
Walvax 2v	*<u>Licensed in China (March 2022)</u>* *Adjuvant: Alum* *Schedule: 2 doses (girls 9-14) or 3 doses (women 15-30)* *Presentation: 1 dose vial*
SII **4v**	*<u>Phase III – ongoing*</u>* *Adjuvant: Alum* *Schedule: 2 or 3 doses* *Presentation: 1,2,5 doses vial*
CNBG **4v**	*<u>Phase III – ongoing*</u>* *Adjuvant: Alum* *Schedule: 3 doses* *Presentation: 1, 3, 5 doses vial*

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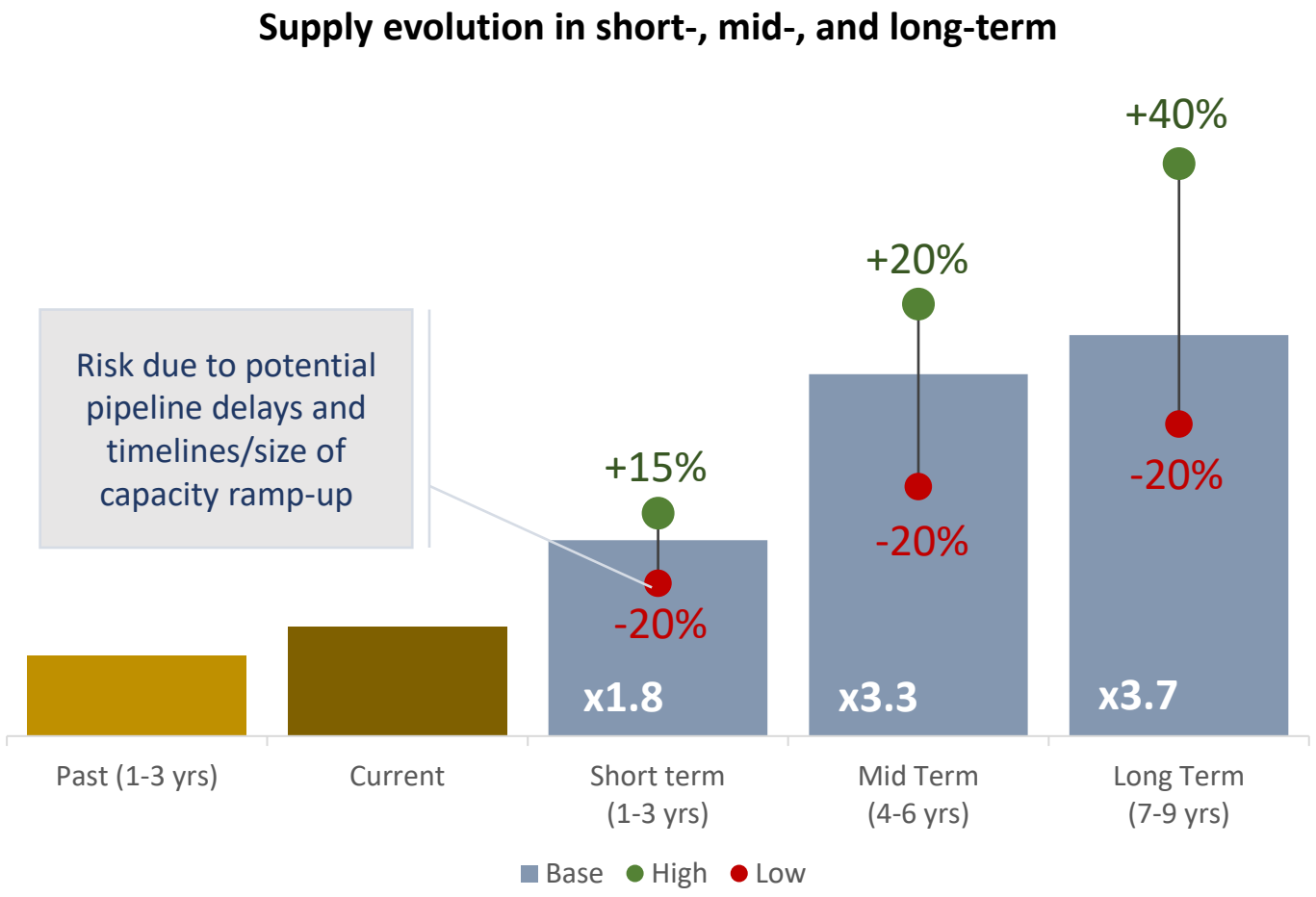
Disclaimer: map does not reflect the WHO / UN views
** Immunobridging study is sufficient for licensure in India - CIN2 efficacy is required in China*
*** Product in clinical development based on tech transfer*
BLA: Biologics License Application

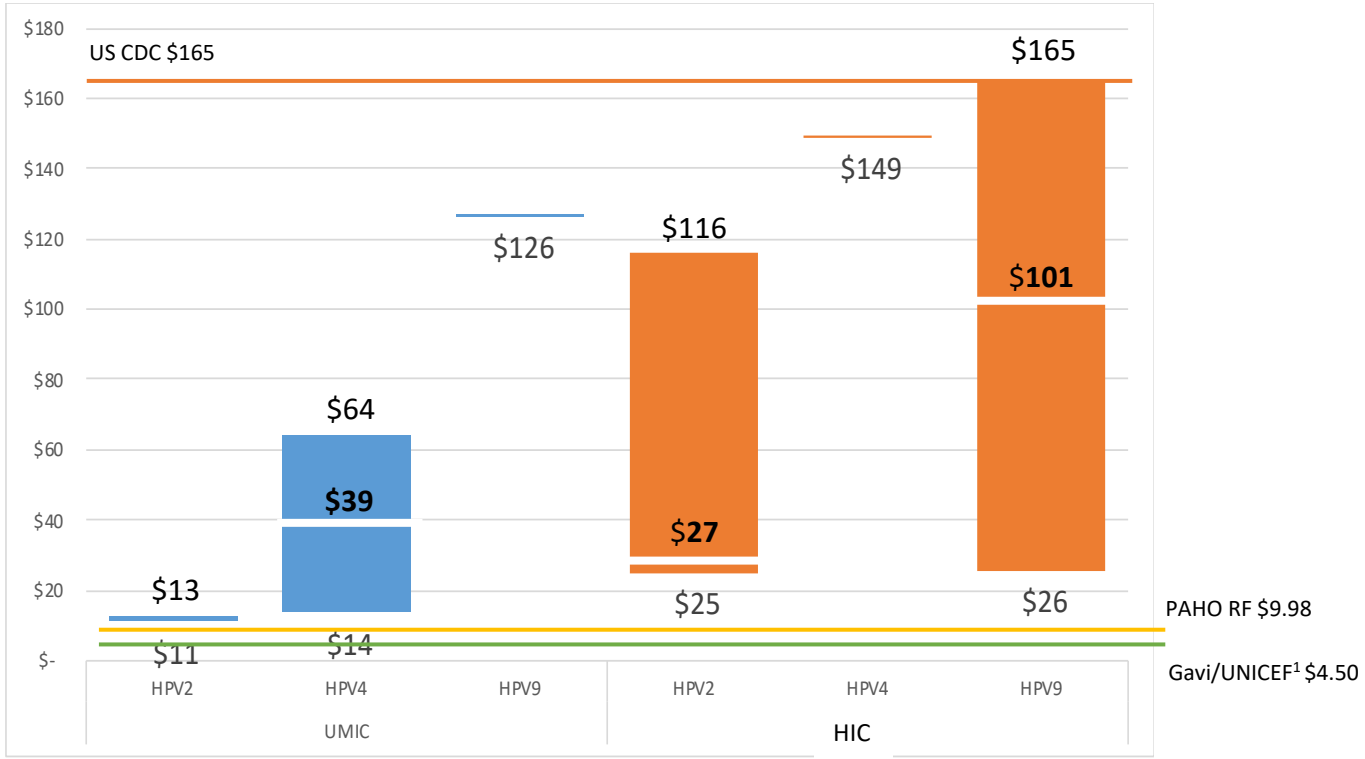
Updated as per March 2022

Available supply expected to increase with steep mid-term ramp-up



- In recent years, **Available supply for commercialization (ASC) grew approximately 15% per year**, but insufficiently to serve demand.
- Some moderate impact of delays in pipeline/registration and slower capacity dev. have been recorded lately.
- In **mid-long-term, available supply will increase significantly**, driven by manufacturer's development/scale-up efforts (ultimate size of increase will be influenced by demand)
- Currently, **supply dominated by one manufacturer**. In second half of decade, 9 valent to become dominant with entrance of new manufacturers (up to 4)

HPV Vaccine Prices



- The reported price per dose of HPV vaccines shows a **tiered structure by procurement method and income group**, though with important overlap
- The self-procuring MICs median price is significantly higher than Gavi and PAHO, creating **affordability barriers** for some
- HPV **price is also tiered by valency** albeit with significant overlaps
- UNICEF'S **contracted price for Innovax's product starting in 2022 is $2.90 per dose –** not yet leveraged

Median values in bold
Source: 2021 MI4A Purchase Data (country-reported)
Note: Reduction in Gavi/UNICEF price is the result of new products being available. Gavi/UNICEF will pay this price when countries elect to introduce the relevant product into their national immunization systems.

Global Demand

Programmatic Dose Requirement

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Health agents are pictured during the first day of the yellow fever vaccination campaign in Kinshasa, on August 17, 2016.

© WHO /Eduardo Soteras Jalil

HPV global demand has been on a steady rise even if historically constrained by supply

Global demand has grown throughout the last decade to exceed 80m doses. After the impact of the COVID-19 pandemic, **demand is expected to start recovering its growth starting from 2022-23**.

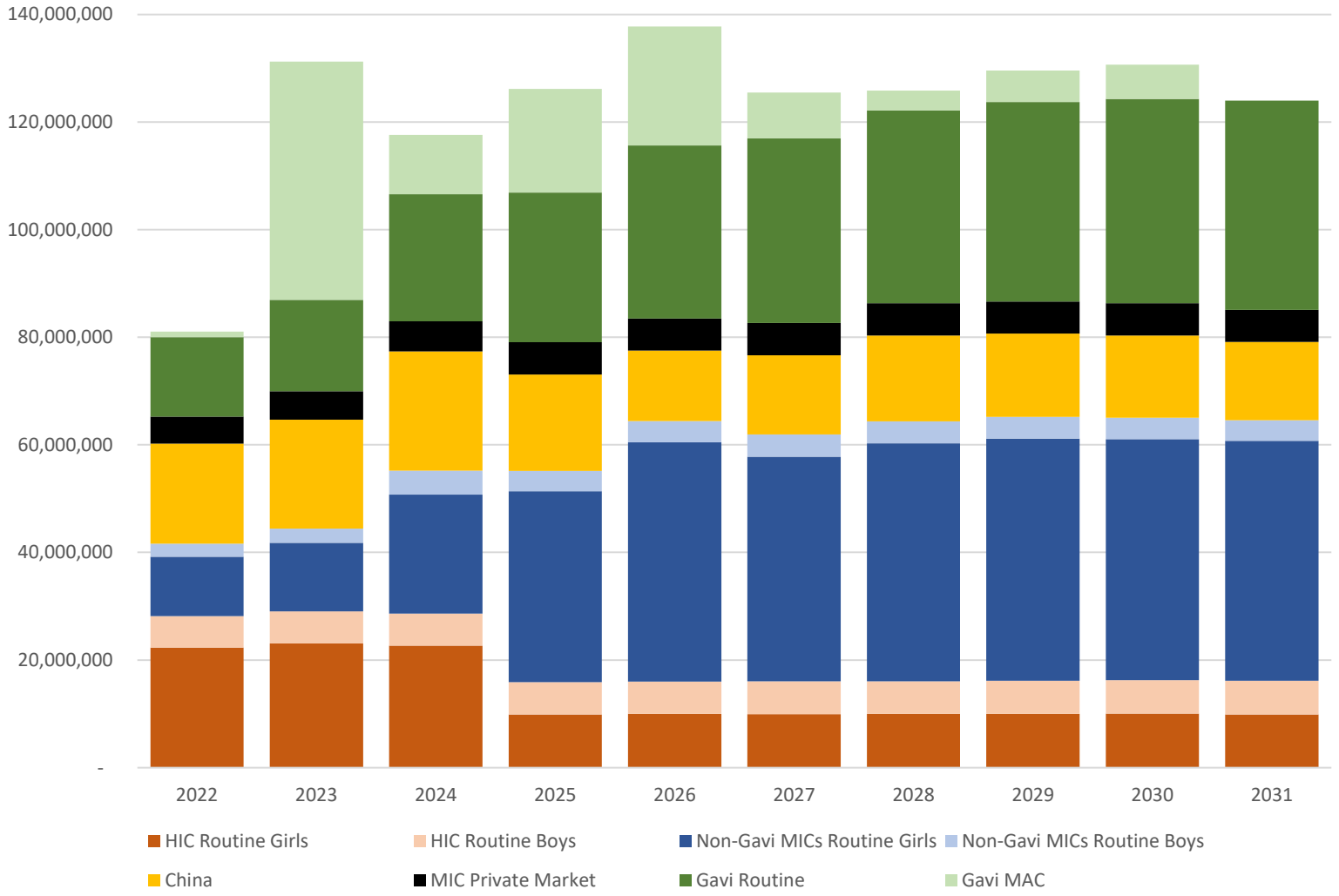
The future evolution of demand and market dynamics in short and long term can shape differently depending on key policy decisions. The following scenarios have been simulated:

	Routine	MACs	Boys
Base case	2-dose (age 9, interval 0,6 months)	2-dose (10-14 years)	Only currently active programs
Base case + Boys	2-dose (age 9, interval 0,6 months)	2-dose (10-14 years)	All HICs and MICs from 2023*
1 dose	1 dose (age 9) from 2023	1-dose (10-14 years) from 2023	Only currently active programs
1 dose + Boys	1 dose (age 9) from 2023	1-dose (10-14 years) from 2023	All countries from 2023*
Elimination	2-dose (age 9, interval 0,6 months) All countries reach 90% coverage	No	Only currently active programs

*with gradual rampup over 3 years

Base case to stabilize on 125m doses PDR*

Unconstrained



Assumptions:

- All countries introduce by 2028[1,2]
- Gender neutral only in countries with existing recommendations[3]
- China switch from 3-dose to 2-dose schedule in 2025

Results:

- PDR to reach ~140M in 2026 and **stabilizes at ~125M** doses by 2031
- **MACs remain an important contributor to dose requirement**
- **Most demand growth** outside of HIC countries (i.e. **in non Gavi MICs and Gavi-supported** countries)
- Forecasted boys vaccination requires approx. 10M doses per year, comprising ~ 10% of total PDR

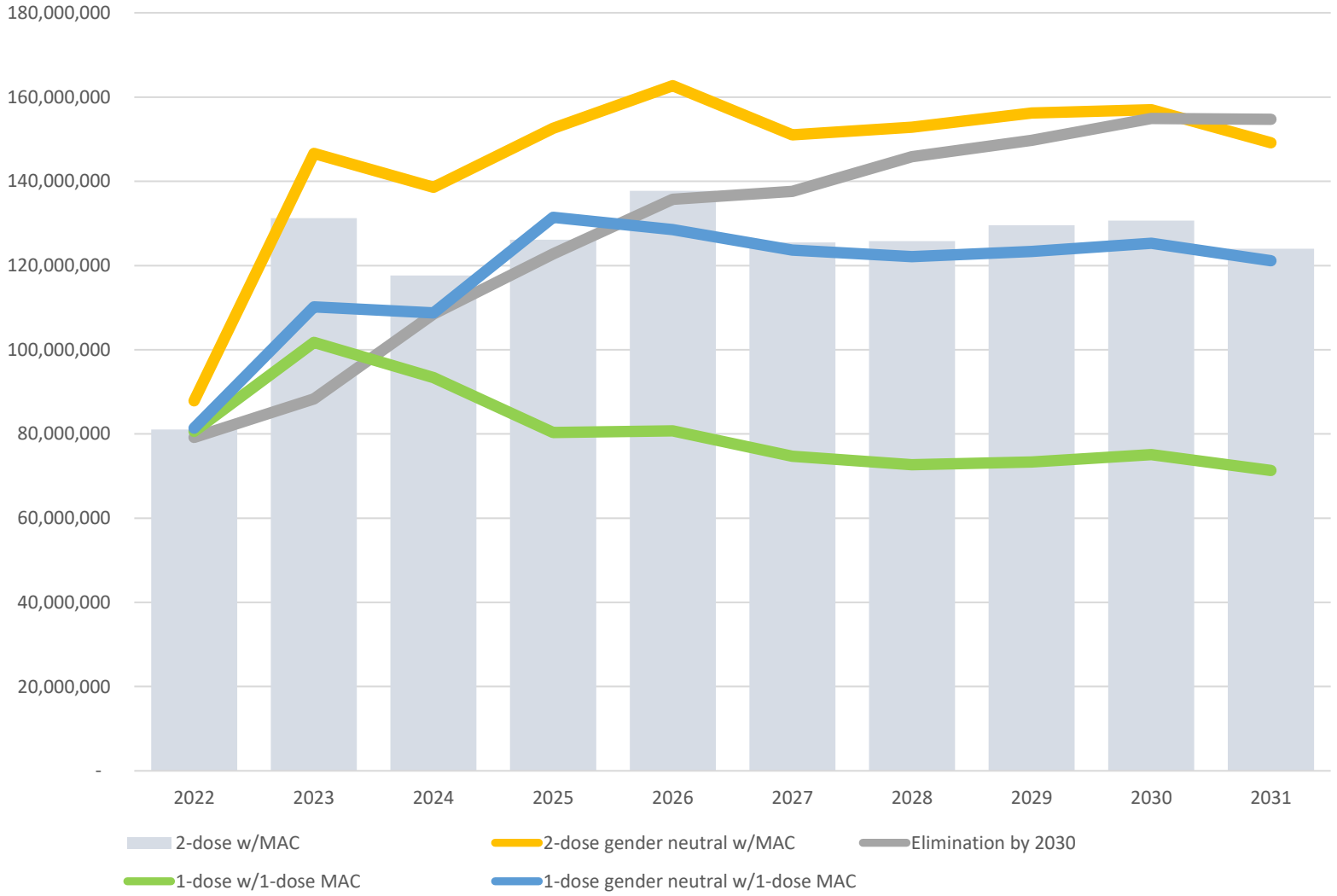
Note: Gavi demand is comprised of 72 Member States and does not include India

1. China: national, girl-only introduction in 2025, assumes switch to 2-dose schedule
2. India: phased, girl-only introduction between 2024-2026
3. Gender neutral strategies are recommended exclusively in some HICs and UMICs

*PDR = Programmatic dose requirement

Comparison of HPV PDR between key scenarios

Unconstrained



- **Boys' vaccination in all HICs and UMICs** increases PDR by 18% between 2022-2031 compared to base case
- **1-dose** (routine and MAC) scenario stabilizes at ~70M doses by 2028
- **1-dose (routine and MACs) with boys' vaccination** stabilizes at ~120M doses by 2031 - at the same level as base case
- **Elimination scenario** grows steadily to above 150M doses

PDR = Programmatic dose requirement

Global supply-demand balance

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Decreases in demand coupled with supply increases led to reduction in risk of global shortages included in short/term

	Base Supply			Low Supply		
Demand Scenarios	**Short-Term (1-3)**	**Mid-Term (4-6)**	**Long-Term (6-9)**	**Short-Term (1-3)**	**Mid-Term (4-6)**	**Long-Term (6-9)**
2-doses (routine & MACs) *Base case*						
2-doses (routine & MACs) & Boys						
1-dose (routine & MACs)						
1-dose (routine & MACs) & Boys						

Insufficient supply
Supply <1.1X Demand

Some risk of shortages
Supply <1.3X Demand

No risk of shortages
Supply >1.3X Demand

Excess supply
Supply > 2X Demand

Important assumptions of global supply/demand balance: No mismatch between available products and country preferences

*Single dose schedule supporting data assumed available since 2022 only for a limited number of products

Key takeaways

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Key takeaways from updated market study

Decreases in demand due to active demand management and the impact of COVID-19, coupled with supply increases over recent years led to **significant reduction in the risk of <u>global</u> shortages**

Short term

Supply remains tight and given limited buffer, **careful phasing of MACs and countries willingness to use any of the available HPV vaccines** will be the most critical aspects to ensure all countries can access supply

Attention also required to the implementation of **large catch-up campaigns in older age cohorts** and to the widespread adoption of strategies **targeting boys vaccination**

Mid-term

A healthy supply situation will likely be reached in 2024 with comfortable buffer as result of existing suppliers capacity expanding and success of pipeline candidates achieving licensure and WHO prequalification (albeit with small volumes)

Mid- long- term

Active management of supplier base required from 2026-27 when significant excess supply is expected to avoid supply disruption and reduction of competition as result of potential unforeseen market exits

Impact of widespread adoption of 1-dose schedule

Short term

Further **improvement of the supply-demand balance**, allowing for higher supply flexibility

Expansion of the HPV program with available supply (adoption of boy vaccination and/or older age cohorts), or

Mid- long- term

Rapid **reduction in global programmatic dose requirement**

Could impact the sustainability of the HPV market including through price changes and/or market exits. **Requires careful management**, including through generation of evidence for single-dose efficacy for all products.

Thank you

For more information see full **HPV Global Market Study 2022 Update** here:

https://www.who.int/publications/m/item/who-hpv-vaccine-global-market-study-april-2022

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Evidence from clinical trials to inform decision-making on reduced dose HPV vaccination schedules

Summary of key data

Lauri Markowitz, MD

SAGE HPV Work Group Member

SAGE Meeting, April 6, 2022

Efficacy and immunogenicity data for initial licensure of HPV vaccines, 3-dose schedules

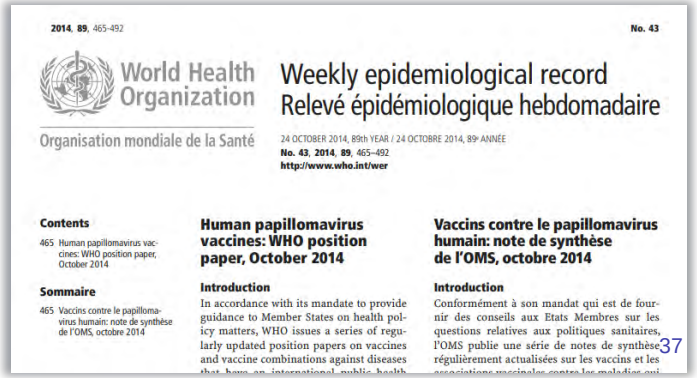
- **Randomized controlled trials in ~15–26-year-old women**
  - Trial endpoints: cervical precancer lesions*
  - Efficacy against vaccine-type endpoints over 96% in per protocol analyses
  - Seroconversion one month after last dose close to 100%

- **Bridging immunogenicity trials in 9–15-year-olds**
  - Licensure/authorization in this age group based on non-inferior antibody response compared with that in young adult women in efficacy trials

*Future II Study Group, NEJM 2007; Garland, et al. NEJM 2007; Paavonen, et al. Lancet 2007
Quadrivalent vaccine trials had other outcomes as well including, vulvar, vaginal precancers in females, genital warts

Transition from 3-dose to 2-dose schedule for persons who initiate vaccination before age 15 years

- **Interest stimulated by post-hoc analyses of 3-dose RCT in which not all individuals completed a 3-dose schedule***
  - Efficacy against incident persistent HPV16/18 infections similar after 3, 2, 1 doses
- **Non-inferiority immunogenicity studies then conducted to evaluate 2-doses in 9–14-year-olds vs 3-doses in ~15–26-year-olds**
  - Seroconversion and geometric mean titers non-inferior in 2-dose group compared with 3 doses in women aged 16–26 years
- **WHO recommendation change in 2014**
  - 2 doses for persons aged 9–14 years


2014, 89, 465-492 No. 43

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

24 OCTOBER 2014, 89th YEAR / 24 OCTOBRE 2014, 89e ANNÉE
No. 43, 2014, 89, 465–492
http://www.who.int/wer

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Human papillomavirus vaccines: WHO position paper, October 2014

Introduction
In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and vaccine combinations against diseases

Vaccins contre le papillomavirus humain: note de synthèse de l'OMS, octobre 2014

Introduction
Conformément à son mandat qui est de fournir des conseils aux Etats Membres sur les questions relatives aux politiques sanitaires, l'OMS publie une série de notes de synthèse régulièrement actualisées sur les vaccins et les

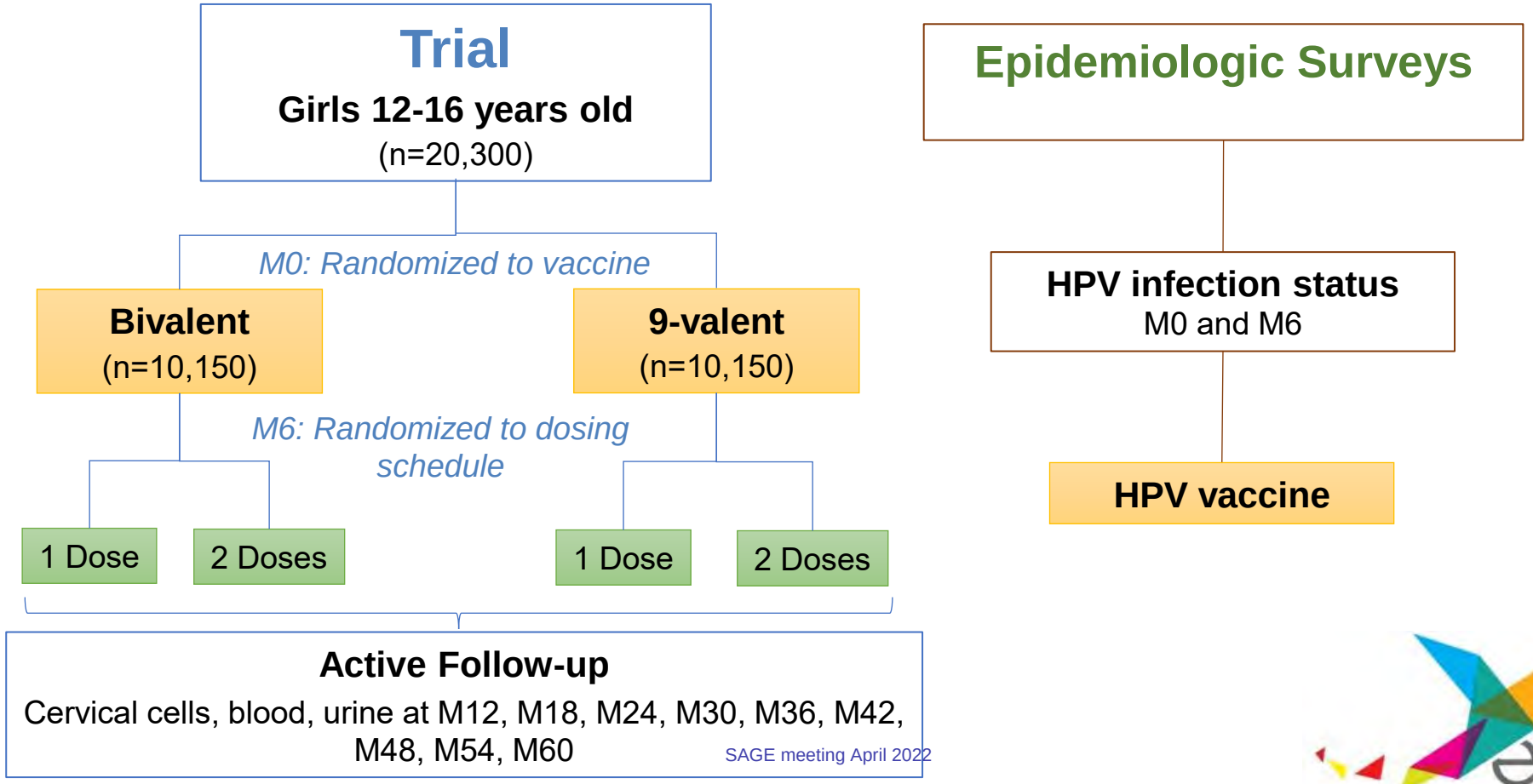
*Kreimer, et al. JNCI 2011

Evidence regarding single-dose HPV vaccination

- **Same studies that stimulated interest in a 2-dose schedule led to interest in single-dose vaccination**
- **Noninferiority immunogenicity studies not possible because single-dose HPV vaccination results in lower antibody titers than 2 or 3 doses**
  - While the basis of protection after HPV vaccination thought to be neutralizing antibody, no established minimum antibody threshold for protection
  - Very low levels of antibody thought to be protective
- **Efficacy studies needed for evaluation of single dose vaccination**

ESCUDDO, Costa Rica

- RCT to evaluate non-inferiority of one versus two doses of 2vHPV and 9vHPV for prevention of new cervical HPV16/18 infections that persist 6+ months
- Evaluate one dose compared to zero doses



Evidence on single-dose HPV vaccination

- Meanwhile, interest in single-dose HPV vaccination increased
- Global HPV vaccine supply/demand imbalance recognized
- Studies that initially provided data on reduced dose HPV vaccination continued follow-up and have additional data
- Additional studies initiated to evaluate single-dose HPV vaccination

Trials with data on single-dose vaccination

Trial/Country	Evidence	Vaccine	Age Group (yrs)	Description
CVT Costa Rica	Efficacy/ Immunogenicity	2vHPV	Females 18–25	Post-hoc analyses: participants randomized to 3 doses or control, but analyzed as 1-, 2-, 3-dose groups
India IARC India	Efficacy/ Immunogenicity	4vHPV	Females 10–18	Post-hoc analyses: participants randomized to 2 or 3 doses but analyzed as 1-, 2-, 3-dose groups
KEN SHE Kenya	Efficacy	2vHPV 9vHPV	Females 15–20	RCT: 1 dose of 2vHPV, 9vHPV, MenA
DoRIS Tanzania	Immunogenicity	2vHPV 9vHPV	Females 9–14	RCT: 1-, 2-, 3-dose groups
Thailand Impact Thailand	Effectiveness/ Impact	2vHPV	Females grade 8	Girls in one province received 1 dose; in another 2 doses. Baseline and post-vaccination prevalence surveys

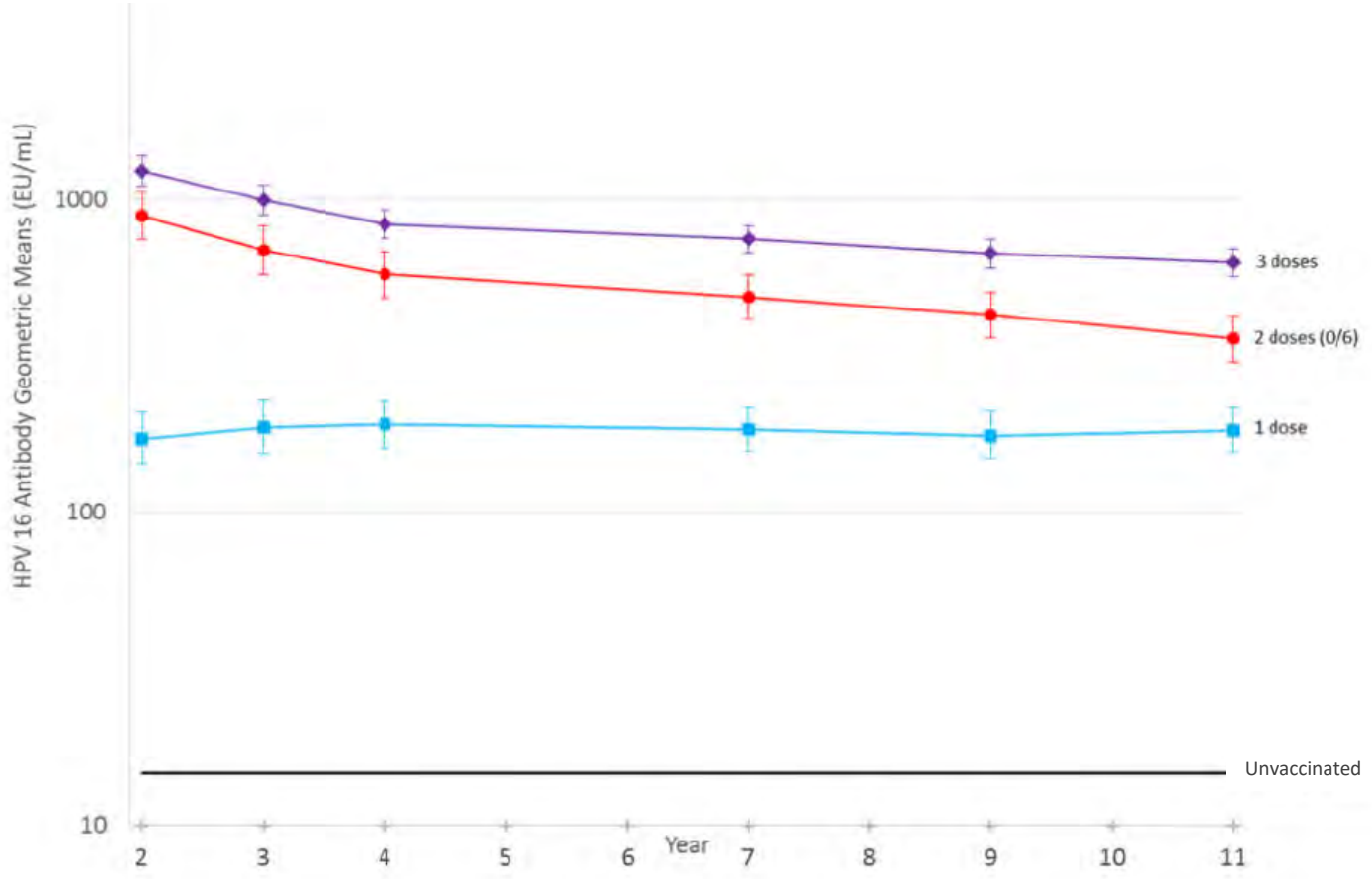
Protection after 1, 2 or 3 doses of 2vHPV through 11 years, Costa Rica Vaccine Trial

Post-hoc analysis of RCT: women vaccinated at age 18–25 years randomized to receive 3 doses of 2vHPV or control, but not all completed series

Doses	Number	Prevalent 16/18 HPV % (95% CI)	Vaccine efficacy % (95% CI)
3 doses	1365	2.0 (1.3–2.8)	**80.0%** (70.7–87.0)
2 doses	62	1.6 (0.1–7.7)	**83.8%** (19.5–99.2)
1 dose	112	1.8 (0.3–5.8)	**82.1%** (40.2–97.0)
Control	1783	10.0 (8.7–11.4)	Reference

Kreimer, et al. J Natl Cancer Inst 2020

HPV 16 antibody after 1, 2 or 3 doses of 2vHPV through 11 years, Costa Rica Vaccine Trial

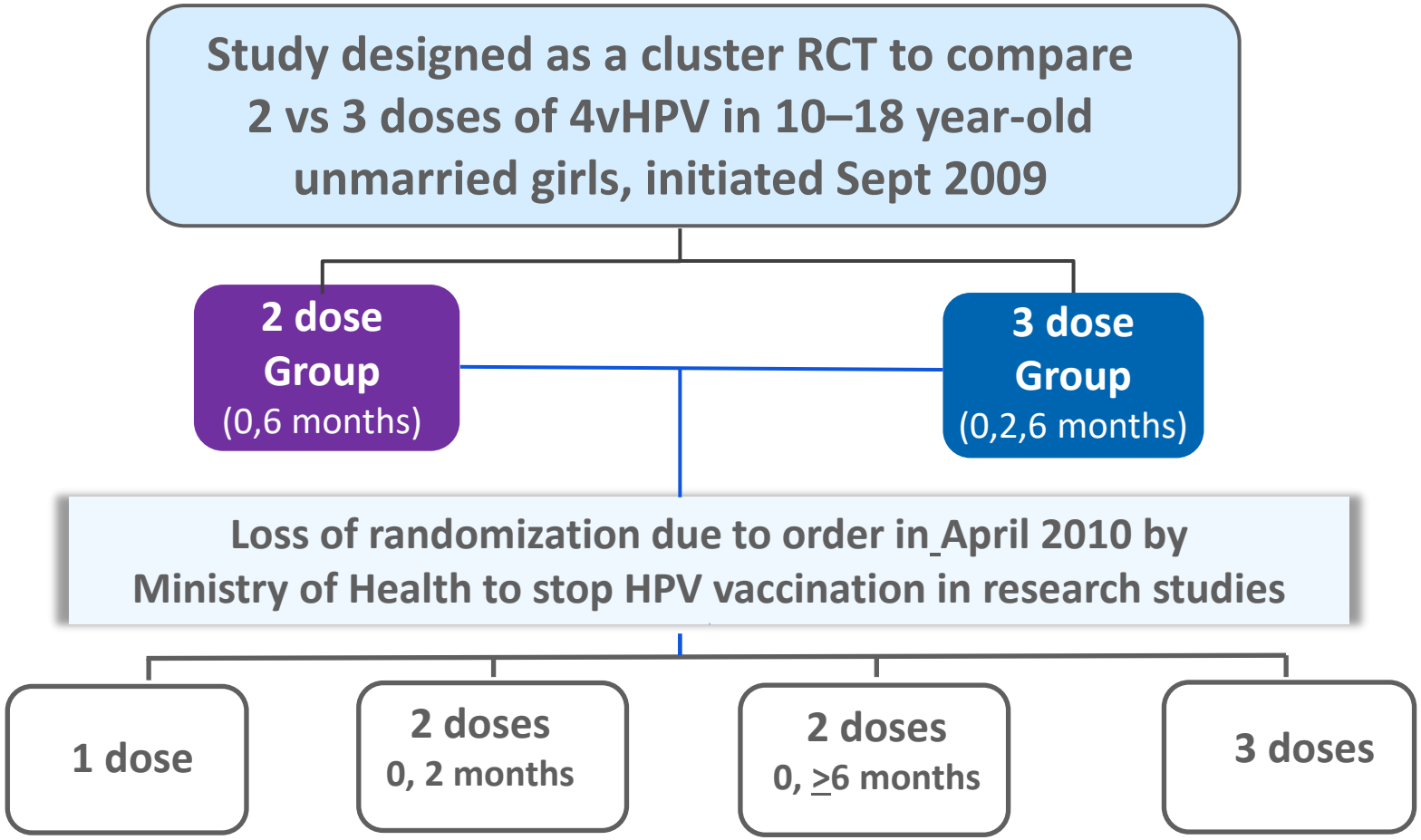


Stable HPV 16 and 18 antibody levels through 11 years post vaccination with different dosing schedules, at least 10-fold above levels in unvaccinated

Antibody by VLP-based ELISA at the NCI HPV Immunology Laboratory
Kreimer, et al. J Natl Cancer Inst 2020

Immunogenicity and efficacy of 1, 2 and 3 doses of 4vHPV, India IARC Trial

Randomized trial design lost and analyzed as observational cohort



Sankaranarayanan, et al. Lancet Oncol 2016

Protection after 1, 2 or 3 doses of 4vHPV through 10 years, India IARC Trial

Doses	Number	Incident 16/18 HPV % (95% CI)	Persistent 16/18 HPV % (95% CI)	VE against persistent infection % (95% CI)
3 doses	1649	3.0 (2.3–3.8)	0.1 (0.0–0.4)	**91.2%** (75.3–98.7)
2 doses (0, 6 months)	1685	2.6 (2.0–3.3)	0.1 (0.0–0.4)	**94.5%** (82.4–99.8)
1 dose	2454	3.1 (2.6–3.8)	0.0 (0.0–0.3)	**94.2%** (83.7–99.1)
Control	1268	9.7 (8.2–11.3)	2.7 (1.9–3.7)	Reference

Post-hoc analysis; women vaccinated at age 10-18 years, randomized to receive 3 or 2 4vHPV doses
Unvaccinated women age-matched to married vaccinated participants recruited as controls
Persistent infection defined as the same HPV type detected in consecutive samples at least 10 months apart
VE adjusted for background HPV infection frequency, time between date of marriage and first cervical specimen collection, and number of cervical specimens per participant

Basu, et al. Lancet Oncology 2021, with updated data

KEN SHE

- Randomized trial of 1 dose of 9vHPV or 2vHPV or meningococcal vaccine
  - 2250 Kenyan women aged 15–20 years; 1-5 lifetime partners; HIV negative
- 1458 girls evaluated for efficacy at month 18 in mITT HPV 16/18 cohort

Study arm	Number	Incident persistent HPV 16/18	Incidence/ 100 PY	VE % (95% CI)
9vHPV	496	1	0.17	**97.5%** (81.7–99.7)
2vHPV	489	1	0.17	**97.5%** (81.6–99.7
MCV	473	36	6.83	Reference

Enrollment between December 2018 and June 2021
mITT, modified intention to treat: HPV 16/18 HPV DNA negative (external genital and cervical swabs) at enrollment and month 3 (self-collected vaginal swab) and HPV antibody negative at enrollment

Barnabas, et al. DOI 10.21203/rs.3.rs-1090565/v1; accepted for publication at NEJM Evidence

DoRIS

Dose **R**eduction **I**mmunobridging & **S**afety Study of 2vHPV and 9vHPV in Tanzanian girls

- 930 girls aged 9–14 years randomized to 1, 2 or 3 doses of 2vHPV or 9vHPV
- Objectives:
  - Demonstrate non-inferiority of HPV 16/18 antibody response after 1 dose compared with 2 or 3 doses of same vaccine at month 24
  - Demonstrate non-inferiority of HPV 16/18 GMCs comparing 1 dose in DoRIS with historical efficacy cohorts that received 1 dose (CVT, India IARC, KEN SHE).

DoRIS: seroconversion results

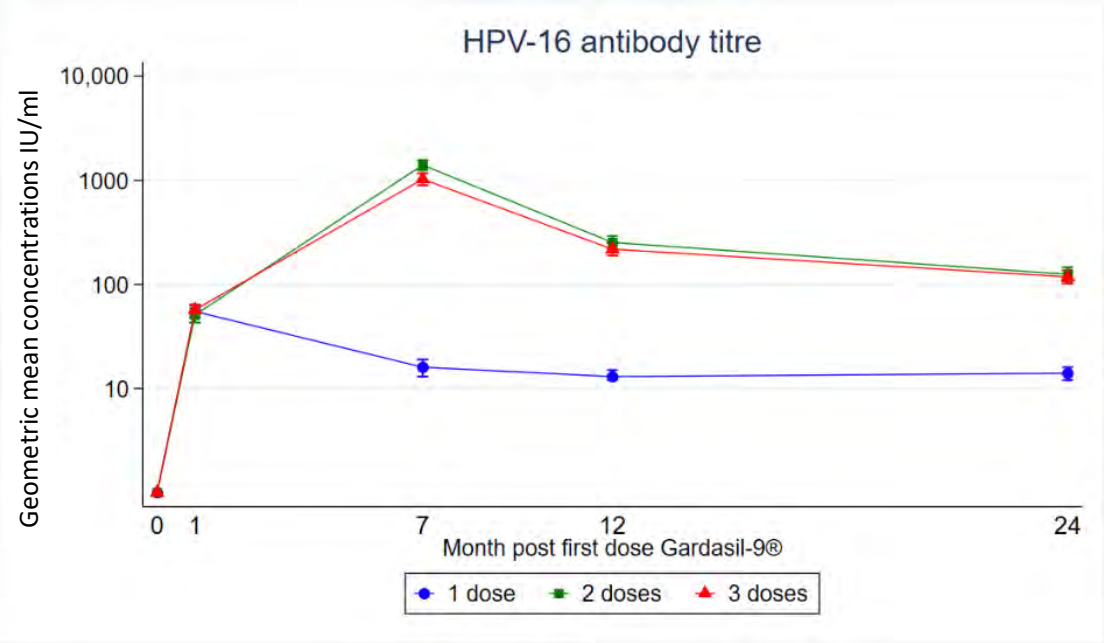
	1 dose		2 doses		3 doses	
	N	Seropositive (%)	N	Seropositive (%)	N	Seropositive (%)
		2vHPV (**Cervarix**)				
HPV-16	148	147 (99.3%)	141	141 (100%)	141	141 (100%)
HPV-18	141	139 (98.6%)	140	140 (100%)	136	136 (100%)
		9vHPV (**Gardasil-9**)				
HPV-16	145	144 (99.3%)	141	141 (100%)	140	140 (100%)
HPV-18	136	133 (97.8%)	136	136 (100%)	142	141 (99.3%)

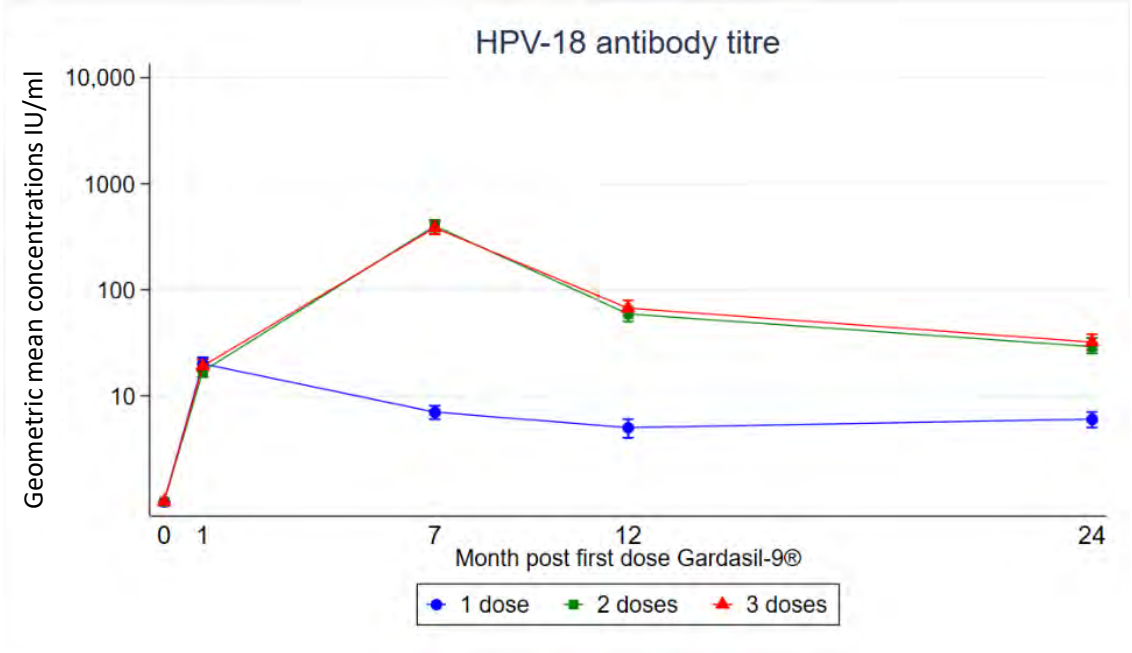
- HPV 16: non-inferiority criteria met for 1 dose compared with 2 or 3, both vaccines
- HPV 18: non-inferiority criteria not met for 1 dose compared with 2 or 3 doses

VLP-based ELISA at the NCI HPV Immunology Laboratory

Watson-Jones, et al. http://dx.doi.org/10.2139/ssrn.4055429

DoRIS: geometric mean concentrations, 9vHPV



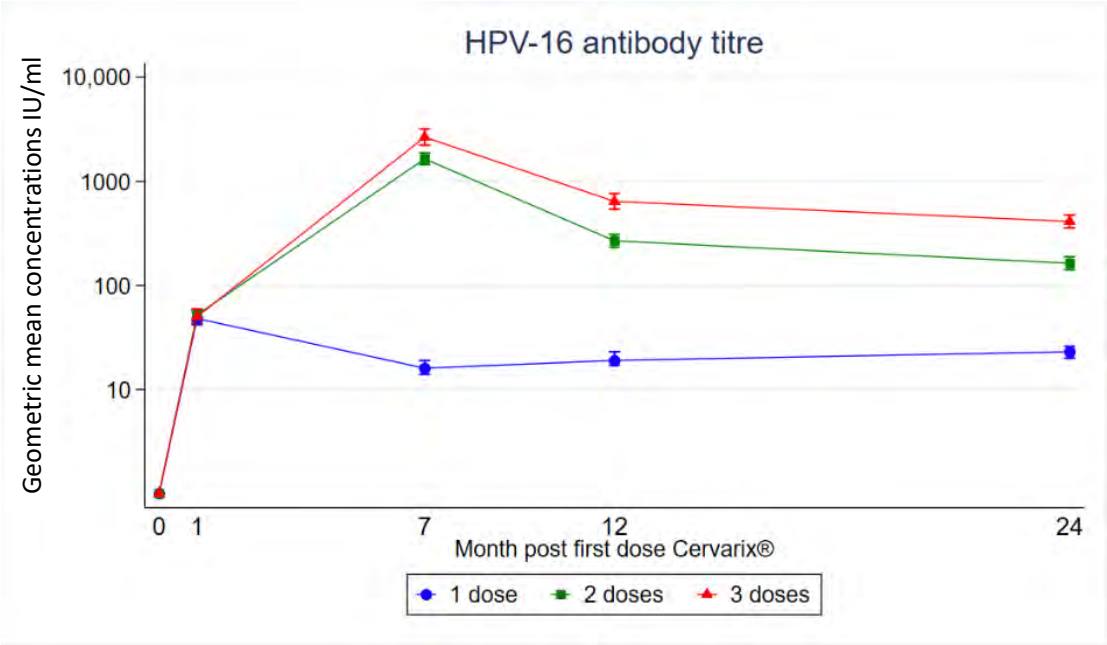


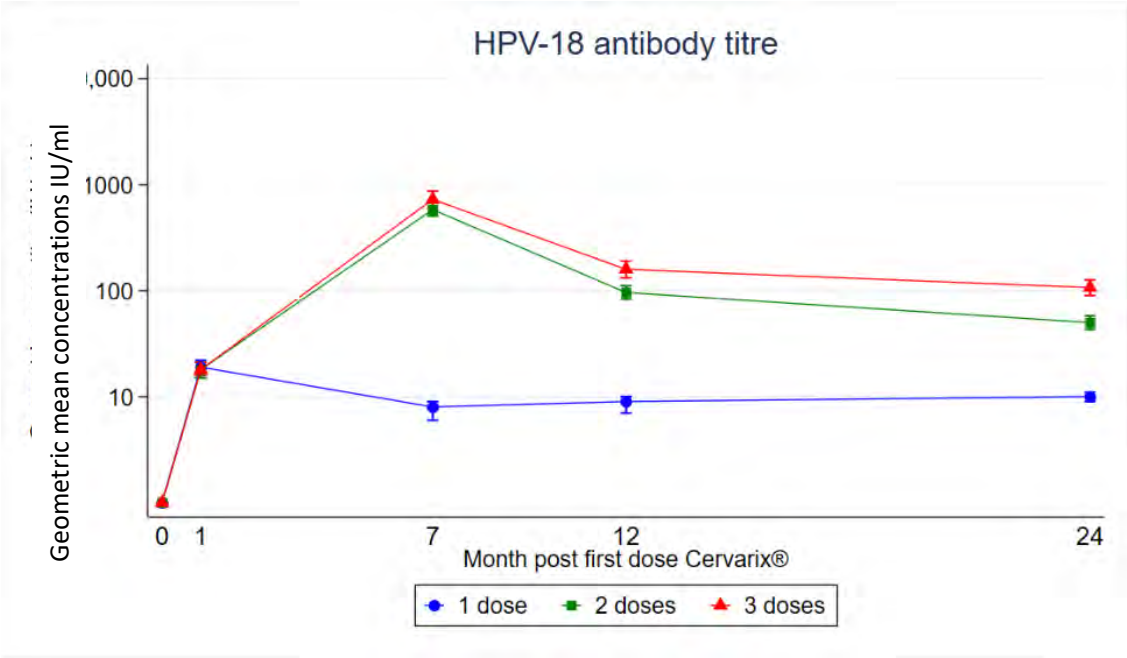
- 2-dose and 3-dose levels decline after peak at month 7
- 2-dose and 3 dose levels similar at month 24
- 1-dose levels lower than 2-dose or 3-dose levels; relatively stable from month 12 (plateau)

VLP-based ELISA at the NCI HPV Immunology Laboratory

Watson-Jones, et al. http://dx.doi.org/10.2139/ssrn.4055429

DoRIS: geometric mean concentrations, 2vHPV





- 2-dose and 3-dose levels decline after peak at month 7
- 3-dose levels higher than 2-dose levels at month 24
- 1-dose levels lower than 2 or 3-dose levels; relatively stable between months 12 and 24

VLP-based ELISA at the NCI HPV Immunology Laboratory

Watson-Jones, et al. http://dx.doi.org/10.2139/ssrn.4055429

DoRIS: immunobridging to efficacy studies (CVT and India)

	N	GMC (IU/mL)	GMC ratio[1] (95% CI)	Seroconversion	Difference[2] (95% CI)
HPV-16					
DoRIS (Cervarix®)	148	22.9		147 (99.3%)	
CVT (Cervarix®)	97	17.7	1.30 (1.00 -1.68)	96 (99.0%)	0.4% (-3.1- 5.1)
DoRIS (Gardasil-9®)	145	13.7		144 (99.3%)	
India (Gardasil®)	131	6.7	1.29 (0.91 -1.82)[3]	121 (92.4%)	6.9% (2.4-13.1)
HPV-18					
DoRIS (Cervarix®)	141	9.9		139 (98.6%)	
CVT (Cervarix®)	97	8.0	1.23 (0.95 -1.60)	96 (99.0%)	-0.4% (-4.4- 4.4)
DoRIS (Gardasil-9®)	136	5.7		133 (97.8%)	
India (Gardasil®)	129	2.2	1.75 (1.22 -2.50)[3]	99 (76.7%)	21.0% (13.5-29.5)

[1]Ratio of geometric mean concentrations (DoRIS / historical cohort). [2]Difference in seroconversion (DoRIS - historical cohort). [3]Adjusted for age.

1 dose in DoRIS is non-inferior to 1 dose in historical cohorts at month 24, for HPV-16 & HPV-18, for both 2vHPV & 9vHPV

Baisley, et al. http://dx.doi.org/10.2139/ssrn.4055428

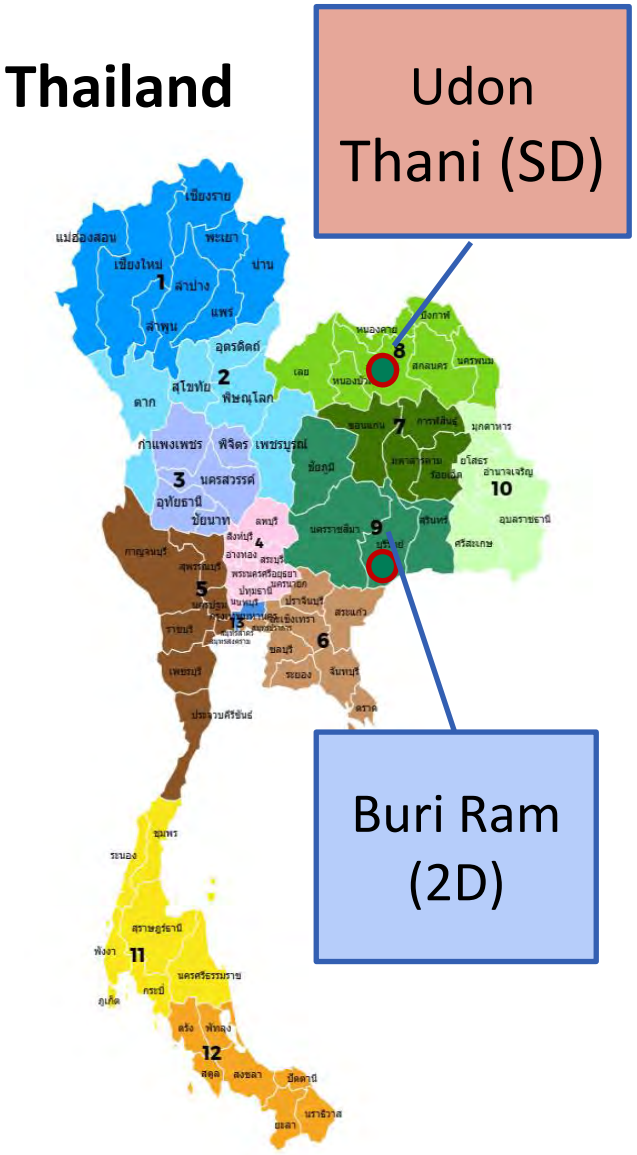
DoRIS conclusions

- Seropositivity >97.5% for all doses of both vaccines
- Antibody levels by dose, vaccine, and kinetics over time similar to those in other HPV vaccine studies
- Avidity (not shown) - no difference between dose groups or vaccines
- Immunobridging showed that 1-dose responses were non-inferior in DoRIS compared with those in studies where 1-dose efficacy observed

Thailand Impact Study

- Observational study of 1 dose and 2 doses of 2vHPV given to Grade 8 girls (age <15 years) in two similar Thai provinces

- Primary objectives:
  - Demonstrate HPV vaccine effectiveness of 1 dose and 2 doses
    - Year 2 and Year 4 post-vaccination
    - Effectiveness by a reduction in vaccine-type HPV prevalence* (HPV 16 and 18) compared to prevalence among unvaccinated same grade female students collected in a baseline survey
  - Evaluate if HPV vaccine effectiveness of 1 dose is non-inferior to 2 doses by comparing reductions in vaccine-type prevalence
    - Year 4 post-vaccination



*Measured in urine, by COBAS

Selected other trials evaluating single-dose vaccination, data forthcoming

Trial/Country	Evidence	Vaccine	Age Group (yrs)	Description
HOPE South Africa	Impact/ Effectiveness	2vHPV	Females 15–16	Girls in one district received 1 dose as catch-up in grade 10. Baseline and post-vaccination cross sectional prevalence surveys; includes WLWH
HANDS The Gambia	Immunogenicity	9vHPV	Females 4–8, 9–14 and 15–26	RCT: 1 or 2 doses 3 doses in 15–26-year-olds
ESCUDDO Costa Rica	Efficacy/ Immunogenicity	2vHPV 9vHPV	Females 12–16	RCT: 1 or 2 doses of 2vHPV or 9vHPV

Cochrane Response

Updated systematic review on the immunogenicity and efficacy of a single dose of HPV vaccine

April 2022
SAGE Working Group Human Papillomavirus Immunization

Trusted evidence.
Informed decisions.
Better health.

Cochrane Response

Methods

- Update of 2019 review on single dose HPV vaccine
  - One dose HPV vaccine vs no vaccine
  - One dose HPV vaccine vs two/three doses HPV vaccine
- Electronic searches were conducted on PubMed, CENTRAL, and EMBASE.
- Search was updated from February 2019 to January 2022.
- Two reviewers independently screened all studies, extracted data, and assessed risk of bias for included studies.

Cochrane Response

Included studies (n = 55)

- 3 RCTs were identified evaluating one dose (Kenya, China, Tanzania)
- 4 post-hoc analyses of RCTs (CVT, India, CVT/PATRICIA, Canada)
- 3 case-control studies
- 45 observational cohort studies

- 20 new studies since 2019 review
- Only three studies included males
- 10 studies on bivalent (Cervarix), 36 quadrivalent (Gardasil), 8 studies more than one type HPV vaccine, 1 study Cecolin

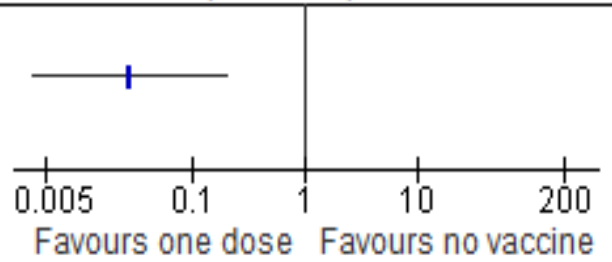
Cochrane Response

One dose of HPV vaccine vs no vaccine

– clinical outcomes

Persistent HPV infections following bivalent vaccine (Cervarix) - RCT

Study or Subgroup	One dose Events	Total	No vaccine Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.1.1 Incident detection of HPV 16/18 that persisted for at least 6 months							
Kenya1 (RCT, 15-20 years old) (1)	1	489	36	473	0.03 [0.00, 0.20]		+ + ? + + ?



Footnotes

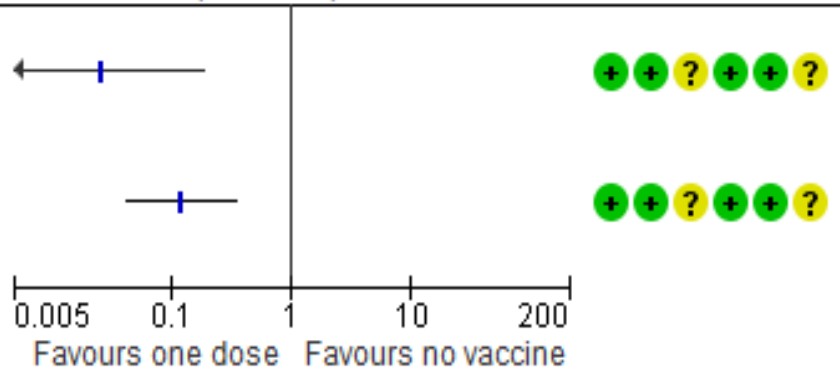
(1) 18 months follow-up; VE = 97.5% (81.6% to 99.7%)

mITT population: negative for HPV 16/18 antibodies and DNA at enrolment

VE = **97.5% (81.6% to 99.7%)**

Persistent HPV infections following nonavalent vaccine (Gardasil9) – RCT

Study or Subgroup	One dose Events	Total	No vaccine Events	Total	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
2.1.1 Incident HPV 16/18 infections that persisted for 6 months						
Kenya1 (RCT, 15-20 years old) (1)	1	496	36	473	0.03 [0.00, 0.19]	+ + ? + + ?
2.1.2 Incident HPV 16/18/31/33/45/52/58 infections that persisted for 6 months						
Kenya1 (RCT, 15-20 years old) (2)	4	325	29	290	0.12 [0.04, 0.35]	+ + ? + + ?



Footnotes
(1) 18 months follow-up; VE = 97.49% (81.66% to 99.66%)
(2) 18 months follow-up; VE = 88.91% (68.45% to 96.10%)

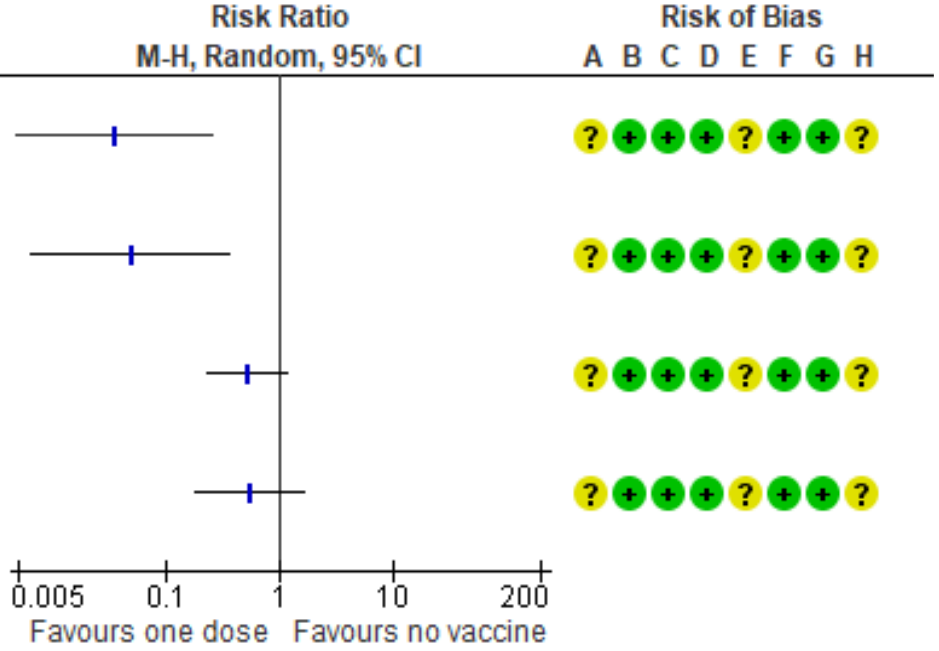
mITT population: negative for HPV 16/18/31/33/45/52/58 antibodies and DNA at enrolment

- HPV 16/18: VE = **97.5% (81.7% to 99.7%)**
- HPV 16/18/31/33/45/52/58: VE = **88.9% (68.5% to 96.1%)**

1 vs 0 dose

Persistent HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses

Study or Subgroup	One dose Events	Total	No vaccine (HAV) Events	Total	Risk Ratio M-H, Random, 95% CI
1.2.1 Incident HPV 16/18 infections that persisted for 6 months					
CVT/PATRICIA (post-RCT, 15-25 years) (1)	1	1234	24	1017	0.03 [0.00, 0.25]
1.2.2 Incident HPV 16/18 infections that persisted for 12 months					
CVT/PATRICIA (post-RCT, 15-25 years) (2)	1	1234	17	1021	0.05 [0.01, 0.37]
1.2.3 Incident HPV 31/33/45 infections that persisted for 6 months					
CVT/PATRICIA (post-RCT, 15-25 years) (3)	9	1222	15	1043	0.51 [0.23, 1.17]
1.2.4 Incident HPV 31/33/45 infections that persisted for 12 months					
CVT/PATRICIA (post-RCT, 15-25 years) (4)	5	1230	8	1061	0.54 [0.18, 1.64]



Footnotes
(1) 47.6 months follow-up
(2) 47.6 months follow-up
(3) 47.6 months follow-up
(4) 47.6 months follow-up

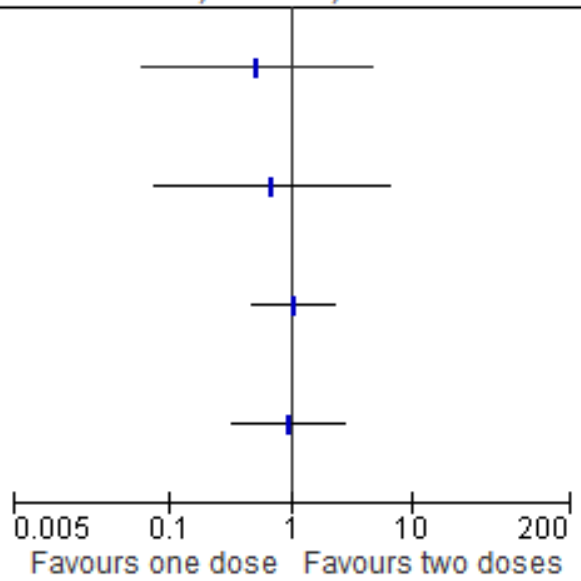
Cochrane Response

One dose of HPV vaccine vs two doses HPV vaccine

– clinical outcomes

Persistent HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses

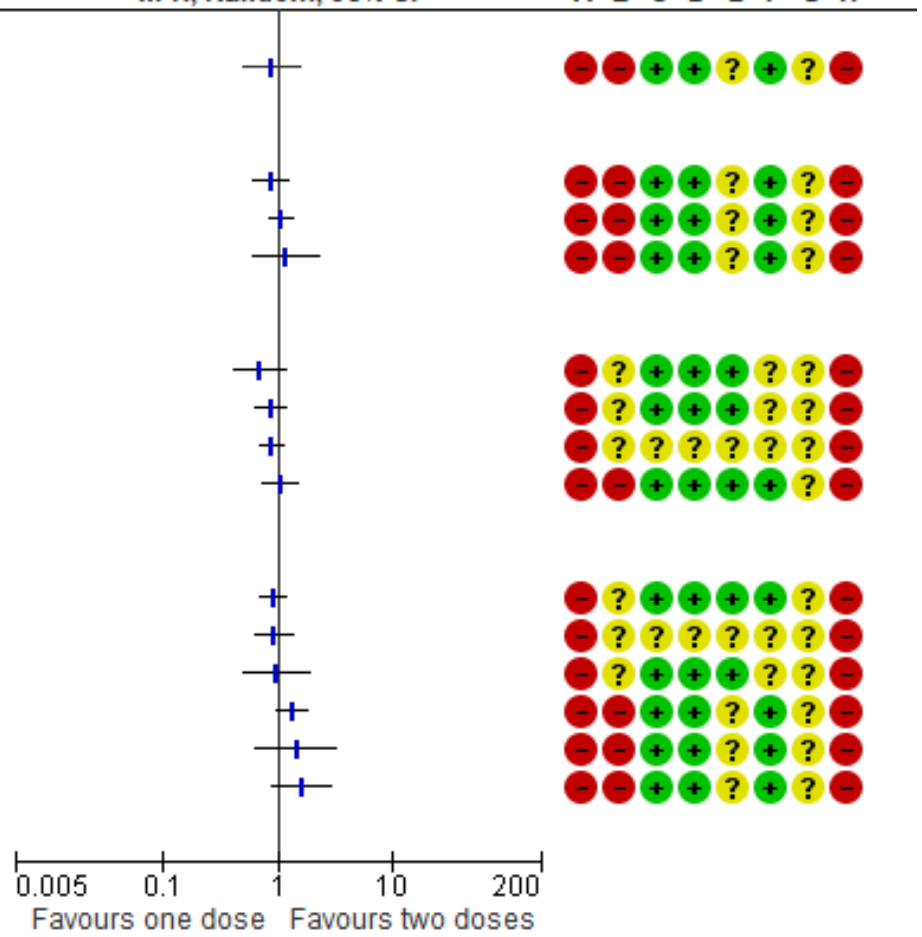
Study or Subgroup	One dose Events	Total	Two doses Events	Total	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G H
3.1.1 incident HPV 16/18 infections that persisted for 6 months						
CVT/PATRICIA (post-RCT, 15-25 years) (1)	1	1234	4	2573	0.52 [0.06, 4.66]	? + + + ? + + ?
3.1.2 incident HPV 16/18 infections that persisted for 12 months						
CVT/PATRICIA (post-RCT, 15-25 years) (2)	1	1234	3	2576	0.70 [0.07, 6.68]	? + + + ? + + ?
3.1.3 Incident HPV 31/33/45 infections that persisted for 6 months						
CVT/PATRICIA (post-RCT, 15-25 years) (3)	9	1222	18	2549	1.04 [0.47, 2.31]	? + + + ? + + ?
3.1.4 Incident HPV 31/33/45 infections that persisted for 12 months						
CVT/PATRICIA (post-RCT, 15-25 years) (4)	5	1230	11	2569	0.95 [0.33, 2.73]	? + + + ? + + ?



Footnotes
(1) 47.6 months follow-up
(2) 47.6 months follow-up
(3) 47.6 months follow-up
(4) 47.6 months follow-up

CIN following quadrivalent vaccine (Gardasil) – observational studies

Study or Subgroup	One dose Events	One dose Total	Two doses Events	Two doses Total	Risk Ratio M-H, Random, 95% CI
4.7.1 CIN1					
Australia3 (retrospective cohort, 12-19 yrs) (1)	20	2568	30	3412	0.89 [0.50, 1.56]
4.7.2 CIN2					
Australia1 (retrospective cohort, 12-26 yrs) (2)	54	6938	77	8638	0.87 [0.62, 1.23]
Australia4 (retrospective cohort, 15 yrs) (3)	89	18104	174	37819	1.07 [0.83, 1.38]
Australia3 (retrospective cohort, 12-19 yrs) (4)	16	2568	18	3412	1.18 [0.60, 2.31]
4.7.3 CIN2+					
Denmark3 (retrospective cohort, 16 yrs) (5)	18	27334	83	88029	0.70 [0.42, 1.16]
USA22 (retrospective cohort, 9-26 yrs) (6)	64	7099	85	8147	0.86 [0.63, 1.19]
USA9 (case-control, 14-21 yrs) (7)	118	638	97	457	0.87 [0.69, 1.11]
USA21 (test-negative, 12-26 yrs) (8)	47	136	35	108	1.07 [0.75, 1.52]
4.7.4 CIN3+					
USA24 (retrospective cohort, 15-20 yrs) (9)	112	43245	98	34401	0.91 [0.69, 1.19]
USA9 (case-control, 14-21 yrs) (10)	47	239	36	168	0.92 [0.62, 1.35]
Denmark3 (retrospective cohort, 16 yrs) (11)	11	27346	36	88100	0.98 [0.50, 1.93]
Australia1 (retrospective cohort, 12-26 yrs) (12)	78	6938	72	8638	1.35 [0.98, 1.86]
Australia3 (retrospective cohort, 12-19 yrs) (13)	12	2568	11	3412	1.45 [0.64, 3.28]
Australia4 (retrospective cohort, 15 yrs) (14)	19	4035	25	8641	1.63 [0.90, 2.95]



Cochrane Response

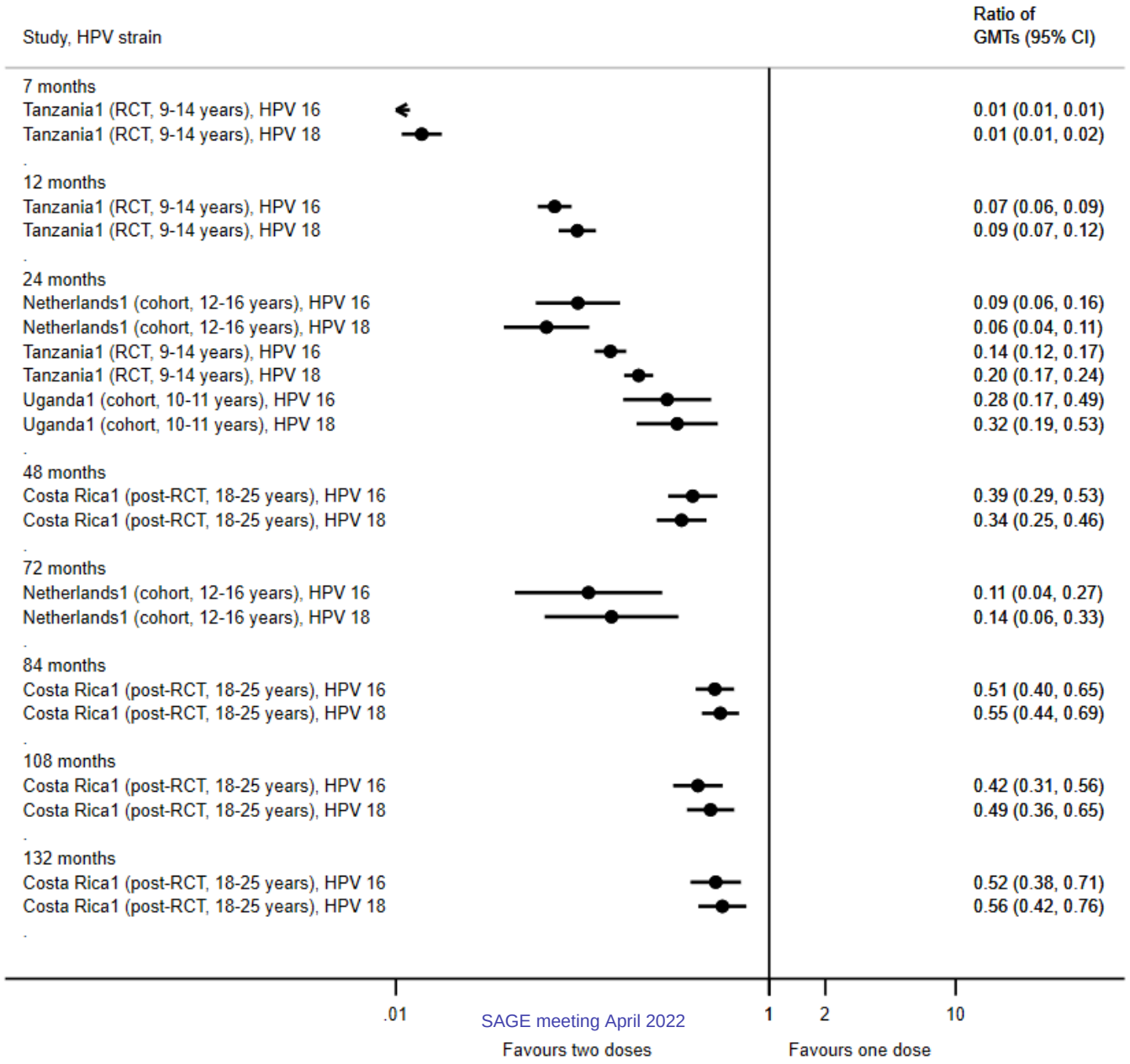
One dose of HPV vaccine vs two doses HPV vaccine

– immunological outcomes

Immunogenicity – seropositivity following bivalent (Cervarix) vaccine

Study	HPV type	Timepoint (months)	One dose		Two doses		Three doses	
			N	% seropositive	N	% seropositive	N	% seropositive
Tanzania1	16	7	148	99.3%	142	100%	141	99.3%
	18	7	141	98.6%	141	100%	136	99.3%
	16	12	147	99.3%	140	100%	141	100%
	18	12	140	99.3%	139	100%	136	100%
	16	24	148	99.3%	141	100%	141	100%
	18	24	141	98.6%	140	100%	136	100%
Uganda1	16	24	36	100%	145	98.6%	195	99.5%
	18	24	36	97.2%	145	98.6%	195	99.5%
Netherlands1	16	24	48	97.9%	51	100%	51	100%
	18	24	48	89.6%	51	100%	51	100%
Costa Rica1	16	48	78	100%	140	100%	120	100%
	16	108	118	100%	66	100%	1365	100%
	18	108	118	100%	66	100%	1365	100%
	16	132	118	100%	66	100%	1365	100%
	18	132	118	100%	66	100%	1365	100%

Immunogenicity – 1 vs 2 dose ratio of GMTs – bivalent (Cervarix) vaccine



Cochrane Response

Summary one dose efficacy/effectiveness

One dose of HPV vaccine vs no vaccine

Immunogenicity

- One dose of HPV vaccine resulted in higher GMTs and seropositivity for HPV 16 and 18 than no vaccine and this was sustained for up to 5-11 years (high certainty).

HPV infections

- One dose HPV vaccine resulted in a large reduction in persistent HPV 16/18 infections compared with no vaccine over the short term (high certainty).
- One dose HPV vaccine resulted in fewer persistent HPV 16/18 infections compared with no vaccine over the long term (moderate certainty).

Other clinical outcomes

- Evidence suggests that one dose of HPV vaccine may reduce the incidence of genital warts, abnormal cytology, and CIN compared with no vaccine, but this is based on observational studies at serious risk of bias.

Evidence profile 1: Effectiveness and immunogenicity of one dose of HPV vaccine compared with no HPV vaccination

№ of studies	Certainty
Persistent HPV 16/18 infections: short term follow-up, 18 months	
1 RCT	⊕⊕⊕⊕ High
Persistent HPV 16/18 infections: long term follow-up, 4-10 years	
2 post-hoc analyses of RCTs	⊕⊕⊕◯ Moderate[1]
Seroconversion to HPV 16: follow-up 6 months to 11 years	
2 RCTs, 1 post-hoc analysis of RCT, 3 obs studies	⊕⊕⊕⊕ High
Seroconversion to HPV 18: follow-up 6 months to 11 years	
2 RCTs, 1 post-hoc analysis of RCT, 3 obs studies	⊕⊕⊕⊕ High
Geometric mean titres (GMT) for HPV 16: follow-up 4-6 years	
1 post-hoc analysis of RCT, 3 obs studies	⊕⊕⊕⊕ High
Geometric mean titres (GMT) for HPV 18: follow-up 4-6 years	
1 post-hoc analysis of RCT, 3 obs studies	⊕⊕⊕⊕ High

[1]Downgraded one level due to some concerns with bias due to confounding and selection of the reported result.

Cochrane Response

Summary one dose efficacy/effectiveness

One dose vs 2 or 3 doses of HPV vaccine

Immunogenicity

- One dose resulted in lower GMTs for HPV 16 and 18 than two or three doses (high certainty)
- One, two, or three doses resulted in similarly high rates of seropositivity to HPV 16 and 18 (high certainty)

HPV infections

- One dose resulted in little to no difference in persistent HPV 16/18 infections compared with two or three doses (low certainty)

Other clinical outcomes

- The estimates of effect between one, two, and three doses come mostly from observational studies that are at serious risk of bias due to confounding.

Evidence profile 2: Effectiveness and immunogenicity of one dose of HPV vaccine compared with two doses HPV vaccine

№ of studies	Certainty
Persistent HPV 16/18 infections: long term follow-up, 4-10 years	
2 post-hoc analyses of RCTs	⊕⊕◯◯ Low[1,2]
Seroconversion to HPV 16: follow-up 6 months to 11 years	
2 RCTs, 1 post-hoc analysis of RCT, 2 obs studies	⊕⊕⊕⊕ High
Seroconversion to HPV 18: follow-up 6 months to 11 years	
2 RCTs, 1 post-hoc analysis of RCT, 2 obs studies	⊕⊕⊕⊕ High
Geometric mean titres (GMT) for HPV 16: follow-up 6 months to 11 years	
2 RCTs, 1 post-hoc analysis of RCT, 1 obs studies	⊕⊕⊕⊕ High
Geometric mean titres (GMT) for HPV 18: follow-up 4-6 years	
2 RCTs, 1 post-hoc analysis of RCT, 1 obs studies	⊕⊕⊕⊕ High

[1] Downgraded one level due to some concerns with bias due to confounding and selection of the reported result.
[2] Downgraded one level due to imprecision, few events and a 95% confidence interval that encompasses a benefit, no effect, and a harm.

Cochrane Response

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Conflict of interest statement

No financial or non-financial conflicts of interest declared

Potential impact of 1-dose HPV vaccination in low and middle income countries (LMICs)

A modeling analysis using HPV-ADVISE LMIC

Marc Brisson, PhD
Full Professor, Université Laval

SAGE meeting
April 6, 2022

Modeling Team

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Conflicts of interest statements

- Single-Dose HPV vaccine evaluation consortium

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UNIVERSITÉ LAVAL

IRSC CIHR
Instituts de recherche en santé du Canada
Canadian Institutes of Health Research

Single-Dose HPV Vaccine
EVALUATION CONSORTIUM

Question considered by the Working Group

- Should an off-label, permissive one-dose HPV vaccine schedule be recommended for use:
  - In multi-age cohort (MAC) catch-up?
  - In routine cohorts?

Objectives

- Examine & compare the population-level impact and efficiency of:
  - 1-dose vs 2-dose MAC strategies
  - 1-dose vs 2-dose routine girls-only strategies

Using 4 LMICs that represent different country profiles (sexual behaviour, HPV epidemiology)

Methods

Model overview

- HPV-ADVISE LMIC (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[&]

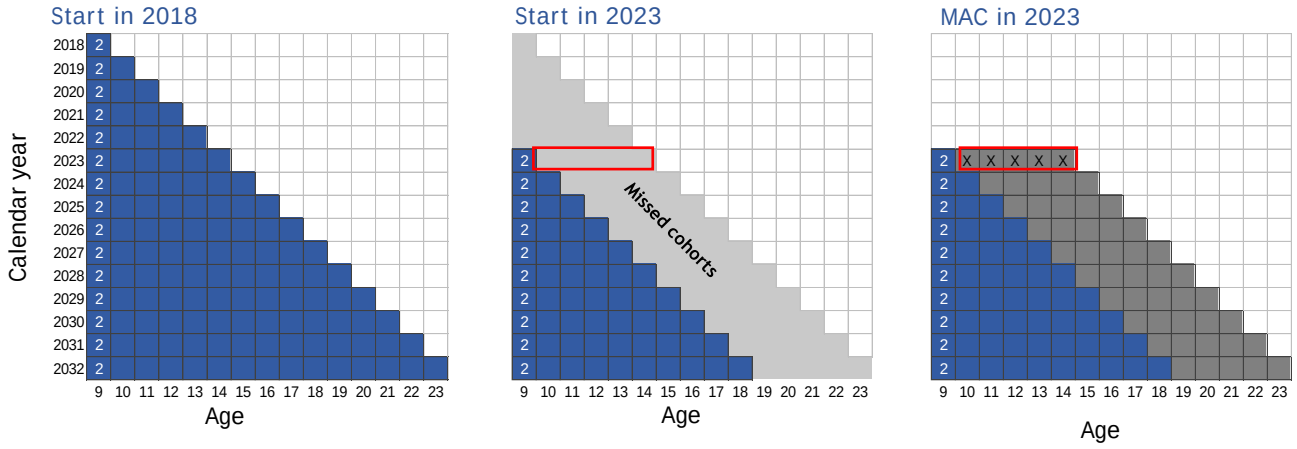
REF: 1. Drolet, Laprise et al., *Lancet ID* 2021; &: Demographic and Health Surveys, Multiple Indicator Survey, ICO information Centre on HPV and Cancer, United Nations Statistics Division, HIV and AIDS HUB for Asia Pacific-Evidence to action, WHO Global Health Observatory data repository, literature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

Question 1a

Could Multiple Age Cohort (MAC) vaccination mitigate the impact of delays in HPV vaccine introduction?

Why MACs?

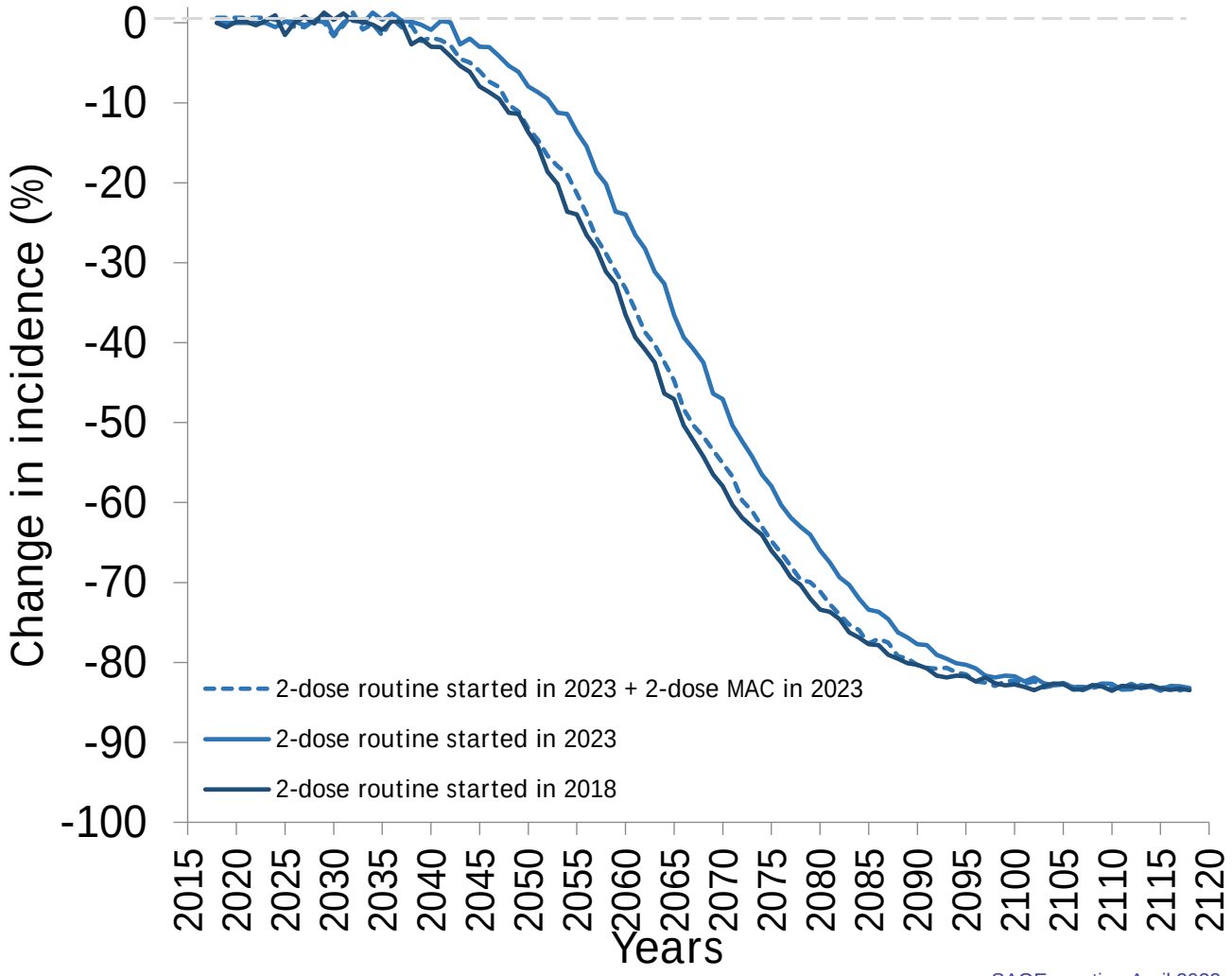
- Introduction of HPV vaccination has been delayed in low- and middle-income countries (LMIC)
  - resource constraints, shortage of HPV vaccine supply, COVID-19 disruptions
- Many LMICs have recently started or will start HPV vaccination in the next few years
  - LMICs that started recently with routine 9-year-old vaccination have cohorts aging out of the 9 to 14-year-old vaccination window and/or may have recent lower coverage
  - LMICs that have yet to start will have potentially lost the opportunity to vaccinate 5 cohorts of girls (prior to age 15 years) before they age out the 9-14 year old vaccination window



Impact of MACs to mitigate delays in HPV vaccine introduction

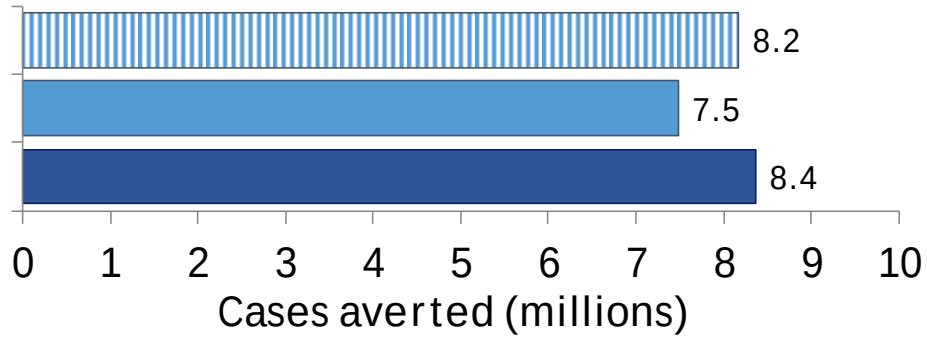
Country profile: INDIA

Girls-only vaccination, Routine = 9 yrs old, MACs = 10-14 yrs old, Vaccination coverage = 80%, Vaccine efficacy (VE) = 100%



If high coverage is achieved, MACs can mitigate the impact of delays in HPV vaccine introduction.

However, MACs with 2 doses may worsen vaccine supply issues

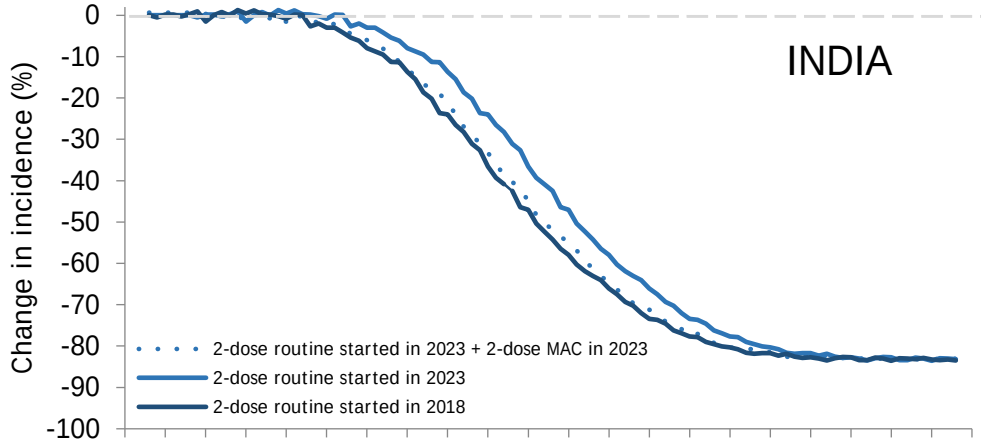


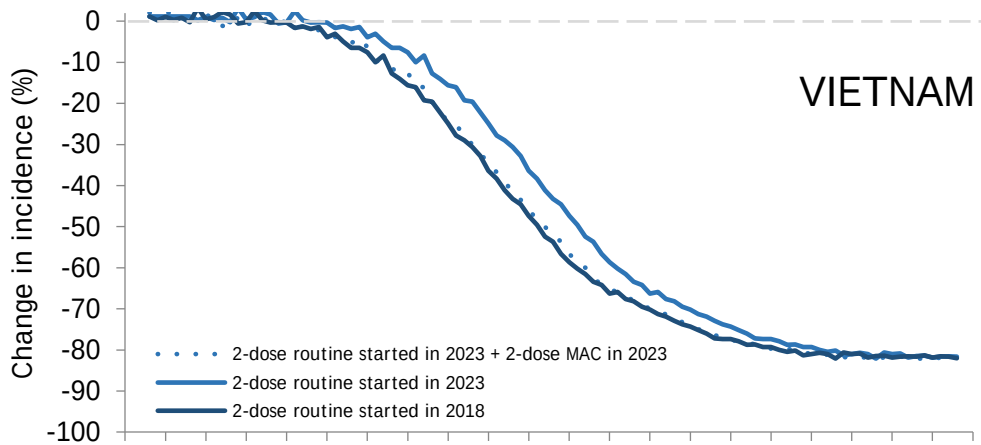
Age-standardized cervical cancer incidence rate, UN World Population prospect 2015; Cancers averted based on population UN prospect projections from 2018 to 2118

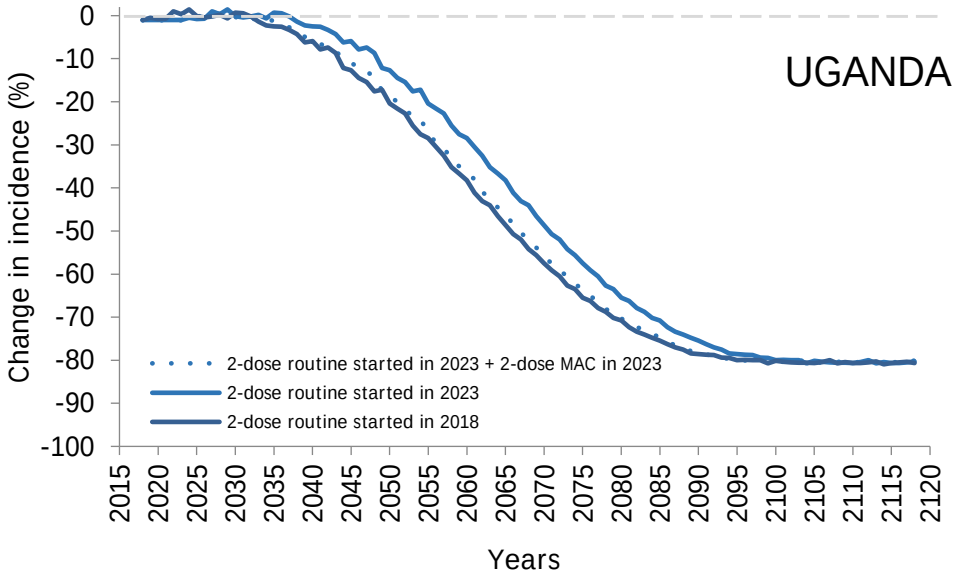
Impact of MACs to mitigate delays in HPV vaccine introduction

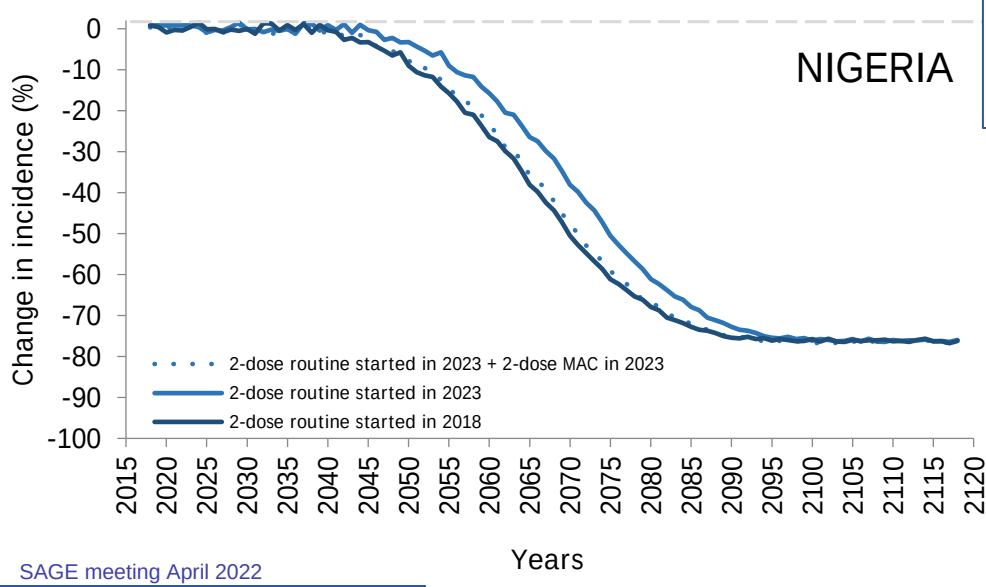
4 country profiles

Girls-only vaccination, Routine = 9 yrs old, MACs = 10-14 yrs old, Vaccination coverage = 80%, Vaccine efficacy (VE) = 100%









Conclusions are the same for the 4 country profiles

Age-standardized cervical cancer incidence rate, UN World Population prospect 2015

Question 1b

Given limited resources & limited vaccine supply, could MAC vaccination with 1 dose be an efficient strategy?

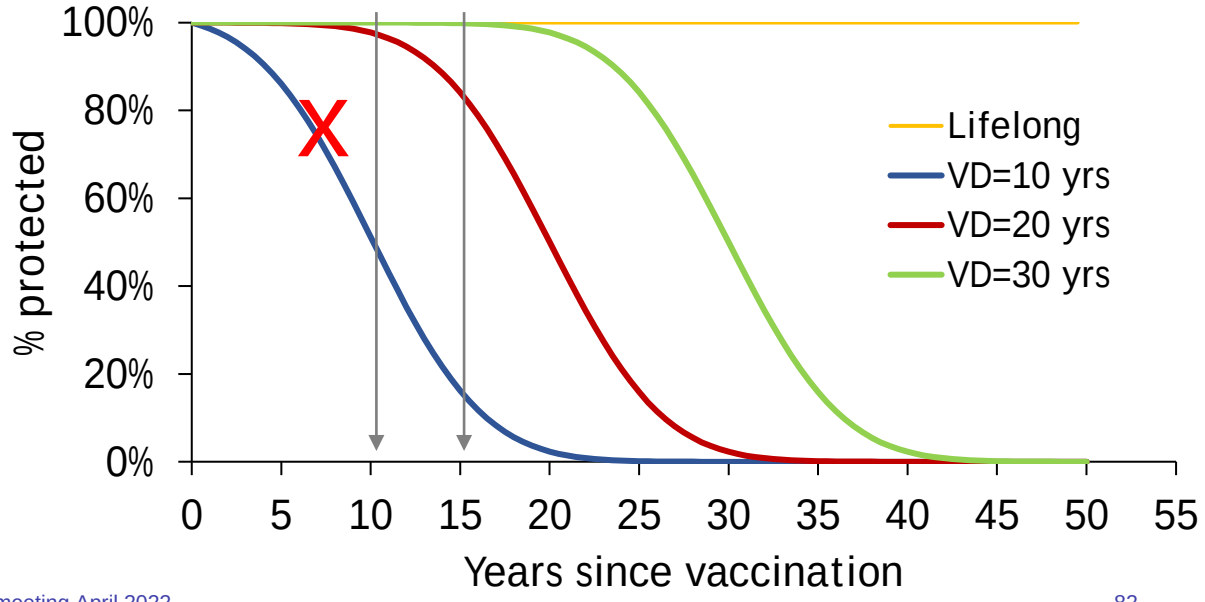
Will depend on 1-dose vaccine efficacy and duration of protection

1-dose vaccine efficacy (VE) scenarios

- Best case: VE 1 dose = 2 doses = 100%
  - India IARC Trial: 95.4% against HPV16/18 persistent infections[1]
  - Kenya KEN-SHE RCT: 97.5% against HPV16/18 persistent infection[2]
- Worst case: VE 1 dose ≈ 85%
  - Lower bound of the India IARC Trial 95% confidence interval: 85%[1]
  - Thailand Impact Study: 83.3% against HPV16/18 (unpublished data)

1-dose duration of vaccine protection (VD) scenarios

- Sustained protection of 1 dose through 10 years in India[1] (if average duration was 10 years we would already be seeing a decline)
- Based on these results, 3 scenarios of 1-dose duration:
  - Lifelong (same as assumption for 2 doses)
  - 30 years
  - 20 years (within the next 5 years we would start seeing a decline in efficacy)

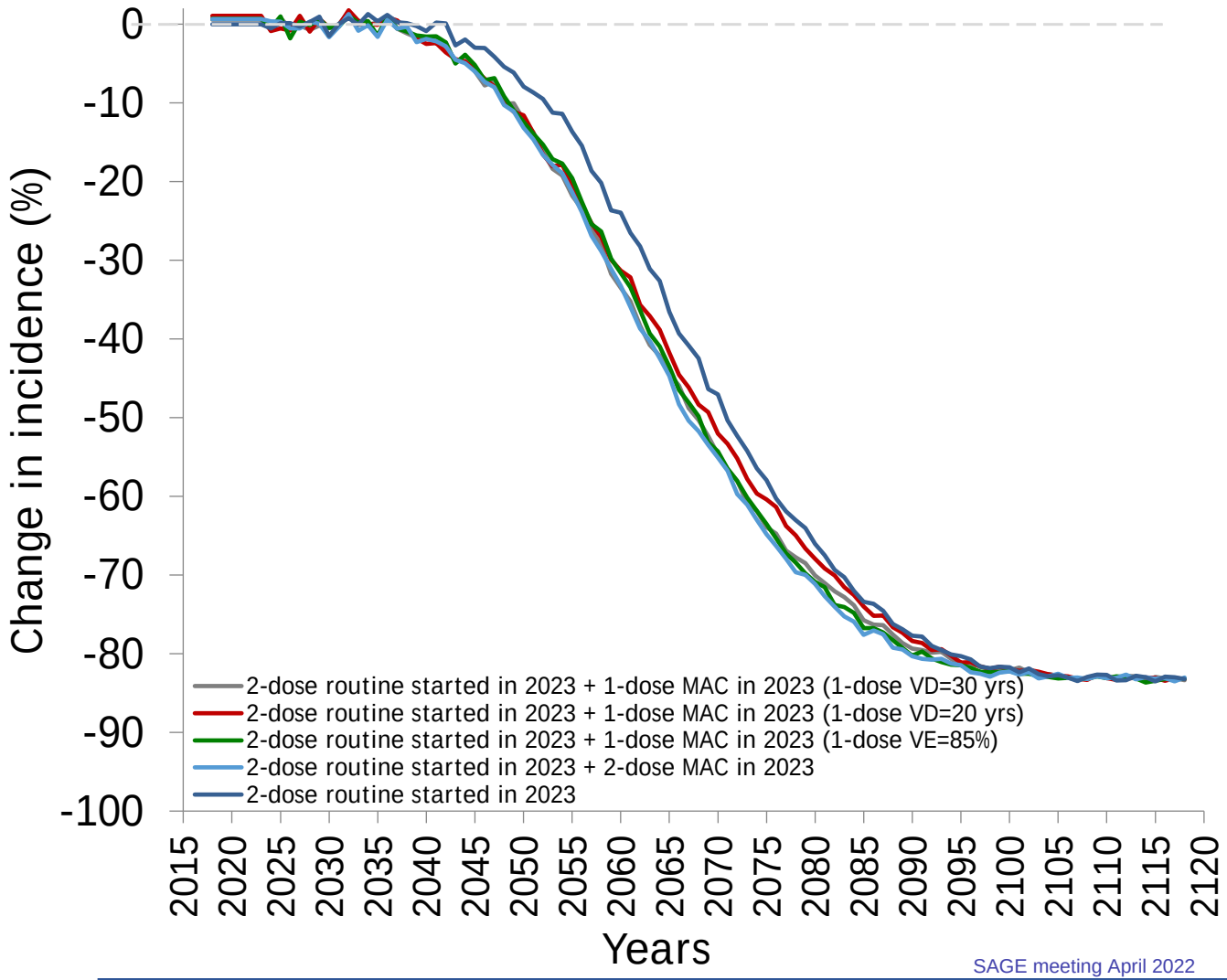


REF: 1. Basu, Lancet Oncol 2021, 2. Barnabas, DOI 10.21203/rs.3.rs-1090565/v1; Duration of protection is modelled using a normal distribution (Standard Deviation = 5 years)

Impact 1-dose vs 2-dose MACs

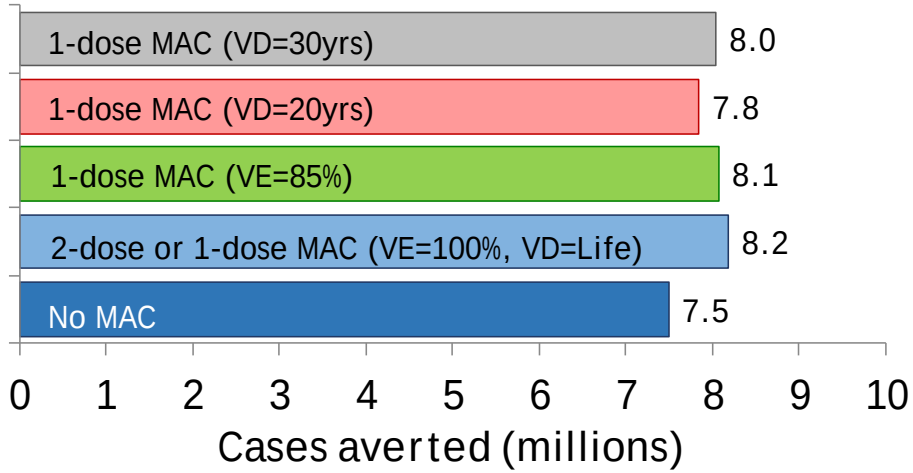
Country profile: INDIA

Girls-only, Routine = 9 yrs old, MACs = 10-14 yrs old, Vaccination coverage = 80%, 2-dose VE = 100%, 2-dose VD = Life



1-dose MACs would:

- Prevent a substantial additional number of cervical cancer cases and accelerate elimination vs routine vaccination
- Provide similar additional cervical cancer cases averted as a 2-dose MAC vaccination, if duration is greater than 20-30 years
- Herd immunity from 2-dose routine would mitigate the impact if 1-dose efficacy is lower



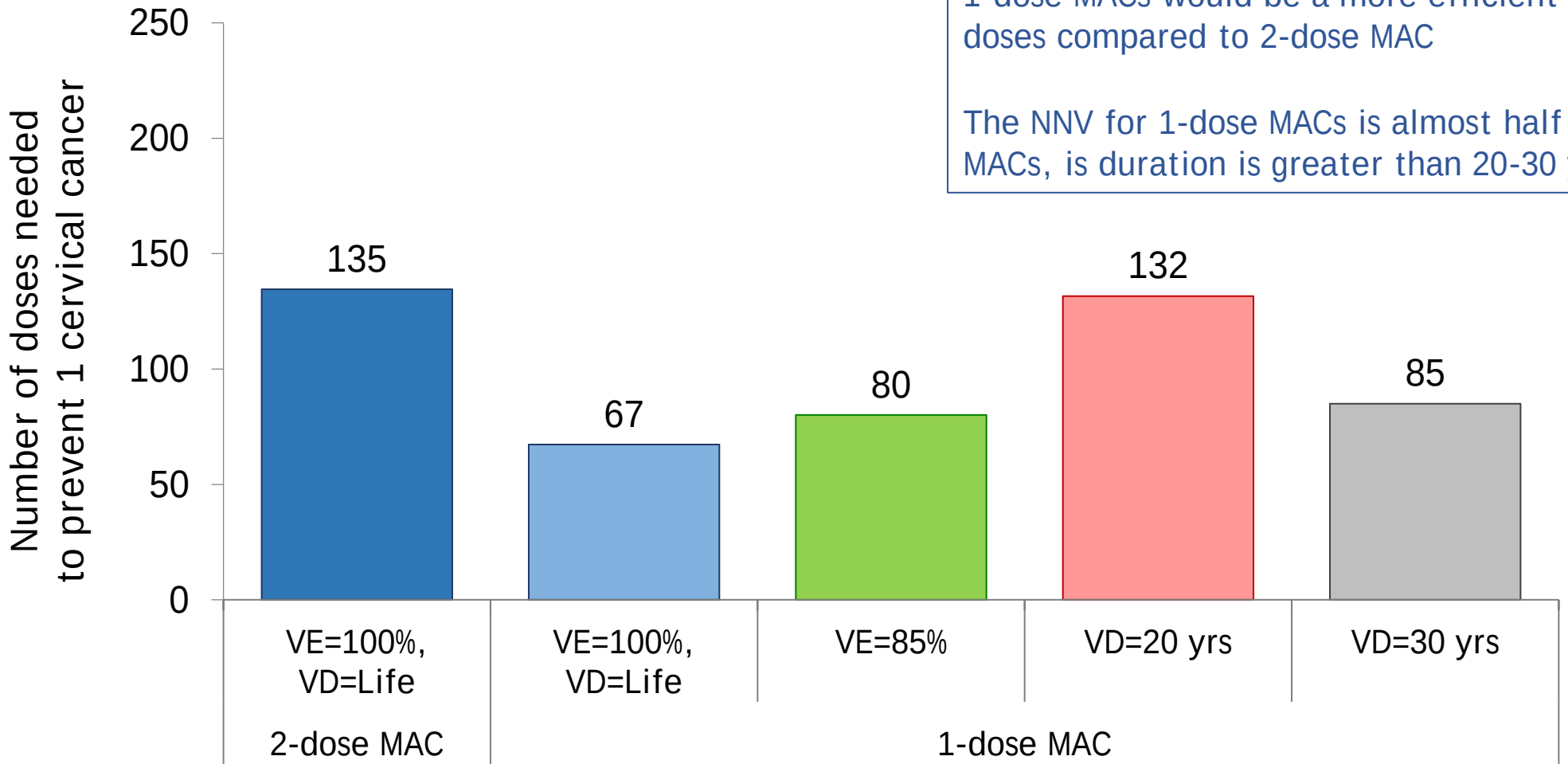
Age-standardized cervical cancer incidence rate, UN World Population prospect 2015; Cancers averted based on population UN prospect projections from 2018 to 2118

Number of doses needed to prevent 1 cervical cancer (NNV) through MAC vaccination vs 2-dose Routine

Country profile: INDIA

1-dose MACs would be a more efficient use of doses compared to 2-dose MAC

The NNV for 1-dose MACs is almost half 2-dose MACs, is duration is greater than 20-30 years

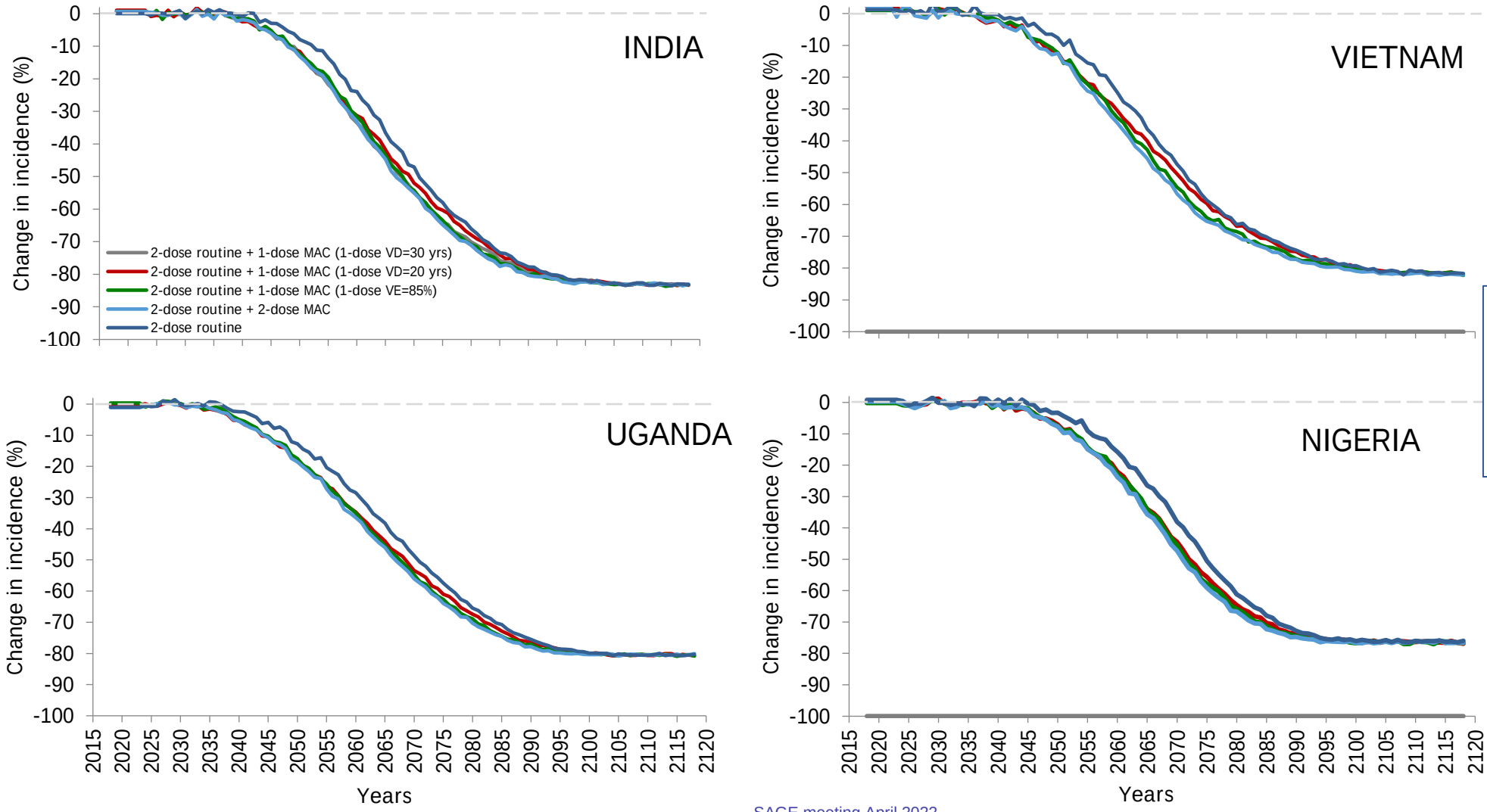


Time horizon=2018-2118; Cancers averted based on population UN prospect projections from 2018 to 2118; Girls-only, Routine = 9 yrs old, MACs = 10-14 yrs old, Vaccination coverage = 80%, 2-dose VE = 100%, 2-dose VD = Life

Impact of 1-dose vs 2-dose

4 country profiles

Girls-only, Start in 2023, Routine=9 yrs old, MACs=10-14 yrs old, Coverage=80%, 2-dose VE = 100%, 2-dose VD = Life



Conclusions are the same for the 4 country profiles

Age-standardized cervical cancer incidence rate, UN World Population prospect 2015

Question 2

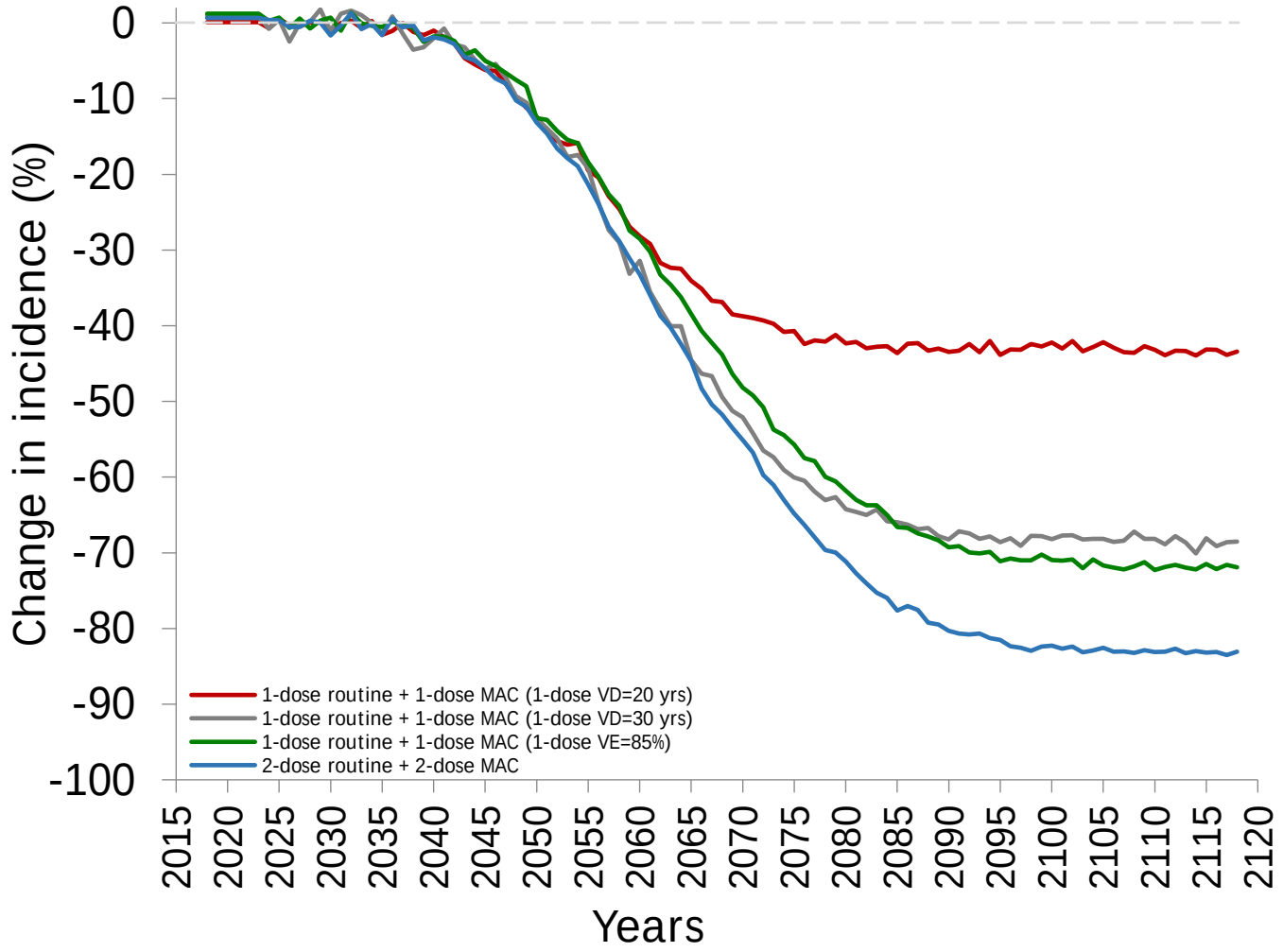
What could be the population-level impact and efficiency of 1-dose vs 2-dose routine HPV vaccination?

Will depend on 1-dose vaccine efficacy and duration of protection

Impact 1-dose vs 2-dose routine vaccination

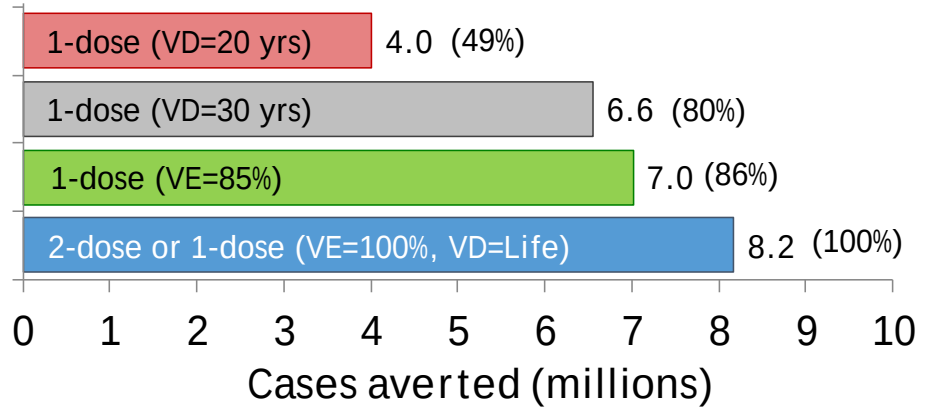
Country profile: INDIA

Girls-only, Start in 2023, Routine = 9 yrs old, MACs = 10-14 yrs old, Coverage = 80%, 2-dose VE = 100%, 2-dose VD = Life



1-dose routine vaccination reduces cervical cancers substantially, if duration is greater than 20-30 years

Under pessimistic assumptions of vaccine efficacy (85% VE or 30 years duration of protection), 1-dose would prevent 80-86% of the cervical cancer cases averted from 2-dose vaccination with half the number of doses

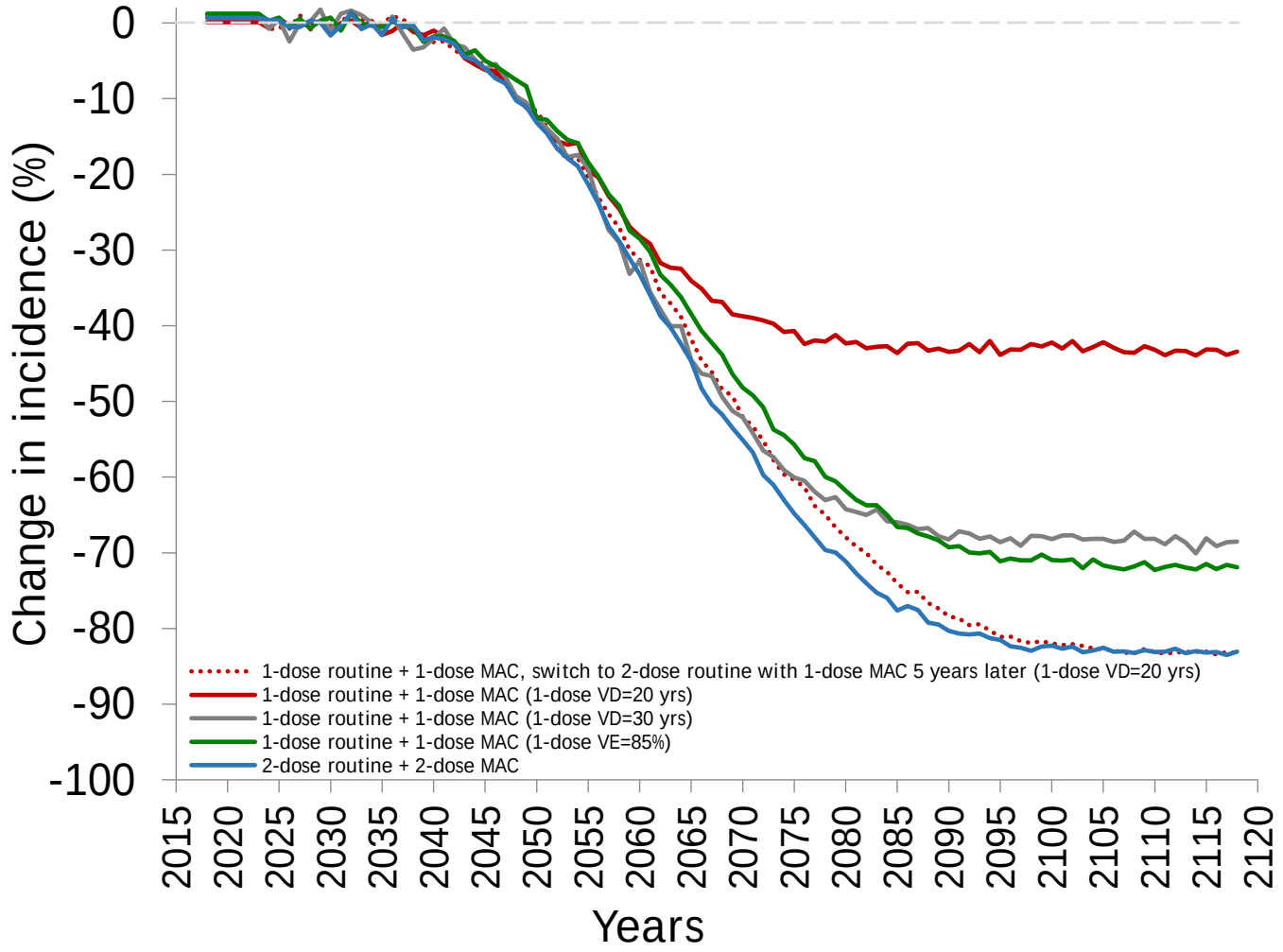


Age-standardized cervical cancer incidence rate, UN World Population prospect 2015; Cancers averted based on population UN prospect projections from 2018 to 2118

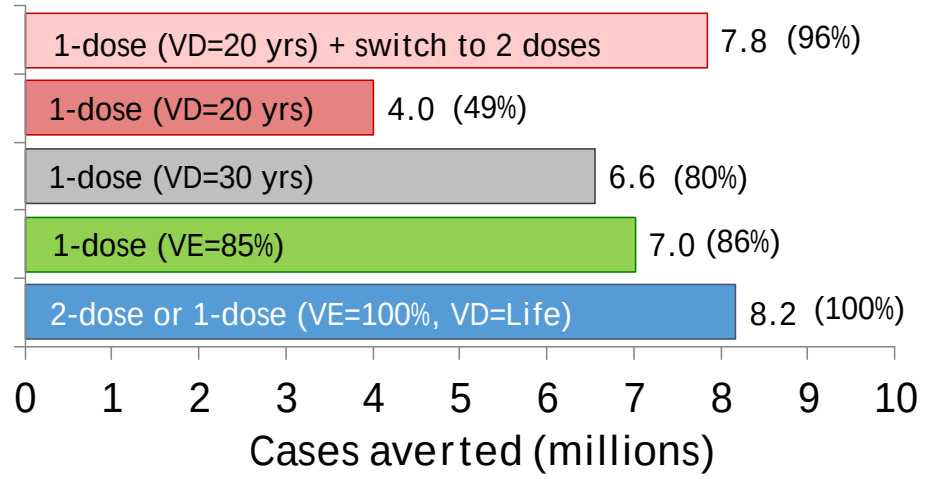
Impact 1-dose vs 2-dose routine vaccination

Country profile: INDIA

Girls-only, Start in 2023, Routine = 9 yrs old, MACs = 10-14 yrs old, Coverage = 80%, 2-dose VE = 100%, 2-dose VD = Life



If 1-dose protection is shown to start to wane in the next 5 years, switching to 2-dose routine vaccination (with a 1-dose MAC with high coverage) would mitigate loss in cancer prevention

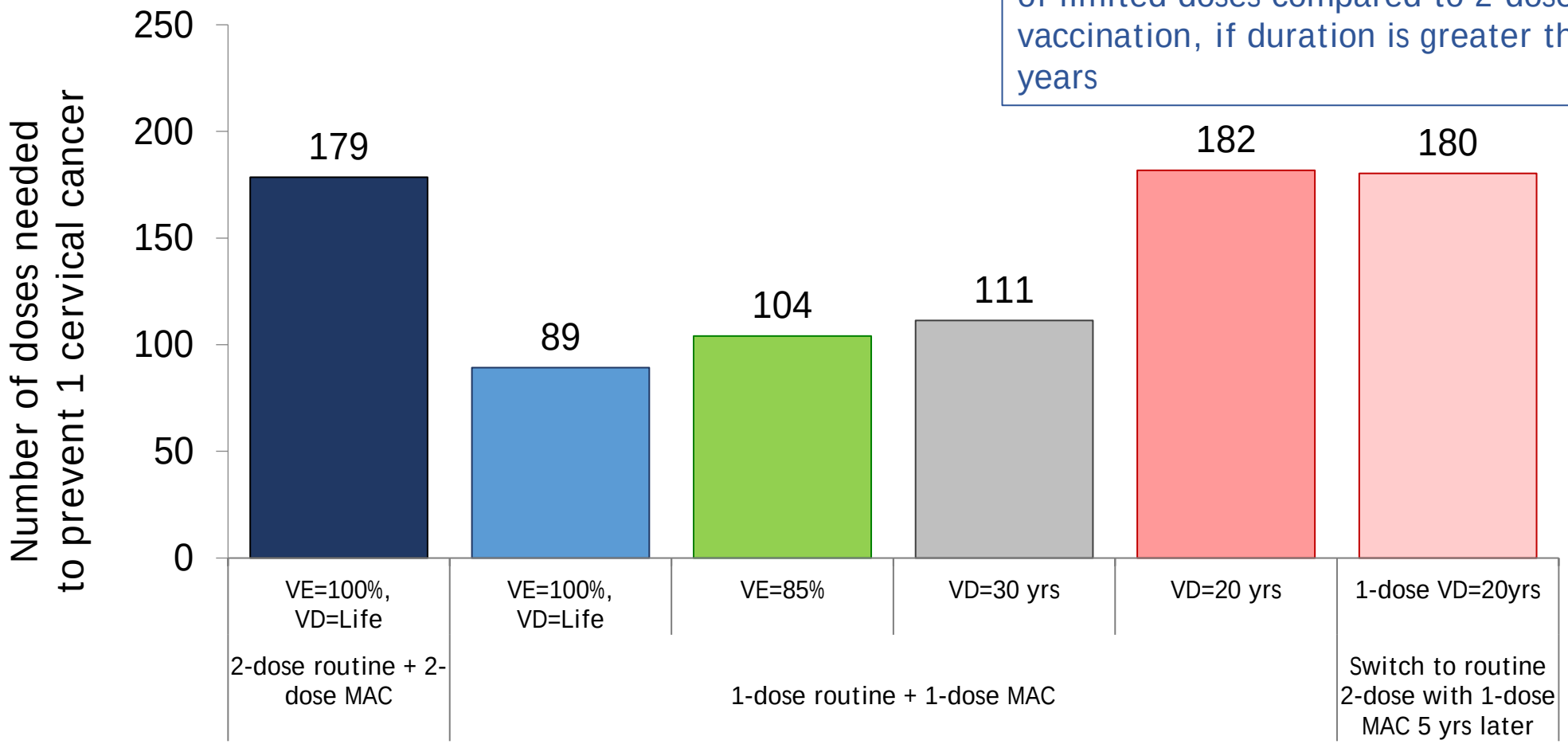


Age-standardized cervical cancer incidence rate, UN World Population prospect 2015; Cancers averted based on population UN prospect projections from 2018 to 2118

Number of doses needed to prevent 1 cervical cancer (NNV) versus no vaccination

Country profile: INDIA

1-dose routine would be a more efficient use of limited doses compared to 2-dose routine vaccination, if duration is greater than 20-30 years

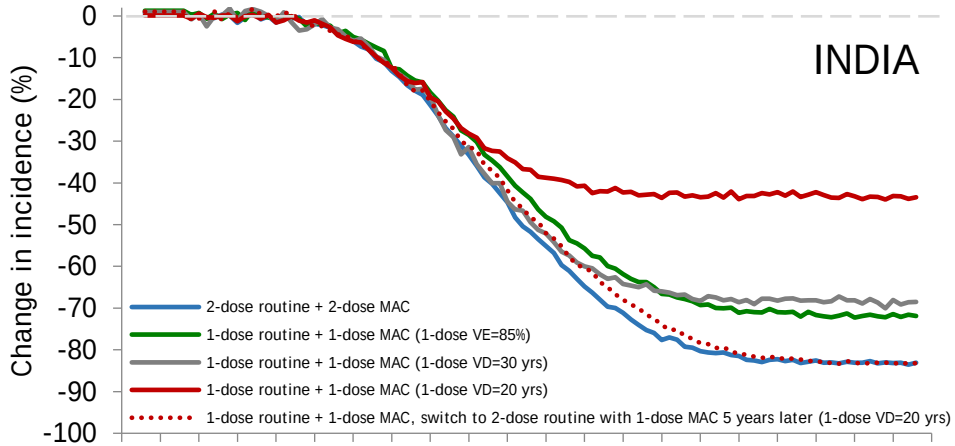


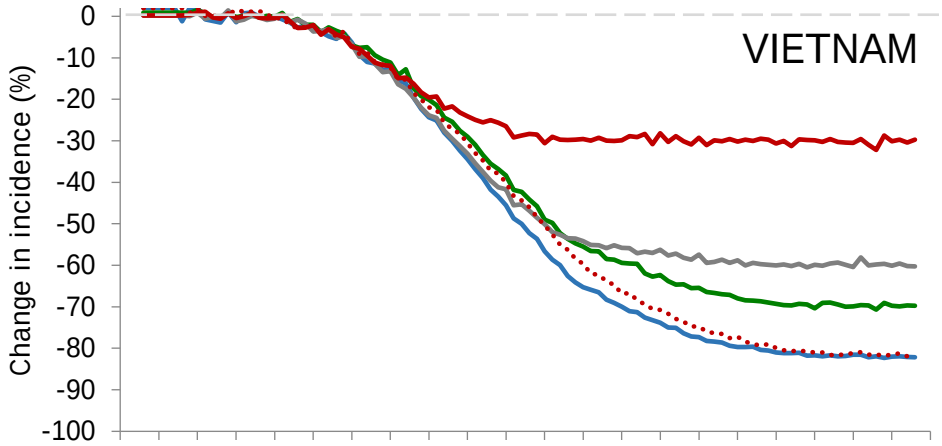
Time horizon=2018-2118; Cancers averted based on population UN prospect projections from 2018 to 2118; Girls-only, Routine = 9 yrs old, MACs = 10-14 yrs old, Vaccination coverage = 80%, 2-dose VE = 100%, 2-dose VD = Life

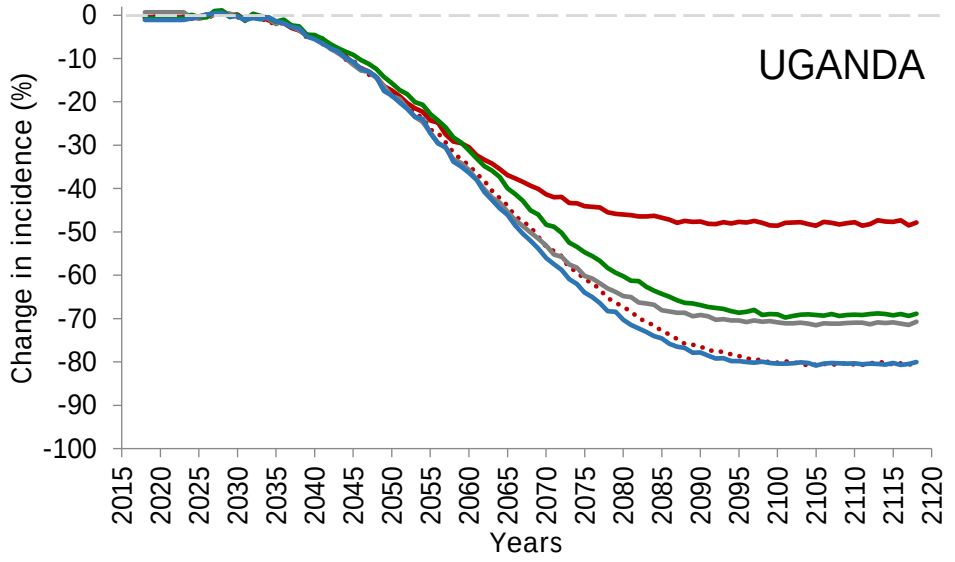
Impact of 1-dose vs 2-dose routine vaccination

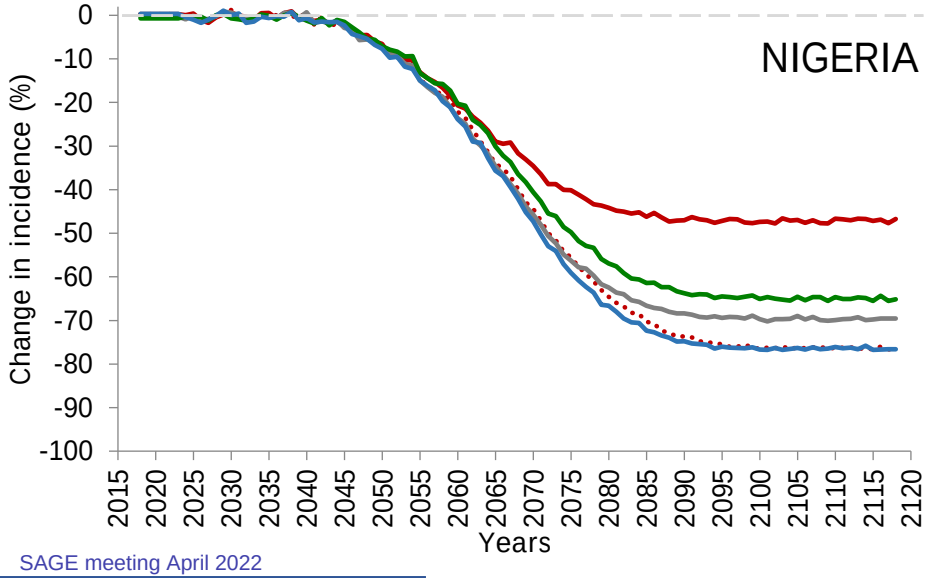
4 country profiles

Girls-only, Start in 2023, Routine=9 yrs old, MACs=10-14 yrs old, Coverage=80%, 2-dose VE = 100%, 2-dose VD = Life









Conclusions are the same for the 4 country profiles

Age-standardized cervical cancer incidence rate, UN World Population prospect 2015

Question 1: Should 1-dose HPV vaccine schedule be recommended for use in multi-age cohort (MAC) catch-up?

Multiple Age Cohort (MAC) vaccination with 1 dose would:

- Prevent a substantial additional number of cervical cancer cases and accelerate reductions in incidence (accelerate elimination) vs routine vaccination only
  - by protecting girls that would be aging out of the 9-14 age window
- Provide similar additional cervical cancer cases averted as a 2-dose MAC catch-up
  - Herd immunity from 2-dose routine would mitigate the impact if 1-dose efficacy is lower
- Would be a more efficient use of limited doses compared to 2-dose MAC

Currently we are losing girls who are aging out of the 10-14 year old vaccination window.

For these girls, 1-dose vaccination is better than no vaccination, is a more efficient use of limited vaccine doses than 2-doses and likely will provide similar impact than 2-doses.

Question 2: Should 1-dose HPV vaccine schedule be recommended for routine vaccination?

1-dose routine HPV vaccination:

- reduces cervical cancers substantially, if duration is greater than 20-30 years
  - would prevent about at least 80-86% of the cervical cancer cases averted by 2-dose vaccination, under pessimistic assumptions (85% VE or 30 years duration of protection)
- would be a more efficient use of limited doses compared to 2-dose routine vaccination, if duration is greater than 20-30 years

Key issue: Duration of vaccine protection

If 1-dose protection is shown to wane within the next 5 years (at which time more than 15 years of follow-up will be available), switching to 2-dose routine vaccination (with a 1-dose MAC for 10-14 year olds with high coverage) could mitigate losses in cervical cancer prevention&.

&. Conclusions are consistent with comparative modeling work conducted by Harvard, Université Laval and LSHTM (Burger *et al*. (under review)).

Summary of key evidence

Rakesh Aggarwal

SAGE member

Overview of key evidence on 1-dose HPV vaccination

Outcome		Results	Key study	GRADE
Immunogenicity	**Seroconversion**	One, two and three doses similar (> 97%) (HPV2/9)	DORIS (RCT)	High
	Antibody titers	Lower GMC with 1 dose (vs. 2 or 3 doses) (HPV2/9)	DORIS (RCT)	High
	Persistence of antibody	GMTs stable up to 11 years, and comparable for 1, 2 and 3 doses (HPV2/4)	CVT, IARC (Post-RCT) DORIS (RCT)	Moderate High
Protection in trials (vaccine efficacy)	**Protective efficacy against** • Persistent infection (HPV 16/18) • Persistent infection (HPV 16/18/31/33/45/52/58)	**VE for one-dose vs. 0 dose** • 97.5% (HPV2/9) • 88.9% (HPV9)	KEN SHE (RCT) KEN SHE (RCT)	High
	• Persistent infections (HPV 16/18) • Prevalent infections (HPV 16/18)	• 94.2% (Similar to 2 & 3 doses) (HPV4) • 82.1% (Similar to 2 & 3 doses) (HPV2)	IARC (Post-RCT) CVT (Post-RCT)	Low Low
	Duration of protection	Up to 10 years against HPV16/18 (HPV4) Up to 11 years against HPV16/18 (HPV2)	IARC (Post-RCT) CVT (Post-RCT)	High