HPV vaccines schedule optimization

Update on April 2022 SAGE advice on HPV schedule optimization and the permissive single dose recommendation in younger women

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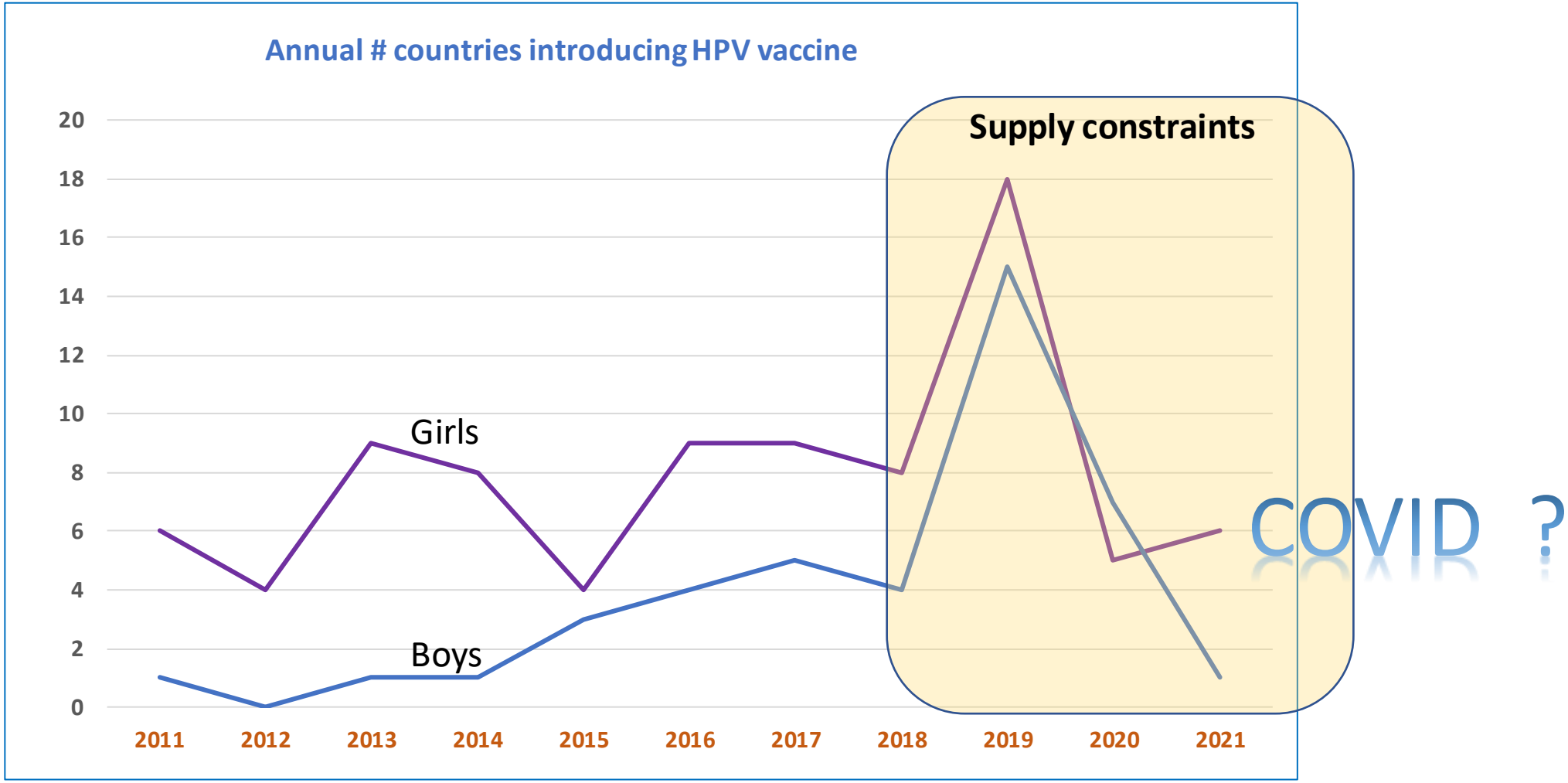
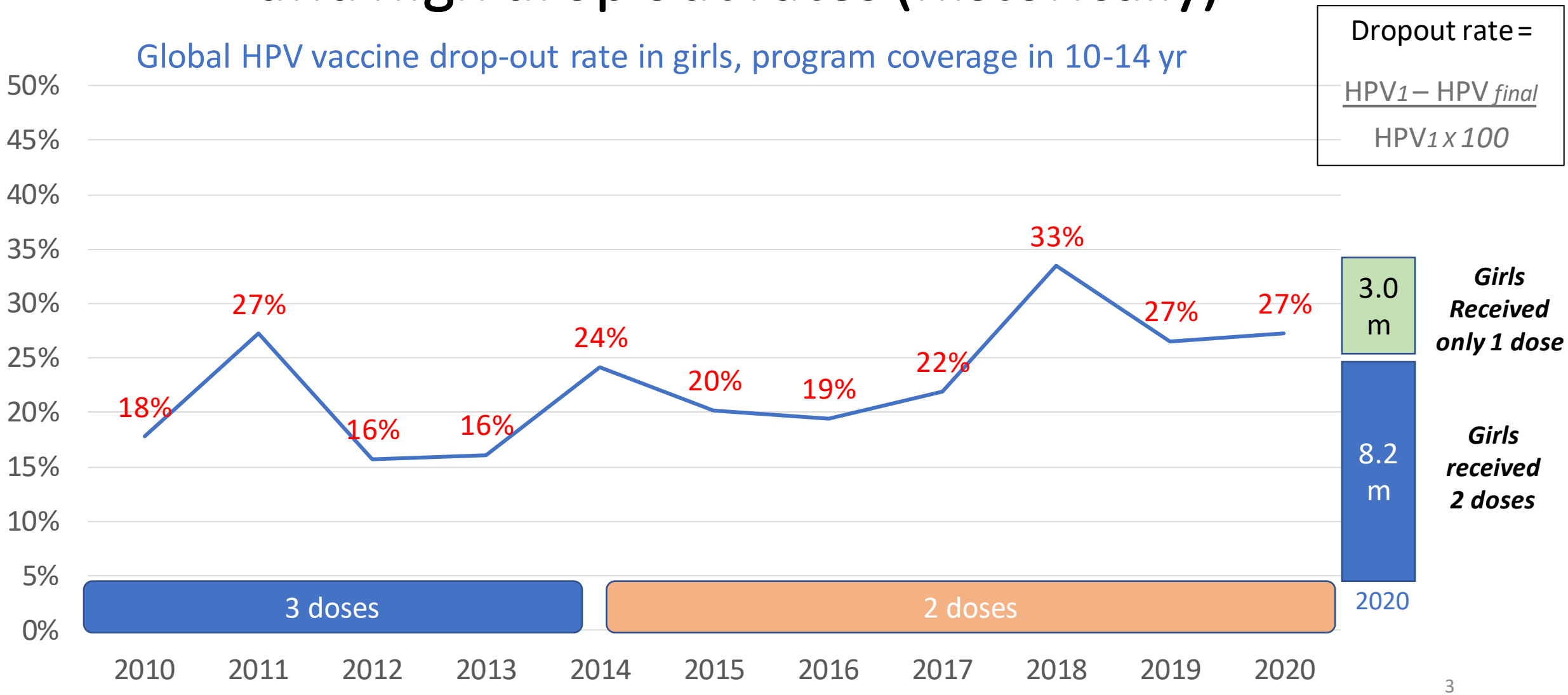
WHO IVB
2 June 2022

Stagnation in HPV vaccine introductions



HPV vaccination context :

Introduction rate slowing, low coverage and high drop out rates (historically)



Supply: Decreases in demand coupled with producion increases led to reduction in risk of global shortages included in short term

FIG. 3: SUPPLY/DEMAND BALANCE[21,22]

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)
2-doses +2ds MACs (base case)						
2-doses +2ds MACs & gender neutral						
2-doses no MACs high coverage (Elimination)						
1-dose +1d MACs						
1-dose +1d MACs & gender neutral						

- Excess supply — Supply >2X Demand
- No risk of shortages — Supply >1.3X Demand
- Some risk of shortages — Supply <1.3X Demand
- Insufficient supply — Supply <1.1X Demand

1d: one dose; 2ds: two doses; MACs: multi-age cohorts.

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

Market health: manufacturer base broadening

- Third Manufacturer on global market - WHO PQ-ed (Innovax, Cecolin)
- Fourth new manufacturer licensed in China (Walvax)

WHO HPV Vaccine Global Market Study April 2022

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

Questions considered by the SAGE *HPV Working Group*

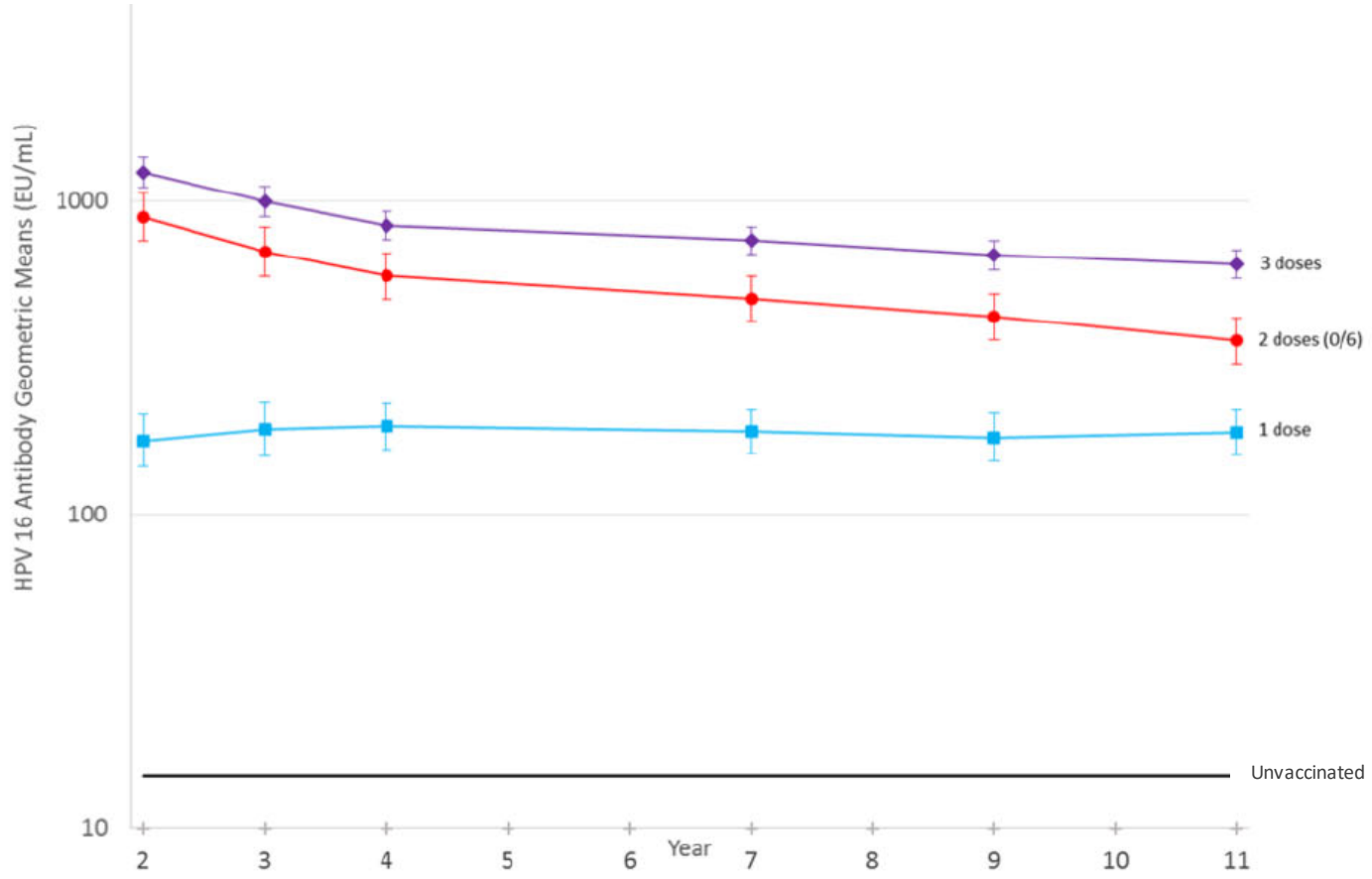
1. What evidence gaps exist and what research is recommended to enable SAGE to make a universal one-dose HPV schedule recommendation?

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?

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

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

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 presented to SAGE HPV Work Group

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

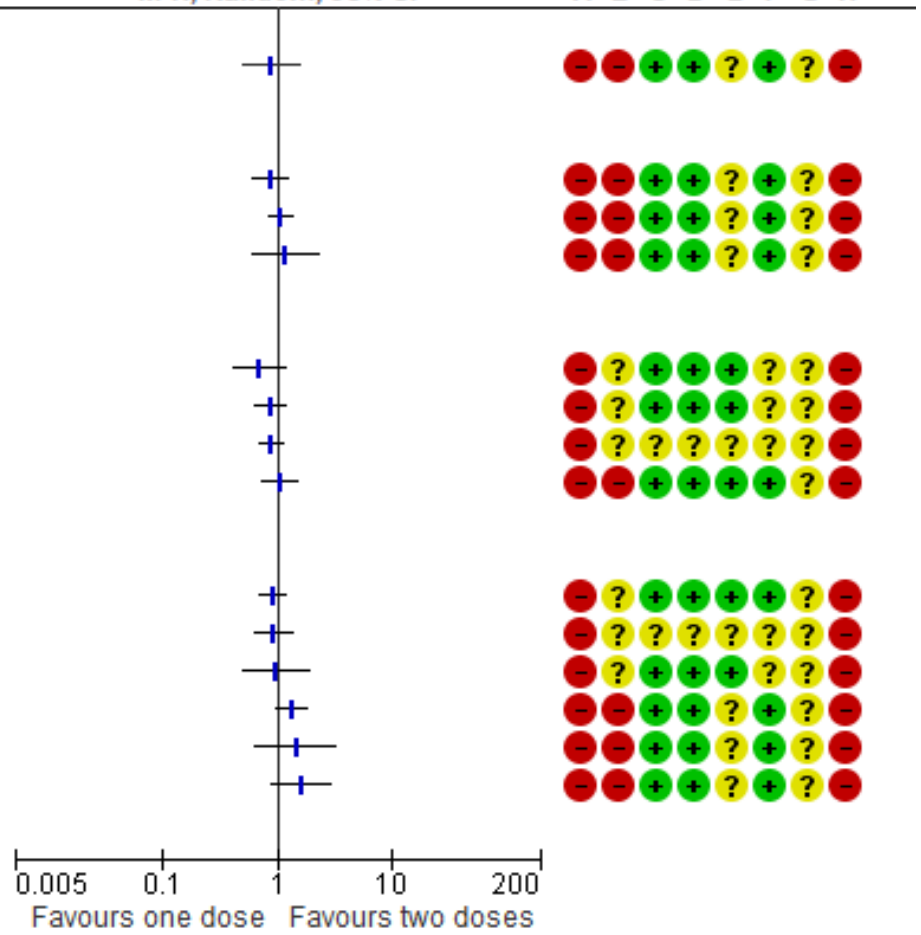
Study arm	Number	Incident persistent HPV 16/18	Incidence/ 100 PY	VE % (95% CI)
9vHPV	496	1	0.17	**97.5%** (81.7–99.7)
2vHPV	489	1	0.17	**97.5%** (81.6–99.7)
MCV	473	36	6.83	Reference

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

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]



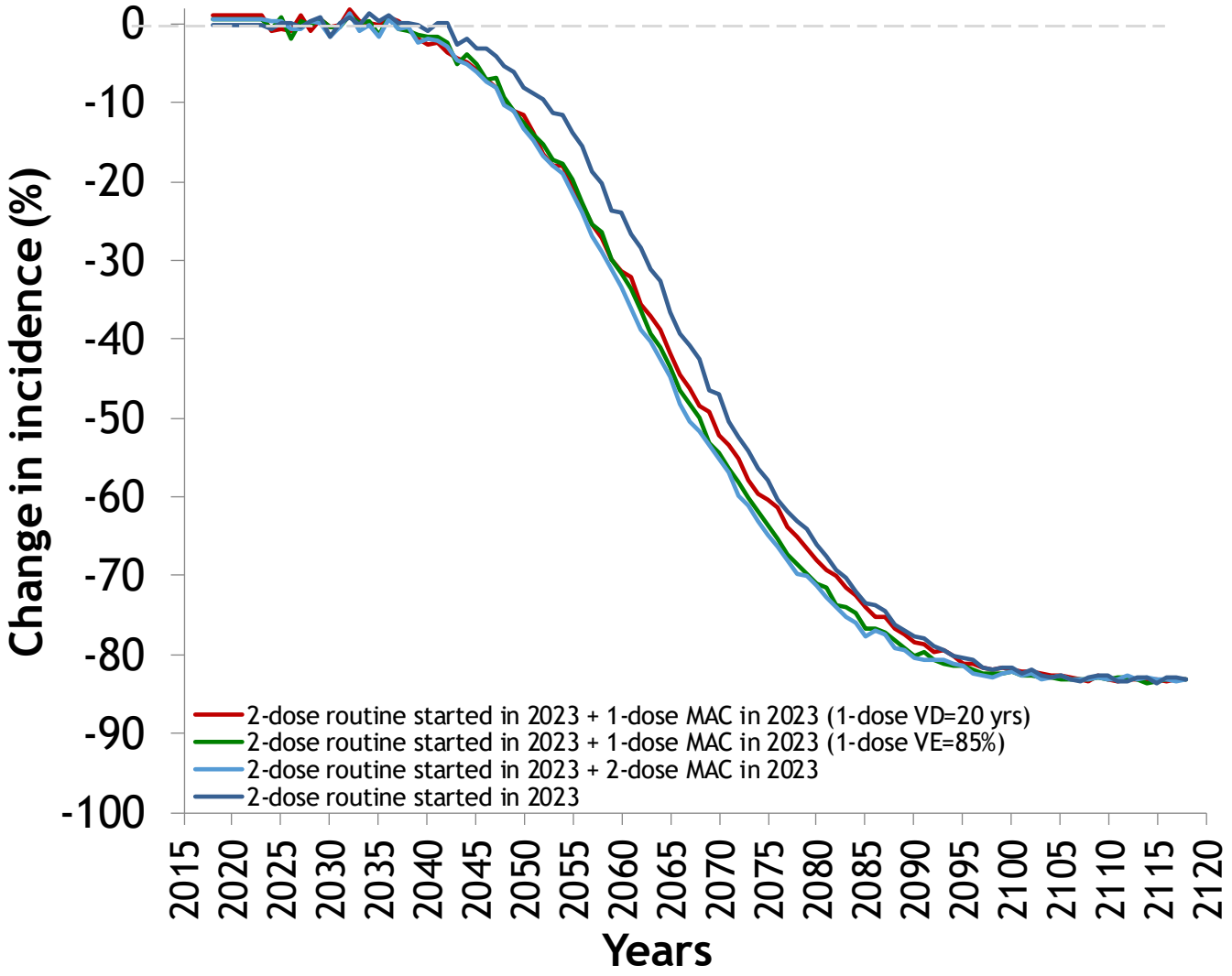
Cochrane Response

SAGE : https://www.who.int/news-room/events/detail/2022/04/04/default-calendar/sage_meeting_april_2022

Impact 1-dose vs 2-dose MACs

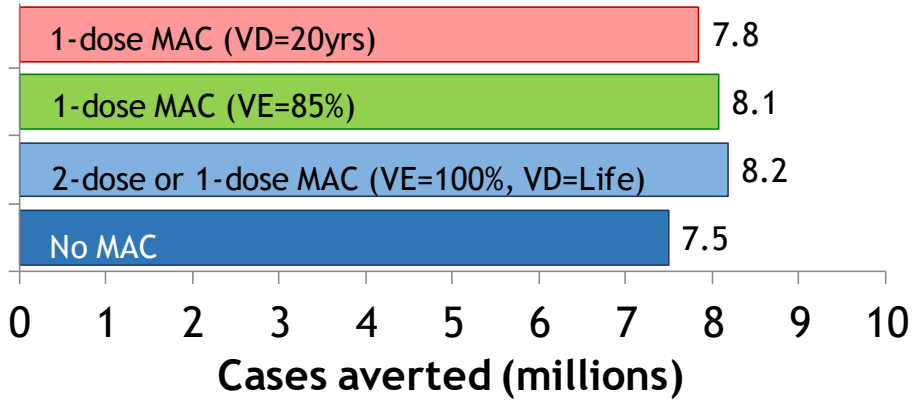
Country profile: INDIA

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

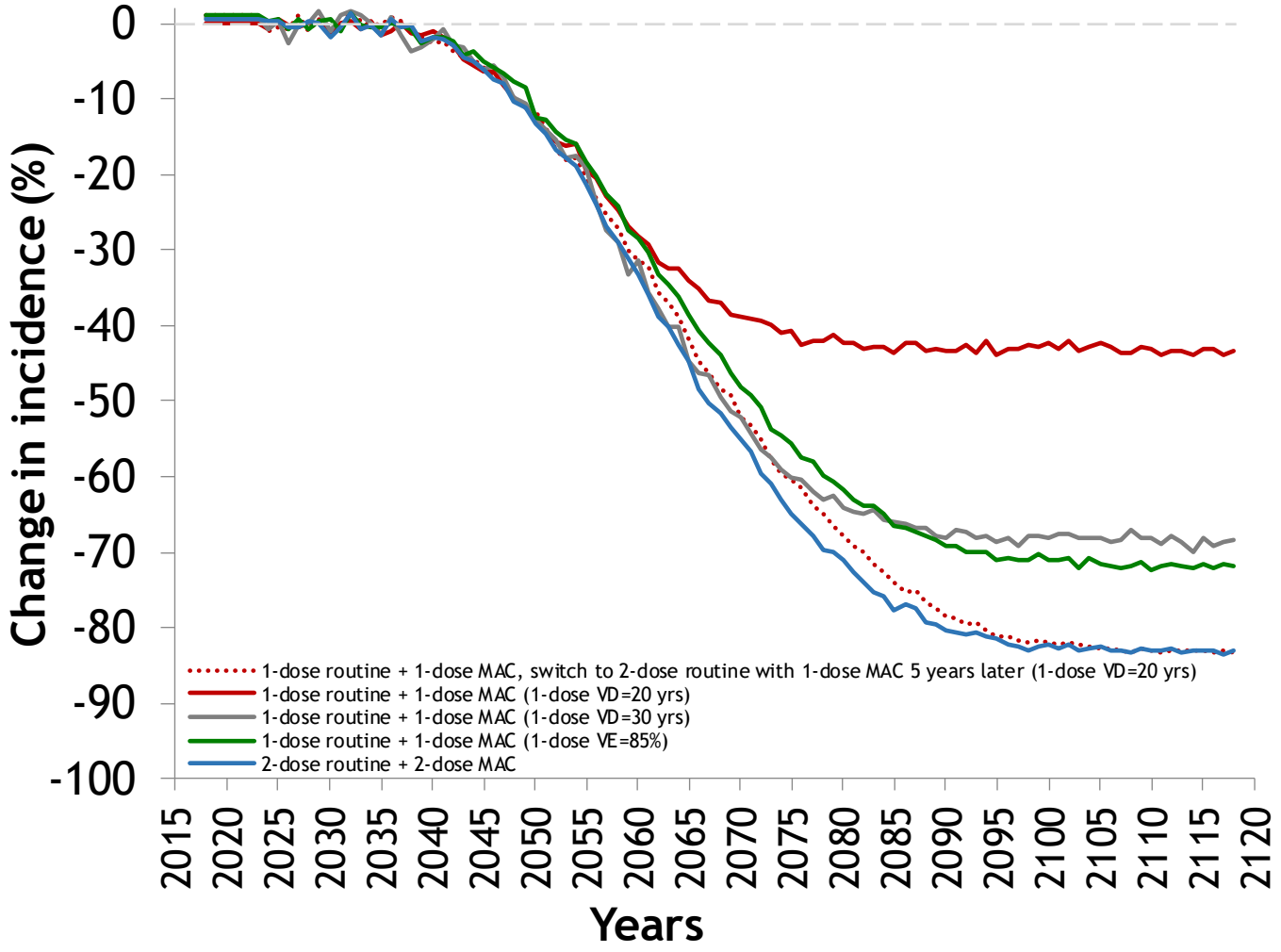


Age-standardized cervical cancer incidence rate, UN World Population prospect 2015; Cancers averted based on population UN prospect projections from 2018 to 2118

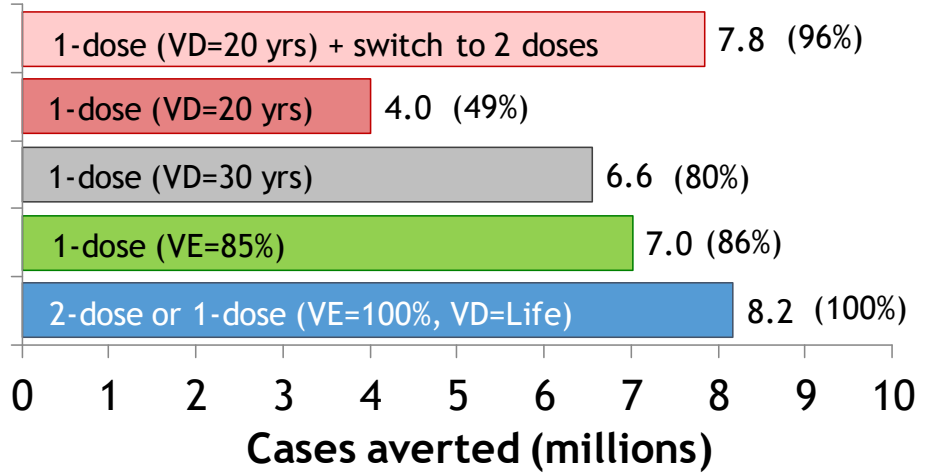
Impact 1-dose vs 2-dose routine vaccination

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

SAGE Advise … Comparison with the current WHO position

Current WHO position			SAGE Advises
Primary target group		Girls aged 9-14 years old	Girls aged 9-14 years old
Vaccination Schedule	**9-14 years old**	2-dose schedule	Either a 1-dose* or a 2-dose vaccination schedule can be used
	15-20 years old	3-dose schedule	Either a 1-dose* or a 2-dose vaccination schedule can be used
	≧21 years old	3-dose schedule	2-dose schedule can be used
	Immuno-compromised (any age)	3-dose schedule	Should be prioritized and should receive <u>at least 2 doses</u> but <u>ideally 3 doses,</u> if programmatically feasible. Immunocompromised persons, including HIV+, should receive vaccination against HPV both within and outside of standard eligibility age-range.

* For products for which efficacy data is available, or immunogenicity has been bridged to vaccines with proven single-dose efficacy.

SAGE Advises … Comparison with the current WHO position

Current WHO position			SAGE Advise
Vaccination prioritization	MAC	*Temporarily postpone*	SAGE recommends countries, where feasible and affordable, to prioritize catch-up of older cohorts and missed girls through multi-age cohort (MAC) vaccination
	Boys	*Temporarily postpone*	Males can receive same schedule as females
	Older age cohorts	*Temporarily postpone*	Introducing the vaccination of boys and older females should be carefully managed until the global supply situation is fully unconstrained.

Further evidence needed:

- Immunogenicity, protective efficacy and duration of protection, with reduced-dose schedules in immunocompromised individuals
  - In particular: protection when HIV seroconversion happens after 1 dose HPV vaccine

- Long-term immunogenicity, efficacy and duration of protection of one-dose HPV vaccine schedule in girls 9-14 year old, in boys as well as the use of single-dose schedules in older adults and children below 9 years of age

- Implementation research to identify strategies to improve HPV vaccine coverage, including among populations at high risk of early HPV infection and immunocompromised individuals

Next steps

1. WER 10 June 2022 publication of SAGE meeting outcomes with full SAGE advice on HPV vaccine schedule

2. Stakeholder consultation process
   - Evidence, research needs and regulation - Manufacturers & Researchers
   - Clarifying criteria, challenges and guidance needed for decision making - EPI programs & NITAGs

3. A revised WHO Position Paper on HPV vaccines planned for Dec 2022

4. Development of a “prioritization framework “ for secondary targets