Single Dose Scientific Evidence Data & Implementation Progress

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CHIC HPV vaccination in Southeast Asia and West Pacific Region, Manila. 2 October 2024

Disclosures

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee
GSK Biologicals			X				
MSD			X				

Cervical cancer and benefits of a dose reduction

- WHO target - cervical cancer elimination by 2030
- 2023 worldwide vaccine coverage in girls <15 years of age was ~27% [2]
- Single dose could lead to equitable delivery of HPV vaccination by:
  - reducing costs, simplifying delivery and encouraging HPV vaccine programme introduction and multi-age cohort (MAC) vaccine delivery & thereby
  - Increase vaccine uptake and help to reduce cervical cancer rates and cervical cancer-related deaths [3]

1. Cervical Cancer Elimination Initiative. WHO.
2. WHO/UNICEF Estimates of National Immunization Coverage, 2023 Revision
3..Stanley M, Dull P. HPV single-dose vaccination: Impact potential, evidence base and further evaluation. *Vaccine* 2018;36(32):4759–60. https://doi.org/10.1016/j.vaccine.2018.02.076 .

Studies with single-dose data reviewed by SAGE

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, vs 0 dose (MenA group)
DoRIS Tanzania	Immunogenicity	2vHPV 9vHPV	Females 9–14	RCT: 1-, 2-, 3-dose groups *Bridging : -> KEN SHE -> CVT -> India IARC*
Thailand Impact Thailand	Impact/ effectiveness	2vHPV	grade 8	Observational Study: Grade 8 Students in one province received 1 dose; in another district 2 doses

Courtesy of P. Bloem (WHO)

Other studies with single-dose data

Trial/Country	Evidence	Vaccine	Age Group (yrs)	Description
Cecolin/Gardasil RCT: Bangladesh & Ghana	Immunogenicity	2vHPV Cecolin 4vHPV Gardasil	9-14 females	RCT of delayed dose 2; SD data to M6.
HOPE (S. Africa)	Vaccine effectiveness	Cervarix	SD catch up vaccination of 15-16 yo girls	Cross-sectional study of HPV 16/18 prevalence following catch-up campaign. Includes HIV+
Phase 2 delayed 2nd dose (USA)	Immunogenicity	Gardasil-9	Females & males 9-11	SD offered to all participants

Courtesy of P. Bloem (WHO)

Costa Rica Vaccine trial (CVT)

- Randomised, double-blind trial of 3 doses of Cervarix®; women aged 18-25 years randomised to 3 doses Cervarix® or control vaccine (Havrix®)
  - Not all completed vaccine series; some received only 1 or 2 doses
- 1st evidence of single dose protection - no evidence of a difference in HPV 16/18 VE or prevalent infection rates across dose groups
- Data at 10 years of follow-up

HPV16/18 infection endpoint	% infection (95% CI)			
	3-dose N=1365	2-dose N=62	1-dose N=112	Control N=1783
Prevalent HPV 16/18	2.0 (1.3 – 2.8)	1.6 (0.1 – 7.7)	1.8 (0.3 – 5.8)	10.0 (8.7 – 11.4)
Vaccine efficacy	**80.0% (70.7-87.0)**	**83.8% (19.5-99.2)**	**82.1% (40.2-97.0)**	**Reference**

Kreimer et al. *J Natl Cancer Inst* 2020

IARC India study

- Cluster randomised trial of 2 vs. 3 doses of 4vHPV (Gardasil®)
  - Girls aged 10-18 years randomised to 2 (0, 6m) or 3 doses (0, 2, 6m)
  - MOH India suspended all HPV vaccination trials in April 2010
  - 17,729 randomised; 4949 received 1 dose; analysed as an observational cohort
  - Age- & site- matched unvaccinated controls recruited post-hoc after suspension
- Followed for efficacy for ~12 years (samples collected from married girls/women)
  - VE against incident and persistent HPV 16/18 infection similar across dose groups

HPV16/18 infection endpoint	N and % infection (95% CI)			
	3-dose 2172	2-dose 2311	1-dose 3022	Control 1268
Persistent HPV 16/18				
N & % infection (95% CI)	2 (0.1; 0.0 – 0.3)	2 (0.1; 0.0 – 0.3)	4 (0.0; 0.0 – 0.3)	35 (2.7; 1.9 – 3.8)
VE (persistent HPV 16/18)	**95.3% (90.9-97.5)**	**94.8% (90.9-97.3)**	**92.0% (87.0-95.0)**	

Sankaranarayanan, et al. Lancet Oncol2016; Basu et al. JNCI in press

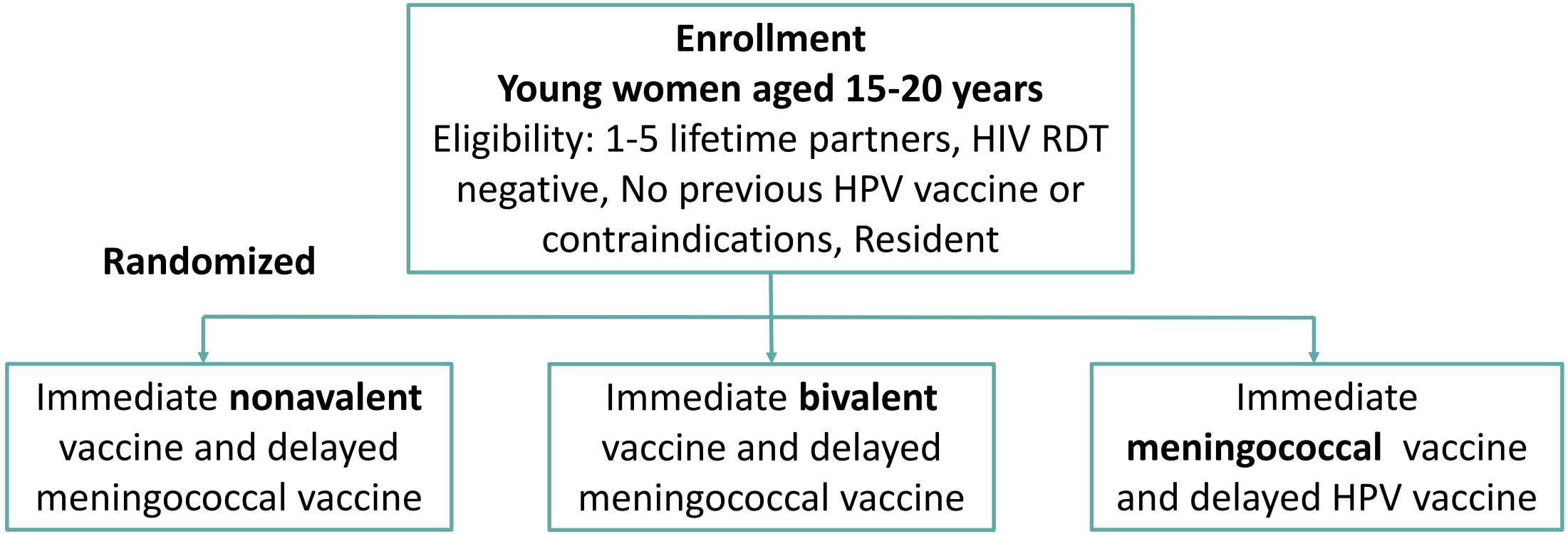
Analysis of cervical screening outcome IARC/India study

Study Group	Women screened	Positive on HPV test (%)		Positive for HPV 16 &/or 18 (among HPV +ve)	CIN 2/3 associated with HPV 16/18
Unvaccinated	4,734	374	(7.9)	28.3%	8
All vaccinated	8,012	375	(4.6)	9.4%	0
3- dose	2,418	96	(5.2)	10.0%	0
2- dose	2,607	123	(6.1)	9.2%	0
1- dose	2,987	106	(4.3)	9.2%	0

Slide courtesy of Basu et el. (Malvi SG et al. JNCI – In Press)

KEN SHE Study Design

- Individually randomized, double-blind, controlled trial
- Multi-center: Three KEMRI locations in Kenya



Slide courtesy of Barnabas RV et al

KEN SHE – M36 vaccine efficacy for incident persistent HPV 16/18 infections*

	mITT No.	No. events	Incidence/ 100 woman yr	VE (%)	VE 95% CI
Delayed Vaccination N = 757	473	72	6.70	Ref	Ref
Single dose Cervarix® N = 760	489	2	0.16	97.5	90.0; 99.4
Single dose Gardasil®9 N = 758	496	1	0.08	98.8	91.3; 99.8

mITT cohort: HPV antibody negative & HPV DNA negative for the relevant genotypes at enrolment and m3 on external genital and cervical swabs;

* Defined as vaccine type specific HPV detected at two consecutive time points no less than 4 months apart after M3 up to & including M18

CI: confidence interval; mITT: modified intent-to-treat; VE: vaccine efficacy; yo: year of age

Barnabas, et al. Nat Med 2023; https://doi.org/10.1038/s41591-02 02658-0

KEN SHE – M36 Gardasil-9® VE for incident persistent HPV 16/18/31/33/45/52/58 infections

	Number of mITT	Number events	Incidence/ 100 woman yr	VE (%)	VE 95% CI
Delayed Vaccination N = 757	290	84	13.8		
Single dose Gardasil®9 N = 758	325	5	0.61	95.5	89.0; 98.2

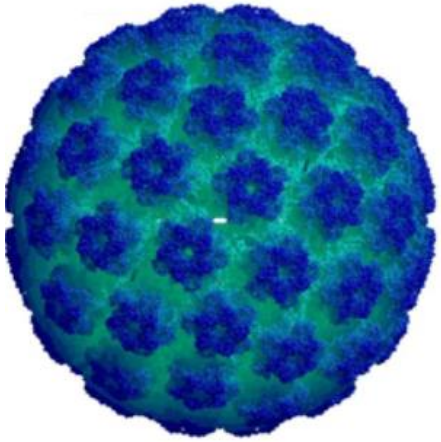
mITT cohort
No vaccine-related SAEs

VE: vaccine efficacy

Barnabas, et al. Nat Med 2023; https://doi.org/10.1038/s41591-023-02658-0

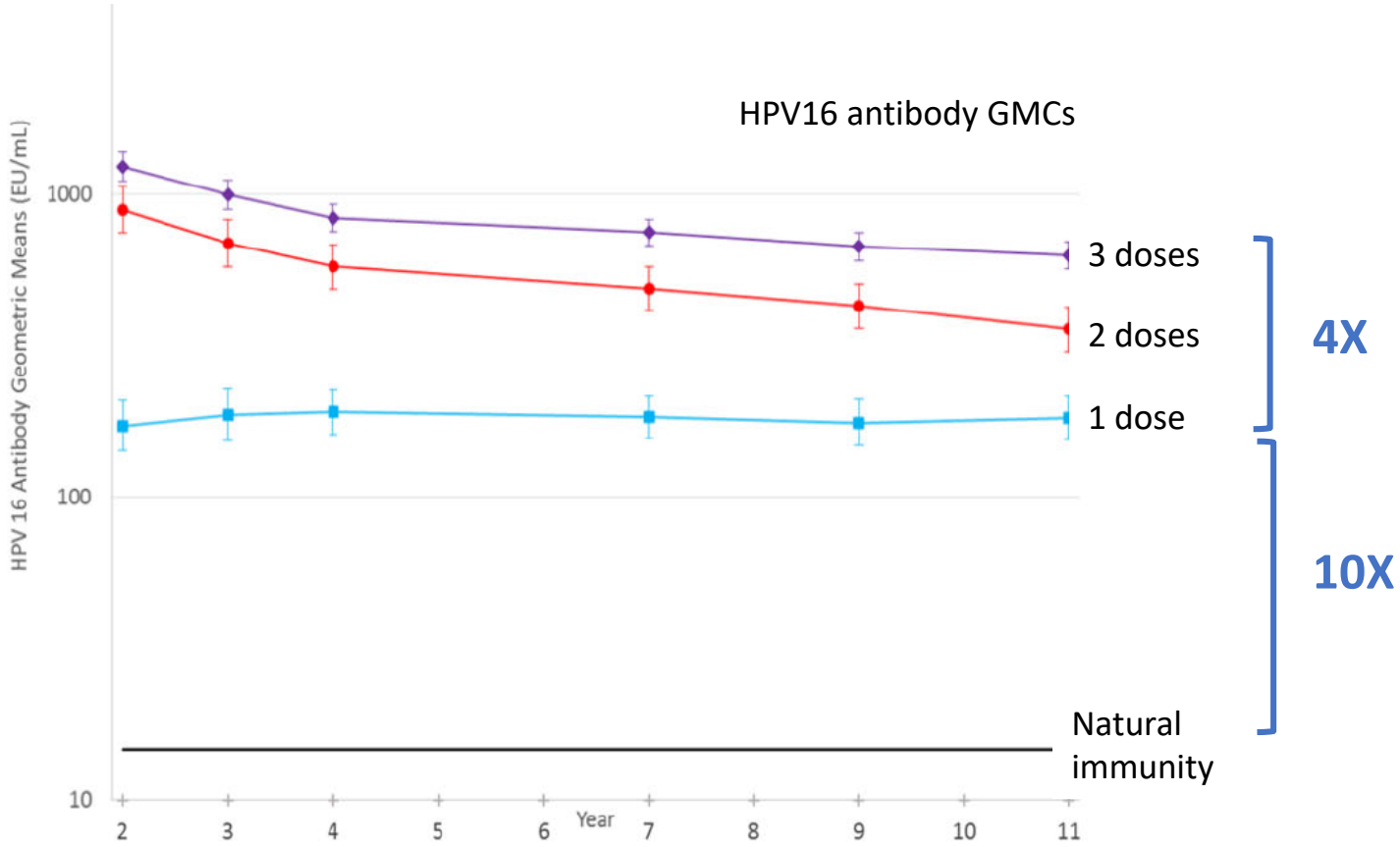
Biological plausibility for a single dose of HPV vaccine

- Antibodies – main method of protection
- VLP epitope structure (densely ordered, repetitive arrays of B cell epitopes) and size (50-55 nm) ideal for stimulating the immune system
- Efficient generation of long-lived, antigen-specific antibody-producing plasma cells
- Results in durable (>10 years) and stable antibody levels
- A minimum antibody level required for protection not yet established but low level of antibodies are protective in animal models.



Schiller J, Lowy D. Explanations for the high potency of HPV prophylactic vaccines. *Vaccine*. 2018;36(32 Pt A):4768-4773. doi: 10.1016/j.vaccine.2017.12.079.

CVT - Immune responses to 11 years post-vaccination

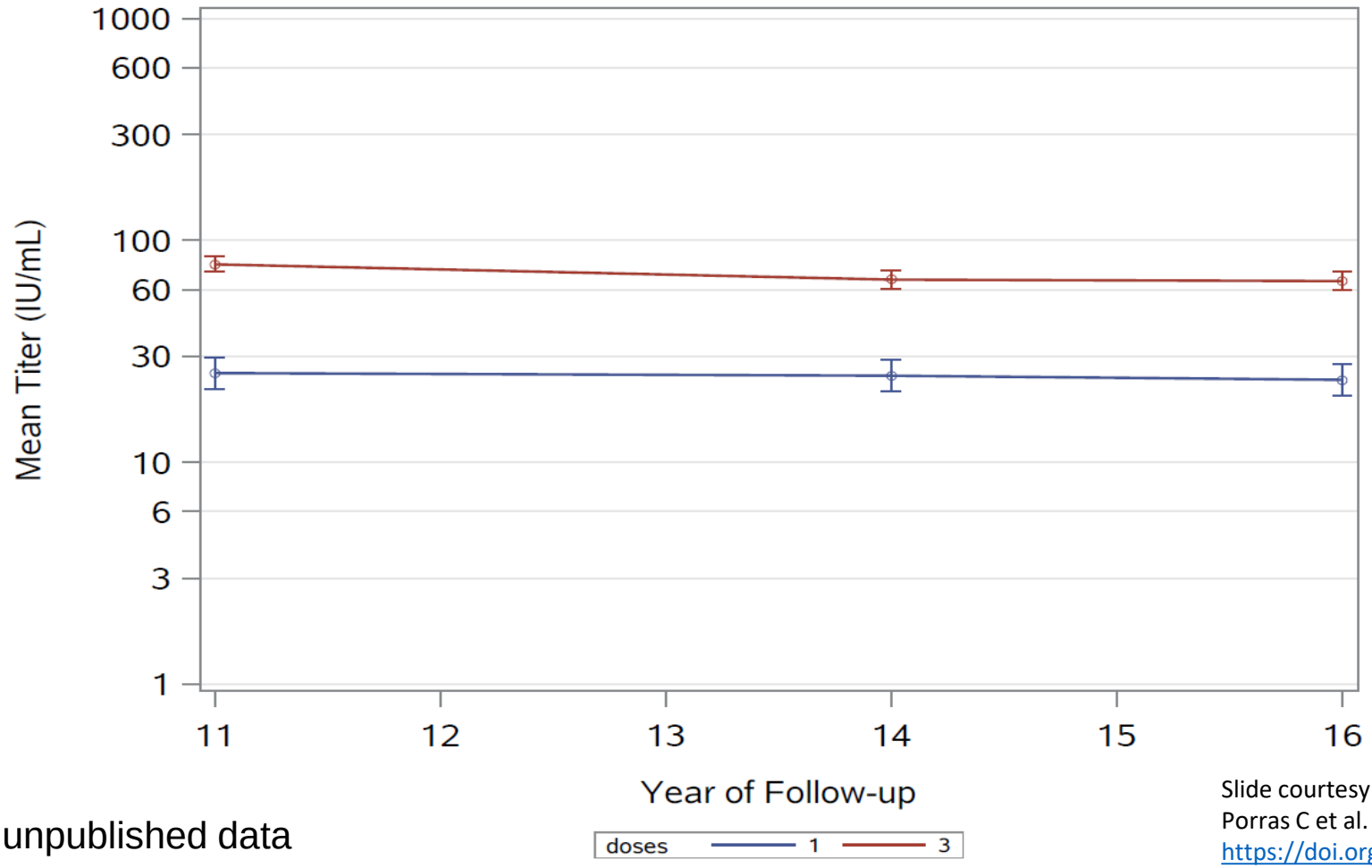


Stable antibody levels for HPV-16 and HPV-18 antibodies up to 11 years post-vaccination at leat 10-fold greater than levels generated by natural infection

Kreimer A. et al, JNCI (2020) Oct 1;112(10):1038-1046. doi: 10.1093/jnci/djaa011.

HPV-16 Antibody Geometric Mean Concentration by visit year for CVT 1- and 3-dose groups to 16 years

CVT extension: to assess long-term stability of HPV-16/18 antibody levels; N=991



Romero B et al unpublished data

Slide courtesy of C. Porras & A. Kreimer ; data presented at IPVC 2023
Porras C et al. JNCI 2024, 2024(67), 329–336,
https://doi.org/10.1093/jncimonographs/lgae032

IARC/India study: immune responses for HPV 16 and 18 over time in single-dose or three dose recipient (M9ELISA)

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HPV 16 Ab response at 10 yr:

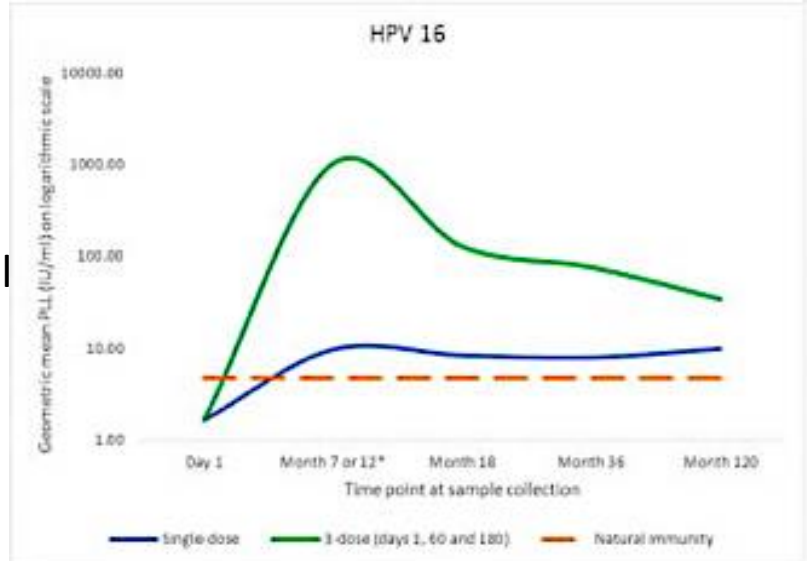
96% 1D recipients -detectable antibody

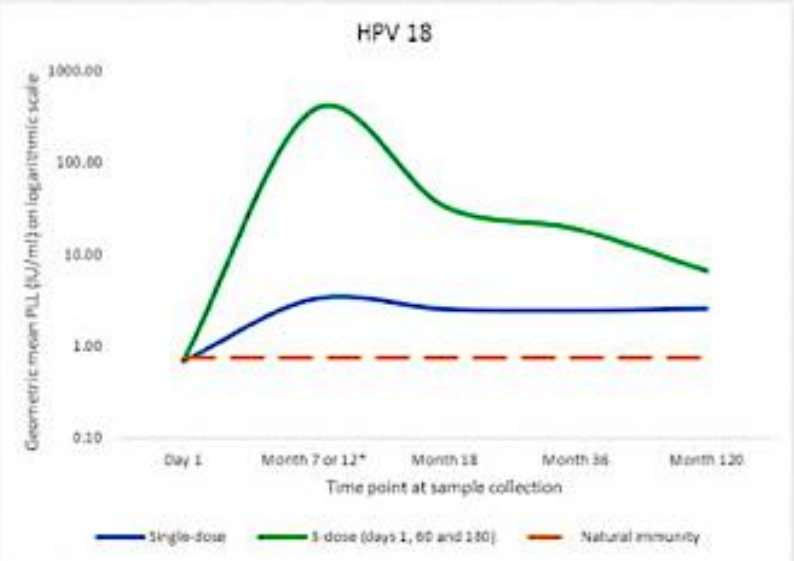
Ab titre in 1D recipients 15x higher than natural immunity

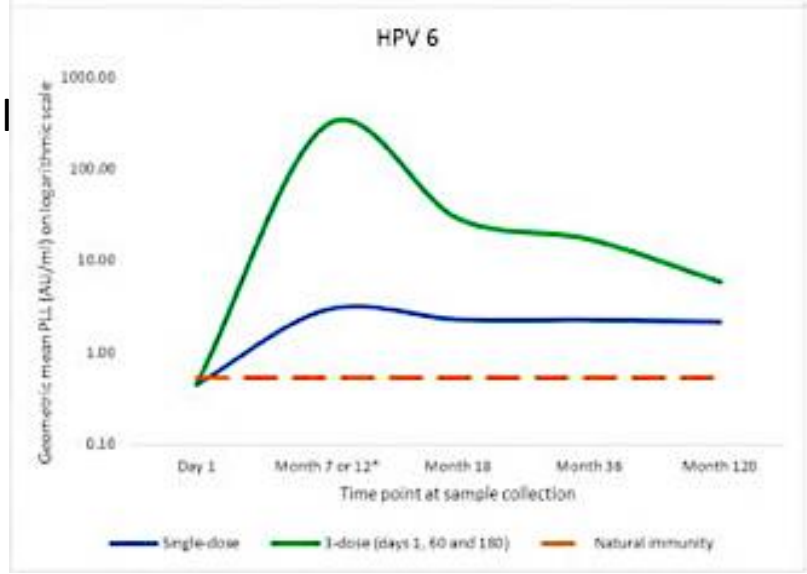
HPV 18 Ab response at 10 yr

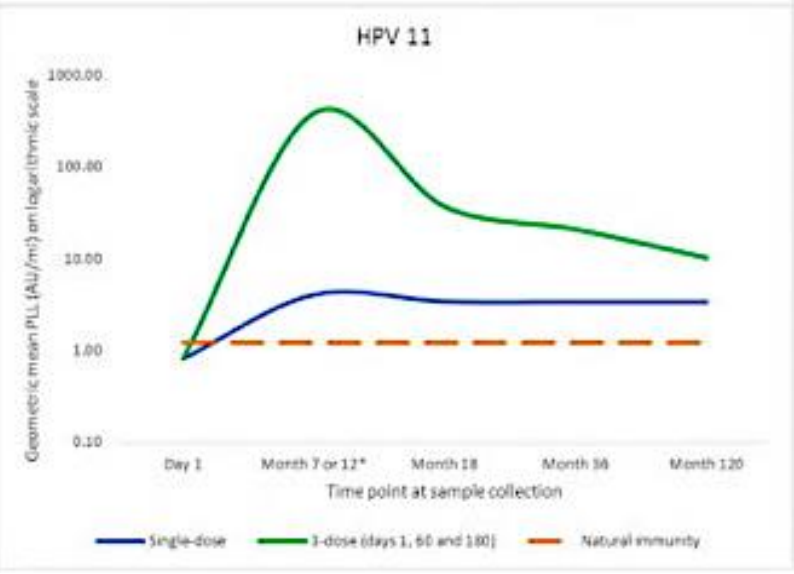
97% 1D recipients - detectable antibody

Ab titre in 1D recipients 10x higher than natural immunity









Vaccine. 2023 Jan 4;41(1):236-245. doi: 10.1016/j.vaccine.2022.11.044.

DoRIS trial - Tanzania

Description	A study to compare the immunogenicity and safety of 1, 2 & 3 doses of 2 HPV vaccines
Trial Centre	Mwanza Intervention Trials Unit (MITU), Mwanza, Tanzania
Trial Design	Randomised unblinded phase IIb/III trial
Population	Healthy HIV-negative females, **aged 9-14 years**
Sample size	930 (155 per arm)
Duration	1, 2 & 3 dose arms followed up to M36 Trial extension: 1 & 2 dose arms followed up to M108

Cervarix®			**Gardasil-9®**		
1 dose	2 doses	3 doses	1 dose	2 doses	3 doses
N = 155	N = 155	N = 155	N = 155	N = 155	N = 155

Samples tested at Leidos, Maryland by L1 VLP ELISA

HPV 16/18 antibody concentrations over time

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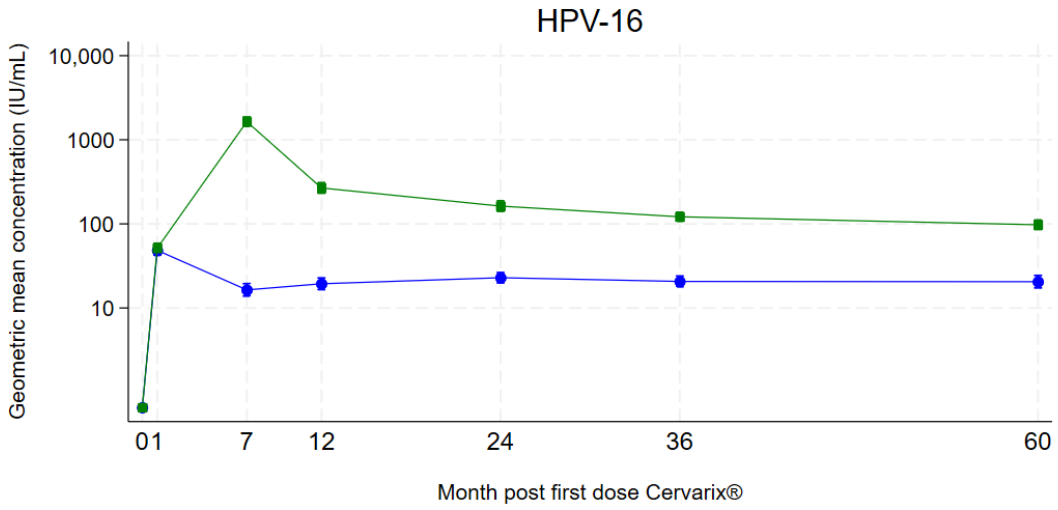
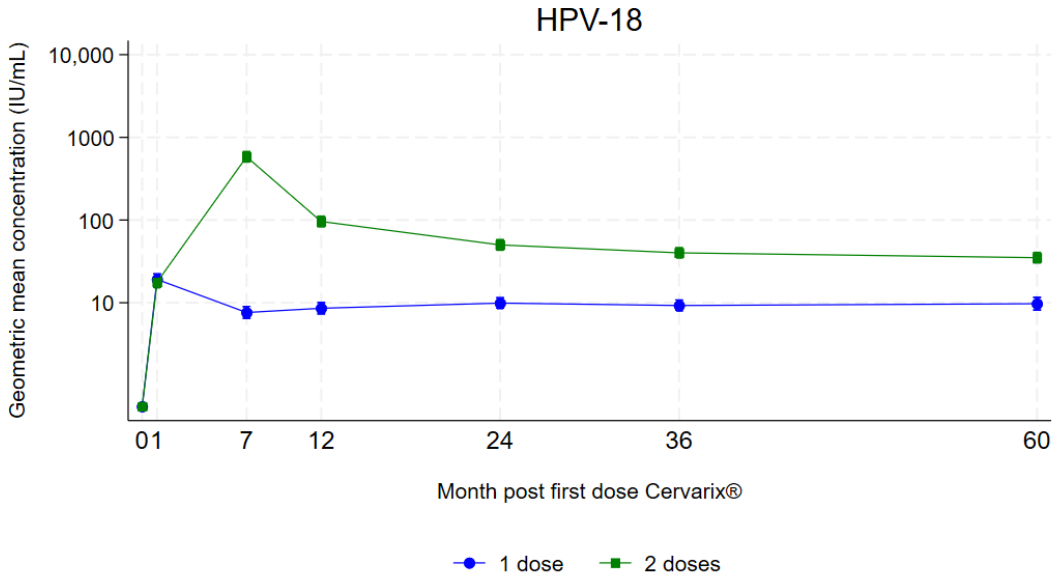
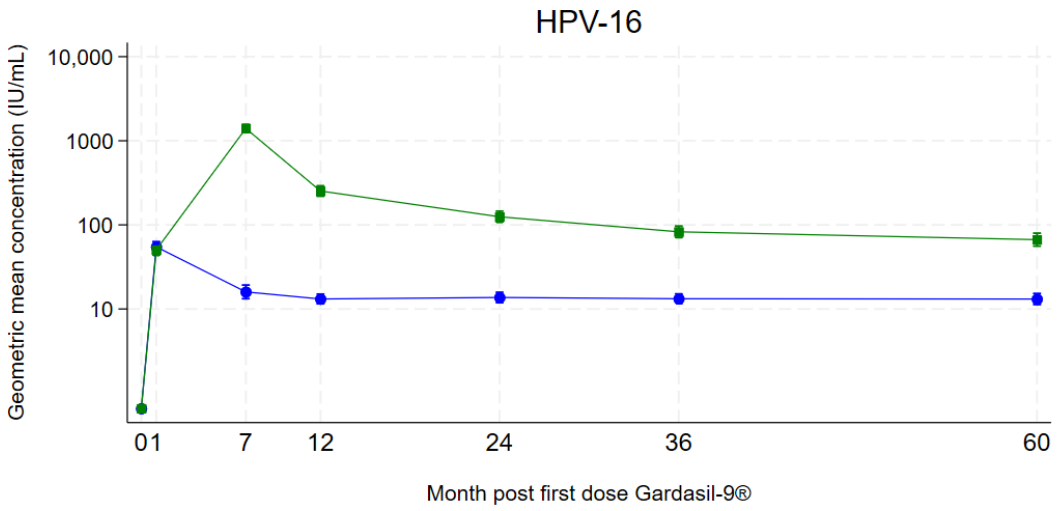
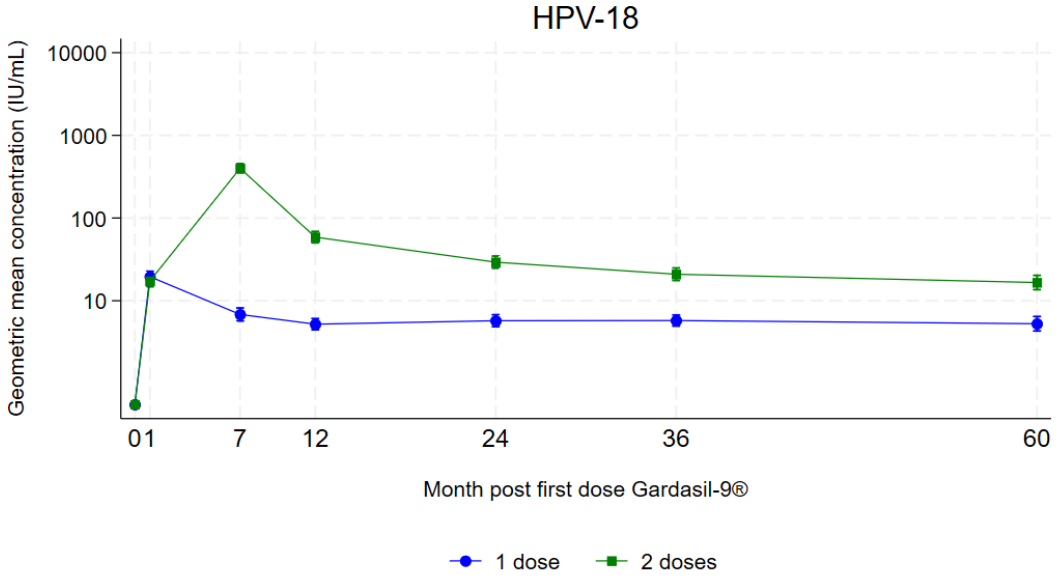
Cervarix®



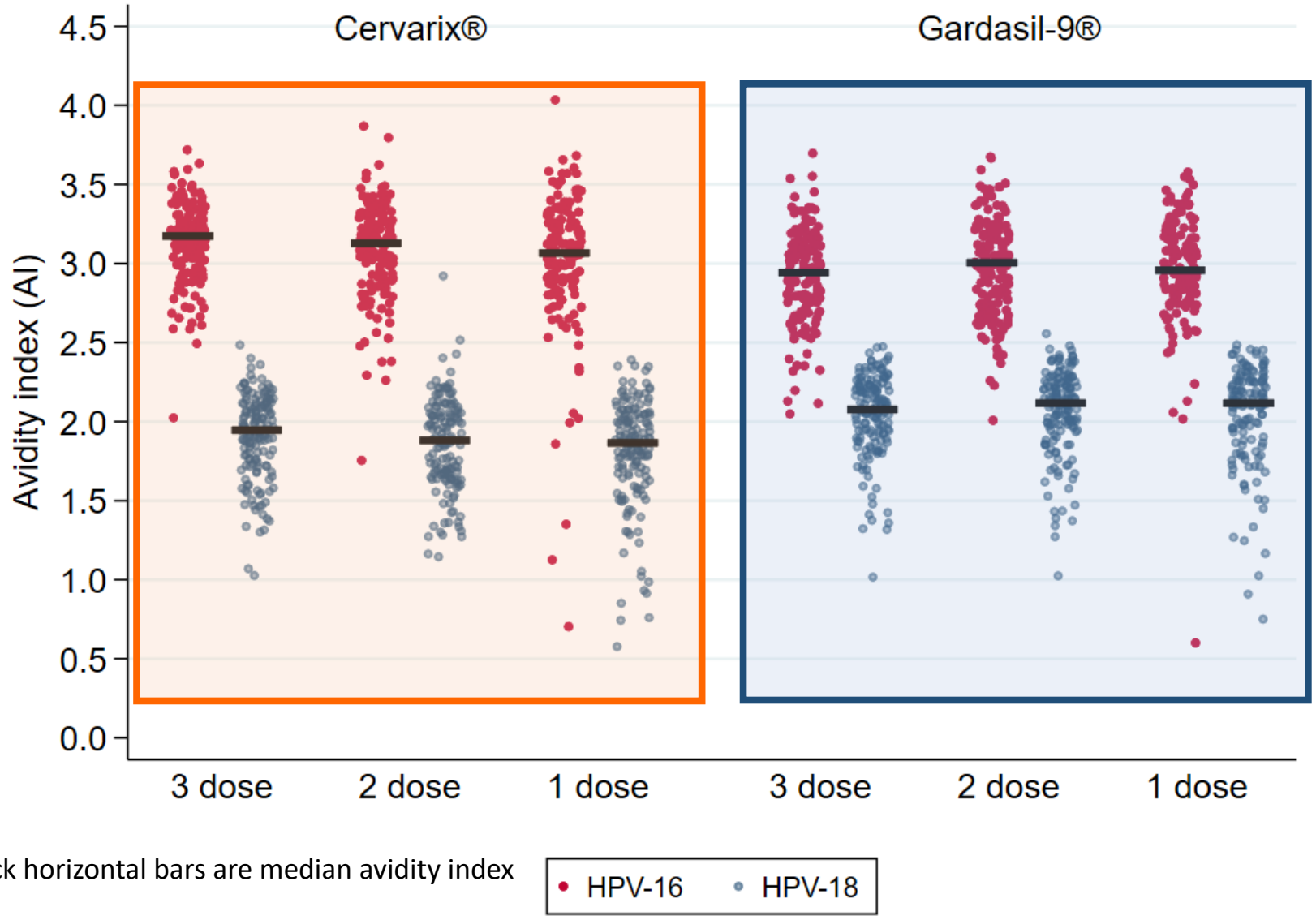


Gardasil-9®





Distribution of HPV 16/18 avidity index at M36



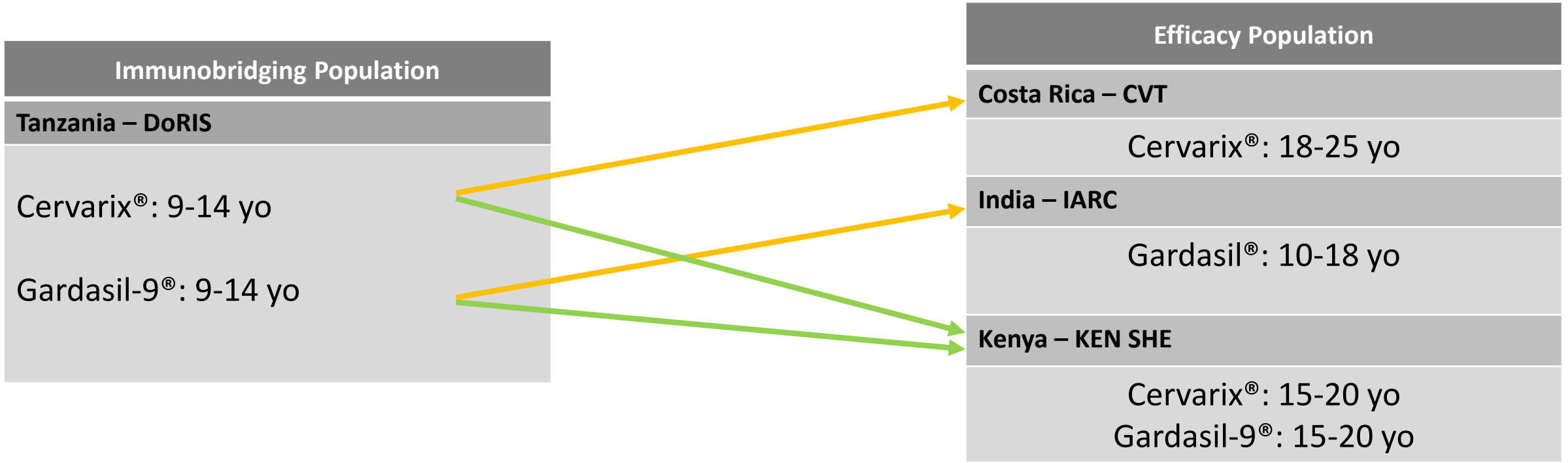
Black horizontal bars are median avidity index

Antibody avidity is an indicator of strength of binding of antibody to antigen

HPV 16/18-specific antibody avidity index (AI) determined in ELISA by the ratio of antibody concentrations in serum samples treated or not treated with Guanidine-HCl

Results at M24 the same

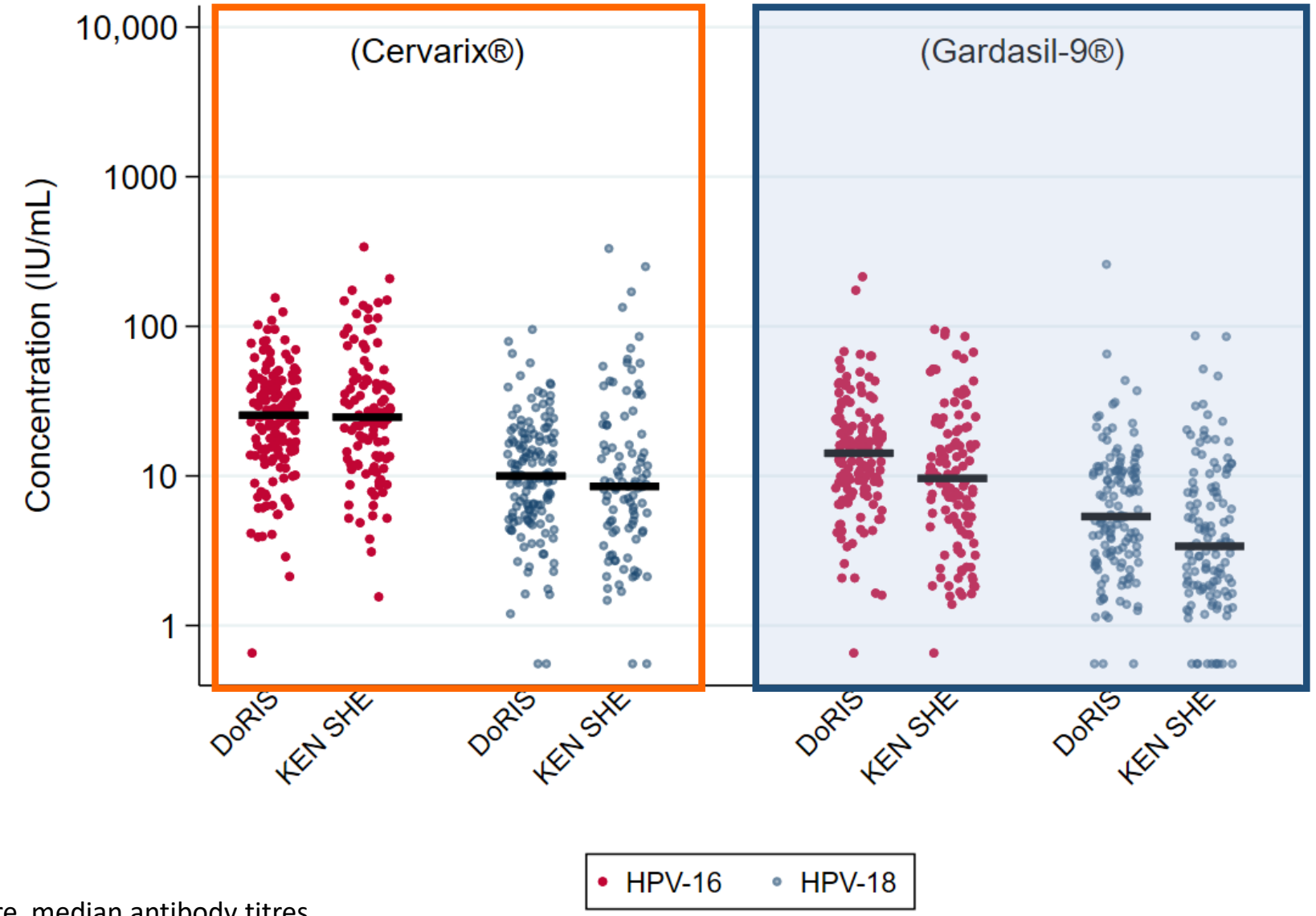
DoRIS Trial – Immunobridging



- Bridge DoRIS immune responses to populations where efficacy has been shown
- VLP ELISA for HPV 16/18 antibody levels; samples from trials tested together in same batch (Frederick National Laboratory for Cancer Research, USA)
- Primary analyses excluded girls HPV DNA or seropositive at baseline

CVT: Costa Rica Vaccine Trial; DoRIS: Dose Reduction Immunobridging and Safety; yo: year of age

DoRIS and KEN SHE one-dose M24 immunobridging



Black horizontal bars are median antibody titres

Baisley K et al. Lancet Global Health. 2024

Cecolin® / Gardasil ® CHOISE study – M6 results

- Phase 3 open label trial; Ghana and Bangladesh; Sponsor: PATH
- Safety and immunogenicity of **Cecolin® [Innovax] cf. Gardasil® [MSD]**
  - Extended 2D schedule 0,6M 0,12M 0,24M (non-inferiority of Cecolin® cf. Gardasil® for each regimen)
  - Mixed schedule
    - Dose 1 Cecolin®, dose 2 Cecolin® at M6 or M12 or M24
    - Dose 1 Gardasil®, dose 2 Gardasil® at M6 (referent)
    - Dose 1 Gardasil®, dose 2 Cecolin® at M24
  - Data on immunogenicity of 1D Cecolin® to M6
- 9-14 yo girls
- L1 VLP ELISA for IgG antibodies
- 1D data to be collected to M24

Zaman et al. Vaccine 2024, 42; 2290-2298

ELISA HPV-16 and HPV-18 IgG antibody responses (per protocol population) 6m post-dose 1

Outcome	Cecolin®	95% CI	Gardasil®	95% CI
HPV 16 seropositivity	100%	(98.2; 100)	99.5%	(97.2; 100)
HPV 18 seropositivity	98.5%	(95.7; 99.7)	96.0%	(92.2; 98.2)
HPV 16 GMC IU/ml	18.2	(16.3; 20.4)	12.0	(10.8; 13.3)
HPV 18 GMC IU/ml	6.8	(6.1; 7.5)	4.2	(3.8; 4.7)

HPV16 GMC ratio Cecolin/Gardasil : 1.5 (1.3, 1.8); HPV18 GMC ratio Cecolin/Gardasil : 1.6 (1.4, 1.9)

Non-inferiority of Cecolin to Gardasil demonstrated for 0, 6m schedule; persistence of Cecolin immune response 6m after dose 1

WHO has now reviewed 1D Cecolin data.

Antibody seropositivity defined as antibody levels equal to or greater than assay thresholds (for IgG concentrations: 1.41 IU/mL for HPV-16 and 1.05 IU/mL for HPV-18; for neutralizing antibodies: titers equal to or higher than 21 for HPV-16 and 16 for HPV-18).

Zaman et al. Vaccine 2024, 42; 2290-2298

HPV 9-valent Vaccine Delayed Booster Immunogenicity Study (DEBS)

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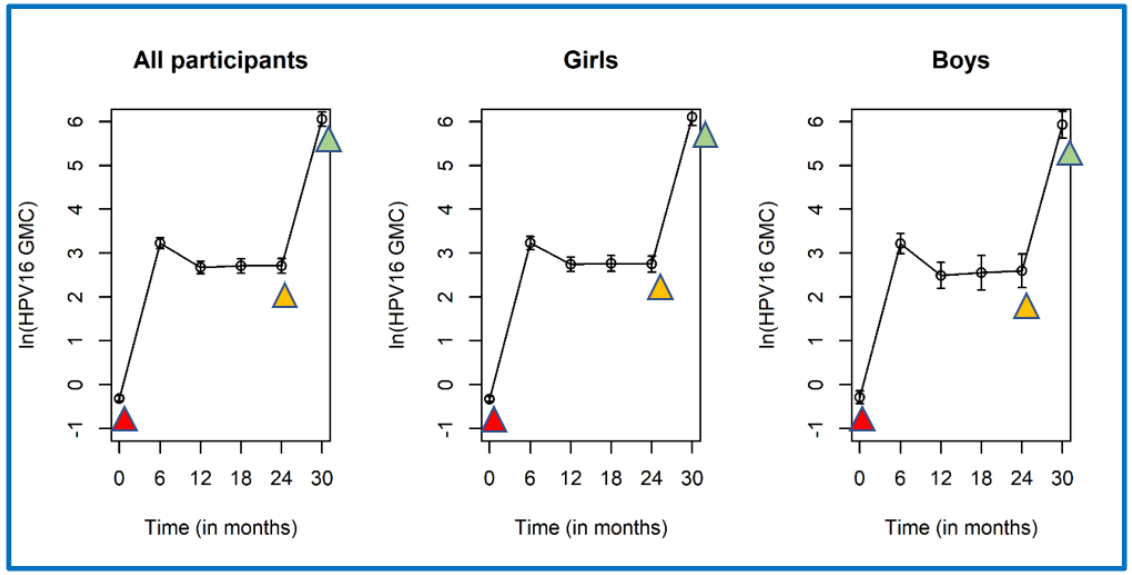
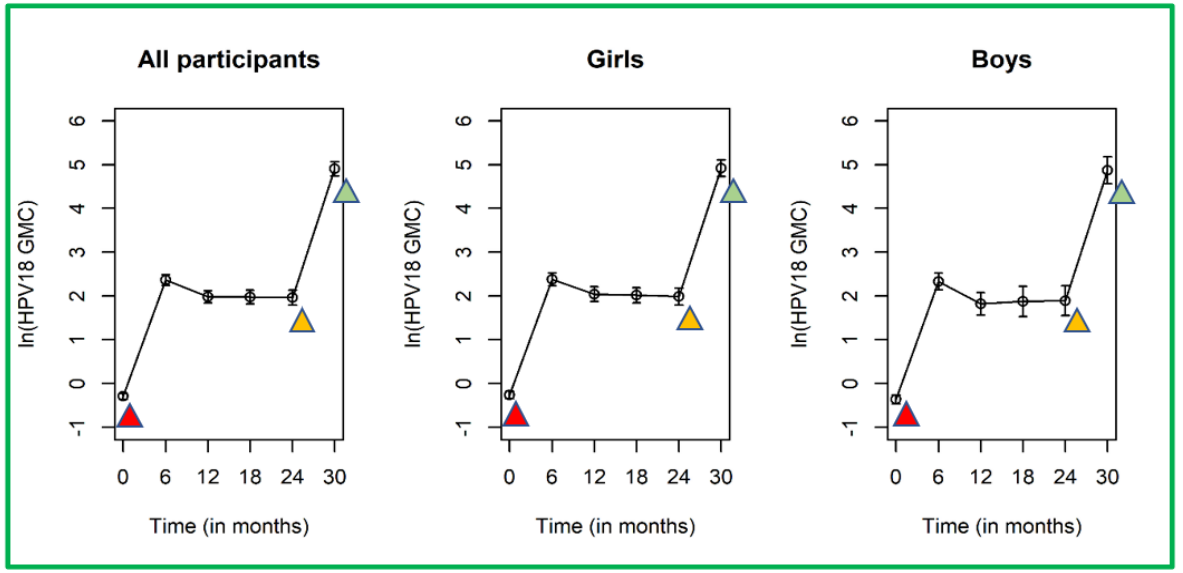
Plot of HPV16 antibody GMC levels by study visit for all participants, girls and boys



Plot of HPV18 antibody GMC levels by study visit for all participants, girls and boys



prime dose delayed booster: 24 months optional booster: 30 months

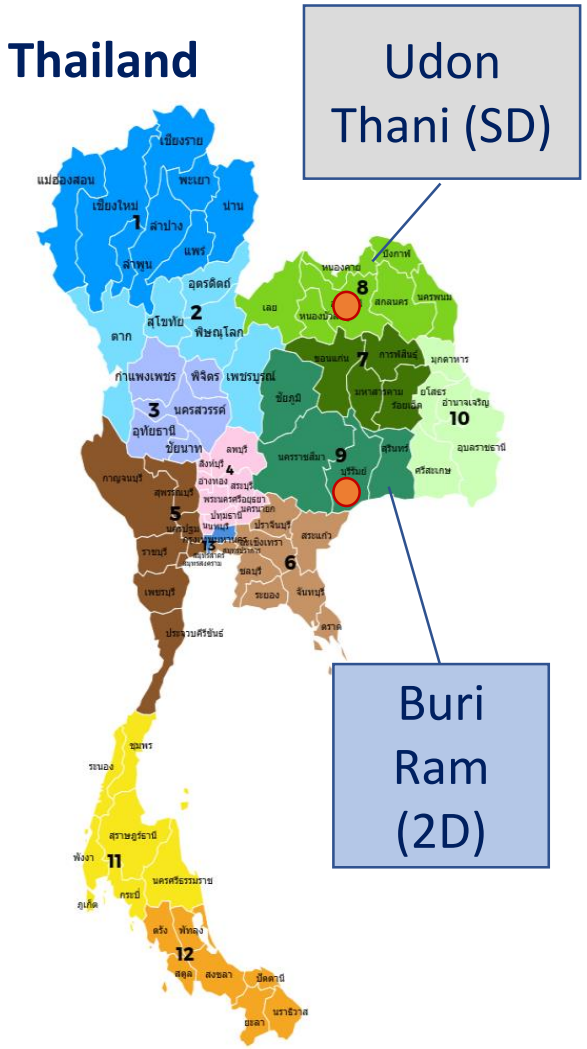
ClinicalTrials.gov NCT02568566

- 9-v vaccine: girls and boys aged 9-11 yrs (USA)
- HPV16 and HPV18 antibody titers (HPV VLP IgG ELISA) - stable and persistently high *(at 20- and 10-times those at baseline for HPV16 and HPV18, respectively)* between 12, 18, and 24 months after single dose of Gardasil9 in boys and girls
- HPV16 and HPV18 antibody responses - anamnestic boosting effect at 30-months after delayed (24-month) booster dose.

Zeng Y, Moscicki A-B, Woo H, Hsu C-H, Kemp TJ, Pinto LA, Szabo E, Dimond E, Bauman J, Sahasrabuddhe VV, Chow S. *Pediatrics 2023.152 (1): e2022060301*

A community intervention effectiveness study of single dose or two doses of bivalent HPV vaccine (CERVARIX) in female school students in Thailand

IVI Grant PI: Dr Julia Lynch; MOPH Study Protocol PI: Dr Suchada Jiamsiri



Year 4 data presented at EUROGIN 13 March 2023; in press (JNCI)

Intervention:

- Cervarix administered to 8th grade (G8) girls in a school-based campaign in two provinces: Udon Thani (**Single Dose**) and Buri Ram (**Two-dose**)
  - Matched: socioeconomics, grade cohort size (8-9000 students per grade), prevalence of sexual activity by grade
  - Offered to all eligible students (under 15 years, non-pregnant); required parental consent and student assent
  - Selected G8 students receiving vaccine completed SBQ (Serology subset N=200)

Outcome Measured through sequential Cross-Sectional Surveys (CSS) at Baseline (G10/V1 and G12/V3), 2-Years (G10/V1) and 4-Years (G12/V3) post-vaccination:

- CSS Methodology:
  - Systematic sampling of schoolgirls at all schools
  - HPV prevalence assessed by single time point collection of urine using Coli-pee
  - Self-administered web-based Sexual Behavior Questionnaire (SBQ)
  - Serology subset (N=200)

Crude 2-year and 4-year post-vaccination vaccine effectiveness - compared prevalence of HPV 16 and/or 18 between **unvaccinated schoolgirls** in baseline CSS (2018) and **vaccinated schoolgirls** (single dose (SD)for Udon Thani, 2D for Buri Ram) in Year-2 CSS (2020) and Year-4 CSS (2022)

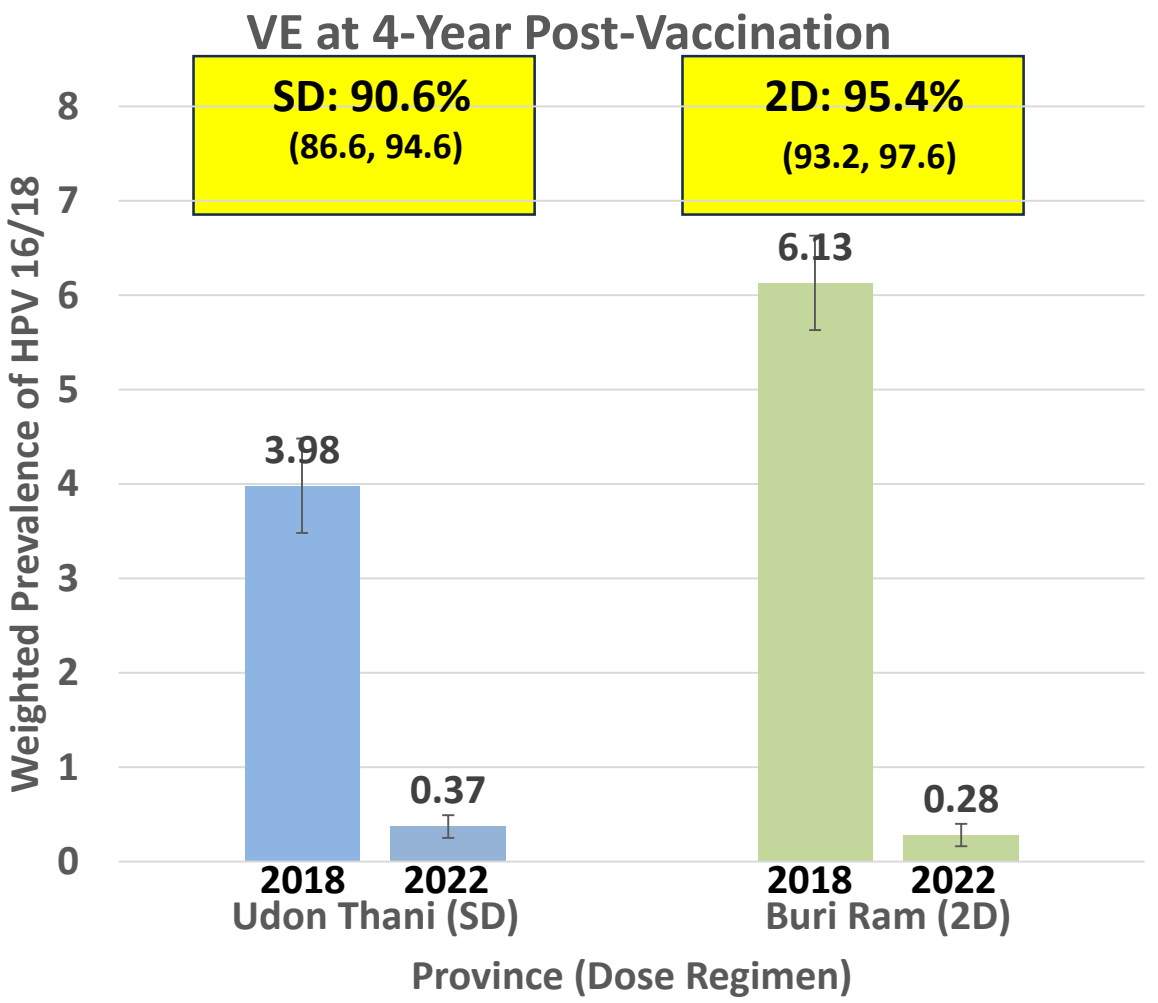
VE at 4-Year Post-Vaccination Comparison

Province	School Type	Grade 12 Schoolgirls					
		Unvaccinated in 2018			Vaccinated in 2022		
		N	HPV 16/18	Prevalence (95% CI)	N	HPV 16/18	Prevalence (95% CI)
Udon Thani (SD)	General High School	988	21	2.13 (1.39, 3.23)	995	2	0.20 (0.06, 0.73)
	Vocational School	836	62	7.42 (5.83, 9.39)	861	6	0.70 (0.32, 1.51)
	Weighted Total [a]			**3.98 (3.52, 4.49)**			**0.37 (0.25, 0.56)**
Buri Ram (2D)	General High School	988	34	3.44 (2.47, 4.77)	997	1	0.10 (0.02, 0.57)
	Vocational School	729	81	11.1 (9.03, 13.6)	801	5	0.62 (0.27, 1.45)
	Weighted Total [a]			**6.13 (5.56, 6.75)**			**0.28 (0.18, 0.45)**

N: Total number of Schoolgirls, Case: Total number of Schoolgirls who were HPV16/18 positive, Prevalence: Proportion of Schoolgirls who were HPV16/18 positive, SD: Single Dose, 2D: Two Dose

[a] Weighted total : weighted total derived by direct standardization

95% CI was derived by Wilson method for prevalence



1D & 2D significantly reduced HPV16/18 point prevalence at 2 & 4 years post-vaccination in schoolgirls aged <15 years at vaccination.

The HOPE study – South Africa

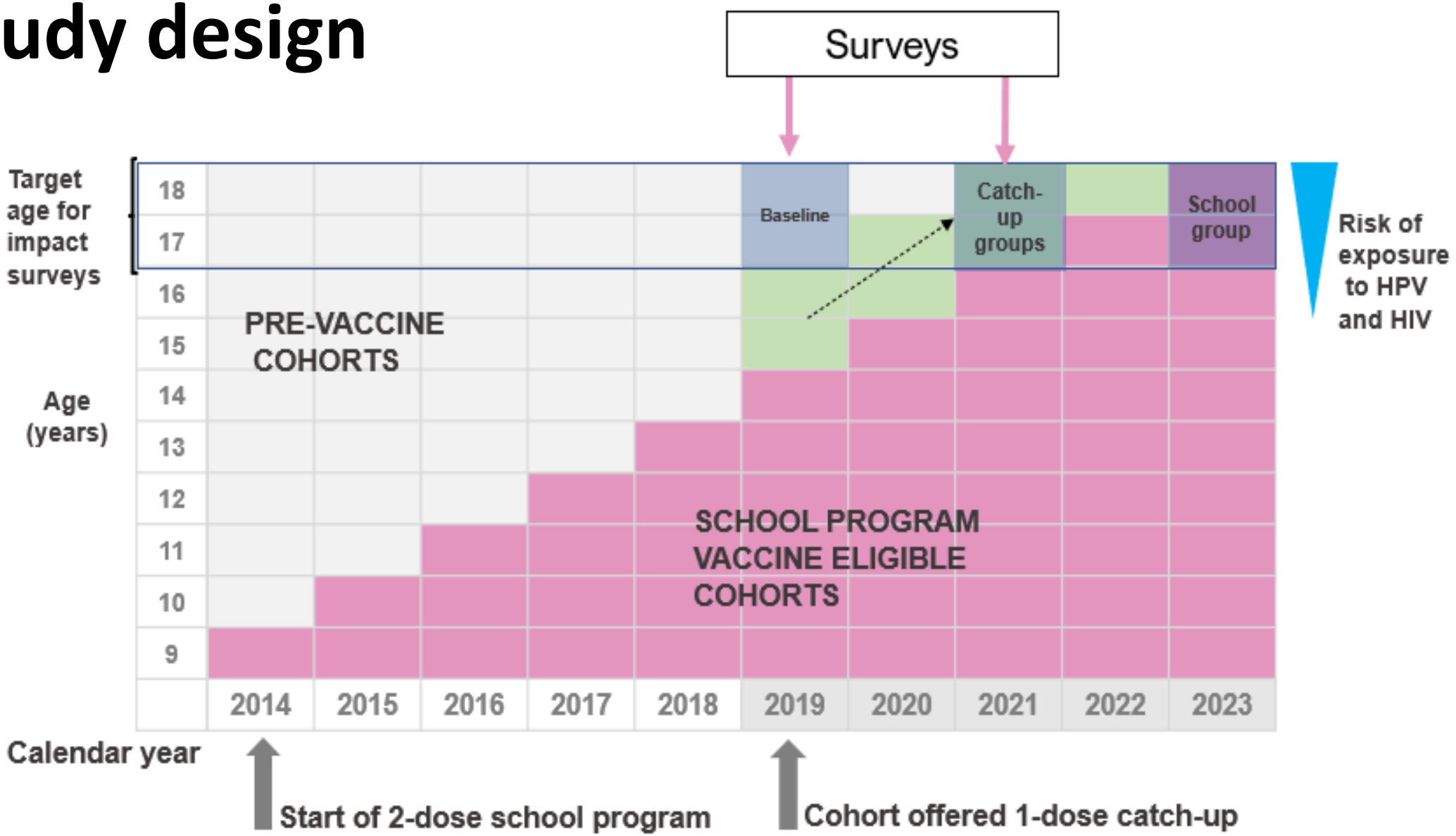
Sinead Delany-Moretlwe, Dorothy Machalek, Richard Munthali, Danielle Travill, Kathy Petoumenos, Helen Rees, John Kaldor, HOPE study group

AIMS

- To measure the population impact of a **1-dose vaccine schedule**, delivered as a catch-up to adolescent girls & young women in Grade 10 in one district, in protecting against infection with HPV 16 and 18

- To determine whether **HIV infection** status affects the impact of a 1-dose vaccine schedule.

Study design



HOPE Study Results: HPV 16/18 prevalence, overall

Single-dose vaccination campaign coverage 72%
HPV 16 and 18 prevalence 35% lower in the post-vaccine survey

HPV type	Crude prevalence				
	Pre-vaccine sample N=506 n (%)	Post-vaccine sample N=892 n (%)	Prevalence ratio (PR) (95% CI)	Adjusted* PR (95% CI)	p-value
HPV 16/18	117 (23)	108 (12)	0.52 (0.41-0.66)	0.65 (0.51-0.83)	<0.001
HPV 16	75 (15)	65 (7)	0.49 (0.36-0.67)	0.59 (0.43-0.82)	0.002
HPV 18	56 (11)	50 (6)	0.51 (0.35-0.73)	0.67 (0.46-0.98)	0.037

*Adjusted for HIV status, being in school, relationship status, smoking, drinking, lifetime number of partners, reported vaginal sex, contraception use

Slide courtesy of S. Delany-Moretlwe

Results: HPV 16/18 prevalence, HIV only

HPV 16 and 18 prevalence 37% lower in HIV-infected girls in the post-vaccine survey

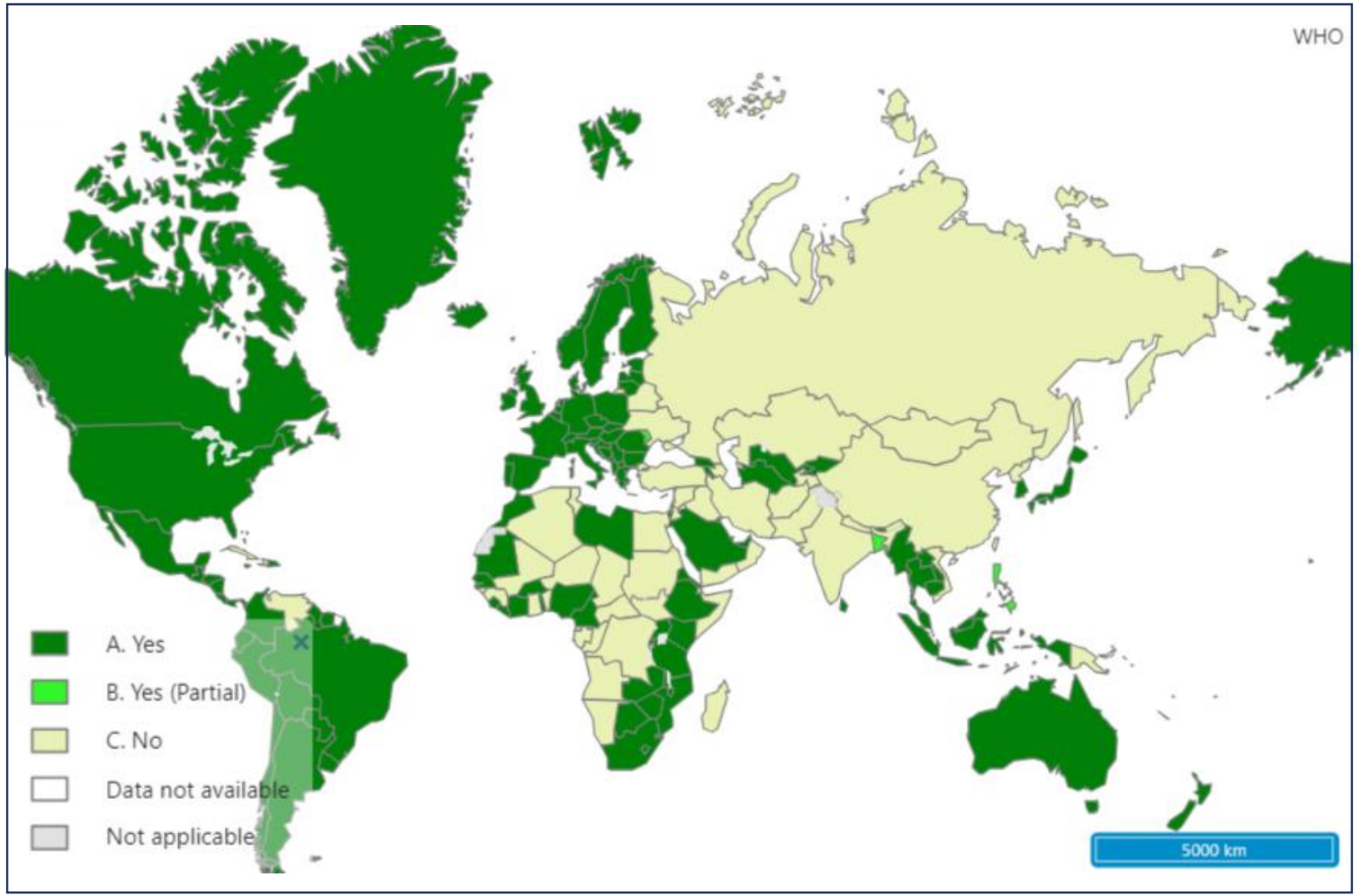
HPV type	Crude prevalence				
	Pre-vaccine sample N=157 n (%)	Post-vaccine sample N=117 n (%)	Prevalence ratio (PR) (95% CI)	Adjusted* PR (95% CI)	p-value
HPV 16/18	52 (33)	24 (21)	0.62 (0.41-0.94)	0.63 (0.41-0.95)	0.026
HPV 16	29 (19)	15 (13)	0.69 (0.39-1.23)	0.71 (0.40-1.24)	0.228
HPV 18	29 (19)	13 (11)	0.61 (0.33-1.12)	0.72 (0.39-1.33)	0.291

*Adjusted for being in school, smoking, lifetime number of partners, reported vaginal sex, contraception use

Slide courtesy of S. Delany-Moretlwe

HPV Vaccine introductions

- 141 / 194 (73%) countries that reported data to WHO have HPV vaccine included in national vaccination programmes (12 Sept 2024)
- 50 countries - no HPV vaccination programme
- April 2024 - 54 countries offered gender-neutral vaccination



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Global HPV vaccine schedule update to 9 Sept 2024

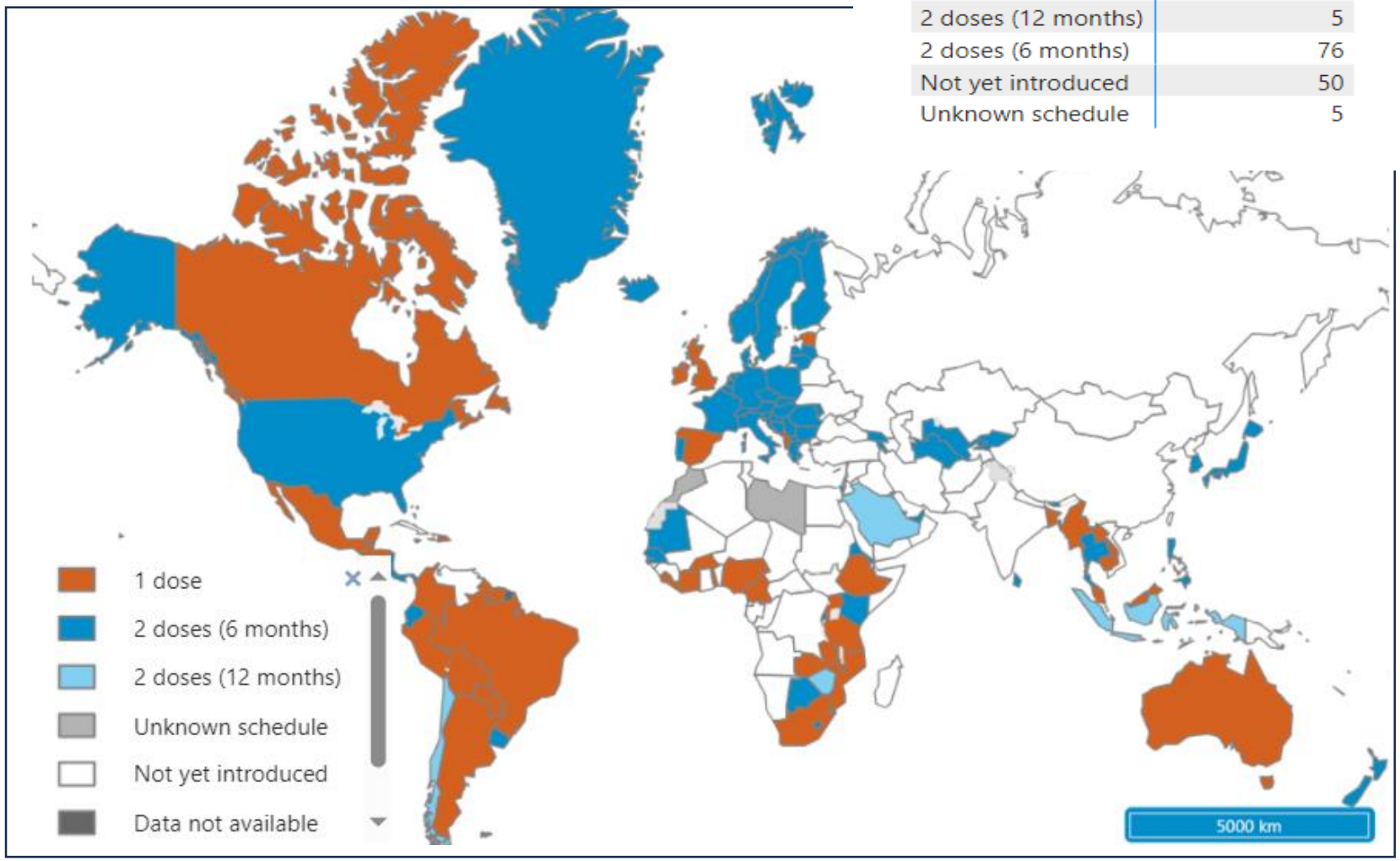
58 countries have adopted a single dose (SD) schedule.

Rise in **global HPV vaccine coverage** to 27% in 2023 cf. 20% in 2022 [1,2]

10/18 countries improved HPV coverage (average 8%) when changing to SD

SD implementation allowed introduction with MACS (e.g. Nigeria, Bangladesh, Togo, Zambia), or switching from 2 to 1 dose and adding MACs to current programmes (e.g. Tanzania)

Interval_doses	No. of countries
1 dose	58
2 doses (12 months)	5
2 doses (6 months)	76
Not yet introduced	50
Unknown schedule	5



1. WHO. Microsoft Power BI

2. https://www.who.int/news/item/15-07-2024-global-childhood-immunization-levels-stalled-in-2023-leaving-many-without-life-saving-protection

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Nigeria

- 224 million people; 36 states
- Estimated 17,106,577 girls aged 9-14 years targeted during 1st HPV vaccine introduction; free vaccine
- Staged introduction Oct 2023 & May 2024 then routine vaccination implementation
- 2023: 5-day MAC campaign (9-14 years) in 16 selected states. In-school (59%) and out-of-school (41%) strategies
- Coverage in 2023 campaign ranged from 98%-36%
- Challenges: low awareness, rumours, hesitancy, operational reasons

Morhason-Bello IO, J Obstet Gynaecol Res. 2015 Oct;41(10):1621-9. doi: 10.1111/jog.12775. Epub 2015 Aug 26. PMID: 26310912.
Wallis S, Adedokun B, Adewole IF. Household survey on Human Papilloma Virus vaccine awareness among women of reproductive age in Ibadan, Nigeria. Afr J Med Med Sci. 2015 Mar;44(1):61-9. PMID: 26548117.

Tanzania

- 65.5 million people; 31 regions
- 4th highest incidence of cervical cancer [1]
- 2019 – launch of 2-dose routine HPV immunization schedule in 14 yo girls
- Coverage variable and lower for dose 2
- Disruption by COVID-19
- April 2024 – one week MAC campaign of 9-14 yo girls with single dose [1]
- 5 million girls targeted; 97% of girls reached in one week (87% at school)
- Will offer 9-14 yo vaccine in routine services and in hard-to-reach populations with periodic intensification of activities until Dec 2024 then switch 1D in 9 yo girls as routine delivery

1. UNICEF, https://www.gavi.org/vaccineswork/tanzanias-5-million-girls-hpv-vaccination-campaign-success

Forthcoming data

- ESCUDDO – Costa Rica: RCT efficacy trial - non-inferiority of 1 or 2 doses of Gardasil9® or Cervarix ®
- PRISMA – Costa Rica: Efficacy of HPV vaccination in older women and 1-dose protection at anal and oral sites
- HANDS trial – Gambia: immunogenicity of single dose Gardasil9® in younger children
- DoRIS trial – 9 year single dose immunogenicity data

Summary - existing Single-Dose Evidence

- 1-dose efficacy demonstrated for prevention of persistent infection with vaccine-related genotypes
- Efficacy sustained until 10-12 years (2-valent and 4-valent vaccines)
- 1 dose immune responses stable up to 16 years and, in the current target age for vaccination, are non-inferior to cohorts where efficacy has been shown
- Reduction in population prevalence of HPV16/18 following 1 dose, including a population with high HIV prevalence
- 1-dose has comparable immunogenicity in girls and boys 9-11 years of age
- Data from multiple geographies
- Supports the WHO 2022 off-label recommendation for 1 dose in 9-20 yo.

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- ❑ Study participants & investigators & research teams
- ❑ Trial funders
- ❑ **Single-Dose HPV Vaccine Evaluation Consortium**

- Collates, assesses and synthesizes existing published evidence on single-dose human papillomavirus (HPV) vaccination
- Evidence summaries, slide decks, and other resources, including translations, available at the Consortium website: www.path.org/singledosehpv