OPTIMISING VACCINE REGIMENS

- HPV VACCINES

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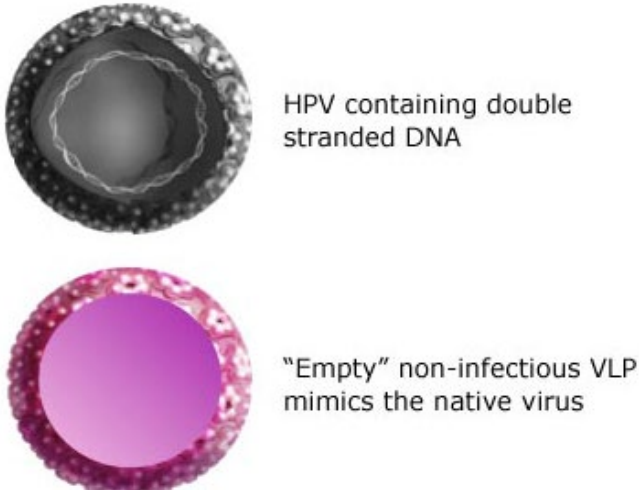
Disclosures

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

HPV vaccines

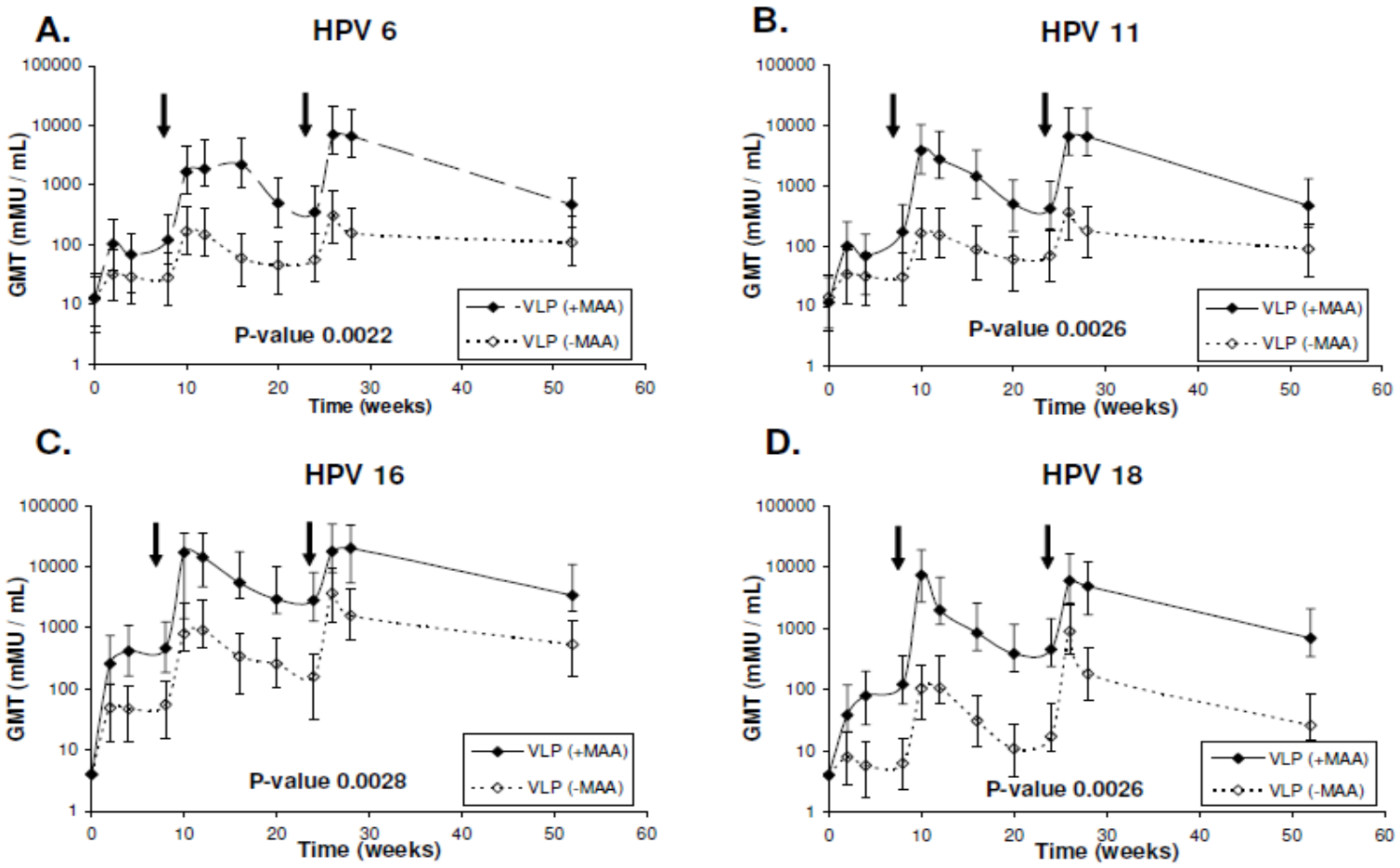
- 1st licensed prophylactic virus-like particle (VLP) vaccine in 2006
- Prepared from the L1 structural protein; recombinant DNA & cell culture technology used to manufacture L1 VLPs
- 6 VLP vaccines currently licensed
- Main indication - prevention of cervical pre-malignant lesions and cancers caused by HR HPV genotypes (+/- some other indications)



HPV containing double stranded DNA

"Empty" non-infectious VLP mimics the native virus

Benefit of multi-dose regimen shown among NHPs in early HPV vaccine development



- 2 doses > 1 dose and 3 doses slightly better than 2 doses
- Clear benefit of inclusion of alum (stability of VLP versus adjuvant?)
- Suggestion of improved durability

Ruiz W et al., Journal of Imm based Therapies and Vaccines. 2005

3 dose HPV vaccine schedules

- No known immune correlate of protection to guide development of HPV vaccines then (or now) - aim was to provide long-term protection

- Start with classic prime, prime, boost schedule with 3 doses
- L1 HPV16 vaccines – 100% efficacy with 3 doses[1]
- Optimal schedule for a subunit protein vaccine (e.g. HBV) – aimed to generate high affinity, high avidity antibodies & large memory B cell pool

- Efficacy studies in 15-25 yo females used 3 dose schedules (0,1,6 m for Cervarix; 0,2,6 m for Gardasil & Gardasil-9).

1 Koutsky et al. NEJM 2002; 347

Phase 3 HPV vaccine trials

- 3 doses – HPV vaccine type negative women aged 15/16 to 25 years

VE – HPV 16/18	Persistent infection	CIN2+
Bivalent vaccine (Cervarix)®	94% *(92-96%)*	98% *(88 -100%)*
Quadrivalent vaccine (Gardasil®)	96% *(83-100%)*	98% *(94-100%)*

- 3 doses - women aged 15/16 to 25 years; HPV 31/33/45/52/58 VE

VE – HPV 16/18	Persistent infection	CIN2+
Nonavalent vaccine (Gardasil-9®)	96% *(94-98%)*	100% *(varied by type)*

Harper, DeMars. HPV Vaccines –a review of the first decade. Gynec. Oncol. 2017

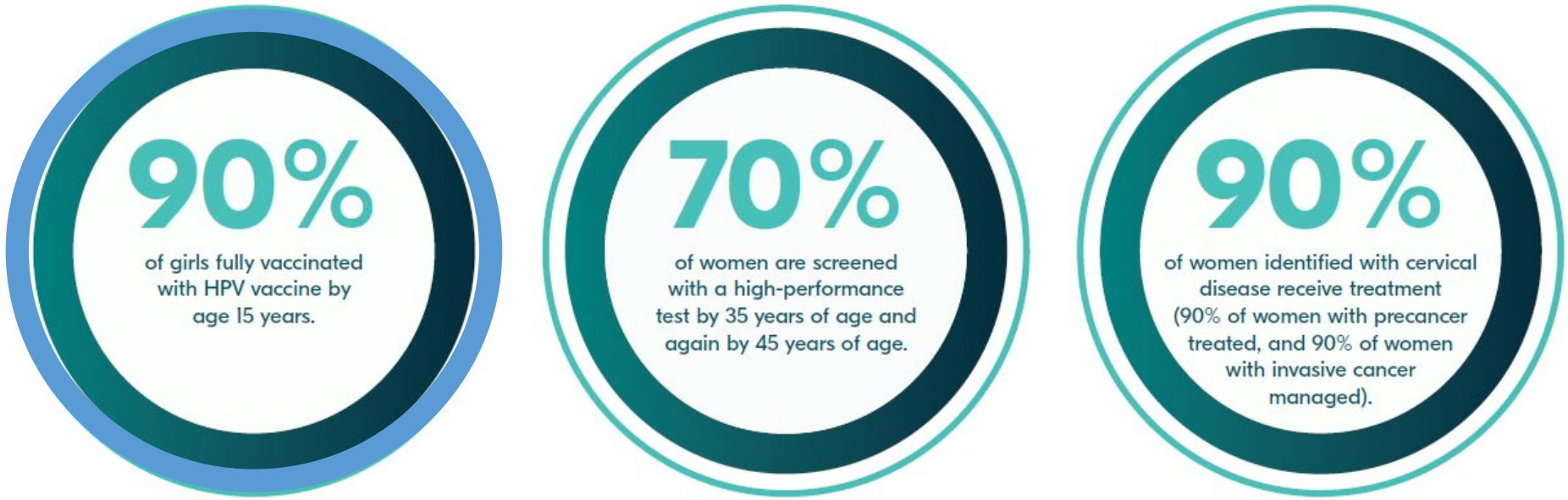
Recommendation changes

- Immunobridging studies used to license for 9-14 year olds (*for 3-dose*)
- 2014 immunobridging studies to license 2-dose regimen in 9-14 year olds
  - 2 doses of 2-valent vaccine given to 9-14 yo girls at months 0 & 6 was immunologically non-inferior for HPV16/18 to 3 doses given to women aged 15-25 years; antibody titres comparable 5 years post-vaccination [1]
  - Similar results with the 4-valent vaccine [2]
- Efficacy against persistent infection or immunobridging considered sufficient for licensing (WHO) [3]

1. Romanowski et al. Human Vaccines & Immunotherapeutics 2016; 12:20-29. 2. Dobson et al. JAMA 2013. 309.1793-1802. 3. Primary end-points for prophylactic HPV vaccine trials / IARC HPV Working Group (2013: Lyon, France).

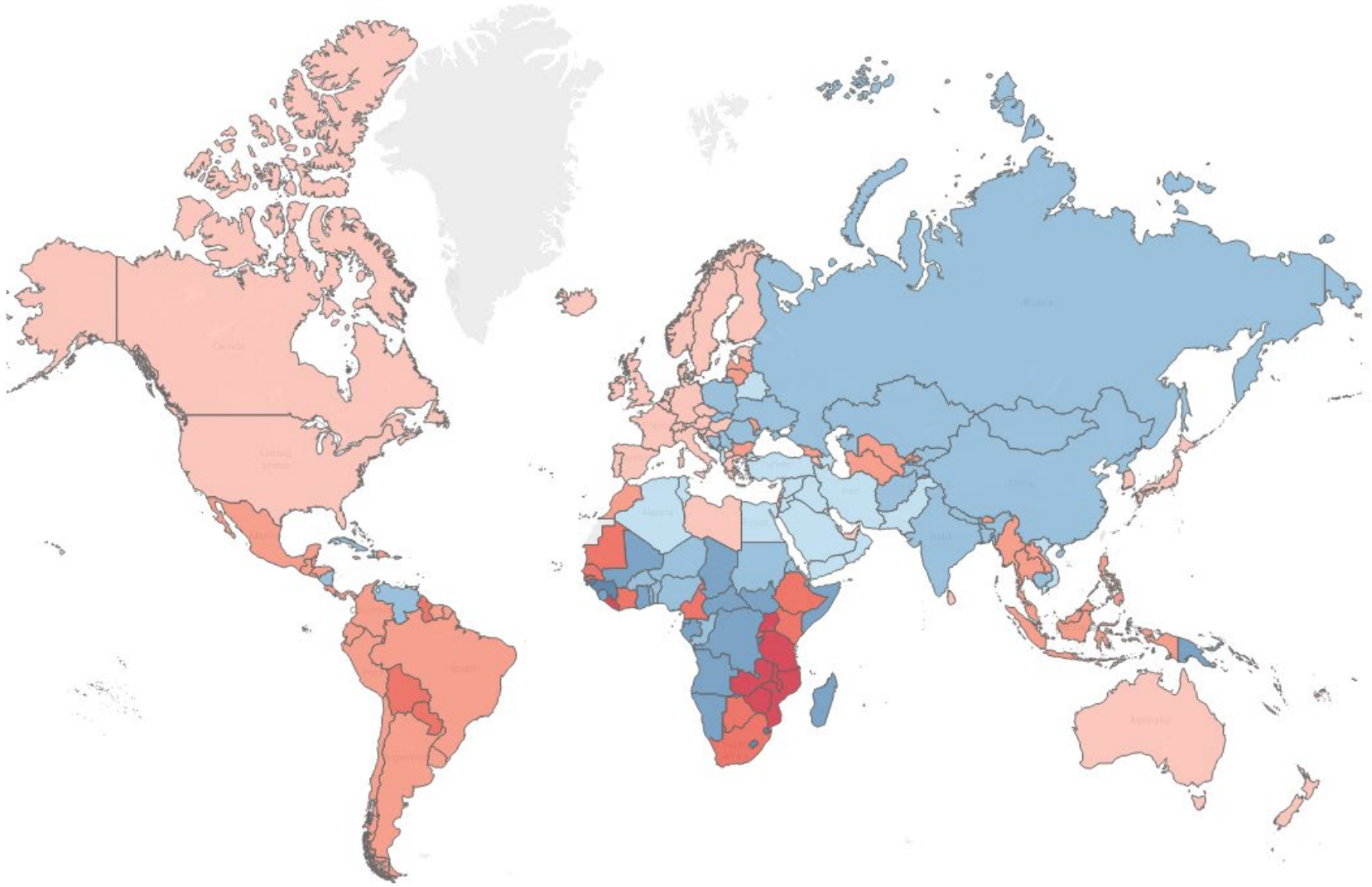
Cervical cancer elimination initiative

- November 2020, WHO launched global strategy to accelerate the elimination of cervical cancer as a public health problem; three 2030 targets[2]
- SDG 2030: target 3.41 – 30% reduction in mortality from cervical cancer



1. Global Cancer Observatory website. Cervix uteri page. https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf. Accessed May 16, 2022. | 2. World Health Organization (WHO). *Global strategy to accelerate the elimination of cervical cancer as a public health problem*. Geneva: WHO; 2020. https://www.who.int/publications/i/item/9789240014107.

Global HPV vaccine introductions by burden of disease



KEY

Mortality rate (ASR)*

National introduction		No introduction
	<5	
	5 - 14.9	
	15 - 29.9	
	≥30	

**rates per 100,000 women per year; estimated 2020 cervical cancer mortality rates from IARC Globocan data*

As of 17 Mar 2022

PATH. *Global HPV Vaccine Introduction Overview*. Seattle: PATH; 2022, Available at https://path.azureedge.net/media/documents/Global_Vaccine_Intro_Overview_Slides_Final_PATHwebsite_MAR_2022_qT92Wwh.pdf.

HPV vaccine in national immunisation programmes

- 60% of cervical cancer cases occur in countries that have not yet introduced HPV vaccination
- <1/3 of the world's population of girls 9-14 yo live in countries providing HPV vaccines
- Mean coverage is 57% for Dose 1 and 45% for a full vaccination regimen
- **=> Global HPV vaccine coverage was 15% in 2019 and declined to 13% in 2020**
- Challenges to introductions include costs, competing priorities and vaccine supply constraints

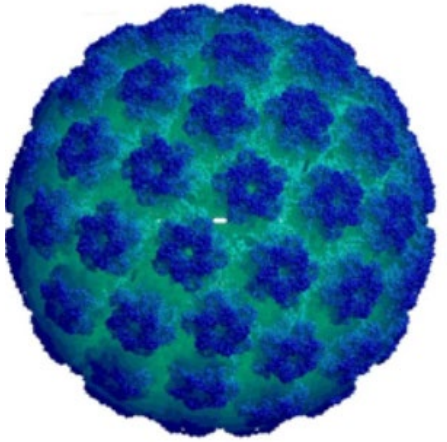
Benefits of a single dose regimen

Single-dose HPV vaccination could:

- ❑ accelerate introduction for countries that have yet to introduce the vaccine
- ❑ simplify delivery/programme costs and potentially lead to a higher coverage e.g. through MACs
- ❑ reduce the potential for supply shortages and delivery challenges, such as those faced during the COVID-19 pandemic
- ❑ Accelerate achieving the vaccination target of WHO's cervical cancer elimination strategy

Biological plausibility for a single dose of HPV vaccine

- Vaccines - virus-like particles (VLP)
- 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.

Trials 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 : -> Kenshe -> 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)

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

- Followed for efficacy for 11+ years

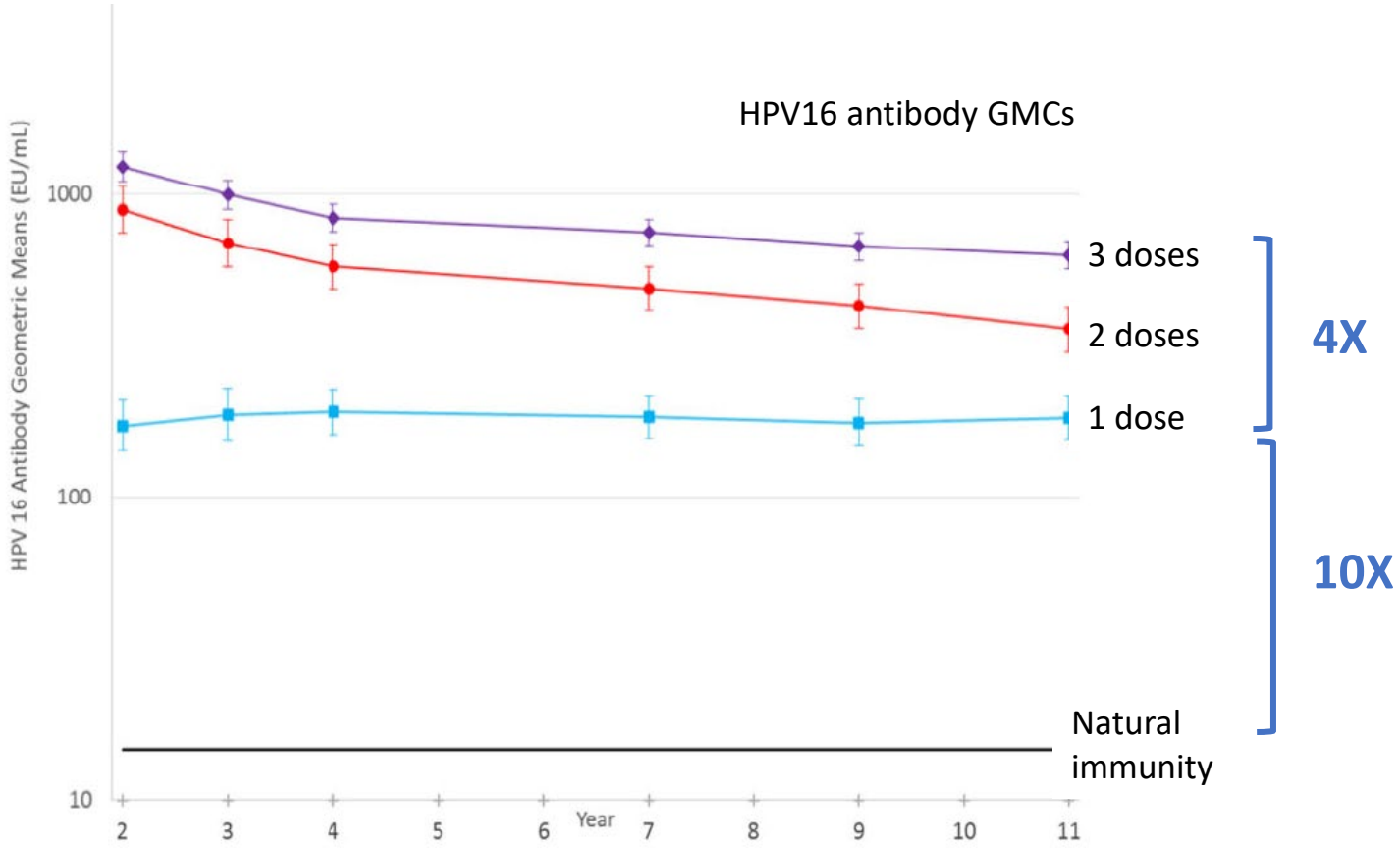
  - No evidence of a difference in VE or infection rates across dose groups

HPV16/18 infection endpoint	% infection (95% CI)			
	3-dose N=1365	2-dose N=62	1-dose N=112	Control N=1783
Prevalent HPV	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)**	

  - Prevalence of infection with non-vaccine HPV genotypes similar across groups

Kreimer et al. *J Natl Cancer Inst* 2020

Immune responses over time post-vaccination in CVT



Stable antibody levels for HPV-16 and HPV-18 antibodies up to 11 years post-vaccination several times above natural immunity

Kreimer A., JNCI (2020)

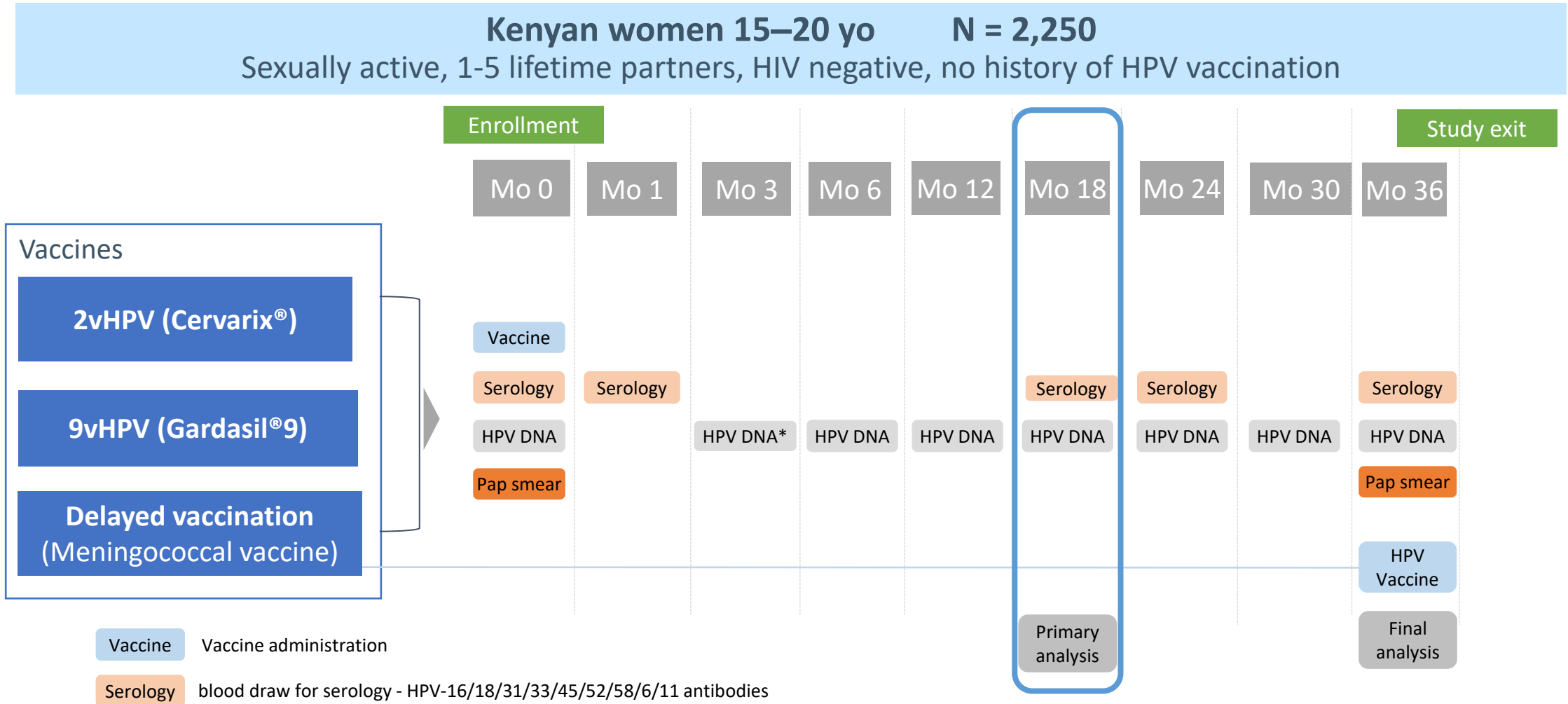
IARC India trial

- 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; 4950 received 1 dose; analysed as observational cohort
  - Age-matched unvaccinated controls recruited post-hoc after suspension
- Followed for efficacy for 9+ years
  - VE against incident and persistent HPV 16/18 infection similar across dose groups

HPV16/18 infection endpoint	% infection (95% CI)			
	3-dose 1649	**2-dose 1685**	**1-dose 2454**	**Control 1268**
Incident	3.0 (2.3 – 3.8)	2.7 (2.1 – 3.5)	3.2 (2.6 – 3.9)	9.4 (7.9 – 11.0)
Persistence	0.1 (0.0 – 0.4)	0.1 (0.0 – 0.4)	0.0 (0.0 – 0.3)	2.5 (1.7 – 3.6)
VE (persistent HPV)	**93.3% (77.5-99.7)**	**93.1% (77.3-99.8)**	**95.4% (85.0-99.9)**	

Sankaranarayanan, et al. Lancet Oncol2016; Basu et al. *Lancet Oncology* Oct 2021

KEN SHE trial – first RCT designed to assess 1 dose efficacy (vs 0)



Mo: month; N: number of participants; yo: year of age

Courtesy of P. Bloem (WHO)

KEN SHE – M18 vaccine efficacy incident persistent HPV 16/18 infections*

	mITT No.	No. events	Incidence/ 100 woman yr	VE (%)	VE 95% CI
Delayed Vaccination N = 757	473	36	6.83	Ref	Ref
Single dose Cervarix® N = 760	489	1	0.17	97.5	81.6; 99.7
Single dose Gardasil®9 N = 758	496	1	0.17	97.5	81.7; 99.7

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

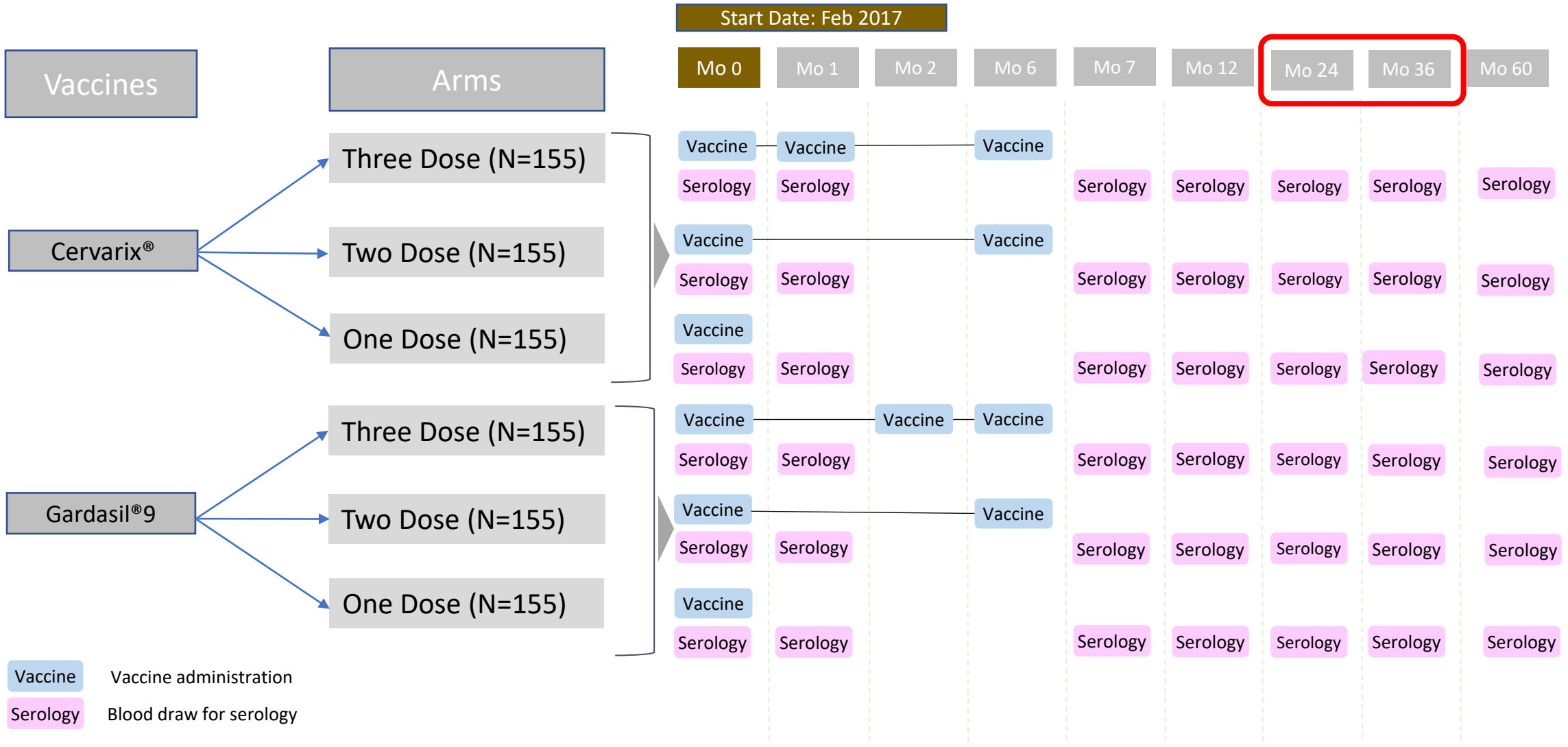
* Defined as vaccine type specific HPV detected at two consecutive time points no less than 4 months apart after M3 up to & including M18

Barnabas, et al. April 12 2022, NEJM Evid 2022; 1 (5)
DOI:https://doi.org/10.1056/EVIDoa2100056

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

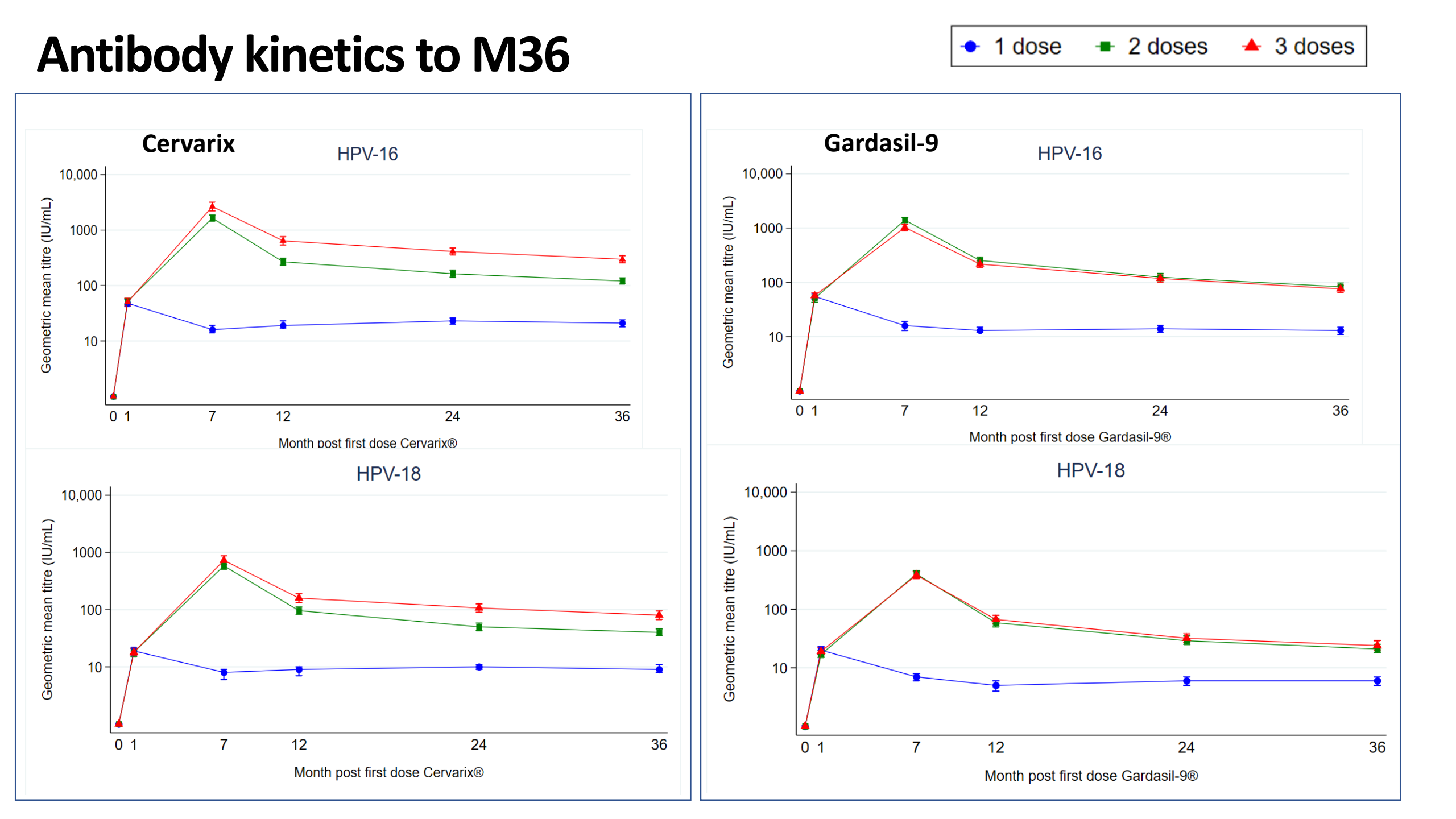
DoRIS Trial – Study Schematic

Tanzanian girls 9-14 yo; N = 930
unblinded, individually-randomized trial, randomly allocated into one of 6 arms; 2 HPV vaccines

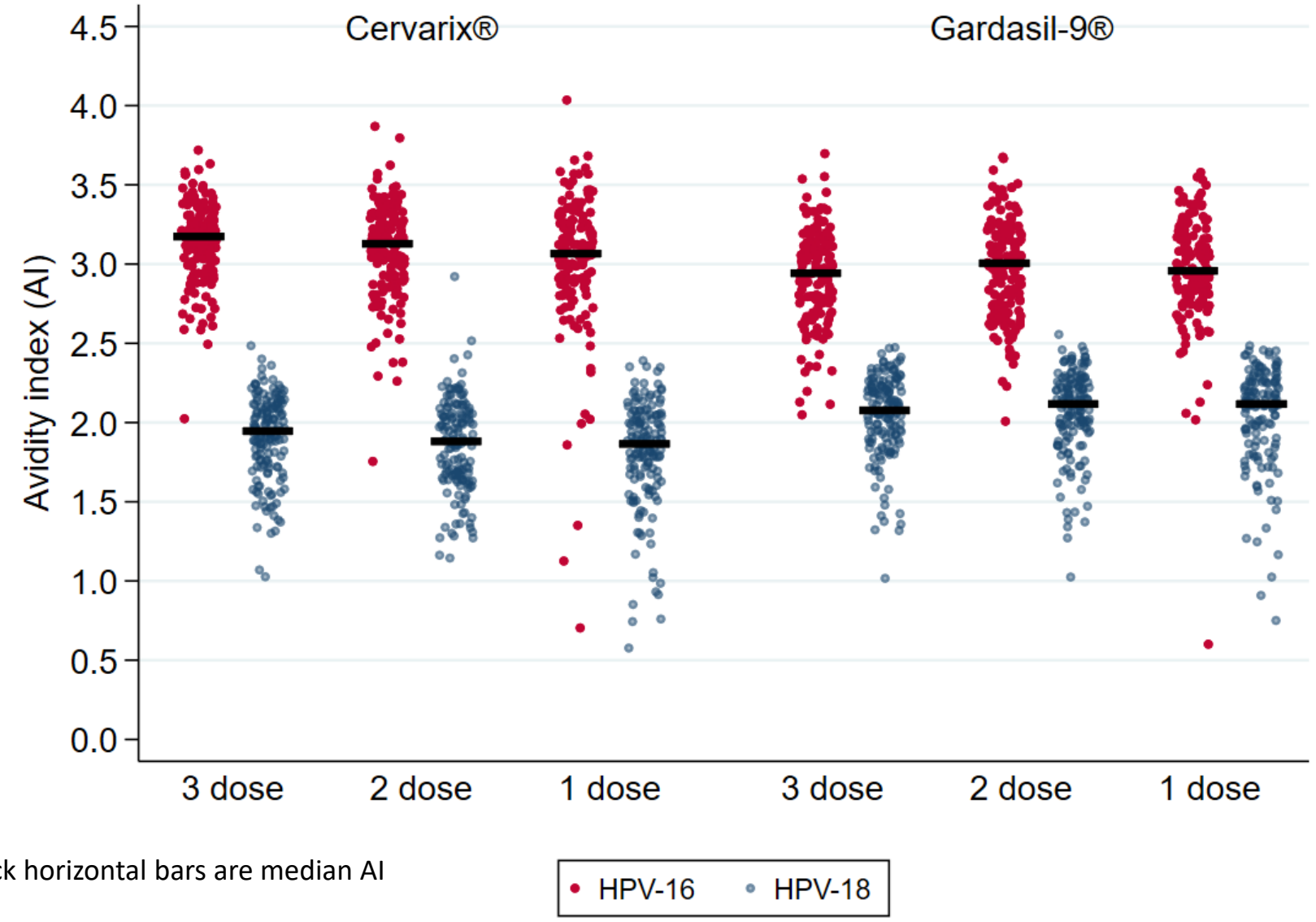


Courtesy of P. Bloem (WHO)

Antibody kinetics to M36



Distribution of HPV 16/18 avidity index at M36



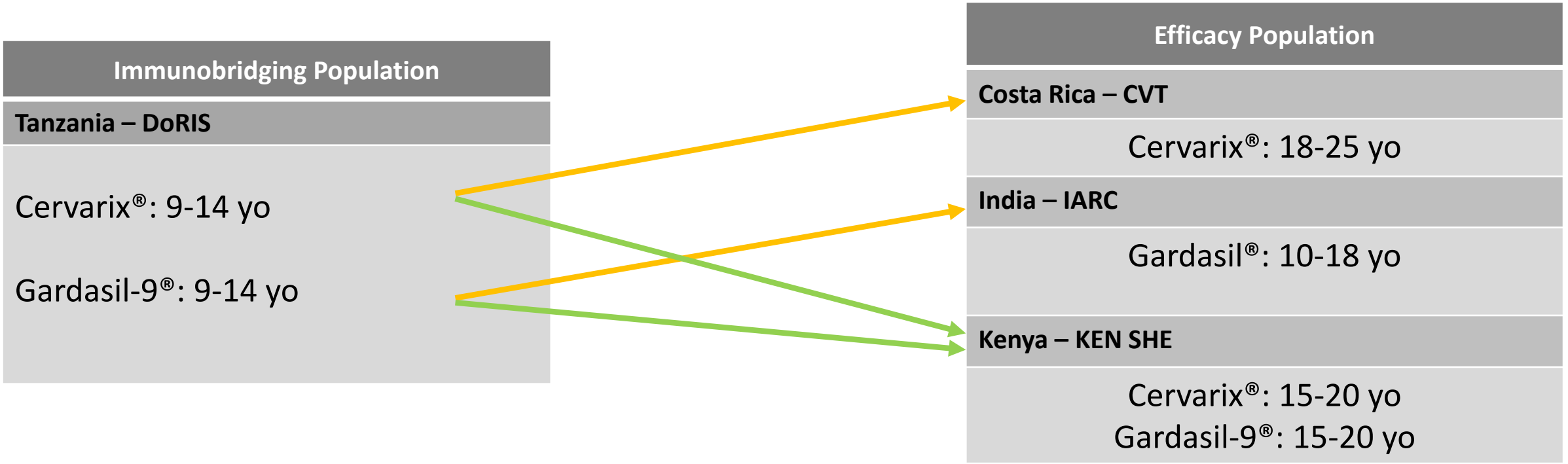
Black horizontal bars are median AI

Antibody avidity - 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

Watson-Jones D, et al. Lancet Glob Health, 2022

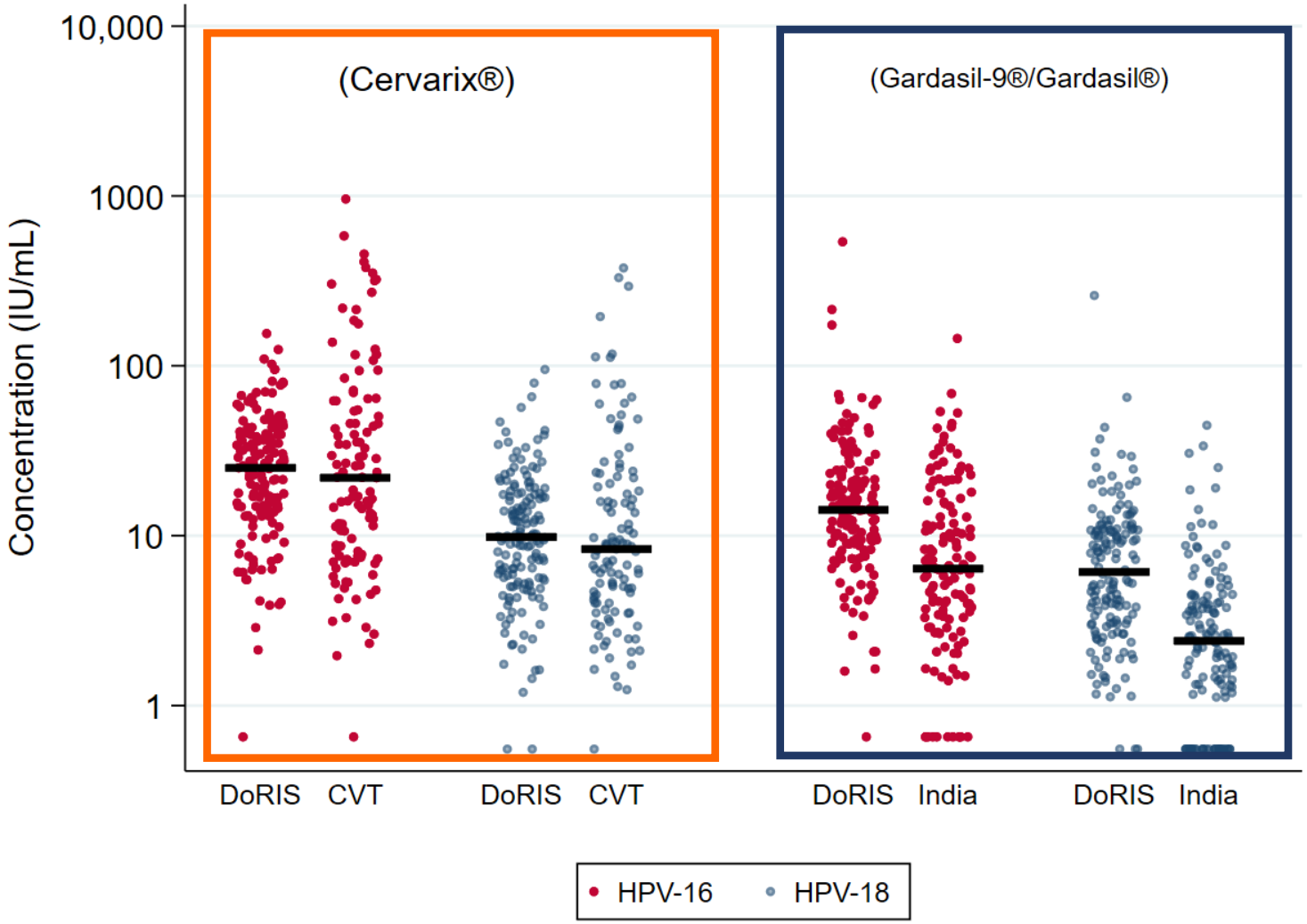
DoRIS Trial – Immunobridging



- 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 Trial M24 one-dose immuno-bridging



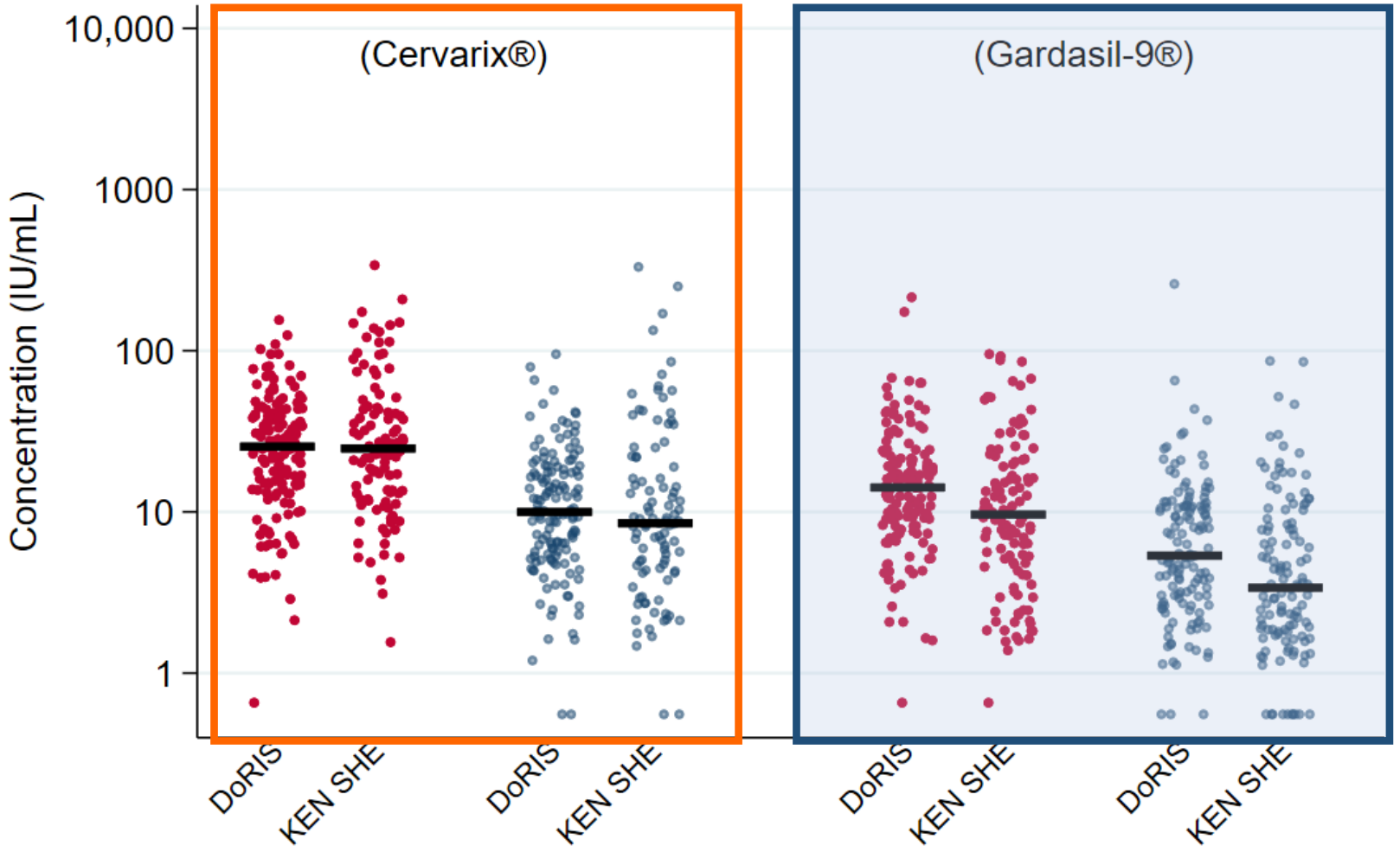
Black horizontal bars are median antibody titers

- 1D in DoRIS is non-inferior to 1D in historical cohorts at M24, for HPV-16 & HPV-18, for both vaccines

CVT: Costa Rica Vaccine Trial; DoRIS: Dose Reduction Immunobridging and Safety Study

Baisley K et al. Lancet Glob Health, 2022

DoRIS and KEN SHE one-dose M24 immunobridging



Black horizontal bars are median antibody titres

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Summary - existing Single-Dose Evidence

- Efficacy with a single dose for prevention of persistent infection with vaccine-related genotypes from a recent RCT and from high quality longitudinal cohort studies where 1-dose efficacy was comparable to efficacy with 2 and 3 doses of vaccine
- Efficacy against HPV 16/18 prevalent and incident infection sustained until 10-11 years for the 2-valent and 4-valent vaccines
- Immune responses following 1 dose stable over time to 10-11 years
- Immune responses in the target age for vaccination non-inferior to cohorts where efficacy has been shown, with similar kinetics and high avidity for all doses
- Data from multiple geographies

Forthcoming data

SAGE reviewed studies

Efficacy/immunogenicity data

- ❑ CVT to 20 years
- ❑ India/IARC CIN2+ data to 12 years
- ❑ KEN SHE M36 data

Immunogenicity

- ❑ DoRIS M36 and M60 data (and data to 9 years)

Effectiveness

- ❑ Thailand impact 4 year data

Other studies

Efficacy/immunogenicity

- ❑ ESCUDDO (Costa Rica): RCT of 1 or 2 doses of 2vHPV or 9HPV

Immunogenicity

- ❑ HANDS (Gambia): includes 4-8 yo (9vHPV)
- ❑ Primavera (Costa Rica): 2vHPV/9HPV

Impact/effectiveness

- ❑ HOPE (S Africa); 2vHPV; incl. HIV-infected participants

Modelling summary

Introducing 2-dose routine vaccination with no MAC prevents fewer cases and is less efficient, cost-effective and equitable than many alternatives e.g. immediate 1-dose (allowing accelerated introduction) or 1/2-dose MAC

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

If 1-dose protection wanes within 20 years, then switching to 2-dose routine vaccination (with a 1-dose MAC with high coverage) would mitigate loss in cancer prevention

The difference between current and optimal strategies can exceed 1m deaths over the next 10 vaccinated cohorts

Similar conclusions from 3 models (Harvard, HPV-ADVISE, PRIME), different approaches to the question, includes many countries

Kim J. Could 1 dose be less efficacious than 2 doses but still be a great public health intervention? . HPV World 2017;24:26-8; Burger E. Now or later: health impacts of delaying 1-dose HPV vaccine implementation in a high-burden setting. Int J Cancer 2022. https://doi.org/10.1002/ijc.34054.; Drolet et al. Optimal human papillomavirus vaccination strategies to prevent cervical cancer in low-income and middle-income countries in the context of limited resources: a mathematical modelling analysis. Lancet Inf Dis 2021; 21:1598-1610. https://doi.org/10.1016/S1473-3099(20)30860-4

Summary of WHO position on HPV vaccines (Dec 2022)

Primary target group		• Girls, 9-14 years old
Vaccination Schedule (F = M)	**≧ 9 years old** *=> 26/45yr*	• 2 doses, *min interval 6m, 12 recommended, no maximum interval**
	9-20 years old	• 1-dose*
	Immuno-compromised & HIV+ individuals *(any age)*	• Minimum 2 doses*, ideally 3 doses
Vaccination prioritization	**Multi Age Cohort Catch-up**	• Prioritize multi-age cohort (MAC) vaccination at introduction or catch-up missed girls through 18 years of age • Offer multiple opportunities to receive at least 1 dose before age 15
	Immunocompromised /HIV+ and sexually abused individuals	• Prioritize vaccination of immunocompromised/ PLWHIV and children or adolescents who faced sexual abuse
	Boys	• Introducing the vaccination of boys and older females should be carefully managed until the global supply situation is fully unconstrained.
	Older age cohorts	

* Off-label recommendations

Slide courtesy of P. Bloem (WHO)

Countries switching to one dose

Region	Country (intro year)	WB	Policy change
AFR	**Cape Verde (2021)**	LMIC	Switch to 1-dose, extended MAC to 14 yo girls
AMR	**Mexico (2008)**	UMIC	Switch to 1-dose in routine programme
EUR	**UK (2008)** **Ireland (2009)** **Albania (2022)**	HIC HIC HIC	Switch to 1-dose, 9-25 yo girls and boys Switch to 1-dose, 9-24 yo girls and boys New introduction with 1-dose in 13 yo girls
WPR	**Tonga (2022)** **Solomon Island (2019)** **Australia (2007)**	LMIC LMIC LMIC	New introduction with 1-dose; catch-up extended →14 yo Switch to 1-dose in routine cohorts Switch to 1-dose in routine programme girls and boys
Planned intros	NITAGS in several GAVI-eligible countries (LMIC) have recommended a 1-dose HPV vaccine schedule		**Bangladesh (2023/24)** **Nigeria (2023/24)** **India (2023/24)**

Information courtesy of P. Bloem (WHO)

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- Paul Bloem (WHO); Margaret Stanley (Univ. Cambridge)
- **Single-Dose HPV Vaccine Evaluation Consortium**

www.path.org/singledosehpv