THE DoRIS TRIAL

RESULTS TO M36 – IMMUNOGENICITY OF 1 DOSE OF GARDASIL-9® AND CERVARIX® IN TANZANIAN GIRLS AGED 9-14Y:

AND

M24 IMMUNOBRIDGING RESULTS

Deborah Watson-Jones

On behalf of DoRIS and immunobridging investigators

London School of Hygiene & Tropical Medicine

& Mwanza Intervention Trials Unit, Mwanza, Tanzania

DoRIS trial

Study Title	**Dose Reduction Immunobridging & Safety Study of two HPV vaccines in Tanzanian girls**
Principal Investigator(s)	D.Watson-Jones, K. Baisley, J Changalucha
Study Centers	Mwanza Intervention Trials Unit, National Institute for Medical Research, Mwanza, Tanzania
Study Design	**Open label, randomised study of 2 different HPV vaccines**
Study population	**930 HIV negative girls aged 9-14 years living in Mwanza city**
Intervention	**1 or 2 or 3 doses of 1 of 2 HPV vaccines; 6 arms; 155 girls per arm**
Study duration	**Follow up to Month 60 (M36 results available)**
Study Vaccines	**Cervarix® & Gardasil®9**

DoRIS trial objectives

Primary Objectives

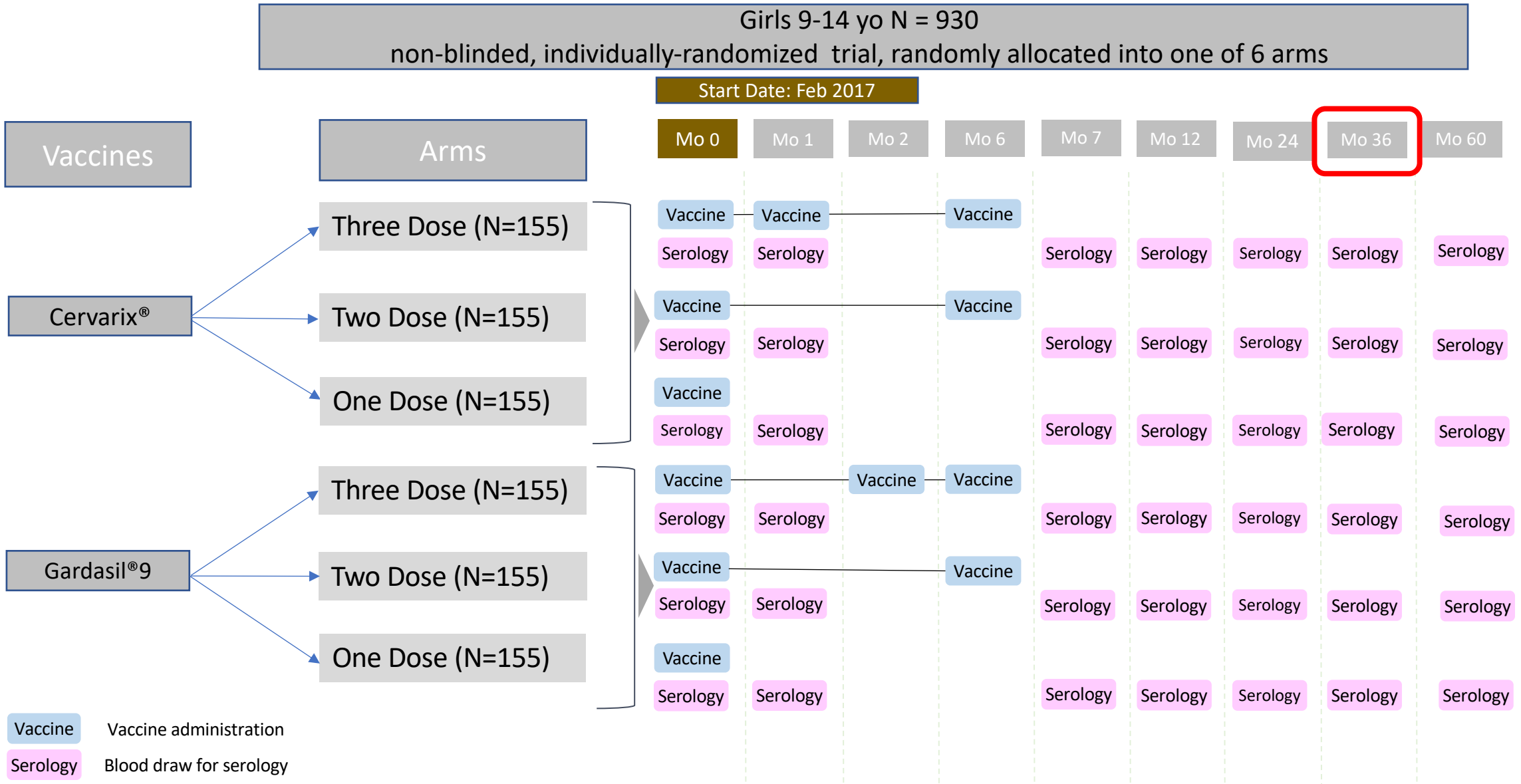
Demonstrate non-inferiority of HPV 16/18 seroconversion after 1 dose compared with 2 or 3 doses of same vaccine at M24

Primary immunobridging objective: Demonstrate non-inferiority of HPV 16/18 antibody GMT at M24, comparing 1 dose in DoRIS with historical efficacy cohorts who received only 1 dose

Secondary objectives

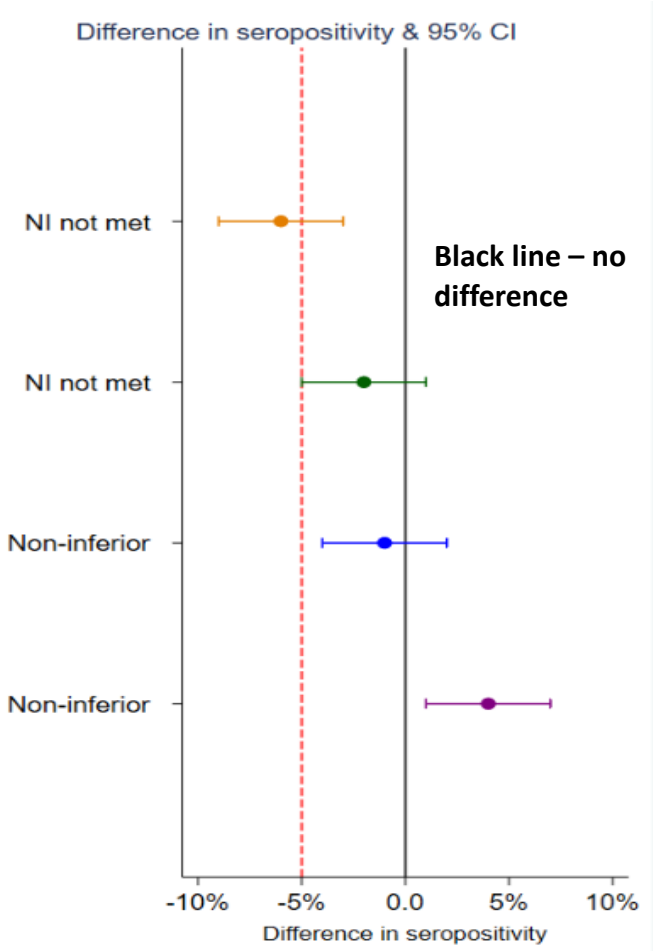
- Safety and tolerability
- HPV 16/18 seropositivity and GMTs comparing same dose regimen between the 2 vaccines
- HPV 16/18 antibody avidity & memory B cell responses between dose regimens & vaccines
- Antibody levels of the HPV genotypes in 9-valent vaccine
- Effect of malaria on antibody GMTs

DoRIS Trial – Study Schematic



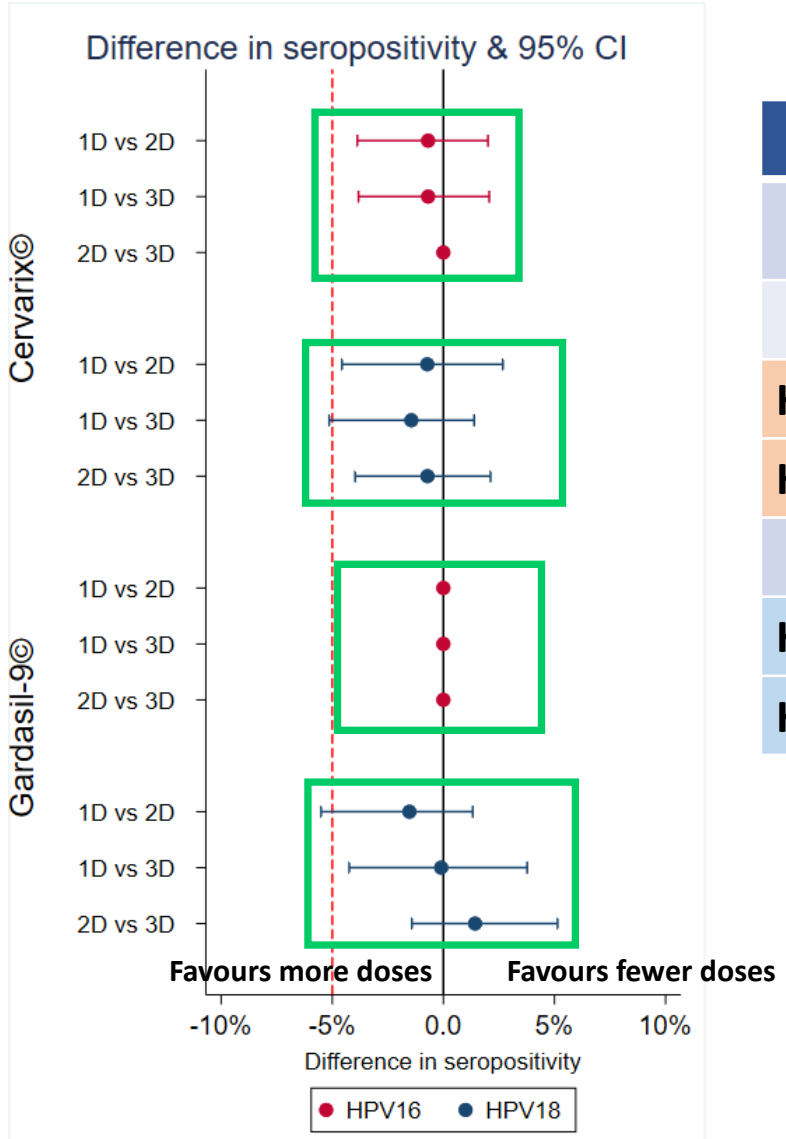
Non-inferiority (NI) objectives - definitions

- For seroconversion, use **NI margin of -5%**
  - **Lower CI for difference in seroconversion (reduced dose regimen – standard regimen) must be above -5%**
  - i.e. reduced dose regimen does not decrease seroconversion by more than 5%
- For ratio of geometric mean concentrations (GMC), use **NI margin of 0.50**
  - **Lower CI for GMC ratio [reduced dose/standard regimen] must be above 0.50**
  - i.e. reduced dose regimen does not decrease antibody titres by more than 50%
- Standard NI margins used in many HPV vaccine trials



Red line – NI margin

Non-inferiority of seropositivity at M36

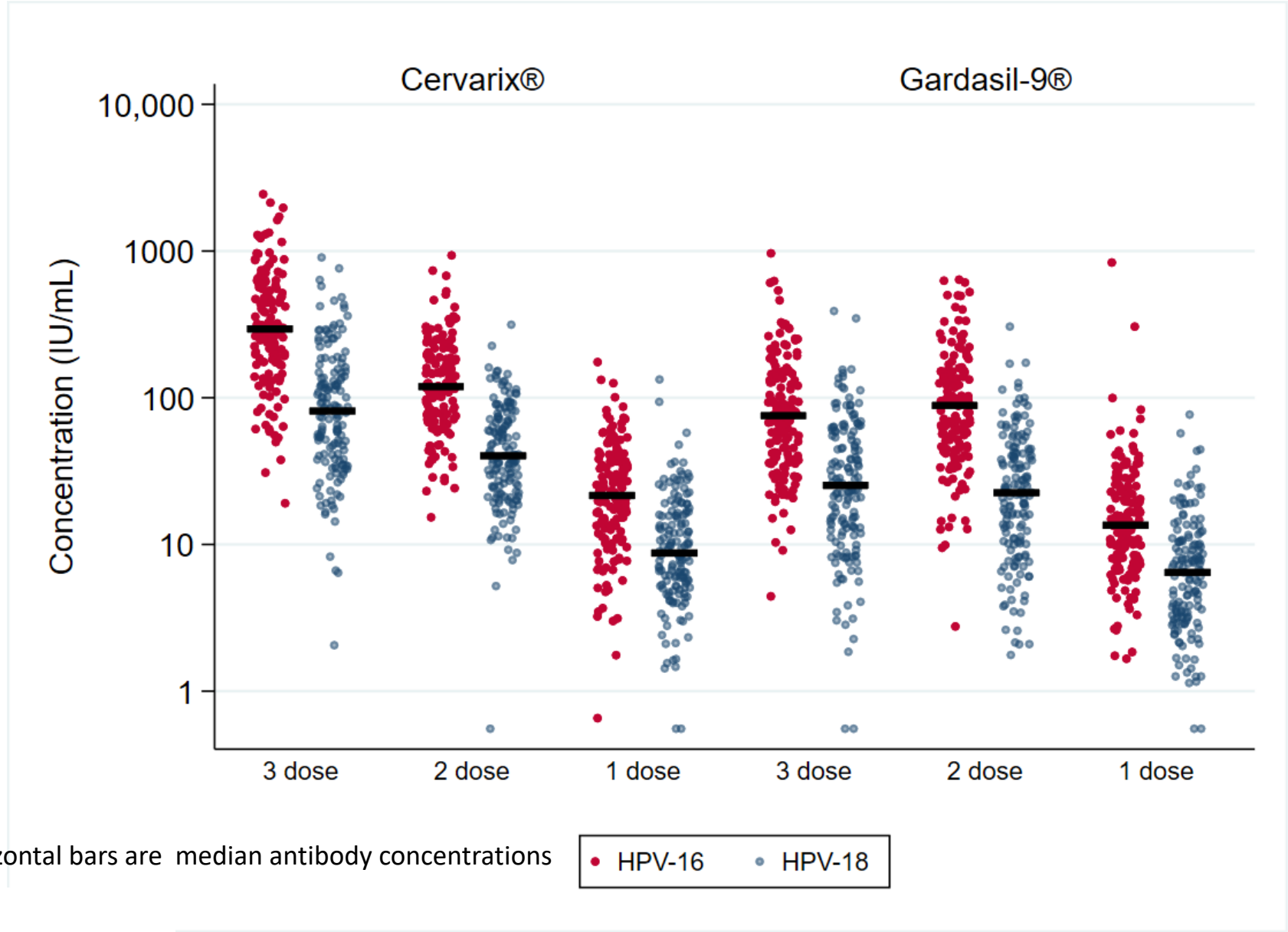


	1 dose		2 doses		3 doses	
	N	Seropositive (%)	N	Seropositive (%)	N	Seropositive (%)
		Cervarix©				
HPV-16	146	145 (99.3%)	141	141 (100.0%)	140	140 (100.0%)
HPV-18	139	137 (98.6%)	140	139 (99.3%)	135	135 (100.0%)
		Gardasil-9©				
HPV-16	140	140 (100.0%)	140	140 (100.0%)	139	139 (100.0%)
HPV-18	131	129 (98.5%)	135	135 (100.0%)	140	138 (98.6%)

- >99% HPV 16 seropositive and >98% HPV 18 seropositive
- 1D is non-inferior to 2D and 3D for HPV16 for both vaccines
- For HPV18, non-inferiority met for 2D vs 3D

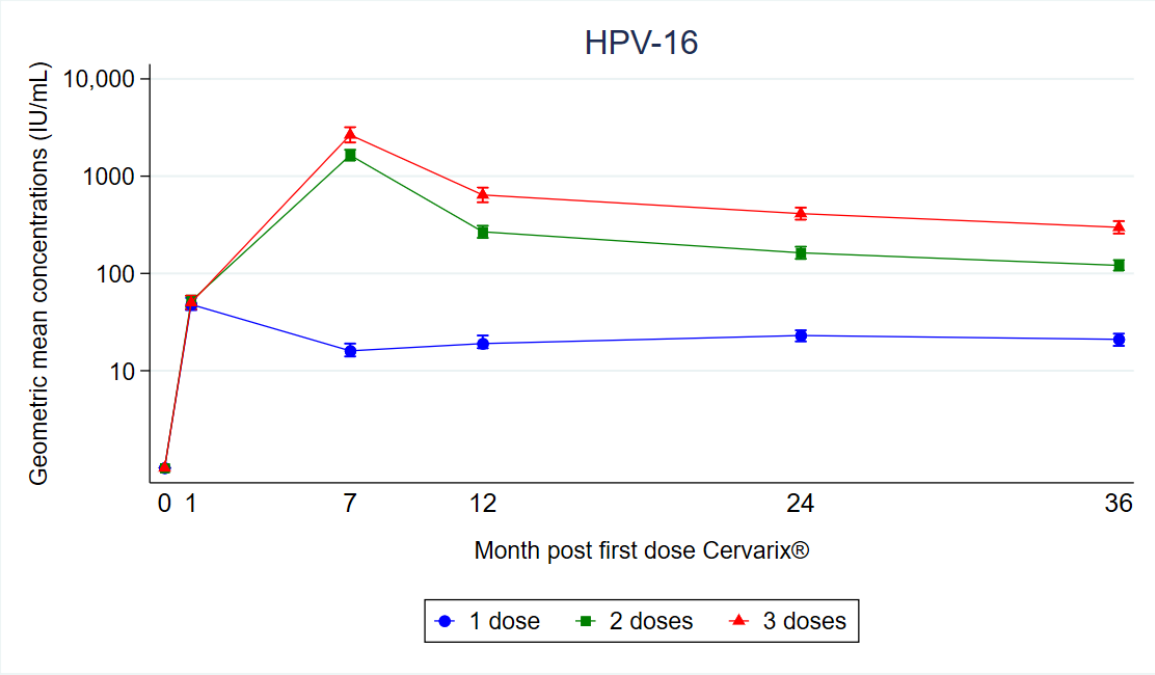
- **Solid black line: 0 - no difference in seropositivity between arms**
- **Dashed red line: NI margin - lower CI for difference above 5%**

HPV 16/18 antibody concentrations at M36



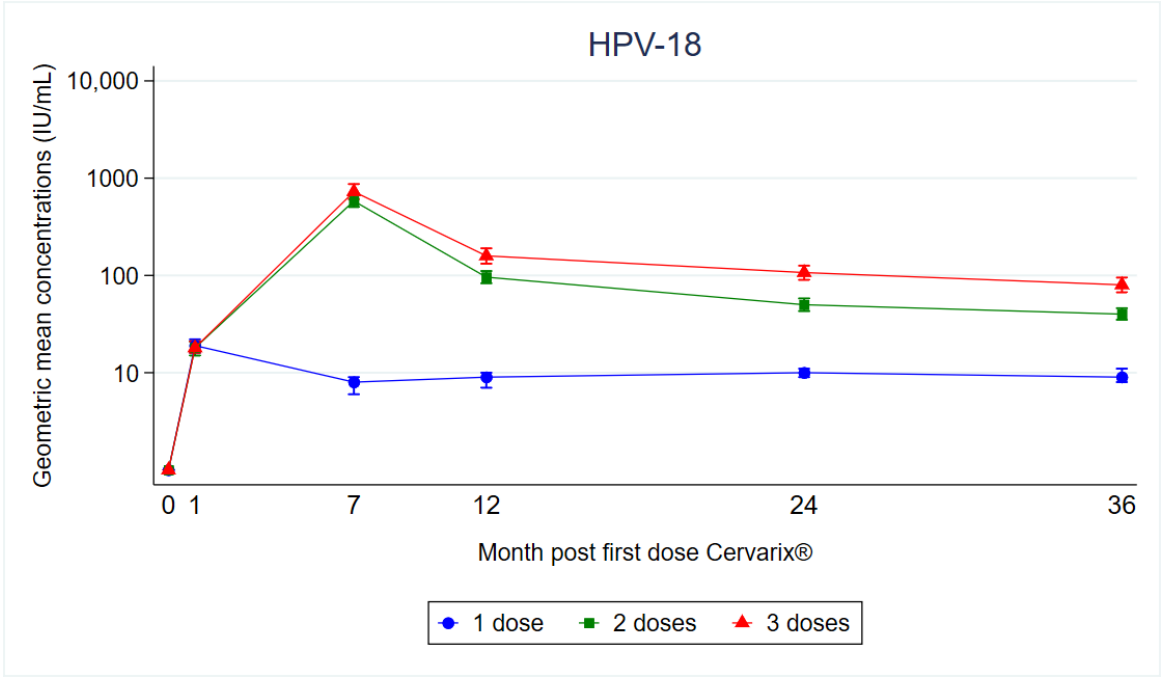
Black horizontal bars are median antibody concentrations

HPV 16/18 antibody concentrations over time – Cervarix®

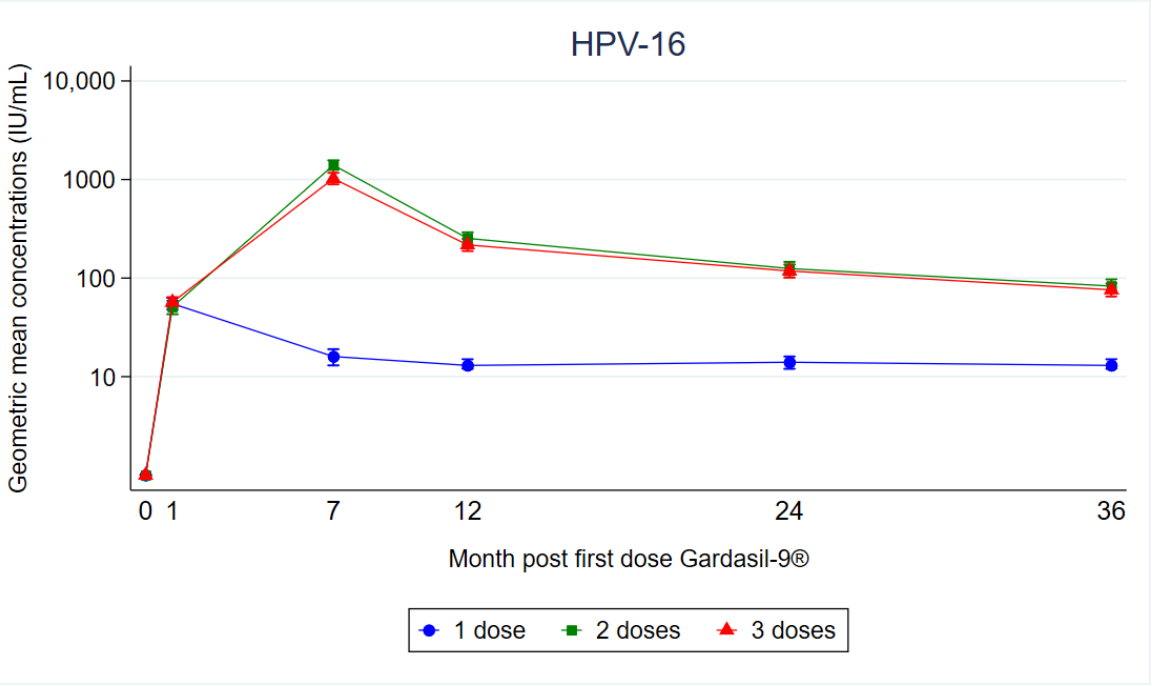


- In 2D and 3D arms, levels decline after peak at M7 (last dose at M6)
- 3D arm levels remain higher than 2D at M36
- In 1D arm, levels relatively constant from M12 (plateau)

- Similar to observations in other HPV vaccine studies

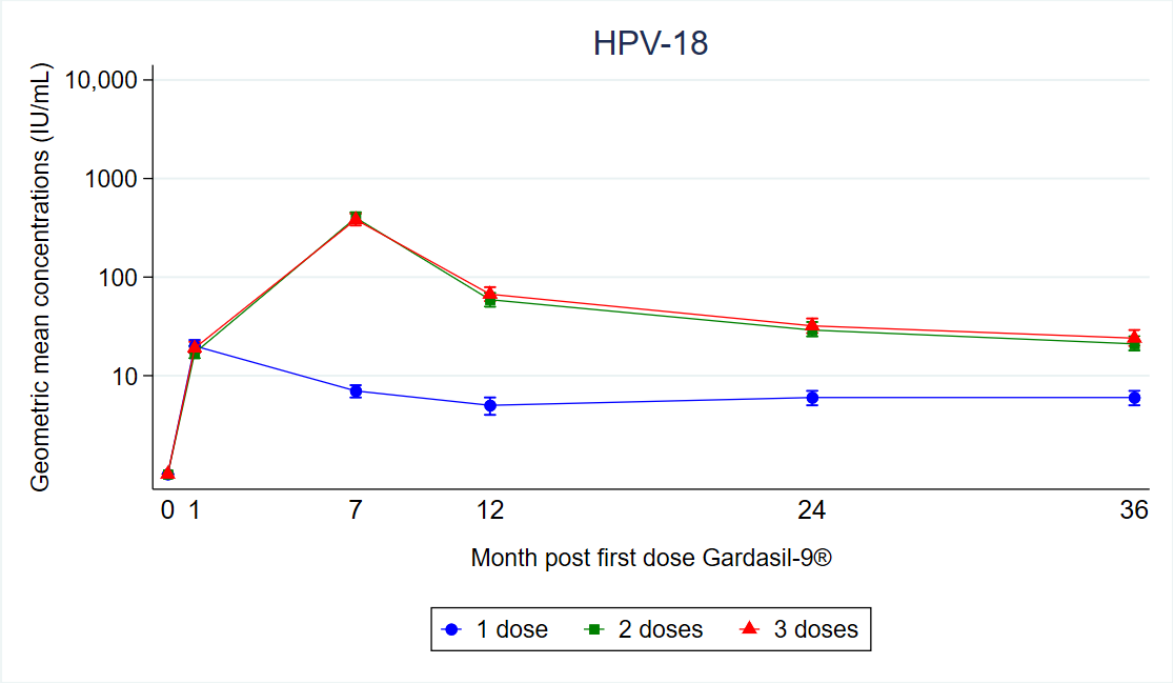


HPV 16/18 antibody concentrations over time – Gardasil-9®

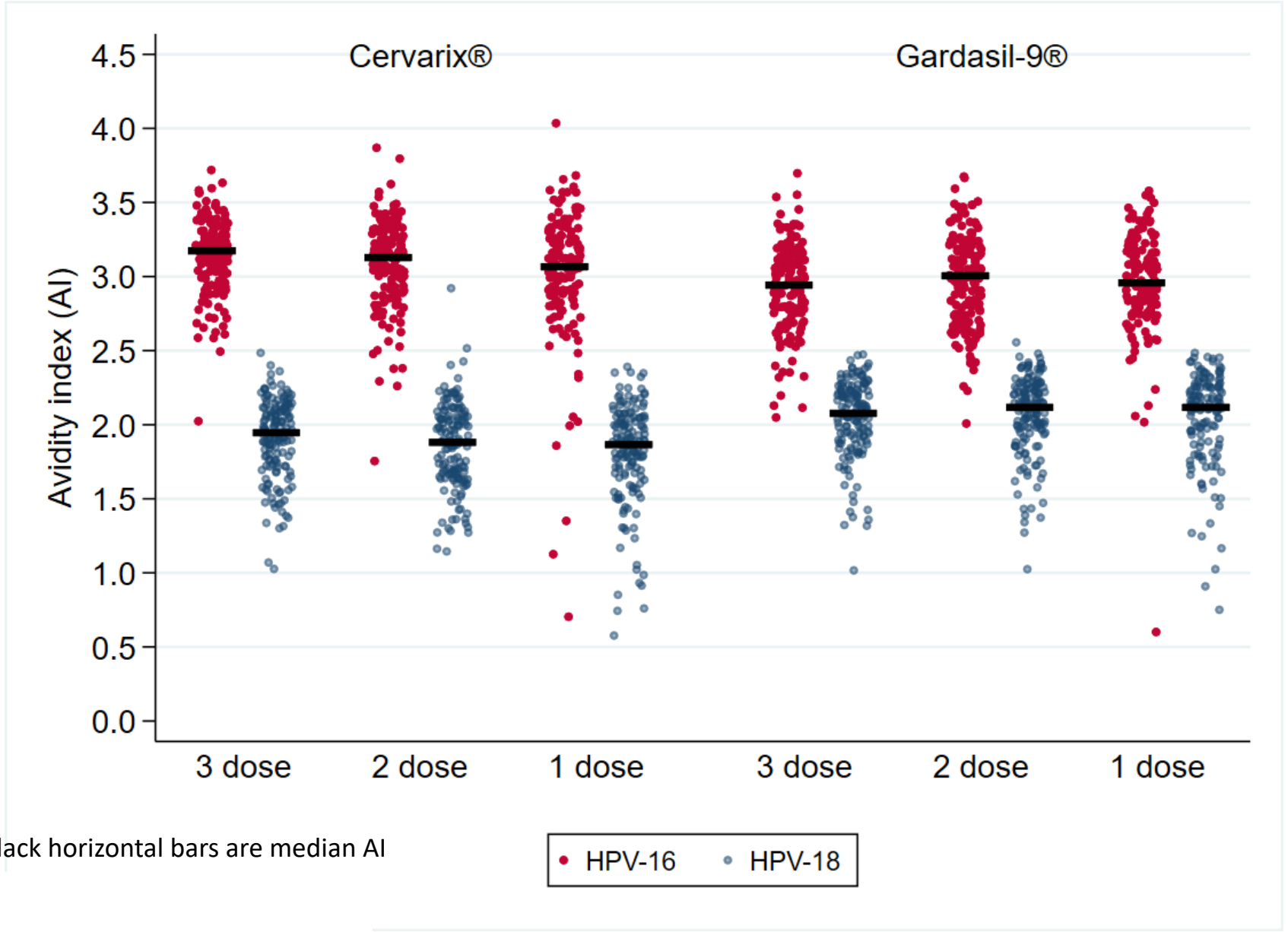


- In 2D and 3D arms, levels decline after peak at M7 (last dose at M6)
- 2D and 3D levels similar at M24 and M36
- In 1D arm, levels relatively constant from M12 (plateau)

- Similar to observations in other HPV vaccine studies



Distribution of HPV 16/18 avidity index at M36

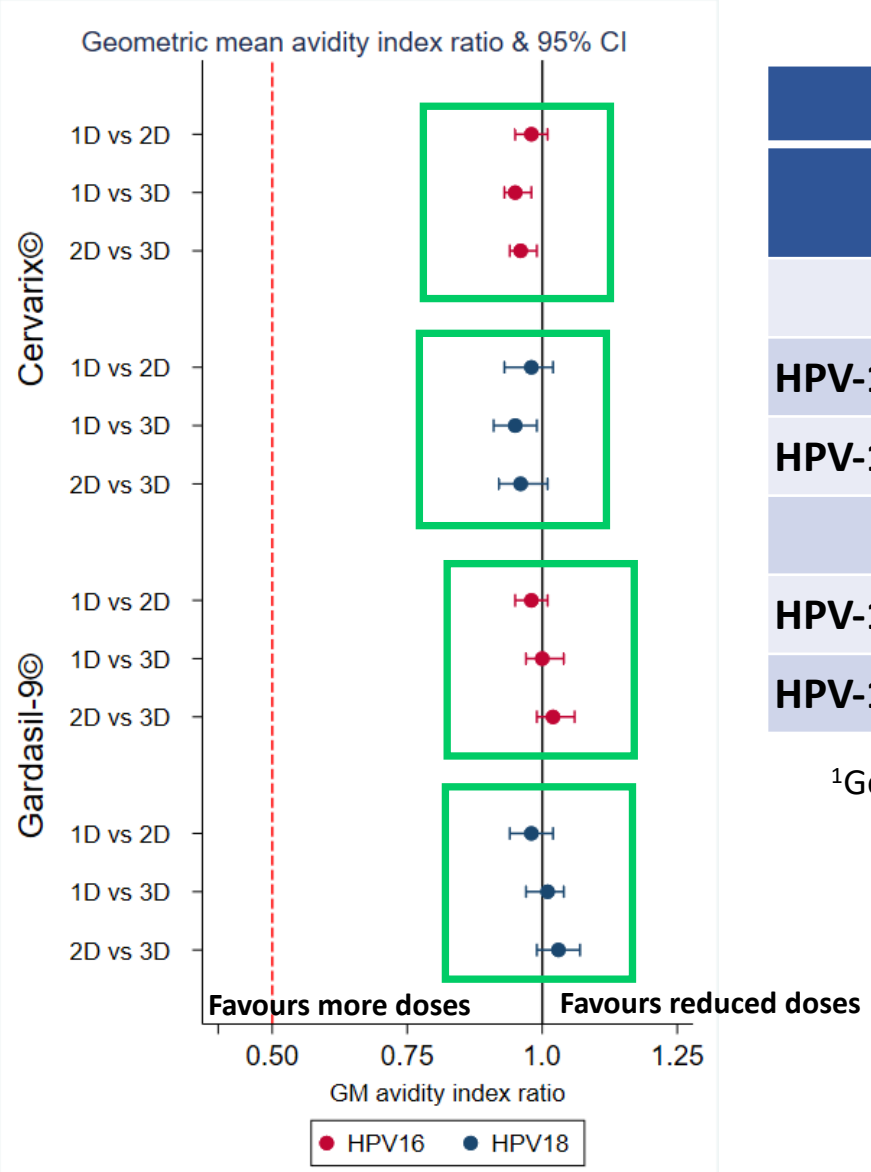


Black horizontal bars are median AI

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

Avidity index at M36 – between dose groups



	1 dose		2 doses		3 doses	
	N	GM avidity index[1] (95% CI)	N	GM avidity index[1] (95% CI)	N	GM avidity index[1] (95% CI)
		Cervarix©				
HPV-16	146	2.99 (2.91-3.09)	141	3.06 (3.01-3.12)	140	3.14 (3.10-3.18)
HPV-18	139	1.80 (1.74-1.87)	140	1.83 (1.78-1.88)	135	1.88 (1.83-1.93)
		Gardasil-9©				
HPV-16	140	2.92 (2.84-3.01)	140	2.98 (2.92-3.04)	139	2.91 (2.86-2.96)
HPV-18	131	2.04 (1.98-2.11)	135	2.08 (2.03-2.13)	140	2.03 (1.98-2.08)

[1]Geometric mean avidity index (AI)

- Avidity index similar between dose groups, for HPV16 and HPV18, for both vaccines (ratios close to 1 – i.e. no difference)
- No formal NI comparison, but lower CI of GM avidity index ratio >0.8 in all cases

Immunobridging rationale and procedures

- Difficult to evaluate efficacy for HPV vaccines in young girls of target age for vaccination - time needed for HPV infection endpoints

WHO recommendation: immunobridging studies[1]

- 'Bridge' immune responses to population where efficacy has been shown
- Non-inferiority is an appropriate trial endpoint
- Non-inferiority of immune responses used to infer efficacy

[1] http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk7/Prophylactic_HPVVaccineTrials.pdf

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®)
  - Some women missed visits and received only 1 or 2 doses
  - 7466 randomised; 549 received 1 dose (275 in Cervarix® arm)
- 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	2-dose	1-dose	Control
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)**	

Kreimer et al. *J Natl Cancer Inst* 2020

IARC India trial

- Cluster randomised trial of 2 vs 3 doses of Gardasil®
  - Girls aged 10-18 years randomised to 2 or 3 doses Gardasil®
  - India suspended all HPV vaccination trials - led to some girls receiving only 1 dose
  - 17,729 randomised; 4950 received 1 dose
  - 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	2-dose	1-dose	Control
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)**	

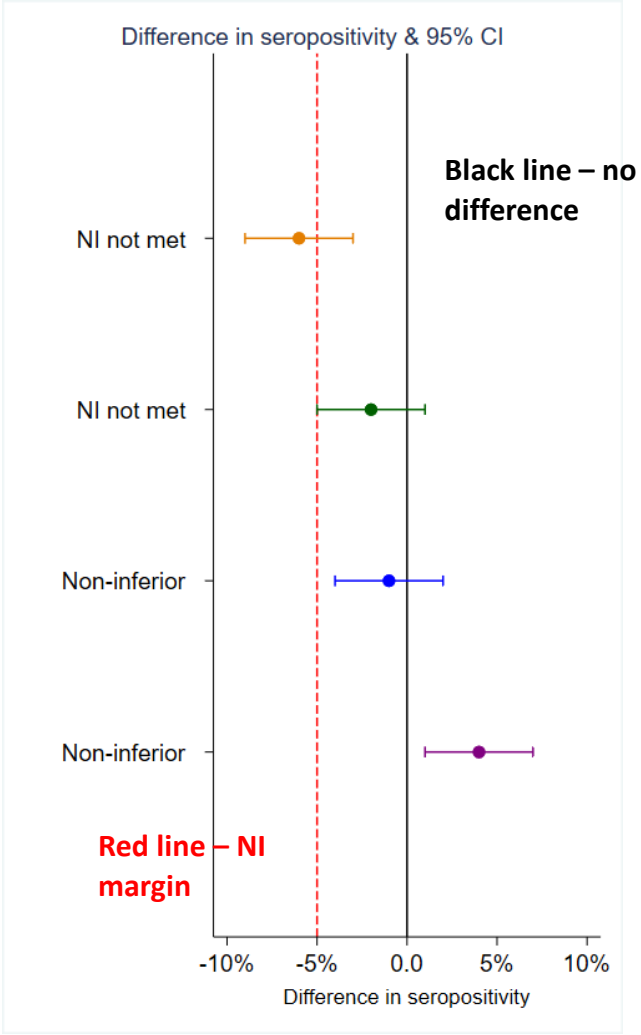
Basu et al. *Lancet Oncology* Oct 2021

Immunobridging analyses

- Immunobridged DoRIS M24 antibody levels to CVT, India/IARC and KEN SHE studies
- VLP ELISA for HPV 16/18 antibody levels; samples from 3 studies tested together in same batch (Frederick National Laboratory for Cancer Research, USA)
- Primary analyses excluded girls HPV DNA or seropositive at baseline
- Antibody levels $\log_{10}$-transformed for all analyses; those below the assay cut-off given value of half the cut-off before log transformation
- Difference in HPV 16/18 seropositivity – with 95% confidence intervals (CI) using exact methods

Non-inferiority (NI) objectives - definitions

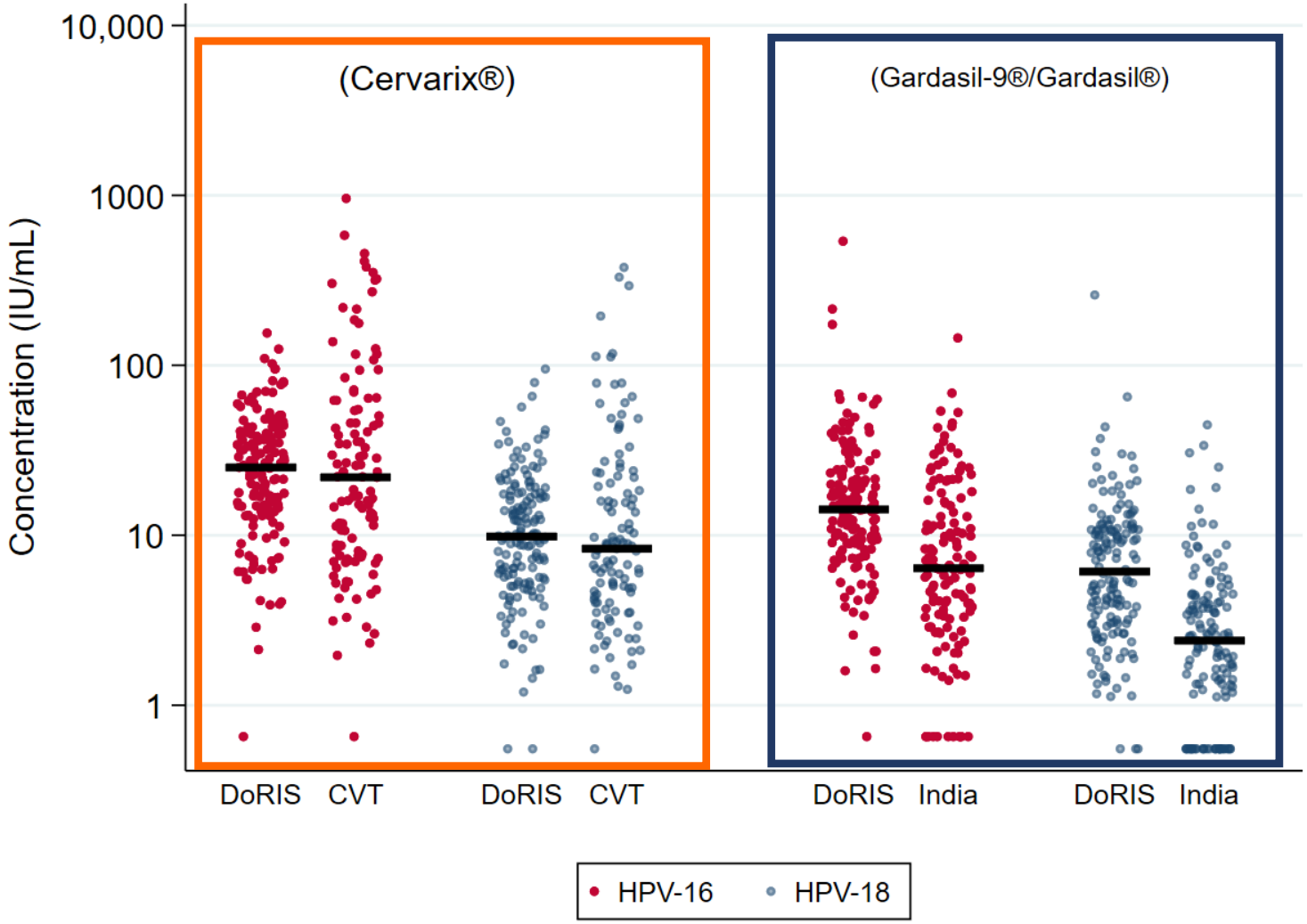
- For seroconversion, use **NI margin of -5%**
  - **Lower CL for difference in seroconversion (1D DoRIS – 1D historical cohort) must be above -5%**
  - i.e. Seroconversion after 1D in DoRIS is not reduced by more than 5%
- For ratio of geometric mean concentrations (GMC), use **NI margin of 0.50**
  - **Lower CL for GMC ratio [1D DoRIS/1D historical cohort] must be above 0.50**
  - i.e. antibody titre after 1D in DoRIS is not decreased by more than 50%



Immunobridging DoRIS to CVT and India – baseline characteristics

	1 dose DoRIS Cervarix® N=155	1 dose CVT Cervarix® N=115	1 dose DoRIS Gardasil-9® N=155	1 dose India Gardasil® N=139
Median (IQR) age (yrs)	10 (9-12)	21 (19-23)	10 (9-12)	14 (13-16)
9-14 years	155 (100%)	0	155 (100%)	74 (53.2%)
15-25 years	0	115 (100%)	0	65 (46.8%)
HPV16 DNA positive	0	3 (2.6 %)	1 (0.6 %)	N/A
HPV18 DNA positive	0	4 (3.5 %)	1 (0.6 %)	N/A
HPV16 seropositive	6 (3.9 %)	16 (13.9%)	7 (4.5 %)	8 (5.8 %)
HPV18 seropositive	13 (8.4 %)	16 (13.9%)	16 (10.3%)	9 (6.5 %)

DoRIS Trial Month 24 1-dose Immuno-bridging

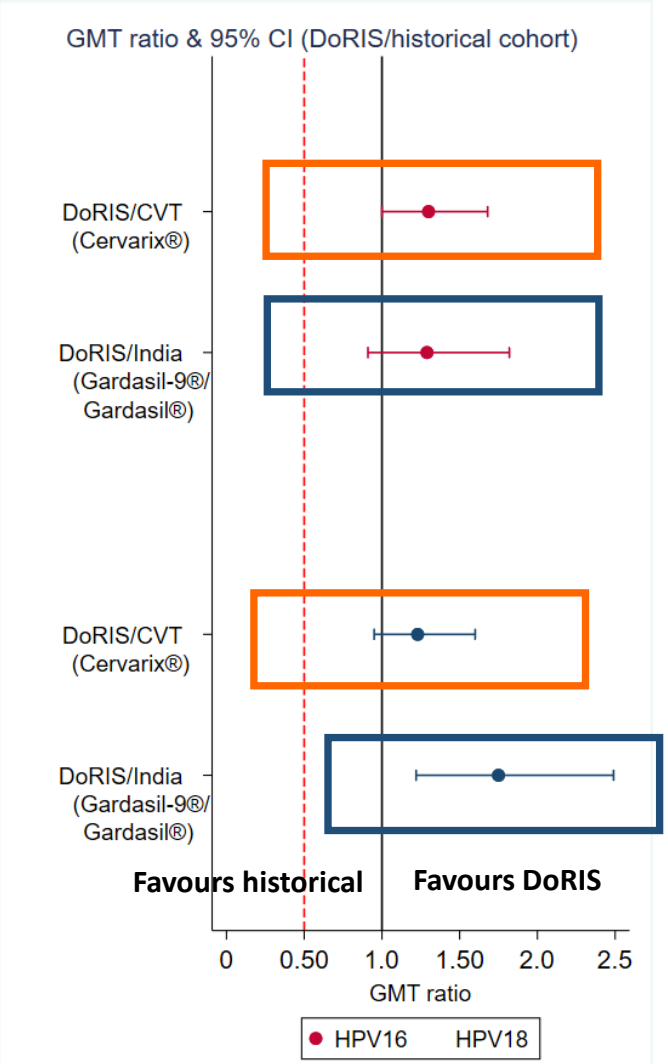


Black horizontal bars are median antibody titers

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

Data presented at IPVC, 2021; Baisley et al: (Pre-print) https://ssrn.com/abstract=4055428

1º immunobridging objective – NI of GMCs at M24



Solid black line: GMC ratio = 1 (no difference between groups)

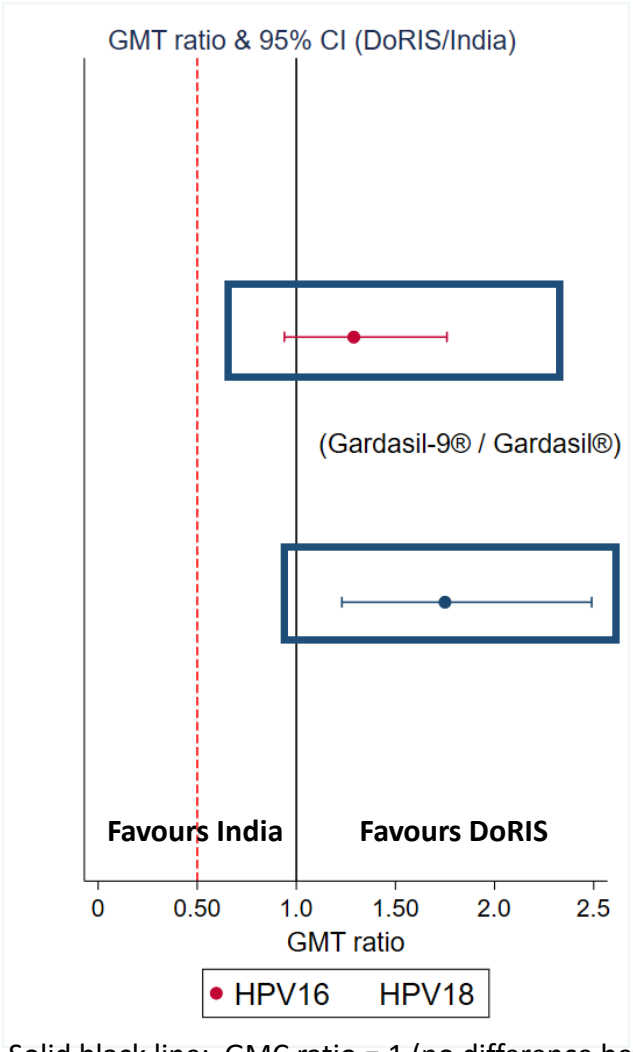
Non-inferiority margin (dashed red line): lower CI for GMT ratio above 0.50

	N	GMT (IU/mL)	GMT 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 titres (DoRIS / historical cohort). [2]Difference in seroconversion (DoRIS - historical cohort). [3]Adjusted for age.

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

1D DoRIS vs 1D IARC/India – younger girls (9-14 years)



Solid black line: GMC ratio = 1 (no difference between groups)

Non-inferiority margin (dashed red line): lower CI for GMT ratio above 0.50

	N	GMC (IU/mL)	GMC ratio[1] (95% CI)	Seroconversion	Difference[2] (95% CI)
HPV-16					
DoRIS (Gardasil-9®)	145	13.7		144 (99.3%)	
India (Gardasil®)	68	9.7	1.29 (0.94 -1.76)[3]	68 (100.0%)	-0.7% (-4.0- 5.0)
HPV-18					
DoRIS (Gardasil-9®)	136	5.7		133 (97.8%)	
India (Gardasil®	69	2.7	1.75 (1.23 -2.49)[3]	57 (82.6%)	15.2% (6.1-26.3)

[1]Ratio of geometric mean tconcentrations (DoRIS / India). [2]Difference in seropositivity (DoRIS - India). [3]Adjusted for age.

- 1D in DoRIS is non-inferior to 1D in IARC/India trial at M24, for HPV-16 & HPV-18, when restricted to same age range

IMMUNOBRIDGING TO KEN SHE TRIAL

Study Title	**The KEN SHE study on HPV vaccine efficacy**
Principal Investigator(s)	R. Barnabas, N. Mugo
Study Centers	Kenya: Thika, Nairobi, Kisumu
Study Design	1st prospective, blinded, randomised study of single-dose HPV vaccination
Study population	HIV negative, sexually active females 15-20 yo; 1-5 lifetime sexual partners
Intervention	1 dose Cervarix® or Gardasil®9 or Meningococcal vaccine [delayed HPV vaccination] N= up to 2,250 (750/ study arm
Study duration	Follow up to Month 36
Study Vaccines	Cervarix® & Gardasil®9

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

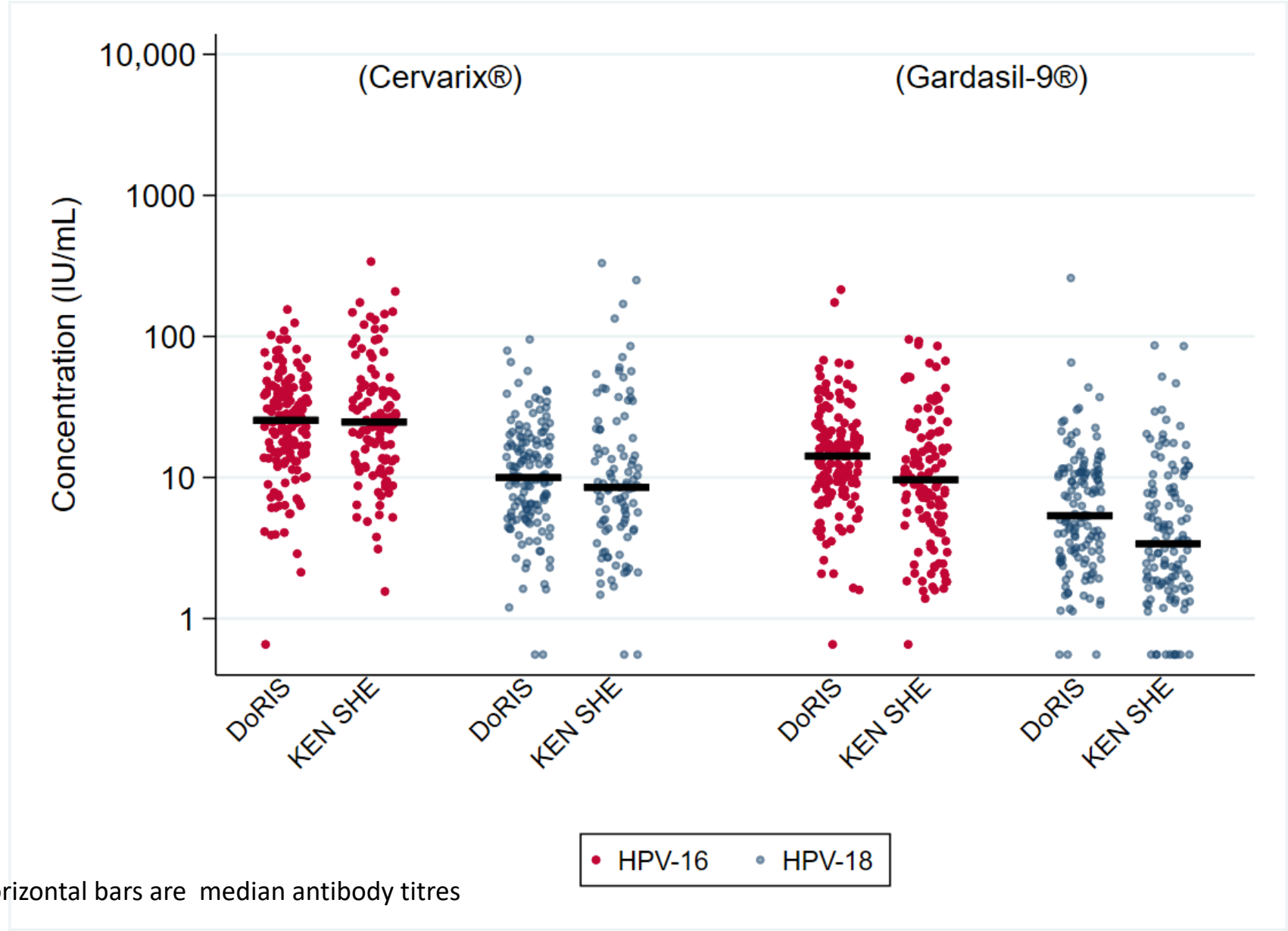
	mITT No.	No. events	Incidence/ 100 woman yr	VE (%)	VE 95% CI
Delayed Vaccination N = 757	473	36	6.83		
Single dose Cervarix® N = 760	489	1	0.17	97.5	81.6; 99.7
Single dose Gardasil®9 N = 758	496	1	0.17	97.5	81.7; 99.7

mITT cohort: HPV antibody negative & HPV DNA negative for the relevant genotypes at enrolment 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

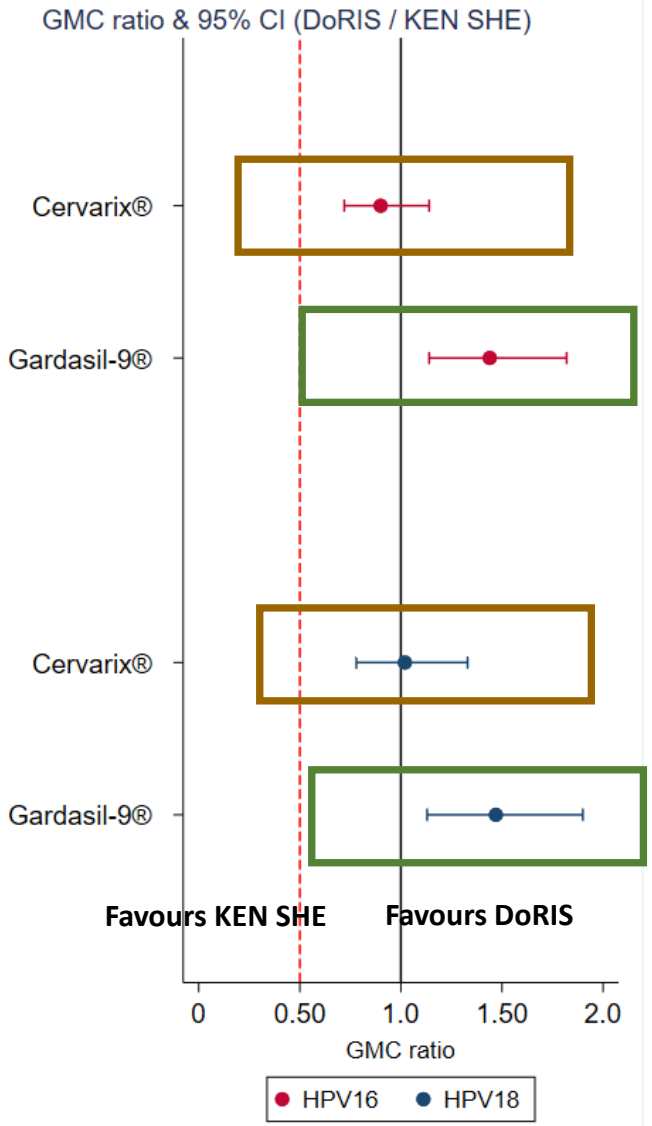
CI: confidence interval; mITT: modified intent-to-treat; VE: vaccine efficacy; yo: year of age

DoRIS and KEN SHE at M24



Black horizontal bars are median antibody titres

Immunobridging 1D DoRIS vs 1D KEN SHE – M24



	N	GMC (IU/mL)	GMC ratio[1] (95% CI)	Seropositive	Difference[2] (95% CI)
HPV-16					
DoRIS (Cervarix®)	148	22.9		147 (99.3%)	
KEN SHE (Cervarix®)	109	25.3	0.90 (0.72 -1.14)	109 (100.0%)	-0.7% (-3.9- 3.0)
DoRIS (Gardasil-9®)	145	13.7		144 (99.3%)	
KEN SHE (Gardasil-9®)	121	9.5	1.44 (1.14 -1.82)	120 (99.2%)	0.1% (-3.2- 4.1)
HPV-18					
DoRIS (Cervarix®)	141	9.9		139 (98.6%)	
KEN SHE (Cervarix®)	99	9.7	1.02 (0.78 -1.33)	97 (98.0%)	0.6% (-3.5- 6.0)
DoRIS (Gardasil-9®)	136	5.7		133 (97.8%)	
KEN SHE (Gardasil-9®)	123	3.9	1.47 (1.13 -1.90)	113 (91.9%)	5.9% (0.5-12.5)

[1]Ratio of geometric mean concentrations (DoRIS / KEN SHE). [2]Difference in seropositivity (DoRIS – KEN SHE). [3]Adjusted for age.

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

Solid black line: GMC ratio = 1 (no difference between arms)

Non-inferiority margin (dashed red line): lower CI for GMT ratio above 0.50

Conclusions

- Seropositivity >98% all doses of both vaccines for both genotypes
- Antibody levels by dose, vaccine, and trajectories over time follow those seen in other HPV vaccine studies and plateau from M12-M36
- Avidity - no difference between dose groups and vaccines
- Immunobridging objectives met; 1D immune responses non-inferior in DoRIS to studies where 1D efficacy observed
- Issues/lessons:
  - number of available samples; may not allow random selection
  - Age differences
  - Testing samples together
  - Immunobridging data – critical in discussions with policy-makers.

Acknowledgements - Investigators

DoRIS Investigators	Institute
John Changalucha, Deborah Watson-Jones*, Saidi Kapiga*, Paul Mutani, Jackton Indangasi*,	Mwanza Intervention Trials Unit, Tanzania
Kathy Baisley, Philippe Mayaud, Hilary Whitworth, Richard Hayes	LSHTM, UK (*joint affiliation)
Ligia Pinto, Troy Kemp	Frederick National Laboratory, Maryland, USA
Charles Lacey	University of York, UK
Silvia de SanJosé	Catalan Institute of Oncology, Spain
Joakim Dillner, Carina Eklund	Karolinska Institute, Sweden
Immunobridging partners	
Ruanne Barnabas	Harvard, USA
Nelly Mugo	KEMRI, Kenya & University of Washington, USA
Aimee Kreimer	Division of Cancer Epidemiology and Genetics, NCI
Partha Basu, Eric Lucas	International Agency for Research on Cancer (IARC)
Caroline Porras	Agencia Costarricense de Investigaciones Biomédicas (ACIB)-Fundación INCIENSA (FUNIN), Costa Rica

Acknowledgements

- Funders: MRC Joint Global Health Trials; Bill & Melinda Gates Foundation
- DoRIS participants and parents
- MITU study and data teams, NIMR Mwanza Centre laboratory team, LSHTM project management team
- DoRIS TSC and DSMB members.