Clinical Vaccine Trials for Infectious Diseases at LSHTM

HPV & Ebola vaccine trials & policy implications

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LSHTM Trials Day
6 November 2023

HPV and vaccine roll-out

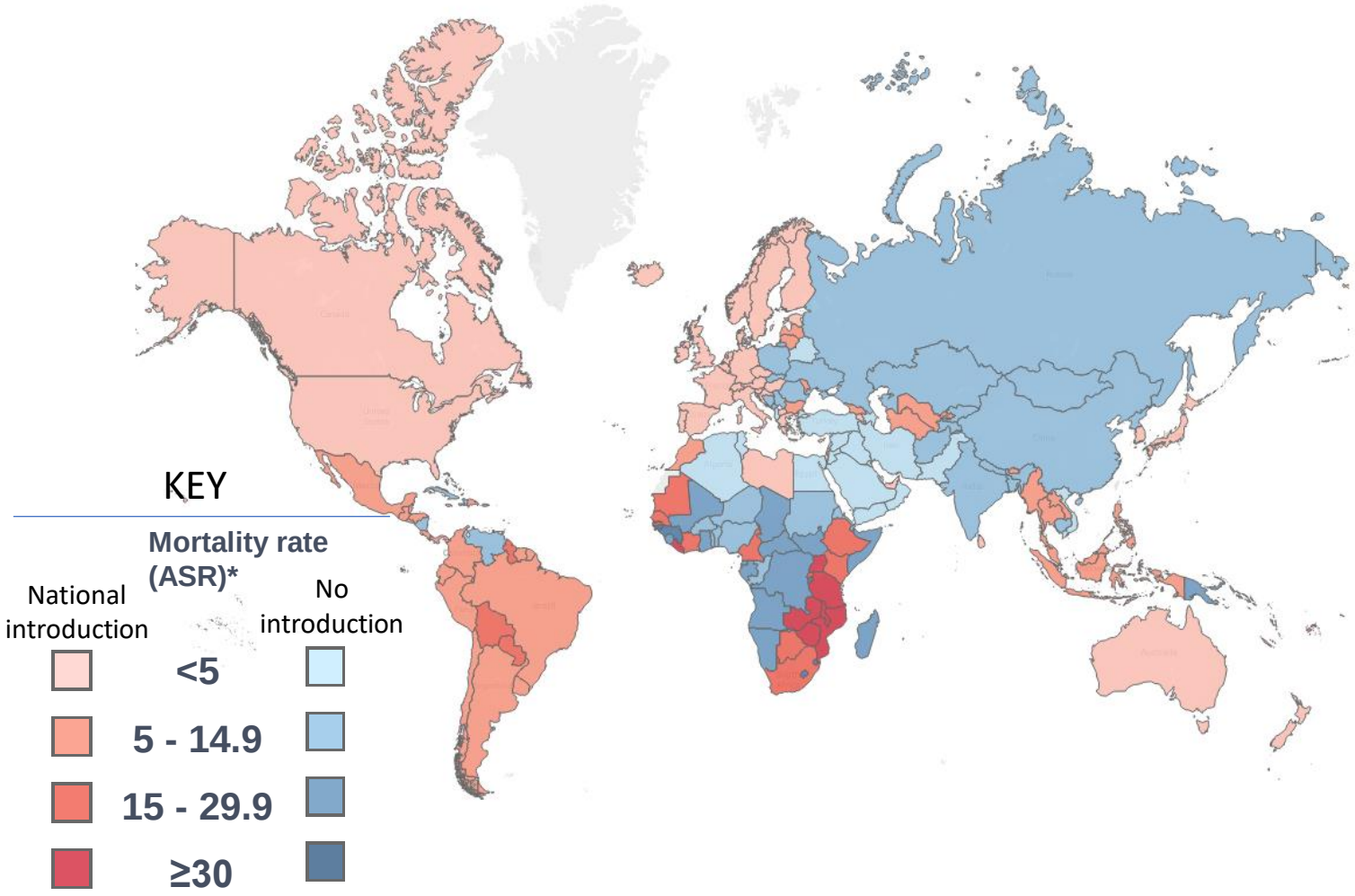
- Human papillomavirus (HPV) – most common STI; cause of cervical cancer
- 4 prophylactic HPV vaccines: highly efficacious; originally licensed as multidose regimens
- WHO – cervical cancer elimination target (including 90% of 15 yr old girls vaccinated) by 2030

Long way to go:

- 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 yrs live in countries providing HPV vaccines
- Mean coverage: 59% for dose 1 and 45% for a full vaccination regimen [1];
  many countries face problems achieving high coverage of dose 2 [2]
- **=> Global HPV vaccine coverage: 15% in 2019; 12% full regimen in 2021** [3]
- Challenges to introductions include costs, competing priorities and vaccine supply constraints

1 WHO Sept 2023; 2. Bruni Prev Med 2021; 144: , 3. WHO

Global HPV vaccine introductions & benefits of single dose



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

As of 17 Mar 2022

Single-dose HPV vaccination could:

- ❑ accelerate introduction
- ❑ simplify delivery/programme costs and potentially lead to a higher coverage e.g. through MACs
- ❑ reduce the potential for supply shortages and delivery challenges
- ❑ Accelerate achieving the vaccination target of WHO's cervical cancer elimination strategy

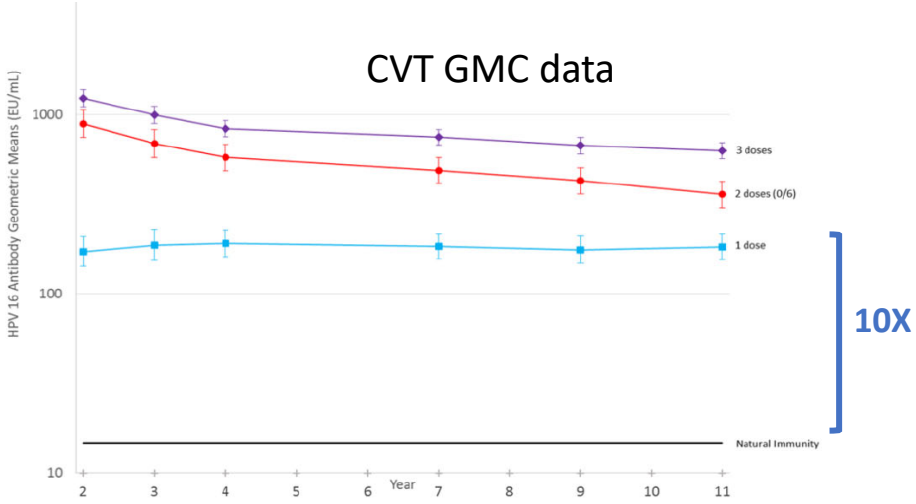
PATH. *Global HPV Vaccine Introduction Overview*. Seattle: PATH; 2022, Available at https://path.azureedge.net/media/documents/Global_Vaccine_Intro_Overview_Slides_Final_PATHwebsite_MAR_2022_qT92Wwh.pdf.

Original observational data supporting 1-dose VE:

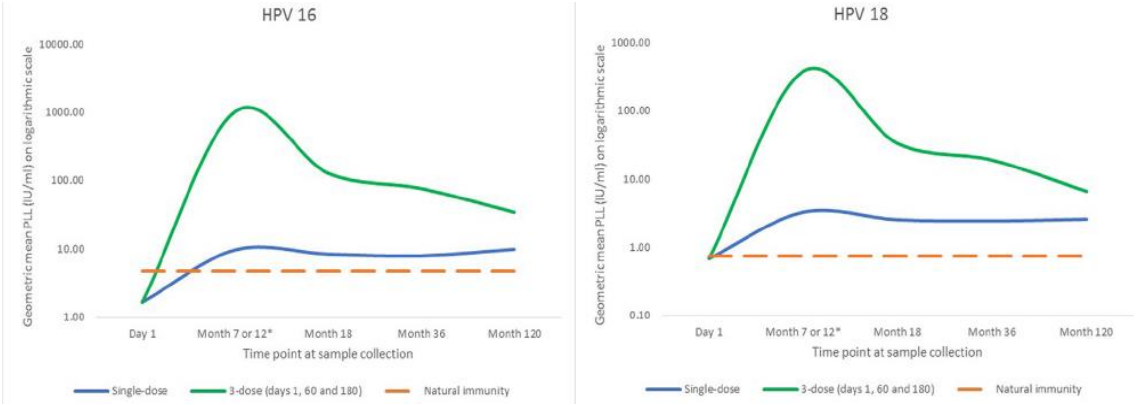
Costa Rica Vaccine trial (CVT) and India/IARC study

- 2 trials - some women did not complete vaccine series and only received 1 dose
- Dose groups analysed as observational cohorts
- Rates of HPV 16/18 infection and VE for prevention of prevalent & persistent HPV infection - no difference by dose; VE >80%
- Followed for 11+ years; no waning VE
- 1 dose - lower titres cf. 2 and 3 doses but stable concentrations going out to 11 years

CVT GMC data



India/IARC GMC data

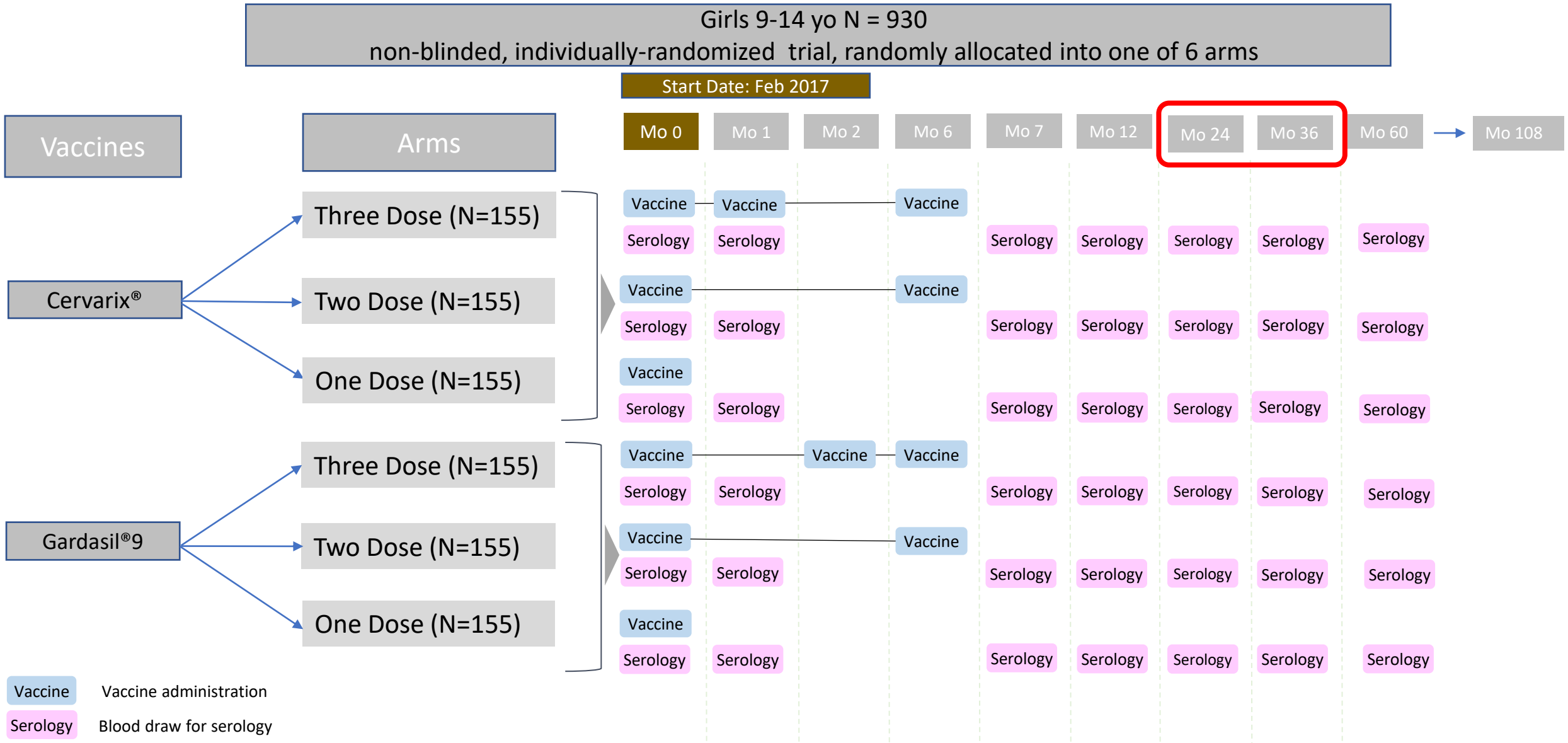


Kreimer et al. *J Natl Cancer Inst* 2020
Joshi et al. Vaccine. 2023; 41: 236-245

DoRIS (Dose Reduction Immunobridging & Safety) Trial

- First randomised trial of 1 dose in girls in the target age range for vaccination (9-14 years)
- 930 girls aged 9-14 years in Tanzania randomly allocated to 6 arms (155 per arm): 1, 2 or 3 doses of either Cervarix® and Gardasil-9®

DoRIS Trial – Study Schematic



DoRIS trial safety and seropositivity at M36

Objectives: to demonstrate

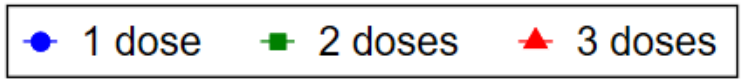
1) Non-inferiority of HPV16/18 antibody seroconversion for 1 dose cf.2 or 3 doses of same HPV vaccine at M24
2) Non-inferiority of HPV16/18 antibody GMT at M24, comparing 1 dose in DoRIS with historical efficacy cohorts who received only 1 dose

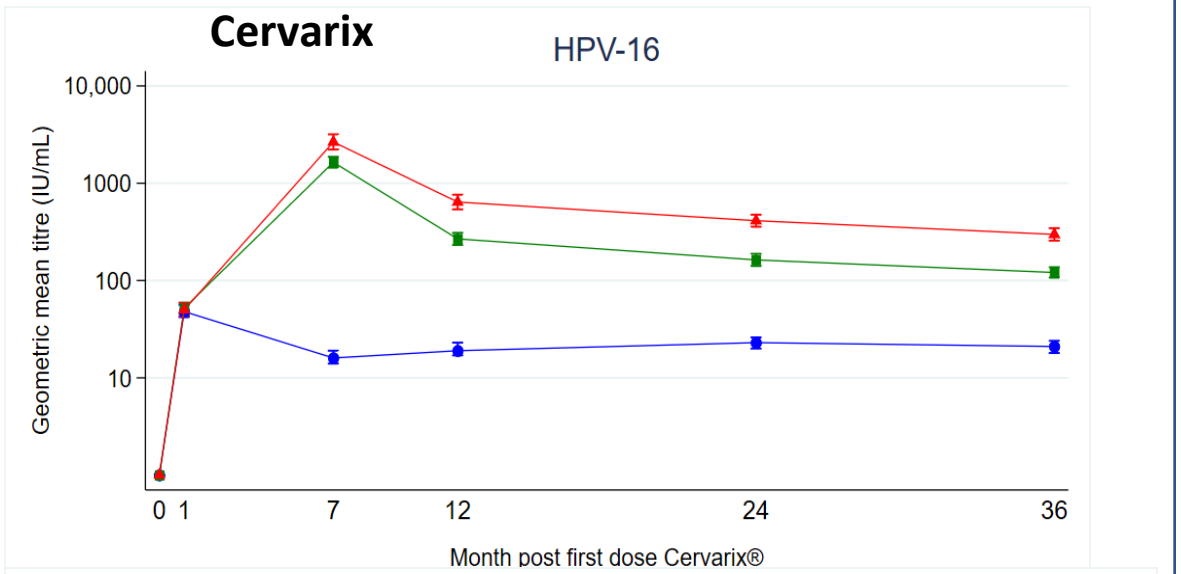
- 99.4% received all doses
- Retention 98.7% at M24
- No SAE related to vaccine irrespective of dose
- 3 years after 1st dose
  - >99% HPV 16 seropositive ; >98% HPV 18 seropositive, similar to M24*
  - M36 1D seropositivity non-inferior to 2D and 3D for HPV16 for both vaccines, similar to M24*

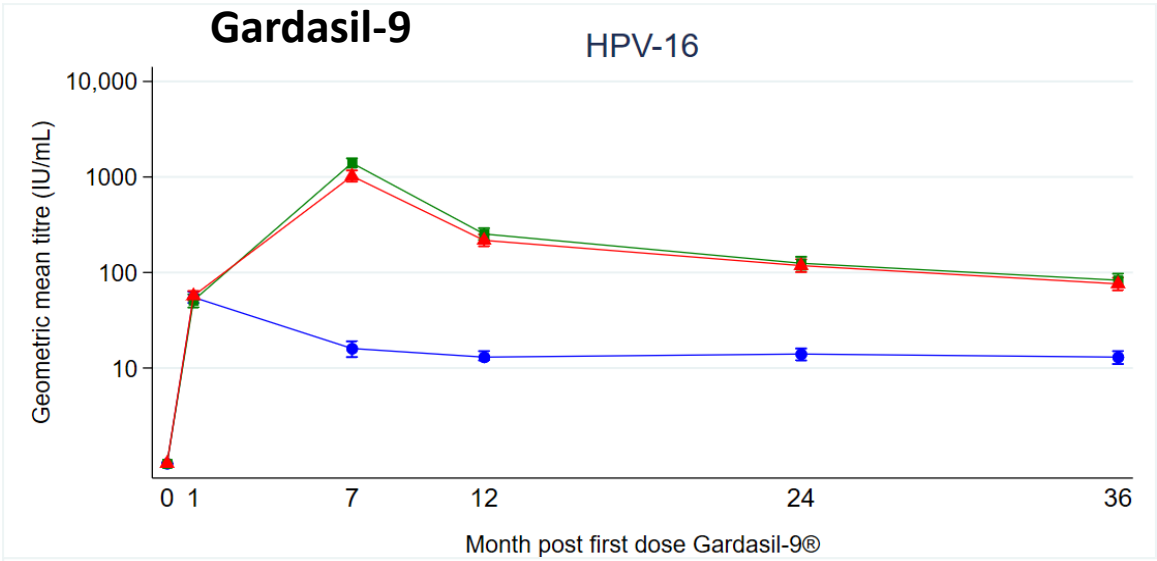
* Watson-Jones et al, Lancet Global Health 2022

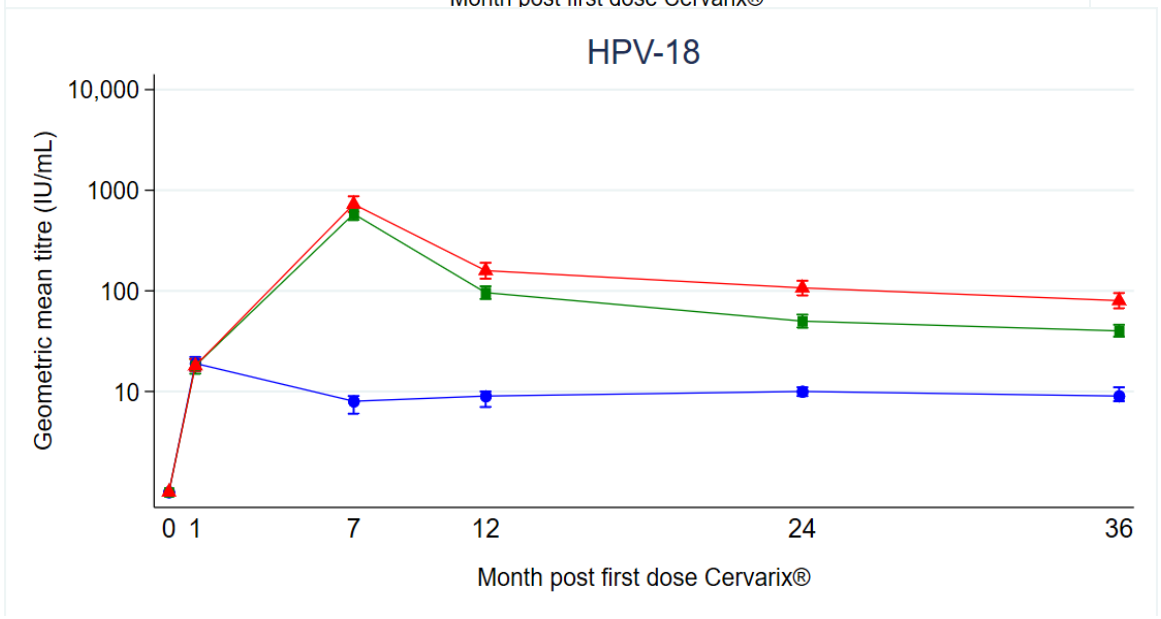
Antibody kinetics to M36

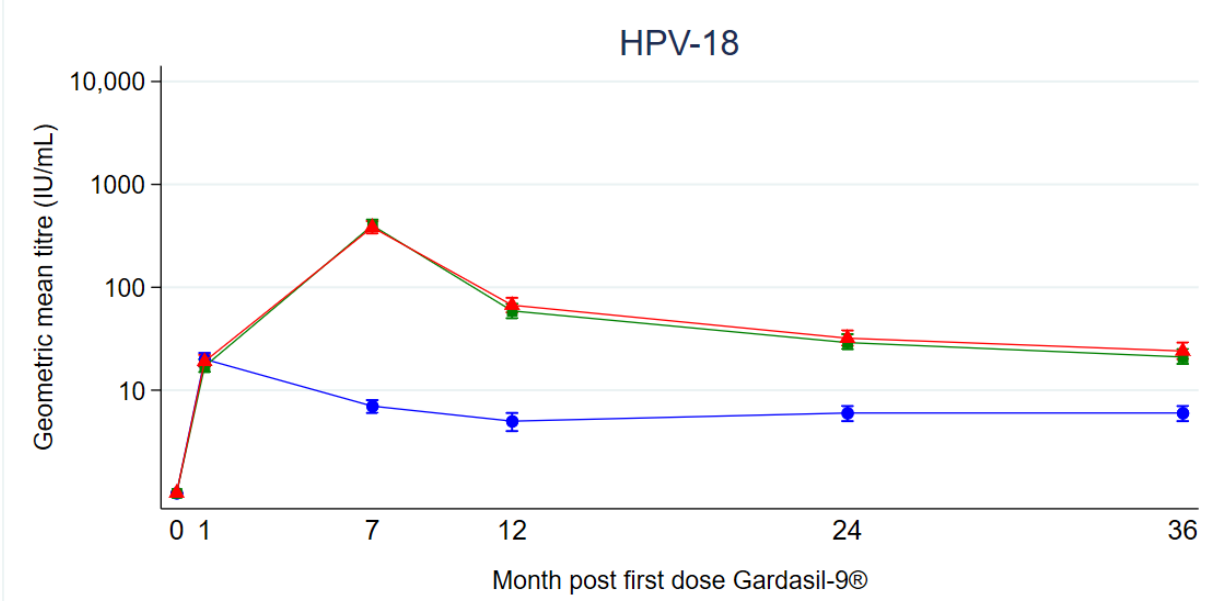
Unpublished data





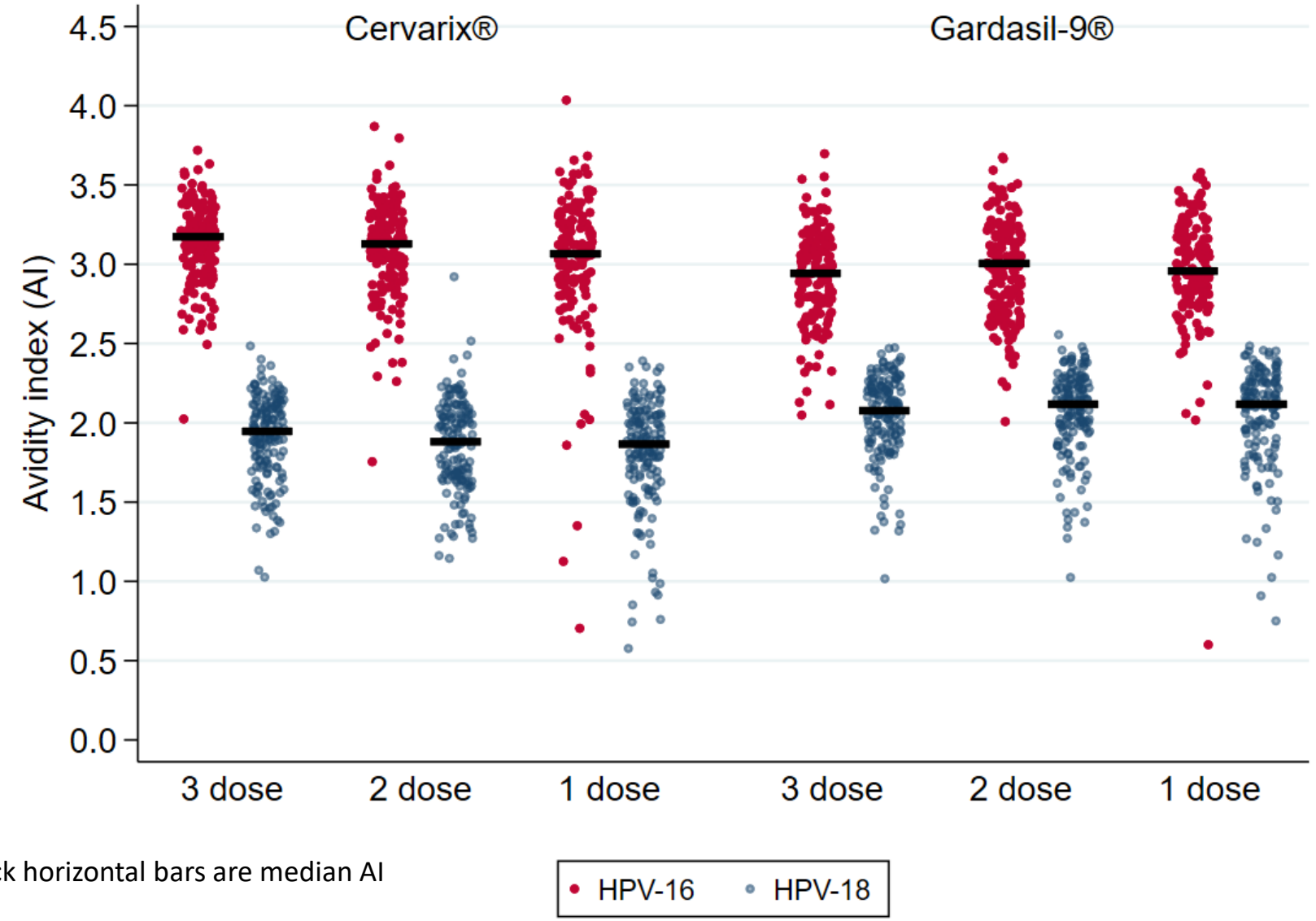






Distribution of HPV 16/18 avidity index at M36

Unpublished data



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

Design of KEN SHE trial and efficacy results

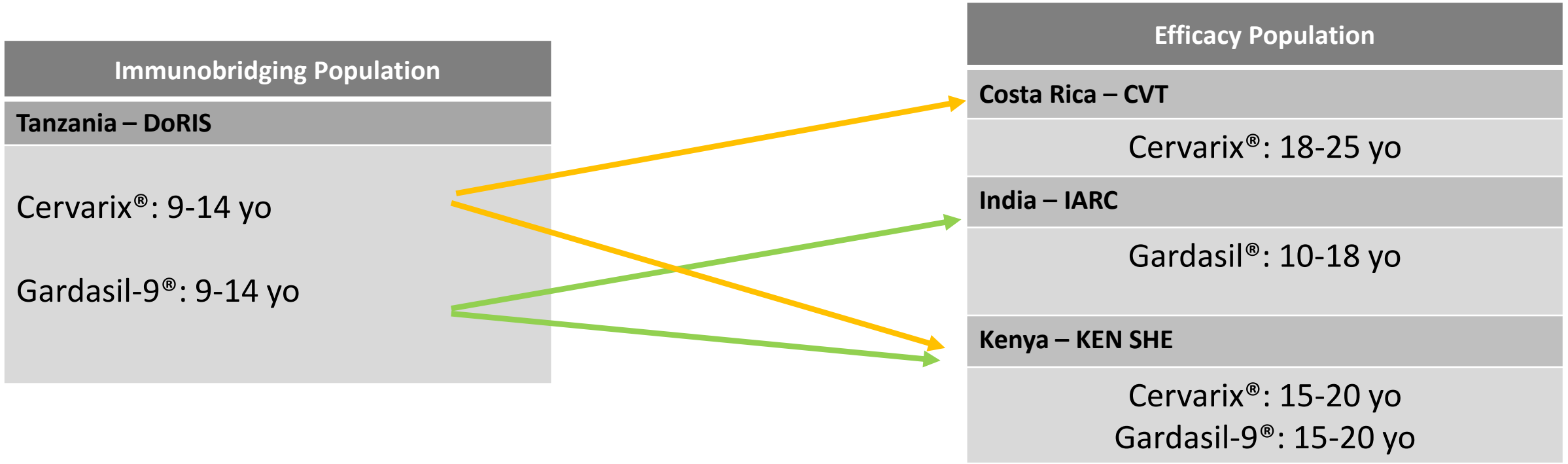
- First randomised trial to evaluate VE of 1 dose regimen

- Efficacy of 1 dose of 9-valent or 2-valent HPV vaccine to prevent incident persistent HPV 16/18 infection and HPV16/18/31/33/45/52/58 (9-valent vaccine)
- 2275 sexually active women aged 15-20 years randomised to 3 arms:
  9-v vaccine; 2-v HPV vaccine; meningococcal vaccine
- M18 HPV-16/18 VE >97%, in keeping with licensure trials for 3 doses

HPV16/18 infection endpoint	1 dose Cervarix® N=496	1 dose Gardasil-9® N=489	Control (MCV) N=473
Cases (incident persistent HPV)	1	1	36
Incidence	0.17 (0-0.93)	0.17 (0-0.95)	6.83 (4.78-9.45)
Vaccine efficacy	**97.5% (81.7-99.7)**	**97.5% (81.6-99.7)**	

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

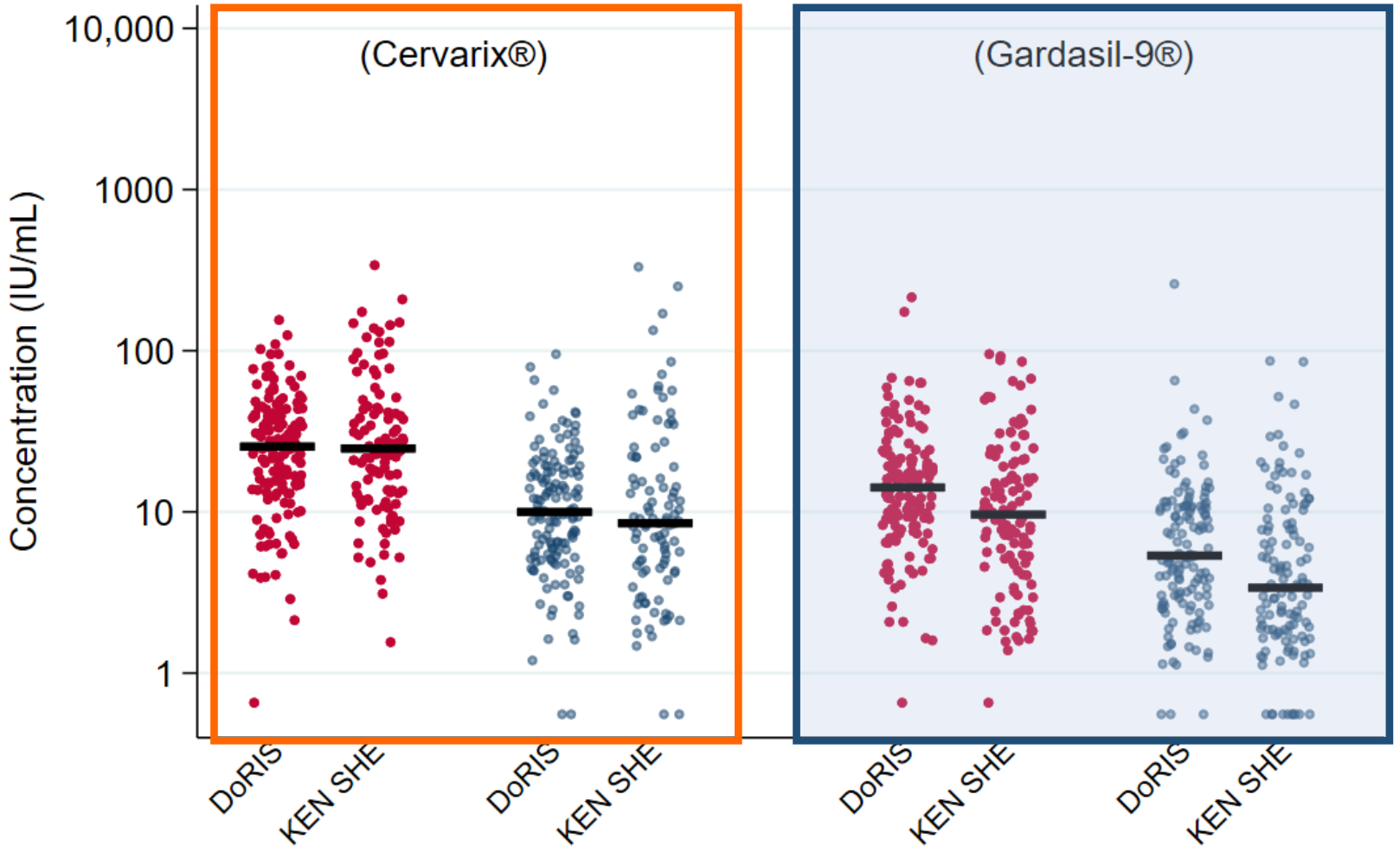
DoRIS Trial – Immunobridging



- 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

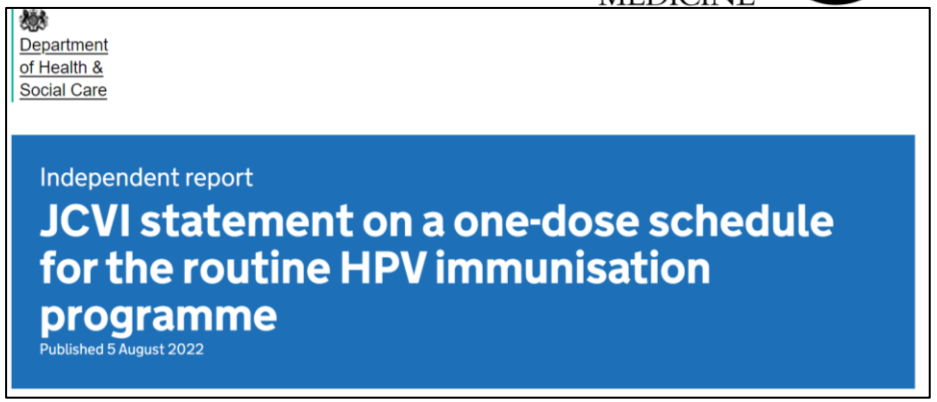
Unpublished data

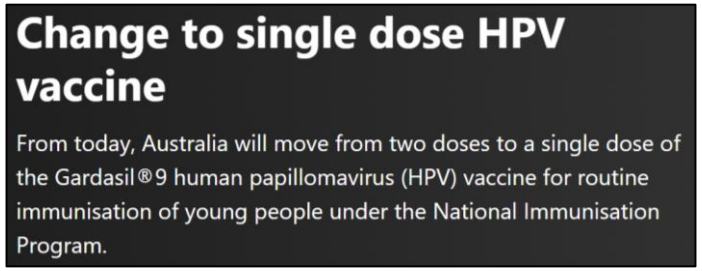
Summary of DoRIS results

- Single dose – high HPV 16/18 seropositivity rates
- Induces stable antibody concentrations out to 3 years
- Similar kinetics to those seen India and CVT
- High avidity for all doses
- Immune responses in DoRIS in the target age for vaccination non-inferior to cohorts where efficacy has been shown (CVT, India/IARC, KEN SHE).

Impact on policy

- Results contributed to:
- UK's decision to change to a single dose in 2022
- WHO Dec 2022 – off label recommendation for single dose in 9-20 year olds; HIV+ to continue with 2 (ideally) 3 doses
- Australia's decision to change to a single dose
- New HPV vaccine introductions





Countries that have switched to 1-dose HPV schedule *or 2-dose vaccination schedule in secondary targets ≥15 yr*

Region	Country (intro year)	WB group	Policy change
AFR	• Cap Verde (2021) • Burkina Faso (2022) • Sierra Leone (2020) • Malawi (2019) • Tanzania (2018) • Zambia (2019)	LMIC LMIC LMIC LMIC LMIC LMIC	• Switch to 1-dose • Switch to 1-dose • Switch to 1-dose • Switch to 1-dose • Switch to 1-dose • Switch to 1-dose
AMR	• Bolivia (2017) • Guatemala (2018) • Guyana (2011) • Jamaica (2017) • Mexico (2008) • Peru (2015) • Quebec (Canada)	LMIC UMIC UMIC UMIC UMIC UMIC HIC	• Switch to 1-dose in routine programme • Switch to 1-dose in routine programme • Switch to 1-dose in routine programme ♂ • Switch to 1-dose in routine programme ♀♂ • Switch to 1-dose in routine programme ♀♂ • Switch to 1-dose in routine programme • Switch 2 dose in 18 yr and older females/males in catch-up
EUR	• UK (2008) • Ireland (2009) • Albania(2022) • Netherlands (2008) • Sweden (2010)	HIC HIC LMIC HIC HIC	• Switch to 1-dose, 9 - 25 year old ♀♂ ; MSM>25yr: 2 doses • Switch to 1-dose, 9 - 25 year old ♀♂ ; MSM>25yr: 2 doses • Introduction with 1-dose in 13-year-old girls • 15-26 year ♀♂ in catch-up: 2-doses • 15 year and older females in catch-up: 2-doses
WPR	• Solomon Islands • Tonga (2022) • Australia (2007)	LMIC LMIC HIC	• Introduction with 1-dose in girls • Introduction with 1-dose in girls • Switch to 1-dose dose in routine programme ♂
GAVI Countries	*NITAGs in several GAVI-supported countries (LMICs) have recommended 1-dose HPV schedule for upcoming introductions*		• Bangladesh (2023/24) Cambodia (2023) • Nigeria (2023/24) – introduced in Oct 2023 • India (2023/24) • Togo (2023)

Prophylactic Ebola vaccine trials

- West African Ebola epidemic in 2014-16; >11,000 deaths [1]
- Dec 2014: EBOVAC1 - Janssen (industry lead), LSHTM (consortium coordinator), Inserm, Univ. Oxford, College of Medicine & Allied Health Sciences, Sierra Leone
- Aim: Accelerate vaccine development & trials of Ad26.ZEBOV /MVA-BN-Filo regimen
  - Janssen's AdVac® technology encoding Zaire EBOV Mayinga variant GP
  - Bavarian Nordic's MVA-BN® technology encoding GP of EBOV, SUDV, MARV & NP of TAFV
- 4 consortia over past 9 years:
  - EBOVAC1/2/3
  - PREVAC/PREVAC-Up : evaluate rVSV.ZEBOV (replication-competent, live, attenuated recombinant vesicular stomatitis virus vaccine) & Ad26.ZEBOV /MVA-BN-Filo (Inserm/LSHTM/NIH with Sierra Leone, Liberia, Mali and Guinea)

1 CDC, 2014-2016 Ebola Outbreak in West Africa

Since 2015 - 13 Ebola vaccine studies (EBOVAC1/3, PREVAC & DRC)

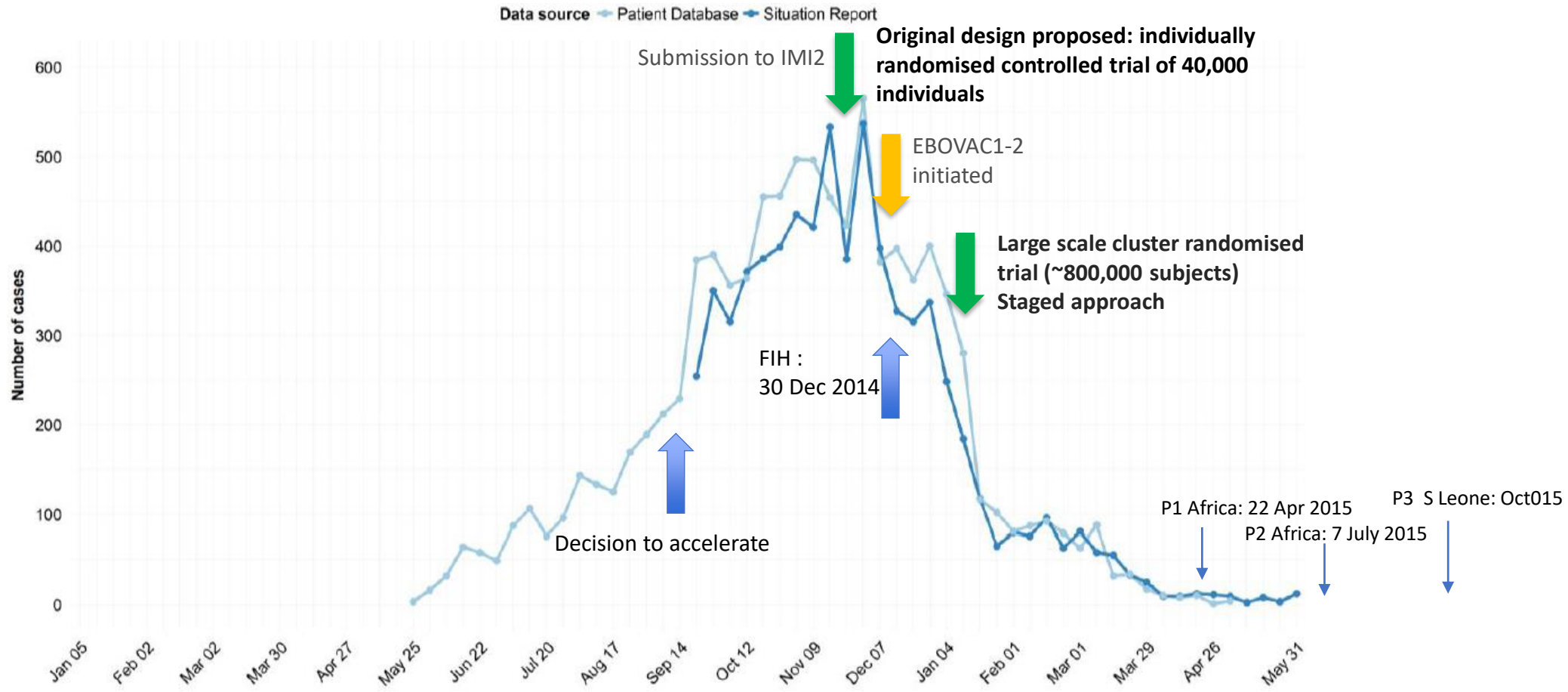
Study	Design	Comparisons / IMP	Participants	Sites
EBL1002 (phase 1)	RCT	Randomised to placebo or Ad26.ZEBOV and MVA-BN-Filo, with 28 or 56-day intervals.	**72** adults	United Kingdom
EBL1003 (phase 1)	RCT	Randomised to placebo or Ad26.ZEBOV and MVA-BN-Filo, with 28 or 56-day intervals.	**72** adults	Kenya
EBL1004 (phase 1)	**RCT**	**Same as EBL1003**	**72 adults**	**Uganda, Tanzania**
EBL3001 stage 1 (phase 1)	**Open label**	**Ad26.ZEBOV, MVA-BN-Filo with 56-day interval.**	**43 adults**	**Sierra Leone**
EBL3001 stage 2	**RCT**	**Randomised to either Ad26.ZEBOV, MVA-BN-Filo or MenACWY, placebo, 56-day interval.**	**400 adults & 576 children (aged 1-17 years)**	**Sierra Leone**
PREVAC phase 2; PREVAC-Up	**RCT**	**Randomised to Ad26.ZEBOV, MVA-BN-Filo or rVSV-ZEBOV, placebo or rVSV-ZEBOV,rVSV-ZEBOV, 56-day interval. Long term follow up for 5 years**	**1400 adults & 1401 children (aged 1-17 years)**	**Sierra Leone (Guinea, Liberia, Mali sponsored by others)**
EBL3005	**Cohort follow-up**	**No vaccination; long term follow-up of EBL3001**	**653 adults and children**	**Sierra Leone**
EBL2005	**RCT**	**Randomised to either Ad26.ZEBOV, MVA-BN-Filo or MenACWY, MenACWY , 56-day interval.**	**61 infants (4-11 months)**	**Guinea, Sierra Leone**

Ebola/COVID-19 vaccine trials since 2015

Study	Design	Comparisons	Participants	Sites
EBL2011 (booster study in children)	Open label	Ad26.ZEBOV booster in participants previously vaccinated with the Ad26.ZEBOV, MVA-BN-Filo	50 healthy children (4-15 years)	Sierra Leone
EBL2010	Open label	Ad26.ZEBOV booster in participants previously vaccinated with the Ad26.ZEBOV, MVA-BN-Filo	26 HIV+ adults	Uganda Kenya
EBL2012	Open label	Ad26.ZEBOV, MVA-BN-Filo with 56-day interval.	133 adults and children	Sierra Leone
DRC-EB-001	Open label	Vaccine effectiveness (test negative case control) trial	20,408 (6635 children)	North Kivu. DRC
Solidarity Vaccine Trial (STV)	RCT	Placebo-controlled trial of intra-nasal live prophylactic COVID-19 vaccines	3000 adults and adolescents	Sierra Leone

EBL3001 trial design and the epidemic

- Planned initial study design during epidemic did not necessarily mean that this design would be used. Animal model and immunobridging used to infer efficacy in the end.



Ebola case incidence and EBOVAC timelines. Courtesy of EBOVAC2

- Immunobridging: Roozendaal R et al., npj Vaccines, 2020; 5, 112
- EMA Zabdeno, Public assessment report, https://www.ema.europa.eu/en/documents/assessment-report/zabdeno-epar-public-assessment-report_en.pdf

Key results

- Safety and immunogenicity in adults, children & infants in Ebola-affected areas in Sierra Leone and Guinea [1-4] (EBL3001/2005/PREVAC)
- Safety and immunogenicity of a boost showing strong anamnestic response:
  - HIV+ adults in East Africa (EBL2010) [5]
  - Children in Sierra Leone. [6]
- Safety in adults and pregnant women & immunogenicity of delayed 2nd dose in DRC (DRC-EB-001) [7,8]
- Social science research on acceptability of trials, reasons for participation, communication technologies, participant identification technologies e.g. iris scanning, etc. [9-11]
- Community engagement through IMI-funded EBODAC consortium

1 Ishola et al. Lancet Infect Dis 2022
2 Afolabi et al. Lancet Infect Dis 2022
3 Choi et al. Lancet Glob Health 2023
4 PREVAC Study Team NEJM 2022
5 Choi et al. Vaccine 2023 (in press)
6 Manno et al. Lancet Infect Dis 2023
7 Kasonia at al. ASTMH 2022
8 Choi et al. ASTMH 2023
9 Enria et al. BMC Public Health 2016
10 Tengbeh et al. Social Science & Medicine 2018
11 Matuvanga et al. J Med Internet Res. 2021

Safety

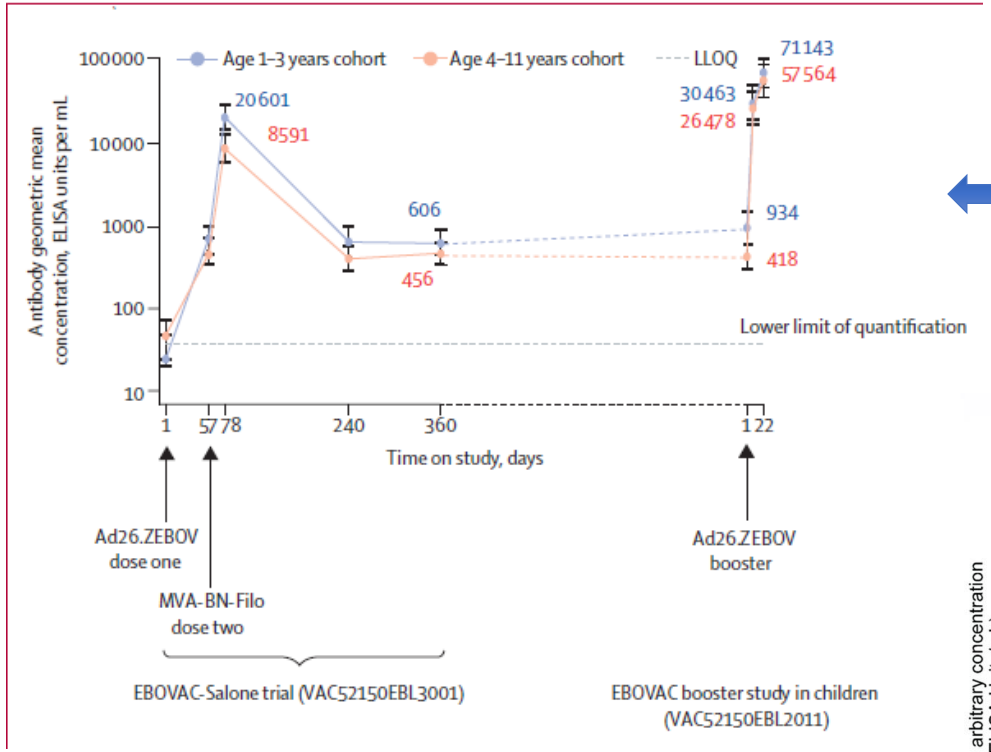
Safety and tolerability (diary card and investigator inquiry to collect local and overall body symptoms)

Ad26.ZEBOV, MVA-BN-Filo vaccine regimen is safe and well tolerated in:

- adults; adverse events similar to experience with other vaccines [1-7]
- children down to 1 year of age; adverse events generally similar to other paediatric vaccines [7-9]
- infants down to 4 months of age [10]

1 Milligan et al. JAMA 2016
2 Mutua et al. JID 2019
3 Anywaine et al. JID 2019
4 Pollard et al. Lancet Infect Dis 2021
5 Barry et al. PLoS Med 2021
6 Ishola et al. Lancet Infect Dis 2022
7 PREVAC Study Team NEJM 2022
8 Afolabi et al. Lancet Infect Dis 2022
9 Anywaine et al. PLoS Med 2022
10 Choi et al. Lancet Glob Health 2023

Immunogenicity and boosting



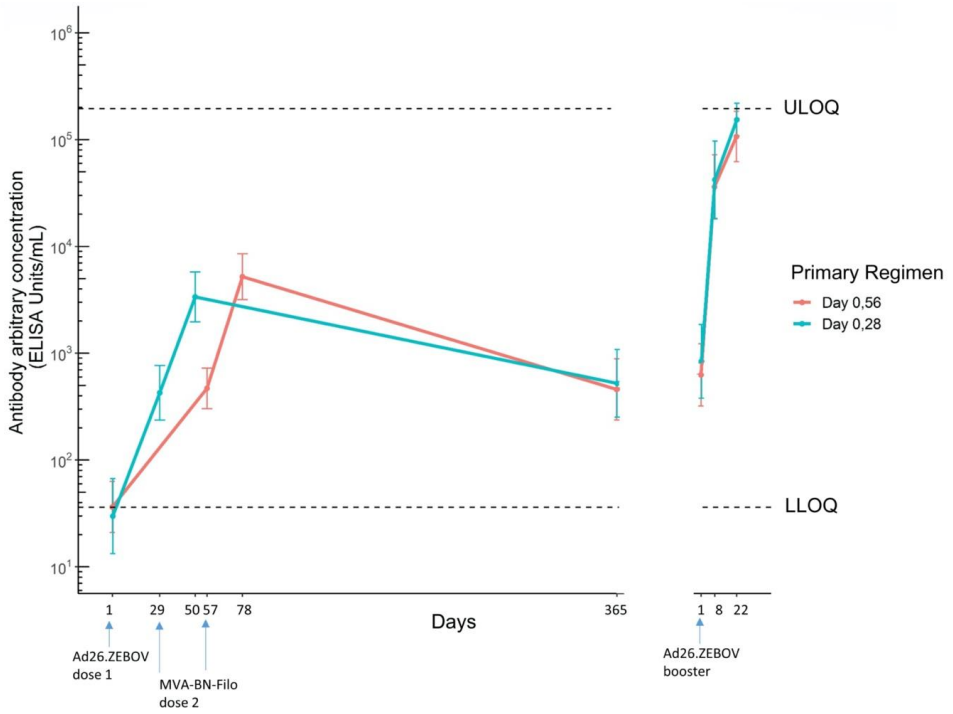
Persistence of Binding Antibody Response

Results in children, boosted ~3 years post primary series

Manno et al, LID 23: 352-60, 2023

Results in HIV+ Adults, boosted ~3 years post primary series

Choi et al Vaccine 2023 (in press)



Impact

- Regulatory approval status

Zabdeno® (Ad26.ZEBOV), Mvabea® (MVA-BN-Filo) vaccine regimen indicated for active immunization to prevent disease caused by Ebola virus (Zaire) in individuals ≥1 year of age in the EU

EU Marketing Authorization obtained 01 July 2020 (EC Decision)

- Approval pathway: exceptional circumstances

WHO prequalification in April 2021

- Based on EMA dossier
- Parallel review with two National Regulatory Authorities in Africa

Approvals now in 5 African countries

- Ghana, Cote D'Ivoire, Uganda, Rwanda, DRC

PREVAC - Contribution towards the licensure of the Merck Ervebo (rVSVΔG-ZEBOV-GP) Ebola vaccine in children (sites passed FDA inspection in Jan 2023)

*Annex I to Directive 2001/83/EC – Marketing Authorisation under exceptional circumstances
https://www.ema.europa.eu/en/documents/assessment-report/zabdeno-epar-public-assessment-report_en.pdf
https://www.ema.europa.eu/en/documents/product-information/zabdeno-epar-product-information_en.pdf
https://www.ema.europa.eu/en/documents/product-information/mvabea-epar-product-information_en.pdf
WHO list of prequalified vaccines: https://extranet.who.int/pqweb/vaccines/prequalified-vaccines

Experiences of epidemic/emerging infection vaccine trial research in an emergency situation

Pros
Exciting, topical research that can impact policy quickly
Industry interest; training; technical support; skill building
Fast-track funding
Budgets may allow capital costs, vehicles, construction etc.
Ethics and regulators understand urgency; can expedite reviews
Assistance by AVAREF* – helpful to inexperienced ECs and regulators
Good will; team members willing to go the extra mile
Site/country can build research experience quickly.

*African Vaccine Regulatory Forum

Lessons learnt in emergency epidemic vaccine trials - challenges

Little time - partners and teams may not know each other
Straight to phase 3 trials in a new/research naïve site
Limited experienced research sites, especially in epidemics vs. pandemics
Study location may not be ideal - infrastructure limited
Limited clinical trials experience at site but need to get going (Ebola task force)
Staff recruitment challenges (e.g. HCW deaths in Ebola). Consider skilled expatriates, especially at start, including QA manager.
External support e.g. mobile phone messaging; cold chain support
Urgency to complete contracts, procure quickly; little time for quotations; may need capital expenditure & vehicles
Logistics workload heavy if new site; consider NGO partners
Epidemic can decline before trial gets started; modelling helpful
Loss of funding interest as epidemic/pandemic drags on.

Nyaragongo volcano eruption, Goma 2021

DRC-EB-001 trial - OVD data centre fire, Strasbourg 2021

Conclusions

- For emerging infections - be prepared to go to settings where no/limited research has been done
- Be flexible – epidemics can change quickly
- Opportunities for new partnerships and to conduct different phases of vaccine research.
- Infectious disease vaccine trial research is rewarding and can impact policy quickly

Acknowledgements – DoRIS trial

- Study participants & research teams
- Trial funders: MRC Joint Global Health Trials; Bill & Melinda Gates Foundation
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- Single-Dose HPV Vaccine Evaluation Consortium

www.path.org/singledosehpv

Ebola Vaccine LSHTM – acknowledgments

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RGIO: Patricia Henley. Naomi Pantelli.

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DRC-EB-001 trial & STV – acknowledgments

DRC-EB-001 trial, LSHTM INRB Goma
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Thank you

First Ad26/MVA Vaccinee in Sierra Leone, Idrissa Kamara, on a billboard in Times Square, New York