Review of Existing Evidence on Single-Dose HPV Vaccination

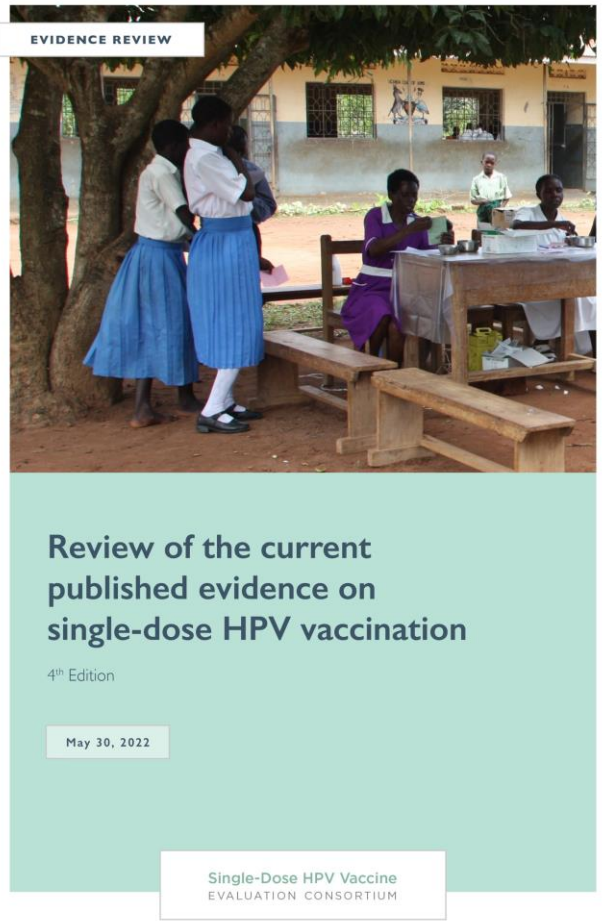
Single-Dose HPV Vaccine
EVALUATION CONSORTIUM

Presentation Outline

- Key messages
- Cervical cancer, HPV, and HPV vaccines
- Current evidence supporting single-dose HPV vaccination
  - Clinical trials (key topics and questions, summary, and key takeaways)
  - Supporting evidence from observational studies
  - Forthcoming evidence from clinical trials
  - Supporting evidence from modeling analyses

About the Single-Dose HPV Vaccine Evaluation Consortium

- Collates, assesses and synthesizes existing published evidence from clinical trials, observational studies, and impact and economic modeling work on the potential for single-dose human papillomavirus (HPV) vaccination
- Evidence is summarized in one paper; Fourth edition released May 2022; each edition is companied by a synthesis and summary (available in English, French, and Spanish) *(4th edition accompaniments and translations are forthcoming)*
- The Consortium will continue to assess newly published studies and perform quality assessments of the evidence with a fifth edition to be available in 2023.



Single-dose HPV vaccination key messages

Executive Summary

Problem statement

HPV causes almost all cases of cervical cancer, and the burden is disproportionate. Approximately **90% of cervical cancer deaths occur in low- and middle-income countries (LMICs).** Additionally, **worldwide vaccine coverage in girls under 15 years of age is only about 13%.**

Potential solution

Recent studies provide high-quality data showing ~**98% efficacy**[1] and **durable protection** for a **single-dose regimen**. There is strong evidence that single-dose HPV vaccines could substantially **reduce the incidence of HPV-attributable cervical precancer and cancer**.

The overall case for single-dose regimen

Ultimately, a single-dose regimen will likely **increase vaccine uptake** and help **decrease rates of cervical cancer and cervical cancer-related deaths** in high-burden, low-income regions.

1. Barnabas R, Brown E, Onono M, et al. Efficacy of Single-Dose HPV Vaccination Among Young African. *NEJM Evidence*. 2022. doi: 10.1056/EVIDoa2100056.

Substantial evidence supporting the benefits of a single-dose HPV vaccine regimen

Evidence for a single dose:

A single dose delivers high levels of protection similar (98% efficacy) in magnitude to multidose regimens.

Single-dose schedules may present significant cost savings and can help with overall delivery challenges.

Single-dose regimens promote global health equity and will help increase access and uptake.

Reaching more girls with a single dose will avert much more cervical cancer cases than vaccinating fewer girls with a second dose.

Data from clinical studies across multiple geographies suggest a single-dose regimen provides significant protection against HPV

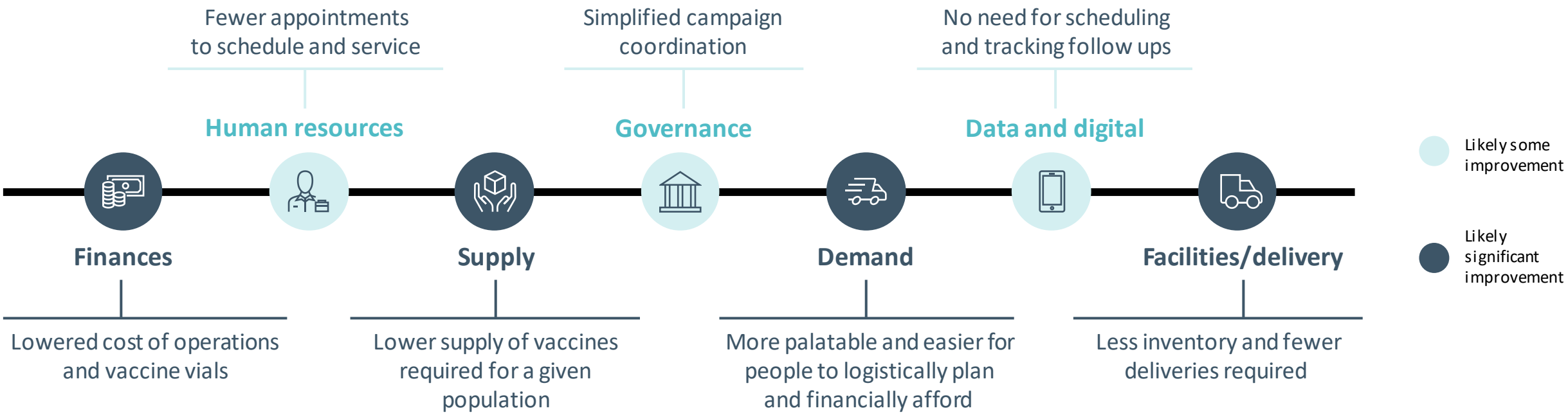
A single dose delivers high levels of protection similar in magnitude to multidose regimens

Study*	**KENya Single-dose HPV-vaccine Efficacy (KEN SHE)[1]**	**Dose Reduction Immunobridging and Safety (DoRIS)[2]**	**International Agency for Research on Cancer (IARC)[3]**	**Costa Rica HPV Vaccine Trial (CVT)[4]**
Start year	**2018**	**2017**	**2009**	**2004**
Location	**Kenya**	**Tanzania**	**India**	**Costa Rica**
Key findings	Single-dose vaccination with Gardasil®9 or Cervarix® was **~98% effective in preventing new onset persistent HPV 16/18 infection among African adolescent girls and young women**	**Antibody levels among girls receiving a single** dose of Gardasil®9 or Cervarix® **were at least as high as those in women from the CVT or IARC studies where efficacy was shown** Data suggest the efficacy of a single dose of HPV vaccine **may apply to additional geographies in the targeted 9–14-year-old age group**	Single dose showed **~95% efficacy with Gardasil®** against persistent HPV 16/18 infection **for at least 10 years** **Comparable vaccine efficacy regardless of the dose regimen** with Gardasil® (1, 2 or 3 doses)	**Comparable efficacy from one and three doses of Cervarix®** in protecting against HPV 16/18 infection after 10 years post-vaccination **10X the level of antibody induced** after a single dose, compared to after natural infection

*All studies in long-term follow-up.

1. Barnabas R, Brown E, Onono M, et al. Efficacy of Single-Dose HPV Vaccination Among Young African. *NEJM Evidence*. 2022. doi: 10.1056/EVIDoa2100056. | 2. Watson-Jones D, Changalucha J, Whitworth H, et al. Immunogenicity and Safety Results Comparing Single Dose Human Papillomavirus Vaccine with Two or Three Doses in Tanzanian girls - the DoRIS Randomised Trial. *Lancet*. Preprint posted online March 11, 2022. https://dx.doi.org/10.2139/ssrn.4055429. | 3. Basu P, Malvi SG, Joshi S, et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study [published correction appears in Lancet Oncol. 2022 Jan;23(1):e16]. *Lancet Oncology*. 2021;22(11):1518-1529. doi:10.1016/S1470-2045(21)00453-8. | 4. Kreimer AR, Sampson JN, Porras C, et al. Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial. *Journal of the National Cancer Institute*. 2020;112(10):1038-1046. doi:10.1093/jnci/djaa011.

A single dose regimen could address implementation challenges



A single-dose regimen addresses several obstacles disproportionately felt by LMICs

by reducing the quantity of doses to be procured and subsequently distribute, store, track, and administer

"Data accumulated to date from clinical trials and high-quality observational clinical studies provide **strong evidence that single-dose HPV vaccination could substantially reduce the incidence of HPV-attributable cervical precancer and cancer**. With greatly reduced costs and simplified implementation potentially allowing more countries to introduce HPV vaccination or increase coverage, health and economic impact analyses show that **single-dose HPV vaccination could be a high-value public health intervention**."

--Single-Dose HPV Vaccine Evaluation Consortium, Jan. 2022

HPV vaccination schedules

Current World Health Organization Strategic Advisory Group of Experts on Immunization (WHO SAGE) recommendations (Weekly Epidemiological Record [WER] June 2022)*:

- One or two-dose schedule for the primary target of girls aged 9-14 years old
- One or two-dose schedule for young women aged 15-20 years old
- Two doses with a 6-month interval for women over 21 years old
- Immunocompromised individuals, including those with HIV, should receive three doses if feasible, and if not, at least two doses

SAGE urged all countries to introduce HPV vaccine for the primary target group of girls aged 9-14 years old and, where feasible and affordable, prioritize catch-up in older cohorts and missed girls through multi-age cohort (MAC) vaccination up to the age of 18.

**subject to change pending formal WHO endorsement and inclusion in HPV position paper*

The UK Issues Advice to Adopt a Single-Dose HPV Vaccine Schedule

Context

In **August 2022,** the **Joint Committee on Vaccination and Immunization (JCVI)**, an expert scientific committee for the UK government, **issued advice on a move to a single-dose vaccine regimen**.[1]

To inform the recommendation, the committee conducted a detailed review of the available evidence showing that **single-dose HPV vaccination provides similar protection to two doses.**

The UK has implemented a **highly successful HPV vaccination program**, consistently achieving greater than 80% uptake prior to the COVID-19 pandemic.

JCVI Recommendation

- A one-dose schedule for the routine adolescent program
- A one-dose schedule for men who have sex with men (MSM) program before the 25th birthday
- a two-dose schedule from the age of 25 in the MSM program
- a three-dose schedule for individuals who are immunosuppressed and those known to be HIV-positive

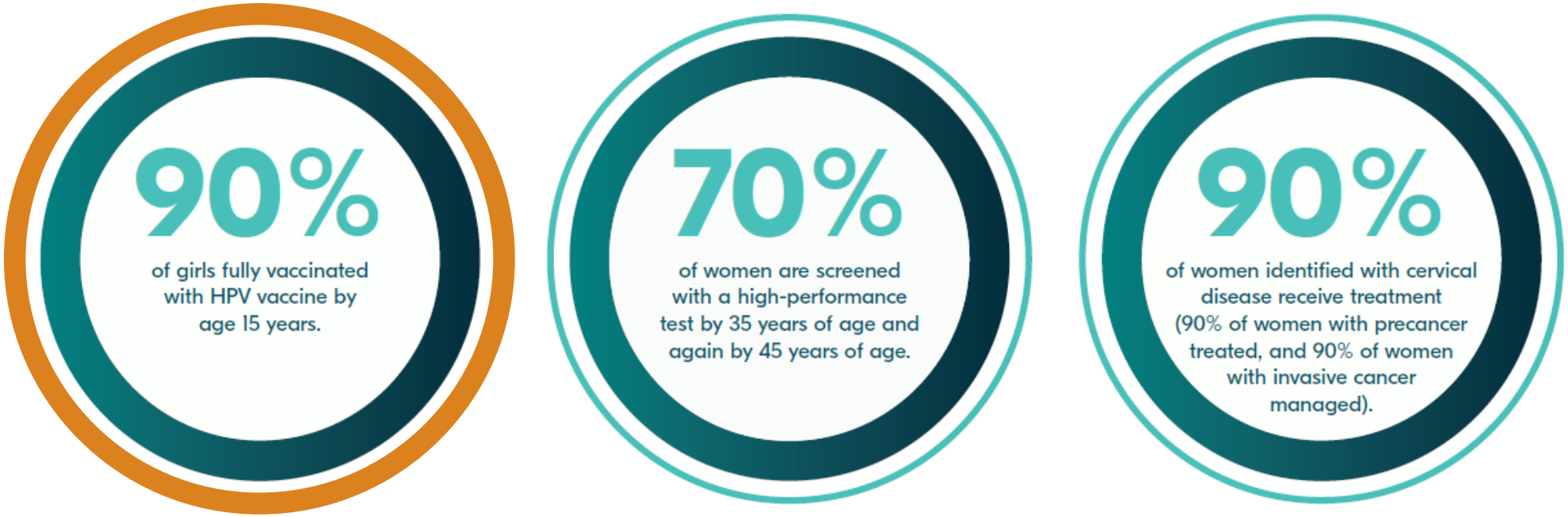
JCVI's recommendation is pending a final policy decision. If a decision is made in agreement with JCVI advice, the earliest implementation of a one-dose program is 2023-2024.

1. JCVI website. https://www.gov.uk/government/publications/single-dose-of-hpv-vaccine-jcvi-concluding-advice/jcvi-statement-on-a-one-dose-schedule-for-the-routine-hpv-immunisation-programme Accessed August 10, 2022

Cervical cancer, HPV, and HPV vaccines

Cervical cancer elimination initiative

- Cervical cancer is a leading cause of cancer deaths among women in LMICs.
- More than 604,000 cases and 341,000 deaths occur annually, with more than 90% of deaths occurring in LMICs.[1]
- HPV is present in virtually all cervical cancers and is a necessary cause of cervical cancer
- In November 2020, WHO launched the global strategy to accelerate the elimination of cervical cancer as a public health problem with the following 2030 targets[2]:



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.

HPV infection can progress to cervical cancer and untimely death, especially in lower-income countries

HPV is a common viral infection to which **almost all cervical cancers can be attributed, most of the burden lies in LMICs***

2nd

most common cancer in Africa and 4th among women worldwide[1]

~342K

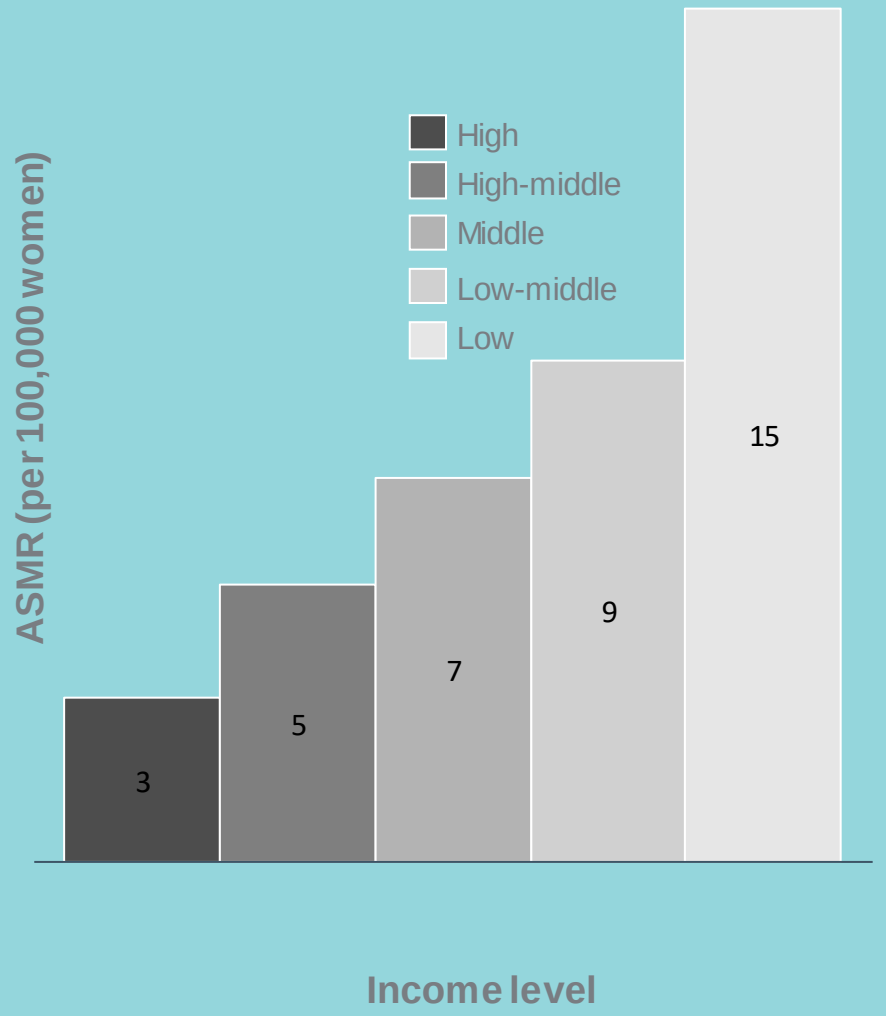
annual deaths caused by cervical cancer[2]

~90%

of those deaths happen LMICs

*HPV types 16 and 18 are responsible for over 70% of cases

2019 Age-standardized mortality rate (ASMR) for cervical cancer by socio-demographic index areas[2]



1. Zhang X, Zeng Q, Cai W, Ruan W. Trends of cervical cancer at global, regional, and national level: data from the Global Burden of Disease study 2019. *BMC Public Health*. 2021;21(1):894. doi:10.1186/s12889-021-10907-5. | 2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*. 2021;71(3):209-249. doi: 10.3322/caac.21660.

HPV vaccines

- Current HPV vaccines are prophylactic, i.e., to be administered prior to exposure with HPV
- HPV vaccines were first introduced in 2006 on a three-dose schedule
- In 2014, the WHO reduced the schedule from three doses to two in pre-adolescents/ adolescents, following an evidence review by SAGE
- Evidence today shows comparable efficacy and effectiveness between single- and multi-dose schedules in preventing HPV-16/18 infections, lasting up to 10 years following vaccination
- In June 2022, WHO SAGE endorsed the optimization of HPV vaccine schedules, noting that a single dose offers solid protection against cervical cancer

Four safe and highly efficacious HPV vaccines are WHO prequalified

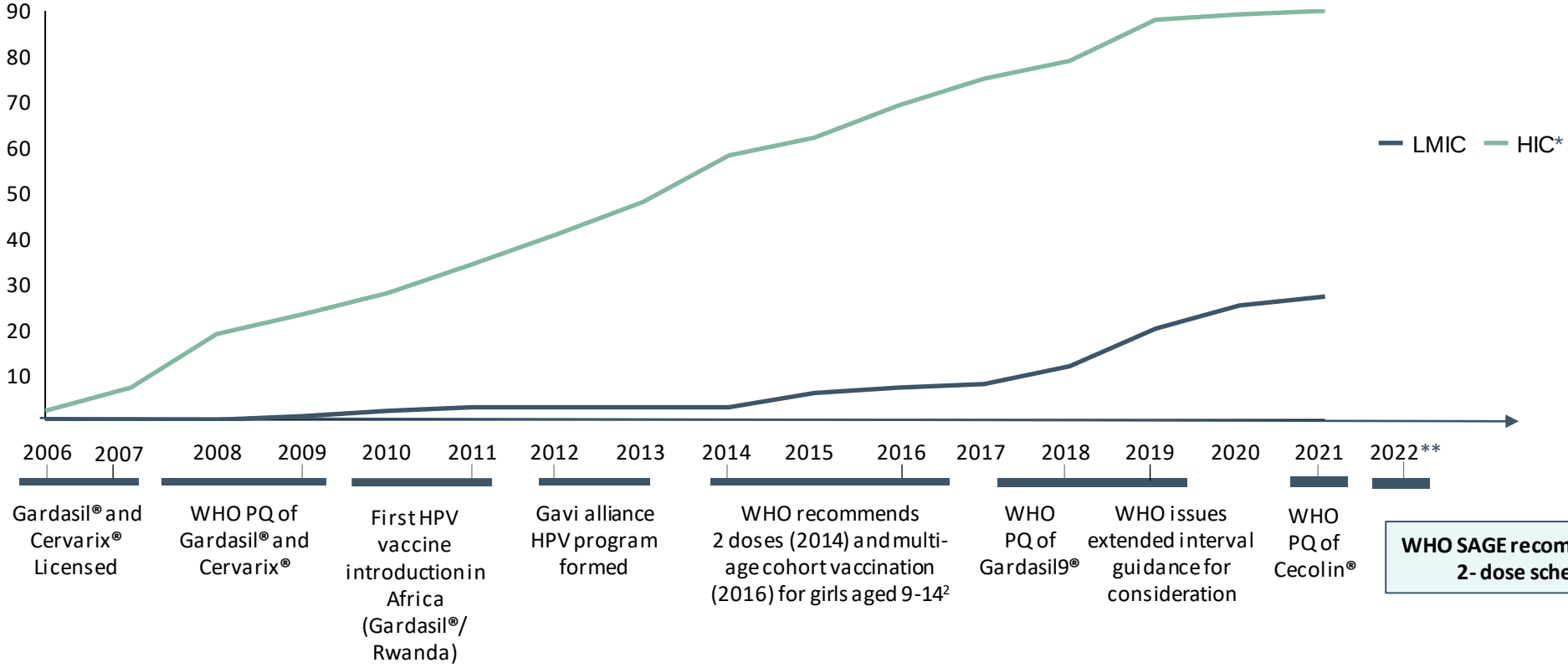
	WHO prequalified HPV vaccines[1]			
	Quadrivalent (4vHPV, Gardasil®)	Bivalent (2vHPV, Cervarix®)	Nonavalent (9vHPV, Gardasil®9)	Bivalent (2vHPV, Cecolin®)
HPV types covered	6, 11, 16, 18	16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58	16, 18
Efficacy	>95%			
Dosage*	2			
Year of initial registration	2006	2007	2014	2019
WHO Prequalification	2009	2009	2018	2021
Distributed by Gavi	✓	✓	Contingent on having an appropriately priced product	Contingent on country program discussions

*For females less than 15 yo; 3 doses for females 15 yo or older, HIV positive, or immunocompromised.

1. HPV working group – Gavi Secretariat and partners. Gavi-supported HPV vaccines profiles to support country decision making, May 2021. Available at https://www.gavi.org/sites/default/files/support/Gavi_HPV_vaccine_profiles.pdf.

In the past 16 years, national HPV vaccination programs have been introduced, but global coverage remains low and varies by income

Number of countries who have introduced a vaccine program on a national scale[1] (#)



Global coverage is ~13% worldwide and only 8% in LMICs[4]

*For US populations covered, approvals/recommendations are not shown for 9-valent if already shown in the past for 4-valent vaccine.
**Projected country introductions by PATH

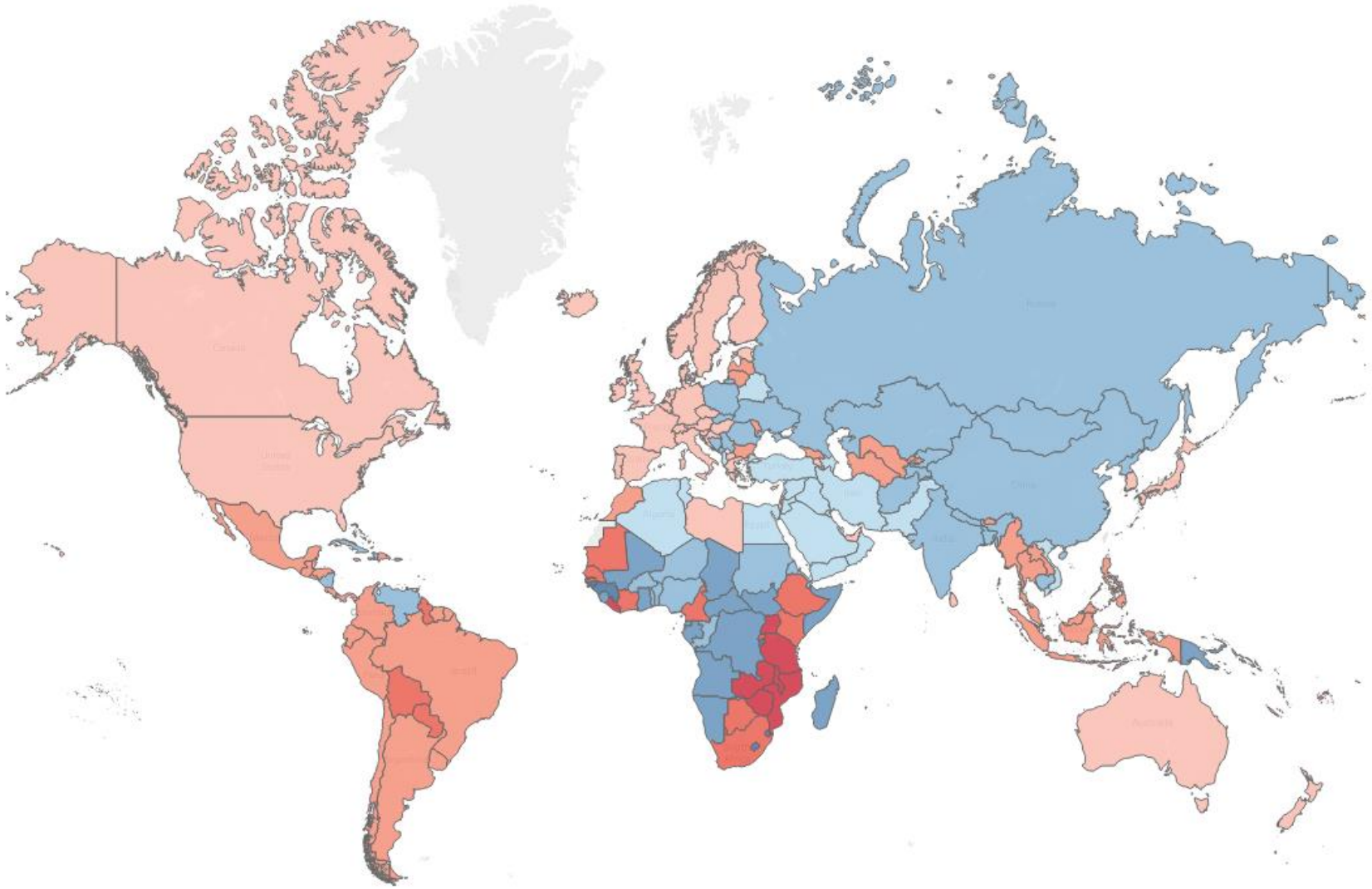
1. PATH. *Global HPV Vaccine Introduction Overview*. Seattle: PATH; 2022, Available at https://path.azureedge.net/media/documents/Global_Vaccine_Intro_Overview_Slides_Final_PATHwebsite_MAR_2022_qT92Wwh.pdf | 2. World Health Organization (WHO). *Meeting of the Strategic Advisory Group of Experts on immunization, April 2014 — conclusions and recommendations*. Weekly Epidemiological Record, 89 (21), 221 - 236. https://apps.who.int/iris/handle/10665/242217. | 3. One-dose Human Papillomavirus (HPV) vaccine offers solid protection against cervical cancer [press release]. Geneva, Switzerland: WHO; April 11, 2022. Available at https://www.who.int/news/item/11-04-2022-one-dose-human-papillomavirus-(hpv)-vaccine-offers-solid-protection-against-cervical-cancer. 4. HPV vaccine cuts cervical cancer cases by nearly 90% [blog]. Geneva, Switzerland; November 8, 2021. Available at https://www.gavi.org/vaccineswork/hpv-vaccine-cuts-cervical-cancer-cases-nearly-90.

HPV vaccine in national immunization programs

- As of March 2022, 149 countries have national programs in place[1].
- 60% of cervical cancer cases occur in countries that have not yet introduced HPV vaccination.
- Less than a third of the world's population of girls aged 9-14 years old live in countries providing HPV vaccines.
- Mean coverage is 57% for Dose 1 and 45% for a full vaccination regimen[2,3].
- **Global HPV vaccine coverage was 15% in 2019 and declined to 13% in 2020**[2]

1. 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 | 2. Immunization Data website. Human papillomavirus (HPV) vaccination coverage page. https://immunizationdata.who.int/pages/coverage/hpv.html?CODE=Global&ANTIGEN=PRHPV1_F&YEAR=. Accessed May 19, 2022. | 3. WHO (World Health Organization). 2020 WHO/UNICEF Estimates of National Immunization Coverage. Presented at: Gavi HPV Subteam Meeting, July 15, 2021; Geneva, Switzerland.

Global HPV vaccine introductions by burden of disease



KEY

Mortality rate (ASR)*

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

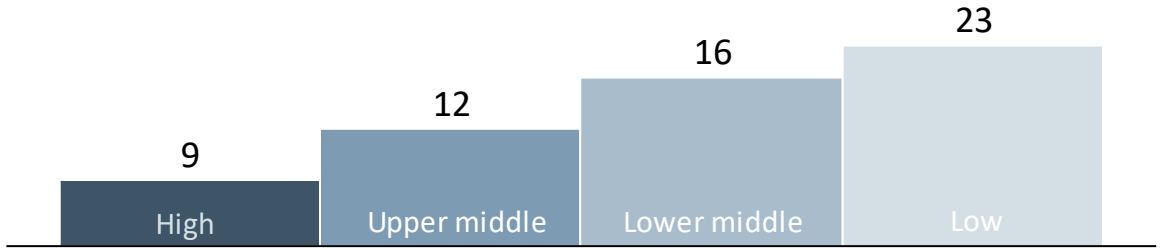
**rates per 100,000 women per year; estimated 2020 cervical cancer mortality rates from IARC Globocan data*

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.

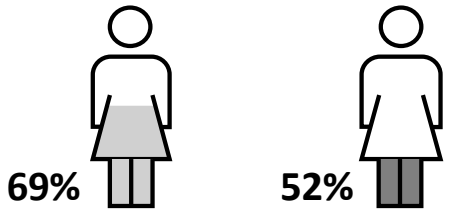
In addition to vaccine introduction, both vaccine uptake and cervical cancer burden differ significantly between HICs and LMICs

Cervical cancer incidence rate per 100,000 females, 2019[1]

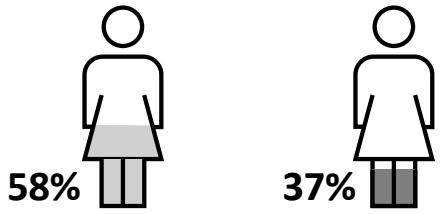


Vaccine uptake in HICs and LMICs, 2020[2]

Percentage of eligible women who receive a **first dose**



Percentage of eligible women who receive a **second dose**



HICs LMICs

Cervical cancer incidence is inversely correlated to the income level of countries **and** their **rate of vaccination**

Eligible **women from HICs are 3X more likely to receive HPV vaccines** than their LMIC counterparts[3]

1. Zhang X, Zeng Q, Cai W, Ruan W. Trends of cervical cancer at global, regional, and national level: data from the Global Burden of Disease study 2019. *BMC Public Health*. 2021;21(1):894. doi:10.1186/s12889-021-10907-5. | 2. WHO (World Health Organization). 2020 WHO/UNICEF Estimates of National Immunization Coverage. Presented at: Gavi HPV Subteam Meeting, July 15, 2021; Geneva, Switzerland. | 3. Spayne J, Hesketh T. Estimate of global human papillomavirus vaccination coverage: analysis of country-level indicators. *BMJ Open*. 2021;11(9):e052016. doi:10.1136/bmjopen-2021-052016.

Expanding access to HPV vaccines

Single-dose HPV vaccination will likely:

- Accelerate introduction for countries that have yet to introduce the vaccine.
- Facilitate new options for current national programs by simplifying delivery, lowering program costs, and potentially increasing coverage.
- 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 Initiative.

Current evidence supporting single-dose HPV vaccination

Single Dose – Key topics & questions

Biological plausibility

Single dose level of protection

Is single-dose protection similar to multi-dose regimens?

Durability of protection after a single dose

Would a single dose regimen be applicable to different populations?

- Across age-groups
- Across geographies

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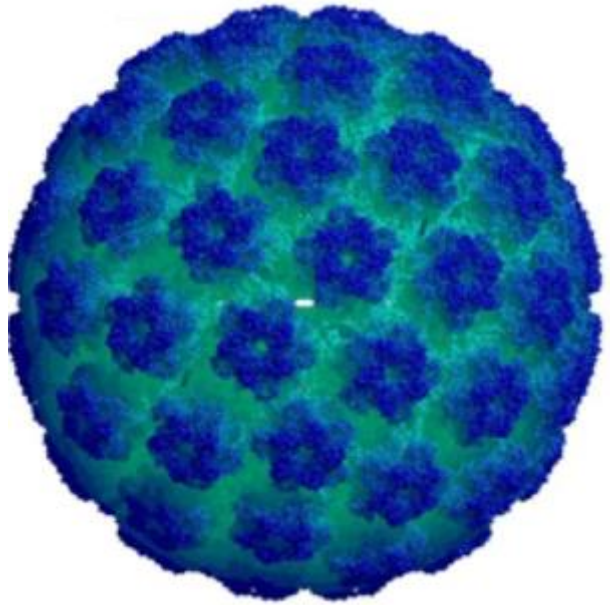
High potency of HPV vaccines

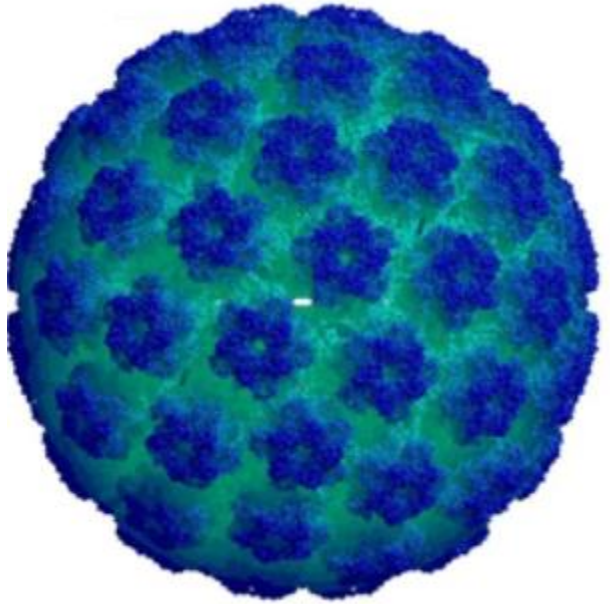
- Antibodies are the prime mediators of protection for L1 HPV VLP vaccines.
- Particle size (50-55 nm) and geometry (repetitive epitopes) of the VLPs are optimal for stimulating the immune system, including efficient generation of long-lived, antigen-specific antibody-producing cells.
- Durable (>10 years) and stable antibody levels are indicative of induction of long-lived plasma cells.
- HPV virus is exceptionally susceptible to antibody-inhibition at the site of infection.
- A minimum antibody level required for protection has not been established yet.
- Low level of antibodies are protective *in vivo* (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.

High immunogenicity of L1 HPV VLP vaccines

- Particle size is optimal (50-55 nm) for stimulating the immune system (uptake by dendritic cells; migration to lymph node).
- Particle geometry is critical: densely ordered repetitive display of B cell epitopes on surface [360 copies of L1 arranged in 72 pentamers] (danger signal to immune system; promote antigen presentation and antibody induction)
- Optimal display and spacing of neutralizing epitopes are critical for B-cell activation, strength, and quality of antibody response.

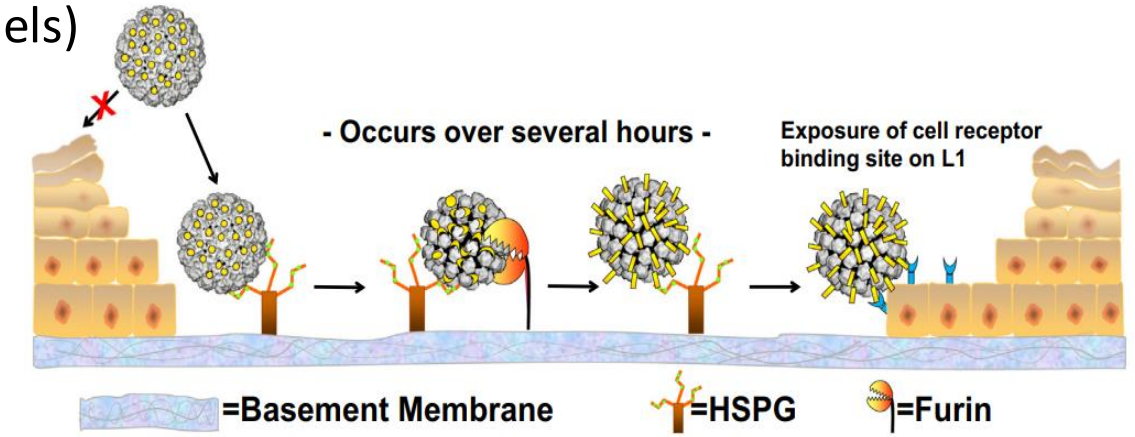


Resulting in efficient generation of long-lived antigen-specific antibody-producing cells

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.

Antibodies are the prime mediators of protection for L1 HPV VLP vaccines

- Vaccine-elicited antibodies shown to neutralize the virus in *in vitro* assays.
- Protection can be passively transferred through serum of vaccinated individuals in animal challenge models.
- Durable (>10 years) and stable antibody levels (indicative of induction of long-lived plasma cells)
- A minimum antibody level required for protection has not been established yet
- Low level of antibodies are protective *in vivo* (animal models)
- Infection initiated in basal epithelial cells
  - Disruption of epithelium required => exudation of antibodies at the infection site
  - Slow internalization process (several hours) => long exposure to antibodies



Exceptional susceptibility of the virus to antibody-inhibition at site of infection

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.

Single Dose – Key topics & questions

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Durability of protection after a single dose

Would a single dose regimen be applicable to different populations?

- Across age-groups
- Across geographies

KEN SHE trial

Study Title	Single-dose HPV catch-up vaccination efficacy
Principal Investigator(s)	R. Barnabas, N. Mugo
Study Centers	Kenya Medical Research Institute in Thika, Nairobi, Kisumu; Kenya
Study Design	Prospective, double-blind, randomized, controlled trial of single-dose HPV vaccination
Study population	Sexually active females 15-20 yo; N= 2,275 (~750/ study arm; 1 dose Cervarix® or Gardasil®9 or Meningococcal vaccine [delayed HPV vaccination])
Study duration	Primary outcome at Mo 18; follow up to Mo 36
Study Vaccines	Cervarix® & Gardasil®9
Primary objectives	1. Efficacy of single dose vaccination (2vHPV or 9vHPV) in preventing **incident persistent* HPV-16/18 infections** compared to delayed vaccination 2. Efficacy of single dose 9vHPV in preventing **incident persistent HPV-16/18/31/33/45/52/58 infections** compared to delayed vaccination * Defined as vaccine type specific HPV detected at two consecutive time points no less than 4 months apart
Secondary objectives	1. Non-inferiority of HPV antibody responses after single-dose vaccination (Cervarix® or Gardasil®9) in 9-14 yo (DoRIS trial) compared to 15-20 yo (KEN SHE trial) 2. Cost, cost-effectiveness, and budget impact of single-dose HPV vaccination 3. Evaluate B cell markers as a proxy for central immune memory following single-dose Cervarix® or Gardasil®9 vaccination

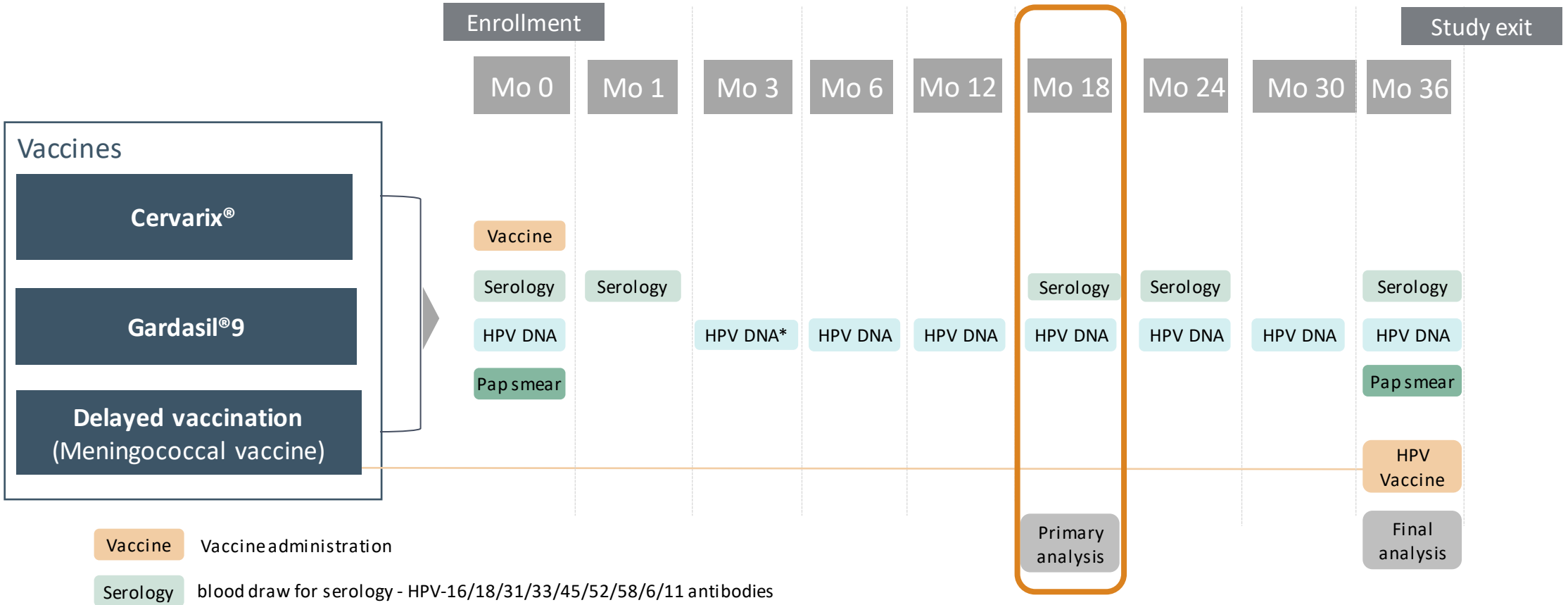
DoRIS: Dose Reduction Immunobridging and Safety; KEN SHE: KENya Single-dose HPV-vaccine Efficacy; Mo: month; N: number of participants; v: valent; yo: year of age

Barnabas R, Brown E, Onono M, et al. Efficacy of Single-Dose HPV Vaccination Among Young African. *NEJM Evidence.* 2022. doi: 10.1056/EVIDoa2100056.

KEN SHE trial – Study schematic

Women 15-20 yo N = 2,250

Sexually active, 1-5 lifetime partners, HIV negative, no history of HPV vaccination



Vaccine — Vaccine administration

Serology — blood draw for serology - HPV-16/18/31/33/45/52/58/6/11 antibodies

HPV DNA — Cervical, vulval-vaginal swabs; testing for HPV-16/18/31/33/45/52/58/6/11; *: self sampling

Pap smear — Liquid-based cytology

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

KEN SHE – Vaccine efficacy
Incident persistent HPV 16/18 infections mITT

	Number of mITT	Number of events	Incidence/ 100 woman years	VE (%)	VE 95% CI
Delayed Vaccination N = 757	473	36	6.83	Referent	
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: seronegative at baseline and HPV-DNA negative at baseline and Mo3 for types considered in analysis

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

Barnabas R, Brown E, Onono M, et al. Efficacy of Single-Dose HPV Vaccination Among Young African. *NEJM Evidence*. 2022. doi: 10.1056/EVIDoa2100056.

KEN SHE – Vaccine efficacy Incident persistent HPV 16/18/31/33/45/52/58 infections mITT

	Number of mITT	Number of events	Incidence/ 100 woman years	VE (%)	VE 95% CI
Delayed Vaccination N = 757	290	29	9.42	Referent	
Single dose Gardasil®9 N = 758	325	4	1.03	88.9	68.5; 96.1

mITT: seronegative at baseline and HPV-DNA negative at baseline and Mo3 for types considered in analysis

CI: confidence interval; mITT: modified intent-to-treat; VE: vaccine efficacy

2vHPV participants are not included in the HPV 16/18/31/33/45/52/58 analysis as the study was not powered to detect cross-protection

Barnabas R, Brown E, Onono M, et al. Efficacy of Single-Dose HPV Vaccination Among Young African. *NEJM Evidence*. 2022. doi: 10.1056/EVIDoa2100056.

KEN SHE – Vaccine efficacy
Incident persistent HPV 16/18 infections ITT

	Number of events	Incidence/ 100 woman years	VE (%)	VE 95% CI
Delayed Vaccination N = 757	96	9.65	Referent	
Single dose Cervarix® N = 760	34	3.18	66.6	50.5; 77.4
Single dose Gardasil®9 N = 758	38	3.58	62.3	45.1; 74.1

CI: confidence interval; ITT: intent-to-treat; VE: vaccine efficacy

Barnabas R, Brown E, Onono M, et al. Efficacy of Single-Dose HPV Vaccination Among Young African. *NEJM Evidence*. 2022. doi: 10.1056/EVIDoa2100056.

KEN SHE– Vaccine efficacy Incident persistent HPV 16/18/31/33/45/52/58 infections ITT

	Number of events	Incidence/ 100 woman years	VE (%)	VE 95% CI
Delayed Vaccination N = 757	186	20.61	Referent	
Single dose Gardasil®9 N = 758	98	9.78	51.9	38.5; 62.3

CI: confidence interval; ITT: intent-to-treat; VE: vaccine efficacy

2vHPV participants are not included in the HPV 16/18/31/33/45/52/58 analysis as the study was not powered to detect cross-protection

Barnabas R, Brown E, Onono M, et al. Efficacy of Single-Dose HPV Vaccination Among Young African. *NEJM Evidence*. 2022. doi: 10.1056/EVIDoa2100056.

KEN SHE – Incident persistent non-vaccine HPV type infections mITT*

	Number of mITT	Number of events	Incidence/ 100 woman years	95% CI
Delayed Vaccination N = 757	250	53	22.6	17; 29.6
Single dose Cervarix® N = 760	241	55	24.5	18.5; 31.9
Single dose Gardasil®9 N = 758	247	53	22.2	16.6; 29.0

mITT: seronegative at baseline and HPV-DNA negative at baseline and Mo3 for types considered in analysis

CI: confidence interval; mITT: modified intent-to-treat

Similar cumulative incidence of persistent nonvaccine HPV types across the study groups

Barnabas R, Brown E, Onono M, et al. Efficacy of Single-Dose HPV Vaccination Among Young African. *NEJM Evidence*. 2022. doi: 10.1056/EVIDoa2100056.

KEN SHE Trial – Conclusions

Single-dose GSK's bivalent and Mercks' nonavalent HPV vaccines were **highly effective** in preventing incident persistent oncogenic HPV infection among African adolescent girls and young women

Efficacy in this randomized single-dose clinical trial appears similar in magnitude to multi-dose regimens

Single Dose – Key topics & questions

Biological plausibility

Single dose level of protection

Is single-dose protection similar to multi-dose regimens?

Durability of protection after a single dose

Would a single dose regimen be applicable to different populations?

- Across age-groups
- Across geographies

Efficacy/Effectiveness from studies with available data

Study / design	Primary objectives / timelines
India-IARC Follow-up of RCT of 2 vs 3 doses (after Indian MoH decision to suspend HPV vaccination in all trials); Gardasil® Females 10-18 yo (~5,000 SD recipients)	Endpoint: Persistent HPV Infections Vaccine efficacy in prevention of persistent infections up to 10 years post-vaccination with 1-, 2- and 3-dose regimens
CVT-extension trial, Costa Rica Females 18-25 yo; Cervarix® N = 3,727 (196 SD)	Endpoint: Prevalent HPV Infections Efficacy in prevention of prevalent infections at Y9 and Y11 (1-, 2- and 3-dose)

CVT: Costa Rica Vaccine Trial; IARC: International Agency for Research on Cancer; MoH: Ministry of Health; N: number of participants; RCT: Randomized-control trial; SD: single dose; Y: Year; yo: year of age

IARC-India Trial – Study schematic

2009/2010 Cluster randomized trial 2- vs 3-dose Gardasil® 10-18 yo

2-dose (0,6 Mo): **10,000**

3-dose (0,2,6 Mo): **10,000**

April 2010: **Indian MoH suspends HPV vaccination in all trials**

=> Longitudinal, prospective cohort study

3-dose **4,348**

2-dose (0,6 Mo) **4,980**

2-dose (0,2 Mo) **3,452**

1-dose **4,949**

Yearly cervical specimen collection/
Luminex for 4 years (18 Mo after marriage/ 6 Mo post delivery)

1,541 matched unvaccinated cohort **1**
(2013-2015)

CC screening (HCII) at 25 and 30 yo (married women);
if+, HPV genotyping/ colposcopy

3,631 matched unvaccinated cohort **2**
(2017-2019)

Median duration of follow-up (vaccinated): 9 years (IQR 8.2; 9.6)

CC: Cervical cancer; HCII: hybrid capture II; Mo: month; MoH: Ministry of Health; yo: year of age;

IARC-India Trial – Virological efficacy
Persistent HPV 16/18 infections

	Number of women assessed	Number of events	Crude Attack rates (%)	Adjusted VE point estimate	Adjusted VE 95% CI
Unvaccinated	1,260	32	2.54	Referent	
Single dose	2,135	1	0.05	95.4	85.0; 99.9
2-dose (0,6 Mo)	1,452	1	0.07	93.1	77.3; 99.8
3-dose	1,460	1	0.07	93.3	77.5; 99.7

CI: confidence interval; Mo: month; VE: vaccine efficacy

Basu P, Malvi SG, Joshi S, et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, ¿o, and three doses of quadrivalent HPV vaccine in girls in India: amulticentre, prospective, cohort study [published correction appears in Lancet Oncol. 2022 Jan;23(1):e16]. *Lancet Oncology*. 2021;22(11):1518-1529. doi:10.1016/S1470-2045(21)00453-8.

IARC-India Trial – attack rate non-vaccine HPV types suggesting similar exposure across vaccine groups

	Number of women assessed	Number of events	Attack rates (95% CI)
Single dose	2,135	68	3.2% (2.5; 4.0)
2-dose (0,6 Mo)	1,452	47	3.2% (2.4; 4.3)
3-dose	1,460	49	3.4% (2.5; 4.4)

Non-vaccine targeted HPV infections excluding 31, 33 and 45 in participants with ≥ 2 samples tested

CI: confidence interval; Mo: month: VE: vaccine efficacy

Basu P, Malvi SG, Joshi S, et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 yearsafter one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study [published correction appears in Lancet Oncol. 2022 Jan;23(1):e16]. *Lancet Oncology*. 2021;22(11):1518-1529. doi:10.1016/S1470-2045(21)00453-8.

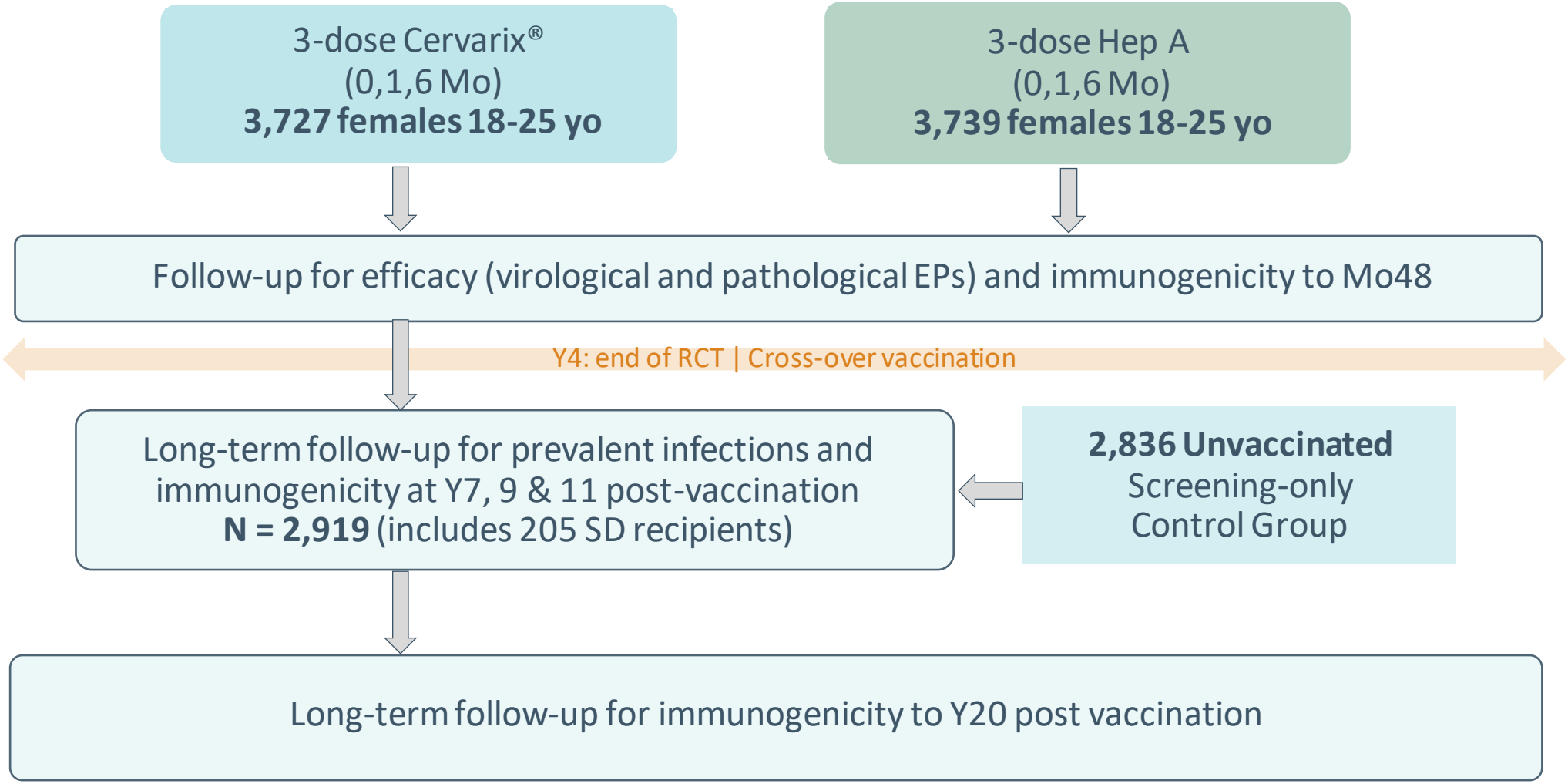
IARC-India Trial – Efficacy screening populations

	Number of women screened	Number of women positive for HPV-16/18+	Number of HPV-16/18 associated CIN2+
Unvaccinated	4626	63 (1.4%)	3
Single dose	1511	2 (0.1%)	0
2-dose (0,6 Mo)	1143	4 (0.3%)	0
3-dose	1037	1 (0.1%)	0

CI: confidence interval; Mo: month; VE: vaccine efficacy; yo: year of age

Basu P, Malvi SG, Joshi S, et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study [published correction appears in Lancet Oncol. 2022 Jan;23(1):e16]. *Lancet Oncology*. 2021;22(11):1518-1529. doi:10.1016/S1470-2045(21)00453-8.

Costa Rica HPV Vaccine trial – Study schematic



Mo: month; N: number of participants; RCT: Randomized-control Trial; SD: Single Dose; Y: Year; yo: year of age

Combined analysis at Month 48 post-vaccination
Costa Rica HPV Vaccine trial & PATRICIA trial

Dose-stratified vaccine efficacy against incident persistent (at least 6 months) HPV-16/18 infections

	Groups	Number of women	Number of events	Rate/ 100 person-years (95% CI)	VE (%)	VE 95% CI
3-dose	HPV	11,104	114	0.26 (0.22; 0.31)	89.1	86.8; 91.0
	Control	11,209	1,000	2.39 (2.24; 2.54)		
Single-dose	HPV	292	1	0.08 (0.00; 0.40)	96.6	81.7; 99.8
	Control	250	24	2.36 (1.55; 3.46)		

CI: confidence interval; PATRICIA: PApilloma TRIal against Cancer In young Adults; VE: vaccine efficacy

Kreimer AR, Struyf F, Del Rosario-Raymundo MR, et al. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA Trials. *Lancet Oncol*. 2015;16(7):775-786. doi:10.1016/S1470-2045(15)00047-9.

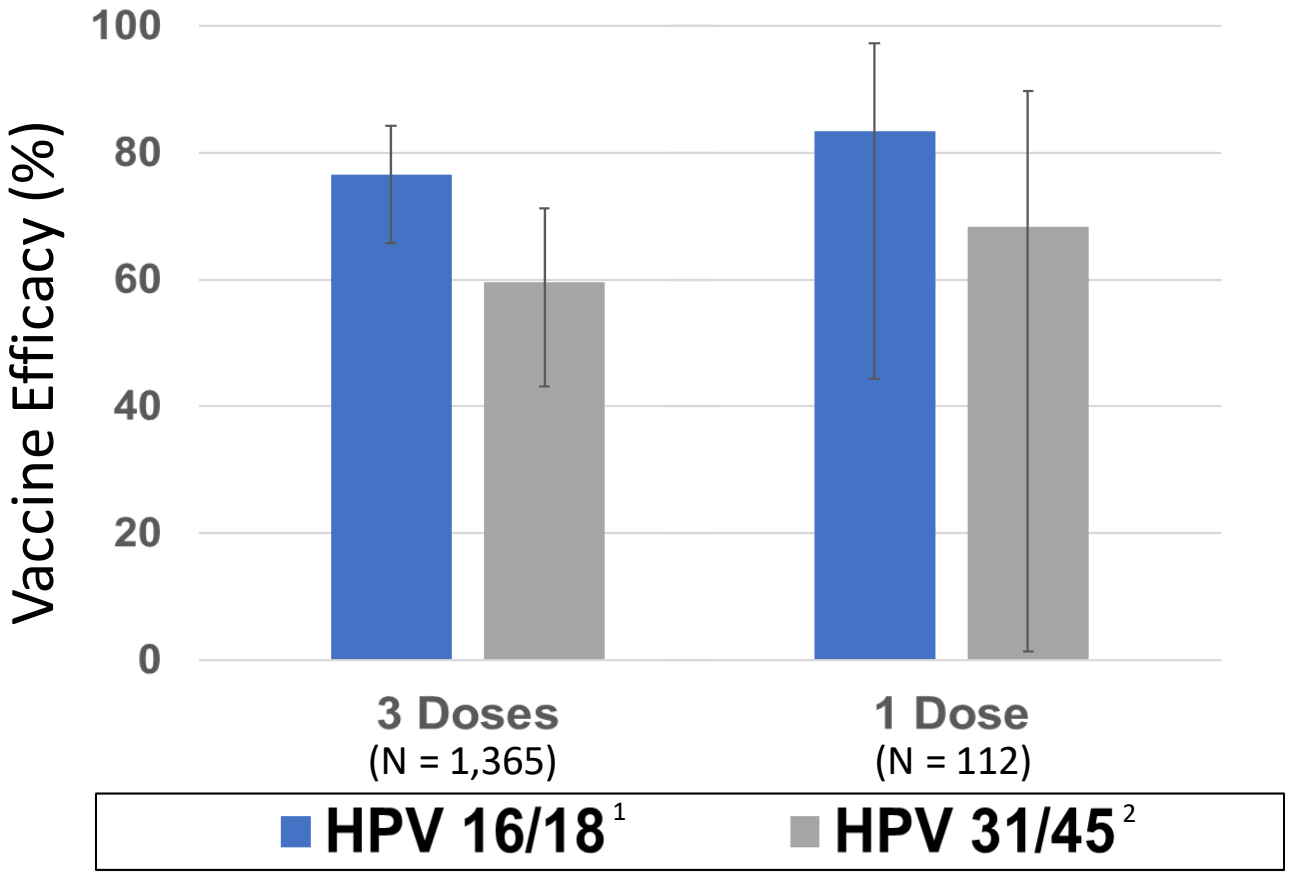
Costa Rica HPV Vaccine trial - Vaccine efficacy
Prevalent HPV 16/18 infections at Years 9 or 11

	Number subjects	Number events	% HPV positive	VE 95% CI
Unvaccinated	1,783	178	10.0	Referent
Single dose	112	2	1.8	82.1 (40.2; 97.0)
3-dose	1,365	27	2.0	80.2 (70.7; 87.0)

CI: confidence interval; VE: vaccine efficacy

Kreimer AR, Sampson JN, Porras C, et al. Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial. *J Natl Cancer Inst*. 2020;112(10):1038-1046. doi:10.1093/jnci/djaa011.

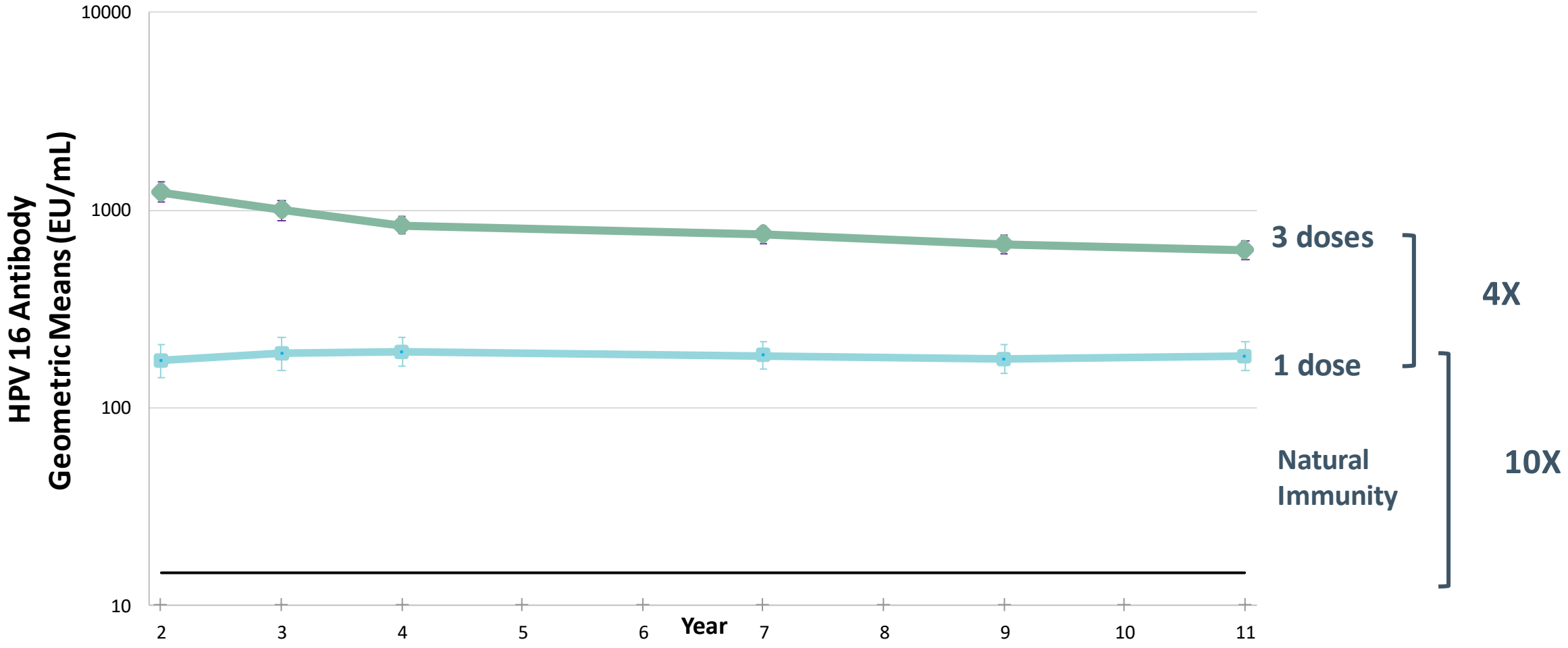
Costa Rica HPV Vaccine trial – efficacy (final)
Prevalent infections >10 years post-vaccination (TVC)



N: number of participants; TVC: total vaccinated cohort

1. Kreimer AR, Sampson JN, Porras C, et al. Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial. *Journal of the National Cancer Institute.* 2020;112(10):1038-1046. doi:10.1093/jnci/djaa011. | 2 Tsang SH, Sampson JN, Schussler J, et al. Durability of Cross-Protection by Different Schedules of the Bivalent HPV Vaccine: The CVT Trial. *J Natl Cancer Inst.* 2020;112(10):1030-1037. 10.1093/jnci/djaa010.

Costa Rica HPV Vaccine trial – 11-year immunogenicity



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

Kreimer AR, Sampson JN, Porras C, et al. Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial. *Journal of the National Cancer Institute*. 2020;112(10):1038-1046. doi:10.1093/jnci/djaa011.

Single Dose – Key topics & questions

Biological plausibility

Single dose level of protection

Is single-dose protection similar to multi-dose regimens?

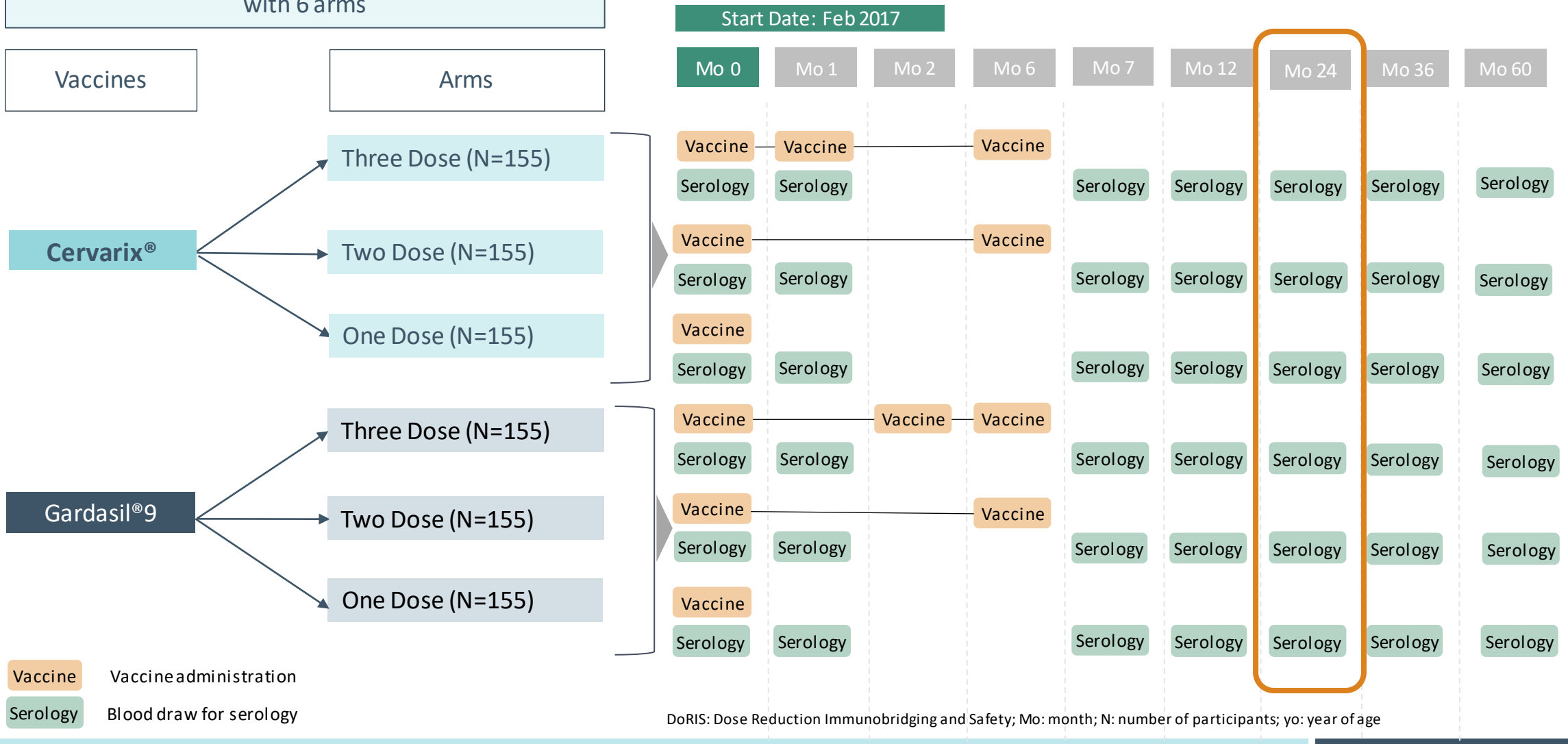
Durability of protection after a single dose

Would a single dose regimen be applicable to different populations?

- **Across age-groups**
- Across geographies

DoRIS Trial – Study Schematic

Women 9-14 yo N = 930
non-blinded, individually-randomized trial,
with 6 arms



DoRIS: Dose Reduction Immunobridging and Safety; Mo: month; N: number of participants; yo: year of age

DoRIS Trial – Month 24 Immunogenicity data (ATP)

	1-dose		2-dose		3-dose	
	Number	Seropositive (%)	Number	Seropositive (%)	Number	Seropositive (%)
Cervarix®						
HPV-16	148	147 (99.3%)	141	141 (100%)	141	141 (100%)
HPV-18	141	139 (98.6%)	140	140 (100%)	136	136 (100%)
Gardasil®9						
HPV-16	145	144 (99.3%)	141	141 (100%)	140	140 (100%)
HPV-18	136	133 (97.8%)	136	136 (100%)	142	141 (99.3%)

ATP: seronegative at baseline and HPV-DNA negative at baseline for types under analysis

Non-inferiority 1-D versus 2-D and 3-D = lower limit of 95% CI for difference in SCR >-5%
HPV-16: met for both vaccines
HPV-18: not met for both vaccines (LL>-10 but<-5%)

ATP: according to protocol; CI: confidence interval; D: dose; DoRIS: Dose Reduction Immunobridging and Safety; SCR: seroconversion rates

Watson-Jones D, Changalucha J, Whitworth H, et al. Immunogenicity and Safety Results Comparing Single Dose Human Papillomavirus Vaccine with Two or Three Doses in Tanzanian girls - the DoRIS Randomised Trial. *Lancet*. Preprint posted online March 11, 2022. https://dx.doi.org/10.2139/ssrn.4055429.

DoRIS Trial – Month 24 Immunogenicity data (ATP)

	1-dose		2-dose		3-dose	
	Number	GMC (95% CI) IU/mL	Number	GMC (95% CI) IU/mL	Number	GMC (95% CI) IU/mL
Cervarix®						
HPV-16	148	23 (20; 26)	141	163 (141; 188)	141	412 (357; 475)
HPV-18	141	10 (9; 11)	140	50 (43; 58)	136	107 (90; 126)
Gardasil®9						
HPV-16	145	14 (12; 16)	141	125 (107; 146)	140	118 (102; 137)
HPV-18	136	6 (5; 7)	136	29 (25; 35)	142	32 (27; 38)

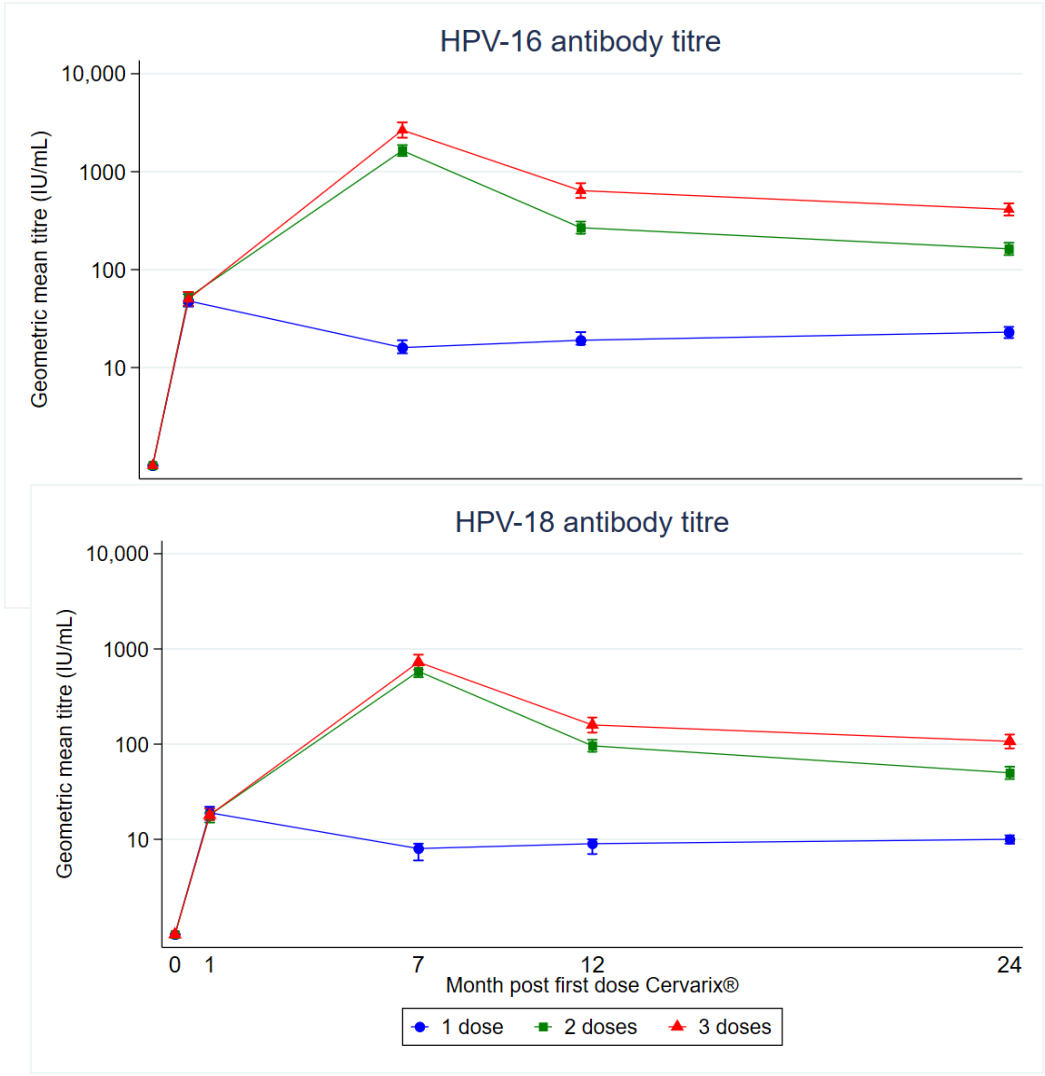
ATP: seronegative at baseline and HPV-DNA negative at baseline for type under analysis

ATP: according to protocol; CI: confidence interval; D: dose; GMC: geometric mean concentrations; IU: International Unit; mL: millimeter

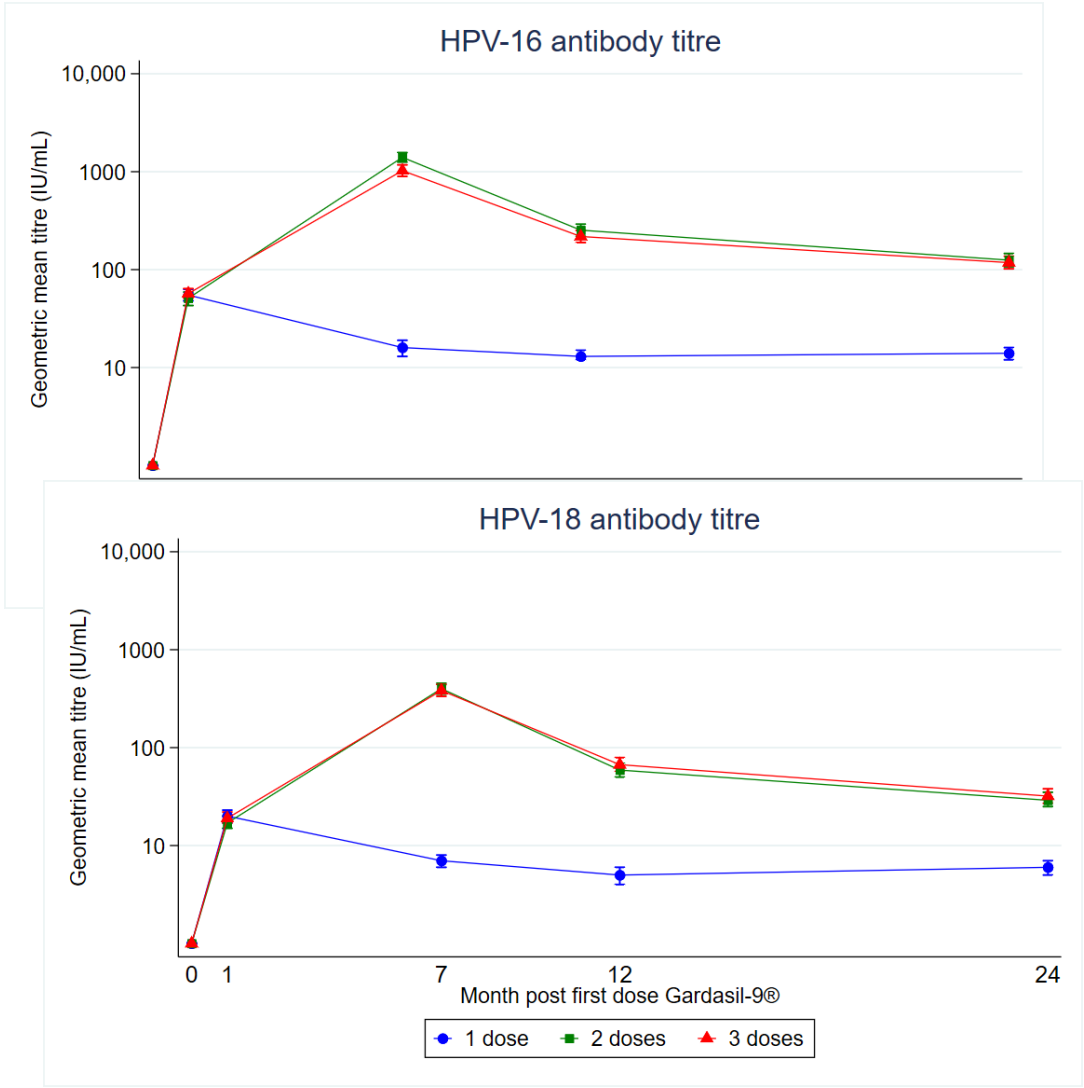
Watson-Jones D, Changalucha J, Whitworth H, et al. Immunogenicity and Safety Results Comparing Single Dose Human Papillomavirus Vaccine with Two or Three Doses in Tanzanian girls - the DoRIS Randomised Trial. *Lancet*. Preprint posted online March 11, 2022. https://dx.doi.org/10.2139/ssrn.4055429.

DoRIS Trial – Kinetic immune response

Cervarix®

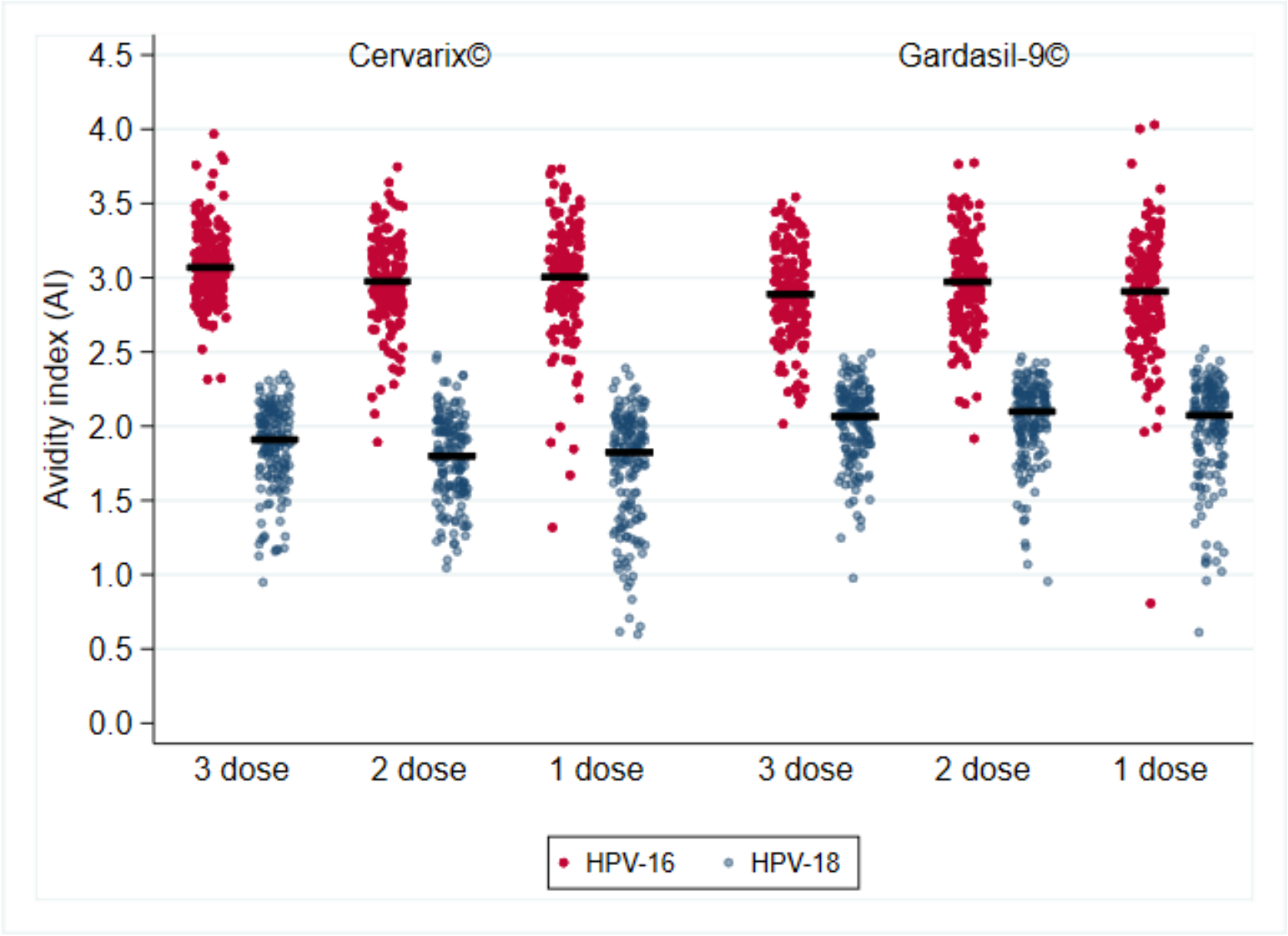


Gardasil®9



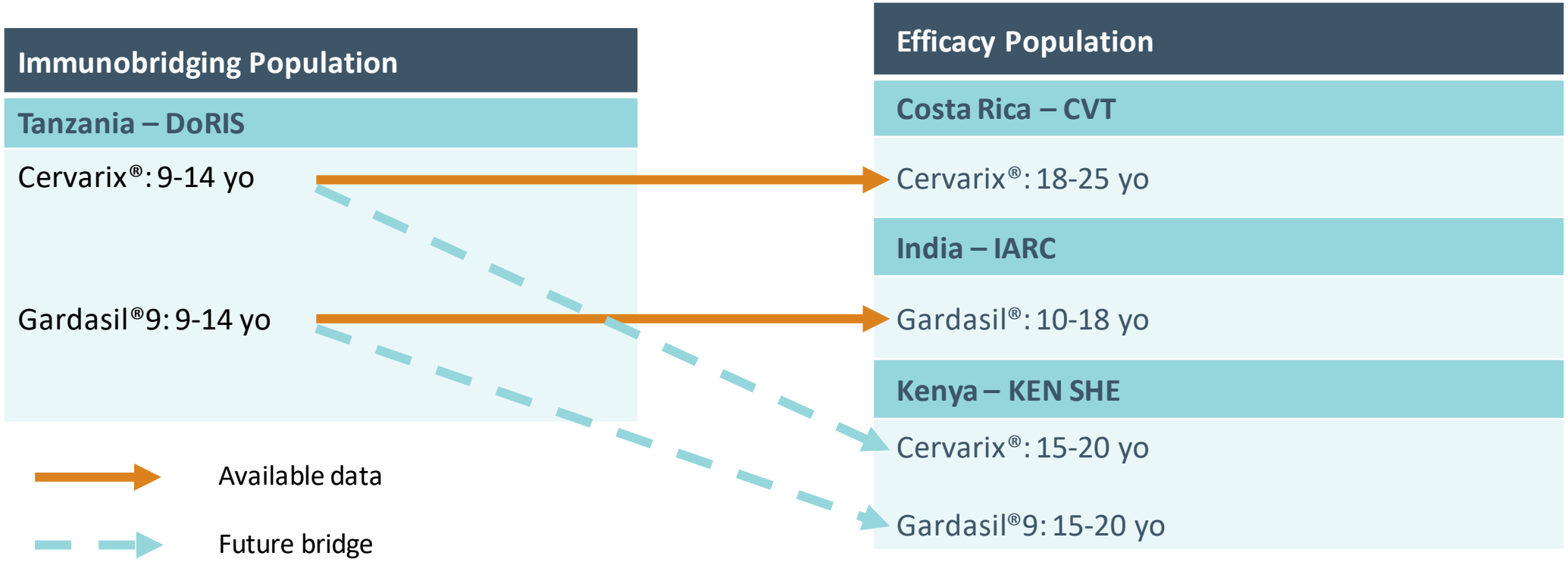
Watson-Jones D, Changalucha J, Whitworth H, et al. Immunogenicity and Safety Results Comparing Single Dose Human Papillomavirus Vaccine with Two or Three Doses in Tanzanian girls - the DoRIS Randomised Trial. *Lancet*. Preprint posted online March 11, 2022. https://dx.doi.org/10.2139/ssrn.4055429.

DoRIS Trial – Month 24 Avidity Index



Watson-Jones D, Changalucha J, Whitworth H, et al. Immunogenicity and Safety Results Comparing Single Dose Human Papillomavirus Vaccine with Two or Three Doses in Tanzanian girls - the DoRIS Randomised Trial. *Lancet*. Preprint posted online March 11, 2022. https://dx.doi.org/10.2139/ssrn.4055429.

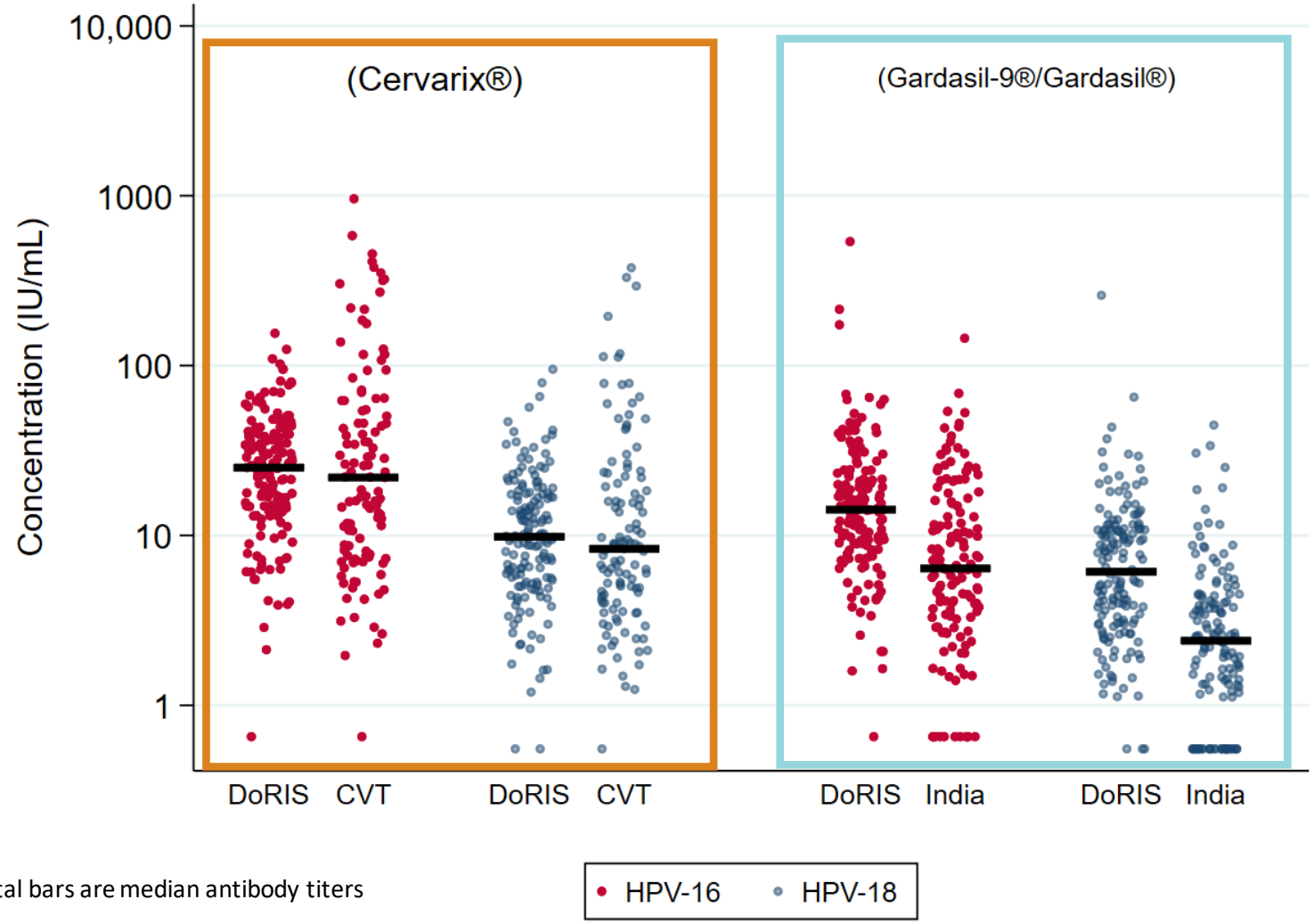
DoRIS Trial – Immuno-bridging



Primary immuno-bridging objective: NI of HPV-16/18 GMC at month 24
Secondary immuno-bridging objective: NI of HPV-16/18 seropositivity at month 24

CVT: Costa Rica Vaccine Trial; DoRIS: Dose Reduction Immunobridging and Safety; GMC: geometric mean concentrations; IARC: International Agency for Research on Cancer; KEN SHE: KEN SHE: KENya Single-dose HPV-vaccine Efficacy; NI: Non-inferiority; yo: year of age

DoRIS Trial – Month 24 Immuno-bridging



Black horizontal bars are median antibody titers

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

Baisley K, Kemp T, Kreimer A, et al. Comparison of Immune Responses after One Dose of HPV Vaccine in a Dose-Reduction HPV Vaccine Trial in Adolescent Girls in Tanzania to the Costa Rica Vaccine and India HPV Vaccine Trials. *SSRN*. Preprint posted online March 11, 2022. https://dx.doi.org/10.2139/ssrn.4055429.

DoRIS Trial – Month 24 Immuno-bridging (PPP)

	Number	GMC (IU/mL)	GMT ratio (95% CI)	SCR	SCR difference (95% CI)
HPV-16					
DoRIS-Cervarix®	**148**	22.9	**1.30 (1.00;1.68)**	147 (99.3%)	**0.4% (-3.1; 5.1)**
CVT-Cervarix®	**97**	17.7		96 (99.0%)	
DoRIS-Gardasil®9	**145**	13.7	**1.29 (0.91; 1.82)***	144 (99.3%)	**6.9% (2.4; 13.1)**
India-Gardasil®	**131**	6.7		121 (92.4%)	
HPV-18					
DoRIS-Cervarix®	**141**	9.9	**1.23 (0.95; 1.60)**	139 (98.6%)	**-0.4% (-4.4; 4.4)**
CVT-Cervarix®	**97**	8.0		96 (99.0%)	
DoRIS-Gardasil®9	**136**	5.7	**1.75 (1.22; 2.50)***	133 (97.8%)	**21.0% (13.5; 29.5)**
India-Gardasil®	**129**	2.2		99 (76.7%)	

CI: confidence interval; GMC: geometric mean conversations; IU: International Unit; mL: millimeter; SCR: seroconversion rate

PPP: seronegative at baseline and HPV-DNA negative (DoRIS and CVT) at baseline for type under analysis
GMT Ratios and SCR differences: Doris vs Historical cohorts *adjusted for age

Non-inferiority margin: lower CI for GMT ratio above 0.50

Baisley K, Kemp T, Kreimer A, et al. Comparison of Immune Responses after One Dose of HPV Vaccine in a Dose-Reduction HPV Vaccine Trial in Adolescent Girls in Tanzania to the Costa Rica Vaccine and India HPV Vaccine Trials. *SSRN*. Preprint posted online March 11, 2022. https://dx.doi.org/10.2139/ssrn.4055429.

Single Dose – Key topics & questions

Biological plausibility

Single dose level of protection

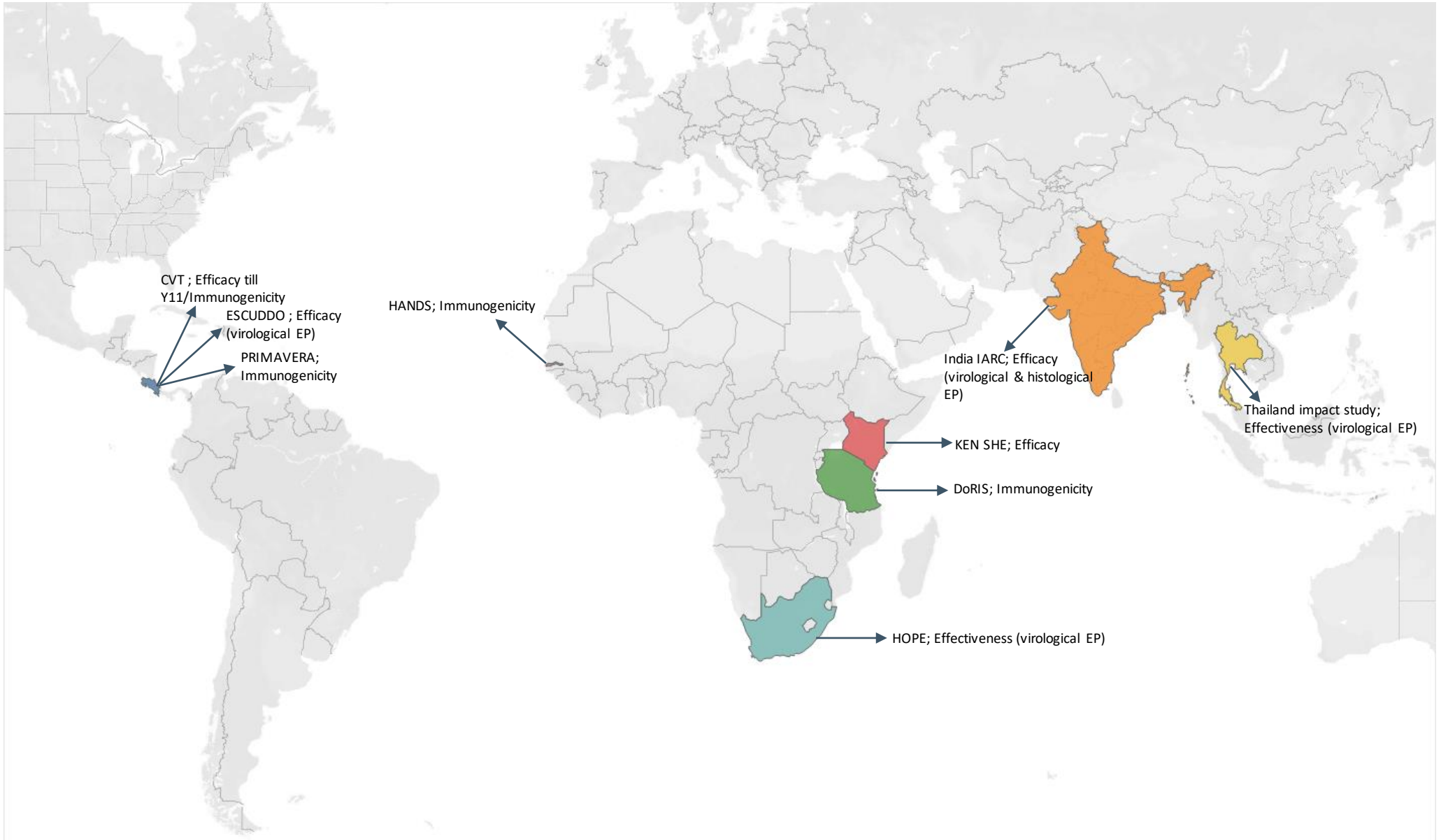
Is single-dose protection similar to multi-dose regimens?

Durability of protection after a single dose

Would a single dose regimen be applicable to different populations?

- Across age-groups
- **Across geographies**

Location of single-dose HPV vaccine clinical trials



Location of clinical trials

- Costa Rica
- India
- Kenya
- South Africa
- Tanzania
- Thailand
- The Gambia

Summary of current evidence from clinical trials supporting single-dose HPV vaccination

Conclusions from available data from clinical trials

- In a randomized control trial assessing single-dose vaccination versus no vaccination, a single dose of Cervarix® and Gardasil®9 HPV vaccines were shown to be highly effective in preventing persistent vaccine-type related oncogenic HPV infections

- A single dose of Cervarix® and Gardasil® HPV vaccines were shown to elicit a level of protection similar to a 3-dose vaccination schedule in preventing HPV-16/18 infections; the level of protection was sustained up to at least 10 years post-vaccination

- A single dose of Cervarix® and Gardasil®9 HPV vaccines in girls 9-14 years of age was non-inferior to 1-dose in a historical cohort at Month 24 post-vaccination (CVT for Cervarix®, 18-25 years of age and India-IARC for Gardasil®, 10-18 years of age)

- The immune response after a single dose of Cervarix® or Gardasil®9 HPV vaccines is lower than after multi-dose regimens but remain stable up to at least Year 10 post-vaccination

- Single-dose data has been generated in different geographies, including in African girls and young women

Key takeaways from ongoing clinical trials

Key takeaways on existing single-dose evidence

- A randomized controlled trial in women 15-20 years of age (KEN SHE) showed that a single dose of Cervarix® & Gardasil®9 was highly effective in preventing HPV infections
- The immune response 24 months post-vaccination of a single dose of Cervarix® or Gardasil®9 in girls 9-14 years of age was non-inferior to a single dose in historical cohorts for which single-dose efficacy was shown (CVT for Cervarix®, 18-25 years of age and India-IARC for Gardasil®, 10-18 years of age)
- A single dose of Cervarix® or Gardasil® was shown to elicit a similar level of protection compared to a three-dose vaccination schedule in high-quality observational clinical studies (India-IARC, CVT) up to at least ten years post-vaccination

Single-dose efficacy data from clinical trials

Study	Objectives	VE % (95% CI)	Reference
KEN SHE 18 Mo Cervarix® Gardasil®9 Gardasil®9	≥ 4 Mo Persistent Infections HPV-16/18 HPV-16/18 HPV-16/18/31/35/45/52/58	 97.5 (81.6; 99.7) 97.5 (81.7; 99.7 88.9 (68.5; 96.1)	Barnabas R., NEJM Evidence 2022 doi: 10.1056/EVIDoa2100056
India- IARC 10Y Gardasil®	≥ 10 Mo Persistent Infections HPV-16/18	95.4 (85.0; 99.9)	Basu P., Lancet Oncol 2022 doi:10.1016/S1470-2045(21)00453-8
CVT Y9 or Y11 Cervarix®	Prevalence HPV-16/18	82.1 (40.2; 97.0)	Kreimer A., JNCI J Natl Cancer Inst 2020 doi:10.1093/jnci/djaa011

CI: Confidence Interval; CVT: Costa Rica Vaccine Trial; IARC: International Agency for Research on Cancer; KEN SHE: KENya Single-dose HPV-vaccine Efficacy; Mo: month; VE: vaccine efficacy; Y: year

Single-dose immunogenicity data from clinical trials

Study	Objectives	Findings	Reference
DoRIS 24 Mo Cervarix® Gardasil®9	Immuno-bridging CVT India-IARC	NI met NI met	Watson-Jones D., Lancet 2022 (*preprint*) https://dx.doi.org/10.2139/ssrn.4055429
India- IARC 4Y Gardasil®	Persistence	No waning	Sankaranarayanan Vaccine 36 (2018) 4783-4791
CVT 11Y Cervarix®	Persistence	No waning	Kreimer A., JNCI J Natl Cancer Inst 2020 doi:10.1093/jnci/djaa011

CVT: Costa Rica Vaccine Trial; DoRIS: Dose Reduction Immunobridging and Safety; IARC: International Agency for Research on Cancer; Mo: month; NI: Non-inferiority

Supportive evidence from observational studies

Observational studies – Effectiveness

A systematic review through September 2021 included HPV vaccine effectiveness studies by the number of doses

Results from 35 studies in 12 countries:
HPV infections [9]; anogenital warts [10]; cervical abnormalities [16]

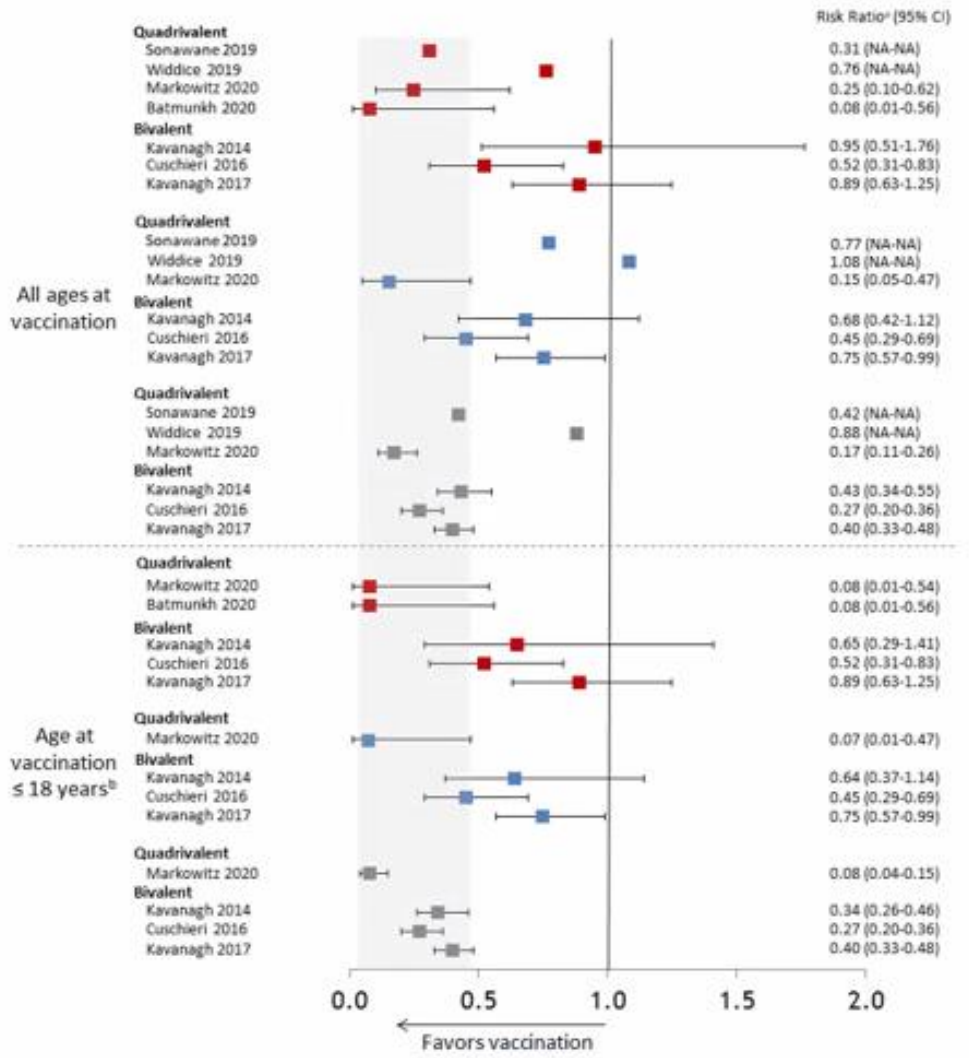
- Most of the studies found highest effectiveness with 3 doses, followed by 2 doses, and then 1 dose
- Biases in many studies; most that would result in apparent lower effectiveness with fewer doses
- Higher effectiveness estimates and decreased differences between dose groups in some studies, when analyses were limited to younger age at vaccination or when using longer buffer period
- More recent studies with younger vaccine recipients, or with analyses stratified by age at vaccination, have found high effectiveness with one dose or similar effectiveness for one, two, and three doses

Observational studies – Effectiveness HPV Infections

Systematic Review Effectiveness against vaccine-type infections

by number of doses overall and limited to age at vaccination ≤18 years

- 1 dose
- 2 doses
- 3 doses



- Risk ratio includes a variety of different measures used in studies
- Gray area indicates the range of the CIs from the published studies for effectiveness of 3 doses among girls aged 18 or younger when vaccinated.

CI: Confidence Interval

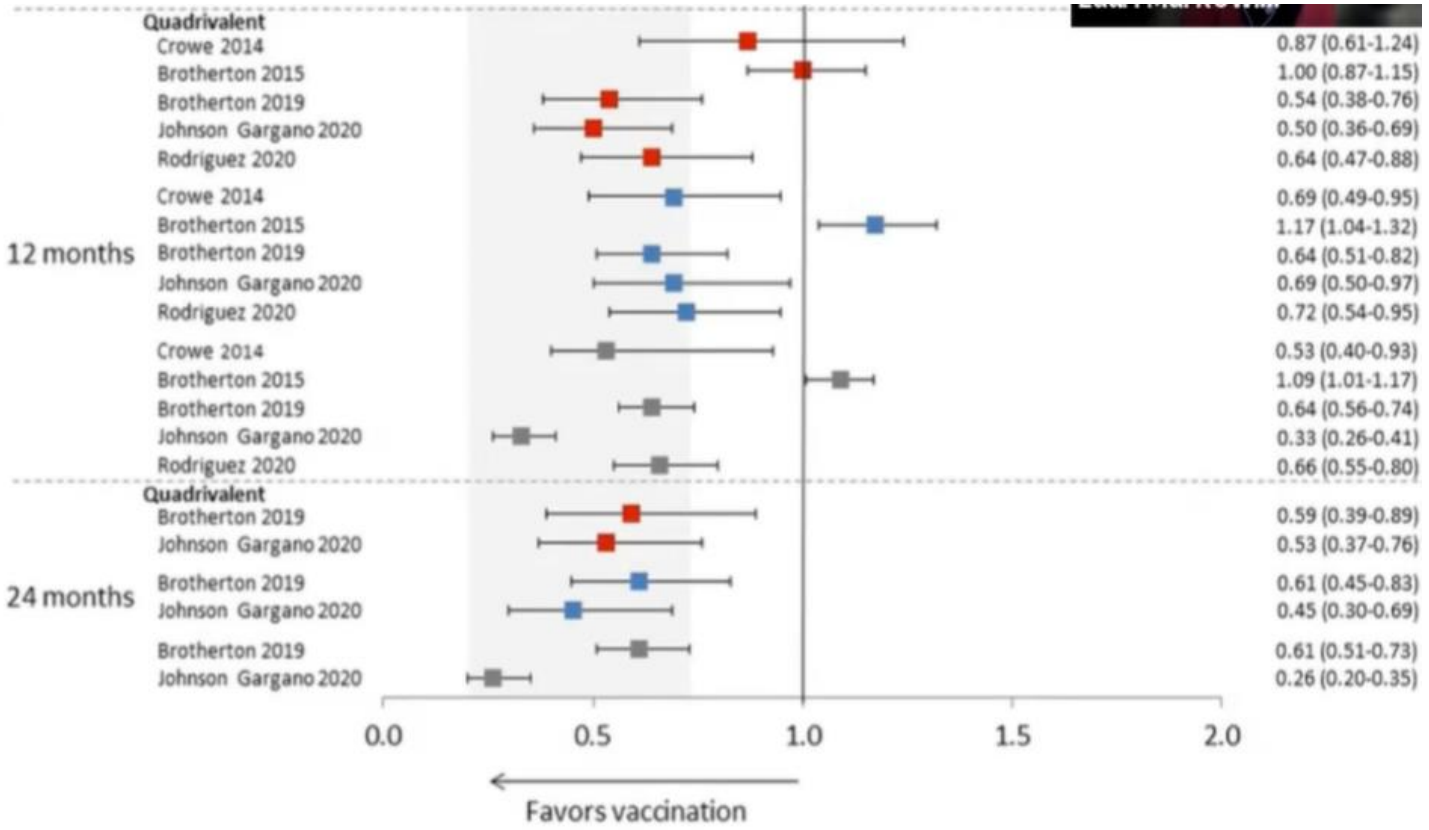
Markowitz, L, Presentation at IPVC conference, 2021 [virtual presentation].

Observational studies – Effectiveness High Grade Cervical Lesions

Effectiveness against CIN2+

by number of doses and duration of buffer period

- 1 dose
- 2 doses
- 3 doses



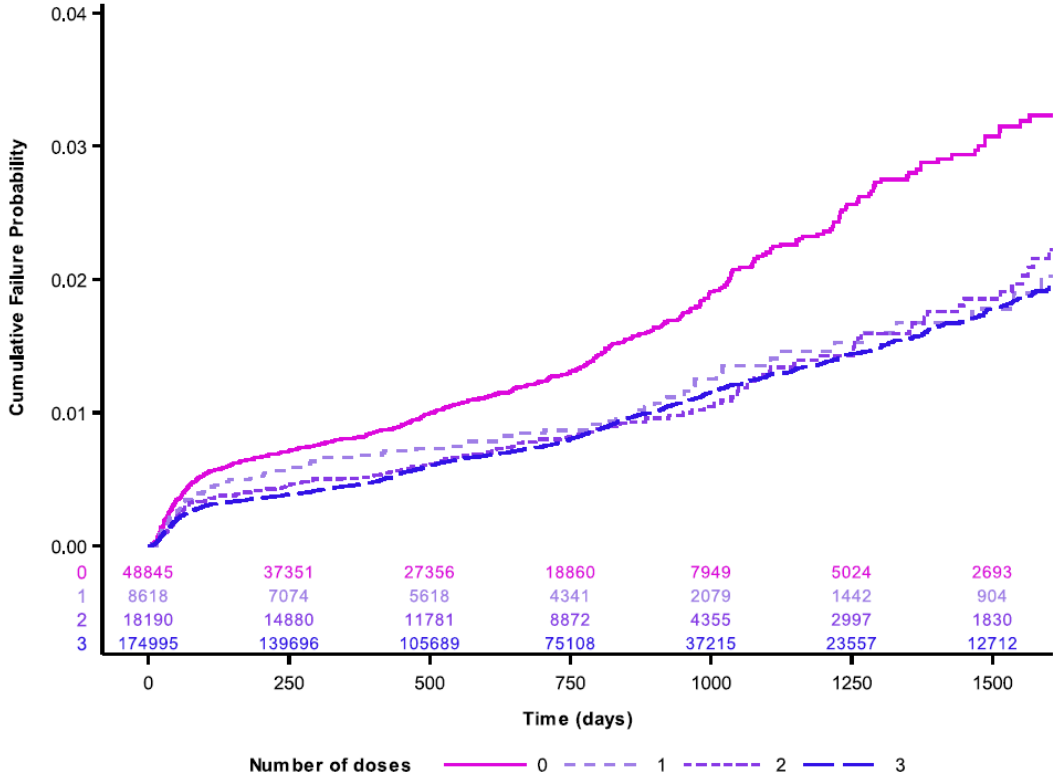
Risk ratio includes a variety of different measures used in studies
Gray area indicates the range of the CIs from the published studies for effectiveness of 3 doses using the longest buffer period.

CI: Confidence Interval; CIN2+: cervical intraepithelial neoplasia grade 2+

Markowitz, L, Presentation at IPVC conference, 2021 [virtual presentation].

Protection against high grade cervical lesions after single dose of 4vHPV National cohort analysis - Australia

Cumulative failure probability plot for CIN2/AIS+ among 250,648 screening women



Hazard ratio for
1 dose compared to
3 doses: 1.01
(95% CI 0.81–1.26)

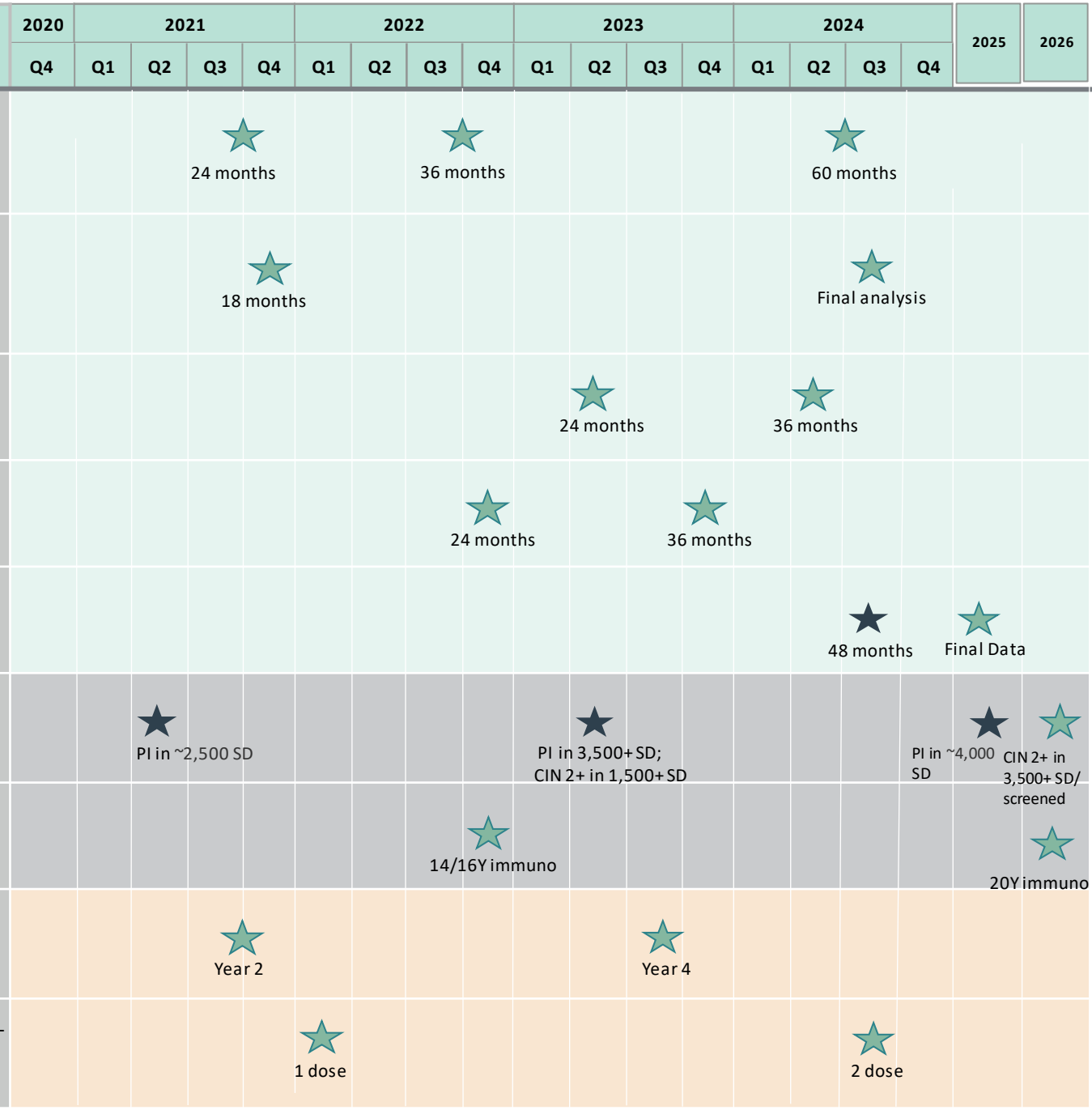
One dose had comparable effectiveness as two or three doses in preventing high-grade disease in a high-coverage setting in women vaccinated ≤ 15 yo

CI: Confidence Interval; yo: year of age; CIN: cervical intraepithelial neoplasia; AIS: adenocarcinoma in situ

Brotherton JM, Budd A, Rompotis C, et al. Is one dose of human papillomavirus vaccine as effective as three?: A national cohort analysis. *Papillomavirus Res.* 2019;8:100177. doi:10.1016/j.pvr.2019.100177.

Forthcoming evidence from ongoing clinical trials

Study name (country)	Evidence type	Vaccine(s)	Brief description
DoRIS Tanzania	Immunogenicity	HPV2 and HPV9	Girls 9-14 yo randomized to 1, 2, or 3 doses of HPV2 or HPV9, N=155 each arm
KEN SHE Kenya	Efficacy (virological EP)	HPV2 and HPV9 vs MenACWY (delay HPV)	Girls 15-20 yo randomized to 1 dose of HPV2, HPV9, or MenACWY; N=750 each arm; delayed dose 2 planned
HANDS The Gambia	Immunogenicity	HPV9	Girls 4-8 yo randomized to 1 or 2 doses; girls 15-26 yo given 3 doses; N=344 each arm
Primavera Costa Rica	Immunogenicity	HPV2 and HPV4	Girls 10-13 yo 1-dose HPV2 immunobridge to women 18-25 yo 3-doses HPV4; N=520 each arm
ESCUDDO Costa Rica	Efficacy (virological EP)	HPV2 and HPV9	Girls 12-16 yo randomized to 1 or 2 doses of HPV2 or HPV9; N=5,000 each arm
India IARC India	Efficacy (virological & histological EP)	HPV4	Girls 10-18 yo received 1, 2, 3 doses of HPV4; N=17586, 1-dose N=4,980
CVT Costa Rica	Efficacy till Y11 / Immunogenicity	HPV2 vs control	Women 18-25 yo received 1, 2, or 3 doses of HPV2; N=3,727, 1-dose N=196
Thailand impact study Thailand	Effectiveness (virological EP)	HPV2	Girls in grade 8 given 1 or 2 doses; N=~8,000 each arm| prevalence surveys of girls grade 10, 12; N=2,400 each grade x 2 provinces
HOPE South Africa	Effectiveness (virological EP)	HPV2	Girls 17-18 yo serial prevalence surveys: unvaccinated (17-18 yo), 1-dose catch up (15-16 yo), and 2-dose routine (9 yo) cohorts; N≥3,260



CIN: cervical intraepithelial neoplasia; immuno: immunogenicity; MenACWY: Meningococcal ACWY; N: number; SD: single dose; PI persistent Infections; RCT: Randomized-control Trial ; Y: year; yo: year of age

RCTs *Non-randomized RCTs* *Impact effectiveness studies* *Interim results* *Final results*

Efficacy data against persistent HPV infections - Future

Study / design	Primary objectives/ timelines
KEN SHE, Kenya Prospective, blinded, randomized Females 15-20 yo N= 2,250 in 3 arms: Cervarix®; Gardasil®9; delayed vaccination	Vaccine Efficacy at Mo 18 and end of study Anticipated data: **Final analysis 2024**
ESCUDDO trial, Costa Rica Females 12-16 yo 4 arms: 1 or 2-dose Cervarix®; 1 or 2-doses Gardasil®9; (N=5,000/arm) Epi survey: 4,000 women 17-20 yo	Non-inferiority of 1- to 2-dose regimens Vaccine Efficacy in each arm compared to unvaccinated Early analysis at 4 years post-vaccination Final analysis at 5 years post-vaccination Anticipated data: **Mo 48 data 3Q2024; Final data: 3Q2025**
India-IARC Follow-up of RCT of 2 vs 3 doses after suspension of Gardasil® Females 10-18 yo (~5,000 SD recipients)	Vaccine Efficacy (virological and histopathological endpoints) for 1-, 2- and 3-dose regimens up to 15 years post-vaccination Anticipated data: **Y15 data 2026**

DoRIS: Dose Reduction Immunobridging and Safety; IARC: International Agency for Research on Cancer; KEN SHE: KENya Single-dose HPV-vaccine Efficacy; Mo: month; N: number of participants; yo: year of age

Effectiveness Data

Study / design	Primary objectives/ timelines
Thailand Impact Trial Cross-sectional surveys in girls grade 10/ VS Y1 (N~2,600) and grade 12/ VS Y2 (N~2,000) Females <15 yo; Cervarix® 1 or 2 doses	Effectiveness of single dose 2vHPV at Y2 and Y4 compared to unvaccinated same grade students Effectiveness of single dose compared to 2-dose regimens in terms of reduction of vaccine type prevalence at Y4 Anticipated data: **Y2 data 2Q2022, Y4 data 3Q2023**
HOPE trial, South Africa Repeat cross-sectional surveys in girls 17-18 yo N ≥ 3,260 Females; Cervarix®	Population impact of the national 2-dose vaccine schedule (delivered at age 9) in protecting against HPV16 and 18 infections Population impact of single-dose vaccine schedule (demonstration project in grade 10 school-girls) in protecting against HPV16 and 18 infections To determine whether HIV infection status affects the impact of HPV vaccines Anticipated data: **1-dose data 1Q2022; 2-dose data 3Q2024**

HOPE: HPV One and two dose Population Effectiveness; N: number of participants; v: valent; VS: Vocational School; Y: Year; yo: year of age

Immunogenicity Data

Study / design	Primary objectives/ timelines
DoRIS, Tanzania Randomised, unblinded Females 9-14 yo; N=930 in 6 arms: 1, 2, 3, doses of Cervarix® or Gardasil®9	Immunological Non-Inferiority 1 dose vs 2-3 doses (seropositivity) at Mo 24 Immunological NI Non-Inferiority 1 dose vs historical controls 10-25 yo (GMTs) at Mo 24 (immuno-bridging to CVT, India IARC and ESCUDDO) Immuno-persistence at Mo 36 for 1-, 2- and 3-dose regimens Anticipated data: **Mo 36 3Q2022; Mo 60: 2024**
Primavera trial, Costa Rica Females; 2 arms (520 each): 1 dose Cervarix® in 9-14 yo; 3 doses of Gardasil® in 18-25 yo	Non-inferiority of 1 dose of Cervarix® in 9-14 yo to 3-doses of Gardasil® in 18-25 yo (efficacy population) Anticipated data: **Mo 24 data 4Q2022; Mo 36 data: 4Q2023**

CVT: Costa Rica Vaccine Trial; DoRIS: DoRIS: Dose Reduction Immunobridging and Safety; GMT: geometric mean titer; IARC: International Agency for Research on Cancer; Mo: month; N: number of participan ts; NI: Non-inferiority: SD: Single Dose; yo: year of age

Immunogenicity Data (Cont.)

Study / design	Primary objectives/ timelines
CVT-extension trial, Costa Rica Females 18-25 yo; Cervarix® N=3,727 (196 SD)	Immuno-persistence up to 20Y post vaccination (1-, 2- and 3-dose) Anticipated data: **Y14 & 16 4Q2022; Y20: 2026**
HANDS trial*, The Gambia Females; Gardasil®9; 5 groups (344 each): 1 or 2 doses 4-8 yo; 1 or 2 doses 9-14 yo; 3 doses 15-26 yo	Non-inferiority of 2 doses in 4-8 yo to 3-doses in 15-26 yo (GMT) Comparison of 1 dose in 4-8 yo to 3-doses in 15-26 yo (GMT) Non-inferiority of 2 doses in 9-14 yo to 3-doses in 15-26 yo (GMT) Anticipated data: **Mo 24 data 2Q2023; Mo 36 data: 2Q2024**

CVT: Costa Rica Vaccine Trial; GMT: geometric mean titer; Mo: Month; N: number of participants; SD: Single Dose; Y: Year; yo: year of age

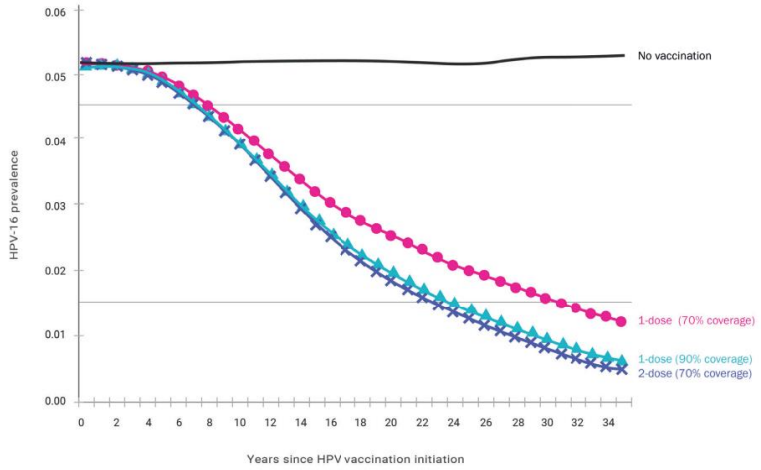
Supportive evidence from modeling analysis

Modeling on single-dose vaccination

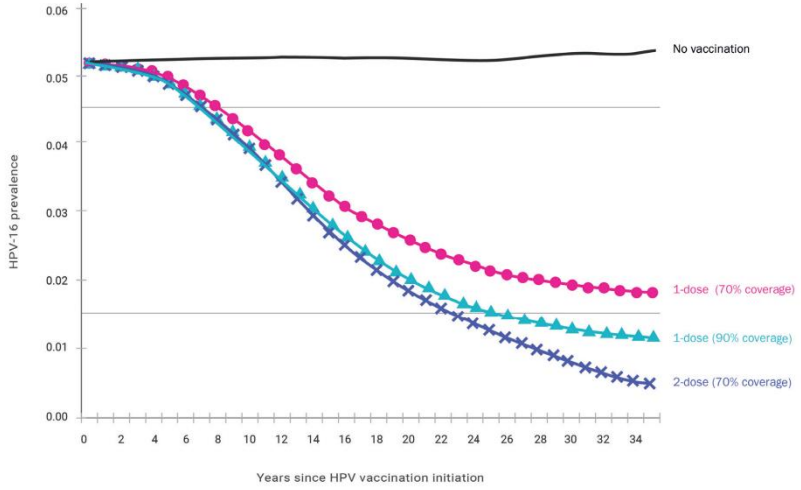
- HPV's natural history takes decades from infections to cervical carcinogenesis
- Empirical studies rely on surrogate measures of vaccine efficacy and effectiveness (infections or HPV-associated lesions)
- By simulating the disease burden of HPV in populations, mathematical models can project longer-term health and economic outcomes (cancer cases and deaths averted, life years gained, disability-adjusted life years (DALYs) and costs averted) under different scenarios about vaccine efficacy and duration
  - evaluate the health and epidemiologic impacts
  - budget impacts
  - cost-effectiveness
  - best vaccination strategies in different settings

Population-level benefit of a single-dose schedule

Model-projected HPV16 prevalence over time, 1-dose no waning



Model-projected HPV16 prevalence over time, 1-dose waning after 15 years



Question: What is the epidemiologic impact of single-dose vaccination under varied assumptions of duration of single-dose protection and coverage?

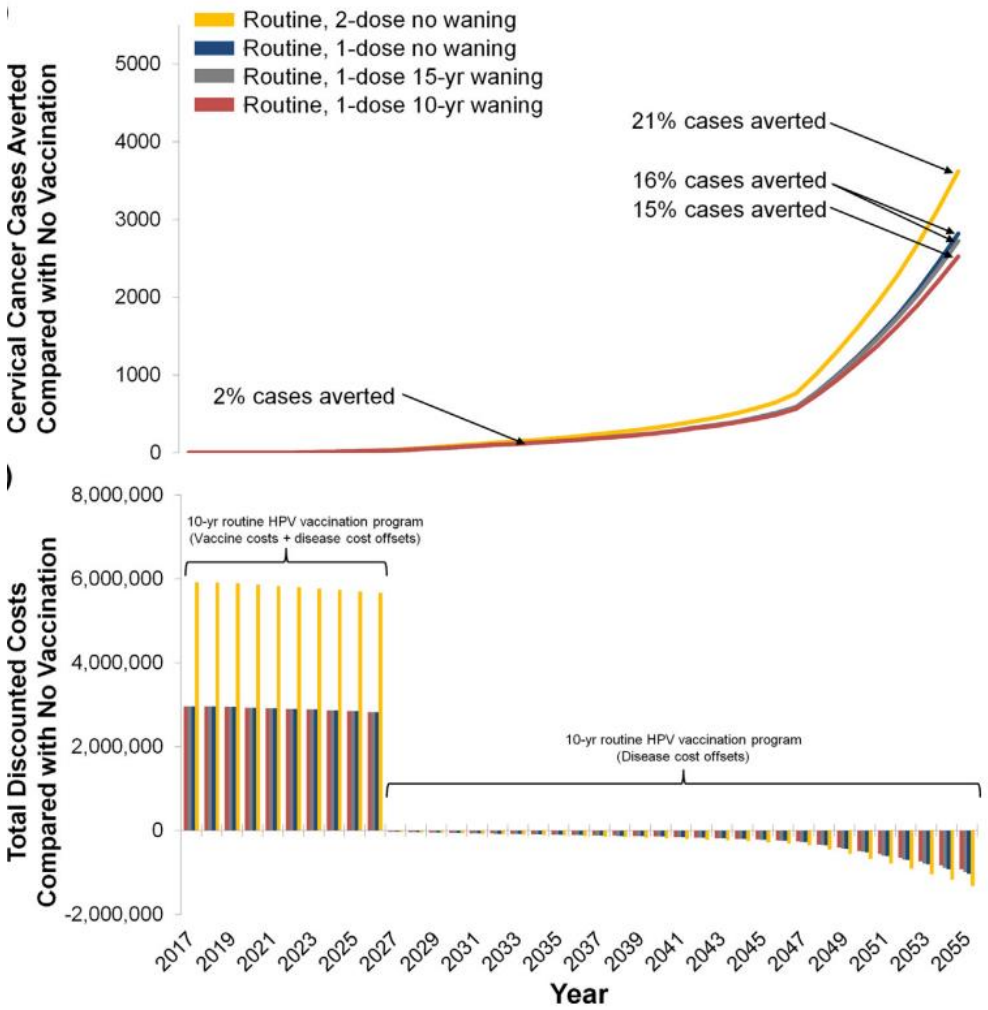
Models: Dynamic model of HPV-16 & 18 infections

Assumptions: Routine vaccination girls; 1-dose 80% efficacy/ 3 waning scenarios; 2-dose 100% efficacy over lifetime

Key message: One-dose vaccination can substantially reduce infection in population HPV-16 prevalence over time, even when protection with one dose is not lifelong. Increasing one-dose vaccination coverage can offset a presumed lower efficacy or durability of single-dose vaccination.

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

Long-term health benefits and cost-effectiveness of a single-dose schedule



Question: What are the long-term health and economic impacts of routine 1-dose HPV vaccination compared to no vaccination and 2-dose HPV vaccination regimen in a Gavi-eligible country?

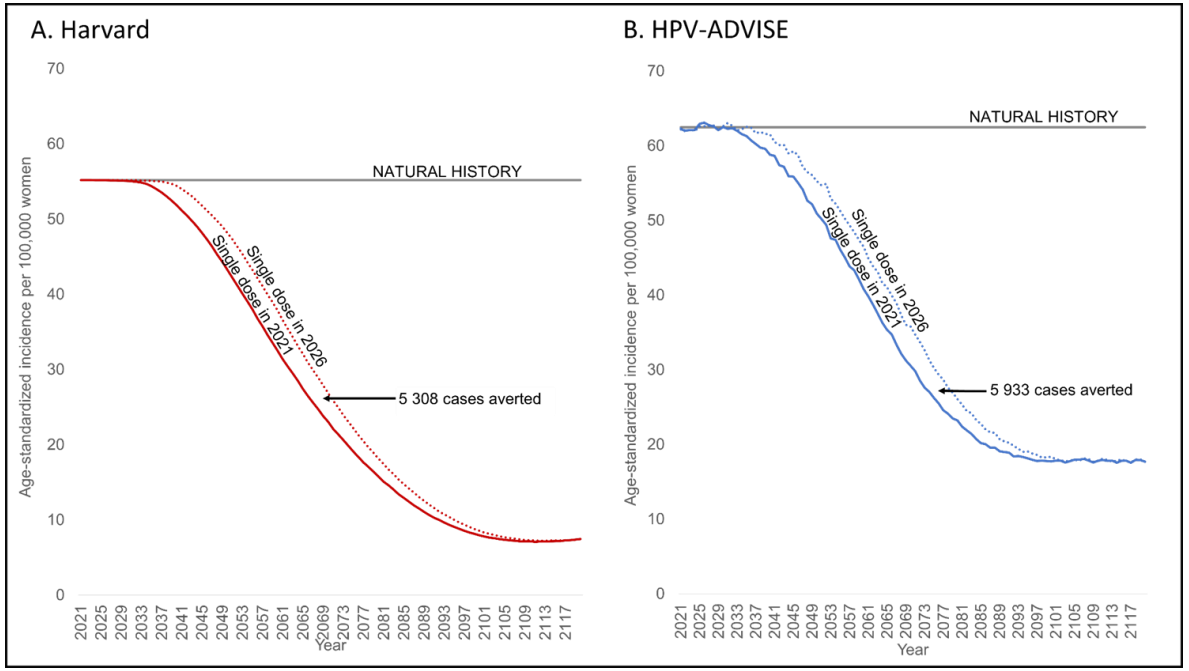
Models: three-tiered hybrid modeling approach/Harvard
Assumptions: 1-dose 80% efficacy/ 3 waning scenarios;
2-dose: 100% efficacy over lifetime

Key message: One-dose HPV vaccination resulted in cost-savings compared to no vaccination and could be cost-effective compared to two-dose vaccination, if protection is longstanding and higher coverage can be achieved.

Burger E. Health and economic benefits of single-dose HPV vaccination in a Gavi-eligible country Vaccine 36 (2018) 4823–4829 doi: 10.1016/j.vaccine.2018.04.061

Health impacts of delaying 1-dose HPV vaccine implementation in a high-burden setting

Aged standardized incidence cervical cancer averted following single dose (100% lifelong efficacy) vaccination implemented in year 2021 compared to delayed implementation in 2026



Immediate single-dose vaccination avoided health losses for those aging out of vaccine eligibility

Question: What are the quantified health impacts of delayed implementation of single-dose HPV vaccination?

Models: two independent dynamic models calibrated to a setting with a high cervical cancer burden

Assumptions: 70% coverage of girls 9 years and 1-year campaign for girls 10-14 years

Key message: Models projected that early implementation of single-dose vaccination resulted in greater health benefits than delayed implementation even up to five years, with 7-10% more cancer cases averted. Even with reduced efficacy of 80%, the earlier implementation of single-dose vaccination would offset any loss in health benefits due to efficacy.

Burger E. Now or later: health impacts of delaying 1-dose HPV vaccine implementation in a high-burden setting. *International Journal of Cancer* (In-Press) DOI: 10.1002/ijc.34054

Key takeaways on Single-Dose modelling analyses

- Compared to no vaccination, single-dose HPV vaccination will lead to substantial reduction in cervical cancer and is a high-value public health intervention
- Reaching more girls with a single dose will avert a much greater number of cervical cancer cases than vaccinating fewer girls with a second dose
- Immediate implementation of a single-dose HPV vaccination program leads to greater health benefits than delaying implementation

Single Dose – Open Questions

Would a single-dose regimen be applicable to different populations?

- HIV/ immuno-deficient
- Males

A single-dose schedule should be considered for those HPV vaccine products for which data on efficacy or immunobridging to vaccines with proven single-dose efficacy are available: currently Cervarix®, Gardasil® and Gardasil®9 [WER June 2022]

- For new L1 VLP vaccines, such data will need to be generated

Additional Resources

Visit: www.path.org/singledosehpv

- Review of the current published evidence for single-dose HPV vaccination
  - Technical Synthesis
  - General Summary
  - Two-page brief and presentation resources
  - Consortium statement on current evidence and its implications for policy
  - JCVI statement

- Relevant publications
  - Efficacy of single-dose HPV vaccination among young African women. *NEJM Evidence.* April 2022
  - Immunogenicity and Safety Results Comparing Single Dose Human Papillomavirus Vaccine with Two or Three Doses in Tanzanian Girls - the DoRIS Randomised Trial. *Lancet Global Health.* October 2022.
  - Comparing one dose of HPV vaccine in girls aged 9–14 years in Tanzania (DoRIS) with one dose of HPV vaccine in historical cohorts: an immunobridging analysis of a randomised controlled trial. *Lancet Global Health.* October 2022.
  - Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study. *Lancet Oncology.* November 2021.
  - Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial. *Journal of the National Cancer Institute.* October 2020.

Thank you!
Questions?

PATH on behalf of
Single-Dose HPV Vaccine Evaluation Consortium

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