Single-dose HPV Vaccine Studies

Aimée R. Kreimer

on behalf of Single-dose HPV Vaccine Evaluation Consortium*

WHO SAGE

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NIH NATIONAL CANCER INSTITUTE

***Member institutions**

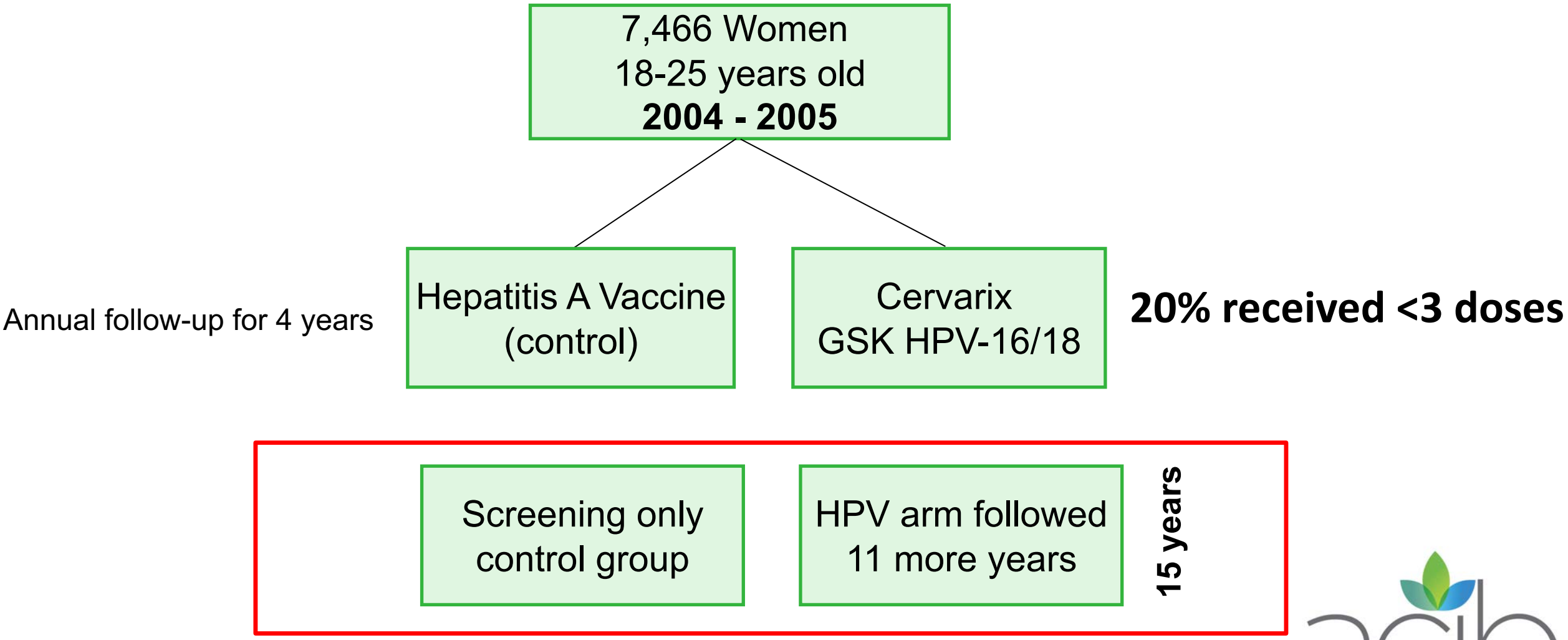
Harvard University
London School of Hygiene & Tropical Medicine
PATH (consortium secretariat)
Université Laval
University of British Columbia
US Centers for Disease Control and Prevention
US National Cancer Institute
Wits Reproductive Health and HIV Institute

Funded by the Bill & Melinda Gates Foundation

Summary of single dose HPV vaccine studies

1. Non-randomized data from trials (additional data accumulating)
   - Bivalent HPV Vaccine- Costa Rica HPV Vaccine Trial
   - Quadrivalent HPV Vaccine- India HPV Vaccine Trial
2. Vaccine registry/phase 4 studies (more to come)
3. Trials to investigate single-dose efficacy
4. Effectiveness Data

NCI Costa Rica Vaccine Trial (CVT)



Research questions shift to DURABILITY of HPV vaccination:
CVT Long-term Follow-up

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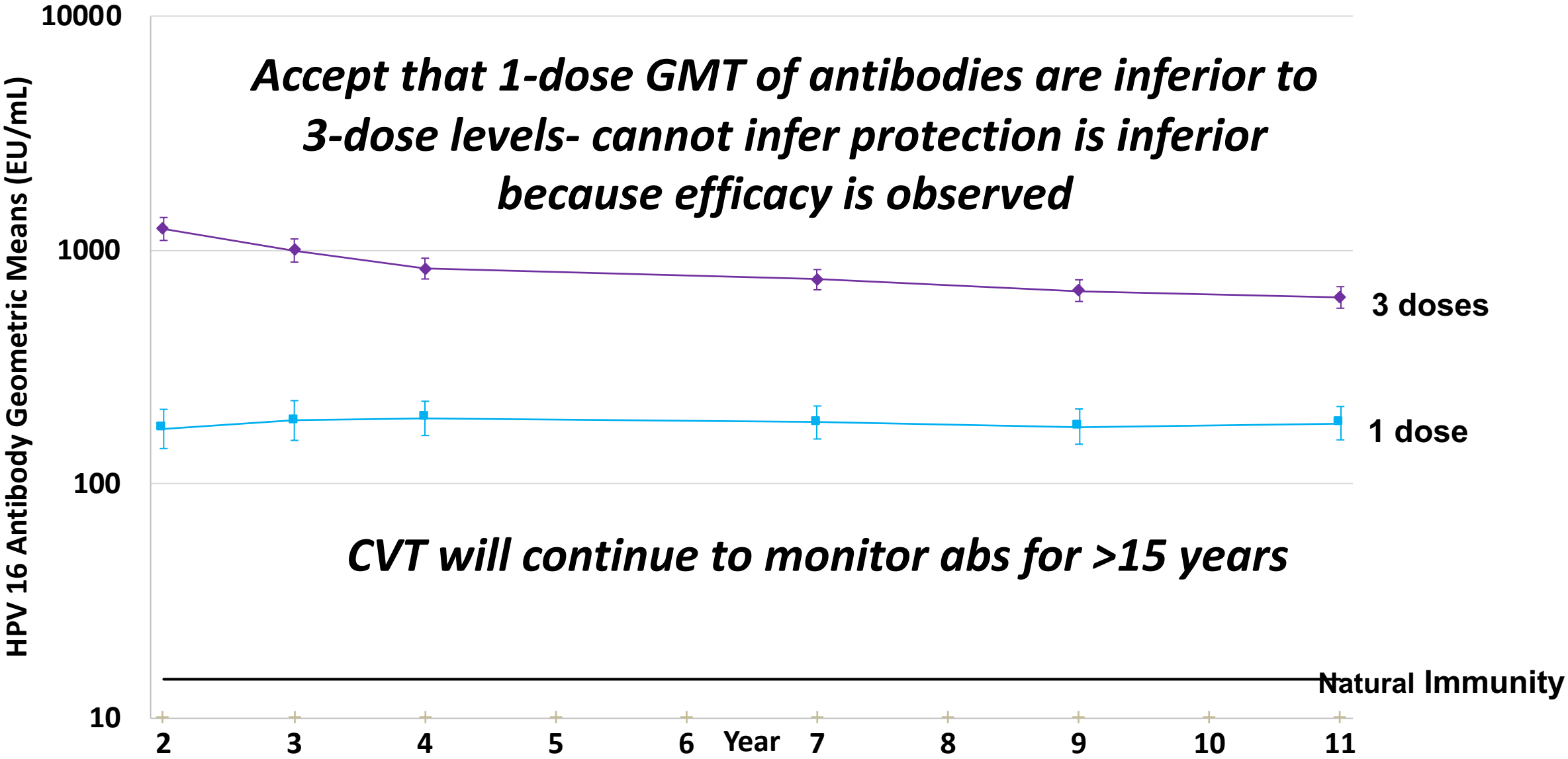
CVT: Stable HPV16 serum antibodies for 11 years

Results similar for HPV18

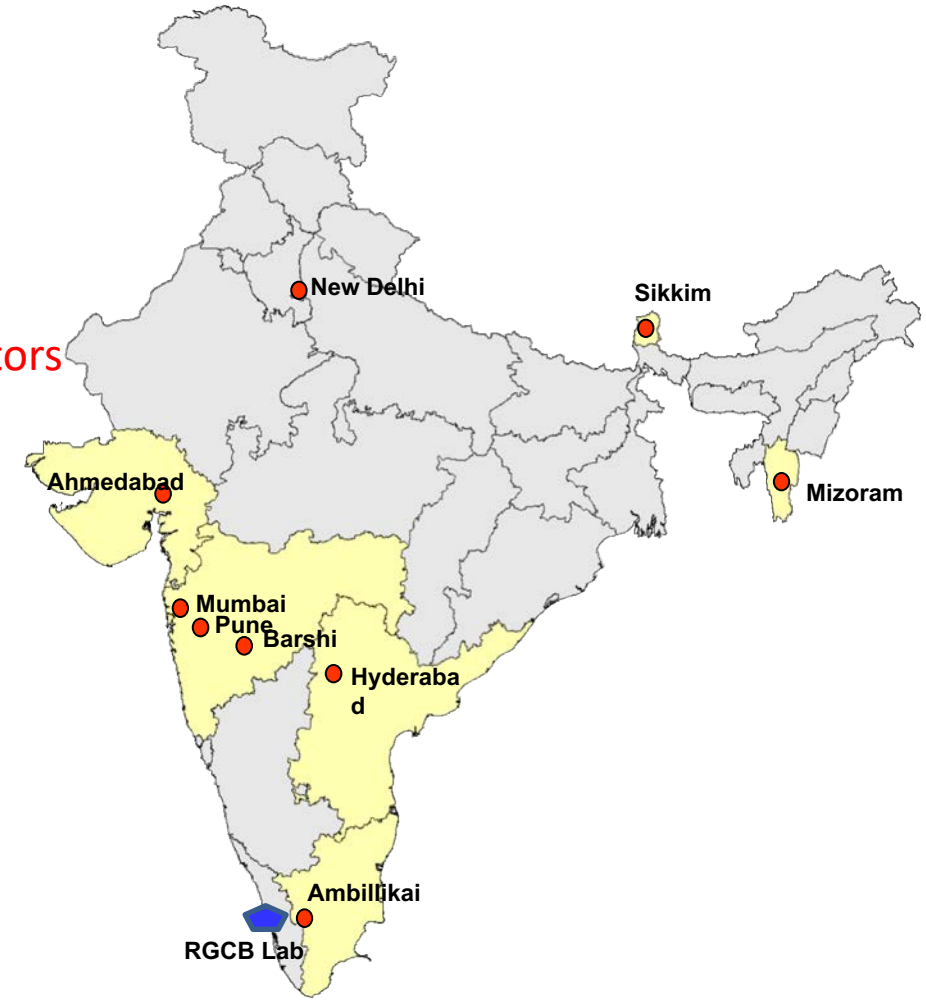


Kreimer AR et al, Revise & resubmit

IARC 2- vs 3- dose 4v HPV Vaccine randomized clinical trial –

(Aimed at recruiting 20,000 unmarried girls aged 10-18 years)

- Recruitment initiated in 2009
- **17,729** girls (89% of target)
- Recruitment suspended due to Ministry directive, April 2010
- RCT converted to a cohort study
- Neither the participants nor the investigators controlled dose group allocation



World Health Organization (WHO)
International Agency for Research on Cancer (IARC)
Lyon, France

In collaboration with

TMH-Mumbai
NDMCH-Barshi
JCDC-Pune
CFCHC-Ambillikai
GCRI-Ahmedabad
AIIMS-New Delhi
MNJ Institute of Oncology and RCC, Hyderabad
Cancer Foundation of India (CFI), Kolkata
and
Rajiv Gandhi Centre for Biotechnology (RGCB), Trivandrum
German Cancer Research Institute (DKFZ), Heidelberg

ClinicalTrials.gov registration number NCT00923702

IARC HPV Vaccine clinical trial

Vaccinated
N=17,064

Received
1 dose
(day 1)
N=4672

Unvaccinated age-match

Additional unvaccinated

HPV SINGLE-DOSE DATA – CONTINUING TO ACCUMULATE

IARC INDIA HPV STUDY – PERSISTENT INFECTIONS (>12M) IN TARGETED / NON-TARGETED HPV TYPES

Study Group	Women assessed (N)	Persistent HPV 16/18 infection N (%; 95%CI)		Persistent non-targeted excluding HPV 31/33/45 infection N (%; 95% CI)	
Unvaccinated	1242	28	(2.3; 1.5-3.2)	57	(4.6; 3.5-5.9)
3- dose (Days 1, 60 & 180+)	1056	1	(0.1; 0.0-0.5)	31	(2.9; 2.0-4.1)
2- dose (Days 1 and 180+)	1055	3	(0.2; 0.0-0.7)	27	(2.1; 1.4-3.1)
1- dose	1643	1	(0.1; 0.0-0.3)	47	(2.9; 2.1-3.8)

~3000 women followed for persistent infection assessment by 2021 with > 10 years since vaccination

Non-randomized data from RCTs provide compelling evidence of single-dose protection

1. Reasons for missing doses are known and usually unrelated to randomization and subsequent risk of HPV acquisition
2. Trials have pre-vaccination information (i.e.: HPV status at time of HPV vaccination, important for vax of older girls)
3. Trials contain in-depth information on covariates
4. Non-vaccine HPV infection can be used as internal control to evaluate infection risk profile by dose group

Robust comparisons between vaccinated and unvaccinated

Long-term data will continue to accumulate

Summary of single dose HPV vaccine studies

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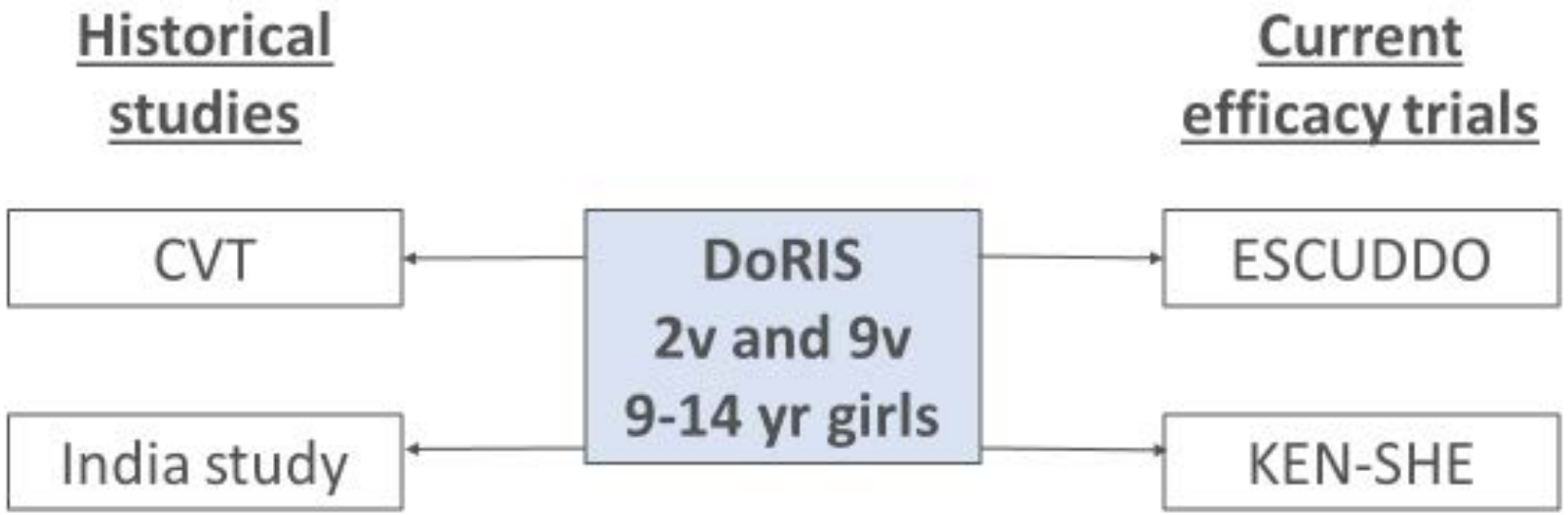
2. Vaccine registry/phase 4 studies (more to come)
3. Trials to investigate single-dose efficacy
   - KenSHE- Efficacy in Kenya
   - ESCUDDO- Efficacy in Costa Rica
   - DoRIS- Immunogenicity in Tanzania (efficacy through immunobridging)
   - Primavera- Immunobridging in Costa Rica
   - HANDS- Immunobridging in the Gambia
4. Effectiveness Data- South Africa and Thailand

Clinical trials investigating 1 dose of HPV vaccination

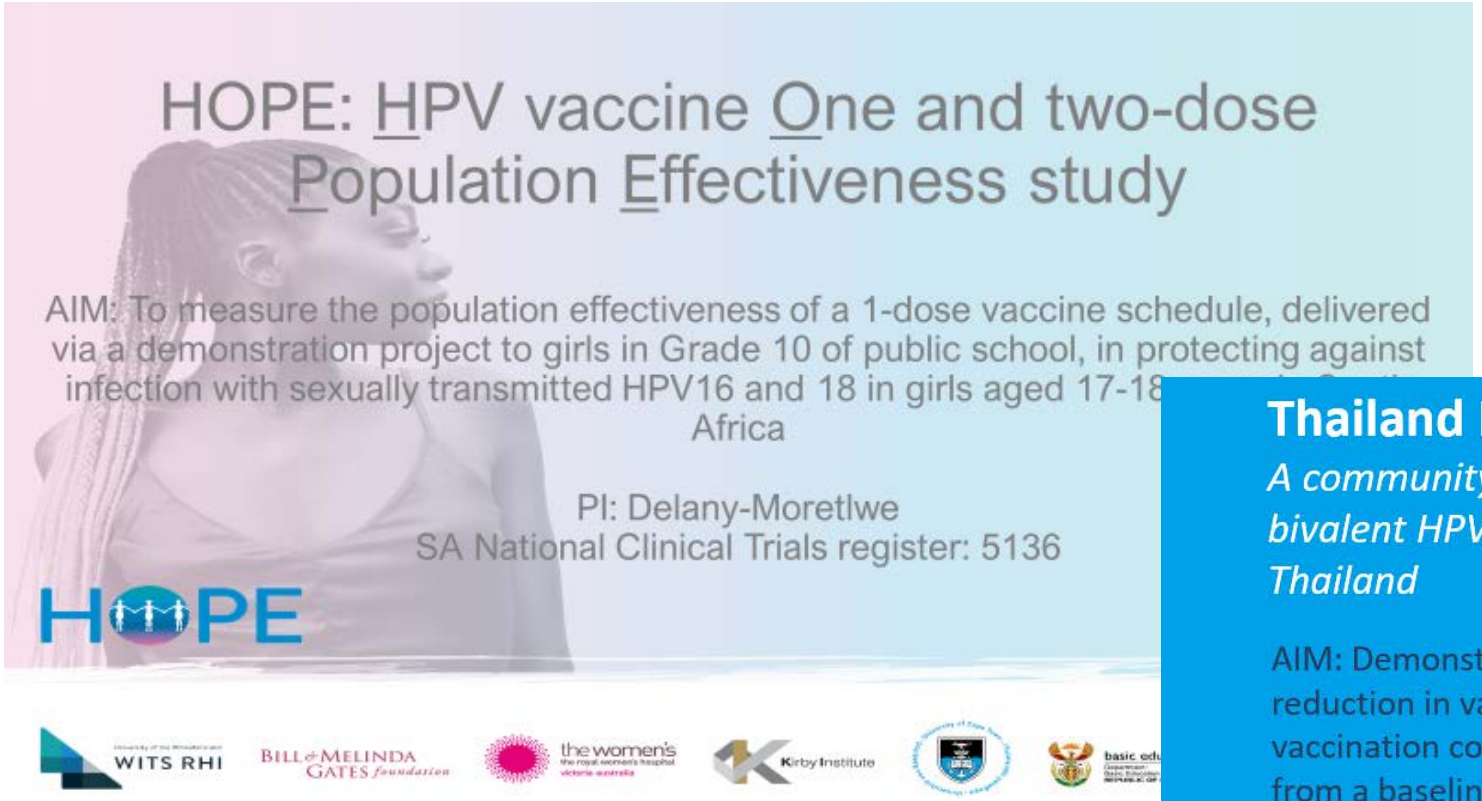
Study name Country	Design	Vaccine	Brief description
KEN SHE Kenya			2, HPV9, or planned
ESCUDDO Costa Rica			f HPV2 or
DoRIS Tanzania			of HPV2 or
Primavera Costa Rica			o women
HANDS The Gambia	Immunogenicity	HPV9	Girls 4-8 yo and 9-14 yo randomized to 1 or 2 doses; girls 15-26 yo given 3 doses; n=344 each arm

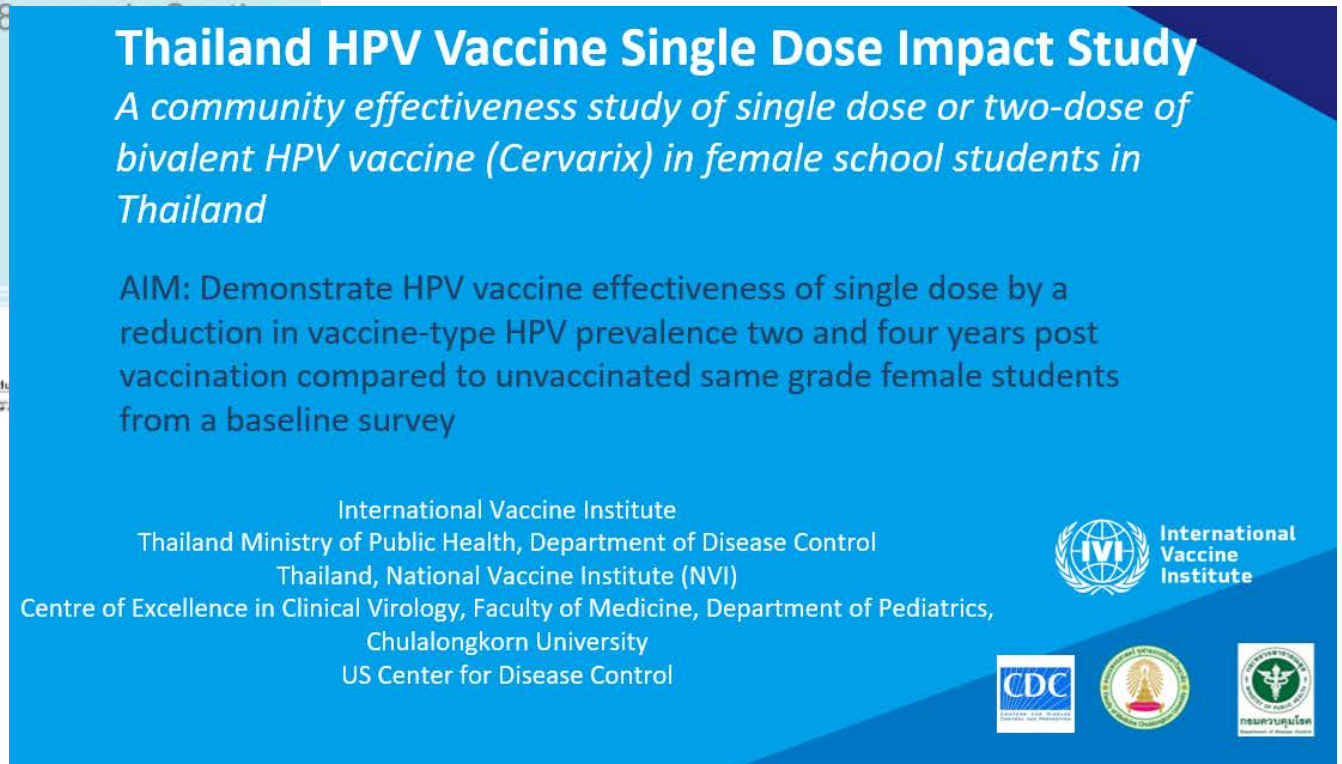


Summary of single dose HPV vaccine studies

1. Existing non-randomized data on single-dose protection from RCTs
   - Bivalent HPV Vaccine- Costa Rica HPV Vaccine Trial
   - Quadrivalent HPV Vaccine- India HPV Vaccine Trial
2. Phase 4 studies based on registry data
3. Trials designed to investigate single-dose protection
   - DoRIS- Immunogenicity in Tanzania
   - Primavera- Immunobridging in Costa Rica
   - KenSHE- Efficacy in Kenya
   - ESCUDDO- Efficacy in Costa Rica
   - HANDS- Immunobridging in the Gambia
4. Effectiveness Data- HOPE in South Africa and another in Thailand

Two effectiveness studies investigating population-based impact of single-dose (i.e., not individually randomized).





Study name (country)	Evidence type	Vaccine(s)	Brief description	2019 Q4	2020 Q1	2020 Q2	2020 Q3	2020 Q4	2021 Q1	2021 Q2	2021 Q3	2021 Q4	2022 Q1	2022 Q2	2022 Q3	2022 Q4	2023 Q1	2023 Q2	2023 Q3	2023 Q4	2024	2025
KEN SHE Kenya	Efficacy	HPV2 vs HPV9 vs MenACWY (delay HPV)	Girls 15-20 yo randomized to 1 dose of HPV2, HPV9, or MenACWY; n=750 each arm								★ 18 months							☆ Year 3		
ESCUDDO Costa Rica	Efficacy	HPV2 and HPV9	Girls 12-16 yo randomized to 1 or 2 doses of HPV2 or HPV9; n=5000 each arm																	☆
DoRIS Tanzania	Immunogenicity	HPV2 and HPV9	Girls 9-14 yo randomized to 1, 2, or 3 doses of HPV2 or HPV 9; n=155 each arm				★ 24 months											☆		
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												★ 24 months				☆ 36 months	
HANDS The Gambia	Immunogenicity	HPV9	Girls 4-8 yo and 9-14 yo randomized to 1 or 2 doses; girls 15-26 yo given 3 doses; n=344 each arm								★ 24 months			★ 36 months	☆					
India IARC India	Efficacy	HPV4	Girls 10-18 yo received 1, 2, 3 doses of HPV4; n=17586, 1-dose n=4980	★ 10 yr f/u				★ 11 yr f/u	☆	Persistent infection endpoint from 3000+ 1-dose recipients						☆	CIN 2+ endpoint from 10,000+ women screened			
CVT Costa Rica	Efficacy / Immunogenicity	HPV2 vs control	Women 18-25 yo received 1, 2, or 3 doses of HPV2; n=3727, 1-dose n=196	★ 13 yr f/u							☆ 15 yr f/u									
Thailand impact study Thailand	Effectiveness	HPV4	Girls in grade 8 given 1 or 2 doses; n=~8000 each arm| prevalence surveys of girls grades 10, 12; n=2,400 each grade x 2 provinces								★ Year 2							☆ Year 4		
HOPE South Africa	Effectiveness	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≥3260									★								☆

RCTs *Non-randomized RCTs* *Impact effectiveness studies*

★ *Interim results* ☆ *Final results*

Summary of single-dose HPV vaccine studies

- Continuing post-hoc analyses of two RCTs suggest that HPV vaccines may generate long-term protection after a single dose
- Vaccine registry studies that control for bias support the possibility of substantial single-dose protection in national immunization programs
- Individual studies answer specific scientific/programmatic questions, e.g. carefully exclude the impact of herd immunity, HIV acquisition, and other factors that may limit an individual study's findings
- A series of efficacy, immunobridging and demonstration trials has been initiated that will provide increasingly robust data over the next 5+ years

BACK-UP SLIDES

Single-dose HPV catch-up vaccination efficacy: A blinded, randomized study of single-dose HPV vaccination among adolescent girls and young women in Kenya

KENya Single-dose HPV vaccine-Efficacy (KEN SHE) Study

Ruanne Barnabas, MBChB, MSc, DPhil & Nelly Mugo, MBChB, MMed, MPH

KEN SHE

KENYA MEDICAL RESEARCH INSTITUTE KEMRI

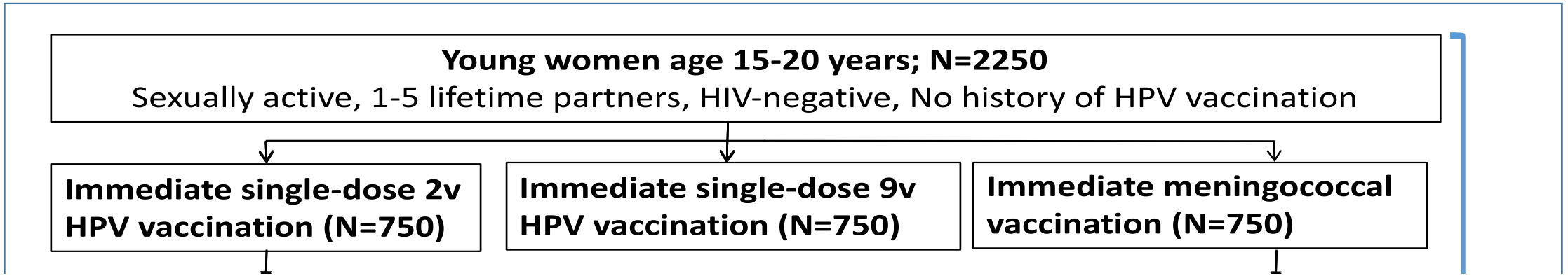
ClinicalTrials.gov: NCT03675256

UNIVERSITY OF WASHINGTON
INTERNATIONAL CLINICAL RESEARCH CENTER

BILL & MELINDA GATES *foundation*

Study Design

Prospective, blinded randomized study that will test the efficacy of immediate single-dose bivalent and nonavalent HPV vaccination as a catch-up immunization strategy compared to immediate meningococcal vaccine and delayed HPV vaccination



Arm 1) immediate nonavalent HPV vaccination and delayed meningococcal vaccination,

Arm 2) immediate bivalent HPV vaccination and delayed meningococcal vaccination,

Arm 3) immediate meningococcal vaccination and delayed HPV vaccination.

KEN SHE

A scientific evaluation of one or two doses of the HPV vaccines

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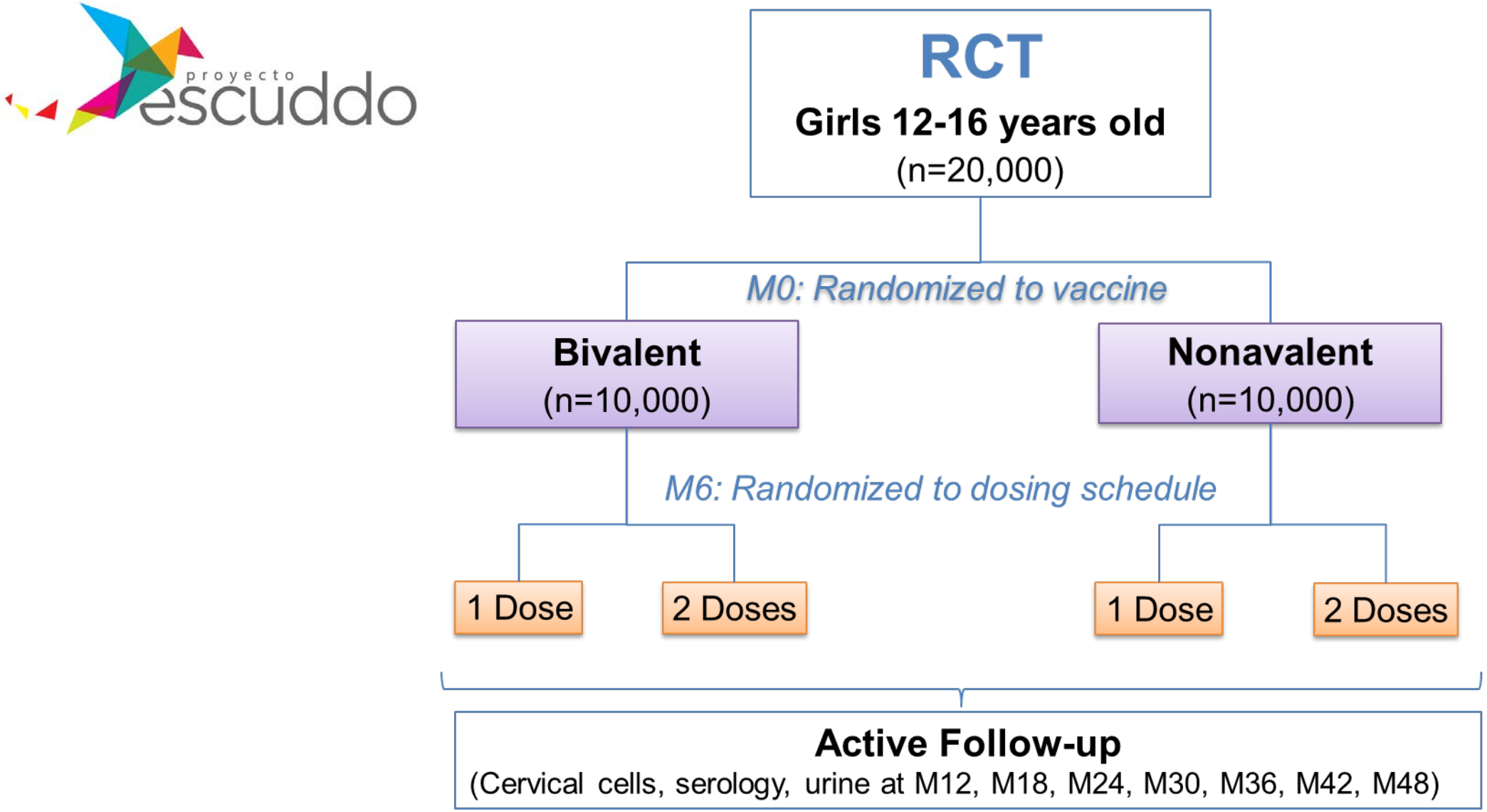
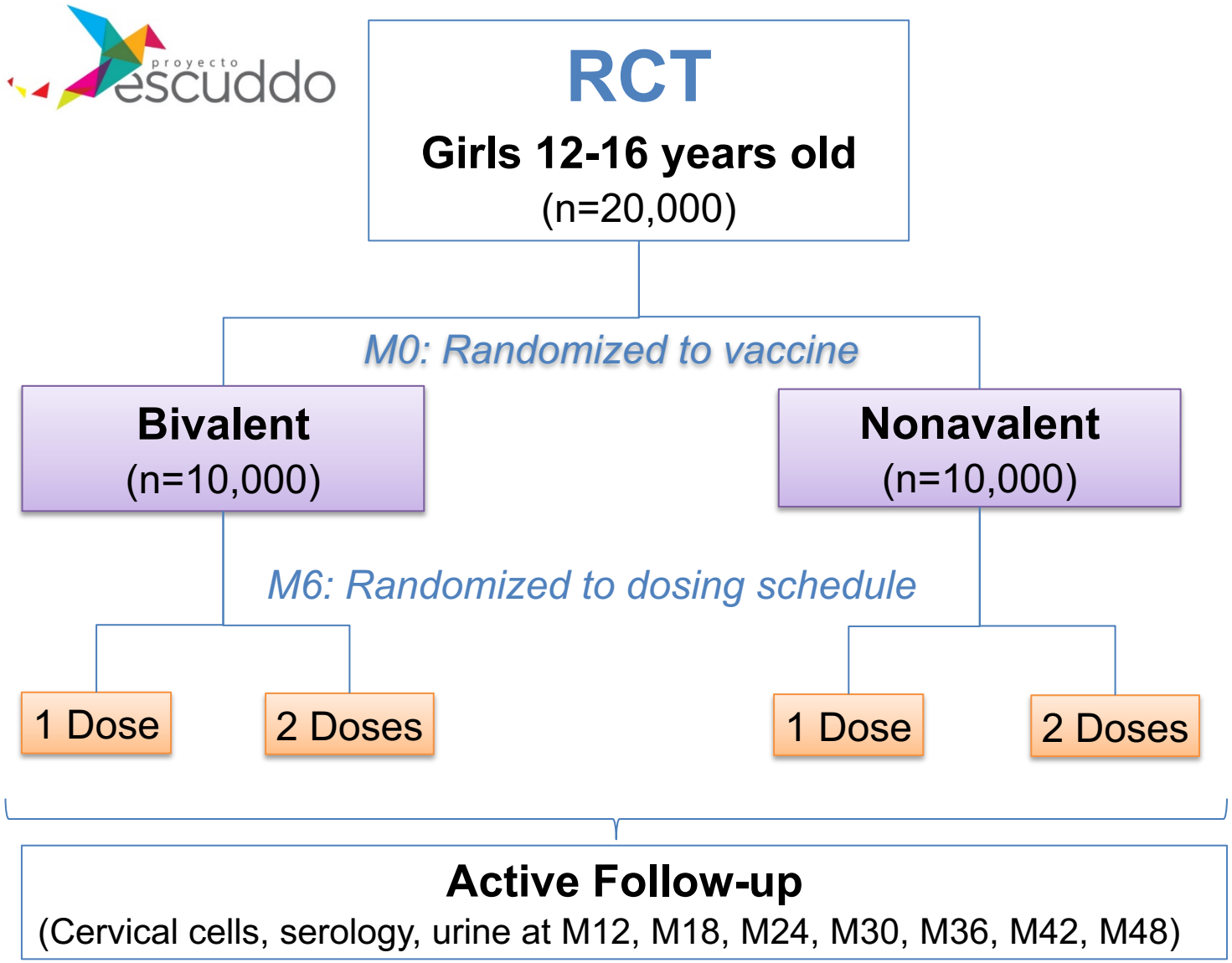
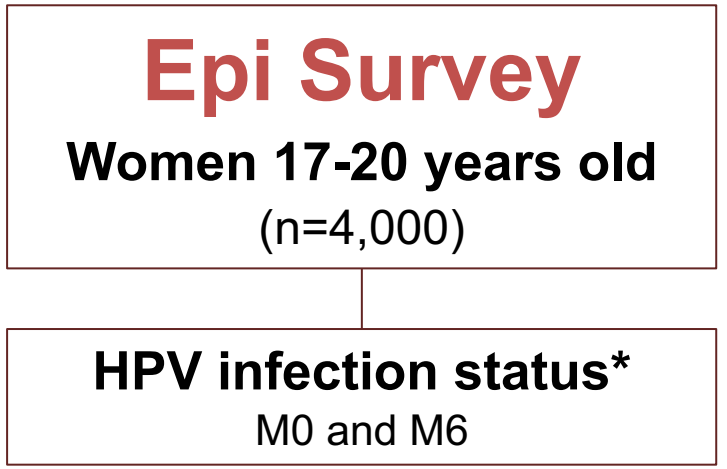
Clinicaltrials.gov identifier: NCT03180034

AIM: Evaluate non-inferiority of one versus two doses in the prevention of new cervical HPV16/18 infections that persist 6+ months



AIM: Evaluate one dose of HPV vaccination compared to zero doses





**Receive HPV vaccine after assessment of HPV infection status*

A Dose Reduction Immunobridging and Safety Study of Two HPV vaccines in Tanzanian Girls (DoRIS Trial)

Deborah Watson-Jones, Kathy Baisley , Richard Hayes – LSHTM
John Changalucha – National Institute for Medical Research, Mwanza
Charles Lacey – University of York, UK
Silvia de SanJosé – Catalan Institute of Oncology, Spain
Joakim Diller – Karolinska Institute, Sweden
Wilm Quentin – Technical University, Berlin, Germany
Kirstin Mitchell - University of Glasgow, UK

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

DoRIS

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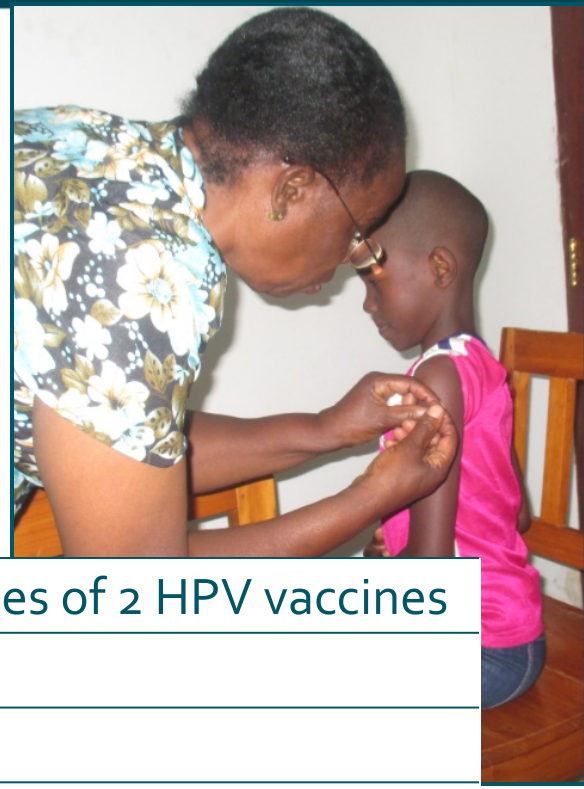
Co-Primary Objectives:

1) Demonstrate non-inferiority of HPV 16/18-specific seropositivity for 1d vs 2 / 3d at M24
2) Demonstrate non-inferiority of HPV 16/18 antibody GMT for 1d in DoRIS vs 1d in historical cohorts (10-25y) at M24



Description	A study to compare the immunogenicity and safety of 1, 2 & 3 doses of 2 HPV vaccines
Trial Centre	Mwanza Intervention Trials Unit (MITU)
Trial Design	Randomised unblinded phase IIb/III trial
Population	Females, aged 9-14 years
Sample size	930
Duration	Follow up to M36

ARM A	ARM B	ARM C	ARM D	ARM E	ARM F
Cervarix®			Gardasil-9®		
3 doses	2 doses	1 dose	3 doses	2 doses	1 dose
N = 155	N = 155	N = 155	N = 155	N = 155	N = 155

National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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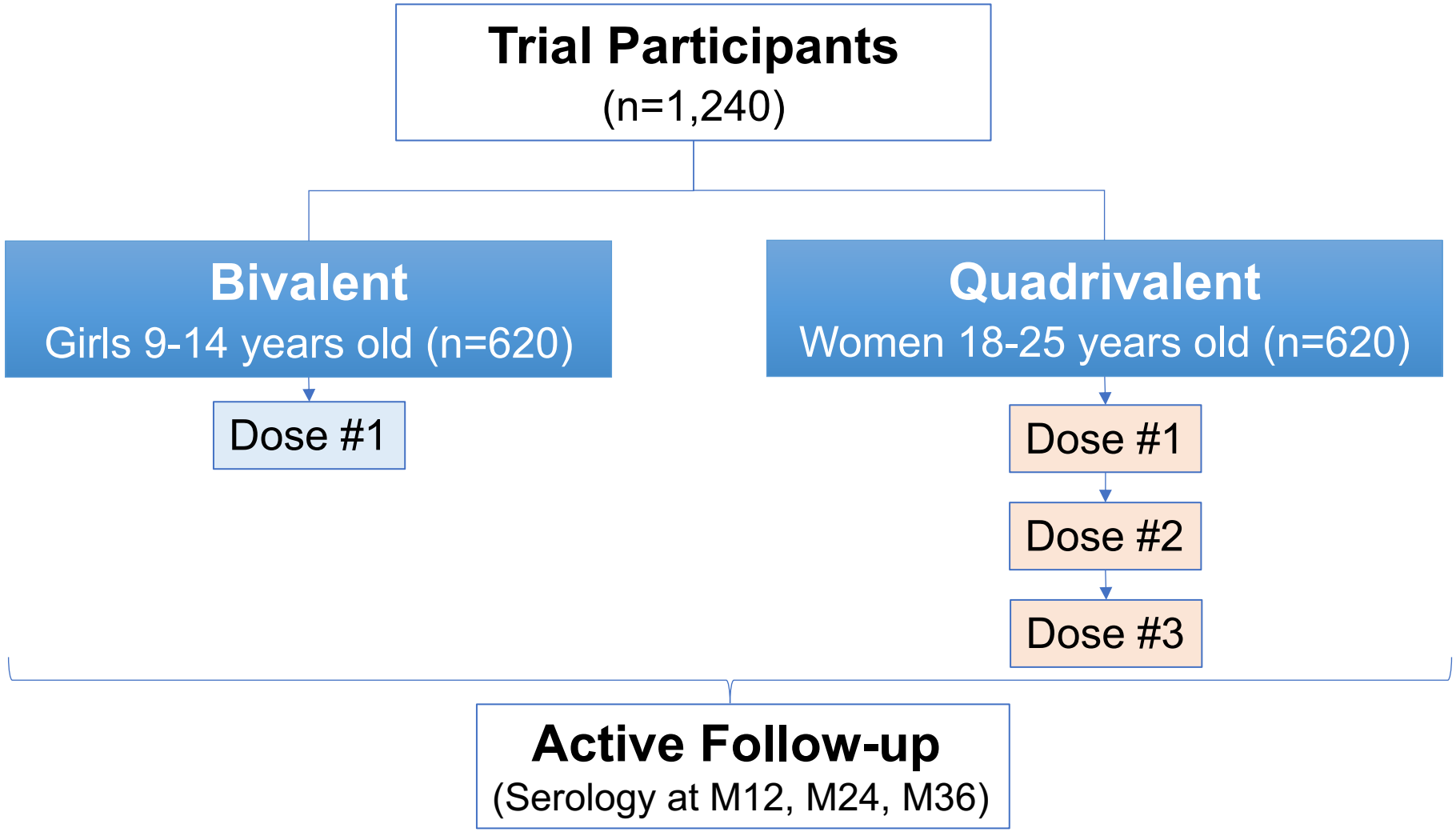
Non-inferiority trial comparing immunogenicity from 1-dose of bivalent HPV vaccine in girls to 3-doses of quadrivalent vaccine in women: The PRIMAVERA-ESCUDDO Trial

primavera

Puente de Respuesta Inmunológica para Mejorar el Acceso a Vacunas y ERradicar el cAncer.

Clinicaltrials.gov identifier: NCT03728881

AIM: Evaluate non-inferiority of HPV16/18 antibodies in girls who received 1 dose of Cervarix compared to women who received 3 doses of Gardasil



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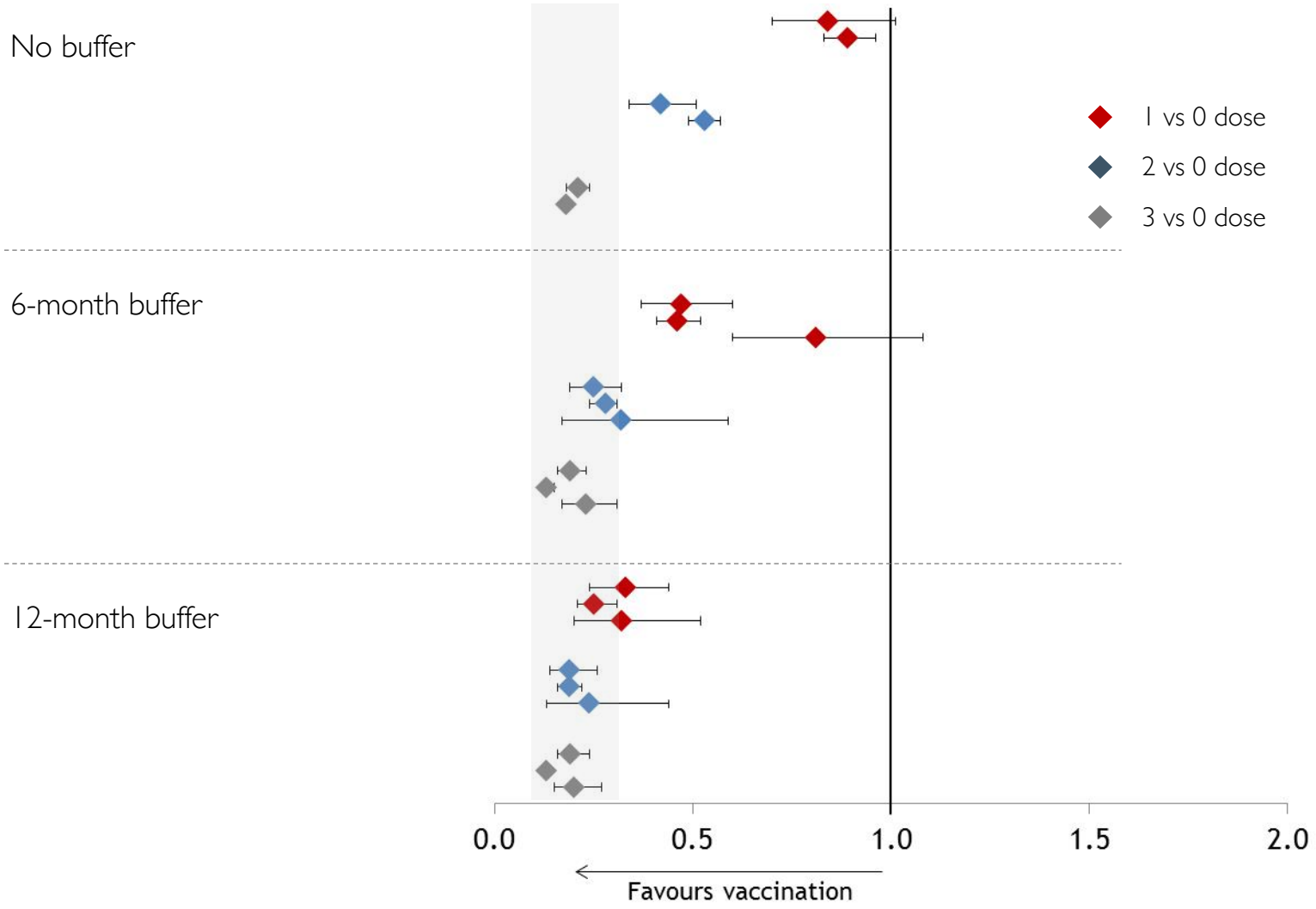
Effectiveness against AGW by number of doses

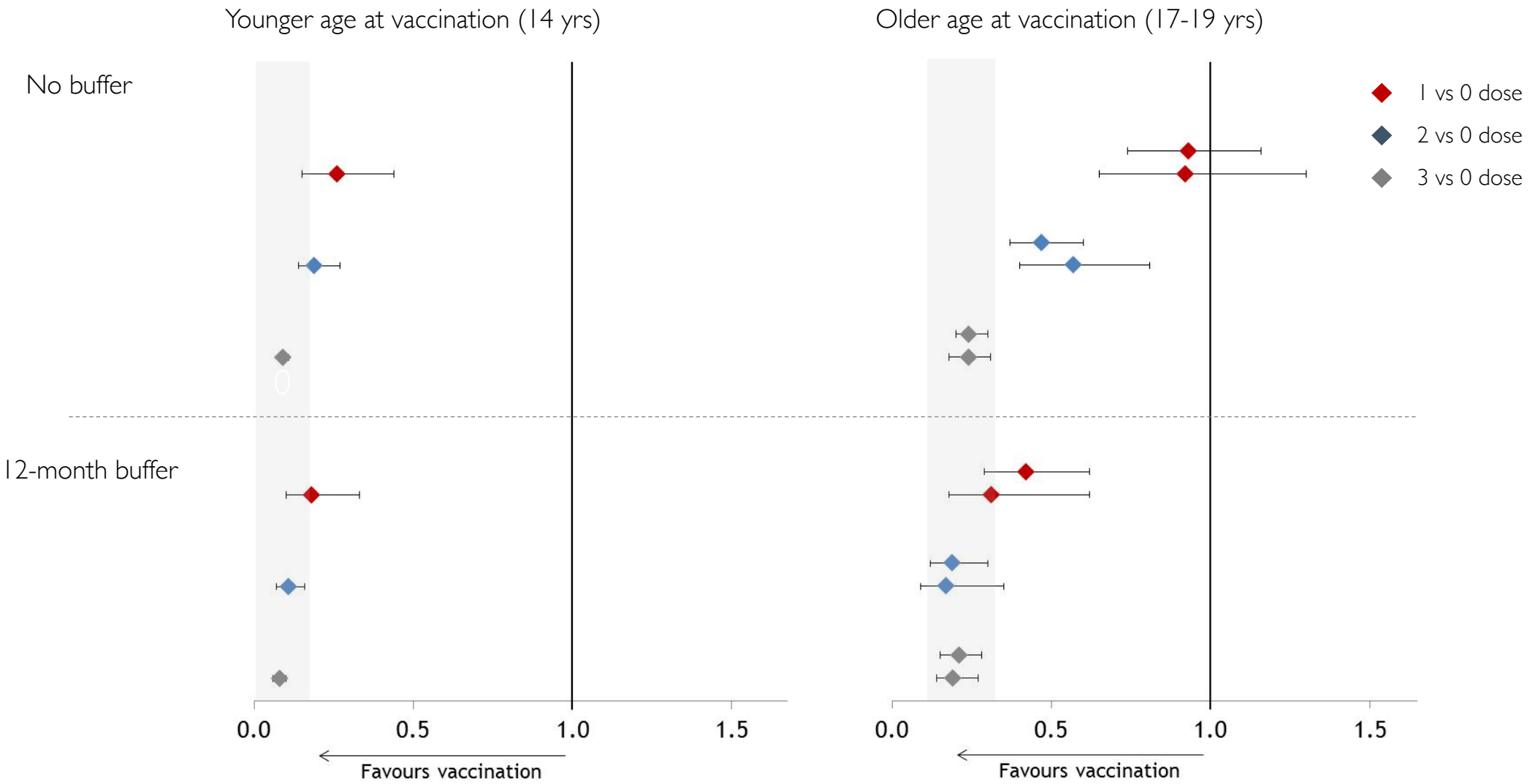
Impact of buffer period



References: Herweijer JAMA 2014, Blomberg CID 2015 (personal communication), Hariri Am J Epidemiol 2017

Effectiveness against AGW by number of doses

Impact of buffer period and age at vaccination

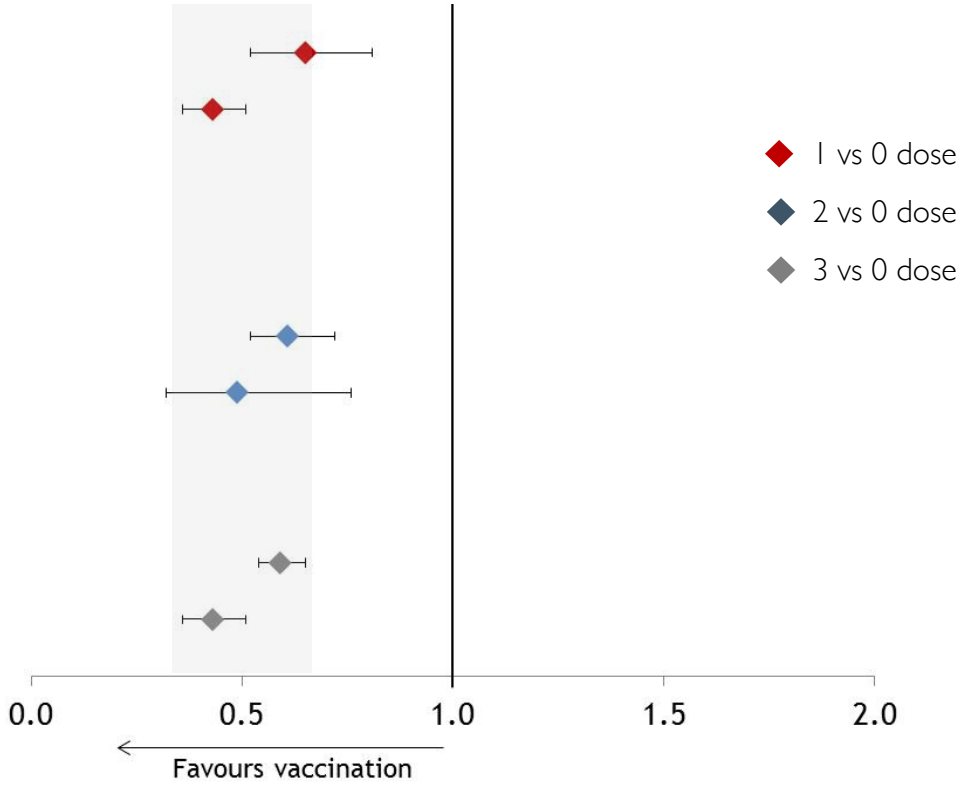


References: Herweijer JAMA 2014, Blomberg CID 2015 (personal communication)

Effectiveness against CIN2+ by number of doses

Findings from recent studies

- Restricted to girls vaccinated **≤15 yrs old (Australia), ≤16 yrs old (Denmark)**
- 1-2 dose effectiveness less likely to be affected by prevalent infections given young age at vaccination and the long delay between vaccination and outcome assessment



References: Brotherton IPV 2018 & personal communication, Verdoodt CID 2019

Brotherton: RR adjusted for socio-economic status, remoteness, attained age ; Verdoodt: RR adjusted for maternal education and attained age