# Disclosure Statement

**Dr. Margaret Stanley** has acted as a consultant and advisor for Merck Sharp & Dohme, GlaxoSmithKline, and Sanofi Pasteur Merck Sharp & Dohme, Innovio, Vaccitech.

# HPV Vaccination:
# Prospect of moving to a one and only dose schedule

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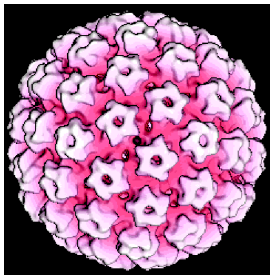


# Prophylactic HPV VLP Vaccine Profiles

| | Cervarix<br>Bivalent vaccine | Gardasil<br>Quadrivalent vaccine | Gardasil9<br>Nonavalent vaccine |
|---|---|---|---|
| **Manufacturer** | Glaxo Smith Kline | Merck | Merck |
| **Volume** | Per dose 0.5ml | Per dose 0.5ml | Per dose 0.5ml |
| **Adjuvant** | ASO4:<br>$Al(OH)_3$ 500mg<br>MPL® 50mg | Amorphous<br>Aluminium 225mg<br>Hydroxyphosphate<br>sulphate® | Amorphous<br>Aluminium 500mg<br>Hydroxyphosphate<br>sulphate® |
| **Antigens** | L1 HPV16 20µg<br>L1 HPV18 20µg | L1 HPV6 20µg<br>L1 HPV11 40µg<br>L1 HPV16 40µg<br>L1 HPV18 20µg | L1 HPV6 30µg<br>L1 HPV11 40µg<br>L1 HPV16 60µg<br>L1 HPV18 40µg<br>L1 HPV31 20µg<br>L1 HPV33 20µg<br>L1 HPV45 20µg<br>L1 HPV52 20µg<br>L1 HPV58 20µg |
| **Expression system** | Hi-5 Baculovirus | Yeast: Saccharomyces cereviseae | Yeast Saccharomyces cereviseae |
| **Schedule**<br>**9-26yrs (initial)**<br>**>15 years (2014)**<br>**9-15 years** | Intra muscular<br>0, 1, 6 months<br>0, 1, 6 months<br>0,6 to 12 months | Intra muscular<br>0,2,6 months<br>0,2,6 months<br>0,6 to 12 months | Intra muscular<br>0,2,6 months<br>0,2,6 months<br>0,,6 to 12 months |
| **FDA licensed** | **2009** | **2006** | **2014** |
| **EMA licensed** | **2007** | **2007** | **2015** |

## Immunobridging trials 9-15 year olds vs 16-23 year olds

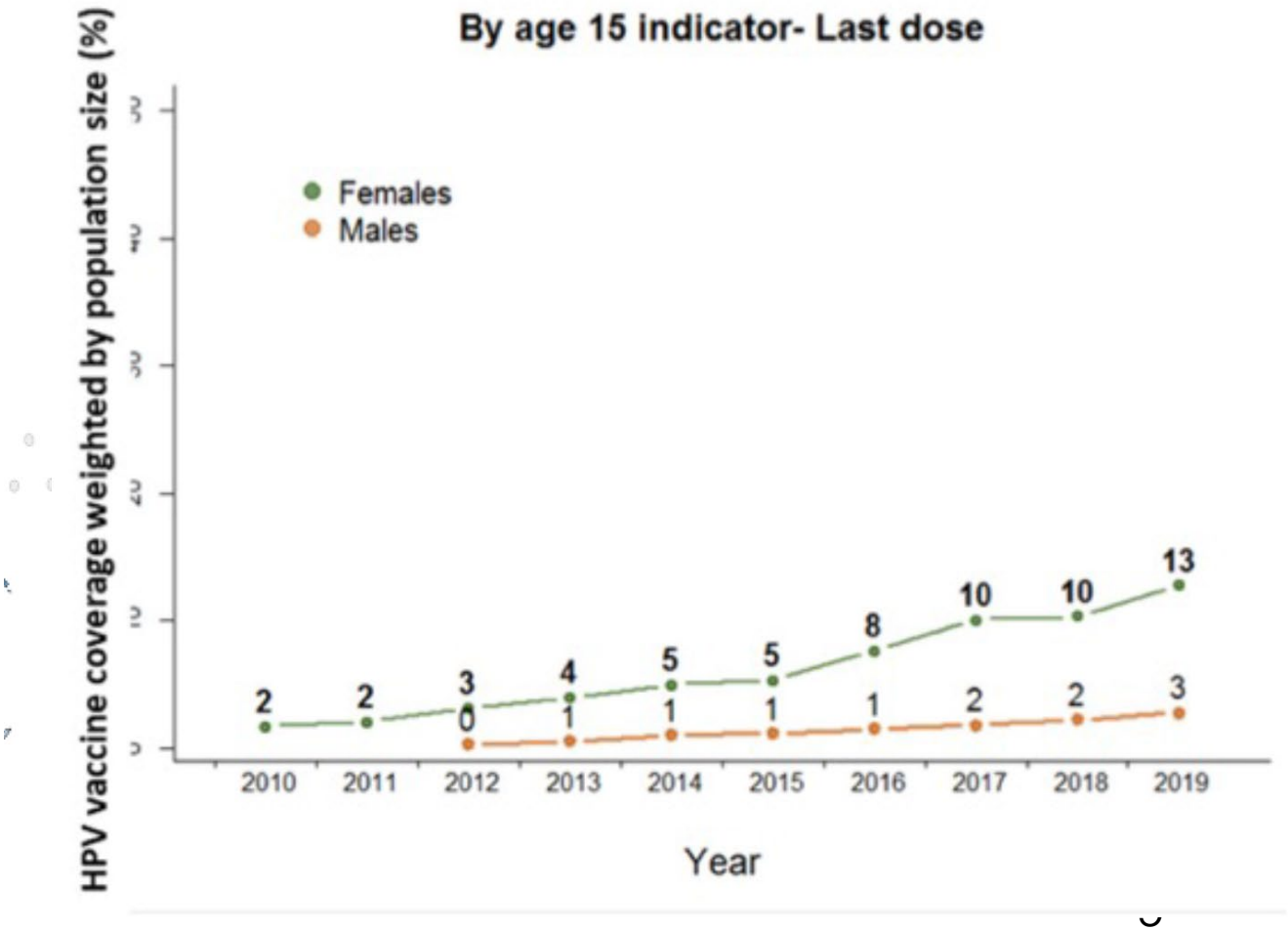
The antibody quantity and quality in 9-13 year olds after 2 vaccine doses *at 0-6months is as good as that generated after 3 doses 0,1/2,6 months in 16-23 year olds in whom efficacy has been shown*

## WHO SAGE April 2014 meeting

Upon review of the evidence, SAGE recommended

- a 2-dose schedule for girls, if vaccination is initiated prior to 15 years of age.
- The recommended minimal interval between the 2 doses is 6 months.
- A 3-dose schedule remains necessary if immunization is initiated after the girls' 15th birthday.
- This interval may be extended to 12 months if this facilitates administration
- A 3-dose schedule (i.e. at 0, 1-2, and 6 months) remains recommended for immunocompromised individuals, including those known to be HIV-infected."

# Global HPV vaccine coverage (2019)




Bruni et al 2019 Preventive Medicine:144

# Hurdles for HPV vaccine programmes

**Cost**

- vaccine cost
- implementation and administrative costs

**Logistics**

- difficulty of delivering 2 doses over 6 months
- no infrastructure for adolescent immunization

**Inflexibility of a 2 dose schedule for the adolescent**

# Alternative dosage schedules

## What is sufficient for protection?

efficacy and duration of 1 dose of 2v,4v or 9v vaccines
- nation wide cohort studies
- post hoc analysis of RCTs
- observational studies of effectiveness by dose number
- RCT

Immunogenicity and duration of protection
- post hoc analysis of RCTs

# Rate of histologically confirmed CIN3 and vaccine dose National screening cohort 2007-2014 women born 1992 or earlier Australia

| Abnormality | Vaccination number of doses | Number of women | Number of cervical abnormalities | Rate/1000 women years | Hazard Ratio |
|---|---|---|---|---|---|
| CIN/AIS | 0 | 48845 | 645 | 7.6 | 1.0 |
| CIN/AIS | 1 | 8618 | 89 | 4.9 | 0.65 (0.52-0.81) |
| CIN/AIS | 2 | 18190 | 174 | 4.6 | 0.61 (0.52-0.72) |
| CIN/AIS 2007-2014 | 3 | 174995 | 1496 | 4.5 | 0.59 (0.54-0.65) |

Brotherton etal 2019 PVR 8

# Trials with data on 1 dose of HPV vaccine

| Trial Country | Outcome | Vaccine | Cohort Age (yrs) | Description |
|---|---|---|---|---|
| * CVT Costa Rica | Efficacy immunogenicity | 2v | 18-25 Female | Post hoc analysis |
| IARC India | Efficacy immunogenicity | 4v | 10-18 Female | Observational Cohort from an original RCT |
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| Thailand Impact | Effectiveness - Impact | 2v | Grade 8 females | Girls in one province received 1 dose; in another 2 doses. Baseline and post-vaccination prevalence surveys |

Vaccine efficacy in women against persistent infection with HPV 16/18 after 3,2 or 1 dose of 2v vaccine -36 months follow up

*Kreimer et al JNCI 103 2011*

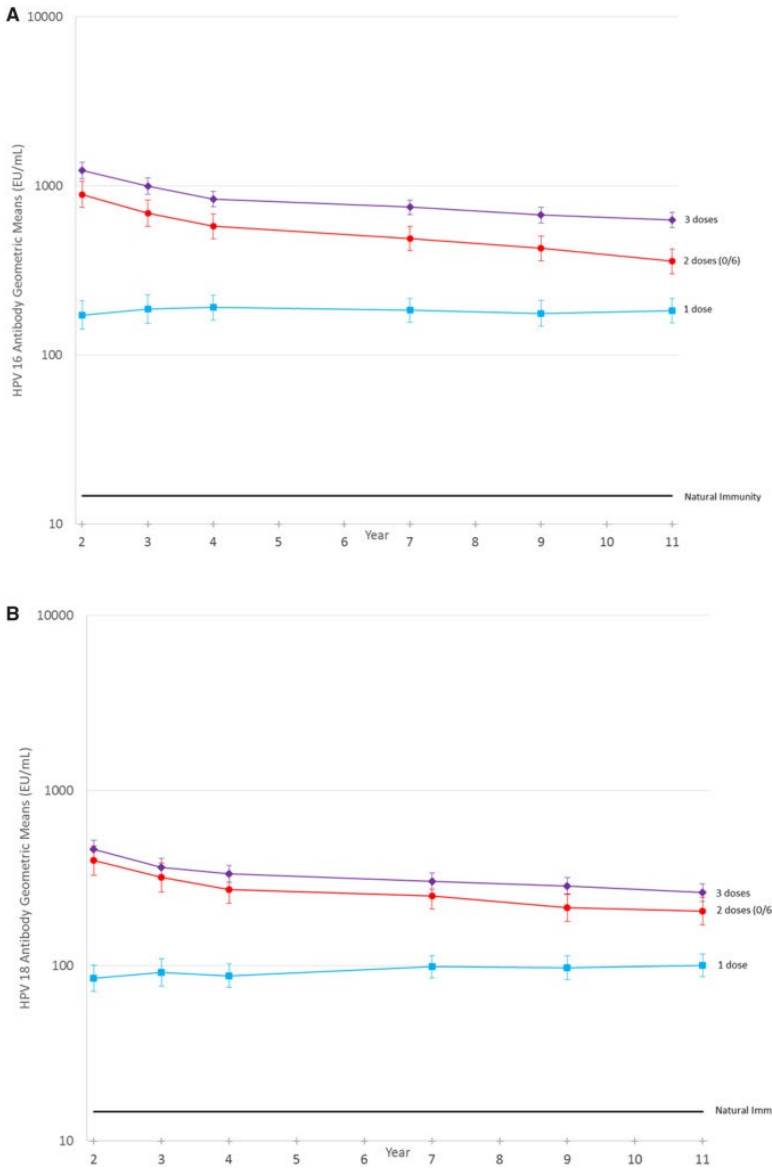
| Doses | Trial arm | Events | % PI 95% CI | Vaccine efficacy 95% CI | |
|---|---|---|---|---|---|
| 3 dose 0,1,6 | Unvacc n=3010<br>Vacc n=2957 | 133<br>25 | 4.4 *(3.7-5.2)*<br>0.85 *(0.56-1.2)* | **80.9** *(71.1-87.7)* | |
| 2 dose 0,1 | Unvacc N=380<br>Vacc N=422 | 17<br>3 | 4.5 *(2.7-6.9)*<br>0.7 *(0.18-1.9)* | **84.1** *(54.2-96.3)* | |
| 1 dose | Unvacc n=188<br>Vacc N=196 | 10<br>0 | 5.3 *(2.7-9.3)*<br>0.0 *(0.0-1.5)* | **100** *(66.5-100)* | |

Post hoc analysis of RCT: women (18-25 years) randomized to receive 3 doses of 2v vaccine or control but not all completed full series but available for follow up

Vaccine efficacy in women against persistent infection with HPV 16/18 after 3,2 or 1 doses of 2vHPV vaccine – CVT trial 11 years follow up

| Doses | Number of subjects | % Prevalent HPV 16/18 (95% CI) | % Vaccine Efficacy (95% CI) |
|---|---|---|---|
| 3 | 1365 | 2.0 (1.3-2.8) | **80.0** (70.7-87.0) |
| 2 | 62 | 1.6 (0.1-7.7) | **83.8** (19.5-99.2) |
| 1 | 112 | 1.8 (0.3-5.8) | **82.1** (40.2-97.3) |
| Control | 1783 | 10.0 (8.7-11.4) | **Referent** |

*Kreimer et al JNCI 2020 112(10):1038–1046*




**One dose of bivalent HPV vaccination induces stable HPV16 serum antibodies for 11 years: Costa Rica vaccine trial**

Kreimer, et al. J Natl Cancer Inst 2020

# Trials with data on 1 dose of HPV vaccine

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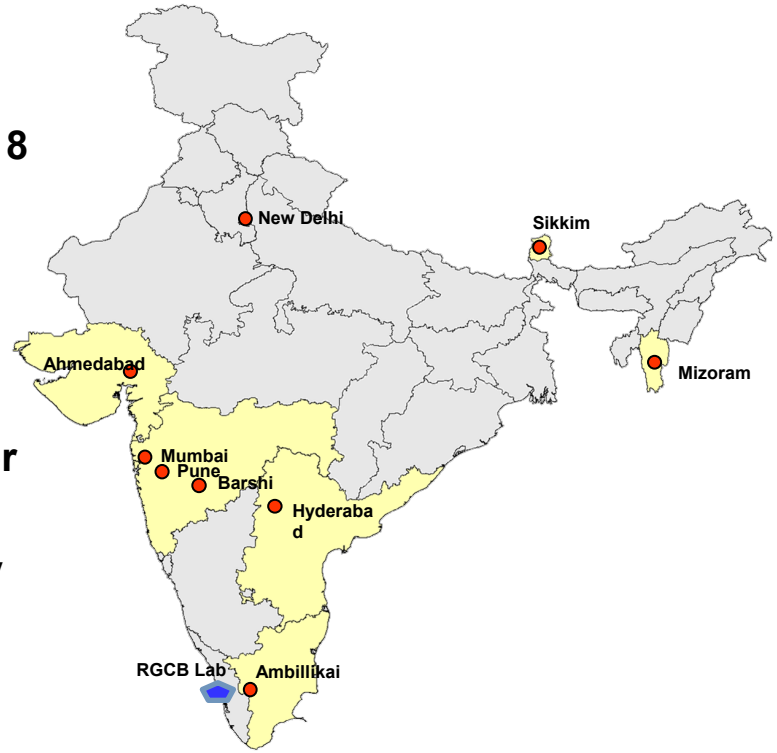
# Planned 2- vs 3- dose 4-HPV Vaccine multi-centric RCT

- Study was planned as an RCT to compare 2 vs. 3 doses of 4-HPV
- Eligibility: Unmarried, unvaccinated girls between 10 & 18 yrs of age
- Plan was to recruit 10,000 girls in each arm
- Total 9 sites participated
- Recruitment initiated in September 2009
- Government of India stopped HPV vaccination in all trials in April 2010
- Till then 17,729 (88.6% of the target) girls were already vaccinated




HPV 3-dose
N=4348 (24.5%)

HPV 2-dose (0,6)
N=4979 (28.1%)

HPV 2-dose D (0,2)
N=3452 (19.5%)

HPV 1-dose
N=4950 (27.9%)

International Agency for Research on Cancer

World Health Organization

Courtesy Dr Partha Basu

# India IARC trial: protection after 1,2 or 3 doses of 4v vaccine through 10 years

| Dose | Number of subjects | %Persistent 16/18 HPV infection (95% CI) | %VE against persistent infection (95% CI) |
|---|---|---|---|
| 3 (0,2,6) | 1649 | 0.1 (0.0-0.4) | 91.2% (75.3-98.7) |
| 2 (0,6) | 1645 | 0.1 (0.0-0.4) | 94.5% (82.4-99.8) |
| 1 | 2454 | 0.0 (0.0-0.3) | 94.2% (83.7-99.1) |
| Control | 1268 | 2.7 (1.9-3.7) | Referent |

Subjects

- Women vaccinated age 10-18 years randomized to receive 2 or 3 doses 4v vaccine
- Control unvaccinated age matched to married vaccinated subjects recruited as controls

Persistent infection

- defined as same HPV type detected in consecutive samples at least 10 months apart

Vaccine efficacy

- Adjusted for background HPV infection frequency
- time between marriage and first specimen collection
- Number of cervical specimens per subject

Basu et al
Lancet Oncology
2021;22:1518-29

# Trials with data on 1 dose of HPV vaccine

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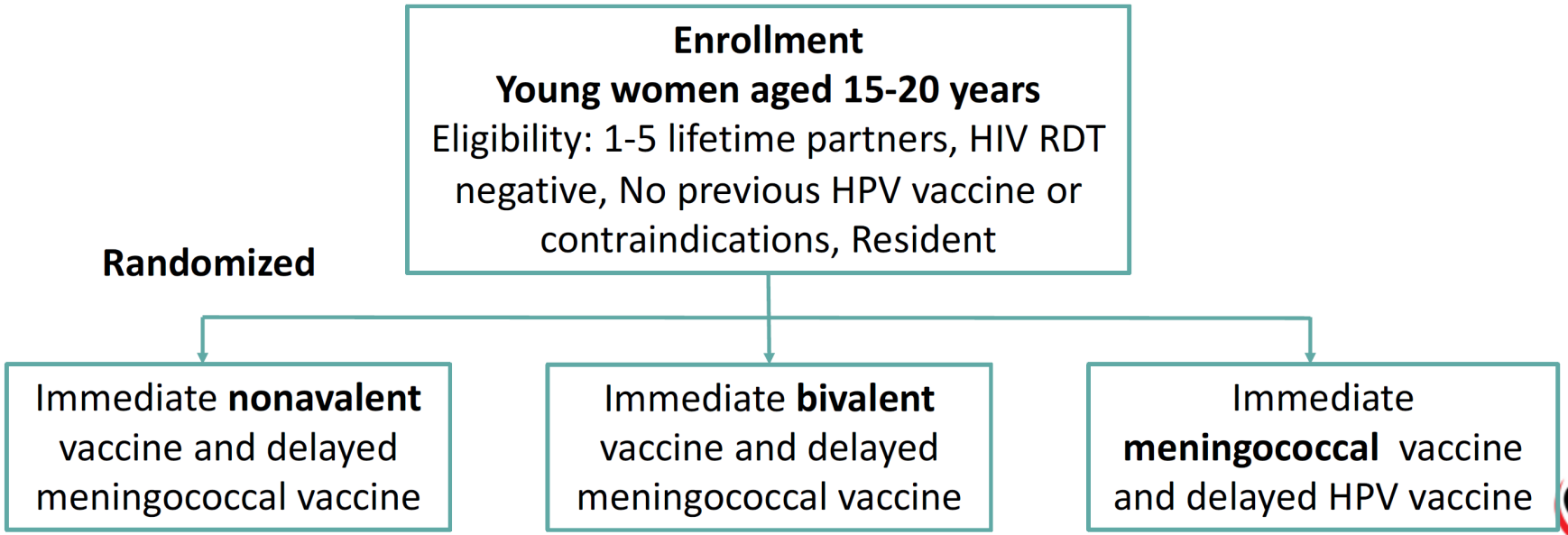
*

# KEN SHE Trial
# Efficacy of single dose HPV vaccination among young African women

## Study Design

- Individual randomized, double-blind, control, three group trial
- Multi-center: Three KEMRI Center locations in Kenya




KEN SHE

Courtesy Dr Ruanne Barnabas, Dr Nelly Mugo and the KenShe investigators

Barnabas, et al. DOI 10.21203/rs.3.rs-1090565/v1; accepted for publication at NEJM Evidence

# Efficacy of single dose HPV vaccination among young African women

Barnabas, et al. DOI 10.21203/rs.3.rs-1090565/v1; accepted for publication at NEJM Evidence

| Vaccine | Number subjects | %Persistent HPV 16/18 infection | Incidence/ 100PY | %Vaccine efficacy (95% CI) |
|---|---|---|---|---|
| 9vHPV | 496 | 1 | 0.17 | 97.5 (81.7-99.7) |
| 2vHPV | 489 | 1 | 0.17 | 97.5 (81.6-99.7) |
| MCV | 473 | 36 | 6.83 | Referent |

Randomised Trial – 1 dose 2vHPV or 9vHPV or meningococcal vaccine

- 2250 Kenyan women 15-20yrs:1-5 lifetime partners; HIV-ve
- 1458 evaluated at month 18 for efficacy in mITT HPV16/18 cohort

mITT: modified intention to treat

- HPV 16/18-ve (external genital and cervical swabs) at enrollment and month 3
- HPV antibody negative at enrollment



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## HPV 16/18/31/33/45/52/58 mITT eficacy

| Vaccine | Number of subjects | Cases persistent HPV | Incidence/ 100 PY | % VE (95% CI) |
|---|---|---|---|---|
| 9vHPV | 325 | 4 | 1.03 | 88.9 (68.5-96.1) |
| MCV | 490 | 29 | 9.42 | |

Barnabas, et al. DOI 10.21203/rs.3.rs-1090565/v1; accepted for publication

- Adolescent girls and young women were effectively protected from HPV infection over the first 18 months post vaccination

- VE was >97% - in keeping with licensure trials for three doses

- 9v hr vaccine-type HPV incidence is high (~9/100 woman-years) – 1/3 higher than previous vaccine trials

- Rigorous design, high fidelity to the protocol, high retention, clear ascertainment of outcomes

# Trials with data on 1 dose of HPV vaccine

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# DoRIS

**Do**se **R**eduction **I**mmunobridging & **S**afety Study of 2vHPV and 9vHPV in Tanzanian girls

- 930 girls aged 9–14 years randomized to 1, 2 or 3 doses of 2vHPV or 9vHPV
- Objectives:
  - Demonstrate non-inferiority of HPV 16/18 antibody response after 1 dose compared with 2 or 3 doses of same vaccine at month 24
  - Demonstrate non-inferiority of HPV 16/18 GMCs comparing 1 dose in DoRIS with historical efficacy cohorts that received 1 dose (CVT, India IARC, KEN SHE).

Interim findings

- Seropositivity >97.5% for all doses of both vaccines
- Antibody levels by dose, vaccine, and kinetics over time similar to those in other HPV vaccine studies
- Avidity no difference between dose groups or vaccines
- Immunobridging showed that 1-dose responses were non-inferior in DoRIS compared with those in studies where 1-dose efficacy observed

# Alternative dosage schedules

## What is sufficient for protection

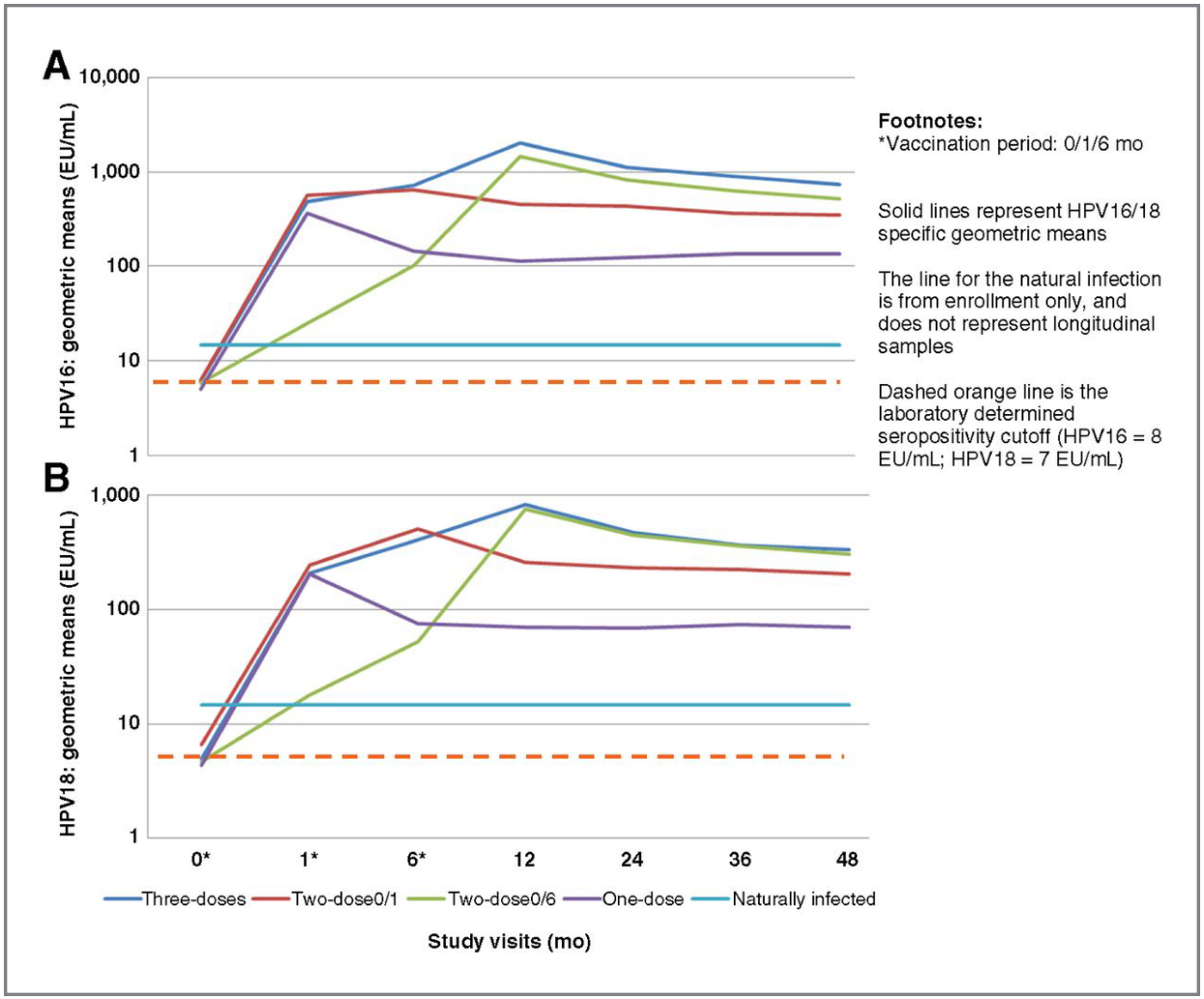
efficacy and duration of protection with 1 dose of bi- or quadri-valent vaccine

- post hoc analysis of RCTs
- nation wide cohort studies
- observational studies of effectiveness by dose number
- KEN-SHE RCT

Immunogenicity and duration of protection

- post hoc analysis of RCTs

# A and B, HPV16 (top) and HPV18 (bottom) specific antibody geometric means: by number of vaccine doses and study visit.

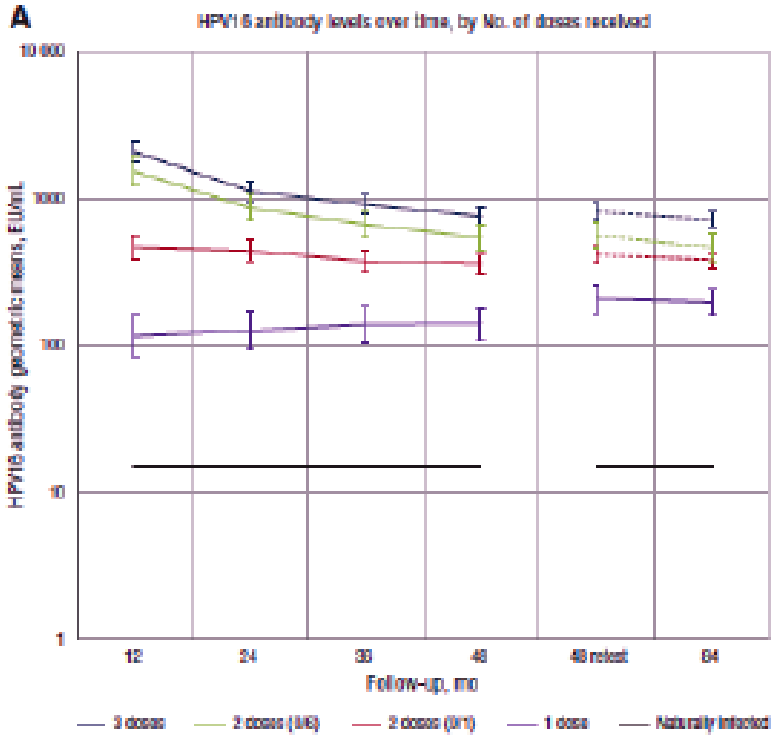



Safaeian M et al. Cancer Prev Res 2013;6:1242-1250



Cancer Prevention Research

# Costa Rica Vaccine Trial: 7 year immunogenicity data

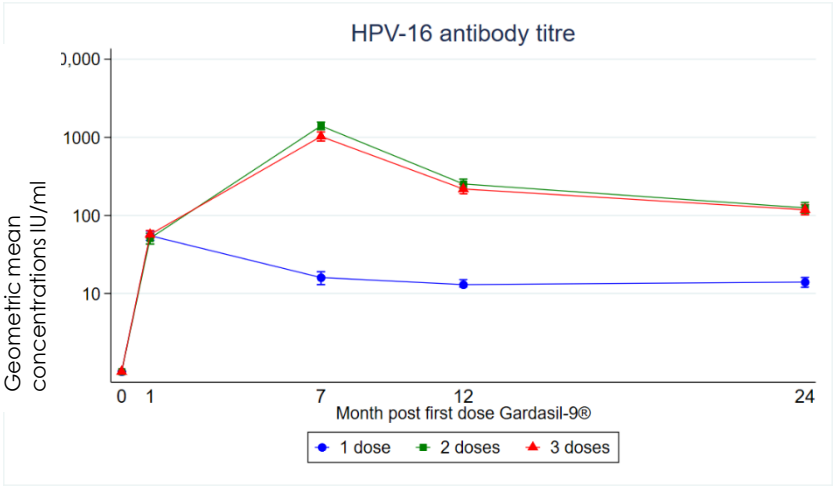



- HPV antibody level by ELISA
- Sample size n = 104, 156, 61 and 165 from 1d, 2d (0,6), 2d (0,1) and 3d, respectively
- 100% of all doses groups seropositive,

| Serum antibody avidity at 7 years post-vax (HPV16) | | |
|---|---|---|
| 3 doses | 2.5 | (2.4-2.6) |
| 2 doses (0/6m) | 2.3 | (2.1-2.6) |
| 2 doses (0/1m) | 2.3 | (2.1-2.4) |
| 1 dose | 2.0 | (1.8-2.4) |

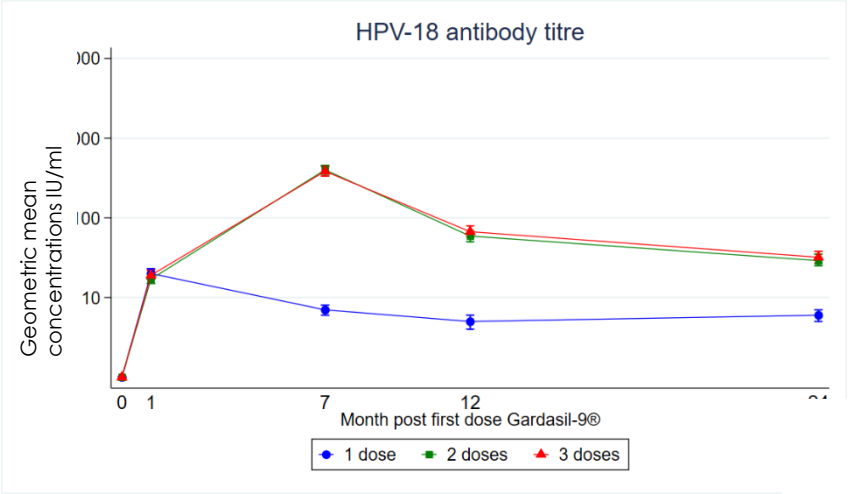
Safaiean etal JNCI Feb 2018

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




- Similar to observations in other HPV vaccine studies

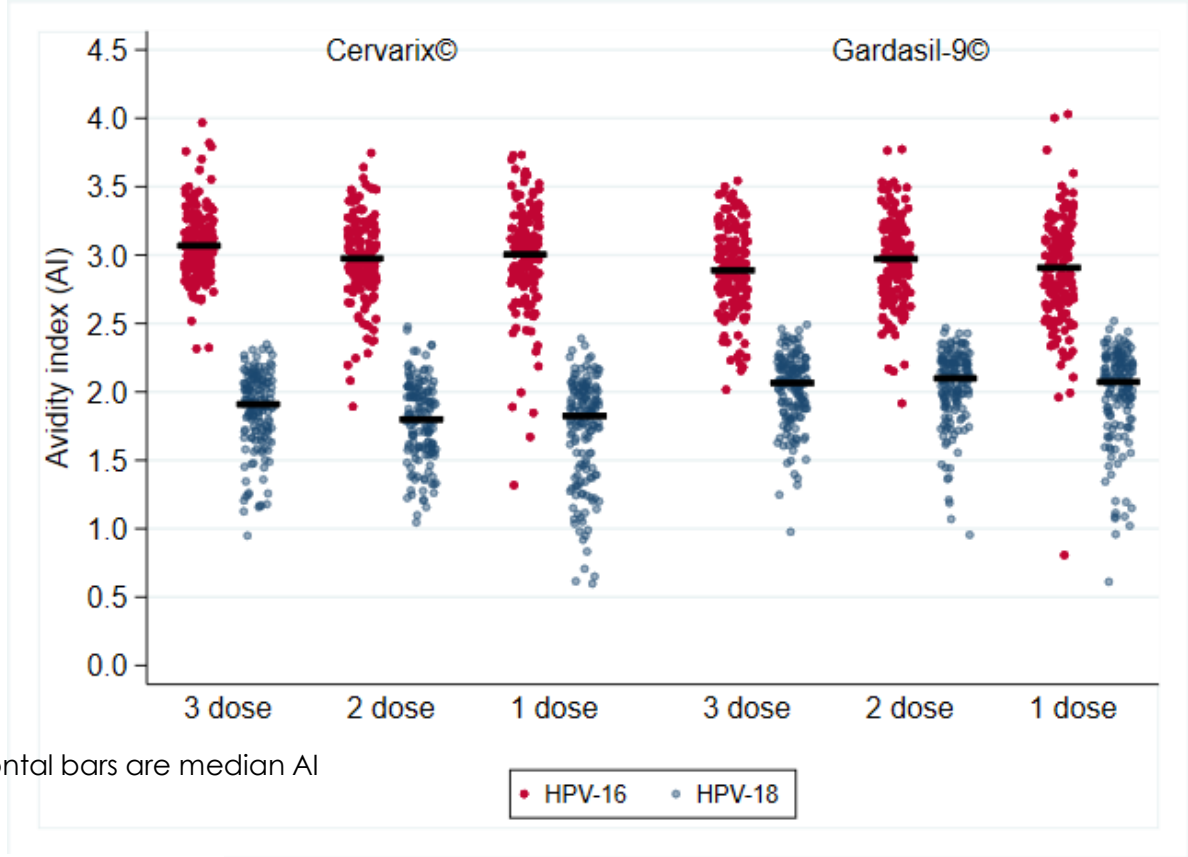
- In 2D and 3D arms, levels decline after peak at M7 (last dose at M6)
- 2D and 3D levels similar at M24
- In 1D arm, levels relatively constant from M12 (plateau)




Courtesy Dr Deborah Watson Jones, Dr Kathy Baisley and the DoRIS investigators

Watson-Jones, et al. http://dx.doi.org/10.2139/ssrn.4055429

# Distribution of HPV 16/18 avidity index at M24




Black horizontal bars are median AI

Antibody avidity is an 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

Courtesy Dr Deborah Watson Jones and the DoRIS investigators

# Antibody responses in natural HPV infection and after HPV VLP vaccination

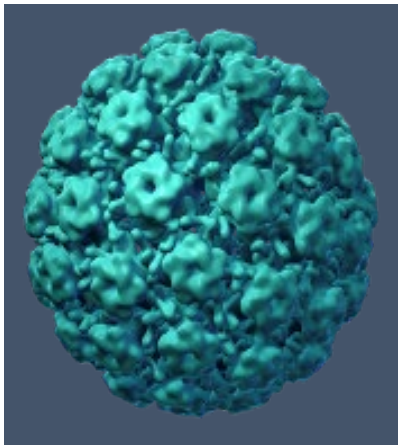
## Natural infection

- 70-80% women 20-30% men sero-convert
- Antibody response to HPV infection is typically slow and weak
- Neutralising antibody responses are to L1
- Cross neutralising antibodies not detected
- Antibody generated in natural infections in women is partially protective against subsequent incident infection but not in men
- Avidity index very variable

## HPV L1 VLP vaccination

- In clinical trials 100% women and men sero-convert
- Peak antibody titres are 2-3 logs greater than in natural infections
- Neutralising antibody persists for >16 years post immunisation
- Both type specific and cross neutralising antibodies detected
- No breakthrough disease caused by vaccine HPV types detected after 16 years follow up in RCTs
- Avidity index consistently high
- No antibody threshold level for the protection provided by HPV vaccines has been identified
- No immune correlate

# Why are HPV vaccine antibody responses so much stronger than natural infection – its all about the VLP



## Size 50-55nm

- optimal for entry into lymphatics,migration to the draining lymph node, take up by subcapsular sinus macrophages,transport to B cell follicles
- particles in this size range most readily taken up by dendritic cells

## Geometry of the VLP is critical

- A multivalent protein antigen 360 copies of L1 assembled as pentamers in a highly dense repetitive crystalline array
- neutralising epitopes displayed and spaced at the optimal distance of 8-10nm across the L1 pentamers crosslinks BCRs efficiently
- BCR crosslinking and clustering are attributes known to be critical for B cell activation, and the induction of high affinity, high avidity antibody

Induce innate and adaptive immune responses

Evoke robust memory responses –long lived plasma cells reactive memory B cells

| | |
|---|---|
| Serological memory | persistence of antibody |
| Reactive memory | anamnestic or recall response |

# Why are vaccine antibody responses so much stronger than natural infection

## Context: Route of Immunisation

**Natural infection - poor access of virus to lymph nodes**

- intra-epithelial infectious cycle -no viraemia
- infectious virus shed from mucosal surfaces[1]

**VLP vaccines delivered intramuscularly**

- rapid access of VLPs to blood vessels,
- local lymph nodes, spleen (access to all B cell subsets)
- avoids virus immune evasion strategies[1]

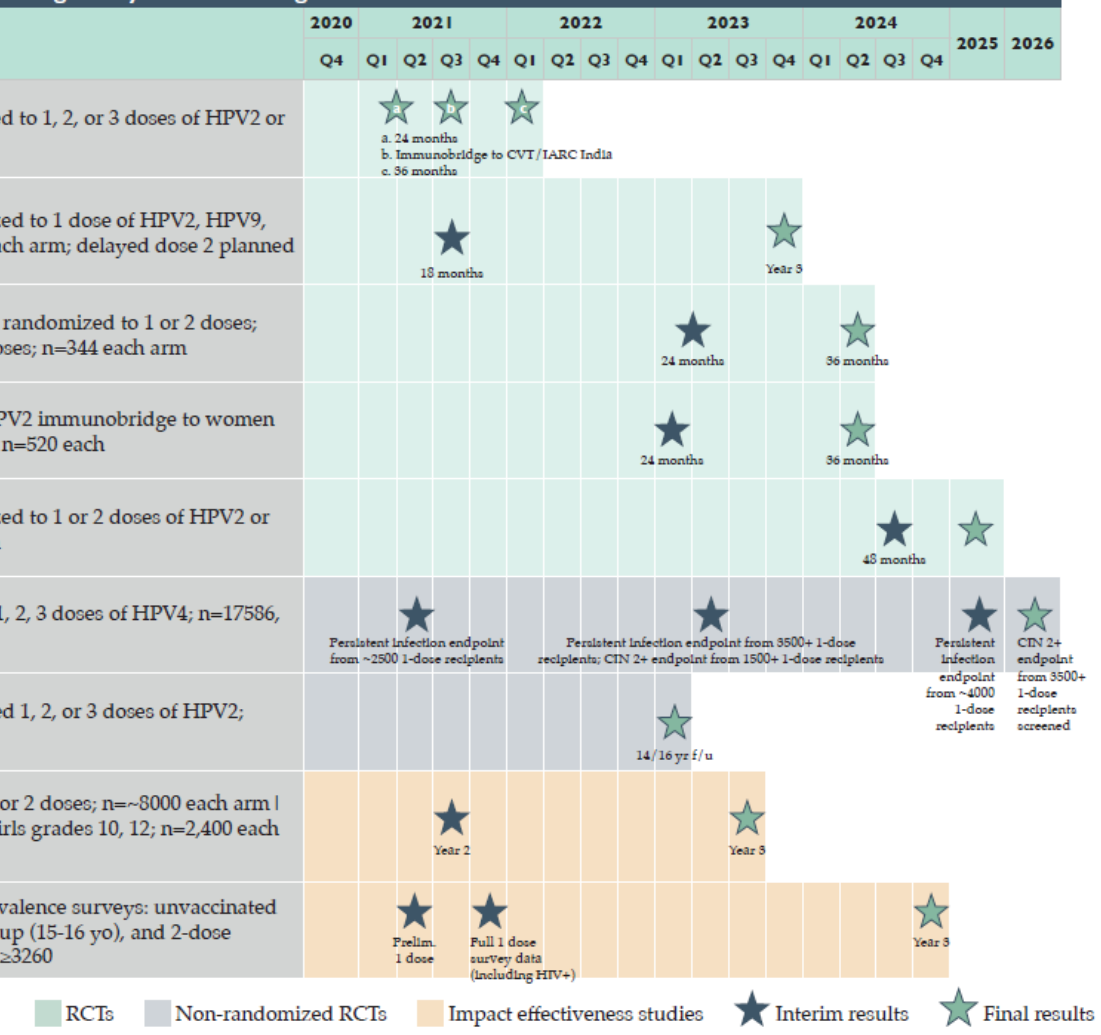
**Evokes robust memory responses**

| | |
|---|---|
| Serological memory | persistence of antibody |
| Reactive memory | anamnestic or recall response |

[1]*Stanley MA Vaccine 2006.*

## Ongoing and forthcoming efficacy, effectiveness, and immunogenicity studies of single-dose HPV vaccination

| | Study name (country) | Evidence type | Vaccine(s) | Brief description |
|---|---|---|---|---|
| * | **DoRIS** Tanzania | Immuno-genicity | HPV2 and HPV9 | Girls 9-14 yo randomized to 1, 2, or 3 doses of HPV2 or HPV 9; n=155 each arm |
| * | **KEN SHE** Kenya | Efficacy *(virological EP)* | HPV2 vs 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 | Immuno-genicity | 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 |
| | **Primavera** Costa Rica | Immuno-genicity | HPV2 and HPV4 | Girls 10-13 yo 1-dose HPV2 immunobridge to women 18-25 yo 3-doses HPV4; n=520 each |
| * | **ESCUDDO** Costa Rica | Efficacy *(virological EP)* | HPV2 and HPV9 | Girls 12-16 yo randomized to 1 or 2 doses of HPV2 or HPV9; n=5000 each arm |
| * | **India IARC** India | Efficacy *(virological and histological EP)* | HPV4 | Girls 10-18 yo received 1, 2, 3 doses of HPV4; n=17586, 1-dose n=4980 |
| * | **CVT** Costa Rica | Efficacy *till Y11* / Immuno-genicity | HPV2 vs control | Women 18-25 yo received 1, 2, or 3 doses of HPV2; n=3727, 1-dose n=196 |
| | **Thailand impact study** Thailand | Effectiveness *(virological EP)* | HPV2 | 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 |
| | **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≥3260 |



# Where next

**Formal evidence for 1 dose for boys**

**One dose efficacy in older age groups**

**Immunocompromised**
**HIV –the elephant in the room**

**Coverage is crucial 1 dose removes hurdles but achieving >80-90% vaccine coverage is needed for disease elimination**

# Thank you