Single-dose HPV Vaccine Studies

Aimée R. Kreimer
on behalf of Single-dose HPV Vaccine Evaluation Consortium*

WHO SAGE
October 9, 2019

*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)

- 7,466 Women
- 18-25 years old
- 2004 - 2005

Annual follow-up for 4 years

- Hepatitis A Vaccine (control)
- Cervarix GSK HPV-16/18

20% received <3 doses

Screening only control group
HPV arm followed 11 more years

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

15 years
CVT: Stable HPV16 serum antibodies for 11 years

Results similar for HPV18

Accept that 1-dose GMT of antibodies are inferior to 3-dose levels- cannot infer protection is inferior because efficacy is observed

CVT will continue to monitor abs for >15 years
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

ClinicalTrials.gov registration number NCT00923702
Received 1 dose (day 1) N=4672

Received 2 doses (days 1-60) N=3300

Vaccinated N=17,064

Received 3 doses (days 1-60-180+) N=4242

Received 2 doses (days 1-180+) N=4850

IARC HPV Vaccine clinical trial

Unvaccinated age-matched (to married vaccinated) women recruited in 2012-15 as controls N=1460

Additional unvaccinated age-matched (to married 25+ yr old vaccinated women) recruited in 2017-18 as controls N=3702

HPV SINGLE-DOSE DATA – CONTINUING TO ACCUMULATE

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

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Women assessed (N)</th>
<th>Persistent HPV 16/18 infection N (%)</th>
<th>Persistent HPV 16/18 infection (%; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated</td>
<td>1242</td>
<td>28</td>
<td>(2.3; 1.5-3.2)</td>
</tr>
<tr>
<td>3- dose (Days 1, 60 &amp; 180+)</td>
<td>1056</td>
<td>1</td>
<td>(0.1; 0.0-0.5)</td>
</tr>
<tr>
<td>2- dose (Days 1 and 180+)</td>
<td>1055</td>
<td>3</td>
<td>(0.2; 0.0-0.7)</td>
</tr>
<tr>
<td>1- dose</td>
<td>1643</td>
<td>1</td>
<td>(0.1; 0.0-0.3)</td>
</tr>
</tbody>
</table>

~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

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
   - 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

<table>
<thead>
<tr>
<th>Study name</th>
<th>Country</th>
<th>Design</th>
<th>Vaccine</th>
<th>Brief description</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEN SHE</td>
<td>Kenya</td>
<td>Efficacy</td>
<td>HPV2 vs HPV9</td>
<td>Girls 15-20 yo randomized to 1 dose of HPV2, HPV9, or MenACWY; n=750 per arm; delayed dose 2 planned</td>
</tr>
<tr>
<td>ESCUDDO</td>
<td>Costa Rica</td>
<td>Efficacy</td>
<td>HPV2 and HPV9</td>
<td>Girls 12-16 yo randomized to 1 or 2 doses of HPV2 or HPV9; n=5000 per arm</td>
</tr>
<tr>
<td>DoRIS</td>
<td>Tanzania</td>
<td>Immunogenicity</td>
<td>HPV2 and HPV9</td>
<td>Girls 9-14 yo randomized to 1, 2, or 3 doses of HPV2 or HPV9; n=155 per arm</td>
</tr>
<tr>
<td>Primavera</td>
<td>Costa Rica</td>
<td>Immunogenicity</td>
<td>HPV2 and HPV4</td>
<td>Girls 9-14 yo 1-dose HPV2 immunobridge to women 18-25 yo 3-doses HPV4; n=620 per arm</td>
</tr>
<tr>
<td>HANDS</td>
<td>The Gambia</td>
<td>Immunogenicity</td>
<td>HPV9</td>
<td>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</td>
</tr>
</tbody>
</table>
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).

**HOPE: HPV vaccine One and two-dose Population Effectiveness study**

AIM: To measure the population effectiveness of a 1-dose vaccine schedule, delivered via a demonstration project to girls in Grade 10 of public school, in protecting against infection with sexually transmitted HPV16 and 18 in girls aged 17-18 in Africa.

PI: Delany-Moretlwe
SA National Clinical Trials register: 5136

**Thailand HPV Vaccine Single Dose Impact Study**

A community effectiveness study of single dose or two-dose of bivalent HPV vaccine (Cervarix) in female school students in Thailand.

AIM: Demonstrate HPV vaccine effectiveness of single dose by a reduction in vaccine-type HPV prevalence two and four years post vaccination compared to unvaccinated same grade female students from a baseline survey.

International Vaccine Institute
Thailand Ministry of Public Health, Department of Disease Control
Thailand, National Vaccine Institute (NVI)
Centre of Excellence in Clinical Virology, Faculty of Medicine, Department of Pediatrics, Chulalongkorn University
US Center for Disease Control
<table>
<thead>
<tr>
<th>Study name (country)</th>
<th>Evidence type</th>
<th>Vaccine(s)</th>
<th>Brief description</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
<th>2024</th>
<th>2025</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KEN SHE</strong> Kenya</td>
<td>Efficacy</td>
<td>HPV2 vs HPV9 vs MenACWY (delay HPV)</td>
<td>Girls 15-20 yo randomized to 1 dose of HPV2, HPV9, or MenACWY; n=750 each arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ESCUDDO</strong> Costa Rica</td>
<td>Efficacy</td>
<td>HPV2 and HPV9</td>
<td>Girls 12-16 yo randomized to 1 or 2 doses of HPV2 or HPV9; n=5000 each arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DoRIS</strong> Tanzania</td>
<td>Immunogenicity</td>
<td>HPV2 and HPV9</td>
<td>Girls 9-14 yo randomized to 1, 2, or 3 doses of HPV2 or HPV 9; n=155 each arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primavera</strong> Costa Rica</td>
<td>Immunogenicity</td>
<td>HPV2 and HPV4</td>
<td>Girls 10-13 yo 1-dose HPV2 immunobridge to women 18-25 yo 3-doses HPV4; n=520 each</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HANDS</strong> The Gambia</td>
<td>Immunogenicity</td>
<td>HPV9</td>
<td>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</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>India IARC</strong> India</td>
<td>Efficacy</td>
<td>HPV4</td>
<td>Girls 10-18 yo received 1, 2, 3 doses of HPV4; n=17586, 1-dose n=4980</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CVT</strong> Costa Rica</td>
<td>Efficacy / Immunogenicity</td>
<td>HPV2 vs control</td>
<td>Women 18-25 yo received 1, 2, or 3 doses of HPV2; n=3727, 1-dose n=196</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thailand impact study</strong> Thailand</td>
<td>Effectiveness</td>
<td>HPV4</td>
<td>Girls in grade 8 given 1 or 2 doses; n=8000 each arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HOPE</strong> South Africa</td>
<td>Effectiveness</td>
<td>HPV2</td>
<td>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</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

ClinicalTrials.gov: NCT03675256
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.

**Young women age 15-20 years; N=2250**
- Sexually active, 1-5 lifetime partners, HIV-negative, No history of HPV vaccination

**Immediate single-dose 2v HPV vaccination (N=750)**

**Immediate single-dose 9v HPV vaccination (N=750)**

**Immediate meningococcal vaccination (N=750)**

Follow-up visits - 6 monthly (month 6 and 12)

**Endpoint visit – 36 months after enrollment**
- HPV 16/18/31/33/45/52/58/6/11 DNA (clinician-collected cervical, vulvar-vaginal swab), HPV antibodies (serum), Pap smear (liquid-based cytology)

Comprehensive sexual and reproductive health (SRH) services will be offered at all study visits.

Month 1:
- HPV antibodies (serum) for immunobridging study N=900 (N=300 per arm)

Month 24:
- HPV antibodies (serum) for immunobridging study N=900 (N=300 per arm)

Follow-up visits - 6 monthly (month 24 and 30)

**Immediate meningococcal vaccination (N=750)**
A scientific evaluation of one or two doses of the HPV vaccines

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

**RCT**
Girls 12-16 years old
(n=20,000)

- **M0: Randomized to vaccine**
  - **Bivalent**
    - (n=10,000)
  - **Nonavental**
    - (n=10,000)

- **M6: Randomized to dosing schedule**
  - 1 Dose
  - 2 Doses
  - 1 Dose
  - 2 Doses

**Active Follow-up**
(Cervical cells, serology, urine at M12, M18, M24, M30, M36, M42, M48)

**Epi Survey**
Women 17-20 years old
(n=4,000)

- HPV infection status*
  - M0 and M6

*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
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

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

<table>
<thead>
<tr>
<th>ARM A</th>
<th>ARM B</th>
<th>ARM C</th>
<th>ARM D</th>
<th>ARM E</th>
<th>ARM F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervarix®</td>
<td>Gardasil-9®</td>
<td>3 doses</td>
<td>2 doses</td>
<td>1 dose</td>
<td>3 doses</td>
</tr>
<tr>
<td>N = 155</td>
<td>N = 155</td>
<td>N = 155</td>
<td>N = 155</td>
<td>N = 155</td>
<td>N = 155</td>
</tr>
</tbody>
</table>
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

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.
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
   - KenSHE- Efficacy in Kenya
   - ESCUDDO- Efficacy in Costa Rica
   - DoRIS- Immunogenicity in Tanzania (efficacy through immunobridging)
   - Primavera- Immunobridging in Costa Rica

4. Effectiveness Data- South Africa and Thailand
Effectiveness against AGW by number of doses

Impact of buffer period

Effectiveness against AGW by number of doses

Impact of buffer period and age at vaccination

No buffer

12-month buffer

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, Verdooodt CID 2019
Brotherton: RR adjusted for socio-economic status, remoteness, attained age; Verdooodt: RR adjusted for maternal education and attained age