Current state of evidence on single-dose HPV vaccination and its implications for policy

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Currently, the World Health Organization (WHO) recommends two doses of the human papillomavirus (HPV) vaccine for girls aged 9 to 14 years, with flexibility in administration of dose 2 from six months up to three to five years after the first dose. Girls aged 15 years and older and girls who are immunocompromised, including those living with HIV, should receive three doses under current guidelines.

In the fifteen years since licensure of the first HPV vaccine, worldwide vaccine coverage in girls under 15 years of age has increased very slowly, reaching only about 15% globally in 2019. This is far below WHO's cervical cancer elimination initiative goal of 90% coverage by 2030. Many country programs struggle to achieve high coverage with two-dose schedules and countries that self-finance are reluctant to introduce a comparatively expensive vaccine. HPV vaccine supply constraints have also impeded widespread coverage and introduction in recent years.

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.

While additional clinical trial and observational study data in the coming years are expected to provide more information on the duration of protection and relative efficacy/effectiveness of single-dose relative to current multidose schedules, the current evidence supports the conclusion that single-dose vaccination of the bivalent (Cervarix®), quadrivalent (Gardasil®), and nonavalent (Gardasil® 9) vaccines for immunocompetent girls would give equivalent or near-equivalent protection to two-dose vaccination.

The Consortium, coordinated by PATH, includes Harvard University, London School of Hygiene & Tropical Medicine, Université Laval, University of British Columbia, US Centers for Disease Control and Prevention, US National Cancer Institute, Wits Reproductive Health and HIV Institute, and the Kirby Institute at University of New South Wales.

For information about the Single-Dose HPV Vaccine Evaluation Consortium, visit path.org/singledosehpv or contact Evan Simpson at esimpson@path.org. March 2022.

A single-dose HPV vaccination schedule is further supported by model-based evidence which consistently shows that single-dose vaccination in settings that have not yet introduced HPV vaccines will lead to substantial reduction in cervical cancer cases. Additionally, reaching more girls with a single dose will avert many more cervical cancer cases than vaccinating fewer girls with a second dose.

Brief summary of evidence pertaining to a single dose of HPV vaccine

In reaching the conclusion above, the Single-Dose HPV Vaccination Evaluation Consortium reviewed the evidence of several clinical trials that examined efficacy, immunogenicity, and effectiveness of single-dose HPV vaccination. Below are summaries and references for all such studies with publicly available data. In addition, the Consortium reviewed and assessed the cumulative evidence on single-dose HPV vaccination from observational studies as well as modeling analyses. These assessments can be found in the Evidence Review produced by the Consortium.

KEN-SHE, Kenya (Efficacy)

- Prospective, blinded, randomized study of single-dose HPV vaccination in females 15-20 years of age (yoa)
- N= 2,250 were equally randomized to 3 arms: Cervarix; Gardasil 9; delayed vaccination
- Study duration: data from month 18 analysis is available; follow-up ongoing till Month 36

Study objectives:

- Vaccine efficacy of single dose HPV vaccination in preventing persistent HPV infections with Cervarix or Gardasil 9 compared to delayed vaccination
- Bridging of 24-month immunogenicity data to the Dose-Reduction Immunobridging and Safety Study (DoRIS) trial data (9-14yoa)

Summary of results at Month 18[1]:

- Single-dose Cervarix and Gardasil 9 vaccines were highly effective in preventing incident persistent oncogenic HPV infection in African adolescent girls and young women; 97.5% vaccine efficacy for HPV-16/18 persistent infections at Month 18 for both vaccines.
- Efficacy estimates were similar to those reported for multidose regimens

[1] Barnabas RV, Brown ER, Onono M, et al. Efficacy of single-dose HPV vaccination among young African women. *Research Square*. Published 2021 Nov 19.doi:10.21203/rs.3.rs-1090565/v1. [Pre-print].

DoRIS, Tanzania (Immunogenicity)

- Randomised open-label trial in females 9-14 years of age;
- N=930 were equally randomized to 6 arms: 1, 2, 3, doses of Cervarix or Gardasil 9
- Study duration: Month 24 data available; follow-up for immuno-persistence up to Month 60

Study objectives:

- Immunological Non-Inferiority 1 Dose vs 2-3 doses (seropositivity) at Month 24
- Immunological Non-Inferiority 1 Dose vs historical controls 10-25ya (GMTs) at Month 24 (immuno-bridging to Costa Rica Vaccine Trial [CVT], India IARC)
- Immuno-persistence at Month 36 for 1-, 2- and 3-dose regimens

Summary of results at Month 24[2]:

- Single-dose of Cervarix is non-inferior to 1-dose in historical cohort (CVT)
- Single-dose Gardasil 9 is non-inferior to 1-dose in historical cohort (India-IARC)

India-IARC (Efficacy)

- Study participants, females 10-18 years of age, enrolled (2009/2010) in a randomized clinical trial comparing 2 versus 3 dose-regimens of Gardasil were followed up for efficacy and immunogenicity, with a substantial portion (~5000 subjects) having received only a single dose of vaccine after the trial was interrupted for reasons unrelated to the study
- Study duration: 10-year efficacy and immunogenicity data are available; follow-up ongoing till 15 years post vaccination

Study objectives:

- Efficacy of four-valent HPV vaccination in preventing persistent HPV-16/18 infections

Summary of results at Year 10[3]:

- Interrupted randomized trial with allocation to single-dose regimen independent from sponsor, investigators, and participants
- Across the different schedules (single dose, 2-doses on 0,6 months and 3-dose on 0,1,6 months schedule) Gardasil VE against HPV-16/18 infections remains similarly high (>90%) up to at least 10 years post vaccination.

Costa Rica HPV Vaccine Trial (Efficacy/Immunogenicity)

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[2] Watson-Jones D. Presentation to the International Papillomavirus Conference, November 2021.

[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. *Lancet Oncol*. 2021;22(11):1518-1529. https://doi.org/10.1016/S1470-2045(21)00453-8.

- Follow-up of study participants enrolled (2004/2005) in a randomized clinical trial comparing 3 dose-regimen of Cervarix to active control (Hep A vaccine)
- 7,466 women 18-25yoa enrolled; 277 participants received a single dose of 2vHPV

Study objectives:

- Efficacy of two-valent vHPV vaccination in preventing HPV-16/18 infections at more than a decade after HPV vaccination
- Durability of antibody response up to 20 years post-vaccination

Summary of results[4]:

- HPV-16 and HPV-18 antibodies in all subjects shown to persist several times above natural infection up to 11 years post-Cervarix single dose administration
- Efficacy estimates against prevalent HPV 16/18 infections similar to multi-dose regimen after a single dose of Cervarix, albeit small numbers.

Observational Studies

Data are from studies that included persons who were non-compliant with a recommended three-dose vaccination series in national programs; most of whom were vaccinated as part of catch-up vaccination. The findings are subject to substantial bias (mainly information bias and confounding). In a few studies among girls vaccinated at younger ages, less likely to be affected by serious biases, there was high effectiveness against infection and disease endpoints with one dose, or similar effectiveness irrespective of number of doses received.

Modelling Studies[5,6,7,8,9]:

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[4] 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. https://doi.org/10.1093/jnci/djaa011.

[5] Kim J. Could 1 dose be less efficacious than 2 doses but still be a great public health intervention? *HPV World*. 2017;1(30):26–28. https://www.hpvworld.com/media/29/media_section/0/5/1605/kim.pdf

[6] Burger E, Campos N, Sy S, Regan C, Kim J. Health and economic benefits of single-dose HPV vaccination in a GAVI-eligible country. *Vaccine*. 2018;36(32 Pt A):4823–4829. https://doi.org/10.1016/j.vaccine.2018.04.061.

[7] Prem K, Choi YH, Bénard É, et al. Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis. *medRxiv*. 2021. https://doi.org/10.1101/2021.02.08.21251186. [Preprint].

[8] Drolet M, Laprise JF, Martin D, et al. Optimal human papillomavirus vaccination strategies to prevent cervical cancer in low-income and middle-income countries in the context of limited resources: a mathematical modelling analysis. *Lancet Infect Dis*. 2021;21(11):1598-1610. https://doi.org/10.1016/S1473-3099(20)30860-4.

[9] Drolet et al. Extended Dose Schedule. Pending

- Compared to no vaccination, single-dose HPV vaccination yields substantial health benefits and is good value for money, even at a lower vaccine efficacy level of 80% or shorter duration of protection of ten years.
- The impact and cost-effectiveness of adding a second dose are driven by the duration of single-dose HPV vaccine protection and, possibly, the ability to achieve higher coverage with single-dose versus multiple doses.
- For cervical cancer prevention, a 2-dose schedule would avert only slightly more cases than a single-dose schedule.
- The current approach (routine vaccination with a 2-dose regimen and without multi-age cohort) prevents fewer cases, is less efficient and less equitable than a single-dose vaccination strategy or single-dose multi-age cohort.
- Immediate implementation of a single-dose HPV vaccination program leads to greater health benefits than delaying implementation until more conclusive information on vaccine efficacy is available from ongoing clinical trials.

The Consortium will release a fourth edition of the evidence review in 2022.

Signed,

The Single-Dose HPV Vaccine Evaluation Consortium