

# A general summary of current published evidence for single-dose HPV vaccination

**Cervical cancer is a leading cause of cancer death among women in low- and middle-income countries (LMICs). More than a half-million new cases and 266,000 deaths occur annually, with more than 85% of deaths occurring in LMICs.**

Accumulating evidence suggests a single dose of human papillomavirus (HPV) vaccine may elicit an immune response to protect against incident and persistent HPV infection, which are the necessary prerequisites to the development of cervical lesions and, in the longer term, cervical cancer.

Clinical trials, observational studies, and modeling analyses are being conducted to evaluate the efficacy, immunogenicity, effectiveness, and cost-effectiveness of single-dose HPV vaccination. If demonstrated to be effective, single-dose HPV vaccination could facilitate new options for current national programs by simplifying delivery and lowering

program costs. For LMICs that have delayed introducing HPV vaccines because of financial, logistical, or other barriers, a single-dose HPV vaccination schedule could accelerate introduction of HPV vaccines into national immunization schedules, potentially protecting even more girls against cervical cancer and other HPV-related diseases.

This brief summarizes a comprehensive review and assessment of current, published evidence for a single-dose HPV vaccination schedule. The review was undertaken by researchers in the Single-Dose HPV Vaccine Evaluation Consortium.



Photo: PATH/Aaron Joel Santos

## About the Single-Dose HPV Vaccine Evaluation Consortium

The Single-Dose HPV Vaccine Evaluation Consortium encompasses nine leading independent research institutions working together to collate and synthesize existing evidence and evaluate new data on the potential for single-dose HPV vaccination. The consortium's goal is to evaluate this evidence to inform global policy discussions and program guidance, as well as to raise awareness and understanding of its implications.

As the project unfolds, the consortium is coordinating relevant scientific groups and evaluating new data as they become available. Modeling experts within the consortium are generating new evidence through meta analyses of existing data and conducting exploratory analyses to estimate the impact and cost-effectiveness of single-dose schedules to alternative dosing schedules to inform decision-making. The consortium will annually update the evidence base throughout the project period (2018–2021).

Consortium members work collaboratively with the World Health Organization and Gavi, the Vaccine Alliance, to share and discuss the evidence base. The consortium will also engage regional and national-level stakeholders to gather perspectives on the potential implications of single-dose HPV vaccination for countries.

Photo:

## Background

### HPV Vaccines and Schedule

Preventing the development of cervical cancer is now possible through vaccination with any of three licensed vaccines: the bivalent vaccine (2vHPV), the quadrivalent vaccine (4vHPV), and the nonavalent vaccine (9vHPV).

Currently, the World Health Organization (WHO) recommends two doses of HPV vaccine for girls aged 9 to 14 years, with dosing flexibility for dose 2 as early as 5 months after dose 1. Girls aged 15 years or older and girls who are immune-compromised, including those who are HIV-infected, should continue to receive three doses per the original dosage recommendations.

## Current evidence

### Immunogenicity of HPV vaccines

HPV vaccines are highly effective and since introduction, have significantly reduced vaccine-type HPV infections and precancerous cervical lesions. The strong, consistent, and durable antibody responses to the three HPV vaccines is well documented. In healthy, previously uninfected young women, HPV vaccines provide close to 100% protection against cervical precancers and some against genital warts. Immune responses in pre-adolescent girls and boys are even stronger. The stability of antibody responses, now observed for over 10 years post vaccination, is unprecedented for a subunit vaccine. This pattern of antibody response is evident even after a single-dose of HPV vaccine as seen in observational data from several clinical studies.

### Clinical trials

As of April 2018, there were no data on the immunogenicity, efficacy, or effectiveness of a single-dose HPV vaccination schedule compared to two- or three-dose schedules that originated from specifically designed randomized studies comparing one-dose to two- or three-dose groups.

Observational data from the following randomized control trials where participants failed to complete their schedule of two or three doses provide some evidence that a single dose of HPV vaccine may protect against persistent HPV infection with vaccine-genotypes and generate protective immune responses.

### Efficacy studies of single-dose HPV vaccine



**Costa Rica HPV Vaccine Trial.** Post hoc proof-of-principal analyses indicated that women who received only one dose of 2vHPV had similar vaccine efficacy as those who received three doses, four years after vaccination. This finding was bolstered by immunogenicity data showing stable antibody titers for single-dose recipients over the same time period. At an

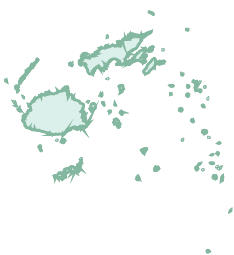
average of seven years of follow-up, similarly low rates of HPV infections and slight, if any, decreases in HPV antibody levels by dose group were observed. A combined post hoc analysis with the PATRICIA trial, a separate efficacy trial of the 2vHPV, also suggested that one dose had similar efficacy as three doses.



**India HPV vaccine trial.** The study population was followed up for seven years of observation comparing girls who received one dose, those that received two doses either two or six months apart, and those that received all three doses. The frequency of incident HPV infections was similar irrespective of the number of vaccine doses received, and no persistent HPV 16 infections were detected in any dose group. Antibody response after a single dose of 4vHPV was also measured in an observational cohort study of multiple HPV dosing groups in India, which included a large number of single-dose HPV vaccine recipients.

## Immunogenicity studies of single-dose HPV vaccine

**Uganda study.** Geometric mean neutralization titers (GMT) after one and two doses of 2vHPV measured about three years after the last dose did not meet the threshold to be declared non-inferior to three doses. However, GMT levels among adolescents who received only a single dose in Uganda were still higher than women who received a single dose of 2vHPV in the Costa Rica trial, among whom vaccine efficacy four years after vaccination has been observed. Furthermore, in Uganda, even though immune responses were inferior in the single-dose group, they were still four-fold higher than natural infection.



**Fiji study.** The primary analysis was the comparison of the GMTs of the HPV-specific neutralizing antibodies (NAb) against HPV 6, 11, 16, and 18 in girls who previously received one or two doses of 4vHPV with girls who received three doses. One dose recipients of 4vHPV vaccine had significantly lower NAb titers than two- or three-dose recipients; titers were 5- to 30-fold higher than unvaccinated girls. There were no differences in titers in two-dose girls who received dose 1 and dose 2 less or more than six months apart. After an additional dose of 2vHPV was administered six-years post vaccination of 4vHPV, NAb titers for HPV 16 and 18 in the one dose group increased

46- and 84-fold suggesting a strong anamnestic response, and were not significantly different from the two-dose and three-dose groups.

## Non-trial observational studies, registry linkages, and other studies

A recent, systematic literature review was conducted on the effectiveness of HPV vaccination by the number of doses from studies published between January 1, 2007 and June 15, 2017.

The main outcome measured was effectiveness of HPV vaccination comparing the incidence or prevalence of HPV-related endpoints between individuals vaccinated with different number of doses (three vs none, two vs none, one vs none, three vs two, three vs one, two vs one) of 4vHPV or 2vHPV vaccine. Most post-licensure studies examining HPV vaccine effectiveness by number of doses report highest effectiveness with three doses, but some found no statistically significant difference between two and three doses.

In six studies (including studies for both vaccines), significant vaccine effectiveness was observed for single-dose HPV vaccination in some analyses. The systematic review also summarized the various biases in these studies due to differences between persons who received a complete vaccination series and those who did not.

Further prospective studies of real-world HPV vaccination effectiveness, examining persons vaccinated prior to sexual activity and using methods to reduce potential sources of bias and confounding, may help inform vaccine policy.

## Modeling evidence

Modeling analyses have been used extensively to evaluate the health and epidemiologic impacts, budget impacts, and cost-effectiveness of strategies to prevent HPV-related diseases globally. Limited modeling analyses evaluating single-dose HPV vaccination exist and those that do used data from high-income country settings. Initial analyses indicate that if the choice is between no vaccination and a single dose, a single dose is likely to provide health benefits and be good value for the cost. This applies even if the vaccine has a lower vaccine efficacy than two or more doses, as long as one dose protection lasts at least 10 years. If the choice is between one-dose and two-dose vaccination, then the second dose becomes the most cost-effective option if it can extend protection up to at least 20 years.

The emerging evidence on vaccine efficacy and durability from the ongoing studies—and the extension of these analyses into settings with more variable epidemiological, demographic, and behavioral profiles—will be critical to fill important evidence gaps regarding the impact and value of reduced-dose HPV vaccination.

## Forthcoming evidence

More evidence is still needed to determine if a single dose of HPV vaccine can provide a sufficient and durable level of efficacy against persistent HPV infection to support a recommendation in policy change to a single-dose vaccination strategy.

Prospective, randomized controlled trials will provide more definitive data on whether a single dose of HPV vaccine can protect against HPV persistent infection and provide immunobridging data to trials where efficacy has been demonstrated.

Trials are underway in Costa Rica (ESCUDDO), The Gambia (HANDS), and Tanzania (DoRIS), and will begin soon in Kenya (KEN-SHE). Large-scale impact studies will be conducted in Armenia and Thailand. ESCUDDO and KEN-SHE will randomize young women to single-dose schedules. HANDS, DoRIS, and KEN-SHE will immunobridge to efficacy trials, and a

common immunoassay will be used across vaccines to directly compare immune response regardless of vaccine received. Additionally, longer term immune response data will still be forthcoming from the Costa Rica Vaccine Trial and the India Vaccine Trial, as well as longer term efficacy observations.

In addition, the next systematic literature review will examine the immunogenicity of one dose compared to two or three doses of HPV vaccines, and the efficacy of one-dose compared to two- or three-dose HPV vaccine regimens against HPV infection, anogenital warts, and HPV-associated disease endpoints. The consortium will also repeat the systematic literature review as new studies are published and new evidence will be strengthened by meta-analysis of population impact studies to increase the robustness of the analysis with larger samples, especially for single-dose groups.

Evidence generated by future modeling work will focus on integrating new trial, non-trial, and effectiveness data into existing models, as well as conducting model-based analyses in LMICs with different sexual behavior and epidemiological profiles.

The evidence for single-dose schedule HPV vaccination is encouraging. Limitations of previous studies are being overcome by new studies, stronger data analyses, and broader dissemination of the evidence. The Single-Dose HPV Vaccine Evaluation Consortium will continue to monitor the evidence base, update it annually, and share results widely.



Photo: PATH/Mike Wang

## Single-Dose HPV Vaccine EVALUATION CONSORTIUM

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 World Health Organization.

In addition to the consortium members, representatives from the following institutions serve as advisors: International Agency for Research on Cancer; Medical Research Council Unit, The Gambia at LSHTM; Instituto Nacional de Salud Pública de Mexico; Quebec Institut National de Santé Publique; Victoria Cytology Services, Australia; University of Washington, USA; and International Vaccine Institute, South Korea.

**Disclaimer:** The content, findings, and conclusions of this report are those of the authors and do not necessarily represent the official position of their agencies or institutions of employ.

For information about the Single-Dose HPV Vaccine Evaluation Consortium and access to the full review of current evidence, visit [RHO.org/singledosehpv](http://RHO.org/singledosehpv).

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