

Technical synthesis of current, published evidence on single-dose HPV vaccination



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Introduction

Prophylactic human papillomavirus (HPV) vaccines have been licensed for over ten years, initially as a three-dose regimen offered over six months and more recently as a two-dose regimen for individuals less than 15 years of age, following a review of the evidence for this dose reduction by the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization in 2014. Recent evidence has emerged to suggest that a single dose of HPV vaccine may be sufficient to elicit a protective immune response against incident and persistent HPV infections, which are the necessary prerequisites to further development of cervical lesions and, in the longer term, cervical cancer.

The Single-Dose HPV Vaccine Evaluation Consortium was formed to collate and synthesize existing evidence and evaluate new data on the potential for single-dose HPV vaccination. The consortium compiles the current, published evidence on single-dose HPV vaccination, including data from trials, immunogenicity studies, other observational studies, and impact modeling. It also provides commentary on the strength of that evidence and the gaps that remain. 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.

This summary provides an overview of the key findings of the consortium's evidence review—known as the White Paper (see sidebar).

Burden of HPV-related disease and cervical cancer

Invasive cervical cancer, caused by persistent infection with HPV, is a major public health problem, especially in developing countries [1]. As of 2018, the International Agency for Research on Cancer (IARC) estimates that there are nearly 570,000 new cases of cervical cancer and more than 311,000 cervical cancer-related deaths per annum globally, with over 85% of deaths occurring in low- and middle-income countries (LMICs) [2, 3]. In settings where effective cervical cancer screening programs are available, the incidence of and mortality from cervical cancer have markedly decreased [3, 4]. However, in many developing countries, screening programs are not in place or are only available on a limited scale and women frequently present late with the disease, leading to high associated morbidity and mortality rates.



Review of the current, published evidence on single-dose HPV vaccination (White Paper)

The white paper (WP) is a comprehensive assessment of (i) the current evidence on single-dose schedules of HPV vaccine, (ii) the strength of that evidence, and (iii) the gaps in the evidence.

The WP provides a detailed summary and interpretation of published evidence relevant to single-dose HPV vaccination. This includes vaccine efficacy, immunogenicity, and effectiveness; mathematical modeling of impact of reduced-dosing schedules; identification of gaps in the evidence; and discussion of studies underway addressing these gaps. These data are necessary to inform policy and program decisions about single-dose or alternative schedules of HPV vaccine. The complete WP can be found at path.org/singledosehpv.

HPV vaccines

Primary prevention for cervical cancer is now possible through vaccination with one of three licensed HPV vaccines (Table 1). These vaccines are highly efficacious against persistent infection with vaccine genotypes, a necessary pre-requisite for the development of cervical cancer and related cervical lesions [5]. Currently, WHO recommends two doses of HPV vaccine for girls aged 9 to 14 years, with dosing flexibility for dose 2 as early as five months after dose 1. Girls aged 15 years or older and girls who are immune-compromised, including those HIV infected, should continue to receive three doses as per original dosage recommendations.

Table 1. Summary of the targets and schedules of available HPV vaccines.

	Bivalent HPV vaccine	Quadrivalent HPV vaccine	Nonavalent HPV vaccine
Manufacturer	GlaxoSmithKline	Merck & Co., Inc.	Merck & Co., Inc.
Trade name	Cervarix®	GARDASIL®	GARDASIL®9
Schedule 9–14 years of age: 2 doses	0, 6–12 months	0, 6–12 months	0, 6–12 months
Schedule ≥ 15 years of age: 3 doses	0, 1, 6 months	0, 2, 6 months	0, 2, 6 months

Note: HPV, human papillomavirus.

When given as a two-dose schedule, HPV vaccines have demonstrated a strong immune response that is non-inferior to that from a three-dose schedule, where protection against HPV infection and related HPV disease has been shown. 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.

Current evidence on a single dose of HPV vaccine

Sources of evidence covered in the White Paper include publicly available, peer-reviewed scientific publications on:

- The rationale for protection with a single dose of HPV vaccine based on vaccine immune response and virological information.
- Nonrandomized data from partially vaccinated participants in clinical trials.
- Data from postlicensure vaccine effectiveness evaluations and other observational studies.
- Mathematical modeling of the impact of reduced dosing schedules for HPV vaccines.

Rationale on single-dose HPV vaccination

Plausible biological explanations for the unexpected potency of HPV vaccines have been reviewed following observational data from several clinical studies that suggested a single dose of HPV vaccine could provide protection against HPV infection [6].

The strong, consistent, and durable antibody responses to the three HPV vaccines are well documented [7]. In healthy young women, seroconversion rates are virtually 100%. Responses in pre-adolescent girls and boys are even stronger [8, 9]. The stability of antibody responses now observed almost ten years after vaccination is unprecedented for a subunit vaccine [10, 11]. This pattern of antibody response is observed even after a single dose of the vaccine [12, 13].

Observational data from partially vaccinated participants in clinical trials of HPV vaccine efficacy and immunogenicity

As of March 2019, there are no data on the immunogenicity, efficacy, or effectiveness of a one-dose HPV vaccination schedule compared to two- or three-dose schedules that originated from specifically designed randomized controlled trials (RCTs). However, observational data from RCTs where participants failed to complete their schedule of two or three doses provide some evidence that one dose of HPV vaccine may provide protection against persistent HPV infection with vaccine genotypes and generate protective immune responses.

A systematic review by the London School of Hygiene & Tropical Medicine (LSHTM) of data on the efficacy and immunogenicity of a single HPV vaccine dose compared to multidose schedules (and compared to no HPV vaccination) from clinical trials was conducted. In addition, a systematic review from the Cochrane Review Group includes data on the efficacy of one or more HPV vaccine doses; however, the review did not compare a one-dose schedule to two- or three-dose schedules.

LSHTM systematic review

The systematic review examined literature published between January 1, 1999, and August 14, 2018, from RCTs on the immunogenicity and efficacy of single-dose HPV vaccination compared to either no vaccination or to multidose schedules [14]. The systematic review was specifically designed to identify clinical trials that randomized participants to receive one dose of HPV vaccine versus no dose or multiple doses, as well as trials in which some participants received only one dose due to non-completion of a multi-dose schedule. Of 6,523 unique records identified from the database and hand searches, seven articles were included in this review; of these, six were considered as observational studies because allocation to the dosing schedule arms (i.e., one dose versus alternative schedules or no vaccination) was according to what participants actually received rather than participants being prospectively allocated to a specific dosing schedule. The other study included in the review was a small randomized study which prospectively allocated participants to one HPV vaccine dose versus no vaccination [12, 13, 15–19].

All six observational studies were based on data from three clinical trials. Two studies were based on the IARC India HPV Trial. Three studies were based on the Costa Rica Vaccine Trial (CVT). One was based on combined data from CVT and the PApilloma TRIal against Cancer In young Adults (PATRICIA) [12, 13, 16–21].

An updated literature search for articles published between August 2018 and March 2019 did not yield any further data from RCTs.

Cochrane review

The Cochrane review of clinical trial data on the efficacy and safety of HPV vaccines compares at least one dose of HPV vaccine (bivalent or quadrivalent) to placebo [22]. The specific objective of the Cochrane review was to evaluate the harms and benefits of prophylactic HPV vaccines against cervical precancer and HPV 16 and 18 infection in adolescent girls and women. The review included articles that were published up to June 2017 about phase II and III RCTs that enrolled female participants of any age who had received HPV vaccine or placebo.

The review included trials of three vaccine doses. Therefore, women who received only one or two doses were those who did not complete their allocated three-dose schedule. While primarily presenting data for at least one dose, the review also stratified results by actual number of doses received.

The Cochrane review included 56 references describing 26 randomized trials of a three-dose HPV vaccination regimen. Of these, only four articles reported efficacy data on single-dose HPV vaccination compared to comparator groups [16–19]. These articles were derived from the IARC India HPV Trial, CVT, and PATRICIA; they are included in the results of the LSHTM systematic review described above.

The most significant efficacy data on single-dose HPV vaccination are from nonrandomized observational data in two independent trials from Costa Rica and India, launched in 2004 and 2009, respectively.



Costa Rica Vaccine Trial (CVT). Conducted by the US National Cancer Institute and the Agencia Costarricense de Investigaciones Biomédicas, the CVT trial was a community-based, randomized phase III clinical trial that was initiated prior to licensure; it also included an additional long-term follow-up study. A total of 7,466 women aged 18 to 25 years were enrolled and randomized to receive either the bivalent HPV vaccine (2vHPV) or a control hepatitis A vaccine in a 1:1 ratio on a three-dose schedule at 0, 1, and 6 months. Of these women, 20% did not receive three doses. Participants were followed at least annually for four years and were invited to stay in a long-term follow-up observational study [16, 23]. During this observational study, HPV-vaccinated participants were followed biennially for up to seven additional years.

Four years after initial vaccination, one dose of the 2vHPV had comparable efficacy to three doses of the vaccine using an endpoint of cumulative persistent HPV infection [15]. The four-year efficacy against HPV 16 or 18 infections that persisted for at least six months among women who were HPV DNA negative for these types at first vaccination was as follows: three doses = 84% (95% CI = 77% to 89%; two doses = 81% (95% CI: 53% to 94%); and one dose = 100% (95% CI: 79% to 100%).

Protection for HPV 16 and 18 at four years was extended to seven years. Additionally, the CVT found that the prevalence of HPV 31, 33, and 45 was similar between the three-dose (2.3%; 95% CI: 1.8% to 3.1%), two-dose (0.6 month schedule; 0.0%; 95% CI: 0.0% to 3.7%; $p = 0.26$ compared to three doses), and one-dose groups (1.5%; 95% CI: 0.3% to 4.8%; $p = 0.77$ compared to three doses) seven years following initial HPV vaccination [18].

Results of the CVT were confirmed through analysis of another trial, the PATRICIA trial, which was sponsored by GlaxoSmithKline Biologicals. A combined, post hoc analysis of 12,013 women aged 15 to 25 years enrolled in Costa Rica and in the PATRICIA cohort compared those who received fewer than the recommended number of doses with those who completed the three-dose vaccine course. The results suggested equivalent efficacy of one, two, and three doses of the 2vHPV against vaccine-type persistent infection over a median follow-up of four years [17].



IARC India HPV Trial. The IARC India HPV Trial was a multicenter cluster-randomized trial that evaluated the comparative efficacy of two versus three doses of the quadrivalent HPV vaccine (4vHPV). The initial study design called for 20,000 girls, aged 10 to 18 years, to be randomly allocated to receive either two or three doses. However, the study was suspended in April 2010 due to unrelated events, resulting in broken randomization and some trial participants not completing, or not completing on time, the vaccination schedule assigned. This meant that the study, which had enrolled 17,739 girls before suspension, had four groups of vaccine recipients: 4,348 (25%) girls received three doses (according to schedule); 4,979 (28%) received two doses (according to 0, 6 month schedule); 3,452 (19%) received two doses by default (approximately two months apart); and 4,950 (28%) received one dose by default. Those in the default groups were the girls who were unable to complete their allocated vaccination schedules.

The frequencies of cumulative incident HPV 16 and 18 infections over seven years after vaccination were similar and uniformly low in all the study groups; the frequencies of HPV 16 and 18 infections were higher in unvaccinated women (6.2%) than among the vaccine recipients (0.9% in the three-dose, 0.9% in the two-dose, 1.7% in the two-dose (default), and 1.6% in the one-dose groups).

Based on a comparison of the rate of persistent infection in 2,989 vaccinated women who had provided at least two cervical samples with the rate in 1,141 unvaccinated women, findings from the IARC India HPV Trial suggest high vaccine efficacy in preventing persistent HPV 16 and 18 infections regardless of the number of doses received. There was a total of 4 (0.1%) persistent HPV 16 and 18 infections among the vaccine recipients and 14 (1.2%) persistent HPV 16 and 18 infections among unvaccinated control women. No persistent HPV 16 and 18 infections were detected in 959 women in the single-dose group [19].

Immunogenicity evidence from clinical trials

Immunogenicity evidence after receipt of a single dose of HPV vaccine was also assessed in the CVT and IARC India HPV Trial.

CVT: In the CVT, among women who received a single dose, 100% seroconverted and HPV 16 and HPV 18 antibody titers (assessed by enzyme-linked immunosorbent assay or ELISA) were substantially higher than those among naturally infected, unvaccinated women four years after initial vaccination [13]. HPV 16 virus-like particle antibody avidity, a measure of the quality of the antibody response, was measured at years 4 and 7. The data for three doses showed that avidity increases considerably over the first four years and then stabilizes at year 7, and avidity for one dose was similar to three doses at year 4 [16].

IARC India HPV Trial: All vaccinated girls in the study groups seroconverted against HPV 16 and 18 after vaccination, and all remained seropositive at 48 months regardless of the number of doses received. The values for geometric mean avidity index for HPV types 16 and 18 for the one-dose group at 18 months were non-inferior to the values after the three-dose regimen at 18 months [12]. One dose induced detectable concentrations of neutralizing antibodies to HPV 16 and 18, but at lower concentration than two or three doses.

Strengths and limitations of evidence on single-dose HPV vaccination from clinical trial data

There are several strengths in the evidence on single-dose HPV vaccination derived from observational data from clinical trials:

- Both the CVT and IARC India HPV Trial have high retention, blinded lab measures, and frequent immunogenicity and efficacy measures.
- For the CVT, a concurrent control group was enrolled, and extensive analyses were conducted to rule out much of the potential bias and confounding that could have been related to an underlying characteristic shared by women who had received only a single dose. The later analysis of the IARC India HPV Trial was improved with the enrollment of an unvaccinated control group, allowing comparison of HPV infection outcomes and controlling for visit attendance.
- The IARC India HPV Trial includes a large sample size across all arms (including the single-dose arm). Since randomization was stopped, women did not choose to have fewer doses.

Using observational data from clinical trials where participants were not randomized specifically to single-dose HPV vaccination has some weaknesses:

- For CVT and PATRICIA, the group of women who had received a single dose of the 2vHPV was relatively small.
- Although the IARC India HPV Trial was originally a randomized trial, the original dose randomization could not be maintained after the trial enrollment stopped. The different vaccine dose cohorts were comparable by age and balanced by HPV attack by non-vaccine types, but there were differences in several sociodemographic factors at enrollment [19]. Clinical outcomes were only measured in married women for cultural reasons, which reduced the sample size for analysis. The unvaccinated cohort was created post hoc by selecting married women matched to married participants. Biases in selection of this cohort cannot be ruled out.

Evidence from immunogenicity studies of partially vaccinated non-trial populations

As of March 2019, seven observational studies have reported immunogenicity results after receipt of a single dose of HPV vaccine: one in Uganda and two each in Fiji, Canada, and the United States [24–30]. In all studies, single-dose participants received only one HPV vaccine dose due to non-completion of the intended multi-dose schedule.

Uganda study: A cross-sectional non-inferiority immunogenicity study was conducted among girls aged 10 to 11 years vaccinated between October 2008 and October 2009 through a government-run HPV vaccination demonstration program. The study recruited girls who had received one ($n = 36$), two ($n = 145$), or three ($n = 195$) doses of 2vHPV and measured antibody responses about three years after vaccination. Geometric mean titers (GMTs) of HPV 16 and 18 after one or two doses of 2vHPV did not meet the threshold for non-inferiority to three doses; however, the immune responses in the single-dose group were fourfold higher than those elicited from natural infection. Of note, GMTs among girls who received a single dose were higher than among women who received only a single dose of 2vHPV in the CVT in whom efficacy was demonstrated [24].

Fiji study: In 2015, girls were recruited into an observational study designed to compare antibody responses of vaccinees who received one or two doses of HPV vaccine compared to those who received three doses through a Fiji Ministry of Health and Medical Services vaccination campaign. All enrollees had been eligible to receive the recommended three-dose schedule of 4vHPV; however, some received only one or two doses. This follow-up study enrolled 200 girls 15 to 19 years of age (who were aged 9 to 12 at vaccination): 66 in the three-dose group, 60 in the two-dose group, 40 in the one-dose group, and 34 in an unvaccinated control group.

At enrollment six years after initial vaccination, GMTs for all 4vHPV types were not statistically different between two- and three-dose recipients. As found in the Uganda study, one-dose recipients had significantly lower neutralizing antibody titers than two- or three-dose recipients; however, titers among the one-dose group were fivefold to thirtyfold higher than those among unvaccinated girls. The single-dose group who received an additional dose of 2vHPV six years after the initial 4vHPV vaccination demonstrated a robust anamnestic response [25, 26].

Canada studies: The first Quebec study was a small, single-group study of 31 girls aged 13 to 18 years who had received a single dose of 4vHPV between three and eight years prior to enrollment through a school-based national vaccination program. At the time of entry into the study, the girls were given a boost dose of nonavalent HPV vaccine (9vHPV). The objectives of the study were twofold: to assess persistence of HPV-specific antibodies after a single dose of 4vHPV and to assess the effect of an additional dose of 9vHPV given several years later [27].

The second Quebec study was a post hoc comparison of antibody responses among the 31 girls included in the first study and those from an independent cohort of 88 girls and 85 boys aged 9 to 10 years who received two doses of 9vHPV six months apart through a clinical HPV vaccine trial [28].

All participants in both studies were seropositive for all four 4vHPV types prior to receiving their second dose. Titers were significantly higher among those in the post hoc analysis compared to the single-group study for HPV 18 but not for the other three types (HPV 6, 11, and 16). Of note, between 58% and 87% of participants in the single-group study were also seropositive to non-4vHPV types prior to administration with 9vHPV.

Following vaccination with the second vaccine dose, all participants in both cohorts were seropositive for the nine 9vHPV types.

US Department of Defense study: The US Department of Defense study was a retrospective cohort analysis of women aged 17 to 26 years who had received one, two, or three doses of 4vHPV through a routine US Department of Defense vaccination program.

In this study, 1,260 women completed the intended three-dose schedule, 420 received two doses, and 411 received only one dose. Prevacination, 62.1% of women tested positive for at least one HPV type (of HPV 6, 11, 16, and 18).

Nearly all three-, two-, and one-dose recipients who were seronegative prevaccination seroconverted for all four HPV types after vaccination. There was no statistical difference in the proportion of seronegative women seroconverting for all four HPV types after vaccination between vaccine dosage groups ($p = 1.0$) [29].

US Pediatric HIV/AIDS Cohort Study (PHACS): This was a prospective observational cohort study of children who received one, two, or three doses of 4vHPV at an average age of 13 years through a national vaccination program. The study included children who were either perinatally HIV infected (PHIV) or perinatally HIV exposed but not infected (PHEU). The study evaluated 4vHPV-type antibody seropositivity and titers approximately three years after the last vaccine dose.

The authors reported antibody seropositivity and titer data for 310 PHIV and 148 PHEU children. Among those PHIV, 90 received three doses, 34 received two doses, 154 received one dose, and 32 were unvaccinated. Among those PHEU, 11 received three doses, 13 received two doses, 91 received one dose, and 33 were unvaccinated.

Overall seropositivity rates for HPV 6, 11, 16, and 18 among PHIV children who received at least one dose of 4vHPV were 83%, 84%, 90%, and 62%, respectively. Among PHEU children, corresponding proportions were 94%, 96%, 99%, and 87%. Seropositivity rates did not vary considerably by number of doses received within either PHIV or PHEU children, but they were significantly higher among vaccine recipients (regardless of the number of doses received) compared to unvaccinated participants.

GMTs for the four 4vHPV types also did not differ considerably between three-, two-, and one-dose recipients, and GMTs were significantly higher for all vaccine recipients (regardless of number of doses received) than for unvaccinated participants [30].

Strengths and limitations of immunogenicity studies of partially vaccinated populations

These immunogenicity studies have several strengths and limitations.

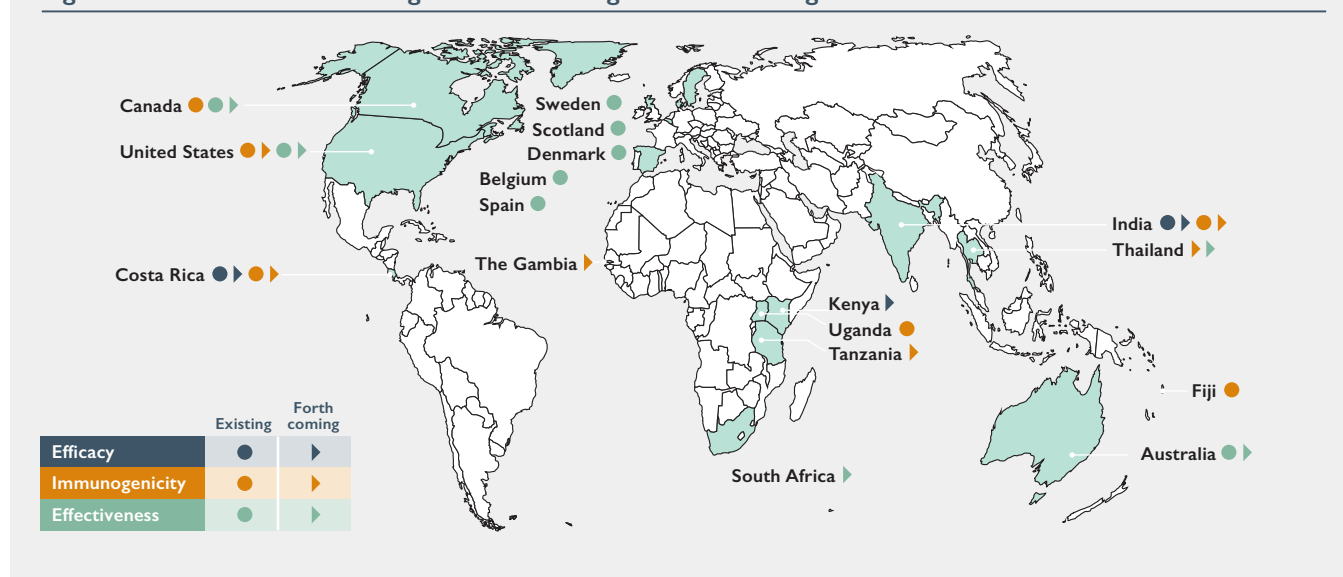
Strengths include:

- Some used the same laboratory assay to assess immune responses as previous clinical HPV vaccine trials, which allowed for comparison to antibody titers reported from clinical trials of adult women who had received single-dose HPV vaccine and among whom efficacy had been demonstrated.
- Some studies had long follow-up time to accommodate an immunogenicity plateau observed 24 months after initial vaccination.
- Where included, non-HPV vaccinated participants had lower antibody titers than single-dose recipients. Furthermore, three-, two-, and one-dose recipients from these immunogenicity studies had higher antibody titers than naturally infected women from prior trials of HPV vaccine.

Limitations include:

- None of the studies was an RCT; therefore, participants might have differed by dose group.
- Neither the Uganda nor the Fiji study reported data on sexual behavior, but all girls in the Uganda study were aged 10 or 11 years at the time of vaccination, and prevalent infections prior to vaccination are highly unlikely in this context.
- The US PHACS did report data on sexual activity and age at sexual debut, and data were not stratified by number of doses received.
- The first Quebec study included only a single group of participants, all of whom received one dose of 4vHPV and were boosted with a dose of 9vHPV. Therefore, no comparisons in immune response can be made with either unvaccinated individuals or multidose recipients within the study.
- Sample sizes were relatively small in all the studies, except the US Department of Defense study, especially among single-dose groups.

Figure 1. Countries with existing and forthcoming evidence on single-dose HPV vaccination.



Data from postlicensure vaccine effectiveness evaluations and other observational studies

Evidence of HPV vaccine effectiveness by number of doses has been compiled through a systematic review of studies that had been published through March 20, 2019 [31]. In total, 23 papers were identified; these are summarized in Table 2.

The main study characteristics included the country, study design, age of study population at vaccination and outcome assessment, sample size according to the number of doses received, case definition, and statistical analyses. Information on use of buffer periods (lag time between vaccination and counting of outcomes) was also collected. All studies were conducted in the setting of national three-dose vaccination programs.

The main outcomes measured were effectiveness of HPV vaccination against HPV infections, anogenital warts, or cervical abnormalities, comparing the incidence or prevalence of HPV-related endpoints between individuals vaccinated with different number of doses of 4vHPV or 2vHPV. Studies were excluded if the vaccine was administered as part of an RCT (e.g., post hoc evaluations of clinical trials).

HPV prevalence

Four studies were identified that reported vaccine effectiveness for reduction of prevalent vaccine-type infection (HPV 16 or 18). Three were from Scotland, which were conducted in the context of a three-dose 2vHPV vaccination program, and one was from the United States, which evaluated vaccine effectiveness among males [32–35].

The first study from Scotland found statistically significant effectiveness for three doses but not for two doses or one dose [32]. The analysis was also stratified by age at vaccination and results were similar, with effectiveness significant only for three doses. In the second study, the authors selected women who were partially vaccinated [33]. In this study, statistically significant effectiveness was found for three doses, two doses, and one dose. However, there was no formal comparison of effectiveness of three doses versus fewer doses in either study; confidence intervals for the effectiveness estimates of three, two, and one dose(s) overlapped.

The third study identified from Scotland used the same surveillance as the first two but included data through 2015. Statistically significant effectiveness was found for three and two doses but not one dose [34].

One small study from the United States was conducted among men. There was no statistically significant effectiveness for at least one dose and no difference in effectiveness by number of doses [35].

Anogenital warts

The review found nine evaluations of anogenital wart outcomes. These were retrospective cohort studies among women from countries that had introduced 4vHPV vaccination [36–44]. The nine studies of anogenital warts were from six different countries. All studies adjusted or stratified analyses for age at vaccination, and some were able to adjust for educational level or markers of socioeconomic status. Most two-dose vaccine recipients received doses separated by two months. Three of the nine studies also included assessment of different buffer periods, and five included assessment of different intervals between doses in two-dose vaccine recipients.

Seven of the nine studies included a comparison of three, two, and one dose(s) with no dose. All seven found the highest point estimate of effectiveness with three doses, and six found lower point estimates but significant effectiveness with two doses. Five of the seven studies found significant effectiveness with one dose [36, 37, 40, 42, 43]. Six studies also formally compared three and two doses, finding no significant difference in either the primary analysis or in analyses

with different buffer periods or two-dose intervals [36, 37, 39, 41–43]. Three studies examined different buffer periods; a longer buffer period decreased differences in effectiveness between three and two doses in one study [37, 39, 41]. In the five studies that explored the interval between doses in two-dose vaccine recipients, two found that a longer interval changed effectiveness estimates or resulted in no difference between three and two doses [36, 39, 41–43].

All five studies that stratified by age at vaccination found higher vaccine effectiveness point estimates with younger age at vaccination, although the differences were not all formally tested [36, 37, 41, 43, 44]. One study was limited to those vaccinated at age 14 years due to the structure of the national vaccination program and found similar effectiveness estimates by number of doses [40]. One study found similar point estimates of effectiveness with three, two, and one doses among those vaccinated at age 15 to 19 years and no significant difference in effectiveness between one and three doses [43].



Photo: PATH

Cervical cytological and histological abnormalities

A total of ten studies evaluated vaccine effectiveness for prevention of cervical cytological or histological abnormalities, including eight for 4vHPV and two for 2vHPV [45–54]. The ten studies were from five different countries. Characteristics of women differed by number of doses in most studies, including for age at first vaccine dose.

Among the ten studies, all found effectiveness for three doses. Five studies found some effectiveness for prevention of high-grade histological abnormalities with two doses, and three studies found effectiveness with one dose among some age groups or in analyses with longer buffer periods [46–48, 53, 54]. Most two-dose vaccine recipients received two doses at one- or two-month intervals. Two studies examined intervals between two doses: One found no impact on the effectiveness estimate. The other found that longer intervals decreased the difference between two and three doses in those vaccinated at age 20 years or younger [47, 53].

Five studies that stratified by age at vaccination found higher vaccine effectiveness point estimates with younger age at vaccination, although not all differences were formally tested [46–48, 51, 53]. In four studies that evaluated effectiveness by number of doses stratified by age at vaccination, differences by number of doses remained in three studies [46–48]. One study found similar point estimates by number of doses when stratifying by age at vaccination, but it only found significant effectiveness for three doses [51]. However, in a large study that was limited to those vaccinated at age 16 years or younger, effectiveness was found for three, two, and one doses, and there was no difference between number of doses [54].

Strengths and limitations of data from postlicensure observational studies

Strengths of the data from the observational studies included the size of the studies, data on buffer periods for some studies, and some information on intervals between doses. Some studies stratified by age at vaccination or limited analyses to those vaccinated at younger ages.

Important weaknesses of the available postlicensure studies and caveats that should be considered when interpreting the findings include:

- The postlicensure studies were all conducted in settings of a national three-dose recommendation. Girls who received one or two doses differed from those completing the recommended schedule. Because of these differences, girls who received fewer doses were likely to be at higher risk of incident HPV infection or have history of prevalent HPV infection. This biased results toward greater effectiveness of three doses compared to one or two doses.
- Since all postlicensure studies published to date were conducted in settings of a national three-dose recommendation, most individuals vaccinated with two doses had received doses at a 0, 1-month or 0, 2-month intervals. However, immunogenicity studies have found non-inferior results with two doses compared to three doses when the two doses were separated by about six months [8, 55, 56]. The longer interval is thought to allow maturation of B cells and the second vaccination to act as a booster dose.
- In most retrospective studies, it was not possible to identify individuals who were already infected with HPV at the time of vaccination. Since girls vaccinated with one or two doses in the studies were often older when vaccinated, prevalent infections at the time of vaccination could have biased results toward lower vaccine effectiveness of fewer than three doses.

Mathematical modeling of impact of reduced-dosing schedules

The limited number of published studies on modeling of reduced-dose strategies (three to two doses) for the 2vHPV, 4vHPV, and 9vHPV were examined in order to identify key factors related to the impact of reduced dosages and their cost-effectiveness. Specifically, four published analyses have addressed the question of reducing from three to two doses in the context of high-income settings, three with either the 2vHPV or 4vHPV and one with the 9vHPV [57–60]. These analyses explored the impact of duration of protection, with equivalent or shorter duration for two doses compared to three doses; quality-adjusted life years (QALYs); and cancer incidence reduction.

Comparative analyses of two-dose 2vHPV and 4vHPV vaccination using independent dynamic transmission models fitted to the United Kingdom (Public Health England model) and Canada [HPV-ADVISE (Agent-based Dynamic model for Vaccination and Screening Evaluation) model] found that the health benefits in terms of cancer incidence reduction and QALYs gained were substantial with two-dose HPV vaccination, even when vaccine protection waned at 30, 20, or 10 years [57, 58]. However, the incremental benefit of adding a third dose varied greatly dependent on duration of two-dose protection. These initial studies suggest that the duration of protection afforded by reduced dosages is a critical factor in determining the impact and cost-effectiveness of HPV vaccination.

Additional findings were consistent across analyses evaluating two-dose HPV vaccination.

- Compared to no vaccination, two-dose HPV vaccination yields substantial health benefits and is good value for money, even when the duration of reduced-dose protection is only ten years.
- The health impact and cost-effectiveness of adding a third vaccine dose hinge on the relative duration of protection for two doses versus three doses.
- The relative gain in health impact by adding a third vaccine dose will be minimal if two-dose protection is 20 to 30 years and assuming no initial waning in the first 10 years for either two or three doses.
- If two-dose protection is less than ten years, adding a third vaccine dose will have greater health impact and is likely to be cost-effective.

Two analyses have evaluated single-dose HPV 16 and 18 vaccination, both in the context of routine girls-only vaccination in high-income countries (United Kingdom and United States) [61, 62]. A third analysis extended the findings from the US-based analysis to evaluate the health impact and cost-effectiveness of single-dose HPV 16 and 18 vaccination in Uganda [24]. The following themes emerged from the limited analyses of evaluating single-dose HPV vaccination.

- 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% and lower duration of protection of only ten years.
- The impact and cost-effectiveness of adding a second dose are driven by the duration of single-dose vaccine protection and, possibly, the ability to achieve higher coverage with single-dose versus multiple doses.

One published modeling study evaluated the population-level impact of single-dose 9vHPV vaccination on reducing cervical cancer incidence and mortality in South Africa, taking into consideration HIV status, CD4 count, and antiretroviral therapy coverage [63]. The analysis used a dynamic HIV transmission model calibrated and validated to data from KwaZulu-Natal, South Africa. This model was adapted to include not only sexual transmission of HIV but also high-risk HPV and the natural history of cervical precancerous lesions and invasive cancer. HIV infection impacted HPV transmission, as well as progression and regression of HPV and precancer, as a function of CD4 count.

This analysis did not compare the effectiveness or cost-effectiveness of two doses versus one dose; rather, it was used to project the long-term effects of single-dose 9vHPV vaccination of 9-year-old girls on cervical cancer incidence and mortality by age and over time. The authors concluded that single-dose 9vHPV vaccination in a high HIV prevalence setting can yield high reductions in cervical cancer incidence and mortality, and these relative reductions are similar irrespective of HIV status, CD4 count, or ART coverage.

Gaps in the evidence, research priorities, and forthcoming evidence

Several clinical studies have examined single-dose regimens and demonstrated results that challenge the prevailing dogma that all protein-based subunit vaccines require a multidose regimen. These observations and the potential public health impact of an effective single-dose HPV vaccination strategy suggest that further studies on the efficacy of single-dose HPV vaccines are warranted. Several evidence gaps and research questions are being addressed or will need to be addressed in the coming years. Below are some, but not all, of the critical gaps and key questions that remain, and the studies currently in progress to address them. The new and ongoing studies and their methods are summarized in Table 3.

- 1. Durability of protection:** Will a single dose of HPV vaccine provide sufficient protection for a long enough period of time to have an impact on HPV infection and/or HPV disease outcomes?

Currently, it is not known if a single dose of HPV vaccine will provide a sufficient and durable enough level of efficacy against persistent HPV infection to support a recommendation for a policy change to a single-dose vaccination strategy.

Longer-term immune response data are still forthcoming from CVT and the India IARC HPV Trial, as well as longer-term efficacy observations. These studies will help to determine the duration of efficacy (and levels of efficacy over time).

- 2. Single-dose efficacy:** Will a single dose of HPV vaccine provide efficacy against clinical 6- or 12-month persistent infection and/or clinical disease?

Prospective RCTs will be able to provide more definitive data on whether single-dose HPV vaccination can protect against HPV-persistent infection and provide immunobridging data to other trials without efficacy endpoints. Several ongoing trials are investigating efficacy and/or immune responses and safety of a single dose of HPV vaccine compared to recommended dose regimens or controls.

In Costa Rica, **ESCUDDO** (Estudio de Comparacion de Una y Dos Dosis de Vacunas Contra el Virus de Papiloma Humano) aims to find out if one dose of either the 2vHPV or 9vHPV is as effective as two doses of these vaccines [64].

In Kenya, the **KEN-SHE** (Kenya Single-dose HPV vaccine Efficacy) study is randomizing participants to receive either immediate single-dose HPV vaccination (2vHPV or 9vHPV) and delayed second dose of meningococcal vaccine or immediate meningococcal vaccine and delayed HPV vaccine (9vHPV) [65].

3. Single-dose effectiveness: Will population-level HPV prevalence after a single dose of HPV vaccine be similar to population-level HPV prevalence after two doses of HPV?

In Thailand, the **IVIHPV I** (Effectiveness of Single Dose or Two Doses of Bivalent HPV Vaccine in Thailand) study is a community intervention study. Grade 8 female students from two provinces will be vaccinated with either one or two doses of HPV vaccine (2vHPV), and a series of cross-sectional surveys will provide population-level impact [66].

In South Africa, the **HOPE** (HPV One/Two Dose Population Effectiveness) study also aims to assess the population-level effectiveness of one versus two HPV vaccine doses. The study is embedded within the South African national HPV vaccination program, which has been administering two doses of 2vHPV to girls aged 9 years since 2014 [67].

4. Single-dose immunogenicity: Will a single dose of HPV vaccine provide a sufficiently robust immune response, in terms of antibody titers, memory B-cell response, and T-cell activation, that could “bridge” to levels measured among populations where efficacy is demonstrated?

In Tanzania, **DoRIS** (Dose Reduction Immunobridging and Safety Study of Two HPV Vaccines in Tanzanian Girls) is an ongoing RCT intended to establish whether a single dose of HPV vaccine (2vHPV and 9vHPV) produces immune responses that are likely to be effective in preventing cervical cancer [68].

In The Gambia, the **HANDS** (HPV Vaccination in Africa – New Delivery Schedules) study is a second immunogenicity trial that will compare one and two doses of 9vHPV in 4- to 8-year-old girls and 9- to 14-year-old girls with three doses in 15- to 26-year-old women [69].

5. Standardization of laboratory assays: How do we measure seropositivity and immune responses comparatively between 2vHPV, 4vHPV, and 9vHPV?

The inability to compare immune responses of a single-dose HPV vaccine across studies due to heterogeneity in laboratory methods and cutoff thresholds for seropositivity creates a significant gap in the evidence. Efforts are now underway to standardize the immunological testing for antibody titers so that the results of the CVT and IARC India HPV Trial can be compared directly as well as the results of future trials (including ESCUDDO, DoRIS, and KEN-SHE).

Effectiveness data from postlicensure surveillance and ecological studies

Further findings from surveillance and ecological studies evaluating the effectiveness of single-dose HPV vaccination are expected to be published over the year ahead, including studies from the United States, Canada, and Australia. The systematic review of effectiveness studies will be updated regularly, allowing inclusion of these and other newly published studies.

Systematic reviews of the literature conducted to date identified studies that used different outcomes, buffer periods, and/or age groups at vaccination and at outcome assessment. Therefore, it was not possible to pool the results from the different studies.

Until recently, there has not been a suitable tool for assessing the quality of evidence and risk of bias derived from postlicensure surveillance and ecological studies comparing single-dose HPV vaccination to either no vaccination or multidose schedules. There is an ongoing effort to adapt the ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) framework to take into account the characteristics of reduced-dose observational studies (e.g., different types of study design, use of buffer periods to control for prevalent infection at first dose, etc.) to formally assess the quality of these studies [70].

Modeling studies

Given the ongoing activities related to evaluating single-dose vaccination, several important research priorities exist for future modeling studies. First, it will be critical for the models to continue to synthesize and integrate new data as they emerge from the ongoing studies and trials.

Results from the long-term follow-up of the CVT and IARC India HPV Trial will continue to refine the plausible lower limits of duration of protection. Model-based impact and cost-effectiveness analyses are already included as part of the existing single-dose HPV vaccine trials. The close involvement of modelers in the ongoing efficacy and immunogenicity trials will enable timely and relevant model updates and analyses. It also will provide a forum for the modelers to share assumptions and explorations and perform comparative modeling exercises to unveil important similarities and differences in results.

Given the limited clinical trial settings, it will also be important to conduct modeling extrapolations and analyses in different countries with varied epidemiological profiles, population demographics, and sexual behaviors in order to continue to identify important factors and uncertainties that could inform decision-making in a particular setting. Likewise, it will be essential to explore single-dose vaccination in the context of both settings that have already initiated multidose HPV vaccination programs (the one- versus two- or three-dose scenario), as well as settings in which HPV vaccination has not yet been adopted (the single-dose versus no-vaccine scenario). Moreover, the models can be used to explore opportunities for, and design of, innovative strategies for vaccine delivery given the unconventional target age group of adolescents and the requirement for multiple doses over multiple contacts.

In South Africa and other countries with high prevalence of HIV infection, it will be critical to generate more evidence on the health and economic impacts of reduced dose HPV vaccination in HIV-positive individuals.

The evidence on single-dose schedule HPV vaccination is encouraging. The limitations of previous studies are being overcome by new studies with more robust data. The Single-Dose HPV Vaccine Evaluation Consortium will continue to monitor and update the evidence base and share results widely.



Photo: PATH/Scott LaMontagne

Table 2.
Studies that evaluated HPV vaccine effectiveness by number of doses: main findings.

Endpoint/ Authors	Study population age (years) at vaccination (V) & outcome (O)	Country/ Vaccine	n	Formal comparison of 3 vs 2 or 1 doses	Main findings
Efficacy/Immunogenicity					
Kreimer 2011 [16]	V: 18–25 O: 28–35	Costa Rica (CVT) Bivalent	3,727	Yes	<ul style="list-style-type: none"> The 4-year analysis found that fewer than 3 doses (2 or 1) of the vaccine protect as well as the full 3-dose series for 4 years. Antibody titers achieved following 2 doses (0 and 6 months) of the HPV vaccine are high and only slightly lower than those observed after 3 doses (1-dose antibody titers were lower than those of 2 and 3 doses, but higher than natural infection levels and remained stably elevated over 4 years).
Sankaranarayanan 2016 [12]	V: 10–18 O: 12–20	India Quadrivalent	17,729	Yes	<ul style="list-style-type: none"> Immune response in the 2-dose HPV vaccine group was non-inferior to the 3-dose group at 7 months but was inferior in the 2-dose default and 1-dose default groups at 18 months. Fewer than 3 doses by design and default induced detectable concentrations of neutralizing antibodies to all 4 vaccine-targeted HPV types, but at much lower concentration after 1 dose. Cervical samples from 2,649 participants were tested, and the frequency of incident HPV 16, 18, 6, and 11 infections were similar irrespective of the number of vaccine doses received. The testing of at least 2 samples from 838 participants showed that there were no persistent HPV 16 or 18 infections in any study group at a median follow-up of 4 to 7 years.
LaMontagne 2014 [24]	V: 11–12 O: 13–16	Uganda Bivalent	376	Yes	<ul style="list-style-type: none"> GMT ratio for 1:3 doses for HPV 16 and HPV 18 was inferior, but absolute GMTs for 1 dose were higher than adult women who received 1 dose (where efficacy has been demonstrated). Even though immunogenicity with fewer than 3 doses did not meet prior non-inferiority thresholds, antibody levels measured ≥ 24 months after last dose were similar to those of adult women who had been followed for more than 8 years for efficacy.
Toh 2017 [25]	V: 9–12 O: 15–19	Fiji Quadrivalent	200	Yes	<ul style="list-style-type: none"> After 6 years, the geometric mean NAb titers for all 4 HPV types were not statistically different between 2-dose and 3-dose recipients: HPV 6 (3:2,216 [95% CI], 1,695–2,896]; 2:1,476 [95% CI, 1,019–2,137]; P = .07), HPV 11 (3:4,431 [95% CI, 3,396–5,783]; 2:2,951 [95% CI, 2,452–4,373]; P = .89); HPV 18 (3:628 [95% CI: 445–888]; 2:606 [95% CI, 462–862] P = .89). Although 1-dose recipients had significantly lower NAb titers than 2- or 3-dose recipients, their NAb titers were fivefold to thirtyfold higher than unvaccinated girls. 2 doses of 4vHPV provide similar NAb titers as 3 doses for 6 years. 1 dose of 4vHPV elicits antibodies that persisted for at least 6 years and induced immune memory.

Endpoint/ Authors	Study population age (years) at vaccination (V) & outcome (O)	Country/ Vaccine	n	Formal comparison of 3 vs 2 or 1 doses	Main findings
Toh 2018 (26)	V: 9–12 O: 15–19	Fiji Quadrivalent	59	Yes	<ul style="list-style-type: none"> Examined the cellular immunity of 0, 1, 2, and 3 doses 4vHPV after 6 years and responses to a subsequent dose of 2vHPV. After 6 years, the HPV 18-specific responses were significantly lower in the 1- and 2-dose compared with 3-dose recipients: 2: IFNγ-ELISPOT: P = .008; cytokines, IFNγ: P = .002; IL-2: P = .022; TNFγ: P = .016; IL-10: P = .018; IL-2: P = .031; IL-10: P = .014. These differences were no longer significant post-2vHPV. No significant differences in HPV 16 responses were observed between the 2- or 1-dose recipients and 3-dose recipients.
Gilca [1] 2019 (27)	V: 13–18 (4vHPV) V: 16–26 (9vHPV) O: 16–26	Canada Quadrivalent Nonavalent	31	No	<p>After 1 dose of 4vHPV:</p> <ul style="list-style-type: none"> All participants were seropositive to the HPV types included in the 4vHPV administered 3 to 8 years earlier, and 58% to 87% had antibodies to the 5 other HPV types included in the 9vHPV. GMTs were 6.1 AU/ml, 7.7 AU/ml, 20.1 IU/ml, and 6.3 IU/ml for HPV 6, HPV 11, HPV 16, and HPV 18, respectively. <p>After 1 dose of 9vHPV:</p> <ul style="list-style-type: none"> 1-month post administration 100% of the participants were seropositive to all 9 HPV types with a 36.1 to 89.1-fold increase of GMTs. The GMTs to HPV types 31, 33, 45, 52, and 58 were slightly higher (all p > 0.05) in subjects seropositive pre-9vHPV dose administration, increasing 24.3- to 82.1-fold in those seropositive and 62.1 to 236.0-fold in those seronegative.
Gilca [2] 2019 (28)	V: 8–9 girls and boys (9vHPV)	Canada Nonavalent	88 girls 85 boys	No	<ul style="list-style-type: none"> Cohort was compared to the cohort in Gilca [1] above. All participants were seropositive to HPV 6, 11, 16, and 18 prior to receiving dose 2. Following dose 2, all participants were seropositive for the 9 9vHPV types.
Mosckicki 2019 (30)	V: 7–16	United States Quadrivalent	458	No	<ul style="list-style-type: none"> Compared antibody titers to HPV 6, 11, 16, and 18 between PHIV and PHEU youth. 83%, 84%, 90%, and 62% were seropositive for HPV 6, 11, 16, and 18 among PHIV participants compared to 94%, 96%, 99%, and 87% of PHEU. Fewer vaccinated PHIV than PHEU were seropositive across all dose categories and HPV types, which was statistically significant among those receiving 1 dose for HPV 11, 16, and 18. Within each cohort, GMTs were similar for 1, 2, or 3 doses. PHIV had lower GMTs, regardless of doses, than PHEU.

Endpoint/ Authors	Study population age (years) at vaccination (V) & outcome (O)	Country/ Vaccine	n	Formal comparison of 3 vs 2 or 1 doses	Main findings
Anogenital warts					
Herweijer 2014 [37]	V: 10–19 O: 10–24	Sweden Quadrivalent		Yes	<ul style="list-style-type: none"> Statistically significant effectiveness against first occurrence of condyloma (warts) for 3, 2, and 1 doses compared to 0 doses: 3: aRR = .20 (CI .17, .23), 2: aRR = .32 (CI .26, .40), 1: aRR = .54 (CI .43, .68). Significantly higher effectiveness of 3 compared to 2 and 1 doses. With buffer periods >4 months, no significant difference between 3 and 2 doses. Similar results for age groups 10–16 years and 17–19 years, except effectiveness for 1 dose without buffer period statistically significant for 10–16-year olds.
Blomberg 2015 [36]	V: 12–27 O: 12–27	Denmark Quadrivalent		Yes	<ul style="list-style-type: none"> Statistically significant effectiveness for reducing risk of genital warts; 1 compared to 0 dose: RR = .51 (CI .46, .56). Effectiveness not reported for 3 and 2 doses compared to 0 doses. Effectiveness significantly increased with each dose: RR 2 vs 1 dose = .44 (CI .37, .51); RR 3 vs 2 doses = .46 (CI .39, .54). With dose interval >4 months, no significant difference between 3 and 2 doses. Similar results when stratified by age at vaccination.
Dominiak- Felden 2015 [38]	V: 10–23 O: 16–23	Belgium Quadrivalent		No	<ul style="list-style-type: none"> Statistically significant effectiveness against incidence of genital warts for 3 and 2 doses, but not 1 compared to 0 doses: 3: aRR = .12 (CI .07, .21); 2: aRR = .34 (CI .14, .83); 1: aRR = .63 (CI .35, 1.16). Effectiveness CI overlap for 3 and 2 doses; no overlap for 3 and 1 doses.
Perkins 2017 [39]	V: 9–25 O: 9–25	United States Quadrivalent		Yes	<ul style="list-style-type: none"> Statistically significant effectiveness against incidence of anogenital warts for 3 doses compared to 0 dose: aRR = .52 (CI .46, .60). Effectiveness not reported for 2 and 1 doses compared to 0 dose. Higher effectiveness for 3 compared with 1 dose: aRR = .82 (CI .71, .95); but no significant difference between 3 and 2 doses: aRR = .89 (CI .78, 1.03). With buffer period of 1 year; no change in findings (data not shown). Similar results with dose interval >5 months for 2 doses.
Navarro- Illana 2017 [40]	V: 14 O: 14–19	Spain Quadrivalent		No	<ul style="list-style-type: none"> Statistically significant effectiveness against incident cases of anogenital warts for 3, 2, and 1 doses compared to 0 dose: 3: aRR = .24 (CI .15, .34); 2: aRR = .36 (CI .14, .68); 1: aRR = .39 (CI .13, .80). Effectiveness CI overlap for 3, 2, and 1 doses.

Endpoint/ Authors	Study population age (years) at vaccination (V) & outcome (O)	Country/ Vaccine	n	Formal comparison of 3 vs 2 or 1 doses	Main findings
Lamb 2017 [41]	V: 10–19 O: 10–27	Sweden Quadrivalent		Yes	<ul style="list-style-type: none"> Effectiveness against incidence of genital warts not reported for 3, 2, and 1 doses compared to 0 doses. Higher effectiveness of 3 doses compared to 2 doses, when 2 doses administered either 0–3 months or >8 months apart; whereas no significant difference between 3 and 2 doses when the 2 doses administered within 4–7 months. Similar results when stratified by age at vaccination.
Hariri 2017 (42)	V: 16–17 O: 11–22	United States Quadrivalent		No	<p>6-month buffer from last dose</p> <ul style="list-style-type: none"> Significant effectiveness for 3 and 2 doses, but not for 1 dose compared to 0 dose: 3: aHR = .23 (CI .17, .31); 2: aHR = .32 (CI .17, .59); 1: aHR = .81 (CI .60, 1.08). No significant difference for effectiveness of 3 vs 2 doses: aHR = .74 (CI .38, 1.43) when 2 doses \geq 6-month interval. Significantly greater effectiveness of 3 doses vs 1 dose: aHR = .29 (CI .20, .42) <p>12-month buffer from first dose</p> <ul style="list-style-type: none"> Significant effectiveness for 3, 2, and 1 doses compared to 0 dose: 3: aHR = .20 (CI .15, .27); 2: aHR = .24 (0.13, .44); 1: aHR = .32 (CI .20, .52). No significant difference for effectiveness of 3 doses vs 1 dose: aHR = .63 (CI .37, 1.09).
Zeybek 2018 (43)	V: 9–26 O: 10–31	United States Quadrivalent		No	<p>Results for those vaccinated at age 15–19 years: no significant effectiveness in older or younger age groups.</p> <ul style="list-style-type: none"> Significant effectiveness for 3, 2, and 1 doses compared to 0 dose: 3: aRR = .58 (CI .49, .70); 2: aRR = .67 (CI .51, .89); 1: aRR = .65 (CI .49, .85). Similar results with dose interval \leq 6 or >6 months for 2 doses. No significant differences for effectiveness of 3 vs 1, 3 vs 2, or 2 vs 1 doses.
Willows 2018 (44)	V: 9–26 O: 10–33	Canada Quadrivalent		No	<p>Results for those vaccinated at age 9–18 years: no significant effectiveness for those vaccinated at older ages.</p> <ul style="list-style-type: none"> Significant effectiveness for 3, but not 2 or 1 doses compared to 0 dose: 3: aHR = .4 (CI .3, .7); 2: aHR = 1.4 (CI .6, 3.3); 1: aHR = .6 (CI .2, 1.8). Effectiveness CI overlap for 3, 2, and 1 doses.

Endpoint/ Authors	Study population age (years) at vaccination (V) & outcome (O)	Country/ Vaccine	n	Formal comparison of 3 vs 2 or 1 doses	Main findings
Cervical abnormalities					
Gertig 2013 (45)	V: 12–19 O: 12–21	Australia Quadrivalent		No	<p>Outcome summarized: CIN3/AIS</p> <ul style="list-style-type: none"> Statistically significant effectiveness for 3, but not 2 and 1 doses compared to 0 dose: 3: aRR = .53 (CI .36, .77); 2: aRR = .87 (CI .46, 1.67); 1: aRR = 1.40 (CI .75, 2.61). Effectiveness CI overlap for 3, 2, and 1 doses.
Crowe 2014 (46)	V: 12–26 O: 11–31	Australia Quadrivalent		No	<p>Outcome summarized: High-grade histological lesions.</p> <ul style="list-style-type: none"> Statistically significant effectiveness for 3 and 2 doses, but not 1 compared to 0 dose: 3: aOR = .54 (CI .43, .67); 2: aOR = .79 (CI .64, .98); 1: aOR = .95 (CI .77, 1.16). Effectiveness CI overlap for 3 and 2 doses, no overlap for 3 and 1 doses. Buffer periods from 1 to 12 months: no consistent impact on 3, 2, and 1 dose effectiveness estimates. Similar results when stratified by age at vaccination.
Pollock 2014 (50)	V: 15–17 O: 20–21	Scotland Bivalent		No	<p>Outcome summarized: CIN3</p> <ul style="list-style-type: none"> Statistically significant effectiveness for 3, but not 2 and 1 doses compared with 0 dose: 3: aRR = .45 (CI .35, .58); 2: aRR = .77 (CI .49, 1.21); 1: aRR = 1.42 (CI .89, 2.28). Effectiveness CI overlap for 3 and 2 doses, no overlap for 3 and 1 doses.
Brotherton 2015 (47)	V: 12–26 O: 12–30	Australia Quadrivalent		No	<p>Outcome summarized: CIN3/AIS</p> <ul style="list-style-type: none"> Statistically significant effectiveness for 3, but not 2 and 1 doses compared to 0 dose: 3: aRR = .69 (CI .58, .81); 2: aRR = 1.17 (CI .92, 1.48); 1: aRR = 1.41 (CI 1.12, 1.77). Effectiveness CI for 3, 2, and 1 doses do not overlap. With increasing buffer periods, some effectiveness for 2 and 1 doses in several age groups. No difference in effectiveness by interval between two doses. Similar results when stratified by age at vaccination.
Hofstetter 2016 (48)	V: 11–20 O: 11–27	United States Quadrivalent		No	<p>Outcome summarized: Any abnormal cytology.</p> <ul style="list-style-type: none"> Statistically significant effectiveness for 3 and 2 doses, but not 1 dose compared to 0 dose: 3: aRR = .58 (CI .48, .69); 2: aRR = .81 (CI .66, .99); 1: aRR = 1.05 (CI .88, 1.26) Effectiveness CI overlap for 3, 2, and 1 doses. Similar results when stratified by age at vaccination, although effectiveness of 2 doses compared to 0 dose not always significant.

Endpoint/ Authors	Study population age (years) at vaccination (V) & outcome (O)	Country/ Vaccine	n	Formal comparison of 3 vs 2 or 1 doses	Main findings
Kim 2016 (49)	V: 10–15 O: 18–21	Canada Quadrivalent		No	<p>Outcome summarized: High-grade cytology.</p> <ul style="list-style-type: none"> Statistically significant effectiveness for 3, but not 2 and 1 doses compared with 0 dose: 3: aOR = .48 (CI .28, .81); 2: aOR = .17 (CI .02, 1.20); 1: aOR = .45 (CI .11, 1.83) Effectiveness CI overlap for 3, 2, and 1 doses.
Cameron 2017 (52)	V: 15–17 O: 20–21	Scotland Bivalent		No	<p>Outcome summarized: CIN 2/CIN 3.</p> <ul style="list-style-type: none"> Significant effectiveness with 3 doses in all deprivation categories compared with unvaccinated in most deprived; no significant effectiveness with 1 or 2 doses.
Silverberg 2018 (51)	V: 14–21 O: 18–26	United States Quadrivalent		No	<p>Outcome summarized: CIN2, CIN3, adenocarcinoma in situ, or CIN2+ and CIN3+.</p> <ul style="list-style-type: none"> 1 or more HPV vaccine doses conferred protection against CIN2+ RR 0.82 (CI 0.73–0.93) and CIN3+ 0.77 (CI 0.64–0.94). Strongest protection against CIN2+ in 3 doses with dose 1 at age 14–17 years: RR 0.52, (CI 0.36–0.74) or aged 18–20 years RR 0.65 (CI 0.49–0.88). No significant protection in 21 years or older at time of dose 1 RR 0.94 (CI 0.81–1.09). Inferences were similar for CIN3+, but with stronger with 3 doses with dose 1 at 14–17 years (0.27, 0.13–0.56) or 18–20 years (0.59, 0.36–0.97).
Dehlendorff 2018 (53)	V: 13–30 O: 13–30	Denmark/ Sweden Quadrivalent		No	<p>Outcome summarized: CIN2 or CIN2+.</p> <ul style="list-style-type: none"> 3 doses showed a reduced risk of CIN2+ if vaccinated <20 years; further reduced risk if vaccinated before 17 years. 2 doses, with dose 2 at 5 months or longer after 1 dose did not yield an increased risk of CIN2+, compared to 3 doses. <16 years: 3 doses IRR .23 (CI .11–.49); 2 doses IRR .44 (CI .1–2.07); 1 dose IRR .23 (CI .01–5.24). 17–19 years: 3 doses IRR .65 (CI .41–1.03); 2 doses IRR .65 (CI 1.25–1.74); 1 dose IRR .58 (CI .15–2.19) 20–29 years: 3 doses IRR 1.31 (CI .97–1.76); 2 doses IRR 1.56 (CI 1.15–2.11); 1 dose IRR 1.56 (CI 1.13–2.15)
Verdoordt 2019 (54)	V: 12–16 O: 17–25	Denmark		No	<p>Outcome summarized: CIN2+ and CIN3+.</p> <ul style="list-style-type: none"> 3 doses IRR 0.37 (CI .30–.45); 2 doses IRR 0.38 (CI .22–.66); 1 dose IRR 0.38 (CI .14–.98). Results were similar for CIN2+.

Endpoint/ Authors	Study population age (years) at vaccination (V) & outcome (O)	Country/ Vaccine	n	Formal comparison of 3 vs 2 or 1 doses	Main findings
HPV prevalence					
Kavanagh 2014 (32)	V: 15–17 O: 20–21	Scotland Bivalent		No	<ul style="list-style-type: none"> Statistically significant vaccine effectiveness against HPV prevalence for 3, but not 2 or 1 doses compared to 0 dose: 3: aOR = .43 (CI .34, .55); 2: aOR = .68 (CI .42, 1.12); 1: aOR = .95 (CI .51, 1.76). Effectiveness CI overlap for 3, 2, and 1 doses. Similar results when stratified by age at vaccination.
Cuschieri 2016 (33)	V: 15–17 O: 20–21	Scotland Bivalent		No	<ul style="list-style-type: none"> Statistically significant vaccine effectiveness against prevalent HPV infection for 3, 2, and 1 doses compared to nonvaccinated population: 3: aOR = .27 (CI .20, .37); 2: aOR = .45 (CI .29, .69), 1: aOR = .52 (CI .31, .83). Effectiveness CI overlap for 3-, 2-, and 1-dose groups.
Kavanagh 2017 (34)	V: 12–18 O: 20–21	Scotland Bivalent		No	<ul style="list-style-type: none"> Significant effectiveness for 3 and 2 doses but not 1 dose compared to 0 dose: 3: aOR=.40 (CI .33, .48); 2: aOR=.75 (CI .57, .99); 1: aOR=.89 (CI .63, 1.25). Effectiveness CI do not overlap for 3 vs 2 and 1 doses.
Chandler 2018 (35)	V: NA O: 13–26	United States Quadrivalent		No	<ul style="list-style-type: none"> Study conducted among males only. No significant effectiveness for at least 1 dose compared to 0 dose. No significant differences for effectiveness of 3 vs 1, or 3 vs 2 doses.

Note: 2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent vaccine; AIS, adenocarcinoma in situ; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted relative risk; CI, confidence interval; CIN, cervical intraepithelial neoplasia; GMT, geometric mean titer; HPV, human papillomavirus; IRR, incidence rate ratio; Nab, neutralizing antibody; O, outcome; PHEU, perinatally HIV exposed but not infected; PHIV, perinatally HIV infected; RR, relative risk; V, vaccination; vs, versus.

Table 3.
Ongoing and forthcoming efficacy, effectiveness, and immunogenicity studies of single-dose HPV vaccination.

Study	Country	Study population	Vaccine(s)	Study design	Key endpoint(s)	Start date & FU / duration
Efficacy/Immunogenicity						
CVT EXTEND (71, 72)	Costa Rica	1,000 females vaccinated aged 18–25 y	2vHPV	Long-term follow-up study of participants previously vaccinated with 1 v 2 v 3 doses through an RCT	Humoral immunogenicity	Start: July 2018 Follow-up: To 15 years post first vaccination
DoRIS (68)	Tanzania	930 females aged 9–14 y	2vHPV & 9vHPV	RCT of 1 v 2 v 3 doses	Humoral & cellular immunogenicity; Cost-effectiveness; Acceptability	Start: February 2017 Follow-up: 36 months
ESCUDDO (64)	Costa Rica	20,000 females aged 12–16 y (RCT) & 4,000 females aged 17–20 y (epi study)	2vHPV & 9vHPV	RCT of 1 v 2 doses & epidemiological study of 1 dose v no vaccination	Vaccine efficacy against HPV infection; Humoral immunogenicity	Start: November 2017 Follow-up: 48 months
HANDS (69)	The Gambia	1,720 females aged 4–26 y	9vHPV	RCT of 1 v 2 v 3 doses	Humoral immunogenicity; Safety; Tolerability	Start: July 2019 Follow-up: 36 months
HOPE (67)	South Africa	~7,000 girls aged 15–16 y (1-dose catch up) & ≥3,260 sexually active girls aged 17–18 y per surveys	2vHPV	Intervention study of 1-dose catch-up v 2-dose national program, using repeat cross-sectional surveys	Population effectiveness against HPV infection; Cross-protection; Herd protection; Sociodemographic & behavioral correlates of uptake & impact	Start: February 2018 Duration: 48 months
IARC India HPV-vaccine efficacy study (73)	India	17,729 vaccinated females aged 10–18y & 1,540 age-matched unvaccinated females	4vHPV	Observational cohort study of 1 v 2 v 3 doses, and v no vaccination (extended follow-up)	Vaccine efficacy against HPV infection; Humoral immunogenicity	Start: September 2009 Follow-up: To 11 years post first vaccination
IVIHPV1 (66)	Thailand	~18,000 female students (intervention) & between ~4,000 and 9,200 female students per survey	2vHPV	Intervention study of 1 v 2 doses, using repeat cross-sectional surveys	Population effectiveness against HPV infection; Humoral immunogenicity	Start: December 2018 Duration: 48 months
KEN-SHE (65)	Kenya	2,250 sexually active females aged 15–20 y	2vHPV & 9vHPV	RCT of 1 dose v delayed vaccination	Vaccine efficacy against HPV infection; Humoral & cellular immunogenicity; Cost-effectiveness	Start: December 2018 Follow-up: 36 months
US study (74)	US	200 males and females aged 9–11 y	9vHPV	Intervention study of 1 dose v deferred-booster dosing schedule	Immunogenicity	Start: March 2016 Follow-up: 48 months

Note: 2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent vaccine; CVT, Costa Rica Vaccine Trial; DoRIS, Dose Reduction Immunobridging and Safety Study of Two HPV Vaccines in Tanzanian Girls; ESCUDDO, Estudio de Comparación de Una y Dos Dosis de Vacunas Contra el Virus de Papiloma Humano; HANDS, HPV Vaccination in Africa – New Delivery Schedules; HOPE, HPV One/Two Dose Population Effectiveness; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; IVIHPV1, Effectiveness of Single Dose or Two Doses of Bivalent HPV Vaccine in Thailand; KEN-SHE, Kenya Single-dose HPV vaccine Efficacy; RCT, randomized controlled trial; v, versus; y, years.

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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, and Wits Reproductive Health and HIV Institute.

In addition to the consortium members, representatives from the following institutions serve as advisors: the World Health Organization, International Agency for Research on Cancer; Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine; Instituto Nacional de Salud Pública de Mexico; Quebec Institut National de Santé Publique; Victorian Cytology Service, Australia; University of Washington, USA; and International Vaccine Institute, South Korea.

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For information about the Single-Dose HPV Vaccine Evaluation Consortium and access to the full review of current evidence, visit path.org/singledosehpv.

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