4TH EDITION | TECHNICAL SYNTHESIS

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 10 years, initially as a three-dose regimen offered over 6 months, and then as a two-dose regimen for individuals aged younger than 15 years. The reduced dose schedule came in 2014 after a review of the evidence by the World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization. Evidence today shows that a single dose of HPV vaccine provides protection against HPV infection comparable to a multidose regimen. As a result, in June 2022, WHO's SAGE issued an updated recommendation for one or two doses of HPV vaccine for girls and young women 9-20 years of age.

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. Since 2018, the Consortium has compiled an Evidence Review of the current, published evidence on single-dose HPV vaccination, including data from efficacy trials, immunogenicity studies, other observational studies, and mathematical impact modeling. The Consortium also provides commentary on the strength of that evidence and the gaps that remain. Its 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 synthesis provides an overview of the Evidence Review's 4th version, which can be accessed at path.org/singledosehpv.

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 low- and middle-income countries (LMICs) (1). In 2020, the International Agency for Research on Cancer (IARC) estimated that there were nearly 605,000 new cases of cervical cancer and over 341,000 cervical cancer–related deaths per annum globally, with greater than 85% of invasive cases occurring in LMICs (2). 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 LMICs, 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.

In November 2020, WHO launched the global strategy to accelerate the elimination of cervical cancer as a public health problem, with the following targets by 2030: (a) vaccination of 90% of girls with HPV vaccine by 15 years of age, (b) screening of 70% of women for cervical cancer by 35 and 45 years of age, and (c) treatment of 90% of women diagnosed with cervical disease (5). In 2019, it was estimated that only 15% of the world's age-eligible female population was fully vaccinated against HPV (5).

HPV vaccines

Primary prevention for cervical cancer is now possible through vaccination with one of four licensed HPV vaccines (Table 1). These vaccines are highly efficacious against persistent infection with vaccine genotypes, a necessary prerequisite for the development of cervical cancer and related cervical lesions (6).

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

Table 1. Summary of available HPV vaccines

	Cervarix™ [a]	GARDASIL® [b]	GARDASIL9® [b]	Cecolin® [c]
Manufacturer	GlaxoSmithKline	Merck & Co., Inc.	Merck & Co., Inc.	Xiamen Innovax Biotech Co. Limited
HPV VLPs included	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58	16, 18
Injection Schedule [d] (2 doses)	0, 6–12 months	0, 6–12 months	0, 6–12 months	0, 6 months
Injection Schedule [d] (3 doses)	0, 1, 6 months	0, 2, 6 months	0, 2, 6 months	0, 1, 6 months

Note: HPV, human papillomavirus; VLP, virus-like particle.

[a] Cervarix is a trademark of GlaxoSmithKline Biologicals, Belgium.

[b] Gardasil and Gardasil-9 are registered trademarks of Merck Sharp & Dohme Corp., United States.

[c] Cecolin is a registered trademark of Xiamen Innovax Biotech Co. Limited, China.

[d] In some countries, the vaccines are also licensed and recommended for boys, in the same dosing schedules as for girls.

In June 2022, based on current evidence on the immunogenicity, efficacy, and effectiveness of single-dose HPV vaccination compared with no vaccination, and multidose schedules, WHO's SAGE endorsed the optimization of HPV vaccine schedules (7) as follows:

- *One- or two-dose schedule for the primary target of girls aged 9-14 years.*
- *One- or two-dose schedule for young women aged 15-20 years.*
- *Two doses with a 6-month interval for women > 21 years.*
- *Immunocompromised individuals, including those with HIV, should receive three doses if feasible, and if not at least two doses*

SAGE urged countries to introduce HPV vaccine for the primary target group of girls aged 9–14 years and, where feasible and affordable, prioritize catch-up in older cohorts and missed girls through multi-age cohort (MAC) vaccination up to the age of 18 years. (8)

A single dose of HPV vaccine should 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 can accelerate introduction of HPV vaccines into national immunization schedules. Single-dose HPV vaccination can also help reduce the potential for supply shortages seen in the recent past and alleviate delivery challenges such as those encountered during the COVID-19 pandemic.

Current evidence on a single dose of HPV vaccine

Sources of evidence in this review include publicly available, peer-reviewed scientific publications on:

- The biological rationale for protection with a single dose of HPV vaccine based on vaccine immune response and virological information.
- Efficacy, effectiveness, and immunogenicity of a single HPV vaccine dose from clinical trials.
- Data from post-licensure vaccine effectiveness and immunological evaluations and other observational studies.
- Mathematical modeling of the impact of reduced dosing schedules for HPV vaccines.

Rationale for a single-dose HPV vaccination

Strong, consistent, and durable antibody responses to the three widely licensed HPV vaccines are well documented (9). In healthy young women, seroconversion rates are virtually 100%. Responses in preadolescent girls and boys are even stronger (9-11). The stability of antibody responses now observed up to 10 years after vaccination is unprecedented for a subunit vaccine (12,13). This pattern of antibody response is observed in a single dose of the vaccine (14, 15).

Clinical trials of HPV vaccines

Researchers from the London School of Hygiene & Tropical Medicine (LSHTM) and collaborators conducted a systematic review of the literature published between January 1, 1999, and August 14, 2018 (16). Subsequent searches were conducted to identify relevant articles that became available between August 14, 2018, and February 4, 2022. The systematic review was specifically designed to identify clinical trials that randomized participants to receive a single dose of HPV vaccine versus no dose or multiple doses, as well as trials of other dosing schedules in which some participants received only a single dose due to noncompletion of a multidose schedule. Of 6,523 unique records identified from the database and hand searches, seven articles were identified and included in the review. The updated 2021 and 2022 searches identified three additional relevant articles, all of which described observational evaluations nested within clinical trials. Thus, in total, ten manuscripts were identified that reported results on single-dose HPV vaccination.

At the time that the systematic review was conducted, there were 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 clinical trials (RCTs). One small, randomized study of ten women in the United States prospectively allocated participants to receive a single HPV vaccine dose versus no vaccination to evaluate whether women with evidence of natural immunity had improved antibody response after single-dose HPV vaccination. The study concluded that single-dose HPV vaccination does indeed augment the existing natural immunity (17).

The other nine manuscripts identified in the reviews described observational data from RCTs where some participants failed to complete their allocated schedule of two or three doses. All nine reports were from observational studies nested within three clinical trials: three manuscripts were based on the IARC India HPV Trial (18-20), five manuscripts were based on the Costa Rica Vaccine Trial (CVT) (21-23), and one manuscript was based on combined data from CVT and the PApilloma TRIal against Cancer In young Adults (PATRICIA) (24). The data from these studies were considered as observational because the number of HPV vaccine doses received (i.e., single dose versus alternative schedules) was not what they were randomized to receive.

Two prospectively randomized trials of single-dose HPV vaccination were recently published and included in this synthesis. Those were not captured by the systematic review as they did not have published, peer-reviewed data available at the time of the most recent database search. Those studies, the KENya Single-dose HPV vaccine Efficacy (KEN SHE) (25) and Dose Reduction Immunobridging and Safety study of two HPV vaccines in Tanzanian girls (DoRIS) (26, 27) trials, are the first studies to report results from prospectively randomized participants who received one dose of HPV vaccine versus a comparator (active control vaccine in KEN SHE; two or three HPV vaccine doses in DoRIS). KEN SHE is the first randomized trial to report efficacy data and DoRIS the first to report immunogenicity data from individuals randomized to receive a single dose of the HPV vaccines.

Efficacy data from clinical trials

The most impactful efficacy data on single-dose HPV vaccination are from the KEN SHE trial launched in 2018 and further supported by nonrandomized observational data in two independent trials from Costa Rica (the CVT) and India (the IARC India HPV Trial), launched in 2004 and 2009, respectively.

The KEN SHE trial is a multi-center randomized, controlled and double-blind efficacy trial comparing a single dose of the Merck nine-valent HPV vaccine (9vHPV) or GSK bivalent HPV vaccine (2vHPV) vaccine with a non-HPV vaccine control (single-dose meningococcal vaccination) conducted in Kenya (28). A total of 2,275 sexually active girls and women aged 15 to 20 years were enrolled.

Single-dose HPV vaccination was

~98%

effective

in preventing new onset persistent HPV 16/18 infection

At Month 18, a total of 38 incident persistent infections were detected in the HPV 16/18 modified intention-to-treat (mITT) cohort: one each among participants assigned to the 2vHPV and 9vHPV vaccine groups and 36 among those assigned to the meningococcal vaccine group. The incidence of persistent HPV 16/18 was 0.17 per 100 woman-years in the HPV vaccine groups, compared to 6.83 per 100 woman-years in the meningococcal vaccine control group. 2vHPV vaccine effectiveness (VE) was 97.5% (95% confidence interval [CI]: 81.7%–99.7%, p=<0.0001) and 9vHPV VE was 97.5% (95% CI: 81.6%-99.7%, p=<0.0001). In the HPV 16/18/31/33/45/52/58 mITT cohort, 33 incident persistent infections were detected: four in the 9vHPV vaccine group and 29 in the meningococcal vaccine group. The incidence of persistent HPV 16/18/31/33/45/52/58 was 1.03 per 100 woman-years in the 9vHPV vaccine group compared to 9.42 per 100 woman-years in the meningococcal group. 9vHPV VE for HPV 16/18/31/33/45/52/58 was 88.9% (95% CI: 68.5%-96.1%, p<0.0001) (28).

The study is currently ongoing with KEN SHE trial participants to continue efficacy follow-up until 36 months post-vaccination.

CVT was conducted by the US National Cancer Institute and the Agencia Costarricense de Investigaciones Biomédicas. It was a community-based, randomized phase III clinical trial that was initiated prior to licensure of the HPV vaccines; 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 GSK 2vHPV vaccine 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 4 years (29). At the end of the randomized, blinded phase of the study, the majority of the participants of the HPV arm were enrolled into an unblinded long-term follow-up for a total of 11 years after the initial dose. A new screening-only control group was enrolled, with demonstrated similarities to the HPV arm on important characteristics that determine risk for HPV acquisition (30).

Four years after initial vaccination, one dose of the GSK 2vHPV had comparable efficacy to three doses of the vaccine using an endpoint of cumulative HPV infection that persisted 12 months or more (17). Comparing the HPV arm to the control arm, the 4-year efficacy against HPV 16 or 18 infections that persisted for at least 6 months among women who were HPV DNA negative for these types at first vaccination was as follows: three doses = 84% (95% CI: 77%–89%); two doses = 81% (95% CI: 53%–94%); and one dose = 100% (95% CI: 79%–100%).

Results suggesting protection against HPV 16 and 18 at 4 years was extended to 7 years following initial vaccination. 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%–3.1%), two-dose (0-, 6-month schedule; 0.0%; 95% CI: 0.0%–3.7%; p = 0.26 compared to three doses), and one-dose groups (1.5%; 95% CI: 0.3%–4.8%; p = 0.77 compared to three doses) 7 years following initial HPV vaccination (31).

After 11 years of follow-up, vaccine efficacy against prevalent HPV 16 or 18 infection was 80% (95% CI: 70.7%–87.0%) among three-dose, 84% (95% CI: 19.5%–99.2%) among two-dose, and 82% (95% CI: 40.2%–97.0%) among one-dose women. Partial protection against HPV 31, 33, and 45 persisted. Importantly, acquisition of nonprotected HPV types was similar between vaccinated and unvaccinated women, indicating that the difference in HPV infection rates was not attributable to differential genital HPV exposure (21, 23, 30).

Single-dose HPV vaccine efficacy for the GSK 2vHPV vaccine was similarly noted in 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 the CVT 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 no differences in the efficacy of one, two, and three doses of the GSK 2vHPV vaccine against vaccine-type persistent infections over a median follow-up of 4 years (24) independently confirming the original observation in CVT.

The IARC India HPV trial was a multi-center cluster-randomized trial that evaluated the comparative efficacy of two versus three doses of the quadrivalent HPV (Merck 4vHPV) vaccine. 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. This resulted in some trial participants failing to complete, or failing to complete on time, the vaccination schedule assigned to them. However, these participants remained in follow-up for the efficacy evaluation. This meant that the study, which had enrolled 17,739 girls before suspension, had four groups of vaccine recipients: 4,348 girls (25%) who received three doses (according to schedule); 4,979 (28%) who received two doses (according to a 0-, 6-month schedule); 3,452 (19%) who received two doses by default (approximately 2 months apart); and 4,950 (28%) who received one dose by default. Those in the default groups were the girls who were unable to complete their allocated vaccination schedules. Study participants who were followed, continued per protocol with no further vaccination (20).

Incident and persistent HPV 16/18 infection over 10 years from vaccination were uniformly low in all the vaccinated study groups, and considerably lower in vaccinated participants compared to unvaccinated controls. HPV 16/18 infections that persisted for 10 or more months were detected in just one participant from each of the one-dose (0.0%, 95% CI: 0.0%-0.3%), two-dose (0.1%, 95% CI: 0.1%-0.4%) and three-dose groups (0.1%, 95% CI: 0.0-0.4%), compared with 32 unvaccinated controls (2.5%, 95% CI: 1.7%-3.6%). Adjusted for a disease risk score, VE against persistent HPV 16/18 infection was 95.4% (95% CI: 85.0%-99.9%) with one vaccine dose, 93.1% (95% CI: 77.3%-99.8%) with two doses, and 93.3% (95% CI: 77.5%-99.7%) with three doses (20).

Vaccine efficacy was comparable

regardless of the dose regimen

(1, 2 or 3 doses)

Among women who were eligible for cervical cancer screening, there was no case of HPV 16/18-positive CIN2 or CIN3 or invasive cervical cancer. For comparison, there were three cases of HPV 16/18-positive CIN2 and CIN3 among unvaccinated controls. One case of invasive cervical cancer was identified in the control group, but it was not associated with HPV 16/18 (20).

Immunogenicity data from clinical trials

Immunogenicity evidence after receipt of a single dose of HPV vaccine was evaluated in the DoRIS trial (26, 27), and also assessed in the CVT (31) and the IARC India HPV Trial (20).

The DoRIS trial is an unblinded randomized, controlled immunogenicity and immunobridging trial comparing one versus two versus three doses of either the Merck 9vHPV vaccine or the GSK 2vHPV vaccine among girls aged 9 to 14 years in Tanzania. The co-primary trial objectives were: (a) to determine whether a single dose of HPV vaccine produces immune responses that are non-inferior to those following two and three doses when given to HIV-negative girls aged 9 to 14 years in a malaria-endemic region, and (b) to demonstrate non-inferiority of HPV 16/18 antibody geometric mean titers (GMTs) at Month 24 when comparing the single-dose regimen of either vaccine with historical cohorts of women aged 10 to 25 years who received one dose, in whom efficacy has been demonstrated.

A total of 930 girls were enrolled. Non-inferiority of seroconversion for anti-HPV 16 antibodies was met for one dose compared with two or three doses of both vaccines at Month 24. Although non-inferiority was not met for seroconversion for anti-HPV 18 antibodies, ≥98% of girls in the single-dose arms of both vaccines were anti-HPV 18 antibody positive at Month 24. HPV 16/18 antibody titers were lower for single-dose arms compared to multidose arms. However, there was no difference between the one-, two-, and three-dose schedules in the geometric mean antibody avidity index for HPV 16 or HPV 18 for both vaccines (26).

Data suggest single-dose HPV vaccine efficacy may apply to additional geographies in the targeted

9–14

year-old age group.

For the immunobridging objective, CVT and the IARC India HPV trial were selected because they are the only two large-scale studies that evaluated a one-dose schedule (albeit not randomized) with long-term (9-11 year) efficacy follow-up. Antibody levels among single-dose recipients in DoRIS were higher and were non-inferior to those among single-dose 2vHPV recipients in CVT with GMT ratios (DoRIS/CVT) of 1.30 (95% CI: 1.00-1.68) for HPV 16 and 1.23 (95% CI: 0.95-1.60) for HPV 18, and to those among single-dose 4vHPV recipients in the India trial, with GMT ratios (DoRIS/IARC India) of 2.05 (95% CI: 1.61-2.61) for HPV 16, and 2.57 (95% CI: 2.02-3.27) for HPV 18 (27).

10x

level of antibody induced *after single-dose HPV vaccine, compared to after natural infection*

Further immunobridging is planned between the DoRIS and KEN SHE trials.

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 4 years after initial vaccination (31). HPV 16 or 18 antibody levels did not qualitatively decline between years 4 and 11 regardless of the number of doses given, although one-dose titers continue to be statistically significantly lower compared with two- and three-dose titers. One-dose titers were approximately fourfold lower than those among women receiving three doses but remained stable up to 11 years post vaccination (22). HPV 16 virus–like particle antibody avidity, a measure of the quality of the antibody response, was measured at years 4 and 7. Antibody avidity increased with the number of HPV vaccine doses received, but within a dose level, avidity remained stable between years 4 and 7 (31).

In the 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 (19). 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 (15). One dose induced detectable concentrations of neutralizing antibodies to HPV 16 and 18, but at lower concentrations than those found in 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 clinical trials:

- The KEN SHE and DoRIS trials are the first prospectively randomized trials of single-dose HPV vaccination. Prospective allocation to a single dose versus comparator groups considerably reduces the risk of bias seen in many of the observational studies.
- KEN SHE was a placebo-controlled, blinded trial and evaluated persistent cervical HPV infection as the primary outcome measure, allowing direct measurement of VE.
- The KEN SHE and DoRIS trials evaluated the GSK 2vHPV and Merck 9vHPV vaccines
- All trials (KEN SHE, DoRIS, CVT, and IARC India HPV trial) have high retention and blinded lab measures.
- CVT and IARC India HPV trial have frequent efficacy and immunogenicity measures over an extended period post vaccination.
- For the CVT, a concurrent control group was enrolled at the end of the randomized phase, 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 bolstered by 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.

There are also several limitations in the evidence on single-dose HPV vaccination derived from randomized control trials:

- The KEN SHE trial did not compare single-dose HPV vaccination to a multidose schedule, but efficacy of one dose against incident persistent HPV infection was ~98%.
- The CVT and IARC India HPV trial provide observational evaluations nested within clinical trials where participants were not randomized specifically to single-dose HPV vaccination.
- For CVT and PATRICIA, the group of women who had received a single dose of the GSK 2vHPV vaccine 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 (18). 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.

Non-trial immunogenicity studies of partially vaccinated populations

The Consortium comprehensively reviewed the published literature for data comparing cellular or humoral immunogenicity responses after one versus two or three doses of HPV vaccine (in any schedule), or versus no HPV vaccination. As of August 2020, 11 published articles have reported immunogenicity results after receipt of a single dose of HPV vaccine: one each from Uganda, the Netherlands, and Mongolia; two from the United States; and three each from Canada and Fiji (32-42).

In all studies, single-dose participants received only one HPV vaccine dose due to noncompletion of an intended multidose schedule. All studies measured binding and/or neutralizing antibody seropositivity rates for the HPV genotypes targeted by the HPV vaccine administered; and all except the US Department of Defense (DoD) study measured antibody levels. However, time points evaluated and methods used varied across studies. Two studies evaluated cellular immunogenicity outcomes: the Fiji and the Netherlands study.

Together, these studies demonstrate that single-dose HPV vaccination can lead to high rates of seroconversion and sustained seropositivity to vaccine-type HPV over time. In several studies in adolescents, GMTs, after one dose of HPV vaccine, were lower than after two or three doses. However, a minimal antibody titer sufficient for protection has not been identified, so the clinical relevance of these differences is unclear, and the lower antibody levels observed in the one-dose groups may still be protective against HPV infection. GMTs with a single dose were considerably higher than with natural infection. Immune memory, as measured in the Fiji and Canada studies by a humoral anamnestic response after a challenge HPV vaccine dose, was evident in all participants who had previously received at least one dose.

The US Pediatric HIV/AIDS Cohort Study (PHACS) and DoD studies extended the available evidence to populations infected with or exposed to HIV and to older women, respectively. Interestingly, the PHACS found that, among HIV-infected or HIV-exposed participants, seropositivity rates and antibody titers did not differ significantly between those who received one, two, or three vaccine doses. Seroconversion rates among sero-naïve women aged 17 to 26 years in the DoD study were very high (approaching 100%) and, also, did not differ by number of vaccine doses received.

Cellular immune responses were detectable among Merck 4vHPV vaccine recipients in the Fiji subcohort 6 years after vaccination, regardless of number of doses received. HPV 16–specific responses were generally similar between the dosage groups, but some HPV 18–specific responses were lower among one- or two-dose groups compared to the three-dose groups. Cellular responses (both HPV 16– and HPV 18–specific) were mostly similar between dosage groups after a dose of GSK 2vHPV vaccine was administered. The Netherlands study found a trend for increasing magnitude of memory B-cell and T-cell responses with increasing numbers of vaccine doses. However, as for humoral analyses, the clinical implications of these cellular results are unclear.

Strengths and limitations of non-trial immunogenicity studies of partially vaccinated populations

Strengths of non-trial immunogenicity studies of partially vaccinated populations include the following:

- Some studies used the same laboratory assay to assess immune responses as they had used for 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, among whom efficacy had been demonstrated.
- Some studies had a long follow-up time to evaluate the 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.
- The US PHACS provides data for a cohort of HIV-positive adolescents, a subgroup for whom data have been lacking, while the US DoD study provides data for women vaccinated at an older age compared to other immunogenicity studies.

Limitations of these studies include the following:

- None of the studies was an RCT; therefore, participants might have differed by dose group. Further, in all studies, single-dose recipients were those that did not complete a multidose schedule.

- 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, but data were not stratified by number of doses received.
- The first Quebec study included only a single group of participants, all of whom received a single dose of Merck 4vHPV vaccine and were boosted with a dose of nonavalent HPV (Merck 9vHPV) vaccine. Therefore, no comparisons in immune response can be made with either unvaccinated individuals or multidose recipients within the study.
- In the Netherlands study, the one- and two-dose participants were aged 12 years at vaccination, whereas three-dose participants were aged 16 years at vaccination. Thus, differences in immune responses to one or two doses versus three doses may appear smaller than they would if the groups were comparable in age.
- The Mongolia study did not compare single-dose HPV vaccination to multidose schedules.
- Sample sizes were relatively small in all the studies, except the US DoD study, especially among single-dose groups.
- Several studies measured immune responses at only one time point following vaccination, and thus the kinetics of the response over time cannot be evaluated.

Post-licensure vaccine effectiveness evaluations and other observational data

A systematic review of studies on HPV vaccine effectiveness by number of doses through August 2020 resulted in 32 published studies. The current update of that review, through September 2021, identified 3 additional studies for a total of 35 papers (summarized in Table 2) (43). All evaluations except one were conducted within the context of a recommended three-dose schedule of either the GSK 2vHPV and/or Merck 4vHPV vaccine. One study evaluated the effectiveness of a recommended two-dose schedule.

The main study characteristics were abstracted from the papers, including study design, age of study population at vaccination and outcome assessment, case definition, statistical analyses, and information on the use of buffer periods (lag time between vaccination and counting of outcomes). The main outcomes measured were the effectiveness of HPV vaccination against HPV infections (9 articles), anogenital warts (10 articles), or cervical abnormalities (16 articles), comparing the incidence or prevalence of HPV-related endpoints between individuals vaccinated with zero, one, two, or three doses. Studies were excluded if the vaccine was administered as part of an RCT (e.g., post hoc evaluations of clinical trials).

HPV prevalence

Nine studies were identified that reported vaccine effectiveness for reduction of prevalent vaccine-type infection (HPV 16 or 18 or HPV 6, 11, 16, or 18). Three were from Scotland, conducted in the context of a three-dose GSK 2vHPV vaccination program; one was from the Netherlands, conducted in the context of a two-dose GSK 2vHPV vaccination program; and four from the United States, plus one from Mongolia, were conducted in the context of a Merck 4vHPV vaccination program (42, 44-51).

Overall, among the nine studies, seven were among women. Two studies among women in the United States found similar effectiveness with three-, two-, and one-dose schedules in all or some analyses (48, 50). The Mongolia study included women who were part of a pilot Merck 4vHPV vaccination campaign, conducted by the Mongolian Ministry of Health (42). Approximately 6 years after initial vaccination, the study included 118 girls who received only a single-dose of vaccine, plus a group of 357 unvaccinated girls, frequency-matched on age. Vaccinated girls had lower vaccine-type prevalence; the adjusted prevalence ratio was 0.08 (95%; 95% CI: 0.01–0.56). Among the three studies conducted in Scotland, the first study found statistically significant effectiveness for three doses but not for two doses or one dose (44). 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 (45). 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 vaccination overlapped. The third study 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 for one dose (46). In the study from the Netherlands, conducted after a two-dose schedule of 2vHPV was implemented in that country, girls who were vaccinated at age 12-13 years were followed prospectively with self-collected vaginal swabs for HPV DNA. The adjusted VE of two doses was 84% (95% CI: 27.0%–96.5%) against incident HPV 16/18 infection (51).

The two studies among men in the United States found no effectiveness with at least one dose and no difference in HPV prevalence by number of doses (47, 49). In both studies, the number of vaccinated men was small; in one, almost half had initiated sexual activity at the same age or before being vaccinated.

Anogenital warts

The ten studies of anogenital warts identified 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. The more recent studies adjusted for more characteristics, and several attempted to adjust for sexual behavior by various composite measures. Most two-dose vaccine recipients received doses separated by 2 months.

Of the ten studies, seven included a comparison of three-, two-, and one-dose vaccinations with no dose. All seven found a highest-point estimate of effectiveness with three doses, and six found lower-point estimates but still significant effectiveness with two doses. Five of the seven studies found significant effectiveness with one dose (52-56). Six studies also formally compared three and two doses, finding either no significant difference in the primary analysis or in analyses with different buffer periods or two-dose intervals (52, 54, 55 57-59). Three studies examined different buffer periods (52, 55, 58); a longer buffer period decreased differences in effectiveness between three and two doses in one study (52). In the five studies that explored the interval between doses in two-dose vaccine recipients (54, 55, 57–59), three found that a longer interval changed effectiveness estimates or resulted in no difference between three and two doses (54, 57, 59).

All six studies that stratified by age at vaccination found higher vaccine effectiveness with younger ages at vaccination, although the differences were not all formally tested (52, 55–57, 59, 60). 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 (53). One study found similar point estimates of effectiveness with one, two, and three doses among those vaccinated at age 15 through 19 years (55).

Cervical cytological and histological abnormalities

Among the 16 studies, 15 found effectiveness for three doses; eight studies found some effectiveness with two doses (61-68); and seven found effectiveness with one dose among some age groups or in analyses with longer buffer periods (62-67, 69). Most two-dose vaccine recipients received two doses at a 1- or 2-month interval. Five studies examined intervals between two doses; of those, three studies found no impact on the effectiveness estimate (65-67), and one found that longer intervals decreased the difference between two and three doses in those vaccinated at age 16 years or younger (70) and another only in one of the age groups examined (68).

In ten studies that evaluated effectiveness by number of doses stratified by age at vaccination, age at vaccination program implementation, or birth cohort or that were limited to younger age at vaccination, three studies found significant effectiveness with one, two, and three doses with similar point estimates by number of doses in some groups (63, 65, 66) These studies, published in 2019 and 2020, were from Denmark, Australia, and the United States. The study from Denmark was a retrospective cohort study using linked national registry data, limited to those vaccinated at age 16 years or younger. Using an outcome of CIN3+ / adenocarcinoma in situ, compared with no vaccination, adjusted incident rate ratios were similar for three, two, and one doses. The study from Australia was a retrospective cohort study. Using an outcome of CIN2+, the adjusted hazard ratios (aHRs) were similar for all doses: three doses, 0.59 (95% CI: 0.54–0.65); two doses, 0.61 (95% CI: 0.52–0.72); and one dose, 0.65 (95% CI: 0.52–0.81). The study from the United States was a retrospective matched cohort study using a database for health insurance claims. Among those vaccinated at ages 15–19 years, hazard ratios (HRs) for CIN2+ were similar for all doses: three doses, 0.66 (95% CI: 0.55-0.80); two doses, 0.72 (95% CI: 0.54-0.95); and one dose, 0.64 (95% CI: 0.47-0.88). An additional study found similar point estimates by number of doses when stratifying by age at vaccination but significant effectiveness only for three doses (70). In the remaining six studies, differences in effectiveness remained between some or all dose groups (62, 64, 67–69, 71).

Strengths and limitations of data from post-licensure 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 post-licensure studies and caveats that should be considered when interpreting the findings include the following:

- All post-licensure studies, except one, were conducted in settings of a 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.
- In the post-licensure studies that were conducted in settings of a three-dose recommendation, most individuals vaccinated with two doses had received doses at 0- and 1-month or 0- and 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 6 months (11, 72, 73). The longer interval is thought to allow the B cells to mature 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.

Important findings regarding effectiveness by number of doses emerged from some of the recent studies identified which either stratified by age at vaccination or were limited to those vaccinated at younger ages. Along with a study that was limited to persons vaccinated in a younger age group in the first review (53), these studies found high effectiveness with one dose or similar effectiveness for one, two, and three doses (48, 55, 63, 65, 66). These studies overcome some of the limitations of earlier studies, which likely included more women who had prevalent infection at the time of vaccination. Continued review of future published reports on vaccine effectiveness by number of doses will be important as studies are able to focus analyses on persons vaccinated in early adolescence.

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 GSK 2vHPV, Merck 4vHPV, and Merck 9vHPV vaccines were examined 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 GSK 2vHPV or Merck 4vHPV vaccine and one with the Merck 9vHPV one (74-77). These analyses explored (a) the impact of duration of protection, with equivalent or shorter duration for two doses compared to three doses, (b) quality-adjusted life years, and (c) cancer incidence reduction.

Comparative analyses of two-dose GSK 2vHPV and Merck 4vHPV vaccination using independent dynamic transmission models fitted to the United Kingdom (Public Health England model) and Canada (HPV Agent-based Dynamic model for Vaccination and Screening Evaluation) found that the health benefits in terms of reduction in cancer incidences and gains in quality-adjusted life years were substantial with two-dose HPV vaccination, even when vaccine protection waned at 30, 20, or 10 years (78, 79). However, the incremental benefit of adding a third dose varied greatly depending 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 10 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 10 years, adding a third vaccine dose will have greater health impact and is likely to be cost-effective.

Single-dose regimens will likely present

significant cost savings

and help with overall delivery challenges

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) (76, 77). 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 vaccinations in Uganda (80). A comprehensive literature search of model-based analyses conducted since the completion of the last edition of the Evidence Review included four additional global analyses (one new peer-reviewed publication and three analyses available as preprint articles in medRxiv and SSRN) (81-84). The following themes emerged from the growing analyses 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 10 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.*
- *Most health benefits associated with two-dose vaccination are achieved with one-dose vaccination, even with lower efficacy or duration of protection.*
- *The number needed to vaccinate to avert one cervical cancer case is far lower in low-income than high-income countries; in all settings, the number needed to vaccinate with a second dose to avert one cervical cancer case was excessively high.*
- *Vaccination with a single dose at age 9 years and a second dose at age 14 years (i.e., an extended dose interval of 5 years) can be as effective as the current two-dose schedule, and may be among the most efficient strategies.*
- *Immediate implementation of single-dose HPV vaccination leads to greater health benefits than waiting until more information on vaccine efficacy is available from ongoing clinical trials, expected in 5 years. Health benefits are maximized when cohorts are reached that would otherwise exceed vaccine age eligibility in those 5 years.*

One published modeling study evaluated the population-level impact of single-dose Merck 9vHPV vaccination on reducing cervical cancer incidence and mortality in South Africa, taking into consideration HIV status, cluster of differentiation 4 (CD4) count, and antiretroviral therapy coverage (85).

This analysis did not compare the relative effectiveness or cost-effectiveness of two doses versus one dose; rather, it was used to project the long-term effects of single-dose Merck 9vHPV vaccination on cervical cancer incidence and mortality, by age and over time, for girls aged 9 years. The authors concluded that single-dose Merck 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 antiretroviral therapy 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. Below are some of the gaps and key questions that remain regarding a single-dose strategy, as well as the studies currently in progress to address them (new and ongoing studies and their methods are summarized in Table 3):

- **Durability of protection:** Current data demonstrates that a single dose of HPV vaccine will provide a durable level of efficacy against persistent HPV infection and/or HPV disease outcomes for at least 10 years post vaccination. The KEN SHE trial is ongoing and will provide additional data on duration of protection. The IARC India HPV trial is also ongoing and will follow the study population up to 15 years post vaccination. These studies will help to determine the duration of efficacy (and levels of efficacy over time). Longer-term immune response data are still forthcoming from the DoRIS, CVT, and the India IARC HPV trial.
- **Single-dose efficacy:** KEN SHE demonstrated that a single dose of HPV vaccine provides high efficacy against clinical persistent infection 18 months post vaccine administration; this study is ongoing and will generate additional data in the near future (25).

  Several additional, ongoing prospective RCTs are investigating efficacy and/or immune responses of a single dose of HPV vaccine compared to recommended dose regimens or controls and will also provide immunobridging data to other trials without efficacy endpoints.

  In Costa Rica, ESCUDDO (Estudio de Comparacion de Una y Dos Dosis de Vacunas Contra el Virus de Papiloma Humano [comparison study of one or two doses of the bivalent or nonavalent prophylactic HPV vaccines]) aims to find out if one dose of either the GSK 2vHPV or Merck 9vHPV vaccine is as effective as two doses of these vaccines (86).
- **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 IVIHPV1 (Effectiveness of Single Dose or Two Doses of Bivalent HPV Vaccine in Thailand) study is a community intervention study. The study involves vaccination of grade 8 female students from two provinces with either one or two doses of HPV vaccine (GSK 2vHPV), and a series of cross-sectional surveys to measure the population-level impact on HPV prevalence, with DNA being measured in, and genotyped from, urine (87).

  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 GSK 2vHPV vaccine to girls aged 9 years since 2014 (88).

  In Costa Rica, the PRIMAVERA (Puente de Respuesta Inmunológica para Mejorar el Acceso a Vacunas y ERrAdicar el cancer) trial is comparing immune responses following one dose of the GSK 2vHPV vaccine to three doses of the Merck 4vHPV vaccine. The primary aim is to evaluate whether HPV 16 and 18 antibody responses among one-dose GSK 2vHPV recipients aged 9–14 years are non-inferior to those aged 18–25 years, three-dose Merck 4vHPV recipients at 24 and 36 months after first vaccine dose (89).
- **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, the DoRIS trial demonstrated that a single dose of HPV vaccine (GSK 2vHPV and Merck 9vHPV) produces immune responses at Month 24 that are likely to be effective in preventing cervical cancer (26). Further immunobridging is planned between the DoRIS and KEN SHE trials.

  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 Merck 9vHPV vaccine in girls aged 4 to 8 years and aged 9 to 14 years with three doses in females aged 15 to 26 years (90).

Effectiveness data from post-licensure 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. 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. There is ongoing work to formally assess the quality of these studies.

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 the 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. The Consortium also has provided 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 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 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 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.

Conclusion

The 2022 SAGE recommendation of one or two doses of HPV vaccine for girls and young women aged 9-20 is based on sound evidence from rigorous clinical trials and high-quality observational clinical studies, including evaluation of durability, that 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 represents a high-value public health intervention.

The Single-Dose HPV Vaccine Evaluation Consortium will continue to monitor and update the evidence base and share results widely.

Table 2.
Studies that evaluated HPV vaccine efficacy, effectiveness, and/or immunogenicity 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 against HPV infection and immunogenicity					
Barnabas 2022 (25)	V: 15-20 O: 16-22	**Kenya** GlaxoSmith-Kline 2vHPV Merck 9vHPV GlaxoSmith-Kline 2vHPV Merck 9vHPV	2,275	No	• HPV 16/18 VE (mITT): 2vHPV: 97.5% (95% CI: 81.7-99.7%, p=<0.0001) 9vHPV: 97.5% (95% CI: 81.6-99.7%, p<0.0001). • HPV 16/18/31/33/45/52/58 (mITT): 2vHPV: NA 9vHPV: 88.9% (95% CI: 68.5-96.1%, p<0.0001).
Kreimer 2011 (21) Safaeian 2013 (22) Safaeian 2018 (31) Kreimer 2020 (23)	V: 18–25 O: 22–29	**Costa Rica** (CVT) GlaxoSmith-Kline 2vHPV	3,727	Yes	• Similar protection against HPV 16/18 infection in 1-, 2- and 3-dose recipients at Y4 and Y11. • 1-dose antibody titers were lower than 2 and 3 doses, but higher than natural infection levels and stable at Y4 to Y11.
Basu 2021 (20)	V: 10–18 O: Year 10	**India** Merck 4vHPV	17,729	Yes	• Cervical samples from 5,047 vaccinees tested; adjusted VE against persistent HPV 16/18 infections: 95.4% (95% CI: 85.0-99.9%) in 1-dose; 93.1% (95% CI: 77.3-99.8%) in 2-dose (Mo6); 93.3% (95% CI: 77.5-99.7%) in 3-dose.
Sankaranarayanan 2016 (15)	V: 10–18 O: 12–20	**India** Merck 4vHPV	17,729	Yes	• Non-inferior immune response in 2-dose to 3-dose at 7 months but inferior in the 2-dose and 1-dose default groups at 18 months. • Detectable neutralizing antibodies to 4 vaccine-targeted HPV types with lower concentrations after 1 dose.
Immunogenicity					
Watson-Jones 2022 (26)	V: 9-14 O: 11-16	**Tanzania** GlaxoSmith-Kline 2vHPV Merck 9vHPV	930	Yes	• HPV 16 SCR: Non-inferiority met for 1-dose compared to 2- or 3-dose at months 7, 12 and 24 for both vaccines. • HPV 18 SCR: Non-inferiority not met; ≥98% of girls in 1-dose anti-HPV 18 antibody positive at Mo24. • HPV 16/18 antibody titers were lower for 1-dose arms compared to multidose arms. • No difference between the dosing schedules in HPV 16/18 GMT antibody avidity index for both vaccines.

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
Baisley 2022 (27)	DoRIS: V: 9-14 O: at Month 24 CVT: V: 18-25 O: at Month 24 IARC India: V:10-18 O: at Month 24	**Tanzania** GlaxoSmith-Kline 2vHPV Merck 9vHPV	DoRIS (one dose): 2vHPV: 155 9vHPV: 155 CVT (one dose): 2vHPV: 115 IARC India (one dose): 9vHPV: 139	Yes	• HPV 16/18 GMTs: Non-inferiority met (GMT ratios 1-dose 2vHPV recipients DoRIS/ 1-dose 2vHPV recipients in CVT: 1.30 (95% CI: 1.00-1.68) for HPV 16 and 1.23 (95% CI: 0.95-1.60) for HPV 18. • HPV 16/18 GMTs: Non-inferiority met (GMT ratios 1-dose 9vHPV recipients DoRIS/ 1-dose 4vHPV recipients in IARC India: 2.05 (95% CI: 1.61-2.61) for HPV 16, and 2.57 (95% CI: 2.02-3.27) for HPV 18.
LaMontagne 2014 (32)	V: 10-11 O: 13–15	**Uganda** GlaxoSmith-Kline 2vHPV	376	Yes	• HPV 16/18 GMT ratio for 1:3 doses inferior, but absolute GMTs for 1 dose higher than adult women who received 1 dose (where efficacy has been demonstrated). • Antibody levels measured ≥24 months after last dose similar to those of adult women followed for efficacy for > 8 years.
Toh 2017 (39)	V: 9–12 O: 15–19	**Fiji** Merck 4vHPV	200	Yes	• After 6 years, the geometric mean NAb titers for all 4 HPV types were not statistically different between 2-dose and 3-dose recipients. • Significantly lower NAb titers in 1-dose recipients than in 2- or 3-dose recipients, but NAb titers 5 to 30 fold higher in 1-dose than unvaccinated girls. • 1 dose of Merck 4vHPV induced immune memory.
Toh 2018 (41)	V: 9–12 O: 15–19	**Fiji** Merck 4vHPV	59	Yes	• After 6 years, HPV 18 responses significantly lower in the 1- and 2-dose compared with 3-dose recipients. • No significant differences in HPV 16 responses between the 2- or 1-dose recipients and 3-dose recipients.

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
Gilca [1] 2019 (38)	V: 9–15 (1 dose 4vHPV) V: 13–18 (1 dose Merck 9vHPV) O: 13–18	**Canada** Merck 4vHPV Merck 9vHPV	31	No	**After 1 dose of Merck 4vHPV:** • All participants seropositive to the HPV-vaccine types 3 to 8 years after vaccination. • 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. **After challenge dose of Merck 9vHPV:** • 1-month post administration 100% of the participants were seropositive to all 9 HPV-vaccine types with 60- to 82-fold increase for four 4vHPV-vaccine types.
Gilca [2] 2019 (36)	V: 9-10 girls and boys (2 doses Merck 9vHPV)	**Canada** Merck 9vHPV	173	No	• Cohort was compared to the cohort in Gilca [1] above. • All participants seropositive to HPV 6, 11, 16, and 18 prior to receiving dose 2. • Following dose 2, all participants seropositive for the 9vHPV-vaccine types.
Sauvageau 2020 (37)	V: 9-10 girls and boys GSK 2vHPV / Merck 9vHPV or 1 dose Merck 9vHPV	**Canada** Merck 4vHPV Merck 9vHPV	86: mixed schedule 88: 1 dose		• Cohort was compared to the cohort in Gilca [1] above. • All participants were seropositive for antibodies to HPV 31, 33, 45, 52, and 58 after vaccination with Merck 9vHPV. • For all of the HPV types evaluated except HPV 58, participants with prior GSK 2vHPV or Merck 4vHPV vaccination had significantly higher antibody titers following vaccination with Merck 9vHPV than previously vaccine-naïve participants.

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
Mosckicki 2019 (35)	V: 13 (mean) O: 16 (mean)	**United States** Merck 4vHPV (PHACS)	458	No	**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. • Seropositivity rates did not vary considerably by number of doses received within either PHIV or PHEU groups. **GMTs for the four Merck 4vHPV types did not differ considerably between 3-dose and 1-dose recipients and were significantly higher for vaccine recipients than in unvaccinated participants.** • Within each cohort, GMTs were similar for 1, 2, or 3 doses. PHIV had lower GMTs, regardless of doses, than PHEU.
Pasmans 2019 (33)	V: 12 (1 and 2 doses) 16 (3 doses)	**Netherlands** GlaxoSmith-Kline 2vHPVt	890		• 100% of multidose recipients and 87% of 1-dose recipients seropositive for antibodies to HPV 16/18. • Antibody titers significantly higher with 2 or 3 doses compared to 1 dose. • HPV 16/18 seropositivity and titers significantly higher in 1-dose participants compared to unvaccinated controls. • Weaker B- and T-cell responses with 1- dose compared to 2 or 3 doses.
Batmunkh 2020 (42)	V: 11-17	**Mongolia** Merck 4vHPV	118		• For 1-dose recipients, 90% seropositive for neutralizing antibodies to HPV 16, and 58% for antibodies to HPV 18. • Corresponding seropositivity rates were 25% and 10%, respectively, among unvaccinated women. • Antibody GMTs significantly higher in vaccinated compared to unvaccinated women.
Hurt 2016 (34)	V: 17-26	**United States (DoD)** Merck 4vHPV	2091		• Of the participants who were HPV 6, 11, 16, and 18 seronegative pre-vaccination, 99.8% of 3-dose, 100% of 2-dose, and 100% of 1-dose recipients seroconverted to all 4 HPV types post-vaccination.

Endpoint/ Authors	Study population age (years) at vaccination (V) & outcome (O)	Country/ Vaccine	n (by dose number)	Formal comparison of 3 vs 2 or 1 doses	Main findings
Effectiveness against HPV infection					
Kavanagh 2014 (44)	V: 15–17 O: 20–21	**Scotland** GlaxoSmith-Kline 2vHPV	0: 3,418 1: 55 2: 106 3: 1,100	No	• Statistically significant vaccine effectiveness against HPV prevalence for 3, but not 2 or 1 doses compared to 0 dose: 3: aOR = 0.43 (CI: 0.34–0.55); 2: aOR = 0.68 (CI: 0.42–1.12); 1: aOR = 0.95 (CI: 0.51–1.76). • Similar results when stratified by age at vaccination.
Cuschieri 2016 (45)	V: 15–17 O: 20–21	**Scotland** GlaxoSmith-Kline 2vHPV	0: 3,619 1: 177 2: 300 3: 1,853	No	• Statistically significant vaccine effectiveness against prevalent HPV infection for 3, 2, and 1 doses compared to 0 dose: 3: aOR = 0.27 (CI: 0.20–0.36); 2: aOR = 0.45 (CI: 0.29–0.69); 1: aOR = 0.52 (CI: 0.31–0.83).
Kavanagh 2017 (46)	V: 12–18 O: 20–21	**Scotland** GlaxoSmith-Kline 2vHPV	0: 4,008 1: 223 2: 391 3: 3,962	No	• Significant effectiveness for 3 and 2 doses but not 1 dose compared to 0 dose: 3: aOR = 0.40 (CI: 0.33–0.48); 2: aOR = 0.75 (CI: 0.57–0.99); 1: aOR = 0.89 (CI: 0.63–1.25).
Chandler 2018 (47)	V: ≤26 O: 14–26	**United States** Merck 4vHPV	400	No	• 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.
Widdice 2019 (49)	V: Mean 15-16 O: 13-26 (men only)	**United States** Merck 4vHPV	0: 471 1: 58 2: 37 3: 143	No	• No significant effectiveness for at least 1 dose. • Similar results for the analysis restricted to men vaccinated at age ≥15 years and men vaccinated before sexual initiation, and men vaccinated after sexual initiation.
Sonawane 2019 (50)	V: <26 O: 18-26	**United States** Merck 4vHPV	0: 1,004 1: 106 2: 126 3: 384	Yes	**Difference in predicted probability compared to unvaccinated:** • 3 doses: aPD = –4.3 (–4.6, –4.0); 2 doses: aPD = –1.7 (–2.4, –0.1); 1 dose: aPD = –5.0 (–5.6, –4. 5).

Endpoint/ Authors	Study population age (years) at vaccination (V) & outcome (O)	Country/ Vaccine	n (by dose number)	Formal comparison of 3 vs 2 or 1 doses	Mainfindings
Markowitz 2020 (48)	V: ≤29 O: 20-29	**United States** Merck 4vHPV	0: 1,052 1: 303 2: 304 3: 2,610	Yes	**Overall results compared to unvaccinated:** • 3 doses: aPR = 0.17 (0.11–0.26); 2 doses aPR = 0.15 (0.05–0.47); 1 dose aPR = 0.25 (0.10–0.62). **Results for those with first dose at age ≤ 18 yrs:** • 3 doses: aPR = 0.08 (0.04–0.15); 2 doses: aPR = 0.07 (0.01–0.47); 1 dose: aPR = 0.08 (0.01–0.54). • Similar effectiveness with 3-, 2-, and 1-dose schedules.
Batmunkah 2020 (42)	V: 11-17 O: 16-26	**Mongolia** Merck 4vHPV	0: 357 1: 118	No	• 1 dose aPR = 0.08 (0.01–0.56) compared to unvaccinated.
Hoes 2021 (51)	V: 12-13 O: 14-17	**Netherlands** GlaxoSmith-Kline 2vHPV	0: 929 2: 1098	No	• Study conducted when routine 2-dose vaccination program recommended: • 2 doses aHR = 0.16 (0.035–0.73).

Endpoint/ Authors	Study population age (years) at vaccination (V) & outcome (O)	Country/ Vaccine	n (by dose number)	Formal comparison of 3 vs 2 or 1 doses	Main findings
Effectiveness against anogenital warts					
Herweijer 2014 (52)	V: 10–19 O: 10–24	**Sweden** Merck 4vHPV	0: 1,045,157 1: 115,197 2: 107,338 3: 89,836	Yes	• Statistically significant effectiveness against first occurrence of condyloma (warts) for 3, 2, and 1 doses compared to 0 doses: 3 doses: aIRR = 0.20 (CI: 0.17–0.23); 2 doses: aIRR = 0.32 (CI: 0.26–0.40); 1 dose: aIRR = 0.54 (CI: 0.43–0.68). • 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. • Significantly higher effectiveness of 3 compared to 2 and 1 doses. • With buffer periods >4 months, no significant difference between 3 and 2 doses.
Blomberg 2015 (57)	V: 12–27 O: 12–27	**Denmark** Merck 4vHPV	0: 188,956 1: 55,666 2: 93,519 3: 212,549	Yes	• Statistically significant effectiveness for reducing risk of genital warts; 1 compared to 0 dose: IRR = 0.51 (CI: 0.46–0.56). • Effectiveness significantly increased with each dose: IRR 2 vs 1 dose = 0.44 (CI: 0.37–0.51); IRR 3 vs 2 doses = 0.46 (CI: 0.39–0.54). • With dose interval >4 months, no significant difference between 3 and 2 doses. • Similar results when stratified by age at vaccination.
Dominiak-Felden 2015 (91)	V: 10–21 O: 16–23	**Belgium** Merck 4vHPV	0: 63,180 1: 4,020 2: 3,587 3: 35,792	No	• Significant effectiveness against incidence of genital warts for 3 and 2 doses, but not 1 compared to 0 doses: 3: aIRR = 0.12 (CI: 0.07–0.21); 2: aIRR = 0.34 (CI: 0.14–0.83); 1: aIRR = 0.63 (CI: 0.35–1.16).
Perkins 2017 (58)	V: 9–25 O: 9–25	**United States** Merck 4vHPV	0: 201,933 1: 30,438 2: 36,583 3: 118,962	Yes	• Significant effectiveness against incidence of anogenital warts for 3 doses compared to 0 dose: aIRR = 0.53 (CI: 0.46–0.60). • Higher effectiveness for 3 compared with 1 dose: aIRR = 0.82 (CI: 0.71–0.95); no significant difference between 3 and 2 doses: aIRR = 0.89 (CI: 0.78–1.03). • With buffer period of 1 year, no change in findings. • Similar results with dose interval >5 months for 2 doses.
Navarro - Illana 2017 (54)	V: 14 O: 14–19	**Spain** Merck 4vHPV	0: 607,006 1: 18,142 2: 31,420 3: 153,296 (person-yrs)	No	• Significant effectiveness against incident cases of anogenital warts for 3, 2, and 1 doses compared to 0 dose: 3 doses: aIRR = 0.24 (CI: 0.15–0.34); 2 doses: aIRR = 0.36 (CI: 0.14–0.68); 1 dose: aIRR = 0.39 (CI: 0.13–0.80).
Lamb 2017 (59)	V: 10–19 O: 10–27	**Sweden** Merck 4vHPV	2: 79,042 3: 185,456	Yes	• Higher effectiveness of 3 doses compared to 2 doses, when 2 doses administered either 0-3 months or >8 months apart; 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.

Endpoint/ Authors	Study population age (years) at vaccination (V) & outcome (O)	Country/ Vaccine	n (by dose number)	Formal comparison of 3 vs 2 or 1 doses	Main findings
Hariri 2018 (54)	V: 16–17 (mean) O: 11–28	**United States** Merck 4vHPV	0: 31,563 1: 5,864 2: 5,459 3: 21,631	Yes	**6-month buffer from last dose:** • Significant effectiveness for 3 and 2 doses, but not for 1 dose compared to 3 doses: aHR = 0.23 (CI: 0.17–0.31); 2 doses: aHR = 0.32 (CI: 0.17–0.59); 1 dose: aHR = 0.81 (CI: 0.60-1.08). • No significant difference for effectiveness of 3 vs 2 doses: aHR = 0.74 (CI: 0.38–1.43) when 2 doses ≥ 6-month interval. • Significantly greater effectiveness of 3 doses vs 1 dose: aHR = 0.29 (CI: 0.20–0.42). **12-month buffer from first dose:** • Significant effectiveness for 3, 2, and 1 doses compared to 0 dose: 3 doses: aHR = 0.20 (CI: 0.15–0.27); 2 doses: aHR = 0.24 (CI: 0.13–0.44); 1 dose: aHR = 0.32 (CI: 0.20–0.52). • No significant difference for effectiveness of 3 doses vs 1 dose: aHR = 0.63 (CI: 0.37–1.09).
Zeybek 2018 (55)	V: 9–26 O: 10–31	**United States** Merck 4vHPV	0: 286,963 1: 54,280 2: 55,632 3: 177,051	No	**Results for those vaccinated at age 15-19 years:** • Significant effectiveness for 3, 2, and 1 doses compared to 0 dose: 3 doses: aRR = 0.58 (CI: 0.49–0.70); 2 doses: aRR = 0.67 (CI: 0.51–0.89); 1 dose: aRR = 0.65 (CI: 0.49–0.85). • Similar results with dose interval <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 (60)	V: 9–26 O: 10–33	**Canada** Merck 4vHPV	0: 94,327 1: 3,521 2: 6,666 3: 21,277	No	**Results for those vaccinated at age 9-18 years:** • Significant effectiveness for 3, but not 2 or 1 doses compared to 0 dose: 3 doses: aHR = 0.4 (CI: 0.3–0.7); 2 doses: aHR = 1.4 (CI: 0.6–3.3); 1 dose: aHR = 0.6 (CI: 0.2–1.8).
Baandrup 2021 (56)	V: 12–30 O: 12–30	**Denmark** Merck 4vHPV	0: 1,904,895 1: 235,653 2: 460,978 3: 1,934,589 (person-yrs)	Yes	**Results for first dose at age 12-14 years:** • Significant effectiveness for 3, 2, and 1 doses compared to 0 doses: 3 doses: aIRR = 0.16 (0.15–0.18); 2 doses: aIRR = 0.22 (0.18–0.26); 1 dose: aIRR = 0.29 (0.22–0.38). • Significant effectiveness for 3 vs 1 dose (aIRR = 0.56 [0.43–0.73]) but not 2 vs 1 dose (aIRR = 0.76 [0.56–1.03]).
Effectiveness against cervical abnormalities					
Gertig 2013 (61)	V: 12–19 O: 12–21	**Australia** Merck 4vHPV	0: 14,085 1:1,422 2:2,268 3: 21,151	No	**Outcome summarized: CIN3/AIS.** • Statistically significant effectiveness for 3, but not 2 and 1 doses compared to 0 dose: 3 doses: aHR = 0.53 (CI: 0.36–0.77); 2 doses: aHR = 0.87 (CI: 0.46–1.67); 1 dose: aHR = 1.40 (CI: 0.75–2.61).
Crowe 2014 (62)	V: 12–26 O: 11–31	**Australia** Merck 4vHPV	0: 60,282 1: 10,879 2: 12,073 3: 25,119	No	**Outcome summarized: High-grade histological lesions.** • Statistically significant effectiveness for 3 and 2 doses, but not 1 compared to 0 dose: 3 doses: aOR = 0.54 (CI: 0.43–0.67); 2 doses: aOR = 0.79 (CI: 0.64–0.98); 1 dose: aOR = 0.95 (CI: 0.77–1.16). • Buffer periods from 1 to 12 months: no consistent impact on effectiveness estimates. • Similar results when stratified by age at vaccination.

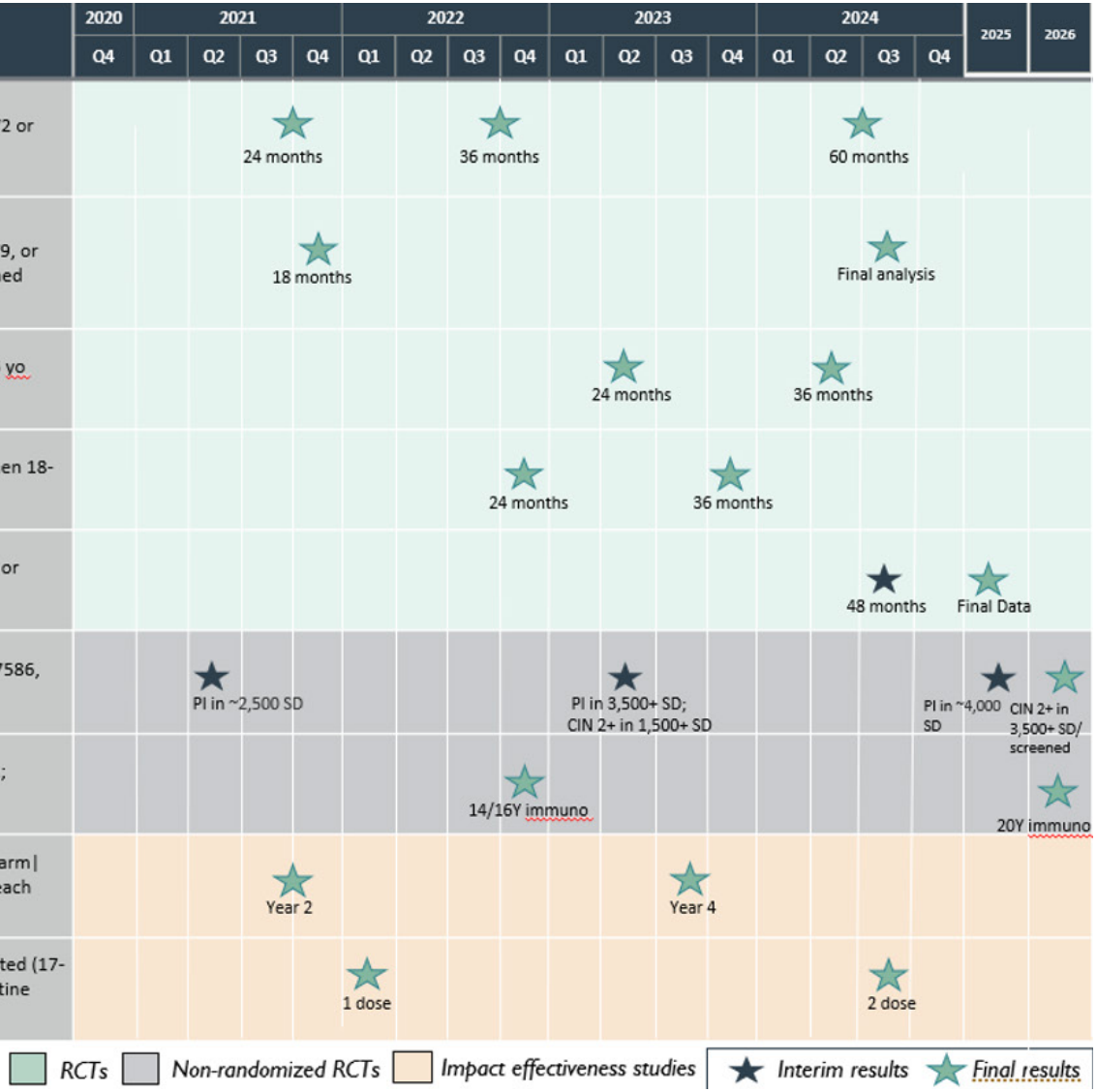
Endpoint/ Authors	Study population age (years) at vaccination (V) & outcome (O)	Country/ Vaccine	n (by dose number)	Formal comparison of 3 vs 2 or 1 doses	Main findings
Pollock 2014 (92)	V: 15–>18 O: 20–21	**Scotland** GlaxoSmith-Kline 2vHPV	0: 76,114 1: 1,315 2: 2,725 3: 25,898	No	**Outcome summarized: CIN3.** • Statistically significant effectiveness for 3, but not 2 and 1 doses compared with 0 dose: 3 doses: aOR = 0.45 (CI: 0.35–0.58); 2 doses: aOR = 0.77 (CI: 0.49–1.21); 1 dose: aOR = 1.42 (CI: 0.89–2.28).
Brotherton 2015 (67)	V: 12–26 O: 12–30	**Australia** Merck 4vHPV	0: 133,055 1: 20,659 2: 27,500 3: 108,264	No	**Outcome summarized: CIN3/AIS.** • Statistically significant effectiveness for 3, but not 2 and 1 doses compared to 0 dose: 3 doses: aHR = 0.69 (CI: 0.58–0.81); 2 doses: aHR = 1.17 (CI: 0.92–1.48); 1 dose: aHR = 1.41 (CI: 1.12–1.77). • 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 (68)	V: 11–20 O: 11–27	**United States** Merck 4vHPV	0: 1,632 1: 695 2: 604 3: 1,196	No	**Outcome summarized: Any abnormal cytology.** • Statistically significant effectiveness for 3 and 2 doses, but not 1 dose compared to 0 dose: 3 doses: aHR = 0.58 (CI: 0.48–0.69); 2 doses: aHR = 0.81 (CI: 0.66–0.99); 1 dose: aHR = 1.05 (CI: 0.88–1.26). • Similar results when stratified by age at vaccination, although effectiveness of 2 doses compared to 0 dose not always significant.
Kim 2016 (93)	V: 10–15 O: 18–21	**Canada** Merck 4vHPV	0: 5,712 1: 327 2: 490 3: 3,675	No	**Outcome summarized: High-grade cytology.** • Statistically significant effectiveness for 3, but not 2 and 1 doses compared with 0 dose: 3 doses: aOR = 0.48 (CI: 0.28–0.81); 2 doses: aOR = 0.17 (CI: 0.02–1.20); 1 dose: aOR = 0.45 (CI: 0.11–1.83).
Cameron 2017 (94)	V: 14–>18 O: 20–21	**Scotland** GlaxoSmith-Kline 2vHPV	0: 75,683 1: 2,258 2: 4,462 3: 55,303	No	**Outcome summarized: CIN3.** • 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 (95)	V: 14–26 O: 18–34	**United States** Merck 4vHPV	0: 23,293 1: 756 2: 554 3: 1,527	No	**Outcome summarized: CIN3+, AIS.** • 3 doses: aRR = 0.64 (CI: 0.48–0.84); 2 doses: aRR = 0.97 (CI: 0.67–1.41); 1 dose: aRR = 0.90 (CI: 0.65–1.24). • Highest 3 dose effectiveness among those vaccinated at youngest ages.
Dehlendorff 2018 (70)	V: 13–29 O: 13–30	**Denmark/ Sweden** Merck 4vHPV	2,253,561	No	**Outcome summarized: CIN2+/ AIS.** • <16 years: 3 doses: IRR = 0.23 (CI : 0.11–0.49); 2 doses: IRR = 0.44 (CI : 0.1–2.03); 1 dose: IRR = 0.23 (CI : 0.01–5.24). • Similar results for those vaccinated at age 17–19 yrs. • No significant difference between 2 doses and 3 doses with dose 2 at 5 months or longer after 1 dose and age of vaccination < 20 yrs.

Endpoint/ Authors	Study population age (years) at vaccination (V) & outcome (O)	Country/ Vaccine	n (by dose number)	Formal comparison of 3 vs 2 or 1 doses	Main findings
Verdoodt 2019 (63)	V: 12–16 O: 17–25	**Denmark** Merck 4vHPV	0: 374,327 1: 10,480 2: 30,259 3: 174,532	No	**Outcome summarized: CIN3+/AIS.** • Overall results compared to unvaccinated: 3 doses: IRR = 0.37 (CI: 0.30–0.45); 2 doses: IRR = 0.38 (CI: 0.22–0.66); 1 dose: IRR = 0.38 (CI: 0.14–0.98). • 3 versus 1 dose: aIRR = 0.95 (CI: 0.60–1.51).
Brotherton 2019 (65)	V: ≤13–22 O: 15–22	**Australia** Merck 4vHPV	0: 48,845 1: 8,618 2: 18,190 3: 174,995	Yes	**Outcome summarized: CIN2+.** • Overall results compared to unvaccinated: 3 doses: aHR = 0.59 (CI: 0.54–0.65); 2 doses: aHR = 0.61 (CI: 0.52–0.72); 1 dose: aHR = 0.65 (CI: 0.52–0.81). • 3 doses versus 1 dose: aHR= 0.91 (0.74 – 1.13). **Outcome summarized: CIN3+/AIS.** • Overall results compared to unvaccinated: 3 doses: aHR = 0.43 (0.35–0.53); 2 doses: aHR = 0.42 (0.27–0.64); 1 dose: aHR = 0.66 (0.41–1.06). • 3 doses versus 1 dose: aHR = 0.66 (0.41–1.05).
Johnson Jones 2020 (64)	V: 12–26 O: 18–39	**United States** Merck 4vHPV	0: 2,731 1: 136 2: 108 3: 325	Yes	**Outcome summarized: CIN2+/AIS.** • 3 doses: aOR = 0.26 (0.20–0.35); 2 doses: aOR = 0.45 (0.30–0.69); 1 dose: aOR = 0.53 (0.37–0.76).
Rodriguez 2020 (66)	V: 9–26 O: 9–31	**United States** Merck 4vHPV	0: 66,541 1: 13,630 2: 14,088 3: 38,823	No	**Outcome summarized: CIN2/3.** • First dose at age 15–19 yrs. • 3 doses: aHR = 0.66 (0.55–0.80); 2 doses: aHR = 0.72 (0.54–0.95); 1 dose: aHR = 0.64 (0.47–0.88).
Innes 2020 (71)	V: 14–21 O: 20–24	**New Zealand** Merck 4vHPV	0: 47,283 1 or 2: 8,317 3: 48,713	No	**Outcome summarized: high-grade histology (at least 1 dose at age <18 yrs).** • 3 doses: IRR = 0.66 (0.60–0.72); 2 doses: IRR = 0.81 (0.63–1.03); 1 dose: IRR = 1.10 (0.85–1.45).
Palmer 2019 (96)	V: 12–>18 O: 20–21	**Scotland** GlaxoSmith-Kline 2vHPV	0: 64,026 1: 2,051 2: 4,135 3: 68,480	No	**Outcome summarized: CIN3+.** • 2 doses: aOR = 0.77 (0.48–1.24); 1 dose: aOR = 1.19 (0.70–2.05).
Acuti Martellucci 2021 (69)	V: 14–>30 O: 17–32	**Italy** GlaxoSmith-Kline 2vHPV & Merck 4vHPV	0: 7,394 1: 212 2: 83 3: 96	No	**Outcome summarized:** • Any abnormal cytology, youngest birth cohort (1990–1993), 1-month buffer duration • 3: aOR = 0.44 (0.14–1.43); 2: aOR = 0.65 (0.20–2.16); 1: aOR = 0.43 (0.17–1.05)

Note: 2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent HPV vaccine; aHR, adjusted hazard ratio; aIRR, adjusted incidence rate ratio; AIS, adenocarcinoma in situ; aOR, adjusted odds ratio; aPD, adjusted difference in predicted probabilities; aPR, adjusted prevalence ratio; aRR, adjusted relative risk; AU, arbitrary unit; CI, confidence interval; CIN2/3(+), cervical intraepithelial neoplasia grade 2 or 3 (or worse); CVT, Costa Rica Vaccine Trial; DoD, Department of Defense; DoRIS, Dose Reduction Immunobridging and Safety; GMT, geometric mean titer; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; IRR, incidence rate ratio; M, month; mITT, modified intent to treat; Nab, neutralizing antibody; O, outcome; PHACS, Pediatric HIV/AIDS Cohort Study; PHEU, perinatally HIV exposed but not infected; PHIV, perinatally HIV infected; PR, prevalence ratio; RR, relative risk; SCR, seroconversion rate; V, vaccination; vs, versus; VE, vaccine efficacy Y, year.

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

Study name (country)	Evidence type	Vaccine(s)	Brief description
DoRIS Tanzania	Immunogenicity	HPV2 and HPV9	Girls 9-14 yo randomized to 1, 2, or 3 doses of HPV2 or HPV9, N=155 each arm
KEN SHE Kenya	Efficacy (virological EP)	HPV2 and HPV9 vs MenACWY (delay HPV)	Girls 15-20 yo randomized to 1 dose of HPV2, HPV9, or MenACWY; N=750 each arm; delayed dose 2 planned
HANDS The Gambia	Immunogenicity	HPV9	Girls 4-8 yo randomized to 1 or 2 doses; girls 15-26 yo given 3 doses; N=344 each arm
Primavera Costa Rica	Immunogenicity	HPV2 and HPV4	Girls 10-13 yo 1-dose HPV2 immunobridge to women 18-25 yo 3-doses HPV4; N=520 each arm
ESCUDDO Costa Rica	Efficacy (virological EP)	HPV2 and HPV9	Girls 12-16 yo randomized to 1 or 2 doses of HPV2 or HPV9; N=5,000 each arm
India IARC India	Efficacy (virological & histological EP)	HPV4	Girls 10-18 yo received 1, 2, 3 doses of HPV4; N=17586, 1-dose N=4,980
CVT Costa Rica	Efficacy till Y11 / Immunogenicity	HPV2 vs control	Women 18-25 yo received 1, 2, or 3 doses of HPV2; N=3,727, 1-dose N=196
Thailand impact study Thailand	Effectiveness (virological EP)	HPV2	Girls in grade 8 given 1 or 2 doses; N=~8,000 each arm| prevalence surveys of girls grade 10, 12; N=2,400 each grade x 2 provinces
HOPE South Africa	Effectiveness (virological EP)	HPV2	Girls 17-18 yo serial prevalence surveys: unvaccinated (17-18 yo), 1-dose catch up (15-16 yo), and 2-dose routine (9 yo) cohorts; N≥3,260



CIN: cervical intraepithelial neoplasia; immuno: immunogenicity; MenACWY: Meningococcal ACWY; N: number; SD: single dose; PI persistent infections; RCT: Randomized-control Trial ; Y: year; yo: year of age

RCTs *Non-randomized RCTs* *Impact effectiveness studies* *Interim results* *Final results*

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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, Wits Reproductive Health and HIV Institute, and the Kirby Institute at University of New South Wales.

In addition to the consortium members, representatives from the following institutions serve as advisors: 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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