Technical synthesis of the current published evidence for single-dose HPV vaccination

Photo: PATH/Will Boase

Introduction

Prophylactic human papillomavirus (HPV) vaccines have been licensed for over 10 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. After review of the evidence, the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization recommended a two-dose schedule in 2014. Recent evidence suggests a single-dose of HPV vaccine may be sufficient to provide protection against incident and persistent HPV infection, which are the necessary prerequisites to further development of cervical lesions and in the longer term, cervical cancer.

In 2018, 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 has compiled the current published evidence on single-dose HPV vaccination, including data from trials, other observational studies, and modeling, and provided 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 initial evidence review, which was published in a white paper (see sidebar) and will be updated annually as new evidence emerges.

Burden of HPV-related disease and cervical cancer

Invasive cervical cancer (ICC), caused by persistent infection with HPV, is a major public health problem, especially in developing countries [1]. In 2012, prior to widespread HPV vaccine introduction, there were estimated to be 528,000 new cases and 266,000 cervical cancer-related deaths per annum globally [2] with over 80% of ICC cases occurring in low and middle income countries (LMIC) [2, 3]. In settings where effective cervical screening programs are available, the incidence of and mortality from cervical cancer has markedly decreased [3, 4]. However, in many developing countries, screening programs are not in place or are available only on a limited scale; women frequently present with advanced disease, leading to high associated morbidity and mortality.

Review of the current published evidence for single-dose HPV vaccination (white paper

The white paper (WP) is a comprehensive assessment of (i) the current evidence on single-dose HPV vaccination, (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 immunogenicity, efficacy and effectiveness; identification of gaps in the evidence; discussion of possible study designs or approaches for filling such gaps; acknowledgment of any known studies or datasets that might be ongoing or available; and an overall summary for the strategic direction needed to inform decisions about HPV single-dose or alternative schedules.

The complete WP can be found at http://www.rho.org/singledosehpv/.

HPV vaccines

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

Table 1. Summary of available HPV vaccines targets and schedule

	Bivalent HPV vaccine (2vHPV)	**Quadrivalent HPV vaccine** (4vHPV)	**Nonavalent HPV vaccine** (4vHPV)
Manufacturer	GlaxoSmithKline	Merck & Co, Inc.	Merck & Co, Inc.
Trade name	Cervarix®	Gardasil4®	Gardasil9®
Schedule ≤ 14 years of age: 2 doses	0, 6 -12 months	0, 6 -12 months	0, 6 -12 months
Injection Schedule ≥ 15 years of age: 3 doses	0, 1, 6 months	0, 2, 6 months	0, 2, 6 months

When given as a two-dose schedule, HPV vaccines elicit a strong immune response that is non-inferior to that from a three-dose schedule, for which 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 for a Single Dose of HPV vaccine

Sources of evidence covered in the WP include publicly available peer reviewed scientific publications on:

- The biological plausibility for protection with a single dose of HPV vaccine based on vaccine immune response and virological information;
- Observational data from partially vaccinated participants in clinical trials of HPV vaccine efficacy and immunogenicity;
- Data from post-licensure vaccine effectiveness evaluations and other observational data; and
- Modeling analyses.

Biological plausibility: the immune response to a single dose of HPV vaccine

Plausible biological explanations for the unexpected potency of HPV vaccines have been examined and recently 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%. Peak *in vitro* neutralizing titers of 1,000-10,000 are generally obtained, and—after a relatively steep 10-fold drop in titer over the first two years—IgG titers plateau or decline very slowly, stabilizing at levels that are substantially higher than the antibody titers induced by natural infection [8]. Responses in pre-adolescent girls and boys are even stronger [9, 10]. The stability of antibody responses now observed almost 10 years post vaccination [11, 12], is unprecedented for a subunit vaccine. This pattern of antibody response is observed even after a single dose of vaccine [13, 14].

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

As of April 2018, there were no data on the immunogenicity, efficacy or effectiveness of a one dose HPV vaccination schedule compared to two and three-dose schedules that originated from specifically designed randomized studies comparing one dose to two or three-dose groups. However, observational data from randomized control trials (RCTs) where participants failed to complete their schedule of two or three doses provide some evidence that a single dose of HPV vaccine may provide protection against persistent HPV infection with vaccine genotypes and protective immune responses. Specific outcomes of interest examined in the observational clinical studies include efficacy and immunogenicity.

Efficacy studies of single-dose HPV vaccine

The most significant efficacy data come from non-randomized observation data in two independent trials, the Costa Rica Vaccine Trial and the IARC India HPV trial. These trials and their findings are summarized below.

Costa Rica Vaccine Trial (CVT). Conducted by the US National Cancer Institute (NCI) and the Agencia Costarricense de Investigaciones Biomédicas, the CVT trial is a community-based, randomized phase III clinical trial that also includes an additional long-term observational study. 7,466 women ages 18–25 years were enrolled and randomized to receive either the 2vHPV (bivalent) 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, a small percentage did not receive three doses; they comprise the group being monitored and observed for efficacy. Participants were followed at least annually for four years and were invited to stay in a long-term follow-up observational study [15,16]. During this observational study, HPV-vaccinated participants were followed annually for six additional years.

Four years after initial vaccination, one dose of the 2vHPV vaccine had comparable efficacy to three doses of the vaccine using an endpoint of cumulative persistent HPV infection [16]. 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%; 37 and 229 events in the HPV [n=2957] and control [n=3010] arms, respectively); two doses = 81% (95% CI: 53 to 94%); 5 and 24 events among HPV [n=422] and control [n=380] arms, respectively); and one dose = 100% (95% CI: 79 to 100%; 0 and 15 events among HPV [n=196] and control [n=188] arms, respectively).

Seven years following initial HPV vaccination, the CVT found that the prevalence of HPV 31,33,45 was similar between the three-dose (2.3%; 95% CI: 1.8 to 3.1%), two-dose (0/6 months; 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) [17].

Results of the CVT were confirmed through analysis of a similarly structured trial, the PATRICIA trial (PApilloma TRIal against Cancer in young Adults), sponsored by GSK biologicals. A combined, post hoc analysis of 12,013 women aged 15–25 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 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 [18].

IARC India HPV trial. Sponsored by the International Agency for Research on Cancer (IARC), the India HPV trial was designed as a multi-center cluster randomized trial to evaluate the comparative efficacy of two versus three doses of 4vHPV (quadrivalent). The initial study design called for 20,000 girls, ages 10-18 years, to be randomly allocated to receive either two or three doses. However, in April 2010, the study was suspended due to events unrelated to the study, resulting in broken randomization and some trial participants not completing or not completing on time the vaccination schedule assigned. As a consequence, the study, which had enrolled 17,739 girls before suspension, resulted in four groups of vaccine recipients; 4,348 (25%) girls received three doses (according to schedule), 4,979 (28%) received two doses (according to schedule), 3,452 (19%) received two doses by default (approximately 2 months apart), and 4,950 (28%) received one dose by default. The default groups included girls who were unable to complete their allocated vaccination schedules.

The frequencies of cumulative incident HPV 16 and 18 infections over seven years from vaccination were similar and uniformly low in all the study groups; the frequencies of HPV 16 and 18 infections were higher in 1,481 unvaccinated women (6.2%) than among the vaccine recipients (0.9% in 1,180 three-dose recipients, 0.9% in 1,179 two-dose recipients, 1.7% in 1,473 two-dose (default) recipients and 1.6% among 1,823 one-dose recipients).

Findings from the India study, based on the comparison of the rate of persistent infection in 2,989 vaccinated women providing at least two cervical samples with that in 1,141 unvaccinated women, suggest high vaccine efficacy in preventing persistent HPV 16 and 18 infections regardless of the number of doses received. There was a total of four (0.1%) persistent HPV 18 infections and no persistent HPV 16 infection among the 2,989 vaccine recipients as opposed to 14 (1.2%) persistent infections with HPV 16 or HPV 18 among 1,141 unvaccinated control women. No persistent HPV 16 and 18 infection was detected in 959 women in the one-dose arm.

Immunogenicity studies of single-dose HPV vaccine

In addition to the efficacy data generated by the CVT and India IARC studies, these studies also reported immunogenicity of a single dose of HPV vaccine during the same follow-up period. Two additional studies of immunogenicity of single-dose HPV vaccine conducted in Uganda [19] and Fiji [20] reported similar findings.

In the CVT trial, among women who received a single dose, 100% seroconverted, and HPV 16 and HPV 18 antibody titers (assessed by ELISA) were substantially higher than those among naturally-infected unvaccinated women (approximately nine-fold higher for HPV 16 and five-fold higher for HPV 18) four years after initial vaccination [14]. HPV 16 VLP 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 [17], and avidity for one dose was similar to three doses at year 4.

In the India IARC study, after four years of follow-up, antibody concentrations for both anti-HPV 16 and anti-HPV 18 were lower among girls receiving one dose compared to three doses. However, the frequency of incident HPV 16, 18, 6, and 11 infections was similar irrespective of the number of vaccine doses received, and no persistent HPV 16 or 18 infections were detected in any dose group over a follow up period of seven years.

Uganda: A cross-sectional immunogenicity study was conducted among 376 adolescent girls (aged 10-11 years at time of vaccination) who received 2vHPV vaccine as part of a government-run HPV vaccination demonstration program implemented between October 2008 and October 2009 in one district of Uganda [19, 21]. Vaccine was administered on a three-dose schedule (0, 1, and 6 months). Three-dose completion among girls aged 10 years was 52-60%. The cross-sectional immunogenicity study recruited girls who had received one, two or three doses and measured antibody responses about three years post-vaccination. Study enrollment and blood draws were completed for 195 three-dose recipients, 145 two-dose recipients, and 36 one-dose vaccine recipients. Study participant demographic characteristics were comparable across dose groups. The geometric mean neutralization titers (GMT) after one or two doses of 2vHPV vaccine did not meet the threshold to be declared non-inferior to three doses. However, GMTs in adolescents who received only one dose were higher than among women who received only one dose of 2vHPV vaccine in the CVT in whom efficacy has been demonstrated. Furthermore, immune responses in the one dose group were four-fold higher than those elicited from natural infection.

Fiji: 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. Girls enrolled had been a part of the government of Fiji's initial effort for national implementation of HPV vaccinations in 2008-09. All had been eligible originally to receive the recommended three-dose schedule of 4vHPV vaccine through a government-administered program; however, some received only one or two doses. This follow-up study enrolled 200 girls 15–19 years of age (9–12 years 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. Girls enrolled in the one-dose group received an additional dose of 2vHPV HPV vaccine to investigate anamnestic responses.

At enrollment six years after initial vaccination, 90–100% of girls were seropositive for HPV 6, 93–100% for HPV 11, 95–100% for HPV 16 and 68–88% for HPV 18. 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 (NAb) titers than two or three-dose recipients; however, titers among the one-dose group were 5- to 30-fold higher than unvaccinated girls. The one-dose group who received an additional dose of 2vHPV six years after the initial 4vHPV vaccination demonstrated a robust anamnestic response and were not significantly different from the two-dose and three-dose groups [20].

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

A recent systematic review summarized the current published literature [22] on evidence on the effectiveness of HPV vaccination by the number of doses, as measured in post-licensure studies. The review summarized the main study characteristics including 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 (three vs none, two vs none, one vs none, three vs two, three vs one, two vs one) of 4vHPV or 2vHPV vaccine. Studies were excluded if the vaccine was administered as part of an RCT (e.g., post-hoc evaluations of clinical trials). The literature search identified 3,787 articles, from which 26 full articles were assessed. After reading full texts, 14 articles were included in the final analyses of effectiveness (Table 2). Of these studies:

- Two examined vaccine effectiveness for reduction of HPV prevalence. One of these studies found statistically significant effectiveness with three doses, but not for two doses or one. The other study found statistically significant effectiveness for three, two, and one doses [22, 23].
- Six evaluated anogenital wart outcomes—four of which included comparison of three, two, and one doses—and found highest effectiveness with three doses and lower but significant effectiveness with two doses. Three of the four studies found significant effectiveness with one dose [24, 25, 26].
- Six studies evaluated vaccine effectiveness in preventing cervical cytological or histological abnormalities. All found effectiveness for three doses, four found some effectiveness for prevention of high-grade histological abnormalities with two doses, and two studies found effectiveness with one dose [27, 28].

Most post-licensure studies examining HPV vaccine effectiveness by number of doses report highest effectiveness with three doses, but some found no statistically significant difference between two and three doses. Additionally, almost half of the studies found some effectiveness for a single dose. The systematic review summarized the various biases in these studies due to differences between persons who received a complete vaccination series and those who did not.

Modeling data and analysis

The limited number of published studies on modeling of reduced dose strategies (three to two doses) for the 2vHPV, 4vHPV and the 9vHPV vaccines 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 vaccines and one with the 9vHPV vaccine [29-32]. 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 2v/4vHPV vaccination using independent dynamic transmission models fitted to the United Kingdom (UK; Public Health England model) and Canada (HPV-ADVISE 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 [29, 30]. 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 impact and cost-effectiveness. 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 duration of reduced-dose protection is only 10 years;
- The impact and cost-effectiveness of adding a third vaccine dose hinges on the relative duration of protection for two versus three doses and will be minimal if two-dose protection is 20–30 years, assuming no initial waning in the first 10 years for either two or three doses; and
- If two-dose protection is only 10 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 (UK and US) [33, 34]. An analysis of single-dose HPV 16 and 18 vaccination in Uganda extends the findings from the US-based analysis to evaluate the impact and cost-effectiveness of single-dose HPV 16 and 18 vaccination in that setting [35]. Themes similar to the two-dose analysis emerged in the limited 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 lower vaccine efficacy (80%) and when duration of reduced-dose protection is only 10 years.
- The impact and cost-effectiveness of adding a second dose is driven by the duration of single-dose vaccine protection and possibly, the ability to achieve higher coverage with a single dose versus multiple doses.
- To date, the model-based evidence on reduced-dose HPV vaccination relies on findings from three independent models that have been developed using data from high-income settings with similar HPV epidemiologic profiles. The emerging evidence on vaccine efficacy and durability from the ongoing studies—and the extension of these analyses into settings with more variable epidemiological, demographic, and behavioral profiles—will be critical to fill important evidence gaps regarding the impact and value of reduced-dose HPV vaccination.

Summary of results

A recent review on the virological and immunological properties of HPV infections and HPV vaccines provides a plausible theoretical mechanism to explain why a single dose elicits a robust immune response and why lower antibody titers observed for one dose compared with two or more doses may still provide protection against HPV [6]. Non-randomized observational data from RCTs comparing one-dose recipients with those who received two or more doses of the 2vHPV and 4vHPV vaccines show consistency in terms of protection against HPV persistent infection.

In the CVT, the initially strong protection by a single dose of the 2vHPV vaccine observed post vaccination indicates no evidence of diminishing at seven years of follow-up. Single time point infection rates by types targeted by the vaccine remain remarkably low. Incident HPV infections in the PATRICIA study were also similar by vaccine dose. In the India HPV vaccine trial of 4vHPV, although antibody concentrations for both anti-HPV 16 and anti-HPV 18 were lower among girls receiving one dose compared to three doses at 48 months, the frequency of incident HPV 16, 18, 6, and 11 infections was similar irrespective of the number of vaccine doses received, and no persistent HPV 16 or 18 infections were detected in any dose group over a follow-up period of seven years.

In both the Uganda and Fiji studies [19, 20], antibody responses after one dose of HPV vaccine were lower than after two or three doses. In the Uganda study, GMTs after one and two doses of 2vHPV vaccine (measured about three years after last dose) did not meet the threshold to be declared non-inferior to three doses. However, GMTs of antibody in adolescents who received only a single dose in Uganda were still higher than women who received a single dose of 2vHPV vaccine in the CVT, among whom there have been no breakthrough cases of persistent infection up to four years after vaccination [14, 36].

Photo: PATH/Doune Porter

A systematic review of 14 studies of HPV vaccine effectiveness by number of doses found the highest effectiveness with three doses, followed by two doses, and one dose. However, few studies directly compared three, two and one dose(s) and some effectiveness estimates had wide confidence intervals due to the small number of outcomes in one- and two-dose vaccine recipients. All found statistically significant effectiveness for three doses and 11 studies found effectiveness for two doses [24-28,37-40, 42-43]. In six studies (including studies for both vaccines) significant effectiveness was observed for a single dose in some analyses [24-25, 27, 37, 39, 42] .

Variation in effectiveness by number of doses was observed across all endpoints (prevalence, AGW and cervical abnormalities). There were generally consistent findings regarding buffer periods in the studies that evaluated this, with three of four studies finding higher effectiveness estimates for one and two doses and a decrease in the differences by number of doses with longer buffer periods. Among studies presenting results stratified by age group, higher effectiveness estimates were generally found with a younger age at vaccination, although the differences were not formally tested. There were differences in the impact of varying time interval between two doses. Two studies of anogenital warts found higher two-dose effectiveness with increasing interval through six or seven months [25, 40]. The one study of cervical abnormalities that evaluated interval between two doses did not find a difference [42].

There are limited modeling analyses evaluating single-dose HPV vaccination and these studies have used data from high-income country settings. However, initial analyses indicate that if the choice is between no vaccination and single-dose, a single dose is likely to provide health benefits and to be good value for money. This applies even if the vaccine has a lower vaccine efficacy than two or more doses, as long as single-dose protection lasts at least 10 years. If the choice is between one-dose and two-dose vaccination, then the second dose becomes the most cost-effective option if it can extend protection up to at least 20 years. Extension of these analyses into settings with more variable epidemiological, demographic, and behavioral profiles will be critical to fill important evidence gaps regarding the impact and value of reduced-dose HPV vaccination.

Strengths

Non-randomized observational data from the CVT, PATRICIA, and India IARC trials have provided encouraging indications that a single dose of the HPV vaccine may provide protection from persistent HPV infections over several years. These are well-conducted prospective studies, implemented in the context of clinical trial protocols, with rigorous enrollment, clinic procedures and laboratory protocols, and good retention to follow-up. The results from these studies have provided the strongest evidence to date to support further investigations on the efficacy and immunogenicity of single-dose HPV vaccine strategies. Analyses from some of these studies are ongoing.

Strengths of the data from other population-based observational studies include the size of the populations included in the studies, inclusion of data on buffer periods in some studies, and some information on intervals between doses.

Mathematical models that simulate the disease burden of HPV in populations complement empirical studies measuring efficacy and effectiveness of HPV vaccination by projecting longer-term outcomes of most interest to decision-makers (e.g., cancer cases and deaths averted or life expectancy gained) and generating evidence under conditions of uncertainty or where data do not exist. Such models have been used extensively to evaluate the health and epidemiologic impacts, budget impacts, and cost-effectiveness of strategies to prevent HPV-related diseases globally.

Limitations

The published studies of the CVT, PATRICIA, and India trials are difficult to cross compare because of their heterogeneous design, vaccine used, and outcomes assessed. Comparisons across the studies of immune response data are also difficult because of the use of different assays, measurement cutoffs for seropositivity, and laboratory procedures in these trials, although clinical data on protection against HPV infection provide consistent results for a single dose of either the 2vHPV or 4vHPV vaccines. It is also important to note that there are no data to date from prospective RCTs specifically designed to answer the question of single-dose protection or immune responses. The number of girls receiving a single dose of the 2vHPV vaccine in the CVT and PATRICIA trials was relatively small, and they were not randomized to a reduced-dosing schedule. The combined analysis of the CVT and PATRICIA trials use one-time detection of HPV incident infection rather than persistent infection. This measurement could also include virus deposition from an infected partner, short-term infections that clear spontaneously or intermittently, and/or activated latent infections that were not detected at vaccination.

Although the IARC India trial was originally an RCT, the original dose randomization could not be maintained. The creation of the single-dose cohort was therefore unintentional, although not controlled by the investigators. The different vaccine dose cohorts were comparable for age but there were differences in several socio-demographic factors at enrollment such as monthly household income, religion, and education [36]. Clinical outcomes were only measured in married women for cultural reasons and this reduced the sample size for analysis. The unvaccinated cohort was created post-hoc in 2011 by selecting married women matched to married participants on age, study site, and time of follow-up. Biases in selection of this cohort cannot be ruled out.

In the Uganda and Fiji immunogenicity studies, sample sizes were small, especially among those who received a single dose. In the Uganda study, the sample size was too small to test the primary hypothesis of non-inferiority of one dose compared with three doses with sufficient statistical power. Neither study was an RCT, therefore girls might have differed by dose group. The results could suffer from selection bias and confounding. The Fiji study had data on participants six years after their initial vaccination, including body mass index (BMI), ethnicity, and some socioeconomic and behavioral characteristics, but data to evaluate comparability across groups were more limited from the Uganda study. Neither study reported data on sexual behavior; however, all girls in the Uganda study were aged 10 or 11 years at time of vaccination, thus prevalent infections prior to vaccination are highly unlikely in this context.

Among the population-based observational studies, a number of possible biases in currently available data may have impacted the estimates, with most biasing the one or two-dose results towards lower vaccine effectiveness.

- Post-licensure studies were all conducted in settings of a national three-dose recommendation and girls who received one or two doses differed from those completing the recommended schedule. These studies also included girls who were vaccinated beyond the routine target age group in the early years of the vaccination programs when catch-up programs had been implemented, girls who were older than three-dose vaccine recipients at the time of vaccination, or girls who had a lower socio-economic status and/or had indicators of earlier sexual exposure.
- Study subjects may have misclassification of vaccination status due to recall and/or misclassification of outcome due to diagnostic bias, interviewer bias, and/or data recording tools used.

Lastly, modeling studies have utilized data only from high-income countries and are reliant on assumptions about the duration of one and two-dose vaccine protection which will ultimately only be confirmed by long-term follow-up of post-vaccination cohorts. It is important to highlight that the model-based evidence on reduced-dose HPV vaccination to date relies on findings from three independent models that have been developed using data from high-income settings with similar HPV epidemiologic profiles. The emerging evidence on vaccine efficacy and durability from the ongoing studies—and the extension of these analyses into settings with more variable epidemiological, demographic, and behavioral profiles—will be critical to fill important evidence gaps regarding the impact and value of reduced-dose HPV vaccination.

Gaps and forthcoming evidence

As of April 2018, there were no data on the immunogenicity, efficacy, or effectiveness of a single-dose HPV vaccination schedule compared to two and three-dose schedules that originated from a randomized comparison of vaccination groups. Therefore, a critical question remains: does a single dose of vaccine provide a sufficient and durable level of efficacy against persistent HPV infection to support a recommendation to support a policy change to a single-dose vaccination strategy?

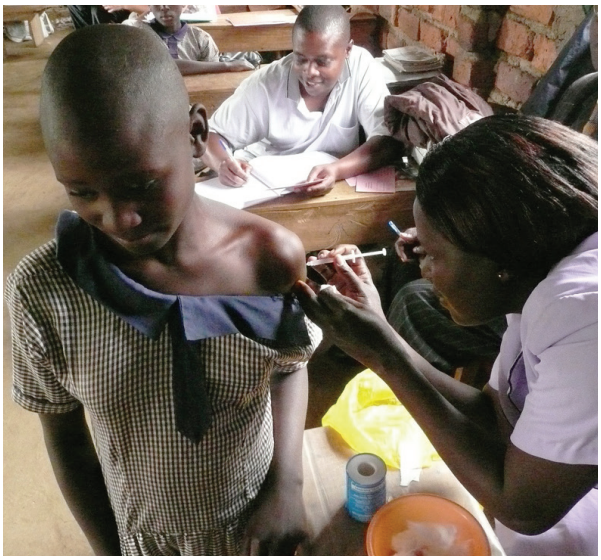

Photo: PATH/Robin Biellik

Prospective randomized trials and large-scale impact studies will provide more definitive data on whether a single dose can protect against HPV persistent infection and provide immunobridging data to trials without efficacy endpoints. These trials are underway in Costa Rica (ESCUDDO), Tanzania (DoRIS), and The Gambia (HANDS), and will begin soon in Kenya (KEN-SHE). The impact studies will also begin soon in Armenia and Thailand.

ESCUDDO and KEN-SHE will randomize young women to single-dose schedules. HANDS, DoRIS, and KEN-SHE will immunobridge to efficacy trials, and a common immunoassay will be used across vaccines to directly compare immune response regardless of vaccine received. Additionally, longer-term immune response data will still be forthcoming from CVT and the India IARC trial, as well as longer-term efficacy observations. These studies will help understand duration of efficacy (and levels of efficacy over time). In addition, efforts are now underway to standardize the immunological testing for antibody levels allowing researchers to directly compare immune responses of a single dose between vaccines and across studies so that the results of the all new trials can be compared directly.

In addition, a separate systematic review of the literature will examine the efficacy and immunogenicity of one dose compared to two or three doses of HPV vaccines from clinical trials or observational studies of partially vaccinated populations. The results will enhance and validate the evidence from individual studies.

The non-trial evidence from population-based observational studies is currently constrained by the studies conducted to date including persons who received catch-up vaccination and difficulties controlling for differences by number of doses received. The work of the consortium will close this gap by doing repeated systematic reviews in hopes of capturing new studies and more studies of effectiveness that have controlled for possible prior infection and other important confounders. In addition, this new evidence will be further strengthened by meta-analyses of population impact studies to increase the robustness of the analysis with larger samples, especially for single-dose groups.

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

While the evidence available to date regading a single-dose schedule of HPV vaccine is encouraging, further data are needed. The Single-Dose HPV Vaccine Evaluation Consortium will continue to monitor the evidence base, update it annually, and share results widely.

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

Endpoint/ Authors [ref.]	Study Population Age (years) at Vaccination (V) & Outcome (O)	Country/ Vaccine	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	Yes	• The four-year analysis found that fewer than 3 doses (2 or 1) of the vaccine protect as well as the full three-dose series for four years [62]; • Antibody levels achieved following two doses (0 and 6 months) of the HPV vaccine are high and only slightly lower than those observed after three doses (one dose antibodies levels were lower than those of two and three doses, but higher than natural infection levels, and remained stably elevated over four years).
Sankaranarayanan 2016 [13]	V: 10-18 O: 12-20	**India** Quadrivalent	Yes	• Immune response in the two-dose HPV vaccine group was non-inferior to the three-dose group at seven months but was inferior in the two-dose default and one-dose default groups at 18 months. • Fewer than three doses by design and default induced detectable concentrations of neutralizing antibodies to all four vaccine-targeted HPV types but at much lower concentration after a single dose. • Cervical samples from 2,649 participants were tested and the frequency of incident HPV 16, 18, 6, and 11 infections was similar irrespective of the number of vaccine doses received. • The testing of at least two samples from 838 participants showed that there was no persistent HPV 16 or 18 infections in any study group at a median follow-up of 4.7 years.
LaMontagne 2014 [19]	V: 11-12 O: 13-16	**Uganda** Bivalent	Yes	• Geometric mean antibody (GMT) ratio for 1:3 doses for HPV 16 and HPV 18 was inferior, but absolute GMTs for one dose were higher than adult women who received one dose (where efficacy has been demonstrated). • Even though immunogenicity with less than three doses did not meet a priori non-inferiority thresholds, antibody levels measured ≥24 months after the last dose were similar to those of adult women who have been followed for more than eight years for efficacy.
Toh 2017 [20]	V: 9-12 O: 15-19	**Fiji** Quadrivalent	Yes	• After six years the geometric mean NAb titers for all four HPV types were not statistically different between two-dose (2D) and three-dose (3D) recipients: HPV 6 (3D: 2216 [95% confidence interval (CI), 1695-2896]; 2D: 1476 [95% CI, 1019-2137]; P=.07), HPV 11 (3D: 4431 [95% CI, 3396-5783]; 2D: 2951 [95% CI, 2452-4373]; P=.89); HPV 18 (3D: 628 {95% CI: 445-888]; 2D: 606 [95% CI, 462-862] P=.89) • Although one-dose recipients had significantly lower NAb titers than two or three-dose recipients, their NAb titers were 5 to 30-fold higher than unvaccinated girls. • Two doses of 4vHPV provide similar NAb titers as three doses for six years. • A single dose of 4vHPV elicits antibodies that persisted for at least six years and induced immune memory.

Endpoint/ Authors [ref.]	Study Population Age (years) at Vaccination (V) & Outcome (O)	Country/ Vaccine	Formal comparison of 3 vs 2 or 1 doses	Main Findings
Effectiveness: Genital warts				
Herweijer 2014 [25]	V: 10-19 O: 10-24	**Sweden** Quadrivalent	Yes	• Statistically significant effectiveness against first occurrence of condyloma (warts) for three, two, and one doses compared to zero. 3: aRR = .20 (CI .17, .23), 2: aRR = .32 (CI .26, .40), 1: aRR = .54 (CI .43, .68). • Significantly higher effectiveness of three compared to two and one doses. • With buffer periods >4 months, no significant difference between three and two doses. • Similar results for age groups 10–16 and 17–19 years, except effectiveness for a single dose without buffer period is statistically significant for 10–16 year olds.
Blomberg 2015 [37]	V: 12-27 O: 12-27	**Denmark** Quadrivalent	Yes	• Statistically significant effectiveness for reducing risk of genital warts; one dose compared to zero, RR = .51 (CI .46, .56). • Effectiveness not reported for three and two doses compared to zero doses. • Effectiveness significantly increased with each dose: RR two vs one dose = .44 (CI .37, .51); RR three vs two doses = .46 (CI .39, .54). • With dose interval >4 months, no significant difference between three and two doses. • Similar results when stratified by age at vaccination.
Dominiak-Felden 2015 [38]	V: 10-23 O: 16-23	**Belgium** Quadrivalent	No	• Statistically significant effectiveness against incidence of genital warts for three and two doses, but not one dose compared to zero. 3: aRR = .12 (CI .07, .21); 2: aRR = .34 (CI .14, .83); 1: aRR = .63 (CI .35, 1.16). • Effectiveness CI overlap for three and two doses; no overlap for three and one doses.
Perkins 2017 [26]	V: 9-25 O: 9-25	**United States** Quadrivalent	Yes	• Statistically significant effectiveness against incidence of anogenital warts for three doses compared to zero, 3: aRR =.52 (CI .46,.60). • Effectiveness not reported for two and one doses compared to zero. • Higher effectiveness for three doses compared with one, aRR = .82 (CI .71, .95); no significant difference between three and two doses, aRR = .89 (CI .78, 1.03). • With buffer period of one year, no change in findings (data not shown). • Similar results with dose interval >5 months for two doses.
Navarro-Illana 2017 [39]	V: 14 O: 14-19	**Spain** Quadrivalent	No	• Statistically significant effectiveness against incident cases of anogenital warts for three, two, and one doses compared to zero. 3: aRR = .24 (CI .15, .34); 2: aRR = .36 (CI .14, .68); 1: aRR = .39 (CI .13, .80). • Effectiveness CI overlap for three, two, and one doses.

Endpoint/ Authors [ref.]	Study Population Age (years) at Vaccination (V) & Outcome (O)	Country/ Vaccine	Formal comparison of 3 vs 2 or 1 doses	Main Findings
Lamb 2017 [40]	V: 10-19 O: 10-27	**Sweden** Quadrivalent	Yes	• Effectiveness against incidence of genital warts not reported for three, two, and one doses compared to zero. • Higher effectiveness of three doses compared to two doses, when two doses administered either 0–3 months or >8 months apart; whereas no significant difference between three and two doses when the two doses administered within 4–7 months. • Similar results when stratified by age at vaccination.
Effectivenss: Cervical Abnormalities				
Gertig 2013 [27]	V: 12-19 O: 12-21	**Australia** Quadrivalent	No	**Outcome summarized: CIN3/AIS** • Statistically significant effectiveness for three, but not two and one doses compared to zero. 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 three, two, and one doses.
Crowe 2014 [28]	V: 12-26 O: 11-31	**Australia** Quadrivalent	No	**Outcome summarized: High-grade histological lesions** • Statistically significant effectiveness for three and two doses, but not one dose compared to zero. 3: aOR = .54 (CI .43, .67); 2: aOR = .79 (CI .64, .98); 1: aOR = .95 (CI .77, 1.16). • Effectiveness CI overlap for three and two doses, no overlap for three and one doses. • Buffer periods from 1–12 months; no consistent impact on three, two, and one-dose effectiveness estimates. • Similar results when stratified by age at vaccination.
Pollock 2014 [41]	V: 15-17 O: 20-21	**Scotland** Bivalent	No	**Outcome summarized: CIN3** • Statistically significant effectiveness for three, but not two and one doses compared with zero. 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 three and two doses; no overlap for three and one doses.
Brotherton 2015 [42]	V: 12-26 O: 12-30	**Australia** Quadrivalent	No	**Outcome summarized: CIN3/AIS** • Statistically significant effectiveness for three, but not two and one doses compared to zero. 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 three, two, and one doses do not overlap. • With increasing buffer periods, some effectiveness for two and one doses in several age groups. • No difference in effectiveness by interval between two doses. • Similar results when stratified by age at vaccination.

Endpoint/ Authors [ref.]	Study Population Age (years) at Vaccination (V) & Outcome (O)	Country/ Vaccine	Formal comparison of 3 vs 2 or 1 doses	Main Findings
Hofstetter 2016 [43]	V: 11-20 O: 11-27	**United States** Quadrivalent	No	**Outcome summarized: Any abnormal cytology** • Statistically significant effectiveness for three and two doses, but not one dose compared to zero. 3: aRR = .58 (CI .48, .69); 2: aRR = .81 (CI .66, .99); 1: aRR = 1.05 (CI .88, 1.26). • Effectiveness CI overlap for three, two, and one doses. • Similar results when stratified by age at vaccination, although effectiveness of two doses compared to zero is not always significant.
Kim 2016 [44]	V: 10-15 O: 18-21	**Canada** Quadrivalent	No	**Outcome summarized: High-grade cytology** • Statistically significant effectiveness for three doses, but not two and one doses compared with zero. 3: aOR = .48 (CI .28, .81); 2: aOR = .17 (CI .02, 1.20); 1: aOR = .45 (CI .11, 1.83). • Effectiveness CI overlap for three, two, and one doses.
Effectivenss: HPV prevalence				
Kavanagh 2014 [23]	V: 15-17 O: 20-21	**Scotland** Bivalent	No	• Statistically significant vaccine effectiveness against HPV prevalence for three doses, but not two or one doses compared to zero. 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 one doses. • Similar results when stratified by age at vaccination.
Cuschieri 2016 [24]	V: 15-17 O: 20-21	**Scotland** Bivalent	No	• Statistically significant vaccine effectiveness against prevalent HPV infection for three, two, and one doses compared to non-vaccinated population. 3: aOR = .27 (CI .20, .37); 2: aOR = .45 (CI .29, .69), 1: aOR = .52 (CI .31, .83). • Effectiveness CI overlap for three, two, and one-dose groups.

Adapted from [22].

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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 World Health Organization.

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

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

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