

EVIDENCE REVIEW



Photo: PATH

Review of the current published evidence on single-dose HPV vaccination

3rd Edition

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Single-Dose HPV Vaccine
EVALUATION CONSORTIUM

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Abbreviations

2vHPV	bivalent HPV [vaccine]
4vHPV	quadrivalent HPV [vaccine]
9vHPV	nonavalent HPV [vaccine]
ADVISE	Agent-based Dynamic model for VaccInation and Screening Evaluation
AGW	anogenital warts
aHR	adjusted hazard ratio
aIRR	adjusted incident rate ratio
AIS	adenocarcinoma in situ
aOR	adjusted odds ratio
aPR	adjusted prevalence ratio
aRR	adjusted relative risk
ART	antiretroviral therapy
AS04	Adjuvant System 04
AU	arbitrary unit
BCR	B-cell receptor
BPV	bovine papillomavirus
CC	cervical cancer
CD4/8	cluster of differentiation 4 or 8
CI	confidence interval
CIN(1/2/3)	cervical intraepithelial neoplasia (grade 1/2/3)
CIN2(or 3)+	cervical intraepithelial neoplasia grade 2 (or grade 3) or worse
cLIA	competitive Luminex immunoassay
COVID-19	coronavirus disease 2019
CT	<i>Chlamydia trachomatis</i>
CV	Coefficient of variation
CVT	Costa Rica [HPV] vaccine trial
DEIA	direct enzyme immunoassay
DNA	deoxyribonucleic acid
DoD	Department of Defense
DoRIS	Dose Reduction Immunobridging and Safety study of two HPV vaccines in Tanzanian girls
ED50	effective dose for 50% of the population
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunosorbent spot
ESCUDDO	Estudio de Comparación 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]
EU	ELISA unit
F	indigenous Fijians
FU	follow-up
GM	geometric mean
GMT	geometric mean titer
GSK	GlaxoSmithKline
GST	glutathione-S-transferase

GuHCl	guanidine hydrochloride
HAV	Hepatitis A vaccine
HIC	high-income countries
HIV	human immunodeficiency virus
HOPE	HPV One/two dose Population Effectiveness
HPV	human papillomavirus
HR	hazard ratio
HSIL	high-grade squamous intraepithelial lesion
HSPG	heparan sulfate proteoglycan
I	Fijians of Indian descent
IARC	International Agency for Research on Cancer
IC50	half maximal inhibitory concentration
ICD-9/10	International Classification of Diseases, 9th/10th revision
IFNγ	interferon gamma
IgG	immunoglobulin G
IL	interleukin
IQR	interquartile range
IRR	incident rate ratio
IVI	International Vaccine Institute
KEN-SHE	Kenya Single-dose HPV vaccine Efficacy [study]
LIC	low-income countries
LLPC	long lived plasma cell
LMIC	low- and middle-income countries
LTFU	long-term follow-up
LSIL	low-grade squamous intraepithelial lesion
MeSH	Medical Subject Headings
MFI	median fluorescence intensity
mMU	milli-Merck unit
MSD	Meso Scale Discovery
MSM	men who have sex with men
NAb	neutralizing antibody
NCI	[US] National Cancer Institute
OR	Odds ratio
PATRICIA	PApilloma TRIal against Cancer In young Adults
PBMC	peripheral blood mononuclear cell
PBNA	pseudovirion-based neutralization assay
PCR	polymerase chain reaction
PHACS	Pediatric HIV/AIDS Cohort Study
PHEU	perinatally HIV-exposed but uninfected
PHIV+	perinatally HIV-infected
PR	prevalence ratio
PRIMAVERA	Puente de Respuesta Inmunológica para Mejorar el Acceso a Vacunas y ERradicar el cancer
PSV	pseudovirion
QALY	quality-adjusted life year
RCT	randomized controlled trial
ROBINS-I	Risk Of Bias In Non-randomized Studies - of Interventions
RR	risk ratio

SAGE	Strategic Advisory Group of Experts
SD	standard deviation
SEAP	secreted alkaline phosphatase
SES	socioeconomic status
STD/I	sexually transmitted disease/infection
Th	T-helper
TU	transducing unit
U	international unit
UK	United Kingdom
US	United States
VE	vaccine efficacy
VLP	virus-like particle
WHO	World Health Organization

1 Introduction and background

1.1 Overview

Prophylactic human papillomavirus (HPV) vaccines have been licensed for over ten years. They were initially administered as a three-dose regimen over a six-month period. In 2014, following a review of the evidence for dose reduction by the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization, a two-dose regimen for individuals aged younger than 15 years was recommended. Since that time, evidence from observational studies suggests that a single-dose HPV vaccine may also provide protection against HPV infection and its sequelae.

The primary objective of this paper is to summarize and assess the current evidence for a single-dose HPV vaccination schedule. We also identify gaps that remain in determining whether a single dose could be sufficiently protective to have a major impact against HPV infection and its sequelae within the context of immunization programs.

The evidence has been compiled by a working group of the Single-Dose HPV Vaccine Evaluation Consortium, whose members represent technical depth, a wide global reach, and extensive expertise in immunization programs, HPV vaccine introductions, and vaccine policy. Coordinated by PATH, the Consortium includes the London School of Hygiene & Tropical Medicine, the US Centers for Disease Control and Prevention, Harvard University, the US National Cancer Institute, Université Laval, the University of British Columbia, and the Wits Reproductive Health and HIV Institute at the University of Witwatersrand.

The Consortium leverages the experience of expert groups working in HPV vaccine and other vaccine introductions. Members represent groups that have actively generated evidence for HPV vaccine safety and efficacy, as well as post-licensure effectiveness and delivery. They have implemented HPV vaccine delivery programs in numerous countries, comprehensively evaluated the delivery and impact of HPV vaccines, and contributed to global vaccine policy processes led by both the WHO and Gavi, the Vaccine Alliance.

The agencies also complement each other at both the global and country level through their existing work with the WHO, SAGE, Gavi, ministries of health, Regional Immunization Technical Advisory Groups, National Immunization Technical Advisory Groups, and National Expanded Programs on Immunization. Specific contributors are listed in [Appendix 1](#).

1.2 Cervical cancer burden

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

In 2018, the director-general of the WHO issued a global call for action to eliminate CC as a public health problem within the 21st century. A subsequent Global Strategy, aimed at aligning and accelerating efforts in order to enable elimination, requires of countries that 90% of girls are vaccinated for HPV by age 15 years, 70% of women are screened for CC by age 35 and 45 years, and 90% of women identified with cervical disease are treated by 2030 (5).

1.3 Licensed HPV vaccines

Primary prevention for CC is now possible through vaccination with one of four licensed vaccines. The two bivalent HPV (2vHPV) vaccines, CervarixTM (GlaxoSmithKline [GSK] Biologicals, Belgium) and Cecolin[®] (Xiamen Innovax Biotech Co. Limited, China), contain L1 antigens from HPV 16 and 18. The quadrivalent HPV (4vHPV) vaccine, Gardasil[®], contains L1 antigens from HPV 6, 11, 16, and 18; and the nonavalent HPV (9vHPV) vaccine, Gardasil-9[®], contains L1 antigens from HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 (both Merck Sharp & Dohme Corp., United States). Cervarix and Gardasil received WHO prequalification in 2009, and Gardasil-9, in 2018; and all three are licensed in many countries worldwide. Cecolin is licensed in China and currently under review for WHO prequalification (expected 2021). The vaccines are highly efficacious against persistent infection with vaccine genotypes, a necessary prerequisite for the development of CC and related cervical lesions (6).

All four vaccines contain virus-like particles (VLPs) of the L1 protein produced in cultured cells and are formulated with adjuvants to increase their immunogenicity. The vaccines differ in several aspects, including HPV types targeted, valency, dose, substrate, and adjuvant (summarized in **Table 1**).

Although the Merck 4vHPV and 9vHPV vaccines are produced by the same manufacturer with similar substrate and adjuvant, there are several differences between the two. In addition to the five

additional VLPs, the 9vHPV has an increased amount of VLPs for HPV 6, 16, and 18 compared to the 4vHPV (7). While the 4vHPV and 9vHPV vaccines contain the same adjuvant (amorphous aluminum hydroxyphosphate sulfate), the 9vHPV vaccine contains more than twice the adjuvant content of the 4vHPV vaccine (500 µg versus 225 µg).

The GSK 2vHPV vaccine has the lowest VLP dose of the four vaccines. It contains a novel adjuvant for enhanced immunogenicity called the Adjuvant System 04. This system is a combination of the Toll-like receptor 4 agonist monophosphoryl lipid A and aluminum hydroxide, which provides direct stimulation of antigen-presenting cells, pronounced cellular and humoral immune responses, and long-lasting antibody responses (8). The GSK 2vHPV vaccine contains a similar amount of aluminum salt as the Merck 9vHPV vaccine. The new Inovax 2vHPV vaccine contains 40 µg HPV 16 VLP and 20 µg HPV 18 VLP. It uses an aluminum hydroxide adjuvant. None of the vaccines contains a preservative.

Currently, there is no immune correlate, antibody concentration, or other immune measurement that has been defined that correlates with vaccine protection against HPV infection. The pseudovirion-based neutralization assay (PBNA) is the “gold standard” for detection of HPV antibodies, although comparisons between sero-epidemiological studies are difficult due to the use of different serological assays and lack of a reference serum for establishing cutoff values (9). The search for an immune correlate of protection has been hampered because there are very few clearly documented “vaccine failures” among vaccine recipients where prior infection could be conclusively excluded and where relevant blood samples were also collected for immunological assessments.

Immune parameters other than functional (neutralizing) and binding antibody levels, which might correlate with protection, have not been defined; and data on antibody avidity are scarce (10).

Antibody avidity indicates the degree of antibody affinity maturation and generally increases over time following an encounter with an antigen. Memory responses are characterized by the production of high-avidity antibodies. Vaccine-derived neutralizing antibody (NAb) levels correlate with antibody avidity at both six months and one year after HPV vaccination (10, 11).

1.4 HPV vaccine schedules and introduction

Uptake of HPV vaccines since their introduction in 2006 has been highly variable and broadly correlated with country income levels. Programs were initially predominated by high-income countries (HIC) in Europe, the Americas, and Australia. Tiered pricing later facilitated introduction in middle-income countries, but for several years, introduction in low-income countries (LIC) was largely dependent on external support for limited-scale demonstration projects. In 2012, Gavi initiated support for HPV vaccination to encourage introduction in LIC.

In 2014, the WHO SAGE on Immunization revised its recommendations from a schedule of three doses to one of two doses, administered with an interval of at least six months, for the GSK 2vHPV and Merck 4vHPV vaccines for girls aged 9–14 years (12). This revised recommendation was based on evidence of non-inferior VLP antibody responses in female adolescents aged 9–14 years compared with women for whom efficacy was demonstrated in clinical trials with a three-dose schedule (13-15). WHO guidelines allow for dosing flexibility for the second dose of the two-dose schedule, as early as five months after the first dose, and with no maximum recommended interval (though up to 12 to 15 months is suggested) (16). According to the recommendations, persons aged 15 years or older, or those who are immunocompromised, including those who are HIV infected, should continue to receive three doses as per original dosage recommendations (12).

Despite the fact that LMIC bear the greatest burden of CC and the highest mortality rates due to the disease (2), introduction of the HPV vaccine has been substantially more widespread among HIC than LIC. This, combined with a wider age range targeted in HIC countries (compared to single- or more restricted-year cohorts in LMIC, such as 9-year-old cohorts or 12-to-13-year-old cohorts), has meant that the proportion of vaccinated females aged 10–25 years is substantially higher in HIC and upper-middle-income countries than in LIC (17).

A number of factors have influenced the slower introduction of HPV vaccines in LMIC. These include the initial cost of the vaccines and a delay in provision of financial mechanisms to support countries in obtaining the vaccine, which was partly due to the financial climate when HPV vaccines became available. Other challenges have included absence of a mechanism for rapid vaccine introduction, previous Gavi requirements that demonstration projects be conducted if the country had no prior experience of HPV vaccine delivery or adolescent multidose schedules, low prioritization of CC as a public health problem, and perceptions that the vaccine is difficult and expensive to deliver (18).

A recent study collating evidence and lessons learned from HPV vaccine delivery in 37 LMIC found that the countries that did introduce the HPV vaccine, either through demonstration projects or national programs, achieved high coverage, especially if their programs or demonstration projects incorporated school-based delivery strategies (19).

However, key informants from LMIC reported that the sustained financial commitment for the cost of vaccine procurement and vaccine delivery has been a key factor in their governments' hesitancy to commit to national HPV vaccine introduction (19). Various approaches to making the HPV vaccine more affordable for LMIC have been suggested, including integrating vaccination into existing adolescent or school-health programs. Integration has proved challenging in many settings since these programs may be vertically funded, only operating in selected districts of a country or not functioning effectively (19).

More recently, a global HPV vaccine shortage has been a barrier to introduction and expansion of national vaccination programs in some countries (20), and it is likely that the COVID-19 pandemic (caused by the severe acute respiratory syndrome coronavirus 2) will have further impact on HPV vaccine rollout (21, 22).

A single-dose regimen for HPV vaccines could be another way to reduce costs and simplify delivery. A dose-reduction recommendation to a single-dose regimen could potentially reduce the costs of vaccine supply and delivery since different delivery strategies might be available for a single-dose schedule (e.g., integration with measles campaigns). This could, in turn, increase accessibility and sustainability of the vaccination programs in both Gavi-eligible and non-Gavi-eligible countries. Single-dose delivery of HPV vaccines is now of interest for a number of reasons following accumulating evidence along several lines: biologic plausibility based on understanding of host-virus interactions at the mucosal level; data from randomized, observational and registry studies; and vaccine impact modeling assessments. These topics are reviewed below.

1.5 Rationale for this evidence review

As discussed above, the cost of the HPV vaccine and its delivery in a multidose schedule have created barriers to HPV vaccine introduction and program sustainability in LMIC. Some observational data and biologically plausible mechanisms exist to suggest that a single dose of HPV vaccine may be sufficient to elicit a protective immune response against incident and persistent HPV infection, which are the necessary prerequisites to further development of cervical lesions and, in the longer term, CC. Randomized controlled trials (RCT) are underway to provide high-quality evidence to assess this hypothesis (23-26).

This paper is an updated version (3rd edition) of previous editions (1st edition, April 30, 2018; 2nd edition, June 30, 2019) (27, 28), aiming to assess (i) the current evidence on efficacy, effectiveness, immunogenicity, and modeling of single-dose schedules of HPV vaccine, (ii) the strength of that evidence, and (iii) the gaps in the evidence. The 3rd edition builds on previous versions by including further evidence published up to August 10, 2020. Significant updates from previous editions are listed in [Appendix 2](#). It presents the current evidence base together in one document to facilitate access to and understanding of the myriad of individually published scientific studies that comprise the evidence base as a whole.

It is envisaged that this evidence could be used in early policy conversations with key global stakeholders, such as the WHO Immunization and Vaccines Implementation Research Advisory Committee and SAGE. It may help to highlight what information is needed for policy deliberations

and help clarify a timeline for when new evidence addressing critical unanswered questions will become available for use in these discussions.

This paper includes a detailed summary of published evidence; interpretation of the implications of the results relevant to single-dose HPV vaccine immunogenicity, efficacy, or effectiveness; identification of gaps in the evidence; discussion of possible approaches (and the ethical considerations therein) to fill such gaps; description of any known studies or datasets that might be ongoing or available that could address evidence gaps; and an overall conclusion for the strategic direction needed to inform decisions about HPV single-dose or alternative schedules.

Sources of evidence covered in this paper include publicly available peer-reviewed scientific publications on the biological plausibility for protection with single-dose HPV vaccine, based on vaccine immune response and virological data; non-randomized data from partially vaccinated participants in clinical trials and immunogenicity studies; data from post-licensure vaccine effectiveness evaluations and other observational data; and mathematical modeling of the impact of reduced dosing schedules for HPV vaccines.

Table 1. Summary of available HPV vaccines

	Cervarix™^a	Gardasil®^b	Gardasil-9®^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
L1 protein dose	20 µg HPV 16 20 µg HPV 18	20 µg HPV 6 40 µg HPV 11 40 µg HPV 16 20 µg HPV 18	30 µg HPV 6 40 µg HPV 11 60 µg HPV 16 40 µg HPV 18 20 µg HPV 31 20 µg HPV 33 20 µg HPV 45 20 µg HPV 52 20 µg HPV 58	40 µg HPV 16 20 µg HPV 18
Substrate	<i>Trichoplusia ni</i> (Hi 5) insect cell line infected with L1 recombinant baculovirus	<i>Saccharomyces cerevisiae</i> (baker's yeast) expressing L1	<i>Saccharomyces cerevisiae</i> (baker's yeast) expressing L1	<i>E.coli</i> expressing L1
Adjuvant	500 µg aluminum hydroxide and 50 µg 3-O-desacyl-4'-monophosphory lipid A (GSK AS04 adjuvant)	225 µg amorphous aluminum hydroxyphosphate sulfate (Merck aluminum adjuvant)	500 µg amorphous aluminum hydroxyphosphate sulfate (Merck aluminum adjuvant)	208 µg of aluminum hydroxide
Injection Schedule (2 doses) ^{d, e}	0, 6-12 months	0, 6-12 months	0, 6-12 months	0, 6 months
Injection Schedule (3 doses) ^{e, f, g}	0, 1, 6 months	0, 2, 6 months	0, 2, 6 months	0, 1, 6 months

Abbreviations: AS04, Adjuvant System 04; GSK, GlaxoSmithKline; 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 A two-dose schedule is recommended for girls aged 9–14 years (for GSK 2vHPV or Merck 9vHPV) or aged 9–13 years (for Merck 4vHPV). SAGE recommends that the second dose should be administered between months 5 and 13 for GSK 2vHPV and Merck 9vHPV and at month 6 for Merck 4vHPV. If the second dose is administered earlier than recommended, a third dose should be given (12, 29).

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

^f A three-dose schedule is recommended for girls aged ≥15 years (for GSK 2vHPV or Merck 9vHPV) or aged ≥14 years (for Merck 4vHPV). For GSK 2vHPV, SAGE recommends that the second and third doses are administered between months 1 and 2.5 and months 5 and 12, respectively. For Merck 4vHPV and Merck 9vHPV, the second dose should be given at least one month after the first, and the third dose should be given at least three months after the second (12).

^g The Innovax 2vHPV is recommended in a two-dose schedule at 0 and 6 months or a three-dose schedule at 0, 1, and 6 months for girls aged 9–14 years. For girls aged >14 years, a three-dose schedule at 0, 2, and 6 months is recommended.

Source: Table adapted from (6) and updated for dosing schedule licensure modifications and global vaccination recommendations (12).

2 Evidence from studies on single-dose HPV vaccination

2.1 Biological plausibility for single-dose protection

Plausible biological explanations for the unexpected potency of HPV subunit vaccines, based on vaccine immune response and virological data, were examined and recently reviewed after observational data from several clinical studies suggested that a single dose of HPV vaccine could provide protection against HPV infection (30). Below, we provide a summary of a comprehensive review published in 2018 (30).

2.1.1 Mechanism of vaccine-induced protection

All four available vaccines are produced using recombinant, genotype-specific, viral outer coat L1 proteins. During a natural infection, the L1 protein is only "visible" to the immune system prior to cell invasion; once a cell is invaded by the virus, the L1 protein locates in the nucleus and is not displayed on the cell surface. Vaccine-induced antibodies to the L1 protein are therefore likely to elicit protection against infection by preventing initial cell invasion events. This mechanism of protection would also explain why already established infections are unaffected by vaccination. The principal mediator of HPV vaccine-induced protection seems to be humoral; however, given the high immunogenicity of the vaccine and the rarity of "breakthrough" infections, the minimum systemic or mucosal antibody level required for protection has not yet been established.

Additionally, it is unknown whether persistent levels of antibodies need to be maintained long term or whether an anamnestic response, mediated by memory B cells, can elicit protection from persistent infection and subsequent disease. It is likely that NAbs need to be present at the time of exposure for the HPV vaccines to be most effective (31). Therefore, "long-lived plasma cells (LLPCs) that continuously produce antigen-specific antibodies are likely to be the key immune effectors that underlie the strong type-restricted protection induced by the HPV vaccines. It is possible that even the few vaccine recipients with undetectable levels of anti-HPV antibody four years after vaccination remain protected by circulating antibodies, because very low levels of VLP antibodies appear to be sufficient for protection against infection of cervicovaginal tissue" (32).

2.1.2 The immunogenicity of a single vaccine dose

This section was excerpted from a review of evidence on the immunologic considerations of HPV vaccination (15) and edited and updated for this paper.

The exceptionally strong, consistent, and durable antibody responses to the three HPV vaccines is well documented (33). 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 tenfold drop in titer over the first two years, immunoglobulin G (IgG) titers plateau or decline very slowly, stabilizing at levels that are substantially higher than the antibody titers induced by natural infection (34). Responses in preadolescent girls and boys are even stronger (13, 35). The stability of antibody responses, now observed for almost ten years post-vaccination (36-38), is unprecedented for a subunit vaccine.

Surprisingly, this pattern of antibody response is observed even after a single-dose vaccine, with stable geometric mean (GM) IgG binding and in vitro neutralizing titers that are about fourfold lower than the plateau titers measured after the standard three doses (38-40). Avidity, as measured in a VLP-based chaotrope enzyme-linked immunosorbent assay (ELISA), similarly rose over the first four years after immunization with one or three doses of GSK 2vHPV and then stabilized for both dose regimens (41). The long-term antibody levels, regardless of dose number, are almost certainly due to efficient induction of LLPCs, which primarily reside in the bone marrow and continuously produce antibodies, probably independent of additional antigen exposure (42). It is unlikely that successive rounds of memory B-cell activation from putative secondary exposure to virion antigens are primarily responsible for the durable levels, as intermittent increases and decreases in antibody levels would be expected if repeated episodic antigen exposure were involved, while the antibody levels in individuals generally remain constant or decrease at a slow rate. In addition, essentially all vaccinees maintain a stable level of antibodies against the VLP types in the vaccine, and it is doubtful that virtually all the women would have experienced immunizing levels of environmental exposure to each of the multiple genital HPV types targeted by the vaccines. Therefore, the central immunological question is why the HPV vaccines are such potent inducers of LLPCs. The specific structure of the VLPs that comprise the HPV vaccine may be key to their ability to efficiently induce LLPCs.

HPV VLPs are composed of 360 ordered protein subunits that form a particulate 55 nm structure displaying a repetitive array of epitopes on their surface. Particles of this size efficiently enter the lymphatic system and traffic to lymph nodes, where they induce primary antibody responses (43). The closely spaced arrangement of determinants on the VLP surface can lead to the stable binding of natural low-avidity IgM and complement, thereby

promoting acquisition of the VLPs by follicular dendritic cells, which present antigens for the induction of B-cell responses in the lymph node (44). Particles in this size range are also efficiently taken up and processed by phagocytic antigen-presenting cells for major histocompatibility complex Class II presentation, leading to the induction of potent T-helper (Th) responses (45). Polyvalent binding of the HPV VLPs to human monocytes, macrophages, and dendritic cells induces the release of a variety of cytokines that may promote antibody induction (46). The ordered display of epitopes at intervals of 50 to 100 Å on the VLP surface is a pathogen-specific danger signal to the humoral immune system (47). Epitope spacing at this distance is found on the surface of most viruses—HIV being a notable exception (48)—and on other microbial structures, such as bacterial pili. Binding and subsequent cross-linking of the B-cell receptors (BCRs) on the surface of naïve B cells by these ordered repetitive antigens transmit exceptionally strong activation and survival signals (49).

The high-density display on a VLP surface can efficiently break B-cell peripheral tolerance and even reactivate anergic self-reactive B cells (50, 51). The BCRs on a majority of newly produced B cells are thought to bind self-antigens, which renders them functionally anergic (52, 53). The polyvalent interaction of repetitive VLP epitopes might also lead to stable engagement and subsequent B-cell activation through BCRs whose affinity, if they were engaged by a monomeric antigen, would be too low to be activating. These conjectures that identify potential mechanisms for activating a large variety of distinct naïve B-cell clones can provide a mechanistic explanation for the remarkable consistency of VLP antibody responses across individuals.

The above considerations may also help to explain the patterns of antibody responses observed for other classes of vaccines compared to the HPV VLPs. Other subunit vaccines composed of monomer or low-valency antigens, such as bacterial toxoids and polysaccharide/protein conjugates, only induce protective antibody responses after several doses and require periodic boosting, as the antibody titers continue to wane over time. This is presumably because these antigens do not deliver the strong signals induced by BCR oligomerization that promote differentiation into LLPCs. Hepatitis B vaccines are multivalent particulate antigens; however, they often do not induce seroconversion after a single dose and generally fail to induce stable antibody responses (54). Induction of LLPCs may be limited because the HBV particles are only 22 nm in diameter, the surface antigen in the HBV particles have both protein and lipid components, and there are a relatively small number of repetitive elements (24 knuckle-like protrusions of the surface antigen for HBV compared to 360 L1 molecules arranged into 72 pentamers for HPV) (55). Each of

these factors could limit the potentially critical oligomerization and downstream signaling through the BCRs.

Inactivated virus vaccines are particulate and have a dense array of repetitive surface elements and yet are administered in multiple doses and generally fail to induce stabilizing antibody responses. However, it is likely that the inactivation process (e.g., protein cross-linking with formalin) disrupts the dense repetitive array of their surface epitopes to ablate their “virus-like” character (56). An exception may be the hepatitis A inactivated virus vaccine (HAV), which appears to induce durable protective antibody responses after a single dose and therefore may retain a sufficient number of repetitive surface epitopes after inactivation to retain its virus-like character (57).

The observation that live attenuated vaccines, such as yellow fever and vaccinia, induce potent, durable antibody responses and immunity to infection after the primary inoculation in most vaccinees (58) has previously been attributed to the infectious nature of the inoculum. In light of the findings with the HPV vaccines, the alternative explanation—that they are highly immunogenic primarily because they contain authentic virion surface structures—should now be considered.

2.1.3 Virologic considerations

This section was also excerpted from a review of evidence on the virologic considerations of HPV vaccination (15) and edited for this paper.

Papillomaviruses have a unique life cycle in which production of virions occurs only in the terminally differentiated layer of a stratified squamous epithelium. However, completion of its productive life cycle depends upon establishing infection in the cells of the basal layer of the epithelium (59). To ensure that initial infection occurs only in basal epithelial cells, the virus cloaks its cell surface receptor binding domain until after it has undergone a series of conformational changes. These changes are induced by binding specifically modified forms of heparan sulfate proteoglycans specific to the basement membrane that separates the dermis from the epithelium (60) (Figure 1).

This unusual strategy of initiating infection on an acellular surface may substantially increase the susceptibility of the virus to serum-derived NAbs for a number of reasons (61).

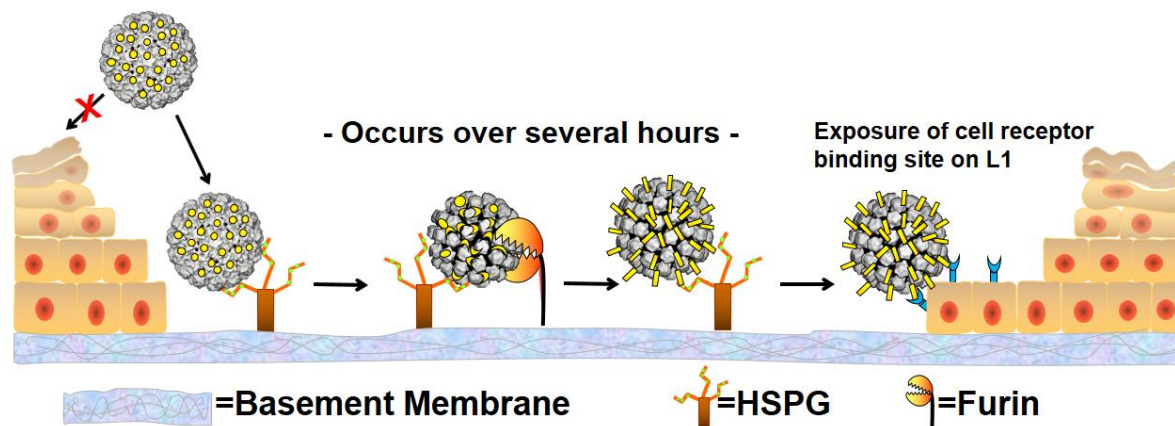
First, exposure of the basement membrane to the virus requires disruption of the epithelial barrier, which results in direct exudation of capillary and interstitial antibodies at these sites. A consequence of this event is that HPV encounters systemic antibodies at potential

sites of infection. This mechanism can explain why induction of systemic antibodies via intramuscular vaccination can be so effective in preventing a mucosal infection. There is also significant transudation of systemic antibodies via the neonatal Fc receptor in the female genital tract (62). However, this latter mechanism may play a secondary role in protection, because levels of transudated VLP-specific antibodies in cervical mucus of vaccinated women are tenfold to a hundredfold lower than serum levels (depending on the stage of the menstrual cycle) (63) and because the vaccines are highly protective against infections of cutaneous epithelia (e.g., external genital warts), which are not routinely bathed in mucus.

Secondly, the factor that contributes to increased susceptibility of the virus to NAbs is the exceptional slowness of the initial stages of the papillomavirus life cycle. In a mouse cervicovaginal challenge model, HPV virions remain on the exposed basement membrane for hours before they attach to the epithelial cells that migrate in to close the disrupted tissue; internalization of the cell-bound virus takes a further several hours (60). Thus, the virions are exposed to NAbs for an exceptionally long time. High concentrations of passively transferred VLP antisera can prevent infection by inhibiting basement membrane binding; lower doses that permit basement membrane binding are nonetheless effective at preventing infection (64). The long exposure of antibody-bound virions on the basement membrane and cell surface may make the complexes highly susceptible to opsonization by phagocytes which would also be attracted to the sites of trauma (61). The observation that antibody levels that are more than a hundredfold lower than the minimum level detected in the in vitro neutralizing assay are able to prevent in vivo infection is consistent with the idea that there are potent antibody-mediated mechanisms relevant to in vivo inhibition that are not detected in vitro (65).

Thirdly, remarkably low levels of VLP antibodies are protective in vivo. For example, in the mouse cervicovaginal model, circulating antibody levels in recipient mice that were 10,000-fold lower than in the donor HPV 16 VLP-vaccinated rabbit potently inhibited infection from high-dose HPV 16 cervicovaginal pseudovirus challenge (64). Although the titers of in vitro NAbs induced by HPV VLP vaccination are approximately tenfold lower in humans than in rabbits, it is plausible that the levels of VLPs antibodies in human vaccinees considerably exceed the minimum level required for prevention of genital infection and that protective levels are lower than those that can be reproducibly detected in current in vitro antibody binding and neutralizing assays. Therefore, the fourfold lower, but readily detectable, plateau titers induced by one-dose compared with three-dose vaccine regimens discussed below might not substantially reduce the long-term protection induced by the HPV VLP vaccines.

Figure 1. In vivo murine model of vaginal HPV infection



In Vivo Murine Model of Vaginal HPV Infection. A disrupted cervicovaginal epithelium is depicted. “X” indicates the inability of virions to bind the apical surface of intact epithelium. The L2 minor capsid protein, cleaved by furin after a HSPG binding-induced conformational change in the capsid, is shown in yellow.

Abbreviation: HSPG, heparan sulfate proteoglycan.

Source: Figure adapted from (30).

2.2 Clinical trials of HPV vaccines

2.2.1 Overview

This section summarizes evidence on the efficacy, effectiveness, and immunogenicity of a single HPV vaccine dose compared to multidose schedules (and compared to no HPV vaccination) from clinical trials of HPV vaccines. Specific outcomes of interest include efficacy or effectiveness against HPV infection (genotype-specific prevalence, incidence and/or persistence) or clinical outcomes (e.g., anogenital warts [AGW] and cervical intraepithelial neoplasia [CIN]), as well as HPV vaccine-type antibody seropositivity or levels (used as the primary immunogenicity endpoint), antibody avidity, and B- or T-cell responses (used as secondary immunological endpoints). Published data (from any geographical location and in any population) that compare at least one of the outcomes of interest after one versus two or three doses of HPV vaccine (in any schedule), or versus no HPV vaccination, were compiled.

Evidence is primarily derived from a systematic review, conducted in 2018–2019, that evaluated the literature on single-dose HPV vaccination from clinical trials (66). When the database search for the systematic review was conducted (August 2018), there were no data comparing the immunogenicity, efficacy, or effectiveness of a one-dose versus two- or three-dose HPV vaccination schedule that originated from specifically designed RCTs comparing one-dose to two- or three-dose groups. Only one small randomized, unblinded pilot intervention study in ten individuals compared immunological

responses in HPV 16-seropositive women after a single dose with no vaccination (67). Thus, most evidence comes from comparisons made between clinical trial participants who completed or failed to complete standard two- or three-dose schedules. Further data have become available from one of the studies since the systematic review was completed. These are included in the information provided below.

Additional information is included from a 2018 Cochrane review on the efficacy of HPV vaccines, which presents data on "at least one" dose of HPV vaccine compared to non-HPV vaccinated controls (68).

2.2.2 Systematic review of evidence on single-dose HPV vaccination from clinical trials

2.2.2.1 DESIGN

The available literature from RCTs on the immunogenicity and efficacy of single-dose HPV vaccination compared to either no vaccination or multidose schedules was evaluated in a systematic review (66). The research questions were as follows:

- Does a one-dose HPV vaccination schedule provide equivalent efficacy against HPV infection and associated clinical outcomes compared to a two- or three-dose schedule?
- Does a one-dose HPV vaccination schedule produce non-inferior immune responses compared to a two- or three-dose schedule?
- Does a single-dose HPV vaccine provide efficacy against HPV infection and associated clinical outcomes compared to no HPV vaccination?

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 in which some participants received only a single dose due to non-completion of a multidose schedule.

The following sections include excerpts from systematic review of the trials (66). The content was edited for this paper and updated to include newly available data.

2.2.2.2 SEARCH STRATEGY

Medline, EMBASE, Global Health Database, and Cochrane Central Register of Controlled Trials were searched systematically for publications and conference abstracts using Medical Subject Headings (MeSH) and non-MeSH terms under the following themes: human papillomavirus AND vaccines AND (immunogenicity OR efficacy OR effectiveness) AND dosage. MeSH terms and operators were adapted as required for each database searched. Searches were limited to articles published between January 1, 1999, and August

14, 2018, and (where allowed by the database) studies conducted in humans. No language restrictions were applied. Reference lists of relevant review articles and all full-text articles identified for inclusion through the database searches were additionally hand-searched.

An updated literature search (not using the full systematic review process) was conducted for the purpose of this paper to identify any further relevant articles that became available between August 2018 and October 2020.

2.2.2.3 ELIGIBILITY SCREENING

Search results were screened using predefined eligibility criteria based on the population, intervention, comparison, outcome (PICO) format. Titles and abstracts of all search results were double-screened for eligibility based on a limited number of eligibility criteria; articles were excluded if they did not describe a research study of human participants who had received GSK 2vHPV, Merck 4vHPV, or Merck 9vHPV and/or did not generate data on immunogenicity, infection, and/or disease outcomes. Full texts of all remaining and potentially relevant publications were subsequently double-screened against full eligibility criteria.

2.2.2.4 DATA EXTRACTION, QUALITY ASSESSMENT, DATA SYNTHESIS AND ANALYSIS

Data were extracted using a standardized extraction form. Extracted data included the following: publication details; target population and setting; study design; study population; intended and actual intervention and comparators; evaluated outcomes; results and findings; and authors' conclusions.

Included studies were assessed for selection bias (i.e., the selection of participants in each dose group); confounding, retention, and survival bias; misclassification of exposure and outcome; and statistical analysis approach. Study populations were evaluated for generalizability. Where articles described a sub- or post hoc analysis of a clinical trial cohort, the "parent" clinical trial population was additionally assessed for generalizability. Biases were specifically assessed for the probability that they would artificially increase the vaccine efficacy (VE) in the one-dose group or artificially decrease the VE in the three-dose group.

A narrative synthesis of the data was conducted using three elements: (i) development of a preliminary synthesis of findings of included studies; (ii) exploration of relationships within and between studies; and (iii) assessment of the robustness of the synthesis.

Infection endpoints evaluated in this review were as reported in included studies. To standardize statistical reporting of incidence risk, persistence, and prevalence, event and denominator data extracted from each article were used to calculate proportions, expressed as percentages (%), and 95% confidence interval (CI), using the exact (Clopper-Pearson) method for calculating CIs for proportions, assuming a binomial distribution. Unadjusted infection risk ratios (RRs) and prevalence ratios (PRs) were calculated for one-versus two- or three-dose HPV vaccine arms and for single-dose HPV vaccine versus control (no HPV vaccine) arms. The Haldane-Anscombe correction was used for calculation of RRs and PRs where no events were detected in one or both comparison arms. Fisher's exact test (2-sided) was used to assess for statistical significance between the groups and compute p values. RRs and PRs calculated for one versus two or three doses must be interpreted with caution because of potential for selection bias due to differences in follow-up between the groups.

In the absence of a known correlate of protection for HPV vaccination, data capture for this systematic review was not limited to a specified humoral immunogenicity endpoint and instead included any data on binding and/or neutralizing antibody seropositivity, titers, and/or avidity. To standardize statistical reporting of seropositivity results, extracted data on numbers of participants seropositive for HPV 16/18 antibodies and denominator data were used to calculate seropositivity proportions (%) and 95% CIs, as above.

Pooling and meta-analysis of data from multiple studies were not considered appropriate due to the small number of contributing studies and heterogeneity in study designs and methods.

2.2.2.5 SEARCH RESULTS

Of 6,523 unique records identified from the database and hand searches, seven articles were included in the systematic review (39, 40, 67, 69-72) (Figure 2; Table 2). Of these, six were considered as observational studies because allocation to the dosing schedule arms (i.e., single-dose versus alternative schedules or no vaccination) was according to what participants actually received rather than what they were prospectively allocated to receive (39, 40, 67, 69-72). One small, randomized study prospectively allocated participants to receive a single-dose HPV vaccine versus no vaccination (67).

Since the systematic review was conducted, two further relevant articles have become available, both of observational evaluations from the same trial (38, 73).

2.2.2.6 NESTED OBSERVATIONAL STUDIES OF SINGLE-DOSE HPV VACCINATION

All six observational studies included in the systematic review were based on data from three clinical trials. Two studies (39, 72) were based on the IARC trial of two versus three doses of HPV vaccine in India (39). Three studies (40, 69, 71) were based on the Costa Rica vaccine trial (CVT) for HPV (74), and one (70) was based on combined data from CVT and the PApilloma TRIal against Cancer In young Adults, or PATRICIA (75).

The two new articles both present further analyses from the CVT (38, 73).

IARC India HPV vaccine trial

This study was originally designed as an open-label cluster-randomized trial, aiming to compare two versus three doses of the Merck 4vHPV among healthy unmarried females aged 10–18 years in India (39, 76). Participants were recruited from 188 geographical clusters across nine locations from September 2009 and randomized to either two- or three-dose arms. However, in April 2010, the Indian government suspended all HPV vaccine trials for reasons not related to the IARC India HPV vaccine trial, and enrollment into the trial therefore stopped early. At the point of suspension, 17,729 participants had been recruited (88.6% of the targeted recruitment of 20,000 girls), but many had not yet completed their full dose schedules. Thus, the clinical trial of two versus three HPV vaccine doses became a prospective observational cohort study of one versus two versus three vaccine doses.

Of the two identified publications arising from the IARC India HPV vaccine trial, the first presents HPV infection and immunogenicity data up to 48 months following the first vaccine dose for participants who received one dose (at day 0), two doses (at day 0 and either month 2 or month 6), and three doses (at day 0, month 2, and month 6) (39). The second presents immunogenicity data up to 48 months and HPV infection data up to seven years, following the first vaccine dose for the same dosing schedules (72). A supplementary cohort of married, unvaccinated females aged 18–23 years (corresponding to the age of the married vaccinated females at the time of follow-up) was recruited from different study sites in India from 2012 to 2015, allowing comparison of HPV infection data between participants vaccinated with one, two, or three doses and those who had not received any vaccine doses.

CVT

This was a community-based, double-blind RCT aimed at evaluating the efficacy of a three-dose regimen of the GSK 2vHPV against persistent vaccine type-specific HPV infection and subsequent development of HPV-associated precancerous lesions among healthy women

aged 18–25 years in two regions of Costa Rica (74, 77). A total of 7,466 women were recruited from seven study clinics between June 2004 and December 2005, all of whom were randomized to receive three doses of either HPV vaccine or hepatitis A vaccine, or HAV (control). Some women did not complete their full vaccination schedule for reasons including pregnancy, colposcopy referral, other medical conditions, vaccine refusal, or missed study visits.

The first identified one-dose study arising from CVT describes a post hoc analysis of HPV infection data up to 48 months following first vaccine dose in participants who received one dose (at day 0), two doses (at day 0 and either month 1 or month 6), and three doses (at day 0, month 1, and month 6) (69). The second study describes a post hoc analysis of HPV vaccine-induced immunogenicity up to month 48 for the same dosing schedules (40). A subsequent analysis extends the HPV infection and immunogenicity data from this study to seven years following the first vaccine dose. At the completion of the randomized, blinded phase of CVT, control participants were offered the HPV vaccine (71). Thus, for the 2018 study, a new cohort of 2,836 unvaccinated women, age-matched to the trial participants, were recruited to replace the original control group.

Of the two most recently published articles arising from CVT that compare a single-dose HPV vaccine to multidose schedules, one extends the HPV 16/18 infection and immunogenicity data up to 11 years post-vaccination (38), and the other evaluates cross protection against HPV 31/33/45 up to the same time point (73).

PATRICIA

This was a large-scale, phase III, double-blind RCT among healthy women aged 15–25 years from 14 countries in Asia Pacific, Europe, Latin America, and North America, also aiming to evaluate the efficacy of a three-dose regimen of the GSK 2vHPV (75). PATRICIA enrolled 18,729 women between May 2004 and June 2005, all of whom were randomized to receive three doses of HPV or HAV (control). Of those, 18,644 received at least one vaccine dose; some participants did not receive all scheduled doses for similar reasons as in the CVT.

One study identified for inclusion in the systematic review reports a post hoc analysis of combined CVT and PATRICIA data (70). This publication describes HPV infection data up to 48 months following the first vaccine dose in participants who received one dose (at day 0), two doses (at day 0 and either month 1 or month 6), and three doses (at day 0, month 1 and month 6).

2.2.2.7 RANDOMIZED INTERVENTION STUDY OF SINGLE-DOSE HPV VACCINATION

The only randomized intervention study was a small pilot study conducted in the United States, aimed at evaluating whether a single-dose HPV vaccine in participants with prior HPV 16 infection just boosts antibody levels or also improves the quality of the B-cell memory (67). The study randomized ten healthy HPV 16–seropositive women aged 27–45 years at day 0 to receive either a single dose of the Merck 4vHPV or no intervention. Humoral and cellular immunogenicity results for the two arms are presented up to month 6.

2.2.2.8 HPV 16 AND HPV 18 INFECTION RESULTS

Summary

*HPV 16/18 infection results for participants who received a single HPV vaccine dose compared to any comparator group are reported in six of the above studies (38, 39, 69–72). HPV infection–related outcome measures most commonly reported include one-time or cumulative incident infection and 6- or 12-month persistent infection. Three studies report results up to 4 years post-vaccination (69, 70), two up to 7 years (71, 72), and one up to 11 years (38). Methods used for detection of infection and definitions of endpoints reported by each of the five studies are summarized in **Table 3**.*

***Table 4** summarizes efficacy results for each of the six studies. In brief, incident, persistent, and prevalent infections with HPV 16/18 were extremely low in all participants who received any HPV vaccine, and significantly lower in those participants than in ones who either were unvaccinated or received HAV. All studies reported comparable efficacy against HPV 16/18 infection in one-dose versus two- or three-dose arms.*

HPV infection and vaccine protection data from CVT and PATRICIA

This section was excerpted from a review of evidence of single-dose HPV vaccine protection from the CVT and future research studies (54). The content has been edited for this paper and updated to include the CVT data up to 11 years of follow-up.

After four years of follow-up, in the HAV (control) arm the attack rates of incident HPV 16 or HPV 18 infections that persisted for at least six months were similar among women who received three doses (7.6%; 95% CI: 6.7 to 8.6%), two doses (6.3%; 95% CI: 4.2 to 9.1%), or one dose (8.0%; 95% CI: 4.7 to 12.5%), indicating that they were at similar risk for acquiring HPV infections regardless of the number of HAV doses they received (69). Since balance in enrollment characteristics was observed between the HPV and HAV arms, indicating successful randomization, it could be inferred that there is likely balance in HPV 16/18 exposure by dose group among the HPV-vaccinated arms. Assessment of HPV

genotypes not protected by the GSK 2vHPV vaccine showed balance across dose groups at both years 4 and 7, indicating continued equality in HPV exposure (69, 71). At year 4 (69), the cumulative detection of carcinogenic HPV types, excluding HPV 16/18/31/33/45, was 14.9% (95% CI: 13.6 to 16.2%) for women who received three doses, 14.1% (95% CI: 11.0 to 17.6%) for women who received two doses, and 12.7% (95% CI: 8.6 to 17.9%) among women who received one dose. At year 7 (71), the point prevalence for the same group of HPV types was 15.2% (95% CI: 13.7 to 16.8%) for women who received three doses, 14.3% (95% CI: 10.5 to 18.9%) for women who received two doses (at 0 and 6 months), and 13.4% (95% CI: 8.4 to 20.0%) for women who received one dose.

Single-dose efficacy of the GSK 2vHPV was assessed at several time points: first, during the initial four-year randomized blinded phase that included the randomized control arm (although not randomized by dose) to assess background rates of HPV infection; and then, at years 7, 9, and 11 in the long-term follow-up (LTFU) study that included a new control arm. At year 4, cumulative HPV infections over the four-year follow-up were assessed. At the year 7 data point, point prevalence of HPV was assessed in order to determine continued duration of protection.

Four years after initial vaccination, one dose of the GSK 2vHPV vaccine had comparable efficacy to three doses of the vaccine using an endpoint of cumulative persistent HPV infection (71). 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 the following: for three doses = 84% (95% CI=77 to 89%; 37 and 229 events in the HPV [n=2957] and control [n=3010] arms, respectively); for 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).

The CVT has published data following up to 11 years. Among the participants who received one dose, no HPV 16/18 cervical infections were detectable at year 7 (among 134 women), and only 2 (1.8%) at years 9 or 11 (among 112 women). This was similar to women who received the three-dose regimen, where there were 20/2,043 (1.0%) HPV 16/18 infections at year 7, and 27/1,365 (2.0%) at years 9 or 11. For comparison, there was a 6.6% HPV 16/18 prevalence among the unvaccinated women at year 7 and 10.0% at years 9 or 11, suggesting that a single dose continued to provide protection against HPV 16/18 infection. Again, carcinogenic HPV types not protected by the HPV vaccine were detected with similar frequency among vaccinated (year 7, 15.0%; year 9/11, 25.2%) and unvaccinated (year 7, 13.0%; year 9/11, 23.9%) women, indicating similar exposure to HPV infections.

In a recent analysis, cross protection of the GSK 2vHPV against incident HPV 31/33/45 infections at 2 to 11 years after vaccination was comparable in three-dose participants (average VE: 64.4%; 95% CI: 57.7 to 70.0%) and one-dose participants (average VE: 54.4%; 95% CI: 21.0 to 73.7%), albeit with very wide confidence limits in the one-dose arm.

Data from another trial, the PATRICIA, indicated that women who received one dose had the same VE as two and three doses (70). The PATRICIA was a phase III, randomized, double-blind placebo-controlled trial of GSK 2vHPV, conducted in 18,644 women aged 15–25 years who were enrolled between May 2004 and June 2005 (78). VE for one-time detection of incident HPV 16 and 18 infection in the PATRICIA was 76.8% (95% CI 74.2–79.2) for three doses, 73.3% (40.4–89.2) for two doses, and 72.2% (13.6–92.4) for one dose (78).

The four-year efficacy against an endpoint of cumulative incident HPV 16/18 infection hovers around 80% for all dose groups in the PATRICIA and CVT and demonstrates that one-dose HPV VE is not inferior to three-dose VE among the same analytic population and using the same endpoint for analyses.

HPV infection and vaccine protection data from IARC India vaccine trial

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 single-dose recipients).

Findings from the India study—based on the comparison between the rate of persistent infection in 2,989 vaccinated women who provided at least two cervical samples and the rate in 1,141 unvaccinated women providing at least two samples—suggest high VE in preventing persistent HPV 16 and 18 infections, regardless of the number of doses received. There was a total of 4 (0.1%) persistent HPV 18 infections and no persistent HPV 16 infection among the 2,989 vaccine recipients compared to 14 (1.2%) persistent infections with HPV 16 or 18 among 1,141 unvaccinated control women. No persistent HPV 16/18 infection was detected in 959 women in the single-dose arm.

2.2.2.9 IMMUNOGENICITY RESULTS

Trials review summary

The following text is excerpted from systematic review of the trials (66). The content was edited for this paper and updated to include the most recently published studies from the CVT.

*HPV 16/18 humoral immunogenicity results for participants who received a single-dose HPV vaccine compared to any comparator group are reported in six of the above studies (39, 40, 67, 71, 72). HPV 16/18 immunogenicity-related outcome measures most commonly reported include the following: seropositivity, GM antibody levels (titers or median fluorescence intensity [MFI]) and antibody stability. Some studies additionally reported on antibody avidity or NAb seropositivity/titers. Methods used for measurement of immune responses and, where applicable, definitions of endpoints reported by each of the five studies are summarized in **Table 5**.*

***Table 6** summarizes seropositivity and antibody-level results for the five studies comparing a single-dose schedule versus other vaccine dosage schedules. In brief, the proportions of participants reportedly seroconverting to HPV 16/18 antibody-positive levels were high in all HPV vaccine arms, reaching 100% in some studies. However, the definition of seroconversion differs between studies (**Table 5**). Antibody levels were lower with one dose than for two or three doses. However, while levels for two- and three-dose arms declined following an initial increase, plateauing thereafter, this trend was typically less pronounced in the one-dose arms, in which levels remained more stable throughout follow-up (Figures 3 and 4). Furthermore, antibody levels were significantly higher in participants vaccinated with a single dose of HPV vaccine compared to pre-vaccination levels in participants with natural infection (**Table 6**).*

Immunogenicity data from the CVT

This section was excerpted from a review of evidence of single-dose-HPV-vaccine protection from the CVT and future research studies (54). The content was edited for this paper and updated to include the 11-year data.

Among women who received one dose in the CVT, 100% seroconverted and remained seropositive up to 11 years post-vaccination. HPV 16 and 18 antibody titers (assessed by ELISA) were substantially higher than those among naturally infected unvaccinated women (approximately ninefold higher for HPV 16 and fivefold higher for HPV 18) four years after initial vaccination (40). Titers remained stably elevated at 11 years post-vaccination at approximately two- to fourfold lower levels than for three doses (38).

NAbs measured at year 4 were highly correlated with levels measured by ELISA. Spearman correlations were high for three-dose (0.87), two-dose (0/1; 0.72), two-dose (0/6; 0.80), and one-dose (0.79) groups, although decreased correlation was noted for the one-dose group compared to the three-dose group (40). By the secreted alkaline phosphatase assay

(a form of PBNA), HPV 16 seropositivity was greater than 95% for all HPV-dose groups and was no different by dose group ($p=0.6$).

In the CVT, 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 by year 7. Since the avidity for one dose was similar to three doses at year 4, we assume that avidity similarly increased during this period after one dose. These results suggest that HPV 16 antibody quality is not substantially increased by boosting (69, 71).

Immunogenicity data from IARC India vaccine trial

Follow-up data are available up to 48 months. All vaccinated girls in the study groups seroconverted against HPV 16 and 18 after vaccination, and all remained seropositive at 48 months regardless of the number of doses received.

The immune response in the two-dose HPV vaccine group was non-inferior to the three-dose group at month 7 (the MFI ratio was 1.12 [95% CI 1.02–1.23] for HPV 16 and 1.04 [0.92–1.19] for HPV 18), but it was inferior in the two-dose default group (0.33 [0.29–0.38] for HPV 16 and 0.51 [0.43–0.59] for HPV 18) and one-dose default group (0.09 [0.08–0.11] for HPV 16 and 0.12 [0.10–0.14] for HPV 18) at 18 months (39) and continued to be inferior by month 48. Although the MFI values for HPV 16 and 18 L1 antibodies for the single-dose group had values equivalent to or lower than the seropositivity cutoff, they are several times higher than the baseline values.

The values for GM 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 (39): the avidity index ratio of the one-dose default group compared with the three-dose group for HPV 16 L1 was 1.10 (95% CI 1.01–1.19). One dose induced detectable concentrations of NAb to HPV 16 and 18 but at lower concentration than did two or three doses. The geometric mean titer (GMT) ratio of HPV 16 L1 neutralization titers was 0.06 (0.04–0.08) for the one-dose default group compared with the three-dose group at 18 months (0.08 [0.05–0.13] for HPV 18 L1 and 0.06 [0.04–0.09] for HPV 6 L1).

Immunogenicity data from a US randomized pilot intervention study in women with prior HPV 16 infection

The following text has been excerpted from the systematic review of the trials (66). The content was edited for this paper.

In the small randomized study (67), four of the five HPV 16–seropositive women receiving a single dose of the 9 HPV vaccine exhibited increases in HPV 16 and HPV 18 binding antibody levels and neutralization against HPV 16 by one month following vaccination, and

responses remained increased compared to baseline at month 6 (67). Two women had observed increases in HPV 16/18 antibody binding levels at one-week post-vaccination. Increases in memory B-cells numbers were also observed. Conversely, non-NABs were observed in women with natural HPV infection, and no changes in antibody responses or memory B-cell numbers were seen among the five infected women who did not receive any HPV vaccine dose.

2.2.2.10 RESULTS OF QUALITY ASSESSMENT

The quality of evidence from all seven studies was assessed, and a descriptive synthesis is presented in **Table 7** for the CVT, PATRICIA, and IARC India trials. The presence of enrolled comparator groups of young women who did not receive HPV vaccine in these trials allowed authors to assess the risk of bias and the presence of a number of confounders that could have artificially inflated the VE in the one-dose group or deflated the VE in the three-dose group. Sociodemographic characteristics (e.g., age, household income, education level), HPV seropositivity at baseline, and the incidence of non-vaccine-type HPV infections during follow-up (proxy measures for participants' risk of HPV 16/18 exposure during follow-up) were very similar across comparator groups (dose groups and control groups). Participants' reasons for non-completion of the vaccination schedule and rates of loss to follow-up (indicators of survival bias) were also very similar across all comparator groups and were controlled for in some analyses conducted by the authors of the included studies. The risk of exposure or outcome misclassification was low, and the included analyses were appropriate.

The intervention study by Scherer et al. was a very small ($n=5$ per arm) pilot study among HPV 16 seropositive women, limiting the precision of estimates and generalizability of results. Allocation to one-dose HPV vaccine versus no intervention was randomized but not blinded; however, the latter point likely has little implication as the study endpoints were immunological.

2.2.3 Data on “one or more” HPV vaccine doses from Cochrane review

2.2.3.1 OVERVIEW

A Cochrane review of clinical trial data on the efficacy and safety of HPV vaccines (monovalent, GSK 2vHPV, Merck 4vHPV, or Merck 9vHPV) compares "at least one" dose of HPV vaccine (2vHPV or 4vHPV) to placebo (vaccine adjuvants or another control vaccine) (68). The specific objective of the Cochrane review was "to evaluate the harms and protection of prophylactic human papillomaviruses (HPV) vaccines against cervical precancer and HPV 16/18 infection in adolescent

girls and women." The review included phase II and III RCTs that enrolled female participants of any age receiving the HPV vaccine or a placebo and that had results published before June 2017.

The review included trials of three vaccine doses. Therefore, women who received only one or two doses were those who did not complete their allocated three-dose schedule. Efficacy outcomes evaluated by the review included high-grade CIN—or worse, invasive CC—and incident and persistent infections with vaccine HPV types. While primarily presenting data for "at least one" dose, the review also stratified results by actual number of doses received, as follows: one dose, two doses, three doses, and two or three doses (calculated as the difference between three-dose and "at-least-one" dose participants in a post hoc analysis).

2.2.3.2 SINGLE-DOSE VERSUS COMPARATOR GROUPS

The Cochrane review included 56 references describing 26 randomized trials of a three-dose HPV vaccination regimen comprising a total of 73,428 women. Of these, only three articles report efficacy data for single-dose HPV vaccination compared to comparator groups (69-71). These three articles were derived from the CVT and PATRICIA and are included in the results of the systematic review described above (66) (Section 2.2.2). The IARC India HPV vaccine trial (39) was not included in the Cochrane review, presumably because, due to suspension of the trial midway through randomization, it could no longer be reported as an RCT and/or because no placebo group was included.

Since the three articles identified by the Cochrane review were also identified by the systematic review of evidence on single-dose HPV vaccination from clinical trials described above, and the corresponding studies are already presented in Section 2.2.2, the results are not repeated here.

2.2.3.3 "ONE OR MORE" DOSE VERSUS PLACEBO GROUPS

The main comparison in the Cochrane review was "at least one" HPV vaccine dose versus placebo (vaccine adjuvants or another control vaccine, such as HAV). The usefulness of these data for evaluating a single-dose regimen is limited because the vast majority of participants received three doses (i.e., completed their allocated schedule). However, in a post hoc analysis, the review authors determined measures of effect and association for participants who received one or two vaccine doses (combined) by calculating the difference between three-dose and "at-least-one-dose" groups (where reported) (69, 75, 78-96). Among one- or two-dose recipients, significant protection was seen, compared to women receiving a placebo, against HPV 16-/18-associated cervical intraepithelial neoplasia grade 2 or worse and grade 3 or worse, or CIN2+ and CIN3+ (2vHPV and 4vHPV vaccines, with women aged 16–25 years) (75, 78-80, 84-96); incident HPV 16/18 infection (2vHPV vaccine, with women aged 15–26 years) (79, 80, 87-89, 92-94); and six-month persistent HPV 16/18 infection (2vHPV and 4vHPV vaccines, with women aged 15–45 years) (79, 80, 84, 85, 87-89, 95, 96). Again,

these data are limited in terms of evaluating efficacy of single-dose HPV vaccination as some (presumably most) participants included in the post hoc "one- or two-dose" groups received two doses of vaccine.

2.2.4 Strengths and weaknesses of evidence from clinical trials

2.2.4.1 STRENGTHS AND WEAKNESSES OF SYSTEMATIC REVIEW OF EVIDENCE ON SINGLE-DOSE HPV VACCINATION FROM CLINICAL TRIALS

The systematic review of trials data described in Section 2.2.2 provides a rigorous search and evaluation of the published literature on single-dose HPV vaccination compared to no vaccination or standard dosing regimens among clinical trial participants. The study's strengths include having a robust and comprehensive search strategy; searches of multiple scientific databases, as well as clinical trial registers; duplicate screening of all abstracts and full-text articles by two authors; independent verification of extracted data and STATA calculations by a separate author; and a quality assessment of included studies, specifically evaluating biases that might lead to increased efficacy in the single-dose arms or reduced efficacy in the standard-dose arms.

The systematic review of evidence on single-dose HPV vaccination from clinical trials also has several limitations. The following text contains excerpts from a systematic review of the trials (66). The content was edited for this paper.

This systematic review is limited by the small number of studies reporting clinical trial-based evaluations of single-dose HPV vaccination and, in some studies, limited sample size of the one-dose group. The review identified only seven publications describing studies of one-dose HPV vaccination compared to either no vaccination or two- or three-dose schedules. Six were observational studies arising from three randomized clinical trials (that were investigating efficacy and immune responses in three doses versus control, or two versus three doses), with participant allocation to one-dose or comparator arms occurring retrospectively (due to non-completion of originally allocated schedules). Only one very small pilot study allocated participants to single-dose versus no-dose arms prospectively.

Furthermore, the systematic review was not able to evaluate the effects of gender, age, or HIV status, as proposed in the study protocol, as all studies conducted to date have been in young, healthy females. This highlights a paucity of evidence in potential alternative target populations. Additionally, all trial-based data of single-dose HPV vaccination published to date come from Cervarix and Gardasil recipients; no studies have evaluated Gardasil-9. While most national program-based studies included in the published review by Markowitz

et al. report on VE against AGW and cervical abnormalities, the trial-based efficacy studies in the trials-based review reported only on HPV-infection endpoints.

Studying cohorts derived from the CVT, PATRICIA, and IARC India HPV vaccine trial for evaluation of single versus multidose vaccination schedules minimizes many of the biases that confound the national program-based studies, despite the retrospective allocation to exposure versus comparator arms. However, retrospective allocation is still suboptimal, so this approach does not preclude the requirement for gold-standard, purpose-designed RCTs. Also, although the point estimates of vaccine effectiveness in the trial-based observational studies are high, the CIs around the estimates are very wide, which limits any strong conclusions from these data on whether a single dose is sufficient for protection. It was not possible to combine results of the included studies and perform a meta-analysis in this review due to considerable heterogeneity between the studies.

While a quality assessment of included studies was conducted, this did not use a standardized risk of bias tool due to the lack of availability of a suitable tool. Coauthors of the systematic review have developed an adapted ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool to account for the characteristics of reduced-dose observational studies (e.g., different types of study design, use of buffer periods to control for prevalent infection at 1st dose) to formally assess the quality of these studies. It is expected that a formal quality assessment of studies included in the systematic review will become available in a future edition of this evidence review.

Specific quality considerations for CVT, the IARC India HPV vaccine trial, and PATRICIA are provided below in [Section 2.2.4.3](#).

2.2.4.2 STRENGTHS AND WEAKNESSES OF THE COCHRANE REVIEW ON “ONE OR MORE” HPV VACCINE DOSES

The Cochrane review has several strengths, including a high-quality review of the trials-based evidence on the safety and efficacy of HPV vaccines and inclusion of data from a large number of studies. However, the review did not specifically aim to evaluate single-dose HPV vaccination and so has a number of limitations in relation to this question. First, the main comparison, "one or more" doses versus a placebo, only includes trials randomizing participants to receive three doses of vaccine or a placebo, so the majority of participants included in the analyses received three doses. Only a proportion received one dose, and we do not know who these participants are. The post hoc analyses that the authors conducted enabled evaluation of VE among participants who received one or two doses (combined) versus a placebo but did not examine efficacy for one-dose participants. The authors did present data by number of doses received where provided in included studies (CVT, PATRICIA). However, the review was limited to phase II and III RCTs of three-dose HPV vaccine

versus placebo or other control vaccine and so would not capture trials of other designs that could provide informative data on efficacy on single-dose HPV vaccination. While an assessment of risk of bias for studies was included in the Cochrane review, this did not include an evaluation of the risk of bias due to differences in reduced-dose and placebo/control participants. Finally, the review did not present any immunogenicity data from the included RCTs.

2.2.4.3 STRENGTHS AND WEAKNESSES OF CVT, IARC INDIA HPV VACCINE TRIAL, AND PATRICIA STUDIES

A quality assessment of the CVT, IARC India HPV vaccine trial, and PATRICIA studies is summarized in [Section 2.2.2.10](#) and [Table 7](#), both of which are extracted from the systematic review of evidence on single-dose HPV vaccination from clinical trials. Given that, at present, the majority of trials-based evidence for single-dose HPV vaccination is derived from the CVT, PATRICIA, and IARC India trials, their strengths and weaknesses are described here in more detail. Portions of this section were excerpted from a review of evidence of single-dose HPV vaccine protection from the CVT, as well as future research studies (54). The content was edited for this evidence review.

Strengths of studies

For the CVT, a concurrent control group was enrolled, and extensive analyses were conducted to rule out much of the potential bias and confounding that could relate to an underlying characteristic shared by women who received only a single dose. The findings on the protection conferred by single-dose vaccination were consistent in the PATRICIA study before the combined analysis with CVT was done.

Several metrics were used to evaluate potential biases and confounding in the CVT and PATRICIA data, including by-dose assessment of the following:

- *Demographic and HPV-related differences at enrollment, including sexual behavior and presence or absence of *Chlamydia trachomatis* by dose group.*
- *Follow-up time and reasons for missed visits and doses.*
- *Vaccine antibody response elicited one month after the first dose, when all women received the same number of doses irrespective of the total number of doses they received.*
- *Prevalence of HPV genotypes not protected by the vaccine, as an indicator of genital HPV exposure, accumulated over the four years of follow-up.*

For the India HPV vaccine trial, strengths of the study include a large sample size across all arms (including the single-dose arm), high cohort retention (over 80%) at seven years after recruitment, the

frequency of the immunogenicity and efficacy measures, and the fact that laboratory analyses were performed in a blinded manner. The original allocation to two versus three doses was cluster randomized—although, the halt to enrollment resulted in formation of new study groups (one- versus two- versus three-dose arms), and this "reallocation" was determined by time of enrollment (and not controlled by the investigators). Thus, it is unlikely to be linked to any preexisting HPV-risk status.

In all three studies, the incidence of infection with HPV vaccine genotypes not targeted by the Merck 4vHPV was similar across vaccinated participants, regardless of the number of doses received. This provides some reassurance against potential bias and confounding relating to underlying characteristics of participants not completing their allocated vaccine schedule.

Weaknesses of studies

For the CVT and PATRICIA studies, the group of women receiving a single dose of the GSK 2vHPV vaccine was relatively small, and they were not randomized to a reduced-dose schedule. The combined analysis of the CVT and PATRICIA studies used 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 activated latent infections that were not detected at vaccination.

Although the India HPV vaccine trial was originally a randomized trial, the original dose randomization could not be maintained. The different vaccine dose cohorts were comparable for age, but there were differences in several sociodemographic factors at enrollment, such as monthly household income, religion, and education (72). However, as described above, the frequency of detection of HPV genotypes not targeted by the Merck 4vHPV were similar across the vaccinated and unvaccinated women (97). Clinical outcomes were measured only 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 and time of follow-up. Biases in selection of this cohort cannot be ruled out.

2.2.5 Summary of observational data from clinical trials

The following text contains excerpts from the systematic review of evidence on single-dose HPV vaccination from clinical trials (66). The content was edited for this paper and updated to reflect recently available data from the CVT.

The systematic review of the literature on single-dose HPV vaccination from clinical trials supports the premise that one dose may be as effective in preventing HPV infection as two or three doses in healthy young females up to 11 years post-vaccination. Incident,

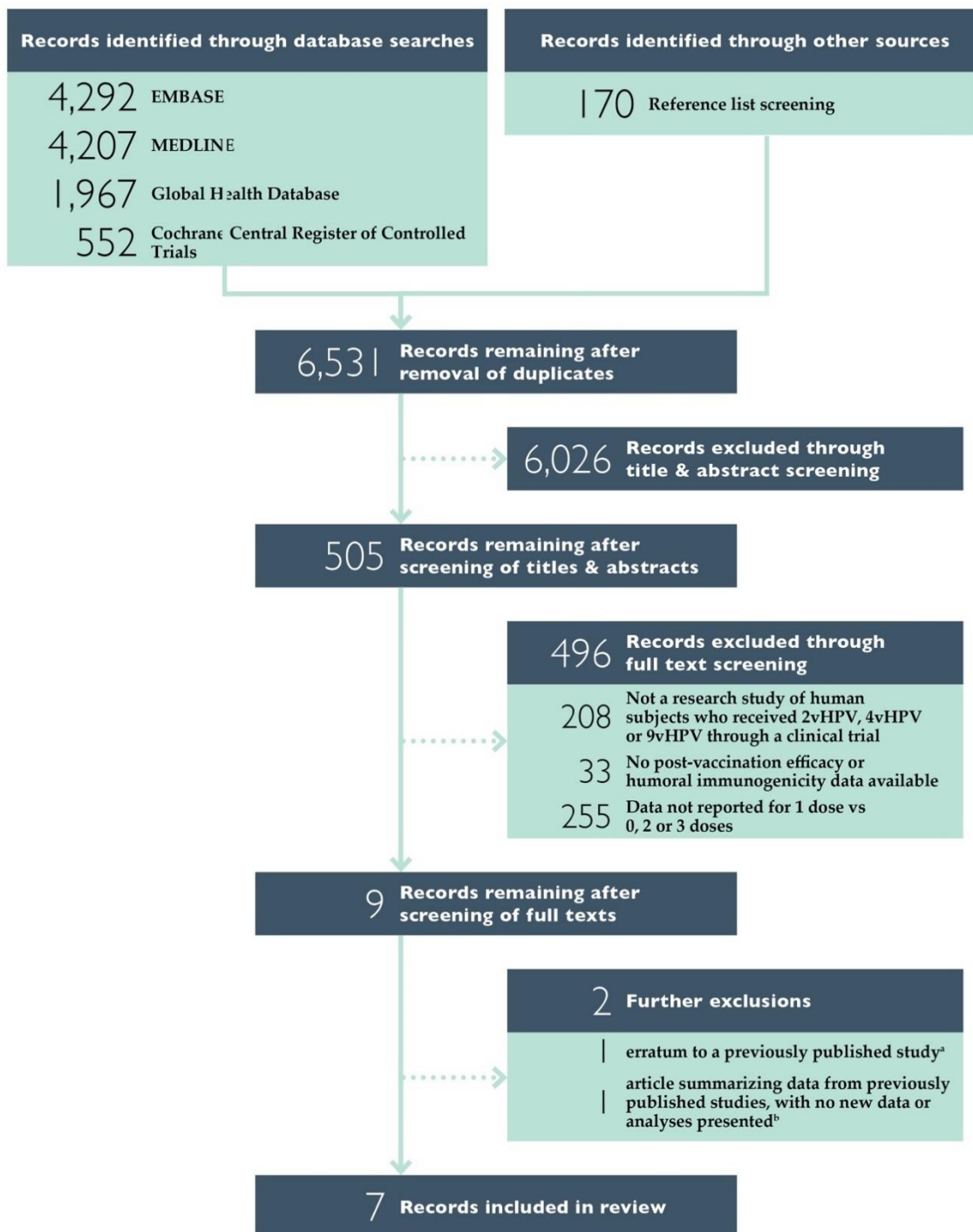
persistent, and prevalent infections with HPV 16/18 were extremely low in all efficacy trial participants who received any HPV vaccine, and significantly lower versus ones who were unvaccinated or received a control vaccine, such as HAV. All included efficacy studies reported comparable efficacy against HPV 16/18 infection in one-dose versus two- or three-dose arms.

The Cochrane review (68) did not identify any studies contributing evidence specifically on efficacy of single-dose HPV vaccination beyond those captured by the systematic review of trials on single-dose HPV vaccination. However, the authors' post hoc analysis demonstrated high efficacy of one or two doses (combined analysis) of HPV vaccine compared to control using data from eight studies. As described above, these data must be interpreted with caution, as one- and two-dose participants cannot be disaggregated, and there is already strong evidence for efficacy of two doses.

Across studies reporting immunogenicity outcomes, the proportions of participants reportedly seroconverting to HPV 16/18 antibody positive were generally high in all HPV vaccine dosage arms, reaching 100% in some studies. However, the definition of seroconversion differs between studies (Table 5), so caution must be applied in interpreting these results. Antibody levels were lower with one dose than with two or three doses, but levels in one-dose arms remained stable throughout follow-up. Furthermore, antibody levels were significantly higher in participants vaccinated with a single dose of HPV vaccine compared to pre-vaccination levels in participants with natural infection (66).

While producing promising results, the systematic review also highlighted the existing paucity of available evidence appropriate for informing policies and guidelines on HPV vaccination strategies. Ongoing clinical trials assessing the efficacy and immunogenicity of single-dose HPV vaccination compared to currently recommended schedules will go a long way toward addressing this knowledge gap for the target populations in those trials. However, research on efficacy of, and immune responses to, single-dose HPV vaccination may need to be expanded to other target groups—such as boys, alternative age groups, and HIV-positive individuals—and should evaluate all licensed HPV vaccines, as well as new vaccines currently in development.

Figure 2. Clinical trials systematic review flow diagram



Note: Two further relevant articles were identified in an updated literature search performed since the systematic review search was conducted.

^a Corrected results presented in the erratum (98) were incorporated into data extraction for the corresponding article (40).

^b Article (99) presents previously published data from the CVT (40, 69-71).

Source: Figure adapted from (66).

Table 2. Summary of studies comparing one HPV vaccine dose to no vaccination or multidose schedules among clinical trial participants

Reference	Study design, location	HPV-vaccinated population (healthy females in all studies)							Control group
		No. in efficacy cohort	No. in immuno. cohort	Age at vaccination (years)	Baseline HPV 16/18 DNA status ^a	Baseline HPV 16/18 serology ^a	Vaccination schedule(s)	Follow-up duration	
GlaxoSmithKline 2vHPV vaccine									
<i>Kreimer 2011^b</i> (69)	Post hoc analysis of RCT (CVT); Costa Rica	3,575	NA	18–25	HPV 16 and 18 positive excluded; unstated proportion HPV 16 or 18 positive	Unstated proportion positive (<i>method not stated</i>)	3d (M 0,1,6), 2d (M 0,1/0,6) 1d (M 0)	Efficacy: 4y	3,578 healthy females receiving HAV in CVT
<i>Sfaeian 2013^c</i> (40)		NA	390		5% HPV 16 or 18 positive	15% HPV 16 positive (<i>by IgG ELISA</i>)		Immuno: 4y	115 healthy HPV 16/18 seropositive females in CVT, pre-vaccination
<i>Sfaeian 2018^d</i> (71)	2,449	486	8% HPV 16/18 positive		38% HPV 16/18 positive (<i>by IgG ELISA</i>)	Efficacy & immuno: 7y		2,836 age-matched healthy unvaccinated females	
<i>Kreimer 2020</i> (38)	Prospective observational cohort study of prior CVT participants; Costa Rica	1,539	NA		Not stated	Efficacy & immuno: 11y	1,783 age- & geography-matched healthy unvaccinated females		
<i>Tsang 2020</i> (73)		2,974	NA		8% HPV 16/18 positive ^e	38% HPV 16/18 positive (<i>by IgG ELISA</i>) ^e	Efficacy: 11y	3,315 healthy females receiving HAV in CVT and 2,619 age-matched healthy unvaccinated females	
<i>Kreimer 2015^f</i> (70)	Combined retrospective analysis of CVT and PATRICIA data; Multiple LMIC & HIC worldwide	12,159	NA	15–25	HPV 16 and 18 positive excluded; unstated proportion HPV 16 or 18 positive	Unstated proportion positive (<i>method not stated</i>)	3d (M 0,1,6), 2d (M 0,1/0,6) 1d (M 0)	Efficacy: 4y	12,194 healthy females receiving HAV in CVT or PATRICIA
Merck 4vHPV vaccine									
<i>Sankaranarayanan 2016^g</i> (39)	Prospective observational cohort study; India	2,649	1,552 – 1,937	10–18	Not measured; unmarried	5% of immuno. cohort HPV 16 positive, 5% HPV 18 positive; not reported for efficacy cohort (<i>by Luminex</i>)	3d (M 0,2,6), 2d (M 0,2/0,6) 1d (M 0)	Efficacy: 4y Immuno: 3y	None
<i>Sankaranarayanan 2018^g</i> (72)		5,655	879 – 1,937					Not reported	Efficacy: 7y Immuno: 4y
<i>Scherer 2016^h</i> (67)	Randomized unblinded pilot intervention study; United States	NA	5	27–45	Not measured	HPV 16 positive (<i>by IgG binding assay</i>)	1d (M 0)	Immuno: 6y	5 healthy HPV 16-seropositive unvaccinated females

Abbreviations: 2vHPV, bivalent HPV [vaccine]; 4vHPV, quadrivalent HPV [vaccine]; CVT, Costa Rica vaccine trial; d, dose; DNA, deoxyribonucleic acid; ELISA, enzyme-linked immunosorbent assay; HAV, hepatitis A vaccine; HIC, high-income countries; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; IgG, immunoglobulin G; Immuno, immunogenicity; LMIC, low- and middle-income countries; M, month; NA, not available; PATRICIA, PApilloma TRial against Cancer In young Adults; RCT, randomized controlled trial; y, years.

- ^a HPV 16/18 DNA status refers to polymerase chain reaction / genotyping results in cervical samples; HPV 16/18 serology refers to antibody seropositivity results in serum or plasma. Baseline refers to pre-vaccination.
- ^b Analytic cohort included all 7,153 CVT participants who were seen each year during four years of follow-up and who were not HPV 16 and 18 DNA positive at baseline. At enrollment, participants were randomized to receive HPV vaccine (n = 3,575) or HAV (3,578). HAV control arms received the vaccine and were followed up according to the same schedule as HPV vaccine arms.
- ^c Included all 270 CVT participants who received one or two HPV vaccine doses and a random selection of 120 participants who received three HPV vaccine doses, all with sera available for each study visit. Pre-vaccination samples from 115 HPV 16-/18-seropositive CVT participants (DNA status not reported) were used as single time point controls.
- ^d Efficacy cohort included all 2,449 HPV-vaccinated CVT participants who agreed to enter the long-term follow-up study at the end of the four-year trial. The immunogenicity cohort included a subset of 321 one- or two-dose participants who were tested previously and had sufficient available sera, and a random subset of 165 three-dose participants. Additionally, 2,836 age-matched healthy and HPV-unvaccinated women were enrolled at the start of the long-term follow-up study and followed up for three years.
- ^e Baseline HPV 16/18 DNA status and serology are presented for consistency with other studies in the table; but the aim of the study was to evaluate cross protection against HPV 31, 33, and 45.
- ^f Analytic cohort included all 25,055 CVT and PATRICIA participants who had adequate follow-up and available HPV DNA results at baseline and who were not HPV 16 and 18 DNA positive at baseline. Inadequate follow-up was defined as no month 12 or later visit, or <300 days between the month 12 (or later) visit and the last study visit. At enrollment, participants were randomized to receive the HPV vaccine (n = 21,013) or HAV (12,042). HAV control arms received vaccine and were followed up according to the same schedule as HPV vaccine arms. Results were additionally reported in the study for a "naïve" cohort excluding women who were HPV DNA positive for any of 14 high-risk HPV types, HPV 16/18 seropositive, and cytology positive at enrollment. Results from the "naïve" cohort are not included in the systematic review.
- ^g Efficacy cohort included all IARC India HPV vaccine trial participants (all unmarried at enrollment) who received one or more dose of HPV vaccine and had at least one cervical sample collected during follow-up (2,649 up to year 4; 5,655 up to year 7). Collection of cervical samples commenced six months after delivery of a baby or 12 months after marriage, whichever was earlier. Participants for the immunogenicity cohort were selected by convenience sampling; numbers of samples vary at each time point. Additionally, 1,481 age-matched healthy married and HPV-unvaccinated control participants were enrolled two years after the start of enrollment into the IARC India HPV vaccine trial and followed up for four years.
- ^h Included ten HPV 16-positive females with ≤5 heterosexual lifetime partners. Five were randomized to receive a single dose of Merck 4vHPV and five to receive no vaccine. Both arms were enrolled together and followed up at the same time points.

Source: Table adapted from (66).

Table 3. Sampling, laboratory methods, and definitions used and reported by each study for HPV 16/18 infection-associated endpoints

Study	Sampling	Methods	Endpoints reported (measure/unit) ^a	Endpoint definitions
Kreimer 2011 (69) and Safaian 2018 (71)	Vaccinated cohort: Cervical cell samples collected from sexually experienced women at enrollment, M 6, and then annually (from day 0) for 4 y. Thereafter, samples collected biennially up to Y 7 from all women in FU study. Unvaccinated cohort: Cervical cell samples collected biennially.	SPF ₁₀ PCR DEIA ^b and LiPA ₂₅ ^c	6 m persistent infection (% risk, 95% CI)	New infection detected at M 6 or later and persisting for ≥ 4 m, confirmed by 2 samples collected ≥ 4 m apart and testing positive for the same HPV type, with no intervening negative tests
			12 m persistent infection (% risk, 95% CI)	New infection detected at M 6 or later and persisting for ≥ 10 m (as above, with samples collected ≥ 10 m apart)
			One-time incident infection (% risk, 95% CI)	All infections detected at Y 7 that were not detected at Y 4
			Cumulative incident infection (% risk, 95% CI)	All detectable infection between M 12 and Y 7 among women type-specific negative at enrollment
			One-time prevalent infection (% risk, 95% CI)	All infections detected at Y 7
Kreimer 2020 (38) and Tsang 2020 (73)	As above, up to Y 11 time point.	SPF ₁₀ PCR DEIA ^b and LiPA ₂₅ ^{c,d} and TypeSeq PCR ^e	Prevalent infection	Type-specific infection detected at a given study visit (73), or infection detected at the Y 9 and/or Y 11 study visit (38)
			Incident infection	A prevalent infection detected at a given study visit, which was not present at the prior study visit
			≥ 6 m persistent infection	An incident infection that is also detected at any visit >150 days later, with no intervening negative tests
Kreimer 2015 (70)	CVT vaccinated cohort: as above, up to Y 4 time point. PATRICIA vaccinated cohort: Cervical samples collected from sexually experienced women at enrollment and biennially thereafter for 4 y.	SPF ₁₀ PCR DEIA ^b and LiPA ₂₅ ^c	One-time incident infection (% rate, 95% CI)	All first detectable infections occurring from M 12, accumulated up to Y 4
			6 m persistent infection (% rate, 95% CI)	New infection detected at M 12 or later and persisting for ≥ 6 m, confirmed by 2 samples collected ≥ 150 days apart and testing positive for the same HPV type, with no intervening negative tests
			12 m persistent infection (% rate, 95% CI)	New infection detected at M 12 or later and persisting for ≥ 12 m (as above, with samples collected ≥ 300 days apart)
Sankaranarayanan 2016 (39) and 2018 (72)	Vaccinated cohort: Cervical samples collected 18 m after marriage or 6 m after first childbirth ^f and annually thereafter until 4 consecutive yearly samples obtained. Unvaccinated cohort: Cervical samples collected at enrollment and annually thereafter for up to 4 collections.	HPV type-specific E7 PCR bead-based multiplex genotyping ^g	Cumulative first incident infection (% risk, 95% CI)	All first detectable infections accumulated during FU
			12 m persistent infection (% risk, 95% CI)	Presence of type-specific HPV DNA on repeated cervical samples over ≥ 12 m interval (in women with ≥ 2 samples tested)
			Cumulative incident infection (% risk, 95% CI)	All detectable infections at any visit up to Y 7

Abbreviations: CI, confidence interval; CVT, Costa Rica vaccine trial; DEIA, direct enzyme immunoassay; DNA, deoxyribonucleic acid ; FU, follow-up; HPV, human papillomavirus; M/m, month/months ; PATRICIA, PApilloma TRIal against Cancer In young Adults; PCR, polymerase chain reaction ; Y/y, year/years.

- ^a Incidence risk denotes the number of new cases occurring per population at risk (i.e., using the number of women in the analytical population as the denominator). Incidence rate denotes the number of new cases per population at risk in a given time period (i.e., using person-years as the denominator).
- ^b SPF₁₀ PCR DEIA: SPF₁₀ PCR primer system and DNA enzyme immunoassay detection of amplimers (DDL Diagnostic Laboratory, Voorburg, the Netherlands).
- ^c LiPA²⁵: HPV line probe assay containing probes for 25 HPV genotypes (Labo Biomedical Products, Rijswijk, the Netherlands).
- ^d Used in Tsang et al. 2020 (73) only.
- ^e US National Cancer Institute's newly developed in-house assay that detects 51 HPV genotypes (100).
- ^f Whichever occurred earlier.
- ^g For 19 high-risk and 2 low-risk HPV types.

Source: Table adapted from (66).

Table 4. Summarized HPV 16/18 infection results from clinical trial participants

Reference	Follow-up duration	Infection endpoint ^a	3-dose HPV arm		2-dose HPV arm ^b		1-dose HPV arm		Control arm ^c		RR or PR (95% CI), <i>p</i> value ^d		
			Events / N	% (95% CI) ^d	Events / N	% (95% CI) ^d	Events / N	% (95% CI) ^e	Events / N	% (95% CI) ^d	1 dose / 3 doses ^e	1 dose / 2 doses ^e	1 dose / control
GlaxoSmithKline 2vHPV													
One-time incident and cumulative incident infections													
<i>Kreimer 2015 (70)</i>	Mean: 4.0y SD: 0.7y	One-time incident	529 / 11,110	4.8 (4.4–5.2)	22 / 611	3.6 (2.3–5.4)	8 / 292	2.7 (1.2–5.3)	45 / 251	17.9 (13.4–23.2)	0.6 (0.3–1.1) <i>0.12</i>	0.8 (0.3–1.7) <i>0.56</i>	0.2 (0.1–0.3) <i><0.01</i>
<i>Safaeian 2018 (71)</i>	Median: 6.9y IQR: 6.5–7.3y	One-time incident	9 / 2,042	0.4 (0.2–0.8)	0 / 78	0.0 (0.0–4.6)	0 / 134	0.0 (0.0–2.7)	-	-	0.8 (0.0–13.6) <i>1.0</i>	0.6 (0.0–29.2) <i>UTCⁱ</i>	-
		Cumulative incident	88 / 2,036	4.3 (3.5–5.3)	3 / 78	3.8 (0.8–10.8)	2 / 133	1.5 (0.2–5.3)	-	-	0.3 (0.1–1.4) <i>0.17</i>	0.4 (0.1–2.3) <i>0.36</i>	-
<i>Kreimer 2020 (38)</i>	Median: 11.3y IQR: 10.9–11.7y	One-time incident	8 / 1,365	0.6 (0.3–1.2)	1 / 62	1.6 (0.04–8.7)	2 / 112	1.8 (0.2–6.3)	69 / 1,783	3.9 (3.0–4.9)	3.0 (0.7–14.2) <i>0.17</i>	1.1 (0.1–12.0) <i>1.00</i>	0.5 (0.1–1.9) <i>0.44</i>
Prevalent infections													
<i>Safaeian 2018 (71)</i>	Median: 6.9y IQR: 6.5–7.3y	One-time prevalent	20 / 2,043	1.0 (0.6–1.5)	1 / 79	1.3 (0.0–6.9)	0 / 134	0.0 (0.0–2.7)	158 / 2,382	6.6 (5.7–7.7)	0.4 (0.0–6.1) <i>0.63</i>	0.2 (0.0–4.8) <i>0.37</i>	0.1 (0.0–0.9) <i><0.01</i>
<i>Kreimer 2020 (38)</i>	Median: 11.3y IQR: 10.9–11.7y	Y9 and/or Y11 prevalent	27 / 1,365	2.0 (1.3–2.9)	1 / 62	1.6 (0.04–8.7)	2 / 112	1.8 (0.2–6.3)	178 / 1,783	10.0 (8.6–11.5)	0.9 (0.2–3.7) <i>1.00</i>	1.1 (0.1–12.0) <i>1.00</i>	0.2 (0.04–0.7) <i><0.01</i>
Persistent infections^h													
<i>Kreimer 2011 (69)</i>	Median: 4.2y ^g	6m persistent	37 / 2,957	1.3 (0.9–1.7)	5 / 422	1.2 (0.4–2.7)	0 / 196	0.0 (0.0–1.9)	15 / 188	8.0 (4.5–12.8)	0.2 (0.0–3.2) <i>0.17</i>	0.2 (0.0–3.5) <i>0.18</i>	0.0 (0.0–0.5) <i><0.01</i>
		12m persistent	25 / 2,957	0.9 (0.6–1.2)	3 / 422	0.7 (0.1–2.1)	0 / 196	0.0 (0.0–1.9)	10 / 188	5.3 (2.6–9.6)	0.3 (0.0–4.8) <i>0.40</i>	0.3 (0.0–5.9) <i>0.56</i>	0.0 (0.0–0.8) <i><0.01</i>
<i>Kreimer 2015 (70)</i>	Mean: 4.0y SD: 0.7y	6m persistent	114 / 11,104	1.0 (0.8–1.2)	4 / 611	0.7 (0.2–1.7)	1 / 292	0.3 (0.0–1.9)	24 / 250	9.6 (6.2–13.9)	0.3 (0.0–2.4) <i>0.37</i>	0.5 (0.1–4.7) <i>1.00</i>	0.0 (0.0–0.3) <i><0.01</i>
		12m persistent	84 / 11,104	0.8 (0.6–0.9)	3 / 611	0.5 (0.1–1.4)	1 / 292	0.3 (0.0–1.9)	17 / 249	6.8 (4.0–10.7)	0.5 (0.1–3.2) <i>0.72</i>	0.7 (0.1–6.7) <i>1.00</i>	0.1 (0.0–0.4) <i><0.01</i>
Merck 4vHPV													
One-time incident and cumulative incident infections													
<i>Sankaranarayanan 2016 (39)</i>	Median: 4.7y IQR: 4.2–5.1y	Cumulative first incident	2 / 536	0.4 (0.0–1.3)	4 / 526	0.8 (0.2–1.9)	10 / 870	1.1 (0.6–2.1)	-	-	3.1 (0.7–14.0) <i>0.17</i>	1.5 (0.5–4.8) <i>0.059</i>	-
<i>Sankaranarayanan 2018 (72)</i>	Up to 7y ^f	Cumulative incident	11 / 1,180	0.9 (0.5–1.7)	11 / 1,179	0.9 (0.5–1.7)	30 / 1,823	1.6 (1.1–2.3)	92 / 1,481	6.2 (5.0–7.6)	1.8 (0.9–3.5) <i>0.1</i>	1.8 (0.9–3.5) <i>0.1</i>	0.3 (0.2–0.4) <i><0.01</i>
Persistent infections^h													
<i>Sankaranarayanan 2018 (72)</i>	Up to 7y ^f	12m persistent	1 / 604	0.2 (0.0–0.9)	0 / 608	0.0 (0.0–0.6)	0 / 959	0.0 (0.0–0.4)	14 / 1,141	1.2 (0.7–2.1)	0.2 (0.0–5.1) <i>0.39</i>	0.6 (0.0–31.9) <i>UTCⁱ</i>	0.0 (0.0–0.7) <i><0.01</i>

Abbreviations: 2vHPV, bivalent HPV [vaccine]; 4vHPV, quadrivalent HPV [vaccine]; CI, confidence interval; HPV, human papillomavirus; IQR, interquartile range; M; Month; N: Number of participants in group; PR, prevalence ratio; RR, risk ratio; SD, standard deviation; UTC, unable to compute; y, year.

^a Definitions of infection endpoints used in each study are provided in Table 3.

^b Results are shown only for two-dose arms where participants received dose one at day 0 and dose two at day 180.

^c Results are shown for one-dose control vaccine (HAV) arms for Kreimer et al. (2011) and Kreimer et al. (2015), and unvaccinated control arms for Sankaranarayanan et al. (2018) and Safaiean et al. (2018; persistent infection only). Comparison of the single-dose HPV vaccine arm with the single-dose HAV (rather than multidose HAV) arm in the Costa Rica trial minimizes the potential for selection bias due to differences in follow-up. No control arm was reported in Sankaranarayanan et al. (2016).

^d Proportions (%), unadjusted RRs and PRs, 95% CIs and 2-sided Fisher's exact p values were calculated by the authors of the systematic review using data provided in the included articles. Haldane-Anscombe correction was used for calculation of RRs and PRs where no events were detected in one or both comparison arms. In most cases, the 95% CIs for proportions calculated by the authors of this review matched those reported in the included studies. Where they do differ, the 95% CIs calculated in this review are wider than those reported in the articles.

^e Risk and prevalence ratios calculated for one versus two or three doses must be interpreted with caution because of potential for selection bias due to differences in follow-up between the groups.

^f Mean, median, IQR, or SD were not reported for this study.

^g IQR or SD were not reported for this study.

^h Sankaranarayanan et al. (2016) detected no persistent infections in any arm up to the median follow-up of 4.7 years among 838 women with two or more samples available for analysis.

ⁱ STATA does not compute a p value using Fisher's exact test where both numerators are 0.

Source: Table adapted from (66).

Table 5. Sampling, laboratory methods, and definitions used and reported by each study for HPV 16/18 immunogenicity-associated endpoints

Study	Sampling	Methods	Endpoints reported (measure/unit) ^a with definitions where applicable
Safaeian 2013 (40) and 2018 (71), and Kreimer 2020 (38)	Vaccinated cohort: Serum collected at enrollment and at M 1, 6, 12, 24, 36, and 48. Serum additionally collected at Y 4, 7, 9, 11. Naturally infected cohort: Serum collected at baseline, pre-vaccination.	HPV 16/18 L1 VLP ELISA	- Antibody titers (GM EU/ml, 10 th , 25 th , 75 th and 90 th percentiles, 95% CI) - HPV 16/18 seropositivity (% of analytical population seroconverting) <i>Laboratory-determined seropositivity cutoffs (8 EU/ml for HPV 16, 7 EU/ml for HPV 18)</i> - Antibody stability (% of analytical population with stable GMTs; Safaeian 2013 only) <i>Stability defined as titers not declining by \geq twofold between two specified time points</i>
		PSV-based SEAP neutralization assay	- HPV 16 neutralizing antibody seropositivity (% of analytical population seroconverting) <i>Laboratory-determined seropositivity cutoff (25.1 TU/ml)</i>
		GuHCl-modified HPV L1 VLP avidity ELISA	- Antibody avidity levels (GM avidity level, 95% CI, IQR)
Sankaranarayanan 2016 (39) and 2018 (72)	Plasma collected from convenience sample at enrollment and M 7, 12, 18, 24, 36, 48, and 60.	Luminex-based multiplex binding assay	- Antibody levels (GM MFI, 95% CI) - HPV 16/18 seropositivity (% of analytical population seroconverting) <i>Seropositivity cutoffs (100 for HPV 16, 41 for HPV 18) calculated based on MFI values of plasma samples from study participants at baseline after allowing for 5% seropositivity</i>
		Modified HPV-L1 genotype-specific binding antibody assay	- Antibody avidity index (GM avidity index (%), 95% CI)
		Automated PSV-based neutralization assay	- Antibody titers (GMT, 95% CI) - HPV 16/18 neutralizing antibody seropositivity (% of analytical population with neutralization titers) <i>Seropositivity defined as sample titer \geq50 and \geq2x control (BPV) titer</i>
Scherer 2016 (67)	PBMCs and plasma collected 6 m prior to vaccination, on day of vaccination, and at 1 w, 1 m, and 6 m post-vaccination.	Anti-L1 binding assay using GST-HPV L1 fusion proteins on BioPlex with magnetic beads	- Antibody levels (MFI converted to U/ml) - HPV 16 seropositivity <i>Seropositivity cutoff (3 U/ml) based on 3x SD above mean for sera from sexually unexperienced controls</i>
		293TT PSV-based SEAP neutralization assay	- HPV 16 neutralizing antibody levels (IC50 plasma dilution, ^a SD)
		Flow cytometry	- HPV 16-specific memory B-cell responses (frequency)

Abbreviations: BPV, bovine papillomavirus; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; EU, ELISA unit; GM, geometric mean; GST, glutathione-S-transferase; GuHCl, guanidine hydrochloride; HPV, human papillomavirus; IC50, half-maximal inhibitory concentration; M/m, Month/months; MFI, mean fluorescent intensity; M, month; PBMC, peripheral blood mononuclear cell; PSV, pseudovirion; SD, standard deviation; SEAP, secreted alkaline phosphatase; TU, transducing unit; U, international unit; VLP, virus-like particle; w, week; Y/y, Year/years.

^a Plasma dilution at which half-maximal inhibition occurred.

Source: Table adapted from (66).

Table 6. Summarized HPV 16/18 seropositivity and GM antibody-level results from clinical trial participants

Reference	Time point	# seropositive ^b / participants (% Seropositive, 95% CI ^c)			GM titers / MFI (95% CI)			
		3 doses	2 doses ^a	1 dose	3 doses	2 doses ^a	1 dose	Naturally infected
GlaxoSmithKline 2vHPV								
HPV 16								
Safaeian 2013 ^d (40)	D0	18 / 120 (15.0, 9.1–22.7)	-	6 / 78 (7.7)	<LOD	<LOD	<LOD	-
	M6	-	-	-	724 EU/ml	102 EU/ml	145 EU/ml	-
	M12	-	-	-	2,034 EU/ml	1,484 EU/ml	115 EU/ml	-
	M24	-	-	-	1,115 EU/ml	837 EU/ml	124 EU/ml	-
	M36	-	-	-	899 EU/ml	642 EU/ml	136 EU/ml	-
	M48	78 / 79 (98.7, 93.1–100.0)	52 / 52 (100.0, 93.2–100.0)	120 / 120 (100, 97.0–100.0)	748 EU/ml (648–865)	520 EU/ml (422–641)	137 EU/ml (106–178)	15 EU/ml (11–19)
Safaeian 2018 (71)	M48	2,043 / 2,043 (100.0, 99.8–100.0)	79 / 79 (100.0, 95.4–100.0)	134 / 134 (100.0, 97.3–100.0)	803 EU/ml (708–909)	555 EU/ml (447–690)	205 EU/ml (165–255)	-
	M84	2,043 / 2,043 (100.0, 99.8–100.0)	79 / 79 (100.0, 95.4–100.0)	134 / 134 (100.0, 97.3–100.0)	716 EU/ml (630–814)	460 EU/ml (367–576)	194 EU/ml (158–237)	-
Kreimer 2020 (38)	M108	1,365 / 1,365 (100.0, 99.7–100.0)	62/62 (100.0, 94.2–100.0)	112 / 112 (100.0, 96.8–100.0)	699 EU/ml (606–807)	414 EU/ml (328–524)	172 EU/ml (141–209)	-
	M132	1,365 / 1,365 (100.0, 99.7–100.0)	62/62 (100.0, 94.2–100.0)	112 / 112 (100.0, 96.8–100.0)	664 EU/ml (570–772)	340 EU/ml (267–434)	176 EU/ml (145–214)	-
HPV 18								
Safaeian 2013 ^d (40)	D0	-	-	-	<LOD	<LOD	<LOD	-
	M6	-	-	-	408 EU/ml	53 EU/ml	76 EU/ml	-
	M12	-	-	-	827 EU/ml	763 EU/ml	71 EU/ml	-
	M24	-	-	-	471 EU/ml	446 EU/ml	69 EU/ml	-
	M36	-	-	-	369 EU/ml	358 EU/ml	74 EU/ml	-
	M48	-	-	-	335 EU/ml (285–392)	305 EU/ml (238–391)	70 EU/ml (54–91)	15 EU/ml (12–19)
Safaeian 2018 (71)	M48	2,043 / 2,043 (100.0, 99.8–100.0)	79 / 79 (100.0, 95.4–100.0)	134 / 134 (100.0, 97.3–100.0)	360 EU/ml (313–414)	296 EU/ml (240–366)	112 EU/ml (93–134)	-
	M84	2,043 / 2,043 (100.0, 99.8–100.0)	79 / 79 (100.0, 95.4–100.0)	134 / 134 (100.0, 97.3–100.0)	322 EU/ml (281–369)	270 EU/ml (221–330)	125 EU/ml (105–150)	-
Kreimer 2020 (38)	M108	1,365 / 1,365 (100.0, 99.7–100.0)	62/62 (100.0, 94.2–100.0)	112 / 112 (100.0, 96.8–100.0)	292 EU/ml (249–342)	210 EU/ml (171–259)	102 EU/ml (83–125)	-
	M132	1,365 / 1,365 (100.0, 99.7–100.0)	62/62 (100.0, 94.2–100.0)	112 / 112 (100.0, 96.8–100.0)	275 EU/ml (234–323)	194 EU/ml (156–241)	109 EU/ml (89–133)	-
Merck 4vHPV								
HPV 16								
Sankaranarayanan 2016 ^e (39)	D0	46 / 1,000 (4.6, 3.4–6.1)	52 / 937 (5.5, 4.2–7.2)	-	MFI 11 (10–12)	MFI 9 (8–10)	-	-
	M7	308 / 308 (100.0, 98.8–100.0)	316 / 317 (99.7, 98.3–100.0)	-	MFI 5,460 (5,195–5,738)	MFI 6,125 (5,785–6,485)	-	-
	M12	-	-	260 / 528 (49.2, 44.9–53.6)	-	-	MFI 106 (96–116)	-
	M18	311 / 313 (99.4, 97.7–99.9)	312 / 314 (99.4, 97.7–99.9)	255 / 476 (53.6, 49.0–58.1)	MFI 1,209 (1,105–1,323)	MFI 1,222 (1,116–1,338)	MFI 113 (102–126)	-
	M36	225 / 271 (83.0, 78.0–87.3)	197 / 278 (70.9, 65.1–76.1)	166 / 510 (32.5, 28.5–36.8)	MFI 221 (197–247)	MFI 163 (147–181)	MFI 72 (66–78)	-
	M36	271 / 271 (100.0, 98.6–100.0)	278 / 278 (100.0, 98.7–100.0)	510 / 510 (100.0, 99.3–100.0)	MFI 221 (197–247)	MFI 163 (147–181)	MFI 72 (66–78)	-

Reference	Time point	# seropositive ^b / participants (% Seropositive, 95% CI ^c)			GM titers / MFI (95% CI)			
		3 doses	2 doses ^a	1 dose	3 doses	2 doses ^a	1 dose	Naturally infected
<i>Sankaranarayanan 2018 (72)</i>	M48	239 / 239 (100.0, 98.5–100.0)	243 / 243 (100.0, 98.5–100.0)	397 / 397 (100.0, 99.1–100.0)	MFI 196 (170–226)	MFI 197 (172–225)	MFI 86 (75–99)	-
HPV 18								
<i>Sankaranarayanan 2016^e (39)</i>	D0	41 / 1,000 (4.1, 3.0–5.5)	63 / 937 (6.7, 5.2–8.5)	-	MFI 6 (5–7)	MFI 5 (4–5)	-	-
	M7	308 / 308 (100.0, 98.8–100.0)	317 / 317 (100.0, 98.8–100.0)	-	MFI 2,942 (2,733–3,167)	MFI 3,068 (2,812–3,347)	-	-
	M12	-	-	304 / 528 (57.6, 53.2–61.8)	-	-	MFI 50 (45–55)	-
	M18	307 / 313 (98.1, 85.9–99.3)	305 / 314 (97.1, 94.6–98.7)	259 / 476 (54.4, 49.8–59.0)	MFI 377 (337–422)	MFI 269 (241–299)	MFI 46 (40–51)	-
	M36	249 / 271 (91.9, 88.0–94.8)	238 / 278 (85.6, 80.9–89.5)	271 / 510 (53.1, 48.7–57.5)	MFI 184 (162–208)	MFI 117 (104–132)	MFI 45 (41–49)	-
<i>Sankaranarayanan 2018 (72)</i>	M36	271 / 271 (100.0, 98.6–100.0)	278 / 278 (100.0, 98.7–100.0)	510 / 510 (100.0, 99.3–100.0)	MFI 184 (162–208)	MFI 117 (104–132)	MFI 45 (41–49)	-
	M48	239 / 239 (100.0, 98.5–100.0)	243 / 243 (100.0, 98.5–100.0)	397 / 397 (100.0, 99.1–100.0)	MFI 133 (115–154)	MFI 120 (105–136)	MFI 47 (41–53)	-

Abbreviations: 2vHPV, bivalent HPV [vaccine]; 4vHPV, quadrivalent HPV [vaccine]; CI, confidence interval; D, day; EU, ELISA unit; GM(T), geometric mean (titer); HPV, human papillomavirus; M, month; MFI, median fluorescence intensity; RR, risk ratio.

^a Results are shown only for two-dose arms where participants received dose one at day 0 and dose two at day 180.

^b Definitions of seropositivity used in each study are provided in **Table 5**.

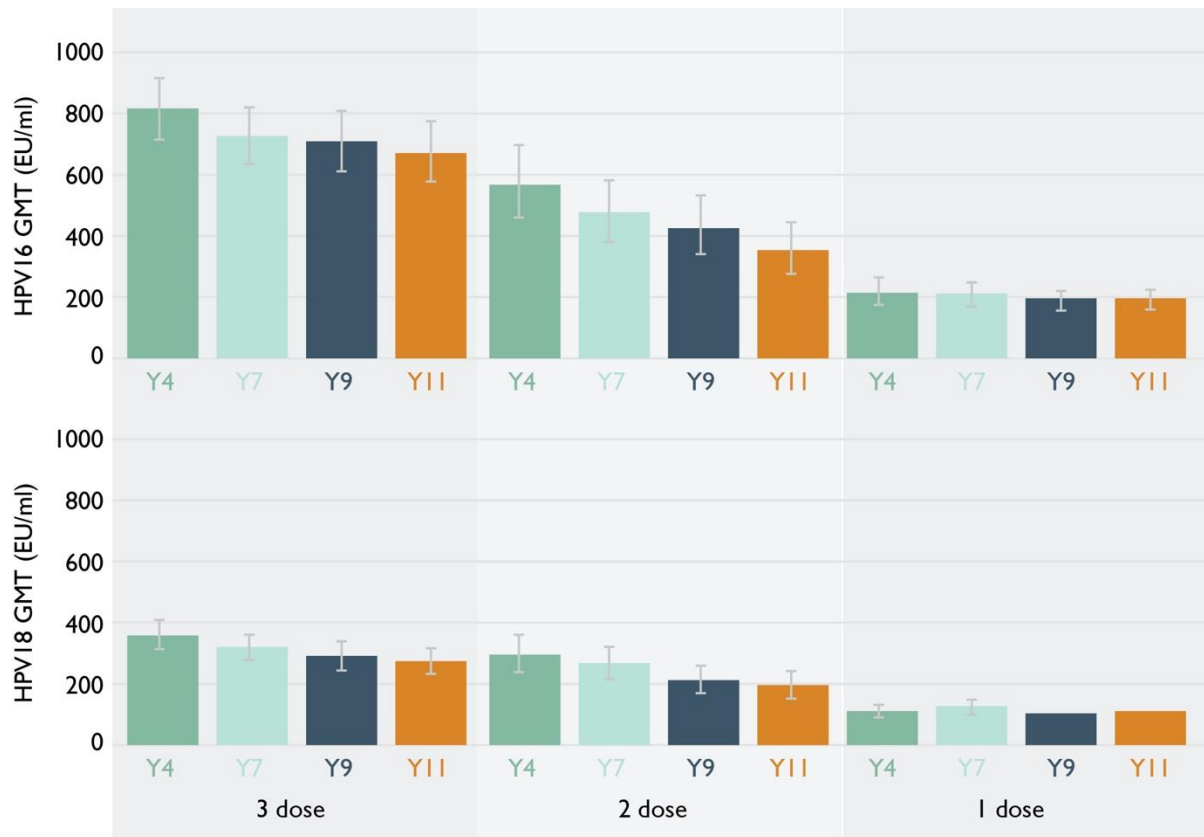
^c Seropositivity proportions (%) and 95% CIs, and percentage change in GM levels, were calculated by the authors of the systematic review using data provided in the included articles.

^d HPV GMTs (95% CI) among 113 unvaccinated but naturally infected controls were 15 (11–19) for HPV 16 and 15 (12–19) for HPV 18.²² This article did not report rates of seropositivity for months 6, 12, 24, or 36 for HPV 16 or for any time point for HPV 18. It also did not report 95% CIs for HPV 16/18 antibody titers prior to month 48; 10th, 25th, 75th, and 90th percentiles were reported in the article but not presented in the systematic review.

^e Month 48 results not shown as reported only for two- and three-dose arms, not for the one-dose arm.

Source: Table adapted from (66).

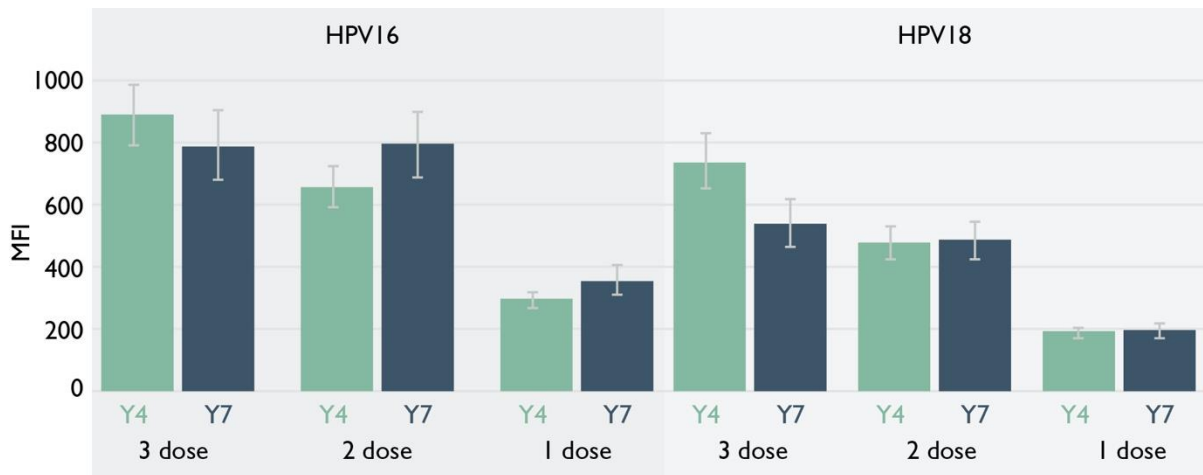
Figure 3. HPV 16 and HPV 18 GMTs up to 11 years post-vaccination in three-, two-, and one-dose HPV vaccine recipients in the CVT



Abbreviations: CVT, Costa Rica vaccine trial; ELISA, enzyme-linked immunosorbent assay; EU, ELISA unit; GMT, geometric mean titer; HPV, human papillomavirus; Y, year.

Source: Figure adapted from (66).

Figure 4. HPV 16 and HPV 18 MFI up to 7 years post-vaccination in three-, two-, and one-dose HPV vaccine recipients in the IARC India vaccine trial



Abbreviations: HPV, human papillomavirus; IARC, International Agency for Research on Cancer; MFI, mean fluorescent intensity; Y, year.
Source: Figure adapted from (66).

Table 7. Quality assessment of studies in the trials-based evidence for single-dose HPV vaccination versus multidose schedules

Studies	Parameter	Summary (including adjustment or consideration by study authors)
<i>Kreimer 2011 (69)</i> <i>Kreimer 2015 (70)</i> <i>Safaeian 2013 (40)</i> <i>Safaeian 2018 (71)</i> <i>Kreimer 2020 (38)</i> <i>Tsang 2020 (73)</i>	Selection bias	CVT and PATRICIA were individually randomized trials of 3d HPV vaccination compared to control HAV. Participants were blinded to vaccine allocation. The "1d" HPV vaccine group were non-completers of the 3d schedule (due to pregnancy, referral to colposcopy, medical conditions, refusal of subsequent vaccinations or missed study visits). Confounding factors could differentially affect whether a participant completed the schedule and her risk of HPV infection during FU (e.g., pregnancy and colposcopy may indicate higher levels of sexual activity and greater exposure to HPV). However, the prevalence of chlamydia infection, pregnancy and colposcopy were balanced between the HPV 1d group and the HAV 1d control group, against which 1d HPV efficacy was estimated; therefore, pregnancy and colposcopy did not appear to be associated with higher rates of HPV infection during FU. Analyses also assessed whether groups were comparable with respect to sexual activity by looking at HPV DNA or antibody positivity at enrollment. The 1d group had slightly higher HPV DNA detection at enrollment but similar rates of HPV seropositivity as the 3d group (i.e., the 1d group may have been more sexually active on average, and in theory, this would lead to lower VE in the 1d group), yet the data appear to suggest very high VE in the 1d group despite these differences at baseline.
	Retention / survival bias	Kreimer <i>et al.</i> 2011 set the primary endpoint as newly detected HPV 16/18 at the 6m visit or later. The 6m visit was the time of 3 rd d administration, so it is likely that those who missed their 3 rd d in the 1d or 2d groups missed this study visit and therefore had a lower probability of detection of incident HPV detection than the 3d group. However, the VE calculated for the 1d group may still be unbiased as it was calculated against a subset of the HAV control group that attended/missed the same study visits. The later analysis of the same data, combined with the PATRICIA trial data (Kreimer <i>et al.</i> 2015), addressed this limitation by assessing HPV outcomes at the 12m visit or later, the first visit at which women in the different dose groups may have had an equal chance of attending. The limitation of this later analysis was that LTFU at 12m was higher in the 1d group than in the 2d or 3d groups. This could have again introduced bias; however, the VE was calculated within each dose group compared to the HAV group, controlling for the differential likelihood of HPV detection due to visit attendance. The dose groups and their control groups had very similar prevalence of the different reasons for non-completion and study visit attendance and were balanced with respect to other confounders measured, leading us to believe the VEs of each dose group are unbiased. When we compare the VEs of the different dose groups we may be comparing slightly different populations (i.e., the 1d VE was calculated in a group of trial enrollees who did not attend every visit and may, on average, have lower health-seeking behavior and be less healthy than the population who attended all study visits). Conversely, the 3d VE was calculated in a group of trial participants who attended all study visits and could be healthier on average than the 1d group (the "healthy vaccinee" effect). If these imbalances between the trial groups were borne in reality, we would expect a lower VE in the 1d arm; however, even in the presence of this potential bias, the VE of 1d is still high.
	Misclassification	Misclassification of the exposure (the number of vaccine doses received) is unlikely across all analyses as the vaccine was not freely available to trial participants outside of the studies. However, none of the texts mention whether there was any verification of vaccination status at FU visits. All studies used highly sensitive HPV assays and standardized assays for the assessment of IgG. Misclassification of HPV incident or persistent infection is possible if HPV is simply undetectable within the cervix at the time of sampling yet latently infecting the epithelial cells. This is an unavoidable problem given the limitations of HPV sampling techniques and would likely be non-differential across comparison groups.
	Statistical analysis	Appropriate comparisons were made among CVT and PATRICIA trial participants using the HAV control group. It is legitimate to restrict analysis to those who are HPV negative at enrollment given that is the population targeted for vaccination.
	Generalizability	The trial recruited generally healthy, HIV-negative young women with few exclusion criteria and were therefore relatively pragmatic and representative of the general population. However, trial participants are, in general, healthier and less heterogenous than the general population.
<i>Sankaranarayanan 2016 (39)</i> <i>Sankaranarayanan 2018 (72)</i>	Selection bias	In the IARC India vaccine trial, the number of doses a participant received was dependent on her time of enrollment onto the study. It is unlikely that time of enrollment would have significantly affected the distribution of relevant confounders between the groups (e.g., their risk of HPV exposure). The 3d group was, on average, slightly poorer, potentially predisposing them to poorer HPV infection outcomes and poorer immunogenicity. However, both the 3d and 1d groups had similar rates of non-vaccine type infection over the full period of FU (excluding types 31, 33, 45).

Studies	Parameter	Summary (including adjustment or consideration by study authors)
	Retention / survival bias	The lack of a control group in the early analyses of the India vaccine trial makes differential rates of LTFU across comparison groups a problem. At m36, 75% of the 1d group remained in FU, compared to 88% of the 3d group. No analysis of whether those LTFU were different with respect to baseline characteristics is available in the published texts. Differential LTFU could decrease the rate of HPV detection in the 1d arm simply because the cervical sample was not available, which therefore biases the VE estimate higher than the true value. However, in the later analysis with FU to 48m, retention rates had become more similar (75% in the 1d group vs. 78% in the 3d group), reducing the risk of survival bias when comparing VE across groups.
	Misclassification	Misclassification of the exposure (the number of vaccine doses received) is unlikely across all analyses as the vaccine was not freely available to trial participants outside of the studies. However, none of the texts mention whether there was any verification of vaccination status at FU visits. All studies used highly sensitive HPV assays and standardized assays for the assessment of IgG. Misclassification of HPV incident or persistent infection is possible if HPV is simply undetectable within the cervix at the time of sampling yet latently infecting the epithelial cells. This is an unavoidable problem given the limitations of HPV sampling techniques and would be non-differential across comparison groups.
	Statistical analysis	The later analysis of the India vaccine trial was improved with the enrollment of an unvaccinated control group, allowing comparison of HPV infection outcomes and controlling for visit attendance. Marriage and sexual activity may have influenced both the sampling time points for HPV infection (6m after first delivery or 18m after marriage) and risk of HPV acquisition (due to exposure), so the control group of unvaccinated married women is necessary to control for confounding by sexual activity.
	Generalizability	The trial recruited generally healthy, HIV-negative young women with few exclusion criteria and were therefore relatively pragmatic and representative of the general population. However, trial participants are, in general, healthier and less heterogenous than the general population.

Abbreviations: CVT, Costa Rica vaccine trial; d, dose; DNA, deoxyribonucleic acid; FU, follow-up; HAV, hepatitis A vaccine; HIV, human immunodeficiency virus; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; IgG, immunoglobulin G; LTFU, loss to follow-up; m, month(s); PATRICIA, PApilloma TRIal against Cancer In young Adults Trial; VE, vaccine efficacy.

Source: Table adapted from (66).

2.3 Non-trial immunogenicity studies of partially vaccinated populations

This section summarizes evidence on the immunogenicity of a single HPV vaccine dose compared to multidose schedules (and compared to natural HPV infection) from observational studies of partially vaccinated populations. Outcomes of interest include HPV vaccine-type binding or neutralizing of antibody seropositivity or levels, antibody avidity, and B- or T-cell responses. Published data that compare cellular or humoral immunogenicity responses after one versus two or three doses of HPV vaccine (in any schedule), or versus no HPV vaccination, were identified through comprehensive literature searches by the authors of this paper and compiled.

In the previous edition of this paper, we reported on seven non-trial observational studies presenting relevant immunogenicity data. Four new studies have been published since the last edition. The 11 articles and their results are summarized below and in [Table 8](#) and [Table 9](#).

2.3.1 Evidence from non-trial immunogenicity studies

2.3.1.1 IMMUNOGENICITY STUDY DESIGNS

The two early immunogenicity studies of single-dose HPV vaccination were conducted in Uganda and Fiji. The Uganda study was a cross-sectional non-inferiority immunogenicity study among 376 adolescent girls (aged 10–11 years at the time of vaccination) who had been vaccinated with the GSK 2vHPV as part of a government-run HPV vaccination demonstration program implemented between October 2008 and October 2009 in one district of the country (101, 102). HPV vaccine was administered by immunization program vaccinators in a three-dose schedule (months 0, 1 and 6), but three-dose completion among girls aged 10 years was only 52% to 60%. This immunogenicity study compared HPV 16/18 binding antibody responses in girls who had received one, two, or three doses according to vaccine registries (though final vaccine status was based on information in vaccination cards, provided by parents).

The Fiji study (103) was a follow-up study of 200 girls aged 15–19 years who had been vaccinated with the Merck 4vHPV vaccine in 2008 and 2009. At that time, all girls aged 9–12 years were eligible to receive the recommended three-dose schedule (0, 2, 6 months); however, as in the Uganda study above, some received only one or two doses due to non-completion of the vaccine schedule. In 2015, girls were recruited into a study designed to compare NAb responses to vaccine-type HPV genotypes among vaccinees who received one, two, or three doses of HPV vaccine, based on Ministry of Health immunization lists. Responses in vaccinated girls were also compared with those from a group of

unvaccinated girls. The study also assessed whether vaccination with different dosing schedules elicited immune memory by administering a challenge dose of GSK 2vHPV to vaccinated girls and measuring subsequent NAb responses.

Two further articles presented additional immunological evaluations of participants in the Fiji study. One (which is new to this edition) described cross-neutralizing antibody responses among the full cohort (104), and the other described cellular immune responses in a small subset of the cohort (105).

Subsequent to the Uganda and Fiji studies, several articles were published on single-dose HPV vaccination evaluations in Canada. The first of these described a small single-group study of girls aged 13–18 years who received a single dose of the Merck 4vHPV between three and eight years prior to enrollment through a school-based national vaccination program (106). As for the immunogenicity studies above, the reason for only receiving a single dose was non-completion of the intended three-dose schedule. Immunization status was determined from regional vaccination registry data and vaccination cards and confirmed with participants and their parents. At the time of entry into the study, the girls were given a boost dose of Merck 9vHPV. The objectives of the study were twofold: to assess persistence of HPV-specific antibodies after a single dose of Merck 4vHPV (using blood samples collected prior to the boost dose of Merck 9vHPV) and to assess the effect of a dose of Merck 9vHPV given several years later (using blood samples collected one month following the boost dose of Merck 9vHPV).

The second Canadian study was a post hoc analysis comparing antibody responses among the girls included in the study above with those from an independent cohort of girls and boys aged 9–10 years who received two doses of the Merck 9vHPV six months apart (107). This independent cohort was from a clinical trial of a two-dose Merck 9vHPV or a mixed GSK 2vHPV / Merck 9vHPV schedule conducted by the same authors (108). Clinical trial participants were eligible for inclusion in this post hoc comparison if they had blood samples available before and one month following their second vaccine dose.

A third analysis by the same research group in Canada (new to this edition) compared antibody responses in (1) girls aged 13–18 years who received a single dose of Merck 4vHPV through the Canadian national program and a single dose of GSK 2vHPV three-to-eight years later through the first intervention study described above, (2) girls and boys aged 9–10 years who received a mixed GSK 2vHPV / Merck 9vHPV vaccination schedule with a six-month interval through the second intervention study described above, and (3) vaccine-naïve girls and boys aged 9–10 years who received a single dose of Merck 9vHPV through the second intervention study described above (109).

Two studies conducted in the United States evaluated single-dose HPV vaccination in alternative populations: one in HIV-infected or exposed girls and boys and the other in older women. The US

Pediatric HIV/AIDS Cohort Study (PHACS) study was a prospective observational cohort study of children who received one, two, or three doses of Merck 4vHPV at an average age of 13 years through a US national vaccination program (110). The study was conducted within the PHACS Adolescent Master Protocol and included children who were either perinatally HIV-infected (PHIV+) or perinatally HIV-exposed but uninfected (PHEU). Non-completion of the intended three-dose schedule led to some participants receiving one or two doses. The study evaluated Merck 4vHPV-type antibody seropositivity and titers approximately three years after the last vaccine dose. Sexually active but non-HPV vaccinated children of the same age as the vaccinated children at the time of enrollment were additionally included as a control group to allow evaluation of natural seroconversion.

The US Department of Defense (DoD) study was a retrospective cohort analysis of women vaccinated at age 17 to 26 years with one, two, or three doses of Merck 4vHPV (70, 111). HPV vaccine was provided through a routine DoD vaccination program, which administers a three-dose HPV vaccination schedule. Thus, again, one- and two-dose recipients were non-completers of the intended three-dose schedule. The study obtained records of vaccinated women using routine data from the Defense Medical Surveillance System, which maintains medical records, immunization records, and demographic data for US military personnel. Women were included if routine serum samples collected within one year prior to vaccination and four to six years post-vaccination were available in the DoD Serum Repository.

The two additional new studies were conducted in the Netherlands (112) and Mongolia (113). The Dutch study compared humoral and cellular immune responses among 890 girls who received one, two, or three doses of GSK 2vHPV through the Dutch national HPV vaccination program (112). A series of cross-sectional surveys (up to 150 girls per survey) were performed yearly from one to seven years post-vaccination in girls vaccinated between 2009 and 2016. Eligible girls were identified through the Dutch vaccination registry. One- and two-dose participants were vaccinated at age 12 years, and three dose participants were vaccinated at age 16 years. At the time of vaccination, the Dutch national program was administering a three-dose schedule, so one- and two-dose recipients were non-completers. A group of unvaccinated girls were included as controls.

The Mongolia study was a retrospective cohort study of single-dose HPV vaccination versus no vaccination among 475 women aged 16–26 years (113). Vaccinated participants received Merck 4vHPV through a pilot vaccination campaign, conducted when the Mongolian Ministry of Health was donated almost 50,000 doses in 2012. The intended schedule was for three doses, but vaccine uptake and schedule completion were very low due to community resistance. The study recruited 118 girls who had received a single vaccine dose in 2018 or 2019 (identified through immunization records), approximately six years prior to the study, plus a group of 357 unvaccinated girls who were

frequency-matched on age. The primary outcome of this study was prevalent HPV 16/18 infection (described in Section 3.4, below). NAb responses were a secondary outcome, measured in a subset of participants.

2.3.1.2 IMMUNOGENICITY ASSESSMENTS

All 11 studies measured binding and/or NAb seropositivity rates for the HPV genotypes targeted by the HPV vaccine administered; and all except the US DoD study measured antibody levels. However, time points evaluated, and methods used varied across studies.

The Uganda, Fiji, and Mongolia studies all collected sera at enrollment. In the Uganda study this was approximately three years after vaccination (101); in the Fiji and Mongolia studies, it was approximately six years after vaccination (103-105, 113). The Fiji study additionally collected sera 28 days after the challenge dose of GSK 2vHPV. The Uganda study tested sera for HPV 16 and 18 antibodies by ELISA, using the same laboratory, assay, and seropositivity cutoffs as those used in the CVT and subsequent studies of the trial cohorts (described above). The first Fiji study measured NAbs against HPV types 6, 11, 16, and 18 using the PBNA. The later Fiji study—which measured cross-neutralizing NAbs against HPV types 31, 33, 45, 52, and 58—used the same assay, as did the Mongolian immunogenicity substudy, which measured NAbs against HPV 16 and 18.

The three Canadian studies used harmonized methods for blood collection and antibody testing (106, 107, 109). Sera were collected before and one month following vaccination with the boost dose of Merck 9vHPV; and Merck 9vHPV vaccine-type antibody titers were measured using multiplex direct IgG ELISA on a Meso Scale Discovery (MSD) platform. The PHACS study collected sera from vaccinated participants at least 20 days after their most recent HPV vaccine dose (110). For control, non-vaccinated participants, sera were collected after sexual debut. Samples were tested for neutralizing IgG to the Merck 4vHPV genotypes using a competitive Luminex immunoassay. HPV 18 antibody titers were additionally measured using an anti-HPV IgG enzyme immunoassay. The Dutch study collected sera at one to seven years post-vaccination and measured HPV 16, 18, 31, 33, 45, 52, and 58 antibody seropositivity and titers, as well as HPV 16 and 18 antibody avidity, using a VLP-based multiplex immunoassay (112).

The DoD study was the only study to use routinely collected, previously stored samples (111). Sera collected within one year prior to vaccination and four to six years post-vaccination were used to test for seropositivity with each of the Merck 4vHPV types by VLP ELISA.

Two studies evaluated cellular immunogenicity outcomes: the Fiji substudy and the Dutch study (105, 112). In the Fiji substudy, peripheral blood mononuclear cells (PBMCs) collected at the same time points as the sera were isolated from whole blood, and cellular responses were evaluated through

interferon-gamma (IFN γ) enzyme-linked immunosorbent spot (ELISpot), Th1/Th2 cytokine multiplex bead array and flow cytometry. In the Dutch study, PBMCs collected at selected serological time points were used to measure memory B-cell responses by B-cell ELISpot, T-cell responses by IFN γ ELISpot, and other stimulated cellular cytokine responses by Th-cytokine multiplex bead array.

2.3.1.3 RESULTS OF NON-TRIAL IMMUNOGENICITY STUDIES

Overview

Most studies were relatively small in size, including approximately 200 to 500 participants. The US DoD study was the largest, with 2,091 participants, though a large proportion (over 60%) of women in this study were excluded from analyses as they were seropositive to vaccine-type HPV genotypes pre-vaccination (111). In some of the studies, most notably the Uganda and Fiji studies, the one-dose group was particularly small (101, 103). However, these studies benefited from analyses demonstrating that dosing groups were largely comparable in terms of baseline characteristics and demographics.

Most studies found very high rates of seropositivity for HPV genotypes protected against by the vaccine type administered, regardless of the number of doses received; and few found a difference in seropositivity rates between participants who received one, two, or three vaccine doses. Most studies found that antibody levels were lower in the single-dose arms compared to the multidose arms. However, where unvaccinated groups were included, antibody levels were higher in study participants who had received a single vaccine dose compared to no vaccination. The Fiji study demonstrated similar cellular immune responses among one-, two-, and three-dose recipients (105), but the Dutch study found a trend for weaker B- and T-cell responses with one dose compared to two or three doses (112).

Further details on the humoral and cellular immunogenicity results for each study are provided below.

Humoral immunogenicity results

The Uganda study enrolled 195 three-dose, 145 two-dose, and 36 one-dose vaccine recipients (101). Participant demographic characteristics were comparable across dose groups. The mean time between last dose and blood collection was 33, 39, and 33 months, respectively, for three-, two-, and one-dose groups. Overall, 99% were HPV 16 and HPV 18 seropositive. HPV 16 antibody GMTs ranged from 230 ELISA units (EUs) / mL in single-dose recipients to 1,607 EU/mL in three-dose recipients. HPV 18 antibody GMTs ranged from 87 EU/mL in one-dose recipients to 296 EU/mL in three-dose recipients. However, in a cross-study comparison, GMTs for one-dose recipients were not lower in the Ugandan girls than in adult women who received one dose in the CVT (HPV 16, 124 EU/mL; HPV 18, 69 EU/mL), in whom efficacy had been demonstrated (69).

Two hundred girls were enrolled in the Fiji study: 66 had received three doses, 60 had received two doses, 40 had received one dose, and 34 were unvaccinated (103). Baseline characteristics did not differ by vaccine group, except for small differences in time since last vaccine dose and in timing of doses one and two in the three- and two-dose groups. Compared with vaccinated groups, unvaccinated participants were older at enrollment, and a larger proportion attended university. At enrollment, six years after initial vaccination, 90% to 100% of girls were seropositive for HPV 6, 93% to 100% for HPV 11, 95% to 100% for HPV 16, and 68% to 88% for HPV 18. GMTs for all Merck 4vHPV types were similar in three- and two-dose recipients. One-dose recipients had significantly lower NAb titers than two- or three-dose recipients. However, among all vaccinated groups, titers were fivefold to thirtyfold higher than in unvaccinated girls. After a boost dose of GSK 2vHPV, NAb titers for HPV 16 and 18 in the one-dose group increased 46- and 84-fold, respectively, and were similar to those observed in the two- and three-dose groups, suggesting that one dose of Merck 4vHPV may be sufficient to prime for immunologic memory to HPV 16 and HPV 18.

In the subsequent Fiji evaluation of cross-neutralizing responses, HPV 31 antibody seropositivity and titers were higher in participants vaccinated with at least a single dose of Merck 4vHPV six years earlier compared to unvaccinated participants, though both measures were significantly lower with one dose compared to three doses (104). There were no differences in antibody seropositivity or titers for other HPV types (HPV 33, 45, or 52) between vaccinated and unvaccinated participants. After vaccination with a boost dose of GSK 2vHPV, seropositivity rates for the five HPV types increased in all groups, with no differences in seropositivity or titers observed in participants who had previously received one, two, or three doses.

Thirty-one girls were included in the first Canadian study (106), and these, along with a subset of 173 girls and boys from an independent vaccine trial, were included in the second study (107). All participants in both studies were seropositive to HPV 6, 11, 16, and 18 after receiving their first vaccine dose, which was given three to eight years ago in the first group and less than six months ago in the second. Titers were significantly higher in the second group compared to the first for HPV 18 but not for the other three types (HPV 6, 11, and 16). Of note, between 58% and 87% of participants in the first group were also seropositive to non-Merck 4vHPV types prior to administration with Merck 9vHPV, with GMTs ranging from 2.0 to 5.2 AU (arbitrary units) / ml. Following vaccination with the second vaccine dose (Merck 9vHPV), all participants in both groups were seropositive for the nine vaccine HPV types. In the first group, GMTs increased 60-to-82-fold for the four types included in both vaccines, indicating that long-term memory is induced after a single dose of Merck 4vHPV.

The most recent Canadian study included the 31 girls above who received a 4v/Merck 9vHPV mixed schedule with a three-to-eight-year interval, 86 boys and girls who received a 4v/Merck 9vHPV

mixed schedule with a six-month interval, and 88 girls and boys who received a single dose of Merck 9vHPV (109). 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.

The US PHACS study included 310 PHIV+ participants and 148 PHEU ones (110). Among the PHIV+, 90 received three doses, 34 received two doses, 154 received one dose, and 32 were unvaccinated. Among PHEU, 11 received three doses, 13 received two doses, 91 received one dose, and 33 were unvaccinated. Overall seropositivity rates for HPV 6, 11, 16, and 18 among PHIV+ who received at least one dose of Merck 4vHPV were 83%, 84%, 90%, and 62%, respectively. Among PHEU, corresponding proportions were 94%, 96%, 99%, and 87%. Seropositivity rates did not vary considerably by number of doses received within either PHIV+ or PHEU groups. For example, among PHIV+ participants, seropositivity to HPV 16 was 87.7% in the one-dose arm and 92.2% in the three-dose arm. Among PHEU participants, seropositivity to HPV 16 was 98.9% in the one-dose arm and 100% in the three-dose arm. Furthermore, seropositivity rates were significantly higher among vaccine recipients, regardless of the number of doses received, compared to unvaccinated participants. Similarly, GMTs for the four Merck 4vHPV types did not differ considerably between three-dose and one-dose recipients and were significantly higher for vaccine recipients than in unvaccinated participants. For example, among the PHIV+, HPV 16 GMTs were 430 milli-Merck units (mMU) / mL in three-dose participants, 519 mMU/mL in one-dose participants, and 19 mMU/mL in unvaccinated participants. Among the PHEU, HPV 16 GMTs were 1,367 mMU/mL in three-dose participants, 1,464 mMU/mL in one-dose participants, and 39 mMU/mL in unvaccinated participants.

Of 2,091 women who received Merck 4vHPV through the US DoD vaccination program and had pre- and post-vaccination serum samples available, 1,260 completed the intended three-dose schedule, 420 received two doses, and 411 received one dose (111). Pre-vaccination, 61.9% of three-dose recipients, 60.5% of two-dose recipients, and 64.5% of one-dose recipients tested positive for at least one of the four HPV types. There was no statistical difference in pre-vaccination seropositivity rates between vaccine dosage arms. Of the participants who were HPV 6, 11, 16, and 18 seronegative pre-vaccination, 99.8% of three-dose recipients, 100% of two-dose recipients, and 100% of single-dose recipients seroconverted to all four HPV types post-vaccination. Antibody titers were not evaluated in the study.

A total of 890 girls were included in the Dutch study; 90 to 150 were included per cross-sectional survey (112). At each time point, the authors aimed to include at least 47 girls per dosage group. At the earliest and latest time points, achieving this number was difficult, particularly for the one- and

two-dose groups. At the three-to-four-year time point, 45 girls were enrolled in the one-dose arm, 52 in the two-dose arm, and 50 in the three-dose arm. At this time, 100% of multidose recipients and 87% of one-dose recipients were seropositive for antibodies to HPV 16/18. Antibody titers were significantly higher with two or three doses compared to one dose. However, HPV 16/18 seropositivity and titers were significantly higher in single-dose participants compared to unvaccinated controls. Data from other time points (albeit with varying numbers per arm) were similar.

The Mongolia immunological substudy included 30 women who received a single dose of HPV vaccine six years earlier and 28 unvaccinated women (113). Women were selected for the substudy based on area of residence: only women residing in the capital city were included for ease of sample processing logistics. Of the vaccinated women, 90% were seropositive for neutralizing antibodies to HPV 16, and 58% for antibodies to HPV 18. Among unvaccinated women, corresponding seropositivity rates were 25% and 10%, respectively. Antibody GMTs were significantly higher among vaccinated compared to unvaccinated women.

Cellular immunogenicity results

Fifty-nine girls were included in the cellular substudy of the Fiji cohort: 15 three-dose participants, 14 two-dose participants, 15 one-dose participants, and 15 unvaccinated participants (105). Flow cytometry was performed for fewer participants (7 per group or fewer) due to limited availability of cells. Baseline characteristics were similar in the substudy cohort compared to the full Fijian cohort, except that the three-dose participants in the substudy cohort were older at the time of first vaccination with Merck 4vHPV and at enrollment into the study. At six years post-Merck 4vHPV vaccination (and pre-GSK 2vHPV vaccination), numbers of HPV 16-specific IFN γ -producing cells were similar among one-, two-, and three-dose participants. Numbers of HPV 18-specific IFN γ -producing cells were lower among two-dose participants (but not one-dose participants) compared to three-dose participants. Post-boost vaccination with GSK 2vHPV, HPV 16- and HPV 18-specific IFN γ -producing cells were similar among participants previously receiving one, two, and three doses of Merck 4vHPV. No significant differences in HPV 16- and HPV 18-specific memory cluster of differentiation 4 (CD4 $^{+}$) cells were observed between the different dosage groups, either pre- or post-GSK 2vHPV administration. Low levels of HPV 16- and HPV 18-specific memory CD8 $^{+}$ cells were observed across all groups at both time points. Levels of a few cytokines released in response to HPV 16 and HPV 18 stimulation (such as IL [interleukin] 2 and IL10) were lower in the one-dose group compared to the three-dose group, but others were similar.

In the Dutch study, cellular responses were measured at one, three, and five/six years post-vaccination. Numbers of HPV-specific memory B cells and IFN γ -producing cells were lower in one-dose recipients compared to two- or three-dose recipients. Differences were not significant, but

numbers of participants per group were low. Notably, there were also no differences in these measures between single-dose recipients and unvaccinated controls. Levels of Th1 and Th2 cytokines released following stimulation of PBMCs with HPV 16 tended to be higher with increasing numbers of doses received. Significantly lower IL5, IL13, IFN γ , and tumor necrosis factor alpha responses were seen in one-dose participants compared to two- and three-dose ones. Stimulation with other HPV types (HPV 18, 31, or 45) produced similar results.

2.3.2 Strengths and weaknesses of non-trial immunogenicity studies

There are several strengths of these observational studies. Some of the studies used the same laboratory assay to assess immune responses as previous clinical HPV vaccine trials, which allowed for comparison to antibody titers reported from clinical trials of adult women receiving single-dose schedules, among whom efficacy had been demonstrated. The Fiji and Mongolia studies measured NAb seropositivity and titers using the same assay at approximately the same time point post-vaccination. NAb GMTs among one-dose participants in the Fiji study were higher than in the Mongolia study, which found that a single dose of HPV vaccine was significantly protective against prevalent HPV 16 and 18 infection compared to no vaccination (see Section 3.4 below). The lack of WHO international standards for HPV 16- and 18-genotype assays until recently meant that earlier immunogenicity studies could not use these standard assays.

Some studies had long follow-up time to accommodate an immunogenicity plateau observed 24 months after initial vaccination. The Canadian study evaluated persistence of HPV-specific antibodies between three and eight years after vaccination with a single dose of Merck 4vHPV.

Where included (e.g., in the Fiji, US PHACS, Dutch, and Mongolia studies), unvaccinated participants had lower antibody titers than single-dose recipients. Furthermore, single-dose recipients from these immunogenicity studies had higher antibody titers than naturally infected women from prior trials of HPV vaccine. The US PHACS study 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. A major strength of the US DoD study was the availability of pre-vaccination serum samples for all study participants, enabling the authors to determine HPV seropositivity status and, thus, numbers of seronegative women who seroconverted after vaccination, according to the number of vaccine doses received.

These observational studies also have a number of limitations. None of the studies was an RCT, and therefore, participants 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, ethnicity, and some socioeconomic and behavioral characteristics. Many

of these data were also available for the US PHACS cohort; however, they were not stratified by number of doses received (only by PHEU versus PHIV+). Data to evaluate comparability across groups were more limited from the Uganda study. While neither the Uganda nor the Fiji study reported data on sexual behavior, 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 study did report data on sexual activity and age at sexual debut, but again, data were not stratified by number of doses received. The US DoD study used routine data obtained from the Defense Medical Surveillance System, so available data on potential confounders, or data that could be used to assess for biases due to differing characteristics between dosage arms, were limited.

The first Canadian study included only a single group of participants, all of whom received a single dose of Merck 4vHPV and were boosted with a dose of Merck 9vHPV. Therefore, no comparisons in immune response can be made with either multidose recipients or unvaccinated individuals within the study. Participants were non-completers of a national three-dose HPV program. In the second Canadian study, results from the single-dose Merck 4vHPV cohort who received a delayed second dose of Merck 9vHPV were compared with those from a cohort of adolescents who received two doses of Merck 9vHPV vaccine. While laboratory methods were harmonized between the two studies, there may be differences in the two cohorts that could lead to bias or confounding.

A key limitation of the Dutch study was that one- and two-dose participants were aged 12 at vaccination, whereas three-dose participants were aged 16 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. A limitation of the Mongolian study is that it did not compare single-dose HPV vaccination to multidose schedules.

Sample sizes were relatively small in most of the immunogenicity studies, especially among single-dose groups, thus limiting the statistical precision of estimates. 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 power. Nevertheless, in a cross-study comparison among girls who received only a single dose in Uganda, GMTs were not lower than those in women who received a single HPV vaccine dose in the CVT, among whom no breakthrough cases have been detected four years after vaccination. While the US PHACS study followed up participants to obtain incidence rates of cervical abnormalities and genital warts, the authors were not able to compare these between dosage arms due to the small numbers of participants in each group. While the overall number of participants in the Dutch study was quite large, numbers per survey were small.

Finally, several studies measured immune responses at only one time point following vaccination, and thus the kinetics of the response over time cannot be evaluated.

2.3.3 Summary of non-trial immunogenicity studies

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 of vaccination 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 one 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 PHACS and DoD studies extended the available evidence to populations infected with or exposed to HIV and to older women, respectively. Interestingly, the PHACS study 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 17–26 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 recipients in the Fiji subcohort six 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 was administered. The Dutch study found a trend for increasing magnitude of memory B-cell and T-cell responses with increasing the dose number. However, as for humoral analyses, the clinical implications of these cellular results are unclear.

Table 8. Summary of non-trial immunogenicity studies

Reference, location	Study design	Study population	Vaccination setting	Vaccination schedule(s) evaluated	Age at vaccination	Sampling	Endpoint(s)	Method(s)
GlaxoSmithKline (GSK) 2vHPV vaccine								
<i>LaMontagne 2014; Uganda (101)</i>	Cross-sectional study of girls with prior HPV vaccination	376 girls aged 13–15 y	Government demonstration program of 3d GSK 2vHPV	3d GSK 2vHPV (n=195) 2d GSK 2vHPV (n=145) 1d GSK 2vHPV (n=36)	10 y	Serum collected at enrollment	HPV 16/18 seropositivity & titers	ELISA; Cutoffs for seropositivity – HPV 16: 8 EU/mL; HPV 18: 7 EU/mL
<i>Pasmans 2019; Netherlands (112)</i>	Repeated cross-sectional surveys of participants with prior HPV vaccination	890 girls aged 13–21 y (n=90 to 150 per survey)	National vaccination program of 3d GSK 2vHPV	3d GSK 2vHPV (n=378) 2d GSK 2vHPV (n=222) 1d GSK 2vHPV (n=239) 0d HPV vaccine (n=51)	1d & 2d participants: 12 y; 3d participants: 16 y	Serum collected in yearly cross-sectional surveys up to 7 y post-vaccination; PBMCs collected at some time points	HPV 16/18/31/33/45/52/58 binding seropositivity & titers & HPV 16/18 avidity; HPV 16/18/31/45 specific memory B-cell and T-cell responses	VLP-based multiplex immunoassay; Cutoffs for seropositivity – HPV 16: 9 LU/mL; HPV 13: 10 LU/mL ELISpot; Multiplex bead array
Merck 4vHPV vaccine								
<i>Hurt 2016; United States (111)</i>	Retrospective cohort routine data study of women with prior HPV vaccination	2,091 women aged 17–26 y	US Department of Defense vaccination program of 3d Merck 4vHPV	3d Merck 4vHPV (n=1,260) 2d Merck 4vHPV (n=420) 1d Merck 4vHPV (n=411)	17–26 y	Serum collected within 1 y prior to first dose and 4–6 y after last dose	HPV 6/11/16/18 seropositivity	ELISA; Cutoffs for seropositivity not stated
<i>Mosckicki 2019; United States (110)</i>	Prospective cohort study of adolescents with prior HPV vaccination, embedded in PHACS cohort	310 PHIV+ & 148 PHEU girls & boys aged 7–16 y at time of entry into PHACS cohort	National vaccination program of 3d Merck 4vHPV	3d Merck 4vHPV (n=101) 2d Merck 4vHPV (n=47) 1d Merck 4vHPV (n=245) 0d HPV vaccine (n=65; sexually active)	Mean: 13 y; IQR: 11–15 y	Serum collected ≥20 days after last vaccine dose; age at sampling: mean = 16 y, IQR = 13–18 y	HPV 6/11/16/18 binding & neutralizing seropositivity & titers	Direct IgG EIA; Cutoffs for seropositivity – HPV 6: 15 mMU/mL; HPV 11: 15 mMU/mL; HPV 16: 7 mMU/mL; HPV 18: 10 mMU/mL cLIA; Cutoffs for seropositivity – HPV 6: 20 mMU/mL; HPV 11: 16 mMU/mL; HPV 16: 20 mMU/mL; HPV 18: 24 mMU/mL
<i>Batmunkh 2020; Mongolia (113)</i>	Retrospective paired cohort study of women with prior HPV vaccination	475 women aged 16–26 y, with 58 in immunogenicity substudy	National vaccination campaign of 3d Merck 4vHPV	1d Merck 4vHPV (n=118) 0d HPV vaccine (n=357)	11–17 y	Serum collected from subset at enrollment ^a	HPV 16/18 neutralizing seropositivity & titers ^a	PBNA; Cutoff for seropositivity – ED50 ≥100 ^a

Reference, location	Study design	Study population	Vaccination setting	Vaccination schedule(s) evaluated	Age at vaccination	Sampling	Endpoint(s)	Method(s)
Mixed vaccination schedule								
<i>Toh 2017; Fiji (103)</i>	Intervention study of girls with prior HPV vaccination who are administered a challenge dose	200 girls aged 15–19 y	Prior vaccine: National vaccination campaign of 3d Merck 4vHPV; Challenge vaccine: Study intervention	Prior to study: 3d Merck 4vHPV (n=66) 2d Merck 4vHPV (n=60) 1d Merck 4vHPV (n=40) 0d HPV vaccine (n=32); Challenge vaccine: 1d GSK 2vHPV (all subjects)	Previous vaccine: 9–12 y; Challenge vaccine: 15–19 y	Serum collected at enrollment & 28 days after challenge dose of GSK 2vHPV	HPV 6/11/16/18 neutralizing seropositivity & titers	PBNA; Cutoff for seropositivity – ED50 ≥100
<i>Toh 2019; Fiji (104)</i>				0d HPV vaccine (n=32); Challenge vaccine: 1d GSK 2vHPV (all subjects)			HPV 31/33/45/52/58 neutralizing seropositivity & titers	PBNA; Cutoff for seropositivity – ED50 ≥25
<i>Toh 2018; Fiji (105)</i>		59 girls aged 15–19 y		As above: 3d (n=15); 2d (n=14); 1d (n=15); 0d (n=15)		PBMCs collected at enrollment & 28 days after challenge dose of GSK 2vHPV	HPV 16–/18–specific IFNy-producing cells (& memory CD4+/ CD8+ cells)	ELISpot; Flow cytometry; Multiplex bead array
<i>Gilca 2019 (1); Canada (106)</i>	Intervention study of girls with prior HPV vaccination who are administered a boost dose	31 girls aged 13–18 y	Prior vaccine: School-based national vaccination program of 3d Merck 4vHPV; Challenge vaccine: Study intervention	Prior to study: 1d Merck 4vHPV (n=31); Challenge vaccine: 1d Merck 9vHPV (all subjects)	Previous vaccine: 9–14 y; Challenge vaccine: 13–18 y	Serum collected before & one month after 2 nd vaccine dose	HPV 6/11/16/18/31/33/45/52/58 seropositivity & titers	Multiplex direct IgG ELISA on MSD platform; Cutoffs for seropositivity – HPV 6: 0.1 AU/mL ; HPV 11: 0.1 AU/mL HPV 16: 0.5 AU/mL; HPV 18: 0.4 AU/mL
<i>Gilca 2019 (2); Canada (107)</i>	Post hoc comparison of two HPV-vaccinated groups	Group 1: As above, n=31; Group 2: 173 girls & boys aged 9–10 y	Group 1: As above Group 2: Prior intervention study of 2d Merck 9vHPV	Group 1: 1d Merck 4vHPV & 1d Merck 9vHPV 3–8 y later (n=31) Group 2: 2d Merck 9vHPV (n=173)	Group 1: As above; Group 2: 9–10 y			
<i>Sauvageau 2020; Canada (109)</i>	Post hoc comparison of two HPV-vaccinated groups	Group 1: As above, n=31; Groups 2 & 3: 174 girls & boys aged 9–10 y	Group 1: As above Groups 2 & 3: Prior intervention study of 2d Merck 9vHPV or mixed 2v/Merck 9vHPV schedule	Group 1: 1d Merck 4vHPV & 1d Merck 9vHPV 3–8 y later (n=31) Group 2: 1d GSK 2vHPV & 1d Merck 9vHPV 6 m later (n=86) Group 3: 1d Merck 9vHPV (n=88)	Group 1: As above; Groups 2 & 3: 9–10 y			

Abbreviations: 2vHPV, bivalent HPV [vaccine]; 4vHPV, quadrivalent HPV [vaccine]; AU, arbitrary unit; CD4/8, cluster of differentiation 4 or 8; cLIA, competitive Luminex immunoassay; d, dose; ED50, effective dose for 50% of the population; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immunosorbent spot; EU, ELISA unit; HPV, human papillomavirus; IFNy, interferon gamma; IgG: immunoglobulin G; IQR, interquartile range; mMU, milli-Merck unit ; MSD, Meso Scale Discovery; PBMC, peripheral blood mononuclear cell; PBNA, pseudovirion-based neutralization assay; PHACS, Pediatric HIV/AIDS Cohort Study; PHEU, perinatally HIV-exposed but uninfected; PHIV+, perinatally HIV-infected; VLP, virus-like particle; y, years.

^a Information provided for the immunogenicity subset only. Details of effectiveness evaluations are presented in Section 3.4.

Table 9. Summarized HPV 16/18 seropositivity and antibody level results from non-trial immunogenicity studies

Reference	Antibody response measured	Time since last vaccine dose	HPV type	# Seropositive / total (%)				GM titers (95% CI)			
				3 doses	2 doses	1 dose	0 dose	3 doses	2 doses	1 dose	0 dose
GlaxoSmithKline 2vHPV											
<i>LaMontagne 2014 (101)</i>	Binding	Mean (IQR) – 3d group: 38m (29–43 m) 2d group: 39m (29–49 m) 1d group: 33m (17–48 m)	HPV 16	Individual results not provided; 99.25% of all participants seroconverted				1,607.92 EU/mL (1,381.78–1,871.07)	808.38 EU/mL (631.86–1,034.22)	229.86 EU/mL (139.27–379.38)	NA
			HPV 18					395.51 EU/mL (331.15–472.37)	270.21 EU/mL (213.15–342.55)	86.87 EU/mL (54.98–137.23)	NA
<i>Pasmans 2019^a (112)</i>	Binding	3–4 y	HPV 16	50 / 50 (100%)	52 / 52 (100%)	43 / 45 (95.6%)	1 / 51 (2.0%)	2155.0 LU/mL (1764.0–2631.0)	1523.0 LU/mL (1177–1971)	148.7 LU/mL (93.9–235.2)	0.7 LU/mL (0.5–1.0)
			HPV 18	50 / 50 (100%)	52 / 52 (100%)	39 / 45 (86.7%)	1 / 51 (2.0%)	668.5 LU/mL (498.6–896.4)	676.0 LU/mL (495.6–922.0)	83.0 LU/mL (51.5–133.8)	1.2 LU/mL (0.9–1.6)
Merck 4vHPV											
<i>Hurt 2016^b (111)</i>	Binding	4–6 y	HPV 16	917 / 928 (99%)	294 / 303 (97%)	237 / 264 (90%)	596 / 2,091 (29%)	NA	NA	NA	NA
			HPV 18	839 / 1,054 (80%)	287 / 354 (81%)	291 / 352 (83%)	331 / 2,091 (16%)	NA	NA	NA	NA
<i>Gilca 2019^c (106)</i>	Binding	Mean (IQR) – 65.3m (36–96 m)	HPV 16	NA	NA	31 / 31 (100%)	NA	NA	NA	20.1 AU/mL (12.0–33.7)	NA
			HPV 18	NA	NA	31 / 31 (100%)	NA	NA	NA	6.3 AU/mL (3.8–10.2)	NA
<i>Toh 2017^d (103)</i>	Neutralizing	Median (IQR) – 3d group: 5.8y (5.7–5.8 y) 2d group: 5.8y (5.4–6.3 y) 1d group: 6.3y (6.3–6.3 y)	HPV 16	66 / 66 (100%)	60 / 60 (100%)	38 / 40 (95%)	2 / 32 (6%)	F: 2,095 (1,461–3,004) I: 5,971 (3,942–9,046)	F: 2,030 (1,405–2,934) I: 5,655 (3,865–8,273)	F: 1,359 (536–3,447) I: 1,018 (572.4–1,811.0)	F: 54.84 (44.98–66.87) I: 54.25 (45.64–64.49)
			HPV 18	58 / 66 (88%)	54 / 60 (90%)	27 / 40 (68%)	1 / 32 (3%)	F: 392.4 (248.3–620.0) I: 1,106 (687.9–1,777)	F: 358.9 (223.1–577.5) I: 1,104 (701.1–1,738.0)	F: 384 (174–847.5) I: 1,88.3 (102.3–345.1)	F: 52.36 (47.42–57.82) I: 50 (50–50)
<i>Moscicki 2019^e (110)</i>	Neutralizing	Mean (IQR) – 2.9y (18–4.1y)	HPV 16	94 / 101 (93%)	44 / 47 (94%)	225 / 245 (92%)	14 / 65 (22%)	PHIV+: 430 mMU/mL PHEU: 1,367 mMU/mL	PHIV+: 497 mMU/mL PHEU: 2,129 mMU/mL	PHIV+: 519 mMU/mL PHEU: 1,464 mMU/mL	PHIV+: 19 mMU/mL PHEU: 39 mMU/mL
			HPV 18	64 / 101 (63%)	33 / 47 (70%)	175 / 245 (71%)	11 / 65 (17%)	PHIV+: 57 mMU/mL PHEU: 142 mMU/mL	PHIV+: 71 mMU/mL PHEU: 245 mMU/mL	PHIV+: 67 mMU/mL PHEU: 165 mMU/mL	PHIV+: 16 mMU/mL PHEU: 23 mMU/mL
<i>Batmunkh 2020 (113)</i>	Neutralizing	6y	HPV 16	NA	NA	27 / 30 (90%)	7 / 28 (25%)	NA	NA	470.2 (272.2–812.3)	82.0 (56.2–119.8)
			HPV 18	NA	NA	17 / 30 (58%)	3 / 28 (10%)	NA	NA	128.9 (86.5–192.2)	56.6 (48.0–66.7)

Abbreviations: 2vHPV, bivalent HPV [vaccine]; 4vHPV, quadrivalent HPV [vaccine]; CI, confidence interval; d, dose; EU, ELISA [enzyme-linked immunosorbent assay] unit; F, indigenous Fijians; GM, geometric mean; HPV, human papillomavirus; I, Fijians of Indian descent; IQR, interquartile range; m, months; mMU, milli-Merck unit; NA, not applicable; PHIV+: perinatally HIV-infected; PHEU: perinatally HIV-exposed but uninfected; y, years.

- ^a The three-to-four-year time point was selected for presentation here because antibody levels are expected to have reached plateau levels, and numbers of participants per survey are reduced at later time points. Results from this time point are representative of those seen at other time points. Data in parentheses for this study are the ranges, not the 95% CIs.
- ^b Seropositivity results shown for "0 dose" are pre-vaccination results for the vaccinated cohort in the Hurt et al. study (111). Seropositivity results for 1-, 2-, and 3-dose recipients are shown for participants who were seronegative to the corresponding HPV type pre-vaccination.
- ^c Results are shown for the intervention study of 31 girls with prior single-dose HPV vaccination (106). Results shown are those measured prior to the boost dose of Merck 9vHPV.
- ^d Results are shown only for Toh et al. 2017, which provides humoral immunogenicity results (103). Humoral immunogenicity results shown are those measured prior to the challenge dose of GSK 2vHPV. Neutralizing titers (ED50, or effective dose for 50% of the population) are shown for two ethnicity groups: indigenous Fijians (F) and Fijians of Indian descent (I). Results are not shown for Toh et al. 2018, which provides cellular immunogenicity results (105).
- ^e Antibody titer data are shown separately for PHIV+ and PHEU participants; 95% CIs are not provided in the publication (110).

2.4 Post-licensure vaccine effectiveness evaluations and other observational data

This section summarizes evidence on the effectiveness by number of doses from post-licensure observational studies of HPV vaccines. Outcomes of interest include effectiveness against HPV infection (genotype-specific prevalence, incidence, and/or persistence) or clinical outcomes (e.g., AGW, CIN).

Evidence is derived from a systematic review—conducted initially in 2017, published in 2018 (114), and updated twice subsequently (updates unpublished)—aimed at evaluating the published literature on single-dose HPV vaccination from post-licensure observational studies (66). This section summarizes and includes excerpts from the published systematic review (114), combined with updates, on evidence of the effectiveness of HPV vaccination by number of doses from 32 eligible articles (23 included in the previous edition of this paper, and a further 9 published since then).

2.4.1 Systematic review of evidence on single-dose HPV vaccination from non-trial observational studies

2.4.1.1 STUDY SELECTION

Studies were eligible if they fulfilled the following inclusion criteria: (1) reported effectiveness of HPV vaccination (GSK 2vHPV or Merck 4vHPV) on vaccine-type HPV infections, AGW, or cervical abnormalities (based on cytological or histopathological results) or (2) assessed effectiveness of HPV vaccination by the number of doses received (one, two, or three). Studies were excluded if vaccine was administered as part of an RCT (e.g., post hoc evaluations of clinical trials).

Through the original systematic review (comprising the period from January 2007 to June 2017) and two subsequent updates (extending first from June 2017 to March 2019 and then from March 2019 to August 2020), Medline and EMBASE databases were searched for studies published between January 1, 2007, and August 10, 2020, using a combination of MeSH terms, titles, or abstract words, without restriction on the language of publications. These included:

- *"papillomavirus vaccines," "HPV vaccine," "HPV vaccination," "papillomavirus vaccine," or "papillomavirus vaccination";*

- *"program evaluation," "immunization programs," "population surveillance," "sentinel surveillance," "incidence," "prevalence," "rate," "rates," "effectiveness," or "doses"; and*
- *"papillomavirus infections," "HPV," "uterine cervical neoplasms," "cervical intraepithelial neoplasia," "HPV related diseases," "condylomata acuminata," or "genital warts."*

The selection of eligible articles was performed independently by two authors first on title and abstract and second on the full-text article (full authorship in "Acknowledgments" section).

2.4.1.2 DATA EXTRACTION

Two authors independently extracted the main study characteristics and outcomes using standardized forms. One author resolved any discrepancy between extractions. The main study characteristics were 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 (procedure used to assign the number of doses and adjust for potential confounders). Information was also collected on use of buffer periods (lag time between vaccination and counting of outcomes). Buffer periods delay the case counting to try to exclude conditions caused by a prevalent infection at the time of vaccination.

Sources of bias in post-licensure studies examining the effectiveness by number of doses include the following: (1) differences in the characteristics and age at vaccination between groups vaccinated with different number of doses; (2) likelihood of prevalent infection at the time of vaccination; and (3) interval between the first and second dose of the HPV vaccine among two-dose vaccine recipients. Since one of the aims of the systematic review was to discuss the limitations of these studies, no studies were excluded on the basis of the methodological quality.

The main outcome of the review was effectiveness of HPV vaccination, comparing the incidence or prevalence of HPV-related endpoints between individuals vaccinated with different numbers of doses (three vs none, two vs none, one vs none, three vs two, three vs one, and two vs one) of the Merck 4vHPV or GSK 2vHPV vaccine. Because eligible studies used different buffer periods or age groups at vaccination and at outcome assessment, it was not possible to pool results from the studies.

2.4.1.3 RESULTS

Overview

The first literature search identified 3,787 articles, from which 26 full articles were assessed. After reading full texts, 12 articles were excluded, leaving 14 (29, 115-127) (**Figure 5**). These publications were published between January 2013 and June 2017 and included studies from Australia (3), Scotland (3), United States (2), Sweden (2), and 1 each from Belgium, Canada, Denmark, and Spain (**Table 10**). The second literature search identified an additional 1,626 articles, from which 50 full articles were assessed. After reading full texts, 41 articles were excluded, leaving 9 new papers (128-136) (**Figure 6**). These included studies from Scotland (2), United States (4), Canada (1), Denmark/Sweden (1), and Denmark (1). The third literature search identified an additional 1,152 articles, from which 48 full articles were assessed. After reading full texts, 39 articles were excluded, leaving 9 new papers (113, 137-144) (**Figure 7**). These included studies from United States (5), Australia (1), Mongolia (1), New Zealand (1), and Scotland (1). The three literature searches identified a total of 32 eligible articles. All evaluations were conducted within the context of a recommended three-dose schedule of either the GSK 2vHPV or Merck 4vHPV vaccine.

Overall, the articles included analyses of effectiveness for prevention of HPV infection (8 articles), AGW (9 articles), or cervical cytological or histological abnormalities (15 articles) (**Table 11**). All investigators attempted to control for or stratify by potentially important variables, such as age at vaccination. However, there were few other variables available in many studies (**Table 10**). Seven studies also evaluated the impact of buffer periods for case counting, and 10 studies evaluated different intervals between doses for two-dose vaccine recipients.

HPV prevalence

The last systematic review included three studies from Scotland that reported vaccine effectiveness for reduction of prevalent vaccine-type infection in women, conducted in the context of a three-dose GSK 2vHPV vaccination program, and one study from the United States that reported vaccine effectiveness in men, conducted in the context of a three-dose Merck 4vHPV vaccination (115, 116, 128, 129). In this updated systematic review, four additional studies were identified: three from the United States and one from Mongolia; three among women and one among men; and all with 4vHPV (113, 137, 140, 141).

The two new studies among women in the United States found similar effectiveness with three-, two-, and one-dose schedules in all or some analyses (137, 141). One study evaluated HPV prevalence on discarded specimens from women screened for CC and used provider-verified vaccination records. Among women aged 18 years or younger with the first vaccine dose, the adjusted PRs were similar for three doses (0.08 [95% CI 0.04–0.15]), two doses (0.07 [95% CI 0.01–0.47]), and one dose (0.08

[95% CI 0.01–0.54]). The Mongolian study included women who were part of a pilot Merck 4vHPV vaccination campaign, conducted by the Mongolian Ministry of Health (113). The intended schedule was for three doses, but vaccine uptake and schedule completion were low. The study included 118 girls who received only one vaccine dose (identified through immunization records), approximately six years after vaccination, plus a group of 357 unvaccinated girls, frequency-matched on age. The adjusted PR was 0.08 (95% [95% CI 0.01–0.56]).

The study among men in the United States found no effectiveness with at least a single dose and no difference in prevalence by number of doses, similar to the report from the same study in our last review (129, 140). Of note, the more recent report included more men, but the number of vaccinated men was still small in both, and at least 48% had initiated sexual activity at the same age or before being vaccinated.

The three studies among women identified previously were all from Scotland. The first found statistically significant effectiveness for three doses but not for two doses or one (115). The analysis was also stratified by age at vaccination; results were similar, with effectiveness significant only for three doses. In the second study, the authors overselected women who were partially vaccinated (116). Statistically significant effectiveness was found for three doses, two doses, and one dose. There was no formal comparison of effectiveness of three doses versus fewer doses in either study; CIs for the effectiveness estimates of three-, two-, and one-dose schedules overlapped. The additional study identified from Scotland used the same surveillance as the first two but included data through 2015 (128). Statistically significant effectiveness was found for three and two doses but not for one dose.

AGW

We identified no new studies of AGW outcomes beyond the nine in the last systematic review. The nine studies of AGW identified previously 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, or SES (**Table 10**). 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 two months. Three of the nine studies also included assessment of different buffer periods (117, 119, 130), and five included assessment of different intervals between doses in two-dose vaccine recipients (29, 119, 121, 130, 131).

Of the nine studies, seven included a comparison of three-, two-, and one-dose vaccination with no vaccination. All seven found the highest point estimate of effectiveness with three doses, and six found lower point estimates but significant effectiveness with two doses. Five of the seven studies found significant effectiveness with one dose (29, 117, 120, 130, 131). 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 (29, 117, 119, 121, 130, 131). Three studies examined different buffer periods (117, 119, 121); a longer buffer period decreased differences in effectiveness between three and two doses in one study (117). In the five studies that explored the interval between doses in two-dose vaccine recipients (29, 119, 121, 130, 131), two found that a longer interval changed effectiveness estimates or resulted in no difference between three and two doses (29, 130).

All five studies that stratified by age at vaccination found higher point estimates of vaccine effectiveness with younger age at vaccination, although the differences were not all formally tested (29, 117, 121, 131, 132). 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 (120). One study found similar point estimates of effectiveness with one, two, and three doses among those vaccinated at age 15–19 years and no significant difference in effectiveness between one and three doses (131).

Cervical cytological and histological abnormalities

The last systematic review included 10 studies that evaluated vaccine effectiveness for prevention of cervical cytological or histological abnormalities, including 8 for the Merck 4vHPV vaccine and 2 for the GSK 2vHPV vaccine (122-127, 133-136). In this updated systematic review, 5 additional studies were included (4 for Merck 4vHPV and 1 for GSK 2vHPV) (138, 139, 142-144) (Table 10). Overall, the 15 studies included data from seven different countries.

Among the 15 studies, all found effectiveness for three doses, 5 found some effectiveness with two doses (123, 136, 138, 143, 144), and 6 found effectiveness with one dose among some age groups or in analyses with longer buffer periods (123, 124, 136, 138, 143, 144). Most two-dose vaccine recipients received two doses at a one- or two-month interval. Four studies examined intervals between two doses: three found no impact on the effectiveness estimate (124, 143, 144), and one found that longer intervals decreased the difference between two and three doses in those vaccinated at age 16 years or younger (135).

Nine studies that stratified by age at vaccination found higher vaccine effectiveness point estimates with younger age at vaccination, although the differences were not all formally tested (123-125, 133, 135, 139, 142-144). In six studies that evaluated effectiveness by number of doses stratified by age at vaccination, differences by number of doses remained in four (123-125, 139). One study found similar point estimates by number of doses when stratifying by age at vaccination but significant effectiveness only for three doses (135).

Three studies that were limited to those vaccinated at younger ages, or that were able to stratify by age at vaccination, found similar effectiveness for one, two, and three doses in some age-at-

vaccination groups (136, 143, 144). These studies, published in 2019 and 2020 (including two identified in the most recent search), 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 those unvaccinated, adjusted incident rate ratios were similar for three, two, and one doses. The study from Australia was a retrospective cohort study using linked regional data registries. 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]).

Two other studies of cervical precancer outcomes identified in the most recent search did not find effectiveness with a single dose, and one study found one-dose effectiveness that was lower than for three doses (138, 139, 142). The New Zealand study stratified by age at vaccination; among those aged younger than 18 years with the first dose, the incident rate ratio differed by number of doses (three doses, 0.66 [95% CI 0.60–0.72]; two doses, 0.81 [95% CI 0.63–1.03]; and one dose, 1.1 [95% CI 0.85–1.45]) (139). The Scotland study found no effectiveness with two doses or one; due to high compliance with the complete vaccination series, the authors were able to stratify by age at vaccination only for three-dose vaccine recipients (142). The study from the United States used a test-negative design to determine vaccine effectiveness for prevention of HPV 16/18 CIN2+. The analysis was not stratified by age at vaccination; the adjusted odds ratio for three-, two-, and one-dose schedules were 0.26 (95% CI 0.20–0.35), 0.45 (95% CI 0.30–0.69), and 0.53 (95% CI 0.37–0.76), respectively (138).

2.4.2 Strengths and weaknesses of data from non-trial 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. The following include important weaknesses of the available post-licensure studies and caveats that should be considered when interpreting the findings:

- The 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. Most studies included girls who were vaccinated beyond the routine target age as part of catch-up vaccination programs. In several studies, fewer-than-three-dose vaccine recipients were older than three-dose vaccine recipients at the time of vaccination, had

lower SES, and/or had indicators of earlier sexual exposure. Because of these differences, girls who received fewer doses were likely to be at higher risk of incident HPV infection, as well as presence or history of prevalent HPV infection, which biases results toward a greater effectiveness of three doses compared to one or two doses. Most studies adjusted analyses for some risk factors; however, it is highly likely that residual confounding remained.

- In most retrospective studies, it is impossible 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 a lower vaccine effectiveness of less than three doses. Some researchers used buffer periods in the analyses, which delay case counting to exclude conditions caused by a prevalent infection. The importance of buffer periods might differ by the condition evaluated. Longer buffer periods might be more helpful for evaluation of vaccine effectiveness against cervical high-grade histological abnormalities than AGW, since the former takes more time to develop after infection (145). In addition, buffer periods could be of greater importance at an older age at vaccination compared to those of a younger age who are more likely to be HPV negative at vaccination. A disadvantage of buffer periods in effectiveness studies is that they reduce the number of person-years with one or two doses, resulting in low statistical power.
- Since all post-licensure studies published to date were conducted in settings of a national three-dose recommendation, most individuals vaccinated with two doses had received doses at a 0- 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 six months (13, 146, 147). The longer interval is thought to allow maturation of B cells and the second vaccination to act as a booster dose. Results of the immunogenicity studies led to the recommendation for a two-dose schedule administered at 0 and 6–12 months for females aged 9–14 years at the time of their first dose (12, 148).

Although the number of girls vaccinated with two doses separated by at least six months was small in the studies identified in the review, ten studies evaluated the interval between doses (29, 119, 121, 124, 125, 130, 131, 135, 143, 144). Three of five studies evaluating AGW outcomes (117, 119, 130), and one of three studies evaluating cervical outcomes (135) found that increasing the interval increased effectiveness estimates. It is possible that the finding of higher effectiveness with a longer interval between two doses in these observational studies is the result of the longer interval acting as a buffer period and not related to the spacing between doses. If so, the inconsistent findings by interval between doses could be due to differing importance of buffer periods for the endpoints and age groups evaluated.

- The accuracy of vaccine history is important for vaccine effectiveness studies. Most studies included in this review were conducted in countries with national vaccine registries. However, underreporting of vaccinations to registries can occur (123, 124). In studies using claims or insurance data, vaccination history could be incomplete if girls moved or changed insurers during the vaccination series. Incomplete vaccination histories could lead to overestimating effectiveness of fewer than three doses.

2.4.3 Summary of non-trial observational studies

In this systematic review of 32 studies of HPV vaccine effectiveness by number of doses, the 29 studies that evaluated three doses all found significant effectiveness, except 2 small studies among males (129, 140); 17 of 28 studies found effectiveness for two doses (116-118, 120, 122-125, 128, 130, 131, 136-138, 141, 143, 144). In 16 of 30 studies, significant effectiveness was observed for a

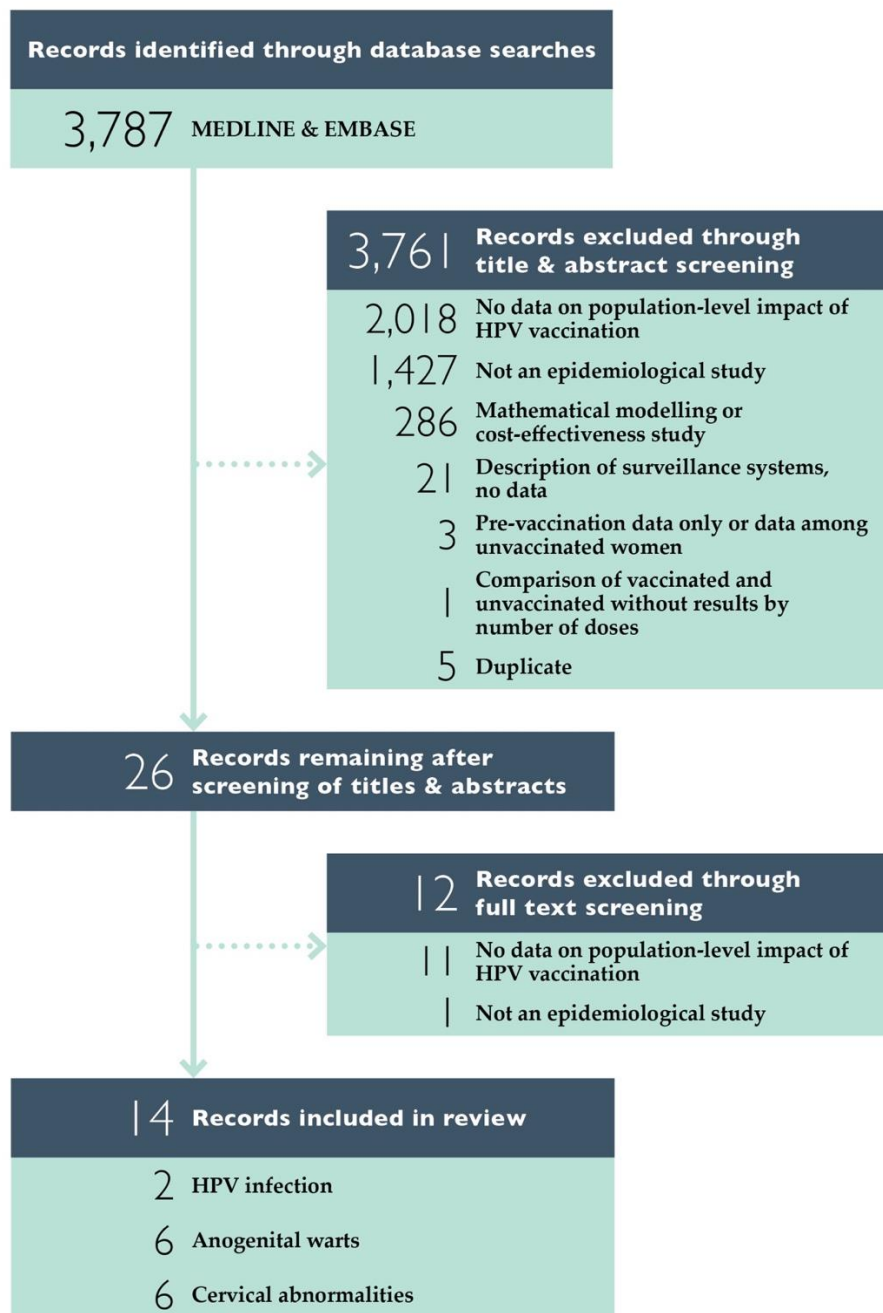
single dose in some or all analyses (29, 113, 116, 117, 120, 122, 124, 128, 130, 131, 136-138, 141, 143, 144). Few studies directly compared three-, two-, and one-dose schedules, and some effectiveness estimates had wide CIs due to the small number of outcomes in one- and two-dose vaccine recipients.

Although most studies found the highest point estimate of effectiveness with three doses, the variation in effectiveness by number of doses was diminished or eliminated in studies when the analyses were stratified by age at vaccination. Furthermore, a few studies that included only persons who received vaccine at a younger age found small or no differences by number of doses. One study reported high effectiveness after one dose but did not include analyses of three or two doses (113); the authors previously reported effectiveness among three-dose recipients (PR=0.25), but there was no formal comparison between doses (149).

There were generally consistent findings among studies that used buffer periods. With longer buffer periods, five of seven studies found higher effectiveness and a decrease in the differences by number of doses (117, 119, 123, 124, 130, 138, 143). Findings related to interval between two doses were less consistent, as noted above: four of eight reported higher two-dose effectiveness with increasing intervals (117, 121, 130, 144). There were also consistent findings among studies that presented results stratified by age at vaccination, with higher effectiveness estimates found with younger age at vaccination, although the differences were not all formally tested.

Important findings for effectiveness by number of doses emerged from some of the recent studies identified that 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 (120), these studies found high effectiveness with one dose or similar effectiveness for one, two, and three doses (131, 136, 137, 143, 144). 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.

Figure 5. Non-trial observational studies systematic review flow diagram (January 2007 to June 2017)



Source: Figure adapted from (114).

Figure 6. Non-trial observational studies systematic review flow diagram, 2019 update (June 2017 to March 2019)

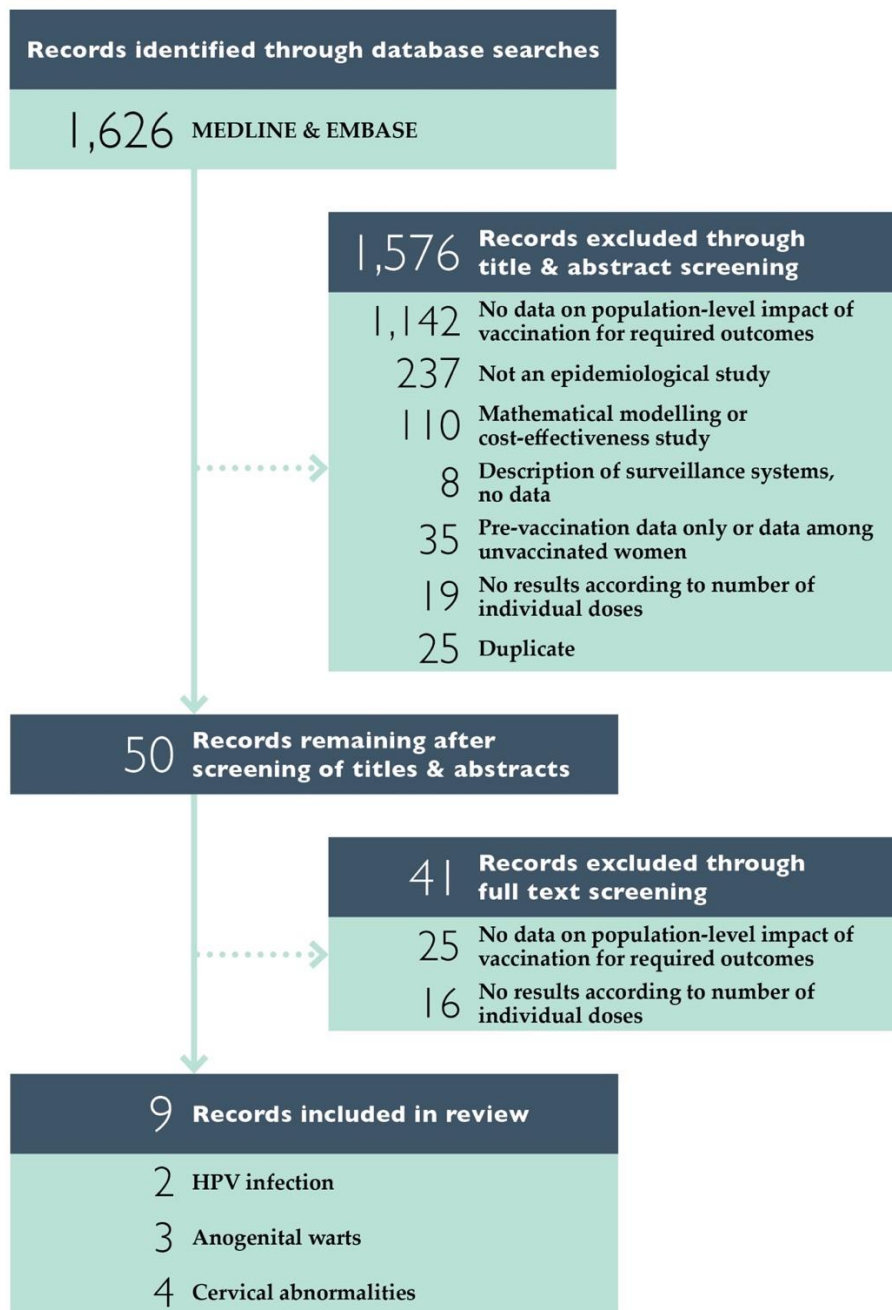


Figure 7. Non-trial observational studies systematic review flow diagram, 2020 update (March 2019 to August 2020)

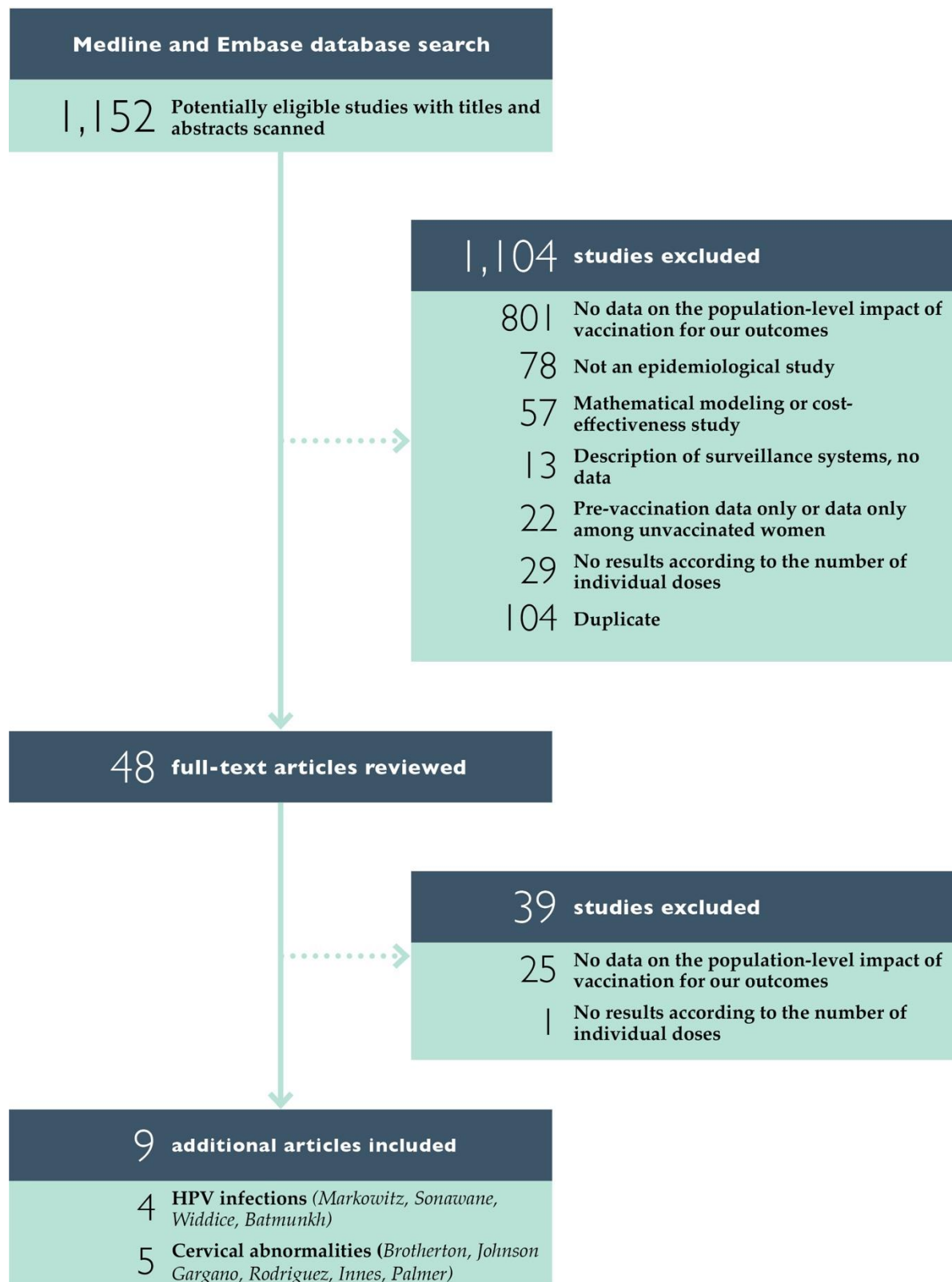


Table 10. Characteristics of studies that evaluated HPV vaccine effectiveness by number of doses

References	Country	Study Design	Study population age (years) at		Vaccination	Case definition	Statistical analyses		
			vaccination	out-come	N by dose number		Assignment of dose number	Buffer periods ^a (months)	Adjustment or stratification
Vaccine Type HPV Prevalence									
Quadrivalent vaccine									
<i>Chandler 2018</i>	United States	Cross-sectional study using self-reported data - men	NA	14–26	0: 82 1: NA 2: NA 3: NA	HPV 6,11,16, or 18 DNA positivity in self-collected penile and perianal/anal swabs ^b	Final status	0	None
<i>Widdice 2019</i>	United States	Cross-sectional study using self-reported data - men	Mean: 16.2 wave 1; 15.1 wave 2	13–26	0: 471 1: 58 2: 37 3: 143	HPV 6, 11, 16, or 18 DNA positivity in genital and perianal/anal swabs ^b	Final status	0	Age at vaccination, sexual initiation before or after vaccination
<i>Sonawane 2019</i>	United States	Cross-sectional study of a nationally representative sample	NA	18–26	0: 1,004 1: 106 2: 126 3: 384	HPV 6, 11, 16, or 18 DNA positivity in self-collected cervicovaginal samples ^b	Final status	0	Age, race/ethnicity, age at sexual debut, lifetime number of male sexual partners
<i>Markowitz 2020</i>	United States	Cross-sectional study of women enrolled in an integrated health-care delivery system	9–26	20–29	0: 1,052 1: 303 2: 304 3: 2,610	HPV 6, 11, 16, or 18 DNA positivity in liquid-based cytology samples ^b	Final status	1	Age at vaccination, screening year, race/ethnicity, age at screening
<i>Batmunkh 2020</i>	Mongolia	Cross-sectional study of women	11–17	16–26	0: 357 1: 118	HPV 16, 18 DNA positivity in self-collected swabs ^c	Final status	0	Age at assessment, sexual behavior, education, income, employment status, tobacco and alcohol use, pregnancy
Bivalent vaccine									
<i>Kavanagh 2014</i>	Scotland	Cross-sectional study using screening registry data	15–17	20–21	0: 3,418 1: 55 2: 106 3: 1,100	HPV 16 or 18 DNA positivity in liquid-based cytology samples ^d	Final status	0	Birth year cohort, deprivation score
<i>Cuschieri 2016</i>	Scotland	Cross-sectional study using screening registry data with additional sampling of those with <3 doses	15–17	20–21	0: 3,619 1: 177 2: 300 3: 1,853	HPV 16 or 18 DNA positivity in liquid-based cytology samples ^e	Final status	0	Birth year cohort, deprivation score, age at first dose
<i>Kavanagh 2017</i>	Scotland	Cross-sectional study using screening registry data	12–18+	20–21	0: 4,008 1: 223 2: 391 3: 3,962	HPV 16 or 18 DNA positivity in liquid-based cytology samples ^e	Final status	0	Age at vaccination, birth year cohort, deprivation score

Anogenital Warts									
Quadrivalent vaccine									
<i>Herweijer 2014</i>	Sweden	Retrospective cohort study using population-based health registries	10–19	10–24	0: 1,045,157 1: 115,197 2: 107,338 3: 89,836	First observed diagnosis: ICD-10 code A63.0 or podophyllotoxin/ imiquimod prescription	Time-dependent Final status	0 to 12	Age at first vaccination, age at outcome, parental education
<i>Blomberg 2015</i>	Denmark	Retrospective cohort study using population-based health national registries	12–27	12–27	0: 188,956 1: 55,666 2: 93,519 3: 212,549	First diagnosis: ICD-10 code A63.0 or podophyllotoxin prescription	Time- dependent	1	Attained age, age at vaccination, maternal education disposable income, calendar year
<i>Dominiak-Felden 2015</i>	Belgium	Retrospective cohort study using sick-fund/ insurance reimbursement database	10–21	16–23	0: 63,180 1: 4,020 2: 3,587 3: 35,792	First prescription of imiquimod and reimbursement	Time- dependent	1	Age at first dose
<i>Perkins 2017</i>	United States	Retrospective cohort study using commercial claims database	9–25	9–25	0: 201,933 1: 30,438 2: 36,583 3: 118,962	ICD-9 and CPT codes and prescriptions ^f	Final status	0, 12	Age, regions, SES indicators, calendar year, differential observation periods
<i>Navarro-Illana 2017</i>	Spain	Retrospective cohort study using national registries	14	14–19	0: NA ^g 1: NA 2: NA 3: NA	First diagnosis of ICD-9-CM code 078.11	Time- dependent	0	Age, calendar year, health department
<i>Lamb 2017</i>	Sweden	Retrospective cohort study using national registries	10–19	10–27	2: 79,042 3: 185,456	First diagnosis of ICD-10 code A63.0 or podophyllotoxin / imiquimod prescription	Time- dependent	0	Age at outcome, time between doses
<i>Hariri 2017</i>	United States	Retrospective cohort study in integrated health-care delivery systems	16–17 mean	11–28	0: 31,563 1: 5,864 2: 5,459 3: 21,631	ICD-9 code 078.10, 078.11, 078.19), specialty of diagnosing provider, and STI tests ordered	Final status	6 from last dose; 12 from first dose	Race/ethnicity, health plan, age at enrollment in health plan, age at beginning of study period, evidence of sexual activity (as defined by composite measure), age at first evidence of sexual activity, age at first dose, continuous enrollment indicator, months enrolled in health plan, Medicaid enrollment
<i>Zeybek 2018</i>	United States	Matched retrospective cohort study using health insurance claims databases (males and females)	9–26	9–31	0: 286,963 1: 54,280 2: 55,632 3: 177,051	ICD-9-CM or 10 code 078.11 or A63.0	Final status	3	Age group, sex, region of residence, history of STDs, enrollment history.
<i>Willows 2018</i>	Canada	Matched retrospective cohort study using linked vaccine registry and claims and population-based databases	9–26	10–33	0: 94,327 1: 3,521 2: 6,666 3: 21,277	ICD-9-CM or 10 code 078.11 or A63.0 and related procedure code	Final status	0	Age at vaccination, place of residence, area-level income, birth date, previous hospitalizations and physician visits, history of chronic diseases, sexual activity (based on evidence using a composite measure)

Cervical Abnormalities									
Quadrivalent vaccine									
<i>Gertig 2013</i>	Australia	Retrospective cohort study using linked data from registries	12–19	12–21	0: 14,085 1: 1,422 2: 2,268 3: 21,151	Histology: CIN3/AIS, CIN2, CIN1, any high grade; Cytology: low grade and high grade	Time-dependent Final status	0	Age at first screen, remoteness area, SES
<i>Crowe 2014</i>	Australia	Case control study using linked data from registries	12–26	11–31	0: 60,282 1: 10,879 2: 12,073 3: 25,119	Histology: CIN2+/AIS	Final status	0, 1, 6, 12	Year of birth, remoteness area, SES, FU time
<i>Brotherton 2015</i>	Australia	Retrospective cohort study using linked regional data registries	12–26	12–30	0: 133,055 1: 20,659 2: 27,500 3: 108,264	Histology: CIN3/AIS, CIN2, any high grade; Cytology: low grade and high grade	Final status	0, 1, 6, 12, 24	Age, remoteness, SES, screening start (before or after vaccination)
<i>Hofstetter 2016</i>	United States	Retrospective cohort study using medical center records	11–20	11–27	0: 1,632 1: 695 2: 604 3: 1,196	Cytology: any abnormal and high grade ^h	Final status	1	Age, insurance, language, clinic type, CT screening, and baseline cytology
<i>Kim 2016</i>	Canada	Nested case-control study using linked data from registries	10–15	18–21	0: 5,712 1: 327 2: 490 3: 3,675	Cytology: low grade and high grade ⁱ	Final status	0	Age, urban/rural, laboratory site, neighborhood income
<i>Silverberg 2018</i>	United States	Nested case-control study of women enrolled in an integrated health-care delivery system	14–26	18–34	0: 23,293 1: 756 2: 554 3: 1,527	Histology: CIN2+/AIS	Final status	6	Smoking, parity, recent outpatient visits, race/ethnicity, STIs, hormonal contraceptives, immunosuppression
<i>Dehlendorff 2018</i>	Denmark, Sweden	Retrospective cohort study using linked national registry data	13–30	13–30	0: 2,091,579 1: NA 2: NA 3: NA	Histology: CIN2+/AIS	Time- dependent	0	Attained age, age at vaccination, maternal education
<i>Verdoordt 2019</i>	Denmark	Retrospective cohort study using linked national registry data	12–16	17–25	0: 374,327 1: 10,480 2: 30,259 3: 174,532	Histology: CIN2+ CIN3+	Time- dependent (final status for the comparison between doses)	0; 6 in secondary analysis	Attained age, maternal education
<i>Brotherton 2019</i>	Australia	Retrospective cohort study using linked regional data registries	≤13–22	15–22	0: 48,845 1: 8,618 2: 18,190 3: 174,995	Histology: CIN2+ CIN3+	Final status (time-varying as a sensitivity analysis)	0, 12, 24	Birth cohort, age at study entry, area of residence, SES, age
<i>Johnson Gargano 2020</i>	United States	Retrospective cohort study using medical records data from 5 US sites; test-negative design	12–26	18–39	0: 2,731 1: 136 2: 108 3: 325	Histology: HPV type-specific CIN2+	Final status	1, 12, 24, 36	Birth cohort, geographic site, race/ethnicity, insurance status, age at vaccination

<i>Rodriguez 2020</i>	United States	Retrospective matched cohort study using health insurance claims database	9–26	9–31	0: 66,541 1: 13,630 2: 14,088 3: 38,823	Histology: CIN2/3 Cytology: HSIL/ASC-H (atypical squamous cells, cannot rule out HSIL)	Final status	12	Age at vaccination, region, history of STDs and pregnancy, length of enrollment, history and results of pap test, US census region, age at beginning of FU
<i>Innes 2020</i>	New Zealand	Retrospective cohort study using linked national registry data	14–21	20–24	0: 47,283 1 or 2: 8,317 3: 48,713	Histology: CIN1 CIN2+ Cytology: low grade and high grade ⁱ	Final status	0	Age at first dose, birth year cohort
Bivalent vaccine									
<i>Pollock 2014</i>	Scotland	Retrospective cohort study using linked national registry data	15–17	20–21	0: 76,114 1: 1,315 2: 2,725 3: 25,898	Histology: CIN1, CIN2, CIN3	Final status	0	Age, birth year cohort year, deprivation score
<i>Cameron 2017</i>	Scotland	Retrospective cohort study using linked national registry data	14–17	20–21	0: 75,683 1: 2,258 2: 4,462 3: 55,303	Histology: CIN1, CIN2, CIN3	Final status	0	Deprivation score, birth year cohort
<i>Palmer 2019</i>	Scotland	Retrospective cohort study using linked national registry data	12–18+	20–21	0: 64,026 1: 2,051 2: 4,135 3: 68,480	Histology: CIN1, CIN2, CIN3 Cytology: Low grade, moderate grade, severe grade	Final status	0	Age at vaccination, deprivation score, rurality

Abbreviations: AIS, adenocarcinoma in situ; CT, *Chlamydia trachomatis*; CIN, cervical intraepithelial neoplasia; CIN1/2/3, cervical intraepithelial neoplasia grade 1/2/3; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; FU, follow-up; HSIL, high-grade squamous intraepithelial lesion; ICD-9/10, International Classification of Diseases 9th/10th revision; NA, not available; SES, socioeconomic status; STD/I, sexually transmitted disease/infection.

^a Buffer period is the lag time between vaccination and counting of outcomes.

^b By Roche Linear Array assay detecting 37 types.

^c By Xpert HPV assay and Anypex II detecting 28 types.

^d By multimetrix HPV assay detecting 24 types.

^e By Optiplex HPV assay detecting 24 types.

^f Three possible scenarios: (a) ≥ 1 diagnosis of ICD-9 code 078.1; (b) ≥ 1 diagnosis of ICD-9 code 078.1, 078.10, 078.19 plus destruction/excision procedure or ICD-9 code 211.4, 216.5, 221.8, 222.9; and (c) ≥ 1 prescription for anogenital warts plus destruction/excision procedure or ICD-9 code 211.4, 216.5, 221.8, 222.9.

^g Presented as person-years in this article.

^h Low-grade cytology defined as atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion (LSIL). High-grade cytology defined as atypical squamous cells, cannot rule out a high-grade lesion, or HSIL.

ⁱ High-grade cytology defined as possible HSIL, HSIL, HSIL with possible microinvasion/invasion, squamous cell carcinoma, possible high-grade endocervical glandular lesion, AIS, AIS with possible microinvasion/invasion and adenocarcinoma. Low-grade cytology defined as possible LSIL, LSIL, and atypical endocervical cells of uncertain significance.

Source: Table adapted from (114).

Table 11. Studies that evaluated HPV vaccine effectiveness by number of doses: analyses and main findings

Reference	Study population age (years) at		Buffer ^a (months)	Sensitivity analyses by age group/ buffer/ dose interval ^b	Comparison with unvaccinated		Formal comparison between doses
	vaccination	outcome			Effect (95% CI)	Comments	
HPV Prevalence							
Quadrivalent vaccine							
<i>Chandler 2018</i>	NA	14–26	0	No/No/No	No significant effectiveness for ≥ 1d		1d vs 3d: OR = 0.99 (0.33–2.96) 2d vs 3d: OR = 0.60 (0.17–2.12)
<i>Widdice 2019</i>	Mean: 16.2 wave 1; 15.1 wave 2	13–26	0	Yes/No/No	No significant effectiveness for ≥ 1d	<ul style="list-style-type: none"> 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 	Number of doses (0,1,2,3) not associated with ≥1 vaccine-type HPV or HPV 16 and/or 18
<i>Sonawane 2019</i>	NA	18–26	0	No/No/No	Difference in predicted probability: 3: aPD = -4.3 (-4.6, -4.0) 2: aPD = -1.7 (-2.4, -0.1) 1: aPD = -5.0 (-5.6, -4.5)		1d vs 3d: p-value = 0.70 2d vs 3d: p-value = 0.40 1d vs 2d: p-value = 0.12
<i>Markowitz 2020</i>	≤29	20–29	1	Yes/No/No	Overall results: 3: aPR = 0.17 (0.11–0.26) 2: aPR = 0.15 (0.05–0.47) 1: aPR = 0.25 (0.10–0.62) Results for those with first dose at age ≥ 18 yrs: 3: aPR = 0.08 (0.04–0.15) 2: aPR = 0.07 (0.01–0.47) 1: aPR = 0.08 (0.01–0.54)	<ul style="list-style-type: none"> Similar results for unadjusted analyses and controlling for race/ethnicity and age at screening 	3d vs 1d: PR = 1.06 (0.14–8.09) 3d vs 2d: PR = 1.17 (0.15–8.96) 2d vs 1d: PR = 0.90 (0.06–14.36)
<i>Batmunkh 2020</i>	11–17	16–26	0	No/No/No	1: aPR = 0.08 (0.01–0.56)	<ul style="list-style-type: none"> Adjusted for income and employment status 	No
Bivalent vaccine							
<i>Kavanagh 2014</i>	15–17	20–21	0	Yes/No/No	3: aOR = 0.43 (0.34–0.55) 2: aOR = 0.68 (0.42–1.12) 1: aOR = 0.95 (0.51–1.76)	<ul style="list-style-type: none"> Differences by number of doses still observed when stratified by age at vaccination 	No

<i>Cuschieri 2016</i>	15–17	20–21	0	No/No/No	3: aOR = 0.27 (0.20–0.36) 2: aOR = 0.45 (0.29–0.69) 1: aOR = 0.52 (0.31–0.83)		No
<i>Kavanagh 2017</i>	12–18+	20–21	0	Yes/No/No	3: aOR = 0.40 (0.33–0.48) 2: aOR = 0.75 (0.57–0.99) 1: aOR = 0.89 (0.63–1.25)	<ul style="list-style-type: none"> When stratified by age at first dose, 3d VE was highest in the youngest group and lower with age, but all were significant (range: 28.9%–89.1%) 	No
Anogenital warts							
Quadrivalent vaccine							
<i>Herweijer 2014</i>	10–19	10–24	3	Yes/Yes/No	3: aIRR = 0.20 (0.17–0.23) 2: aIRR = 0.32 (0.26–0.40) 1: aIRR = 0.54 (0.43–0.68)	<ul style="list-style-type: none"> Similar results for age groups 10–16 and 17–19 yrs Similar results for buffers of 0–12 months, except effectiveness for 1d was not significant among those vaccinated at age 17–19 yrs using buffers of 0 and 1 month(s) 	3d vs 1d: aIRR = 0.37 (0.28–0.48) 3d vs 2d: aIRR = 0.63 (0.48–0.82) 2d vs 1d: aIRR = 0.59 (0.43–0.81) <ul style="list-style-type: none"> With buffer periods >4 months, no significant difference between 3d and 2d
<i>Blomberg 2015</i>	12–27	12–27	1	Yes/No/Yes	1: IRR = 0.51 (0.46–0.56)		3d vs 2d: IRR = 0.46 (0.39–0.54) 2d vs 1d: IRR = 0.44 (0.37–0.51) <ul style="list-style-type: none"> With dose interval >4 months, no significant difference for 3d vs 2d Similar results when stratified by age at vaccination
<i>Dominiak-Felden 2015</i>	10–21	16–23	1	No/No/No	3: aIRR = 0.12 (0.07–0.21) 2: aIRR = 0.34 (0.14–0.83) 1: aIRR = 0.63 (0.35–1.16)	<ul style="list-style-type: none"> 3d VE estimates were higher for those vaccinated at age <15 and 15–17 yrs than ≥18 yrs 3d VE estimates higher with buffers >1 yr 	No
<i>Perkins 2017</i>	9–25	9–25	0	No/Yes/Yes	3: aIRR = 0.53 (0.46–0.60)		3d vs 1d: aIRR = 0.82 (0.71–0.95) 3d vs 2d: aIRR = 0.89 (0.78–1.03) <ul style="list-style-type: none"> With 1-yr buffer period, no change in findings (data not shown) Similar results with interval >5 months for 2d
<i>Navarro-Illana 2017</i>	14	14–19	0	No/No/No	3: aRR = 0.24 (0.15–0.34) 2: aRR = 0.36 (0.14–0.68) 1: aRR = 0.39 (0.13–0.80)		No

<i>Lamb 2017</i>	10–19	10–27	0	Yes/No/Yes	No analyses of 3d, 2d or 1d compared to 0		<ul style="list-style-type: none"> • Higher effectiveness of 3d vs 2d when 1std and 2ndd administered 0–3 or >8 months apart but not 4–7 months • Similar results stratified by age at vaccination
<i>Hariri 2017</i>	16–17 (mean)	11–28	6 from last dose 12 from first dose	No/Yes/Yes	6-month buffer from last dose: 3: aHR = 0.23 (0.17–0.31) 2 ^c : aHR = 0.32 (0.17–0.59) 1: aHR = 0.81 (0.60–1.08) 12-month buffer from first dose: 3: aHR = 0.20 (0.15–0.27) 2 ^c : aHR = 0.24 (0.13–0.44) 1: aHR = 0.32 (0.20–0.52)		6-month buffer from last dose: 3d vs 1d: aHR = 0.29 (0.20–0.42) 3d vs 2d ^c : aHR = 0.74 (0.38–1.43) 2d ^c vs 1d: aHR = 0.39 (0.20–0.76) 12-month buffer from first dose: 3d vs 1d: aHR = 0.63 (0.37–1.09) 2d vs 1d: aHR = 0.74 (0.35–1.60)
<i>Zeybek 2018</i>	9–26	9–31	3 from last dose	Yes/No/Yes	Results for age 15–19 yrs: 3: aRR = 0.58 (0.49–0.70) 2: aRR = 0.67 (0.51–0.89) 1: aRR = 0.65 (0.49–0.85)	<ul style="list-style-type: none"> • No significant effect in older or younger age groups • Similar results with 2d interval <6 or ≥6 months 	<ul style="list-style-type: none"> • No significant differences for 3d vs 1d, 3d vs 2d, or 2d vs 1d (only p-values reported)
<i>Willows 2018</i>	9–18	10–32	0	Yes/No/No	Results for those vaccinated at age 9–18 yrs: 3: aHR = 0.4 (0.3–0.7) 2: aHR = 1.4 (0.6–3.3) 1: aHR = 0.6 (0.2–1.8)	<ul style="list-style-type: none"> • No significant effect in those vaccinated at older ages 	No
Cervical abnormalities^d							
Quadrivalent vaccine							
<i>Gertig 2013</i>	12–19	12–21	0	No/No/No	Outcome summarized: CIN2+ 3: aHR = 0.61 (0.48–0.78) 2: aHR = 1.02 (0.68–1.53) 1: aHR = 1.47 (0.97–2.23) Outcome summarized: CIN3/AIS 3: aHR = 0.53 (0.36–0.77) 2: aHR = 0.87 (0.46–1.67) 1: aHR = 1.40 (0.75–2.61)	<ul style="list-style-type: none"> • Similar results for CIN2 as an outcome 	No
<i>Crowe 2014</i>	12–26	11–31	0	Yes/Yes/No	Outcome summarized: high-grade histological lesions 3: aOR = 0.54 (0.43–0.67) 2: aOR = 0.79 (0.64–0.98) 1: aOR = 0.95 (0.77–1.16)	<ul style="list-style-type: none"> • Buffer periods from 1 to 12 months, no consistent impact on estimates • Similar results among those vaccinated at ages 15–18 and 19–22 yrs 	No

<i>Brotherton 2015</i>	12–26	12–30	0	Yes/Yes/Yes	Results for those vaccinated prior to screening: Outcome summarized: CIN2+ 3: aHR = 0.71 (0.64–0.80) 2: aHR = 1.21 (1.02–1.44) 1: aHR = 1.19 (0.99–1.43) Outcome summarized: CIN3/AIS 3: aHR = 0.69 (0.58–0.81) 2: aHR = 1.17 (0.92–1.48) 1: aHR = 1.41 (1.12–1.77)	<ul style="list-style-type: none"> • Similar results for those vaccinated after screening, stratified by age at vaccination • With longer buffer periods, some effectiveness for 2d and 1d • No difference by interval between 2d 	No
<i>Hofstetter 2016</i>	11–20	11–27	1	Yes/No/No	Outcome summarized: any abnormal cytology 3: aHR = 0.58 (0.48–0.69) 2: aHR = 0.81 (0.66–0.99) 1: aHR = 1.05 (0.88–1.26)	<ul style="list-style-type: none"> • Similar results when stratified by age at vaccination, although 2d not always significant • Highest effectiveness, although only significant for 3d, for those vaccinated at ages 11–14 yrs compared to those vaccinated at older ages 	No
<i>Kim 2016</i>	10–15	18–21	0	No/No/No	Outcome summarized: high-grade cytology 3: aOR = 0.48 (0.28–0.81) 2: aOR = 0.17 (0.02–1.20) 1: aOR = 0.45 (0.11–1.83)		No
<i>Silverberg 2018</i>	14–26	18–34	6	Yes/No/No	Outcome summarized: CIN3+/AIS 3: aRR = 0.64 (0.48–0.84) 2: aRR = 0.97 (0.67–1.41) 1: aRR = 0.90 (0.65–1.24)	<ul style="list-style-type: none"> • Highest 3d effectiveness among those vaccinated at youngest ages 	No
<i>Dehlendorff 2018</i>	13–30	13–30	0	Yes/No/Yes	Outcome summarized: CIN2+/AIS (aged ≤ 16 yrs) 3: aIRR = 0.23 (0.11–0.49) 2: aIRR = 0.44 (0.10–2.03) 1: aIRR = 0.23 (0.01–5.24)	Similar results for those vaccinated at age 17–19 yrs	2d vs 3d: aIRR = 1.60 (1.05–2.24) <ul style="list-style-type: none"> • No significant difference between 2d and 3d when interval between 1d and 2d > 5 months and age at vaccination < 20 yrs
<i>Verdoodt 2019</i>	12–16	17–25	0 (6 months for comparison between doses)	Yes/No/No	Outcome summarized: CIN3+/AIS 3: aIRR = 0.37 (0.30–0.45) 2: aIRR = 0.38 (0.22–0.66) 1: aIRR = 0.38 (0.14–0.98)	<ul style="list-style-type: none"> • Similar results by age at vaccination, but only significant for those aged <23 yrs 	Outcome summarized: CIN3+/AIS 3d vs 1d: aIRR = 0.95 (0.60–1.51) 2d vs 1d: aIRR = 0.89 (0.53–1.52)
<i>Brotherton 2019</i>	≤ 13 –22	15–22	0	Yes/Yes/Yes	Outcome summarized: CIN2+ 3: aHR = 0.59 (0.54–0.65) 2: aHR = 0.61 (0.52–0.72) 1: aHR = 0.65 (0.52–0.81) Outcome summarized: CIN3+/AIS 3: aHR = 0.43 (0.35–0.53) 2: aHR = 0.42 (0.27–0.64) 1: aHR = 0.66 (0.41–1.06)	<ul style="list-style-type: none"> • Similar results for time-varying dose status, CIN3+, buffers of 0 and 12 months, and alternate status based on timing between 1d and 2d 	Outcome summarized: CIN2+ 3d vs 1d: aHR = 0.91 (0.74–1.13) 3d vs 2d: aHR = 0.97 (0.83–1.14) 2d vs 1d: aHR = 0.94 (0.73–1.21) Outcome summarized: CIN3+/AIS 3d vs 1d: aHR = 0.66 (0.41–1.05)

							3d vs 2d: aHR = 1.04 (0.68–1.57) 2d vs 1d: aHR = 0.64 (0.35–1.16)
<i>Johnson Gargano 2020</i>	12–26	18–39	24	Yes/Yes/No	Outcome summarized: CIN2+/AIS 3: aOR = 0.26 (0.20–0.35) 2: aOR = 0.45 (0.30–0.69) 1: aOR = 0.53 (0.37–0.76)	<ul style="list-style-type: none"> aORs were slightly higher using 1 and 12 month buffer periods and lower using a 36-month buffer period, but all showed significant effectiveness Effectiveness was higher in earlier birth cohort and lower in later one 	3d vs 1d: aOR = 0.61 (0.38–0.99) 3d vs 2d: aOR = 0.64 (0.39–1.05) 2d vs 1d: aOR = 0.96 (0.55–1.68)
<i>Rodriguez 2020</i>	9–26	9–31	12	Yes/No/Yes	Outcome summarized: CIN2/3 First dose at age 15–19 yrs: 3: aHR = 0.66 (0.55–0.80) 2: aHR = 0.72 (0.54–0.95) 1: aHR = 0.64 (0.47–0.88)	<ul style="list-style-type: none"> Study underpowered for those aged <15 yrs No vaccine effectiveness against high-grade cytology or against CIN2/3 for those who received first dose at age ≥20 yrs 	No
<i>Innes 2020</i>	14–21	20–24	0	Yes/No/No	Outcome summarized: high-grade histology (min. 1d at age <18 yrs) 3: IRR = 0.66 (0.60–0.72) 2: IRR = 0.81 (0.63–1.03) 1: IRR = 1.10 (0.85–1.45)	<ul style="list-style-type: none"> No significant effectiveness against high-grade histology for ≥1d among women vaccinated at age ≥18 yrs 	No
Bivalent vaccine							
<i>Pollock 2014</i>	15–17	20–21	0	No/No/No	Outcome summarized: CIN3 3: aOR = 0.45 (0.35–0.58) 2: aOR = 0.77 (0.49–1.21) 1: aOR = 1.42 (0.89–2.28)		No
<i>Cameron 2017</i>	14–17	20–21	0	No/No/No	Outcome summarized: CIN3 Significant effect only with 3d	<ul style="list-style-type: none"> Vaccinated in each deprivation category, compared with unvaccinated in most deprived 	No
<i>Palmer 2019</i>	12–18+	20–21	0	No/No/No	Outcome summarized: CIN3+ 2: aOR = 0.77 (0.48–1.24) 1: aOR = 1.19 (0.70–2.05)	<ul style="list-style-type: none"> Effect of 3d vaccination larger with younger age at vaccination, ranging from 0.14 to 0.85 	No

Abbreviations: aHR, adjusted hazard ratio; aIRR, adjusted incidence rate ratio; AIS, adenocarcinoma in situ; Significant; aOR, adjusted odds ratio; aPR, adjusted prevalence ratio; aRR, adjusted relative risk; CI, confidence interval; CIN2/3, cervical intraepithelial neoplasia grade 2/3; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; d, dose; HR, hazard ratio; IRR, incidence rate ratio; NA, not available; OR, odds ratio; RR, relative risk; VE, vaccine efficacy. 95% CI does not include 1.

^a Buffer period is the lag time between vaccination and counting of outcomes. This column shows buffer period in main analysis.

^b Interval between doses for two-dose vaccine recipients.

^c Data presented for two doses are those with an interval ≥6 months between doses.

^d Several outcomes were presented in some articles for cervical cytological or histological abnormalities. We summarized results for the outcome most proximal to cervical cancer.

Source: Table adapted from (114).

2.5 Mathematical modeling of the impact of reduced dosing schedules

This section summarizes evidence derived from mathematical modeling of the impact of reduced dosing schedules for HPV vaccines. In the previous editions of this paper, we examined and summarized the published studies of reduced-dose strategies for the GSK 2vHPV, Merck 4vHPV, and Merck 9vHPV vaccines to identify key factors related to the impact of reduced dosages and their cost-effectiveness. A comprehensive literature search conducted since completion of the last edition did not identify any further relevant evidence.

2.5.1 Overview

Given the long natural history process of HPV and cervical carcinogenesis, empirical studies have relied on intermediate endpoints as measures of efficacy and effectiveness of HPV vaccination, such as the incidence of persistent HPV infection and CIN. Mathematical models that simulate the disease burden of HPV in populations can be used to complement these data 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.

Important features of different model types, attributes, functionalities, and structures have been covered extensively elsewhere (150-154). The best suited models for questions related to HPV vaccination are “dynamic” transmission models that explicitly simulate the acquisition of HPV infections through sexual behavior in the population and can therefore capture both direct and indirect (i.e., herd protection) effects. Given the increased use of mathematical models to inform decisions globally, ensuring appropriate model adaptation to different populations (i.e., model calibration), assessing the quality of predictions (i.e., model validation), and comparing predictions across independent models (i.e., comparative modeling) are important to enhance credibility of findings (150, 155, 156). Standardization of model reporting to increase transparency and interpretability of model assumptions, inputs, and outputs is also critical (157).

In contrast to the large body of model-based evidence on the impact and cost-effectiveness of three-dose HPV vaccination (158-162), analyses evaluating reduced-dose vaccination schedules are limited. To date, most have focused on two-dose vaccination; however, an increasing number of analyses on the impact and value of single-dose vaccination is anticipated, corresponding with the growing empirical data summarized in [sections 2.2, 2.3, and 2.4](#).

2.5.2 Models of two-dose HPV vaccination

Four published analyses have addressed the question of reducing vaccination from three to two doses in the context of high-income settings; three with either the GSK 2vHPV or Merck 4vHPV vaccines and one with the Merck 9vHPV vaccine (163-166). These analyses explored the impact of duration of protection, with equivalent or shorter duration for two doses compared to three doses. Consistent with observed data, they assumed equivalent VE between the dose regimens (95% to 100% efficacy) in base-case scenarios but explored differential VE in sensitivity analyses.

Comparative analyses of two-dose 2v/Merck 4vHPV vaccination using independent dynamic transmission models fitted to the United Kingdom (Public Health England model) and Canada (HPV-ADVISE [Agent-based Dynamic model for Vaccination and Screening Evaluation]) found that the health benefits, in terms of cancer incidence reduction and quality-adjusted life years (QALYs) gained, were substantial with two-dose HPV vaccination, even when vaccine protection waned at 30, 20, or 10 years (163, 164). However, the incremental benefit of adding a third dose varied greatly dependent on duration of two-dose protection. For example, in the UK model, at 80% vaccination coverage with two-dose protection lasting 30 years, the added CC incidence reduction from the third dose (assuming lifelong protection) at 70 years post-vaccination was only 1% (90% range, 0% to 6%) of pre-vaccination incidence; however, when two-dose protection was only 10 years, the added incidence reduction was 17% (5% to 23%) (163).

The Canadian model projected similar cancer incidence reductions as the UK model, except it estimated a lower benefit from two-dose vaccination when protection lasted only 10 years, which made the incremental benefit associated with the third dose greater than in the UK model (49% in the Canada model versus 17% in the UK model). These trends were similar when vaccination coverage was 40% (although with lower absolute benefit) and when results were reported in terms of the number needed to vaccinate to prevent an additional cancer.

Despite different cost inputs and willingness to pay thresholds in the two countries, the cost-effectiveness results of two-dose (GSK 2vHPV or Merck 4vHPV) HPV vaccination in the United Kingdom and Canada were also qualitatively similar. The UK analysis evaluated routine vaccination of girls aged 12 years plus a one-year catch-up campaign to age 18 years and included health benefits and costs related to all HPV-related diseases (i.e., cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancers, as well as AGW and respiratory papillomatosis) (164). The model estimated that two-dose HPV vaccination was cost-effective compared to no vaccination at the United Kingdom's willingness-to-pay threshold (£30,000 per QALY gained), even when the duration of protection was only 10 years and at a vaccine cost up to £300 per dose (much higher than list price at the time of £86.50 per dose). Similar to the health benefits, the cost-effectiveness of adding a third dose depended heavily on the assumption of duration of two-dose protection; for example, three-dose

vaccination (assuming lifelong protection) was not cost-effective when two-dose vaccination provided at least 20 years of protection. However, if two-dose protection was only 10 years, three-dose vaccination was cost-effective, provided the vaccine cost was less than £147 per dose. These results were robust irrespective of vaccine type (GSK 2vHPV versus Merck 4vHPV) and assumptions on cross protection against non-vaccine types; they were replicated when using HPV-ADVISE and adapted to include UK cost and cancer inputs.

In the Canadian analysis using the HPV-ADVISE model (165), routine vaccination was targeted to children aged 9 years and included a five-year, three-dose catch-up campaign; strategies of two- and three-dose vaccination were also evaluated for girls only or with girls and boys and included outcomes related to all HPV diseases. As in the UK analysis, two-dose vaccination was found to be cost-effective (versus no vaccination) at a willingness-to-pay threshold of gross domestic product per capita in Canada (i.e., \$40,000 per QALY gained). Adding a third dose for girls was not cost-effective unless protection of two-dose vaccination was 10 or 20 years and the third dose would extend protection by 10 years; if two-dose vaccine protection was 30 years, the third vaccine dose was not cost-effective unless the cost for the third dose was drastically reduced below the base case cost per dose (i.e., \$85).

Extending vaccination to girls and boys at either two or three doses was uniformly cost-ineffective unless vaccinating boys at a substantially reduced cost (10% to 40% of the cost for vaccinating girls) or under other extreme conditions, including a high prevalence of men who have sex with men (MSM), much higher relative risk of disease among MSM (versus heterosexual men), and no effect of girl-only vaccination on MSM disease risk. Interestingly, vaccinating both girls and boys with two doses was found to be dominated by vaccinating girls only with three doses, given the similar health gains but higher cost of extending two doses to all boys versus adding one more dose to all girls (165).

One US-based analysis using the HPV-ADVISE model (calibrated to US HPV epidemiology and sexual behavior) evaluated reduced doses in the context of the Merck 9vHPV vaccine for girls only, assuming comparable VE (95%) between two and three doses, vaccine cost of US\$158 per dose, and variable duration of two-dose protection (10 years to lifelong) (166). Despite a greater absolute benefit from the Merck 9vHPV vaccine on all HPV-related diseases, the findings regarding two-dose vaccination were qualitatively similar to the previous analyses assuming the GSK 2vHPV or Merck 4vHPV vaccines in the United Kingdom and Canada. Compared to no vaccination, two-dose HPV vaccination was found to be cost saving or cost-effective, even when duration of protection from two doses was short (10 years). As in the other analyses, adding a third dose was unlikely to be cost-effective if duration of two-dose protection was at least 20 years. Unlike previous studies, this analysis explored modest increases in vaccination coverage with a two-dose regimen and found that

an increased uptake of 5% to 15% of two-dose vaccination could compensate for the loss in not administering the third dose. Given the higher cost, three-dose vaccination was therefore found to be dominated (i.e., costlier and less effective).

2.5.3 Models of single-dose HPV vaccination

Two analyses, one in the United Kingdom and one in the United States, have evaluated single-dose HPV 16 and 18 vaccination in the context of routine girls-only vaccination in HIC (167, 168). An analysis published in the *Vaccine* theme issue on single-dose HPV vaccination extends the findings from the US-based analysis to evaluate the impact and cost-effectiveness of single-dose HPV 16 and 18 vaccination in the setting of Uganda (169).

The UK analysis involved comparative modeling using the Public Health England (UK) and the Canadian HPV-ADVISE models, in which one dose was assumed to have equivalent efficacy against HPV 16 and 18 as two doses but to be varied in terms of duration of protection (10 or 20 years) and cross protection against HPV 31, 33, and 45 (167). Results for one-dose vaccination were qualitatively consistent with findings regarding two-dose vaccination. Compared to no vaccination, single-dose vaccination resulted in substantial reductions in CC incidence (range 18% to 74%) and was highly cost-effective, even when protection was only 10 years and did not include cross protection. Adding a second dose resulted in additional cancer reductions ranging from 4% to 44% and was cost-effective if one-dose protection was only 10 years and the second dose extended protection to 20 years, irrespective of cross protection. In contrast, adding a second dose was not cost-effective if one-dose vaccination protected for 20 years, even if the second dose extended protection over the lifetime. The large uncertainty intervals in predictions are driven, at least partly, by uncertainty around sexual behavior and suggest that information about these parameters will be key to comparing the impact of different vaccine schedules.

The US analysis explored the epidemiologic impact of single-dose vaccination under varied assumptions of duration of single-dose protection (10 years, 15 years, and lifetime) and achievable vaccination coverage (70% and 90%) (168). This analysis also assumed lower VE for one dose (80% against HPV 16 and 18 infections) than for two doses (100%). The analysis projected that both one-dose and two-dose vaccination provide substantial reductions in population HPV 16 prevalence over time, even when protection with one dose is not lifelong. When no waning of protection after one-dose vaccination was assumed, HPV 16 prevalence reductions over time were lower for one-dose vaccination than two-dose vaccination, as expected with the lower efficacy; however, this loss in benefit was almost completely offset when there was an increase in one-dose vaccination coverage from 70% to 90%. The ability for increased coverage to compensate for decreased efficacy was diminished under assumptions of waning protection.

When these model assumptions and projections of one-dose and two-dose vaccination effects were applied to the burden of HPV and CC in the setting of Uganda (169), one-dose vaccination was found to be cost saving or very cost-effective compared to no vaccination, consistent with prior analyses. Adding a second dose was found to be cost-effective unless one-dose vaccination was accompanied by higher coverage and had equivalent (i.e., lifelong) protection.

One published modeling study evaluated the population-level impact of single-dose Merck 9vHPV vaccination on reducing CC incidence and mortality in South Africa, taking into consideration HIV status, CD4 count, and antiretroviral therapy (ART) coverage (170). The analysis used a dynamic HIV transmission model that was calibrated and validated to data from KwaZulu-Natal, South Africa. This model was adapted to include not only sexual transmission of HIV but also high-risk HPV and the natural history of cervical precancerous lesions (i.e., CIN1, CIN2, CIN3) and invasive cancer. HIV infection impacted HPV transmission, as well as progression and regression of HPV and precancer, as a function of CD4 count.

Unlike previous analyses of single-dose vaccination, this analysis did not compare the comparative 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 of girls aged 9 years on CC incidence and mortality by age and over time, varying important vaccine characteristics and programmatic assumptions. In the base case, vaccination coverage of 90% for girls aged 9 years was assumed starting in year 2018, with 80% protection over the lifetime against 90% (i.e., approximate type distribution of Merck 9vHPV) of CC cases. Sensitivity analysis examined the impacts of vaccination coverage (50% and 70%) and duration of vaccine protection (waning at 10, 15, and 20 years of full protection, followed by linear decline to no protection over 20 years).

Assuming 80% lifetime protection and 90% coverage, CC incidence for all women irrespective of HIV status was reduced by 74% (CC mortality reduced by 71%) after 70 years of the start of Merck 9vHPV vaccination in South Africa. As expected, lower vaccination coverage resulted in lower incidence and mortality reductions; with 50% coverage and lifelong protection, reductions in CC incidence and mortality decreased to 48% and 45%, respectively. Waning protection at 10 to 20 years also reduced benefits, ranging from 72% CC incidence reduction among all women when full protection lasted only 20 years down to 67% CC incidence reduction when full protection lasted only 10 years (decreases in CC mortality reductions were also similar). Interestingly, the impact of HIV status (and CD4 count among HIV-positive women) on relative reductions in incidence and mortality was minimal—roughly 2% to 3% for CC incidence and 2% to 5% for CC mortality—at all included levels of coverage and vaccine waning.

The study did not evaluate costs and did not vary CC screening but identified cost-effectiveness analysis of single-dose HPV vaccination, including threshold analysis for the cost of Merck 9vHPV in

an HIV-endemic setting, as a priority for future work. The authors concluded that single-dose Merck 9vHPV vaccination has the potential to achieve high reduction in CC burden, even with lower efficacy (80%) and possible waning protection (10 to 20 years) and despite a high prevalence of HIV among women in South Africa.

2.5.4 Strengths and weaknesses of model-based evidence

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 VE 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.

The latest analysis (170) makes several contributions to the limited literature on reduced-dose HPV vaccination. First and foremost, the study is the first of its kind to take into consideration the comorbidity of HPV and HIV when evaluating the impact of single-dose Merck 9vHPV vaccination. The explicit modeling of the interactive effects of HPV and HIV is critical to understand the mediating or exacerbating effects of CC prevention strategies in many LMIC where HIV is highly prevalent. Second, the model was adapted to the setting of South Africa, leveraging rich data on sexual behaviors, the natural history of HIV and HPV, and longstanding programs in both HIV and CC prevention and control. Third, the study was led by a modeling group that was independent from the other model-based studies, adding to the number of different research groups assessing the impacts of single-dose HPV vaccination. Continued model-based work evaluating the relative trade-offs of multiple doses (at recommended or delayed schedules) and integrating emerging evidence on the efficacy, costs, and acceptability of single-dose HPV vaccination can inform various stakeholders and decision-makers on the value of HPV vaccination in different settings.

2.5.5 Summary of model-based evidence

These initial studies suggest that the duration of protection afforded by reduced dosages is a critical factor in determining impact and cost-effectiveness. Several findings were consistent across analyses evaluating two-dose HPV vaccination, including the following:

- 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 health impact and cost-effectiveness of adding a third vaccine dose hinges on the relative duration of protection for two 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, 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.

Similar themes 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 a lower VE (level of 80%) and a lower duration of protection of 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.
- Single-dose Merck 9vHPV vaccination in a high-HIV-prevalence setting can yield high reductions in CC incidence and mortality, and these relative reductions are similar irrespective of HIV status, CD4 count, or ART coverage.

3 Summary of the available evidence

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 of HPV vaccine should be able to elicit a robust immune response and why lower antibody titers observed for one dose, compared with two or more doses (which are higher than those following natural infection), may still provide protection against HPV.

A systematic review (and subsequent updated literature review) of data on single-dose HPV vaccination from participants vaccinated through clinical trials supports the premise that a single HPV vaccine dose may be as effective in preventing HPV infection as multidose schedules in healthy young females. The reviews identified seven articles describing six nested observational studies from three clinical trials (CVT, PATRICIA, and the IARC India HPV vaccine trial) and one small pilot intervention study. Participants receiving HPV vaccine through the clinical trials had very low rates of HPV 16/18 infection up to 11 years post-vaccination, regardless of the number of doses received. Furthermore, participants receiving only a single HPV vaccine dose had significantly lower infection rates than control participants who did not receive any HPV vaccine. Rates of HPV 16/18 antibody seropositivity were very high among participants receiving one, two, or three HPV vaccine doses. However, seropositivity data must be interpreted with caution due to differences in methodologies and definitions between studies. HPV 16/18 antibody titers were consistently lower for single-dose arms compared to multidose arms, though this may have limited clinical significance if the titers induced by a single dose are sufficient to confer long-term protection against infection, as the evidence suggests. Even in single-dose arms, the data indicate that HPV 16/18 antibodies are sustained to at least 11 years post-vaccination.

A number of non-randomized observational studies have recently been published that compare immune responses among adolescents receiving three-, two-, or one-dose HPV vaccine through national vaccination campaigns or programs. Most of these evaluate humoral immune responses to the vaccines, though two also present cellular immunogenicity data. The published studies demonstrate high rates of seroconversion for vaccine-type HPV antibodies in all dosage groups, albeit with the same caveat as trial-derived data, whereby methodologies used and definitions of seropositivity are variable. Again, antibody titers were mostly lower for single-dose recipients compared to multidose recipients. However, where immunogenicity studies have used the same laboratory methods as the clinical trials described above, they have been able to demonstrate higher antibody titers among adolescents receiving a single dose of HPV vaccine through national campaigns or programs than the titers associated with protection in previous clinical trial participants of older

age. Furthermore, the immunogenicity studies present evidence of a sustained immune response to single-dose HPV vaccination into the mid- to long term, with one study presenting data up to eight years post-vaccination.

Most post-licensure studies examining HPV vaccine effectiveness by number of doses report highest effectiveness with three doses, though some found no statistically significant difference between two and three doses. Almost half of the studies found some effectiveness after one dose. Importantly, more recent studies with younger vaccine recipients have found minimal or no differences in effectiveness by number of doses. Several biases in available data impact estimates, with most biasing two-dose and one-dose results away from showing effectiveness. Future studies of real-world HPV vaccination effectiveness, which examine people vaccinated prior to sexual activity and use methods to reduce potential sources of bias, are warranted.

Modeling analyses have evaluated single-dose HPV vaccination in the United States, United Kingdom, South Africa, and Uganda. Initial analyses indicate that, if the choice is between no vaccination and a single dose, a single dose is likely to provide health benefits and be good value for money. This applies even if the vaccine has a lower VE than two or more doses, as long as one-dose protection lasts at least 10 years. Single-dose Merck 9vHPV vaccination in a high-HIV-prevalence setting can yield high reductions in CC incidence and mortality, and these relative reductions are similar irrespective of HIV status, CD4 count, or ART coverage. 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.

4 Strengths and weaknesses of the evidence

To date, two high-quality and purpose-designed systematic reviews of the evidence on single-dose HPV vaccination compared to either no vaccination or to multidose schedules have been conducted. One systematic review presented evidence on efficacy and immunogenicity derived from clinical trials and the other from post-licensure observational (surveillance and ecological) studies of national HPV vaccination programs. Both reviews used a robust and comprehensive search strategy and encompassed data from multiple sources. A limitation of the reviews was that, while the authors evaluated the quality of the included studies, they did not use a formal quality assessment tool due to the previous lack of availability of a suitable tool. Members of the Single-Dose HPV Vaccine Evaluation Consortium have adapted the Risk of Bias 2.0 framework to allow a formal quality assessment of the studies included in the two reviews. Thus, a formal quality assessment using a standardized framework will be included in future updates to the evidence base.

To date, there has been no systematic review of the evidence derived from observational immunogenicity studies of participants who received different dosing schedules of HPV vaccine through national programs or campaigns. The evidence presented in this edition comes from a literature search (not using systematic review methodology) conducted by Consortium members.

Data from the non-randomized studies included in the trials-based systematic review (derived from the CVT, PATRICIA, and IARC India HPV vaccine trial), have provided encouraging indications that a single dose of the HPV VLP vaccine may provide protection from HPV infections over several years. These are well-conducted, prospective studies implemented in the context of clinical trial protocols with rigorous enrollment, clinical procedures, and laboratory protocols and with good retention to follow-up. Their results 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. These published studies are, however, heterogeneous in design and outcome assessment. Immune response data are difficult to compare across these studies because of the different assays and laboratories used for these trials, although clinical data on protection against HPV infection provide consistent results for a single dose of either GSK 2vHPV or Merck 4vHPV vaccine. It is also important to note that no data are yet available from prospective randomized controlled studies that are specifically designed to answer the question of single-dose protection or immune responses.

The immunogenicity studies identified through literature searches have also provided useful data. In Uganda, among adolescents who received only single-dose HPV vaccine, the GMTs measured nearly three years after vaccination were no different compared to those observed in CVT women who received single-dose HPV vaccine, for which no breakthrough cases have been detected four years after vaccination. Furthermore, the Uganda study has shown the importance of consistency in laboratory methods for the outcome measurements in using the same ELISA and calibrated standards to measure immunogenicity as those used in the CVT. A unique aspect of the Fiji study was the ability to examine the immunogenicity of mixed HPV vaccine schedules comprising both Merck 4vHPV and GSK 2vHPV; the study reported that a single dose of Merck 4vHPV elicits antibodies that persist for at least six years and also induced immune memory. NAb GMTs measured in the single-dose arm of the Fiji study were higher than those measured at the same time point (and with the same assay) in the vaccinated immunogenicity subset of the Mongolia study, among whom a single dose of Merck 4vHPV was associated with a 92% reduction in prevalent HPV 16/18 infection six years post-vaccination compared to unvaccinated peers.

A strength of the US DoD study was the availability of seropositivity results pre-vaccination, but the study suffered from the limitations of using routine data. The first study from Canada demonstrated sustained antibody responses to a single dose of Merck 4vHPV three to eight years post-vaccination in a small cohort of 31 girls but was unable to compare results for a single dose versus either no dose or multiple doses. Subsequent comparisons were made with cohorts of adolescent girls and boys who received two doses of vaccine with a six-month interval through a clinical trial. The US PHACS study presented immunogenicity data following one, two, or three doses of Merck 4vHPV (as well as no vaccination) for HIV-infected adolescents, an important population who is at particularly high risk of HPV infection and related clinic sequelae, yet for whom there is currently little evidence base in regards to HPV vaccine dosing schedules.

In the majority of trial and immunogenicity studies comparing participants who received single versus multidose HPV vaccination schedules, a major limitation was sample size, particularly for the single-dose groups, limiting statistical precision of estimates.

Strengths of the data included in the systematic review of evidence from the post-licensure observational studies included the overall size of the studies, data on buffer periods for some studies, and some information on intervals between doses. Several limitations were noted: 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, in the early years of the vaccination programs when catch-up programs had been implemented, girls who were vaccinated beyond the routine target age group and thus were older than three-dose vaccine recipients at the time of vaccination, who had lower SES, and/or who had

indicators of earlier sexual exposure. A third limitation was information bias—for example, misclassification of vaccination status due to recall, misclassification of outcome due to diagnostic bias, interviewer bias, or tools used.

Three of the five identified modeling studies have only used data from HIC and are reliant on assumptions about the duration of one-dose and two-dose vaccine protection. The South Africa modeling study is the first to consider HPV and HIV comorbidity when evaluating single-dose Merck 9vHPV vaccination impact, which is critical to understanding the effects of HIV infection on CC prevention strategies in many LMIC where HIV is highly prevalent. Ultimately, modeling results will only be confirmed by LTFU of post-vaccination cohorts.

Table 12. Threats to validity of single-dose HPV protection from previous clinical trials and evaluations of bias and confounding within these rubrics

Threat to validity	Evaluation of bias and confounding
Are girls/women who received a single dose of the HPV vaccine different from women who received a single dose of the control vaccine?	Within the single-dose arms of the CVT and PATRICIA, women who were in the HPV and control arms were similar with regard to age, number of clinic visits, HPV16/18 DNA and seropositivity/negative status, and prevalence of other surrogates of infection risk, such as <i>Chlamydia trachomatis</i> .
Did single-dose girls/women receive less than a complete schedule for reasons related to HPV vaccination?	<p>In the CVT and PATRICIA, assessment of reasons for missed doses revealed that most reasons were involuntary and unrelated to the randomization arm, such as pregnancy and colposcopy referral. It was less common for participants to refuse the vaccine or have a medical condition that was contraindicated to vaccination.</p> <p>For the IARC India study, subjects received only a single dose due to a government-requested halt to enrollment (for reasons unrelated to the study itself).</p>
Are girls/women who received a single dose of the HPV vaccine immunologically different from girls/women who received multiple doses of the HPV vaccine?	In the CVT, women in the one-dose HPV group had similar HPV antibody titers compared to the two- and three-dose groups following the initial HPV vaccine dose, when all women received the same number of doses.
Is HPV exposure during the FU phase similar among girls/women who received a single dose of the HPV vaccine compared to the control HPV vaccine or other dose groups?	<p>Cumulatively over the first four years of FU, women in the active control arms of the CVT and PATRICIA had the same HPV attack rate regardless of the number of doses received. At 7, 9, and 11 years after initial vaccination, prevalence of infection with non-vaccine HPV genotypes (a metric of HPV exposure) was similar across HPV vaccine dosing groups and unvaccinated women.</p> <p>Similarly, girls who received HPV vaccine in the IARC India study had similar rates of cumulative incident infections with non-vaccine HPV types over seven years of FU.</p>

Abbreviations: CVT, Costa Rica vaccine trial; DNA, deoxyribonucleic acid; FU, follow-up; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; PATRICIA, PApilloma TRIal against Cancer In young Adults.

Source: Table adapted from (99).

5 Gaps in the evidence, research priorities & forthcoming evidence

5.1 Efficacy and immunogenicity data from RCTs and observational studies

Several clinical studies have examined single-dose regimens and demonstrated results that challenge the prevailing dogma that protein-based subunit vaccines require a multidose regimen. These observations and the potential public health impact of an effective single-dose strategy suggest that further studies on single-dose efficacy of the HPV vaccines—including cross-protective efficacy and duration of protection, as well as data from different study populations—are warranted. Several evidence gaps are being addressed or will need to be addressed in the coming years. These are discussed below, and new and ongoing studies are summarized in [Table 13](#).

5.1.1 Durability of protection

Currently, it is not known if a single dose of HPV vaccine will provide a sufficient and durable enough level of efficacy against persistent HPV infection to support a recommendation for a policy change to a single-dose vaccination strategy. This question is being addressed through the CVT and continued follow-up of the India study cohort.

In the CVT, analysis of efficacy is published out to 11 years, and a subset of participants will be followed out to 18 to 20 years for immunogenicity outcomes in a study called CVT EXTEND (77, 171, 172).

Additional data on incident persistent infections in the IARC India HPV vaccine study will be obtained from at least 2,500 additional women who are initiating sexual activity over the next few years, including women in the single-dose arm (76). Data from these women will be used to compare the efficacy of one dose of Merck 4vHPV against persistent infection compared to the two- and three-dose vaccine recipients and unvaccinated women. The Indian study will provide robust evidence on the protection offered by a single dose beyond 16 to 17 years post-vaccination.

The India study will also generate data on the efficacy of a single dose to protect against cervical sequelae of HPV infection by comparing rates of CIN2+ in one-dose recipients (compared to unvaccinated women and women receiving two or three doses) who initiate CC screening within the

next few years. To date, 1205 women in the single-dose group have initiated CC screening (using Hybrid Capture II HPV assay). A further 400 women per year will be screened up to 2022. Many of these women will have a second round of screening in the subsequent years. The screening outcomes in the vaccinated women will be compared with that of 4,598 unvaccinated age-matched women who have been screened with the same HPV test.

Durability of efficacy and immunogenicity will also be addressed through new randomized and non-randomized prospective intervention studies, which are described below.

5.1.2 Evidence from purpose-designed intervention studies of single-dose HPV vaccine versus no vaccination or multidose schedules

The systematic and Cochrane reviews of trials data highlighted a paucity of evidence from RCTs that specifically randomized participants to receive a single HPV vaccine dose versus either no HPV vaccine dose or multidose schedules. Randomized trials will be able to provide more definitive data on whether single-dose HPV vaccination can protect against HPV-persistent infection and provide immunobridging data to other trials without efficacy endpoints. Several ongoing trials are investigating the efficacy and/or immune responses and safety of a single dose of HPV vaccine compared to recommended dose regimens or controls ([Table 13](#), [Figure 8](#)).

A large-scale RCT is underway in Costa Rica. The Estudio de Comparacion de Una y Dos Dosis de Vacunas Contra el Virus de Papiloma Humano (ESCUDDO) trial [comparison study of one or two doses of the bivalent or nonavalent prophylactic HPV vaccines] (24) 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 among young women in Costa Rica. The study is a four-arm trial of approximately 20,000 girls aged 12–16 years to formally evaluate the non-inferiority of one versus two doses of each the Merck 9vHPV and GSK 2vHPV vaccines. The participants have been randomized into two stages to receive one or two doses of the vaccines and to be followed initially for four years. As a primary endpoint, the trial will focus on the prevention of new, persistent infection by HPV types 16 and 18. The trial will also evaluate protection against the other cancer- and genital wart-causing HPV types, while documenting infection by non-vaccine-preventable HPV types to verify continued exposure among trial participants. A group (approximately 4,000) of initially HPV-unvaccinated women are recruited to provide control estimates of HPV persistent infection in order to estimate VE. In addition to the evaluation of efficacy against HPV infection, the immunological response to vaccination will be monitored to demonstrate robust, stable, and durable antibody responses following one- and two-dose vaccination and to enable studies to compare immune responses induced by the two vaccines, which contain different adjuvants. The ESCUDDO trial completed enrollment this year (2020), with four-year follow-up data available in 2025 ([Figure 8](#)).

A second single-dose efficacy RCT commenced in Kenya in December 2018. The Kenya Single-dose HPV vaccine Efficacy (KEN-SHE) study is enrolling 2,250 sexually active females aged 15–20 years and randomizing participants to receive either immediate one-dose HPV vaccination (GSK 2vHPV or Merck 9vHPV) and delayed second dose of meningococcal vaccine or immediate meningococcal vaccine and delayed HPV vaccine (Merck 9vHPV) (177). Study participants will be followed until month 36 to assess VE against HPV infection and measure humoral immune responses. The delayed vaccine will be administered at the end of follow-up.

While not randomized, three further intervention studies evaluating the efficacy or effectiveness of single-dose HPV vaccination are also underway: the PRIMAVERA [Puente de Respuesta Inmunológica para Mejorar el Acceso a Vacunas y ERrAdicar el cancer] study in Costa Rica, the International Vaccine Institute (IVI) HPV1 study in Thailand, and the HPV One/two dose Population Effectiveness (HOPE) study in South Africa.

PRIMAVERA is a clinical trial in Costa Rica comparing immune responses following one dose of the GSK 2vHPV vaccine among 520 girls aged 9–14 years (the intervention arm) to three doses of the Merck 4vHPV vaccine in 520 women aged 18–25 years (the control arm), the trial population in which efficacy was initially proven (173). The primary aim is to demonstrate that 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. Efficacy of three doses of Merck 4vHPV has already been demonstrated among women of this age group, and thus non-inferior immune responses among the younger age group would imply protection against HPV 16/18 and associated precancerous lesions following a single dose of GSK 2vHPV. This study started in March 2019.

The study in Thailand on the effectiveness of one or two doses of 2vHPV vaccine (IVIHPV1) (25) is a community intervention study of female students in Thailand, which started in December 2018. The study involves vaccination of grade 8 female students (aged 13–14 years) from two provinces with either one or two doses of HPV vaccine (GSK 2vHPV) and a series of cross-sectional surveys (at baseline, year 2, and year 4) among grade 10 and 12 female students (aged 15–18 years) to measure the population-level impact on HPV prevalence, with DNA being measured in, and genotyped from, urine. Immune responses will be measured in a subset of vaccinated participants, as well as a subset of survey participants.

The HOPE study also aims to assess the population-level effectiveness of one versus two HPV vaccine doses and is embedded within the South African national HPV vaccination program, which has been administering two doses of GSK 2vHPV to girls aged 9 years since 2014 (174). In 2019, HOPE performed a one-year catch-up demonstration project among girls aged 17 and 18 years in one South African district, administering a single dose of GSK 2vHPV to approximately 7,000 girls.

Cross-sectional surveys of at least 3,260 girls aged 17–18 years across districts was offered by the national program alone, and the district-level single-dose catch-up vaccination will be used to determine HPV prevalence at baseline and follow-up time points, enabling measurement of population effectiveness of the two-dose national program and the one-dose demonstration project. The impact of HIV infection on the protective effectiveness of HPV vaccination will additionally be determined.

Randomized, controlled immunogenicity trials are also underway. The Dose Reduction Immunobridging and Safety study of two HPV vaccines in Tanzanian girls (DoRIS) is an ongoing RCT among Tanzanian girls aged 9–14 years, intended to establish whether a single dose of HPV vaccine (GSK 2vHPV and Merck 9vHPV) produces immune responses that are likely to be effective in preventing CC (178). The trial has randomized 930 girls to six groups, which are being followed for 36 months. Girls received the GSK 2vHPV or the Merck 9vHPV vaccine in one, two, or three dose schedules. Immune responses of girls receiving one or two doses will be compared with those receiving three doses of the same vaccine. Results from the DoRIS trial will be used to immunobridge to historical cohorts, such as the CVT and the IARC India HPV vaccine trial, where a single dose has been shown to be protective, as well as to the new RCTs, ESCUDDO and KEN-SHE.

Immunobridging analyses will support efficacy claims across different geographies (among an African population) and age groups (among girls as young as aged 9 years). This study will be one of the first randomized trials of one and two doses of any HPV vaccine in Africa. The DoRIS trial cohort completed the second year of follow-up in January 2020, and month 36 will be available in 2021. Follow-up will be extended for immunogenicity for the one-dose and two-dose arms to 60 months.

The HPV vaccination in Africa—New Delivery Schedules (HANDS) trial (26) is an immunogenicity trial in The Gambia which will compare one and two doses of Merck 9vHPV in children aged 4–8 years and 9–14 years with three doses in those aged 15–26 years. This trial began in 2019. This randomized, open-label, single-center, phase III non-inferiority trial will recruit 1,720 female participants. The primary and secondary immunogenicity objectives will be analyzed based on serological samples taken four to six weeks after the last dose of vaccine received according to group. A substudy will be undertaken within the main trial to compare early immunological events.

Finally, a non-randomized delayed second-dose immunogenicity trial in the United States, where 200 male and female subjects aged 9–12 years receive a second dose of Merck 9vHPV at 24 months, determine the persistence and stability of serologic GMT of HPV 16/18 between 6, 12, 18, and 24 months after the prime dose and prior to the administration of the second dose, thus also providing some limited information on immune responses to a single dose up to two years after the first dose (175).

5.1.3 Evidence from different populations and using different vaccines

It is important that research on a single dose of HPV vaccine is carried out across a wide range of age groups and populations. Undertaking multiple, large-scale efficacy and effectiveness studies across numerous countries is challenging, but current studies (including CVT, India, ESCUDDO, KEN-SHE, IVIHPV1, and HOPE) are already being conducted across multiple continents. Immunobridging studies will be important to allow conclusions to be drawn about the potential efficacy of a single dose across further populations and age groups. The current prospective studies are working across a wide age range, from 4 to 26 years, and are covering study populations on five continents (**Table 13**).

While the evidence base to date is largely derived from studies of the 2vHPV and 4vHPV vaccines, new and ongoing research on single-dose vaccination spans the three widely available commercial vaccines (GSK 2vHPV, Merck 4vHPV, and Merck 9vHPV).

5.1.4 Standardized measurement and reporting of immunogenicity outcomes

The inability to compare immune responses of a single-dose HPV vaccine across studies due to heterogeneity in laboratory methods and cutoff thresholds for seropositivity creates a significant gap in evidence. Efforts are now underway to standardize the immunological testing for antibody levels so that the results of the CVT and India trials can be compared directly, as well as for future trials (including ESCUDDO, DoRIS, and KEN-SHE). Antibody avidity indicates the degree of antibody affinity maturation and generally increases over time following encounter with an antigen. Avidity data are available from the CVT and India studies and will be collected in the ESCUDDO and DoRIS trials. Studies are also underway in the DoRIS trial to compare cellular immune responses following one, two, and three doses of HPV vaccines.

To date, there has been no systematic review of immunogenicity data from observational studies of participants receiving a single dose of HPV vaccine versus either no vaccination or multidose schedules through national programs or campaigns. However, a systematic review of immunogenicity data among vaccine recipients, stratified by number of doses received, is currently underway. This review is being conducted by the Strategic Analysis, Research & Training Center at the University of Washington. Once results are available, these will enhance the evidence base regarding the immunogenicity of single-dose HPV vaccination.

5.2 Effectiveness data from post-licensure observational studies

The systematic review of the literature conducted to date identified studies that (1) reported the effectiveness of HPV vaccination (GSK 2vHPV or Merck 4vHPV vaccine) on HPV infections, AGW, or cervical lesions abnormalities; and (2) assessed the effectiveness of HPV vaccination by the number of doses received (one, two, and three). However, because eligible studies used different vaccines, outcomes, buffer periods, and/or age groups at vaccination and at outcome assessment, it was not possible to pool the results from the different studies.

The systematic review of effectiveness studies will be updated regularly, allowing inclusion of newly published studies, and it is anticipated that future updates will include meta-analyses of the population-level effectiveness of HPV vaccination (GSK 2vHPV or Merck 4vHPV or Merck 9vHPV vaccine) with reduced doses. This work will include contacting authors of eligible studies to request supplementary data extractions in order to standardize data stratifications between studies for comparison and pooling (e.g., same age at first vaccination, buffer periods, and outcomes).

Until recently, there has not been a suitable tool for assessing the quality of evidence and risk of bias derived from post-licensure surveillance and ecological studies comparing single-dose HPV vaccination to either no vaccination or multidose schedules. There is an ongoing study to adapt the ROBINS-I framework (176) to account for the characteristics of reduced-dose observational studies (e.g., different types of study design and use of buffer periods to control for prevalent infection at 1st dose) to formally assess the quality of these studies. This quality assessment will be presented in future editions of this paper.

5.3 Modeling studies

5.3.1 Factors influencing modeling results

The early studies on reduced-dose vaccination have revealed several key issues and areas of uncertainty that the models can continue to explore as data emerge. Collectively, the analyses demonstrate that the duration of vaccine protection with reduced-dose regimens is a key determinant of impact and value and that the function of waning protection is important. Most analyses assume fixed duration with or without a gradual decline, based on sustained efficacy from over ten years of trials of three-dose regimens and three years of trials of two-dose regimens.

Efficacy of single-dose vaccination will also have a key influence on overall effectiveness, although preliminary results suggest that it could be less important than duration of protection. Small changes

in efficacy (5% to 10%) had little impact on results in the context of two versus three doses (165, 166). Likewise, cross protection, which in previous analyses has been shown to be potentially influential in the choice of vaccine (GSK 2vHPV versus Merck 4vHPV, and incremental value of Merck 9vHPV), thus far has not been shown to have much effect in analyses of reduced doses. However, that could change as evidence regarding the efficacy and duration of cross protection associated with reduced doses emerges. It currently remains unclear whether the difference in the plateauing of GMTs will influence long-term efficacy; however, ongoing clinical trials (summarized in [Section 5.1](#)) are expected to provide stronger evidence on the magnitude of efficacy.

The impact of duration of protection and efficacy will also undoubtedly be influenced by the level of vaccination coverage achievable and possible increase in coverage with reduced-dose schedules. Preliminary analyses showed that modest increases in coverage with reduced doses can compensate for waning protection and/or lower efficacy (166, 168).

In the South African modeling study, the authors found that changes in vaccination coverage was influential in reductions in CC incidence and mortality, whereas the duration of vaccine protection ranging from 10 to 20 years (followed by a linear decline over 20 years) did not degrade the level of health benefits as much as in previous studies evaluating reduced-dose HPV vaccination.

5.3.2 Future modeling priorities

Given the ongoing activities related to evaluating single-dose vaccination, several important priorities exist for future modeling work. 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 LTFU of the CVT and Indian trials 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, being led by the three modeling groups in this Consortium. The close involvement of the modelers in the ongoing efficacy and immunogenicity trials will enable timely and relevant model updates and analyses. The Consortium will provide a venue for the modelers to share assumptions and explorations and, under agreed-upon circumstances, perform comparative modeling exercises to unveil important similarities and differences in results.

Given the limited clinical trial settings, it will also be important to conduct modeling extrapolations and analyses in different countries with varied epidemiological profiles, population demographics, and sexual behaviors in order to continue to identify important factors and uncertainties that could inform decision-making in a particular setting. Likewise, it will be essential to explore single-dose vaccination in the context of both settings that have already initiated multidose HPV vaccination programs (the one- versus two-/three-dose scenario), as well as settings in which HPV vaccination has

not yet been adopted (the single-dose versus no-vaccine scenario). Moreover, the models can be used to explore opportunities for, and design of, innovative strategies for vaccine delivery given the unconventional target age group of adolescents and the requirement for multiple doses over multiple contacts.

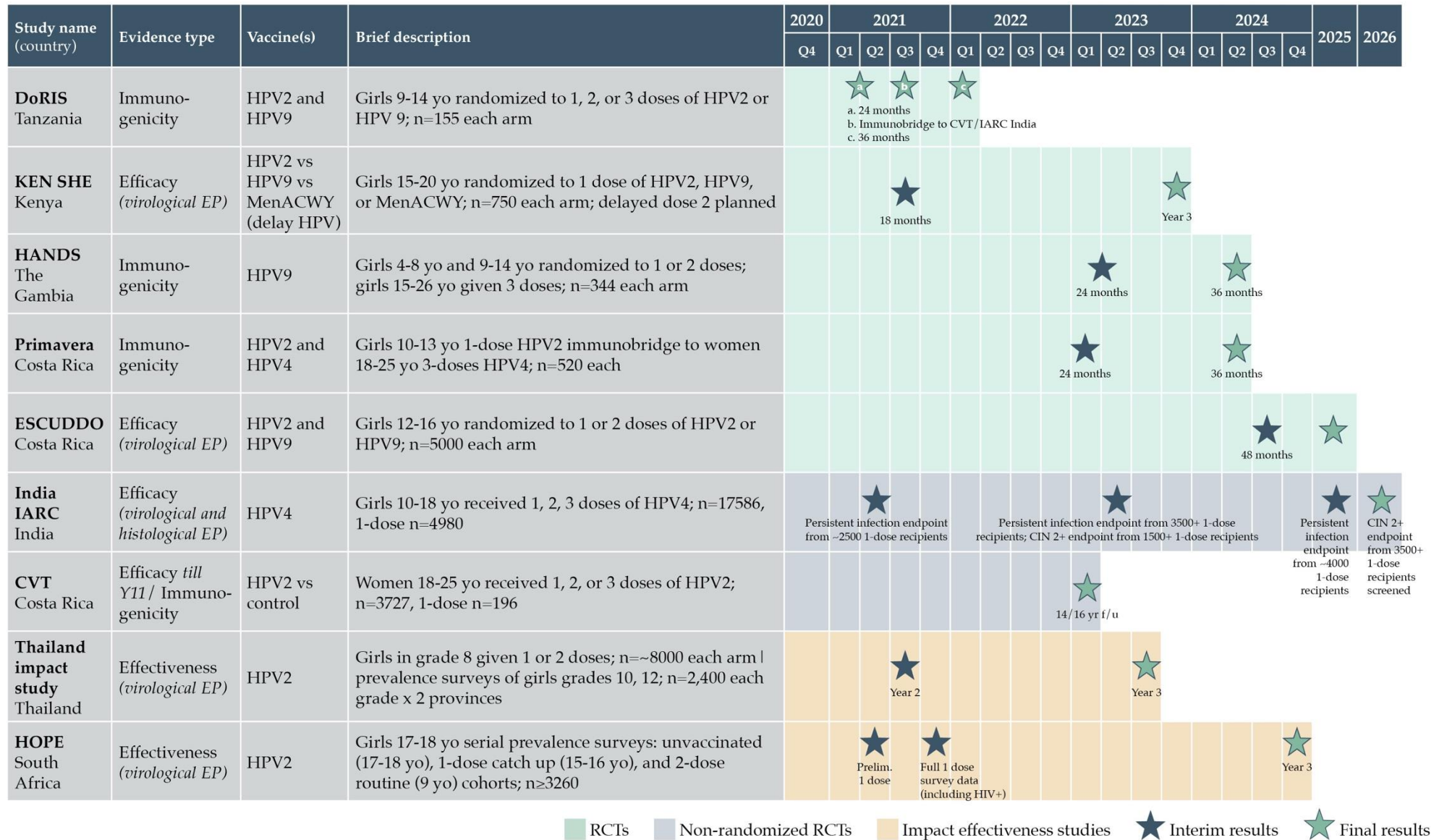
The South African study found that the relative reductions in CC incidence and mortality did not vary substantially across HIV-negative and HIV-positive women (irrespective of CD4 count or ART coverage). However, the analysis assumed the same efficacy across all vaccinated girls. Given current recommendations for HPV vaccination with a full three-dose series for HIV-positive individuals, it will be critical to generate more evidence on the health and economic impacts of reduced-dose HPV vaccination in this population. Model-based analyses that are in the context of settings with high HIV prevalence will need to revisit assumptions regarding vaccine characteristics as data become available from clinical trials on VE and durability in HIV-positive women.

Table 13. Ongoing and forthcoming efficacy, effectiveness, and immunogenicity studies of single-dose HPV vaccination

Study	Country	Study population	Vaccine(s)	Study design	Key endpoint(s)	Start date & FU / duration
CVT EXTEND (171, 172)	Costa Rica	1,000 females vaccinated aged 18–25 y	GSK 2vHPV	Long-term FU study of participants previously vaccinated with 1d v 2d v 3d through an RCT	Humoral immunogenicity	Start: July 2018 FU: To 18/20 years post first vaccination
DoRIS (178)	Tanzania	930 females aged 9–14 y	GSK 2vHPV & Merck 9vHPV	RCT of 1d v 2d v 3d	Humoral & cellular immunogenicity; cost-effectiveness; acceptability	Start: Feb 2017 FU: 36 months
ESCUDDO (24)	Costa Rica	20,000 females aged 12–16 y (RCT) & 4,000 females aged 17–20 y (epi study)	GSK 2vHPV & Merck 9vHPV	RCT of 1d v 2d, & epidemiological study of 1d v no vaccination	VE against HPV infection; humoral immunogenicity	Start: Nov 2017 FU: 48 months
HANDS (26)	Gambia	1,720 females aged 4–26 y	Merck 9vHPV	RCT of 1d v 2d v 3d	Humoral immunogenicity; safety; tolerability	Start : Jul 2019 FU: 36 months
HOPE (174)	South Africa	~7,000 girls aged 15–16 y (1d catch-up) & ≥3,260 sexually active girls aged 17–18 y per surveys	GSK 2vHPV	Intervention study of 1d catch up v 2d national program, using repeat cross-sectional surveys	Population effectiveness against HPV infection; cross protection; herd protection; sociodemographic & behavioral correlates of uptake & impact	Start: Feb 2018 Duration: 48 months
IARC India HPV-VE study (76)	India	17,729 vaccinated females aged 10–18 y & 1,540 age-matched unvaccinated females	Merck 4vHPV	Observational cohort study of 1d v 2d v 3d, and v no vaccination (extended FU)	VE against HPV infection; humoral immunogenicity	Start: Sep 2009 FU: To 16/17 years post first vaccination
IVIHPV1 (25)	Thailand	~18,000 female students (intervention), & between ~4,000 and 9,200 female students per survey	GSK 2vHPV	Intervention study of 1d v 2d, using repeat cross-sectional surveys	Population effectiveness against HPV infection; humoral immunogenicity	Start: Dec 2018 Duration: 48 months
KEN SHE (177)	Kenya	2,250 sexually active females aged 15–20 y	GSK 2vHPV & Merck 9vHPV	RCT of 1d v delayed vaccination	VE against HPV infection; humoral & cellular immunogenicity; cost-effectiveness	Start: Dec 2018 FU: 36 months
PRIMAVERA (173)	Costa Rica	520 girls aged 9–14 y & 520 women aged 18–25 y	GSK 2vHPV & Merck 4vHPV	Non-inferiority trial of 1d GSK 2vHPV in girls v 3d Merck 4vHPV in women	Immunogenicity	Start: Mar 2019 FU: 36 months
US study (175)	United States	200 males and females aged 9–11 y	Merck 9vHPV	Intervention study of 1d v deferred-booster dosing schedule	Immunogenicity	Start: Mar 2016 FU: 48 months

Abbreviations: CVT, Costa Rica vaccine trial; d, dose; DoRIS, Dose Reduction Immunobridging and Safety study of two HPV vaccines in Tanzanian girls; ESCUDDO, Estudio de Comparación de Una y Dos Dosis de Vacunas Contra el Virus de Papiloma Humano [comparison study of one or two doses of the bivalent or nonavalent prophylactic HPV vaccines]; FU, follow-up; GSK, GlaxoSmithKline; HANDS, HPV vaccination in Africa—New Delivery Schedules; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; IVI, International Vaccine Institute; KEN-SHE, Kenya Single-dose HPV vaccine Efficacy; PRIMAVERA, Puente de Respuesta Inmunológica para Mejorar el Acceso a Vacunas y ERrAdicar el cancer; RCT, randomized controlled trial; VE, vaccine efficacy; y, year.

Figure 8. Timing of data from new and ongoing studies evaluating single-dose HPV vaccination



Note: The information provided in this schematic is correct as of November 9, 2020, but may be subject to change.

Abbreviations: 2v, bivalent; 4v, quadrivalent; 9v, nonavalent; CVT, Costa Rica vaccine trial; DoRIS, Dose Reduction Immunobridging and Safety study of two HPV vaccines in Tanzanian girls; ESCUDDO, Estudio de Comparación de Una y Dos Dosis de Vacunas Contra el Virus de Papiloma Humano [comparison study of one or two doses of the bivalent or nonavalent prophylactic HPV vaccines]; f/u, follow-up; HANDS, HPV vaccination in Africa—New Delivery Schedules; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; IVI, International Vaccine Institute; KEN-SHE, Kenya Single-dose HPV vaccine Efficacy; PRIMAVERA, Puente de Respuesta Inmunológica para Mejorar el Acceso a Vacunas y ERrAdicar el cancer; Q, quarter; RCT, randomized controlled trial; v, versus; VE, vaccine efficacy; y/yo, year.

6 References

1. Bosch FX, Broker TR, Forman D, et al. Comprehensive control of human papillomavirus infections and related diseases. *Vaccine*. 2013;31(Suppl 7):H1–H31. <https://doi.org/10.1016/j.vaccine.2013.10.003>.
2. Globocan W-I. Cervical Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2018. <https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf> 2018.
3. Parkin DM, Bray F. Chapter 2: the burden of HPV-related cancers. *Vaccine*. 2006;24(Suppl 3:S3):11–25. <https://doi.org/10.1016/j.vaccine.2006.05.111>.
4. Denny L, de Sanjose S, Mutebi M, et al. Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries. *Lancet*. 2017;389(10071):861–870. [https://doi.org/10.1016/s0140-6736\(16\)31795-0](https://doi.org/10.1016/s0140-6736(16)31795-0).
5. World Health Organization (WHO) website. Newsroom page: World Health Assembly adopts global strategy to accelerate cervical cancer elimination. August 20, 2020. <https://www.who.int/news-room/detail/19-08-2020-world-health-assembly-adopts-global-strategy-to-accelerate-cervical-cancer-elimination>.
6. Schiller JT, Castellsague X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. *Vaccine*. 2012;30(Suppl 5):F123–F138. <https://doi.org/10.1016/j.vaccine.2012.04.108>.
7. Harper DM, DeMars LR. HPV vaccines - a review of the first decade. *Gynecologic Oncology*. 2017;146(1):196–204. <https://doi.org/10.1016/j.ygyno.2017.04.004>.
8. Giannini SL, Hanon E, Moris P, et al. Enhanced humoral and memory B cellular immunity using HPV16/18 L1 VLP vaccine formulated with the MPL/aluminium salt combination (AS04) compared to aluminium salt only. *Vaccine*. 2006;24(33-34):5937–5949. <https://doi.org/10.1016/j.vaccine.2006.06.005>.
9. Scherpenisse M, Schepp RM, Mollers M, et al. Comparison of different assays to assess human papillomavirus (HPV) type 16- and 18-specific antibodies after HPV infection and vaccination. *Clinical and Vaccine Immunology*. 2013;20(8):1329–1332. <https://doi.org/10.1128/cvi.00153-13>.
10. Kemp TJ, Hildesheim A, Garcia-Pineros A, Williams MC, Shearer GM, Rodriguez AC, et al. Elevated systemic levels of inflammatory cytokines in older women with persistent cervical human papillomavirus infection. *Cancer Epidemiology, Biomarkers & Prevention*. 2010;19(8):1954–1959. <https://doi.org/10.1158/1055-9965.epi-10-0184>.
11. Dauner JG, Pan Y, Hildesheim A, Harro C, Pinto LA. Characterization of the HPV-specific memory B cell and systemic antibody responses in women receiving an unadjuvanted HPV16 L1 VLP vaccine. *Vaccine*. 2010;28(33):5407–5413. <https://doi.org/10.1016/j.vaccine.2010.06.018>.
12. WHO position paper on human papillomavirus vaccines - October 2014. *Weekly Epidemiological Record*. 2014;89(43):465–492. <https://www.who.int/wer/2014/wer8943/en/>.
13. Dobson SR, McNeil S, Dionne M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. *JAMA*. 2013;309(17):1793–1802. <https://doi.org/10.1001/jama.2013.1625>.
14. Lazcano-Ponce E, Stanley M, Munoz N, et al. Overcoming barriers to HPV vaccination: non-inferiority of antibody response to human papillomavirus 16/18 vaccine in adolescents vaccinated with a two-dose vs. a three-dose schedule at 21 months. *Vaccine*. 2014;32(6):725–732. <https://doi.org/10.1016/j.vaccine.2013.11.059>.

15. Toh ZQ, Licciardi PV, Fong J, et al. Reduced dose human papillomavirus vaccination: an update of the current state-of-the-art. *Vaccine*. 2015;33(39):5042–5050. <https://doi.org/10.1016/j.vaccine.2015.07.102>.
16. Strategic Advisory Group of Experts (SAGE) on Immunization. Working Group on Potential Contribution of Human Papillomavirus (HPV) Vaccines and Immunization Towards Cervical Cancer Elimination: Background Document and Report to SAGE. Geneva: WHO; 2019. https://www.who.int/immunization/sage/meetings/2019/october/1_HPVS_SAGE2019WG_for_SAGE.pdf.
17. Bruni L. Global vaccine uptake and projected cervical cancer disease reductions. *HPV World*. 2017;Year 1(18):6-9. <https://www.hpvworld.com/articles/global-vaccine-uptake-and-projected-cervical-cancer-disease-reductions/>.
18. LaMontagne DS, Gallagher KE, Watson-Jones D. Why has global HPV vaccine uptake lagged? A contextual reframing of vaccine introduction. *HPV World*. 2017;Year 1(19):10–12. https://www.hpvworld.com/media/29/media_section/1/4/1114/LaMontagne.pdf
19. Gallagher KE, Howard N, Kabakama S, et al. Lessons learnt from human papillomavirus (HPV) vaccination in 45 low- and middle-income countries. *PLoS One*. 2017;12(6):e0177773. <https://doi.org/10.1371/journal.pone.0177773>.
20. Garland SM, Stanley MA, Giuliano AR, et al. IPVS statement on "temporary HPV vaccine shortage: implications globally to achieve equity." *Papillomavirus Research*. 2020;9:100195. <https://doi.org/10.1016/j.pvr.2020.100195>.
21. WHO website. Newsroom page: WHO and UNICEF warn of a decline in vaccinations during COVID-19. July 15, 2020. <https://www.who.int/news-room/detail/15-07-2020-who-and-unicef-warn-of-a-decline-in-vaccinations-during-covid-19>.
22. Abbas K, Procter SR, van Zandvoort K, et al. Routine childhood immunisation during the COVID-19 pandemic in Africa: a benefit-risk analysis of health benefits versus excess risk of SARS-CoV-2 infection. *Lancet Global Health*. 2020;8(10):e1264–e1272. [https://doi.org/10.1016/s2214-109x\(20\)30308-9](https://doi.org/10.1016/s2214-109x(20)30308-9).
23. Scherer LD, Shaffer VA, Patel N, Zikmund-Fisher BJ. Can the vaccine adverse event reporting system be used to increase vaccine acceptance and trust? *Vaccine*. 2016;34(21):2424–2429. <https://doi.org/10.1016/j.vaccine.2016.03.087>.
24. ClinicalTrials.gov. NCT03180034: A Scientific Evaluation of One or Two Doses of Vaccine Against Human Papillomavirus: the ESCUDDO Study. <https://clinicaltrials.gov/ct2/show/NCT03180034>. Accessed June 30, 2019.
25. ClinicalTrials.gov .NCT03747770: A Community Intervention Effectiveness Study: Single Dose or Two Doses of Bivalent HPV Vaccine (CERVARIX) in Female School Students in Thailand. <https://clinicaltrials.gov/ct2/show/NCT03747770>. Accessed June 30, 2019.
26. ClinicalTrial.gov. NCT03832049: A Randomized, Observer-blind, Non-inferiority Trial to Evaluate Alternative Human Papillomavirus (HPV) Vaccination Schedules in Females in West Africa. <https://clinicaltrials.gov/ct2/show/NCT03832049>. Accessed June 30, 2019.
27. Single-Dose HPV Vaccine Evaluation Consortium. Review of the Current Published Evidence for Single-Dose HPV Vaccination. 1st ed. Seattle: PATH; 2018. https://path.azureedge.net/media/documents/SingleDoseHPV_WhitePaper_2018.pdf.
28. Single-Dose HPV Vaccine Evaluation Consortium. Review of the Current Published Evidence for Single-Dose HPV Vaccination. 2nd ed. Seattle: PATH; 2019. https://path.azureedge.net/media/documents/SDHPV_Whitepaper_2019Final.pdf.
29. Blomberg M, Dehlendorff C, Sand C, Kjaer SK. Dose-related differences in effectiveness of human papillomavirus vaccination against genital warts: a nationwide study of 550,000 young girls. *Clinical Infectious Diseases*. 2015;61(5):676–682. <https://doi.org/10.1093/cid/civ364>.
30. Schiller J, Lowy D. Explanations for the high potency of HPV prophylactic vaccines. *Vaccine*. 2018;36(32 Pt A):4768–4773. <https://doi.org/10.1016/j.vaccine.2017.12.079>.

31. Stanley M. Prophylactic HPV vaccines. *Journal of Clinical Pathology*. 2007;60(9):961–965. <https://doi.org/10.1136/jcp.2006.040568>.
32. Stanley M. HPV - immune response to infection and vaccination. *Infectious Agents and Cancer*. 2010;5:19. <https://doi.org/10.1186/1750-9378-5-19>.
33. Stanley M, Pinto LA, Trimble C. Human papillomavirus vaccines--immune responses. *Vaccine*. 2012;30(Suppl 5):F83–F87. <https://doi.org/10.1016/j.vaccine.2012.04.106>.
34. Einstein MH, Takacs P, Chatterjee A, et al. Comparison of long-term immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18–45 years: end-of-study analysis of a Phase III randomized trial. *Human Vaccines & Immunotherapeutics*. 2014;10(12):3435–3445. <https://doi.org/10.4161/hv.36121>.
35. Schwarz TF, Huang LM, Lin TY, et al. Long-term immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in 10- to 14-year-old girls: open 6-year follow-up of an initial observer-blinded, randomized trial. *Pediatric Infectious Disease Journal*. 2014;33(12):1255–1261. <https://doi.org/10.1097/inf.0000000000000460>.
36. Nygard M, Saah A, Munk C, et al. Evaluation of the long-term anti-human papillomavirus 6 (HPV6), 11, 16, and 18 immune responses generated by the quadrivalent HPV vaccine. *Clinical and Vaccine Immunology*. 2015;22(8):943–948. <https://doi.org/10.1128/cvi.00133-15>.
37. Roteli-Martins CM, Naud P, de Borja P, et al. Sustained immunogenicity and efficacy of the HPV-16/18 AS04-adjuvanted vaccine: up to 8.4 years of follow-up. *Human Vaccines & Immunotherapeutics*. 2012;8(3):390–397. <https://doi.org/10.4161/hv.18865>.
38. Kreimer AR, Sampson JN, Porras C, et al. Evaluation of durability of a single dose of the bivalent HPV vaccine: the CVT trial. *Journal of the National Cancer Institute*. 2020;112(10):1038–1046. <https://doi.org/10.1093/jnci/djaa011>.
39. Sankaranarayanan R, Prabhu PR, Pawlita M, et al. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. *Lancet: Oncology*. 2016;17(1):67–77. [https://doi.org/10.1016/s1470-2045\(15\)00414-3](https://doi.org/10.1016/s1470-2045(15)00414-3).
40. Safaeian M, Porras C, Pan Y, et al. Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial. *Cancer Prevention Research*. 2013;6(11):1242–1250. <https://doi.org/10.1158/1940-6207.capr-13-0203>.
41. Kemp TJ, Safaeian M, Hildesheim A, et al. Kinetic and HPV infection effects on cross-type neutralizing antibody and avidity responses induced by Cervarix (®). *Vaccine*. 2012;31(1):165–170. <https://doi.org/10.1016/j.vaccine.2012.10.067>.
42. Amanna IJ, Slifka MK. Mechanisms that determine plasma cell lifespan and the duration of humoral immunity. *Immunological Reviews*. 2010;236(1):125–138. <https://doi.org/10.1111/j.1600-065x.2010.00912.x>.
43. Reddy ST, Rehor A, Schmoekel HG, Hubbell JA, Swartz MA. In vivo targeting of dendritic cells in lymph nodes with poly(propylene sulfide) nanoparticles. *Journal of Controlled Release*. 2006;112(1):26–34. <https://doi.org/10.1016/j.jconrel.2006.01.006>.
44. Link A, Zabel F, Schnetzler Y, Titz A, Brombacher F, Bachmann MF. Innate immunity mediates follicular transport of particulate but not soluble protein antigen. *Journal of Immunology*. 2012;188(8):3724–3733. <https://doi.org/10.4049/jimmunol.1103312>.
45. Bachmann MF, Jennings GT. Vaccine delivery: a matter of size, geometry, kinetics and molecular patterns. *Nature Reviews: Immunology*. 2010;10(11):787–796. <https://doi.org/10.1038/nri2868>.
46. Lenz P, Thompson CD, Day PM, Bacot SM, Lowy DR, Schiller JT. Interaction of papillomavirus virus-like particles with human myeloid antigen-presenting cells. *Clinical Immunology*. 2003;106(3):231–237. [https://doi.org/10.1016/s1521-6616\(02\)00039-6](https://doi.org/10.1016/s1521-6616(02)00039-6).
47. Bachmann MF, Rohrer UH, Kundig TM, Burki K, Hengartner H, Zinkernagel RM. The influence of antigen organization on B cell responsiveness. *Science*. 1993;262(5138):1448–1451. <https://doi.org/10.1126/science.8248784>.

48. Schiller J, Chackerian B. Why HIV virions have low numbers of envelope spikes: implications for vaccine development. *PLoS Pathogens*. 2014;10(8):e1004254. <https://doi.org/10.1371/journal.ppat.1004254>.
49. Jegerlehner A, Storni T, Lipowsky G, Schmid M, Pumpens P, Bachmann MF. Regulation of IgG antibody responses by epitope density and CD21-mediated costimulation. *European Journal of Immunology*. 2002;32(11):3305–3314. [https://doi.org/10.1002/1521-4141\(200211\)32:11%3C3305::aid-immu3305%3E3.0.co;2-j](https://doi.org/10.1002/1521-4141(200211)32:11%3C3305::aid-immu3305%3E3.0.co;2-j).
50. Chackerian B, Durfee MR, Schiller JT. Virus-like display of a neo-self antigen reverses B cell anergy in a B cell receptor transgenic mouse model. *Journal of Immunology*. 2008;180(9):5816–5825. <https://doi.org/10.4049/jimmunol.180.9.5816>.
51. Chackerian B, Lenz P, Lowy DR, Schiller JT. Determinants of autoantibody induction by conjugated papillomavirus virus-like particles. *Journal of Immunology*. 2002;169(11):6120–6126. <https://doi.org/10.4049/jimmunol.169.11.6120>.
52. Wardemann H, Yurasov S, Schaefer A, Young JW, Meffre E, Nussenzweig MC. Predominant autoantibody production by early human B cell precursors. *Science*. 2003;301(5638):1374–1377. <https://doi.org/10.1126/science.1086907>.
53. Yarkoni Y, Getahun A, Cambier JC. Molecular underpinning of B-cell anergy. *Immunological Reviews*. 2010;237(1):249–263. <https://doi.org/10.1111/j.1600-065x.2010.00936.x>.
54. Mendy M, Peterson I, Hossin S, et al. Observational study of vaccine efficacy 24 years after the start of hepatitis B vaccination in two Gambian villages: no need for a booster dose. *PloS One*. 2013;8(3):e58029. <https://doi.org/10.1371/journal.pone.0058029>.
55. Zhao Q, Li S, Yu H, Xia N, Modis Y. Virus-like particle-based human vaccines: quality assessment based on structural and functional properties. *Trends in Biotechnology*. 2013;31(11):654–663. <https://doi.org/10.1016/j.tibtech.2013.09.002>.
56. Amanna IJ, Raue HP, Slifka MK. Development of a new hydrogen peroxide-based vaccine platform. *Nature Medicine*. 2012;18(6):974–979. <https://doi.org/10.1038/nm.2763>.
57. Uruena A, Gonzalez JE, Rearte A, et al. Single-dose universal hepatitis A immunization in one-year-old children in Argentina: high prevalence of protective antibodies up to 9 years after vaccination. *Pediatric Infectious Disease Journal*. 2016;35(12):1339–1342. <https://doi.org/10.1097/inf.0000000000001322>.
58. Amanna IJ, Carlson NE, Slifka MK. Duration of humoral immunity to common viral and vaccine antigens. *New England Journal of Medicine*. 2007;357(19):1903–1915. <https://doi.org/10.1056/nejmoa066092>.
59. Doorbar J, Quint W, Banks L, et al. The biology and life-cycle of human papillomaviruses. *Vaccine*. 2012;30(Suppl 5):F55–F70. <https://doi.org/10.1016/j.vaccine.2012.06.083>.
60. Kines RC, Thompson CD, Lowy DR, Schiller JT, Day PM. The initial steps leading to papillomavirus infection occur on the basement membrane prior to cell surface binding. *Proceedings of the National Academy of Sciences of the United States of America*. 2009;106(48):20458–20463. <https://doi.org/10.1073/pnas.0908502106>.
61. Schiller JT, Lowy DR. Understanding and learning from the success of prophylactic human papillomavirus vaccines. *Nature Reviews: Microbiology*. 2012;10(10):681–692. <https://doi.org/10.1038/nrmicro2872>.
62. Li Z, Palaniyandi S, Zeng R, Tuo W, Roopenian DC, Zhu X. Transfer of IgG in the female genital tract by MHC class I-related neonatal Fc receptor (FcRn) confers protective immunity to vaginal infection. *Proceedings of the National Academy of Sciences of the United States of America*. 2011;108(11):4388–4393. <https://doi.org/10.1073/pnas.1012861108>.
63. Nardelli-Haeffliger D, Wirthner D, Schiller JT, et al. Specific antibody levels at the cervix during the menstrual cycle of women vaccinated with human papillomavirus 16 virus-like particles. *Journal of the National Cancer Institute*. 2003;95(15):1128–1137. <https://doi.org/10.1093/jnci/djg018>.

64. Day PM, Kines RC, Thompson CD, et al. In vivo mechanisms of vaccine-induced protection against HPV infection. *Cell Host & Microbe*. 2010;8(3):260–270. <https://doi.org/10.1016/j.chom.2010.08.003>.
65. Longet S, Schiller JT, Bobst M, Jichlinski P, Nardelli-Haeffliger D. A murine genital-challenge model is a sensitive measure of protective antibodies against human papillomavirus infection. *Journal of Virology*. 2011;85(24):13253–13259. <https://doi.org/10.1128/jvi.06093-11>.
66. Whitworth HS, Gallagher KE, Howard N, et al. Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to no vaccination or standard three and two-dose vaccination regimens: a systematic review of evidence from clinical trials. *Vaccine*. 2020;38(6):1302–1314. <https://doi.org/10.1016/j.vaccine.2019.12.017>.
67. Scherer EM, Smith RA, Gallego DF, et al. A single human papillomavirus vaccine dose improves B cell memory in previously infected subjects. *EBioMedicine*. 2016;10:55–64. <https://doi.org/10.1016/j.ebiom.2016.06.042>.
68. Arbyn M, Xu L, Simoons C, Martin-Hirsch PPL. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. *Cochrane Database of Systematic Reviews*. 2018;5(5):CD009069. <https://doi.org/10.1002/14651858.cd009069.pub3>.
69. Kreimer AR, Rodriguez AC, Hildesheim A, et al. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. *Journal of the National Cancer Institute*. 2011;103(19):1444–1451. <https://doi.org/10.1093/jnci/djr319>.
70. Kreimer AR, Struyf F, Del Rosario-Raymundo MR, et al. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA Trials. *Lancet: Oncology*. 2015;16(7):775–786. [https://doi.org/10.1016/s1470-2045\(15\)00047-9](https://doi.org/10.1016/s1470-2045(15)00047-9).
71. Safaeian M, Sampson JN, Pan Y, et al. Durability of protection afforded by fewer doses of the HPV16/18 vaccine: the CVT trial. *Journal of the National Cancer Institute*. 2018;110(2):205–212. <https://doi.org/10.1093/jnci/djx158>.
72. Sankaranarayanan R, Joshi S, Muwonge R, et al. Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study. *Vaccine*. 2018;36(32 Pt A):4783–4791. <https://doi.org/10.1016/j.vaccine.2018.02.087>.
73. Tsang SH, Sampson JN, Schussler J, et al. Durability of cross-protection by different schedules of the bivalent HPV vaccine: the CVT trial. *Journal of the National Cancer Institute*. 2020;112(10):1030–1037. <https://doi.org/10.1093/jnci/djaa010>.
74. Herrero R, Hildesheim A, Rodriguez AC, et al. Rationale and design of a community-based double-blind randomized clinical trial of an HPV 16 and 18 vaccine in Guanacaste, Costa Rica. *Vaccine*. 2008;26(37):4795–4808. <https://doi.org/10.1016/j.vaccine.2008.07.002>.
75. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet*. 2009;374(9686):301–314. [https://doi.org/10.1016/s0140-6736\(09\)61248-4](https://doi.org/10.1016/s0140-6736(09)61248-4).
76. ClinicalTrials.gov. NCT00923702: Randomised Trial of Two Versus Three Doses of Human Papillomavirus (HPV) Vaccine in India. <https://clinicaltrials.gov/ct2/show/NCT00923702>. Accessed June 30, 2019.
77. ClinicalTrials.gov. NCT00128661: A Double-Blind, Controlled, Randomized, Phase III Study of the Efficacy of an HPV16/18 VLP Vaccine in the Prevention of Advanced Cervical Intraepithelial Neoplasia (CIN2, CIN3, Adenocarcinoma In Situ [AIS] and Invasive Cervical Cancer) Associated With HPV 16 or HPV 18 Cervical Infection in Healthy Young Adult Women in Costa Rica. <https://www.clinicaltrials.gov/ct2/show/NCT00128661>. Accessed June 30, 2019.
78. Paavonen J, Jenkins D, Bosch FX, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an

- interim analysis of a phase III double-blind, randomised controlled trial. *Lancet*. 2007;369(9580):2161–2170. [https://doi.org/10.1016/s0140-6736\(07\)60946-5](https://doi.org/10.1016/s0140-6736(07)60946-5).
79. Zhu FC, Chen W, Hu YM, et al. Efficacy, immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese women aged 18-25 years: results from a randomized controlled trial. *International Journal of Cancer*. 2014;135(11):2612–2622. <https://doi.org/10.1002/ijc.28897>.
 80. Zhu FC, Hu SY, Hong Y, et al. Efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine in Chinese women aged 18-25 years: event-triggered analysis of a randomized controlled trial. *Cancer Medicine*. 2017;6(1):12–25. <https://doi.org/10.1002/cam4.869>.
 81. Herrero R, Wacholder S, Rodriguez AC, et al. Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: a community-based randomized clinical trial in Guanacaste, Costa Rica. *Cancer Discovery*. 2011;1(5):408–419. <https://doi.org/10.1158/2159-8290.cd-11-0131>.
 82. Hildesheim A, Wacholder S, Catteau G, et al. Efficacy of the HPV-16/18 vaccine: final according to protocol results from the blinded phase of the randomized Costa Rica HPV-16/18 vaccine trial. *Vaccine*. 2014;32(39):5087–5097. <https://doi.org/10.1016/j.vaccine.2014.06.038>.
 83. Lang Kuhs KA, Porras C, Schiller JT, et al. Effect of different human papillomavirus serological and DNA criteria on vaccine efficacy estimates. *American Journal of Epidemiology*. 2014;180(6):599–607. <https://doi.org/10.1093/aje/kwu168>.
 84. Castellsague X, Munoz N, Pitisuttithum P, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. *British Journal of Cancer*. 2011;105(1):28–37. <https://doi.org/10.1038/bjc.2011.185>.
 85. Munoz N, Manalastas R Jr, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. *Lancet*. 2009;373(9679):1949–1957. [https://doi.org/10.1016/s0140-6736\(09\)60691-7](https://doi.org/10.1016/s0140-6736(09)60691-7).
 86. Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *New England Journal of Medicine*. 2007;356(19):1915–1927. <https://doi.org/10.1056/nejmoa061741>.
 87. Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus type 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: final analysis of a phase 2 double-blind, randomized controlled trial. *International Journal of Gynecological Cancer*. 2010;20(5):847–855. <https://doi.org/10.1111/igc.0b013e3181da2128>.
 88. Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: interim analysis of a phase 2 double-blind, randomized, controlled trial. *International Journal of Gynecological Cancer*. 2010;20(3):404–410. <https://doi.org/10.1111/igc.0b013e3181d373a5>.
 89. Konno R, Yoshikawa H, Okutani M, et al. Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical intraepithelial neoplasia and cervical infection in young Japanese women. *Human Vaccines & Immunotherapeutics*. 2014;10(7):1781–1794. <https://doi.org/10.4161/hv.28712>.
 90. Lehtinen M, Paavonen J, Wheeler CM, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet: Oncology*. 2012;13(1):89–99. [https://doi.org/10.1016/s1470-2045\(11\)70286-8](https://doi.org/10.1016/s1470-2045(11)70286-8).
 91. Szarewski A, Poppe WAJ, Skinner SR, et al. Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in women aged 15-25 years with and without serological evidence of previous exposure to HPV-16/18. *International journal of cancer*. 2012;131(1):106–116. <https://doi.org/10.1002/ijc.26362>.

92. Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. *New England Journal of Medicine*. 2002;347(21):1645–1651. <https://doi.org/10.1056/nejmoa020586>.
93. Mao C, Koutsky LA, Ault KA, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. *Obstetrics and Gynecology*. 2006;107(1):18–27. <https://doi.org/10.1097/01.aog.0000192397.41191.fb>.
94. Rowhani-Rahbar A, Mao C, Hughes JP, et al. Longer term efficacy of a prophylactic monovalent human papillomavirus type 16 vaccine. *Vaccine*. 2009;27(41):5612–5619. <https://doi.org/10.1016/j.vaccine.2009.07.027>.
95. Skinner SR, Szarewski A, Romanowski B, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. *Lancet*. 2014;384(9961):2213–2227. [https://doi.org/10.1016/s0140-6736\(14\)60920-x](https://doi.org/10.1016/s0140-6736(14)60920-x).
96. Wheeler CM, Skinner SR, Del Rosario-Raymundo MR, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. *Lancet: Infectious Diseases*. 2016;16(10):1154–1168. [https://doi.org/10.1016/s1473-3099\(16\)30120-7](https://doi.org/10.1016/s1473-3099(16)30120-7).
97. Sankaranarayanan R, Bhatla N, Nene BM, Basu P. Single-dose efficacy using the bivalent HPV vaccine: Early results from an Indian study. *HPV World*. 2017;1(22):20-2. <https://www.hpvworld.com/articles/single-dose-ef-cacy-using-the-bivalent-hpv-vaccine-early-results-from-an-indian-study/>
98. Zanoni BC, Archary M, Buchan S, Katz IT, Haberer JE. Systematic review and meta-analysis of the adolescent HIV continuum of care in South Africa: the Cresting Wave. *BMJ Global Health*. 2016;1(3):e000004. <https://doi.org/10.1136/bmjgh-2015-000004>.
99. Kreimer AR, Herrero R, Sampson JN, et al. Evidence for single-dose protection by the bivalent HPV vaccine-Review of the Costa Rica HPV vaccine trial and future research studies. *Vaccine*. 2018;36(32 Pt A):4774–4782. <https://doi.org/10.1016/j.vaccine.2017.12.078>.
100. Wagner S, Roberson D, Boland J, et al. Development of the TypeSeq assay for detection of 51 human papillomavirus genotypes by next-generation sequencing. *Journal of Clinical Microbiology*. 2019;57(5):e01794-18. <https://doi.org/10.1128/jcm.01794-18>.
101. LaMontagne DS, Mugisha E, Pan Y, et al. Immunogenicity of bivalent HPV vaccine among partially vaccinated young adolescent girls in Uganda. *Vaccine*. 2014;32(47):6303-11. <https://doi.org/10.1016/j.vaccine.2014.08.071>.
102. LaMontagne DS, Barge S, Le NT, et al. Human papillomavirus vaccine delivery strategies that achieved high coverage in low- and middle-income countries. *Bulletin of the World Health Organization*. 2011;89(11):821–830b. <https://doi.org/10.2471/blt.11.089862>.
103. Toh ZQ, Russell FM, Reyburn R, et al. Sustained antibody responses 6 years following 1, 2, or 3 doses of quadrivalent human papillomavirus (HPV) vaccine in adolescent Fijian girls, and subsequent responses to a single dose of bivalent HPV vaccine: a prospective cohort study. *Clinical Infectious Diseases*. 2017;64(7):852–859. <https://doi.org/10.1093/cid/ciw865>.
104. Toh ZQ, Kosasih J, Russell FM, et al. Selective persistence of HPV cross-neutralising antibodies following reduced-dose HPV vaccine schedules. *Vaccines*. 2019;7(4):200. <https://doi.org/10.3390/vaccines7040200>.
105. Toh ZQ, Cheow KWB, Russell FM, et al. Cellular immune responses 6 years following 1, 2, or 3 doses of quadrivalent HPV vaccine in Fijian girls and subsequent responses to a dose of bivalent HPV vaccine. *Open Forum Infectious Diseases*. 2018;5(7):ofy147. <https://doi.org/10.1093/ofid/ofy147>.
106. ClinicalTrials.gov. NCT03431246: Persistence of Anti-HPV After a Single Dose of Gardasil and the Effect of a Dose of Gardasil-9 When Administered 3-8 Years Later. <https://clinicaltrials.gov/ct2/show/NCT03431246>. Accessed June 30, 2019.

107. Gilca V, Sauvageau C, Panicker G, et al. Long intervals between two doses of HPV vaccines and magnitude of the immune response: a post hoc analysis of two clinical trials. *Human Vaccines & Immunotherapeutics*. 2019;15(7–8):1980–1985. <https://doi.org/10.1080/21645515.2019.1605278>.
108. ClinicalTrials.gov. NCT02567955: Immunogenicity and Safety of Gardasil-9 and Cervarix When Administered to 9-10-year-old Subjects According to 0-6 Month Schedule. <https://clinicaltrials.gov/ct2/show/NCT02567955>. Accessed June 30, 2019.
109. Sauvageau C, Panicker G, Unger ER, et al. Priming effect of bivalent and quadrivalent vaccine for HPV 31/33/45/52: an exploratory analysis from two clinical trials. *Human vaccines & immunotherapeutics*. 2020;16(3):590–594. <https://doi.org/10.1080/21645515.2019.1669413>.
110. Moscicki AB, Karalius B, Tassiopoulos K, et al. Human papillomavirus antibody levels and quadrivalent vaccine clinical effectiveness in perinatally human immunodeficiency virus-infected and exposed, uninfected youth. *Clinical Infectious Diseases*. 2019;69(7):1183–1191. <https://doi.org/10.1093/cid/ciy1040>.
111. Hurt L, Nsouli-Maktabi H, Rohrbeck P, Clark LL. Use of quadrivalent human papillomavirus vaccine and the prevalence of antibodies to vaccine-targeted strains among female service members before and after vaccination. *MSMR*. 2016;23(2):6–13. <https://pubmed.ncbi.nlm.nih.gov/26930146/>.
112. Pasmans H, Schurink-Van't Klooster TM, Bogaard MJM, et al. Long-term HPV-specific immune response after one versus two and three doses of bivalent HPV vaccination in Dutch girls. *Vaccine*. 2019;37(49):7280–7288. <https://doi.org/10.1016/j.vaccine.2019.09.066>.
113. Batmunkh T, Dalmau MT, Munkhsaikhan ME, et al. A single dose of quadrivalent human papillomavirus (HPV) vaccine is immunogenic and reduces HPV detection rates in young women in Mongolia, six years after vaccination. *Vaccine*. 2020;38(27):4316–4324. <https://doi.org/10.1016/j.vaccine.2020.04.041>.
114. Markowitz LE, Drolet M, Perez N, Jit M, Brisson M. Human papillomavirus vaccine effectiveness by number of doses: systematic review of data from national immunization programs. *Vaccine*. 2018;36(32 Pt A):4806–4815. <https://doi.org/10.1016/j.vaccine.2018.01.057>.
115. Kavanagh K, Pollock KGJ, Potts A, et al. Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. *British Journal of Cancer*. 2014;110(11):2804–2811. <https://doi.org/10.1038/bjc.2014.198>.
116. Cuschieri K, Kavanagh K, Moore C, Bhatia R, Love J, Pollock KG. Impact of partial bivalent HPV vaccination on vaccine-type infection: a population-based analysis. *British Journal of Cancer*. 2016;114(11):1261–1264. <https://doi.org/10.1038/bjc.2016.97>.
117. Herweijer E, Leval A, Ploner A, et al. Association of varying number of doses of quadrivalent human papillomavirus vaccine with incidence of condyloma. *JAMA*. 2014;311(6):597–603. <https://doi.org/10.1001/jama.2014.95>.
118. Dominiak-Felden G, Gobbo C, Simondon F. Evaluating the early benefit of quadrivalent HPV vaccine on genital warts in Belgium: a cohort study. *PloS One*. 2015;10(7):e0132404. <https://doi.org/10.1371/journal.pone.0132404>.
119. Perkins RB, Lin M, Wallington SF, Hanchate A. Impact of number of human papillomavirus vaccine doses on genital warts diagnoses among a national cohort of U.S. adolescents. *Sexually Transmitted Diseases*. 2017;44(6):365–370. <https://doi.org/10.1097/olq.0000000000000615>.
120. Navarro-Illana E, Lopez-Lacort M, Navarro-Illana P, Vilata JJ, Diez-Domingo J. Effectiveness of HPV vaccines against genital warts in women from Valencia, Spain. *Vaccine*. 2017;35(25):3342–3346. <https://doi.org/10.1016/j.vaccine.2017.04.080>.
121. Lamb F, Herweijer E, Ploner A, et al. Timing of two versus three doses of quadrivalent HPV vaccine and associated effectiveness against condyloma in Sweden: a nationwide cohort study. *BMJ Open*. 2017;7(6):e015021. <https://doi.org/10.1136/bmjopen-2016-015021>.
122. Gertig DM, Brotherton JML, Budd AC, Drennan K, Chappell G, Saville AM. Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. *BMC Medicine*. 2013;11:227. <https://doi.org/10.1186/1741-7015-11-227>.

123. Crowe E, Pandeya N, Brotherton JM, et al. Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. *BMJ*. 2014;348:g1458. <https://doi.org/10.1136/bmj.g1458>.
124. Brotherton JML, Malloy M, Budd AC, Saville M, Drennan KT, Gertig DM. Effectiveness of less than three doses of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia when administered using a standard dose spacing schedule: observational cohort of young women in Australia. *Papillomavirus Research*. 2015;1:59–73. <https://doi.org/10.1016/j.pvr.2015.05.005>.
125. Hofstetter AM, Ompad DC, Stockwell MS, Rosenthal SL, Soren K. Human papillomavirus vaccination and cervical cytology outcomes among urban low-income minority females. *JAMA Pediatrics*. 2016;170(5):445–452. <https://doi.org/10.1001/jamapediatrics.2015.3926>.
126. Kim J, Bell C, Sun M, et al. Effect of human papillomavirus vaccination on cervical cancer screening in Alberta. *CMAJ: Canadian Medical Association Journal*. 2016;188(12):E281–E288. <https://doi.org/10.1503/cmaj.151528>.
127. Pollock KGJ, Kavanagh K, Potts A, et al. Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. *British Journal of Cancer*. 2014;111(9):1824–1830. <https://doi.org/10.1038/bjc.2014.479>.
128. Kavanagh K, Pollock KG, Cuschieri K, et al. Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. *Lancet: Infectious Diseases*. 2017;17(12):1293–1302. [https://doi.org/10.1016/s1473-3099\(17\)30468-1](https://doi.org/10.1016/s1473-3099(17)30468-1).
129. Chandler E, Ding L, Gorbach P, et al. Epidemiology of any and vaccine-type anogenital human papillomavirus among 13–26-year-old young men after HPV vaccine introduction. *Journal of Adolescent Health*. 2018;63(1):43–49. <https://doi.org/10.1016/j.jadohealth.2018.01.005>.
130. Hariri S, Schuler MS, Naleway AL, et al. Human papillomavirus vaccine effectiveness against incident genital warts among female health-plan enrollees, United States. *American Journal of Epidemiology*. 2018;187(2):298–305. <https://doi.org/10.1093/aje/kwx253>.
131. Zeybek B, Lin YL, Kuo YF, Rodriguez AM. The impact of varying numbers of quadrivalent human papillomavirus vaccine doses on anogenital warts in the United States: a database study. *Journal of Lower Genital Tract Disease*. 2018;22(3):189–194. <https://doi.org/10.1097/lgt.0000000000000401>.
132. Willows K, Bozat-Emre S, Righolt CH, Kliewer EV, Mahmud SM. Early evidence of the effectiveness of the human papillomavirus vaccination program against anogenital warts in Manitoba, Canada: a registry cohort study. *Sexually Transmitted Diseases*. 2018;45(4):254–259. <https://doi.org/10.1097/olq.0000000000000742>.
133. Silverberg MJ, Leyden WA, Lam JO, et al. Effectiveness of catch-up human papillomavirus vaccination on incident cervical neoplasia in a US health-care setting: a population-based case-control study. *Lancet: Child & Adolescent Health*. 2018;2(10):707–714.
134. Cameron RL, Kavanagh K, Cameron Watt DC, et al. The impact of bivalent HPV vaccine on cervical intraepithelial neoplasia by deprivation in Scotland: reducing the gap. *Journal of Epidemiology and Community Health*. 2017;71(10):954–960. <https://doi.org/10.1136/jech-2017-209113>.
135. Dehlendorff C, Sparen P, Baldur-Felskov B, et al. Effectiveness of varying number of doses and timing between doses of quadrivalent HPV vaccine against severe cervical lesions. *Vaccine*. 2018;36(43):6373–6378. <https://doi.org/10.1016/j.vaccine.2018.09.011>.
136. Verdoodt F, Dehlendorff C, Kjaer SK. Dose-related effectiveness of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia: a Danish nationwide cohort study. *Clinical Infectious Diseases*. 2019;70(4):608–614. <https://doi.org/10.1093/cid/ciz239>.
137. Markowitz LE, Naleway AL, Klein NP, et al. Human papillomavirus vaccine effectiveness against HPV infection: evaluation of one, two, and three doses. *Journal of Infectious Diseases*. 2020;221(6):910–918. <https://doi.org/10.1093/infdis/jiz555>.

138. Johnson Jones ML, Gargano JW, Powell M, et al. Effectiveness of 1, 2, and 3 doses of human papillomavirus vaccine against high-grade cervical lesions positive for human papillomavirus 16 or 18. *American Journal of Epidemiology*. 2020;189(4):265–276. <https://doi.org/10.1093/aje/kwz253>.
139. Innes CR, Williman JA, Simcock BJ, et al. Impact of human papillomavirus vaccination on rates of abnormal cervical cytology and histology in young New Zealand women. *New Zealand Medical Journal*. 2020;133(1508):72–84. <https://pubmed.ncbi.nlm.nih.gov/31945044/>.
140. Widdice LE, Bernstein DI, Franco EL, et al. Decline in vaccine-type human papillomavirus prevalence in young men from a Midwest metropolitan area of the United States over the six years after vaccine introduction. *Vaccine*. 2019;37(45):6832–6841. <https://doi.org/10.1016/j.vaccine.2019.08.052>.
141. Sonawane K, Nyitray AG, Nemutlu GS, Swartz MD, Chhatwal J, Deshmukh AA. Prevalence of human papillomavirus infection by number of vaccine doses among US women. *JAMA Network Open*. 2019;2(12):e1918571. <https://doi.org/10.1001/jamanetworkopen.2019.18571>.
142. Palmer T, Wallace L, Pollock KG, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. *BMJ*. 2019;365:l1161. <https://doi.org/10.1136/bmj.l1161>.
143. Brotherton JMI, Budd A, Rompotis C, et al. Is one dose of human papillomavirus vaccine as effective as three?: a national cohort analysis. *Papillomavirus Research*. 2019;8:100177. <https://doi.org/10.1016/j.pvr.2019.100177>.
144. Rodriguez AM, Zeybek B, Vaughn M, et al. Comparison of the long-term impact and clinical outcomes of fewer doses and standard doses of human papillomavirus vaccine in the United States: a database study. *Cancer*. 2020;126(8):1656–1667. <https://doi.org/10.1002/cncr.32700>.
145. Hariri S, Bennett NM, Niccolai LM, et al. Reduction in HPV 16/18-associated high grade cervical lesions following HPV vaccine introduction in the United States - 2008-2012. *Vaccine*. 2015;33(13):1608–1613. <https://doi.org/10.1016/j.vaccine.2015.01.084>.
146. Leung TF, Liu APY, Lim FS, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine administered according to 2- and 3-dose schedules in girls aged 9-14 years: results to month 12 from a randomized trial. *Human Vaccines & Immunotherapeutics*. 2015;11(7):1689–1702. <https://doi.org/10.1080/21645515.2015.1050570>.
147. Iversen OE, Miranda MJ, Ulied A, et al. Immunogenicity of the 9-valent HPV vaccine using 2-dose regimens in girls and boys vs a 3-dose regimen in women. *JAMA*. 2016;316(22):2411–2421. <https://doi.org/10.1001/jama.2016.17615>.
148. Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination - updated recommendations of the advisory committee on immunization practices. *MMWR Morbidity and Mortality Weekly Report*. 2016;65(49):1405–1408.
149. Batmunkh T, von Mollendorf C, Tulgaa K, et al. HPV genoprevalence and HPV knowledge in young women in Mongolia, five years following a pilot 4vHPV vaccination campaign. *Papillomavirus Research*. 2019;8:100175. <https://doi.org/10.1016/j.pvr.2019.100175>.
150. Brisson M, Benard E, Drolet M, et al. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. *Lancet Public Health*. 2016;1(1):e8–e17. [https://doi.org/10.1016/s2468-2667\(16\)30001-9](https://doi.org/10.1016/s2468-2667(16)30001-9).
151. Jit M, Levin C, Brisson M, et al. Economic analyses to support decisions about HPV vaccination in low- and middle-income countries: a consensus report and guide for analysts. *BMC Medicine*. 2013;11:23. <https://doi.org/10.1186/1741-7015-11-23>.
152. Canfell K, Chesson H, Kulasingam SL, Berkhof J, Diaz M, Kim JJ. Modeling preventative strategies against human papillomavirus-related disease in developed countries. *Vaccine*. 2012;30(Suppl 5):F157–F167. <https://doi.org/10.1016/j.vaccine.2012.06.091>.

153. Brisson M, Van de Velde N, Boily MC. Economic evaluation of human papillomavirus vaccination in developed countries. *Public Health Genomics*. 2009;12(5-6):343–351. <https://doi.org/10.1159/000214924>.
154. Kim JJ, Brisson M, Edmunds WJ, Goldie SJ. Modeling cervical cancer prevention in developed countries. *Vaccine*. 2008;26(Suppl 10):K76–K86. <https://doi.org/10.1016/j.vaccine.2008.06.009>.
155. Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. *Value in Health*. 2012;15(6):843–850. <https://doi.org/10.1016/j.jval.2012.04.012>.
156. Van de Velde N, Brisson M, Boily MC. Understanding differences in predictions of HPV vaccine effectiveness: a comparative model-based analysis. *Vaccine*. 2010;28(33):5473–5484. <https://doi.org/10.1016/j.vaccine.2010.05.056>.
157. Molden T, Nygard JF, Kraus I, et al. Predicting CIN2+ when detecting HPV mRNA and DNA by PreTect HPV-proofer and consensus PCR: a 2-year follow-up of women with ASCUS or LSIL Pap smear. *International Journal of Cancer*. 2005;114(6):973–976. <https://doi.org/10.1002/ijc.20839>.
158. Gervais F, Jiang Y, Langeron N, Nikoglou T. Critical review of cost-effectiveness analyses (CEA) of prevention strategies against diseases associated with human papillomavirus (HPV) infection. *Value in Health*. 2014;17(7):A637. <https://doi.org/10.1016/j.jval.2014.08.2288>.
159. Fesenfeld M, Hutubessy R, Jit M. Cost-effectiveness of human papillomavirus vaccination in low and middle income countries: a systematic review. *Vaccine*. 2013;31(37):3786–3804. <https://doi.org/10.1016/j.vaccine.2013.06.060>.
160. Seto K, Marra F, Raymakers A, Marra CA. The cost effectiveness of human papillomavirus vaccines: a systematic review. *Drugs*. 2012;72(5):715–743. <https://doi.org/10.2165/11599470-000000000-00000>.
161. Armstrong EP. Prophylaxis of cervical cancer and related cervical disease: a review of the cost-effectiveness of vaccination against oncogenic HPV types. *Journal of Managed Care Pharmacy*. 2010;16(3):217–230. <https://doi.org/10.18553/jmcp.2010.16.3.217>.
162. Marra F, Cloutier K, Oteng B, Marra C, Ogilvie G. Effectiveness and cost effectiveness of human papillomavirus vaccine: a systematic review. *Pharmacoeconomics*. 2009;27(2):127–147. <https://doi.org/10.2165/00019053-200927020-00004>.
163. Jit M, Choi YH, Laprise JF, Boily MC, Drolet M, Brisson M. Two-dose strategies for human papillomavirus vaccination: how well do they need to protect? *Vaccine*. 2014;32(26):3237–3242. <https://doi.org/10.1016/j.vaccine.2014.03.098>.
164. Jit M, Brisson M, Laprise J-F, Choi YH. Comparison of two dose and three dose human papillomavirus vaccine schedules: cost effectiveness analysis based on transmission model. *BMJ*. 2015;350:g7584. <https://doi.org/10.1136/bmj.g7584>.
165. Laprise JF, Drolet M, Boily MC, et al. Comparing the cost-effectiveness of two- and three-dose schedules of human papillomavirus vaccination: a transmission-dynamic modelling study. *Vaccine*. 2014;32(44):5845–5853. <https://doi.org/10.1016/j.vaccine.2014.07.099>.
166. Laprise JF, Markowitz LE, Chesson HW, Drolet M, Brisson M. Comparison of 2-dose and 3-dose 9-valent human papillomavirus vaccine schedules in the United States: a cost-effectiveness analysis. *Journal of Infectious Diseases*. 2016;214(5):685–688. <https://doi.org/10.1093/infdis/jiw227>.
167. Jit M, Laprise JF, Choi YH, Brisson M. Fewer than three doses of HPV vaccine. *Lancet: Oncology*. 2015;16(9):e423–e424. [https://doi.org/10.1016/s1470-2045\(15\)00229-6](https://doi.org/10.1016/s1470-2045(15)00229-6).
168. Kim J. Could 1 dose be less efficacious than 2 doses but still be a great public health intervention? *HPV World*. 2017;1(30):26–28. https://www.hpvworld.com/media/29/media_section/0/5/1605/kim.pdf.
169. Burger E, Campos N, Sy S, Regan C, Kim J. Health and economic benefits of single-dose HPV vaccination in a GAVI-eligible country. *Vaccine*. 2018;36(32 Pt A):4823–4829. <https://doi.org/10.1016/j.vaccine.2018.04.061>.

170. Tan N, Sharma M, Winer R, Galloway D, Rees H, Barnabas RV. Model-estimated effectiveness of single dose 9-valent HPV vaccination for HIV-positive and HIV-negative females in South Africa. *Vaccine*. 2018;36(32 Pt A):4830–4836. <https://doi.org/10.1016/j.vaccine.2018.02.023>.
171. ClinicalTrials.gov. NCT03309033: Fifteen Years of Immunologic Follow-Up of Women Who Received One, Two, and Three Doses of the Bivalent HPV Vaccine in the Costa Rica HPV-16/18 Vaccine Trial (CVT): Generating Durability Data: The ESCUDDO-CVT Study. <https://clinicaltrials.gov/ct2/show/NCT03309033>. Accessed June 30, 2019.
172. ClinicalTrials.gov. NCT00867464: Extended Follow-up of Young Women in Costa Rica Who Received Vaccination Against Human Papillomavirus Types 16 and 18 and Unvaccinated Controls. <https://clinicaltrials.gov/ct2/show/NCT00867464>. Accessed June 30, 2019.
173. ClinicalTrials.gov. NCT03728881: Non-Inferiority Trial Comparing Immunogenicity From 1-Dose of Bivalent HPV Vaccine in Girls to 3-Doses of Quadrivalent Vaccine in Women: The PRIMAVERA-ESCUDDO Trial ("Puente de Respuesta Inmunológica Para Mejorar el Acceso a Vacunas y ERradicar el Cancer"). <https://clinicaltrials.gov/ct2/show/NCT03728881>. Accessed June 30, 2019.
174. Wits RHI to Launch the First HPV Vaccine Impact Evaluation Project in Africa. <http://www.wrhi.ac.za/media/detail/wits-rhi-to-launch-the-first-hpv-vaccine-impact-evaluation-project-in-afric05> February 2019. Accessed June 30, 2019.
175. Clinicaltrials.gov. NCT02568566: A Prospective, Single-Arm, Open-Label, Non-Randomized, Phase IIA Trial of a Nonavalent Prophylactic HPV Vaccine to Assess Immunogenicity of a Prime and Deferred-Booster Dosing Schedule Among 9-11 Year-Old Girls and Boys. <https://clinicaltrials.gov/ct2/show/NCT02568566>. Accessed June 30, 2019.
176. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. <https://doi.org/10.1136/bmj.i4919>.
177. Clinicaltrials.gov. NCT03675256: KENya Single-dose HPV-vaccine Efficacy - The KEN-SHE Study. <https://clinicaltrials.gov/ct2/show/NCT03675256>. Accessed June 30, 2019.
178. ClinicalTrials.gov. NCT02834637: A Dose Reduction Immunobridging and Safety Study of Two HPV Vaccines in Tanzanian Girls. <https://clinicaltrials.gov/ct2/show/NCT02834637>. Accessed June 30, 2019.

Appendix 1:

Contributors and acknowledgments

Table 14. Individuals that contributed to the evidence review
(in alphabetical order)

Name	Initials	Institution / Affiliation
Basu, Partha	PB	International Agency for Research on Cancer
Brisson, Marc	MB	Université Laval
Campos, Nicole	NC	Harvard T.H. Chan School of Public Health
Clarke, Ed	EC	London School of Hygiene & Tropical Medicine
Drolet, Mélanie	MD	Université Laval
Gallagher, Katherine	KG	London School of Hygiene & Tropical Medicine
Henão Restrepo, Ana Maria	AMHR	World Health Organization
Howard, Natasha	NH	London School of Hygiene & Tropical Medicine
Hutubessy, Raymond	RH	World Health Organization
Jit, Mark	MJ	London School of Hygiene & Tropical Medicine
Kelly, Helen	HK	London School of Hygiene & Tropical Medicine
Kim, Jane	JK	Harvard T.H. Chan School of Public Health
Kreimer, Aimée	AK	National Cancer Institute
LaMontagne, D. Scott	DSL	PATH
Lewis, Rayleen	RL	Centers for Disease Control and Prevention
Markowitz, Lauri	LM	Centers for Disease Control and Prevention
Mounier-Jack, Sandra	SMJ	London School of Hygiene & Tropical Medicine
Ogilvie, Gina	GO	University of British Columbia
Perez, Norma	NP	Université Laval
Schiller, John	JS	National Cancer Institute
Watson-Jones, Deborah	DWJ	London School of Hygiene & Tropical Medicine
Whitworth, Hilary Sian	HSW	London School of Hygiene & Tropical Medicine

The Costa Rica vaccine trial (CVT) on the human papillomavirus (HPV) is a long-standing collaboration between investigators in Costa Rica and the US National Cancer Institute (NCI). The trial is sponsored and funded by the NCI (contract N01-CP-11005), with funding support from the National Institutes of Health Office of Research on Women's Health. GlaxoSmithKline Biologicals provided vaccine and support for aspects of the trial associated with regulatory submission needs of the company under a Clinical Trials Agreement (FDA BB-IND 7920) during the four-year, randomized, blinded phase of our study.

Investigators in the CVT group are as follows:

- *Proyecto Epidemiológico Guanacaste, Fundación INCIENSA, San José, Costa Rica*: Bernal Cortés (specimen and repository manager), Paula González (LTFU: co-principal investigator), Rolando Herrero (CVT: co-principal investigator), Silvia E. Jiménez (trial coordinator), Carolina Porras (coinvestigator), Ana Cecilia Rodríguez (coinvestigator).
- *US NCI, Bethesda, MD, United States*: Allan Hildesheim (co-principal investigator & NCI co-project officer), Aimée R. Kreimer (LTFU: co-principal investigator & NCI co-project officer), Douglas R. Lowy (HPV virologist), Mark Schiffman (CVT: medical monitor & NCI co-project officer), John T. Schiller (HPV virologist), Mark Sherman (CVT: quality control pathologist), Sholom Wacholder (statistician).
- Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, MD, United States (HPV Immunology Laboratory): Ligia A. Pinto, Troy J. Kemp.
- Georgetown University, Washington, DC, United States: Mary K. Sidawy (CVT: histopathologist).
- DDL Diagnostic Laboratory, Netherlands (HPV DNA Testing): Wim Quint, Leen-Jan van Doorn, Linda Struijk.
- *University of California, San Francisco, CA, United States*: Joel M. Palefsky (expert on anal HPV infection and disease diagnosis and management), Teresa M. Darragh (pathologist and clinical management).
- University of Virginia, Charlottesville, VA, United States: Mark H. Stoler (quality control pathologist).

Appendix 2:

Summary of updates

Newly available information provided in this 3rd edition compared to the 2nd edition is summarized below.

Table 15. Summary of new information

SECTION	SUMMARY OF NEW INFORMATION
1 – INTRODUCTION AND BACKGROUND	
1.1 Cervical cancer burden	Information has been provided on the Global Strategy for cervical cancer elimination, including 2030 targets.
1.2 Licensed HPV vaccines	Information on the new bivalent vaccine, Cecolin® (Xiamen Inovax Biotech Co. Limited, China), has been added. Table 1 has been updated accordingly.
1.3 HPV vaccine schedules and introduction	Reference has been made to the impact of the global HPV vaccine shortage and COVID-19 pandemic on HPV vaccine introduction and rollout.
1.4 Rationale for this evidence review	The scope of the 3rd edition of the evidence review has been described.
2 – EVIDENCE FROM STUDIES ON SINGLE-DOSE HPV VACCINATION	
2.1 Biological plausibility for single-dose protection	No new information has been provided.
2.2 Clinical trials of HPV vaccines	Two new relevant studies, published since the 2nd edition of the evidence review, have been described. Both of the new studies evaluate further observational data arising from the Costa Rica vaccine trial (CVT). Tables 2 to 7 have been updated accordingly.
2.3 Non-trial immunogenicity studies of partially vaccinated populations	Four new relevant studies, published since the 2nd edition of the evidence review, have been described. One of the new studies evaluates further data arising from the Fijian study, and one evaluates further data from the Canadian study. The other two studies are from Mongolia and the Netherlands. Tables 8 and 9 have been updated accordingly.
2.4 Post-licensure vaccine effectiveness evaluations and other observational data	Results from an update to the previously described systematic review are presented. The updated search found nine new relevant studies: five from the United States, and one each from Australia, New Zealand, Scotland, and Mongolia. Tables 10 and 11 have been updated accordingly.
2.5 Mathematical modeling of the impact of reduced dosing schedules	No new information has been provided.
3 – SUMMARY OF THE AVAILABLE EVIDENCE	
-	This summary has been updated to reflect the newly available evidence described in sections 2.2 to 2.4.
4– STRENGTHS AND WEAKNESSES OF THE EVIDENCE	
-	This section has been updated to reflect the strengths and limitations of the newly available evidence described in sections 2.2 to 2.4. Table 12 has been updated accordingly.
5 – GAPS IN THE EVIDENCE, RESEARCH PRIORITIES & FORTHCOMING EVIDENCE	
5.1 Efficacy and immunogenicity data from randomized controlled trials and observational studies	Updated information has been provided as applicable for ongoing studies, including the International Agency for Research on Cancer's India HPV vaccine trial, CVT, and DoRIS. Figure 5 has been updated accordingly.
5.2 Effectiveness data from post-licensure observational studies	No new information has been provided.
5.3 Modeling studies	No new information has been provided.

Abbreviations: DoRIS, Dose Reduction Immunobridging and Safety study HPV, HPV, human papillomavirus.

Single-Dose HPV Vaccine
EVALUATION CONSORTIUM

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

For information about the Single-Dose HPV Vaccine Evaluation Consortium, visit path.org/singledosehpv.

Inquiries about this project can be directed to Evan Simpson at PATH, 2201 Westlake Avenue, Suite 200, Seattle, WA 98121, USA, esimpson@path.org. November 2020.