EVIDENCE REVIEW

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

4th 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	*Chlamydia trachomatis*
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
IFNy	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 15 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 suggests that a single dose of 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. It also identifies remaining gaps for single-dose HPV vaccination within the context of immunization. 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, the Wits Reproductive Health and HIV Institute at the University of Witwatersrand, and the Kirby Institute at University of New South Wales.

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.

Note to reader: This evidence review draws information directly from other publications, including previous evidence reviews, and is edited for use in this paper. Text that appears in bold type is information new to this 4th edition.

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 2020, the International Agency for Research on Cancer (IARC) estimated that there were nearly 605,000 new cases of CC and over 341,000 CC–related deaths per annum globally, with greater than 85% of invasive CC cases occurring in LMIC (2). 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 November 2020, WHO launched the global strategy to accelerate the elimination of cervical cancer as a public health problem, with the following targets by 2030: (a) vaccination of 90% of girls with HPV vaccine by 15 years of age, (b) screening of 70% of women for CC by 35 and 45 years of age, and (c) treatment of 90% of women diagnosed with cervical disease (5). In 2019, it was estimated that only 15% of the world's age-eligible female population was fully vaccinated against HPV (5).

1.3 Licensed HPV vaccines

Primary prevention of CC is possible through vaccination with one of four licensed vaccines. The two bivalent HPV (2vHPV) vaccines, Cervarix™ (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; 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 (referred to hereafter as the GSK 2vHPV and Merck 4vHPV vaccines, respectively) received WHO prequalification in 2009, and Gardasil-9 (referred to hereafter as the Merck 9vHPV vaccine) received prequalification in 2018; these vaccines are licensed in many countries worldwide. **Cecolin (referred to hereafter as the Innovax 2vHPV vaccine) is licensed in China and received WHO prequalification in October 2021.** The vaccines are highly efficacious against persistent infection with vaccine genotypes (6, 7).

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. In addition to the five additional VLPs, the 9vHPV vaccine has an increased amount of VLPs for HPV 6, 16, and 18 compared to the 4vHPV vaccine (8). 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 Adjuvant System 4, which is a combination of the Toll-like receptor 4 agonist monophosphoryl lipid A and aluminum hydroxide, and which provides direct stimulation of antigen-presenting cells, pronounced cellular and humoral immune responses, and long-lasting antibody responses (9). The GSK 2vHPV vaccine contains a similar amount of aluminum salt as the Merck 9vHPV vaccine. The Innovax 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.

1.4 HPV vaccine schedules and introduction

The 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 its introduction in LIC.

In 2014, the WHO SAGE on Immunization revised its recommendations from a schedule of three doses to a schedule of two doses, administered with an interval of at least six months, for the GSK 2vHPV and Merck 4vHPV vaccines, for girls aged 9 to 14 years (10). This revised recommendation was based on evidence of non-inferior antibody responses in female adolescents aged 9 to 14 years compared with women for whom efficacy was demonstrated in clinical trials with a three-dose schedule (11-13). WHO guidelines allow for flexibility in the timing of 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) (14). 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 (14, 15).

Even though LMIC bear the greatest burden of CC and the highest mortality rates due to the disease (16), the 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 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 to 25 years is substantially higher in HIC and upper-middle-income countries than in LIC (5, 17).

Several factors have influenced the slower introduction of HPV vaccines in LMIC. These include the initial cost of the vaccines and a delay in the provision of financial mechanisms to support countries in obtaining the vaccine, which was partly due to the economic climate when HPV vaccines became available. Other challenges have included the absence of a mechanism for rapid vaccine introduction, previous Gavi requirements that demonstration projects are 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 had 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 the introduction and expansion of national HPV vaccination programs in some countries (20). The COVID-19 pandemic (caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) has had a further impact on HPV vaccine rollout. It is now estimated that only 13% of the targeted population is fully vaccinated globally, a decrease from the 15% pre-pandemic coverage (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 the 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 several reasons following accumulating

evidence along several lines: biologic plausibility based on an 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 Immune markers of HPV vaccine-induced protection

Currently, no immune marker, antibody concentration, or other immune measurement has been defined that correlates with vaccine protection against HPV infection. The pseudovirion-based neutralization assay (PBNA) is the "gold standard" for the detection of HPV antibodies. However, comparisons between seroepidemiological studies are difficult due to the use of different serological assays and the lack of a reference serum for establishing cutoff values (23). 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 relatively scarce (24). 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 six months and one year after HPV vaccination (24, 25).

1.6 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 many LMIC. Clinical trial data, 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. Ongoing randomized controlled trials (RCT) will provide further high-quality evidence regarding the efficacy and immunogenicity of a single dose schedule (26-29).

This paper is an updated version (4th edition) of previous editions (1st edition, April 30, 2018; 2nd edition, June 30, 2019; 3rd edition, November 30, 2020) (30-32), aiming to assess and summarize (i) the current published evidence on the efficacy, effectiveness, immunogenicity, impact and cost-effectiveness of single-dose schedules of HPV vaccine; (ii) the strength of that evidence; and (iii) the gaps in the evidence and how these are being addressed through new and ongoing research. 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. As noted in the overview, significant updates made in this 4th edition of the evidence review are highlighted in **bold**.

Sources of evidence covered in this paper include publicly available scientific publications on: (1) the biological plausibility for protection with single-dose HPV vaccine, based on vaccine immune response and virological data; (2) efficacy and immunogenicity data from clinical trials in which participants were prospectively randomized to receive a single HPV vaccine dose versus a comparator vaccine or vaccine schedule; (3) non-randomized data from partially vaccinated participants in clinical trials and immunogenicity studies; (4) data from post-licensure vaccine effectiveness evaluations and other observational data; and (5) mathematical modeling of the impact of reduced dosing schedules for HPV vaccines. The 4th edition of this paper builds on previous versions by including further evidence published up to January 2022. Key updates presented in this edition are highlighted in the box below.

It is envisaged that this evidence could be used in policy conversations with key global stakeholders, such as the WHO Immunization and Vaccines Implementation Research Advisory Committee and SAGE, as well as national level policy bodies such as National Immunization Technical Advisory Groups.

KEY UPDATES IN THIS EDITION OF THE EVIDENCE REVIEW

- Results are presented from the KEN-SHE trial—the first prospectively randomized, controlled trial to evaluate the efficacy of a single dose of HPV vaccine (the GSK 2vHPV vaccine or the Merck 9vHPV vaccine). KEN-SHE randomized 2,275 sexually active Kenyan women aged 15 to 20 years to receive HPV vaccine or a control vaccine and assessed vaccine efficacy against incident persistent vaccine-type HPV infection at 18 months post-vaccination. (Section 2.2.3.1)
- Results are presented from the DoRIS trial—the first prospectively randomized trial to compare immunological responses to single versus multidose HPV vaccination (using the GSK 2vHPV vaccine or the Merck 9vHPV vaccine). DoRIS was conducted in Tanzania among 930 schoolgirls aged 9 to 14 years, and is therefore also the first prospectively randomized trial of single-dose HPV vaccine in the target age range for vaccination. Girls received one, two or three vaccine doses, and antibody responses to vaccine type HPV were evaluated up to 24 months post-vaccination. (Section 2.2.3.2)
- Long term (≥9 year) observational data are presented on vaccine-induced protection against HPV infection, CIN and invasive CC outcomes, and on durability and stability of immune responses, following one, two or three doses of HPV vaccine among participants from earlier clinical trials (the Costa Rica Vaccine Trial (CVT) and the IARC India HPV Vaccine Trial) who completed or failed to complete an allocated multidose schedule. (Section 2.2.2)

KEY UPDATES IN THIS EDITION OF THE EVIDENCE REVIEW (cont.)

- Findings are presented from an updated systematic review on the effectiveness of one versus two versus three doses of HPV vaccine from post-licensure observational studies. Newly included articles (added since the systematic review was presented in the previous editions of this paper) address some of the biases observed in earlier studies, for example by evaluating individuals vaccinated at a younger age or stratifying analyses by age at vaccination. A formal quality assessment of studies included in the review is also presented. (Section 2.4.1)
- Evidence is summarized from four new studies that used mathematical modeling to evaluate the impact and cost-effectiveness of reduced dose HPV vaccine schedules. These studies: evaluated HPV vaccination strategies under various scenarios, including single-dose vaccination, extended dose schedules and catch-up vaccination; projected the impact and cost-effectiveness of one-dose versus two-dose 9vHPV vaccination in 192 countries; and estimated the impact of delaying implementation of single-dose HPV vaccination. (Section 2.5.3)

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	*Trichoplusia ni* (Hi 5) insect cell line infected with L1 recombinant baculovirus	*Saccharomyces cervisiae* (baker's yeast) expressing L1	*Saccharomyces cervisiae* (baker's yeast) expressing L1	*E.coli* 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 (10, 33).

[e] In some countries, Cervarix™, Gardasil®, and Gardasil-9® 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 (14, 15).

[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, 1 and 6 months is recommended.

Source: Table adapted from (6) and updated for dosing schedule licensure modifications and global vaccination recommendations (14, 15).

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 reviewed after observational data from several clinical studies suggested that a single dose of HPV vaccine could provide protection against HPV infection (34). Below, we provide a summary of a comprehensive review published in 2018 (34); sections 2.1.2 and 2.1.3 were excerpted from the review and edited and updated for this paper.

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 (see Section 1.5).

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 (35). 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” (36).

2.1.2 The immunogenicity of a single vaccine dose

The exceptionally strong, consistent, and durable antibody responses to the three HPV vaccines is well documented (37). In healthy young women, seroconversion rates are virtually 100%, peak in vitro neutralizing titers of 1,000 to 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 (38). Responses in preadolescent girls and boys are even stronger (11, 39). The stability of antibody responses, now observed for over ten years post-vaccination (40-42), is unprecedented for a subunit vaccine.

Surprisingly, this pattern of antibody response is observed even after a single dose of vaccine, with stable geometric mean (GM) IgG binding and in vitro neutralizing titers that are about four-fold lower than the plateau titers measured after the standard three doses (42-44). 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 (45). The long-term antibody levels, regardless of dose number, are almost certainly due to efficient induction of LLPC, which primarily reside in the bone marrow and continuously produce antibodies, probably independent of additional antigen exposure (46). 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 (47). 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 (48). 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 (49). 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 (50). 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 (51). Epitope spacing at this distance is found on the surface of most viruses—HIV being a notable exception (52)—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 (53).

The high-density display on a VLP surface can efficiently break B-cell peripheral tolerance and even reactivate anergic self-reactive B cells (54, 55). The BCRs on a majority of newly produced B cells are thought to bind self-antigens, which renders them functionally anergic (56, 57). 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 (58). 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 pentameters for HPV) (59). 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 (60). 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 (61).

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 (62) has previously been attributed to the infectious nature of the inoculum. Considering 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

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 (63). 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 (64) (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 (65).

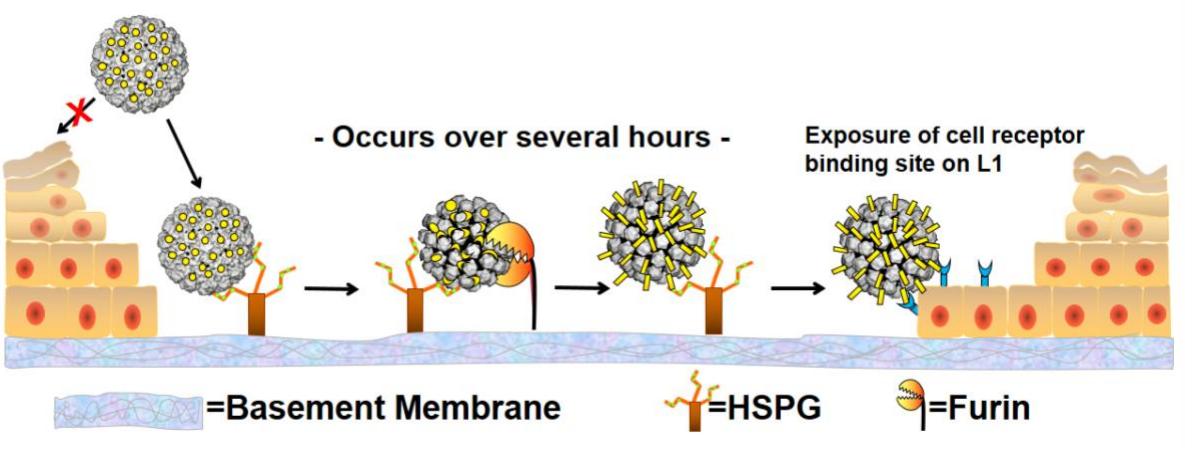
First, exposure of the basement membrane to the virus requires disruption of the epithelial barrier, which results in direct exudation of capillary and interstitial antibodies at these sites. A consequence of this event is that HPV encounters systemic antibodies at potential sites of infection. This 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 (66). 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) (67) 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 (64). 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 (68). 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 (65). The observation that antibody levels that are more than a hundredfold lower than the minimum level detected in the in vitro neutralizing assay can 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 (69).

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 (68). 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 (34).

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, levels, or avidity. 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 derived from a systematic review, conducted initially in 2018–2019 and subsequently updated in 2021 and 2022, that evaluated the peer-reviewed, published literature on single-dose HPV vaccination from clinical trials (70). When the database searches for the systematic review were conducted (August 2018, July 2021, and February 2022), there were no published, peer-reviewed 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 and unblinded pilot intervention study in ten individuals compared immunological responses in HPV 16-seropositive women after a single dose with no vaccination (71). Thus, most evidence in the systematic review comes from comparisons made between clinical trial participants who completed or failed to complete standard two- or three-dose schedules.

Importantly, additional data have recently become available from two randomized trials evaluating single-dose HPV vaccination in East Africa. These are the first RCT data from girls or women who were prospectively randomized to receive one dose of HPV vaccine versus a comparator. The two clinical trials were not included in the systematic review described above as they did not have published, peer-reviewed data available at the time of the most recent database search.

2.2.2 Systematic review of evidence on single-dose HPV vaccination from clinical trials up to February 2022

2.2.2.1 DESIGN

The available published and peer-reviewed 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 (70). 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?
- How do immune responses to a one-dose HPV vaccination schedule compare to those induced by 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 (sub-sections within Section 2.2.2) include excerpts from the published systematic review of the trials data (70), as well as excepts from an earlier narrative review on the evidence for single dose protection from the GSK 2vHPV vaccine (72). 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.

Updated searches were conducted to identify any further relevant articles that became available between August 14, 2018 and February 4, 2022.

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.

In the 2021 and 2022 updates to the systematic review, articles related to studies in which participants received the Innovax 2vHPV vaccine were also eligible for inclusion.

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 intervals (CIs), 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 articles 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 2018 database and hand searches, seven articles were included in the systematic review (43, 44, 71, 73-76) (Figure 2; Table 2). Of these, six were considered to describe 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 (43, 44, 71, 73-76). One small, randomized study prospectively allocated participants to receive a single-dose HPV vaccine versus no vaccination (71). **The updated 2021 and 2022 searches identified three additional relevant articles, all of which described observational evaluations nested within clinical trials (Figure 3; Table 2) (42, 77, 78).**

2.2.2.6 NESTED OBSERVATIONAL STUDIES OF SINGLE-DOSE HPV VACCINATION

All six articles of observational evaluations included in the initial systematic review were based on data from three clinical trials. Two articles (43, 76) were based on the IARC trial of two versus three doses of HPV vaccine in India (43). Three articles (44, 73, 75) were based on the Costa Rica vaccine trial (CVT) for HPV (79), and one (74) was based on combined data from CVT and the PApilloma TRIal against Cancer In young Adults, or PATRICIA (80).

Two of the new articles from the systematic review updates present further analyses from the CVT (42, 77). The third and most recent article, published in October 2021, presents further analyses from the IARC India trial.

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 to 18 years in

India (43, 81). 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 articles arising from the IARC India HPV vaccine trial identified in the 2018 systematic review search, 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) (43). 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 (76). A supplementary cohort of married, unvaccinated females aged 18 to 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 2013 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.

The most recent article arising from the IARC India HPV vaccine trial presents data up to 10 years post vaccination. As at earlier timepoints, HPV infection data were evaluated using cervical specimens collected at 18 months after marriage or 6 months after first childbirth (whichever was earlier). In addition, cervical screening was conducted among married participants as they turned 25 years of age and among an age-matched control group of unvaccinated women, allowing evaluation of CIN and invasive cancer outcomes.

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 to 25 years in two regions of Costa Rica (79, 82). 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 potential for one-dose efficacy was first described in CVT in a post-hoc analysis of incident, 12-month persistent HPV infection detected 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) (73). Subsequent articles describe HPV vaccine-induced immunogenicity up to four years following the first vaccine dose for the same dosing schedules (44) and HPV infection and immunogenicity data up to seven years (75). At the completion of the randomized, blinded phase of CVT, control participants were offered the HPV vaccine. Thus, for the 2018 evaluation, 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 single-dose HPV vaccination to multidose schedules, one evaluates single-dose vaccine efficacy against HPV 16/18 infection and immunogenicity data more than a decade post-vaccination (42), and the other evaluates cross protection against HPV 31/33/45 up to the same time point (77).

PATRICIA

This was a large-scale, phase III, double-blind RCT among healthy women aged 15 to 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 (80). 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 article identified for inclusion in the systematic review reports a post-hoc analysis of combined CVT and PATRICIA data (74). This article 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 identified by the systematic review was a small pilot study conducted in the United States, aimed at evaluating whether a single dose of HPV vaccine in participants with prior HPV 16 infection just boosts antibody levels or also improves the quality of the B-cell memory (71). The study randomized ten healthy HPV 16–seropositive women aged 27 to 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

HPV 16/18 infection results for participants who received a single HPV vaccine dose compared to any comparator group are reported in seven of the above articles (42, 43, 73-76, 78). HPV infection–related outcome measures most commonly reported include one-time or cumulative incident infection

and 6- or 12-month persistent infection. Three articles report results up to 4 years post-vaccination (43, 73, 74), two up to 7 years (75, 76), one up to 10 years (78) and one up to 11 years (42). 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 seven articles. 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

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, two doses, or one dose, indicating that they were at similar risk for acquiring HPV infections regardless of the number of HAV doses they received (73). 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 (73, 75).

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 7-year 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 against cumulative persistent HPV infection (75). The four-year efficacy against HPV 16 or 18 infections that persisted for at least six months among women who were HPV DNA negative for these types at first vaccination was as follows: 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).

Data from the long-term follow up study showed sustained protection from reduced-dose schedules. Among the participants who received one dose, no HPV 16/18 cervical infections were detectable at year 7 (among 134 women), and only 2 infections were detectable at years 9 or 11 (1.8% among 112 women). This was similar to women who received the three-dose regimen, where there were 20 HPV 16/18 infections among 2,043 women (1.0%) at year 7, and 27 infections among 1,365 women (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 and unvaccinated 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.

HPV infection and vaccine protection data from IARC India vaccine trial

Incident and persistent HPV 16/18 infection over ten years from vaccination were uniformly low in all the vaccinated study groups, and considerably lower in vaccinated participants compared to unvaccinated controls. Incident infections were detected in 3.2% (95% CI 2.6-3.9%) of one-dose participants, 2.7% (95% CI 2.1-3.5%) of two-dose (0,6m) participants, 3.0% (95% CI 2.3-3.8%) of three-dose participants and 9.4% (95% CI 7.9-11.0%) of unvaccinated controls. HPV 16/18 infections that persisted for 10 or more months were detected in just one participant from each of the one-dose (0.0%, 95% CI 0.0-0.3%), two-dose (0.1%, 95% CI 0.0.1-0.4%) and three-dose groups (0.1%, 95% CI 0.0-0.4%), compared with 32 unvaccinated controls (2.5%, 95% CI 1.7-3.6). Adjusted for a disease risk score (described below), VE against persistent HPV 16/18 infection was 95.4% (95% CI 85.0-99.9%) with one vaccine dose, 93.1% (95%CI 77.3-99.8%) with two doses, and 93.3% (95% CI 77.5-99.7%) with three doses.

Among women who were eligible for cervical cancer screening, two (0.1%) single-dose recipients, four (0.3%) two-dose recipients, one (0.1%) three-dose recipient and 63 (1.4%) unvaccinated controls tested positive for HPV 16/18 infection. There was only one case of HPV 16/18-positive CIN1 (in the two-dose arm) among vaccinated participants, and no cases of HPV 16/18-positive CIN2 or CIN3 or invasive cervical cancer. For comparison, there were eight cases of HPV 16/18-positive CIN (5x CIN1, 2x CIN2, 1x CIN3) among unvaccinated controls. One case of invasive cervical cancer was identified in the control group, but it was not associated with HPV 16/18.

2.2.2.9 IMMUNOGENICITY RESULTS

Trials review summary

HPV 16/18 humoral immunogenicity results for participants who received a single dose of HPV vaccine compared to any comparator group are reported in six of the above articles (43, 44, 71, 75, 76). HPV 16/18 immunogenicity-related outcome measures most commonly reported include 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 articles are summarized in **Table 5**.

Table 6 summarizes seropositivity and antibody-level results for the five articles comparing a single-dose schedule versus other 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 articles. 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. 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

Among women who received one HPV vaccine 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 nine-fold higher for HPV 16 and five-fold higher for HPV 18) four years after initial vaccination (44). Titers remained stably elevated at 11 years post-vaccination at approximately two- to four-fold lower levels than for three doses (42).

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 (44). 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 ($p=0.6$).

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 those tested were 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 (43) 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 (43): 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 NAbs to HPV 16 and 18 but at lower concentration than 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

In the small randomized study (71), 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 (71). Two women had 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 articles 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 articles. 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 New data from prospectively randomized trials of single-dose HPV vaccination

2.2.3.1 THE KEN-SHE TRIAL

The KEN-SHE trial is a multi-center randomized, controlled and double-blind efficacy trial comparing a single dose of the Merck 9vHPV or GSK 2vHPV vaccine with a non-HPV vaccine placebo (single-dose meningococcal vaccination) among sexually active girls and women aged 15 to 20 years in Kenya (83, 84). The following text on the trial design, methods and results (within Section 2.2.3.1) is an excerpt from a publication for the primary trials results up to 18 months post vaccination (83) and was edited for this paper.

KEN-SHE design and methods

The study was conducted at three KEMRI clinical sites in Thika, Nairobi, and Kisumu. Participants were recruited through community outreach. Participants were eligible for randomization if they were able to provide informed consent, age 15 to 20 years old, of female sex assigned at birth, sexually active with one to five lifetime partners, and resident within the study area. Study ineligibility criteria were a positive HIV diagnostic test, history of HPV vaccination, allergies to vaccine components or latex, current pregnancy, hysterectomy, or history of immunosuppressive conditions.

Participants were randomized to 1) immediate Merck 9vHPV vaccination and delayed (36 months after enrollment) meningococcal vaccination, 2) immediate GSK 2vHPV vaccination and delayed meningococcal vaccination, or 3) immediate meningococcal vaccination and delayed HPV vaccination. Study staff, participants, investigators, clinic staff, lab technicians,

and other study team members did not have access to the randomization codes, except for the unblinded statistical analysts and unblinded pharmacists at each site.

Participants were seen at months 3, 6, 12 and 18 post-vaccination. Cervical and/or vaginal swabs were collected six-monthly. HPV DNA genotyping was conducted in Kenya using the Anyplex II HPV28 assay (Seegene, Seoul, South Korea), a multiplexed type-specific real-time PCR based assay. Serum specimens were shipped to the UW, Seattle, WA, US, and tested at the Galloway Lab, Fred Hutchinson Cancer Research Center. HPV IgG antibodies were detected using a multiplex Luminex assay.

The primary trial endpoint was incident persistent cervical HPV infection among participants who tested HPV DNA negative at enrollment and month 3 and HPV antibody negative at enrollment (the modified intent-to-treat (mITT) cohort). For inclusion in the HPV 16/18 mITT cohort, participants had to be HPV 16/18 naive. Similarly, for the HPV 16/18/31/33/45/52/58 mITT cohort (9vHPV participants only), participants were HPV 16/18/31/33/45/52/58 naive. Persistent HPV, a surrogate marker for cervical dysplasia/precancer, was defined as high-risk vaccine type specific HPV detected at two consecutive time points ≥4 months apart after month 3 and up to and including month 18 (same HPV type at both time points) for the primary analysis. Cervical swabs were tested for the primary endpoint; vaginal swabs were substituted if necessary.

Sensitivity analysis was planned on participants who tested HPV DNA negative at enrollment, month three and month six, and antibody negative at enrollment (extended sensitivity cohort), to match the analysis cohort for HPV vaccine licensure trials. The extended sensitivity cohort analysis used all available data, including visits after the pre-specified month 18 data cut.

KEN-SHE trial results

Between December 20, 2018, and November 15, 2019, 3,090 participants were screened for study eligibility and 2,275 (74%) were enrolled. Among 1,458 participants meeting criteria for the primary HPV 16/18 mITT analysis, 496 were in the Merck 9vHPV group, 489 were in the GSK 2vHPV group, and 473 were in the meningococcal group. Of 615 participants eligible for the primary HPV 16/18/31/33/45/52/58 analysis, 325 were in the 9vHPV and 290 were in the meningococcal vaccine group. The median age was 17 years for both mITT cohorts; and, overall, the baseline characteristics by study groups were comparable. By the month 18 visit, retention for assessment of the primary endpoints was 98% for two swabs and 94% for three swabs. The cumulative incidence of chlamydia and gonorrhea was comparable across the three study groups.

A total of 38 incident persistent infections were detected in the HPV 16/18 mITT cohort: one each among participants assigned to the 2vHPV and 9vHPV vaccine groups and 36 among those assigned to the meningococcal vaccine group. The incidence of persistent HPV 16/18 was 0.17 per 100 woman-years in the HPV vaccine groups, compared to 6.83 per 100 woman-years in the meningococcal vaccine control group. 2vHPV VE was 97.5% (95% CI 81.7-99.7%, p=<0.0001) and 9vHPV VE was 97.5% (95% CI 81.6-99.7%, p=<0.0001).

Thirty-three incident persistent infections were detected in the HPV 16/18/31/33/45/52/58 mITT cohort: four in the 9vHPV vaccine group and 29 in the meningococcal vaccine group. The incidence of persistent HPV 16/18/31/33/45/52/58 was 1.03 per 100 woman-years in the 9vHPV vaccine group compared to 9.42 per 100 woman-years in the meningococcal group. 9vHPV VE for HPV 16/18/31/33/45/52/58 was 88.9% (95% CI 68.5-96.1%, p<0.0001).

In the extended sensitivity analysis, there were a total of 16 incident persistent infections in the HPV 16/18 mITT cohort: 0 among participants assigned to the HPV vaccine groups and 16 among those assigned to the meningococcal vaccine group. HPV 16/18 incidence was 0 per 100 women-years in the HPV vaccine groups and 3.9 per 100 women years in the meningococcal control group; HPV vaccine VE was 100% (p<0.0001). There was a total of 15 incident persistent infections in the HPV 16/18/31/33/45/52/58 mITT cohort: one among participants assigned to the 9vHPV group and 14 among those assigned to the meningococcal group; 9vHPV VE was 95.0% (95% CI 62.1-99.4%, p=<0.0001).

2.2.3.2 THE DORIS TRIAL

The DoRIS trial (full title: 'A Dose Reduction Immunobridging and Safety Study of two HPV vaccines in Tanzanian girls') is an unblinded randomized, controlled immunogenicity and immunobridging trial comparing one versus two versus three doses of either the Merck 9vHPV vaccine or the GSK 2vHPV vaccine among girls aged 9 to 14 years in Tanzania (85, 86). The following text on the trial design, methods and results (within Section 2.2.3.2) has been excerpted from a non-peer reviewed pre-print article describing the primary within-trial immunogenicity results up to 24 months post-vaccination (86). The content was edited for this paper.

DoRIS trial design and methods

The co-primary trial objectives of the DoRIS trial were: (1) to determine whether a single dose of HPV vaccine produces immune responses that are non-inferior to those following two and three doses when given to HIV negative girls aged 9 to 14 years in a malaria-endemic region of Tanzania, and (2) to demonstrate non-inferiority of HPV 16/18 antibody GMTs at M24 when comparing the single-dose regimen of either vaccine with historical cohorts of women aged 10 to

25 years who received one dose, in whom efficacy has been demonstrated (described below in section 2.2.3.3).

Participants were recruited from primary and secondary government schools in Mwanza city. Girls were eligible for inclusion if they were healthy, HIV-negative, aged 9 to 14 years, planning to be resident in Mwanza for 36 months, and willing to give informed assent following informed consent from a parent or guardian. Participants were randomly allocated to one of 6 arms comprising three different dose schedules of the GSK 2vHPV vaccine or the Merck 9vHPV vaccine, administered as three doses over 6 months, two doses given 6 months apart or a single dose.

Before the first vaccine dose was given, blood samples were collected for immunogenicity assays and HSV-2 serology. In addition, girls were asked to collect two nurse-assisted, self-administered vaginal swabs for baseline HPV DNA testing and genotyping. Subsequent blood samples were collected for immunogenicity assays at M1, 7, 12, 24 and 36.

The Anyplex II HPV28 detection assay (Seegene, South Korea) was used for baseline vaginal swabs HPV DNA detection and genotyping at the Catalan Institute of Oncology in Barcelona. HPV 16/18 IgG serostatus using an L1 VLP enzyme-linked immunosorbent assay (ELISA) was determined at the HPV Immunology Laboratory of the Frederick National Laboratory for Cancer Research in Maryland, USA. HPV 16/18 specific antibody avidity index was determined by the ratio of antibody concentrations in serum samples treated or not treated with Guanidine-HCl (GuHCl) in ELISA.

The primary outcome was non-inferiority of HPV 16/18-specific seropositivity following one dose of HPV vaccine compared with two or three doses of the same vaccine at M24. Secondary outcomes included HPV 16/18 antibody GMTs and seropositivity at other timepoints, antibody avidity, comparison of immune responses after two versus three doses, and comparisons of the same dose regimen between vaccine types.

For each vaccine type and HPV genotype, the difference (with 95% CIs) in the proportion of girls who were seropositive were calculated for one versus two doses and for one versus three doses. Non-inferiority of seropositivity was concluded if the lower bound of the two-sided 95% CI for the difference was above –5%. Non-inferiority of the antibody GMT was concluded if the lower bound for the two-sided 95% CI for the GMT ratio for one versus two doses or for one versus three doses was above 0.50. The primary immunogenicity analyses were done in the per-protocol cohort, i.e., participants who received the allocated doses of HPV vaccine in the protocol-defined window and who were HPV antibody negative and HPV DNA negative at enrolment for the specific HPV genotype under analysis. As a sensitivity analysis, analyses were

repeated in participants who received at least one dose of HPV vaccine (total vaccinated cohort).

DoRIS trial results

Overall, 995 individuals were screened for eligibility between February 2017 and January 2018, of whom 930 (93%) were enrolled and randomized. Retention at M24 was 99%. Only 20 (2%) girls had evidence for any HPV infection on their vaginal swabs at baseline, of whom 4 girls were positive for HPV 16 or HPV 18 DNA. In total, 57 girls (6%) were HPV 16 seropositive and 81 (9%) were HPV 18 seropositive.

At M24, 918 and 831 girls were included in the per-protocol analysis of antibody responses to HPV 16 and HPV 18, respectively. All but 2 participants (>99%) were seropositive for anti-HPV 16 IgG antibodies at M24; one in each of the single-dose arms were seronegative. All but 6 participants were seropositive for anti-HPV 18 IgG antibodies at M2: 2 in the single-dose 2vHPV vaccine arm, 3 in the single-dose 9vHPV vaccine arm, and 1 in the three-dose 9vHPV vaccine arm. Non-inferiority of seroconversion for anti-HPV 16 antibodies was met for one dose compared with two or three doses of both vaccines at months 7, 12 and 24. Although non-inferiority was not met for seroconversion for anti HPV 18 antibodies, ≥98% of girls in the single-dose arms of both vaccines were anti-HPV 18 antibody positive at M24.

Antibody GMTs at M24 among girls in the per-protocol cohort who received one dose of the 2vHPV vaccine were 23 IU/mL (95% CI=20-26) for HPV 16 and 10 IU/mL (95% CI=9-11) for HPV 18. Among those receiving one dose of the 9vHPV vaccine, GMTs were 14 IU/mL (95%CI=12 -16) and 6 IU/mL (95%CI=5-7), respectively. HPV 16 and HPV 18 GMTs were higher among girls receiving two and three doses of vaccine compared to those receiving one dose and were higher for HPV 16 compared to HPV 18. Among girls receiving two doses of the 2vHPV vaccine, HPV 16 and HPV 18 GMT levels were 163 IU/mL (95% CI=142 -188) and 50 IU/mL (95% CI=43-58), respectively, and for those receiving two doses of the 9vHPV vaccine, they were 126 IU/mL (95% CI=108 -146) and 29 IU/mL (95% CI=25-35), respectively.

For both vaccines and HPV genotypes, GMTs among the two dose and three dose recipients peaked at M7 and declined thereafter up until M24. Among the single-dose recipients, GMTs remained relatively constant over time from M7 through M24, for both vaccine types.

In contrast with antibody GMTs, there was no evidence of a difference between the one, two and three dose schedules in the geometric mean antibody AI for HPV 16 or HPV 18 for both vaccines. AI ratios were around 1.0 for all comparisons, with the lower limit of the 95% CI exceeding 0.90 in all but one comparison (GM avidity index ratio comparing one dose with three doses of the 2-valent vaccine=0.93, 95%CI=0.88-0.97).

Immunogenicity results were similar among the total vaccinated cohort, for both vaccines and both HPV genotypes.

2.2.3.3 IMMUNOBRIDGING BETWEEN THE DORIS, CVT AND IARC INDIA TRIALS

An immunobridging study was conducted to compare vaccine-induced immune responses in DoRIS trial single-dose participants with those in historical cohorts of girls and young women who received only one HPV vaccine dose, in whom efficacy has been demonstrated. Specifically, HPV 16 and HPV 18 antibody responses results from the DoRIS trial were compared with those from the CVT and the IARC India trial (both of which were included in the above systematic review of single-dose HPV vaccination). CVT and the India trial were selected for immunobridging because they are the only two large-scale studies that evaluated a one-dose schedule (albeit non-prospectively) with long-term (9-11 year) efficacy follow-up. The following text on the study design, methods and results (within Section 2.2.3.3) has been excerpted from a non-peer reviewed pre-print article describing the immunobridging results at 24 months post-vaccination (87). The content was edited for this paper.

Immunobridging methods

As described above, the primary immunobridging objective was to demonstrate non-inferiority of HPV 16/18 antibody GMT at M24 post-vaccination. A secondary immunobridging objective was to demonstrate non-inferiority of HPV 16/18 seropositivity at M24.

The immunobridging analysis included all girls in the single dose arms in the DoRIS trial who had a blood sample taken at M24 (within the allowable window of 22-28 months), and a similar number (n=140) of randomly selected samples from participants in the CVT and India trials who received only one dose of HPV vaccine, had a blood sample taken at M24, had sufficient serum available at D0 and M24 for re-testing, and had efficacy data available. The one dose 2vHPV vaccine arm in DoRIS was compared with one dose 2vHPV vaccine in the CVT; the one dose 9vHPV vaccine arm in DoRIS was compared with one dose 4vHPV vaccine in the India trial.

Antibodies to HPV 16 and HPV 18 were measured in samples from all three trials by the anti-VLP ELISA assay at the Frederick National Laboratory for Cancer Research HPV Immunology Laboratory in Maryland, USA. Samples for the immunobridging analyses (D0 and M24) from the three trials were batched and tested together.

The primary immunobridging analysis was in the per-protocol cohort: participants who received only one dose of HPV vaccine and who were HPV antibody negative (for the DoRIS/CVT and the DoRIS/India comparisons), and HPV DNA negative (DoRIS/CVT

comparison) at enrolment for the specific genotype under analysis. Secondary analyses included all participants who received one dose of HPV vaccine irrespective of baseline antibody or HPV DNA status.

For each vaccine type and HPV genotype, the M24 GMT ratios with 95% CIs were calculated for one dose DoRIS versus one dose CVT, and for one dose DoRIS versus one dose India. Non-inferiority of the antibody response was concluded if the lower bound for the two-sided 95% CI for the GMT ratio was above 0.50, Similarly, the difference (one dose DoRIS minus one dose comparison cohort) in the proportion seropositive was calculated with 95% CI, and non-inferiority of seropositivity was concluded if the lower bound of the two-sided 95% CI for the difference was above –5%.

In a secondary analysis, comparisons between DoRIS and India were adjusted for age. In addition, a post-hoc sub-group analysis was done restricted to girls who were aged less than 15 years at the time of vaccination. Since there was no overlap between DoRIS and CVT in the age ranges, no adjustment for age was done.

Immunobridging results

Overall, 154 (99.4%) DoRIS participants in the single-dose 2vHPV vaccine arm and 152 (98.1%) in the single-dose 9vHPV vaccine arm attended the M24 visit within the 22 to 28 month window and thus were eligible for the immunobridging analysis. In the CVT, 115 of 277 single-dose recipients met the eligibility requirements and were included in the immunobridging analysis. In the India trial, 139 single-dose recipients were randomly sampled from the 150 who met the eligibility requirements. Baseline characteristics were similar between the two single-dose arms in the DoRIS trial, but DoRIS participants were younger (median (IQR) = 10 years (9-12)) than the single-dose recipients in the CVT (median = 21 years (19-23)) and India trial (median = 14 years (13-16)). Baseline HPV 16/18 seropositivity was similar between the DoRIS and India trial participants, and lower in DoRIS than in CVT, consistent with the older age range of the latter trial.

The primary immunobridging analysis at M24 included 521 (92.4%) participants from the 3 trials for HPV 16, and 503 (89.2%) for HPV 18. Antibody levels among single-dose 2vHPV recipients in DoRIS were higher and were non-inferior to those among single-dose 2vHPV recipients in CVT for both HPV genotypes, with GMT ratios (DoRIS/CVT) of 1.30 (95% CI=1.00-1.68) for HPV 16 and 1.23 (95% CI=0.95-1.60) for HP V18. Non-inferiority was also met for seropositivity, with a difference in seroconversion (DoRIS/CVT) of 0.4% (95% CI= -3.1-5.1) for HPV 16 and -0.4% (95% CI = -4.4-4.4) for HPV 18.

For both HPV genotypes, antibody levels among single-dose 9vHPV recipients in DoRIS were higher and non-inferior to those among single-dose 4vHPV recipients in the India trial, with GMT ratios (DoRIS/India) of 2.05 (95% CI=1.61-2.61) for HPV 16, and 2.57 (95% CI=2.02-3.27) for HPV 18. After adjusting for age, the GMT ratios were 1.29 (95% CI=0.91-1.82) and 1.75 (95% CI=1.22-2.50) for HPV 16 and HPV 18, respectively. Seropositivity rates at M24 were also higher in the DoRIS trial than in the India trial, with a difference (DoRIS-India) of 6.9% (95% CI= 2.4-13.1) for HPV 16 and 21.0% (95% CI=13.5-29.5) for HPV 18.

Similar results were seen among the total vaccinated cohort, for both vaccines and both HPV genotypes. In the sub-group analysis restricted to girls aged less than 15 years in the India trial, the results were also similar, with age-adjusted GMT ratios (DoRIS/India) of 1.29 (95% CI=0.94-1.76) for HPV 16, and 1.75 (95% CI=1.23-2.49) for HPV 18. Although the power calculations were based on a non-inferiority margin of 0.5 for the GMT ratio, the lower limit of the 95% CI of the GMT ratio was above the more stringent margin of 0.75 in all comparisons, for both vaccines and HPV genotypes.

2.2.4 Other relevant immunogenicity data from clinical trials

Merck has recently published results comparing two versus three doses of their 9vHPV vaccine over three years of follow-up in a multi-national, randomized, open-label trial of both girls and boys aged 9 to 14 years (88). The study was not included in the systematic review above because it did not compare participants receiving a single dose of vaccine to unvaccinated participants or to those receiving a multidose schedule. However, the authors did conduct a post-hoc analysis of antibody responses following the first vaccine dose, before administration of the second dose, among participants receiving a two-dose schedule with a 6- or 12-month interval.

The study used two different assays to measure vaccine induced antibody responses. Using the HPV competitive Luminex immunoassay (cLIA), the proportion of participants who were seropositive to HPV 16 was 95.6% and 98.1% at month 6 in boys and girls, respectively, receiving a 0- and 6-month schedule, and 89.7% at month 12 in boys and girls receiving a 0- and 12-month schedule. Using the HPV IgG LIA, the corresponding proportions who were seropositive were higher at 100.0%, 99.6% and 98.8%. Seropositivity for HPV 18 was considerably lower when using the HPV cLIA, at 60.9% and 72.1% for boys and girls, respectively at month 6, and at 56.6% at month 12. However, HPV 18 seropositivity was high using the HPV IgG LIA at 97.7%, 98.4% and 88.8%, respectively. Numbers of participants contributing to analyses at one month post dose one were very small (just n=2 in some cases) and the resulting wide confidence intervals mean that results from this timepoint are difficult to interpret.

Using both assays, antibody GMTs were similar at 1- and 6-months post dose one in participants receiving a 0- and 6-month schedule (again with the caveat that confidence intervals at month 1 were very wide due to small participant numbers). Overall, antibody GMTs were lower at month 12 in participants receiving a 0- and 12-month schedule than at month 6 in those receiving a 0- and 6-month schedule. However, month 6 GMTs were lower in boys than in girls, and GMTs were comparable between boys at month 6 and boys and girls at month 12.

2.2.5 Strengths and weaknesses of evidence from clinical trials

2.2.5.1 STRENGTHS AND WEAKNESSES OF THE DORIS AND KEN-SHE TRIALS

The KEN-SHE and DoRIS trials are the first studies to prospectively randomize participants to receive one dose of HPV versus a comparator (placebo in KEN-SHE; two or three vaccine doses in DoRIS); KEN-SHE is the first randomized trial to provide efficacy data, and DoRIS the first to provide immunogenicity data. KEN-SHE included sexually active girls and women aged 15 to 20 years, allowing sufficient accumulation of HPV infection events to provide crucial efficacy data within a relatively short follow up time. Conversely, this meant that the age range of the KEN-SHE study population was outside the target age range for HPV vaccination (9 to 14 years). The age range was dictated by the need to assess a sexually active population and collect efficacy endpoints following exposure to the virus. However, the analyses aimed to assess the performance of the vaccine in a population presumed naïve to the vaccine types. The DoRIS trial, on the other hand, is the first trial of single-dose HPV vaccination in this target age range.

The KEN-SHE trial compared single-dose HPV vaccination to placebo, but not to two or three dose vaccine schedules. An efficacy trial evaluating non-inferiority of one dose versus a multidose schedule (as is taking place in the ongoing 'ESCUDDO' trial, described below in Section 5.1) would be considered the "gold standard"; however, this would require considerably higher participant numbers and longer follow up duration in view of the very high VE of single-dose HPV vaccination demonstrated in KEN-SHE. Given the global HPV elimination goal, and the ongoing inequalities in HPV vaccine introduction and coverage in LMIC compared to HIC, single-dose HPV vaccine efficacy data are urgently needed. Regardless of the lack of intra-study comparison with multidose schedules, KEN-SHE demonstrated very high efficacy (almost 98%) of single-dose HPV vaccination, comparable to efficacy estimates of multidose schedules from previous RCTs.

To date, follow-up of KEN-SHE participants is complete to 18 months post-vaccination. Earlier studies have demonstrated that antibody GMTs plateau by 18 months and are durable up to 11 years post-vaccination. Nonetheless, KEN-SHE trial participants will continue in efficacy

follow-up until 36 months post-vaccination. DoRIS trial participants have completed immunogenicity follow up to month 36 to date, and the one and two dose arms will continue in follow up to 5 years post-vaccination.

Further strengths of both trials include a head-to-head comparison of two licensed HPV vaccines (the GSK 2vHPV and the Merck 9vHPV) and excellent retention up to and including the primary outcome visit. Both trials compared sexually transmitted infection (albeit restricted to HSV-2 and HPV in DoRIS) and sexual behavior data at baseline across arms; the lack of significant differences across arms provides confidence in the randomization processes. KEN-SHE benefited from measurement of cervical HPV DNA as the outcome and determination of persistent HPV infections. DoRIS benefited from measurement of antibody avidity and memory B cell responses (not yet reported), as well as antibody seropositivity and GMTs. Furthermore, the DoRIS trial is also evaluating the impact of malaria parasitemia (a known immunomodulator) at the time of vaccination on immune responses to single- and multi-dose HPV vaccination (not yet reported). However, neither study included boys or HIV-positive females, meaning that a paucity of RCT evidence on single-dose HPV vaccination remains for these groups. The KEN-SHE trial was blinded, whilst the DoRIS trial was not; however, this is unlikely to result in systematic biases within an immunogenicity trial.

Immunobridging of month 24 results to those from CVT and the IARC India trial was a major strength of the DoRIS trial, and further immunobridging is planned between DoRIS and KEN-SHE. A limitation of the DoRIS versus India comparison was the difference in vaccines used (4vHPV in the India trial; 9vHPV In DoRIS). However, both vaccines have the same manufacturer (Merck), use the same adjuvant (aluminum hydroxyl-phosphate sulfate, albeit with a higher dose in the 9-valent vaccine), and have similar immunogenicity and efficacy for the shared HPV types. Notably, the basis for licensure of the Merck 9vHPV vaccine was the demonstration of non-inferiority of immune responses to the 4vHPV vaccine; a formal comparison of efficacy was not conducted.

A further limitation of the immunobridging was the difference in age ranges of the DoRIS (9 to 14 years), India (10 to 18 years) and CVT cohorts (18 to 25 years) at vaccination. However, antibody GMTs in DoRIS participants were the same as or higher than antibody GMTs in the India trial and CVT (as would be expected in younger participants), and efficacy was demonstrated among India and CVT participants. Nonetheless, the DoRIS versus India comparisons were recalculated adjusted for age and within an age-restricted group of 10 to 14-year-olds, and results of both analyses were consistent with those from the main analyses.

2.2.5.2 STRENGTHS AND WEAKNESSES OF THE CVT, IARC INDIA HPV VACCINE TRIAL, AND PATRICIA TRIAL

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. Further information is provided here.

A major strength of the CVT and the combined CVT/PATRICIA evaluation is that extensive analyses were performed to eliminate much of the potential bias and confounding that may arise from underlying characteristic of women who received only a single dose. These included by-dose comparisons of: demographics 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 responses 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; and prevalence of HPV genotypes not protected by the vaccine, as an indicator of genital HPV exposure, accumulated over the four years of follow-up. Key limitations of these studies include the relatively small numbers of women receiving a single dose of the GSK 2vHPV vaccine and lack of prospective randomization to a reduced-dose schedule.

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%) up to ten 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; whereas the halt to enrollment resulted in formation of new study groups (one- versus two- versus three-dose arms), this “reallocation” was determined by time of enrollment (not controlled by the investigators or participants). Thus, it is unlikely to be linked to any preexisting HPV-risk status. However, although the different vaccine dose cohorts were comparable for age, there were differences in several sociodemographic factors at enrollment, such as monthly household income, religion, and education (76). Nonetheless, the incidence of infection with HPV vaccine genotypes not targeted by the Merck 4vHPVwas similar across vaccinated participants, regardless of the number of doses received, providing some reassurance against potential bias and confounding relating to underlying characteristics of participants not completing their allocated vaccine schedule.

The unvaccinated cohorts in the India HPV vaccine trial were created post-hoc in 2013 to 15 and 2017 to 19 by selecting married women matched to married participants on age and time of follow-up, and thus biases in their selection cannot be ruled out. In the 10-year analysis, the frequency of infection with non-vaccine type HPV infection (excluding HPV 31, 33 and 45) was higher in the unvaccinated group (incident infection: 27.2%, 95% CI: 24.9-29.5%; persistent infection: 5.6%, 95% CI 4.4-7.0%) compared to the vaccinated group (incident infection: 16.6%, 95% CI 15.8-17.3%;

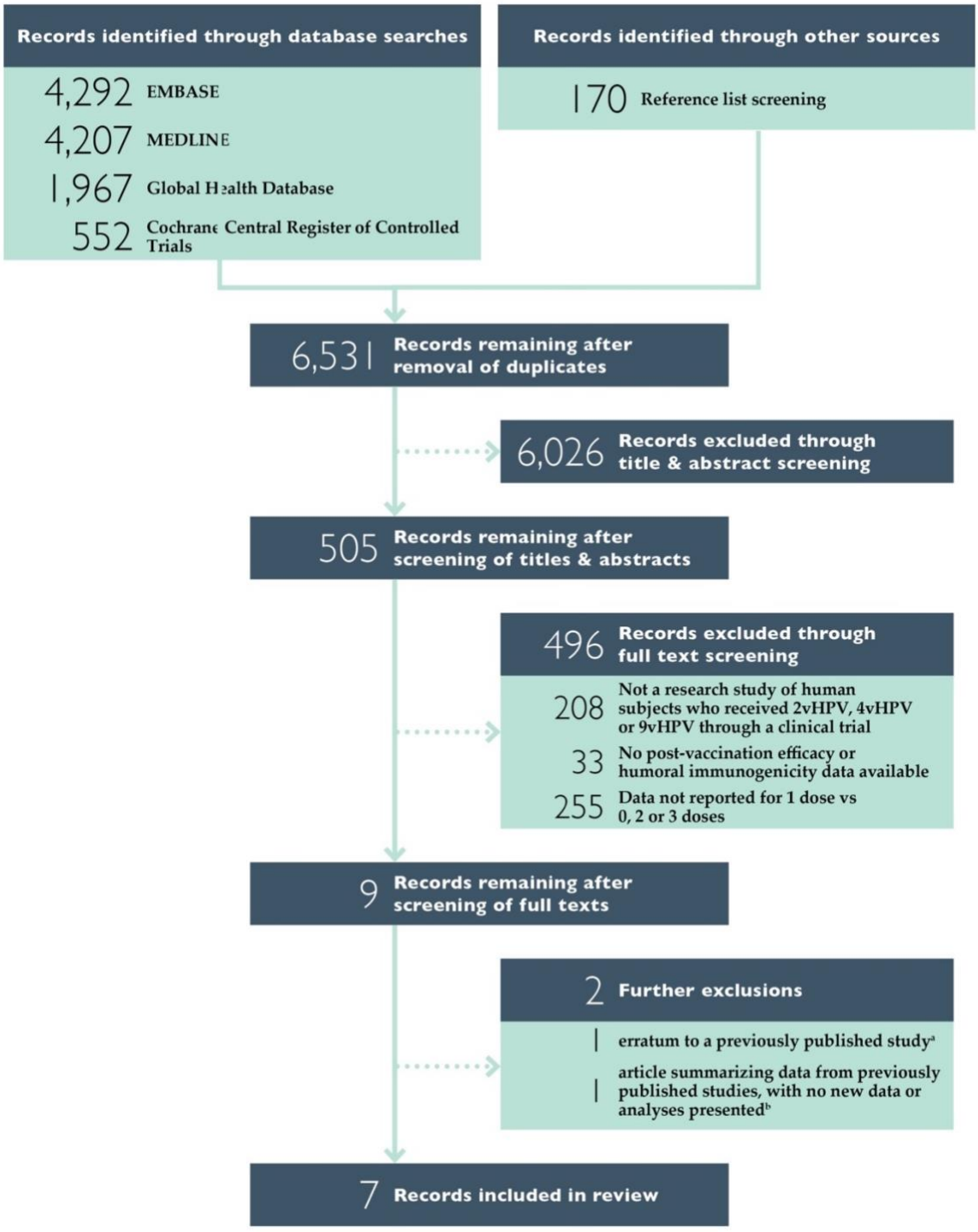
persistent infection: 3.2%, 95% CI 2.8-3.6%). However, as described above, the frequency of infection was similar among vaccinated participants who received one, two or three doses, and the authors adjusted VE estimates by a disease risk score that was calculated based on predictors of non-vaccine type HPV infection (excluding HPV 31, 33 and 45).

2.2.6 Summary of evidence from clinical trials

The data described in this chapter (Chapter 2.2) provide robust evidence that a single-dose HPV vaccination strategy may be as effective as multidose schedules in preventing HPV infection in healthy girls and young women up to 11 years post-vaccination. The frequency of infection (incident, persistent or prevalent) with HPV 16 or HPV 18 was very low in all efficacy trial participants who were vaccinated against HPV, regardless of the number of doses received, and significantly lower in participants who received one dose compared to those who were unvaccinated or received a control vaccine. Results from the prospectively-randomized KEN-SHE trial indicate that a single dose of the 2vHPV vaccine or the 9vHPV vaccine has almost 98% efficacy against incident persistent HPV 16 or 18 infection in sexually active young Kenyan women up to 18 months post-vaccination.

The proportions of participants with detectable antibodies to HPV 16 and HPV 18 were high (reaching 100% in some studies) in all HPV vaccine recipients, again regardless of the number of doses received. The DoRIS trial, conducted among Tanzania girls in the primary target age range for HPV vaccination, found that at least 98% of participants seroconverted to HPV 16 and 18 following a single dose of the 2vHPV or 9vHPV vaccine, and HPV 16 seropositivity following one dose was non-inferior to that following two or three doses. Whereas antibody levels were higher with multidose HPV vaccine schedules compared to a single dose across all immunogenicity studies, antibody levels following a single vaccine dose were found to be durable (up to 11 years post-vaccination in CVT) and higher than levels observed in natural infection. **Furthermore, antibody seropositivity and GMTs among one-dose recipients in the prospectively-randomized DoRIS trial were non-inferior to those among one-dose participants in CVT and the IARC India vaccine trial, among whom efficacy has been demonstrated.**

Figure 2. Clinical trials systematic review flow diagram (2018).



[a] Corrected results presented in the erratum (89) were incorporated into data extraction for the corresponding article (44).

[b] Article (90) presents previously published data from the CVT (44, 73-75).

Source: Figure adapted from (70).

Figure 3. Clinical trials systematic review flow diagram (2018-2022 updates).

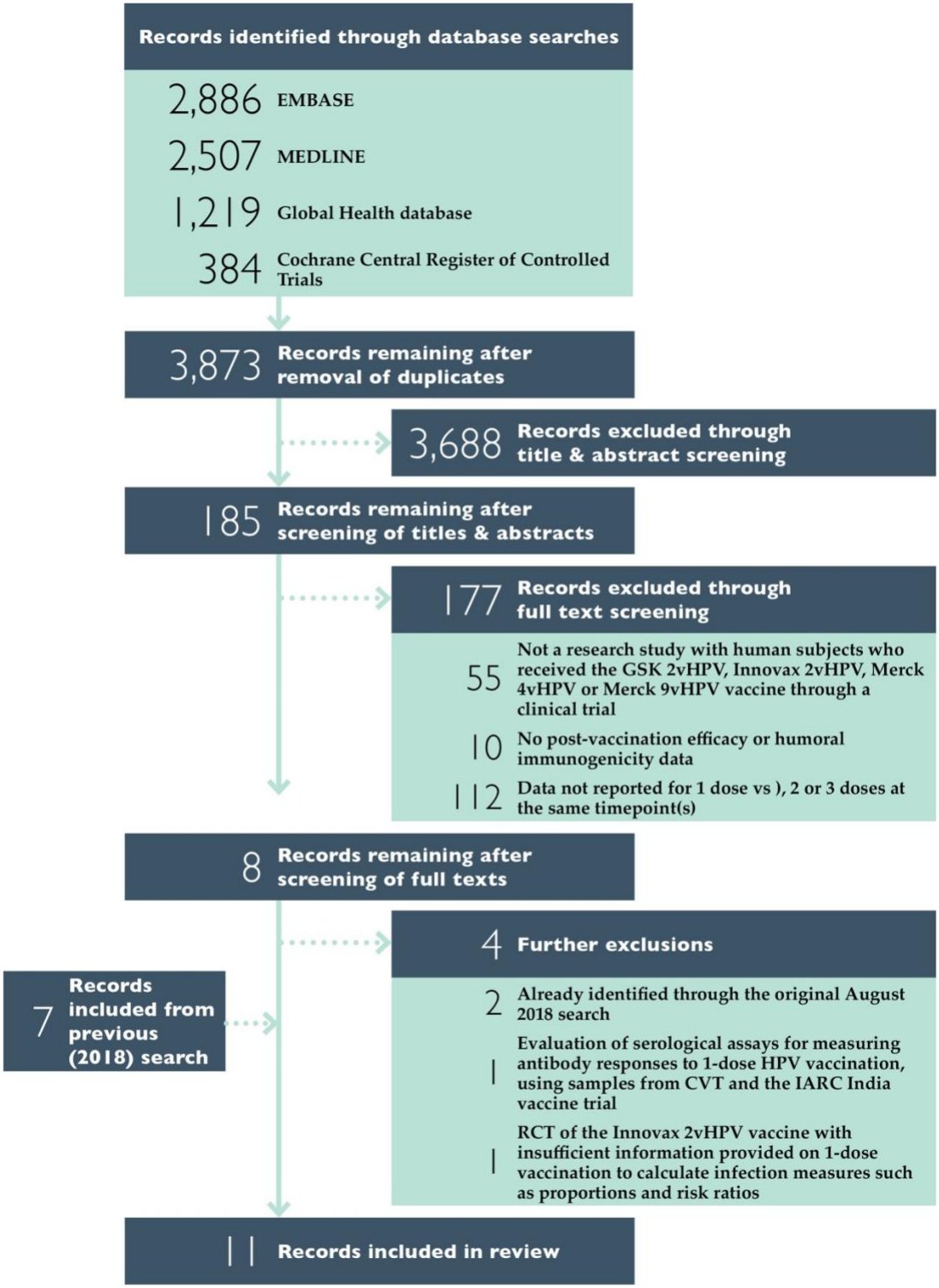


Table 2. Summary of studies included in the systematic review that compared one HPV vaccine dose to no vaccination or multidose schedules among clinical trial participants.

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									
Kreimer 2011[b] (73)	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 *(method not stated)*	3d (M 0,1,6), 2d (M 0,1/0,6) 1d (M 0)	Efficacy: 4y	3,578 healthy females receiving HAV in CVT
Safaeian 2013[c] (44)		NA	390		5% HPV 16 *or* 18 positive	15% HPV 16 positive *(by IgG ELISA)*		Immuno: 4y	115 healthy HPV 16/18 seropositive females in CVT, pre-vaccination
Safaeian 2018[d] (75)	Prospective observational cohort study of prior CVT participants; Costa Rica	2,449	486		8% HPV 16/18 positive	38% HPV 16/18 positive *(by IgG ELISA)*		Efficacy & immuno: 7y	2,836 age-matched healthy unvaccinated females
Kreimer 2020 (42)		1.539	448		Not stated			Efficacy & immuno: 11y	1,783 age- & geography-matched healthy unvaccinated females
Tsang 2020 (77)		2,974	NA		8% HPV 16/18 positive[e]	38% HPV 16/18 positive *(by IgG ELISA)*[e]		Efficacy: 11y	3,315 healthy females receiving HAV in CVT and 2,619 age-matched healthy unvaccinated females
Kreimer 2015[f] (74)	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 *(method not stated)*	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									
Sankaranarayanan 2016[g] (43)	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 *(by Luminex)*	3d (M 0,2,6), 2d (M 0,2/0,6) 1d (M 0)	Efficacy: 4y Immuno: 3y	None
Sankaranarayanan 2018[g] (76)		5,655	879 – 1,937			Not reported		Efficacy: 7y Immuno: 4y	1,481 age-matched healthy unvaccinated females
Basu[g] *2021*		10,915	NA			Not reported		Efficacy: 10y	(1) 1,484 age-matched healthy unvaccinated females (2) 4,626 age-matched healthy unvaccinated females

Scherer 2016[h] (71)	Randomized unblinded pilot intervention study; United States	NA	5	27–45	Not measured	HPV 16 positive *(by IgG binding assay)*	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; 10,915 up to year 10). 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, a cohort of 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 to the 10y timepoint (n=1,481 at the 7y timepoint; 1,484 at the 10y timepoint). For the most recent analysis, a second cohort of 4,626 unvaccinated females age-matched to the married females was recruited.

[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 (70).

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

Study	Sampling	Methods	Endpoints reported (measure/unit)[a]	Endpoint definitions
Kreimer 2011 (73) **and Safaeian 2018** (75)	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 (%, 95% CI)	All infections detected at Y 7
Kreimer 2020 (42) and Tsang 2020 (77)	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 (77), or infection detected at the Y 9 and/or Y 11 study visit (42)
			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 (74)	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 (43) **and 2018** (76), Basu 2021	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]; HC-II and	Cumulative first incident infection (% risk, 95% CI)	All first detectable infections accumulated during FU
			10 or 12 m persistent infection (% risk, 95% CI)	Presence of type-specific HPV DNA on repeated cervical samples over ≥10 or 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

	In 10-year analysis: Cervical samples collected from married women at 25 years of age for cervical cancer screening	*digene* HPV genotyping PS test	One-time incident infection (% risk, 95% CI)	Detection of an HPV type in any one sample

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] SPF_{10} PCR DEIA: SPF_{10} PCR primer system and DNA enzyme immunoassay detection of amplimers (DDL Diagnostic Laboratory, Voorburg, the Netherlands).

[c] $LiPA^{25}$: HPV line probe assay containing probes for 25 HPV genotypes (Labo Biomedical Products, Rijswijk, the Netherlands).

[d] Used in Tsang et al. 2020 (77) only.

[e] US National Cancer Institute's newly developed in-house assay that detects 51 HPV genotypes (91).

[f] Whichever occurred earlier.

[g] For 19 high-risk and 2 low-risk HPV types.

Source: Table adapted from (70).

Table 4. Summarized HPV 16/18 infection results from participants of studies included in the systematic review.

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), *p 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													
Kreimer 2015 (74)	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) *0.12*	0.8 (0.3–1.7) *0.56*	0.2 (0.1–0.3) *<0.01*
Safaeian 2018 (75)	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) *1.0*	0.6 (0.0–29.2) *UTC*[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) *0.17*	0.4 (0.1–2.3) *0.36*	-
Kreimer 2020 (42)	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) *0.17*	1.1 (0.1–12.0) *1.00*	0.5 (0.1–1.9) *0.44*
Prevalent infections													
Safaeian 2018 (75)	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) ***0.63***	0.2 (0.0–4.8) ***0.37***	0.1 (0.0–0.9) ***<0.01***
Kreimer 2020 (42)	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) *1.00*	1.1 (0.1–12.0) *1.00*	0.2 (0.04–0.7) *<0.01*
Persistent infections[h]													
Kreimer 2011 (73)	Median: 4.2y[g]	6m persistent	37 / 2957	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) ***0.17***	0.2 (0.0–3.5) ***0.18***	0.0 (0.0–0.5) ***<0.01***
		12m persistent	25 / 2957	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) ***0.40***	0.3 (0.0–5.9) ***0.56***	0.0 (0.0–0.8) ***<0.01***
Kreimer 2015 (74)	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) ***0.37***	0.5 (0.1–4.7) ***1.00***	0.0 (0.0–0.3) ***<0.01***
		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) ***0.72***	0.7 (0.1–6.7) ***1.00***	0.1 (0.0–0.4) ***<0.01***
Merck 4vHPV													
One-time incident and cumulative incident infections													
Sankaranarayanan 2016 (43)	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) ***0.17***	1.5 (0.5–4.8) ***0.059***	-
Sankaranarayanan 2018 (76)	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) ***0.1***	1.8 (0.9–3.5) ***0.1***	0.3 (0.2–0.4) ***<0.01***
Basu 2021	Median:9.0y IQR: 8.2-9.6y	One-time incident	60 / 2,019	3.0 (2.3-3.8)	59 / 2,166	2.7 (2.1-3.5)	92 / 2,858	3.2 (2.6-3.9)	139 / 1,484	9.4 (7.9-11.0)	1.1 (0.8-1.5) ***0.62***	1.2 (0.9-1.6) ***0.31***	0.3 (0.3-0.4) ***<0.01***
Persistent infections[h]													

Sankaranarayanan 2018 (76)	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) ***0.39***	0.6 (0.0–31.9) ***UTC***[i]	**5.0** (0.0–0.7) ***<0.01***
Basu 2021	Median:9.0y IQR: 8.2-9.6y	10m persistent	1 / 1,460	0.1 (0.0-0.4)	1 / 1,452	0.1 (0.0-0.4)	1 / 2,135	0.0 (0.0-0.3)	32 / 1,265	2.5 (1.7-3.6)	0.7 (0.0-10.9) ***0.79***	0.7 (0.0-10.9) ***0.78***	0.0 (0.0-0.1) ***<0.01***

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 Safaeian 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 (70).

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

Study	Sampling	Methods	Endpoints reported (measure/unit)[a] with definitions where applicable
Safaeian 2013 (44) **and 2018** (75), **and Kreimer 2020** (42)	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, 10th, 25th, 75th and 90th percentiles, 95% CI) - HPV 16/18 seropositivity (% of analytical population seroconverting) *Laboratory-determined seropositivity cutoffs (8 EU/ml for HPV 16, 7 EU/ml for HPV 18)* - Antibody stability (% of analytical population with stable GMTs; Safaeian 2013 only) *Stability defined as titers not declining by ≥ twofold between two specified time points*
		PSV-based SEAP neutralization assay	- HPV 16 neutralizing antibody seropositivity (% of analytical population seroconverting) *Laboratory-determined seropositivity cutoff (25.1 TU/ml)*
		GuHCl-modified HPV L1 VLP avidity ELISA	- Antibody avidity levels (GM avidity level, 95% CI, IQR)
Sankaranarayanan 2016 (43) **and 2018** (76)	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) *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*
		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) *Seropositivity defined as sample titer ≥50 and ≥2x control (BPV) titer*
Scherer 2016 (71)	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 *Seropositivity cutoff (3 U/ml) based on 3x SD above mean for sera from sexually unexperienced controls*
		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 (70).

Table 6. Summarized HPV 16/18 seropositivity and GM antibody-level results from participants of studies included in the systematic review.

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] (44)	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 (75)	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 (42)	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] (44)	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 (75)	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 (42)	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] *(43)*	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)	-

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
Sankaranarayanan 2018 (76)	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)	-
	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								
Sankaranarayanan 2016[e] (43)	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)	-
Sankaranarayanan 2018 (76)	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 (70).

Table 7. Quality assessment of studies included in the systematic review.

Studies	Parameter	Summary (including adjustment or consideration by study authors)
Kreimer 2011 (73) *Kreimer 2015 (74)* *Safaeian 2013 (44)* *Safaeian 2018 (75)* *Kreimer 2020 (42)* *Tsang 2020 (77)*	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 *et al.* 2011 set the primary endpoint as newly detected HPV 16/18 at the 6m visit or later. The 6m visit was the time of 3rdd administration, so it is likely that those who missed their 3rdd 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 *et al.* 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.
Sankaranarayanan 2016 (43) *Sankaranarayanan 2018 (76)* *Basu 2021 (78)*	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). The IARC 10-year analyses were adjusted for predictors of non-vaccine type HPV infection (78).
	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.

Studies	Parameter	Summary (including adjustment or consideration by study authors)
	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. In the IARC 10-year analyses, the authors adjusted VE estimates by a disease risk score that was calculated based on predictors of non-vaccine type HPV infection (excluding HPV 31, 33 and 45) (78).
	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 (70).

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 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. The 11 identified articles and their results are summarized below and in **Table 8** and **Table 9.**

In December 2020, a systematic review was published that evaluated the immunogenicity of alternative dosing schedules for HPV vaccines among adolescent girls and young women (92). The review identified three eligible articles that evaluated the immunogenicity of single-dose HPV vaccination, all of which are already presented in detail in this review.

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 to 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 (93, 94). 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 (95) was a follow-up study of 200 girls aged 15 to 19 years who had been vaccinated with the Merck 4vHPV vaccine in 2008 and 2009. At that time, all girls aged 9 to 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 described cross-neutralizing antibody responses among the full cohort (96), and the other described cellular immune responses in a small subset of the cohort (97).

After 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 to 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 (98). 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 to 10 years who received two doses of the Merck 9vHPV six months apart (99). 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 (100). Clinical trial participants were eligible for inclusion in this post-hoc comparison if they had blood samples available before and 1 month following their second vaccine dose.

A third analysis by the same research group in Canada compared antibody responses in (1) girls aged 13 to 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 to 10 years who received a mixed GSK 2vHPV / Merck 9vHPV vaccination schedule with a 6-month interval through the second intervention study described above, and (3) vaccine-naïve girls and boys aged 9 to 10 years who received a single dose of Merck 9vHPV through the second intervention study described above (101).

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 (102). 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 (74, 103). 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 studies were conducted in the Netherlands (104) and Mongolia (105). 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 (104). 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 to 26 years (105). 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. In 2018 or 2019, the study

recruited 118 girls who had received a single vaccine dose (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 (93); in the Fiji and Mongolia studies, it was approximately six years after vaccination (95-97, 105). 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 (98, 99, 101). 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 (102). 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 (104).

The DoD study was the only study to use routinely collected, previously stored samples (103). 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 (97, 104). 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 (IFNy) 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 IFNy 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 (103). In some of the studies, most notably the Uganda and Fiji studies, the one-dose group was particularly small (93, 95). 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. 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 (97), but the Dutch study found a trend for weaker B- and T-cell responses with one dose compared to two or three doses (104).

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 (93). Participant demographic characteristics were comparable across dose groups. The mean time between last dose and blood collection was 38, 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 396 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 (95). 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 (96). 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 (98), and these, along with a subset of 173 girls and boys from an independent vaccine trial, were included in the second study (99). 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 2v/9vHPV mixed schedule with a 3- to 8-year interval, 86 boys and girls who received a 2v/9vHPV mixed schedule with a 6-month interval, and 88 girls and boys who received a single dose of Merck 9vHPV (101). All participants were seropositive for antibodies to HPV 31, 33, 45, 52, and 58 after vaccination with Merck 9vHPV. For all 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 (102). 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 (103). 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 (104). 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 (105). 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 (97). 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 IFNy-producing cells were similar among one-, two-, and three-dose participants. Numbers of HPV 18–specific IFNy-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 IFNy-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 IFNy-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, IFNy, 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 and18 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 several 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 4 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 to 26 years in the DoD study were very high (approaching 100%), and 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								
LaMontagne 2014; Uganda *(93)*	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
Pasmans 2019; Netherlands *(104)*	Repeated cross-sectional surveys of participants with prior HPV vaccination	890 girls aged 13–21 y cumulative across all time points (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 specifc 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								
Hurt 2016; United States *(103)*	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
Mosckicki 2019; United States *(102)*	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
Batmunkh 2020; Mongolia *(105)*	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								
Toh 2017; Fiji *(95)*	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=34; 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
Toh 2019; Fiji *(96)*							HPV 31/33/45/52/58 neutralizing seropositivity & titers	PBNA; Cutoff for seropositivity – ED50 ≥25
Toh 2018; Fiji *(97)*		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
Gilca 2019 (1); Canada *(98)*	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 2nd 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
Gilca 2019 (2); Canada *(99)*	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			
Sauvageau 2020; Canada *(101)*	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		HPV 31/33/45/52/58 seropositivity & titers	Multiplex direct IgG ELISA on MSD platform; Cutoffs for seropositivity – HPV 31: 0.5 AU/mL ; HPV 33: 1.3 AU/mL HPV 45: 2.5 AU/mL; HPV 52: 0.7 AU/mL; HPV 58: 1.2 AU/mL

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											
LaMontagne 2014 (93)	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
Pasmans 2019[a] *(104)*	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											
Hurt 2016[b] (103)	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
Gilca 2019[c] *(98)*	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
Toh 2017[d] *(95)*	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)	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) I: 1,106 (687.9–1,777)	F: 358.9 (223.1–577.5) I: 1,104 (701.1–1,738)	F: 384 (174–847.5) I: 188.3 (102.3–345.1)	F: 52.36 (47.42–57.82) I: 50 (50–50)
Moscicki 2019[e] *(102)*	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
Batmunkh 2020 (105)	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 (103). Seropositivity results for 1-, 2-, and 3-dose recipients are shown for participants who were seronegative to the corresponding HPV type pre-vaccination. 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.

c Results are shown for the intervention study of 31 girls with prior single-dose HPV vaccination (98). 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 (95). 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 (97).

[e] Antibody titer data are shown separately for PHIV+ and PHEU participants; 95% CIs are not provided in the publication (102).

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 (106), and updated three times subsequently (updates unpublished)—aimed at evaluating the published literature on single-dose HPV vaccination from post-licensure observational studies (106). **This section summarizes and includes excerpts (Section 2.4.1.1) from the published systematic review (106), combined with updates, on evidence of the effectiveness of HPV vaccination by number of doses from 35 eligible articles (32 included in the previous edition of this paper, and a further 3 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 three subsequent updates (extending first from June 2017 to March 2019, then from March 2019 to August 2020, and finally from August 2020 to September 2021), Medline and EMBASE databases were searched for studies published between January 1, 2007, and September 29, 2021, 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, QUALITY ASSESSMENT, DATA SYNTHESIS

Three 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.

The main outcome of the review was the effectiveness of HPV vaccination—comparing the incidence or prevalence of HPV-related endpoints between individuals vaccinated with different numbers of doses (three versus none, two versus none, one versus none, three versus two, three versus one, and two versus 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.

The consortium adapted the ROBINS-I framework (107) by using the same main sources of biases and ratings as the ROBINS-I but modifying for reduced dose observational studies. For selection bias, we examined whether selection of participants could be influenced by participants' characteristics or outcome. For information bias, we examined potential biases in measurement of intervention and in measurement of outcome (e.g., validity of the algorithm used to identify outcomes, use of lag time or buffer period between time of vaccination and counting of outcome to exclude outcomes originating from prevalent infections at a given dose). For confounding, we examined the likelihood of differences between dose groups in: 1) prevalence of HPV infection at first dose, 2) risk of HPV acquisition during study follow-up, and 3) immunogenicity (for studies with formal comparisons between three, two and one doses). We also examined methods used to control for these potential confounders. Quality assessment findings have been compiled in a descriptive synthesis and included in a submitted manuscript. Because one of the aims of the systematic review was to discuss the limitations of these studies, no studies were excluded based on the methodological quality.

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 (33, 108-120). These publications were published between January 2013 and June 2017. 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 (121-129). 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 (105, 130-137). Figure 4 summarizes these three literature searches. Finally, the fourth literature search identified an additional 1,006 articles, from which 18 full articles were assessed. After reading full texts, 15 articles were excluded, leaving 3 new papers (138-140). Overall, a total of 35 eligible articles are included in this review (Figure 5). All evaluations except one (139) were conducted within the context of a recommended three-dose schedule of either the GSK 2vHPV and/or Merck 4vHPV vaccine. This study evaluated the effectiveness of a recommended two-dose schedule (139).

The articles included analyses of effectiveness for prevention of HPV infection (9 articles), AGW (10 articles), or cervical cytological or histological abnormalities (16 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). **Eight 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 eight studies that reported vaccine effectiveness for reduction of prevalent vaccine-type infection in women or men conducted in the context of a three-dose GSK 2vHPV or a three-dose Merck 4vHPV vaccination program (105, 108, 109, 121, 122, 130, 133, 134). The studies were from Scotland (n=3), the United States (n=4) and Mongolia (n=1). **In this updated systematic review, one additional study was identified (139). This study, from the Netherlands, was conducted after a two-dose schedule of 2vHPV was implemented in that country.** Girls who were vaccinated age 12 to 13 years were followed prospectively with self-collected vaginal swabs for HPV DNA. The adjusted VE of two doses was 84% (95% CI 27.0– 96.5) against incident HPV 16/18 infection.

Overall, among the nine studies, seven were among women; two studies among women in the United States found similar effectiveness with three-, two-, and one-dose schedules in all or some analyses (130, 134). 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 at 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 other used self-reported vaccination history. One study conducted in Mongolia only looked at one dose vaccine effectiveness; that study included women who were part of a pilot Merck 4vHPV vaccination campaign, conducted by the Mongolian Ministry of Health (105). 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% CI 0.01–0.56).

There were three studies among women from Scotland using data from the same surveillance system. The first found statistically significant effectiveness for three doses but not for two doses or one (108). 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 over sampled women who were partially vaccinated (109). 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 third study included data from additional years through 2015 (121). Statistically significant effectiveness was found for three and two doses but not for one dose.

Two studies were conducted among men, both from the United States. These found no effectiveness with at least a single dose and no difference in prevalence by number of doses (122, 133). In both studies, the number of vaccinated men was small; in one, almost half had initiated sexual activity at the same age or before being vaccinated.

Anogenital warts

The last evidence review included nine studies of AGW and were from six different countries (Belgium (n=1), Canada (n=1), Denmark (n=1), Sweden (n=2), Spain (n=1), United States (n=3)) **(33, 110-114, 123-125). We identified one new study of AGW outcomes beyond the nine in the last review. The study, conducted in Denmark, was a retrospective cohort study using population-based health national registries (138)**. Results were stratified by age at vaccination; among those with first dose at age 12 to 14 years, adjusted IRR was 0.16 (95% CI 0.15–0.18) for three doses, 0.22 (95% CI 0.18–0.26) for two doses and 0.29 95% CI (0.22–0.38) for one dose. The study also formally compared three versus one doses and two versus one doses. There was a significant difference between three doses versus one dose but not for two doses versus one dose.

In all 10 studies, analyses were adjusted or stratified 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 ten studies included assessment of different buffer periods (110, 112, 123), and five included assessment of different intervals between doses in two-dose vaccine recipients (33, 112, 114, 123, 124).

Of the ten 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 (110, 113, 123, 124, 138). 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 (33, 110, 112, 114, 123, 124). Three studies examined different buffer periods (110, 112, 123); a longer buffer period decreased differences in effectiveness between three and two doses in one study (110). In the five studies that explored the interval between doses in two-dose vaccine recipients (33, 112, 114, 123, 124), three found that a longer interval changed effectiveness estimates or resulted in no difference between three and two doses (33, 114, 123).

All six 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 (33, 110, 114, 124, 125, 138). 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 (113). One study found similar point estimates of effectiveness with one, two, and three doses among those vaccinated at age 15 to 19 years and no significant difference in effectiveness between one and three doses (124).

Cervical cytological and histological abnormalities

The last systematic review included 15 studies that evaluated vaccine effectiveness for prevention of cervical cytological or histological abnormalities, including 12 for the Merck 4vHPV vaccine and 3 for the GSK 2vHPV vaccine (115-120, 126-129, 131, 132, 135-137) (Table 10). Overall, the 15 studies included data from seven different countries. **We identified one new study of cervical outcomes which was conducted in Italy; this was a retrospective cohort study using administrative data (140).** Both Merck 4vHPV and GSK 2vHPV had been used in that country (in different areas). The outcome was abnormal cytology, and the analysis was stratified by birth cohort; in the youngest birth cohort (1990–1993), the adjusted OR for was 0.44 (95% CI 0.14–1.43) for three doses; 0.65 (95% CI 0.20–2.16) for two doses and 0.43 (95% CI 0.17–1.05) for one dose.

Among the 16 studies, 15 found effectiveness for three doses, eight found some effectiveness with two doses (115-118, 129, 131, 136, 137), and seven found effectiveness with one dose among some age groups or in analyses with longer buffer periods (116, 117, 129, 131, 136, 137, 140). Most two-dose vaccine recipients received two doses at a one- or two-month interval. Five studies examined intervals between two doses: three found no impact on the effectiveness estimate (117, 136, 137); one found that longer intervals decreased the difference between two and three doses in those vaccinated at age 16 years or younger, (128) and another only in one of the age at vaccination groups examined (118).

In ten studies that evaluated effectiveness by the number of doses stratified by age at vaccination, age at vaccination program implementation, or birth cohort or that were limited to younger age at vaccination, three studies found significant effectiveness with one, two, and three doses with similar point estimates by number of doses in some groups (129, 136, 137). These studies, published in 2019 and 2020, were from Denmark, Australia, and the United States. The study from Denmark was a retrospective cohort study using linked national registry data, limited to those vaccinated at age 16 years or younger. Using an outcome of CIN3+ / adenocarcinoma in situ, compared with no vaccination, adjusted incident rate ratios were similar for one, two or three 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 to 19 years, hazard ratios (HRs) for CIN2+ were similar for all doses (three doses, 0.66 (95% CI, 0.55-0.80); two doses, 0.72 (95% CI, 0.54-0.95); and one dose, 0.64 (95% CI, 0.47-0.88)). An additional study found similar point estimates by number of doses when stratifying by age at vaccination but significant effectiveness only for three doses (128). In the remaining six studies, differences in effectiveness remained between some or all dose groups (116-118, 131, 132, 140).

Quality assessments

Overall, all 35 studies were determined to be at moderate or serious risk of bias (**Figure 6**; **Figure 7**; **Figure 8**). No study had a domain rated as critical. Comparisons involving one and two doses were more likely to be affected by serious biases. Of seven potential sources of biases, three were more likely to be rated at serious risk of bias. These serious biases fell in two broad categories—i.e., information bias and confounding—each are likely to underestimate the effectiveness of one and two doses.

First, the majority of studies were deemed at moderate or serious risk of information bias for measurement of outcome. This is because prevalent infections at a given dose could cause an attribution of outcome to the wrong dose if outcomes are detected after a given dose but originate from an infection acquired before that dose. Studies using buffer periods to exclude outcomes originating from prevalent infections (≥12 months for infection, ≥ six months for anogenital warts, ≥24 months for cervical abnormalities) or restricting analyses to girls vaccinated at an age when they were less likely to have prevalent infections were deemed at lower risk of information bias.

Second, studies examining two-dose effectiveness were deemed at serious risk of information bias in the measurement of intervention if the interval between the two doses was less than five months. Because the majority of studies were conducted when a three-dose schedule was recommended, the interval between the first and second dose was often only one or two months; longer intervals were found when individuals were late for the second dose in a recommended three-dose series.

Third, the majority of studies were at moderate or serious risk of confounding due to differences between dose groups in the prevalence of HPV infection at first dose or the start of follow-up and/or in risk of HPV acquisition during follow-up. The use of buffer periods or restriction of analysis to younger age groups could control for differences in prevalent infection at the first dose between dose groups. More recent studies tended to include individuals vaccinated at a younger age and were less likely to be affected by biases related to prevalent infections at vaccination. Very few studies were able to control for the potential difference in risk of HPV acquisition between dose groups by adjusting for sexual activity during follow-up.

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 includes important weaknesses of the available post-licensure studies and caveats that should be considered when interpreting the findings:

- Except for one study, 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 some 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 and 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 the one study that focused on girls vaccinated under a routine two-dose recommendation, there was only a two-dose group and no comparison group of girls who received one or three doses.

- 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 fewer 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 outcome evaluated. Longer buffer periods might be more helpful for the evaluation of vaccine effectiveness against cervical high-grade histological abnormalities than AGW since the former takes more time to develop after infection (141). 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.
- Because almost 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 0- and 1-month or 0- and 2-month intervals. However, immunogenicity studies had found non-inferior results with two doses compared to three doses when the two doses were separated by about six months (11, 142, 143). The longer interval is thought to allow the 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 to 14 years at the time of their first dose (10, 144).
- 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 (33, 112, 114, 117, 118, 123, 124, 128, 136, 137). Three of five studies evaluating AGW outcomes (33, 112, 123), and two of five studies evaluating cervical outcomes (118, 128) 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 is not related to the spacing between doses. If so, the inconsistent findings by the interval between doses could be due to the 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 (116, 117). 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 the effectiveness of fewer than three doses.

- More recent studies tended to include individuals vaccinated at a younger age and were less likely to be affected by biases related to prevalent infections at vaccination. Among 22 studies published before 2019, less than 50% were rated at moderate risk of bias or had only one category rated at serious risk of bias, compared with 77% of 13 studies published in 2019 through 2021.

2.4.3 Summary of non-trial observational studies

In this updated systematic review of HPV vaccination effect by number of doses, we included 35 observational studies that evaluated outcomes of vaccine-type HPV infection, anogenital warts or cervical abnormalities. Among 29 studies that evaluated three doses, 28 found evidence of significant effectiveness. Among 29 studies that evaluated two doses, 19 found significant effectiveness (109-111, 113, 115-118, 121, 123, 124, 129-131, 134, 136-139). In 18 of 30 studies, significant effectiveness was observed for one dose in some or all analyses (33, 105, 109, 110, 113, 115-117, 123, 124, 129-131, 134, 136-138, 140). Across all endpoints (infection, anogenital warts, and cervical abnormalities), variation in effectiveness by number of doses was observed in most of the earliest published studies, with the highest effectiveness with three doses. 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.

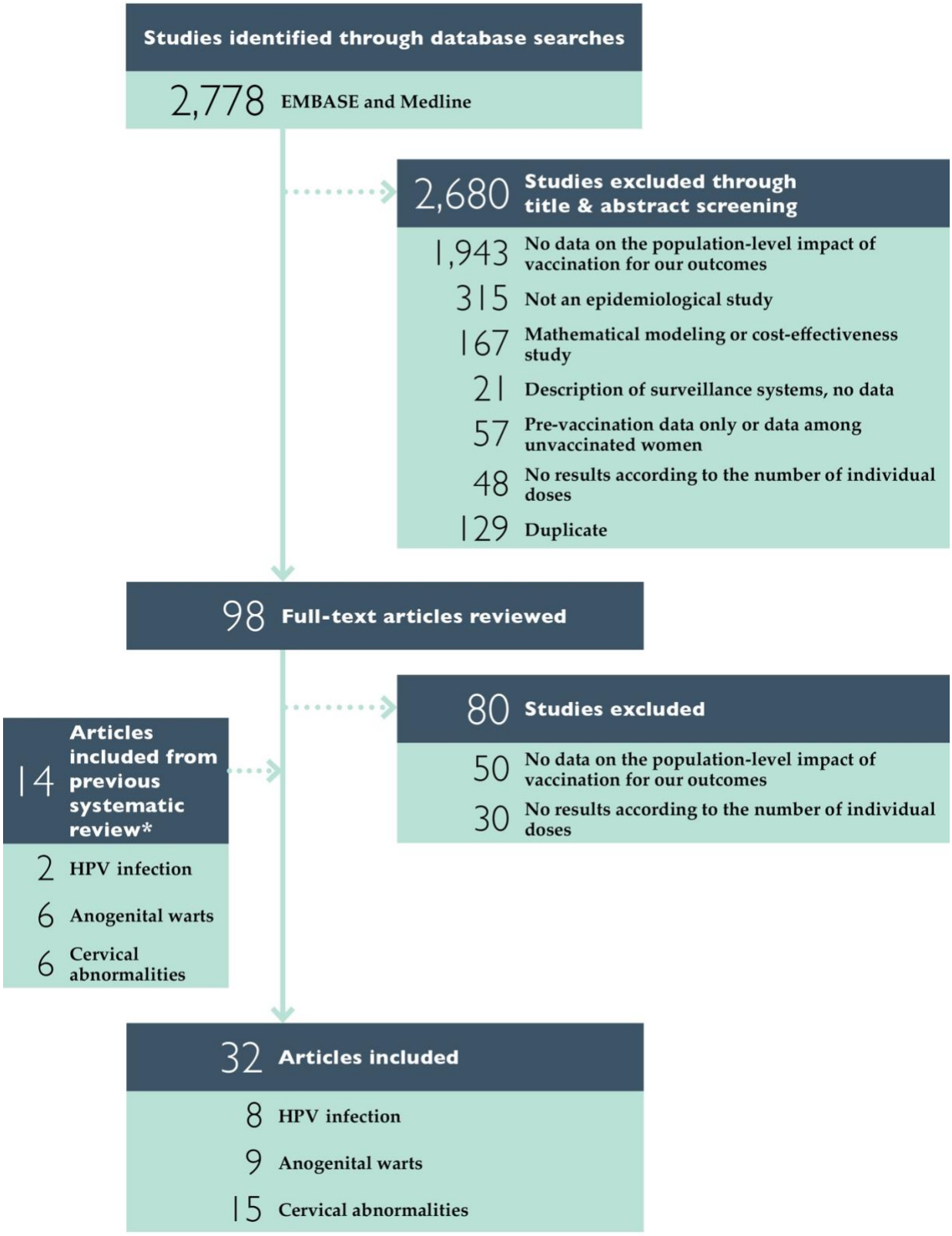
A significant feature of many studies was the inclusion of women vaccinated at ages older than the target age of routine programs who were more likely to have a prevalent infection at the time of vaccination. More recent studies have begun to address this limitation by including persons vaccinated at younger ages or restricting analyses by age at vaccination. 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.

There were generally consistent findings among studies that used buffer periods. With longer buffer periods, among eight studies that evaluated this (110, 112, 116, 117, 123, 131, 136, 140), five found higher effectiveness and a decrease in the differences by number of doses (110, 117, 123, 131, 136). Findings related to the interval between two doses were less consistent, as noted above: five of ten studies reported higher two-dose effectiveness with increasing intervals (33, 114, 118, 123, 137). 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 the number of doses emerged from some studies that either stratified by age at vaccination or were limited to those vaccinated at younger ages. These studies found high effectiveness with one dose and similar effectiveness for one, two, and three doses (110, 113, 124, 129, 130, 136-138). These studies overcome some limitations of earlier studies, which likely included more women who had a prevalent infection at the time of vaccination. Continued review of future published reports on vaccine effectiveness by the number of doses will be important as studies are able to focus analyses on persons vaccinated in early adolescence.

Figure 4. Non-trial observational studies systematic review flow diagram (to 11 August 2020).



Source: Markowitz et al. Vaccine 2018. Figure adapted from (106).

Figure 5. Non-trial observational studies systematic review flow diagram (August 11, 2020 to September 29, 2021).

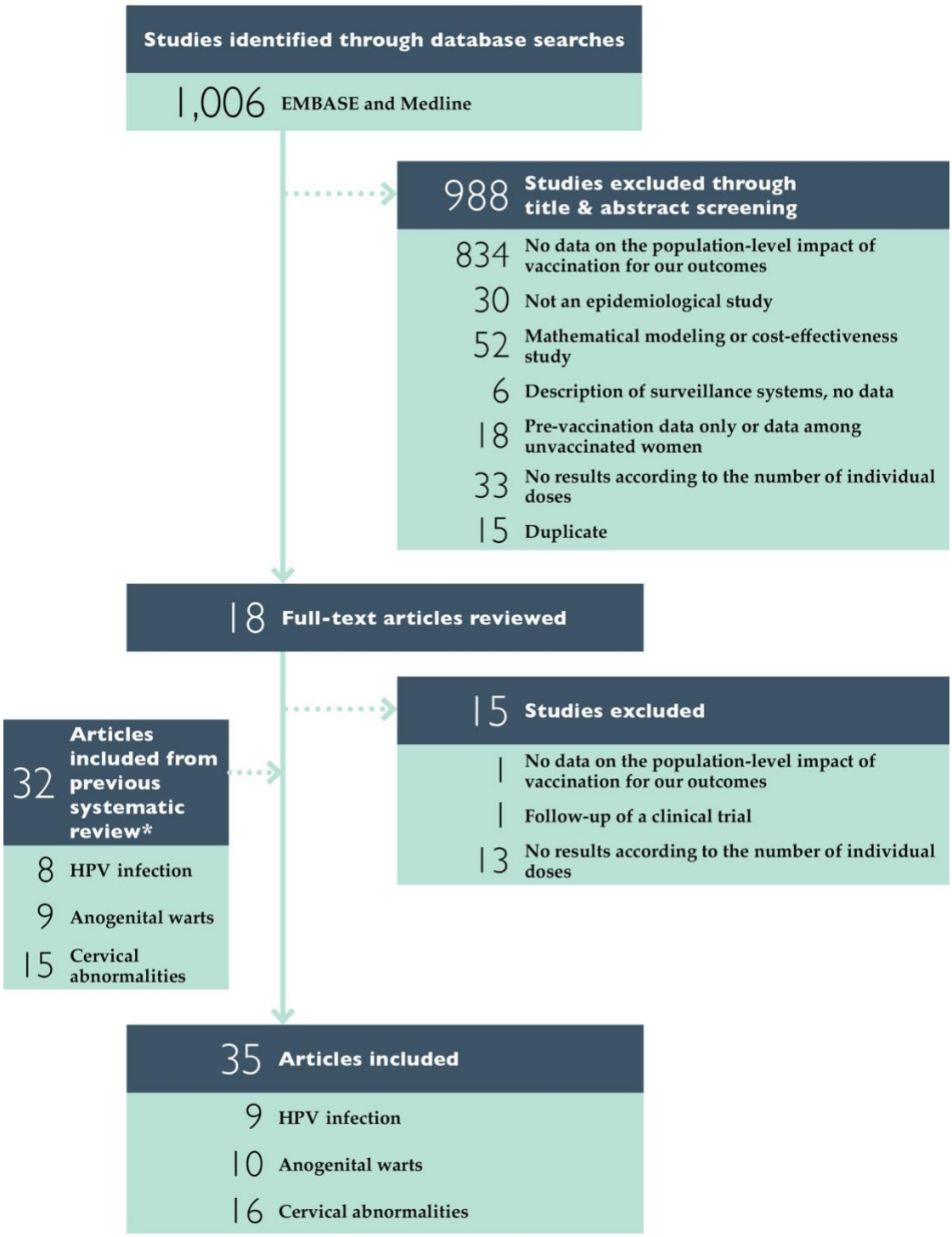


Table 10. Characteristics of studies that evaluated HPV vaccine effectiveness by number of doses.

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									
Chandler 2018	United States	Cross-sectional study using self-reported data - men	≤26	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
Widdice 2019	United States	Cross-sectional study using self-reported data - men	Mean: 16.2 wave 1: 5.1 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
Sonawane 2019	United States	Cross-sectional study of a nationally representative sample	≤26	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	Attained age, race/ethnicity, age at sexual debut, lifetime number of male sexual partners
Markowitz 2020	United States	Cross-sectional study of women enrolled in an integrated health-care delivery system	≤29	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, attained age
Batmunkh 2020	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	Attained age at assessment, sexual behavior, education, income, employment status, tobacco and alcohol use, pregnancy
Bivalent vaccine									
Kavanagh 2014	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
Cuschieri 2016	Scotland	Cross-sectional study using screening registry data with additional sampling of those with <3 doses	15–>18	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
Kavanagh 2017	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

Hoes 2021	Netherlands	Prospective cohort study	12–13	14–17	0: 929 2: 1098[f]	HPV 16 or 18 incident DNA positivity in self- collected vaginal swabs[g]	Final status	0	Attained age, ethnicity, ever had sex, ever used contraception
Anogenital Warts									
Quadrivalent vaccine									
Herweijer 2014	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
Blomberg 2015	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
Dominiak-Felden 2015	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
Perkins 2017	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[h]	Final status	0, 12	Age at start of exposure period, regions, SES indicators, calendar year, differential observation periods
Navarro-Illana 2017	Spain	Retrospective cohort study using national registries	14	14–19	0: 607,006 1: 18,142 2: 31,420 3: 153,296 (person-yrs)	First diagnosis of ICD-9-CM code 078.11	Time- dependent	0	Attained age (time-varying), calendar year, health department
Lamb 2017	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	Attained age, age at vaccination, time between doses
Hariri 2017	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
Zeybek 2018	United States	Matched retrospective cohort study using health insurance claims databases (males and females)	9–26	10–31	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 (based on age at last dose), sex, region of residence, history of STDs, enrollment history.

Willows 2018	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)
Baandrup, 2020	Denmark	Retrospective cohort study using population-based health national registries	12–30	12–30	0: 1,904,895 1: 235,653 2: 460,978 3: 1,934,589 (person-yrs)	First diagnosis: ICD-10 code A63.0 or podophyllotoxin prescription	Time-dependent	1	Attained age, age at vaccination, maternal education, calendar time
Cervical Abnormalities									
Quadrivalent vaccine									
Gertig 2013	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
Crowe 2014	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
Brotherton 2015	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 in 2007, remoteness, SES, screening start (before or after vaccination)
Hofstetter 2016	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[1]	Final status	1	Age at vaccination initiation or first missed opportunity for vaccination for unvaccinated, insurance, language, clinic type, CT screening, and baseline cytology
Kim 2016	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[1]	Final status	0	Attained age, urban/rural, laboratory site, neighborhood income
Silverberg 2018	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
Dehlendorff 2018	Denmark, Sweden	Retrospective cohort study using linked national registry data	13–29	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

Verdoodt 2019	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
Brotherton 2019	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, attained age (time varying)
Johnson Gargano 2020	United States	Case control 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
Rodriguez 2020	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
Innes 2020	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+	Final status	0	Age at first dose, birth year cohort
Bivalent vaccine									
Pollock 2014	Scotland	Retrospective cohort study using linked national registry data	15–>18	20–21	0: 76,114 1: 1,315 2: 2,725 3: 25,898	Histology: CIN1, CIN2, CIN3	Final status	0	Attained age, birth year cohort year, deprivation score
Cameron 2017	Scotland	Retrospective cohort study using linked national registry data	14–>18	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
Palmer 2019	Scotland	Retrospective cohort study using linked national registry data	12–>18	20	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
Acuti Martellucci[k] *2021*	Italy	Retrospective cohort study using administrative data	14–>30	17–32	0: 7,394 1: 212 2: 83 3: 96	Cytology: Any abnormal cytology, low and high grade	Final status	1, 6, 12	Year of birth, residential area, country of birth, screening test kit, number of screens

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] Numbers in first study year; i

[g] By HPV-LIPA25 detecting 25 types

[h] 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.

[i] 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.

[j] 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.

[k] Either bivalent or quadrivalent vaccine

Source: Table adapted from (106).

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							
Chandler 2018	≤26	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)
Widdice 2019	Mean: 16.2 wave 1; 15.1 wave 2	13–26	0	Yes/No/No	No significant effectiveness for ≥ 1d	• 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
Sonawane 2019	≤26	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
Markowitz 2020	≤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)	• 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)
Batmunkh 2020	11–17	16–26	0	No/No/No	1: aPR = 0.08 (0.01–0.56)	• Adjusted for income and employment status	No
Bivalent vaccine							
Kavanagh 2014	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)	• Differences by number of doses still observed when stratified by age at vaccination	No
Cuschieri 2016	15–17	20–21	0	No/No/No	3: aOR = 0.27 (0.20–0.36) 2: aOR = 0.45 (0.29–0.69)		No

					1: aOR = 0.52 (0.31–0.83)		
Kavanagh 2017	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)	• 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
Hoes 2021	12–13	14–17	0	No/No/No	2: aHR = 0.16 (0.035–0.73)	• Study conducted when routine 2-dose vaccination program recommended	No
Anogenital warts							
Quadrivalent vaccine							
Herweijer 2014	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)	• 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) • With buffer periods >4 months, no significant difference between 3d and 2d
Blomberg 2015	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) • With dose interval >4 months, no significant difference for 3d vs 2d • Similar results when stratified by age at vaccination
Dominiak-Felden 2015	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)	• 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
Perkins 2017	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) • With 1-yr buffer period, no change in findings (data not shown) • Similar results with interval >5 months for 2d
Navarro-Illana 2017	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

Lamb 2017	10–19	10–27	0	Yes/No/Yes	No analyses of 3d, 2d or 1d compared to 0		• Higher effectiveness of 3d vs 2d when 1st d and 2nd d administered 0–3 or >8 months apart but not 4–7 months • Similar results stratified by age at vaccination
Hariri 2017	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) 2c: 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) 2c: 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 2dc: aHR = 0.74 (0.38–1.43) 2dc 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)
Zeybek 2018	9–26	10–31	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)	• No significant effect in older or younger age groups • Similar results with 2d interval <6 or ≥6 months	• No significant differences for 3d vs 1d, 3d vs 2d, or 2d vs 1d (only p-values reported)
Willows 2018	9–26	10–33	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)	• No significant effect in those vaccinated at older ages	No
Baandrup 2020	12–30	12-30	1	Yes/No/No	Results for first dose at age 12–14 yrs 3: aIRR = 0.16 (0.15–0.18) 2: aIRR = 0.22 (0.18–0.26) 1: aIRR = 0.29 (0.22–0.38)	• Results presented for 4 age at vaccination groups; in oldest age, ≥19 yrs, significant effect only with 3 doses • Significant but lower effectiveness for 3, 2 and 1 doses in 15–16 and 17–18 yr age groups than 12–14 yrs	Results for first dose at age 12–14 yrs 3 vs 1 dose: aIRR = 0.56 (0.43–0.73) 2 vs 1 dose: aIRR = 0.76 (0.56–1.03)
Cervical abnormalities[d]							
Quadrivalent vaccine							
Gertig 2013	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	• Similar results for CIN2 as an outcome	No

					3: aHR = 0.53 (0.36–0 .77) 2: aHR = 0.87 (0.46–1.67) 1: aHR = 1.40 (0.75–2.61)		
Crowe 2014	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)	• 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
Brotherton 2015	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)	• 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
Hofstetter 2016	11–20	11–27	1	Yes/No/Yes	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)	• 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
Kim 2016	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
Silverberg 2018	14–26	18–34	6	Yes/No/No	Outcome summarized: CIN2+/AIS 3: aRR = 0.78 (0.66–0.91) 2: aRR = 1.02 (0.82–1.28) 1: aRR = 0.89 (0.73–1.09) 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)	• Highest 3d effectiveness among those vaccinated at youngest ages	No
Dehlendorff 2018	13–29	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) • No significant difference between 2d and 3d when interval between 1d and 2d > 5 months and age at vaccination < 20 yrs
Verdoodt 2019	12–16	17–25	0 (6 months for comparison	Yes/No/No	Outcome summarized: CIN2+/AIS 3: aIRR = 0.43 (0.36–0.51) 2: aIRR = 0.49 (0.32–0.76)	• Similar results by age at vaccination, but only significant for those aged <23 yrs	Outcome summarized: CIN2+/AIS 3d vs 1d: aIRR = 0.99 (0.64–1.53)

			between doses)		1: aIRR = 0.34 (0.13–0.87) 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)		2d vs 1d: aIRR = 1.00 (0.61–1.64) Outcome summarized: CIN3+/AIS 3d vs 1d: aIRR = 0.95 (0.60–1.51) 2d vs 1d: aIRR = 0.89 (0.53–1.52)
Brotherton 2019	≤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)	• 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)
Johnson Gargano 2020	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)	• 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)
Rodriguez 2020	9–26	9–31	12	Yes/Yes/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)	• 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
Innes 2020	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)	• No significant effectiveness against high-grade histology for ≥1d among women vaccinated at age ≥18 yrs	No
Bivalent vaccine							
Pollock 2014	15–>18	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
Cameron 2017	14–>18	20–21	0	No/No/No	Outcome summarized: CIN3 Significant effect only with 3d	• Vaccinated in each deprivation category, compared with unvaccinated in most deprived	No

Palmer 2019	12–>18	20	0	YesNo/No	Outcome summarized: CIN3+ 2: aOR = 0.77 (0.48–1.24) 1: aOR = 1.19 (0.70–2.05)	• Effect of 3d vaccination larger with younger age at vaccination, ranging from 0.14 to 0.85	No
Acuti Martellucci[e] *2021*	14–>30	17–32	1,6,12	Yes/Yes/No	Outcome summarized: Any abnormal cytology, youngest birth cohort (1990–1993), 1-month buffer duration 3: aOR = 0.44 (0.14–1.43) 2: aOR = 0.65 (0.20–2.16) 1: aOR = 0.43 (0.17–1.05)	• Sensitivity analyses also for vaccine type (both bivalent and quadrivalent used), high and low grade cytology, and buffer duration	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.

[e] Either bivalent or quadrivalent vaccine

Source: Table adapted from (106).

Figure 6. Specific quality assessment ratings of studies examining HPV infections.

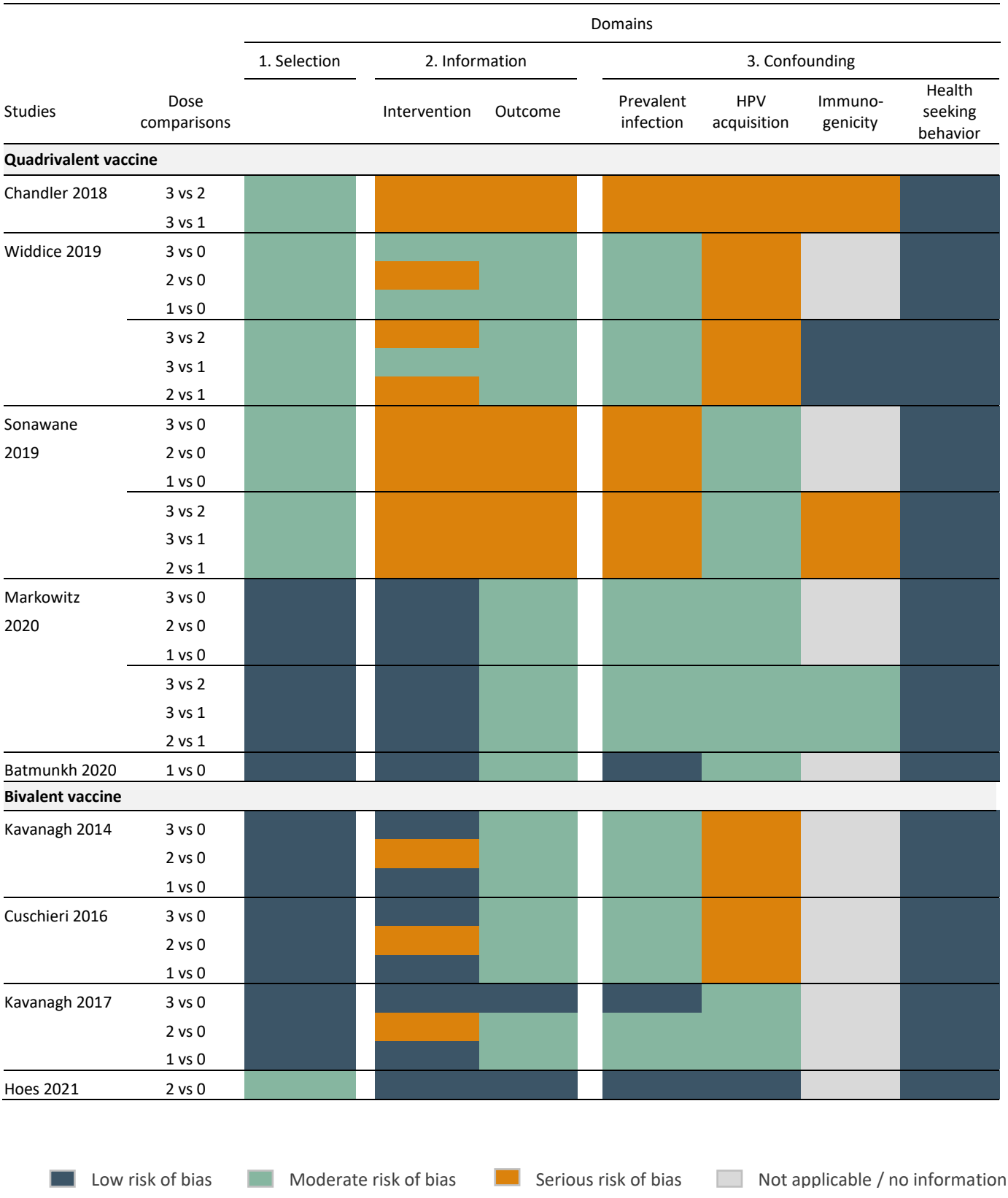


Figure 7. Specific quality assessment ratings of studies examining anogenital warts.

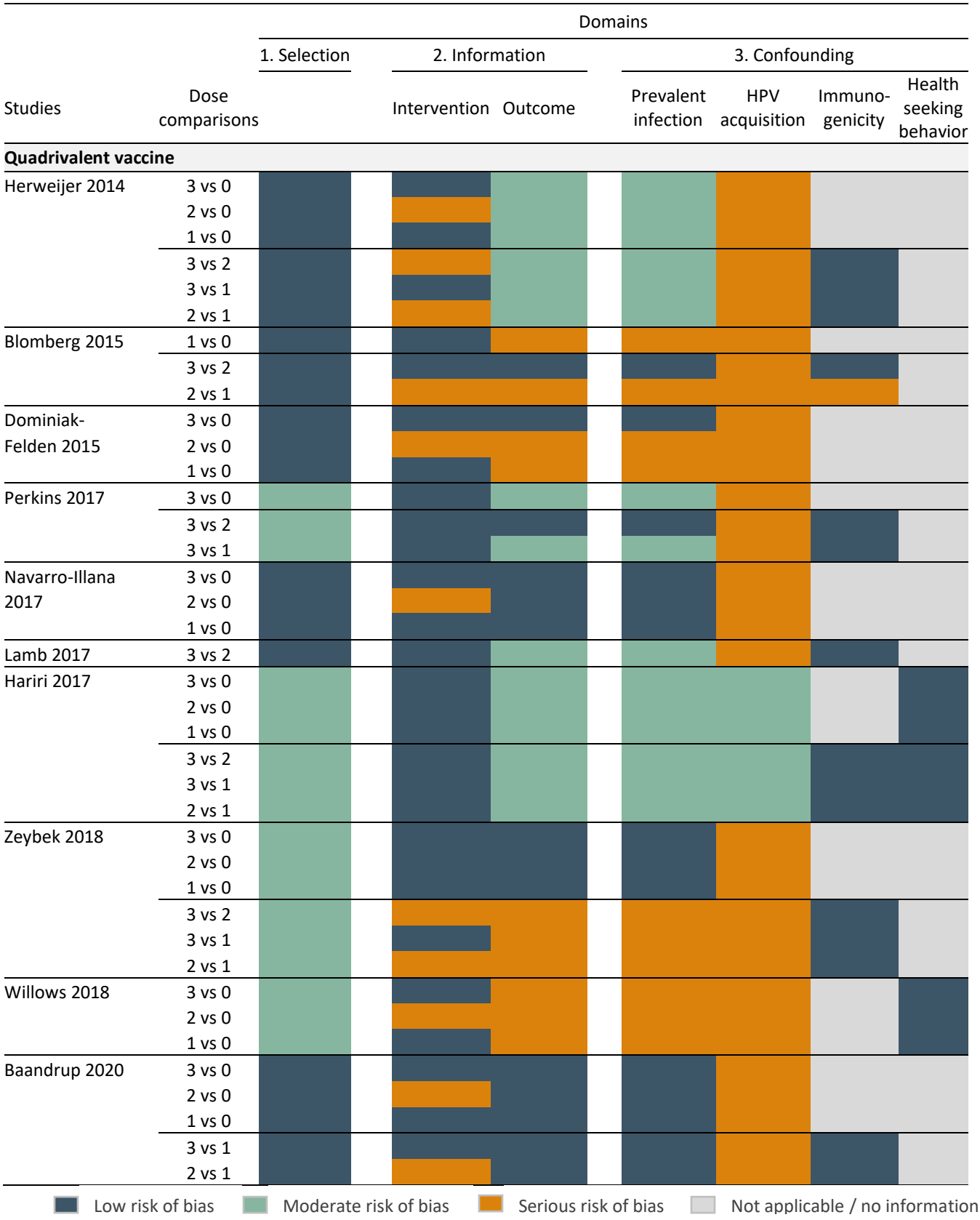
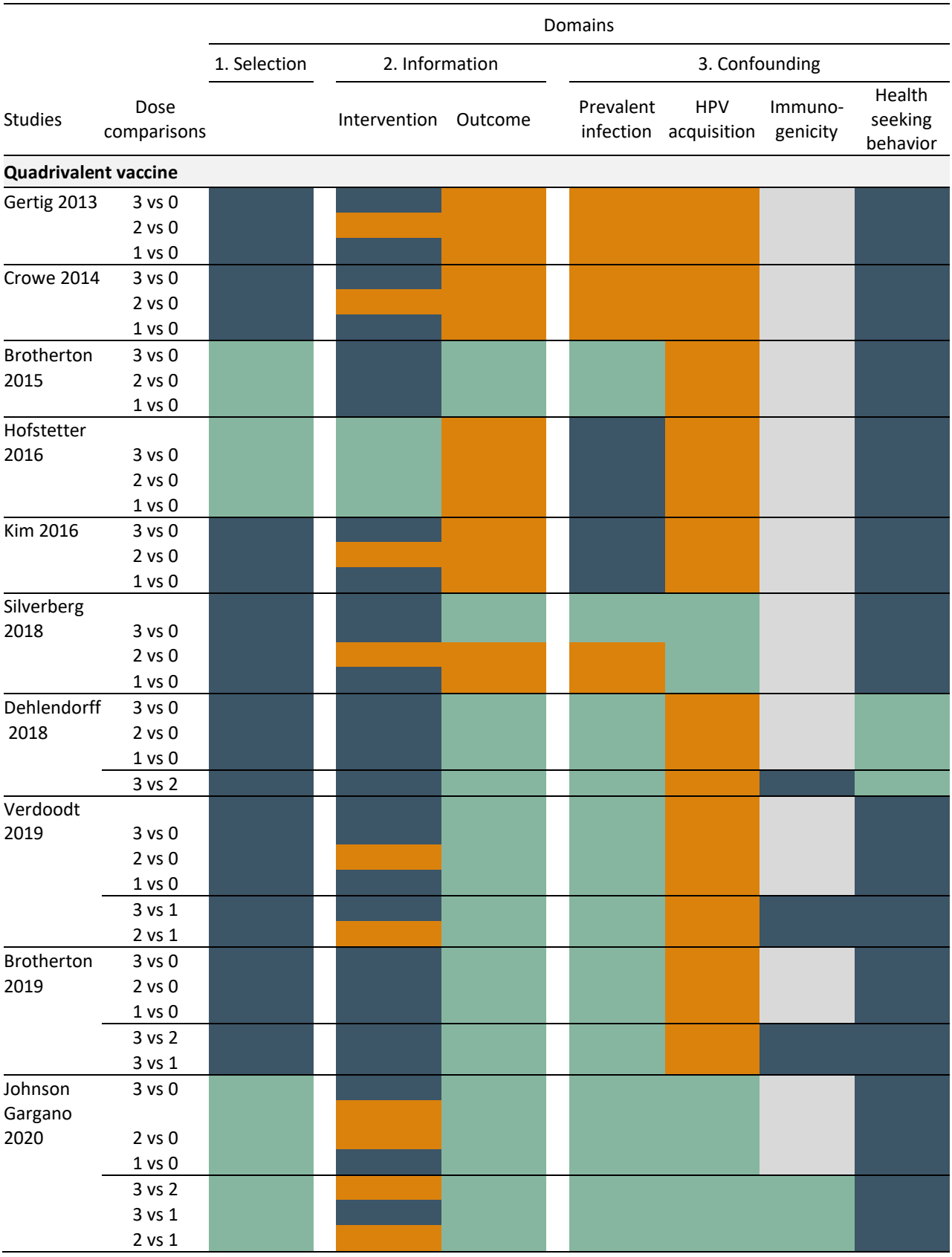


Figure 8. Specific quality assessment ratings of studies examining cervical abnormalities.



		Domains						
		1. Selection	2. Information		3. Confounding			
Studies	Dose comparisons		Intervention	Outcome	Prevalent infection	HPV acquisition	Immuno-genicity	Health seeking behavior
Rodriguez 2020	3 vs 0							
	2 vs 0							
	1 vs 0							
Innes 2020	3 vs 0							
	2 vs 0							
	1 vs 0							
Bivalent vaccine								
Pollock 2014	3 vs 0							
	2 vs 0							
	1 vs 0							
Cameron 2017	3 vs 0							
	2 vs 0							
	1 vs 0							
Palmer 2019	3 vs 0							
	2 vs 0							
	1 vs 0							
Acuti Martelluci 2021*	3 vs 0							
	2 vs 0							
	1 vs 0							

* Bivalent and quadrivalent vaccines were used in this study, but a greater proportion of vaccinated women received the bivalent vaccine

Low risk of bias Moderate risk of bias Serious risk of bias Not applicable / no information

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 the completion of the third edition on single-dose HPV vaccination strategies included one new peer-reviewed publication and three analyses available as preprint articles in medRxiv and SSRN.**

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 (145-149). 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 the credibility of findings (145, 150, 151). Standardization of model reporting to increase transparency and interpretability of model assumptions, inputs, and outputs is also critical (152).

In contrast to the large body of model-based evidence on the impact and cost-effectiveness of three-dose HPV vaccination (153-157), analyses evaluating reduced-dose vaccination schedules are limited. 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 (158-161). 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 (158, 159). However, the incremental benefit of adding a third dose varied greatly, dependent on the 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%) (158).

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 papillomatoses) (159). 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 the 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 (160), 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 (160).

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) (161). 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 (162, 163). An analysis published in the *Vaccine* theme issue on single-dose HPV vaccination extended 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 (164). More recently, several analyses using models calibrated specifically to LMIC have been conducted to examine the global impact and cost-effectiveness of one-dose HPV vaccination in the context of vaccine shortages, extended dose schedules, and delayed implementation (165-168).

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 (162). 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%) (163). 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 (164), 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.

Available in preprint, a recent analysis projected the impact and cost-effectiveness of one-dose versus two-dose 9vHPV vaccination in 192 countries using a comparative modeling approach involving the three modeling platforms described above (Public Health England, HPV-ADVISE, and Harvard models) (165). While the Public Health England model reflected the burden of HPV and cervical cancer in the UK, both the HPV-ADVISE and Harvard models were calibrated to multiple countries reflecting different epidemiological, demographic, and economic profiles (Canada, Uganda, Nigeria, India, and Vietnam for the HPV-ADVISE model; United States, Uganda, India, El Salvador, and Nicaragua for the Harvard model). The projections of direct and indirect benefits of HPV vaccination under a one-dose or two-dose schedule from the 11 country-calibrated models were then extrapolated to the remaining countries in the world using the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model. To consider the most pessimistic scenarios about one-dose protection, one-dose vaccination with 9vHPV was assumed to have either lower efficacy (80% vaccine take) or shorter duration of protection (either 20 or 30 years) for vaccine-targeted types than two-dose vaccination (100% efficacy over the lifetime). Vaccination strategies included routine HPV vaccination of 10-year-old girls, including a one-year multi-age catch-up (MAC) to age 14 years, assuming 80% coverage. Globally, one-dose vaccination was projected to avert 64 to 68.4 million CC cases over 100 years (2021-2120). Importantly, across the models, roughly 93.8-99.9% of the CC cases averted via two-dose vaccination were achieved with one-dose vaccination, even with lower efficacy or shorter duration of protection. Reflecting the stark disparities in CC burden among countries by income group, the number of girls needed to vaccinate (NNV) to prevent one CC case was lowest (and therefore more efficient) in low-income countries (NNV=30) and highest in high-income countries (NNV=81). The NNV with a second dose to avert one CC case was comparatively very high, ranging from 85,800 to 460,000, depending on one-dose efficacy and duration. Likewise, the maximum cost that a country should pay for a second dose was low (US$1.20 in LMIC; US$22.30 in high-income countries, assuming 20-year protection).

A newly published article and a recent pre-print article utilized the HPV-ADVISE model, calibrated to four LMIC (India, Vietnam, Uganda, and Nigeria) to evaluate HPV vaccination

strategies under various scenarios, including single-dose vaccination and extended dose schedules, which involves initially a single-dose followed by a second dose several years later. Drolet et al. primarily focused on examining two-dose vaccination of 9-year-old girls and the incremental benefits and efficiency of including catch-up vaccination to older ages (up to ages 14, 18, and 25 years), adding boys ages 9 to 14 years, and possibly raising the routine target age to 14 years for girls (166). These analyses were also evaluated in the context of one-dose vaccination under the assumption of lower efficacy (95% or 85%) and lower duration (30 or 20 years), as well as increasing the interval between doses up to 5 years. Consistent with prior analyses, routine vaccination of 9-year-old girls with two doses (with 100% lifelong efficacy against seven high-risk HPV types included in 9vHPV) was found to be highly effective in reducing cervical cancer in each of the four countries (ranging from 79-85% reduction in age-standardized incidence rates); comparatively, including catch-up vaccination in the first year accelerated the decrease in incidence but did not change the steady-state incidence reduction, adding boys both accelerated the decrease in incidence and resulted in lower steady-state incidence, and shifting the age of routine vaccination from 9 to 14 years yielded nearly equivalent effectiveness. One-dose vaccination of girls aged 9 to 14 years was found to be cost-effective compared to no vaccination; when assuming lifelong efficacy greater than 85%, the authors found that extending single-dose vaccination to older girls, women, and boys aged 9 to 14 years would be more cost-effective than giving a second dose to the girls aged 9 to 14 years. If a single dose provides a shorter duration of protection (i.e., 20 years), then giving a second dose to girls aged 9 to 14 years was equivalent to extending vaccination to older girls and women. The authors also found that vaccination of girls with one dose at age 9 years and a second dose at age 14 years (i.e., extended interval) was as effective as providing two doses at age 9 years, if vaccine efficacy and coverage achieved were equivalent and was among the most efficient and cost-effective strategies with NNV ranging from 78 to 350 across the four countries.

In the pre-print article using the same calibrated HPV-ADVISE models, Bénard et al. focused on evaluating the potential benefit of extended-dose schedules for HPV vaccination and explored the impact of varying vaccination coverage of the second dose, as well as one-dose efficacy and durability (167). They found that even with lower efficacy of a single dose, vaccination with an extended interval between doses was nearly equivalent to the current two-dose vaccination schedule, provided coverage of the second dose five years later was not low (e.g., 30% coverage). Furthermore, reaching 70% vaccination of 14-year-old girls irrespective of vaccination status would be even more effective than the current two-dose schedule. The authors concluded that extended dose schedules have the potential to provide similar cervical cancer reductions as two-dose schedules, while alleviating the need for vaccine supply in the short-term and offering a 5-year time window to re-assess the necessity of the second dose as we await additional clinical trial data.

In another pre-print analysis, Burger et al. estimated the impact of delayed implementation of single-dose HPV vaccination using two independent models calibrated to a setting with a high cervical cancer burden (168). With clinical trials underway and expected to report final results on the (non-) inferior efficacy of one-dose vaccination within five years, the authors examined two scenarios: (1) assuming non-inferiority of a single dose compared to two doses (i.e., 100% lifelong efficacy), single-dose vaccination implemented in year 2021 compared to delayed implementation of single-dose vaccination in 2026; and (2) assuming an inferior vaccine efficacy of a single dose (80% lifelong efficacy), single-dose vaccination implemented in year 2021, reverting to a two-dose schedule in 2026 (presumed year in which trial results show assumed inferiority). In the second scenario, different assumptions regarding re-vaccination of those who had received one dose in 2021 were explored, including 100% revaccination, 0% revaccination, and multi-age cohort campaign assuming 70% of girls aged 10 to 14 years in 2026 received vaccination, either as a first dose or second dose. In all scenarios, vaccination coverage was assumed to be 70% of girls aged 9 years, with a one-year campaign of girls ages 10 to 14 years. Both models consistently projected that early implementation of single-dose vaccination, ahead of confirmatory trials, resulted in greater health benefits under most scenarios evaluated than delayed implementation even up to five years. Even with a lower, inferior efficacy of 80% for a single dose (increasingly observed to be too pessimistic in clinical and observational studies to date), the earlier implementation offset any loss in health benefits due to efficacy, even if re-vaccination of previously vaccinated girls was not possible. As with prior analyses, the authors note the importance of prioritizing cohorts of girls that would otherwise exceed the age of HPV vaccine eligibility during the 5-year delay window.

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 (169). 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 limitations of model-based evidence

It is important to highlight that the model-based evidence on reduced-dose HPV vaccination to date relies primarily on findings from three independent models (Public Health England, HPV-ADVISE, and Harvard) that have been developed and calibrated using data on the burden of HPV and cervical cancer in different countries.

The most recent analyses contribute to the early modeling studies of one-dose vaccination by expanding the evaluation to settings with varying epidemiological, demographic, and economic profiles, enabling an assessment at the global level. Despite the variability of HPV and CC burden of disease across countries—and analyses conducted across three independent models—the findings consistently showed that most of the health benefits of a two-dose vaccination scenario were achievable with one-dose vaccination, and that one-dose vaccination was far more efficient in preventing CC cases, especially in low-income countries. While each of the four new analyses addressed different questions, they all emerged with consistent messaging that any loss due to decreased efficacy or durability with single-dose vaccination could be offset by

reasonable coverage of a second dose, even five years later, and by focusing on reaching girls and young women before they age out of vaccine eligibility. These findings support the importance of reducing delays in implementing HPV vaccination programs in countries that have not yet introduced them. 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.

The analysis evaluating single-dose vaccination for women living with HIV (169) makes several contributions to the literature on reduced-dose HPV vaccination. Foremost, the study is the first of its kind to consider 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 independent from the other model-based studies, adding to the number of different research groups assessing the impacts of single-dose HPV vaccination. Future analyses that extend the modeling to settings with more variable epidemiological, demographic, and behavioral profiles will further enrich the evidence of the impact of single-dose HPV vaccination in populations with a high HIV burden.

2.5.5 Summary of model-based evidence

These 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 the 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 a greater health impact and is likely to be cost-effective.**

Similar themes emerged in the 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 lower duration of protection of only 10 years.**
- **The impact and cost-effectiveness of adding a second dose are driven by the duration of single-dose vaccine protection and, possibly, the ability to achieve higher coverage with a single dose versus multiple doses.**
- **Most health benefits associated with two-dose vaccination are achieved with one-dose vaccination, even with lower efficacy or duration of protection.**
- **The NNV to avert one CC case is far lower in low-income than high-income countries; in all settings, the NNV with a second dose to avert one CC case was excessively high.**
- **Vaccination with a single dose at age 9 years and a second dose at age 14 years (i.e., an extended dose interval of 5 years) can be as effective as the current two-dose schedule, and to be among the most efficient strategies.**
- **Immediate implementation of a single-dose HPV vaccination leads to greater health benefits than waiting until more information on vaccine efficacy is available from ongoing clinical trials, expected in five years. Health benefits are maximized when cohorts are reached that would otherwise exceed vaccine age eligibility in those five years.**
- **Single-dose Merck 9vHPV vaccination in a high-HIV-prevalence setting can yield high reductions in CC incidence and mortality. These relative reductions are similar irrespective of HIV status, CD4 count, or ART coverage.**

3 Summary of the available evidence

A comprehensive review of 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 protect against HPV. Providing robust evidence in support of this theory, the recent KEN-SHE trial – the first prospectively randomized efficacy trial of single-dose HPV vaccination – demonstrated that a single dose of the 2vHPV vaccine or the 9vHPV vaccine has almost 98% efficacy against incident persistent HPV 16 or 18 infection in sexually-active young Kenyan women. The Tanzanian DoRIS trial—the first prospectively randomized trial of single-dose HPV vaccination in the target age range for HPV vaccination—found that greater than 98% of participants seroconverted to HPV 16 and 18 following a single dose of the 2vHPV or 9vHPV vaccine and HPV 16 seropositivity following one dose was non-inferior to that following 2 or 3 doses. HPV 16 and 18 antibody GMTs in DoRIS were lower with one dose compared to two or three doses, but GMTs with one dose were durable to 24 months post-vaccination.

Results from the KEN-SHE and DoRIS trials are consistent with earlier observational evidence from clinical trials (CVT, PATRICIA and the India HPV vaccine trial) in which some participants received only one HPV vaccine dose due to non-completion of an allocated multidose schedule. Participants receiving HPV vaccine through these clinical trials had very low rates of HPV 16/18 infection and sustained antibody responses up to 11 years post-vaccination, regardless of the number of doses received. Participants receiving only a single HPV vaccine dose had significantly lower infection rates than control participants who did not receive any HPV vaccine. As in the DoRIS trial, HPV 16/18 antibody titers in CVT and the India HPV vaccine trial were lower for single-dose arms compared to multidose arms. However, 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 from CVT and the India HPV vaccine trial suggests. Notably, antibody seropositivity and GMTs among girls who were prospectively randomized to receive a single dose of HPV vaccine in DoRIS were non-inferior to those among one-dose participants in CVT and the IARC India vaccine trial, in whom efficacy has been demonstrated.

Several post-licensure observational studies have been published that compare HPV vaccine effectiveness or immune responses among adolescents receiving one, two or three doses of HPV vaccine through national vaccination campaigns or programs. 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. More than 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. There are 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.

Most of the post-licensure immunogenicity studies evaluated humoral immune responses to the vaccines, though two also present cellular immunogenicity data. As for the trial data, these studies demonstrate high rates of seroconversion for vaccine-type HPV antibodies in all dosage groups. 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.

Modeling analyses have evaluated single-dose HPV vaccination in the United States, United Kingdom, South Africa, Uganda and globally. Analyses consistently 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. If the choice is between one-dose and two-dose vaccination, then the second dose becomes a cost-effective option if it can extend protection up to at least 20 years; however, a recent global analysis suggests that 93-99% of health benefits from two-dose vaccination are achieved through one-dose vaccination. New analyses demonstrated that delays in vaccine implementation, even with a single dose with lower efficacy, can result in substantial forgone health benefits, and that extended dose schedules (e.g., a single vaccine dose at age 9 years followed with a second dose at age 14 years), has the potential to be as effective as the current two-dose schedule. Together these studies suggest that the benefits of immediate introduction of single-dose HPV vaccination, prior to the availability of further clinical trial data, likely outweigh the potential risks. 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. 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

The KEN-SHE and DoRIS trials are the first prospectively randomized trials of single-dose HPV vaccination. Prospective allocation to a single dose versus comparator groups considerably reduces the risk of bias seen in many of the observational studies conducted to date due to differences in participants who received different dosing schedules. Both trials demonstrated consistency across arms in risk factors such as sexual behavior. KEN-SHE was a placebo-controlled, blinded trial and evaluated persistent cervical HPV infection as the primary outcome measure, allowing direct measurement of VE. The trial did not compare single dose HPV vaccination to a multidose schedule, but efficacy of one dose against incident persistent HPV infection was almost 98%. The DoRIS trial was an unblinded trial comparing immune responses to one, two, or three vaccine doses among girls in the target age range for HPV vaccination. Both trials evaluated the GSK 2vHPV and Merck 9vHPV vaccines and had excellent retention to the primary outcome visits. A major strength of the newly available trial data is the immunobridging of results from DoRIS to those from the CVT and Indian trials, and further immunobridging is planned between the DoRIS and KEN-SHE trials.

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, encompassed data from multiple sources, and have been updated at multiple time points to capture new data on single -dose HPV vaccination as it emerges in the literature. A limitation of the previous review versions was that, while the consortium 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. However, in the current evidence review, the non-trials observational studies were reviewed using an adaptation of the ROBINS-I framework to conduct a quality assessment of the studies included. This framework takes into account the particularities of observational studies examining the impact of HPV vaccination by number of doses. The quality assessment is completed for the 35 eligible non-trial observational studies.

Data from the nested observational studies from RCTs included in the trials-based systematic review (derived from the CVT, PATRICIA, and IARC India HPV vaccine trial) provided encouraging indications prior to the emergence of the prospectively randomized trial data that a single dose of

HPV 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. Follow up in the CVT and India HPV vaccine trial 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.

The observational immunogenicity studies identified through literature searches have also provided useful data. For example, 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 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. The US PHACS study presented immunogenicity data following one, two, or three doses of Merck 4vHPV for HIV-infected adolescents, an important population who is at particularly high risk of HPV infection and related clinic sequalae, yet for whom there is currently little evidence base regarding HPV vaccine dosing schedules.

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 (except one) conducted in settings of a national three-dose recommendation, and girls who received one or two doses differed from those completing the recommended schedule as described earlier in this document. More recent studies have examined persons vaccinated prior to sexual activity and used methods to reduce potential sources of bias.

Three of the nine 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 newest analyses

utilize models that are calibrated to specific LMICs that reflect a range of epidemiological, demographic, and behavior profiles. 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.

5 Gaps in the evidence, research priorities & forthcoming evidence

5.1 Efficacy and immunogenicity data from RCTs and observational studies

Several clinical trials and observational studies have examined single-dose regimens and provided results that challenge the prevailing dogma that protein-based subunit vaccines require a multidose regimen. 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 12**.

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

The systematic review 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, and the KEN-SHE and DoRIS trials are the first studies to address this evidence gap. These and other ongoing randomized trials (**Table 12**, Error! Reference source not found.) will be able to provide more definitive data on whether single-dose HPV vaccination can protect against HPV-persistent infection and produce sufficient and durable antibody responses.

Both the KEN-SHE and DoRIS trials are ongoing and will provide results up to 36- and 60-months post-vaccination, respectively. Further trials and population level impact studies are ongoing, the results of which are scheduled to become available within the next few years. These include the Estudio de Comparacion de Una y Dos Dosis de Vacunas Contra el Virus de Papiloma Humano (ESCUDDO) trial, the Puente de Respuesta Inmunológica para Mejorar el Acceso a Vacunas y ERrAdicar el cancer [PRIMAVERA] trial in Costa Rica, the International Vaccine Institute (IVI) HPV1 study in Thailand, the HPV One/two dose Population Effectiveness (HOPE) study in South Africa, and the HPV vaccination in Africa—New Delivery Schedules (HANDS) trial in the Gambia.

The ESCUDDO trial is a large-scale RCT aiming to evaluate 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 (27). The study is a four-arm trial of approximately 20,000 girls aged 12 to 16 years to formally evaluate the non-inferiority of one versus two doses of each the Merck 9vHPV and GSK 2vHPV vaccines. The participants were randomized into two stages to receive one or two doses of the

vaccines and will be followed for five years. As a primary endpoint, the trial will focus on the prevention of new persistent HPV 16/18 infection. 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 of approximately 4,000 initially HPV-unvaccinated women were recruited to provide control estimates of HPV persistent infection 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 in 2020, and four-year follow-up data are expected to be available in 2025 (Error! Reference source not found.).

Results from the DoRIS trial will be immunobridged to those from both KEN-SHE and ESCUDDO.

PRIMAVERA is another clinical trial in Costa Rica comparing immune responses following one dose of the GSK 2vHPV vaccine among 520 girls aged 9 to 14 years (the intervention arm) to three doses of the Merck 4vHPV vaccine in 520 women aged 18 to 25 years (the control arm), the trial population in which efficacy was initially proven (170). The primary aim is to demonstrate that HPV 16 and 18 antibody responses among one-dose GSK 2vHPV recipients aged 9 to 14 years are non-inferior to those among three-dose Merck 4vHPV recipients aged 18 to 25 years at 24 and 36 months after their 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) (28) 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 to 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 to 18 years) to measure the population-level impact on HPV prevalence, with DNA being measured in, and genotyped from, urine. Immune responses are being 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 (171). 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 to 18 years across the intervention (district-level single-dose catch-up vaccination) and control (national program alone) districts 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.

The HANDS trial is an immunogenicity trial in the Gambia comparing one and two doses of Merck 9vHPV in children aged 4 to 8 years and 9 to 14 years with three doses in those aged 15 to 26 years (29). This randomized, open-label, single-center, phase III non-inferiority trial began in 2019. 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 to 12 years will receive a second dose of Merck 9vHPV at 24 months, will 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 (172).

5.1.2 Durability of protection

Robust evidence that a single dose of HPV vaccine will provide a sufficient and durable enough level of efficacy against persistent HPV infection will be crucial to support a recommendation for a policy change to a single-dose vaccination strategy. KEN-SHE will continue efficacy follow up to three years post-vaccination. Thereafter, this question is being addressed through continued follow-up of the CVT and India study cohorts. 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 (82, 173, 174). Data on incident persistent infections in the IARC India HPV vaccine study are currently available up to ten years post-vaccination; and data will continue to be obtained from women who are initiating sexual activity over the next few years, including women in the single-dose arm (81). Data from these women will be used to compare the efficacy of one dose of Merck 4vHPV against persistent infection 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 is also generating 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. Many of those who have initiated CC screening to date will have a second round of screening in the subsequent years. The screening outcomes in the vaccinated women will be compared with that of 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, described above.

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 12).

Currently, all the ongoing prospective studies evaluating single-dose HPV vaccination (described above) are being conducted in females only. However, a new cluster-randomized trial (CRT)—the Add-Vacc trial ("Adding Male Single Dose HPV Vaccination to Female HPV Vaccination in Tanzania"; Clinicaltrials.gov: NCT04953130)—will evaluate the impact of adding one-time, single-dose HPV vaccination among a multi-year cohort of Tanzanian boys aged 14 to 18 years alongside routine annual HPV vaccination of girls aged 14 years on population-level HPV prevalence. The CRT will be conducted in 26 communities in northern Tanzania, randomized 1:1 to either the control arm (national HPV vaccination program in girls alone) or the intervention arm (national HPV vaccination program in girls plus one-time, single-dose catch-up HPV vaccination in boys). Vaccine-type HPV infection prevalence will be measured among 18-to 21-year-old males and females in cross-sectional surveys conducted at baseline and at three years post-vaccination of boys. The trial is due to start in early 2022. Within the Add-Vacc trial, a nested cohort of 200 boys administered a single dose of HPV vaccine will be followed up for immunogenicity up to 36 months following vaccination.

At current, another key evidence gap is the efficacy and immunogenicity of single-dose HPV vaccination in HIV positive girls and young women, a group at particularly high risk of HPV

acquisition and persistence, and CC related morbidity and mortality. This gap will be partially addressed through a new trial, titled "Integration of HPV vaccination and HPV-based cervical screening into ARV clinics" (the "H2VICTORY trial") (175). The H2VICTORY trial is a randomized, hybrid effectiveness-implementation study evaluating a dual intervention of HPV vaccination alongside HPV-triage-treat within ARV clinics. It will be conducted in three countries within Sub-Saharan Arica: South Africa, Kenya and Eswatini. In total, 8,000 HIV-positive women aged 25 to 35 years will be randomized (1:1:1) to receive three doses of HPV vaccine, one dose of HPV vaccine or a placebo; all arms will additionally be screened for HPV according to WHO guidelines. The primary outcome measure is prevalent HPV infection at 24 months post-vaccination; neutralizing antibody titres will be measured at the same time point as a secondary outcome measure. The study is expected to start in July 2022.

The evidence base to date is largely derived from studies of the 2vHPV and 4vHPV vaccines; however, new and ongoing research on single-dose vaccination spans the three widely available commercial vaccines (GSK 2vHPV, Merck 4vHPV, and Merck 9vHPV). Whereas no single-dose study of the new Innovax 2vHPV vaccine has been conducted or planned to date, a new open-label randomized controlled trial titled "Phase 3 trial of a Bivalent HPV vaccine (Cecolin®) in young girls" is evaluating two-dose regimens of the Innovax 2vHPV vaccine with varying interval durations (up to 24 months), thus providing the opportunity to examine persistence and stability of immune responses following the first vaccine dose (176). The study will be conducted among 1,025 girls aged 9 to14 years in Ghana and Bangladesh, who will be randomized to one of five study arms. Arms 1 to 3 will receive two doses of the Innovax 2vHPV vaccine with intervals of 6, 12 or 24 months, respectively; arm 4 will receive two doses of the Merck 4vHPV vaccine with a 6-month interval; and arm 5 will receive a mixed Merck 2vHPV / Innovax 2vHPV vaccine schedule with a 24-month interval. Anti HPV 16 and 18 IgG GMCs will be measured by ELISA and neutralizing antibody GMTs will be measured by PBNA at various timepoints up to month 24.

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 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.

As funding allows, the systematic review of effectiveness studies will be updated regularly, allowing inclusion of newly published studies. If possible, 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.

5.3 Modeling studies

5.3.1 Factors influencing modeling results

The early studies on reduced-dose vaccination 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 (160, 161). 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), has thus far 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. Early analyses showed that modest increases in coverage with reduced doses can compensate for a potential waning protection and/or lower efficacy (161, 163). **The most recent analyses also included multi-cohort catch-up vaccination for girls, inclusion of boys, extended dose schedules, and delayed implementation of HPV vaccination (165, 166).** In addition to the factors mentioned above, the influence of patterns by age (e.g., coverage, sexual behavior, and HPV risk) becomes greater as more specific and targeted strategies are evaluated.

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

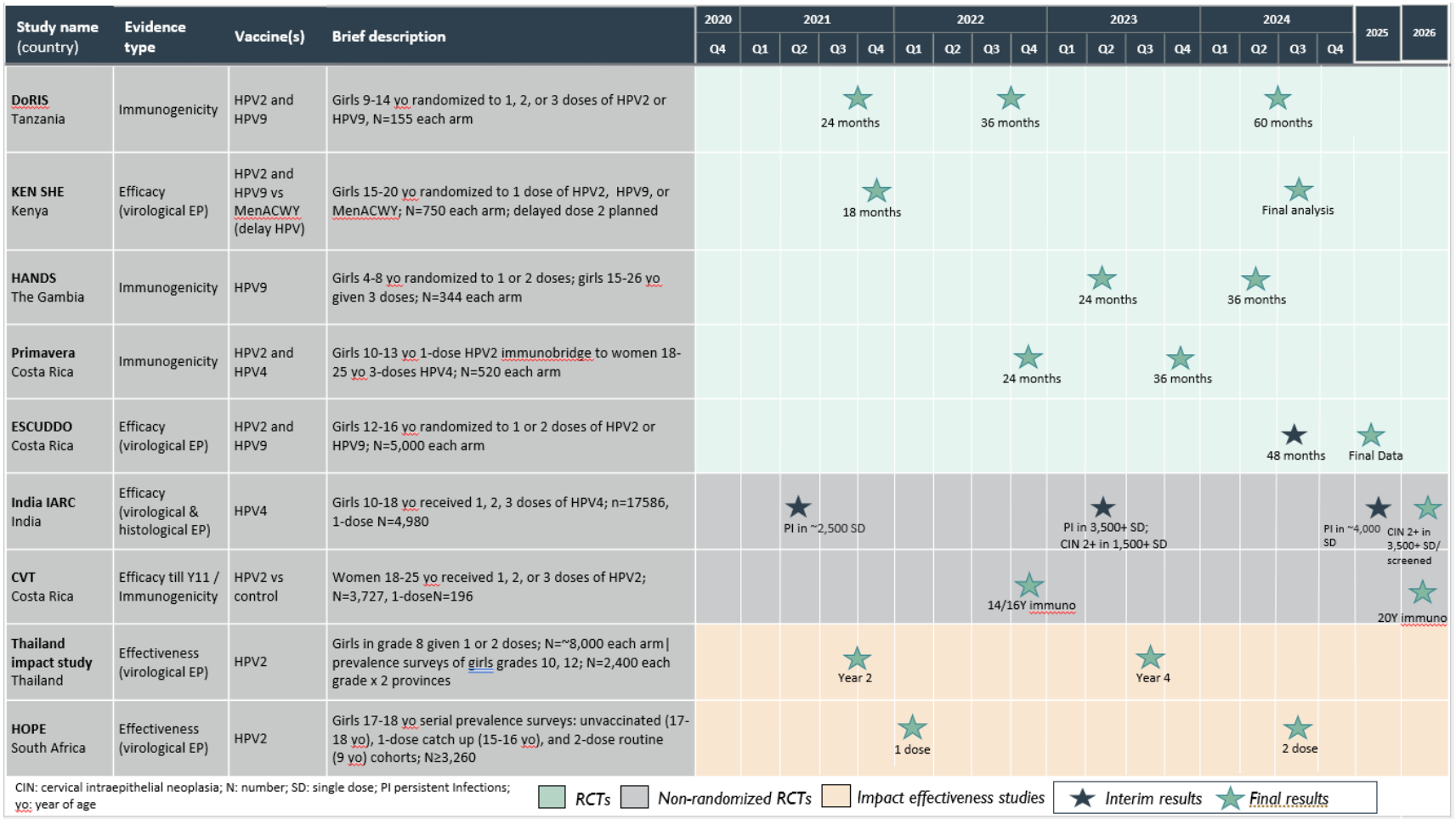
The South African study found that the relative reductions in CC incidence and mortality did not vary substantially across HIV-negative and HIV-positive women (irrespective of CD4 count or ART coverage). However, the analysis assumed the same efficacy across all vaccinated girls. Given current recommendations 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 becomes available from clinical trials on VE and durability in HIV-positive women.

Table 12. 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 (173, 174)	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 (26)	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: 60 months
ESCUDDO (27)	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: 60 months
HANDS (29)	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 (171)	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 (81)	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 (28)	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 (28)	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 (170)	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 (172)	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
Add-Vacc	Tanzania	≤11,440 males vaccinated aged 14-17 y Surveys in 13,000 males and females aged 18-21 y	Merck 4vHPV	CRT of 1d catch up in boys compared to national program, using repeat cross-sectional surveys	Impact on population HPV prevalence; immunogenicity (subset)	Start: Jan 2022 FU: 36 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 9. 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.

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Appendix 1: Contributors and acknowledgments

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

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