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REVIEW

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Review of long-term immunogenicity following HPV vaccination: Gaps in current knowledge

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ABSTRACT

The licensed HPV vaccines are highly efficacious and induce high levels of neutralizing antibody levels, the assumed mediators of protection. However, a correlate of protection against HPV is lacking, and the evidence is still limited as to long-term persistence of antibodies, especially following reduced dosing schedules. The World Health Organization (WHO) urges immunization of young girls as part of the strategy to eliminate cervical cancer, thus long-lasting protection is required. The current review describes long-term follow-up regarding vaccine-induced seropositivity and antibody level development following the different vaccines and dosing schedules. Implications and opportunities of long-term vaccine-induced immune responses are discussed, such as the gaps in monitoring of long-term immunogenicity, the possibilities of reduced dosing schedules, and the importance of evidence for durable immunity.

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Introduction

The human and non-human papillomaviruses can be subdivided into genera. This review focusses on human papillomavirus (HPV) types from the alpha-genus, which are able to infect the human genital tract where they may cause disease.[1] Within this genus, high-risk (hr) and low-risk (lr) types can be distinguished; when hrHPV type infections persist, they have the potential to cause the development of cervical (pre-) cancer, whereas lrHPV types are associated with anogenital warts.[2,3] However, the vast majority of the infections are asymptomatic and clear spontaneously.

HPV is a very common sexually transmitted infection with an estimated cumulative lifetime risk of 80% in Western countries.[4,5] To prevent HPV infection and ultimately preclude the development of cervical cancer, prophylactic HPV vaccines have been developed. The first two were licensed in 2006 and 2007, respectively. The first is the bivalent vaccine (2vHPV), Cervarix®),[6] which targets the most important hrHPV types 16 and 18.The second is the quadrivalent vaccine (4vHPV), Gardasil®,[7] which targets HPV types 6,11,16, and 18. In 2014, a vaccine targeting these four types plus five additional hrHPV types was licensed: the nonavalent vaccine (9vHPV), Gardasil9®.[8] In recent years, vaccine registration has been expanded to protection against non-cervical HPV-associated disease (including other anogenital cancers) and to males as well as females.

High efficacy of the HPV vaccines against cervical infections and lesions was shown by randomized controlled trials (RCTs), indicating protection up to 98% against virological and clinical endpoints caused by the targeted vaccine types.[9] These findings were reiterated in observational research following implementation of HPV vaccines in national immunization programs. For example, a large meta-analysis in high-income countries showed an 83% reduction of HPV16/18 prevalence among girls aged 13–19 y comparing pre- and post-vaccination implementation periods up to 8 y following implementation.[10] This reduction was likewise observed in field efficacy studies; in Australia, the prevalence of HPV16/18 was flat across age groups following vaccination,[11] whereas in Sweden, a substantial risk reduction for cervical cancer was observed among vaccinated women.[12] Furthermore, HPV vaccines are known to be highly immunogenic able to provoke a solid systemic immune response, especially through the formation of antibodies.[13] Virtually all HPV-vaccinated individuals seroconvert[14] and RCTs found peak antibody levels in vaccinated individuals up to 100-fold higher compared to naturally infected individuals.[15]

HPV vaccines can be provided according to a three-dose schedule (0,1–2, and 6 months), currently recommended for those 15 y and above or two-dose schedule (0, 5–13 months), recommended for those 9–14 y of age. After the initial registration of the HPV vaccines according to three-dose schedules, new evidence implied that two doses induce protection equally well. The underlying concept is known as immunobridging: Efficacy against virological and clinical endpoints was first observed among 15–26-y-old women who were vaccinated three times. Among 9-to-14-y-old girls who were vaccinated twice, non-inferior serum antibody responses were observed as compared to the three-dose-vaccinated women. Immunobridging assumes the same efficacy can be expected in groups where non-inferior antibody responses are found. Hence, from 2014 onwards, two–dose schedules were approved and advised for young vaccine recipients by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and World Health Organization (WHO).[6–8]

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Registered HPV vaccines are prophylactic and thus provide optimal protection among HPV-naïve individuals. Since the prevalence of HPV infection starts to rise from the beginning of sexual activity, vaccination in young adolescence is preferable, feasible, and pursued in most countries where HPV vaccination has been implemented. For optimal benefit, the induced protection should ideally cover the entire life period of sexual activity. As of 2018, the WHO has committed to elimination of cervical cancer as a global health problem. To reach this goal, one of the targets proposed for countries is to have 90% of girls fully vaccinated against HPV by age 15.[16] While neutralizing antibodies are the supposed primary mediators of the protection, the minimum level required for protection has not yet been established, nor has the duration of protection.[17] In this review, the current knowledge on long-term immunogenicity following HPV vaccines is described and the implications for global HPV reduction are discussed.

Measurement units and assays

We can roughly distinguish three types of assays that are commonly used in RCTs to evaluate HPV antibodies following vaccination: the pseudovirus-based neutralization assay (PBNA), competitive (epitope-specific) immunoassays (cLIA), and VLP-IgG binding assay (ELISA or MIA). The first is considered relevant for measuring the biological activity, whereas the cLIA reflects neutralizing activity with high affinity. ELISA detects all antibodies regardless of neutralization.[18] Respectively, the methods require pseudovirions, type-specific monoclonal antibodies, and/or intact VLPs, and their quality affects the individual assay quality. WHO suggests PBNA was as the reference standard for assessing HPV-specific neutralizing antibodies. This method is very time-consuming and costly, but a recently developed high-throughput PBNA assay allows more assays to be processed sequentially and also has increased sensitivity.[19] On the other hand, cLIA and ELISA/MIA are fast and suitable for high-throughput but, measure, respectively, a subset of total neutralizing antibodies and the total amount of HPV-specific antibodies.

Variations on these three assays are used in studies because reagents and assay standards are not always available and there are no official guidelines on methods for determining cutoffs. This use of varied techniques gives rise to variation in findings. For example, a comparison study showed that the PBNA is more sensitive than IgG-cLIA for the detection of HPV16- and HPV18-neutralizing antibodies.[20] Another study indicated that assays showed reasonable correlation, but that improvement in correlation could be achieved by small alterations.[21] To overcome such problems, the International Unit (IU) measure has been established for HPV16 and 18. It should be used to express findings in order to facilitate comparability,[18] but not all studies use standardized measurements, and the IU for hrHPV types other than 16 and 18 has yet to be established.

Outcomes used to describe the immunogenicity of the HPV vaccines include the geometric mean concentration or titer (GMC/T), or the percentage of seropositives (i.e., number of study participants with an antibody level above a certain cutoff level). Both provide information on the long-term performance of the vaccine regarding stimulation of antibody production. Arbitrary study-specific cutoffs have been applied to determine seropositivity.[13] Additionally, antibody avidity can be used as a marker to express affinity maturation, i.e., how well an antibody binds to an antigen. This can for instance be measured with the chaotropic thiocyanate ion method in the ELISA/MIA assays.[22,23] Nevertheless, avidity is considered a crude marker for affinity maturation and should therefore be interpreted with caution.

Biological mechanisms underlying HPV vaccination

All three prophylactic HPV vaccines now on the market consist of virus-like particles (VLPs), although these are produced in various expression systems. Also, the vaccines differ in their adjuvant systems (Table 1). The VLPs resemble the L1 protein of HPV, the major capsid protein, which is morphologically indistinguishable from real HPV particles.[24] All the vaccines contain aluminum salts as an adjuvant to ensure a slow release of the antigen and activation of the innate immune system. However, the 2vHPV vaccine uses the AS04 adjuvants system, which contains both aluminum salt and monophosphoryl lipid A (MPL), which is believed to activate the innate immune response.[25]

Table 1. Characteristics of the three available HPV VLP vaccines.

	Cervarix® (bivalent)	Gardasil® (quadrivalent)	Gardasil9® (nonavalent)
Manufacturer	GlaxoSmithKline Biologicals, SA	Merck Sharp & Dohme	Merck Sharp & Dohme
VLP types included	HPV16 and 18	HPV6, 11, 16 and 18	HPV6, 11, 16, 18, 31, 33, 45, 52 and 58
Dose of L1 protein	20 µg (HPV16 and 18)	20 µg (HPV6 and 18), 40 µg (HPV11 and 16)	20 µg (HPV31, 33, 45, 52, 58), 30 µg (HPV6), 40 µg (HPV11 and 18), 60 µg (HPV16)
Registered for	Boys and girls ≥9 yr.	Boys and girls 9-26 yr.	Boys and girls 9-26 yr.
Adjuvant	500 µg aluminium hydroxide and 50 µg 3–0-deacylated-4′ -monophosphoryl lipid A (AS04)	225 µg aluminium hydroxyphosphate sulphate (AAHS)	500 µg aluminium hydroxyphosphate sulphate (AAHS)
Schedule	9-14 years of age: two doses (0, 5-13 months) ≥15 years of age: three doses (0,1,6 months)	9-13 years of age: two doses (0, 6 months) ≥14 years of age: three doses (0,2,6 months)	9-14 years of age: two doses (0, 6 months) ≥15 years of age: three doses (0,2,6 months)

In animal models, vaccination with L1 VLPs has been shown to induce neutralizing antibody levels and protection against an HPV infection.[26] After passive transfer of immune sera, naïve animals were protected against infection.[17] These findings were supportive of the general assumption that protection following HPV vaccination is primarily antibody-mediated. Even more supportive were trials in human participants, which showed high and durable, type-restricted titers of VLP antibodies after vaccination.[22]

Naïve B- and T-cell activation is important in HPV antibody production. Upon entering the body, the VLP antigen part of the vaccine is bound to antigen-presenting cells (APCs). The antigen is then presented to T-cells, which have various functions and can differentiate into one of several T-cell lineages, including cytotoxic, T-helper, or memory T-cells. The T-helper cells in turn stimulate naive B-cells to become either plasma cells or memory B-cells.[27] Long-lived plasma cells (LLPC) are generated upon vaccination and secrete antigen-specific antibodies, thereby enabling the persistence of circulating antibodies. However, circulating memory B-cells can be still detected after vaccination and could therefore also assist in a rapid recall when the HPV antigen is encountered again.[28] Thus, LLPCs, memory B- and T-cells are essential for establishing long-term protection, i.e., by inducing and maintaining high levels of neutralizing antibodies.

Neutralizing antibodies are the assumed mediators of protection following HPV vaccination. They can bind to a virion and prevent it from binding to a cell, thereby neutralizing the toxin. There are various isotype forms of antibodies, IgG and IgA, which can be further subdivided. After HPV vaccination the subclasses IgG1 and IgG3 are most frequently detected.[17] Serum antibodies are thought to arrive at the side of infection via exudate (antibody leak from a damaged blood vessel or membrane) and/or transudate (antibody transfer from the intravascular compartment due to an imbalance of hydrostatic or oncotic pressure or though antibody-transporting receptors) to block HPV binding to the basement membrane.[29] To date, no correlate of protection has been established for HPV, as vaccine efficacy after HPV vaccination is high, with few breakthrough infections and hence few vaccinated individuals who are infected with vaccine types. This limits the opportunities to study which antibody levels are needed to give adequate protection. Also, studies might be biased by the difficulties in distinguishing rare breakthrough infections from emergence of prevalent infection at the time of vaccination or reactivation of latent infection[30]

Unvaccinated individuals acquiring an HPV infection can likewise develop an immune response. However, detectable antibody levels are not always present after a natural infection (not everyone seroconverts), and it is not known whether a previous infection protects against subsequent exposure to the same HPV type.[31] Nonetheless, GMC/Ts reached among naturally infected individuals can provide benchmarks for the evaluation of antibody levels after vaccination.[32]

Long-term immune responses following three doses of HPV vaccination

Seropositivity rates

Given the initial registration for HPV vaccination, the longest follow-up has been reported in studies adhering to this schedule. In Table 2, an overview is given of RCTs conducted for the three different vaccines with follow-up of seropositivity rates. Diverse study populations have been included, both younger and older age groups and women and men. For all three vaccines, follow-up was at least 7.5 y, and the longest was 14 y for the 4vHPV vaccine. ELISA and cLIA were the assays commonly used to assess antibody levels. Although high seroprevalence rates were maintained, a slight decline was observed with increased follow-up, notably for HPV18 after 4vHPV (47.9% seropositive after 4 y).[44] Previous research indicated a decline in seropositivity for HPV18 after 4vHPV vaccination, but no breakthrough infections/lesions were reported.[48] However, follow-up may have been too short and statistical power too limited to fully examine this.

Long-term seropositivity appears to be higher when the vaccine is administered at a younger age as compared to older populations, especially those 25 y or older.[43] In general, males and females were comparable regarding achieved seropositivity rates, but small differences have been observed.[46] This might be due to different populations across studies or minor differences in immune response following vaccination.[49] The 2vHPV and 4vHPV vaccine also induce some cross-protection against non-targeted hrHPV types.[50] For example, after 2vHPV vaccination, seropositivity rates for HPV31 and HPV45 were slightly lower compared to the 9vHPV vaccine and were maintained until at least 10 y.[42] For the 4vHPV vaccine also, cross-protection for these types was observed, although seropositivity rates were slightly lower than for the 2vHPV vaccine.[51,52]

Similar to RCTs, observational studies have been conducted to monitor the long-term immunogenicity following the implementation of HPV vaccination into national immunization programs. High seroprevalence for HPV16 and HPV18 up to 12 y after 2vHPV vaccination was observed.[30,53] Also for cross-protective types HPV31, 33 and 45, persisting seropositivity rates up to 12 y were reported.[53] For the 4vHPV vaccine, comparable vaccine-type immunogenicity following three doses was shown in observational studies.[54] Regarding cross-reactivity, seropositivity rates were generally lower for non-vaccine types following 4vHPV compared to 2vHPV vaccination.[55] A 5-y observational follow-up study of the 9vHPV vaccine indicated long-term seropositivity for all types included in the vaccine, with patterns comparable to those in RCTs.[56]

Antibody levels over time

Antibody levels against HPV16/18 and cross–protective types over time are reported from an observational cohort study in which 15–16-y-old girls received three doses of 2vHPV vaccination (Figure 1).[30] An initial peak is observed, followed by a rapid, significant decline for the vaccine types between y 2 and 3 post-vaccination. Thereafter a more gradual antibody decline is observed as time progresses. Antibody levels against cross-protective types show a comparable pattern at a lower

Table 2. Long-term seropositivity and geometric mean concentration (GMC) following three doses of HPV vaccination (in RCTs).[33–47.]

Vaccine	Study and population (age at vaccination)	Immunogenicity endpoint: percentage seropositive	Immunogenicity endpoint: GMC/T	Techniques	Follow-up
2vHPV	NCT00309166	HPV16 100%	27891.6 EU/mL	ELISA	7m
	♂10-14y	HPV18 100%	10593.7 EU/mL		
	VIVIANE	26-35y: HPV16 100%	n.a.	ELISA	7y
	♀>25y to at least 46y	HPV18 98.0%			
		36-45y: HPV16 100%			
		HPV18 97.1%			
		>45y: HPV16 95.7%			
		HPV18 93.3%			
	CVT	HPV16 100%	716 EU/mL	ELISA	7y
	♀18-25y	HPV18 100%	322 EU/mL		
	HPV001/007/023	HPV16 100%	n.a.	ELISA	9.4y
	♀15-25y	HPV18 100%			
	NCT00196924	HPV16 100%	1589.9 EU/mL	ELISA	10y
	♀10-14y	HPV18 100%	597.2 EU/mL		
		HPV-31 87.7%	242.9 EU/mL		
		HPV-45 85.1%	204.7 EU/mL		
	NCT00196937	15-25y: HPV16 100%	965.4 EU/mL	ELISA	10y
	♀15-55y	HPV18 99.2%	321.1 EU/mL		
		26-45y: HPV16 99.2%	334.4 EU/mL		
		HPV18 93.7%	115.4 EU/mL		
		46-55y: HPV16 96.3%	157.4 EU/mL		
		HPV18 83.3%	69.7 EU/mL		
4vHPV	MAM study	HPV06 100%	419.5 mMu/mL	cLIA	7m
	♂27-45y	HPV11 100%	516.6 mMu/mL		
		HPV16 100%	2228.6 mMu/mL		
		HPV18 100%	300.0 mMu/mL		
	NCT00090285	HPV06 88.9%	71.5 mMu/mL	cLIA	3y
	♂16-26y	HPV11 94.0%	82.6 mMu/mL		
		HPV16 97.9%	293.3 mMu/mL		
		HPV18 57.0%	33.1 mMu/mL		
	NCT00090220	HPV06 91.5%	61.0 mMu/mL	cLIA	4y
	♀24-45y	HPV11 92.0%	66.0 mMu/mL		
		HPV16 97.4%	202.0 mMu/mL		
		HPV18 47.9%	23.0 mMu/mL		
	V501-018	9-12y: HPV06 90.1%	91.4 mMu/mL	cLIA	10.5y
	♀♂9-16y	HPV11 89.7%	78.7 mMu/mL		
		HPV16 97.0%	336.4 mMu/mL		
		HPV18 90.1%	41.0 mMu/mL		
		13-16y: HPV06 86.8%	76.9 mMu/mL		
		HPV11 86.8%	66.9 mMu/mL		
		HPV16 94.0%	289.4 mMu/mL		
		HPV18 86.8%	28.9 mMu/mL		
	FUTURE(I/II)	HPV06 90.6%	78.4 mMu/mL	cLIA	14y
	♀16-23y	HPV11 91.1%	66.8 mMu/mL		
		HPV16 98.3%	291.2 mMu/mL		
		HPV18 52.4%	26.1 mMu/mL		
9vHPV	V503-003, NCT01651949	HPV06 99.6%	782.0 mMu/mL	cLIA	7m
	♂16-26y	HPV11 100%	616.7 mMu/mL		
		HPV16 100%	3346.0 mMu/mL		
		HPV18 99.9%	808.2 mMu/mL		
		HPV31 100%	708.5 mMu/mL		
		HPV33 100%	384.8 mMu/mL		
		HPV45 99.8%	235.6 mMu/mL		
		HPV52 100%	386.8 mMu/mL		
		HPV58 100%	509.8 mMu/mL		
	V503-002	HPV06 98.5%	252.8 mMu/mL	cLIA	3y
	♀9-15y	HPV11 99.3%	145.8 mMu/mL		
		HPV16 99.8%	857.4 mMu/mL		
		HPV18 94.5%	167.8 mMu/mL		
		HPV31 99.3%	216.6 mMu/mL		
		HPV33 98.5%	94.1 mMu/mL		
		HPV45 93.8%	64.7 mMu/mL		
		HPV52 99.0%	109.6 mMu/mL		
		HPV58 99.0%	147.4 mMu/mL		
	V503-002	HPV06 98.7%	262.7 mMu/mL	cLIA	3y

(*Continued*)

Table 2. (Continued).

Vaccine	Study and population (age at vaccination)	Immunogenicity endpoint: percentage seropositive	Immunogenicity endpoint: GMC/T	Techniques	Follow-up
	♂9-15y	HPV11 98.3%	156.6 mMu/mL		
		HPV16 99.6%	944.1 mMu/mL		
		HPV18 96.6%	244.2 mMu/mL		
		HPV31 98.5%	246.3 mMu/mL		
		HPV33 98.7%	120.8 mMu/mL		
		HPV45 93.0%	76.7 mMu/mL		
		HPV52 97.9%	104.9 mMu/mL		
		HPV58 99.1%	170.9 mMu/mL		
	NCT00543543	HPV06 95.0%	143.1 mMu/mL	cLIA	5y
	♀16-26y	HPV11 95.5%	82.9 mMu/mL		
		HPV16 100%	324.4 mMu/mL		
		HPV18 77.5%	62.5 mMu/mL		
		HPV31 96.3%	69.2 mMu/mL		
		HPV33 96.5%	44.7 mMu/mL		
		HPV45 81.1%	20.8 mMu/mL		
		HPV52 91.0%	33.7 mMu/mL		
		HPV58 92.4%	50.9 mMu/mL		
	V503-002; NCT00943722	HPV06 94.0%	135.4 mMu/mL	cLIA	7.5y
	♀9-15y	HPV11 91.1%	87.8 mMu/mL		
		HPV16 99.5%	490.4 mMu/mL		
		HPV18 96.8%	150.0 mMu/mL		
		HPV31 95.9%	125.8 mMu/mL		
		HPV33 95.0%	65.3 mMu/mL		
		HPV45 92.4%	48.9 mMu/mL		
		HPV52 96.8%	69.7 mMu/mL		
		HPV58 98.6%	85.6 mMu/mL		
	V503-002; NCT00943722	HPV06 88.2%	139.0 mMu/mL	cLIA	7.5y
	♂9-15y	HPV11 90.4%	94.6 mMu/mL		
		HPV16 99.5%	497.9 mMu/mL		
		HPV18 96.1%	161.4 mMu/mL		
		HPV31 96.1%	138.8 mMu/mL		
		HPV33 92.8%	76.7 mMu/mL		
		HPV45 96.0%	58.1 mMu/mL		
		HPV52 92.8%	63.8 mMu/mL		
		HPV58 98.5%	103.5 mMu/mL		

n.a. = not available, geometric mean concentration or titer was not specified; EU = ELISA units; mMu = milli-Merck units.

level. GMCs against HPV16 are higher than for other types from the start and remain so over time.[30]

In Table 2, GMC/Ts from the RCTs are included if reported. Although various arbitrary measurement units were used, the pattern of antibody level development for all the vaccines and HPV types is comparable to the one described above.[42,45–47,57,58] However, the initial decline in HPV18 following both the 4vHPV and 9vHPV vaccination seems more pronounced as measured by cLIA assay (less so in the total binding assay), which could also explain the observed faster decline in seropositivity rates. Furthermore, there were small deviations between the 4vHPV and 9vHPV vaccine that could be related to changes in the VLP concentration. Regarding cross-protective types, the observed responses are higher following 2vHPV compared to 4vHPV vaccination.[59] In the first 7 months post-vaccination, the 2vHPV vaccine induced neutralizing HPV31/33/45/52/58 antibodies significantly more often and to higher levels than did the 4vHPV vaccine.[52] Neutralizing antibodies remained detectable up to at least 7–12 y post-vaccination, but with expected three- to fourfold higher titers after 2vHPV vaccination than 4vHPV vaccination.[55,60] Evidenced by clinical trial data, cross protection against HPV31 and HPV45 and subsequent lesions indeed seems to be higher following 2vHPV compared to 4vHPV vaccination,[50] which could be due to the observed higher antibody levels.

Statistical modeling studies indicated that among young girls (10–14 y) receiving timely 2vHPV vaccination, durability of antibody levels above natural infection level was predicted to be 70.1 y for anti-HPV-16 and 78.8 y for anti-HPV–18, or even lifelong, depending on the model used.[42] Another modeling study among older women receiving HPV vaccination (15–55 y) indicated that antibody levels after 2vHPV vaccination for vaccine types HPV16 and 18 would remain higher than after natural infection for up to 30 y. However, the age at which participants received vaccination was important, as with older age the predicted prolonged immune response decreased, probably due to lower initial antibody responses.[43] For the 4vHPV vaccine, the predicted GMTs up to 20 y after vaccination were also above the level induced by natural infection for anti-HPV-16 antibodies but below the natural infection level for anti-HPV–18 antibodies (among 18–45-y-olds). In general, longer durability of antibodies was predicted following 2vHPV than 4vHPV vaccination.[61] This is likely due to the high initial antibody levels after 2vHPV vaccination.

Some RCTs compared the different vaccines directly. In general, they showed that the 2vHPV vaccine induces higher antibody responses for both HPV16 and 18 compared to the 4vHPV vaccine (up to threefold higher as measured by PBNA),[62,63] while 9vHPV vaccination induced anti-HPV16/18 responses similar to the 4vHPV vaccine, as measured by cLIA.[9,64] Especially, the response against HPV18 differs between

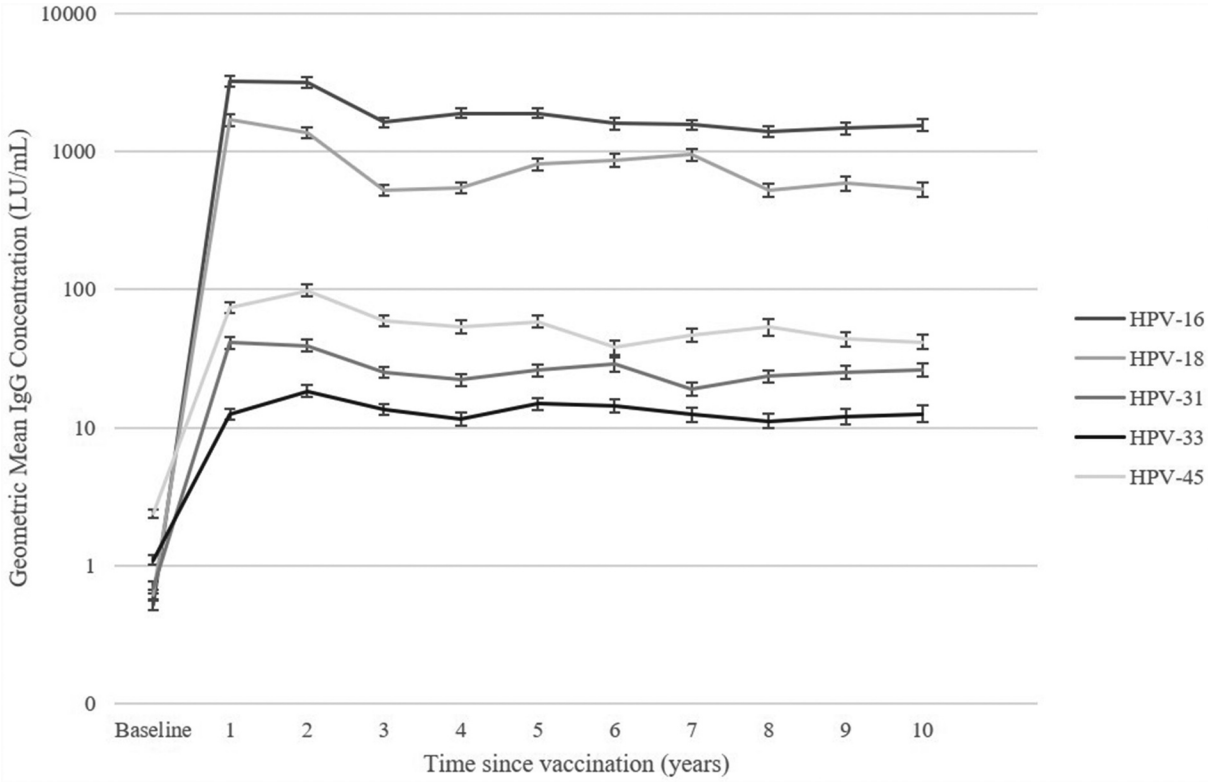

Figure 1. Adapted from Hoes et al.[30] with 1 additional y of follow-up. Geometric mean concentration (GMC) of HPV16, 18, 31, 33, and 45 IgG before and every year after 3 doses of 2vHPV vaccination (declining number of women due to loss-to-follow–up).

the 2vHPV and 4vHPV vaccine, as the 4vHPV vaccine was less immunogenic for HVP18 (shown in lower GMTs in the first year following vaccination).[62] This difference persisted with increased follow-up.[65] A comparison trial between the 2vHPV and 9vHPV vaccine is ongoing (NCT02834637).

Other immune parameters

Besides seroprevalence and antibody levels, other immune parameters may provide an indication of long-term protection following HPV vaccination. Research showed that avidity levels of antibodies against vaccine types increased with every dose of 2vHPV vaccination, peaked after the third, and remained relatively constant up to 3 y post-vaccination.[66] Nevertheless, a correlation between avidity and neutralizing antibody levels could not be established, suggesting that neutralizing activity of antibodies is relatively independent of their avidity (once a threshold level is reached following primary vaccination).[66] Furthermore, a study comparing two and three doses of 2vHPV vaccination indicated no differences in avidity up to four and a half years post-vaccination,[67] leaving the correlation between avidity and number of doses inconclusive.

Another parameter that is less well studied is cellular immunity following HPV vaccination. Research showed that both the 2vHPV and 4vHPV vaccines give an HPV-specific memory B- and T-cell response[68,69] up to at least 4 y post-vaccination.[63] Age at vaccination was found to impact memory B-cell formation, whereas T-cell memory formation influenced by dose number but not by age of vaccination.[70] Recipients of the 2vHPV vaccine showed higher numbers of memory B-cells after vaccination compared to those receiving 4vHPV vaccine.[63,71] Likewise, for HPV31 and HPV45 numbers of both memory T- and memory B-cells were detected up to 36 months post-vaccination for the 2vHPV vaccine. Again, this level of cross-protection was higher for the 2vHPV compared to the 4vHPV vaccine.[72] Generally speaking, although cell-mediated immune effectors provide information on the responsiveness to the vaccine, they do not directly indicate how well the vaccine protects or how long antibodies are maintained (which is due to the production by LLPCs).[22] Nevertheless, further research on the long-term persistence of memory B- and T-cells could provide an indication for the sustainability of protection from disease, as is the case in hepatitis B studies.[73]

Immune responses following fewer than three doses of HPV vaccination

Non-inferiority of the two-dose schedule

To compare immune responses for various dosing schedules, GMT/C ratios are often used (in combination with non-inferiority margins). For all three vaccines, RCTs comparing two (at the required 0-, >5-month interval)- and three-dose schedules have been conducted indicating non-inferiority of the two-dose schedule regarding the vaccine types (among girls aged 9–14 y) according to study-dependent cutoffs, when compared to a three-dose schedule (in women aged 15–26 y).[74–76] The longest follow-up with direct comparison of doses was measured for the 4vHPV

vaccine (up to 10 y post-vaccination), showing sustained immunogenicity for HPV6/11/16/18 and steady seropositivity rates, following two doses.[77] However, a meta–analysis showed that, compared to three doses, two doses of the 4vHPV vaccine could produce an inferior antibody response for HPV18 within 18 months and, likewise, two doses of 2vHPV could produce an inferior responses for HPV16 within 2 y (again, women receiving three doses were older, at 15–26 y, than those receiving two doses, at 9–13 y).[78] Moreover, a study by Leung and colleagues compared the 2vHPV and 4vHPV vaccine in a two-dose schedule and found that, as with three doses, the 2vHPV vaccine elicits antibody responses that are up to sixfold higher for the vaccine types[65] compared to 4vHPV.

Antibody levels and the development of GMC/T over time are comparable following two doses and three doses of the same vaccine, at least for the first period (up to 36 months) post–vaccination.[75,76,79,80] Among young girls (9–14 y) receiving two doses of 2vHPV vaccination, modeling studies predicted lifelong durability of antibody levels above natural infection level, comparable to the three-dose schedule.[75] No differences in avidity following a two-dose 2vHPV schedule were observed at months 7, 24 or 48 post-vaccination, suggesting that the quality of the antibody response in terms of avidity was similar in the two-dose recipients compared to three-dose recipients.[81] Also following two doses, cross-protection against non-vaccine types can be observed. For the 2vHPV vaccine, similar antibody concentrations against HPV31 and HPV45 were measured up to 5 y after both two and three doses of vaccination.[72] For the 4vHPV vaccine, higher antibody concentrations against HPV31 were observed up to 6 y after one-, two-, or three-dose-vaccination as compared to no vaccination, but this was not observed for other cross-protective serotypes.[82] This difference in antibody response against cross-protective types between vaccines might be due to the AS04 adjuvant system used in the 2vHPV vaccine, which is claimed to induce a broader immune response and may hence lead to higher antibody levels.[51]

One-dose HPV vaccination

Besides RCTs, other prospective studies investigated optimal dosing schedules, including one-dose vaccination. This most reduced number of doses makes HPV vaccination cheaper and logistically more accessible, especially for low- and middle-income countries. Nevertheless, one-dose delivery would require sufficiently high efficacy and long-term immunogenicity. Several studies have shown seropositivity for HPV16 and HPV18 following one-dose 2vHPV vaccination (up to 11 y of follow-up), although antibody levels were lower compared to two or three doses.[41,83] With one-dose delivery of 4vHPV, avidity was non-inferior, and detectable concentrations of neutralizing antibodies to all four vaccine-targeted HPV types were present, but at much lower concentration after one dose than after two/three doses (up to 6 y of follow-up) and seropositivity rates decreased rapidly; however, protection from infection seemed comparable between dosing schedules.[54,84,85] Another study indicated that besides lower antibody levels following one-dose 2vHPV, also lower levels of memory B- and T-cells were measured. Altogether, these findings suggest that one-dose vaccine recipients are at higher risk of waning immunity.[86] Despite the potential of the one dose schedule, the trade-off between costs and accessibility on one side and the effectiveness and immunogenicity on the other should be considered carefully, especially regarding long-term protection.

Implications of long-term HPV vaccine-induced immunogenicity

Long–term protection following HPV vaccination is important to prevent people from acquiring an HPV infection throughout their lives. Therefore, protection during sexually active life is desirable, as this reduces lifetime risk of HPV infection and subsequent disease, and supports the WHO goal to eliminate cervical cancer.[16] If protection following vaccination persists for a limited amount of time, the peak prevalence of HPV infections may shift toward older age, influencing the outcomes of and the need for secondary prevention (i.e., screening) of cervical cancer. The pattern in which HPV prevalence peaks and thus protection is needed might differ geographically, causing the HPV burden to be unequally distributed across countries. In higher income countries, the HPV infection prevalence peaks between 20 and 25 y of age and is followed by a decline and finally a plateau in prevalence.[87] However, a large meta–analysis including 1 million women with normal cytology from all over the world indicated that HPV prevalence in less developed countries remains at a higher level following the initial peak. In some cases, a second peak can be observed around age 45-65, although the actual risk of developing cancer from these infections might be limited.[88]

While a correlate of protection is still lacking for HPV, protection is assumed to be antibody-mediated. The three vaccines are very immunogenic and induce solid protection against HPV infections and cervical lesions,[9] which could indicate that protection will last if there is a high and detectable immune response. In general, long-term follow-up studies align with regard to immunogenicity. Following all three vaccines, seropositivity rates for targeted vaccine types remain high up to at least 7.5 y after vaccination, with few indications of waning. This finding is underscored by modeling studies and the development of GMC/Ts over time. Nevertheless, some decline of 4vHPV-induced antibodies against HPV18 is observed with all dosing schedules.[44,78] This could indicate an increased risk of waning immunity, although no supporting evidence in the form of breakthrough cases has been reported.[48] The observation does emphasize the importance of continued immunosurveillance and proper comparisons between vaccines, e.g., between 2vHPV, which induces the highest levels of cross protection, and 9vHPV, which provides broad-spectrum protection.

In Figure 2, the vaccines are summarized as to their dosing schedules and longest reported follow-up of immunogenicity. It shows that the current knowledge gaps mainly concern long-term follow-up of reduced dosing schedules and 9vHPV vaccine, all requiring further research. Despite the benefits of immunosurveillance over clinical surveillance (e.g., less invasive, easier to collect samples, especially from males), vaccine efficacy is often seen as most important outcome, with immunogenicity outcomes considered seperately.[9] Accordingly, research is needed to study the linkage between protection and observed immune responses over time, which can aid in

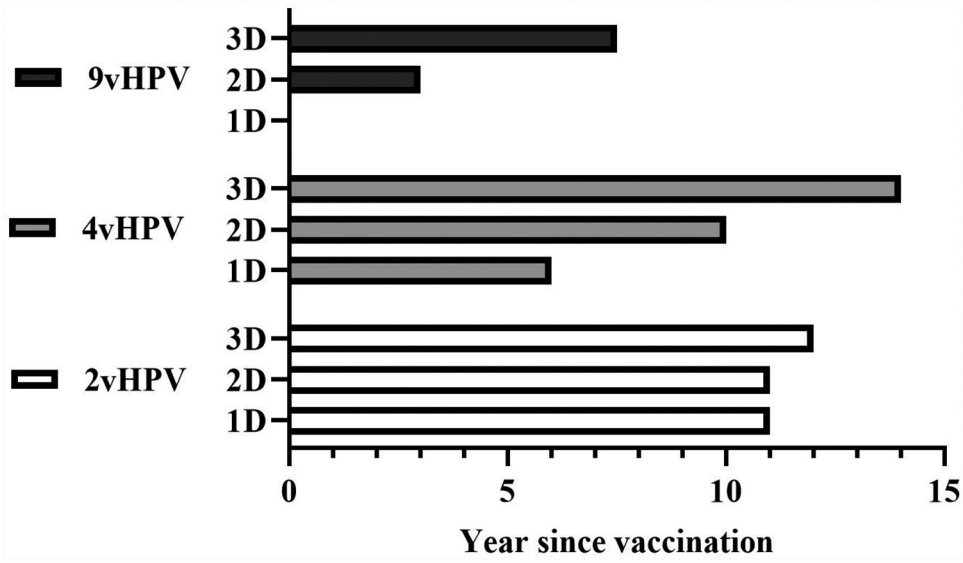

Figure 2. Longest reported follow-up time concerning antibody levels and/or seropositivity rate. Studies can be both RCT or observational. Stratified for HPV vaccine and dosing schedule.[38,47,53,76,77,83,89]

our understanding of long-term efficacy following HPV vaccination. However, such research remains challenging due to the low number of breakthrough infections, the large confidence intervals around effectiveness estimates, and the variety in antibody levels among individuals.[30] In RCTs, prolonged or incidental follow-up of vaccine recipients with relatively low antibody response reveal the individual level of antibodies that must be achieved for protection.

Vaccine uptake, age at vaccination, and the optimal dosing schedule remain critical research areas. Since HPV vaccination was introduced, uptake has remained behind in low- and middle-income countries, although they have the highest burden and minimal screening opportunities.[90] Even in high-income countries uptake has been suboptimal, possibly due to negative media attention or parental concerns.[91] Thus, increased effort is required to offer timely vaccination to young girls around the globe. Age of vaccination remains important, since vaccination at higher ages increases pre-vaccination HPV exposure risk. Moreover, the number of doses might affect GMT/Cs; more evidence is needed on the non-inferiority and long-term follow-up of a one-dose schedule regarding both immunogenicity and effectiveness.[92] Besides RCTs in which some participants received one dose and virological endpoints were evaluated,[41,93] there are ongoing comparison studies between two- and one-dose recipients as to both non-inferiority of immune response and protection against clinical outcomes (NCT03180034 and NCT03675256, both focus on 2vHPV and 9vHPV vaccination). Additionally, some early initiated studies will continue their follow-up and frequently report their findings.[92] Evidence for or against one-dose vaccination, based on efficacy against persistent infection and immunogenicity as to targeted HPV types, will be available from the RCTs and other studies in the coming years, aiding in the evaluation and formal implementation of a one-dose schedule.

To conclude, long-term immunogenicity following HPV vaccination looks promising, with little indication for a decline. Future studies should focus on establishing a correlate of protection in order to optimize dosing schedules and to realize sustained protection through sexually active life. This will aid in reducing HPV infections and subsequent disease, with the ultimate goal of worldwide elimination of cervical cancer.

Disclosure of potential conflicts of interest

The authors have no conflict of interest to disclose.

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