Prophylactic human papillomavirus vaccines to prevent cervical cancer: review of the Phase II and III trials

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Cervical cancer may be substantially prevented by human papillomavirus (HPV) vaccination. The two most common oncogenic HPV types causing 70% of all cervical cancers are represented in the vaccines by synthetic virus-like particles to the L1 protein of HPV 16 and 18. The virus-like particles and adjuvant systems promote long-term antibody response. Phase II trials indicated vaccine efficacy against type-specific infection, initial vaccine immunogenicity and the tolerability of initial vaccination. Although designed to be preliminary evidence of disease prevention, the Phase II trials have become the sentinel beacon of longer-term efficacy for infection and disease outcomes, immunogenicity and safety after at least 5 years of follow-up. Both vaccines were approved for licensure after corroborative favorable Phase III trial data on efficacy, immunogenicity and safety. Vaccination programs targeted to a large age range of women will achieve cervical cancer reductions several decades from now.

Keywords: adolescent females, adult women, Cervarix®, cervical cancer, cervical dysplasia, efficacy, Gardasil®, human papillomavirus vaccines, immunogenicity, menopausal women, middle-age women, safety

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Two human papillomavirus (HPV) vaccines are in the process of review or have been recently approved worldwide for the prevention of cervical cancer: Cervarix® by GlaxoSmithKline (London, UK) and Gardasil® by Merck & Co. (NJ, USA). Both vaccines contain the L1 capsid protein made by recombinant technology to produce virus-like particles (VLPs) of the two most common oncogenic HPV types: HPV 16 and 18. The quantity of VLPs differs in each vaccine (**Table 1**). Likewise, both vaccines contain a proprietary adjuvant system to improve the immunologic response to the VLP antigens. The adjuvant system, AS04, in Cervarix contains both an aluminum salt and a toll-like receptor-4 agonist (monophosphoryl lipid A); the adjuvant system in Gardasil contains an aluminum salt called aluminum hydroxyphosphate sulfate (**Table 1**) [1,2].

Clinical trials in humans show that the HPV 16/18 VLPs adjuvanted with AS04 induce a significantly greater initial antibody response than do the HPV 16/18 VLPs adjuvanted with aluminum hydroxide alone, and this superior response continues for at least 4 years [3]. Experiments in mice show that the Merck proprietary amorphous aluminum hydroxyphosphate sulfate used in Gardasil induces a greater initial antibody response to HPV 16 VLPs than does the aluminum hydroxide adjuvant alone [4].

Safety

Safety issues are addressed in clinical trials as local and systemic. Systemic reactions include both serious adverse events and reproductive reactions. A third mechanism for safety evaluation occurs post-licensure with voluntary reports of vaccine adverse events. Local reactions attributed to both HPV vaccines include pain, erythema and swelling [1,2,5,6]. However, the severity of pain, erythema and swelling was not great enough to preclude compliance with the remaining injections. Systemic adverse events such as myalgias, headaches and gastrointestinal irritability occurred, but their frequencies did not significantly differ between study groups. No fatal adverse events were associated with either HPV vaccine in the Phase II and III trials.

Pregnancy-related events were not associated with either HPV vaccine [5,6]. The number of conceptions, spontaneous abortions, live births, healthy infants and fetal anomalies was proportionately equal in women receiving HPV vaccines as in the control arm for both vaccines.

Long-term health events to be monitored in post-licensure settings include new-onset chronic diseases; data over at least 6.4 years for Cervarix indicate no increase in acquisition of these end points [7]. Post-licensure monitoring of Gardasil indicates vasovagal reactions to be the most common adverse event reported [101]. A small number of peripheral neuropathies/paralyses, including Guillain–Barré Syndrome, have been reported after the administration of Gardasil, but the rate of occurrence has not been more frequent than in the general population [102].

There is little documented on the safety of coadministration of Gardasil with any of the other possible 16 vaccines that young girls may receive

Table 1. Human papillomavirus vaccine composition.

	Cervarix®	Gardasil®
Vaccine type	HPV 16 and HPV 18 VLP L1 capsid component	HPV 6/11/16/18 VLP L1 capsid component
Concentration	20 µg HPV 16 20 µg HPV 18	20 µg HPV 6 40 µg HPV 11 40 µg HPV 16 20 µg HPV 18
Adjuvant	AS04 : 500 µg aluminum hydroxide 50 µg 3-deacylated monophosphoryl lipid A	Alum: 225 µg aluminum hydroxyphosphate sulfate
Recombinant technology substrate system	Baculovirus expression system in *Trichoplusnia ni* insect cells	Yeast expression system in *Saccharomyces cerevisiae*
Ref.	[1]	[2]

HPV: Human papillomavirus; VLP: Virus-like particle.

during adolescence. A trial of 466 women aged 16–23 years showed that the HPV 16 and 18 titers induced 1 month after complete vaccination with Gardasil and after 2 years of follow-up were not affected by co-administration of Gardasil with hepatitis B vaccine [8]. A vaccine co-administration trial in adolescents of Menactra® (meningitis vaccine, MCV4) and Boostrix® (hepatitis B) with Cervarix is ongoing [103].

Efficacy

Efficacy measurements depend on the population studied, the definition of the ethically acceptable end point for efficacy in a study with active follow-up, the duration of end point follow-up and the attack rate of the HPV type over the time course of the study. The Phase II efficacy studies offer the longest duration of follow-up, and the duration of vaccine efficacy is the single most important unresolved parameter in understanding the cost–effectiveness of HPV vaccination [9].

The end points for these trials deserve discussion. Cervical cancer as the ultimate end point takes decades to develop after infection and is not a realistic or ethically acceptable study end point. Hence, surrogate end points along the continuum from infection to cancer must be used. Instead of starting with incident infection, of which the majority of infections are cleared, persistent infection lasting at least 6 months, reflecting the median time of natural regression, becomes the first important surrogate end point [10]. Persistent infection is highly correlated with precancerous lesion development [11], because persistent infection, a continuously episomally replicating infection, is the biological precursor for HPV integration. With HPV integration, precancerous cervical intraepithelial neoplasia grade 2/3 (CIN 2/3) and cancer develop. CIN 2/3 is the target for treatment of all cervical cancer screening programs and serves as the second surrogate end point for cervical cancer development in these trials.

The Phase II efficacy study for Cervarix follows 1002 women (505 in the vaccine arm, 497 in the placebo arm) over 5.5 years [12]; the Phase II efficacy study for Gardasil follows 561 women for 3 years with 241 women (114 in the vaccine arm, 127 in the placebo arm) continuing for the full 5 years [13]. In those women who were negative for the vaccine-related HPV types at the time of first vaccination, the efficacies for preventing incident infection, persistent infection, abnormal cytology and CIN disease associated with the vaccine-related HPV types are very high, regardless of whether they are calculated by the according to protocol/per-protocol analysis or the (modified) intention-to-treat analysis (**Table 2**).

Within the population of women naive to HPV at entry followed for 5.5 years, for an end point of CIN 2, CIN 3, adenocarcinoma *in situ* or squamous cell carcinoma or adenocarcinoma (CIN 2/3+) caused by any oncogenic HPV type, the efficacy of Cervarix has remained higher than expected by epidemiologic estimates at 68% (95% CI: 7–91), with 15 placebo and five vaccine events [12]. By Bayesian analysis, there is an 88% probability that the 68% efficacy demonstrated is indeed above the 50% estimated by the literature. This was the first indicator of evidence for cross-protection to other oncogenic HPV

Table 2. Phase IIb efficacy results.

End point	Cervarix®	Gardasil®
	5.5-year follow-up	*5-year follow-up*
Incident infection with HPV 16/18	96% (95% CI: 88–99) P/V: 66/3 events (n = 776, ATP)	Not study aim
Persistent infection caused by HPV 16/18 6 month – Cervarix 4 month – Gardasil	100% (95% CI: 88–100) P/V: 29/0 events (n = 775, ATP)	96% (95% CI: 83–100) P/V: 45/2 events (n = 468, PP)
Abnormal cytology ≥ASCUS caused by HPV 16/18	96% (95% CI: 86–100) (n = 1002, ITT*) P/V: 51/2 events	Not study aim
CIN 1–3 caused by HPV 16/18	100% (95% CI: 62–100) P/V: 11/0 events (n = 951, ITT*)	100% (95% CI: 32–100) P/V: 7/0 events (n = 514, MITT‡)
Ref.	[12]	[13]

The women represented in these data are those who received all three doses and were HPV DNA 16/18 negative at the time of the first vaccination.

**Intent to treat among women who were DNA negative for 14 high-risk HPV types, seronegative for HPV 16 and 18 at study entry, but who received at least one dose. The ensuing cases were counted starting at day 1* [7].

‡The population included all women in the trial except for those seropositive or DNA positive at study entry for the vaccine-relevant HPV types, had at least one dose and the cases of CIN were counted starting at day 30 [2].

ASCUS: Atypical squamous cells of undetermined significance; ATP: According to protocol; CI: Confidence interval; HPV: Human papillomavirus; ITT: Intent-to-treat; MITT: Modified intent-to-treat; PP: Per-protocol; P/V: Number of events occurring in the placebo arm and the vaccine arm, respectively.

types that has subsequently been corroborated by type-specific cross-protection data in Phase II and the Phase III trials as detailed below.

Efficacy determined from the Phase III trials

The limitation of small numbers of women followed in the Phase II trials is resolved in the Phase III trials, where large numbers of young women (>18,000) of reproductive age (15–25 years for Cervarix and 16–23 years for Gardasil), with an average of two previous lifetime sexual partners, were enrolled. The women in the trials could have been infected with the vaccine-related HPV types at the time of first vaccination, could have been seropositive for the vaccine-related HPV types at the time of first vaccination, or could have had an abnormal cytology screen at study entrance. Over 70% of the women in the trials were HPV DNA negative for the vaccine-related HPV types, seronegative for the vaccine-related HPV types and cytology-screen normal. It is this mix of infection status, serostatus and disease state that allows measuring the vaccine efficacies for different subsets of the population.

The most straightforward vaccine efficacy is defined in the population of women who are HPV DNA negative and seronegative to the HPV vaccine-related types. The primary end point for both trials in this population was the prevention of CIN 2/3 disease associated with HPV 16 and/or 18. Case definition of HPV type attribution has had to include preceding type-specific virologic infections due to the high proportion of multiple HPV types found in the CIN 2/3 lesions in both sets of Phase III trials. Secondary and descriptive analyses demonstrated efficacy against persistent infection, abnormal cytology and any severity of CIN disease caused by HPV 16 and/or 18. The Phase III trials replicate the high vaccine efficacies against CIN 2/3 seen in the Phase II trials for women who had received at least one dose of vaccine (**Table 3**) [6,14]. Both vaccines provide excellent protection against any CIN disease attributed to HPV 16 and 18, individually.

Table 3. Phase III vaccine trial efficacy results.

End point	Cervarix®	Gardasil®
	15-month follow-up N = 18,644	*3-year follow-up N = 5455; N = 12,167*
CIN 2/3+		
Caused by HPV 16/18	90% (97.9% CI: 53–99) P/V: 21/2 events, TVC*	95% (95% CI: 85–99) P/V: 62/3 events, USP§
	100% (97.9% CI: 74–100) P/V: 20/0 events, PPR‡	98% (95% CI: 86–100) P/V: 42/1 events, PPSP¶
CIN 1+		
Caused by HPV 16	94% (97.9% CI: 54–100) P/V: 17/1 events, PPR‡	100% (95% CI: 93–100) P/V: 53/0 events, USP§
Caused by HPV 18	100% (97.9% CI: 34–100) P/V: 9/0 events, PPR‡	95% (95% CI: 72–100) P/V: 22/1 events, USP§
6-month persistent infection		
Caused by HPV 16/18	80% (97.9% CI: 70–87) P/V:193/38 events, TVC*	Not a study aim
Ref.	[6]	[5,14]

The women represented in these data are those who received at least one dose and were HPV DNA 16/18 negative for the corresponding vaccine type at the time of the first vaccination.

**The cohort of women who were seronegative and DNA negative for the corresponding vaccine type at the time of first vaccination whose cytology could be normal or ASCUS/LSIL, who received at least one dose and where cases were counted starting the first day after vaccination* [6].

‡*Per-protocol analysis revised for HPV 16/18 causality case attribution* [6].

§*Unrestricted susceptible population: the cohort of women who were both seronegative and DNA negative for the corresponding vaccine type at the time of first vaccination but whose cytology could be normal or abnormal, who received at least one dose, and where cases were counted starting the first day after vaccination* [5,13].

¶*The cohort of women who received all three doses within 12 months, were seronegative and DNA negative for HPV 16/18 at the time of first vaccination, and were DNA negative at month 7, and where cases were counted starting at 1 month after the third dose* [5].

ASCUS: Atypical squamous cells of undetermined significance; CI: Confidence interval; CIN 1+: Cervical intraepithelial neoplasia of any severity or any cervical cancer; CIN 2/3+: Cervical intraepithelial neoplasia (CIN) grade 2 or grade 3 or squamous cell carcinoma or adenocarcinoma in situ *or adenocarcinoma; HPV: Human papillomavirus; LSIL: Low-grade squamous intraepithelial lesion; PPR: Per-protocol analysis revised; PPSP: Per protocol susceptible population; P/V: Events occurring in the placebo and vaccine arms, respectively; TVC: Total vaccinated cohort; USP: Unrestricted susceptible population.*

When the women are not infected with HPV 16/18 at the time of first vaccination, but have had a past infection resulting in natural infection antibody titers (seropositivity for HPV 16/18) and do not receive vaccine, they do develop new HPV 16/18 CIN 2+ lesions at the same attack rate as for women who are seronegative [15]. On the other hand, these HPV 16/18 DNA-negative, HPV 16/18-seropositive women who received vaccine in Phase III trials for both vaccines were protected from all CIN 2+ lesions caused by HPV 16/18 in this relatively short follow-up time (Table 4) [16,17]. This finding will need further trial data to achieve statistical significance, but underscores the importance of vaccination for all women, regardless of past HPV exposure.

Gardasil's vaccine efficacies were expected to drop when calculated for a mixed population of women with prevalent disease, of whom less than 30% were HPV DNA positive for HPV 16/18 at entry, who received at least one dose of vaccine and were followed for only 3 years. For CIN 2/3+ caused by HPV 16/18 in this mixed population, Gardasil's efficacy is

Table 4. Phase III efficacy results in women seropositive for HPV 16/18 but HPV DNA-negative at study entry.

End point	Cervarix®	Gardasil®
	15-month follow-up N = 18,644	*3-year follow-up N = 20,583*
Efficacy in preventing CIN 2+ caused by HPV 16, 18	100% P/V: 3/0 events	100% P/V: 5/0 events
Ref.	[6,17]	[16]

Event numbers are too small to calculate meaningful confidence intervals around the point estimates of efficacy. CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus; P/V: Events occurring in the placebo and vaccine arms, respectively.

44% (95% CI 26–58), with 148 and 83 cases occurring in the placebo and vaccine arms; furthermore, for protection against CIN 2/3+ caused by any oncogenic HPV type developing within a short 3 years, Gardasil's efficacy drops to 17% (95% CI: 1–31), with 266 and 219 cases occurring in the placebo and vaccine arms [14]. Gardasil is not effective against the development of CIN caused by HPV 16 or 18 if the woman is currently infected with one of these HPV types, but does offer similar CIN efficacy as in the Phase II trials to the HPV type for which she is not infected at the time of first vaccination [18]. Cervarix, likewise, does not promote clearance of epithelium already infected with HPV 16/18 [19].

Cross-protection

Just as surrogate end points are used to assess vaccine efficacy for HPV 16/18-related diseases, surrogate end points of incident infection, persistent infection, CIN lesions and cancer precursors are also appropriate end points for evaluating cross-protection with phylogenetically related HPV types. The enrollment size and duration of the trials to date are limitations in assessing cross-protection in a robust manner. In a mixed population of women who were HPV 16/18 positive and negative at time of first vaccination but of whom most were both HPV 16 and 18 naive, both vaccines showed extended protection against other oncogenic HPV types (**Table 5**) [6,20]. Cervarix shows individual type-specific cross-protection to both HPV 16 and 18 phylogenetically related types (types 31 and 45, respectively) for 6- and 12-month persistent infections (12-month data not shown), whereas Gardasil shows extended protection against groups of HPV 16 phylogenetically related types for 6-month persistent infection and CIN disease. Gardasil does not protect against HPV 45-related infections or disease.

Immunogenicity

Despite both vaccines having a 100% seroconversion 1 month after three doses of vaccine, the mechanism of immunogenicity from a scientific perspective is poorly understood. The measure of antibody induction by geometric mean titers (GMTs) is dependent on the assay system used, and is not comparable between HPV types within one manufacturer or for identical HPV types between manufacturers. Despite these incomparabilities, the peak response to vaccination was robustly 100–200-fold higher than natural infection titers for both vaccines in neutralizing type-specific antibody titers for both HPV 16 and 18. The Phase II trials provide the longest duration of follow-up to evaluate immunogenicity for both vaccines.

Figure 1 shows the Phase II trial antibody titers for HPV 16 and 18 induced by Cervarix over 5.5 years. The antibody titers, measured by an ELISA, then corroborated by the pseudovirion neutralization assay [21], remain more than 11-fold greater than natural infection titers [22]. All women receiving Cervarix remained seropositive for both HPV types 16 and 18 after 6.4 years [7].

The induced immune response to Cervarix in girls aged 10–14 years results in twice the peak antibody titers to HPV 16 and 18 measured 1 month after the three doses of vaccine compared with women aged 15–25 years, at levels hundreds of fold higher than natural infection titers [23]. Continued high titers in young girls are sustained for both HPV 16 and 18 1 year after vaccination, paralleling the sustained response in 15–25-year-old women, creating the immunobridge to efficacy. Likewise, the antibody titers measured in women up to the age of 55 years approach the 100-fold increased titers over natural infection titers at peak and are sustained at more than eight-fold higher than natural infection titers through at least 2 years for both HPV 16 and 18 [24,25].

Table 5. Cross protection evidence of vaccine efficacy in Phase III trials for oncogenic HPV types beyond the vaccine associated types.

Population	Incident infection		6-months persistent infection		CIN 2+	
	Cervarix[*]	*Gardasil*[‡]	*Cervarix*[*]	*Gardasil*[‡]	*Cervarix*[*]	*Gardasil*[‡]
Naive population						
HPV 31			42% (97.9% CI: -17, 72) P/V: 24/14 cases		[§]	75% P/V: 21/5 cases
HPV 45			83% (97.9% CI: 43, 97) P/V: 18/3 cases		[§]	0% P/V: 2/3 cases
HPV 31/45			60% (97.9% CI: 28, 79) P/V: 42/17 cases	45% (95% CI: 18, 63) P/V: 73/41 cases		
HPV 31/33/45/52/58			41% (97.9% CI: 20, 56) P/V: 127/76 cases	28% (95% CI: 7, 44) P/V: 148/109 cases		
Total population						
HPV 31	54% (95% CI: 15, 76) P/V: 35/17 cases		36% (97.9% CI: 1, 60) P/V: 74/47		[§]	
HPV 45	88% (95% CI: 61, 98) P/V: 24/3 cases		60% (97.9% CI: 3, 85) P/V: 25/10 cases		[§]	
Ref.	[6]		[32]	[20]	[6]	[20]

Where there are no confidence intervals noted, the lower bounds exceeded zero

[*]*DNA negative to the corresponding HPV type, >80% DNA negative to HPV 16 or 18, irrespective of serostatus.*

[‡]*DNA negative to the corresponding HPV types, unknown status to HPV 16 or 18, irrespective of serostatus..*

[§]*Data coming.*

CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus; P/V: Events occurring in the placebo and vaccine arms, respectively.

Data taken from [6,11,18,24].

Gardasil also induces initial high peak antibody titers measured with a competitive Luminex immunoassay (cLIA, Luminex Corporation, TX, USA) for HPV 16 and 18 as seen in **Figure 2** [26]. Antibody titers for HPV 16 remain approximately tenfold higher than natural infection titers for 5 years, with more than 98% of the women maintaining their seropositivity. HPV 18 antibody titers dropped as quickly as the HPV 16 titers after the initial three doses of vaccine, but because the initial response to HPV 18 was much lower than the initial response of HPV 16, the long-term antibody levels approached natural infection titers from 18 through 60 months of follow-up. Similarly, more than a third of the women lose all detectable antibodies to HPV 18 over time: 76% remain seropositive at 3 years, dropping to 65% seropositive at 5 years. The attack rate of the vaccine-related HPV types during the last 2 years of the Phase II trial is not reported, making it difficult to gage whether the high efficacy reported at 5 years reflects sufficient HPV 18 challenge to these seronegative subjects to change the vaccine's efficacy.

The peak induced immune response to Gardasil in girls and boys aged 9–15 years shows twice the GMT induced in women aged 15–26 years for HPV 16 and 18 1 month after complete vaccination [27], supporting the immunobridge for efficacy. HPV 16 seropositivity and titers remain high through follow-up to at least 18 months in this young cohort, and, again, HPV 18 seropositivity dropped and titers fell to three-times natural infection titer by month 18 for girls and boys.

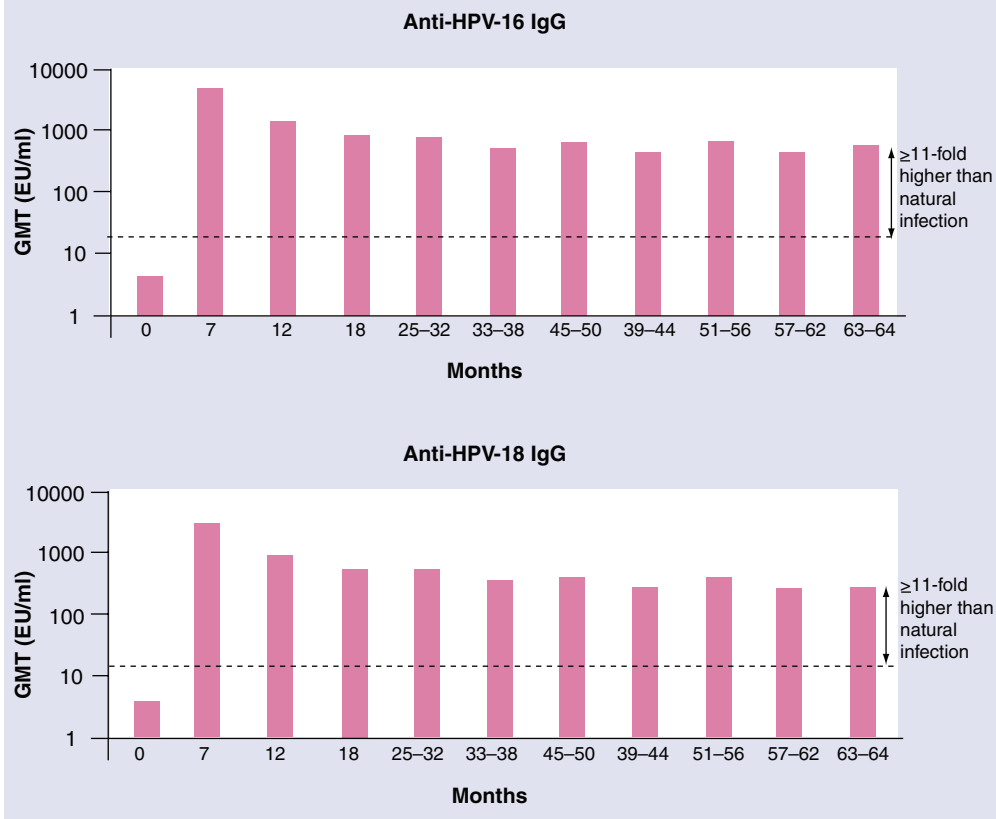
Evidence of immunologic memory

In addition to high circulating levels of serum antibodies, a robust memory B-cell response leading to an anamnestic response would be desirable.

Cervarix

The ELISPOT assay directly measured HPV 16 and 18 type-specific B memory cell induction

Figure 1. The induced antibody titers after vaccination with Cervarix® measured by ELISA compared with natural infection titers over 5.5 years.



GMT: Geometric mean titer; HPV: Human papillomavirus.
Modified from [12,22].

1 month after complete vaccination, showing that the AS04 adjuvant system produced four- to fivefold more B memory cells for both HPV 16 and 18 than did an aluminum salts adjuvant [3]. In women already seropositive for HPV 16/18 but DNA negative at the time of vaccination, Cervarix shows a higher antibody response after initial vaccination compared with seronegative HPV DNA 16/18-negative women [6].

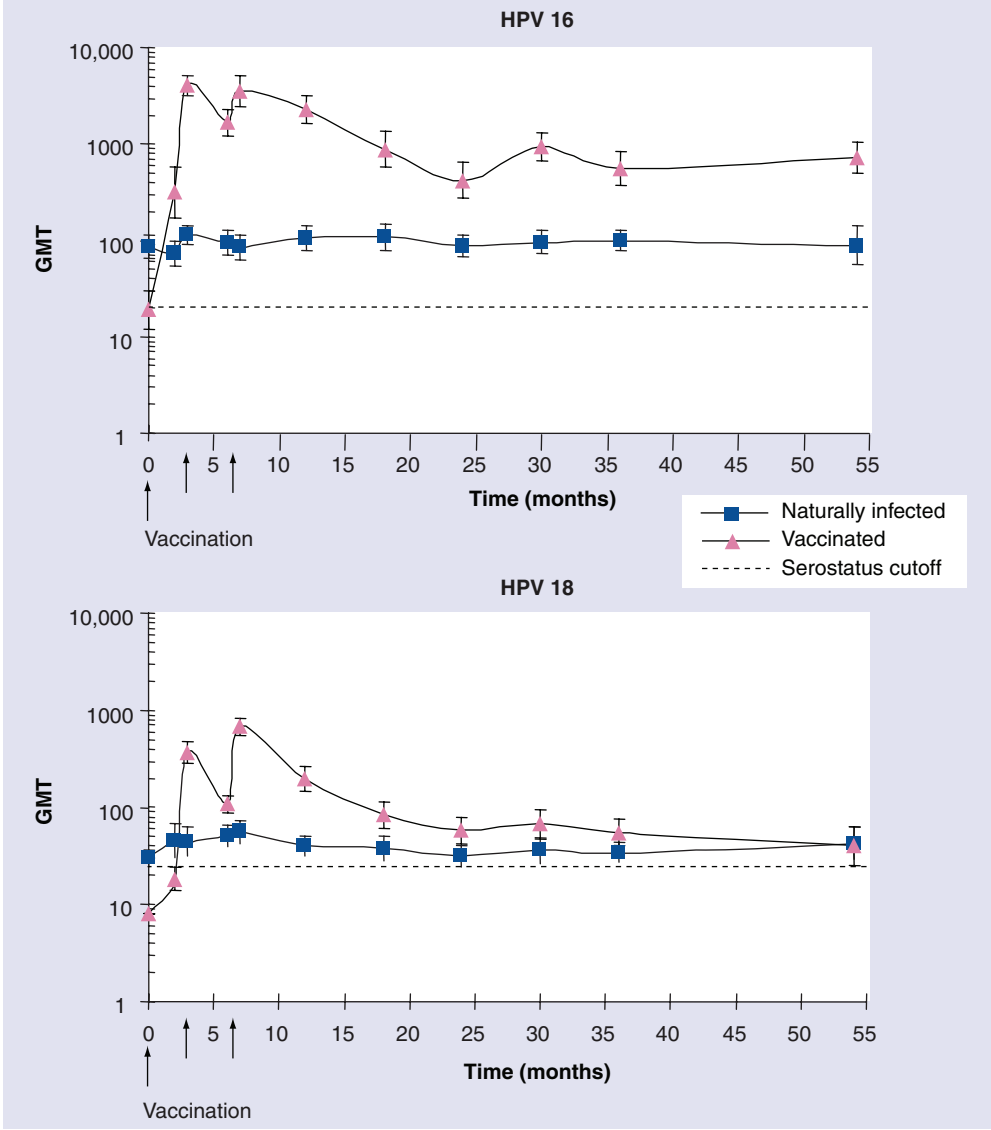
Gardasil

There is no documented direct increased memory B-cell response. Instead, an intramuscular vaccine challenge, a booster (not an epithelial natural infection challenge), was provided to Phase II trial participants with waning antibody titers at 5 years after the first vaccine dose. There was an anamnestic response observed 1 week after the booster challenge that induced titers equivalent to original peak titers for both HPV 16 and 18 [28].

Cervical mucous antibodies

High serum antibody titers are a preliminary indication of protection against infection. However, HPV infections are epithelial and occur at the surface of the cervix. Therefore, the level of transudated type-specific antibodies in the cervical mucous may become more important for immediate virion neutralization. Cervical mucous antibodies to HPV 16 and 18 have only been reported for Cervarix [29]. In women without HPV 16/18 infection, abnormal cytology or CIN lesions, but with antibodies to HPV 16 and 18 whose levels reflected natural infection titers, no HPV 16/18 antibodies were detected in the cervical mucous. In women similarly without HPV disease or CIN lesions and who were vaccinated with Cervarix, the induced antibodies transudated to the cervical mucous in correlatively high titers independent of the woman's age. Even in the perimenopausal age group of women 45–55 years, there are high titers of HPV 16 and 18 antibodies in the cervical mucous [25].

Figure 2. The induced antibody titers after vaccination with Gardasil® measured by competitive Luminex immunoassay compared with natural infection titers over 5 years.



GMT: Geometric mean titer; HPV: Human papillomavirus.
Modified from [26].

Immunologic evidence of cross-protection

Robust immunologic support measured with the pseudovirion assay for the vaccine efficacy demonstrated against HPV 45 and 31 has been reported over at least 5.5 years for an immunologic subset of 46 women receiving Cervarix. Similar to the patterns seen for HPV 16 and 18, Cervarix induces complete seroconversion for HPV 45 and 31 individually, with peak titers 7–13-fold higher than natural infection titers 1 month after complete vaccination. The duration of the immunologic response continues for at least 4.5 years with antibody titers above natural infection titers and seropositivity for HPV 45 and 31 retained at greater than 90% and greater than 70%, respectively [32]. The presence of antibody titers for HPV 45, 31, 52 and 58 was demonstrated 1 month after three doses of Gardasil in a subset of ten women [30]. The cross-protection efficacy studies discussed above corroborate HPV 31-related disease prevention. In women whose antibody response to HPV 18 was at least as robust as the geometric mean titer, a 60% seroconversion for HPV 45

Table 6. Summary of the two commercially available human papillomavirus vaccines.

	Cervarix®	Gardasil®
Safety	Generally safe and well tolerated	Generally safe and well tolerated
Efficacy	100% CIN 2/3 protection caused by HPV 16/18 for at least 5.5 years in a naive population	100% CIN 2/3 protection caused by HPV 16/18 for at least 5 years in a naive population
	–	44% CIN 2/3 protection caused by HPV 16/18 over 3 years in a mixed population
	68% CIN 2/3 protection irrespective of HPV type after 5.5 years in a naive population	17% CIN 2/3 protection caused by any HPV type after 3 years in a mixed population
	88% HPV 45-related incident infection protection for at least 5.5 years in a naive population	HPV 45 protection not demonstrated
	54% HPV 31-related incident infection protection for at least 5.5 years in a naive population	75% HPV 31 CIN 2+ protection for at least 3 years in a naive population
Immunogenicity	**HPV 16:**	**HPV 16:**
	100% seroconversion	100% seroconversion
	Seropositivity remains >98% at 5.5 years	Seropositivity remains >98% at 5 years
	Neutralizing antibody titers remain eightfold higher than natural infection titers at 5.5 years	Antibody titers remain approximately eightfold higher than natural infection titers at 5 years
	HPV 18:	**HPV 18:**
	100% seroconversion	100% seroconversion
	Seropositivity remains >98% at 5.5 years	Seropositivity drops after 2 years
	Neutralizing antibody titers remain eightfold higher than natural infection titers at 5.5 years	Antibody titers approach natural infection titers at 3 years
	HPV 45:	**Some evidence for anti-HPV 45 and 31**
	100% seroconversion	
	Seropositivity remains >98% at 4.5 years	
	Type-specific antibody titers remain higher than natural infection titers at 4.5 years	
	HPV 31:	
	100% seroconversion	
	Seropositivity remains >70% at 4.5 years	
	Type-specific antibody titers remain higher than natural infection titers at 4.5 years	
Cervicovaginal Ab transudation	HPV 16 and 18	

CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus.

was seen, and the HPV 45 antibody titers measured with the pseudovirion assay were 1–2 orders of magnitude less than generated for HPV 18 antibodies [31]. Despite HPV 45 neutralizing antibodies generated by Gardasil, Gardasil does not prevent HPV 45-related disease [20].

Conclusion

There are now two vaccines to prevent the two most common cancer-causing types of HPV designed to be given to women aged 9–55 years. Over at least 5 years, both vaccines show complete efficacy at preventing CIN 2/3 caused by HPV 16 or 18 in women who do not have HPV 16 or 18 infections at the time of first vaccination, regardless of age at vaccine administration. Cervarix alone shows efficacy data against nearly all of the HPV 45 infections and, as with Gardasil, efficacy data against approximately half of the HPV 31 infections, the two next most common cancer-causing HPV types. Neither vaccine will cure women who have HPV 16- or 18-related infection or CIN. Both vaccines are generally safe, but do cause injection-site pain, erythema and edema. The vaccines differ in their antibody responses, with Cervarix having high

and sustained titers for both HPV 16 and 18 throughout 5.5 years, and Gardasil having initial high but waning titers for HPV 18 after 3 years. A head-to-head trial of the immune response of Cervarix and Gardasil is underway that measures the antibody responses in the same assay system for actual GMT value comparison.

A considerable amount of work has been completed by multinational trial sites to accumulate the compelling evidence for HPV vaccination in women to date. The vaccines are generally safe, immunogenic and effective at preventing HPV infections and cervical cancer precursors, but even with extended cross-protection, the vaccines cannot abolish cervical cancer. The true degree to which we will see population protection from cervical cancer by HPV vaccination will depend on the need for boosters, the coverage of the population reached and, where present, the continued participation in cytologic cancer screening programs.

Future perspective

Active surveillance and monitoring systems for population-based vaccination programs is mandatory to evaluate the performance of these HPV vaccines over time. Cervical cancer can not be abolished even with the combination of HPV vaccination and cytology screening programs. The charge to evaluators of the vaccine programs and Pap screening programs over the next decade will be to determine the most cost-effective mix of both of these programs to maximally reduce, in the shortest time frame, the burden of cervical precancers and cancers. This may involve understanding the need for boosters in the face of declining antibody titers, varying the age groups initially targeted for vaccination, evaluating the public-health cost–effectiveness of vaccinating men, including some version of molecular testing with the cytology-based screening system, changing the interval at which screens are performed and possibly changing the ages at which women commence and cease screening. The implementation of second-generation vaccines, unless designed to eliminate all causes of cervical cancer, will be a lesser priority than understanding the mixture of primary and secondary cervical cancer prevention efforts.

In order for vaccination and secondary screening for the early detection and treatment of precancerous lesions to evolve to reduce cervical cancer, the following needs to be evaluated:

- The need for boosters in the face of declining antibody titers, with the identification of the immunological correlate of protection;
- Variation of the age groups initially targeted for vaccination;
- Public-health cost–effectiveness of vaccinating men (determining efficacy at preventing penile and anal male cancers, as well as the efficacy of preventing sexual transmission regardless of partner gender);
- The value of cytology, HPV testing, HPV typing and molecular markers to create an effective secondary screening program;
- Changing the interval at which screens are carried out;
- Changing the ages at which women commence and cease screening.

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