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EXPERT REVIEWS

Currently approved prophylactic HPV vaccines

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Cervarix® and Gardasil® are two prophylactic HPV vaccines designed primarily for cervical cancer prevention. Cervarix is effective against HPV-16, -18, -31, -33 and -45, the five most common cancer-causing types, including most causes of adenocarcinoma for which we cannot screen adequately. Gardasil is effective against HPV-16, 18 and 31, three common squamous cell cancer-causing types. In addition, Gardasil is effective against HPV-6 and -11, causes of genital warts and respiratory papillomatosis. The most important determinant of vaccine impact to reduce cervical cancer is its duration of efficacy. To date, Cervarix's efficacy is proven for 6.4 years and Gardasil's for 5 years.

Keywords: cervical cancer • efficacy • HPV • immunogenicity • safety

Within the last three decades, human papillomavirus (HPV) infection has been found to be necessary but not sufficient for the development of cervical cancer [1]. Cytologic and histologic correlations with cervical cancer were initially described contemporaneously by zur Hausen [2] and by Meisels and Fortin [3,4], with a rapid subsequent increase in knowledge both in the human and animal papillomaviruses. zur Hausen continued to elucidate the oncogenic mechanisms of HPV for which he was awarded the Nobel Prize in 2008 [5]. Several scientists continued to work to isolate and fabricate the L1 virus-like particles (VLPs) [6], which form the basis of the prophylactic HPV vaccines.

Most HPV infections never progress to cancer, but the small fraction of HPV infections that do become cervical cancer cause over 250,000 deaths annually worldwide [7]. HPV infections are common and, most often but not necessarily, are associated with sexual activity. Multiple studies indicate that the rate of oncogenic HPV infection is between 5 and 10% for children prior to sexual activity [8–10]; the incidence increases to 30% when women become sexually active, decreases in their late 30s to 10% and increases again to 15% in women over 60 years of age [11]. HPV vaccines offer the potential to decrease the incidence rate of HPV infection. Where secondary prevention programs (e.g., Pap screening or HPV testing) are not nationally organized, decreasing the baseline rate of HPV infection should lead to population-based reductions in cervical cancer after several decades of widespread female vaccination. Where secondary prevention programs are vigorous and well-attended, prophylactic vaccination should reduce the number of diagnostic work-ups for abnormal screens and decrease the need for excisional therapies for precancerous lesions in as little as 3 years after vaccinating a currently HPV-uninfected sexually active population.

The two vaccines

The two HPV vaccines, Cervarix® (GlaxoSmithKline, Middlesex, UK) and Gardasil® (Silgard®; Merck & Co., Inc., NJ, USA), contain a protein mimic of the L1 outermost protein capsid (VLPs) specific to the two most common HPV types causing cervical cancer, HPV-16 and -18 (Table 1). Gardasil also includes the VLPs for HPV-6 and -11, the most common HPV types causing genital warts. Along with the HPV type-specific VLPs, which direct the antibody response, the vaccines contain an adjuvant whose dual purpose is to prolong the immune response for as long as possible with the smallest amount of antigen (VLP) possible.

The primary mechanism of action of the prophylactic vaccines is the anti-HPV L1 humoral response [12], which has been proven in animal studies to prevent acquisition and disease in unvaccinated animals after a viral challenge. Therefore, one of the goals of the prophylactic vaccines is to induce a robust antibody response that can only be achieved by combining the antigen with an adjuvant.

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Table 1. Vaccine composition.

	Cervarix® (GlaxoSmithKline)	Gardasil® (Merck)
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 *Trichoplusia ni* insect cells	Yeast expression system in *Saccharomyces cerevisiae*

HPV: Human papillomavirus; VLP: Virus-like particle.
Data from [16,73].

The adjuvant systems are different for each vaccine. Gardasil's system is based on the traditional general adjuvant principles while Cervarix's system is based on an adjuvant hypothesized to be targeted to the specific receptors for HPV infection. Cervarix contains monophosphoryl lipid A, a mimic of Toll-like receptor 4, which is hypothesized to function as a link between viruses, such as HPV, and the activation of the innate immune system. Having primed the innate immune system, the antigen-presenting cells stimulate the adaptive immune response by activating T cells, then B cells. The B cells proliferate into plasma cells, immediately making large quantities of antibody, and into memory B cells, which, upon later stimulation, can reactivate the plasma cells to replenish the neutralizing antibodies. This adjuvant system is called the AS04 adjuvant system. The AS04 system provides higher titers of antibodies than an aluminum adjuvant alone in humans, and the titers remain elevated above aluminium-induced antibody titers for at least 48 months [13]. The adjuvant system for Gardasil contains a proprietary aluminum hydroxyphosphate sulfate system which, in mice, provides more superior binding to HPV-16 than a simple aluminum adjuvant [14]. The results of the human trials for these two novel HPV vaccines provides early data upon which to design HPV-associated disease and cancer-prevention strategies.

Vaccine efficacy

Both Cervarix and Gardasil have been found to be highly efficacious in preventing HPV-16/18-associated cervical intraepithelial neoplasias (CINs) (Table 2) in women 15–16 years of age through to 25–26 years of age who were seronegative and DNA negative at study entry for the relevant HPV types associated with each vaccine. [15,16]. Table 2 delineates the differences in efficacy when the study population changes either in terms of baseline characteristics, the number of injections received or when the cases of CIN 2+ begin to be counted (CIN 2+ means CIN 2, CIN 3, adenocarcinoma *in situ*, cervical squamous cell carcinoma and/or cervical adenocarcinoma).

The efficacy of Gardasil changes only slightly when the per-protocol (PP) population includes those who missed their injection at the specified protocol timing (protocol violations), as seen in the unrestricted susceptible population. Over 97% of the subjects received all three doses within 1 year in FUTURE II [17], and over 95% of the subjects received all three doses within 1 year in FUTURE I [18]. The 95% efficacy seen in this population of which the majority received all three doses of vaccine within 1 year indicates that the implementation regimen of the three doses can be quite flexible within a 1-year span without affecting the vaccine efficacy.

When women are included regardless of baseline serologic and HPV status who have received one or more injections (intent-to-treat [ITT] population), the efficacy of Gardasil over an average of 36 months falls to 44% against CIN 2+ caused by HPV-16/18. By counting cases after day 1, the data show that more than one dose of vaccine is necessary to induce a high efficacy, and that the cases counted prior to a full series of vaccination reflect infection and lesion development occurring during the nonprotected state. This is important for public-health tabulations of vaccine coverage – tabulating at least one dose will not reflect any population efficacy; population coverage can only be estimated from those individuals receiving three doses within 1 year. An additional decrease in efficacy is attributed to women already infected or who had already developed a CIN lesion from one of the vaccine-relevant types at the time of first vaccination.

Gardasil's efficacy further falls to 18% for an average of 44 months in the ITT population when the cause of CIN 2+ can be any HPV infection. This low efficacy from simulated real-life populations is expected when evaluating efficacy against CIN 2+ caused by any HPV infection, as 50% of CIN 2+ lesions are caused by high-risk types of HPV other than 16 and 18. Similarly, an additional decrease in efficacy is also expected in the ITT population reflecting conditions of an already actively infected population: 20% of the baseline population were infected with one of the vaccine-relevant HPV types at baseline, had serologic evidence of prior exposure or entered the study with abnormal cytology [17]. Uncharacteristically, however, the cross-protection benefits seen in later Gardasil studies [19,20] are not reflected by any increase in efficacy in this ITT calculation, questioning the clinically measurable benefit of cross-protection by Gardasil.

In comparison to the 18% efficacy seen by Gardasil, the efficacy of Cervarix in the naive total vaccinated cohort was 70% against all CIN 2+ regardless of HPV causation, and 30% in the total vaccinated cohort, which included those with current and past HPV-16/18 infections.

At this time, Cervarix and Gardasil show durations of efficacy lasting 6.4 and 5 years, respectively, from the Phase II trial data (Table 3), with Cervarix trials still ongoing. Gardasil Phase II trials were stopped at 5 years. There are ongoing trials in Costa Rica, the Netherlands, Iceland, Denmark, Sweden and Finland for both Cervarix and Gardasil planned for at least 10 years [21–23].

Table 2. Phase III trial vaccine efficacies by human papillomavirus type causation and by cohort analysis.

Vaccine	CIN 2+ caused by HPV-16/18	CIN 2+ caused by HPV-16/18	CIN 2+ caused by HPV-16/18	CIN 2+ caused by any HPV-type	Ref.
Cervarix®*	93% (96.1% CI: 80–98), ATP-E n = 14,656	98% (96.1% CI: 88–100), ATP-E‡ n = 14,656	98% (96.1% CI: 91–100), TVC-E n = 16,120	30% (96.1% CI: 16–42), TVC n = 17,349 70% (96.1% CI: 55–81), TVC-naive n = 10,885	[26]
Gardasil®§	98% (95% CI: 94–100), PPSP n = 16,957	95% (95% CI: 85–99), USP¶ n = 11,728	44% (95% CI: 26–58), ITT§ n = 12,167	18% (95% CI: 7–28), ITT n = 17,151	[103]

*35-months follow-up [26].
‡Those in the ATP-E but HPV type assignment algorithm were used to resolve causation when multiple HPV types were present.
§44-month close-out analysis [103].
¶36-months follow-up [17].
CIN 2+ = CIN 2/3, adenocarcinoma *in situ*, squamous cell carcinoma and adenocarcinoma.
ATP-E: According to protocol efficacy (efficacy for all women who met eligibility criteria and complied with the protocol, who received three injections, whose baseline Pap was normal, atypical squamous cells of undetermined significance [ASCUS] or low-grade squamous intraepithelial lesion [LSIL]; cases were counted starting the day after the third vaccination); CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus; ITT: Intention-to-treat population (regardless of serostatus or HPV DNA PCR status to vaccine-relevant HPV types at study entry, regardless of entry cytology, regardless of timing and number of injections received; cases were counted from day 1 after the first injection); PPSP: Per protocol susceptible population (for those women who were seronegative and PCR negative for the vaccine-related HPV types at study entry regardless of entry cytology results, and remained PCR negative for the vaccine-relevant HPV types through 1 month after receipt of the third injection; cases were counted 1 month after three doses given); TVC: Total vaccinated cohort (women with at least one injection, seropositive or negative, PCR positive or negative for one or more HPV types at baseline, regardless of Pap result; case counting first day after first injection); TVC-E: Total vaccinated cohort for efficacy (women with at least one injection, baseline Pap of normal, ASCUS or LSIL; case counting began the day after the first injection); TVC-naive: Total vaccinated cohort for naive women (women with at least one injection, baseline normal Pap, PCR DNA negative for all 14 oncogenic HPV types and seronegative for HPV-16 and -18; cases counted first day after first injection); USP: Unrestricted susceptible population (for those women who were seronegative and PCR negative for the vaccine-related HPV types at study entry, regardless of entry cytology results, received one or more injections; cases were counted from the first day after the first injection).

Therapeutic efficacy

It is important to establish with firm data, not just indirect evidence, that neither Cervarix nor Gardasil offers any therapeutic efficacy, nor any acceleration in viral clearance, nor any accelerated progression to cervical cancer. The data available to date are presented in Table 4, showing a lack of therapeutic efficacy in women positive for a vaccine-relevant HPV infection at baseline. Women who had a CIN lesion of any grade attributed to HPV-6, -11, -16 and/or -18 at study entry did not clear their lesion within 3 years after three Gardasil injections [18], nor did they develop an increased number of CIN 2+ lesions over the placebo group. Likewise, in women who already had an active HPV-16/18 infection at the time of vaccination, there was no clearance of the HPV-16/18 infection or acceleration to CIN 2+ within 12 months with Cervarix vaccination [24].

Baseline seropositivity

The highest vaccine efficacies for Gardasil and Cervarix are reported in women 15–26 years of age who are both seronegative and PCR negative for the relevant vaccine types prior to vaccination. The limited but statistically significant data in Table 5 show that despite prior exposure to HPV-16/18 (seropositivity), women without active HPV-16/18 infection at the time of first vaccination continued to have 100% vaccine efficacy to prevent CIN 2+ caused by HPV-16/18. High efficacy in seropositive women without active infection is important to vaccinating young girls, approximately 10% of whom are already seropositive by 10 years of age for at least HPV-16 from unknown causes [8–10], but without active infection. Having confidence that the vaccines perform at high efficacy rates despite prior infection alleviates concerns that vaccine performance might be compromised when targeting a supposedly naive adolescent population that is not actually completely naive. Serendipitously, the continued high efficacy of

Table 3. Duration of efficacy established from Phase II trials.

Vaccine	CIN 1–3 caused by vaccine-relevant HPV type				Vaccine efficacy (%) (95% CI)	Duration of follow-up
	Vaccine (n)	*Vaccine (cases)*	*Placebo (n)*	*Placebo (cases)*		
Cervarix®	481	0	470	15	100 (73–100)	6.4 years
Gardasil®	114	0	127	7	100 (31–100)	5 years

Women in these trials were seronegative and DNA-negative at baseline regardless of sexual activity.
Cervarix: population analyzed in this table were seronegative to HPV-16 and -18, and PCR DNA negative to 14 high-risk HPV types at study entry.
Gardasil: population analyzed in this table were seronegative to HPV-6, -11, -16 and -18, and PCR DNA negative to HPV 6, 11, 16 and 18 at study entry.
CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus.
Data from [15,16].

Table 4. No vaccine efficacy for viral or lesion clearance by human papillomavirus L1 virus-like particle vaccines in women human papillomavirus DNA PCR positive regardless of serostatus to vaccine relevant HPV types at the time of vaccination.

	Vaccine efficacy (95% CI)			Ref.
	Seropositive baseline status: CIN 1+ caused by HPV-6, -11, -16 or -18	*Seronegative baseline status: CIN 1+ caused by HPV-6, -11, -16 -or -18*	*Seropositive or seronegative baseline status: 12-month persistent HPV-16/18 infection*	
Cervarix®			*-7% (-32–13)* n = 345	[24]
Gardasil®	*-20% (<0–27)* n = 293	*19% (<0–54)* n = 445		[18]

Italicized values are not significant.
CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus.

HPV vaccination in women 15–26 years of age who are already seropositive but PCR negative supports targeting vaccination to the newly sexually active population, a population far more accepting of a sexually transmitted infection vaccination than the parents of young adolescent girls [101]. This population of women vaccinated within the first year of sexual activity has a greater prevention of HPV-16/18 persistent infections and CIN 2+ disease within 3 years of vaccination in absolute rate reductions (57/1000 women) than does vaccinating virgins prior to the onset of their sexual activity (17/1000 women) [25].

Cross-protection

Table 6 details the known data for the protection provided against persistent infection of 6 months duration or longer, and for CIN 2+ lesions caused by high-risk types other than HPV-16 and -18 for Cervarix and Gardasil. Cervarix provides individual cross-protection for HPV-31, -33 and -45 persistent infections [26]. Gardasil provides protection against HPV-31. All of the cross-protection provided by Gardasil in grouped classifications is due to the solo strength of HPV-31 coverage [18]. Ongoing trials are evaluating the efficacy of a pentavalent supplemental vaccine to Gardasil explicitly containing HPV-31, -33, -45, -52 and -58 to broaden Gardasil's coverage with eventual replacement of Gardasil with the nonovalent vaccine [102]. In the cross-protection studies, persistent HPV infection outcomes are more appropriate than CIN 2+ end points, as they unequivocally establish that infection has been present for some time, in contrast to the incidental presence of an HPV type in a lesion in which multiple types are also detected, but not necessarily causative [27,28], which occurs in the majority of CIN 2+ lesions [29]. Extrapolating potential reduction in cervical cancers from direct and cross-protection of the HPV vaccines under assumptions of complete vaccine coverage, lifetime duration of efficacy and clinically relevant efficacies, indicates that Cervarix may reduce the incidence of both squamous and adenocarcinoma of the cervix by 81% and Gardasil by 73% (Table 7).

Reductions in use of secondary screening

Both Cervarix and Gardasil have reduced the number of women referred to colposcopy for an abnormal Pap test by 26 and 20%, respectively, within 3 years of vaccine use (Table 8) [26,30]. Because of the additional cross-protection, Cervarix has prevented in 3 years 69% of the excisional therapies associated with reproductive morbidity compared with 42% for Gardasil [26,30]. The rate of loop electrosurgical excision procedures in the USA is currently 500 per 100,000 women screened [31]; this could be reduced to as low as 155 per 100,000 women with universal vaccination coverage (Figure 1).

Protection beyond the cervix for Gardasil

Table 9 details the efficacies against diseases not related to cervical cancer prevention. HPV-6 and -11 are the assumed cause of 90% of genital warts [32]. Vaccine efficacy for protection against the development of condyloma caused by HPV-6, -11, -16 or -18 in women 16–26 years of age lasting on average 44 months was reported at 80% for the ITT population and 99% for the PP population for Gardasil – both very high levels of efficacy [103,104]. Inexplicably, however, one would expect the efficacy of Gardasil against all condyloma regardless of HPV type to be

Table 5. Vaccine efficacy for CIN 2+ caused by HPV-16/18 in women seropositive, but PCR negative for HPV-16/18 at time of vaccination.

	Vaccine cases	Placebo cases	Vaccine efficacy	Ref.
Cervarix®	0	3	100%	[26]
Gardasil®*	0	5	100%	[17]
Combined vaccines: *post hoc* analysis	0	8	100% (95% CI: 63–100)	

*Additional case reported via [Richard Haupt, Merck & Co, USA (2008), Pers. Comm.].
CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus.

Table 6. Cross-protection evidence of vaccine efficacy in Phase III trials for oncogenic human papillomavirus types beyond HPV-16/18 in women DNA negative for the cross-protected types at study entry, regardless of serostatus.

	6 months persistent infection		CIN 2+	
	Cervarix® 35-month follow-up	*Gardasil® 44-month follow-up*	*Cervarix 35-month follow-up*	*Gardasil 44-month follow-up*
HPV-31	79% (96.1% CI: 70–85) P/V: 215/46	46% (95% CI: 15–66) P/V: 57/31	92% (96.1% CI: 66–99) P/V: 25/2	70% (95% CI: 32–88) P/V: 27/8
HPV-45	76% (96.1% CI: 60–86) P/V: 94/23	*8% (95% CI: -67–49) P/V: 26/24*	*100% (96.1% CI: -68–100) P/V: 4/0*	*-52% (95% CI: -1718–83) P/V: 2/3*
HPV-33	46% (96.1% CI: 25–61) P/V: 123/67	*28% (95% CI: -45–66) P/V: 21/15*	*52% (96.1% CI: -3–79) P/V: 25/12*	*24% (95% CI: -71–67) P/V: 16/12*
HPV-31/-33/-45/-52/-58	30% (96.1% CI: 22–38) P/V:755/534	25% (95% CI: 5–41) P/V: 167/127	53% (96.1% CI: 25–71) P/V: 64/30	*33% (95% CI: -0.3–55) P/V: 66/44*

For Cervarix: women were DNA PCR negative at baseline for the nonvaccine-relevant HPV types, regardless of DNA PCR status for vaccine-relevant HPV types at study entry, receiving at least one dose of vaccine, with cases counted after month 7. For Gardasil: women were seronegative and DNA PCR negative for the vaccine-relevant HPV types at study entry, were DNA PCR negative for each of the nonvaccine-relevant HPV types, received at least one dose of vaccine, with cases counted after day 1.
Italicized values are not significant.
CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus; P/V: Cases occurring in the placebo arm/cases occurring in the vaccinated arm.
Data from [19,26].

very similar to the efficacy against condyloma caused by HPV-6 and -11, the purported cause of 90% of genital warts. The data show significantly less efficacy for condyloma caused by all HPV types at 63%. Potentially the attributable proportion of HPV-6 and -11 for genital warts is not 90% as previously thought, but actually much lower.

Protection against condyloma caused by HPV-6, -11, -16 or -18 in boys and men is 89% lasting for 29 months [33]. Unfortunately, there are no reports of efficacy against all condyloma regardless of HPV causation for males to date. We do not know whether there is a similar significant decrease in overall condyloma prevention in men as there is in women.

Table 7. Estimated maximal cervical cancer reduction accounting for significant cross-protection of additional oncogenic human papillomavirus types.

HPV type	Attributed proportion (%) of cervical cancers by cancer type		Reduction in cases (%) after use of Cervarix®		Reduction in cases (%) after use of Gardasil®	
	Squamous cell carcinoma of the cervix	*Adenocarcinoma of the cervix*	*Squamous cell carcinoma of the cervix*	*Adenocarcinoma of the cervix*	*Squamous cell carcinoma of the cervix*	*Adenocarcinoma of the cervix*
16	61.6	47.8	61.6	47.8	61.6	47.8
18	8.2	29.0	8.2	29.0	8.2	29.0
31	4.5	1.2	3.6	0.9	2.1	0.6
33	4.3	1.1	2.0	0.5		
45	5.5	12.3	4.2	9.3		
Total estimated reduction in cervical cancers attributed to vaccination			**79.5%**	**87.6%**	**71.9%**	**77.4%**

Assumptions: 100% female coverage, lifetime duration of vaccine efficacy, 100% efficacy for HPV-16- and -18-associated cancers by both Gardasil and Cervarix. For Cervarix, efficacy values were 76, 79 and 46% for HPV-45, -31 and -33 persistent infections, respectively; based on a population of women who were seronegative for the vaccine-relevant HPV types at study entry, were DNA PCR negative at baseline for the 12 nonvaccine-relevant HPV types regardless of DNA PCR status for vaccine relevant HPV types at study entry, receiving at least one dose of vaccine, with cases counted after month 7 [26]. For Gardasil, efficacy against persistent HPV 31 was assumed to be 46% based on a population of women who were seronegative and DNA PCR negative for the vaccine-relevant HPV types at study entry, were DNA PCR negative for each of the ten nonvaccine-relevant HPV types, received at least one dose of vaccine, with cases counted after day 1 [19]. Attributable proportion data taken from [74].
HPV: Human papillomavirus.

Table 8. 3-year reductions in abnormal Pap tests requiring colposcopy referrals and excisional treatments for CIN 2/3, regardless of HPV type causation after human papillomavirus vaccination.

	Cervarix®				Gardasil®			
	Vaccine n = 5449	*Placebo n = 5436*	*Reduction (%)*	*96.1% CI*	*Vaccine n = 4616*	*Placebo n = 4679*	*Reduction (%)*	*95% CI*
	Cases (n)	*Cases (n)*			*Cases (n)*	*Cases (n)*		
Reduction in number of colposcopy referrals	354	476	26	15–36%	850	1061	20	21–27
Reduction in number of cervical excisional therapies	26	83	69	50–81%	131	229	42	28–54

Women 15–25 years of age (Cervarix) or 16–23 years of age (Gardasil) negative to 14 oncogenic HPV types with normal cytology at baseline followed on average for 40 and 43 months (Cervarix and Gardasil, respectively).
HPV: Human papillomavirus.
Data from [26,30].

Gardasil's efficacy against vulvar intraepithelial neoplasia (VIN) 1 caused by HPV-6, -11, -16 or -18 in an ITT population was not significant after 36 months, trialed in a population of almost 18,000 women [104]. Vaginal intraepithelial neoplasia (VaIN) 1 caused by HPV-6, -11, -16 or -18, on the other hand, showed nonreassuring significant efficacy both in the PP and the ITT populations as both had quite broad confidence intervals [104]. Overall protection from VIN 1, VaIN 1 or condyloma caused by any HPV type was reported at 41% for the ITT population. This overall efficacy is dominated by the protection from condyloma as efficacies for VIN 1 and VaIN 1 contribute little to the overall protection of VIN 1/VaIN 1/condyloma from any HPV type. Gardasil does not have national regulatory approval for the prevention of VIN 1 or VaIN 1.

Gardasil's efficacy against VIN 2/3 and VaIN 2/3 caused by HPV-16/18 after an average of 44 months of follow up is 100% in the PP populations, with small overlapping decreases to 69 and 85%, respectively, in the ITT populations [103]. Both vaginal and vulvar cancer precursors have limited association with HPV infection [34,35], explaining the extremely wide efficacy confidence intervals for VIN 2/3 from any cause and no significant efficacy for VaIN 2/3 from any cause [36]. While Gardasil is approved for and has the potential to reduce vaginal and vulvar cancers caused by HPV-16/18 by two-thirds of their current incidence, it is unlikely that Gardasil will have a measurable clinical effect on the prevention of vaginal cancers from any cause overall based on these nonsignificant data.

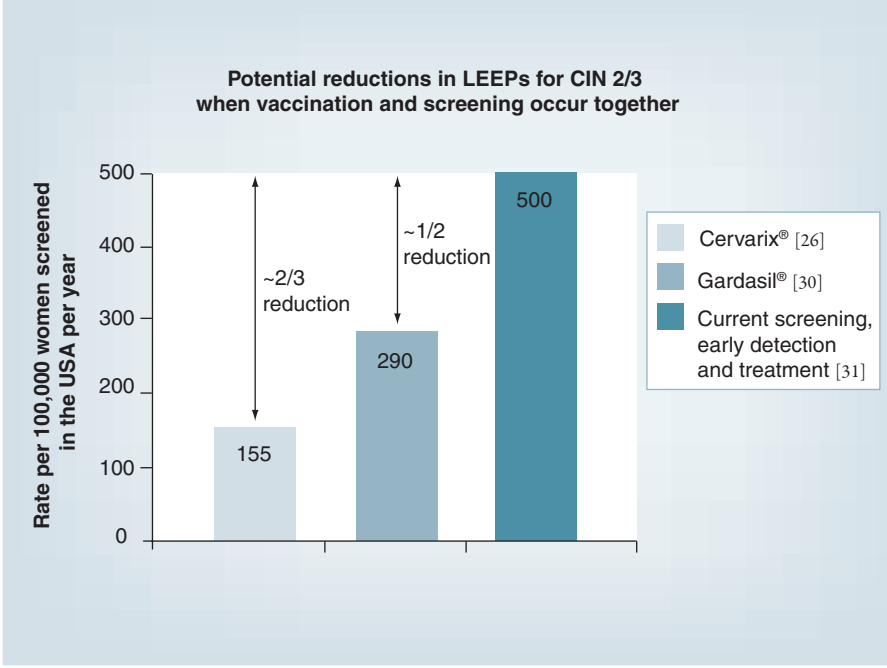

Figure 1. Estimated maximal potential reduction in reproductive morbidity from excisional therapies for CIN 2/3 disease by vaccination, assuming all excisional therapies are associated with reproductive morbidity. Reduction in LEEPs for CIN 2/3 per 100,000 women screened per year in the USA for the current management scenario compared with the potential for reduction if there is 100% vaccination coverage, lifetime vaccine efficacy and 100% continued screening in women who receive either Cervarix® or Gardasil®.
CIN: Cervical intraepithelial neoplasia; LEEP: Loop electrosurgical excision procedure.

Duration of vaccine efficacy

Cost–effectiveness analyses have indicated that the vaccines must last at least 15 years or longer, or there will not be any cases of cervical cancer prevented – they will merely be postponed [37–43]. If the vaccines are given to an age group who is immediately sexually active, then despite not preventing cervical cancers, there will be some protection from the precursor lesions and a reduction in excisional treatments, which are linked to reproductive morbidity [44,45]. If the vaccines are given to the youngest ages approved, the risk of no benefit of any protection is high with a small risk of serious side effects.

Immunogenicity

The purpose of the prophylactic HPV vaccines is to induce antibodies to the specific vaccine-relevant HPV types that will be sustained for the duration of time the woman is susceptible to HPV infections. Both Cervarix and Gardasil induce antibody titers after three doses that far exceed the titers a natural infection induces in women 16–26 years of age who were seronegative and PCR negative for the vaccine-relevant HPV types at baseline.

The antibody titers, measured in ELISA units/ml, induced by Cervarix remain 13- and 12-fold higher than natural infection titers at 6.4 years for HPV-16 and -18, respectively, with over 98% of the women vaccinated maintaining initial seroconversion through 6.4 years. An increased memory B-cell response has been demonstrated in women 18–30 years of age who were seronegative and PCR negative for HPV-16/18 at the time of vaccination at 1 month after the three doses of Cervarix compared with the HPV-16/18 VLPs adjuvanted with aluminum alone [13]. The pseudovirion-based neutralization assay (PBNA, ED_{50} unit) titers for HPV-16 and -18 were likewise high and sustained throughout 6.4 years, and correlated well with the ELISA titers. In addition, the PBNA titers correlated tightly with the measured type-specific cervical mucous antibodies transudating across the basement membrane over 24 months. Antibody titers induced by Cervarix measured in women 15–55 years of age were titers still eightfold higher than natural infection titers for even the oldest 46–55-year-old age cohort after 24 months [46]. The strong and sustained immunogenic properties of Cervarix offer the possibility of long-term protection for women of many ages.

The neutralization antibody titers induced by Gardasil have been measured by competitive Luminex immunoassay (cLIA) for each HPV type 6, 11, 16 and 18 in milliMerck units/ml. Over 99% of women seroconverted for each HPV type after three doses of vaccine. For HPV-18, however, 28% of women lost their initial seroconversion at 2 years, increasing to 35% of women losing their seroconversion by 3 years. Of those with remaining HPV-18 titers, the levels continued to drop through the studies' end. After an average of 44 months of follow up, 40% of women lost all measurable antibody titers to HPV-18. [47]. In over 14,000 women followed for at least 3 years, there were only 60 cases of HPV-18 infection in the placebo arm for a very low attack rate of less than five infections per 1000 woman-years in an age range of maximal HPV exposure. Such a low attack rate does not allow inferences to be drawn about the duration of the vaccine's efficacy or the immunologic correlate of protection, as there has not been much infectious challenge to the women's waning serostatus. Overall, 10% of women lost their antibody titers to HPV-6 and 5% lost them to HPV-11 within 44 months; of those with remaining seropositivity, the titers dropped to natural

Table 9. Vaccine efficacy summary for Gardasil® for lesions other than cervical disease.

Lesion type	Average duration of study	HPV-type causation	Vaccine efficacy (95% CI)		Ref.
			Per protocol	*Intent to treat*	
Condylomas					
Condyloma	44 months	6, 11, 16, 18	99% (96–100) n = 15,802	80% (74–85) n = 17,923	[103]
Condyloma	44 months	Any	83% (74–89) n = 17,622	63% (54–70) n = 17,389	[103]
Male condyloma	29 months	6, 11, 16, 18	89% (66–98) n = 2805		[33]
VIN 1, VaIN 1					
VIN 1	36 months	6, 11, 16, 18	100% (42–100) n = 15,886	*58% (<0–84)* n = 17,916	[104]
VaIN 1	36 months	6, 11, 16, 18	100% (31–100) n = 15,886	76% (28–94) n = 17,916	[104]
VIN 1 or VaIN 1 or condyloma	36 months	Any		41% (28–51) n = 17,916	[104]
VIN 2/3, VaIN 2/3					
VIN 2/3	44 months	16, 18	100% (56–100) n = 15,513	69% (30– 88) n = 17,923	[103]
VaIN 2/3	44 months	16, 18	100% (50–100) n = 15,516	85% (32–98) n = 17,923	[103]
VIN 2/3	44 months	Any		50% (9–73) n = 17,389	[103]
VaIN 2/3	44 months	Any		*46% (-7–74)* n = 17,389	[103]

Italicized values are not significant.
Per protocol means women were seronegative at baseline and PCR negative for each type day 1 through month 7, regardless of entry cytology; cases were counted from the first day after 30 days after the third injection. Intent to treat means women were included regardless of serostatus or HPV DNA PCR status to vaccine-relevant HPV types at study entry, regardless of entry cytology, and regardless of timing and number of injections received; cases were counted from day 1 after the first injection.
HPV: Human papillomavirus; VaIN: Vaginal intraepithelial neoplasia; VIN: Vulvar intraepithelial neoplasia.

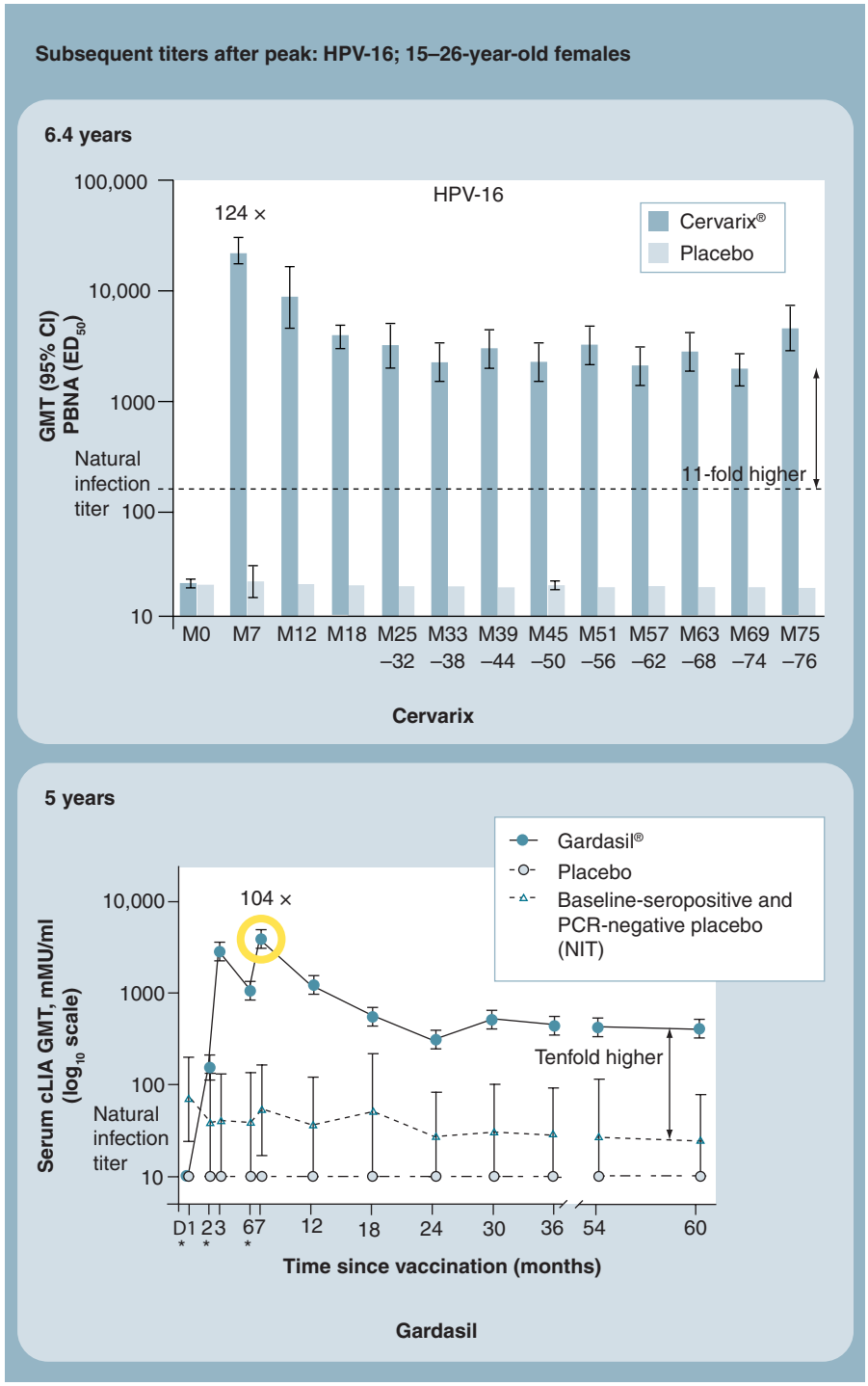

Figure 2. Induced anti-HPV-16 titers after Cervarix® and after Gardasil® administration in women 15–26 years of age. These graphs show the subsequent titers for HVP-16 after peak (month 7) responses over time. For Cervarix, the peak titer is 124-fold higher than natural infection titers and remains 11-fold higher 6.4 years later [15]. For Gardasil, the peak titer is encircled, and is 104-fold higher than natural infection titers and remains tenfold higher 5 years later.
*Denotes when vaccination occurred.
cLIA: Competitive Luminex immunoassay; GMT: Geometric mean titer; HPV: Human papillloma virus; NIT: Natural infection titer; PBNA: Pseudovirion-based neutralization assay (measured in ED_{50} units).
Redrawn with permission from [50,75].

infection titers by 24 months, opening the possibility of waning protection. Strong immunogenicity is seen for HPV-16. Over 98% of women maintained seroconversion to HPV-16 and maintained titers tenfold above natural infection titers at 44 months (Figures 2, 3 & 4).

The neutralizing antibody titers to HPV-16 and -18 have been measured in the same assay in a head-to-head trial of Cervarix and Gardasil [48] in order to remove the confusion of different proprietary measurement systems. In all circumstances, Cervarix produced significantly higher antibody titers for HPV-16 than did Gardasil (3.7-fold higher) at month 7, the peak titers; and even greater fold higher for HPV-18 (7.3-fold higher). As the duration of vaccine efficacy is the most important public-health parameter of mass vaccination programs, and because antibody titers are the closest surrogate measure to efficacy as evidenced by our use of immunobridging, and despite not having a correlative titer identified, it is likely that Cervarix will have a longer duration of efficacy than will Gardasil. Long-term studies are necessary to prove this (Table 10).

The head-to-head trial also reported cervicovaginal mucous antibody titers present in the vaccinated women. Cervicovaginal secretion mucous antibodies are believed to be central for protection against HPV infection and cervical disease, evidenced by natural history studies in which both IgA and IgG antibodies appear several months after HPV clearance, with the IgG antibody action predominating [49]. A similar proportion of HPV-specific neutralizing antibodies transudates from the serum to the mucous for both vaccines. The ratios of titers in the serum to titers in the mucous were threefold higher for Cervarix than for Gardasil as measured by the PBNA.

Memory B cells induced after Cervarix and Gardasil were equivalent for HPV-16 measured at 1 month after the series of three vaccinations at nearly 90%. For HPV-18, nearly 90% of the women vaccinated with Cervarix responded with memory B cells, but only 66% of the women vaccinated with Gardasil had so responded at the time of maximal potential response. This is another indicator of the potential necessity for a booster for HPV-18 durability by Gardasil.

An anamnestic response was elicited by an intramuscular injection of a single dose of Gardasil at the end of the 5-year Phase II trial [50]. Antibodies to HPV-6 were induced in 75% of women who had lost their HPV-6 seropositivity with only a third of the responders mounting titers that exceeded the initial antibody response. Antibodies to HPV-11 were induced in 86% of women who had lost their HPV-11 seropositivity, with 70% of the responders mounting titers that exceeded the initial antibody response. This is worrisome that the boosted titers were not completely regained after only 5 years between the initial series and the booster injection. Antibodies to HPV-18 were induced in 97% of women who had lost their HPV-18 seropositivity, with 73% of the responders mounting titers that exceeded the initial antibody response. It is reassuring to note that the loss of HPV-18 efficacy may be regained by booster shots, certainly within 5 years. The anamnestic studies were not continued to show the rate of decay in the response over time. It is not known how the anamnestic response will behave if the booster is not given until 10 years after the initial vaccination series.

HPV-16 immunogenicity remains strong for Gardasil with anamnestic challenge. There was only one woman who lost her seropositivity to HPV-16 at 60 months, and she responded to the booster shot with titers above the initial antibody response 1 month after the booster. Since no trials of Gardasil have been extended beyond 44 months for the Phase III trials and 5 years for the Phase II trial, the meaning of the loss of antibody titers is unclear for possible future declines in vaccine efficacy.

Both Cervarix and Gardasil were tested in young adolescents 9/10–15 years of age who were seronegative at study entry for the vaccine-relevant HPV types for safety and antibody responses [51–54]. Both studies showed that young adolescents mounted an antibody response that was significantly higher than the response induced in 16–26-year-old seronegative, PCR-negative women. The concept of immunobridging was invoked to infer a similar efficacy for adolescent females to that seen in the 16–26-year-old female cohort because there was a similar or greater immune response in the young adolescents compared with the 16–26-year-old women.

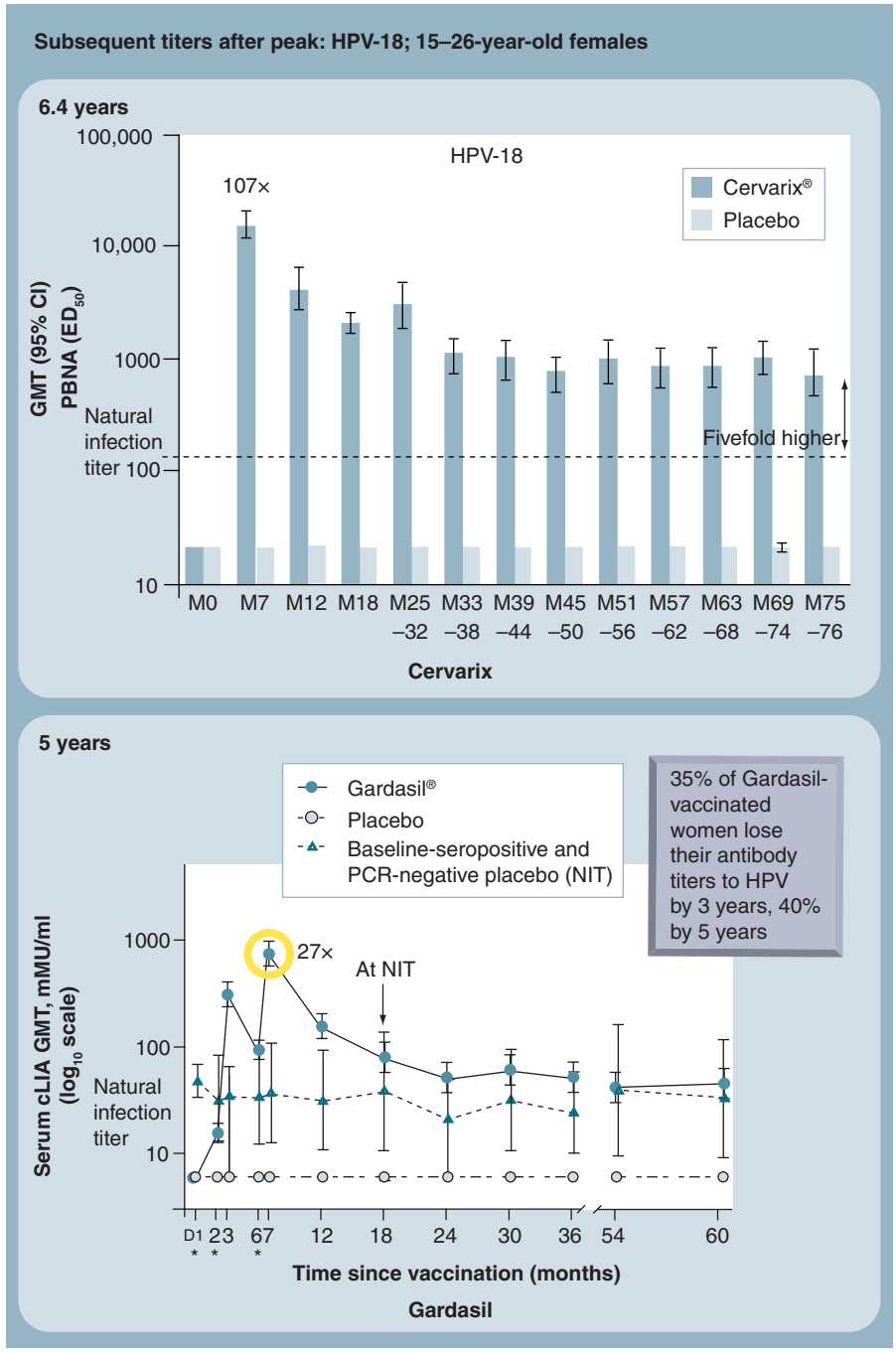

Figure 3. Induced anti-HPV 18 titers after Cervarix® and after Gardasil® administration in women 15–26 years of age. These graphs show the subsequent titers for HVP 18 after peak (month 7) responses over time. For Cervarix, the peak titer is 107-fold higher than natural infection titers and remains fivefold higher 6.4 years later [15]. For Gardasil, the encircled peak titer is 27-fold higher than natural infection titers and returns to natural infection titer levels at 18 months, with 35% of Gardasil-vaccinated women losing their anti-HPV-18 titers by 3 years. Anti-HPV-18 titers for Gardasil become equivalent to natural infection titers at 18 months and remain equivalent to natural infection titers through 5 years.
*Denotes when vaccination occurred.
cLIA: Competitive Luminex immunoassay; GMT: Geometric mean titer; HPV: Human papilloma virus; NIT: Natural infection titer; PBNA: Pseudovirion-based neutralization assay (measured in ED_{50} units).
Redrawn with permission from [50,75].

Table 10. Immunogenicity response of Cervarix® and Gardasil® measured in the same systems for women receiving the complete series of the respective vaccines.

	Peak antibody titer (ED_{50}) at month 7, 18–26-year-old females		Cervicovaginal mucous positivity for neutralizing antibodies (% positivity [95% CI]), 18–45-year-old females		Memory B-cell response (% positivity [95% CI]), 18–45-year-old females		Published years of efficacy [15,16]
	HPV-16	*HPV-18*	*HPV-16*	*HPV-18*	*HPV-16*	*HPV-18*	
Cervarix	31,715	13,732	81% (67–91)	33% (20–48)	90% (79–96)	89% (78–95)	6.4
Gardasil	8682	1886	51% (37–64)	9% (3–19)	94% (84–99)	66% (53–78)	5
Comparison (fold increase, 95% CI)	3.7-fold (2.7–5.0)	7.3-fold (5.2–10.2)					
p-value			Significantly different	Significantly different		p = 0.0041	

Antibody titers measured in the PBNA system for serum and cervicovaginal mucous showed statistically higher induced responses at 7 months post vaccine dose 1 for Cervarix than Gardasil. Memory B-cell responses were identical for both vaccines for HPV-16; but were significantly superior for Cervarix for HPV-18.
HPV: Human papillomavirus; PBNA: Pseudovirion-based neutralization assay (measured in ED_{50} units).
Adapted from [48].

Seropositive & PCR negative for HPV-6, -11, -16 & -18

Data from the Gardasil studies (Table 11) [103] show that the antibody titers for HPV-6, -11 and -18 (not HPV-16) measured at 30 months for the 9–12-year-old girls seronegative and PCR negative to HPV-6, -11, -16 and -18 were half the titers present at 38–50 months for the 16–26-year-old seropositive women who were PCR-negative for HPV-6, -11, -16 and -18 at study entry. On the other hand, the antibody titers for HPV-16 were equivalent for the 9–12-year-old girls and the 16–26-year-old seropositive, PCR-negative women at study end. If the concept of immunobridging is to be believed, this evidence indicates that Gardasil should be equally effective for 16–26-year-old sexually active young women as it is assumed to be in the 9–12-year-old naive cohort, as neither group has an actively replicating vaccine type-specific HPV infection. This will alleviate much of the social and cultural strife of targeting a vaccine for a sexually transmitted infection to young physiologically immature adolescents without removing the possibility of being vaccinated at either a young age or an age postcoital debut. As previously stated, data from the Costa Rica Vaccine Trial supports this concept: protection from persistent HPV-16/18 infections and CIN 2+ disease caused by any HPV type was 57 per 1000 women in those women vaccinated within their first year of sexual activity, whereas it was only 17 per 1000 women in those women vaccinated as virgins who went on to become sexually active [25]. Given the tremendous negative attitude among physicians and patients about Gardasil being marketed to girls too young, there is excellent scientific evidence to emphasize the benefits of vaccinating young women instead of adolescents [105,55].

Safety

Safety documentation is a priority in all phases of the vaccine clinical trials. Safety is categorized as local reactions from the injection itself and as systemic reactions that may occur throughout the trials. The randomized, controlled trials are the appropriate mechanism for determining safety in general for the regulatory licensure process. Postlicensure surveillance is critically important for population-based safety because the more rare adverse events cannot be detected until millions of doses have been administered.

In general, the randomized, controlled trials have shown that both vaccines are safe for the vast majority of recipients when considering pregnancy-related outcomes, fetal and infant morbidity and mortality, as well as new onset of chronic or autoimmune diseases. However, serious adverse events do occur at a low frequency that must be disclosed to the parents and young women prior to vaccination. It is possible that with whole genome-scanning, transcriptomics, epigenetics, proteinomics and newly associated biostatistical approaches, individuals will be screened prior to vaccination to avoid serious adverse events (immunogenetics). Entire populations may be classified by immunogenomics to identify groups of people who are at the highest risk from serious adverse events from vaccination. Despite low-frequency occurrences, the fact that serious adverse events have been reported means that individuals, if not entire subpopulations, will be able to be identified prior to vaccination for maximal vaccine safety [56].

The safety data for 10–14-year-olds were documented from a study of 158 young adolescent girls for Cervarix, and from a study of 1123 girls 9–15 years of age for Gardasil, both studies ending at 1 year after the three-dose series was completed [51,52,54]. The local adverse events reported within the first 5–7 days after vaccination in the adolescent ages included pain in 75–80%, erythema in 20–35% and swelling in 20–30% of the recipients. These local adverse events occurred in the same proportion in the 16–26-year-old women.

Systemic adverse events in the trials of adolescents and young women were reported within 30 days of vaccination and then at intermittent follow-up visits throughout the studies. The most commonly reported adverse events were myalgias, arthralgias, headaches and gastrointestinal symptoms, which occurred equally often in those receiving the control injection [17,26].

The serious adverse events were those medical events that resulted in hospitalization, disability, congenital anomaly or death. Only Gardasil has been subjected to postmarketing surveillance through the US-based Vaccine Adverse Events Reporting System (VAERS), as Cervarix has just been approved in the USA. The VAERS has limitations. If a positive association is found statistically between the events and receiving Gardasil, the association exists. However, the association, *ipso facto*, does not mean causation. Likewise, when no association is found in the analysis of VAERS, there is no reassurance that an association is not present as VAERS is insignificantly powered. Of all the adverse events reported to VAERS, Merck was responsible for 68%, an unusually high proportion of reports coming from industry rather than the physician, patient, pharmacist or other reporter. Frustratingly for the US FDA, 89% of the reports Merck submitted did not contain sufficient information for the US CDC to evaluate; this includes four of the cases of death [57].

Anaphylaxis has been reported at a rate of 2.6 per 100,000 doses in an Australian school-based national vaccination program [58]. Although rare and methodologically disputed by critics [59], this incidence rate is higher than that associated with other routinely given vaccines in this age group. The only published report shows that syncope and venous thromboembolism are occurring at frequencies statistically higher than expected in the general population [60]. FDA warnings about syncope have been issued since 2007 to prevent the falls, contusions, fractures, concussions, lacerations and intracerebral hemorrhages that have ensued after loss of consciousness.

The other remarkable serious adverse events include 12 verifiable cases of Guillain–Barré syndrome (GBS), which were confirmed by the Clinical Immunization Safety Assessment (CISA) network of six academic centers whose mission is to research vaccine adverse events [106]. Of these, nine cases manifested within 41 days of vaccination, the biologically plausible timeframe for GBS to occur. Four cases occurred in women

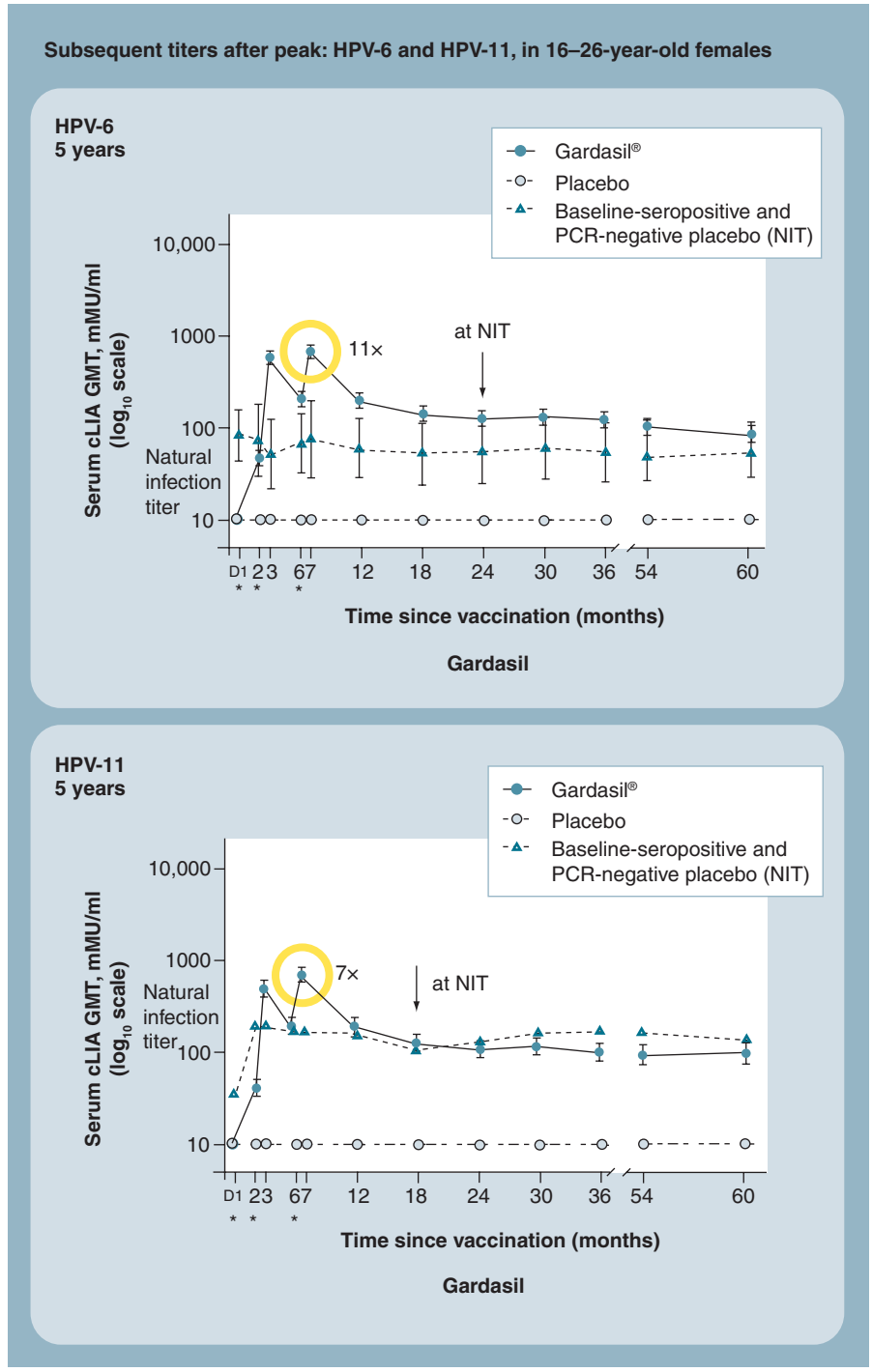

Figure 4. Induced anti-HPV-6 and anti-HPV-11 titers after Gardasil® administration in women 16–26 years of age. These graphs show the subsequent titers for HVP-6 and -11 after peak (month 7) responses over time. The encircled peak titer for HPV-6 is 11-fold higher than natural infection titers. The titers for HPV-6 become statistically indistinguishable from the natural infection titers at 18 months, staying at that level over 5 years. The titers for HPV 11 return to baseline natural infection titers at 18 months, dropping slightly lower than natural infection titers over 5 years.
cLIA: Competitive Luminex immunoassay; GMT: Geometric mean titer; HPV: Human papilloma virus; NIT: Natural infection titer; PBNA: Pseudovirion-based neutralization assay (measured in ED_{50} units).
*Denotes when vaccination occurred.
Redrawn with permission from [50].

Table 11. Ranked anti-HPV competitive Luminex immunoassay geometric mean titers induced by Gardasil® at end of study for females 16–26 years of age and 9–12 years of age by vaccine-relevant serostatus and PCR status at study entry.

Day 1 serostatus for vaccine-relevant HPV type	Day 1 PCR status for vaccine-relevant HPV type	n	GMT (mMU/ml)	95% CI
HPV-6				
Positive 16–26-year-olds	Negative 16–26-year-olds	301	376*	329–431
Positive 16–26-year-olds	Positive 16–26-year-olds	95	256	205–319
Negative 9–12-year-olds	Negative 9–12-year-olds	250	180*	160–202
Negative 16–26-year-olds	Positive 16–26-year-olds	121	111	96–130
Negative 16–26-year-olds	Negative 16–26-year-olds	4230	83	80–85
HPV-11				
Positive 16–26-year-olds	Negative 16–26-year-olds	66	453*	331–619
Positive 16–26-year-olds	Positive 16–26-year-olds	16	239	136–422
Negative 9–12-year-olds	Negative 9–12-year-olds	250	209*	184–238
Negative 16–26-year-olds	Positive 16–26-year-olds	19	187	148–237
Negative 16–26-year-olds	Negative 16–26-year-olds	4231	103	100–106
HPV-16				
Negative 9–12-year-olds	Negative 9–12-year-olds	248	961‡	848–1089
Positive 16–26-year-olds	Negative 16–26-year-olds	290	785‡	679–908
Positive 16–26-year-olds	Positive 16–26-year-olds	204	777	675–895
Negative 16–26-year-olds	Positive 16–26-year-olds	234	423	370–484
Negative 16–26-year-olds	Negative 16–26-year-olds	4088	408	394–422
HPV-18				
Positive 16–26-year-olds	Positive 16–26-year-olds	51	292*	219–388
Positive 16–26-year-olds	Negative 16–26-year-olds	122	211	162–274
Negative 9–12-year-olds	Negative 9–12-year-olds	251	126*	106–151
Negative 16–26-year-olds	Positive 16–26-year-olds	131	78	63–96
Negative 16–26-year-olds	Negative 16–26-year-olds	4522	38	36–40

End of study was 38–50 months for the 16–26-year-old females. End of study was 30 months for the 9–12-year-old females.
*Seropositive, PCR-negative 16–26-year-old females had significantly higher GMT at the end of study than did the seronegative, PCR-negative 9–12-year-old females.
‡No significant difference in GMT at the end of the study for HPV-16 for seropositive, PCR-negative 16–26-year-old females and seronegative, PCR-negative 9–12-year-old females.
GMT: Geometric mean titer; HPV: Human papillomavirus; mMU: milliMerck unit.
Adapted from [103].

where Menactra™ (MCV4) and Gardasil were coadministered. A preliminary analysis by the Vaccine Safety Datalink, a CDC-sponsored surveillance group based at eight managed care organizations throughout the USA, did not find a statistically significant increased risk for GBS in persons who received Gardasil compared with a historic reference population [107]. Nevertheless, Merck has revised the quadrivalent and pentavalent HPV vaccine study consent forms to include a possible low-frequency increased risk of GBS in study participants. If there are multiple opportunities to vaccinate young girls, it would seem wise to separate their vaccinations to different days, to lessen the likelihood of unknown adverse interactions.

Less frequently occurring motor neuron diseases resulting in permanent disability or death have been reported after Gardasil use as well. These events are very rare, but the incidence of juvenile amyotrophic lateral sclerosis (ALS) in the general population, a uniformly fatal disease, is also very rare, at rates similar to the incidence of reported ALS-like symptoms triggered after Gardasil injection. There are four confirmed cases of ALS-like syndromes after Gardasil injection, with two of the four girls already dead [Shapiro B, Pers. Comm.]. Other rare demyelinating, autoimmune diseases and other events have been reported in low frequencies [61–68].

Pregnancy concerns

Clinical recommendations for vaccine administration are split into three conditions:

- Do not vaccinate a woman during pregnancy
- If she has received one dose prior to pregnancy, the series of three doses can be restarted after delivery
- If she has received two doses prior to pregnancy, the final dose can be given after delivery

There is no medical reason to interrupt a pregnancy owing to partial vaccine administration. There are no contraindications to vaccination during lactation. Some would suggest immediately starting the vaccination series postpartum as an effective strategy to ensure completion of the three doses as she will already be interacting with the medical profession for her infant follow-up visits.

Expert commentary

The HPV vaccines neutralize type-specific HPV infections prior to engulfment into the basal cells of the epithelium. Therefore, the vaccines should provide benefit to any epithelium that is at risk for HPV infection, with cervical cancer being the most prevalent HPV-associated cancer. Other cancers less closely associated with HPV occur in the vagina, vulva, penis, anus and oropharynx [7]. Results from the HPV vaccine trials to prevent CIN and cervical cancer should theoretically translate into some level of partial protection from these other HPV-associated cancers. Specific long-term cancer registries or ecologic epidemiological data will be needed to determine the extent of impact, potentially quite small, of the HPV vaccines on these cancers several decades from now.

Likewise, the benefit of Gardasil for the prevention of the noncancerous but lethal juvenile respiratory papillomatosis, caused at minimum by HPV-6 and -11, will require decades of follow-up to ascertain whether efficacy occurs and whether the duration of vaccine efficacy truly prevents this disease or merely prolongs the number and frequency of surgeries with no difference in overall survival. To prevent this disease, the prophylactic vaccines will have to prevent the autoinoculation from the original field infection to prevent further disease. The long-term impact on genital wart prevention could prevent some nonlethal HPV infections. The disutility of genital warts is the replacement of a normally functioning protective epithelium with warty tissue that can be both disfiguring and highly disruptive to normal life activities. Serious doubts about Gardasil's long-term protection are raised by the surprisingly lower efficacy in preventing genital warts of any HPV type, and the rapid fall in antibody titers that do not respond uniformly well to the anamnestic challenge.

Vaccination of 12–15-year-old girls has certainly been shown by cost–effectiveness models to have the potential to reduce cervical cancer incidence many decades in the future [38–43]. The scientific evidence supporting this program is the immunobridging principle and the generally good safety profile, with only rare debilitating neurologic adverse events reported. Despite no efficacy data and no evidence for duration of efficacy past the first decade, public-health bodies recommend young adolescent female vaccination. Should the duration be less than 15 years, cervical cancers will only be postponed at a great cost, not prevented. In addition, there has been very limited public acceptance of vaccinating 10–12-year-olds, with the greatest proportion of vaccinees being 16–20 years of age [55,69].

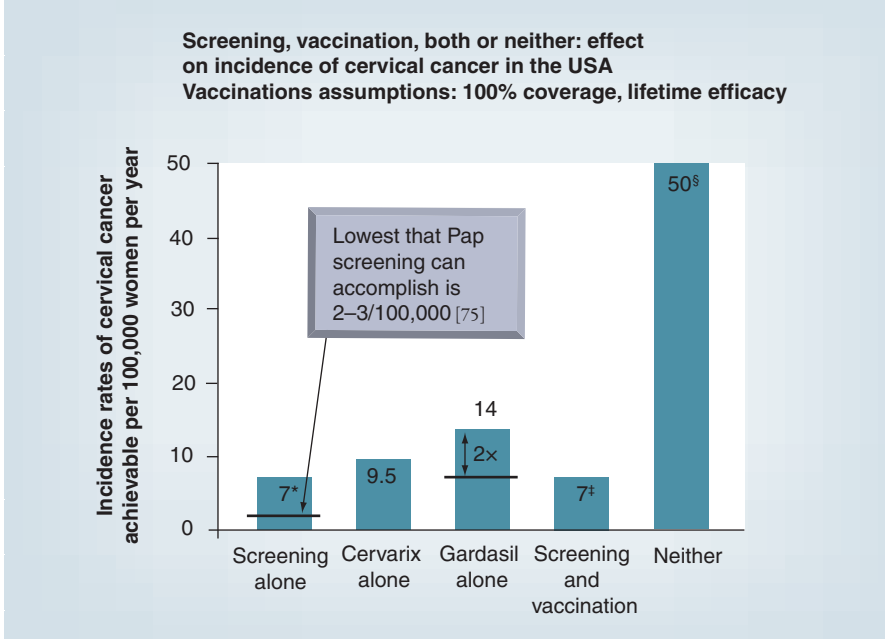

Figure 5. Maximal potential effect of screening, vaccination, both or neither on the incidence of cervical cancer in the USA. The lowest incidence Pap screening can achieve in the nonvaccinated population is two to three per 100,000 [76]. Currently, in the USA, the Pap screening program identifies on average seven per 100,000 new women with cervical cancer every year [108]. Without any screening or vaccination, the yearly incidence rate of cervical cancer will quickly approach 50 per 100,000 [77]. Assuming 100% vaccine coverage, and lifetime efficacy, the incidence of cervical cancer will be higher (in the case of Gardasil®, twice as high) than the rate currently achieved by screening only if vaccinated women cease their Pap screening. Screening and vaccination will not reduce the incidence of cervical cancer by any measurable degree [78], but will provide reassurance to lengthen the screening interval.
*Data from [108].
‡Data from [78].
§Data from [77].

But there are millions of women under 26 years of age who are already sexually active and who may derive immediate benefit from vaccination based on induced antibody titers that exceed the bridging titers induced in adolescents. HPV vaccines cannot stop the progression of HPV disease outcomes in cells already infected with HPV, but induced antibodies should be able to neutralize autoinfecting HPV virions from the original field infection, thereby disrupting the infectious cycle and preventing the recurrence of CIN and anogenital cancers that currently occurs at frequencies up to 12-times the general population rate of disease and as long as 20 years out from the original infection [26,70–72].

In industrialized countries with organized screening, regardless of whether you choose to vaccinate or which vaccine you choose to use for vaccination, the most important message to relay to women is the continued need for cervical cancer screening exams. The vaccines do not replace Pap testing. The incidence of cervical cancer will increase if screening is forgotten after vaccination. The decision to vaccinate in countries with organized, well-attended screening programs must be made by the individual herself or as a shared decision with her provider. Furthermore, the benefits of reducing the number of abnormal Pap screens, the number of colposcopies and the number of excisional treatments necessary must

be weighed against the risks of missing screening exams, booster needs and small but real serious side effects, including death. The incidence of cervical cancer will not be reduced by vaccination alone or vaccination in combination with screening (Figure 5).

In countries without well-attended, organized screening, the lasting effects of HPV vaccination will be completely dependent on the duration of vaccine efficacy and the population coverage achieved, with the potential to save hundreds of thousands of women's lives, balanced against the very small risk of serious adverse events.

Five-year view

It is highly likely that the prophylactic vaccines will be found to be effective at preventing autoinoculation of HPV infections in women already actively infected with HPV. These data are being collected over longer follow-up times than the initial pivotal trials. This would broaden the use of HPV vaccines to infected women and potentially older women to help stem the secondary outbreaks of similar anogenital cancers 10–20 years after the first CIN 3 development.

There is already a supplemental vaccine being trialed for Gardasil recipients that is hypothesized to provide protection against the HPV types for which it does not currently have cross-protection (HPV-31, -33, -45, -52 and -58). The long-term plan is to combine the current four HPV types in Gardasil with these supplemental five oncogenic HPV types to broaden the cancer protection possible for Gardasil. When Merck will withdraw Gardasil for its replacement nonovalent vaccine is unknown.

Therapeutic vaccines have been slower to develop than the prophylactic vaccines. Developing a vaccine whose primary method of action is the cell-mediated immune response with killer T cells actively destroying HPV-infected epithelial cells has been technically more challenging. Several candidate vaccines are in early trials.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Key issues

- In countries with well-attended organized, screening programs, vaccination will not reduce cervical cancer any further than screening has already achieved. Vaccination will reduce the number of diagnostic colposcopies and excisional therapies, thereby reducing some associated psychosocial and reproductive morbidity, but with an attendant risk of very low-frequency serious side effects.
- Attendance at screening programs must continue after vaccination. Without continued screening, the incidence of cervical cancer could increase to more than double (using Gardasil® as the vaccine) the current rate within a decade.
- In countries with little or no organized screening, if the duration of vaccine efficacy is longer than 15 years, cervical cancer can be dramatically reduced to approximately twice the incidence established in countries with screening (from 50 to 15/100,000 women), saving hundreds of thousands of women's lives annually. The small risk of vaccination may be tolerable in populations where so many lives can be saved.
- If the duration of efficacy is less than 15 years, cervical cancers will only be postponed, not prevented.
- Both vaccines are highly effective in preventing persistent human papillomavirus (HPV) infections and cervical intraepithelial neoplasia 2+ in women who are not currently shedding active HPV virus of the vaccine-relevant types. Neither vaccine is effective in women currently shedding active HPV virus of the vaccine-relevant types.
- Cervarix® offers greater opportunity to reduce excisional treatments for precancerous disease, the incidence of adenocarcinoma and squamous carcinomas over time than does Gardasil.
- Gardasil offers protection for men 16–26 years of age against genital warts caused by HPV-6 and -11 for 2.4 years.
- The emerging field of vaccine adverse event immunogenetics may be able to identify individual girls/women prior to vaccination to avoid the rare lethal adverse events that have been reported.
- Immunogenomics may be able to identify entire subpopulations that would suffer the most serious side effects from vaccinations, allowing other screening methods to reduce the cervical cancer rate.
- Cervical cancer eradication is not possible. Cervical cancer control is ongoing and robustly supplemented by vaccination.

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