

# Current prophylactic HPV vaccines and gynecologic premalignancies

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## Purpose of review

Studies of the human papillomavirus (HPV) vaccines, Cervarix and Gardasil provide strong evidence for the recommendation that HPV vaccines may minimize the incidence of cervical cancer over time.

## Recent findings

Both Cervarix and Gardasil provided more than 90% efficacy in preventing cervical intraepithelial neoplasia grade 2+ (CIN 2+) disease caused by HPV 16 and 18 in women 16–26 years who were seronegative and PCR-negative for HPV 16 and 18 at baseline. Cervarix provides more than 75% efficacy in independent cross-protection against persistent HPV 31 and 45, and 47% efficacy against HPV 33; whereas Gardasil offers 50% efficacy only against persistent HPV 31. A reduction in excisional therapies for CIN 2+ is nearly 70% for Cervarix, and 40% for Gardasil. Cervarix efficacy is documented to 6.4 years; Gardasil's to 5 years. Immunologically, Cervarix induces three to nine-fold higher peak-neutralizing antibody titers to HPV 16/18 than Gardasil, has significantly higher cervicovaginal mucus-neutralizing antibody presence than Gardasil, and significantly higher B memory cell response than Gardasil. Safety reports indicate injection site reactions for both Cervarix and Gardasil. Rare serious adverse events have been reported.

## Summary

The benefits and risks of vaccination must be weighed with the benefits and risks of screening to reduce cervical cancer in a cost-effective manner.

## Keywords

adult women, CIN 2+, efficacy, immunogenicity, prophylactic HPV vaccine, safety

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## Introduction

In 2007, human papillomavirus (HPV) was classified as a biologic carcinogen [1] and in 2008, Dr zur Hausen was presented the Nobel prize for proving the association of HPV with cervical cancer [2].

Over the past 60 years, Pap screening has been successful in decreasing the incidence of cervical cancer. The Pap test provided individual protection, but did not reduce the public health burden of cervical cancer until at least 70% of the population was screened with an organized system [3]. Finland has been the exemplary beacon accomplishing a 75% decrease in the incidence of cervical cancer since 1953 [4]. Finland has also provided the sentinel warning that without continued organized screening, the incidence of cervical cancer will quickly return to the 50/100 000 women rate currently seen in countries without Pap screening. In Finland, from 1991 to 2005, the incidence rate of cervical cancer increased five-fold over the expected rate for women 30–39 years old [4,5]. The reason for this quick, sharp increase in inci-

dence was the lack of compliance with cytology screening in all ages of women, with the most egregious lack of screening occurring in the young women 25–30 years old [6]. Lessons we learn from the history of cytology screening programs become critical to the value of HPV vaccination in our populations. We will review the benefits and harms of both Pap screening and HPV vaccination in the quest to minimize the burden of cervical cancer.

## The benefits and risks of routine cytology screening

Globally about 500 000 women develop cervical cancer every year [7]. Over 80% of the cervical cancers occur in countries without organized cytology screening [7]. The phenomenal benefit at extraordinary cost of organized Pap screening systems is the vastly reduced yearly incidence rate of cervical cancer now at 7–9/100 000 women with cancers peaking bimodally at 35 and 65 years [7,8]. Approximately 60% of the women developing cancer every year did not participate or infrequently participated in the Pap screening program [9]. Particularly difficult to

detect are the subset of adeno and adenosquamous carcinomas which are increasing in incidence [10,11]. Approximately 30% of women with cancer participated in Pap screening but had falsely negative reports highlighting that all cervical cancers cannot be detected by routine cytology screening, liquid or conventional [12]. Pap testing cannot bring us to a zero incidence of cervical cancer. The lowest incidence Pap testing can effect is 2–3/100,000 [9].

Quality-of-life harms associated with Pap screening include the falsely positive Pap tests which can engender marked stress and anxiety surrounding the colposcopy appointment. In addition, there is often relationship trauma between partners when she learns that a sexually transmitted infection is the most likely reason for her abnormal Pap test, even if she does not have a cancer precursor [13].

Reproductive morbidity is a second harm associated with the treatment intervention for cervical intraepithelial neoplasia grade 2 (CIN 2) disease, CIN 3, adenocarcinoma *in situ*, squamous cell carcinoma, adenocarcinoma (CIN 2+). Deep excisional therapies are 100% effective for 5 years, but are associated with a 70–300% increased chance of operative delivery, preterm labor and low birth-weight infants in subsequent pregnancies [14\*\*]. Additionally, the risk of recurrence of cervical cancer or other anogenital cancers after CIN 3 treatment is 3–12-fold higher than in the general female population 20 years posttreatment [15,16,17\*,18].

Understanding the natural history of HPV infection and its causal relationship to cervical cancer illustrates when vaccination can contribute. Anogenital oncogenic HPV infections are detected in 5–10% of girls and boys of all ages [19,20,21\*\*,22\*\*]. There is a spiked increase after the onset of sexual activity with incidence rates exceeding 30% by 20 years of age, dropping back to 10% from 35–60 years old, with increases up to 15% for women older than 60 years [23]. About half of HPV infections in adult women resolve spontaneously in 1 year with 90% clearing after 2 years [24,25]. This high clearance rate supports triennial screening for the detection of only those infections which remain persistent. Among women with persistent infections, about half progress to CIN 2/3 disease within 3 years [26\*\*]. Detection and treatment of less than CIN 2/3 is not contributory to cervical cancer prevention. Twenty percent of women with CIN 2/3 disease progress to invasive cancer within 5 years, 30% within 10 years and 40% within 30 years [27\*\*]. This slow time lag from CIN 2/3 to invasive cancer provides years of opportunity to intervene with therapy, hence the tremendous success of Pap screening. In review, the one benefit of Pap screening is early detection and treatment of cervical lesions, significantly reducing cervical cancer

incidence. The six risks/harms of Pap screening include the need for repeated screens, the false negative rate of Pap testing, the false positive rate of Pap testing leading to quality-of-life compromises, the reproductive morbidity from lesion treatment and finally the recurrence of HPV associated cancers many years later.

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### The benefits and risks of the prophylactic human papillomavirus vaccines

Paralleling what we have learned from cytology, we ask similar questions about the prophylactic HPV vaccines, Cervarix and Gardasil: efficacy, extent of cancers covered, limits of duration of efficacy, reductions in harms caused by screening, and harms of vaccination itself.

Both Cervarix and Gardasil have shown a remarkable greater than 90% efficacy for the prevention of CIN 2+ caused by HPV 16/18 in women 15–25 years and 16–26 years, respectively, who were seronegative and PCR-negative for HPV 16/18 at study entry. There was no efficacy for either vaccine in preventing new CIN 2+ disease caused by HPV 16/18 in women who were actively expressing HPV 16/18 DNA at study entry; neither was there acceleration of disease progression in this group of vaccinated women [28]. It is also highly probable that Cervarix and Gardasil will be effective in women who are seropositive but not actively shedding HPV 16/18 at the time of vaccination. The protection offered for CIN 2+ regardless of the responsible HPV type is a notable 70% for Cervarix in 15–25-year-old women naive to HPV, dropping to a still impressive low of 30% if the population is all women irrespective of their serostatus, Pap status, and HPV DNA PCR status [29\*\*]. The efficacy of Gardasil against CIN 2+ regardless of responsible HPV types in naive women is not known, but is 18% for any CIN 2+ in this latter population [30\*\*,31\*\*].

Cross-protection for other oncogenic HPV types is an added bonus for Cervarix. We review that three HPV types account for about 90% of the adeno and adenosquamous carcinomas worldwide: HPV 16, 18 and 45; HPV 31 and 33 contribute an additional 2.3% of the glandular cancers. These same five types account for approximately 84% of the global burden of squamous cell cervical carcinomas [23]. Using the 6-month persistent infection as the most relevant endpoint [32\*–34\*], Cervarix has 79% efficacy against HPV 31, 46% efficacy against HPV 33 and 76% efficacy against HPV 45, whereas Gardasil has a 46% efficacy only against HPV 31. Merck is developing an additional HPV vaccine containing HPV 31, 33, 45, 52, and 58 to supplement those women who have already received Gardasil, recognizing the cross-protection weakness of Gardasil [35]. Extrapolating the potential reduction in cervical cancers from the HPV vaccines

**Table 1 Estimated maximal cervical cancer reduction accounting for significant cross-protection of additional oncogenic HPV types**

HPV type	Attributed proportion (%) of cervical cancers by cancer type [23]		Cervarix [29**]		Gardasil [36*]	
	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 by 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; 46% efficacy against HPV 31 persistent infections for Gardasil; for Cervarix: 76% efficacy against HPV 45, 79% efficacy against HPV 31, 46% for HPV 33 persistent infections [29\*\*]. Based on 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 [36\*]. Based on 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 10 nonvaccine relevant HPV types, received at least one dose of vaccine, with cases counted after day 1. HPV, human papillomavirus.

under assumptions of vaccine coverage, duration and clinically relevant efficacies, indicates that Cervarix may reduce the incidence of both squamous and adenocarcinoma of the cervix more than Gardasil (Table 1) [23,29\*\*,36\*]. In addition, Cervarix also appears to offer substantially better protection from adenocarcinoma than does Pap screening, a major advantage for vaccination.

Another benefit of vaccination is some reduction in the decreased quality of life and reproductive morbidities associated with colposcopy and excisional therapies. Both Cervarix and Gardasil offer about a 20% reduction in colposcopies within 3 years after vaccination [29\*\*,37]. But Cervarix, because of its broader cancer coverage, prevents more excisions, and hence the harm from excisions, than Gardasil: 69 compared to 42%, respectively [29\*\*,37].

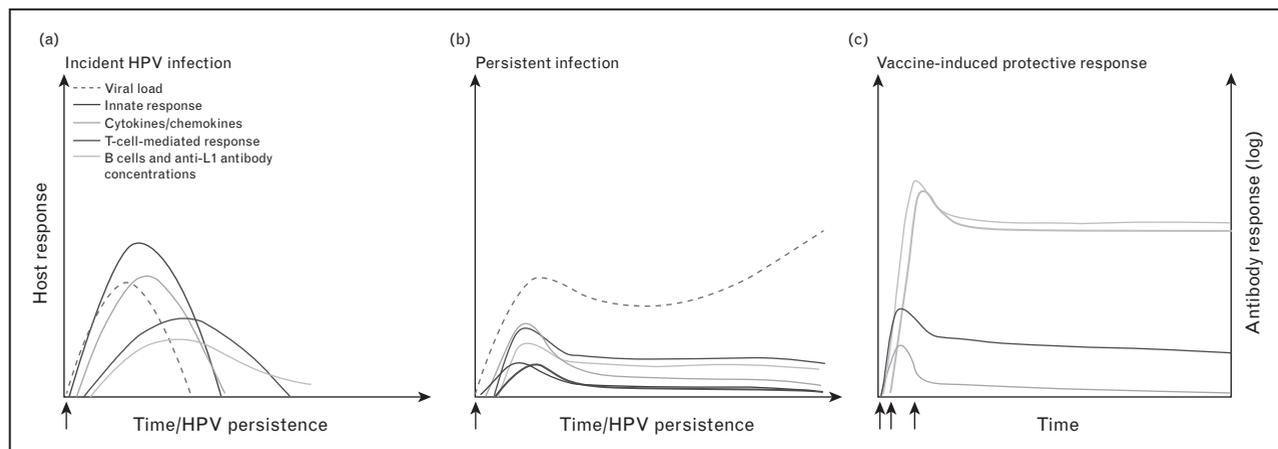
The HPV association and genotype distribution with vulvar and vaginal cancers have only recently been published [38\*,39\*]. Gardasil has documented an additional 50% efficacy against the rare vulvar precancer irrespective of HPV type causation among 16–26-year-old women [30\*\*]; and the 100% efficacy against both rare vulvar and vaginal precancers caused by HPV 16/18 among the baseline HPV 16/18 naive 16–26-year-old women [31\*\*,40\*]. The data from Cervarix are theoretically expected to show similar vulvar and vaginal protection. Vaginal and vulvar cancers are very slow growing cancers with high cure rates for early-stage detection [41\*]. They develop mostly in women older than 50 years, are not usually detected by Pap screening, but during the visual and bimanual examination [40\*]. There are no documented harms with detecting and treating vulvar and vaginal precancers as there are with cervical precancers; the vaccine efficacy would have to last at least 20 years to prevent rather than just postpone these

cancers. Therefore, the value of partial primary prevention (vaccination) against complete secondary prevention strategies (visual exam) must be questioned.

No efficacy studies have been done for either vaccine in women younger than 15 years. Studies of immunogenicity and safety have indicated an acceptable immune response to bridge to younger ages of girls and boys for both Gardasil and Cervarix [42–44,45\*].

Both Cervarix and Gardasil have ongoing trials of efficacy, immunogenicity and safety in women older than 25 years [46,47]. To date there are no published data for discrete outcomes of either persistent infection or CIN 2+ disease prevention. Cost-effectiveness studies indicate that vaccinating older women could substantially decrease cervical cancer incidence if there is associated efficacy, especially if the duration of efficacy is less than 10 years [48].

The critical question of duration of vaccine efficacy is not yet answered by rigorous methodologic trials. Cervarix efficacy is proven for 7.4 years with published data through 6.4 years [49\*\*]; Gardasil efficacy is proven for 5 years [50]. Because 90% of the HPV infections clear spontaneously, because the development of cancer precursors is slow, because the progression from cancer precursors to invasive cancer is slow, vaccination efficacy must last at least 15 years. Any less duration of efficacy and cervical cancers are merely postponed, not prevented [51\*\*]. The cost of vaccination, the cost of implementing booster programs, the risk of interrupted protection allowing new infections, new precancers and cancers to develop, the risks of the vaccination itself, and the risk of noncompliance with continued organized screening after vaccination casts doubt on the benefit of universal early age vaccination programs. Sweden, Denmark, Norway,

**Figure 1 Models of the host immune response against infection with and without vaccination against oncogenic HPV [55\*\*]**

These hypothetical models are based on the available immunological data and represent general immune response patterns in women. (a) Innate immune responses may limit viral load and play a part in clearance of incident oncogenic HPV infection without activation of adaptive immunity. (b) During persistent oncogenic HPV infection, the host immune response is unable to control infection and viral load begins to increase beyond the point of control. The responses of many components of the immune system increase in parallel as infection progresses. In addition, the qualitative nature of the innate and adaptive immune response to persistent infection differs from that of infection associated with clearance. Eventually, HPV overwhelms the immune responses at the cervix. Memory-induced immune responses also seem to be insufficient to control persistent infection. (c) In women who are vaccinated parenterally against oncogenic HPV, the immune response is dominated by a sustained and rapid increase in serum neutralizing antibodies. Moreover, immune responses occur at a rapid and greater amplitude with adjuvanted vaccines. High concentrations of neutralizing antibodies at the site of infection function to prevent oncogenic HPV infection of the cervix. Arrows indicate time of HPV infection or exposure or vaccine doses. HPV, human papillomavirus.

Finland, Iceland and Costa Rica have ongoing rigorously designed population trials to try to determine, among many objectives, the duration of vaccine efficacy [52\*–54\*]. In the meantime, the only remotely possible surrogate method to evaluate vaccine duration is comparing the quantity and quality of the neutralizing antibody responses [55\*\*]. As shown in Fig. 1, there are many immune processes at play during infection, clearance and protection against HPV.

A head-to-head trial measuring induced neutralizing antibodies in the pseudovirion-based neutralization assay (PBNA) [56] has removed the difficulty in comparing the results from proprietary methods [57]. In all age ranges – 18–26 years, 27–35 years, 36–45 years – Cervarix induced a three to nine-fold increase in peak type specific antibodies over Gardasil. In addition, there were significantly higher neutralizing antibodies in the cervicovaginal mucus in Cervarix recipients than in Gardasil recipients [57,58\*\*]. Memory-specific B cells likewise occurred in significantly higher quantities for women vaccinated with Cervarix over Gardasil indicating a possible superior long-term memory response for Cervarix [53\*]. Earlier work showed that 35% of Gardasil recipients lost their seroconversion to HPV 18 and titers decreased to natural infection titers around 36 months after vaccination [59]. Until further data are available, it is reasonable to assume that Cervarix will offer the longer duration of efficacy, maximizing the potential for universal vaccination program success without immediate need for boosters or supplemental injections.

The safety of the vaccines must be considered before any recommendations for vaccination can occur. In general, both vaccines are well tolerated for most women. Both vaccines induce an injection site reaction that usually clears within 2 days [29\*\*,60]. Postmarketing surveillance, through VAERS in the US, has given a more critical examination of Gardasil to which Cervarix has not yet been subjected. Syncope after vaccination has been recognized [61\*]. Serious adverse events [62\*–72\*,73\*\*,74\*\*] including death from amyotrophic lateral sclerosis (ALS)-like syndromes are being given serious consideration as rare but real side effects potentially triggered by the HPV 16 L1 VLP (Frankovich, personal communication). The mechanism for motor neuron interruption also affects the physiologic anticoagulation pathways that could explain the increased statistical signal reported for venous thromboembolism which was discounted because of associated estrogen use, obesity and sedentary lifestyles [75\*\*]. There is insufficient information at this time to be reassured that serious adverse events are not triggered by Gardasil; likewise there is insufficient information that Gardasil is the not the cause of these adverse events. Until further work can be completed, it is necessary to inform parents of a very rare, but real potential, for serious adverse events from vaccination [75\*\*].

### **Offering vaccination requires discussing the benefits and risks of screening and vaccination**

In countries where organized screening has been successful, and HPV vaccine acceptance has been limited

[76–81], the introduction of universal mass vaccination of young girls must be couched in terms of a shared decision: between parents, the girls, their physicians and the recommendations of public health authorities. Each party has a different perspective, a different goal and a different set of priorities. Parents consenting to HPV vaccination must be told that the duration of the vaccine is unknown, and that it is entirely possible that the initial vaccination series will only postpone, not prevent, future cervical cancers in their daughter. They must be told that no substantial public health decrease in cervical cancer will occur until at least 70% of the female population is vaccinated and then the maximal reduction will not be seen until there has been continuous protection in at least 70% of the female population for at least 60 years [82–88]. If boosters are needed [59], there will be a window of vulnerability for HPV infection as booster implementation takes place. As there is no evidence of vaccine efficacy for HPV 16 and 18 in males [89], there is no role for herd immunity in cervical cancer prevention and boys are not included in vaccination recommendations for cervical cancer control.

Parents must be told that vaccination offers protection from HPV infections (not cervical cancer) and only 5% of the oncogenic HPV infections will progress to CIN 2+ disease within an average of 3 years; less than half of women with CIN 2+ then will progress to cancer within another 30 years leaving ample time for detection and treatment if the woman continues routine screening. They must be told that continued routine screening must continue even after vaccination. Without continued screening the number of cancers preventable by vaccination alone is less than the number of cancers prevented by regular screening alone. Parents must be told that vaccination and screening together will not lower the chances of cervical cancer by any appreciable amount [90], but will provide reassurance that the screening interval can lengthen. They must be told that there are very low frequency, rare side effects including death, that have been reported after vaccination [62•–72•,73••–75••].

Parents need to understand that women vaccinated within the first year of sexual activity have an impressive reduction in persistent HPV 16/18 infection and CIN 2+ disease despite being already sexually active at the time of vaccination (57/1000 infections or lesions prevented vs. 17/1000 prevented in virgins who became sexually active after vaccination) [91]. They need to understand that 5–10% of 9–12-year-olds already have genital oncogenic HPV [20,21••,22••] and that the age of vaccination is less important than the duration of efficacy.

Parents must weigh the risks and benefits that vaccination affords. At maximal efficacy, HPV vaccination will reduce the number of abnormal screens by about 55% for

Gardasil and 65% for Cervarix, giving the woman an increased chance that her next screen will be normal. There is a 20% reduction within 3 years of vaccination in abnormal-screening-required colposcopies and a 40–70% reduction in the subsequent excisional therapies [29••,37]. This protection significantly lessens the decreased quality of life and reproductive morbidity associated with colposcopy and treatment.

How parents and women value each of these risks and benefits will inform their decision to be vaccinated and continue screening participation to prevent cervical cancer.

When organized screening for a broad age range of women is not available, vaccination provides the potential for a dramatic decrease from current 30–50/100 000 incidence rates [7] to around 15/100 000 incidence rate if the duration of efficacy is sufficiently long. The small risk of serious adverse events may be tolerable when the mortality from cervical cancer is so much higher than in screened populations.

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## Conclusion

Under the best circumstances in which HPV vaccination has lifetime efficacy and screening is sparse, a vaccination program has the potential to save hundreds of thousands of women's lives. When screening is routinely available, vaccination may decrease the number of diagnostic work-ups and allow the interval between screens to safely increase. Mores, values, ethics, cost-effectiveness, and tolerance for rare but real risks of serious adverse events must be balanced by each potential vaccine recipient in light of the public health guidelines.

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## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 542–543).

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