

Should the HPV vaccine be offered to all women?

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Overview of HPV, the Human Papilloma Virus

More than 40 genital types of HPV have been identified, of which 15 are known to be oncogenic. High risk HPV types cause all cervical cancers and true cervical pre cancer lesions, including cervical intra epithelial neoplasia III.¹ HPV types 16 and 18 are the most common oncogenic HPV types associated with cervical cancer. HPV 16 accounts for nearly 60% of all cervical cancers, and HPV 18 accounts for another 10-20% of cervical cancers. The second most common histological type of cervical cancer, adenocarcinoma of the cervix, is becoming increasingly common in the USA.² The rate of association between HPV 16 and 18 and cervical adenocarcinoma is similar, and in some populations the rate of HPV 18 exceeds that of HPV 16. HPV is also implicated in 30% of oropharyngeal cancer³, 45-95% of anal cancer⁴, 60 to 65% of vaginal cancer and 40 to 60% of vulvar cancer.⁵

Natural History of HPV infection as it relates to cervical cancer

Women with persistent oncogenic HPV infections have the greatest risk of developing cervical pre-cancer and cancer.⁶ Persistent HPV infection is usually regarded as HPV present on the cervix after age 30 years. Not all persistent infections progress to CIN II and CIN III and few precancerous lesions will develop into cancer in a screened population with access to treatment for dysplasia. The longer a HPV infection persists, the less likely a patient is to clear her infection.⁷ Cervical cancer is not likely to follow a stepwise progression of CIN I to CIN II to CIN III followed by invasive cancer. The true pathologic course is most likely based on active HPV infection and its persistence wherein newly acquired HPV infections most often regress and persistent infections have the potential to progress to a higher grade lesion.⁸ In a population based study, women with type specific persistence for more than 2 years were 800 times more likely to develop a high-grade cervical lesion.⁹ It also follows that L-SIL and H-SIL lesions are not necessarily sequences but more likely morphologically related lesions.

The progression from HPV infection to HPV persistence to

the development of HSIL and ultimately invasive cancer appears to take according to the WHO, on average, about 15-20 years, although cases of rapid-onset cancers do occur. The time to invasive cancer reflects the time needed for additional genetic events to occur such as integration of HPV-DNA into the host genome. The relatively slow process of transformation in addition to persistent HPV infection has allowed current screening and treatment programs in developed countries to effectively interfere in this process. However, even in screened populations, cervical adenocarcinoma remains a problem. Given that more than 91% of adenocarcinomas have HPV16 and 18, it is very likely that vaccination against HPV16 and 18 will effectively halt the rising trend in incidence of cervical adenocarcinoma.

Mechanism of action of prophylactic HPV vaccines

The currently available prophylactic HPV vaccines are based on Virus Like Particles composed of HPV L1 proteins. A VLP is geometrically and antigenically identical to the native version. Thus VLPs resemble the actual virus morphologically but cannot induce infections as these do not contain viral DNA. Once introduced intramuscularly, VLP vaccines generate high levels of symptomatic anti-HPV L1 immunoglobulin antibodies.¹⁰ Protection is in principle type specific, but cross reactivity may occur because phylogenetically related HPV types do share cross neutralizations epitopes. The HPV vaccines induce immune memory¹¹, likely providing long-term immunity even when initially induced high IgG antibody titres drop in time.

Virtually all vaccinated individuals (9-55 years) seroconvert and generate high titres of neutralizing IgG antibody against the vaccines type(s). The neutralizing antibodies have shown to persist for at least 5 years after vaccination at measurable levels higher than those found natural infections. Antibody response has shown to be highest in younger (9-15 years) recipients.¹² These findings suggest that an optional immune response to HPV-VLPs occurs at or around puberty, indicating this age category to be a potential target population.

Prevention of HPV infections

Efficacy data of available HPV vaccines demonstrate protection against persistent HPV 16 and/or HPV 18 infections (lasting 6 months or more) of practically 100% up to at least 5

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years after vaccination.¹³ Cross infection was demonstrated for the bivalent vaccine against HPV 31 (HPV 16 related), HPV 45 (HPV 18 related) and HPV 52 (HPV 16 related).¹⁴

In a combining analysis cross-protection against persistent infections with HPV 31/33/35/39/45/51/52/56/58/59, mainly owing to HPV 31/45 was observed for the quadrivalent vaccine.¹⁵ The effect was most pronounced for HPV 31/45.

In both vaccines the level of cross-protection is around 45%.

Prevention of anogenital lesions

Current assessment of the effectiveness of the HPV vaccines relate to the type-specific cervical HPV status after vaccination. For both bivalent and quadrivalent vaccines other clinical trials report on efficacy data preventing HPV 16/18 related disease.¹⁶ In these trials, the efficacy against CIN 2/3 and AIS is documented as intermediate end point because these lesions are the obligate and immediate precursors to invasive cancer.

(a) HPV 16/18 DNA-negative women

These include both HPV negative women and women who have no current infection, but who have been previously exposed to one or more other HPV types. HPV-VLP vaccines demonstrated similarly high clinical efficacy in both groups of women. The current reports of effectiveness against HPV 16/18 are about 100% in HPV 16/18 DNA negative woman.

Current prophylactic HPV vaccines demonstrate valuable preventative efficacy against early clinical complications of HPV 16 and 18 infections and to a certain extent to these associated with some related HPV types and raise prospects for primary prevention of cervical cancer.

(b) HPV 16/18 DNA POSITIVE WOMEN

Protection against disease caused by HPV 16/18 for women who were cervical smear positive is marginally or even non-existent (17). This is not surprising as a prophylactic vaccine requires a type-specific HPV naïve person to be effective. Only among HPV16/18 DNA positive but sero negative woman, a minor reduction (observed efficacy of 31%; 95% CI < 0-54.9)¹⁸ in incident CIN lesions caused by the respective vaccine HPV type was observed while no effect in double HPV 16/18 – DNA positive sero positive women was found.¹⁹ Thus current HPV-VLP vaccines cannot be used to treat existing HPV infections and associated lesions.

From the established phase III trial performed so far, it may be concluded that there are no contra-indications for prophylactic vaccination²⁰ although use in pregnancy is not recommended and there is a debate on its use in patients with AIDS. Follow-up of vaccinated women who were HPV 16/18 DNA positive at the time of vaccination is recommended to monitor their infection and potential emergence of CIN lesions and on the other hand to evaluate potential long-term (positive or negative) effects of the prophylactic vaccination on the existing HPV infection.

Although non therapeutic, prophylactic vaccination could theoretically be beneficial to HPV 16 or HPV 18 DNA positive women by preventing infections with other types represented in the vaccine for with the woman is negative at baseline (e.g. HPV 18 in case of HPV 16 DNA positive women). It may also potentially prevent successive rounds of auto inoculation or

recurrent infections by sexual partner(s) which may decrease the extent and duration of viral infections and consequently reduce progression risk.

Who should be vaccinated?

In June 2006, the federal Advisory Committee on Immunization Practices (ACIP) issued the following recommendations.

1. Routine vaccination of females 11 to 12 years of age with three doses of HPV Vaccines.
2. The vaccination series can be started as young as 9 years of age.

The ACIP endorsed the goal of immunization before the onset of sexual activity but allowed for extended application to capture young woman not previously vaccinated. Therefore, vaccination is also recommended for females 13 to 26 years of age who have not been previously vaccinated (so called catch-up after a new vaccination programme has been instituted). Special circumstances will be encountered with vaccination of sexually active women.

The Society of Gynecologic Oncologists vaccine education resource panel offers the following guidance:

1. Vaccination should be offered to woman 9 to 26 years of age with epifocal or abnormal pap test results, genital warts, and positive test result for high risk HPV types because vaccination will protect against HPV types not already acquired. No data are available to indicate whether the vaccine will have a therapeutic effect, on existing cervical, vaginal or vulvar lesions.
2. Vaccination may be offered to immune suppressed women because of their high risk of persistent HPV infection. However no data support vaccine efficacy or safety in these women. Efficacy is less certain in this group but there should be no special safety issues because this is not a live virus vaccine. The pros and causes of vaccination should be carefully considered for women at risk for graft-versus-host disease because of the unknown effects of vaccine adjuvant in this group.
3. Vaccination during pregnancy should be avoided if possible. Early study results show that conception within 30 days of vaccination may be associated with a small increased risk of congenital abnormalities.
4. Vaccination during lactation is acceptable. Mother should be advised that the risk for respiratory illness in a breast feeding infant may increase within 30 days of the mothers vaccination.
5. In the setting of any moderate to severe acute illness, vaccination should be deferred until the illness subsides.
6. The pros and cons of vaccination should be carefully considered for any patient with a history of hyper sensitivity reaction or severe allergy reaction to yeast or any vaccine component.

Conclusion

Currently no contra-indication for prophylactic HPV vaccination has been recognized. Prophylactic vaccination for any women after sexarche could be applied, taken into consideration the possibility of pre-existing pre cancer

lesions that should be diagnosed and treated according to standard regimes. Continued active follow up of women who are infected with HPV at the time of vaccination or who were previously exposed to HPV is necessary to elucidate potential benefits prophylactic vaccination may confer to them. More research data need to be collected to allow determining correlating of vaccine efficacy in these women, which may include the viral load at time of vaccination.

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