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Age for HPV vaccination

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KEYWORDS

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Summary HPV vaccination of pre-pubescent girls will be effective for many girls. Vaccinating girls and women older than 12 years of age may accelerate the reduction in cervical cancer rates. Currently HPV vaccines are effective for at least 5 years in the prevention of HPV 16 and 18 associated precancerous lesions however the duration of vaccine protection is unknown. The need for booster shots must therefore be addressed with patients as unknown. Continued cervical cancer screening is necessary regardless of vaccination. Vaccination alone will not eliminate cervical cancer.

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Rationale

Historically, vaccination is a prophylactic measure to prevent fatal infectious diseases; and is dispensed when the person is not infected, before the fatal event, at a time when the person is at highest risk of exposure to the infectious disease. Thus, vaccines are typically prophylactic, not therapeutic. In contrast to the typical prophylactic vaccine, the HPV vaccine is designed to prevent a viral infection that may cause cervical cancer many years later. In addition to causing cervical cancer, the second most common cancer in women worldwide, HPV is closely linked to many other cancers including anogenital and oropharyngeal for which prophylactic vaccination may prove effective in future studies.

Current evidence based medicine

How are HPV infections detected?

Two standard laboratory methods have been used in epidemiology studies to identify HPV infection: HPV DNA detection and serum antibody detection. Type specific HPV DNA is identified in exfoliated cells sampled from the cervix or vagina by PCR consensus primers or occasionally performed after detection with a cocktail probe of multiple HPV types (Hybrid Capture[®] 2, Digene, Gaithersburg, MD). Seroprevalence is determined by ELISA to type specific HPV virus-like particles self-assembled in baculovirus manufacturing systems. Sero-epidemiology studies always indicate a lower prevalence than HPV DNA detection for three reasons [1]: (1) less than half of the epithelial HPV infections produce an antibody response, (2) if there will be a serologic response to a natural oncogenic HPV infection, it will occur many months after incident infection (8–12 months later) and usually after the concurrent HPV type specific DNA is no longer detectable, (3) antibody titers to type specific HPV infections can be lost after initial detection. The cumulative probability of losing the type specific antibody response within 3 years is almost 50% [2].

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What genders are infected by oncogenic HPV?

Approximately 90% of the cancers caused by oncogenic HPV affect women only; 2% of the cancers caused by oncogenic HPV affect men only; and 7% cause anal, oropharyngeal and oral cancers in both men and women. Clearly, majority of the fatal disease occurs in women. Genital wart manifestation of non-oncogenic HPV infections is much less common than cytologic manifestations of oncogenic HPV infections reported on Pap screening [3].

At what age are genital oncogenic HPV infections detected?

There is no one age at which all boys or girls are uninfected with oncogenic HPV types. Oncogenic HPV DNA has been reported in the epithelium of young girls and boys at an underlying prevalence between 3 and 10% [4–14]. Proposed, but unproven, transmission modes include vertical transmission during birth [5–7], genital skin to skin contact as well as sexual abuse in children [15]. In adolescence, the point prevalence of high risk HPV types peaks at 30–50% for young women in their second and third decades of life. This is mostly attributed to the onset of sexual exploration with one or more sexual partners, with up to 15% of the remaining infections not associated with penetrative penile intercourse.

The oncogenic HPV population prevalence in women drops to 15–20% for women 26–30 years of age, and 10–20% for women 31–35 years to an underlying population prevalence of 5–15% in later decades of life [16–19]. The cumulative prevalence rate to 50 years of age of oncogenic HPV infections approaches 80% [20–22].

Acquisition of high risk HPV parallels the prevalence statistics reported. Women under 25 years of age have the highest acquisition of high risk HPV at 4.5% per year, with a continuing infection rate of 1% per year for women older than 35 years [20]. At the same time, the risk of not clearing a high risk HPV infection increases with age. In women older than 30 years, 20% of their HPV 16 persistent infections and 15% of their HPV 18 persistent infections progress into CIN 3 lesions within 10 years [23].

The risk of HPV infection, whether from new exposures or auto-inoculated from prior exposure and being detected as incident or persistent infections, continues throughout a woman's lifetime. Past exposure to type specific HPV infections does not confer lifetime protection from future infection with the same HPV type [24].

What is the time from HPV infection to death due to cervical cancer?

Time from HPV infection to high grade precancerous dysplasia ranges from 6 months to decades, on average around 3 years [25]. Because CIN 2/3 triggers medical treatment, it is considered the surrogate clinical precancer marker for invasive cancer. Progression from CIN 2/3 to invasive cervical cancer has been described to take from 5 to 20 years [26].

In screened populations, cervical cancer has been reported, before 20 years of age [27], gradually increasing to a plateau level by the early 30s that does not decrease in the later years [28]. In unscreened populations, the incidence of cervical cancer continues to increase as a woman ages [29].

What determines whether the vaccine will be effective in a particular woman?

DNA negativity for the vaccine associated HPV types at the time of first vaccination is the sole determinant of vaccine efficacy for prevention of disease associated with those HPV types [30–36]. Complete vaccine efficacy for HPV 16 and 18 has been reported for both virgins and sexually active women 15–26 years old when the women are HPV DNA 16/18 negative at the time of vaccination. Vaccine efficacy in women younger than 15 years has not been established, but will be evaluated in upcoming studies.

Does vaccine immunogenicity determine vaccine efficacy?

HPV vaccine trials have established that both vaccines produce an immunologic response within weeks of complete vaccination, and are associated with 100% efficacy for 5 years at all titer responses [30,31,33,34]. Seroconversion is generated by HPV vaccination at any age in both genders. There is no immune correlation for efficacy to date. Vaccine induced immune titers to the specific HPV types are much higher than natural infection titers for 18 months of follow-up for both vaccines. Although each vaccine has a different profile of antibody response over the 5 years reported, the significance of this difference is unknown [37–39].

Do HPV vaccines offer protection for a woman's entire life?

This is unknown. Efficacy evidence of both HPV vaccines shows 100% protection from future disease caused by HPV 16 and 18 for at least 5 years in women negative for HPV 16 and 18 at the time of first vaccination. This is sufficient evidence to initiate vaccination implementation with concurrent surveillance programs. Duration of vaccine efficacy must be established to determine if, when, and for which HPV vaccine booster shots are necessary.

Do HPV vaccines clear current HPV infections or treat current CIN lesions?

No, both vaccines are entirely prophylactic. The HPV vaccines cannot cure current HPV infection [40], nor treat current CIN caused by vaccine associated HPV types [41].

Current recommendations

National regulatory agencies (e.g. FDA, EMEA,) approve commercial products based on safety and efficacy. Public health agencies recommending implementation policies for

vaccination (e.g. ACIP) include cost effectiveness in their deliberations. Gardasil™ has been approved in several countries by regulatory agencies including the FDA and EMEA for use in young women 9–26 years of age. Cervarix™ is currently under review by the FDA and has been approved by the EMEA for women 10–26 years of age. In Australia, Cervarix™ has been approved for women 10–45 years of age and there are approvals with no upper limit of age in several Asian countries. A few countries have approved Gardasil™ and Cervarix™ for use in boys 9–15 years of age.

Directions of future research

The safety and efficacy of co-administration of the HPV vaccines with other childhood and adolescent vaccines need to be established. Safety database reporting systems must be regionally in place to understand the more rare complications from HPV vaccination that could be reported in future years.

Randomized controlled trials provide optimal vaccine efficacy results. Population based trials, such as the NCI-sponsored Costa Rican vaccination trial and the long-term Nordic countries' follow-up studies will provide estimates of vaccine effectiveness in the prevention of cancer. In addition, the 80,000 girls and boys enrolled from the Nordic countries between the age of 12–15 years provide vaccine safety surveillance for rare adverse events to be documented should they occur. Phase IV trials will necessarily broaden the age and gender of populations studied, as well as the underlying co-morbid health states of vaccine recipients (e.g. diabetes, malaria, HIV infection, chronic diseases, etc.).

Implementation research needs to consider vaccination dosage interruptions for non-compliance or intervening health events such as abnormal Paps, pregnancy, lactation, or other disease treatments.

Population based public health research will evaluate the effectiveness of varying the number of initial vaccine doses in the context of the need for boosters and original age at vaccination.

The number and frequency of booster vaccines necessary after the initial series will be important to establish lifetime risk control. The logistics and expense for repeated boosters needs to be addressed scientifically, sociologically, and economically.

The delivery of the vaccine requires cold chain maintenance. Other potential routes of administration (intranasal, transgenic food carriers, topical applications) should be explored.

Clinical perspectives

- (1) Vaccinating pre-pubescent girls will be effective for many girls, and vaccinating women older than 12 years may accelerate the reduction in cervical cancer rates.
- (2) The HPV vaccines are effective for at least 5 years in the prevention of HPV 16 and 18 associated precancerous lesions. Duration of vaccine protection is unknown. The need for booster shots must be addressed with patients as unknown.

- (3) Continued cervical cancer screening is necessary regardless of vaccination. Vaccination alone will not eliminate cervical cancer.

Phase IV studies

As the phase IV studies in older women are published showing immunogenicity, efficacy and safety, as vaccine effectiveness studies of women 18 and older are continued in Costa Rica, and as community randomized trials are undertaken in Finland immunizing 12–15-year-old girls and boys establishing vaccine effectiveness against the development of cancer including duration of vaccine efficacy, we will gain data to understand the differential benefit of vaccinating different ages of women and men. Until then, natural history data and modeling data are useful surrogates to guide recommendations.

Modeling data show that the younger the age of vaccination, the more cervical cancers will be prevented (Fig. 1) [42]. Equally important is the time lapse before reducing the incident cervical cancers. It is estimated to take 100 years to maximally reduce cervical cancer incidence when vaccinating only 12-year-old girls. Modeling data clearly show that it is the duration of vaccine efficacy, not the age of vaccination, which drives the cost effectiveness of cervical cancer prevention in populations [43].

The serendipitous benefit in preventing other HPV associated cancers throughout the body will take decades to prove, but appears likely from early data [44] using surrogate precursor markers for other anogenital sites.

Expert opinion

HPV vaccines have been shown through clinical trials, leading to approval by national regulatory boards, to prevent infection and lesions of vaccine specific HPV types in women 15–26 years of age, who are not currently infected with the vaccine specific HPV types at the time of vaccination.

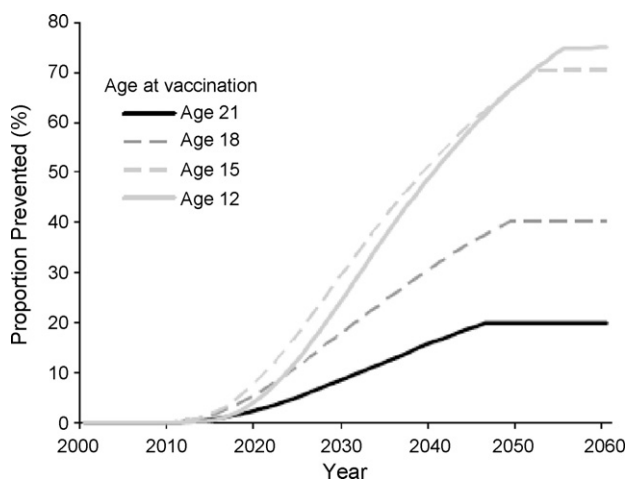


Fig. 1 Assuming 70% population coverage, the proportion of HPV 16 cervical cancers prevented by starting female vaccination at different ages. Model assumptions include 100% vaccine efficacy and lifetime protection with no catch up ages included. Source: French, et al. [42].

Because of the complete set of immunogenicity, safety and efficacy data, public health dollars may be spent to design and implement programs to immunize this group of women.

Immunobridging and safety data exist for females as young as nine years of age. Vaccination of young girls offers possible protection prior to the average age of peak HPV acquisition, but may require boosting to maintain protection throughout the period of acquisition, if started too young. Public health officials have assumed lifelong protection (*no further costs*) from both HPV vaccines and have implemented publicly funded programs to immunize young girls.

Similarly, immunobridging and safety data in women as old as 55 years are also supported by a similar efficacy for those women who are HPV DNA negative for the vaccine specific types at the time of vaccination. Because *the study methodologies are too limited* to determine whether the presence of antibody titers (either naturally induced or vaccine induced) prevents future type specific infections (either novel or by auto-inoculation of latent episomally active field infections), *we are unable to quantify the full benefit of vaccinating women* with prior type specific infections, but not infected at the time of vaccination. HPV vaccination is safe and may possibly offer a great benefit against future anogenital cancers [45,46]. Therefore, at this time, women older than 26 years are entitled to be offered the option of vaccination potentially at their own cost, as public health dollars for population coverage are rationed first to the youngest girls.

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