
HPV VACCINES FOR THE PREVENTION OF CERVICAL CANCER: POTENTIAL IMPACT IN PUBLIC HEALTH

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In many populations, Human Papillomavirus (HPV) infections are common in the adolescent and young age groups, translating their sexual behavior patterns. Most of the infections will clear spontaneously. Persistent carriers of HPV DNA are at high risk of developing intraepithelial cervical lesions and a fraction of them (perhaps 1% of the originally infected women) will develop overt invasive cancer, particularly in the absence of proper screening.

Initial trials with HPV 16 prophylactic vaccines have shown good tolerance, high response rate and high protection against persistent HPV 16 infections. Advanced Phase II and III trials with a bivalent vaccine (HPV 16 and 18) and a quadrivalent vaccine (HPV 6,11, 16 and 18) are currently being published. HPV 16 and 18 are jointly responsible for 70% of the cases of invasive cervical cancer worldwide with small geographical variability. Key results to date can be summarized as follows: Vaccines based on the HPV L1 Virus-like particles (VLP) are highly immunogenic with virtually 100% responses under trial conditions. Antibody titers are several fold higher than titers generated following spontaneous infections and the duration of the high titers has been demonstrated for a follow up time of 4 to 5 years. These vaccines are safe, they generate moderate local and systemic reactions but no attrition has been recorded in the trials due to secondary effects. No evidence of other unwanted reactions has been observed. These vaccines are highly efficacious with demonstrated protection against HPV type specific infection, persistent infection, and related CIN 2/3 lesions in the range of 95 to 100%. The latter were the endpoints set up by the major international regulatory agencies to claim protection against invasive cervical cancer. Results also indicate that these vaccines are protective against the preinvasive stages of the neoplastic lesions in vulva, vagina and against external genital warts (by the vaccine including HPV 6 and 11). From trials of the bivalent vaccine, evidence is being published indicating strong protection against HPV 45 infections and partial protection against HPV 31. The expected impact of currently available HPV vaccines has been estimated as a potential reduction of 70% of invasive cancer, 60% of the high grade lesions (HSIL), 25% of the low grade lesions (LSIL) and 20% of the uncertain findings (ASCUS) among vaccinated women.

Essential questions under active research include the assessment of the duration of protection and the establishment of good correlates of protection (such as thresholds for protection of the antibody titers). These studies should be of great value to

understand the optimal age at vaccination and the need of booster doses later in life. The value of the adjuvants is an issue of considerable interest. Continuous monitoring of long term safety is on going in the large Phase IV trials and demonstration projects. The importance of the results on cross-protection afforded by the bivalent vaccine is being carefully evaluated. Current trials should also provide essential information as to the value of such vaccines in women of other age groups, among males and among persons in special situations such as HIV positives and patients under therapeutic immunosuppression.

It can be anticipated that the future of cervical cancer prevention will include universal vaccination of adolescents followed by a combination of HPV testing and cytological examination. Given the current evidence it would be justified to use HPV tests as the primary form of screening with cytology / colposcopy as the triage method in case of persistency of a high risk HPV type. In developing countries, where regular screening has proven to be of limited use, perhaps a booster dose of HPV vaccines may be considered. HPV vaccines are opening a new frontier in the options for cervical cancer prevention.