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REVIEW ARTICLE

Human Papilloma Virus Vaccines: Implications for use in developing world

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Abstract:
Cervical cancer may be substantially prevented by human papillomavirus (HPV) vaccination. The two most common oncogenic HPV types causing 70% of all cervical cancers are represented in the vaccines by synthetic virus-like particles to the L1 protein of HPV 16 and 18. The virus-like particles and adjuvant systems promote long-term antibody response. Invasive cervical cancer (ICC) is the second most common cancer among women worldwide. Approximately 85% of the disease burden is seen in women in developing nations. India with its highest share of global burden of cervical cancer has to implement a population based cervical cancer control program to reduce the number of deaths. Development of effective vaccines against human papillomavirus, the necessary cause of cervical cancer, has introduced a fresh lease of life to the cervical cancer control strategies. Vaccination programs targeted to a large age range of women will achieve cervical cancer reductions several decades from now.

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Introduction

Persistent infection with human papillomavirus (HPV) is a necessary cause of cervical cancer and is one of the most common sexually transmitted infections (1-3). Most HPV infections never progress to cancer, but the small fraction of HPV infections that do become cervical cancer. HPV infections are common and, most often but not necessarily, are associated with sexual activity. 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 organised, decreasing the baseline rate of HPV infection should lead to population-based reductions in cervical cancer after several decades of widespread female vaccination.

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 (4). Gardasil is effective against HPV-16, 18 and 31, three common squamous cell cancer-causing types (5). In addition, Gardasil is effective against HPV-6 and -11, causes of genital warts. 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 (6, 7). This review focuses on recently published or presented data regarding epidemiology of human papillomavirus and cervical

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cancer, efficacy, immune response, and safety of HPV vaccines, cross-protection against HPV types beyond HPV-16/18 and implications for use in developing nations.

Burden of cervical cancer

Invasive cervical cancer (ICC) is the second most common cancer among women worldwide, with an estimated incidence of 493,000 new cases and mortality of 274,000 each year (8, 9, 10). Approximately 85% of the disease burden is seen in women in developing nations (8, 9). The burden of cervical cancer in India is enormous accounting for about 20 per cent of all cancer related deaths in women and is the number one cause of death in middle aged Indian women (8). In India, there are an estimated 132,000 new cases and 74,000 deaths each year (8).

Persistent infection with carcinogenic human papillomavirus (HPV) types has been recognized as a necessary cause of cervical cancer (11-13). At present, there are about 100 identified genotypes (types) of human papillomavirus (HPV), of which about 40 are genital HPV types that invade the genital organs (14). Genital HPV types are classified into high risk types commonly associated with cervical cancer and low-risk types known causative pathogens of condyloma acuminatum. HPV types 16 /18/31/33/35/39/45/51/52/56/58/66/68 are classified as high-risk and 6/11/40/42/43/44/54/61/72 as low-risk types (13, 14). HPV types 16 and 18 cause about 70% of all cases of invasive cervical cancer worldwide, with type 16 having the greatest oncogenic potential (13, 14). The distribution of HPV types varies among geographical regions, but the dominant oncogenic type in all regions is HPV-16. HPV types-16, -18, -31, -33, and -45 are responsible for 90% of Invasive cervical cancer in India (15).

The HPV vaccines

Currently, 2 HPV vaccines are available and widely marketed internationally. Using recombinant technology, both are prepared from purified L1 structural proteins that self assemble to form HPV type-specific empty shells or virus-like particles (VLPs). Neither vaccine contains live biological products or viral DNA, so they are non-infectious. HPV vaccines are designed for prophylactic use only; they do not clear existing HPV infection or treat HPV-related disease. Cervarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) and Gardasil (Merck, Whitehouse station, 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. 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 adjuvant systems are different for each vaccine. The adjuvant system for Gardasil contains aluminum hydroxyphosphate sulfate system. Cervarix contains a proprietary ASO4 adjuvant system comprising monophosphoryl lipid A (MPL) absorbed upon aluminium hydroxide. Recognizing increased complexity of infectious diseases being prevented, the ASO4 adjuvant was developed to provide innovative ways to control the quality and/or quantity of vaccine antigen-specific immune responses (16, 17).

The efficacy of the AS04-adjuvanted HPV 16/18 vaccine has been evaluated in a randomized, double blind, placebo-controlled, phase II trial and in the large (n = 18 644) phase III PATRICIA trial (HPV-008). The initial phase-2 trial (study HPV-001) and its extension phase (study HPV-007) included only women who were DNA-negative for oncogenic HPV-types, seronegative for HPV-16 and HPV-18, and had normal cytology. Following vaccination, women in study HPV-007 were evaluated for upto 6.4 years after the first vaccine dose. The efficacy of Cervarix against CIN2+ lesions associated with HPV-16 and HPV-18 was 100% (95% CI: 51.3-100) (6).

The final results of study HPV-008 have recently been presented and published (4). Vaccine efficacy was analyzed on average 34.9 months after administration of the third vaccine dose in an according to protocol for efficacy (ATP-E) cohort of women , who, in addition to receiving all three vaccine doses, were seronegative at baseline and DNA-negative at months 0 and 6 for the type analyzed. This population included women with normal cytology or low-grade lesions at baseline. The efficacy of Cervarix against HPV-16 and/or HPV-18-associated CIN2+ lesions in the primary analysis was

92.9% (96.1% CI: 79.9-98.3) and 98.1% when causal HPV type was assigned to lesions containing multiple HPV types. The high HPV-16/18 vaccine efficacy was also confirmed in CIN3+ lesions (100%; 96.1% CI: 64.7-100) (4).

At this time, Cervarix and Gardasil show durations of efficacy lasting 6.4 and 5 years, respectively, from the Phase II trial data, with Cervarix trials still ongoing (6). Gardasil Phase II trials were stopped at 5 years (7).

Cross-protection

Human papillomavirus (HPV)-16 and -18 are responsible for approximately 70% of invasive cervical cancers worldwide. Other oncogenic HPV types account for almost all the remainder. Importantly, HPV-31, -33 and -45 account for approximately 12% (13). HPV-18 and -45, along with HPV-16, are found in over 90% of endocervical adenocarcinomas. HPV-45 is the third most frequent HPV type in cervical carcinoma and adenocarcinoma (13).

The AS04-adjuvanted vaccine Cervarix was developed against HPV-16 and -18 focusing on preventing cervical cancer by inducing durable protection against new infection. In clinical trials, it shows evidence of cross-protection against other important oncogenic HPV types using a range of clinicopathological and virological endpoints. For Cervarix, cross-protective efficacy was seen against species related to both HPV-16 and HPV-18; individual type efficacy in the HPV-008 study was mainly driven by efficacy against HPV-31, -33, and -45 (4). Although efficacy against HPV-45 did not reach significance in the ATP-E cohort, a consistently high efficacy was observed across virological and clinical endpoints, reaching statistical significance in the broadest population, the TVC (vaccine efficacy of 100%, p=0.0312). 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 (5).

Clinically, the protection offered by Cervarix against vaccine and Nonvaccine types resulted in a substantial reduction of the numbers of colposcopy referrals and cervical excision procedures in both the TVC and TVC-naïve (4).

In summary, cross-protective efficacy of Cervarix is mainly driven by efficacy against the Nonvaccine HPV-31, -33, and -45. This could represent 11%-16% additional protection against cervical cancer, in addition to the 70% of cervical cancers that could be prevented by a vaccine offering protection against HPV-16/18 (4).

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. Vaccine-induced antibody responses for Cervarix have been measured primarily by conventional ELISA or PBNA, whereas for Gardasil these were measured by competitive Luminex-based immunoassay.

The neutralizing antibody titers to HPV-16 and -18 have been measured in the same assay in a head-to-head trial (Study HPV-010) of Cervarix and Gardasil in order to remove the confusion of different proprietary measurement systems (18). In the ATP subgroup, Cervarix produced significantly higher antibody titers for HPV-16 than did Gardasil (2.3-4.8 fold higher) at month 7, the peak titers; and even greater fold higher for HPV-18 (6.8-9.1 fold higher). These significantly higher neutralizing antibody titers in the serum were associated with higher positivity rates for anti- HPV-16 and -18 neutralizing antibodies in cervicovaginal secretions (CVS). Differences in immunological responses between both vaccines at month 7 were also characterized by a stronger cellular response and higher circulating HPV-16 and -18 specific memory B-cell and T-cell frequencies for Cervarix compared with Gardasil (18).

In a phase-2b arm of study HPV-007, a sub cohort of 304 women was followed for upto 7.3 years after first vaccination. At this point, 100% women remained seropositive for anti-HPV-16 and -18 antibodies. Antibody levels remained high and well above those observed after natural infection for HPV-16 and -18. This arm of the study is ongoing (19).

Mathematical modeling predicts that, for all antigens contained in the vaccine, Cervarix provides antibody levels above those associated with natural HPV infection for over 20 years (20). Protection with

Cervarix could therefore remain for at least 20 years and may be life-long.

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. In clinical trials, mild and transient local reactions at the site of injection (erythema, pain or swelling) were 10–20% more frequent among those who received the HPV vaccines than in their respective control groups, but no systemic adverse reactions assessed to be causally associated with the HPV immunization have been reported (4, 21).

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 (4, 21).

Data on the safety of HPV vaccination in pregnancy are limited, and HPV vaccination of pregnant women should be avoided. However, no adverse events causally associated with the vaccine have been observed in mothers or their offspring following inadvertent vaccination during pregnancy (4).

Conclusion

Two prophylactic HPV vaccines are licensed in more than 100 countries, and immunization programs have been widely implemented. Cervarix has demonstrated type-specific protection against the five most frequent cancer-causing HPV types (16, 18, 31, 33, and 45) that are responsible for 82% of invasive cervical cancer globally (1, 4). The protection offered by Cervarix against Nonvaccine types should therefore allow for additional protection preventing 11%-16% more cervical cancer (4). Protection against HPV-45 is of particular clinical relevance because HPV-45 is the third most common oncogenic type and plays a major role in the development of adenocarcinomas of the cervix (22). Adenocarcinomas of the cervix frequently evades the usual screening measures and have a poor prognosis than squamous cell carcinomas.

Vaccination with Cervarix has been observed to induce a high-level antibody response against both HPV-16 and HPV-18 that persists for over 7.3 years (19). 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. New and ongoing studies will provide important data on the duration of vaccine-induced protection against oncogenic HPV types, and the populations that will derive most benefit from vaccination.

A program based on vaccinating a target population appears to be logistically simpler than the screening based approach in developing countries. Introduction of HPV vaccine in a country with existing cytology-based screening programme is likely to reduce substantially the number of abnormal Pap smears, number of follow ups due to low grade abnormalities on cytology or histology and number of treatments for cervical precancers. This will not only reduce the logistics and fiscal burden on the programme but will also spare large number of women from unnecessary anxiety related to abnormal screening test results.

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