Evaluation of the current Human Papillomavirus (HPV) vaccines: comparative analysis based on immunogenicity, efficacy, safety, and cost.

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Abstract:

Cervical cancer remains the second leading cause of cancer related deaths amongst women worldwide. A necessary etiological factor for cervical cancers’ pathogenesis is the Human Papillomavirus (HPV). The discovery of the two HPV prophylactic vaccines was a ground-breaking they were able to prevent HPV infections with a very high efficiency level. The vaccine formulation is based on virus-like particles (VLPs) containing recombinant L1 capsid of the HPV. In this review, the two vaccines were compared in detail based on criteria of immunogenicity, efficacy, safety, cost and coverage. The primary objective for the comparative analysis was to enable policymakers depict the better vaccine as well as reveal areas that needed more research and or improvement. Based on the aforementioned criteria, Cervarix was selected as the better vaccine and recommendations on how to improve it were suggested.

Keywords: VLPs: virus-like particles; CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus, GMT: geometric mean titers; RB: retinoblastoma, P53: protein 53; E6, E7: early protein 6 and 7.

Introduction:

Cervical cancer is the second most common cause of cancer-related deaths in women1. With over 500,000 deaths per year2, numerous studies have been conducted to analyze the tumor pathogenesis and determine the etiological factors in order to develop curative treatments. So far, Human Papilloma Virus (HPV) is implicated as the major etiological factor for cervical cancer, as well as for other anogenital cancers (vulva, vaginal, penile, and anal)3. There are five significant oncogenic papillomavirus
strains associated with cervical cancer carcinogenesis: 16, 18, 33, 45, 52 and 58, and they are known as the high risk strains. While strains 16 and 18 are present in 70% of cervical cancer, the other three are present in about 20% of the cervical cancer cases. Papillomavirus is also known to cause non-malignant genital warts (a widely known STD), which is a condition propagated by the low risk papillomavirus strains: 6 and 11.

The induction of cervical cancer by papillomavirus is similar to the induction most cancers in that targeted cells are transformed and immortalized (i.e. proliferate with no regulation). The papillomavirus early proteins (E6 and E7) facilitate cellular transformation and immortalization of target cells by integrating into the hosts’ DNA, which is a process that usually results in the total loss in function of the hosts’ tumor suppressor proteins, pRB and p53. Studies have shown however, that only the E6 and E7 proteins of the high-risk papilloma strains lead to the aforementioned process of integration.

Initial infection with papillomavirus causes inconspicuous squamous epithelial lesions that are not life-threatening and are in most cases subdued by the immune cells. In the event that the immune cells are unable to completely clear these lesions, they could progress into high-grade pre-cancerous lesions called Cervical intraepithelial neoplasia (CIN), and then to adenocarcinoma or squamous-cell carcinoma of the cervix.

The papillomavirus strains causing cervical cancers (and most other anogenital cancers) are mainly transmitted through sexual intercourse and thus predominantly affects sexually active females. These strains are known to reside in and are transmitted from the mucosal regions of the genitals.

Papanicolaou smear and cytology screening are some of the gynecological measures for depicting degree of papillomavirus infection in women before referrals (if necessary) for colposcopy and other surgical interventions are made. Pap smear screening since its discovery in 1970’s have reduced cervical cancer incidence by half, however this screening technique could only detect a pre-existing
papillomavirus infection. With the growing transmission rate of the virus, there was a strong incentive to formulate a prophylactic vaccine or drug that will prevent the infection from occurring, drastically reducing future cervical cases.

The initiative for vaccine development ignited when a strong association was established between papillomavirus and cervical cancer. Gardasil (Merck Frosst) is a quadrivalent vaccine that contains live attenuated forms of four papillomavirus strains: 16, 18, 6, and 11. Strains 16 and 18 are the most significant oncogenic papillomavirus strains, while 6 and 11 are the most important strains causing genital warts. A few years after, Cervarix (GlaxoSmithKline), a bivalent vaccines containing live attenuated strains of types 16, 18 was approved. These two prophylactic vaccines are virus-like particles (VLPs) with recombinant L1- capsids of the specific HPV serotypes they contain. Gardasil has VLPs produced from yeast and is adjuvanated with amorphous aluminum hydroxyphosphate sulfate while Cervarix has VLPs produced Baculovirus expression vector system and is adjuvanated with Adjuvant system 04. Both vaccines have been highly successful in preventing pre-cancerous lesions as evidenced from results of double blind trials conducted globally, as a result have earned the title as the first cancer preventing vaccines. In this review, both vaccines would be evaluated based on efficacy, immunogenicity, safety, and cost. Comparative analysis would enable policy makers to determine the most cost-effective vaccine to use in major HPV vaccination programs: the vaccine that is the safest and confers the longest duration of protection.

**Vaccine immunogenicity:**

Unlike in most vaccines where markers of immunogenicity levels are established, the serological correlates of immunity for the HPV prophylactic vaccines is unknown i.e. the minimum antibody count required for both natural and vaccine-induced immunity is unknown. Thus, most experimenters rely on
number of neutralizing antibody titers and duration of antibody sustenance (long-term protection) as default immunogenicity markers. Large scale immunogenicity trials conducted by PATRICIA/FUTUREI/10,11 as well other major studies13, 14 have shown that Cervarix produces superior geometric mean antibody titers (GMTs) to Gardasil. An explanation to this is attributed to the highly potent adjuvant ASO4 contained in Cervarix9. Other studies have shown that higher level of titers are induced in women vaccinated by both Gardasil and Cervarix than it does in men, which could suggest higher efficacy of vaccine in women15. Furthermore findings from Clark et.al.16 and Rochengue et.al17 amongst other studies indicate that the trend of GMT level remain consistent irrespective of ethnical, cultural, or racial differences of vaccine candidates. However, there has still been no established link between GMT levels and vaccine efficacy i.e. preventing infections and precancerous lesions.

Duration of vaccine protection is another hallmark of immunogenicity. Both vaccines show similar duration of protection of about 4.5 years for Cervarix and 6 years for Gardasil17. Duration of protection for both vaccines is perceived to be relatively transient as it takes 11-20 years from the time of HPV infection to time of invasive cancer progression12.

Vaccine efficacy:

Due to the significant lag (10-20 years) between time of HPV infection and diagnosis of cervical cancer, WHO has declared the outcome of HPV infections as not only presence of invasive cancer, but also persistent HPV infections (6 months or longer) and CIN infections9. Consequently, HPV vaccine primary efficacy endpoints are demonstrated by the rate of reduction of pre-cancerous lesions as well as HPV persistent infections. Both vaccines have shown high efficacy levels in preventing intra-epithelial lesions and persistent infections of the HPV type they contain. Gardasil demonstrates up to 96% efficacy against -16/18 CIN infections, 100% efficacy in vulva, vaginal and genital warts related intra-epithelial lesions, as
well as condylomata accuminata and low grade CIN by 6/11 types. Cervarix is also about 100% efficacious in protecting against 16/18 CIN infections. As the prophylactic vaccines are preventive and not therapeutic, it is important to understand that protection from the aforementioned persistent infections is most effective when the vaccination candidate is either HPV DNA negative or seronegative for the HPV serotypes covered by each individual vaccine.

A secondary endpoint of vaccine efficacy is cross-protection. Cross-protection is this context is defined as vaccine protection against other papillomavirus oncogenic strains not present in the vaccine. Because the less prevalent oncogenic strains account for 20% of cervical cancer induction, protection with one or more of these strains is a hallmark of excellent efficacy. Gardasil is known to induce protection primarily against the viral strains it contains with a slight cross protect against to one of three less prevalent oncogenic strains. However, Cervarix cross-protects against type all of the five oncogenic types, although with a greater affinity for the specific strains it contains. The basis of Cervarix’s extensive cross-protection is explained by three factors. It possesses a modified VLP which allows a less specific antibody-antigen interaction that increases its antigen recognition to a wider array of HPV serotypes. Also, it contains a highly immunogenic adjuvant that generates high level of antibody titers, which is a factor that is proposed to positively influence cross-protection. Lastly it has been proposed that the high levels of titers produced by Cervarix vaccine increasing the level of contact and recognition of other oncogenic strains of the papillomavirus.

Another hallmark of efficacy is indicated by the reduction in colposcopy and other tumor-related surgical excision interventions by vaccinated candidates. Precancerous lesions produced by CIN infections are the lesions often removed by surgery, thus a reduction in these excision procedures indicates that the vaccine slows or inhibits the progression of the viral infection to precancerous cell formation. Major HPV vaccination clinical trials including the experiment conducted by Alexander et.al. show that both vaccines where highly efficacious in preventing the induction of CIN lesions in patients
with already existing persistent papillomavirus infections. It is this prevention of CIN pathogenesis that has led to a significant decrease of the need for surgical excision of viral-induced lesion\textsuperscript{10}.

Lastly current data have shown that the HPV prophylactic vaccines are significantly efficacious against pre-existing HPV infections. The basis of the vaccine design is mimicry of HPV L1 capsid. The recombinant L1 capsid of the VLPs have shown to induce most effective immune response in HPV naïve individuals (HPV DNA negative or seronegative) and induces a negligible (if at all) response in HPV DNA positive individuals. However findings from a major HPV trials conducted by Paavonne et. al.\textsuperscript{11} show that both vaccines (especially Cervarix) are significantly effective in protecting individuals with previous or concurrent HPV infections. In this trial, the vaccines where able to prevent CIN2+ or worse infection by any of the high risk serotypes, however, vaccines protected most effectively against precancerous lesion by 16/18 serotypes\textsuperscript{11}.

Criteria for vaccine efficacy include protection against CIN lesions, cross-protection, reduction in surgical excision, and both vaccines were able to satisfy all criteria, although with different levels of effectiveness.

**Vaccine safety**

Safety is a key pre-licensure consideration with any vaccine formulation. Both prophylactic vaccines have excellent safety profiles by the CDC\textsuperscript{15}. Trials conducted with these vaccines record very few drop-outs due to vaccine adverse effects. Most common adverse effects observed from vaccination include mild to moderate pain and erythema\textsuperscript{18}, fever, diarrhea, vomiting, myalgia, and allergic reactions\textsuperscript{17}. Cervarix, however has shown to induce higher levels of adverse reactions (especially at injection site) most probably attributed to its highly immunogenic ASO4 adjuvant. Gardasil is prohibited for use by pregnant women for unclear reasons. It is speculated that reasons could be associated with the make-up
of the Gardasil’s adjuvant\textsuperscript{16}. In contrast, data show no relevant difference in pregnancy outcomes of the women vaccinated with Cervarix and women vaccinated with a saline placebo in Cervarix trials\textsuperscript{15}.

**Period of vaccine administration**

The HPV prophylactic vaccines are engineered to be most effective in HPV DNA negative and seronegative individuals (HPV naïve individuals). As papilloma infections are contracted via sexual interactions, the seronegative or DNA negative individuals are usually the virgins or sexually inactive people, that is, individuals mostly between the ages of 13-20\textsuperscript{19}. Also, as not all sexually active individuals contract the virus, there are still older individuals that are DNA negative for the virus that should be vaccinated in order to prevent future infection. The seropositive or HPV DNA positive individuals could also receive vaccination, however, vaccine protection within this group is significantly diminished. Cervarix is approved for use between women of ages 15-45, while Gardasil is approved for women of ages 20-45\textsuperscript{20}.

**Cost**

Gardasil, $120 per dose ($360 for 3 doses), is slightly more expensive than Cervarix, $100 per dose ($300 for 3 doses). Both vaccines are a cheaper alternative compared to the Pap smear screening technique that cost upwards $500 per screening procedure. It is hypothesized that Gardasil (quadrivalent) is more expensive because it contains more strain of papillomavirus than does Cervarix (bivalent)\textsuperscript{19}. Some scientist argue that Gardasil is not justified to be more expensive solely for its quadrivalence, as Cervarix though bivalent, is more efficacious against HPV infections, provides higher antibody titers, and confers cross protection\textsuperscript{19}. Other scientist argue that the HPV vaccines are relatively expensive as compared to other regular vaccine and this high cost, have influenced the HPV vaccine availability in developing countries. It is important that HPV vaccines are more accessible to developing countries (areas with high incidences of HPV infection) if the campaign to eradicate cervical cancer is to be achieved.
Conclusion

The two prophylactic vaccines were evaluated in this paper based on their level of immunogenicity, efficacy, safety, periods of administration, and cost. It was found that while both vaccines are extremely effective in all categories, Cervarix seems to be the better vaccine. Cervarix is chosen as it produces higher level of antibody titers, proffers cross-protection against more oncogenic papilloma strains, confers the longest duration of protection and is the cheaper of the two vaccines.

References


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