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Review Article

HPV vaccine: Current status and future directions

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ABSTRACT

HPV Vaccine was introduced to prevent cervical cancer known to be caused by infection with one or more of the high risk subtypes of the Human papilloma virus (HPV). Since introduction, trials have proven its efficacy in preventing Cervical intraepithelial neoplasia (CIN) beyond doubt and its effectiveness in preventing cervical cancer though presumptive is reasonably certain as per mathematical modelling. It also prevents other HPV related anogenital and oropharyngeal malignancies in both sexes. HPV vaccines have courted many controversies related to its efficacy, safety, ideal age of vaccination, use in HPV infected individuals and use in males. The currently available vaccines are based on L1 Viral like particles (VLP) and hence highly species specific, thermolabile, costly and are purely prophylactic. The quest for a cheaper, thermostable and broad spectrum vaccine has led to many newer prophylactic vaccines. Therapeutic vaccines were born out of the inescapable necessity considering high HPV related morbidity projected in the non HPV naïve population. Therapeutic vaccines would immediately reduce this burden and also help in the management of HPV related cancers alone or as part of combination strategies. Ongoing research is aimed at a total control over HPV related malignancies in the near future.

Introduction

HPV (Human Papilloma Virus) has its presence in about 5.2% of cancers in the world, and is proven to cause cervical, anogenital and head and neck cancers.[1] HPV was recognized as a cause of cervical cancer as early as 1992 and almost all cervical malignancies demonstrated oncogenic strains of HPV DNA.[2] While the organized screening programs has brought down the incidence of cancer cervix and associated mortality in the developed world, the lack of the same has increased the burden of the disease in countries like India. Lack of adequate resources and infrastructure are likely to keep cervical screening programs a distant dream in resource starved nations, alternate strategies are needed to reduce the cervical cancer burden in these nations. The recent prophylactic HPV vaccines aimed at preventing cervical cancer and its precursors has thrown in an opportunity for countries like India

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to control this epidemic.[3] Human papilloma Virus (HPV) is a non – enveloped double stranded DNA virus with a genome of 8000 base pairs encoding two protein types – 'Late proteins' L_1 and L_2 which are the structural components of viral capsid and are involved in packaging of the virus, and the 'Early proteins' $E_{1,2,4,5,6,7}$which regulate the replication of viral DNA. While the early proteins are expressed throughout the life cycle of the virus, the late proteins are expressed only during the initial stages of infection fading away later.[4] There are more than 170 different HPV types identified of which 40 are purely mucosal subtypes that includes the 15 high risk oncogenic types[5] (Table 1). The maximum number of HPV infections occur during the early years. Most HPV infections, however are transient and are spontaneously cleared by the immune system of the host except in susceptible individuals and in immunocompromised, when they persist and lead to preinvasive and invasive lesions of the genital tract.[6] The two currently available vaccines against HPV are both prophylactic vaccines meant for HPV naïve individuals – The bivalent vaccine (Cervarix) against HPV 16 & 18 and the quadrivalent vaccine (Gardasil) effective against HPV 16, 18, 6 and 11. The quest for newer vaccines continues with the aim of making it more affordable, more thermostable, more coverage towards larger number of strains and for therapeutic use too.

The vaccine

These vaccines are produced by recombinant DNA technology by incorporating L_1 capsid gene of HPV 16 and 18 into a host cell (Baculovirus/Yeast) which replicates the L_1 proteins which then self-assemble into viral like particles (VLP) or empty viral shells similar in size and shape to HPV viron but non infective and non-oncogenic. The VLP's are mixed with a suitable adjuvant to promote immunogenicity.[3,4] Though the vaccine is species specific and the protection against HPV is limited to the two high risk oncogenetic strains interestingly there is some augmented protection exhibited by the vaccine on account of cross reactivity and the specific adjuvant used. HPV 16 (A9 Species) is phylogenetically related to HPV strains 31, 33, 52, and 58 and HPV 18 (A-7 species) to HPV strain 45 thus providing some protection against these non-vaccine strains too and increasing protection.[7]

Immunogenicity of HPV vaccines

Though HPV infections are very common, they are cleared through an immune response mounted by the body. However natural infections produce only transient local immunity at the level of basal keratinocytes. As the viral capsid and proteins do not reach beyond the basement membrane and do not incite systemic humoral immunity they fail to prevent reinfection with the same species or infection with a different HPV species.[4,8] Prophylactic L_1 based VLP HPV vaccines induce much stronger immunogenicity with a long lasting and effective humoral immunity thus offering prolonged and effective protection from HPV.[8] Unfortunately the vaccines are highly type specific thus narrowing the protection only to the target species.[9]

Drawbacks of current vaccines

Limited species coverage

The L_1 protein being highly type specific, the protection against HPV infection is only against the vaccine strains (HPV 16, 18 in case of the bivalent and HPV 16, 18, 6, 11 in case of the quadrivalent vaccine) with some happenstance protection against a few related species as discussed earlier. Though the vaccine protects against a vast majority of HPV infections (70–80%) the remaining strains still pose the danger of HPV related disease even after vaccination.[7,9]

Absence of therapeutic role

Both the presently available vaccines are L_1 based VLP vaccines which induce only humoral immunity, has only a prophylactic effect against HPV infections and hence effective only in HPV naïve individuals. L_1 proteins being structural capsid proteins involved in packaging of the virus are not expressed once infection is established in the mucosa or after infection becomes systemic and hence L_1 based vaccines have no therapeutic effect. A therapeutic vaccine should target oncogenetic proteins that are expressed throughout the life-cycle of the virus (E6, 7 proteins) and should be capable of inciting cell mediated immunity.[10]

Cost and affordability

L_1 protein based vaccines are highly species specific and the only way to increase the coverage is to produce vaccine separately against each oncogenic species thus increasing the cost of production especially when one relies on the assembly of viral like particles for vaccine production. The addition of suitable adjuvant to enhance the immunogenicity not only increases the cost of production but also makes the vaccine thermolabile thus necessitating an efficient cold chain further adding storage and delivery costs making the vaccine even more expensive and unaffordable to the very population who need it most. Cost reducing strategies tried out include use of a two dose regimen in place of the currently recommended three dose schedule, bacteria based vaccines and L_2 protein based vaccines.

Table 1 – Pathogenic HPV viruses.

Low risk	High risk	Non classified
6, 11, 42, 43, 44, 55	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	2a, 3, 7, 13, 26, 27, 28, 29, 30, 34, 40, 53, 54, 57, 61, 67, 70, 72, 73, 74, 81, 82, 83, 84, 87, 89, 90, 91