Review Article

Indian Journal of Trauma and Emergency Pediatrics
Volume 13 Number 2-3/April-September 2021
DOI: http://dx.doi.org/10.21088/ijtep.2348.9987.132-321.1

HPV Vaccines in Adolesient Girls

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How to cite this article:
Alka Patil, Hetashvi Sudani/HPV Vaccines In Adolesient Girls/Indian J Trauma Emerg Pediatr.2021;13(2-3):43-46.

Abstract

Adolescence is a transitional journey from childhood to adult life along with physical development and sexual maturation. This may be considered as physical, psychological and emotional rebirth. HPV is the cause of variety of proliferative lesions in humans including anogenital warts and neoplasia. Immunization is one of the most important, most beneficial and cost effective disease prevention measures that can be provided for adolescents. Bivalent and quadrivalent vaccines are available. The development of HPV vaccines is a major medical achievement of 21st century. Finally, there is hope that cervical cancer may be controlled globally.

Keywords: Adolescent, vaccine, cervical cancer, HPV, prevention.

Introduction

Adolescence is a transitional journey from childhood to adult life along with physical development and sexual maturation. This may be considered as physical psychological and emotional rebirth.[1] Human Papillomavirus (HPV) a non enveloped DNA papovavirus, is the cause of a variety of proliferative epithelial lesions in humans including anogenital warts and neoplasia.[2] HPV with over 100 types have been characterized. HPV types have been decided as low and high risk depending on the types of lesions caused. Low risk HPV types such as 6 and 11can cause genital warts. HPV types 16,18,45 and 31 are the most important of the high risk or oncogenic types all around the world. Prevalence of HPV is greatest in women aged less than 25 years and can be acquired by skin-to-skin contact.[3] Spread primarily through sexual transmission, the human papilloma virus causes all type of cervical cancer cases a disease that too often, affects relatively young women in the height of their reproductive years. It also causes vaginal cancer in women, penile cancer in men, and throat and anal cancer in both men and women.[4] It causes more years of life lost than any other form of cancer, with immeasurable human costs. Every two minutes somewhere in the world, some women will lose her life to the disease.

High risk HPV are unusual viruses that are confined to the mucosal epithelial cells in the cervix or genital tract and do not spread to the rest of the body. They therefore stimulate epithelial cells that down-regulate the local response, and prior infection with this virus does not induce immunity against subsequent infection. The vaccine is given by intramuscular injection and thus escapes this down

regulation by stimulating a direct systemic response.[3]

Clinical studies carried out to date in 15-25 years old women, have shown that the vaccine prevents HPV 16 or 18 associated persistent infections, abnormal cytologies and CIN lesions.[3]

The immunization is one of the most important, most beneficial and cost-effective disease prevention measures that can be provided for adolescents. The adolescent's vaccination protects most of the world's adolescents from the number of infectious diseases that previously claimed millions of lives each year. Main aims of adolescent's vaccination are: to boost immunity status that is waning after completion of primary immunization or absence of "natural" boosting due exposure to particular disease.[5] Three important infections (Neisseria meningitidis, Pertussis and HPV) for which effective vaccination is now available are especially prevalent in the adolescent years, making the adolescent age group the ideal target age for prevention.

The Primary Objective of an Anti-HPV Vaccine would be:

- *Prophylactic:* To prevent primary infection in susceptible population
- *Therapeutic:* To eliminate infections in populations infected. Two prophylactic vaccines have already been marketed and others are under development. Therapeutic vaccines are still under research.[6]

There no drug therapy available against HPV virus unlike treatment of HIV infection. However prophylactic vaccines are currently marketed. The development of HPV vaccines is a major medical achievement of 21st century. Finally, there is hope that cervical cancer may be controlled globally.[7]

Prophylactic HPV Vaccines

Mechanism of action of Prophylactic HPV Vaccines

The most crucial factor that stimulated interest in HPV vaccine development was the evidence that protection against infection by papillomaviruses could be accomplished successfully. A successful immune response to genital HPV infections is characterized by strong, local cell mediated immunity that is associated with lesion regression and protection against a further infection with the same genotype of HPV. Humoral immunity (antibody) is generated in most, but not all infected individuals. Despite low antibody levels, seropositive individuals are protected, probably for life, against further viral challenge, thus suggesting that vaccines that generate neutralizing antibodies to HPV capsid protein will be effective prophylactically.

In contrast to most viral vaccines which are based on an attenuated form of virus (for example polio vaccine), the development of an attenuated HPV vaccine has been difficult because there is not effective cultural system to propagate the virus. An attenuated vaccine could also potentially cause disease in vaccinated subjects, particularly if they were immunocompromised. Thus, an optional VLP-based (virus like particles) vaccine will require multiple vaccine components to provide good coverage against diseases caused by more than one virus type.

Three doses of both vaccines are recommended.[8]

- *Bivalent vaccine*
  - Cervarix
  - Protect against HPV 16 and 18.
  - Delivered by intramuscular route as a 0.5ml dose.
  - Vaccine Schedule:

Zero point	1st dose
One month	2nd dose
Six months	3rd dose

- *Quadrivalent vaccine*
  - Gardasil
  - Protects against HPV 6, 11, 16 and 18.
  - This vaccine also prevents cancer cervix, genital warts, vaginal intraepithelial neoplasia and vulval epithelial neoplasia.
  - Vaccine Schedule:

Zero point	1st dose
Two months	2nd dose
Six months	3rd dose

It has become a part of routine national health care and cancer screening programme in many countries. They are manufactured by recombinant DNA technique producing non-infectious virus like particles (VPL) with HPVL1 protein. Hence, it is not a live vaccine.

Target Population

Since HPV vaccines are prophylactic vaccines, the most appropriate target population for HPV vaccination will depend on the age at which individuals first get exposed to HPV. This depends on the sociocultural behavior patterns of the region.

The Food and Drug Administration (FDA) has licensed the HPV vaccines for use in girls and women aged 9-26 years.[9] It can be started as early as 9 years but routinely in females at age 11-12 years. Vaccination of sexually active women of any age can be done but the benefits may be less if the subject is already infected with one or the other virus. The

vaccine is also recommended for 13-26 year old girls/women who have not yet received or completed the vaccination series.

Since the vaccine does not protect against all types of HPV, it will not prevent all cases of cervical cancer or genital warts, so it will be important for women to continue getting screened for cervical cancer by regular PAP tests.Thus, even after vaccinations-creening programme should be continued as per schedule.[6] Some countries have licensed the vaccine for use in boys as well. The case for male vaccination against HPV relies on the establishment of herd immunity, thus reducing the chances of an infected individual transmitting the virus to a susceptible person. The quadrivalent vaccine immunize against HPV types that cause genital warts as well, so it may be more likely to be taken up by teenage boys.[6]

Immunogenicity

Protection is observed among women with a wide range of antibody titers. Peak antibody titers in trial are achieved 1 month after dose 3, i.e., at month 7, after which detectable titers decline until about month 18, when the rate of decline decreases considerably and titer appear to stabilize over the next few months at or above titers observed in women with naturally acquired and cleared infections. The total duration of protection is not yet known.[6]

Adverse Effects

- Reaction at injection site: pain, redness or swelling.
- Fever.
- Headache, fatigue, myalgia.
- Gastrointestinal complaints.
- Itching.[10,11]

Most adverse effects are mild to moderate in intensity. Thus, both vaccines generally appear to be safe and well tolerated.

Discussion

The major obstacles to implementation of HPV vaccine programs include:

- Cost.
- Lack of public awareness and infrastructure.
- Concern about unknown side effects, social and religious barriers.
- Parental concerns which include the possibility of change in sexual behavior of teenagers due to a false sense of security against STIs which may lead to an increase in other STIs.
- Since HPV vaccines are cancer prevention vaccines it may be difficult for parents to understand the role of vaccinating 9 to 13 years old girls for a cancer that they are unlikely to develop for at least two to three decades.[6]

Future Prospects

Most countries that introduce HPV vaccination will eventually want to switch to HPV-DNA testing as the primary screening test since it has better performance characteristics than cervical cytology and also using HPV testing for screening coupled with HPV genotyping will provide a simple strategy to monitor long-term protection among vaccinated women. Rapid and cheap HPV testing systems amenable to use in areas with limited health infrastructures are currently being developed and evaluated.[6]

Second Generation Vaccines

The current VLP vaccines have fundamental weakness for achieving their goals, particularly in developing countries, where most cervical cancers occur. Attempts are been made to overcome these short comings. Some of the new generation of vaccines under study are:

- Additional VLP types: (HPV-31, 45, 33, 52 etc.)[12]
- Heat stabilized VLPs.[13]
- Slow-release formulations.[14]
- Oral vaccines.[15]
- Chimeric VLPs.[16]

Chimeric VLPs have been shown in preclinical studies to elicit both neutralizing antibodies to the VLP and T-cell responses to L1 and oncogenic protein E7, thus offering better protection. Polynucleotide vaccines are being considered because of the ease of production and delivery in the developing world and the ability to generate both B and T-cell responses.[17] Capsomere vaccine may offer a simplified, economical alternative to VLPs that is particularly suited to the developing world where the burden of cervical cancer is greatest.

Theraputic Vaccines

Therapeutic vaccines are aimed at eradicating or reducing infected cells. They are based on the generation of cell-mediated immunity. Agents that are in or nearing clinical trials are:

- HPV peptides.
- Fusion protein of HPV-16 L2/E7 and dendritic cells.

Vaccine efficacy in preventing genital warts was 100%. Cross protection has also been reported against other high-risk HPV genotypes. In recent reports, comparable safety, efficacy and immunogenicity of HPV vaccines have been reported in women aged 24 to 45 years.

The ministry of health and family welfare, government of India should make the policy for adolescent vaccination and community at large need to be made more aware about the value of adolescent immunization. There is need to strengthen other areas like health care quality measures, quality surveillance and research.[6]

Building Confidence in the HPV Vaccine

Building public trust is a crucial objective of immunization programs around the world, and this particularly true when a new vaccine is introduced. The vaccine is extremely safe and highly effective in protecting girls against the most dangerous strains of the virus. We must work together to reach women and girls - wherever they live in the world - with effective, high quality prevention including vaccination, screenings and treatment. No women should die from a preventable disease. Benefits of vaccination far outweigh positive risks of potential side effects.

Conclusion

In developing countries, where screening services are sporadic because of unpredictable funding and poor infrastructure. HPV vaccination represents a great hope in the fight against cervical cancer. Public awareness activities are needed aiming to provide parents, young people, schools and health workers with fact-based information on HPV and cervical cancer.

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