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Viewpoint

Human papillomavirus vaccine for cancer cervix prevention: Rationale & recommendations for implementation in India

Burden of cancer cervix and public health interventions

Globally, cervical cancer is the third leading cancer among women in terms of new cases per year. The majority (85%) of the cervical cancer burden is in less developed countries. Cervical cancer accounted for 7.5 per cent of all female cancer deaths globally in 2012, and mortality was substantially higher in less developed countries[1].

Cervical cancer is one of the leading causes of death among women in India. The estimated age-standardized incidence rate was 22.9/100,000 women in 2012[2]. India contributed to one-fourth of the global burden of cervical cancer in 2000. Therefore, researchers emphasized the need for population-based interventions in India to reduce the overall burden of cervical cancer globally[3]. Despite the lack of large scale screening programmes, there was rapid decline noted in the cervical cancer in urban India. The age-adjusted incidence rate in Chennai declined from 42.3 (1982-1983) to 16.7 (2010) per 100,000. In contrast, the decline was much slower in rural areas. Barshi Rural Registry in Maharashtra documented a marginal decline from 23.5 (1988-1989) to 19.5 per 100,000 (2010)[4].

WHO South East Asia Region has recently developed a strategic framework for cervical cancer control in the Region[5]. The framework recommends a multipronged approach towards comprehensive cervical cancer control. Human papillomavirus (HPV) vaccine is one of the recommended interventions for girls aged 9-13 yr for primary prevention. Cervical cancer screening programmes using cost-effective screening tests can be implemented for early detection of pre-cancerous conditions and cancers. Health systems need to be strengthened for preventive, curative and palliative care services for cancers[5].

A multidisciplinary Expert Group constituted by the Secretary, Department of Health Research (DHR) and Director-General (DG), Indian Council of Medical Research, Ministry of Health and Family Welfare, Government of India, reviewed the available evidence globally regarding immunogenicity and efficacy, adverse effects and cost-effectiveness of the HPV vaccine. In addition, burden of HPV infection and status of HPV vaccine in India were also reviewed. The Group discussed the available guidelines and recommendations of WHO[6] for the introduction of HPV vaccine at the country level. Available evidence and the recommendations endorsed by the group are summarized here.

HPV vaccine: Immunogenicity and efficacy

HPV vaccine is one of the recommended interventions for cervical cancer control worldwide. It has been included in the national immunization programmes in more than 60 countries around the world. While the cost of vaccine has been a major challenge, there has been a decline in cost in recent years. Contributions from donors and Global Alliance for Vaccines and Immunization (GAVI), the vaccine alliance have also facilitated the procurement at affordable price for low- and middle-income countries[7].

There are three commercially available vaccines: bivalent, quadrivalent and nonavalent. Quadrivalent vaccine protects against four HPV types (6, 11, 16 and 18) and the bivalent vaccine protects against two HPV types 16 and 18[6]. A recently introduced nonavalent (nine valent) vaccine protects against five HPV types 31, 33, 45, 52 and 58 in addition to the types covered in quadrivalent vaccine[8].

Immunogenicity and efficacy of available vaccines in the clinical trials

All three available vaccines (bivalent, quadrivalent, and nonavalent) are administered intramuscularly.

Data from several clinical trials among young women (15-26 yr) indicated an excellent immunogenicity profile for all vaccines tested[6]. Although the efficacy studies were not carried out in the target adolescent population, immunogenicity-bridging studies documented strong immune response and safety profile[6].

Cancers that could be potentially prevented by the three vaccines were estimated in a study in the US based on the available secondary data from various sources. HPV 16/18 vaccines prevented majority of the invasive cervical (66.2%) and anal (79.4%) cancers; the nonavalent vaccine additionally prevented between 4.2 and 18.3 per cent of cancers[8].

HPV infections, precancerous lesions and anogenital warts

A systematic review of 20 studies from nine high-income countries analyzed the risk reduction in the HPV infection and anogenital warts in the vaccinated cohorts[9]. Pooled duration of follow up across these 20 studies was 140 million years. In countries with >50 per cent coverage among girls, HPV 16 and 18 and anogenital warts declined significantly by 68 per cent [relative risk (RR) 0.32, 95% confidence interval (CI) 0.19-0.52] and 61 per cent (RR 0.39, 95% CI 0.22-0.71), respectively, among girls aged 13-19 years. Only one study reported significant decline in high-grade precancerous cervical lesions among girls aged 15-19 yr (RR 0.69, 95% CI 0.66-0.73)[9].

Two-dose versus three-dose schedule

A systematic review analyzed the data from randomized controlled trials comparing the two-dose and three-dose schedule[10]. The seroconversion and seropositivity were non-inferior in the two-dose group as compared to the three-dose group at all time points. Similar results were also observed in the non-randomized comparisons[10].

A cluster randomized trial was planned in India to measure the efficacy and immunogenicity of two doses versus three doses. The trial was prematurely terminated due to suspension of all HPV-related clinical trials in India in 2010 in response to an unrelated event (concerns about HPV vaccine demonstration study). The data available from the cohort immunized before the suspension of trial were analyzed in an observational study design. Immune response in the two-dose group was non-inferior to the three doses. There was no persistent HPV (16 and 18) infection at the median follow up of 4.7 yr among vaccinated girls[11].

Adverse effects

The Global Advisory Committee on Vaccine Safety (GACVS) released statements in 2013 and 2014 on vaccine safety based on the available evidence. Serious adverse effects such as syncope, anaphylaxis, venous thromboembolism, adverse pregnancy outcomes and stroke were investigated. There was no evidence of association of HPV vaccine with any of these adverse events[12,13]. A recent update from the GACVS issued in December 2015 reiterates the safety of the vaccine based on available data after distribution of more than 200 million doses since 2006[14].

In the programmatic setting, it is important to educate the health staff responsible for vaccine administration regarding common adverse effects of the vaccine. In the clinical trials of bivalent and quadrivalent vaccines, injection site pain ranged from 83 to 93 per cent in the vaccine group for both the vaccines. The proportion reporting pain in the control group ranged from 76 to 87 per cent. Headache and fatigue were also reported by 50-60 per cent in the vaccinated group[15].

Cost-effectiveness

Cost-effectiveness of the HPV vaccine in Asia was estimated in a study that used epidemiological data from 25 Asian countries. The study estimated the averted cervical cancer cases and deaths, disability-adjusted life years and cost-effectiveness ratios for HPV (16 and 18) vaccination among the adolescent girls. The authors concluded that the HPV vaccine would be cost-effective if the cost per vaccinated girl was 10-25 USD (653-1633 INR) or lower in various Asian countries[16].

One study estimated the cost-effectiveness of various cervical cancer control strategies, namely vaccination before 12 yr of age and the cancer screening among women above 30 yr for India[17]. Mean reduction in the lifetime risk of cervical cancer was 44 per cent for HPV (16 and 18) vaccine if vaccine coverage of 70 per cent was assumed. If HPV DNA testing twice in lifetime was added in the analysis, mean risk reduction was 63 per cent. The combination of HPV vaccine and screening (either using VIA or HPV DNA testing) was reported as cost-effective for India if the cost per vaccinated girl was 10 USD (653 INR)[17].

HPV infections and HPV vaccine in India

HPV prevalence among women with and without cervical lesions was estimated in a meta-analysis of nine studies from India[18]. Prevalence of any HPV type was 12 per cent among women with normal cytology. Among women with invasive cervical cancer, 94.6 per cent were positive for HPV and type 16 was most common. HPV prevalence was 86.5 and 65.4 per cent among women with high-grade squamous intraepithelial lesions and low-grade squamous intraepithelial lesions, respectively[18].

There are two types of HPV vaccines, bivalent and quadrivalent; both are licensed and available in India. The vaccines are already in use in the private sector. A demonstration project was initiated at two sites in India. There was a report of a few deaths among vaccinated girls in a southern State[19]. This led to negative media response and the project was stopped in 2010[19]. Subsequent investigations did not prove any causal association between the vaccine and deaths[5]. However, HPV vaccine is yet to be included in the immunization programme in India.

Recommendations for HPV vaccine implementation in India

The WHO issued recommendations for HPV vaccine in October 2014 based on all the available evidence on various aspects of the vaccine[6]. In addition, a strategic framework for cervical cancer control has been developed for the South East Region[5]. The multidisciplinary Expert Group reviewed the recommendations and also held consultative meetings with various stakeholders. The group endorsed the following recommendations for the introduction of HPV vaccine in the programmatic settings in India:

Introduce HPV vaccine within a comprehensive cervical cancer control programme

HPV vaccine is a primary prevention intervention for cervical cancer control. HPV vaccine will only protect young adolescent girls that are not yet exposed to HPV. Protection is for only selected HPV types and does not cover all high-risk types. Therefore, comprehensive cervical cancer control also requires cervical cancer screening for early detection and treatment, even for those cohorts vaccinated against HPV. A comprehensive cervical cancer control programme must include a health promotion programme to increase awareness regarding prevention, risk factors and treatment. While it may not be feasible to introduce all the interventions simultaneously, a long-term plan should be put in place to establish a comprehensive programme. Health promotion and awareness activities must precede the implementation of the HPV vaccine.

Vaccinate the primary target group of girls aged 9-13 years

Primary target group for HPV vaccine is girls aged 9-13 yr as per the WHO recommendations[6]. Other target groups such as adolescent males, older adolescent females or young women can be given lower priority in context of limited resources and high cost of vaccine in India.

Follow two-dose schedule with flexibility in the interval no greater than 12-15 months

WHO revised the recommendation from a three-dose schedule to a two-dose schedule based on the emerging data on the efficacy of the two-dose schedule[6]. The two-dose schedule can be used for both bivalent and quadrivalent vaccines. The maximum interval between the doses should not exceed 12-15 months. The two doses should be given at least six months apart. Among immunocompromised individuals and females aged 15 yr and above, it is preferable to use the three-dose schedule.

Choose vaccine (bivalent/quadrivalent/nonavalent) by considerations of availability and cost

The Group recommends the use of either of the available vaccines (bivalent/quadrivalent/nonavalent) in the programmatic conditions for initiating or completing the vaccine series. The choice of vaccine can be assessed by programme managers considering the availability and cost.

Identify sustainable financing and enhance the capacity of the health system (if required) before introduction of HPV vaccine

A sustainable mode of financing should be identified to ensure the long-term continuity of the programme. Health system capacity in terms of trained human resources to administer the vaccine, delivery infrastructure such as functional cold chain and systems to monitor adverse events after vaccination should be assessed. If there are any gaps, appropriate steps should be taken to strengthen the health system before implementation of the HPV vaccine programme.

Identify appropriate approaches to maximize the coverage in the local context

The majority of programmes globally have used a school-based approach for HPV vaccine programmes.

This is appropriate if the school dropout proportion is not very high. School-based approaches can be supplemented with outreach at the community level to ensure coverage of school dropouts.

Establish a system to monitor for adverse events and vaccine coverage

The adverse events following HPV vaccine are mostly non-serious and of short duration. A system to monitor the adverse events should be in place before the implementation of HPV vaccine. Vaccine coverage should be monitored within the programme framework.

Establish cancer registries to monitor the long-term impact

Prevalence of HPV has been documented in several studies from India[18]. Monitoring of the HPV burden in the population is not required under programmatic settings. Although India already has network of cancer registries, an effort should be made to expand and strengthen the cancer registries to monitor the long-term impact of HPV vaccine and cancer screening programmes.

Conclusion

Cervical cancer is one of the preventable cancers among women. Screening for early detection of the precancerous conditions using cost effective methods and HPV vaccine administration among adolescent girls are the two major interventions for cervical cancer control worldwide. It is recommended that adolescent girls 9-13 yr should be vaccinated with two doses of HPV vaccine. Health system capacity should be assessed before introduction to ensure effective implementation and reliable system should be established to monitor the adverse events. Vaccine coverage should be monitored within the programme framework and cervical cancer trends need to be monitored through network of cancer registries.

***Conflicts of Interest*:** None.

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