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Vaccination programs for men tend to improve population-level control of HPV infection and directly prevent HPV related disease such as anogenital warts and oropharyngeal cancers in males. HPV vaccine does not treat existing infection or lesions/cancer and is intended for individuals before initiation fo sexual activity or any other form of exposure to HPV.

Many programs across the globe do not include vaccination for boys because of the cost and little recognition of the emerging epidemic of HPV associated cancers in men. In the Indian context, as screening is not feasible for non-cervical HPV associated cancers, its incidence mostly among men will continue to rise until the present generation of vaccinated adolescents reaches their middle-age.

Vaccination will reduce transmission rates and increase herd immunity. This in-turn, will prevent not just cervical cancers but also other HPV-associated malignancies among men and women.

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A narrative review on HPV vaccination among boys and men

Vinod K Ramani [α] & Radheshyam Naik [σ]

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I. Introduction

Apart from cervical cancer, Human papillomavirus (HPV) infection is associated with head and neck as well as other anogenital cancers such as vulva, vagina, anus, and penis. Worldwide ~70% of cervical cancer could be attributed to HPV types 16 and 18. HPV vaccine provides specific protection against the disease and its subsequent manifestations[1].

An important etiological agent in squamous cell carcinoma of the tonsil, base of tongue and anus, includes one of a subset of mucosal high-risk human papillomaviruses (HPVs) principally 16 and 18. Apart from causing cervical cancer among women, it significantly contributes to squamous cell carcinoma of the larynx, head and neck, penis, vulva and vagina[2].

In India[1], the crude incidence rate of cervical cancer per 100,000 during 2018 was 14.9, and the age-standardized rate was 14.7. The global measures were 15.1 and 13.1, respectively. It ranks second among the leading causes of female cancers. Among women aged 25-64 years, screening coverage every three years for cervical cancer is 3.1%. The age-standardized rate for cervical cancer mortality in India was 9.2 per 100000 women during 2018. The age - specific mortality rate of cervical cancer among women aged 15-44 years of age in India during 2018 was 3.9%. The demographic profile of India includes 32.7% of its population living in urban areas.

The average worldwide incidence of anal cancer is 1 per 100,000. Its incidence is high among men who have sex with men (MSM), women with a history of cervical or vulvar cancer, the immunosuppressed population including HIV-infected, and patients with a history of organ transplantation. The incidence of anal cancer is high among women when compared with men[1].

Cancers of the vulva and vagina are rare among women with worldwide estimated new cases of 27,000 and 13,000 respectively, in the year 2008. Among vulvar cancers, only the basaloid/warty lesions are often associated with detection of HPV DNA (deoxyribonucleic acid). Penile cancer's incidence worldwide is estimated to be 22,000 cases, strongly correlating with those of cervical cancer[1].

Among the head and neck cancers, current evidence suggests that HPV type 16 is associated with tonsil cancer, the base of tongue cancer, and other oropharyngeal cancers. The crude incidence rate per 100,000 and year 2018 for oropharyngeal cancer in India was 2.6 (Male: 2.2, Female: 0.4)[1]. Among human cancers, ~5% are caused due to HPV infection with HPV16 being the major genotype. HPV infection mainly with the genotype 16 could be attributed to >90% of anal cancers[1].

The peak prevalence of HPV infection among women is in their late teens and twenties and steadily declines throughout the subsequent decades. However, men acquire the infection during the late teens, and there is no change in prevalence during the subsequent decades[2].

Gardasil from Merck company is one of the available prophylactic HPV vaccines, which is approved by the United States Food and Drug Administration (USFDA) during 2006. This quadrivalent vaccine protects against HPV types 6, 11, 16 and 18. During 2009, USFDA approved Cervarix from GlaxoSmithKline company as a bivalent vaccine against genotypes 16 and 18. During 2014, a nine-valent vaccine 'Gardasil 9' from Merck was approved, which offers protection against five additional oncogenic genotypes (31, 33, 45, 52 and 58) in addition to the types 6, 11, 16 and 18. The primary target group for vaccination includes

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adolescents aged 9-13 years, with catch-up vaccination until the age of 26 years[3]. The vaccine is ideally intended for individuals before initiation of sexual activity and exposure to HPV, as it may not benefit existing infection or disease.

The proportion of girls and women as well as boys and men in an Australian study[3], showed a significant reduction in the development of genital warts after the implementation of the National HPV Vaccination program during 2007.

Cost-effectiveness is the primary argument for the HPV vaccination program among males. The recommendation in Countries such as the USA, Canada, Austria, and Australia includes gender-neutral vaccination[4].

II. Methods

'Pubmed' database was used for searching relevant articles. Search terms used include 'HPV vaccination among males'; 'Effectiveness of male HPV vaccination program'; the results of this search yielded research articles that contextually detailed the concerned concepts. The criterion used for reviewing these abstracts includes their relevance to the defined review question. This review includes 13 studies that address the determinants of HPV vaccination uptake.

III. Discussion

In India, screening tests such as PAP smear and HPV testing are already existent for cervical cancer, which is not the case with oropharyngeal cancers. The absence of screening tests results in many such patients presenting with advanced disease involving regional lymph nodes. It is of interest to note the increasing incidence of anal cancer among both the sexes, as well as the presentation of disease in an advanced stage[5]. Some reasons for low vaccination rates in various studies include inadequate provider recommendations, parent opposition, lack of policies mandating HPV vaccination during school enrolment, and absence of school-based immunization program[5].

The sexual behavior with both female and male sexual partners determines the incidence risk of acquiring HPV infection and the likelihood of its clearance. A consequential predictor of both HPV infection and persistence is having either >10-lifetime female sexual partners or >2 recent male anal sex partners[5].

Choi[6] et al.'s study on the 2012-2013 United States National Immunization survey teen dataset shows that 56% of females received at least one dose of HPV vaccine when compared with 28% of males. In this study[6], the interaction between gender and socio-demographic variables in predicting vaccination was found to be significant. Such variables include age, ethnicity, mother's education level, healthcare coverage, and Provider recommendation for vaccination. There has been a lag time of five years for male vaccination to become a routine when compared to female vaccination program. The customary parental reason for avoiding vaccination to their children includes 'healthcare provider not recommended' for males (24%) and 'vaccine not necessary' for females (18%).

Predisposing conditions such as cancer and acquired immunosuppression (among transplant recipients, cancer patients, chronic inflammatory conditions on immunomodulatory drugs, and HIV patients) increase the morbidity of HPV. Such prepubescent boys need to be vaccinated, which could prevent the impact of HPV disease in the future else it becomes a lost opportunity in our fight against HPV disease[4]. There is a scope for post-exposure prophylactic HPV vaccination in boys and men (as well as girls and women). Although direct evidence from clinical trials is limited (given the clinical heterogeneity of the problem and timescale for significant outcomes such as progression to invasive cancer), indirect evidence (women with the cervical disease) provides a compelling rationale regarding the benefits of quadrivalent vaccination[7].

Many programs across the globe do not include vaccination for boys because of the cost and little recognition of the emerging epidemic of HPV associated cancers in men. As screening is not feasible for non-cervical HPV associated malignancies, the incidence of HPV-associated cancers (mostly among men) will continue to rise until the present generation of vaccinated adolescents reaches their middle-age[5]. Primary level of prevention could address this burden, where-in HPV vaccination is provided to both boys and girls.

HPV vaccination program for young adolescent girls leads to dramatic reductions in cervical high-grade precancerous lesions, as well as genital warts. Among girls, sero-surveillance of circulating vaccine-related HPV types also shows a reduction[6]. It is imperative to monitor the incremental impact of universal vaccination of pre-adolescent boys as a component of the immunization schedule. Although population-wide cervical screening programs are currently prevailing, it may not be prudent to advocate screening for HPV infection or related disease in males. The real-time effectiveness of HPV vaccination among males could be monitored through precise surveillance strategies, which in-turn depends on the healthcare infrastructure and existing models of disease surveillance such as sexually transmitted infection (STI) networks[4]. Sentinel surveillance of circulating genital HPV types is a surrogate marker for vaccine effectiveness in males. In such a setting, we need to consider the sampling methods, appropriate anatomical sites for specimen collection, and the sensitive assays which need to be utilized. The epidemiological challenge for assessing the

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impact of HPV vaccination in the male population includes analyzing the effect of herd protection.

An indicator of the vaccine's impact among the male population includes changes in the prevalence of genital HPV genotypes among young, sexually active men. Such markers are more of an indicator of viral deposition than of significant host infection, due to the high rate of HPV DNA clearance detected in males[8]. Surveillance strategies should include a combination of short (HPV prevalence) and long term (anogenital warts, cancers) outcome measures, including those for specific target populations such as MSM and HIV infected men (at high risk for HPV infection and associated disease).

Among heterosexual men, the keratinized epithelial cells from the penile shaft need to be ideally sampled avoiding other deposits from the surface. Comparative studies do not show any difference in the HPV detection rates between swabbing with and without abrasion[8]. This swabbing technique promotes compliance as it is less uncomfortable for participants. Among men who have sex with men (MSM), anal sampling is the ideal site for sampling as HPV is frequently detected here than on the penis or scrotum.

Due to female vaccination, there is a continuing decline in male HPV genoprevalence[8]. This confounding factor is of epidemiological interest when we intend to accurately measure the impact of male vaccination on the male infection (additional decline beyond that due to female vaccination). MSM cannot be covered by such herd protection, and they need to be protected with vaccination.

For measuring the impact of the vaccination programs, sero-surveillance could contribute towards measuring immunological response to vaccination. Exposure to HPV DNA does not always result in a serological response, and vaccination results in higher antibody titers when compared with natural infection. Although geno-prevalence survey is invasive in nature sero-prevalence cannot substitute for geno-prevalence as a measure of circulating virus[8].

Unlike cervical cancer screening, lack of screening tests for anal and oropharyngeal cancers has led to an increase in incidence, particularly among men. Unlike the HPV negative cancers at these sites, HPV positive ones tend to occur in younger age groups (40 to 60 years), present at a later stage leading to higher mortality and cause significant morbidity after therapy, thus impairing the quality of life[2].

The seroconversion rate among women is ≥70% after detectable cervical HPV infection, with antibodies against the major coat protein L1. However among men, this rate is only ≥20-30%. Among girls and women, an effective prophylactic vaccine against HPV 6, 11, 16 and 18 tends to significantly reduce the infection and disease. Even though the antibody response is poor among men for natural infection, the humoral immune response to the virus-like particle vaccine results in 100% seroconversion. Trials with the quadrivalent 'Gardasil' vaccine have shown efficacy against infection and disease, in context to preventing 6/11 genital warts among men who have sex with women and 6/11/16/18 anal intraepithelial neoplasia among men who have sex with men[2].

Some of the determinants which influence compliance among men for vaccination include their attitude towards HPV vaccination and self-efficacy (ability to visit the clinic three times for vaccination). Other socio-psychological determinants such as social influences and specific attitudinal constructs like outcome beliefs and anticipated regret were also significantly associated with an intention for HPV vaccination[8]. As assessed in Marra E. et al.'s study[9],out-of-pocket payment had a significantly negative effect on HPV vaccination intent among male clients of the STI clinic in Amsterdam.

Duncan et al[10] address the gendered influences on the acceptability of HPV vaccination among men. Parents tend to accept the sexuality of adolescent boys to a greater extent when compared with girls and tend to perceive protecting children from harm as their duty. These deliberations reflect on their motivation for HPV vaccination among boys. However, the low awareness about its benefits for boys given the well favored belief that it accords protection to girls, and the stigma in receiving a women's vaccine in conjunction with the lack of Provider recommendation for boys, are the obstacles for HPV vaccine acceptability.

The cost-utility of girls-only HPV vaccination program needs to be input into a model for estimating the quality-adjusted life years (QALYs) gained and the net costs for the health system. Simulation modeling activity for HPV vaccination should include preventing of events such as anogenital warts, cervical intraepithelial neoplasia (CIN) I, II, III, cervical, anal, oropharyngeal, and vulval cancers using the rates of the all-cause mortality, cancer-specific mortality and morbidities[11].

IV. Conclusion

Community based cervical screening programs could detect high grade cervical intra-epithelial neoplasms (CIN), which are the obligate precursors to invasive cancer. The increasing incidence of other HPV-related cancers among both men and women is because these are not amenable to screening. HPV vaccination coverage for males improves population-level control of HPV infection and prevents related diseases such as anogenital warts and anal cancers. Monitoring such a Program faces challenges given the long time-frame for cancer as an outcome and genital specimens among men not being routinely collected for estimating HPV prevalence. Surveillance measures should be directed towards specific targeted

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populations with high risk for HPV infection such as MSM and HIV infected men.

There is a compelling need to quantify the impact of HPV vaccination, and in this regard we need to monitor the cost-effectiveness, conduct operational research, and focus on vaccine development in the future. Unlike the cervical screening programs for females, measuring the effectiveness of a male vaccination program is challenging. Sentinel surveillance programs should compare baseline geno-prevalence with post-vaccine geno-prevalence, and disease end-points need to be monitored through disease registries.

The burden of disease among men needs to be factored in cost-effective models, apart from other inputs such as vaccine price, coverage, and other factors influencing vaccination among males. Gender-neutral vaccination would result in herd immunity, which in-turn could rapidly reduce the viral load in the population. Our failure to implement the male vaccination program will result in a missed public health opportunity.

As HPV sero-prevalence is higher in women than among men and decreases to a greater extent with increasing age respectively, there is a need for different models to understand the whole disease pathway. This in-turn, could channelize various approaches for prevention and treatment. In this regard, male vaccination is a safe and effective option for preventing HPV infection and its consequences.

Since out-of-pocket payment has a negative impact on the intent for HPV vaccination, its inclusion in the Indian Universal immunization program would aid in the higher uptake. Tailored messages need be targeted for Parents, adolescent boys, and Providers to address the multi-level influences. Screening services for non-cervical HPV associated cancers may not be feasible, and its incidence (chiefly among men) is likely to increase.

HPV related cancers are largely preventable, and an aggressive immunization stance and screening schedules are essential in India. Vaccination will reduce transmission rates and increase herd immunity, which will prevent not just cervical cancers but also other HPV-associated malignancies among men and women.

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