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Human Papilloma Virus Vaccination: The ever persisting dilemma still continues

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Abstract

Human Papilloma Virus (HPV) induced chronic diseases have been a huge burden on health system; developing and developed nations equally affected. Among these diseases cervical cancer is the frontrunner malignancy. More than half a million women are diagnosed with cervical cancer worldwide each year with equally threatening mortality figures. Evidence of being HPV in the causal pathway of other cancers like anal and laryngeal cancers has also been generated in the recent path. Like all infectious diseases, these diseases can also be contained employing strategies recommended and proven beneficial for other ailments of infectious origin. In addition the availability of a safe yet efficacious vaccine equips us better to counteract against the HPV linked diseases. However, there are certain conflicting and controversial things like financial implications, adverse effects in few scenarios which disfavor the generalization of vaccines resulting into much dreaded vaccine hesitancy. However it is high time for the nations, stakeholders and health managers to evaluate the pros and cons scientifically and decide accordingly in public interest; ending this debate for once and all.

Keywords: HPV infection; Cervical cancer; HPV vaccination

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Background

Human Papilloma Virus (HPV) is a sexually transmitted virus and its association with chronic cancers such as cervical cancer, ano-genital carcinomas and head-neck malignancies has been well documented [1]. Its association with cervical cancer in particular has been proved scientifically beyond any reasonable doubt.As there are protective measures available in the form of standard precautions, behavior and vaccines; all these cancers can be branded as a largely preventable malignancies. Considering the burden of these malignancies especially the cervical cancer globally, the inclusion-exclusion of HPV vaccination in immunization programs has been much debated; India being no exception. Though there are proven benefits, but there are still some significant reasons to hold back the generalization of this vaccine to the masses and the dilemma of adopting the vaccine without any hesitation still persists.

Burden

All sexually active women are infected with HPV at least once during their lifetime, and the highest prevalence is seen soon after the onset of sexual activities [2]. Human Papilloma Virus (HPV) causes cervical cancer, which is the fourth leading cancer in women [3]. There were 569847 cervical cancer cases worldwide and 96922 in India alone in 2018 [4-5]. It is ranked as second most common female cancer in all age groups across India. Around 85% of the global burden occurs in the developing regions, accounting for almost 12% of all female malignancies.[6]Globally, HPV-16 and 18, the two vaccine-preventable types contribute to over 70% of all cervical cancer cases followed by HPV subtypes 31, 33, 35, 45, 52 and 58; that account for an additional 20% of cervical cancers worldwide [6]. Even though majority of HPV infections remain asymptomatic, longstanding genital infection can ultimately culminate into cervical cancer in women. Virtually all cervical cancer cases are linked to genital infection with HPV and it is the most common viral infection of the reproductive tract. Sexual contact has been determined as the primary mode of transmission of HPV infection. In addition to the cervical cancer, HPV can also cause other types of ano-genital malignancies, head and neck carcinomas and genital warts in both men and women. At present more than 90% of anal cancer cases are linked to HPV infections [7]. The prevalence of laryngeal carcinomas with HPV positivity has varied from 0% to 75% as evident by different studies [8].

Vaccine Status

The first FDA approved quadrivalent HPV vaccine became

available in 2006, followed by a bivalent vaccine in 2009. In 2014, a nonavalent vaccine protecting against nine serotypes was approved. Australia was the first country to introduce a Government-funded National HPV Vaccination Program in 2007 [9]. By 2017, globally 71 countries had introduced HPV vaccine in their national immunization programme for girls, and 11 countries also for boys [10]. India has also attempted to implement the HPV vaccination programs. Two HPV vaccination projects for operational feasibility were launched in Andhra Pradesh and Gujarat provinces of India; while Punjab became the first state in the country to include the vaccine in its universal immunization program in 2016 [9]. All three HPV vaccines were initially licensed and marketed using a 3-dose vaccination schedule which was changed to a 2-dose schedule subsequently as indicated by immunogenicity data [10]. However there are still varying discrepancies regarding initiation or timing of vaccination and different health agencies recommend different schedules. Though recommended in pediatric age, vaccine is more efficacious if the usage is before the sexual debut and the efficacy drops significantly thereafter. High efficacies have been observed for all vaccines in trials. In low resource settings, single dose trials have also been conducted which have also shown promising results. Regarding safety profile of vaccination, even though there have been sporadic instances of adverse events following immunization, there is no strong evidence event against the vaccination [10].

Dilemma concerning the vaccine

Apart from cervical cancer, vaccine has been found to be efficient in preventing persistent infections and lesions from the anus, vagina, and vulva [11]. Furthermore, the implication of HPV in laryngeal carcinoma, extended avenues have opened up for vaccine usage. Therefore the relevance and significance of vaccine cannot be questioned. Due to benefits offered for the diseases involving other systems and regions, now the vaccination is not exclusively for the females only. In addition based on clinical trials and post-introduction impact evaluations, there is evidence that HPV vaccines provide some cross-protection even against HPV types not included in the vaccines [10].

As per GLOBOCAN report 2018, among exclusive female cancers, breast cancer poses a bigger threat than cervical carcinoma [3]. Even in India the incidence of cervical cancer is ranked below the breast cancer, which is change in previous trend [5]. In recent years as the Low and Middle Income Countries (LMIC) are improving on developmental parameters, it will be interesting to see whether these countries are moving towards the trend of cervical cancer in developed countries. If the vaccine is introduced in the universal immunization program, the long term cost effectiveness has to be evaluated in the light of recent report of declining trend of cancer cervix in LMIC countries.

Apart from infection, cervical cancer has other etiologies and risk factors like multiple pregnancies, multiple sexual partners, using oral contraceptives for more than 5 years, early pregnancy, genital herpes infection, chlamydia infection, HIV infection, smoking, economic status and family history; therefore getting vaccination does not guarantee protection against cervical cancer [12]. Moreover as the vaccines addresses only 2, 4 or maximum 9 of the potential 17 carcinogenic strains of HPV and vaccine prevents about 70-80% of cervical cancers; therefore protection against cancer will still be questionable and even women who have received the HPV vaccine need to be screened regularly for cervical cancer [13]. Thus it will be difficult to choose a costlier vaccination program over a relatively less expensive screening program.

Regionally, there have been some issues in the recent past concerning safety of vaccines. In 2009, a vaccination program in India ran into controversy after alleged four deaths and complications among 120 girls were reported after vaccination and the program was terminated. Although the Government enquiry concluded that the deaths were unrelated to the vaccines, still the overall program suffered a huge setback and the pro-vaccination momentum came to an abrupt halt [13-14]. There was also an instance in 2011 in United Sates where baseless remarks implicating vaccine in mental retardation were made publically [15]. As per WHO, barring few minor local and systemic side effects; all approved vaccines have excellent safety profile.There were concerns about association of vaccine with some chronic auto-immune disorders especially Bell's palsy and Guillain-Barré syndrome but scientifically nothing could be proven [10]. However, as it is relatively recent vaccine, so long term studies and post marketing surveillance are still going on. The significant data will only start coming in when we are able to follow up vaccinated cohort for decades; then only we will be able to know the real efficacy and safety profile of the vaccine. The safety of the HPV vaccines in children younger than 9 years has not been established [10].

A significant challenge regarding implementation of vaccination program especially in low resource settings is the relatively high cost of vaccination. Speaking in monetary terms, in an African country, the mean economic cost of vaccine per dose and per fully immunized girl were USD 45 and USD 91.19 respectively [16]. Similar high vaccination costs have also been observed in India too [17]. With multiple doses of both vaccines recommended in schedule the expense reaches even higher making it one of the most expensive vaccines in the history of immunization. Being an expensive vaccine, there has been a suspicion that HPV vaccination is exclusively for profiteering [18].

Depending upon the schedule, vaccination requires multiple doses for desired protection; which can be a huge deterrent for the adequate compliance [10,19-21]. As the vaccination is recommended in the paediatric age group prior to the sexual debut, there would be no guarantee that the vaccine will be effective by the time child reaches adulthood. This will generate requirement for boosters, which will further increase the number of doses. Furthermore, vaccine coverage is hindered by social and cultural norms as HPV induced diseases are deemed as sexually transmitted infections. Therefore a huge media push will be needed get every child to get vaccinated leading to enormous financial burden especially in low resource settings.

Conclusion

The debate of adopting HPV vaccination in national programmes of the countries particularly in LMICs is still persisting, despite the

availability of strong evidence in favour of vaccine. The vaccine itself has seen a developmental course from covering a couple of strains to multiple strains. Though there is proven efficacy of vaccine, yet its usage in real world especially the developing nations is quite limited. Attempts are being made to generalize the vaccination, but not without some complications. Analysis of pros and cons needs to be done at the earliest, so that the much needed benefits of the vaccination can be divulged. A scientific consensus regarding vaccination schedule also needs to be addressed in the wake of multiple varying schedules by different agencies .

Moreover international agencies of health and women welfare also need to be more focussed on vaccination initiatives and definitely aid the developing countries in adopting the standard norms pertaining to HPV vaccination. Recently a HPV vaccination campaign was launched in Punjab province of India with the WHO technical support; about 10,000 girls studying in class six of Government schools were covered reflecting a 95% mobilization highlighting enormous commitment.

Studies highlight that the influence of accurate information about vaccines is maximized and more accepted when conveyed from health care personnel to either a parent or patient. Therefore it is imperative that the health workers should generate awareness among parents and patients regarding preventable nature of cancers and HPV vaccination in order to create vaccine demand from client aspect. In addition, the inclusion of HPV vaccination in national immunization program can definitely reduce the out of pocket expenditure on health care. Single shot schedule may be explored more for efficacy as opposed to multiple dosage schedules. Indigenous manufacturers should be encouraged to produce vaccines in bulk to bring down the cost substantially.

In addition the role of HPV in other chronic diseases and other cancers also need to be explored vastly so that our understanding of phenomenon is enriched. Globally the countries should implement the program taking into consideration of their resources, operational feasibility and sustainability, fiscal capacity, long standing cost-effectiveness, burden of HPV preventable diseases and definitely the safety and efficacy profile of vaccine. The vision of sustainable development and universal health care will only be truly realized if we address the neglected health issues as well. If we head with the right approach and appropriate strategy regarding the HPV Vaccination, we might be able to finally see off this never-ending dilemma.

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