Is human papillomavirus vaccination likely to be a useful strategy in India?

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Abstract

Two vaccines that protect against infection by some of the oncogenic human papillomavirus (HPV) subtypes have recently been licensed for use in population-based vaccination strategies in many countries. However, these products are being promoted as 'cervical cancer vaccines' based on inadequate data. Specifically, there remain several concerns about the duration of immunogenicity, length of follow-up of trial subjects, endpoints chosen in vaccine trials, applicability of trial results to real populations, the safety of these products, and their cost-effectiveness as public health interventions. Furthermore, it is unlikely that vaccination will obviate the need for setting up robust and cost-effective screening programs in countries like India. This article will discuss various aspects of HPV vaccination from a public health perspective, especially from the point of view of its relevance to India and other South Asian countries.

Key words: Human papillomavirus, infection, human papillomavirus, human papilloma virus vaccine, cervical cancer prevention

Introduction

Introduction of the human papillomavirus (HPV) vaccines in India in recent years has led to considerable discussion in the medical and public health community. Arguments have been advanced for and against a population-based mass vaccination strategy. Suspension of field trials of one of the vaccines by the Indian regulators in April 2010 because of alleged irregularities has added grist to the mill. This article will pragmatically review the available evidence for HPV vaccination and assess whether it is relevant to a low-resource country like India. We will consider the end-of-study analyses of the large phase III prophylactic HPV-virus-like-particle (HPV-VLP) vaccines that have been published.

The Vaccines

Cervarix® and Gardasil®, the current HPV vaccines are both available in India. Although conceptually similar, they differ in several aspects. Cervarix® is bivalent and contains VLPs of the high-risk oncogenic subtypes HPV16 and 18, the two types that cause 70% of cervical cancer worldwide.[1,2] Gardasil® also targets HPV 16/18 but also contains VLPs of HPV 6 and 11, which cause approximately 90% of external genital warts in both men and women.[3]

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Trials: The Evidence

Two phase III studies, FUTURE I and FUTURE II[4,5] evaluated Gardasil and two, PATRICIA[6] and the Costa Rica HPV Vaccine Trial (CVT)[7] evaluated Cervarix. All of the trials were relatively large (5,500-18,500 vaccinees), blinded, randomized, and controlled trials of young women (mean age 20, range 15-26). All subjects in both arms of each trial were monitored and high-grade CIN lesions (CIN II/III) were treated as per local management policies. The FUTURE II and PATRICIA considered high-grade dysplasia (CIN II/III), adenocarcinoma-*in-situ* (AIS) and HPV 16/18-associated cervical cancer as primary efficacy endpoints. The FUTURE I trial also included HPV 16/18/6/11 associated anogenital warts and all grades of vulvovaginal dysplasia as primary efficacy end-points.

The final results from the FUTURE I/II and PATRICIA trials results are now available[8-10] and involve analyses of various sub-cohorts of trial participants-namely per protocol cohort, intent to treat (ITT) cohort and the naïve cohort who had no evidence of baseline cytology abnormalities or prevalent HPV infection. The trials measured rate reduction (per 100 subject-years) in their chosen end-points and used this parameter as an estimate of overall vaccine efficacy.

The results showed that prophylactic efficacy against high-grade CIN lesions was high (95-100%) in both trials but only in the per-protocol and naïve cohorts. It was low in the ITT population (45.1-45.7%). Although efficacy figures were impressively high in the naive cohorts, it is highly unlikely that either vaccine will show comparable long-term efficacy if used in preteen/adolescent mass vaccination campaigns. This is because HPV16 and18 are more often present in CIN3 lesions that appear relatively early after incident infection whereas CIN3 caused by non-vaccine HPV types generally appear later, and so are less likely to contribute to this endpoint in a 4-year trial

than they will during a women's lifetime.[11] It should be noted that from a public health perspective, the most relevant figure for vaccine efficacy for the primary endpoint was 47.2% for vaccine-targeted HPV types in the ITT cohort.[8]

With respect to long-term immunogenicity endpoints, for Cervarix, plateau levels above those detected after natural infection have been observed or up to 8.4 years.[12] Similar results have been reported for Gardasil, with some evidence for immune memory in that antibody responses could be boosted by revaccination at month 60.[13]

Is Published Evidence Relevant to Public Health in India?

The age-standardized incidence of invasive cervical cancer in India is 27 per 100,000 women with a mortality of 15.2 per 100,000 women.[14] Robust data from several population-based cancer registries shows that the incidence of cervical cancer has been gradually decreasing in urban and rural India over the past two to three decades in the absence of either screening or vaccination. While the exact reasons for this decline are unclear it is likely to be due to a combination of factors like better hygiene and water supply, better nutrition, changing reproductive patterns, and others. For example a recently published 30-year time trend study from Mumbai revealed an average annual decline in cervical cancer incidence of 1.8% (95% CI 1.6-2.0%) between 1976 and 2005.[15] The average annual decline was even steeper (2.8%) in the most recent period between 1991 and 2005. The age standardized incidence rate (per 100,000 female population in age group 30-64 years) of cervical cancer in Mumbai was 41.1 in 1976 and 26.6 in 2005. Similar results have been reported from several other registries in India. It is self-evident that it would be far more productive to understand and strengthen the reasons behind this trend than to expose an entire population to an uncertain intervention that has not been proven to prevent a single cervical cancer or cervical cancer death to date.

Were HPV Infection and High-Grade CIN Appropriate End-Points in Vaccine Trials?

Prevention of invasive cervical cancer was not considered as an end-point in these trials, by the pharmaceutical industry, because sample size and trial duration would become impractical. But why would trial size be large? Because invasive cancer is a very rare outcome of persistent HPV infection! If cancer is such a rare outcome that it would take a prohibitively large trial to prove benefit, are surrogate endpoints (HPV infection) that rarely lead to the actual outcome of interest (cancer) justified? What about CIN II/III as endpoints? The actual scenario is as follows: About 90% of HPV infections clear over time. Of the remaining 10% that persist (potentially causing CIN I) 85-90% will regress spontaneously. Of the 10-15% (of the 10%) that still persist, only 5% progress to higher grade CIN (II/III). CIN II/III again can stabilize or resolve over time.[16] Of those that do develop CIN III, about 40% will progress to invasive cancer over the next 20-30 years.[17-19] It is clear from this understanding that only very rarely does HPV infection actually lead to invasive cancer in an infected individual and this rare event happens over a period of decades. How justified would it be to vaccinate the overwhelming majority of individuals today to protect the very rare ones who might develop cancer 20 years later? When that happens, it remains unproven that the very rare ones are actually protected from cancer! We have not even begun to consider the fact that only 70% of cancers are actually attributed to the vaccine subtypes.[16,18]

The only reasonable conclusion from the above is that it would be grossly premature to judge the efficacy of these vaccines from a public health perspective.

Are the Trial Results Applicable to Real Populations?

Both trials have shown maximum prophylactic efficacy in preventing CIN III only in the per protocol cohorts. Efficacy falls off sharply in the ITT cohorts. It bears repetition that it is actually the ITT analyses that are likely to reflect the actual efficacy of a healthcare intervention because those are the very characteristics of the population being vaccinated. For example, will women be tested for pre-existing HPV infection prior to vaccination? If not, then the actual efficacy, even for the imperfect endpoints discussed above, would be completely inadequate from a public health perspective.

What about Immunogenicity and the Eventual Impact on Cervical Cancer Incidence? Will Vaccination only Postpone Cervical Cancer and not Prevent it?

At present there are no data to suggest that either Gardasil or Cervarix can prevent invasive cervical cancer as the testing period is too short to evaluate the long-term benefits of HPV vaccination. The longest available follow-up data from phase II trials for Gardasil and Cervarix are 5 and 8.4 years, respectively.[20] Although immunogenicity analyses in the published data suggest continuing antibody responses for 5-8 years post-vaccination, cervical cancer is about two to three decades away from infection. The minimum level of serum antibodies needed to protect women from genital infection has not been established, follow-up is short, we have no information on the duration over which elevated antibody responses are likely to be maintained and there is very little information on the possible need for booster doses and their frequency of administration. If we suppose that immunity wanes after two to three decades of vaccination (it has not yet been proven that it does not), is it possible that the women will

become susceptible to infection/neoplasia/cancer later in their lives? That these fears are not unfounded is shown by the fact that almost 35% of Gardasil recipients have no measurable antibody against HPV-18 after 5 years of vaccination.[21]

Modeling studies have suggested that the vaccines must maintain near 100% efficacy for at least 15 years to prevent invasive disease.[22] Long-term studies that monitor both efficacy and immune titers over at least 15 years are required before the minimum immune titer necessary for protection can be determined.

Do the Vaccines Predispose to Cervical Neoplasia in Women Already Infected with Vaccine Relevant Subtypes?

A fact that has never been openly discussed is the increased risk of developing CIN II/III in those women who were already infected with the strains targeted by the vaccine, if they received Gardasil. Data provided by Merck to US-FDA[23] in a subgroup analysis showed that infected individuals had incidence rate/100000 person years of CIN II/III of 11.1 if they received Gardasil versus 7.7 if they had received placebo. Additional data published later reinforced the impression that women who are already infected with one of the high risk subtypes may be at increased risk of developing CIN II/III after vaccination.[24,25] At a very minimum, studies in these individuals are urgently needed to clarify this potential risk before recommending mass vaccination without prevalent HPV testing.

Are the Vaccines Really Safe?

Because vaccines are administered to healthy individuals the highest standards of safety are (rightly) expected of them. Although both vaccines were reported as being safe, data collected from the Vaccine Adverse Events Reporting System (VAERS) in the USA suggests that the rate of Gardasil-associated SAEs (4.3/100.000 distributed doses) is 2.5 times higher than the age-standardized death rate from cervical cancer. The SAE rate for Cervarix-associated SAEs shows a similar trend. It is estimated that the SAE rates obtained from the VAERS database may actually underestimate the true SAE rate (only 1-10% of all ADRs in the USA) since data collection for VAERS depends largely upon passive self-reporting.[26,27] There are several continuing concerns regarding vaccine safety with several independent reports of serious ADRs related to HPV vaccination. These include deaths, convulsions, syncope, paraesthesia and paralysis, Guillain-Barre syndrome, transverse myelitis, and other autoimmune demyelinating neurological sequelae, GI disturbances, anaphylaxis, and thromboembolism.[28-35]

In this context a healthy 16-year-old is at zero immediate risk of dying from cervical cancer but is faced with a small but real risk of death or serious disability from a vaccine that has yet to prevent a single case of cervical cancer. Physicians have an ethical obligation to provide a comprehensive explanation of the potential benefits and risks associated with vaccination to the potential recipients. Although official guidelines for vaccination are in place in Australia and the UK no such guidelines exist in India and there is genuine cause for concerns regarding mass vaccination in this country.

Are HPV Vaccines Cost-Effective?

The currently licensed HPV vaccines are very expensive and it is highly unlikely that countries with the heaviest burden of cervical cancer mortality (i.e., Uganda, Nigeria, and Ghana) would ever benefit from them, presuming, of course, that these vaccines prove their efficacy in cervical cancer prevention. In low-resource countries like India, not only the cost of the vaccines but the costs incurred in setting up a vaccination program i.e., feasibility, affordability, and logistics of vaccine delivery, etc., must also be considered. Another consideration is the mandated need for ongoing post-vaccination cervical screening which is non-existent in India. It is, thus, difficult to support channeling public funds in India toward mass immunization campaigns with either of the two HPV vaccines. Such a venture will not be justifiable either by the (as yet uncertain) long-term health benefits nor economic viability.

In developed countries on the other hand, with established cervical cancer screening, vaccination programs will only prove to be cost-effective if the vaccine demonstrates complete and life-long efficacy and there is at least 75% coverage of the targeted pre-adolescent population. This is necessary owing to the very low incidence of invasive disease in these countries due to effective Pap screening programs. Thus their cost-effectiveness in these countries is also questionable.

Can HPV Vaccination Replace the Need for a Cervical Cancer Screening Program in India?

There is no data in the literature to suggest that vaccination can replace cervical cancer screening. For any population coverage cervical screening will always detect more precancers and cancers than vaccination can prevent. Cost-effectiveness analyses have shown that cervical screening is more cost-effective than either vaccination alone or vaccination with screening.[36,37]

Conclusions and Questions

There are several relevant questions that the proponents of the available HPV vaccines need to answer:

- How, with zero evidence, are these products being promoted as 'cervical cancer' vaccines?
- Should regulatory and health authorities rely solely on data provided by vaccine manufacturers to make public health decisions?
- If the incidence of cervical cancer is declining in most parts of India (and is already very low in Western

populations) how is mass vaccination to 'prevent' it 30 years from now, justified?
- Should there not be a mandatory requirement to fully convey the small but real and serious risks of vaccination to potential recipients?
- Should the establishment of cost-effective screening and referral programs such as those with cytology and/or visual inspection with acetic acid (VIA)-based techniques not be a much higher public health priority in India?

Unbiased answers to these questions will lead to a meaningful roadmap for cervical cancer control in India and other developing countries that still have a significant burden of mortality from this disease. A step in this direction is the recent presentation of the results of the randomized Mumbai screening study using VIA in the hands of trained health workers, which resulted in a highly significant reduction in cervical cancer mortality in the screened group.[38]

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