## HPV vaccine programmes: Current scenario and recommendations in India

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SUMMARY

Drolet *et al*. did a systematic review and meta-analysis to assess the

population-level impact of the HPV vaccine. The intervention was HPV vaccination using bivalent or quadrivalent vaccine. The meta-analysis included all studies that reported the frequency of any of the listed end-points in a defined population in the pre-vaccination and post-vaccination periods. The outcomes considered were HPV infection (vaccine types HPV 16 and 18, cross-protection for other HPV strains and non-vaccine types), anogenital warts and high-grade cervical lesions. No randomized controlled trials were included.

Summary effects were calculated using the random effects model on a log scale. Heterogeneity was measured using $I^2$ and $\chi^2$ statistics. Analysis was stratified by sex and age (as mostly girls <20 years of age were vaccinated), and type of vaccine for anogenital warts. Subgroup analysis was done by: vaccine type, vaccination coverage, age, years since the vaccination programme was implemented, source of study data and by whether or not the impact measure was adjusted.

The authors identified 661 potentially relevant abstracts from Medline and Embase and 29 potentially relevant abstracts of unpublished data from conferences. Finally, 20 studies were included, of which 7 reported HPV infection, 11 anogenital warts and 2 reported high-grade intra-cervical lesions. All the studies were done in nine high-income countries. The meta-analysis found that there was a 68% decrease in the HPV 16 and 18 infection rates and a 61% decrease in anogenital warts in girls 13–19 years of age. In studies where vaccination coverage was high, cross-protection was found against HPV31, HPV33 and HPV45 infection as well as anogenital warts in men and older women.

## COMMENT

The study found evidence of protection against HPV 16 and 18 infection and anogenital wart diagnosis as a proxy for HPV 6 and 11 in the target population for vaccination, i.e. women <20 years of age. The study also showed herd effects in the form of cross-protection for other HPV types and in unvaccinated individuals, such as men and older women. Potential sources of bias and confounding included increased awareness of anogenital warts after the licensing of HPV vaccine, change in sexual activity, change in detection of vaccine and non-vaccine types of HPV and bias owing to clinic-based studies that measure proportion of clientele attributable to anogenital warts. The generalizability of the findings is also limited to individuals consulting the health system, as these individuals are included in most of the studies. The present meta-analysis includes studies from high-income countries, which may further limit its generalizability to middle- and low-income countries. The ecological fallacy inherent to population-based studies remains. Moreover, the lack of a systematic review registration number casts a shadow of doubt in the reader's mind.

The present study also showed a dose–response association between vaccination coverage and effect, along with evidence from other studies. However, the study reports effects only up to 4 years after vaccination and cannot comment on waning of effect of vaccination or whether there is a true reduction in the incidence of cervical cancer.

Meta-analysis of six randomized controlled trials including 47 000 women found that bivalent and quadrivalent vaccines significantly reduced the rate of lesions in the cervix, vulva, vagina and anogenital region, with efficacy of 93% (95% CI 87%–96%) and 62% (95% CI 27%–70%) and that adverse events were more with bivalent vaccines.[1] A meta-analysis by La Torre *et al*.[2] also found similar results.

Worldwide, cervical cancer is the fourth most frequent cancer in women, with an estimated 530 000 new cases in 2012. However, among women in India, cervical cancer is the most common cancer, with a population of approximately 365.71 million women above 15 years of age, who are at risk of developing it. The current estimates indicate approximately 132 000 new cases diagnosed and 74 000 deaths annually in India, accounting for nearly one-third of the global deaths due to cervical cancer.[3] Sexually transmitted HPV infection is the most important risk factor for cervical intra-epithelial neoplasia (CIN) and invasive cervical cancer. Two HPV types (16 and 18) cause 70% of cervical cancers and precancerous cervical lesions[4] and HPV 6 and 11 cause 85%–95% of anogenital warts.[5] Trials have found that both the bivalent and quadrivalent vaccines of HPV are 93%–100% effective.[6,7] The potential of saving lives as well as costs by introducing HPV vaccination is huge, especially for India.

However, despite what seems to be good evidence to implement a national policy for HPV vaccination, there are many dissenting voices in India. This was subsequent to the suspension of HPV trials in India in April 2010 after allegations of ethical misconduct by Merck.[8] A heated debate followed with the medical fraternity divided over whether or not the vaccine should be recommended.

At that time, two trials of HPV vaccine were being conducted in India—a multicentric clinical trial evaluating the immunogenic efficacy of two doses (6 months apart) *v*. three doses (at 0, 2 and 6 months) of Gardasil; and another in Khammam district (Andhra Pradesh, Gardasil) and Vadodara (Gujarat, Cervarix) to evaluate the operational feasibility of school-based and community-based vaccination against HPV. The state governments, Indian Council of Medical Research (ICMR) and PATH (a US-based non-governmental organization [NGO]) were involved in the trials. No biological outcome was measured in any of the trials. The death of four girls in Khammam caused a public outcry, which led to the suspension of both the trials. Subsequent investigations by the state governments, the Drug Controller General of India (DGCI) and ICMR found that the deaths were not related to the vaccine,[9] but the ban on HPV trials continues.

The Indian Academy of Pediatrics Committee on Immunization (IAP COI) recommends offering HPV vaccine to all girls/women who can afford the vaccine (Category 2 of IAP categorization of vaccines) before sexual debut.[10] It is ironical that trials of HPV vaccine cannot continue, whereas IAP recommends it and 52 countries worldwide have implemented HPV vaccination programmes, with USA and Australia recently including boys as well for vaccination.[11] In view of the large potential benefits, the government must expeditiously resolve the issues related to HPV vaccines.

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