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HPV vaccination in India

Dear Editor,

I read with interest the article by Gupta *et al*.,[1] "Is human papillomavirus (HPV) vaccination likely to be a useful strategy in India". Cervical cancer is the second leading cause of mortality among women in India, just behind breast cancer.[2] In making its arguments against the value of HPV vaccination in India, the authors unfortunately misinterpret much of the existing information.

Gupta *et al*., argue that "it is highly unlikely that either vaccine will show comparable long-term efficacy if used in preteen/adolescent mass vaccination campaigns". This is not the case. The high efficacy in the randomized controlled trials was shown in the per-protocol populations, which mirror the target demographics of mass vaccination campaigns, that is, girls before they initiate sexual activity. The intention-to-treat data are irrelevant in this context.

Gupta *et al*., point to a decline in the incidence of cervical cancer without any obvious intervention as a reason to delay implementation of a vaccination program. There is no country in the world where cervical cancer rates have declined from high levels on their own to acceptable levels in the absence of an organized cervical cancer prevention program. Even if rates have declined without any specific intervention, there is no evidence that this decline will continue. The current rates (22/100,000) are still too high[2] and hundreds of thousands of women are at risk of dying the longer implementation of vaccination and/or routine screening is delayed. The argument that cervical cancer is a rare outcome of HPV infection is accurate but irrelevant. The cancer and mortality statistics speak for themselves. More than 67,000 women die of cervical cancer every year in India.

Gupta *et al*., argue that the duration of protection is unknown and that concerns about loss of protection are justified by data showing that 35% of quadrivalent vaccine recipients have no measurable antibody against HPV-18 after 5 years of vaccination. Published data from both the bivalent and quadrivalent vaccines show continuing protection against HPV-18 after more than 8 years after vaccination and there is still no evidence of loss of protection.[3,4] Women remain protected against HPV 18 despite the absence of detection of antibodies to HPV 18 because the assay only measures antibodies to one neutralizing epitope to HPV 18. There are many antibodies that the assay does not measure and ongoing protection against HPV-18 despite the absence of detectable antibodies is a technical artifact of the assay.[5] Women remain protected against HPV 18.

Gupta *et al*., allude to data that women who are already infected with one of the high-risk subtypes may be at increased risk of developing cervical intraepithelial neoplasia (CIN) II/III after vaccination. There is no evidence of this in follow-up studies. Even if it were the case, vaccination campaigns should be primarily targeted to women who have not yet initiated sexual activity and who will not have HPV-associated CIN of any grade. Likewise, there is no evidence that the serious adverse events (SAEs) are occurring at a rate in vaccinated women that is higher than in unvaccinated populations.[6,7]

The authors allude to the need for ongoing postvaccination cervical screening. Screening guidelines will likely change with the adoption of the nonavalent vaccine, that is, less screening will be needed in women who receive this version of the vaccine since it covers a higher proportion of cancers than the quadrivalent vaccine.

The authors indicate that in developed countries vaccination programs are only cost-effective if the vaccine demonstrates complete and life-long efficacy and there is at least 75% coverage of the targeted preadolescent population. This is simply untrue. In developed countries vaccination is cost-effective at much lower levels than 75% uptake and much of the benefit is in reduced costs of screening for and treating high-grade CIN. There are also benefits beyond the costs of reduced incidence of cervical cancer. It is likely that there will be reduced incidence of vulvar, vaginal and anal cancer, and very possibly oral cancer, which is a serious public health problem in India. The authors also assert that cervical screening is more cost-effective than either vaccination alone or vaccination with screening. Many HPV experts would dispute this statement.[8,9] But even if it were true, how likely is it that effective cervical screening will be implemented in India? If it is simple and cost-effective, why has it not yet been done in India? Why are more than 67,000 women dying every year of cervical cancer in India?

HPV vaccination has consistently been shown to be safe and effective. Delays in implementation in the absence of an effective secondary cervical cancer prevention program will result in unnecessary mortality among Indian women. Policymakers should work closely with vaccine manufacturers and international agencies to ensure that the vaccine can be delivered in a cost-effective manner, as soon as possible.

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