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EDITORIALS

Effect of quadrivalent HPV vaccination on HPV related disease in women treated for cervical or vulvar/vaginal disease

Subsequent disease is reduced in women who undergo treatment post-vaccination

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The two most carcinogenic types of human papillomavirus (HPV) types 16 and 18, are responsible for around 70% of cervical cancers, 85% of anal cancers, and a smaller proportion of other anogenital and oral cancers.[1] Vaccines that target these two sexually transmitted HPV types have consistently shown high efficacy in preventing disease related to those specific HPV types in people who have not yet been exposed.[2-6] In the linked study (doi:10.1136/bmj.e1401), which is a post hoc analysis of the main efficacy trials (FUTURE I and FUTURE II) of the quadrivalent HPV vaccine that also targets non-carcinogenic HPV types 6 and 11 (responsible for most genital warts),[2 3] Joura and colleagues show a reduction in subsequent HPV related disease in vaccinated women who received treatment for cervical, vulvar, or vaginal disease (including genital warts) during the course of the trial.[7] This protection extended to disease associated with not only the four HPV types targeted by the vaccine but also 10 other HPV types that cause cancer.

The study's findings—including reductions in any HPV related disease (irrespective of causal HPV type) of 46.2% after cervical surgery and 35.2% after diagnosis of vulvar or vaginal disease—are welcome, but some important caveats deserve consideration.

Firstly, the authors classified "new" disease as disease detected more than 60 days after surgery or diagnosis on the basis of data from the FUTURE I study, in which 82% of those diagnosed with vulvar or vaginal disease received treatment within 60 days. This 60 day threshold was used to minimise the risk of capturing residual (not new) disease while maximising follow-up time, which was less than four years in both trials. In the subgroup analysis of women in the placebo group who developed cervical disease related to HPV types 6, 11, 16, or 18 after cervical surgery, the authors report that six of nine women had different HPV types from those detected in their surgical specimen, which supports the notion that cases detected after 60 days were indeed "new." However, if the remaining three women had residual disease, the efficacy against subsequent cervical disease would decrease to about 60%, with even wider confidence intervals suggesting substantial uncertainty. The study investigators found similar results when they extended the time interval to 90 days, by which time 91% of women had received treatment in FUTURE I; however, without conclusive diagnosis of new disease, uncertainty in the reported estimates remains appreciable.

Secondly, understanding the subgroup of women being studied—namely, those in the vaccine arm who developed HPV related disease after being vaccinated—is a key factor in putting the study's results into context. Joura and colleagues maintain that cases of disease in the vaccine arm did not result from vaccine failure. Furthermore, all but five women in the study received the full three dose vaccine series as per protocol. Therefore, vaccinated women who developed vaccine type (HPV types 6, 11, 16, and 18) disease during the trial presumably had been exposed to HPV infection(s) of the same type at the time of vaccination. The authors provide an example of two vaccinated women who underwent cervical surgery and then subsequently developed cervical disease; in both of these women the HPV types associated with disease were indeed concordant with those detected at day 1 of vaccination. A closer look at all 26 vaccinated women who developed disease related to HPV types 6, 11, 16, or 18 could further inform the level of concordance between HPV infection(s) at the time of vaccination and in subsequent disease, but this information is not provided. Nonetheless, it can be deduced that any disease that was prevented was associated with HPV infections that were not present at the time of vaccination, which simply reinforces what we already know—that women can benefit from HPV vaccination against unexposed types even if they are exposed to one or more other vaccine types. On one hand, as the authors note, the study corroborates previous findings that the benefits of vaccination are not limited to the primary target group of young sexually naive girls; but on the other hand, the current study's findings further highlight the importance of vaccinating at an early age, when exposure to HPV is minimal, to maximise protection against all HPV types targeted by the vaccine.

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Thirdly, and most importantly, this study examines a unique subgroup of women who were vaccinated before the first treatment for HPV related disease. The findings cannot be generalised beyond this group, specifically to women who are considering HPV vaccination after treatment for HPV related disease, contrary to the authors' suggestion that the women in the current study can serve as a surrogate. Without fully understanding individual characteristics and heterogeneities in these different populations, any inference or extrapolation of the current study's findings is premature. Because previous cervical disease was an exclusion criterion for enrolment in the vaccine trials, only surveillance of vaccinated populations in the real world can provide clear evidence of the effectiveness of the vaccine in women who have been treated before vaccination. As we await this information, it is important to emphasise to providers and decision makers that little, if any, generalisation of study findings can be made.

Half a million new cases of cervical cancer are estimated to occur each year, mostly in resource constrained settings, and HPV vaccination offers a tremendous opportunity for cancer prevention. Worldwide, decision makers who are increasingly considering adopting HPV vaccination programmes need information on the total potential health gains and the priority target groups for vaccination. The current study moves us closer to understanding the full scope of benefits from HPV vaccination by showing for the first time that vaccine protection against disease can endure beyond the management of HPV related disease in women already vaccinated. As evidence of both the efficacy and effectiveness of vaccination continues to emerge, responsible communication of the remarkable yet complex properties of HPV vaccines—specifically information about where the evidence is clear and where it remains uncertain—is crucial.

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