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Adjuvant HPV vaccination: proof or promise?

We read with interest the VACCIN trial by Ralf L O van de Laar and colleagues,[1] published in *The Lancet Obstetrics Gynaecology, & Women's Health*, reporting on adjuvant HPV vaccination after treatment of high-grade cervical intraepithelial neoplasia (CIN 2–3, also known as high-grade squamous intraepithelial lesion). Despite its randomised design, we noticed some limitations that might temper the non-superiority conclusion.

First, the 24-month follow-up is insufficient to capture recurrences from de novo infections. Data from previous vaccine trials show CIN 2–3 often develop 24–36 months after new HPV infection,[2,3] suggesting that the VACCIN trial might underestimate vaccine effect. Second, absence of margin status—an important predictor of recurrence (17% with positive margins *vs* 4% with negative margins[4])—in 33 (83%) of 40 participants is another potential confounder. Another limitation is the absence of HPV-specific genotyping, which precludes distinguishing persistent infection from reinfection. A further weakness is the non-standardised vaccination timing, with vaccinations allowed up to 4 weeks after loop electrosurgical excision procedure. This timing likely diluted protection, as evidence shows that the first dose should be given before surgery to ensure protective antibody levels against new infection, therefore limiting the ability of the trial to show the true benefit of adjuvant vaccination.[5] The under-representation of women younger than 30 years (20 [5%] of 402 participants in the vaccine group were age 18–29 years and the mean age was 39·2 years [SD 8·7]) restricts conclusions for the group most likely to benefit from adjuvant vaccination.

The trial found a 33·7% reduction—which is clinically relevant but underpowered, given design for a 62·5% effect—leaving room for type II error. Although not statistically significant, we calculated that the number needed to vaccinate was approximately 35 in the intention-to-treat analysis and 32 in the per-protocol analysis. This result contrasts with the number needed to vaccinate of 43 from a meta-analysis, suggesting the true effect might be smaller.[1,5] Overall, these limitations preclude definitive conclusions. Until standardised trials are available, adjuvant HPV vaccination should not be dismissed prematurely.

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I read with great interest the randomised controlled trial by Ralf L O van de Laar and colleagues,[1] published in *The Lancet Obstetrics Gynaecology, & Women's Health*, evaluating the efficacy of quadrivalent human papillomavirus (HPV) vaccination after loop electrosurgical excision procedure (LEEP) for prevention of recurrent high-grade cervical intraepithelial neoplasia (CIN 2–3). The authors reported no evidence of benefit, with recurrence rates at 24 months of 6% (23 of

402 participants) in the HPV-vaccinated group versus 9% (25 of 407 participants) in the placebo group.

These findings are consistent with the trial by Firnhaber and colleagues in women who were immunocompromised,[2] which also showed no added benefit of adjuvant HPV vaccination. Conversely, other randomised studies[3,4] suggested some protective effect, whereas a meta-analysis concluded that evidence remains insufficient.[5]

A biological distinction between early and late recurrences could clarify these discrepancies between studies. Early recurrences (12–36 months after LEEP) are usually due to persistence of the same HPV genotype and represent continuity of the initial disease. In this setting, vaccination is ineffective because HPV vaccines are prophylactic, not therapeutic. Late recurrences (5–20 years) after a disease-free HPV-negative period reflect new infection with identical or different genotypes, for which HPV vaccination could plausibly be protective. However, no trial has stratified participants by HPV genotype status before and after LEEP. Short-term follow-up (24–36 months) cannot capture late recurrences, the natural history of which requires 5–10 years to emerge.

In conclusion, current evidence neither supports nor excludes a protective role of adjuvent HPV vaccination after LEEP. A definitive answer would require randomised controlled trials restricted to women who are HPV-negative after LEEP with long-term follow-up.

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Authors' reply

We appreciate the points raised by Wiebren Tjalma and colleagues and Joseph Monsonego about the VACCIN randomised controlled trial,[1] many of which we discussed in the Article. We recognise that our study has limitations and we understand that many who believe in the potential benefits of adjuvant HPV vaccination might feel disappointed by the non-superiority conclusion.

Conducting randomised controlled trials is always challenging, particularly in a multicentre setting. Our study was designed based on the realities of daily clinical practice and with consideration of Dutch guidelines.[2] Some compromises were necessary due to scarce funding, whereas others were made to ensure the feasibility of the study across multiple centres. These decisions were pragmatic, made with real-world complexity in mind.

Regarding 24-month follow-up, this period indeed might not fully capture recurrences from de novo HPV infections; long-term data will be essential to assess the sustained effect of adjuvant vaccination. Our protocol includes planned follow-up at 5 years and 10 years.

According to Dutch guidelines, neither margin status nor HPV-specific genotyping is mandatory in the pathology report because this information does not have clinical implications for patient management. For this reason, and particularly due to financial constraints, we did not include these elements in our study. However, given the randomised design, we expect margin status and HPV type distribution to be balanced across groups. We have requested funding for HPV-specific genotyping on all samples and are planning to do this testing for the long-term samples, to distinguish between new infections or recurrences from the same HPV type.

The timing of vaccination was standardised up to 4 weeks after loop electrosurgical excision procedure (LEEP). Again, this period was chosen to facilitate daily practice in case of a see-and-treat colposcopy. 105 (13%) of 809 enrolled patients had delayed vaccination, with the remainder received vaccination on the day of treatment. In previous studies, first adjuvant HPV vaccination was administered weeks after LEEP.[3,4] We agree that the timing of vaccination remains a topic for discussion.

The under-representation of women younger than 30 years indeed restricts the conclusion for this subgroup. In the Netherlands, population screening for cervical cancer starts at age 30 years, which might account for why this subgroup is small. We found a smaller reduction in high-grade cervical intraepithelial neoplasia (CIN 2–3) recurrences than expected, and we clearly state in our Article that even a more modest reduction can be clinically relevant, but cost-effectiveness remains the most important factor. Based on our findings, we cannot recommend routine HPV vaccination after LEEP, and this conclusion is in line with recently presented data from the NOVEL trial (NCT03979014).

Despite the strength of a well designed randomised controlled trial