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cc Dr Colette Bonner DCMO  
Ms Michael Duffy Principal Officer  
Ms Pauline Brady CMO Office

**RE: Clarification of evidence relating to CIN1 HPV vaccination**

Dear Professor Smyth,

Thank you for your email of 31 January 2023 relating to NIAC advice for HPV vaccination for those with CIN1 and above. We have summarised the evidence for clinical effectiveness used to inform NIAC recommendations below.

On reviewing evidence in this cohort, NIAC considered the role of HPV vaccine from a primary preventative perspective as well as from an adjunctive therapeutic perspective. Additional factors considered include HPV vaccination uptake and the efficacy of the HPV vaccine programme, the potential impact on the cervical screening programme (CervicalCheck), the evolving epidemiological situation, and safety profile of the vaccine.

In Ireland, vaccination of schoolgirls (first years) with quadrivalent HPV (HPV4) vaccine commenced in May 2010. Catch-up programmes were run and continue to run. Since September 2019, the nonavalent HPV (HPV9) vaccine has been administered.

CervicalCheck screens approximately 270,000 women (aged 25-65 years) per year. CervicalCheck currently conducts 6,000 and 6,500 treatments per year for low (CIN1) and high grade lesions (CIN2+), respectively. CervicalCheck quotes a 10% risk of recurrence of CIN.

In England, routine HPV vaccination was first offered to schoolgirls in September 2008. Data pertaining to women between the ages of 20 and 64 years who were resident in England, were extracted from a population-based cancer registry from 1 January 2006 to 30 June 2019. These data demonstrate that the HPV immunisation programme has almost eliminated cervical cancer in women born since 01/09/95 (Falcato et al, 2021). The number of women who developed CIN3 has steadily decreased over time.

Early trends suggest that a similar impact will be seen in Ireland (unpublished data from CervicalCheck). It is anticipated that the number of women with persistent high grade lesions requiring excisional treatment will decrease in the near future. However, in the meantime there is a cohort of women who will need treatment for CIN and who will not have received the HPV vaccine.

The November 2022 NIAC recommendation states:

- **10.5.6 Vaccination within 48 months of treatment of CIN1+ lesions.**

HPV4 or 9 vaccine should be offered to women aged <45 years in this cohort.

This recommendation was primarily based on a 2021 systematic review and meta-analysis (Di Donati et al, 2021) suggesting that giving HPV vaccination within 48 months prior to or after primary surgical excision of CIN1 or greater, in women aged between 15 and 45 years is associated with a significantly decreased risk of recurrent disease in the order of 50%.

Subsequent systematic reviews (Eriksen et al, 2022; Kechagias et al, 2022) support evidence for effectiveness of HPV vaccination post treatment of CIN2 and CIN3 against persistent infection and development of invasive cervical cancer. A benefit was further demonstrated in those with CIN2+ in a 2022 publication in which HPV vaccination was associated with a 57% reduction in persistence or recurrence of high grade lesions after excisional treatment (Casajuana-Perex et al, 2022). However, evidence to support current recommendation for HPV vaccination post excisional treatment of CIN1 is more limited due to the lack of large well controlled randomised trials.

The biological plausibility of a potential benefit of HPV vaccination in those with persistent CIN1 is further highlighted when considering the impact of HPV vaccination in reducing recurrence of other HPV related disease. A 2019 systematic review and metanalysis concluded that in those with recurrent respiratory papillomatosis requiring surgical intervention, HPV vaccination given as an adjunctive therapy led to a significant reduction in the number of surgical interventions required and allowed a longer interval between future surgeries (Rosenberg et al, 2018). In a cohort study of men who have sex with men with previous high grade anal neoplasia, quadrivalent HPV vaccination was found to halve the risk of disease recurrence (Swedish et al, 2012). While this was a relatively small study (n=202) the results were significant.

High quality RCTs will further determine whether post-treatment HPV vaccination should be recommended for all women undergoing excisional treatment for CIN lesions. One such RCT (The NOVEL trial) is underway in the UK, Finland and Norway, the results of which are not anticipated before 2025.

It is important to note that ten to twenty percent of women with CIN1 will progress to high grade disease. Notwithstanding the shortcomings and caveats of study designs published to date, it is reasonable to postulate that the HPV vaccine could plausibly prevent progression in this group. This could have an important impact in terms of avoidance of further surgical interventions and ultimately preventing the development of cervical cancer. The safety profile and durability of protection of the HPV vaccine has been well established. There is a consistency in the direction of all of the study results to date indicating a potential benefit of HPV vaccination to those with CIN at risk of progression.

Since the original recommendation was formulated in November 2022, The Committee has engaged in constructive and informative exchanges with the Cervical Check Programme. Informed by those engagements and the latest evidence as outlined above, NIAC agreed to refine the November 2022 recommendation at the Full Committee Meeting on 27 March 2023 as follows:

**10.5.6 For those who require excisional treatment of CIN lesions;**

- HPV9 vaccine should be offered to previously unvaccinated women aged <45 years with CIN2+ lesions
- HPV9 vaccine may be offered to previously unvaccinated women aged <45 years with CIN1 lesions.

NIAC will continue to monitor emerging evidence in relation to HPV vaccination and recommendations will be updated as further evidence becomes available. Chapter 10 will be updated shortly to include this revised recommendation. NIAC will continue to monitor emerging evidence in relation to HPV vaccination and recommendations will be updated as further evidence becomes available.

Yours Sincerely,



**Prof Siobhán O'Sullivan**  
NIAC Chair



**Dr Bryony Treston**  
Interim NIAC Clinical Lead

## References

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