Dear editor,

The major basis of protection against infection [following vaccination] is neutralising antibodies [1]. HPV vaccination focuses on preventing HPV infection through generation of ‘neutralising’ antibodies which bind to sites on the viral capsid and prevent infection of host cells [2]. Both the bivalent and the quadrivalent HPV vaccines give a 100% seroconversion if measured one month after the completion of three vaccines [3,4].

The mechanism of seroconversion however is poorly understood. After 7.3 years all women vaccinated with the bivalent vaccine remained seropositive for both HPV 16 and 18 [4]. Over time the seroconversion rate for the different HPV types within the quadrivalent vaccine drops [3]. After a mean interval of 44 months the seroconversion rate for HPV 6, HPV 11, HPV 16 and HPV 18 is respectively, 89.7%, 94.5%, 98.4% and 60.3% [3]. Despite the drop of 40% the efficacy against HPV 18-related disease remained high (98.4%; 95% CI: 90.5–100.0).

The authors claim that these results suggest vaccine-induced protection via immune memory [3]. However, there is data to suggest that natural boosting may not occur. First of all there is HPV’s ability to evade the immune detection in the cervix [5], secondly approximately 40–50% of infected women do not make detectable antibodies to HPV [6–8], thirdly only very low numbers of B cells are detectable in the cervical epithelium of healthy women [9], and lastly there is a lack of antibody ‘spikes’ in subjects responses who are reinfected post-vaccination.

But most importantly the follow-up time of the presented study is not long enough to support the statement that immune memory exists.

One should regard the moment were the vaccine induced antibodies cross the “natural” level as new starting point. From this new starting point the protection should be determined. The women of the placebo group (HPV 6/11/16/18 seronegative and DNA negative) in the per protocol analysis started to develop CIN 1 + lesions after 18 months [3]. In a recent analyses is was revealed for the first time that the actuarial estimate of mean time between incident HR-HPV infection in previously uninfected women and onset of cervical lesion development is 44 months [10]. After 24 months 28.4% of the vaccinated women became seronegative for HPV 18, and this number grow to 39.7% after 44 months [3]. The study follow-up ends at 44 months [3]. Based on this information women who got infected with HPV 18 after they became seronegative and subsequently developed a CIN 1 lesion or worse will not be detected before the end of the study. Because, one would expect the development of lesions in vaccinees who were “exposed” to be about 18 to 44 months after they became “seronegative”. The follow-up time simply does not allow the detection of breakthrough infections. The study will never answer this question because it has been stopped and all participant of the placebo arm have been offered the vaccine. The only possible way breakthrough infection of HPV 18 can be detected is by the follow-up of the Nordic registries and registration trials. The question of immune memory remains unanswered until then.

References


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