PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>The impact of HPV vaccination on future cervical screening: a simulation study of two birth cohorts in Denmark</th>
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<td>AUTHORS</td>
<td>Hestbech, Mie; Lynge, Elsebeth; Kragstrup, Jakob; Siersma, Volkert; Vazquez-Prada Baillet, Miguel; Brodersen, John</td>
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VERSION 1 - REVIEW

<table>
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<tr>
<th>REVIEWER</th>
<th>Andrew Hinde</th>
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<td>University of Southampton</td>
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<td>United Kingdom</td>
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<td>REVIEW RETURNED</td>
<td>21-May-2015</td>
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GENERAL COMMENTS

The reviewer also provided a marked copy with detailed comments. Please contact the publisher for full information about it.

VERSION 1 – AUTHOR RESPONSE

1. What is the purpose of the paper? The conclusion is that the advice given to women who are screened following vaccination about the implications of a positive result should be little different from the advice offered to women who are screened without having been vaccinated. I do not have the background to judge whether or not this is an important clinical issue. To me, it would seem more important to make sure that women who have been vaccinated are screened – i.e. to disabuse these women of the notion that their vaccination has reduced the risk of cervical cancer to zero. I am aware that overtreatment, especially of CIN1 women, is an issue – but I am not sure what contribution this research makes to the reduction of that problem.

RE: We have taken note of this comment, that the purpose of the paper is not sufficiently clear, and we have therefore made the revisions below to the introduction, specifying that our main purpose is to investigate the frequency of positive screening outcomes, which is an important attribute of a screening programme.

However, we do not think, that our study contributes directly to the discussion of whether or not to continue screening vaccinated women. That requires more advanced modelling of cost-effectiveness of screening or (ideally) randomised controlled studies of the effect of cervical screening on incidence and mortality of cervical cancer in a context where HPV vaccination is implemented.

Added text:

One of the harms of screening is false positive results. Due to the reduced incidence of cervical
cancer, the predictive value of a positive screening may be reduced and the proportion of false positive results could increase.

The aim of this study was to test these hypotheses and to explore the interplay between primary and secondary prevention of cervical cancer in future primary healthcare by focusing on one of the important aspects of a screening programme: The frequency of positive screening outcomes.

2. The comparability of the 1982 birth cohort and the simulated 1993 birth cohort data is not addressed adequately. To say that 'socio-demographic data support this assumption' on the basis of the proportion of 20-24 year old women who have completed high-school education being 'fairly stable for the last ten years' seems grossly insufficient. I should like to see some evidence about sexual behaviour, age at sexual debut, number of partnerships, etc., in the two cohorts. I do not know whether this information exists, but surely in a country such as Denmark there is more than just information about completed education.

RE: We would like to thank the reviewer for this relevant comment. We have searched the literature on this topic. It has not been possible to find specific data comparing the two cohorts. But we have been able to find three references that suggest that the age at sexual debut in Denmark has been fairly stable over the past 30 years. We have added this to the manuscript.

Added text:
Moreover, studies of sexual habits among young Danish women, suggest that age of sexual debut has been fairly stable over the past 30 years with a mean age of sexual debut around 16 years 17-19

References:

3. I think the way the paper is presented is curious. The main contribution seems to be the calculations you have made of the numbers of false positives and the positive predictive value of the post-vaccination screening, which are reported in Table 3. These calculations seem fine, but the results are completely determined by the parameters of the model, which are the proportions by which vaccination reduces the ASCUS+, CIN2+ and CIN3+ outcomes compared to non-vaccinated cases, and by the input data, which are the results for the 1982 cohort. Much more attention should be given to the likely error in the parameters and the impact of this on the results. Specifically, I should like an account of how the pooled estimates of the reduction in the ASCUS+, CIN2+ and CIN3+ in the bottom row of Table 2 were arrived at. The sample sizes of the five studies whose results form the basis of the estimates are not given, and I should like to know whether you adjusted for the fact that in some instances you have a mixture of hazard ratios and odds ratios as input data. I should also like to see some sensitivity analysis of the results. What would be the impact of a reduction in the CIN2+ and CIN3+ as great as that obtained by Baldur-
Feskov et al. Given the uncertainty surrounding the future efficacy of vaccines, this seems to be at least as important as providing a simple point estimate.

RE: Firstly, the reviewer comments that he would like to see the sample sizes of the five studies that have contributed to the meta-analysis. Indeed, we agree that this is relevant information. However, we have chosen not to put these numbers in table 1, because we believe it will lower the readability of the paper and the table. We have provided the requested numbers in the table uploaded together with the revised manuscript (appendix table). We suggest that it can appear as an appendix to this paper, but we think that the final decision about the placement of this table should be decided by the editor.

Secondly, the reviewer addresses the use of a mixture of odds ratios and hazard ratios. Actually, we did not include odds ratios in our meta-analysis. As stated in the footnote to table 1 for the Crowe et al study the “Relative risk [was] calculated from reported data”, and this relative risk was used in the meta-analysis. This was done to make the different vaccine efficacy estimates as comparable as possible and easier to interpret for the reader. Nonetheless, we are aware that meta-analyses should be performed on ORs. In the meta-analysis we have not directly adjusted for the different effect estimates (RR or HR) that were used in the different studies. However, in the case the outcome (a positive test) is relatively rare in the background population, OR and RR are good estimates for each other, and a HR, also a relative risk of some sort, will also resemble RR and OR. That said, the study horizons differ and the (cohort) studies are adjusted for different variables. The heterogeneity between the studies, also because of the slightly different settings and inclusion criteria, is addressed by the use of random effect meta-analysis.

Added text: Pooling of the different measures of efficacy is justified because of the relatively low outcome incidence in the background populations.

Finally, the reviewer requests to see sensitivity analysis. Indeed we agree that this increases the transparency of our calculations, and we have therefore done sensitivity analysis, and added the text below to the manuscript, where we have also attempted to make clear, that our results are determined by the parameters of the model:

Added text: Sensitivity analyses were conducted using “best case” and “worst case” estimates of vaccine efficacy. (…) Sensitivity analyses using the extreme values of vaccine efficacies resulted in a “best case vaccine effect” estimate of PPV of 16.7% using CIN2+ as cut-off and 9.0% using CIN3+ as cut-off and a “worst case vaccine effect” estimate of 17.4% using CIN2+ as cut-off and 10.4% using CIN3+ as cut-off. (…) Results are obviously determined by the parameters of the model. However, sensitivity analysis substituting the pooled estimates with extreme values of vaccine efficacy resulted in quite similar estimates.

Editorial comments:
The title needs to state the study design, as at present it is confusing. As a suggestion - “The impact of HPV vaccination on future cervical screening: a simulation study of two birth cohorts in Denmark”.

RE: We thank the editor for this excellent suggestion and we have changed the title to “The impact of HPV vaccination on future cervical screening: a simulation study of two birth cohorts in Denmark”.

Otherwise Hinde gives an excellent review and suggests they clarify their message that women who have been vaccinated make sure they are still screened. He says they need to make it clear that their results are completely determined by the parameters of the model.
RE: Considering the first point, please see our reply to comment #1 from the reviewer. Considering the second point, we have tried to emphasize this, as explained in our reply to comment #3 from the reviewer.
The impact of HPV vaccination on future cervical screening: a simulation study of two birth cohorts in Denmark
Mie Sara Hestbech, Elsebeth Lynge, Jakob Kragstrup, Volkert Siersma, Miguel Vazquez-Prada Baillet and John Brodersen

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