Author’s response to reviews

Title: The costs of offering HPV-testing on self-taken samples to non-attendees of cervical screening in Finland

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Author’s response to reviews: see over
Dear Editor,

Please find enclosed our revised manuscript, “The costs of offering HPV-testing on self-taken samples to non-attendees of cervical screening in Finland”, for consideration by your Journal.

We want to thank the reviewer for a thorough analysis and good suggestions focusing on the essentials of the subject.

Here are our responses to the reviewers’ comments:

Reviewer 1:

Reviewer’s comment: It would be helpful for the authors to expand on the statistical analysis methods utilized in their cost-effectiveness analysis. Specifically, what models were used to estimate the costs.

Response: No previously known models were used; but we measured the observed program cost by using the total and average participation rates, follow-up compliance and referral rates and precursor lesion yields documented in the Finnish self-sampling studies and detection rates in routine screening. The costs were presented per invitational strategy in a population of 100,000 women. Lines 88-94.

Reviewer’s comment: The authors conduct a sensitivity analysis of their cost effectiveness estimates based on increased detection of hrHPV by molecular assays as compared to standard cytology. It would be helpful for the authors to provide a reference for the 20% and 50% increased sensitivity estimates they utilize. Furthermore, it is unclear how extensive the authors factored into their analysis the effect of the reduced positive predictive value of HPV testing alone due to a high number of HPV infections that will not progress to cervical pre-cancer. This increased detection of hrHPV and potential overtreatment, while potentially being balanced out by Pap Smear triage, may have an effect on the costs associated with CIN 2+ detection. I believe the authors make mention of this in the discussion, however a further elaboration would be helpful.

Response: The 20% and 50% rates were chosen as examples for alternative sensitivity analyses of program costs, as there is no previous knowledge on this aspect in the Finnish population, and the numbers in the original studies were too small for reliable comparisons in the background cancer risk of the participants by respective interventions or differences in clinical sensitivity by respective testing methods.

On the subject of reduced PPV of HPV-testing (high number of HPV-infections that will no progress into cervical cancer); As the test-positivity rates, referral rates and CIN2+ detection rates were direct observations from the studies conducted within routine screening, this has already naturally been accounted for (although number are small and susceptible for chance, as stated in the ‘Strengths and limitations’ section of the Discussion)
Reviewer’s comment: Did the authors consider differences in non-attendance and the cost-effectiveness of HPV-testing by self-sampling by age group in their analysis? It is unclear if cost-effectiveness estimates, particularly costs associated with CIN 2+, are different among women >30 or >35 years of age as compared to women <30 or <25 years of age. As above, a comment in the discussion section would be informative.

Response: No, due to the small number of CIN2+ lesions or even referrals detected in the original studies, as lack of effectiveness information on cervical cancer outcomes, calculations of this type would have been based simply on various assumptions and we felt that the basis for effectiveness estimates would have been unreliable yet. The reviewer is right that the cost might differ particularly among women aged <30 and <25, but these age groups are not even included in the analysis, as cervical screening in Finland in conducted mainly from age 30 onwards and there are very few cervical cancers in the Finnish female population below age of 30.

Reviewer 2:

Reviewer’s comment: Firstly, the tables are almost incomprehensible to the average reader, and a number of the assumptions in the model are either not up to date or not explained. The Tables should be redone in a publication friendly format and supported by explanatory flow diagrams showing how the composite cost prices have been reached. This at should be done with Table 1 at a minimum, but the top section of Table 3 could also be visualized in a flow diagram facilitating easier understanding.

Response: As per request, a flow chart of the invitational protocols has now been added as Figure 1. Further, to hopefully make the tables more readable, Tables 1 and 2 (methods) have been merged to new Table 1, and Tables 3 and 4 (results) to new Table 2. To further clarify the calculations made in each estimate (/invitational strategy), the costs that contribute to the final cost/strategy have now been marked in new Table 1.

Reviewer’s comment: Secondly, I have open questions: the cost assumption unit price is “1” for a mailed invitation letter. However the same unit cost for a reminder or invitation for self sampling is stipulated at 0.75. Why? I can think of a number of options to explain this, I can not however read it from the Tables or the text.

Response: The cost of a primary screening invitation includes the costs of identifying the screening population from the Population Register Centre and cost of the letter itself. The cost of a reminder letter (or invitation to self-sampling) includes only the cost of the letter itself. Lines 126-128.

Reviewer’s comment: Thirdly, the cost price of HC2 testing is set at 20 Euro. Even modelled at 30 Euro. Yet, the price of HPV testing using HC2 or similar test systems typically is around 14-16 euro in the Scandinavian countries, and with the high throughput of tests in the new Turkish screening program I believe the EU tender price ended at 4.65 Euro. This makes a major difference for the strength of the conclusions, and I assume the authors estimated the HPV test price as in a study, not in full roll out?? Nonetheless, given that the test prices world-wide are decreasing irrespective of HPV test system I strongly feel that the authors should recalculate the costs by assuming an HPV price of, say, 15 Euro as this will be a highly likely price in the Scandinavian markets.

Response: As per suggestion of one of the reviewers, additional analysis has been conducted with the HPV-analysis cost of 15 euros. Lines 121-122, and Table 2.
Reviewer’s comment: Fourth, what monetary unit do the authors use. In the text Euros are mentioned, but in the Tables, no such stipulations are made.

Response: The monetary unit (euro) has now also been clarified in tables

Reviewer’s comment: Fifth, clean up the commas and decimals in the Tables to make the appearance uniform, please.

Response: Done, Tables 1&2.

Lastly, the style of the written English language in the text has been re-checked, hopefully to your satisfaction. If needed, further copyediting can be made.

Once again, we wish to thank the reviewers for a thought provoking review, and hope that the corrections are to your satisfaction.

On the behalf of the working group,

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