Reviewer’s report

Title: Impact of HPV vaccination: health gains in the Italian female population

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Reviewer: Simopekka Vänskä

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In the manuscript "Impact of HPV Vaccination: Health Gains in the Italian Female Population" the author attempts to evaluate the impacts of HPV vaccination in terms of mortality and morbidity in the Italian female population. To this end, the author created a Markov model with diagnostic/observational states for cervical and anal cancers, cervical intraepithelial neoplasia, genital warts, three death states, and health, and use age-specific transition probabilities between the states. The state-specific health measures (QALY, DALY, etc.) were attached to the model outcome. The scenarios with and without HPV vaccination were compared using the above mentioned measures.

The subject is interesting, but the manuscript should not be accepted in the current form. To improve the manuscript, the author should consider at least the following issues:

1. Shorten the text and focus it better. For example, the methods and results sections include quite much discussion or introductory type text, which make it difficult to follow of what is done in the present study. Try to tell simply what was done in the study in the methods, and about results in the results sections. Discuss in the discussion section.

2. Transparency of work. For example, the sources for model parameters are presented in Table 1, but what about the values? The values should be given somewhere.

3. Model foundations: It is hard to believe that the progression from CIN1, or from CIN2/3, to cancer plays an essential role after the stage is diagnosed, as it is the case in the corresponding model states. Women with such diagnoses should be followed up. In contrast, much more important factor is that a woman in the model state "health" can still have an undiagnosed CIN1/2/3 by not attending cervical cancer screening, or by a false negative smear. Such undiagnosed lesions can progress to cervical cancer. Thus, differences in cervical cancer screening attendance, or management, would change drastically the balance between transition probabilities from health to precancerous and cervical cancer states [that is what is aimed with cervical cancer screening!]. Should the local screening attendance rates be included in the model in some way (or are they really uniform in the whole country?)? At least, the author should discuss that the model is not a natural history model but the transition probabilities to the diagnosed states depend heavily on the screening attendance rates in the population (and solely
in CIN1/2/3 cases as these stages induce no symptoms in practice). Are there any potential implications to the results?

4. The formula (5.18) in mid page 11 is essential in setting the effectiveness of vaccination, but many questions remain: A) The reduction rate \( x^*\lambda_{1,j} \) values are given in Figure 3, but the link was not very clearly presented so that I am not sure about this. If so, are the values adapted just as they were in the BASE study (are the study setting so similar that this is feasible?)? B) What does the author mean by a vaccinated cohort - a cohort with 100% coverage of vaccination, or the vaccinated part of a vaccinated birth cohort? C) The dependency between \( \lambda^{\text{Vacc}} \) and the coverage of vaccination \( \pi_{1j} \) is generally not linear by the herd effects. If no herd effects are taken into account, it should be mentioned. Did the BASE study include herd effects? D) Why such complicated notation with * and x in front of the transmission probabilities is used?

5. If no herd effects were included and screening is assumed unchanged, could essentially a similar analysis be done even without a Markov model? Just compute the age-specific health measures, and attach them to the age-specific incidence of the diseases, and use the reduction rates for the vaccination scenario. What would be the difference?

6. The cross-protection of quadrivalent vaccine against the ten HPV types seems very high compared to e.g. [Malagon] - although, the specific level of cross-protection is not clearly presented.

7. Details in figure and table legends are missing. For example, what is the unit of utility (Figure 2)? (1/year per case) or (per case). The main results are collected into Table 3-4. The tables should be combined and add the columns for the difference between the scenarios. Please explain the numbers in the legends.

8. State HEALTH is different from health state, confusing.

9. At the end of manuscript the author claims that the model could be used in developing secondary prevention strategies. Is this really feasible? The natural history of cervical HPV disease was not modeled (i.e., distinction of prevalent and observed cases), which makes it difficult to control the transition probabilities when the cervical cancer screening is changed in some way, see point 3 above.

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1. Employee of Institute for Health and Welfare (Finland), and Tampere University

2. No

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6. Working in the HPV modelling field as well

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