Reviewer's report

Title: Evaluation of primary HPV-DNA testing in relation to visual inspection methods for cervical cancer screening in rural China: an epidemiologic and cost-effectiveness modelling study

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Reviewer: Mari Nygård

Reviewer's report:

Current study by Shi et al., is an extensive evaluation of the effect of different screening tests for cervical cancer in China, as predicted by the mathematical model. The study provides a useful guidance for anyone who would like to make an informed decision regarding different technologies to be considered as options for public health policies. The report consists of: 5257 words as main article; 8 figures and 4 tables; an abstract; and list of references.

- Major Compulsory Revisions

1. I disagree with the authors regarding the conclusion of this study, namely the suggestion to use care HPV screening as a part of the regular screening program. This decision should be made based on the results from a randomized public health trial, where the direct effect of new strategy vs old strategy/no strategy can directly be observed, and NOT on the basis of a cost-effectiveness modelling study. As has been pointed out among the limitations of the study in the discussion on page 21: “... we had very limited data for assessing validity of model predictions against age-specific cancer incidence and mortality in this population” In fact there was no data on observed cause specific mortality, and “observed” incidence was assumed to be 22/105 , the same as in developing countries without substantial screening, which is a rather optimistic assumption, and most likely an underestimation for this high risk rural area. Further the authors state: “…we did not have extensive local data on health state preferences (utilities) or data from comparable populations to use in the calculation of QALYs, and therefore, the primary findings of the current analysis were based on the estimation of life years saved for the various screening strategies”. To implement successful cervical cancer screening has proved to be impossible in many countries. Among important barriers are: availability of the resources; acceptability of the screening method among the population at risk; availability of treatment facilities, i.e. “incomplete patient path or chain of actions”. Without the possibility to demonstrate the direct effect on cervical cancer incidence/mortality one should not suggest screening, but rather suggest this as a method which needs to be evaluated in public health trials and in real life settings.

My suggestion is that the authors revise the article and conclusions accordingly.

2. On page 6, the WHO World Standard Population was used, with ref. to
Ahmad, OB. In fact, Ahmad et al introduces in this publication a new standard population, which has been debated (Bray, F., Guilloux, A., Sankila, R., and Parkin, D. M. Practical implications of imposing a new world standard population. Cancer Causes Control, 13: 175-82, 2002).

Please clarify which standard population has been used in this model. In order to be comparative to the references, you should apply the WHO World Standard Population, not the new one, as indicated by Ahmad.

3. On page 6, you assume 71% as an overall participation rate by referring to Dai et al. and to unpublished data from a governmental project. Dai is reporting data from a study where out of 1668 women, 43.6% did not participate in the study, and out of the 941 who did participate, 197 did not give a smear, leaving about 44 % of the women invited with a smear. This is much lower than the stated 71%. Please provide clarification as to why you have chosen Dai in this context, and/or why you have stated 71%.

4. Results: there seems to be confusion regarding the terms “age-specific” and “age-standardized”:

“The incorporation of the HPV incidence into the model of CIN natural history resulted in a predicted age-specific incidence of invasive cervical cancer of 19 per 100,000 women”. Do you mean crude rate or age-standardized rate?

1. Results: “This is similar to the average age-standardised incidence of 22 per 100,000 and cumulative lifetime incidence of 2.7% observed in developing countries without substantial levels of screening…” and “The model predicts an age-standardised cancer mortality of 15 per 100,000 in the absence of intervention, peaking in the oldest age groups”…” please provide a reference.

5. References: Nr. 13, 17 and 19 are not fully cited. Please add for Ref. nr. 26 in press.

- Minor Essential Revisions

1. General comment: Figures 6 & 7 appear in the text earlier than figure 3. It is commonly accepted that figures are numbered in order of their appearance.

2. Results: §1 “…oncogenic HPV infection” please define this more specifically.

3. Discussion: “Regular screening would reduce cervical cancer mortality by 18-52%, with a CER of US$458-1545…” please correct as in table 3: $1550

4. Figure legend: Figure 2: please add ref.; Figure 3: please revise the legend, as you present as well observed incidences.

5. Figures:

Figure 1: VIA test and VILI test, at the end of the diagram, it is unclear who receives “ECC” and who “End this screening round”;

Headings of the figures 3A an 3B should be improved;

Figure 5 missing A and B labels.

6. Tables: Table 4: Does the Biopsy also includes diagnoses from the ECC? If
yes, please indicate.

Discretionary Revisions
I would expect more clarification regarding terms: undiscounted and discounted life-years saved.
The sensitivity analyses were different for QALY and for LYS (Figure 7 and 8). Please provide more explanation why.
The paper is already very extensive with over 5000 words, therefore clarifications should be incorporated in a manner which does not further increase the report.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests