Author’s response to reviews

Title: Online Cost-Effectiveness ANalysis (OCEAN): A user-friendly interface to conduct cost-effectiveness analyses for cervical cancer

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REVIEWER COMMENTS

Monisha Sharma (Reviewer 1):

This is a very interesting tool for conducting CEAs that has the potential to be highly useful for policy makers. I have some suggestions that would be helpful to address before publication.

We thank the reviewer for her comments and suggestions, that led to a significantly improved version of the manuscript. All specific questions are responded below, and the changes in the manuscript have been highlighted.

Model uses:

It is not clear from the paper who the intended users are of the online CEA tool. The tool is calibrated to Spain, which is a high-income setting. However the vast majority of cervical cancer burden occurs in developing settings. Most HPV modeling groups develop separate models that are used in developed vs developing countries because of the myriad of factors that affect the natural history in different settings. It would be useful to outline specific cases in which the tool could be used to inform policy decisions and to which settings the results can be applied.

We think that the tool will be more safely used by users with a minimum understanding of cost-effectiveness analyses, in order to properly conduct the analyses and interpret the results. Following the reviewer’s suggestion, we have described in more detail the profile of who we think might be the potential user of the presented tool. As the reviewer points out, the included transition probabilities matrix is calibrated to Spanish data, but the users could upload their own HPV prevalence, incidence and mortality data and calibrate the transition probabilities matrix to their own settings. To clarify, the following sentence has been added to the manuscript:
“The default transition probabilities matrix is calibrated to Spanish data, but the users could upload their own HPV prevalence, incidence and mortality data and calibrate the transition probabilities matrix to their own settings.”

Available support from developers:
The authors state "Despite the tool's ease of use and its design, thought to be usable for non-experienced users, the authors are available to provide some guidance in case it is needed." This sentence is a bit vague so it's not clear what level of support is available in parameterizing, conducting, and interpreting a CEA from the tool. Many other simplified models for diseases provide extensive user support. For example the WHO GOALS model for HIV provides a user training on the model and ongoing support use despite the model's ease of use. Although it is relatively easy to run the model, users without a background or understanding of CEAs could make incorrect model assumptions or misinterpret model results leading to potentially negative policy results. What steps will the developers take to prevent these occurrences? Further what level of ongoing developer support will be available to address bugs and issues as they arise?

One of the authors is responsible for the maintaining of the tool, and after acceptance of the paper their email will be published in the tool to encourage users to contact them in order to get advice, address bugs or fix any issues the users may found. Additionally, a specific training program may be prepared if necessary. To prevent misuses of the tool we considered the possibility of requesting a free registration for users in order to use the tool, although we would like to keep it totally open and encouraging contact with the authors in case the user found difficulties in using the tool or interpreting the results.

Correctly specified model inputs:
What data is needed in order to produce accurate results from the model? Currently, the data in the model is populated with costs and incidence/prevalence data from Spain. If a user is not familiar with the inputs that he/she needs to change, it seems they could inadvertently use default inputs from Spain. What steps will the authors take to prevent this from occurring? Would it be possible to pre-populate the model with HPV prevalence and CC incidence data from many countries around the world (using ICO, registry, and Globocan) and allow the user to choose the country from a drop down menu? This is how HIV models including GOALS are set up to minimize errors in model specification. Further, users may not have the clinical or epidemiologic background to manipulate primary data into a form needed by the model or correct for biases (eg the proportion of sexually active young women in HPV prevalence surveys or the sensitivity/specificity of precancer lesion detection). This highlights another reason that technical support from the authors in analyses is important.

The necessary input data for the calibration and cost-effectiveness parts are listed in the manuscript (Sections 2.1.1 and 2.1.2 respectively). The tool shows a pop-up windows with the message “If a needed input file is not provided, the corresponding example file will be used for the analysis.” to warn the user about using default data. To be more specific, this message has been changed to “If a needed input file is not provided, the corresponding example file will be used for the analysis. In particular, the transition probabilities matrix might not be calibrated to your specific settings.” At this point, it is not possible to pre-load data from several countries, but the tool allows the user to include their own data.
Accuracy of model results:
The authors state that the tool output is very similar to that of a more sophisticated model for Spain but it would be useful to have more detail, including graphs comparing the results, or indications of how and why the results of the two models differ. More detail would be useful on the validation of this tool, particularly given its simplicity. It's not possible for a simple tool to match a more complex model exactly, so in what ways are the results inaccurate and how inaccurate? What are the implications of this? Specifically, graphs comparing the projected impact of CC screening on CC burden over time from the tool and a more complex model would be useful.

Although we put a lot of effort into making the tool simple, the underlying mathematical model is not. In fact, the underlying Markov model is essentially the same that was used in reference [7], adapted to include more screening strategies not used in Spain (VIA). This is the main reason why Section 3 (Results) reproduce the analyses reported in [7], so it can be seen that results are pretty much consistent. In particular, the cost-effectiveness summary graph reported in [7] is reproduced using the outcomes from the tool in Figure S2 (Supplementary Material). To clarify, the following sentence has been added to the manuscript (page 4):

“This model is described in detail in [7].”

Lack of herd immunity:
This tool seems very useful to evaluate cervical cancer screening strategies. However, I'm concerned about the implications of using a linear model to assess the cost-effectiveness of HPV vaccination. The authors state several times in the manuscript that they intend to add in 9v-HPV and additional vaccine related cancers for evaluation. Modeling studies evaluating the impact of not considering herd immunity when projecting health benefits from HPV vaccination have found a substantial underestimating of cancers averted and a cost-effectiveness ratio that is too high. It would be useful if the authors could address this limitation and assess the difference between health benefits projected by the tool compared to a dynamic simulation model. My sense is that it would be better for policy makers interested in HPV vaccination to use a very simple dynamic compartmental model to assess projected impact of vaccines rather than a linear model.

We agree with the reviewer that not considering herd immunity is a limitation of the model, and we plan to include it by using a microsimulation model in upcoming versions of the tool. To highlight this point, we have added the following lines to the manuscript (page 12):

“Using a static underlying model has also some relevant limitations as, for instance, not capturing herd immunity benefits due to HPV vaccination, although it can handle complex screening strategies and improves transparency and robustness of the results compared to dynamic models [22]. To overcome this issue, more sophisticated models based on microsimulation will be included in the near future.”

[22] Westra et al. Until which age should women be vaccinated against HPV infection? Recommendation based on cost-effectiveness analyses (2011). The Journal of Infectious Diseases, 204:377-384.
As the reviewer points out, the comparison between dynamic and static models would be of great interest, but we think it is beyond the objectives of the present work.

Supplementary material:
It would be helpful if the supplementary material was more detailed, particularly since this is the first time this new tool is being published. Most modeling papers include supplementary information that is 50-100 pages of model specification, equations, rationale behind model assumptions, validation exercises, etc. References can be included for model parameters and costs reported in the supplement currently.

This is the first publication focused on the OCEAN tool, but the underlying model has been used before and is described in full detail in reference [7]. To clarify, the following sentence has been added to the manuscript (page 4):

“This model is described in detail in [7].”

Language/grammar:
The paper can benefit from careful proofreading and improvements to language and readability. Grammatical editing by a native English speaker would be helpful. For example

Page 6: "That allow the tool to generate" should be "That allows(s) the tool to generate"

This sentence has been corrected and the manuscript has been revised by a native English speaker as suggested.

Further, much of the language could be tightened to be more concise. For example:

"In general, it is known that the mathematical models used in cost-effectiveness analyses are affected by a significant and non-negligible degree of uncertainty at different levels" could be changed to:

"Model-based projections are subject to uncertainty."

This sentence has been rewritten to:

“In general, it is known that mathematical models used in cost-effectiveness analyses are subject to uncertainty at different levels...”

Reviewer 2:
Overview
This manuscript describes an online implementation of a Markov model that can be used to evaluate the cost-effectiveness of HPV vaccination programs. The underlying model has been programmed in R, and a beautiful interface has been programmed in shiny. Users are able to use the fixed model structure but customize the parameterization and calibrate the population. I applaud the authors for making their model available and for the truly impressive online interface they have made that would allow others to use and customize their model. The manuscript itself
has several issues. The language is awkward in places, and difficult to read. In addition, the flexibility and usefulness of the model and online tool are exaggerated in places. And finally, I worry about the motivation for the online tool. It is suggested that this model will allow users without a background in modeling or cost-effectiveness to perform cost-effectiveness analyses of HPV vaccination programs. In reality, users without a background in modeling or cost-effectiveness are not likely to either appreciate what the model can do nor understand how to customize transition probabilities, costs, or utilities in the model. I think there value to having this model available but would urge the authors to re-think who could successfully use it, and how. I have the following suggestions to improve the manuscript.

We thank the reviewer for his or her comments and suggestions, that led to a thorough and deep rethinking of the tool and its objectives. All specific questions are responded below, and the changes in the manuscript have been highlighted.

Major issues
1. The title does not reflect the content of the manuscript. The title implies that the tool is useful for *any* cost-effectiveness analysis. But the tool is only useful for studying cost-effectiveness of HPV vaccination programs in females. Please consider narrowing the focus of the title to a more appropriate scope.

We agree with the reviewer that the title suggests that the tool is useful for any cost-effectiveness analysis, while the model it is based on is focused on cervical cancer. For this reason, the title has been changed to “Online Cost-Effectiveness ANalysis (OCEAN): A user-friendly interface to conduct sophisticated cost-effectiveness analyses for cervical cancer”. However, it is important to notice that it can be used to evaluate cost-effectiveness of most usual screening strategies (cytology, HPV DNA test and VIA) additionally to HPV vaccination programs.

I’m uncomfortable with the motivation that this tool will allow people unfamiliar with decision analysis, Markov models, or cost-effectiveness analysis, to perform this kind of analysis. Without some background in these methods, how will they be able to properly specify transition probabilities, costs, and utilities so that results are meaningful? How will they be able to interpret the results? Is it plausible to think that someone who does not understand cost-effectiveness will be able to produce and interpret an incremental cost-effectiveness ratio or net monetary benefit correctly? It seems to me that the tool is going to be best used by analysts who ARE familiar with these methods.

We agree with the reviewer that the tool will be more safely used by users with a minimum understanding of cost-effectiveness analyses, in order to properly conduct the analyses and interpret the results. Following the reviewer’s suggestion, we have changed the focus on who might be the potential user of the presented tool. Additionally, several sentences in the manuscript have been changed to be as cautious as possible about the flexibility and usefulness of the tool.

Minor issues
[Page 3, line 1] “Professionals that should face these analyses” is unclear. What kind of professionals? And does “face” mean read? Or desire to perform?
We mean professional who would need to perform cost-effectiveness analyses. The sentence in the manuscript has been changed to:

“However, it is not uncommon that professionals that would need to perform these analyses are not familiar with the models.”

[Page 3, line 18] “Quick tool” is misleading. The tool itself is neither quick nor slow. The tool can certainly facilitate CEA, but it is hard to imagine a scenario where doing so will be quick unless only the default parameters are used. And in that case, why is it worth doing since those results are already available?

We agree with the reviewer. This sentence has been changed to:

“… with a useful tool to conduct complex cost-effectiveness analyses…”

[Page 3, line 33] Consider changing “are consistent to” to “are consistent with”.

Changed.

[Page 3, line 35] I disagree that having a tool “will certainly” be an asset. It could be as asset, for some, but this is in no way certain.

We agree with the reviewer and several sentences in the manuscript have been modified in order to be as cautious as possible regarding the usefulness of the tool.

[Page 4, line 3] Consider changing “its efficient” to “their efficient”.

Changed.

[Page 4, line 12] Consider changing “optimum” to “optimal”.

Changed.

[Page 4, line 31] Consider changing “find any pre-cancerous lesions” to “find pre-cancerous lesions”.

Changed.

[Page 4, line 41] I do not understand what you mean by “concrete setting”.

We mean the specific characteristics of the implemented strategies (age at which girls are vaccinated, screening ages…). To clarify, the sentence has been changed to:

“… although details may vary.”

[Page 4, line 48] Consider changing “challenges to be faced” to “challenges faced”.

Changed.
Changed.

[Page 4, line 50] I would recommend qualifying “most cost-effectiveness analysis” to indicate cost-effectiveness analysis of HPV vaccination and cervical cancer prevention.

We agree with the reviewer. The sentence has been changed to:

“Currently, most cost-effectiveness analyses focused on the evaluation of cervical cancer prevention strategies are conducted by means of mathematical models that simulate the natural history of HPV and cervical cancer.”

[Page 5, line 12] It is not true that users of the model can perform cost-effectiveness analysis “without dealing with complex mathematical modelling”. The do still deal with complex modeling. The fact that the model has been pre-specified does not mean it does not have to be dealt with.

We agree with the reviewer. The sentence has been changed to:

“… a new easy to use web application that allow running sophisticated cost-effectiveness analysis based on a pre-specified mathematical model.”

[Page 6, line 39] I would avoid making this bulleted list a specific instruction manual. This should list the inputs without instructions such as ticking boxes.

We appreciate reviewer’s suggestion, but we think that having a brief explanation of what is each input parameter referring to might help the user to use the tool properly.

[Page 7, line 13] The language “used in the cost-effectiveness part” is awkward and unclear.

We agree with the reviewer. To clarify, the sentence has been changed to:

“An Excel file including all calibrated matrices can be downloaded and used as inputs for the cost-effectiveness analyses.”

[Page 8, line 1] Is there a reason undiscounted results are presented by default, when most guidelines for good practice in CEA (e.g. ISPOR guidelines) suggest using a 3% discount rate by default? Even your example later uses a 3% discount rate.

We agree with the reviewer that there is no reason to present undiscounted results unless user explicitly asks for it, as most guidelines recommend using some discount rate. The tool behavior has been changed according to this criterion, so undiscounted results are not presented by default. The corresponding sentence has been changed to:

• “Discount rate: Discount rate to be applied to health and costs (undiscounted results can be obtained by setting the discount rate to 0).”
Consider changing “one...matrices” to “one...matrix”.

Changed.

How is “best-fitting” defined?

To clarify this point, the sentence has been changed to:

“The output is based on the 5 best-fitting (the matrices producing the outcomes that minimize the differences with respect to target HPV infection prevalence and CC incidence) simulations out of 10 demanded with a 10% of change.”

I completely disagree with your characterization of this tool as a “very adaptive and flexible environment”. The model is completely fixed. The population is fixed. Only the parameterization has some flexibility.

The sentence has been changed to:

“… the most common cervical cancer prevention strategies worldwide using their specific parameters.”

Again, I would contest the idea that the tool “will certainly” be an asset. It might be, for some. It has the potential to be an asset to folks that DO have a background in modeling.

We agree with the reviewer and this sentence has been modified in order to be as cautious as possible regarding the usefulness of the tool.

I’d recommend removing “great”. It might be useful, and that is good enough. There is no need to exaggerate.

We agree with the reviewer and the sentence has been changed accordingly.

I suspect you meant “warts” not “wards”.

The reviewer is right. It has been changed in the manuscript.

Consider changing “in the upcoming” to “in upcoming”.

Changed.