PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Organized screening for cervical cancer in France: a cost-effectiveness assessment
AUTHORS	Barré, Stéphanie; Massetti, Marc; Leleu, Henri; De Bels, Frédéric

VERSION 1 – REVIEW

REVIEWER	Didik Setiawan Dept of Pharmacy, Faculty of Science and Engineering, University of Groningen, the Netherlands Dept of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy. Universitas Muhammadiyah Purwokerto, Indonesia
REVIEW RETURNED	09-Feb-2017

GENERAL COMMENTS	- The cost-effectiveness threshold should mentioned in the method section and the decision or recommendation should be based on the threshold. - Table 5 and 6 will be more attractive if it is presented as tornado diagram - Some of the discussion (line 13 to 25) is more suitable in the result section, synthesize the results and create an ultimate discussion based on these results instead of explaining each screening methods. - Further research on HPV vaccination will add some consideration for another researchers in the field

REVIEWER	Monisha Sharma University of Washington, USA
REVIEW RETURNED	04-Mar-2017

GENERAL COMMENTS	General comment: This is a very interesting and timely paper on methods to cost-effectively optimize cervical cancer prevention in France. The authors use a validated model and conduct a robust sensitivity analyses. This paper could benefit from editing by a native English speaker. My major concern is concerning the impact of HPV vaccination and how it is handled in the model. Do the authors assume a certain percentage of women are vaccinated and have a 70% lower risk of

	getting CC? Vaccination is likely to have a large effect on cost-effectiveness of different screening strategies and the proportion of vaccinated women is likely to increase over time. It would be good to have more details about the model in the methods and supplementary appendix. Is the model stochastic or deterministic? What software is it programmed in? Are all HPV types modeled as one infection? Are there additional calibration results for age specific CC incidence and HPV prevalence, CC incidence over time, and prevalence of CIN1 and CIN23? It would be helpful to see how the model predicts health outcomes other than overall CC incidence and mortality. Does the age structure of the 100,000 women match the age structure in France? This would be especially important given that age at model initiation had a large impact on the results. Abstract line 2: “Accordingly to the third Cancer plan”, I think this word should be “according”. Delete “in regard of this objective” I’m unsure what the collective perspective is. Do you mean societal perspective? Define: (Pap, HPV, p16/Ki67), spell out acronyms. More detail is need on “current situation” and screening strategies including coverage and frequency assessed. Line 18: “It is the dominating alternative”. The meaning of this is unclear and could be confused with “dominated”. Perhaps this could be changed to “most efficient” alternative or something similar. Line 22: “The assumption that OS periodicity will be respected”. This is unclear. Background I think the first sentence can be deleted to keep the focus on CC in developed countries, specifically France. Second paragraph: Are screening guidelines different for vaccinated and non vaccinated women? If so, please specify. Although providing HPV vaccination coverage rates would be helpful. Line 21: More detail on these strategies would be helpful. What was the coverage rate of self-testing? How much did it reduce loss to follow up? Does the 13.2% increase in participation refer to the self-sampling coverage or facility based HPV testing? Methods Line 8: positivize—I think this is a typo. “A small fraction of participant was LtFU.” Please specify the loss to follow up rate Table 1: IT would be useful to have more specific inputs on percentage increase in screening coverage and percentage decrease in loss to follow up associated with each strategy. I think it should be stated more clearly if only women who did not participate in regular screening are the only ones targeted for the

	interventions. Results Table 4: I think it would be useful to have the percentage increase in LYs associated with each strategy in addition to the absolute increase. Tables 5 and 6: I think the tables should have the ranges used for sensitivity analyses so they can be understood as stand alone results. A tornado diagram would be a useful depiction of influential parameters. Discussion It would be good to mention the threshold being used for cost-effectiveness. Page 13: “Accetta et al. have found HPV-test every 5 years 1 to be a dominant 2 strategy over triennial Pap-tests in Italy.” The word dominant is confusing here, I think it would be better to say “more cost effective” or “more effective”.

REVIEWER	Gary Ginsberg Ministry of Health, Israel.
REVIEW RETURNED	16-Mar-2017

GENERAL COMMENTS	Major problems Table 2 is very good, except for the fact that it does not include the disability weight/health state valuations given to the various stages of cancers. Please add them into Table 2. If by some chance you only included DALY losses due to mortality, then this is a serious erroneous mistake and you should add morbidity losses via the cancer stages to your model and recalculate your results. Tables 5 and 6 do not contribute much……..it is best to delete them and draw up a new table that presents the lower and upper bounds of the parameter values AS WELL as the resultant ACER (average cost-effectiveness ratio) --- this will enable us to clearly see the relative effects of changes in parameter values…… The English has numerous linguistic mistakes and is also very cumbersome and hard to follow. Some mention could be made in the discussion as to what might consist of a reasonable boundary for achieving cost-effectiveness….maybe 3 x GNP per QALY or $50,000 or ????….thereby maybe showing that 35,846 per QALY as well as 101,389 per QALY ICERs are both cost-effective Minor problems Page 4 line 16: Screening remains the main prevention tool because vaccination is restricted to only younger age groups in ADDITION to the compliancy rates being lower than for screening.

	Page 4 line 28-33 cost-utility analysis should be mentioned somewhere in this paragraph. Page 6 line 40……..delete "all costs…..price index" as these are repeated in lines 5/6 on page 7. Page 10 Table 3. Re-order HPV/Pap by swapping the places of HPV/Pap-5y with HPV/Pap-3y. Supplementary File 2: It is not clear what the RR refers to……is the the RR of participation or the RR of cancer or RR of something else…..please clarify…….

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. The cost-effectiveness threshold should mentioned in the method section and the decision or recommendation should be based on the threshold.

Dear reviewer, thank you for your comments on our manuscript. Please note that no cost-effectiveness threshold is relevant in the French context since HAS (the high health authority, which is the independent agency in charge of health technology assessment, including pharmacoeconomic evaluation) does not wish cost-effectiveness results to be compared to a threshold.

In order to ensure the relevance of our study as a decision-support tool for the French national cancer institute (INCa) and the health ministry, it was performed following the HAS guidelines for health economic assessment. Indeed, in France, cost-effectiveness analyses are not used as a resource allocation tool for health technologies. Instead, cost-effectiveness results are used as indicators of the health-economic value of a technology relatively to its comparators during pricing negotiations between the technology supplier/manufacturer and the health ministry.

Furthermore, our study took place in a context where implementation of organized screening (OS) for cervical cancer was decided upon as part of the national “cancer plan”, with oversight by the President of the Republic. Therefore, our study did not aim to assess whether and how OS was efficient. The goal of the study was rather to determine which screening modality was the most efficient, keeping in mind practical issues, such as the operational feasibility and clinical interest of every assessed OS modality, reduction in social inequalities regarding access to cervical cancer screening and budget constraints.

In this context, our study should be reviewed as a public health analysis based on a modelling methodology, rather than a medico-economic assessment of health technologies. Therefore, we do not feel comfortable with presenting our results relatively to a cost-effectiveness threshold. We feel that this point of view is further reinforced by our results that confirm the legislator’s choice to implement organized screening.

However, mentions of “absolute” cost-effectiveness of strategies (i.e. “strategy X is cost-efficient”) were removed to better comply with our approach.

2. Table 5 and 6 will be more attractive if it is presented as tornado diagram

Results of the DSA are now presented as tornado diagrams.

3. Some of the discussion (line 13 to 25) is more suitable in the result section, synthesize the results and create an ultimate discussion based on these results instead of explaining each screening methods.

Thank you for the suggestion, the manuscript was revised according to your recommendation.

4. Further research on HPV vaccination will add some consideration for another researchers in the field

HPV vaccination is implemented in the model by applying a relative risk of HPV infection in vaccinated women. The parameters associated with vaccinations were tested in sensitivity analyses and had a negligible impact. This is mostly due to the structure of the modelled population that

reflects the actual characteristics of French women eligible for cervical cancer screening and the closed cohort methodology. Scenarios that considered vaccination rates up to 80% in an effort of anticipation of the increasing number of vaccinated women going through cervical cancer screening had a negligible impact on results.
Furthermore, vaccination has had a slow adoption in the French population. In 2015, it was estimated that only 17% of women eligible for vaccination were vaccinated. Therefore the impact of vaccination on the efficiency of cervical cancer screening strategies is not expected to be significant in the forthcoming years.

Reviewer: 2
General comment:
This is a very interesting and timely paper on methods to cost-effectively optimize cervical cancer prevention in France. The authors use a validated model and conduct a robust sensitivity analyses. This paper could benefit from editing by a native English speaker.
Dear reviewer, thank you for your comments on our manuscript. The writing of the manuscript was revised and the manuscript was submitted for English editing to a specialized company before submission.
My major concern is concerning the impact of HPV vaccination and how it is handled in the model. Do the authors assume a certain percentage of women are vaccinated and have a 70% lower risk of getting CC? Vaccination is likely to have a large effect on cost-effectiveness of different screening strategies and the proportion of vaccinated women is likely to increase over time.
Indeed, HPV vaccination is implemented in the model by applying a relative risk of HPV infection in vaccinated women. However, since the modelled population is representative of French women eligible for cervical cancer screening (women aged 25-65 that did not undergo a hysterectomy or trachelectomy), vaccination was limited to women aged 30 or less as it was only recently available in France.
The parameters associated with vaccination (vaccination rate and relative risk of infection) were tested in sensitivity analyses with a negligible impact. This is mostly due to the structure of the modelled population and the closed cohort methodology. Scenarios that considered vaccination rates up to 80% for all ages in an effort of anticipation of the increasing number of vaccinated women going through cervical cancer screening had a negligible impact on results.
Furthermore, vaccination has had a slow adoption in the French population. In 2015, it was estimated that only 17% of women eligible for vaccination were vaccinated, a decreasing trend. Such figures would not allow herd immunity against HPV among women living in France in the forthcoming years/decade. Therefore the impact of vaccination on the efficiency of the tested cervical cancer screening modalities is not expected to be relevant in the timing of cervical cancer OS implementation in France, although it represents a major discussion topic among health practitioners involved.

It would be good to have more details about the model in the methods and supplementary appendix. Is the model stochastic or deterministic? What software is it programmed in? Are all HPV types modeled as one infection?

Are there additional calibration results for age specific CC incidence and HPV prevalence, CC incidence over time, and prevalence of CIN1 and CIN23? It would be helpful to see how the model predicts health outcomes other than overall CC incidence and mortality. Does the age structure of the 100,000 women match the age structure in France? This would be especially important given that age at model initiation had a large impact on the results.
Extended presentation of the model methodology has been added as a supplementary appendix, in particular:
•It is a stochastic model that operates on an individual level.
•The model is programmed in C++. Input data and scenario definition are entered through a Microsoft Excel interface. Model results are then exported to Excel to generate the figures and tables.
•Model calibration was performed in two steps:

-Age-dependent HPV-infection rates were calibrated on age-dependent HPV-infection prevalence observed in France
-Age dependent transition probability from persistent CIN2/3 to cervical cancer was calibrated on age-dependent cervical cancer incidence rate.
Results of both calibration processes are provided in a supplementary appendix.
•Population characteristics, including age, were based on available epidemiologic and demographic data representative of the French population.

Abstract
line 2: “Accordingly to the third Cancer plan”, I think this word should be “according”.
Thank you for the correction.

Delete “in regard of this objective”
OK.

I’m unsure what the collective perspective is. Do you mean societal perspective?
In France, the HAS recommends adopting a collective “all payers” perspective for cost effectiveness analysis that takes account of all the stakeholders involved in the implementation of the health technology assessed.
This leads to differences in the resource utilisation considered compared to the societal perspective: the basecase analysis is limited to direct costs, that is, costs related to the resources used in the production of the intervention: consumption of hospital care, outpatient care, medical goods, transport, organisation of a health care program, time spent by people undergoing the interventions, and time spent by their care givers, as well as costs related to the treated disease during the added life-years. Transition costs must also be presented (resource consumption required for the intervention to be routinely used, including infrastructure modifications).
The indirect costs, which include resources and time used because of mortality/morbidity, measured as the duration of the different categories of activities affected which are typically included in the societal perspective, should not be included in the base case analysis.
To add clarity to the abstract, this was rephrased as follows: “adopting a collective “all payers” perspective.”

Define: (Pap, HPV, p16/Ki67), spell out acronyms.
OK

More detail is need on “current situation” and screening strategies including coverage and frequency assessed.
Given the limitations of the abstract in terms of word count, our goal was to focus on the general results of the analysis (i.e. OS always generates additional patient outcomes and can lead to savings or moderate extra costs compared to the current individual screening only situation).

Since it was decided to implement organised cancer screening as an add-on to existing individual screening by only inviting eligible women who do not participate, OS coverage is a complex parameter that simultaneously depends on participation rate, screening frequency among participants and the impact OS will have on them. Therefore, it would not be possible to explain this in the abstract.

Line 18: “It is the dominating alternative”. The meaning of this is unclear and could be confused with “dominated”. Perhaps this could be changed to “most efficient” alternative or something similar.
Thank you for your suggestion, we used “most efficient” to avoid confusion.

Line 22: “The assumption that OS periodicity will be respected”. This is unclear.

The following wording was used: “OS strategies based on the HPV test appear highly efficient. However, our results rely on the assumption that women and practitioners comply with the recommended OS periodicities (3, 5 and 10 years).”

Background
I think the first sentence can be deleted to keep the focus on CC in developed countries, specifically France.
Thank you for this suggestion. The sentence was removed.

Second paragraph: Are screening guidelines different for vaccinated and non vaccinated women? If so, please specify. Although providing HPV vaccination coverage rates would be helpful.
Current screening practices do not depend on vaccination status. This is a discussion that French practitioners involved in CC screening are having, as HPV vaccination was only recently reimbursed in France. Vaccination has had a slow adoption rate in the French population. In 2015, it was estimated that only 17% of women eligible for vaccination were vaccinated, a decreasing trend. This figure is presented in the manuscript in the methods section, as it is used in the basecase analysis.

Line 21: More detail on these strategies would be helpful. What was the coverage rate of self-testing? How much did it reduce loss to follow up? Does the 13.2% increase in participation refer to the self-sampling coverage or facility based HPV testing?
The wording was revised to avoid confusion, as the 13.2% figure is not to be understood as a relative increase in participating women but as an absolute increase in the rate of eligible women that performed a cervical cancer screening after 3 years.
“Several OS experimentations have been performed in France to assess the efficacy of different screening modalities, including invitation and positive tests follow-up (FU), self-sampling and HPV-testing. Experimentations that consisted of an invitation of non-participants to perform a Pap test allowed to catch up with 13.2% of all eligible women after 3 years and reduced the lost to follow-up (LtFU) rates of women after a positive result. Additionally, primary HPV-testing and self-sampling were shown to be a feasible alternative to the Pap smear in France. Finally, innovative testing, such as p16/Ki67 double-staining, was shown to be a performant alternative for CC screening compared to HPV screening or the Pap test.”

Methods
Line 8: positivize—I think this is a typo.
Indeed, thank you for the correction.

“A small fraction of participant was LtFU.” Please specify the loss to follow up rate
Lost to follow up rates of women and OS impact on this parameter are given in table 2. We did not include it in the paragraph, as the rate differs after positive Pap-tests and positive HPV-tests.

Table 1: IT would be useful to have more specific inputs on percentage increase in screening coverage and percentage decrease in loss to follow up associated with each strategy.
These parameters are reported with all model inputs in table 2. Since OS strategies share the same invitation/recall methods and impact on lost to follow up, inputs would be repeated every row in table 1, which would be redundant.

I think it should be stated more clearly if only women who did not participate in regular screening are the only ones targeted for the interventions.
Thank you for this suggestion. The manuscript now explicitly states that only non-participant women are targeted by these interventions: “These strategies were all based on adding the dispatch of screening invitations (followed by a single recall) to women who did not spontaneously participate in

the last 3 years (non-participant). Hence, women who did not participate in regular screening are the only ones targeted by the interventions."

Results
Table 4: I think it would be useful to have the percentage increase in LYs associated with each strategy in addition to the absolute increase.
The low incidence of cervical cancer screening leads to limited OS outcomes in regard of survival. Therefore, as stated under table 4, extra-survival of OS strategies vs. current situation (individual screening only) is expressed per 10,000 eligible women on a lifetime horizon. Thus, expressing survival gains as a percentage would lead to very low figures (in the 10-3%), interpretation of which would be made even more difficult considering that the extra-survival is a population average obtained in women representative of the population eligible for cervical cancer screening in terms of age, HPV infection and lesions prevalence. This led us to adopt this presentation of results which facilitates ranking of strategies in regard of this outcome.

Tables 5 and 6: I think the tables should have the ranges used for sensitivity analyses so they can be understood as stand alone results. A tornado diagram would be a useful depiction of influential parameters.
In accordance with your comments and the suggestion made by both other reviewers, we replaced tables 5 and 6 by tornado diagrams for the 10 inputs with the biggest impact on QALYs and costs, respectively. Upon your advice, we have added the basecase value and ranges used in SA to the figures.

Discussion
It would be good to mention the threshold being used for cost-effectiveness.
Please note that no cost-effectiveness threshold is relevant in the French context since HAS (the high health authority, which is the independent agency in charge of health technology assessment, including pharmacoeconomic evaluation) does not wish cost-effectiveness results to be compared to a threshold.
In order to ensure the relevance of our study as a decision-support tool for the French national cancer institute (INCa) and the health ministry, it was performed following the HAS guidelines for health economic assessment. Indeed, in France, cost-effectiveness analyses are not used as a resource allocation tool for health technologies. Instead, cost-effectiveness results are used as indicators of the health-economic value of a technology relatively to its comparators during pricing negotiations between the technology supplier/manufacturer and the health ministry.
Furthermore, our study took place in a context where implementation of organized screening (OS) for cervical cancer was decided upon as part of the national "cancer plan", with oversight by the President of the Republic. Therefore, our study did not aim to assess whether and how OS was efficient.

The goal of the study was rather to determine which screening modality was the most efficient, keeping in mind practical issues, such as the operational feasibility and clinical interest of every assessed OS modality, reduction in social inequalities regarding access to cervical cancer screening and budget constraints.
In this context, our study should be reviewed as a public health analysis based on a modelling methodology, rather than a medico-economic assessment of health technologies. Therefore, we do not feel comfortable with presenting our results relatively to a cost-effectiveness threshold. We feel that this point of view is further reinforced by our results that confirm the legislator's choice to implement organized screening.
However, mentions of "absolute" cost-effectiveness of strategies (i.e. "strategy X is cost-efficient") were removed to better comply with our approach.

Page 13: “Accetta et al. have found HPV-test every 5 years 1 to be a dominant 2 strategy over triennial Pap-tests in Italy.” The word dominant is confusing here, I think it would be better to say “more cost effective” or “more effective”.
Thank you for your suggestion. We rephrased the sentence as follows: “Accetta et al. have found that an HPV test every 5 years is more effective and less costly than triennial Pap-tests in Italy.”

Reviewer: 3

Major problems
Table 2 is very good, except for the fact that it does not include the disability weight/health state valuations given to the various stages of cancers. Please add them into Table 2.
Dear reviewer, thank you for your comments on our manuscript. This study was conducted by the French national cancer institute (INCa) within a more comprehensive project that aimed to assist decision makers regarding the implementation of organised cervical cancer screening. In this context, OS implementation was decided upon as part of the national “cancer plan”, with oversight by the President of the Republic, alongside the objectives of a 20% reduction in cervical cancer mortality, a 80% cervical cancer screening coverage among eligible women and the reduction in inequalities of access to screening.
Thus, our study aimed to inform the decision maker on the corresponding outcomes with various OS modalities, keeping in mind practical feasibility of the assessed strategies. This led us to adopt a cost-effectiveness approach instead of a cost-utility framework in this project and in our paper. Even though health utilities are implemented in the model, we do feel that the reporting of results in terms of screening coverage, avoided cancer and survival is more appropriate.

If by some chance you only included DALY losses due to mortality, then this is a serious erroneous mistake and you should add morbidity losses via the cancer stages to your model and recalculate your results.
As stated above, we believe that the cost-utility framework is not appropriate in the context of our work. The cost per avoided cancer as presented in figure 2 of our manuscript and in Goldie et al.’s 2006 article in Vaccine, “Cost-effectiveness of cervical cancer screening”, seemed more appropriate. In our study, survival gains offer a more traditional outcome that allows ICERs determination and the construction of an efficiency frontier.
Implementing utility values in the model does not lead to significant changes in the ICERs or the constitution of the frontier. Considering the low incidence of cervical cancer, the vast majority of modelled women die of general mortality with no impact on modelled morbidity (cervical cancer related utility decrements). Therefore, the following analysis based on age dependent utility values for the French general population (Perneger 2010) and utility decrements corresponding to the precancerous lesions, cervical cancer (Demarteau 2011) and cancer survivorship (Korfage 2009) and its results will be added in a supplementary appendix and the results section now mentions this analysis as follows: “A cost-utility analysis was performed by applying specific health utilities to the health states and utility decrements to non-cancerous and cancerous states.

Its results and the utility values used are available in a supplementary appendix.”

Tables 5 and 6 do not contribute much……..it is best to delete them and draw up a new table that presents the lower and upper bounds of the parameter values AS WELL as the resultant ACER (average cost-effectiveness ratio) --- this will enable us to clearly see the relative effects of changes in parameter values……
In accordance with your comments and the suggestion made by both other reviewers, we replaced tables 5 and 6 by tornado diagrams for the 10 inputs with the biggest impact on QALYs and costs, respectively. Upon your advice, we have added the basecase value and ranges used in SA to the figures.

The English has numerous linguistic mistakes and is also very cumbersome and hard to follow.
The writing of the manuscript was revised and the manuscript was submitted for English editing to a specialized company before submission.

Some mention could be made in the discussion as to what might consist of a reasonable boundary for achieving cost-effectiveness….maybe 3 x GNP per QALY or $50,000 or ????….thereby maybe showing that 35,846 per QALY as well as 101,389 per QALY ICERs are both cost-effective
Please note that no cost-effectiveness threshold is relevant in the French context since HAS (the high health authority, which is the independent agency in charge of health technology assessment, including pharmacoeconomic evaluation) does not wish cost-effectiveness results to be compared to a threshold.
In order to ensure the relevance of our study as a decision tool for the French national cancer institute (INCa) and the health ministry, it was performed following the HAS guidelines for health economic assessment. Indeed, in France, cost-effectiveness analyses are not used as a resource allocation tool for health technologies. Instead, cost-effectiveness results are used as indicators of the health-economic value of a technology relatively to its comparators during pricing negotiations between the technology supplier/manufacturer and the health ministry.
As stated above, our study took place in a context where implementation of organized screening (OS) for cervical cancer was decided upon as part of the national “cancer plan”, with oversight by the President of the Republic. Therefore, our study did not aim to assess whether and how OS was efficient. The goal of the study was rather to determine which screening modality was the most efficient, keeping in mind practical issues, such as the operational feasibility and clinical interest of every assessed OS modality, reduction in social inequalities regarding access to cervical cancer screening and budget constraints.
In this context, our study should be reviewed as a public health analysis based on a modelling methodology, rather than a medico-economic assessment of health technologies. Therefore, we do not feel comfortable with presenting our results relatively to a cost-effectiveness threshold. We feel that this point of view is further reinforced by our results that confirm the legislator’s choice to implement organized screening.
However, mentions of “absolute” cost-effectiveness of strategies (i.e. “strategy X is cost-efficient”) were removed to better comply with our approach.

Minor problems
Page 4 line 16: Screening remains the main prevention tool because vaccination is restricted to only younger age groups in ADDITION to the compliancy rates being lower than for screening.
Thank you for the suggestion, this part was rephrased as follows: “Screening remains the main prevention tool in France, as anti-HPV vaccination is restricted to younger age groups and was recently made available. Furthermore, vaccination has had a slow adoption in the French population. In 2015, it was estimated that only 17% of women eligible for vaccination were vaccinated.”

Page 4 line 28-33 cost-utility analysis should be mentioned somewhere in this paragraph.
Thank you for this suggestion, we added that the study is based on a cost-effectiveness analysis since, as discussed above, we believe that the cost-utility framework is not appropriate in the context of our study. Survival gains offer a more traditional outcome that allows ICERs determination and the construction of an efficiency frontier.

Page 6 line 40……..delete "all costs…..price index" as these are repeated in lines 5/6 on page 7.
Thank you for this correction.

Page 10 Table 3. Re-order HPV/Pap by swapping the places of HPV/Pap-5y with HPV/Pap-3y.
Thank you for this suggestion, which we applied throughout the manuscript and supplementary

appendixes.

Supplementary File 2: It is not clear what the RR refers to……is the the RR of participation or the RR of cancer or RR of something else…..please clarify…….
Indeed, those relative risks are applied to participation and are now explicitly described as “RR of participating vs. average” in the appendix.

VERSION 2 – REVIEW

REVIEWER	Monisha Sharma University of Washington, USA
REVIEW RETURNED	07-May-2017

GENERAL COMMENTS	General comment: The authors have sufficiently addressed the reviewer comments. Abstract: It would be useful to have a description of what the current situation is in the abstract. For example, 70% coverage of eligible women with pap tests every 10 years. Also, the increase in coverage achieved by the intervention strategies (pap, HPV DNA etc) should be specified in the abstract. It would be useful to specify the expected proportion of LTFU reduced by each intervention explicitly in the methods section, although it is presented in a Table. The type of screening used in the current situation should also be mentioned in the methods. Results: Why does a small increase in CC screening coverage (61.9 to 65.5%) result in such large reductions in CC incidence and mortality? Are you assuming only 4% of the population receives the intervention screening strategy or does the current situation screening get replaced with the new screening strategy (i.e. everyone receives HPV, not just those who are lost to follow up and offered the intervention)? It would be useful to mention the lack of consensus on CEA threshold in France. Conclusion: Spelling out TP=transmission probability would be clearer as this is not a widely used abbreviation. Tornado diagram: Having a footnote stating that TP refers to transition probability would be helpful.

REVIEWER	Dr Gary Ginsberg Public Health Service Ministry of Health Israel
REVIEW RETURNED	04-May-2017

GENERAL COMMENTS	The discussion or into could have included a paragraph saying why they only did a cost per life year analysis instead of cost per QALY nalysis.....

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3
Reviewer Name: Dr Gary Ginsberg
Institution and Country: Public Health Service, Ministry of Health, Israel Please state any competing interests: None Declared

Please leave your comments for the authors below

The discussion or into could have included a paragraph saying why they only did a cost per life year analysis instead of cost per QALY analysis.....

Dear reviewer, thank you for your comment. We have added the following justification for this choice in the background section : “In order to assist decision-making regarding the implementation of CC OS, our study’s main outcomes correspond to the objectives of CC OS implementation: participation rate, survival and avoided CC. A cost-utility analysis is provided in a supplementary appendix.”

Reviewer: 2
Reviewer Name: Monisha Sharma
Institution and Country: University of Washington, USA Please state any competing interests: None declared

Please leave your comments for the authors below

General comment:
The authors have sufficiently addressed the reviewer comments.

Abstract:
It would be useful to have a description of what the current situation is in the abstract. For example, 70% coverage of eligible women with pap tests every 10 years. Also, the increase in coverage achieved by the intervention strategies (pap, HPV DNA etc) should be specified in the abstract.

Dear reviewer, thank you for your comments. We have modified the abstract as follows: “Different OS strategies, additive to IndScr with a 61.9% participation rate and based on mailed invitations to perform OS were assessed. 17.3% and 12.1% of women performed a primary test after invitation and recall, respectively. Strategies implied different screening tests (Papanicolaou (Pap) test, HPV test, and p16/Ki67 double-staining) and OS periodicity.”

It would be useful to specify the expected proportion of LTFU reduced by each intervention explicitly in the methods section, although it is presented in a Table.

The relative risk of becoming LtFU was added in the method section as follows: “The participation rates after invitation and recall, LtFU rate associated with IndScr, OS effect on LtFU (RR=0.88), observed lesions on Pap smear and associated care were all based on observational data from French OS experimentations.”

The type of screening used in the current situation should also be mentioned in the methods.

The following sentence was added to the method section: “The primary test modality is the same for IndScr and OS participants.”

Results:
Why does a small increase in CC screening coverage (61.9 to 65.5%) result in such large reductions in CC incidence and mortality?

Indeed the increase in CC screening coverage is limited to 4% at 4 years which is the main indicator to assess the impact of OS implementation on CC screening coverage. However, as explained in the manuscript and detailed in the supplementary appendix 3, screening coverage is handled in a complex manner in order to accurately reflect the current situation in France. Many women are diagnosed every 4+ years which results in cumulative CC IndScr coverage around 80% (see histogram in appendix file 3).
Since most women will eventually perform CC screening, the non-participating women who participate after being invited or recalled represent the majority of women at risk of developing CC without being diagnosed with precancerous lesions. This allows for a greater impact of OS on CC incidence and mortality, compared to the actual increase of CC screening coverage at 4 years.

Are you assuming only 4% of the population receives the intervention screening strategy or does the current situation screening get replaced with the new screening strategy (i.e. everyone receives HPV, not just those who are lost to follow up and offered the intervention)?

Indeed, the project steering committee considered that the organised screening modality would be applied to women participating in IndScr as well, in order to avoid the coexistence of 2 screening systems. Since this was not clearly stated in the manuscript, the following sentence was added in the methods section: “The same primary screening modality is applied to OS and IndScr participants.”

It would be useful to mention the lack of consensus on CEA threshold in France.

We added the following paragraph, based on our answers to your previews comments in the discussion: “Lastly, we do not present our results relatively to a willingness-to-pay threshold. This choice results from the fact that no cost-effectiveness threshold is relevant in France, since the national agency in charge of health technology assessment, including pharmacoeconomic evaluation (HAS) does not wish cost-effectiveness results to be compared to a threshold. Indeed, cost-effectiveness analyses are not used as a resource allocation tool for health technologies in France. Furthermore, since implementation of CC OS was decided, we did not aim to assess whether and how OS was efficient, but to determine which screening modality was the most efficient, keeping in mind practical issues. We feel that this choice is further reinforced by our results that confirm the legislator’s decision to implement OS.”

Conclusion:
Spelling out TP=transmission probability would be clearer as this is not a widely used abbreviation.

Tornado diagram: Having a footnote stating that TP refers to transition probability would be helpful.

This was applied in the manuscript and figure 3.

VERSION 3 – REVIEW

REVIEWER	Monisha Sharma University of Washington, USA
REVIEW RETURNED	30-Jun-2017

GENERAL COMMENTS	Abstract: "Different OS strategies, additive to IndScr with a 61.9% participation rate and based on mailed invitations to perform OS were assessed." I think the authors can clarify the coverage of the intervention—were invitations mailed to the 29.1% of the women not reached in the IndScr or were the mailed to all women resulting in 12-17% increase in uptake for a total coverage of up to 79%? It would be good to state the total coverage achieved in each scenario. "Compared to the current IndScr only situation, all OS strategies were associated with decreased cancer incidence/mortality (from -14.2%/-13.5% to -22.9%/-25.8%)" I don't think a negative sign is needed in the sentence above, if incidence decreased by 14.2% adding a negative actually makes the sentence double negative. "HPV tests every 10 and 5 years were the most efficient strategies, generating more survival at lower costs than Pap-based strategies" Is this in addition to the IndScr? Or instead of pap-based IndScr? If it's the former, why would women responding to a mail invitation be given a different screening than standard of care in France? Methods: Page 9: Change sub-heading "analyses" to Cost-effectiveness analyses". Sub-heading should be capitalized. Results: If invitation lead to an increase of only 3% (65.5% vs. 61.9%) why does the abstract say 12-17% of women attending screening as a result of mailed invitations? It would seem that the majority of those women would have screened anyway in the standard of care. This should be made more clear in the abstract so as not to mislead the reader. How does a 3% increase in screening lead to a 14-26% reduction in mortality? Discussion: "Using a comprehensive, validated microsimulation model that allows for the fine modelling of CC natural history and screening modalities" This sentence may overstate the model. The cohort is quite small (10,000) and the model uses yearly transition rates which do not allow for fine modeling of the natural history as many HIV infections clear in less than one year.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Monisha Sharma
Institution and Country: University of Washington, USA Please state any competing interests: None declared
Please leave your comments for the authors below

Abstract:
1. "Different OS strategies, additive to IndScr with a 61.9% participation rate and based on mailed invitations to perform OS were assessed." I think the authors can clarify the coverage of the

intervention—were invitations mailed to the 29.1% of the women not reached in the IndScr or were the mailed to all women resulting in 12-17% increase in uptake for a total coverage of up to 79%?

Dear reviewer. Thank you for your final comments on our manuscript. The sentence was revised to allow for this precision: “Different OS strategies, additive to IndScr with a 61.9% participation rate and based on mailed invitations to non-participant women to perform OS were assessed.”

2. It would be good to state the total coverage achieved in each scenario.

Since participation rate depends on the periodicity of the OS strategy and the assumption that this periodicity will be respected by women participating in IndScr in the scenarios with strategies based on HPV test as primary screening, HPV tests every 10 and 5 years are associated with low participation rates.
Therefore the comparison of strategies based on the participation rate at 4 years is not informative. The participation rates of strategies based on primary Pap test was given as a result of the addition of invitation + recall of non-participant women to the current participation. The results section was revised to better reflect this.

3. “Compared to the current IndScr only situation, all OS strategies were associated with decreased cancer incidence/mortality (from -14.2%/-13.5% to -22.9%/-25.8%)” I don’t think a negative sign is needed in the sentence above, if incidence decreased by 14.2% adding a negative actually makes the sentence double negative.

Indeed, we made the suggested correction.

4. “HPV tests every 10 and 5 years were the most efficient strategies, generating more survival at lower costs than Pap-based strategies” Is this in addition to the IndScr? Or instead of pap-based IndScr? If it’s the former, why would women responding to a mail invitation be given a different screening than standard of care in France?

It is not. Indeed, it was considered that women participating in IndScr could not be penalized by receiving a less sensitive screening than invited women. The following sentence was added to the abstract: “Similar screening modality was applied to OS and IndScr participants.”

Methods:
5. Page 9: Change sub-heading “analyses” to Cost-effectiveness analyses”. Sub-heading should be capitalized.
The suggested modifications were applied.

Results:
6. If invitation lead to an increase of only 3% (65.5% vs. 61.9%) why does the abstract say 12-17% of women attending screening as a result of mailed invitations?

The increase in participation at 4 years is the result of the hypothesis that non-participant women are not invited every year. The project steering committee considered that invitations would be sent to non-participant women in the manner of prevention campaigns, following the screening recommended frequency (i.e. 3 years in the case of Pap/Pap). This leads to only a fraction of non-participant women being invited every year.

As a result, in the Pap/Pap OS strategy, only a third of non-participant are invited + recalled every year with the corresponding 17%/12% participation rates (to which are applied HR of participation dependant of age and socioeconomic status [CMU-c eligibility]). At the level of the eligible population,

this means that only 13% (38%/3) women are invited, leading to the 3.6% increase in participation rate obtained with this strategy.

Considering the limitations of abstract in terms of word count it is not possible for us to explain this appropriately in this section. To avoid further misunderstanding, the abstract was revised and does not mention the participation rates associated with invitation and recall. Furthermore, the following explanation was added to the methods section:

“Each year, the model determines whether the woman undergoes screening individually or after invitation based on her participation periodicity, time since last screening and participation rates after invitation. Invitations are sent to non-participant women in the manner of prevention campaigns, following the screening recommended frequency (i.e. 3 years in the case of Pap/Pap). Therefore, only a fraction of non-participant women are invited every year. The same primary screening modality is applied to OS and IndScr participants.”

7. It would seem that the majority of those women would have screened anyway in the standard of care. This should be made more clear in the abstract so as not to mislead the reader.

Around 15% of women are generated as non-participant to IndScr. Furthermore, IndScr participant can become non-participant in time to account for the fact that older women are less likely to participate. Therefore, a big part of non-participant women will never be caught up by screening even at long term.

8. How does a 3% increase in screening lead to a 14-26% reduction in mortality?

Since most women will eventually perform CC screening, the non-participating women who participate after being invited or recalled represent the majority of women at risk of developing CC without being diagnosed with precancerous lesions. Given the low mortality by CC in the general population, catching up a small proportion of these particularly at risk women results in such high mortality reduction.

Discussion:

9. “Using a comprehensive, validated microsimulation model that allows for the fine modelling of CC natural history and screening modalities”. This sentence may overstate the model. The cohort is quite small (10,000) and the model uses yearly transition rates which do not allow for fine modeling of the natural history as many HIV infections clear in less than one year.

The sentence was revised as follows: “Using a validated microsimulation model that allows for the fine modelling of screening modalities".

VERSION 4 – REVIEW

REVIEWER	Monisha Sharma University of Washington, USA
REVIEW RETURNED	03-Aug-2017

GENERAL COMMENTS	The authors have sufficiently addressed the reviewer comments. Minor comment: Abstract The authors should specify what indvSr is in the abstract as they do

	in the background. Eg “IndScr is annual Pap testing followed by pap testing every 3 years after two negative Pap tests.”

VERSION 4 – AUTHOR RESPONSE

Dear reviewer, due to wordcount limitations in the abstract, the following addition was brought to it, accordingly to your comment:
"A closed cohort of women eligible for CC screening and representative in terms of age and participation in individual screening (IndScr) by annual Papanicolaou (Pap) testing every 3 years was modelled on a lifetime horizon."