PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Women's acceptability of and experience with primary human papillomavirus testing for cervix screening: HPV FOCAL trial cross-sectional online survey results
AUTHORS	Smith, Laurie W.; Racey, C. Sarai; Gondara, Lovedeep; Krajden, Mel; Lee, Marette; Martin, Ruth Elwood; Stuart, Gavin; Peacock, Stuart; Coldman, Andrew; Franco, Eduardo; van Niekerk, Dirk; Ogilvie, Gina

VERSION 1 – REVIEW

REVIEWER	Galvin, Annalynn University of North Texas Health Science Center, Health Behavior and Health Systems
REVIEW RETURNED	06-Jul-2021

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. With a robust sample of online survey participants recruited through previous enrollment in a large HPV testing randomized control trial, the authors sought to identify acceptability and attitudes toward primary HPV testing versus pap cytology for cervical cancer screening. Canadian women survey responses were also compared to their HPV status. With bivariate and multivariate logistic regression, results demonstrated higher rates of acceptability and 1.41 higher odds of HPV testing acceptability among women with positive HPV test results during the study. I believe the study does build on current literature and appreciate the well-written introduction, details regarding non-participation, and incorporation of participants in the study design. However, I have a few suggestions for the paper. Abstract - Page 2, Line 68-71: "In multivariable regression, women who reported HPV testing as acceptable were more likely to have received an HPV positive screen test result during the trial (OR=1.41 95%CI: 1.11,1.80), and were older (OR= 1.01, 71 95%CI:1.00,1.02)." I would note that logistic regression was performed and change the phrasing: currently, it is phrased like the outcome (acceptability) is a predictor of an HPV+ screening result, instead of vice versa. Methods - Line 172-173: "Patient concerns and questions identified the need for the study. Patients were involved in pilot testing and revision of the survey." How so? If noted in previous literature, please cite.

	- Line 209-212: "Bivariable analysis explored differences in acceptability of HPV testing based on demographics, HPV screening test result, and length of time since study exit. Factors associated with acceptability, such as HPV screening starting at 30 years of age and increased screening interval, were also examined." Could you give more details on variables and rationale for their inclusion, supported from previous literature or pilot testing? - Line 214-216: “Socio-demographics and attitudes towards HPV testing were explored descriptively with Chi square and Fisher’s exact tests (where applicable) for categorical variables and median score test for continuous variables.” Could you provide elaboration on which specific variables needed Fisher's exact tests versus which needed Chi-squared? Presumably, Fisher’s exact tests were used over Chi-squared due to small cell sizes, but it would be interesting to whether these variables affected the multivariable model differently, based on inclusion. - Line 218-220: "Multivariate logistic regression was used to explore the association of the acceptability of HPV testing with a priori identified confounding variables that reached $p<0.2$ in bivariable analysis. Level of significance was 0.05. All statistical analyses were performed in SAS 9.4 and R 4.02." Education was included in multivariable regression model, but per table 1, $p=0.22$ (>0.2). Results - Line 239-241: "Survey respondents and non-respondents were comparable by study arm and marital status, but those who responded to the survey were slightly older than non-responders, although this was not a meaningful difference." Do you have the results listed anywhere? Does meaningful here mean statistically significant? Discussion - Line 304-306: "Regardless of one’s level of agreement with HPV testing for screening, friends and family or social media were not as important as health care providers and BC Cancer for sources of information." This is a stretch to say for results based on bivariate analysis, using p-value, not effect size. If solely based on bivariate analysis, it is interesting that there was not more discussion regarding the significant findings for social media as a source between the outcome, given the proliferation of misinformation on social media regarding HPV vaccination. - Line 329-332: "Those who tested HPV positive would have received additional information and counseling from their healthcare provider and or a Study nurse, which would have included information that would not necessarily have been provided to those who tested HPV negative." Does this extra education also provide rationale for extended intervals? Is there a way to see whether participants with HPV+ screening results also received additional testing for diagnosis of cervical cancer (e.g., colposcopy) prior to survey completion, which may also affect their acceptability and survey participation? - Line 338-339: "One of the concerns with an extended screening interval is if women would be less likely to consult with the health care provider for other medical reasons." Is this a concern from

	piloting or literature or the survey? Indicate and cite, as needed. You may need to introduce this in the methods section as well. To what extent was education about extended intervals provided to participants? - Line 408-409: "The potential lag time between trial entry and survey completion may impact women's attitudes and beliefs surrounding HPV testing." You have this data and can control for the analysis, but initial bivariate analysis showed that it was not statistically significant with the outcome and excluded from multivariable logistic regression. Tables/Figures - Table 1: HPV testing result percentages are confusing – you may need to include a footnote to explain.

REVIEWER	Hamashima, Chisato Teikyo University, Faculty of Medical Technology
REVIEW RETURNED	30-Jul-2021

GENERAL COMMENTS	Thank you for the opportunity to review an interesting manuscript submitted to BMJ open. According to the dissemination of HPV testing, promotion has become a big issue, and thus, the importance of shared decision-making should not be overlooked. Before the discussion, we need information on how patients felt their results and the modality changed for cervical cancer screening. We can find how to communicate with patients with HPV positive results. The manuscript is well written, but questions were raised as follows; 1. The subjects of this study were the same for the FOCAL study. Before the enrollment and randomization, enough information was given for them. This condition was different from actual screening. What information was given to subjects at recruitment of the FOCAL Study? 2. The numbers of responders were aggregated with intervention and control groups in the FOCAL study. Is there any difference in answers between them? 3. The research setting was convenient for questioner survey but not reflect reply from general population. The authors should discuss the influence on which groups were allocated for subjects.

REVIEWER	de Sanjose, Silvia PATH, Seattle
REVIEW RETURNED	03-Aug-2021

GENERAL COMMENTS	This is a well designed study evaluating the acceptability of HPV testing and changes in the age range of screening and interval compared to cervical cytology. The paper is clear in exploring the issue and provides relevant insight of how women may think differently from the scientific community when confronted with changes in screening approaches. I enjoyed reading the manuscript and see how women may not be fully aware of the cytology limitations or the full meaning of a given abnormal cytology result. It is clear that women from the FOCAL study may not be 100% representative of the Canadian population but the study is well designed and useful. The study indicates that maybe the information that is given about performance of Pap smears could be revised, making women more aware of limited

	sensitivity and that a HSIL result may be more indicative of disease than an HPV positive test. Also that a HSIL is a consequence of an STI as much as and HPV positive test is. I do not have any additional comments.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Abstract

1) Page 2, Line 68-71: "In multivariable regression, women who reported HPV testing as acceptable were more likely to have received an HPV positive screen test result during the trial (OR=1.41 95%CI: 1.11,1.80), and were older (OR= 1.01, 71 95%CI:1.00,1.02)." I would note that logistic regression was performed and change the phrasing: currently, it is phrased like the outcome (acceptability) is a predictor of an HPV+ screening result, instead of vice versa.

We have made the following revision to these lines to address the reviewer's comment, lines 69-72: "In multivariable logistic regression, women who received an HPV positive screen test result during the trial (OR=1.41 95%CI: 1.11, 1.80), or were older (OR= 1.01, 95%CI:1.00, 1.02) were more likely to report HPV testing as acceptable".

Methods

2) Line 172-173: "Patient concerns and questions identified the need for the study. Patients were involved in pilot testing and revision of the survey." How so? If noted in previous literature, please cite.

We have added further clarity to this section to address reviewer comments and a citation. Please see lines 187-191.

"Patient concerns and questions raised during the trial period identified the need for the study, but patients were not involved in the construction of the survey. However, a sample of women who undergo cervical cancer screening in BC were involved in pilot testing of the survey for the purposes of face validity, and survey flow and logistics. Based on this feedback, revisions were made to the survey to clarify wording of questions and formatting of layout".

3) Line 209-212: "Bivariable analysis explored differences in acceptability of HPV testing based on demographics, HPV screening test result, and length of time since study exit. Factors associated with acceptability, such as HPV screening starting at 30 years of age and increased screening interval, were also examined." Could you give more details on variables and rationale for their inclusion, supported from previous literature or pilot testing?

To provide more context and support regarding variable selection and address reviewer comment, additional citations have been included and the wording in this section changed as follows (lines 231-233)

"Bivariable analysis explored differences in acceptability of HPV testing based on demographic factors such as age, income, and education, in addition to HPV screening test result, and length of time since study exit. Factors shown to be potentially associated with acceptability, such as HPV screening starting at 30 years of age and increased screening interval, were also examined".

4) Line 214-216: “Socio-demographics and attitudes towards HPV testing were explored descriptively with Chi square and Fisher’s exact tests (where applicable) for categorical variables and median score test for continuous variables.” Could you provide elaboration on which specific variables needed Fisher's exact tests versus which needed Chi-squared? Presumably, Fisher’s exact tests were used over Chi-squared due to small cell sizes, but it would be interesting to whether these variables affected the multivariable model differently, based on inclusion.

We thank the reviewer for identifying this discrepancy. We originally had intended to use Fisher Exact tests, where applicable, but this approach was not necessary, given larger cell sizes were available. We have removed any reference to Fisher’s exact test.

“Socio-demographics and attitudes towards HPV testing were explored descriptively with Chi-square for categorical variables and median score test for continuous variables”.

5) Line 218-220: "Multivariate logistic regression was used to explore the association of the acceptability of HPV testing with a priori identified confounding variables that reached $p<0.2$ in bivariable analysis. Level of significance was 0.05. All statistical analyses were performed in SAS 9.4 and R 4.02." Education was included in multivariable regression model, but per table 1, $p=0.22$ (>0.2).

Again, we thank the reviewer for noting this oversight in our methods section. The wording has been changed to reflect that confounding variables that reached $p<0.2$ (vs $p<0.2$) in bivariable analysis were included (Line 243). Education was included given it was right at the threshold selected for inclusion (based on rounding) and as it is a known confounder of acceptability of HPV (education being a proxy for knowledge, health literacy etc).

Results

6) Line 239-241: "Survey respondents and non-respondents were comparable by study arm and marital status, but those who responded to the survey were slightly older than non-responders, although this was not a meaningful difference." Do you have the results listed anywhere? Does meaningful here mean statistically significant?

We have changed the wording to ensure clarity, recognizing the use of the word “meaningful” could be interpreted in different ways. Please see changes to lines 268-269.

“Survey respondents and non-respondents were comparable by study arm and marital status, but those who responded to the survey were slightly older than non-responders (median of 51 years vs. 49 years), although the difference was not clinically significant.”.

Discussion

7) Line 304-306: "Regardless of one’s level of agreement with HPV testing for screening, friends and family or social media were not as important as health care providers and BC Cancer for sources of information." This is a stretch to say for results based on bivariate analysis, using p-value, not effect size. If solely based on bivariate analysis, it is interesting that there was not more discussion regarding the significant findings for social media as a source between the outcome, given the proliferation of misinformation on social media regarding HPV vaccination.

The findings explained here refer to the effect size, and not the p-values. Proportionally, more people agreed their health care provider and the BC Cancer screening program were important sources of information, than were friends and family and social media (lowest proportion of respondents agreed these sources were important).

In addition, the following statement has been added to the discussion section, lines 440-443.
“In this cohort, the least important sources of information were social media and friends and family, providing reassurance that women in this cohort seek information from reputable sources such as health care providers and the screening program compared to the internet, or friends and family”

8) Line 329-332: "Those who tested HPV positive would have received additional information and counseling from their healthcare provider and or a Study nurse, which would have included information that would not necessarily have been provided to those who tested HPV negative." Does this extra education also provide rationale for extended intervals? Is there a way to see whether participants with HPV+ screening results also received additional testing for diagnosis of cervical cancer (e.g., colposcopy) prior to survey completion, which may also affect their acceptability and survey participation?

We appreciate this observation and have changed the wording of this section to add clarity. All participants who would have required follow-up and or management would have indeed undergone these procedures by the time the survey was administered. See lines 362-372.

“Those who tested HPV positive would have received additional information and counseling from their healthcare provider and or a Study nurse, which would not necessarily have been provided to those who tested HPV negative. This additional information would have reinforced the education participants were provided at trial baseline, including the prevalence of HPV in the population, the transient nature of HPV and the long natural history between HPV infection and cervical dysplasia development. In addition, those with HPV positive results would have received additional follow-up and management by the time the survey was administered. The reinforcement of education, and an opportunity for dialogue when receiving the positive result, and the fact that those with a positive HPV result would have received treatment for detected dysplasia, may have facilitated improvement in knowledge and subsequently, enhanced acceptance of HPV testing. Other findings have indicated that increased HPV and HPV screening knowledge can be a facilitator of HPV screening acceptance”.

9) Line 338-339: "One of the concerns with an extended screening interval is if women would be less likely to consult with the health care provider for other medical reasons." Is this a concern from piloting or literature or the survey? Indicate and cite, as needed. You may need to introduce this in the methods section as well. To what extent was education about extended intervals provided to participants?

A citation has been added to support this statement. In addition, further information has been provided to the methods section (lines 163-165) to add more details regarding the education participants were provided at baseline when they consented to participate in the HPV FOCAL trial.
“Participants were provided with information on HPV, HPV testing (including differences between Pap and HPV testing, and the reasons behind an extended interval between negative HPV screens) and cervical cancer upon enrollment and throughout the trial follow-up period”.

10) Line 408-409: "The potential lag time between trial entry and survey completion may impact women’s attitudes and beliefs surrounding HPV testing." You have this data and can control for the

analysis, but initial bivariate analysis showed that it was not statistically significant with the outcome and excluded from multivariable logistic regression.

To add more detail to this section, this sentence has been revised as follows to address this reviewer's comment. Lines 471-475.
"The potential lag time between trial entry and survey completion may have introduced recall bias and impacted women's attitudes and beliefs surrounding HPV testing; however, the impact of this potential bias would be small as we found no significant difference between acceptability and time between trial entry and survey completion".

Tables/Figures
11) Table 1: HPV testing result percentages are confusing – you may need to include a footnote to explain.

We recognize that the row % in table 1, for HPV testing status was confusing and we have deleted these %. This was oversight on our behalf, and we thank the reviewer for the careful attention that has been taken to review the table.

Reviewer: 2

1) The subjects of this study were the same for the FOCAL study. Before the enrollment and randomization, enough information was given for them. This condition was different from actual screening. What information was given to subjects at recruitment of the FOCAL Study?

Revisions have been made to the methods section (Lines 163-165) to provide additional details regarding the information provided to consented participants at trial entry and provide more details about screening in our province (see response to reviewer #1). Of note, the standard of care in British Columbia at the time of the FOCAL Study, and currently, remains cytology testing (Pap smear) and not primary HPV testing. Therefore, screening program participants not involved in the FOCAL Trial would not be receiving any information regarding HPV testing for cervical cancer screening.

The following sentence in the limitations section has been revised (lines 449-455).
"Survey participants were part of a large clinical trial and were given information about HPV, HPV testing and cervical cancer upon enrollment and, therefore, may not be representative of all people eligible for cervix screening in British Columbia. However, participants of this study are reflective of the current population engaged in the screening program, who receive cytology testing with the Pap smear, and not HPV testing as standard of care. As a result, their concerns and feedback are informative for programs planning for a shift from cytology to HPV-based screening".

2) The numbers of responders were aggregated with intervention and control groups in the FOCAL study. Is there any difference in answers between them?

The survey respondents were comparable to all HPV FOCAL Trial participants. Please see lines 265-269 in the results section:

“Survey respondents were comparable to HPV FOCAL trial participants based on study arm, age at HPV FOCAL trial enrollment, and geographical location. Survey respondents and non-respondents were comparable by study arm and marital status, but those who responded to the survey were slightly older than non-responders (median of 51 years vs. 49 years), although the difference was not clinically significant.”

3) The research setting was convenient for questioner survey but not reflect reply from general population. The authors should discuss the influence on which groups were allocated for subjects.

As indicated in the methods section, the subjects in the HPV FOCAL Study were people currently engaged in the cervical cancer screening program of British Columbia.
The following statement (with citation) has been added to the methods section (lines 159-162)
“Participants of the HPV FOCAL Trial were engaged in cervical cancer screening through a large population-based screening program, and representative of women at average risk of cervical cancer in North America”

In addition, the following section has been revised in the limitations section, lines 449-455:
“Survey participants were part of a large clinical trial and were given information about HPV, HPV testing and cervical cancer upon enrollment and, therefore, may not be representative of all people eligible for cervix screening in British Columbia. However, participants of this study are reflective of the current population engaged in the screening program, who receive cytology testing with the Pap smear, and not HPV testing as standard of care. As a result, their concerns and feedback are informative for programs planning for a shift from cytology to HPV-based screening.

Reviewer: 3
Dr. Silvia de Sanjose, PATH, Seattle
Comments to the Author:
This is a well designed study evaluating the acceptability of HPV testing and changes in the age range of screening and interval compared to cervical cytology. The paper is clear in exploring the issue and provides relevant insight of how women may think differently from the scientific community when confronted with changes in screening approaches.
I enjoyed reading the manuscript and see how women may not be fully aware of the cytology limitations or the full meaning of a given abnormal cytology result. It is clear that women from the FOCAL study may not be 100% representative of the Canadian population but the study is well designed and useful. The study indicates that maybe the information that is given about performance of Pap smears could be revised, making women more aware of limited sensitivity and that a HSIL result may be more indicative of disease than an HPV positive test. Also that a HSIL is a consequence of an STI as much as and HPV positive test is.
I do not have any additional comments.

We are grateful for this reviewer’s comments and feedback. We have added more specifics to the limitations section to address the comment about generalizability and relevance of these findings in a screening program setting. Please see our responses to the point from reviewer #2.

VERSION 2 – REVIEW

REVIEWER	Galvin, Annalynn University of North Texas Health Science Center, Health Behavior and Health Systems
REVIEW RETURNED	17-Sep-2021

GENERAL COMMENTS	Thank you for your resubmission! I appreciate the detail and thoughtful responses provided in the revised draft. I have no additional comments. This study and its findings are very important, and I am grateful to the authors for their work.

REVIEWER	Hamashima, Chisato Teikyo University, Faculty of Medical Technology
REVIEW RETURNED	13-Sep-2021

GENERAL COMMENTS	The manuscript is acceptable for publication of BMJ open because revision is done correctly.