PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A community-randomized controlled trial embedded in the Anishinaabek Cervical Cancer Screening Study: human papillomavirus self-sampling versus Papanicolaou cytology
AUTHORS	Zehbe, Ingeborg; Jackson, Robert; Wood, Brianne; Weaver, Bruce; Escott, Nicholas; Severini, Alberto; Krajden, Mel; Bishop, Lisa; Morrisseau, Kyla; Ogilvie, Gina; Burchill, Ann; Little, Julian

VERSION 1 - REVIEW

REVIEWER	Nathalie BOULLE Laboratoire de Biologie Cellulaire des Tumeurs CHRU de Montpellier Hôpital Arnaud de villeneuve 371, avenue du Doyen G. Giraud
REVIEW RETURNED	30-Mar-2016

GENERAL COMMENTS	Zehbe I, Jackson R, Wood B et al. A community-randomized controlled trial embedded in the Anishinaabek Cervical Cancer Screening Study: human papillomavirus self-sampling versus Papanicolaou cytology. The study presented by Zehbe et al. aims at initiating the implementation of cervical screening in First Nations communities in Canada and at studying the conditions for optimal screening in this population. This controlled trial was based on a partnership with local communities and community health workers through a PAR approach (community-based participatory action research); the study is well designed and analyses qualitative (cervical screening barriers components) as well as quantitative aspects of cervical screening in First Nation Populations. The supplementary data about the trial (Screening Trial Protocol according to the Spirit guidelines) are clearly written. The results presented and the discussion about the limitations of implementing cervical screening in this context are quite interesting. However, several points in this paper raised questions or need precisions: About the results: - The main objective described in the abstract (“offering HPV self-sampling…and reduce cervical cancer rates in this population”) is not addressed in the trial presented as 1) cervical screening uptake prior to this study was not known but only estimated according to 3 scenarios (as stated page 9 in “Sample size and power estimation”) and 2) the population of women targeted in this trial was not defined by their non-participation to cervical screening (inclusion criteria: age, band members and main address in the Thunder Bay). Accordingly, the majority of women who participated to the study (two-thirds) had adequate cervical screening, which may a bias in

	the final results of cervical screening uptake. -To our opinion, the main objective of the study is the feasibility of implementing cervical screening in First nation communities with the help of community members, rather than comparing the efficacy of HPV self –sampling and Pap testing to increase screening participation and reduce cervical cancer rates. The first important result of the trial is thus screening uptake, which as stated by the authors, varies greatly among communities independently of the screening procedure (HPV self-sampling or pap testing). We think that the abstract of the paper should be written in this way, in accordance with the conclusion of the authors ("Cervical screening was successfully…"). In this respect, it would be interesting to indicate in the paper the reasons why Community (Band) 10 withdrew from the trial (this is not clearly explained in the text or in Supplemental Data 3) and to discuss as part of the results, the recruitment strategies for each community underlying the most useful ones as well as the problems encountered by the CBRA, as described in Supplementary Data 3. Similarly, why are the results of Community (Band) 3 in arm A so low (1 questionnaire and 2 screened women for a total of 70 women)? In the discussion, the authors stated that smaller communities get better results for screening uptake than larger ones (page 21). What was the ratio of Community-based research assistant or health worker per women in each community (band)? This could be an important component of screening uptake as shown by Arrossi et al. (2015). A second result of the trial would be better results of screening uptake (although not significant) by proposing HPV self-sampling as compared to Pap testing. Page 8, Interventions, "women were asked how they wished to be contacted in the event of a positive test result". What are the women's responses? This could an important issue if future trials target non-attendee women. What is the % of follow-up of women tested positive for high-risk HPV? We found that the averaged response to baseline questionnaires was 26% in Arm A and 39.7% in arm B. Is this difference statistically significant? And how can you explain this? - Potential bias in the study that should be discussed by the authors: When looking at the women who participated to the study (Table 5), apart from a high proportion of adequately screened women, the authors noted a higher employment rate (57,7%) and for half of the women a high education level (> high school). Moreover, in Supplementary Data 1, it is indicated that every tenth participant could win a grocery gift certificate worth CAD $100. The authors should discuss how these characteristics and this financial incitation constitute potential bias and may overestimate screening uptake response in a real-world setting. In Table 5, 12,8% (Arm A) and 7,7% (Arm B) of women had previous hysterectomy. These cases should also be discussed as in some countries, cervical screening is not recommended after total hysterectomy. - Statistical analyses by ITT and PP: We are not convinced that women from community 10, that withdrew from the trial, should be included in the analysis as having no screening uptake, and treated as ITT results, as the reasons why this community withdrew may be completely independent from health considerations and are not described in the paper. This point should be checked by an independent reviewer, specialized in

	statistical analysis. - Presentation of the results: We found the presentation of the results and especially some Tables confusing. For instance, in Table 2, the number of total women and of women screened is indicated next to a % of women screened, but this % is the averaged - screening uptake for each arm (for instance: in Arm A, 63/404*100 = 15.6% and the mean screening uptake in Arm A is 22.9%). It would be easier for the reader to present only the averaged screening uptake (%) and the corresponding P-values along with Figure 1 (Overview of the Anishinaabek Cervical screening study). In Table 2, we do not find the same results as the authors for Arm B, averaged-screening uptake in Per-Protocole: 14.1% rather than 15.2% as indicated by the authors. Could you detail this? In Figure 1, (overview of the Anishinaabek Cervical screening study), Arm B, 33 instead of 35 ITT screening responders? - References: Some recent references about HPV self-sampling should be added, such as: Arbyn M. et al. Lancet Oncol 2014; 15:172-183. Haguenoer K et al. British Journal of Cancer 2014 ; 111 : 2187-2196. Based on the comments above, we recommend that the authors present their results differently to gain in clarity and precision; this will increase the interest of the study.

REVIEWER	Petignat Patrick University Hospitals of Geneva
REVIEW RETURNED	08-May-2016

GENERAL COMMENTS	The manuscript by Zehbe and colleagues aims to assess if HPV self-sampling improve cervical cancer screening participation in a high risk population for cervical cancer (unscreened or poorly screened). The study has been executed and data analyzed in an appropriate manner. There are a few comments: Uptake between both groups are similar except in women having complete the (baseline) questionnaire (=subgoup). This is a very surprising and interesting point. Hypothesis was that Self-HPV do better but in fact it does not do it. The investigators should explain why Self-HPV does not allow to improve participation Uptake is very low (about 20%) and the author claims in the conclusion "CC screening was successfully implemented"... This should be adapted and this extremely low participation rate should be explained. Have the investigators alternative approach to improve participation rate ? Why the investigators adopted a two-steps strategy (questionnaire/screening) ? Maybe a "screen-and-treat" approach could be more appropriate ?

	As Self-HPV is only one step in the screening process (HPV positive, cytology, colposcopy, biopsy, treat). The results are frustrating, as the reader would like to know how many patients in each group have completed the whole process. Could you please add these data in the paper. The national Canadian guidelines for cervical cancer screening should be reported in the paper. Does the country have an opportunistic screening or a program ? I do not understand why women having had a screening test in the last three years (even less than one year) have been include in this study.

REVIEWER	Richard MUWONGE Scientist International Agency for Research on Cancer, Lyon, FRANCE
REVIEW RETURNED	17-Jun-2016

GENERAL COMMENTS	General comment The manuscript is well written, analyses and discusses the feasibility of implementing and participants acceptability of two cervical cancer screening modalities. This manuscript has important public health implications largely for the under-screened populations of the high-income regions and to some extent most populations of the low-income regions. It brings out the importance of involving the different stakeholders in the setting up and successful implementation of cervical cancer screening programmes. Specific minor comments 1. Page 7, line 11: Not full definition of IZ is given in the text a prior. 2. Page 7, lines 25-35: Were the same women offered HPV testing in phase 1 and cytology in phase 2 in the arm A and vice versa for arm B? If yes, could this have affected the participation especially in phase 2 since a gap of around 2 months between screens may to small especially for those who were screen-negative in the first phase. 3. Page 8, line 4-6: The authors may give a brief description of the Ontario Cervical Screening protocol. 4. Page 11, lines 30-40: It is a general tendency in cluster randomized trials to take the unit of analysis as the cluster instead of the individual. The authors may use the cluster as the unit of analysis even for the descriptive analyses. (ref. Bland and Kerry) 5. Page 12, lines 14-24: This text many be shifted to the methods section. Reference Bland JM, Kerry SM. Statistics notes. Weighted comparison of means. BMJ 1998;316:129.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
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Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
Zehbe I, Jackson R, Wood B et al.
A community-randomized controlled trial embedded in the Anishinaabek Cervical Cancer Screening Study: human papillomavirus self-sampling versus Papanicolaou cytology.
The study presented by Zehbe et al. aims at initiating the implementation of cervical screening in First Nations communities in Canada and at studying the conditions for optimal screening in this population.
This controlled trial was based on a partnership with local communities and community health workers through a PAR approach (community-based participatory action research); the study is well designed and analyses qualitative (cervical screening barriers components) as well as quantitative aspects of cervical screening in First Nation Populations. The supplementary data about the trial (Screening Trial Protocol according to the Spirit guidelines) are clearly written. The results presented and the discussion about the limitations of implementing cervical screening in this context are quite interesting.
However, several points in this paper raised questions or need precisions:

About the results:
- The main objective described in the abstract ("offering HPV self-sampling…and reduce cervical cancer rates in this population") is not addressed in the trial presented as 1) cervical screening uptake prior to this study was not known but only estimated according to 3 scenarios (as stated page 9 in "Sample size and power estimation") and 2) the population of women targeted in this trial was not defined by their non-participation to cervical screening (inclusion criteria: age, band members and main address in the Thunder Bay). Accordingly, the majority of women who participated to the study (two-thirds) had adequate cervical screening, which may a bias in the final results of cervical screening uptake.

Response:

Point 1: Indeed, cervical screening uptake rate was not known. Our hypothesis is that the higher cervical cancer incidence rate in Indigenous people in Canada relates to low screening uptake and/or poor follow up. Hence this statement relates to a long-term outcome. We have added "eventually" in

the Abstract (Objectives) to emphasize that this is long-term. Point 2: As discussed on page 22, last paragraph (Discussion), we are finding new ways to reach this under-screened population. In fact, we had an update community gathering with the participating communities and stakeholders to get their feedback. This work is currently summarized as a manuscript to be submitted in the near future. Briefly, we learned that we have to create awareness for the benefits of screening not only amongst the screening-eligible women but provide education to all community members independent of gender and age. Screening will have to be embedded in health promotion as part of a healthy life style and education will have to be tailored to the communities based on their feedback.

-To our opinion, the main objective of the study is the feasibility of implementing cervical screening in First nation communities with the help of community members, rather than comparing the efficacy of HPV self–sampling and Pap testing to increase screening participation and reduce cervical cancer rates.

Response:

The PAR approach is important but our main objective was to assess whether self-sampling, being a convenience factor, could increase screening uptake. Our pilot study with one community pointed into that direction (Zehbe et al., BMJ Open, 2011).

The first important result of the trial is thus screening uptake, which as stated by the authors, varies greatly among communities independently of the screening procedure (HPV self-sampling or pap testing). We think that the abstract of the paper should be written in this way, in accordance with the conclusion of the authors (“Cervical screening was successfully…”).

Response:

We have indicated that in the Abstract’s Results section: Screening uptake varied between communities (range 0 to 62.1%). We have also revised the concluding sentence in the Abstract.

In this respect, it would be interesting to indicate in the paper the reasons why Community (Band) 10 withdrew from the trial (this is not clearly explained in the text or in Supplemental Data 3) and to discuss as part of the results, the recruitment strategies for each community underlying the most useful ones as well as the problems encountered by the CBRA, as described in Supplementary Data 3. Similarly, why are the results of Community (Band) 3 in arm A so low (1 questionnaire and 2 screened women for a total of 70 women)?
In the discussion, the authors stated that smaller communities get better results for screening uptake than larger ones (page 21).

Response:

As per our mutually signed research agreements between the ACCSS team and the 11 partner communities, any participating community could discontinue their participation without mentioning any reasons. The ACCSS team respected this fact without further due.

We handled the strategies of the community based research assistants (CBRAs) where we felt they are best positioned (namely in the Protocol, Supplementary Data 3, Table A) and to relieve space in the main body text. We also briefly refer to the strategies in ‘Interventions’ of the Methods section (page 8). The CBRAs were all requested to provide an educational event to inform and promote the ACCSS trial. They would also promote the study in community-held events. Engagement of the CBRAs may have been different, which is related to the environment in the community and may differ

largely between communities. As well, situations in communities may change with time, e.g. in correspondence with a change in leadership. For Band 3, the CBRA was new in the community and may not have had the trust that would be needed to recruit women for screening. Indeed, we have discussed this and other facts on page 21-22 (Discussion).

What was the ratio of Community-based research assistant or health worker per women in each community (band)? This could be an important component of screening uptake as shown by Arrossi et al. (2015).

Response:

One CBRA per community was hired on an hourly basis and paid by the ACCSS team; the hours to be worked were directly correlated to the number of women eligible to be screened in that community.

A second result of the trial would be better results of screening uptake (although not significant) by proposing HPV self-sampling as compared to Pap testing.
Page 8, Interventions, “women were asked how they wished to be contacted in the event of a positive test result”. What are the women’s responses? This could an important issue if future trials target non-attendee women. What is the % of follow-up of women tested positive for high-risk HPV?

Response:

As per the Informed consent form, the women could choose between being contacted by their local health care provider or by their family physician. The ACCSS team collaborated with the local health care providers to communicate screening results, i.e. either Pap test results or HPV testing results to the participants. This part was considered part of standard-of-care and due to patient confidentiality, the ACCSS team was not involved in the follow-up. This had also not been negotiated with the communities’ leadership prior to commencing the ACCSS.

We found that the averaged response to baseline questionnaires was 26% in Arm A and 39.7% in arm B. Is this difference statistically significant? And how can you explain this?

Response:

The community-averaged baseline questionnaire response, as the proportion of eligible women within each community, was not statistically significantly different between Arm A and B by permutation test even when the withdrawn community was removed from the analysis. Arm A = 26.0% vs Arm B (including withdrawn community) = 31.7%, difference of -5.7% (95% CI = -38.0 – 15.0, P = 0.703, permutation test). Arm A = 26.0% vs Arm B (excluding withdrawn community) = 39.7%, difference of -13.7% (95% CI = -54.2 – -0.2, P = 0.355, permutation test).

- Potential bias in the study that should be discussed by the authors:
When looking at the women who participated to the study (Table 5), apart from a high proportion of adequately screened women, the authors noted a higher employment rate (57,7%) and for half of the women a high education level (> high school). Moreover, in Supplementary Data 1, it is indicated that every tenth participant could win a grocery gift certificate worth CAD $100. The authors should discuss how these characteristics and this financial incitation constitute potential bias and may overestimate screening uptake response in a real-world setting.

Response:

The ACCSS is a research study and several elements would not be adopted in a real world scenario.

The ACCSS wanted to characterize the cohort and therefore all women who wished to participate in screening had to answer a questionnaire prior to getting screened. This fact per se may have reduced participation willingness. We followed the advice of our community partners to provide an incentive for participation since filling out questionnaires takes the participants' time. This feature should be seen as an appreciation by the ACCSS team and would not likely be adopted in a future screening program.

In Table 5, 12,8% (Arm A) and 7,7% (Arm B) of women had previous hysterectomy. These cases should also be discussed as in some countries, cervical screening is not recommended after total hysterectomy.

Response:

There was no significant difference between Arm A and B for reported hysterectomies, so there does not appear to be a significant bias that is different between the arms. The Ontario screening guidelines recommend cervical screening in the event of a hysterectomy if the cervix is still retained. Hysterectomy was not an exclusion criterion for participation in the ACCSS because it may not be known to some women whether or not their cervix is still intact (cancercare.on.ca).

- Statistical analyses by ITT and PP:
We are not convinced that women from community 10, that withdrew from the trial, should be included in the analysis as having no screening uptake, and treated as ITT results, as the reasons why this community withdrew may be completely independent from health considerations and are not described in the paper. This point should be checked by an independent reviewer, specialized in statistical analysis.

Response:

On the point of including one of the clusters or not, we had substantial discussion as group on this when drafting the manuscript. The interventions were complex and multifaceted—a scenario, which is also addressed by Campbell et al., 2000 (BMJ): http://www.bmj.com/content/321/7262/694 and Craig et al., 2008 (BMJ): http://www.bmj.com/content/337/bmj.a1655). Thus, there was substantial interaction with communities with educational exchange sessions followed by the offer of the alternative sequence of screening tests. We agree that it is unlikely that the withdrawal of one community was related to health outcomes, but the conservative interpretation is that intervention was offered but not accepted. We also recognized that ITT in cluster randomized trials is not straightforward (as documented in references 31-35 in the manuscript) and therefore conducted a per protocol analysis that excluded this community from the analysis. As in most situations in which ITT and PP analyses can be compared, the magnitude of the difference between arms was somewhat greater in the PP analysis. We consider that it is important that the fact that the two analyses were done, and their results, are transparently reported.

- Presentation of the results:
We found the presentation of the results and especially some Tables confusing. For instance, in Table 2, the number of total women and of women screened is indicated next to a % of women screened, but this % is the averaged - screening uptake for each arm (for instance: in Arm A, 63/404*100 = 15.6% and the mean screening uptake in Arm A is 22.9%). It would be easier for the reader to present only the averaged screening uptake (%) and the corresponding P-values along with Figure 1 (Overview of the Anishinaabek Cervical screening study).
In Table 2, we do not find the same results as the authors for Arm B, averaged-screening uptake in Per-Protocole: 14.1% rather than 15.2% as indicated by the authors. Could you detail this?

Response:

We attempted to abide by CONSORT guidelines. This would make Figure 1, which is seen as an overview of the study, too busy since we need to include the differences/confidence intervals between arms. However, we have included mean values in brackets in Table 2, which is also explained accordingly in the footnote text below the table. A recalculation for PP averaged screening values for both initial and cumulative update has been performed and Table 2 has been updated accordingly.

In Figure 1, (overview of the Anishinaabek Cervical screening study), Arm B, 33 instead of 35 ITT screening responders?

Response:

According to Table 1, this should be n=35, as presently displayed in Figure 1. Arm B, phase 1 ITT, sum of screening responders = 8 + 5 + 12 + 0 + 10 = 35.

- References:
Some recent references about HPV self-sampling should be added, such as:
Arbyn M. et al. Lancet Oncol 2014; 15:172-183.
Haguenoer K et al. British Journal of Cancer 2014 ; 111 : 2187-2196.

Response:

The most recent and pertinent reference, i.e. the one by Arbyn is in the reference list of the Protocol.

Based on the comments above, we recommend that the authors present their results differently to gain in clarity and precision; this will increase the interest of the study.

Reviewer: 2

Reviewer Name
Petignat Patrick

Institution and Country
University Hospitals of Geneva

Please state any competing interests or state ‘None declared’:
No competing interests

Please leave your comments for the authors below
The manuscript by Zehbe and colleagues aims to assess if HPV self-sampling improve cervical cancer screening participation in a high risk population for cervical cancer (unscreened or poorly screened). The study has been executed and data analyzed in an appropriate manner.
There are a few comments:

Uptake between both groups are similar except in women having complete the (baseline) questionnaire (=subgoup). This is a very surprising and interesting point. Hypothesis was that Self-HPV do better but in fact it does not do it.
The investigators should explain why Self-HPV does not allow to improve participation.

Response:

Depending on analysis, screening uptake with HPV self-sampling was ~ two- to three-fold higher vs. Pap (ITT and PP, respectively). This was only significant when values of questionnaire participants were compared due to the low amount of participants. However, our qualitative testimonies clearly favour self-sampling: this qualitative perspective has been summarized as a manuscript to be submitted for publication by members of the ACCSS team and some First Nations community members.

Uptake is very low (about 20%) and the author claims in the conclusion "CC screening was successfully implemented"... This should be adapted and this extremely low participation rate should be explained.

Response:

Indeed, the average uptake was low but variation was considerable between communities. We have made corrections in the Abstract (Conclusions) and in the Discussion on page 20, first paragraph. There are structural and cultural barriers such as lack of awareness for the benefit of screening, general fear of cancer, and colonial legacy. Please see Discussion on page 21, second paragraph.

Have the investigators alternative approach to improve participation rate?

Response:

We have obtained feedback from our community partners: More collaborative work and emphasis to embed screening in community-hels health promotion, involve all community members and provide Indigenous knowledge-based education. Please see Discussion, page 22, last paragraph. Please see also response to reviewer 1 above (page 2).

Why the investigators adopted a two-steps strategy (questionnaire/screening)? Maybe a "screen-and-treat" approach could be more appropriate?

Response:

The ACCSS wanted to characterize the cohort and therefore all women who wished to participate in screening had to answer a questionnaire prior to getting screened. Please see also response to reviewer 1 above (page 5).

As Self-HPV is only one step in the screening process (HPV positive, cytology, colposcopy, biopsy, treat). The results are frustrating, as the reader would like to know how many patients in each group have completed the whole process. Could you please add these data in the paper.

Response:

As we have explained to reviewer 1 above, this part was not negotiated with the communities because this was an explorative research study to assess screening uptake related to self-sampling and therefore outside of the scope of the ACCSS.

The national Canadian guidelines for cervical cancer screening should be reported in the paper. Does the country have an opportunistic screening or a program?

Response:

We have complemented the information in the protocol on page 4 and there is also a citation. Cervical screening programs are not alike in all Canadian provinces. In Ontario, for example, it is still opportunistic.

I do not understand why women having had a screening test in the last three years (even less than one year) have been include in this study.

Response

The rationale was to recruit as many women as possible to obtain an answer whether or not self-sampling could be a viable option to standard-of-care screening and to learn about screening habits of First Nations women. We would have lost many voices had we not included these women.

Reviewer: 3

Reviewer Name
Richard MUWONGE

Institution and Country
Scientist
International Agency for Research on Cancer,
Lyon, FRANCE

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
Review comments

General comment
The manuscript is well written, analyses and discusses the feasibility of implementing and participants acceptability of two cervical cancer screening modalities. This manuscript has important public health implications largely for the under-screened populations of the high-income regions and to some extent most populations of the low-income regions. It brings out the importance of involving the different stakeholders in the setting up and successful implementation of cervical cancer screening programmes.

Specific minor comments
1. Page 7, line 11: Not full definition of IZ is given in the text a prior.

Response:

The full name is given where applicable: pages 2 and 7 in the Protocol as well as page 8 of the text body.

2. Page 7, lines 25-35: Were the same women offered HPV testing in phase 1 and cytology in phase 2 in the arm A and vice versa for arm B? If yes, could this have affected the participation especially in phase 2 since a gap of around 2 months between screens may to small especially for those who were screen-negative in the first phase.

Response:

Probably not because only women who had not accepted the initial screening offer were invited for the alternative test in the second round.

3. Page 8, line 4-6: The authors may give a brief description of the Ontario Cervical Screening protocol.

Response:

We have complemented the information in the protocol on page 4 and there is also a citation. Please see also response to reviewer 2 above (page 9).

4. Page 11, lines 30-40: It is a general tendency in cluster randomized trials to take the unit of analysis as the cluster instead of the individual. The authors may use the cluster as the unit of analysis even for the descriptive analyses. (ref. Bland and Kerry).

Response:

We initially attempted this approach, and applied it to the primary outcomes where appropriate, but changed it to individual analysis for these data due to very low numbers and zeroes in some of the cells. As well, given the complexity of applying and presenting both ITT and PP approaches to the levels of stratification of these data, including the socio-economic demographic characteristics, we instead applied standard descriptive statistics to highlight the characteristics within each Arm.

5. Page 12, lines 14-24: This text many be shifted to the methods section.

Response:

We kept the text in the protocol due to space constraints in the main text body.

Reference

Bland JM, Kerry SM. Statistics notes. Weighted comparison of means. BMJ 1998;316:129.

VERSION 2 – REVIEW

REVIEWER	Petignat Patrick University Hospital of Geneva
REVIEW RETURNED	30-Aug-2016

GENERAL COMMENTS	The authors have now correctly answered the questions of reviewers. I have no additional comment to add