

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cervical cancer screening and HPV vaccine acceptability among rural and urban women in Kilimanjaro Region, Tanzania
AUTHORS	Cunningham, Melissa; Skrastins, Emily; Fitzpatrick, Ryan; Jindal, Priya; Oneko, Olola; Yeates, Karen; Booth, Christopher; Carpenter, Jenn; Aronson, Kristan

VERSION 1 - REVIEW

REVIEWER	Polat Dursun Baskent University School of Medicine Gynecologic Oncology
REVIEW RETURNED	08-Jul-2014

GENERAL COMMENTS	this is a very well designed and performed study . In my opinion it should be publish in your journal
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REVIEWER	PARTHA BASU Department of Gynecologic Oncology Chittaranjan National Cancer Institute
REVIEW RETURNED	22-Dec-2014

GENERAL COMMENTS	<p>In the review article the authors have justified conducting a study to evaluate the role of prophylactic ablation of transformation of zone of cervix to prevent development of cervical neoplasia. The authors have reviewed the available evidence, which is limited yet greatly favour prophylactic ablation. This is more relevant in the context of the recent WHO guidelines to perform 'screen and treat' for HPV positive women.</p> <p>FEW COMMENTS:</p> <p>Page 4; discussion on the study by Peyton et al: The number of untreated women developing CIS/CA is very high (27/1000). Were those women attending clinic because of abnormal pap?</p> <p>Page 8; discussion on study by Collins et al: Another reason for difference in susceptibility to HP can be the fact that the TZ is larger in young women few years after monarchy than at monarchy</p> <p>Page 9; conclusions: prophylactic ablation will not be done in women with mature metaplasia-- In real life it will be difficult to distinguish between mature and immature metaplasia by VIA/VILI. More importantly treatment should be offered to all who are positive on HPV test. Subset analysis can be done to find the difference in effect between those apparently having mature and those having immature metaplasia.</p> <p>Other: The authors can also justify prophylactic ablation as it has a potential role to treat those HPV positive women with CIN 2/3 who do not have any visible lesions on colposcopy/VIA (Yang B,</p>
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	Pretorius RG, Belinson JL et al. False negative colposcopy is associated with thinner cervical intraepithelial neoplasia 2 and 3. <i>Gynecol Oncol</i> 2008; 110: 32–36.)
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REVIEWER	Nicole Campos Harvard School of Public Health Boston, MA USA
REVIEW RETURNED	22-Dec-2014

GENERAL COMMENTS	<p>This article represents an important contribution to the literature on awareness of cervical cancer, screening, and HPV vaccination in a low-income country setting. Strengths include the population-based sample and the stratification of respondents by rural/urban setting. The following areas should be addressed to further strengthen the paper:</p> <ol style="list-style-type: none"> 1) Abstract, Conclusions: The authors state that “Although best implemented concurrently, the availability of prophylactic vaccination may provide an effective means of prevention for women who are unable to access screening.” This statement is unclear, and might be interpreted as suggesting that HPV vaccination and cervical cancer screening apply to the same target ages. Furthermore, even if vaccination prevents cancer cases in several decades if administered to adolescents, there will still be many women who die of cancer in the interim if screening is unavailable. 2) Introduction, paragraph 1, line 20: While cervical cancer is a highly preventable disease, it is preventable primarily through identification of precancerous lesions via screening (not early detection of cancer, as the sentence implies) and prophylactic vaccination; I don’t think it is useful to include personal risk factors as modifiable ones in this instance. A similar statement appears on p. 5, line 14, about the “insufficient use of preventative methods in combination with risk factors have resulted in a high cancer-related mortality rate of 32 per 100,000 women per year.” It is not clear what the authors mean by “preventative methods” and “risk factors,” but this statement appears to be misleading, as again, it is lack of screening, late detection, and lack of appropriate cancer treatment that is primarily responsible for the high mortality rate – not personal risk factors. 3) p. 4, p. 14: Why do the authors only refer to the quadrivalent HPV vaccine? It seems the bivalent vaccine should also be described. 4) p. 10, lines 20-34: Where are the results pertaining to perceived barriers to HPV vaccination reported in a table? In line 34, what is meant by “concerns about testing of the vaccine”? Furthermore, on p. 11, lines 5-14, these results do not appear to be included in any of the tables. 5) It would be useful to see the multivariate model results in a table. 6) p. 12, line 25: See #4, above; the endorsement of healthcare providers and the government do not appear in the table on HPV vaccine knowledge and attitudes and has not been previously mentioned. 7) Table 1: It would make more sense to move “Aware of the
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	<p>disease” and “Adequate knowledge of cervical cancer” to the top of the table, before launching into detailed knowledge/attitudes toward screening. Also, how is the difference between disease awareness and adequate knowledge defined?</p> <p>Minor comments: 1) Please provide a reference for p. 4, line 28. 2) p. 8: Section 1.5.2 heading: Please specify that this section applies to screening. 3) The number headings are off on p. 10 (Sections 1.5.4 and 1.5.5).</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer #1 (Polat Dursun)

this is a very well designed and performed study . In my opinion it should be publish in your journal
A: Thank you.

Reviewer #2 (Partha Basu)

Page 4; discussion on the study by Peyton et al: The number of untreated women developing CIS/CA is very high (27/1000). Were those women attending clinic because of abnormal pap?

A: The publication to which the reviewer is referring to is unclear. It is also not clear as to what the question regarding women is referring to. The reviewer has requested no changes to our paper.

Page 8; discussion on study by Collins et al: Another reason for difference in susceptibility to HP can be the fact that the TZ is larger in young women few years after monarchy than at monarchy (menarche?)

A:The issue the reviewer is referring to is not apparent to us, and the reviewer has requested no changes to our paper.

Page 9; conclusions: prophylactic ablation will not be done in women with mature metaplasia-- In real life it will be difficult to distinguish between mature and immature metaplasia by VIA/VILI. More importantly treatment should be offered to all who are positive on HPV test. Subset analysis can be done to find the difference in effect between those apparently having mature and those having immature metaplasia.

A:Same comment as above.

Furthermore, our paper has not discussed HPV testing.

Other: The authors can also justify prophylactic ablation as it has a potential role to treat those HPV positive women with CIN 2/3 who do not have any visible lesions on colposcopy/VIA (Yang B, Pretorius RG, Belinson JL et al. False negative colposcopy is associated with thinner cervical intraepithelial neoplasia 2 and 3. Gynecol Oncol 2008; 110: 32–36.)

A:We do not believe this is relevant to discuss as we have not referenced HPV testing in low-resource areas and were also not trying to justify an approach to treatment.

Reviewer #3 (Nicole Campos)

1) Abstract, Conclusions: The authors state that “Although best implemented concurrently, the availability of prophylactic vaccination may provide an effective means of prevention for women who are unable to access screening.” This statement is unclear, and might be interpreted as suggesting that HPV vaccination and cervical cancer screening apply to the same target ages. Furthermore, even

if vaccination prevents cancer cases in several decades if administered to adolescents, there will still be many women who die of cancer in the interim if screening is unavailable.

A: We agree, thank you for your suggestion.

Page 3, lines 4-6, have been changed to make clear that screening and vaccination are not the same target population for prevention: "Although best implemented concurrently, the availability of prophylactic vaccination for girls may provide an effective means of prevention if they are unable to access screening in the future."

This has also been clarified on Page 4, lines 24-28: "Although organized cervical cancer screening and educational campaigns are recognized as important prevention methods for women today, combining these efforts with prophylactic vaccination is expected to substantially reduce the future burden of disease in low-resource countries."

2) Introduction, paragraph 1, line 20: While cervical cancer is a highly preventable disease, it is preventable primarily through identification of precancerous lesions via screening (not early detection of cancer, as the sentence implies) and prophylactic vaccination; I don't think it is useful to include personal risk factors as modifiable ones in this instance.

A: Thank you for your suggestion – we have changed Page 4, lines 9-11 to reflect that screening is for precancerous lesions and that prevention is primarily accomplished through screening and prophylactic vaccination.

A similar statement appears on p. 5, line 14, about the "insufficient use of preventative methods in combination with risk factors have resulted in a high cancer-related mortality rate of 32 per 100,000 women per year." It is not clear what the authors mean by "preventative methods" and "risk factors," but this statement appears to be misleading, as again, it is lack of screening, late detection, and lack of appropriate cancer treatment that is primarily responsible for the high mortality rate – not personal risk factors.

A: Thank you for your suggestion. We have clarified these statements. "Preventative methods" in this sentence was in reference to screening. "Risk factors" were in reference to factors specific to Tanzania, specifically the high prevalence of HIV/AIDS, which contribute to the higher incidence of HPV and thus cervical cancer in the region. We have amended the statement to also cite the lack of available treatment. (Page 5, lines 6-9)

3) p. 4, p. 14: Why do the authors only refer to the quadrivalent HPV vaccine? It seems the bivalent vaccine should also be described.

A: In order to have a focused paper, we refer and discuss the quadrivalent vaccine ("In 2006, a quadrivalent vaccine protecting against these four strains became commercially available from Merck & Co. (Gardasil®)") because this is the vaccine which is supported by GAVI and the one which will be used in low-resource areas.

4) p. 10, lines 20-34: Where are the results pertaining to perceived barriers to HPV vaccination reported in a table?

A: The barriers reported for HPV vaccination have been added to Table 5 (page 26).

In line 34, what is meant by "concerns about testing of the vaccine"?

A: This has been clarified to "concerns about safety testing of the vaccine" (page 10 lines 16-17)

Furthermore, on p. 11, lines 5-14, these results do not appear to be included in any of the tables.

A: These results have now been added to Table 4 (page 25)

5) It would be useful to see the multivariate model results in a table.

A: We did not wish to go above the maximum allotment of 5 tables. We also believe that we have

written the results in an organized and comprehensive manner for readers on page 10, lines 18-26.

6) p. 12, line 25: See #4, above; the endorsement of healthcare providers and the government do not appear in the table on HPV vaccine knowledge and attitudes and has not been previously mentioned.
 A: This is part of the discussion and refers to results that were not found in this study. A citation has not been added for these findings (Page 12, Line 14).

7) Table 1: It would make more sense to move “Aware of the disease” and “Adequate knowledge of cervical cancer” to the top of the table, before launching into detailed knowledge/attitudes toward screening.

A: Thank you for your suggestion – these have now been moved to the top of the table.

Also, how is the difference between disease awareness and adequate knowledge defined?

A: On Page 6, lines 25-27, we have defined adequate knowledge to mean, “Participants were considered to have an adequate knowledge of cervical cancer if they answered ‘yes’ to “Have you heard of (a) cancer and, (b) the cervix?” and “Have you heard of cervical cancer?” and answered ‘women’ to “Who can develop cervical cancer?”
 Awareness is simply the answer to the item “Have you heard of cervical cancer”

Minor Comments

1) Please provide a reference for p. 4, line 28.

A: This should have been referenced: World Health Organization (WHO). Control of cancer of the cervix uteri. Bull World Health Organ. 1986;64(4):607–18.

We have now added this.

2) p. 8: Section 1.5.2 heading: Please specify that this section applies to screening.

A: This section refers to both screening and vaccination and this has now been noted in the heading.

3) The number headings are off on p. 10 (Sections 1.5.4 and 1.5.5).

A: Thank you; these have been corrected.

VERSION 2 – REVIEW

REVIEWER	Nicole Campos Harvard T.H. Chan School of Public Health Boston, MA USA
REVIEW RETURNED	04-Feb-2015

GENERAL COMMENTS	<p>The paper is improved, but there are still some areas that need to be addressed:</p> <p>1) P. 4, lines 9-11: It would be clearer to say “Cervical cancer is preventable primarily through prophylactic HPV vaccination and screening for precancerous lesions.”</p> <p>2) P. 4, lines 23-24: I don’t believe it is accurate that GAVI only supports Gardasil. Please see: http://www.gavi.org/library/news/press-releases/2013/hpv-price-announcement/. Unless there is a more recent decision you can cite, please do not restrict the Introduction to Gardasil.</p> <p>3) P. 4, line 27: I assume you mean prophylactic vaccination in pre-adolescent girls? Please clarify the target population for prophylactic vaccination.</p> <p>4) P. 5, line 7: “insufficient use of screening methods” seems to imply the women aren’t accessing screening, rather than screening</p>
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	<p>just isn't available. Please re-phrase.</p> <p>5) P. 6, line 27-28: It is still not clear from the text what the distinction is between "awareness" and "adequate knowledge". Please add this information as you did in the response to reviewers. It would also be helpful to include as a footnote in Table 3.</p> <p>6) P. 10, line 20: "safety testing" is not clear. Perhaps you just mean "safety of the vaccine"? Table 5 refers to "Safety of administration". Please use a consistent term and make sure it is defined for readers – whether the question on safety referred to safety of the vaccine or safety of the vaccine administration.</p> <p>7) P. 11, line 9: Please specify that by "their" you mean the husband or partner.</p>
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VERSION 2 – AUTHOR RESPONSE

Thank you for your comments, they are very helpful. We have made changes based on all your responses below:

1) P. 4, lines 9-11: It would be clearer to say "Cervical cancer is preventable primarily through prophylactic HPV vaccination and screening for precancerous lesions."

These lines have been changed to the above.

2) P. 4, lines 23-24: I don't believe it is accurate that GAVI only supports Gardasil. Please see: <http://www.gavi.org/library/news/press-releases/2013/hpv-price-announcement/>. Unless there is a more recent decision you can cite, please do not restrict the Introduction to Gardasil.

Thank you, this has been changed on page 4 to include the other vaccine mentioned. "A quadrivalent vaccine protecting against these four strains is commercially available from Merck & Co. (Gardasil®) and a bivalent vaccine against the cervical cancer strains is available from GalxoSmithKline (Cervarix®)"

3) P. 4, line 27: I assume you mean prophylactic vaccination in pre-adolescent girls? Please clarify the target population for prophylactic vaccination.

Yes, thank you, we have revised this to include the term "pre-adolescent girls".

4) P. 5, line 7: "insufficient use of screening methods" seems to imply the women aren't accessing screening, rather than screening just isn't available. Please re-phrase.

It is not known why women aren't accessing screening (this was one of the reasons this survey was done -- the hospital's screening clinic in Kilimanjaro was not attended by women from the community, nor some of the nurses themselves). We agree with your comment and have revised the statement to be more broad and have simply stated that there is a lack of screening. It now reads, "The comorbid epidemic of HIV/AIDS in the region and lack of screening has contributed to the high incidence of cervical cancer, and late detection and lack of treatment availability have resulted in a high cancer-related mortality rate of 32 per 100,000 women per year (10)."

5) P. 6, line 27-28: It is still not clear from the text what the distinction is between "awareness" and "adequate knowledge". Please add this information as you did in the response to reviewers. It would also be helpful to include as a footnote in Table 3.

Thank you for this comment. We have added this into the Methods section where this was described on page 6, and we have also added it to a footnote on Table 3.

6) P. 10, line 20: "safety testing" is not clear. Perhaps you just mean "safety of the vaccine"? Table 5

refers to "Safety of administration". Please use a consistent term and make sure it is defined for readers – whether the question on safety referred to safety of the vaccine or safety of the vaccine administration.

Thank you for this clarification. These were two separate questions and they have been more clearly described in the paper as "safety of the vaccine's administration" and "previous testing of the vaccine's safety" on page 10, and page 13; this has also been updated to the exact same phrasing for Table 5.

7) P. 11, line 9: Please specify that by "their" you mean the husband or partner.

"Their" did not mean husband or partner, and it is clear that this sentence was unclear. We hope the updated version clarifies any confusion: "Women were also asked to predict their husband or partner's acceptance of the vaccine: while there was no difference across urban/rural strata, women's predictions of their husband or partner's intention to definitely accept the vaccine was lower (64%)."