Format for ANSWERING REVIEWERS

September 3, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 20228-Review.doc).

Title: Cervical cancer screening in developing countries at a crossroad: Emerging technologies and policy choices

Author: Rosa Catarino, Patrick Petignat, Gabriel Dongui, Pierre Vassilakos

Name of Journal: *World Journal of Clinical Oncology*

ESPS Manuscript NO: 20228

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reply to reviewers

1# Reviewed by 03262677

Review Time 2015-06-18 10:44

The aim of the manuscript was to review the challenges of implementing cervical screening adapted by developing countries in particularly the primary rapid HPV-based screening test. The authors discussed the different types of screening test such as the traditional cytology screening, VIA/VILI and HPV genotyping. However, there were little discussed about the potential new biomarkers for cervical screening, briefly touched on page10-11. Considered a more detail discussion and other biomarkers beside HPV proteins. This should be a major component as the title emphasise on emerging technologies. In addition a discussion of mechanisms of how the biomarkers are working, a diagram/figure would help.

R: A more detailed discussion on biomarkers for cervical screening was written on

pages 13 to 15.

Other points to consider:

i) A Table summarising the challenges of implementing cervical screening in developing countries would be useful? Is the challenges country specific? Or a summary section documenting the limitations.

R: We added a table summarising the challenges of implementing cervical screening in developing countries – See table 1.

ii) Also stated in the title is policies - this is not adequately addressed in the review. What are the policies in developing countries, if any? A discussion on this would be useful? How is your review be useful in establishing a universal WHO policy. List potential challenges of implementing cervical screening policies in developing countries (or perhaps a Table format will be useful).

R: Changes have been done accordingly – page 6.

iii) What is the authors' recommendation(s) in cervical screening in developing countries? Is it the proposed Triage test? Which order do the authors recommend and is this feasible economically?

R: We believe that CC screening in developing countries will be based on rapid point-of-care HPV tests that are performed in self-obtained vaginal samples, followed by a triage of HPV-positive women during the same visit. The triage test still needs to be defined, but for the moment we will keep using visual inspection tests in our campaigns.

iv) There should be a short introduction summarising the problem and what to be discussed in the review. Abstract - could be the introduction and the abstract summarise the review with background, what is deficient in the area, how this review can help aid the gap, what will be discussed and have a concluding statement and/or recommendation at the end of the abstract.

R: Changes have been done accordingly – page 3.

2# Reviewed by 00739752

Review Time 2015-08-08 16:15

Indeed the article is very well and it will be useful for most physician.

3# Reviewed by 00558009

Review Time 2015-08-08 21:17

This is a clear and nicely written discussion of the choices and decisions to be made regarding cervical cancer screening in developing countries. It is well constructed, concise, and provides the pros and cones involved in various approaches that may be chosen by each country.

I have a few wording suggestions below, which are meant to clarify.

page 4, line 13 CC screening is one of the most successful disease-prevention programmes.

page 4, line 21 Consequently, implementation and execution of the whole process is too complex and expensive.

page 6, line 16 Highly sensitive tests have been developed and are currently used to replace cervical cytology for primary screening [29].

page 7, line 10 Evidence shows that HPV tests should not only be type specific but also virial region specific (specific regions in the HPV genome are L1, E1/E2 and E6/E7)

page 7, line 14 A test designed only for L1 will miss approximately 10% of all invasive cancers.

Page 7, line 28 Until recently, the greatest limitations of HPV testing was the need for expensive laboratory infrastructure and the 4–7 h time to process the test.

Page 8, lines 3-13 In a cohort of unscreened 30-year old women from South Africa, HPV testing followed by the treatment of women who tested positive at the second visit was the most effective option (27% reduction in the incidence of CC) at a cost of 39 USD/years of life saved (YLS) [38]. VIA coupled with the immediate treatment of women who tested positive at the first visit was cost saving and was the next most effective strategy, with a 26% decrease in the incidence of CC [38]. In another cost-effectiveness analysis in a rural Chinese population, where the careHPV? test (Qiagen, Gaithersburg, MD, USA) was directly compared with VIA, a once-per-lifetime screening at the age of 35 years would reduce CC mortality by 8% combined with VIA (cost of 557 USD/YLS), compared with 12% with the careHPV test (cost of 959 USD/YLS) [39].

Page 9, line 7 If HPV is used as primary screening, recent evidence supports its use in women aged 30 years or older [47, 48].

R: Corrections to the text were done accordingly.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Clinical Oncology*

Sincerely yours,

Catarino Rosa, MD