Author's response to reviews

Title: Human papillomavirus (HPV) genotype distribution in Madrid and correlation with cytological data

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Author's response to reviews: see over
Dear Roselle Pangilinan,

Thank you for your letter and comments from the reviewers. All are well taken. We enclose a revised version with the modifications suggested highlighted in red (with “tracked” changes).

Given the existence of several other reports of type specific HPV prevalence, could the authors please emphasize what new information this report provides, and how it contributes to the field?

Limited data are available describing human papillomavirus (HPV) genotype distributions in Madrid (Spain) and these studies are needed to predict how HPV vaccination and HPV-based screening will influence cervical cancer prevention.

Our study confirms the significant presence of other HPV genotypes (not HPV16/ not HPV18) implicated in cervical infection, with a very low frequency of genotype 18. These data support the necessity of assessing the specific genotype rather than distinguishing between high- or low-risk HPV. The finding of HPV52 as the second most common genotype associated with high grade lesions (HSIL) is a new information that may have relevant implications.

We think that our results (and more studies) are necessary and provide relevant information to evaluate the benefits and the impact of vaccination programs.

Reviewer 1
1- The percentage of cases positive for HPV infection in the different lesions grades has been added to the results section (first paragraph lanes 3-4) clarifying the quality of diagnosis method used.

2- We agree that there is a great variation in HPV type distribution, even between HSIL and cancer. More studies need to be done and the use of histological section instead of cytological specimens for specific HPV genotyping would be very useful in order to understand the role of different HPV types and the impact of HPV vaccination.

**Reviewer 2**

1- A serious statistical treatment of data has been done by a specialist, who has been included as an author of the paper (V. Abraira). Statistical analysis (in methods section) has been corrected, and Chi square test has been added to Table 2 (correlates cytological lesion with age).

2- A new table (Table 4) with cytological lesion and coinfection correlation has been done using the Chi square test.

3- Coinfections of HVP18 with HPV52 have been found in ten cases with the following lesions: three with HSIL, three LSIL and four with ASCUS. We think that they are few cases to do a figure or table for the manuscript. HPV52 is an important and frequent type in samples with lesions (LSIL and HSIL) in our area, more than HPV18, and this is an important point for the HPV vaccination in Spain.

**Reviewer 3**

1- We have included in the paper the cases HPV negative according to each diagnosis (new Table 1).
**COVER LETTER**: point-by-point description of the changes made

**Title page:** Following the recommendation of reviewer 2 a statistical review has been done and a new author from the Biostatistics Unit has been added to the list of authors and affiliations.

**Abstract:** Cases who tested negative for HPV according to each diagnosis have been included to the manuscript (answering to referee 3), hence the total of cases analysed have been changed in methods and results.

**Methods:**

Specimen preparation: Now, the total of cases included is 2,461 (with HPV negatives) and the cytological diagnoses of all cases have been added to the manuscript (referee 3).

Statistical analysis: Logistic regression had not been included in the manuscript, only Chi-square test was used to evaluate association between genotype, lesion, and age. It has been corrected in the paper.

**Results:**

First paragraph: Specimens negative for HPV have been included to the manuscript (answering to referee 3); hence the total of cases has reached 2,461. A phrase with percentage of cases HPV positive in the different cytological diagnosis has been added (referee 1).

Two new tables have been inserted (Table 1 and table 4) to clarify the results. Table 1 and table 2 now are renamed to table 2, and table 3 respectively.

**Discussion:**

Phrase of co infection have been included in the discussion (last paragraph).

**Author’s Contribution:**

VA (as statistical reviewer) has been put in author’s contribution.

We hope we answered all the comments and we look forward for your feedback of this revised version.

Yours sincerely:

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