Reviewer's report

Title: Genotype distribution of human papillomavirus (HPV) in histological sections of cervical intraepithelial neoplasia and invasive cervical carcinoma in Madrid, Spain.

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Reviewer: Helen Trottier

Reviewer's report:

This is a very interesting study and an article of importance in its field. However, a revision would be necessary before I can recommend publication. Essentially, the manuscript needs more concision and precisions. My concerns are described in the comments to authors.

INTRODUCTION

Introduction needs revision.

1) The Introduction needs much more references. For example, the classification of HPVs, the number of mucosal types, the available vaccines, the variation of oncogenic potential, etc, must be supported with references.

2) Second paragraph: Co-infection is known to increase the risk of CIN but not cervical cancer. It is more accepted that co-infection is a marker of immunity. However, in cervical cancer samples, co-infection is rarely detected. Even if a woman is infected with multiple types (showing a potential problem in term of immunity), only type 16 or 18 for example cause cancer. The impact of co-infection should be better explained with references.

3) I suggest reducing the Introduction regarding statement that goes outside the focus of the study. For example, there are statements about the impact of the vaccine on the potential genotype replacement which I think is inappropriate, because this is not the scope of the study but also because it is not really supported by the literature.

4) I do not understand the forth paragraph of the Introduction.

5) The introduction must describe the general epidemiology of HPV in Spain (Spain is well known to have low prevalence of HPV in women with normal cytology). This should be presented.

MATERIAL AND METHODS

Can you give more details about the “stratified and not random consecutive samples”? What is it exactly?

The Method section should provide the details about the analysis. For example, different methods were used to estimate % in tables 2 and 4. This should be
95% confidence intervals should also be provided for estimates (percentage).

Specimen collection and diagnosis

Results about the % of HPV positivity are given in this section but this is an important result and it should be presented in the Result section (not in the method). And this % is estimated at less than 47% (533/1137). It would have been interesting to provide % of HPV positivity for the total number of abnormal specimen (1137) stratified according to lesions (Benign, CIN1, CIN2-3, etc.). Also is 47% is comparable with other studies?

It is stated in this section that Inform consent was not required because that HPV genotyping is routinely performed. Then you described in the next section how the detection and genotyping was done. I don’t understand? Are detection and genotyping done in clinical setting? Or it is because these data were collected in another study? Need more details.

Results

Distribution of viral genotypes

Table 2 needs to be cited in the first sentences. Also, the Result section is written as an output and not as a manuscript. As is, we get lost in the results and it is hard to analyse and compare the data between lesions and genotypes. Authors don’t need to repeat all the data presented in tables. Only essentials should be presented in the Results section. It must be considerably reduced as most of the information is presented in tables.

Table 2 et 4:
replace “genotipe” by genotype.
Replace n# by N and define in the footnote

DISCUSSION

The Discussion is well written. However, results should be discussed and compared considering 95% confidence intervals around their estimates. For example, authors concluded that HPV18 was more prevalent in CIN1 (7.2%) than in CIN 2-3 (5.7%). Authors need to be cautious when comparing similar results. CIs probably overlap (no significant difference).

Important limitations of the study should be discussed:
- Small sample size
- Low external validity (only one site), hard to generalize the results to the entire population of Spain
- Detection of only 20 HPVs genotypes whereas more than 40 mucosal exist. It may underestimate HPV prevalence.
- etc.
Conclusion can be merged with the Discussion.
The last sentence of the conclusion is very strong. Obviously, the effectiveness of the vaccine seems very good in Spain as more than 85% of ICCs are caused by HPV-16/18! I think that one of the most important conclusions here is that the vaccine will be very good in Spain to prevent cervical cancer!

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I have received speaker/consultation fees and travel assistance from Merck Frosst and GlaxoSmithKline Biologicals.