Author’s response to reviews

Title: Human papillomavirus in semen and the risk for male infertility: a systematic review and meta-analysis

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Author’s response to reviews:

Dear Editor,

Thank you very much for your decision letter. We deeply appreciate your and reviewer’s valuable comments. The manuscript has been revised accordingly, with our point-by-point
responses attached below. We thank you again and hope that the latest version will meet with your approval.

Yours sincerely,

Dong Hang, Ph.D.

Comments from Editor:

1. With respect to the paragraph added to define male infertility as per the suggestion of reviewer 1 (Page 6 Line 127-134), the meaning of the figures adjacent to each criteria are unclear. Please clarify this paragraph. It is likely that so much detail is not required as you have referenced the WHO guidelines.

Response: Thanks for your valuable comment. We have revised the paragraph.

“Male infertility is defined based on the following criteria: at least 1 year of unprotected sexual intercourse without conception, and/or abnormal results of semen analysis referring to the standards in the guidelines of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edition) [13].” (Methods section, line 127 - 130, page 6)

2. Please have a fluent English speaker read over your manuscript to correct minor grammatical errors throughout.
Response: Thanks for the advice. We have revised grammatical errors throughout the manuscript.

Comments from Christophe Depuydt (Reviewer 2):

1. "Biological evidences indicate that HPV virions could have been localized at the equatorial region of sperm and affect sperm quality, thereby increasing the risk of male infertility [8]." (Line 95 - 97).

Different groups have shown that HPV virions bind 2 equatorial regions of the sperm head.

Response: Thanks for the reviewer’s valuable advice. We have revised the sentence.

"Biological evidences indicate that HPV virions could bind two distinct equatorial regions of the sperm head and affect sperm quality, thereby increasing the risk of male infertility [8, 9]." (Background section, line 96 - 98, page 5)

2. It should be clear for the readers that the HPV DNA measured mostly originates from virions. It would maybe be more appropriate to mention in the introduction or material and methods that the HPV DNA that is measured in semen primarily originates from virions and is infectious (eg p5 line 92). This would allow to use the term HPV prevalence or HPV DNA in tables and text instead of HPV virion prevalence. The problem in writing HPV virion prevalence is that in fact none of the studies measured virions but measured HPV DNA that almost exclusively originates from virions or will be used to build new virions. In rare cases one cannot exclude that the measured HPV DNA originates from clonal HPV infections.


P7 line 156; p8 line 180; p9 line 192; p11: HPV prevalence

P8 line 184: 738 HPV DNA positive men
Response: Thanks for the reviewer’s valuable advice. We have added the statement in the background section.

“Actually, HPV DNA measured in semen samples primarily originates from HPV virions and is infectious.” (Background section, line 92 - 93, page 5)

We have also revised the descriptions accordingly.

“the clonal HPV E6/E7 transforming pathway” (Background section, line 90, page 4)
“HPV prevalence” (Method section, line 151, page 7)
“HPV DNA positive cases” (Method section, line 151, page 7)
“HPV prevalence” (Results section, line 176, page 8)
“HPV prevalence” (Results section, line 187, page 8)
“HPV prevalence” (Results section, line 217, page 11)
“738 HPV DNA positive men” (Results section, line 179 - 180, page 8)