Reviewer's report

Title: Estimate of the Global Burden of Cervical Adenocarcinoma and Potential Impact of Prophylactic Human Papillomavirus Vaccination

Version: 1 Date: 30 August 2013

Reviewer: Karl-Ulrich Petry

Reviewer's report:

The submitted estimation on the global burden of adenocarcinoma of the uterine cervix is of interest for researchers in this field. In principle I rate the manuscript as suitable for publication in BMC Cancer but it needs some essential major and minor revisions before it could be accepted.

Major compulsory revisions (1, 2, 5)

Minor essential revisions (3.+4, 6-7)

1. 3 out of 4 authors are GSK employees, therefore even the slightest impression of a hidden promotion of a GSK product should be avoided. As there are no head to head efficacy data for Gardasil vs Cervarix and because the FUTURE and PATRICIA study designs are not identical, the true difference in cross-protection may be smaller than observed. To my opinion, the table in the additional file, comparing Gardasil and Cervarix does not add anything essential to the investigation aim of estimating the global burden of ADC and very little on the impact of HPV vaccination but it discredits the scientific neutrality of the paper. Therefore this table should not be published.

2. For the same reason on page 6, first paragraph:

"The quadrivalent HPV-6/11/16/18 vaccine (Gardasil®) significantly reduced persistent infection with HPV-31, but not other oncogenic HPV types"

lacks the neutrality needed. I would advise to state that for gardasil a significant cross-protection was published for HPV31 but so far not for other oncogenic types.

3. Page 9, second paragraph The multiplication by 100/82 to adjust for total HPV prevalence) needs a better explanation because the 82% prevalence is only given in the subsequent results chapter on page 12

4. Page 9, end of second paragraph. The adjustment for multiple HPV infections is better explained but may lead to an overestimation of HPV types that are frequently found in multiple and an underestimation of HPV types with single type detection only. For example if HPVXY is associated with 10% of ADC but only in liason with HPV16 you would calculate an impact of 10/110 for HPVXY although the true impact might be zero. Please address this point

5. Page 9 to 10. The first paragraph of potential impact of HPV vaccination needs to be corrected according to point 1. I would advice to calculate the impact on
non 16/18 ADC based on Cervarix data alone with the argument that the published data on Gardasil’s cross protection is so far inconclusive

6. page 16 the statement about a rise in HPV in head and neck tumours stands alone and should be deleted

7. the assumption that the HPV prevalences in ADC reported in the analysed trials are very likely underestimations is conclusive. Further to the arguments listed by the authors, there are prospective trials on SCC and ADC (e.g Böhmer G et al. Am J Obstet Gynecol 2003 and/or Liebrich C et al Eur J Gyn Oncol 2009) that showed that there is only a tiny subset of truly HPV neg ADC, mostly clear cell ADC, while the rest is explained by false diagnosis, insufficient sample quality and other HPV types. The first IARC analysis detected HPV only in less than 94% of SCC while a revision by J. Walboomer et al showed that finally 99.7% contained HPV. So it seems a sound conclusion that the submitted analysis may even underestimate the true impact of HPV vaccines on ADC but also that a fraction of ADC is probably just a misclassification.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I received occasionally speaker’s honorarium from GSK, was primary investigator in a Cervarix trial run by GSK. My institution receives unrestricted grants from Sanofi Pasteur MSD for an ongoing trial on the epidemiology of HPV in younger women