Reviewer's report

Title: Benefits and harms of the human papillomavirus (HPV) vaccines: comparison of trial data from clinical study reports with corresponding trial register entries and journal publications

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Reviewer: David Fisher

Reviewer's report:

This is an interesting and unusual article. The authors seek to compare data from CSRs, trial registries and journal publications using various metrics, including the efficacy and safety outcomes and the completeness of information on study design, inclusion criteria and risk of bias.

My first comment would be that, although the aim of comparing data on the same trial from different sources is an entirely sensible one, a specific hypothesis (or hypotheses) is not given, and this has an impact on the methodology used. For instance, do the authors hypothesize that efficacy/safety comparisons would be more favourable to the research treatment in CSRs vs in journals? Or that there would be no bias as such, but rather, a certain amount of variation? Or that any bias would be limited to certain types of outcome or participant?

My second comment is regarding the footnote to Table 3a, and Additional File 2. The footnote states that it was "not possible to present [these data] for the 16 subgroups that the 24 included studies comprised (based on age-group, gender, type of HPV vaccine and comparator). And indeed, it is within these subgroups that the meta-analyses in Additional File 2 are presented. But it is not made clear why this should be the case -- particularly when, as a result, there are multiple meta-analysis subgroups with only one (or sometimes two, but no more) study in each. The authors should explain these subgroups, and whether this sparseness of studies was expected. To me, this seems an odd way of presenting this data, not least because of the wasted space, small font and difficulty of interpretation. It may have made sense in the main systematic review; but in this context, some "lumping" of data might be best. And this comes back to my first comment: what are the authors trying to show with these data?
My suggestion would be to try applying the techniques of Bland and Altman, whereby the difference (or ratio, or log ratio, etc. ...) of two measurements (e.g. between CSR and journal publication) is plotted against a convenient metric. By default this metric is the average of the two measurements, but it could also be some characteristic which is hypothesized to vary with either bias or amount of variation in the differences. For instance, in this context, the age group of the participants; but also maybe the size of the study, or the level of detail in the report as measured by page numbers, etc. However, an argument against this approach might be the sparse data, which I shall discuss next.

Considering that one of the main stated aim of the study was to compare pooled estimates, the pooling methodology is fairly simplistic: inverse-variance DerSimonian-Laird random-effects. With such sparse, imbalanced data, Mantel-Haenszel pooling might be a more robust primary choice, possibly with a random-effects model as a sensitivity analysis to assess the effect of heterogeneity. Another alternative might be one-stage modelling, since knowledge of count data enables IPD to be recreated in full. (Other options for handling sparse data might also exist -- that is not my specific field of expertise.)

Finally, a couple of more minor comments:

in the Methods section it states "We did not check for eligible information in additional trial registers (such as the EU Clinical Trials Register) or letters to the editors." -- why not? what effect might this have had?

in the Conclusions, the authors acknowledge that no significant differences were found, but then immediately claim that CSRs "should be used as primary data sources in systematic reviews". Might not an alternative conclusion be that since no significant differences were found, reviewers can be more confident in published data; and that CSRs need only be referred to if they contain additional data that cannot be found elsewhere? To me it seems that the HPV review was particularly complex, with multiple outcomes; do the authors' conclusions necessarily generalize to (clinical) systematic reviews in general?

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