***Q&A BRIEF ON JEFFERSON et al's ork on HPV VACCINES***

BEFORE READING THIS, PLEASE **READ** THE BRIEF (800 WORDS) INTRODUCTION:

*Jefferson T and Jørgensen L. Redefining the 'E' in EBM. BMJ Evid Based Med. 2018 Mar 9;23:46-47. https://doi.org/10.1136/bmjebm-2018-110918.*

IF YOU DO NOT READ IT YOU WILL BE UNABLE TO FOLLOW THE REST.

I will now list and answer some questions. References to the answers are in the document.

1.Can you tell us who you are and describe your work on HPV vaccines?

The human papillomavirus (HPV) vaccines are global interventions given to healthy individuals to prevent HPV-related diseases, such as, cervical cancer. The vaccines are considered "safe and effective" by health care authorities. Benefits on the major outcomes such as cancer and deaths will only be verifiable after decades. However safety signals raised concerns whether selective presentation of the evidence had influenced the authorities' considerations of benefits and harms.
Because of the widely perceived threat by reporting bias to the validity of trial journal publications, we investigated the benefits and harms of the HPV vaccines by building an index of the study programmes, we accessed the clinical study reports from the HPV vaccine study programmes and compared the reports to corresponding study documents—trial register entries and journal publications:

*1 Reconstruction of a study index of all prospective comparative studies of HPV vaccines*: The HPV vaccine study programmes demonstrated deficiencies and variability in the availability of study data in trial register entries and journal publications. Only half of the completed studies listed on ClinicalTrials.gov had results posted and a third of the studies were not published.

*Jørgensen L, Gøtzsche PC and Jefferson T. Index of the human papillomavirus (HPV) vaccine industry clinical study programmes and non-industry funded studies: a necessary basis to address reporting bias in a systematic review. Syst Rev. 2018 Jan 18;7(1):8. https://doi.org/10.1186/s13643-018-0675-z.*

*2 Accessing regulatory data on HPV vaccines from the EMA*: our analysis reporting accessing the HPV vaccines trial data from clinical study reports showed that regulatory policies are in need of change to increase transparency. For example, it was not possible to get a complete set of unredacted clinical study reports of the HPV vaccines.

*Jørgensen L, Doshi P, Gøtzsche PC and Jefferson T. Challenges of independent assessment of potential harms of HPV vaccines. BMJ. 2018 Sep 24;362:k369. https://doi.org/10.1136/bmj.k3694.*

*3 Minimally biased evidence synthesis*: Our systematic review of 24 clinical study reports with nearly 100,000 participants showed that at four years follow-up the HPV vaccines decreased HPV-related precursors to cancer and treatment procedures but increased serious nervous system disorders and general harms. The trials used biased designs and underreported harms, which prevented adequate harm assessment.

*Jørgensen L, Gøtzsche PC and Jefferson T. Benefits and harms of the human papillomavirus (HPV) vaccines: systematic review with meta-analyses of trial data from clinical study reports. Submitted for publication. 2018.*
*Protocol: https://www.crd.york.ac.uk/PROSPEROFILES/56093_PROTOCOL_20170030.pdf. Amendment: https://www.crd.york.ac.uk/PROSPEROFILES/56093_PROTOCOL_20171116.pdf*

*5 Comparison of published trials vs their clinical study report versions*: our comparison of corresponding study documents showed no effect differences of pooled estimates but demonstrated that the clinical study reports were quantitatively and qualitatively superior with more outcome data and information that improved risk of bias judgments. One possible explanation for the finding is that distortions in the trials' design ensures that the same results are reached despite the data source used.

*Jørgensen L, Gøtzsche PC and Jefferson T. Benefits and harms of the human papillomavirus (HPV) vaccines: comparison of clinical study reports with trial registry entries and journal publications. Submitted for publication. 2018.*
*Protocol: https://www.crd.york.ac.uk/PROSPEROFILES/56093_PROTOCOL_20180320.pdf.*

2.What are the main problems with the evidence of efficacy and safety of the papillomavirus vaccines?

It is not clear to what extent the HPV vaccines benefits outweigh their harms, as the study programmes and clinical study reports were influenced by reporting bias and biased trial designs. The clinical study reports were superior study documents that contained better information for risk of bias judgements. Clinical study reports should therefore be used for systematic reviews.

3. What are the main problems with the Cochrane HPV vaccine review published by Arbyn et. al.?

Our main criticisms are listed here:

Jørgensen L, Gøtzsche PC and Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. *BMJ Evid Based Med*. 2018 Oct;23(5):165-168. https://doi.org/10.1136/bmjebm-2018-111012.

Briefly, the reviewers ignored evidence of bias despite being sent our HPV study index 4 months before publication, based their review on journals articles and made crass mistakes such as referring to active comparators as "placebo"and misclassifying 4 deaths.

https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009069.pub3/read-comments

4. What are the current challenges in the paradigm of evidence-based medicine?

These are described in *Jefferson T and Jørgensen L. Redefining the 'E' in EBM. BMJ Evid Based Med. 2018 Mar 9;23:46-47. https://doi.org/10.1136/bmjebm-2018-110918.*

The main challenge is the use of more reliable and detailed sources of evidence than journal publications.

5. How are you following up your HPV vaccines work?

You should be aware that we have received thousands more regulatory files from Health Canada as a consequence of this:

https://blogs.bmj.com/bmj/2018/07/19/precedent-pushing-practice-canadian-court-orders-release-of-unpublished-clinical-trial-data/

Further analysis and integration of the available reviews are possible with an unprecedented level of detail.

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