Appendix – list of the documents related to Cochrane HPV vaccines review published on zenodo.org

Cochrane

1.

Complete email correspondence with Cochrane (2012-2018)

DOI 10.5281/zenodo.1434757

Authors:

Riva C, Tinari S, Spinosa JP, Lippman A, Arya N, Rail G, Spring L, Taillefer A, Biron P, Turcotte F

2012-2013_Cochrane-mails.pdf	22 pages
2014-2015_Cochrane-mails.pdf	30 pages
2017_Cochrane-mails.pdf	30 pages
2018_Cochrane-mails.pdf	36 pages

***Emails sent between 2012 and 2018 to the Cochrane Gynaecological, Neuro-oncology & Orphan Cancer Group (CGNOCG)**, senior editor of the HPV vaccines Cochrane review, to Cochrane Editor in Chief David Tovey and to CGNOCG coordinating Editor Jo Morrison to point at methodological and ethical flaws in the Cochrane HPV vaccines review protocol, in the revised protocol, in the original and reconstituted authors panel, on the published review, and to ask when our June 4th 2018 analysis would be finally published, to insist tables should be made public, and to reiterate our request to receive a feedback from the review authors.*
This email collection includes the exchange of February 2015 about the Cochrane HPV vaccines review' leading author having presented intermediary review results at a congress, although we were informed in December 2014 that the review work hadn't even started. Cochrane replied: ''(..) The protocol was originally published a number of years ago now so it is inevitable that the authors would have commenced work on some, but not all, aspects of the review. We were unaware that the authors had presented preliminary findings of their review. Whilst it is not uncommon for researchers on Cochrane Reviews to present interim findings from their work prior to publication, this is not something which we are in a position to stop or approve. As such so we cannot comment on the presentation of preliminary results of the systematic review by the authors''.
When the emails were sent with attachment, the attachment's content is presented.
Where needed, explanatory notes were added.

2.

Letters to Cochrane - December 10th, 2012 - December 8th, 2013 - December 23rd, 2013 - August 19th, 2014 - April 17th, 2017

DOI 10.5281/zenodo.1434611

Authors:

Riva C, Spinosa JP, Lippman A, Arya N, Rail G, Spring L, Taillefer A, Biron P, Turcotte F

2012-12-10_Letter_Cochrane.pdf	3 pages
2013-12-08_Letter_Cochrane.pdf	2 pages
2013-12-23_Letter_Cochrane.pdf	2 pages
2014-08-19_Letter_Cochrane.pdf	2 pages
2017-04-17_Letter_Cochrane-ToveyD.pdf	2 pages

***Letters sent between 2012 and 2017 to the Cochrane Gynaecological, Neuro-oncology & Orphan Cancer Group (CGNOCG)**, senior editor of the HPV vaccines Cochrane review, and to Cochrane Editor in Chief David Tovey. These letters contain the analysis of Conflicts of Interest (COIs) in the review authors panel and point to methodological flaws in the review protocol. These letters have not been published. Cochrane communicated to us that received our letters and intervened on the most serious cases of conflicts of interest, dismissing some of the authors; in December 2013 the authors' panel was indeed reconstituted. However, two authors, including the lead author, Marc Arbyn with COIs with Merck, Sanofi Pasteur MSD and GSK remained on the panel.*

3.

Comments on COIs of the review's authors (2012) and on Cochrane HPV vaccines review protocol (2014)

DOI 10.5281/zenodo.1434601

Authors:

Riva C, Spinosa JP, Lippman A, Arya N, Rail G, Spring L, Taillefer A, Biron P, Turcotte F

2012-12-10_Cochrane_HPV_authorship.pdf	2 pages

***Comment transmitted to the Cochrane Gynaecological, Neuro-oncology & Orphan Cancer Group (CGNOCG)**, senior editor of the HPV vaccines Cochrane review. It shows that relevant conflicts of interest (COIs) affected the review' authors panel. At least two thirds of the fourteen authors had relevant risk of bias, because of COIs with Merck and GSK, the manufacturers of HPV vaccines. Some of the authors have been supported by Merck and GSK; worked as investigators in company-sponsored clinical trials for the HPV vaccines; stated their positive opinions about vaccines effectiveness and safety in publications; work or have worked for health authorities that recommend this vaccination in the belief that its efficacy and safety are demonstrated and acquired; have otherwise conveyed support for the HPV vaccines and HPV vaccination programs, through continuing medical education activities and/or publications.*

Cochrane communicated to us that received our letters and intervened on the most serious cases of conflict of interest, dismissing some of the authors; in December 2013 the authors' panel was indeed reconstituted. However, two authors, including the lead author, Marc Arbyn with COIs with Merck, Sanofi Pasteur MSD and GSK remained on the panel.
Cochrane did not publish this comment.

2014-08-19_Cochrane-reviewCD009069_comments.pdf 5 pages

***Comment on the Cochrane HPV vaccines review protocol**; it includes specific suggestions to rectify some methodological flaws. Submitted in August 2014, this comment was published in February 2015, five months after submission. It was removed from the Cochrane platform in May 2018, as the Cochrane HPV vaccines review was published.*
CGNOCG and authors' response to our suggestions on the protocol: ''We thank Catherine Riva and colleagues for their helpful suggestions and comments, many of which we plan to address in the full review, since they have commented on the protocol only. In response to their earlier set of comments and on the advice of the Cochrane Funding Arbiter review authors with ties to clinical trials in this area were removed. Although this has reduced our ability to consider extensive unpublished data we have been able to contact investigators of included studies for additional information, where necessary, in accordance with Cochrane guidance. This is not an individual patient data review and to undertake one would be beyond the scope of the original review question and represent an investment of time and resources that we are not in a position to make.''

4.

Exposé (E + F + F Canada) summarizing the issues we encountered in communicating to Cochrane our methodological and ethical concerns on the HPV vaccines review (2015)

DOI 10.5281/zenodo.1434780

Authors:

Riva C, Spinosa JP, Lippman A, Arya N, Rail G, Spring L, Taillefer A, Biron P, Turcotte F

2015-03-16_Cochrane_expose_e.pdf 4 pages
2015-03-16_Cochrane_expose_f.pdf 4 pages
2015-03-16_Cochrane_expose_f-CAN.pdf 4 pages

***This exposé describes background and process of the Cochrane HPV vaccines review** and express our concerns on lack of transparency and reluctance to publish critical comments as we experienced them with Cochrane. This text was sent in March 2015 to several journalists; it was not published.*

5.

Comments on Cochrane HPV vaccines review (June 2018 and September 2018)

DOI 10.5281/zenodo.1434748 (June 2018)
DOI 10.5281/zenodo.1434763 (September 2018)

Authors:

Riva C, Tinari S, Spinosa JP

2018-06-04_RivaC-TinariS-SpinosaJP_ Comment-Cochrane-review-HPV-vaccine.pdf	7 pages
2018-09-12_RivaC-TinariS-SpinosaJP_ Comment-Cochrane-review-HPV-vaccine.pdf	7 pages

Detailed analysis of the Cochrane HPV vaccines review we submitted on June 4th , 2018, as a comment via the Cochrane website. *Our comment highlights relevant methodological flaws in the review: (a) studies' quality not properly assessed; (b) post-hoc subgroup analyses presented as RCT results; (c) reporting bias not acknowledged; (d) selective reporting not taken into consideration; (e) biased trial designs; (f) unpublished data not included; (g) COIs in the authors' group; (h) n=7 studies on Gardasil® included, n=18 for Cervarix® – the latter not being marketed in the U.S. anymore.*

Published on August 9th 2018, two months after submission, as: Riva C, Tinari S, Spinosa JP. Cochrane review on HPV vaccines: Concerns over methodological flaws in the assessment of vaccines' efficacy. Comment on Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database of Systematic Reviews. Available from https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009069.pub3/detailed-comment/en?messageId=154255807

The first version (June 4th, 2018) was amended on September 21st, 2018 to include a minor correction we requested. In our first submission, indeed, we stated wrongfully that Lehtinen's study on Cervarix® mentioned the limitation of the post-hoc subgroup analysis performed as TVC-naïve analysis, whereas Munoz had not mentioned the same issue about Gardasil® data. We corrected this statement and the updated text states as follows: ''The limitation of this type of analysis is not mentioned in Lehtinen's study regarding Cervarix and in Munoz's study regarding Gardasil''. In September 2018 we also reiterated our request to let us publish in this page our conflicts of interest declarations. As in June we submitted our comment to the published HPV vaccines Cochrane review we noticed the publication form didn't prompt the insertion of authors COIs. To our explicit request of letting us declare our COIs, Cochrane replied: ''we do currently only ask for direct financial conflicts of interest, but (...) are reviewing a policy for seeking non-financial conflicts''.

6.

Tables RMITT-2 - 2018

DOI 10.5281/zenodo.1434229

Authors:

Riva C, Tinari S, Spinosa JP

Tables-RMITT-2.pdf 2 pages

Data submitted by Merck to the Food and Drug Administration (FDA) for Gardasil® approval (published and unpublished data). *These tables show that the definition of the subgroup ''negative to 14 HPV types'' population (RMITT-2) changed several times between 2006 and 2010.*

7.

Table efficacy Gardasil

DOI 10.5281/zenodo.1435032

Authors:

Riva C, Spinosa JP

Table_Efficacy-Gardasil.pdf 1 page

This table summarizes all the available analyses (published and unpublished data) about Gardasil's efficacy in preventing all high-risk HPV-associated CIN 2+. *While the vaccine showed a near 100% efficacy in preventing CIN 2+ associated with HPV 16 and 18, the result for all high-risk HPV-associated CIN 2+ was dramatically below the 70% expected by the vaccine manufacturer.*

Gardasil® Approval

1.

Statistical Data Analysis Plan HPV Quadrivalent HPV Vaccine CIN/Wart Efficacy Study (Study 013) - March 2003 / Statistical Data Analysis Plan HPV Quadrivalent HPV Vaccine, Safety, Immunogenicity and Efficacy Study (Study 015) FUTURE II - July 2003

DOI 10.5281/zenodo.1434216

Authors: Railkhar R, Lupinacci L, Merck

2003_FDA_r_s_DAP-Gardasil-HPV-013.pdf 61 pages

Statistical Data Analysis Plan HPV Quadrivalent HPV Vaccine CIN/Wart Efficacy Study (Study 013) March 2003

2003_FDA_r_s_DAP-Gardasil-HPV-015.pdf 78 pages

Statistical Data Analysis Plan HPV Quadrivalent HPV Vaccine, Safety, Immunogenicity and Efficacy Study (Study 015) FUTURE II - July 2003

We obtained Gardasil® Data Analysis Plans (DAPs) from the FDA through Freedom of Information Act (FOIA) request. *The above linked DAPs specified a ‘‘per protocol analysis’’ for the outcome CIN 2+ irrespective of HPV type.*

2.

Statistical Data Analysis Plan Efficacy Merck's HPV Vaccine (Studies 005, 007, 013, and 015) - Amendment 1 - August 2005

DOI 10.5281/zenodo.1434220

Authors:

Lupinacci L, Merck

2005_FDA_r_s_F11-7942 DAP-Efficacy-Studies-005-007-013-015 46 pages

We obtained Gardasil® Data Analysis Plans (DAPs) from the FDA through Freedom of Information Act (FOIA) request. *The above linked DAP introduced modifications in the study participants populations. Instead of ‘‘per protocol analysis’’ for the outcome CIN 2+ irrespective of HPV type, this DAP introduced a post-hoc subgroup analysis (subgroup of subjects negatives to 14 HPV types, called RMITT-2).*

3.

VBPAC background document – 2006

DOI 10.5281/zenodo.1434214

Authors: VRBPAC, FDA

2006-VRBPAC_Background_Document-4222B3.pdf 30 pages

Vaccine and Related Biological Products Advisory Committee (VRBPAC) discussion on the results submitted for the biologics license application (BLA) from the clinical development program of Gardasil® for prevention of HPV diseases in females. *This important background document providing unpublished results was obtained in 2008 by the nonprofit organization Judicial Watch through a Freedom of Information Act (FOIA) request (http://www.judicialwatch.org/documents/2008/JWReportFDAhpvVaccineRecords.pdf).*

While the vaccine showed a near 100% efficacy in preventing CIN 2+ associated with HPV 16 and 18, the result for all high-risk HPV-associated CIN 2+ was dramatically below the 70% expected by the vaccine manufacturer. In fact, the result for the "per protocol" analysis was only 16.9%, and did not reach statistical significance. These results had never been published before, despite their importance; although the FOIA filed by Judicial Watch made these very relevant data available to the public and to the medical and scientific community, they never made it to be part of the conversation around HPV vaccines efficacy.