Note:

On May 9th, 2018 Cochrane published its HPV vaccines review.

On June 4th, 2018 Catherine Riva, Serena Tinari and Jean-Pierre Spinosa submitted a review analysis as a comment via the Cochrane dedicated website.

On June 9th, 2018 Catherine Riva, Serena Tinari and Jean-Pierre Spinosa sent an email to the CGNOCG, stressing they wanted the comment to be published on the Cochrane platform as official feedback. Since the submission form did not allow attachments, they sent via email tables to be transmitted to the authors.

Catherine Riva, Serena Tinari and Jean-Pierre Spinosa informed the CGNOCG they expected a reply from the authors within 60 days and received a feedback stating the comment would be published as soon a new platform was available.

From: Catherine Riva [catherine.riva@re-check.ch]
To: jo.morrison1@nhs.net
Cc: Serena Tinari <serena.tinari@re-check.ch>; Jean Pierre Spinosa <spinosa@deckpoint.ch>

Subject: Cochrane review on HPV vaccine - comment
Attached: 2018-06-04_RivaC-TinariS-SpinosaJP_Comment-Cochrane-review-HPV-vaccine.pdf / 2018-06-04_RivaC-TinariS-SpinosaJP_Tables- Cochrane-review-HPV-vaccine.pdf
Sent: 2018-06-09

Dear Dr. Morrison,

Please find attached our comment to the following review:

> Arbyn M, Xu L, Simoens C, Martin-Hirsch PPL. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD009069. DOI: 10.1002/14651858.CD009069.pub3

We submitted it on June 4, 2018, via the dedicated website (http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009069.pub3/abstract) and we wish for it to be included as official feedback.

Since the contact form for comments does not allow attachments, you find enclosed a document with tables to be transmitted to the authors.
We are expecting from them a reply within 60 days: this seems to us a reasonable period of time to address our questions and remarks.

Could you please tell us when our comment will be available online?

Thank you very much in advance.

Sincerely,

Catherine Riva
Serena Tinari
Jean-Pierre Spinosa

Attachment: 2018-06-04_RivaC-TinariS-SpinosaJP_Comment-Cochrane-review-HPV-vaccine.pdf

Cochrane review on HPV vaccines: Concerns over methodological flaws in the assessment of vaccines' efficacy

Catherine Riva (Re-Check)
Serena Tinari (Re-Check)
Jean-Pierre Spinosa, MD (Lecturer at the Faculty of Medicine, Université de Lausanne)

The usefulness of HPV vaccines is controversial.[1,2] In such context, a Cochrane review plays a leading role in assessing the HPV vaccines' risk-benefit ratio. To achieve this goal, it is essential that the review be carried out with all the necessary rigor, circumspection and impartiality, in accordance with the standards of the Cochrane Collaboration.

We therefore welcomed the publication of "Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors (Review)" by Arbyn et al.[3]

However, we regret the choice of title. Shouldn't this Cochrane Review be called "Prophylactic vaccination against human papillomaviruses to prevent cervical cancer's precursors (Review)"? The randomized controlled trials (RCTs) were indeed conducted on the precursors' outcome; no RCTs ever assessed the impact of HPV vaccines on cervical cancer incidence and its associated mortality. Any conclusion on this matter is therefore purely speculative.

Therefore, it is understandable—although very regrettable—that mainstream media from different countries have been misled by the title

[1] Lippman A, Melnychuk R, Shimmin C, Boscoe M. Human papillomavirus, vaccines and women's health: questions and cautions CMAJ. 2007 Aug 28; 177(5): 484–487. doi: 10.1503/cmaj.070944 Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1950169/

[2] Franco EL, de Pokomandy A, Spence AR, Burchell AN, Trottier H, Mayrand MH, Laus S. Vaccination against human papillomavirus. CMAJ. 2007 Dec 4; 177(12): 1524–1525. doi: 10.1503/cmaj.1070120 Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2096514/

[3] Arbyn M, Xu L, Simoens C, Martin-Hirsch PPL. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD009069. DOI: 10.1002/14651858.CD009069.pub3. Available from http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009069.pub3/full

of Arbyn et al.'s publication and have claimed that, according to a Cochrane review, HPV vaccination prevents cervical cancer.[4,5]

It should be noted that Arbyn et al. have evaluated the efficacy of HPV vaccines in the global prevention of CIN2/3+, irrespective of HPV type, thus honoring a suggestion we made in 2014[6]. This outcome is indeed the only relevant one from a public health perspective because it alone can be used to assess the vaccines' efficacy (prophylactic and no therapeutic) in reducing the global incidence of CIN2/3+ and possibly the global incidence of cervical cancer.

In the context of a competition between several virus strains, it cannot be assumed that by preventing the development of cancers due to HPV 16 and 18 (responsible for 70% of cervical cancers), the overall disease incidence will likewise decrease. Indeed, other high-risk strains may replace HPVs held in check by the vaccination.[7,8] The outcome CIN2/3+ irrespective of HPV type allows to avoid the pitfall of viral replacement.

The efficacy of HPV vaccines in preventing high-grade cervical lesions (CIN2 +, CIN3 + and AIS) due to high-risk HPVs has been established 10 years ago in Phases II and III of FUTURE (Gardasil)[9] and PATRICIA (Cervarix)[10] RCTs. The numerous analyses carried out by Arbyn et al. on these outcomes do not bring any new information.

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[4] HPV vaccines prevent cervical cancer, global review confirms. CNN. May 8, 2018. Available from https://edition.cnn.com/2018/05/08/health/hpv-vaccines-cervical-cancer-review/index.html

[5] Le vaccin contre le papillomavirus prévient le cancer du col de l'utérus. Doctissimo. 9 mai 2018. Available from http://www.doctissimo.fr/sante/news/efficacite-vaccin-anti-hpv-contre-cancer-col-de-l-uterus

[6] Riva C, Spinosa JP, Lippman A, Arya N, Biron P, Rail G, Spring L, Taillefer A, Turcotte F. Feedback on Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. 16 December 2014. Available from http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009069.pub2/full#CD009069-sec1-0006

[7] Murall CL, McCann KS, Bauch CT. Revising ecological assumptions about Human papillomavirus interactions and type replacement. J Theor Biol. 2014 Jun 7;350:98-109. doi: 10.1016/j.jtbi.2013.12.028. Available from https://www.ncbi.nlm.nih.gov/pubmed/24412334

[8] Pons-Salort M1, Letort V, Favre M, Heard I, Dervaux B, Opatowski L, Guillemot D. Exploring individual HPV coinfections is essential to predict HPV-vaccination impact on genotype distribution: a model-based approach. Vaccine. 2013 Feb 6;31(8):1238-45. doi: 10.1016/j.vaccine.2012.11.098. Available from https://www.ncbi.nlm.nih.gov/pubmed/23246257

[9] The Future II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 2007; 369: 1861–68. Available from https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(07)60852-6/fulltext

[10] Paavonen J et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet. 2009 Jul 25;374(9686):301-14. doi: 10.1016/S0140-6736(09)61248-4. Epub

For the outcome "CIN2/3+ irrespective of HPV type", the FUTURE and PATRICIA intent-to-treat results were significantly lower than expected, as analyses 3.7, 3.8 and 3.9 provided by Arbyn et al. clearly show (pp. 143-145). As for the per-protocol results (women who are naive to high-risk HPV types at vaccination onset), they were published in medical journals for Cervarix for CIN2 +, but not for CIN3 + (see analyses 2.13 and 2.14). For Gardasil, no publication in medical journals is available to date. In such selective reporting context, the Cochrane review had a highly relevant role to play. We regret that Arbyn et al. did not attempt to fill this knowledge gap by requesting and analyzing these unpublished data, whereas some of them are available,[11,12] which they had been made aware of in August 2014.[13]

The authors chose instead to examine the results of an analysis on a subgroup of women naive to high-risk HPV types. This choice may seem logical from a public health perspective, as girls who have not yet begun their sex life constitute the HPV vaccines' target population.

However, Arbyn et al.'s decision is methodologically problematic. The studies included for analyses 1.7, 1.8 and 1.9 (Lehtinen 2012[14] for Cervarix and Munoz 2010[15] for Gardasil) are indeed post-hoc subgroup analyses and not pre-specified analyses. In the original protocols, such

2009 Jul 6. Available from https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)61248-4/fulltext

[11] VRBPAC. Background Document, GardasilTM HPV Quadrivalent Vaccine May 18, 2006 VRBPAC Meeting. Table 25. Available from: https://web.archive.org/web/20060815000000*/http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B3.PDF

[12] Spinosa JP, Riva C, Biollaz J. Letter to the editor response to the article of Luisa Lina Villa HPV prophylactic vaccination: the first years and what to expect from now, in press. Cancer Lett. 2011 May 1;304(1):70. doi: 10.1016/j.canlet.2011.01.024. Epub 2011 Feb 19. Available from https://www.cancerletters.info/article/S0304-3835(11)00050-4/fulltext

[13] Riva C, Spinosa JP, Lippman A, Arya N, Biron P, Rail G, Spring L, Taillefer A, Turcotte F. Feedback on Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. 16 December 2014. Available from http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009069.pub2/full#CD009069-sec1-0006

[14] Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland S, Castellsagué X. Overall efficacy of HPV-16/18 ASO4-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncology 2012;13(1):89–99. doi: 10.1016/S1470-2045(11)70286-8. Epub 2011 Nov 8. Erratum in: Lancet Oncol. 2012 Jan;13(1):e1. Available from https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(11)70286-8/fulltext

[15] Munoz N, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. Journal of the National Cancer Institute 2010;102(5):325–39. Available from https://academic.oup.com/jnci/article/102/5/325/889337

analyses were part of neither the FUTURE nor the PATRICIA clinical trials.

While the limitation of this type of analysis is clearly mentioned in Lehtinen's study regarding Cervarix, it is absent in Munoz's study. Most importantly, this limitation does not appear in Arbyn et al.'s review. Mentioning this would have been all the more necessary that Lehtinen and Munoz have not used the tools recommended by good practice to report results of subgroup post-hoc analyses.[16] The latter are strictly exploratory and non-conclusive; they cannot be interpreted as evidence. Basically, the FDA rejects such analysis due to the risk of spurious results. Hindeed, with sufficient covariate measurements, a drug company can always find a subgroup that benefits from a drug.[17]

The above-mentioned publications do not therefore meet the inclusion criteria of this Cochrane review. The results of a subgroup post-hoc analysis cannot be considered equivalent to RCT results. The methodological problem stems from the fact that post-hoc analyses are used to generate a hypothesis and at the same time to verify it. Given this circular situation, they cannot be used as evidence and can only help generating new hypotheses.[18]

The omission of such limitations in Arbyn et al.'s publication is especially problematic considering that Lehtinen and Munoz provide almost 70% of the populations considered by the authors of this Cochrane review for their calculations and their conclusion that "HPV vaccines reduce the risk of any CIN2 + from 287 to 106/10,000 (RR 0.37 (0.25 to 0.55), high certainty)."

Arbyn et al.'s decision to include Munoz in their review is all the more surprising that, as early as August 2014,[19] they had been made aware that this analysis of a subgroup of women naive to 14 HPV types constituted a subgroup post-hoc analysis that was not planned in the initial protocol

---

[16] Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in Medicine ─ Reporting of Subgroup Analyses in Clinical Trials.*NEJM*, 2007 https://www.nejm.org/doi/pdf/10.1056/NEJMsr077003

[17] Malani A, Bembom O, van der Laan M. Reforming Subgroup Analysis. April 13, 2008. Available from SSRN https://ssrn.com/abstract=1119970 or http://dx.doi.org/10.2139/ssrn.1119970

[18] Cucherat M., Interprétation des essais cliniques pour la pratique médicale, Faculté de médecine Lyon Laennec. Available from https://www.scribd.com/document/24698055/Lecture-critique-des-essais-cliniques-pour-la-pratique-medicale [only in French]

[19] Riva C, Spinosa JP, Lippman A, Arya N, Biron P, Rail G, Spring L, Taillefer A, Turcotte F. Feedback on Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. 16 December 2014. Available from http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009069.pub2/full#CD009069-sec1-0006

of the FUTURE trials. The tables we put together and we offer in the appendix show that the composition of this subgroup has changed several times between 2005 and 2010, which increases doubt about the validity of Munoz et al.'s analysis.

The Data Analysis Plans (DAP) that we obtained from the FDA through a FOIA request also show that the problem is even more serious in the case of Gardasil. These documents show that the analysis of a "negative to 14 HPV types" population (RMITT-2) was not planned in the first DAP (2003)[20] and that it was added during the trials, with a new DAP (2005)[21] replacing the per-protocol analysis.

This problem of *outcome switching*, a highly controversial practice,[22] shows that Arbyn et al. did not diligently assess the risk of bias in the studies they decided to include. They didn't even mention this issue in their publication.

We are surprised that they have assessed the PATRICIA and FUTURE studies as being at low risk of bias and bias reporting, while problems have been reported on these specific points at least since 2009.[23,24,25,26] Again, they didn't even mention this issue in their publication. We also regret that Arbyn et al. did not pay attention to the quality of the clinical trials' design and to the choice of outcomes, despite the fact that they had been made aware of these issues.[27]

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[20] Statistical Data Analysis Plan (Protocol 015). V501 Reference P015V1. Appendix 3.11. Prepared by Lisa Lupinacci. 2003 July 21. P. 24.
[21] Statistical Data Analysis Plan (Sudies 005, 007, 013, and 015). V501 Data Analysis Plan. Amendement 1. Prepared by Lisa Lupinacci.2005 Aug 04. P. 24.
[22] Altmann DG, Moher D, Schulz KF. Harms of outcome switching in reports of randomised trials: CONSORT perspective, *BMJ* 2017;356:j396. Available from https://www.bmj.com/content/356/bmj.j396
[23] Therapiekritik Neue Daten zu HPV-IMpfstoffen (CERVARIX, GARDASIL). a-t 2009; 40:71-3. Available from https://www.arznei-telegramm.de/html/htmlcontainer.php3?produktid=071_01&artikel=0908071_01k [only in German]
[24] Riva C, Spinosa JP, La piqûre de trop? Ed. Xenia, 2010. [only in French]
[25] Spinosa JP, Riva C, Biollaz J. Letter to the editor response to the article of Luisa Lina Villa HPV prophylactic vaccination: the first years and what to expect from now, in press. Cancer Lett. 2011 May 1;304(1):70. doi: 10.1016/j.canlet.2011.01.024. Epub 2011 Feb 19. Available from https://www.cancerletters.info/article/S0304-3835(11)00050-4/fulltext
[26] Riva C, Spinosa JP. Prescrire en questions: vaccin papillomavirus : quelle efficacité, quel risque ? La Revue Prescrire 2013;33(357):552-556. Available from http://www.prescrire.org/fr/3/31/49012/0/NewsDetails.aspx [only in French]
[27] Riva C, Spinosa JP, Lippman A, Arya N, Biron P, Rail G, Spring L, Taillefer A, Turcotte F. Feedback on Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. 16 December 2014. Available from http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009069.pub2/full#CD009069-sec1-0006

Moreover, we find the imbalance between the number of studies included for Cervarix (n = 18) and the number of studies included for Gardasil (n = 7) highly problematic, notably as the authors attempted to calculate the "global" efficacy of "the" HPV vaccine while dealing with three hardly comparable products with different valences and adjuvants. We also regret that the authors did not mention this imbalance and the resulting limitations. In addition, Arbyn et al. gloss over the significant differences between placebo groups in the FUTURE and PATRICIA trials. In the FUTURE trials' placebo group, there were proportionately many more cases of precancerous lesions than in the PATRICIA trials' placebo group. Interestingly, the recruitment procedures for the two trials do not explain these differences. Finally, it should be noted that in most Western countries, Gardasil dominates the market in an overwhelming way.[28,29] For example, since 2016,[30] Cervarix is no longer marketed in the United States. From the authors of a Cochrane review, we would have expected a mention and a consideration of such issues, which should have been taken into account when analyzing the supposed benefits of these vaccines.

As a result, the analyses and conclusions put forward by Arbyn et al. regarding the alleged benefits of HPV vaccines are based on data whose quality has not been correctly assessed and put into perspective. We are concerned that despite such methodological limitations and problems, the authors stated that there is "high-certainty evidence that HPV vaccines protect against cervical precancer". For the sake of consistency and credibility, it seems to us essential that this Cochrane review be updated in light of the above-mentioned elements.

We encourage Arbyn et al. to review their analyses and conclusions regarding the efficacy of Gardasil® and Cervarix® in protecting from CIN2/3 regardless of the associated HPV type, and to consider all these comments, particularly regarding data quality assessments, and also the clinical trials' design.

Last but not least, we deplore the multiple conflicts of interest plaguing the group of authors of this Cochrane review. We have signaled such

[28] GlobalData. CERVARIX (prophylactic human papillomavirus vaccines) – Forecas and market analysis to 2022. 2014. Available from https://www.marketresearch.com/product/sample-8275218.pdf
[29] GlobalData. GARDASIL (prophylactic human papillomavirus vaccines) – Forecas and market analysis to 2022. 2014. Available from https://www.marketresearch.com/product/sample-8275165.pdf
[30] Mulcahy N. GSK's HPV Vaccine, Cervarix, No Longer Available in US. Medscape May 14, 2018. Available from https://www.medscape.com/viewarticle/870853

conflicts as early as 2012,[31] however, even in the latest panel composition that has signed the review, they do not seem to be resolved.

[31] Riva C, Spinosa JP, Lippman A, Arya N, Biron P, Rail G, Spring L, Taillefer A, Turcotte F. Feedback on Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. 16 December 2014. Available from http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009069.pub2/full#CD009069-sec1-0006

Table II

Evolution of the subgroup RMITT-2 (number of participants, efficacy)

	Gardasil® N	Lesions N	Placebo N	Lesions N	Efficacy %	95% CI
2006 Name of the subgroup: Partially HPV-Naïve population (*) / RMITT-2 (**) Protocols: 007-013-015 Type of lesion: CIN 2/3+ (*) Briefing Document, presented by Merck to VRBPAC on 18-May-2006 (Table 20, p. 59) (**) VRBPAC. Background Document Gardasil™ HPV Quadrivalent Vaccine May 18, 2006. VRBPAC Meeting. Table 13. CBER. Clinical Review of Biologics License Application for Human Papillomavirus 6, 11, 16, 18 L1 Virus Like Particle Vaccine. 2006 June 8. Table 272.	5638	59	5701	96	37.9%	13.2, 55.9%
2007 Name of the subgroup: RMITT-2 (*) Protocols: 013-015 Type of lesion: CIN 2/3+ (*) E. Barr. Updated Efficacy Data – GARDASIL®. 2007 February 2007. [ACIP PPT-presentation] Slide 18. (**) R. Haupt. GARDASIL® Update. Slide 33 (***)R. Haupt. GARDASIL® Update. Slide 31	4658(**) 4616 (***)	52	4732(**) 4675(***)	97	46%	not specified
2008 Name of the subgroup: RMITT-2, close-out, data (*) Protocols: 005-007-013-015 Type of lesion: CIN 2/3+ (*) CBER. Clinical Review of Biologics License Application Supplement for Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant (Gardasil®). 2008 Sept 11. Table 26.	4616	77	4680	136	42.7%	23.7, 57.3%
2010 Name of the subgroup: 14 HPV-neg (*) Protocols: 013-015 Type of lesion: CIN 2/3+ (*) Munoz N, Kjaer SK, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst. 2010 mar 3;102(5):325-339. Table 3.	4616	77	4680	136	42.7%	23.7, 57.3%

Table III

Evolution and changes in the definition of subgroup RMITT-2

	Seroneg. and PCR-neg. HPV 6-11-16-18	PCR-neg. HPV 31-33-35-39-45-51-52-56-58-59	Pap test normal at day 1	Remained free of infection with the relevant vaccine HPV type during the course of vaccination	Any follow up visit 1 month following first injection	Cases counted starting 30 days after Day 1	Endpoint counting after Day 1	Endpoints between Month 1 and Month 7	Subject received < 3 doses	Subject received at least 1 dose	Subject with major protocol violations	Subjects who became infected with a vaccine type during the vaccination period
2006												
Briefing Document, presented by Merck to VRBPAC on 18-May-2006.	x	--	x	x	x	x	--	x	x	not specified	x	x
VRBPAC. Background Document Gardasil™ HPV Quadrivalent Vaccine May 18, 2006. VRBPAC Meeting	x	--	x	not specified	not specified	x	--	not specified	not specified	not specified	not specified	not specified
CBER. Clinical Review of Biologics License Application for Human Papillomavirus 6, 11, 16, 18 L1 Virus Like Particle Vaccine. 2006 June 8.	x	--	x	not specified	not specified	x	--	not specified	not specified	not specified	not specified	not specified
2007												
E. Barr. Updated Efficacy Data – GARDASIL®. 2007 February 2007. [ACIP PPT-presentation] Slide 18.	x	x	x	not specified	not specified	not specified	--	not specified	not specified	not specified	not specified	not specified
2008												
CBER. Clinical Review of Biologics License Application Supplement for Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant (Gardasil®). 2008 Sept 11.	x	x	x	not specified	x	not specified	--	not specified	not specified	x	not specified	not specified

2010 Munoz N, Kjaer SK, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst. 2010 mar 3;102(5):325-339.	x	x	x	not specified	x	--	x	--	not specified	x	x	not specified

From: gnoc-cochrane (ROYAL UNITED HOSPITALS BATH NHS FOUNDATION TRUST) <ruh-tr.gnoc-cochrane@nhs.net>
To: catherine.riva@re-check.ch
Cc: Serena Tinari <serena.tinari@re-check.ch>; Jean Pierre Spinosa <spinosa@deckpoint.ch>

Subject: PG19 Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors
Sent: 2018-06-09

Dear Catherine Riva, Serena Tinari, Jean-Pierre Spinosa,

Thank you for submitting feedback regarding the recently published Cochrane review of evidence on 'Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors'. This has been shared with the author team.

Cochrane are launching a new feedback platform on the Library which will enable us to facilitate such comments and we will contact you again as soon as the date for this is available.

Best wishes
Cochrane Gynaecological, Neuro-oncology and Orphan Cancers

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Note:

On July 27th, 2018 Lars Jørgensen, Peter C Gøtzsche and Tom Jefferson published in BMJ-EBM the article "The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias" (available from https://ebm.bmj.com/content/early/2018/07/27/bmjebm-2018-111012.info*). Their piece raised other methodological flaws than those contained in our comment. Although we had submitted our piece almost two months before, Cochrane had not published it yet. We wrote again to Cochrane asking for news.*

From: Catherine Riva [catherine.riva@re-check.ch]
To: gnoc--cochrane (ROYAL UNITED HOSPITALS BATH NHS FOUNDATION TRUST)
Cc: Serena Tinari <serena.tinari@re-check.ch>; Jean Pierre Spinosa <spinosa@deckpoint.ch>

Subject: PG19 Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors
Sent: 2018-07-26

Dear Cochrane Gynaecological, Neuro-oncology and Orphan Cancers,

On June 4th, we submitted a comment regarding the Cochrane review 'Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors' via the dedicated website.

On June 9th, we informed Dr. Jo Morrison by email, attaching two documents and stressing that we wished for our comment to be included as official feedback.

On June 16th, you wrote to us that Cochrane were launching a new feedback platform on the Library which will enable us to facilitate such comments.
Could you please tell us if this feedback platform exists now and if our comment will be published by August 9th?
It seems very important to us to make our comment public the latest at this time, since we informed the review's authors that we were expecting a reply within 60 days after posting our comment.

Thank you very much in advance.

Sincerely,

Catherine Riva
Serena Tinari
Jean-Pierre Spinosa

++++++++++++++++++++

From: gnoc-cochrane (ROYAL UNITED HOSPITALS BATH NHS FOUNDATION TRUST) <ruh-tr.gnoc-cochrane@nhs.net>
To: Catherine Riva catherine.riva@re-check.ch

Subject: RE: PG19 Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors
Sent: 2018-07-31

Dear Catherine
Just to say that we have received your email and will be in touch as soon as I have a response from the Cochrane platform.
Best wishes
Tracey

Tracey Harrison
Assistant Managing Editor
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++++++++++++++++++++

From: Catherine Riva [catherine.riva@re-check.ch]
To: 'Cochrane Library Comments' <cochrane_feedback@wiley.com>
Cc: 'ruh-tr.gnoc-cochrane@nhs.net'; Serena Tinari (serena.tinari@re-check.ch); Jean Pierre Spinosa <spinosa@deckpoint.ch>

Subject: Cochrane Library: Your comment has been published
Attached: 2018-06-04_RivaC-TinariS-SpinosaJP_Comment-Cochrane-review-HPV-vaccine.pdf / 2018-06-04_RivaC-TinariS-SpinosaJP_Tables- Cochrane-review-HPV-vaccine.pdf
Sent: 2018-08-09

Thank you very much.
The text as it is published on your platform presents some format issues (no line breaks and no automatic link to the footnotes, for example). It makes it very difficult to read.
Furthermore, only one author is mentioned.
Please find attached the files we sent originally to GNOC-Cochrane. Could you please publish it with the appendix (Tables)?
Thank you very much in advance.
Best regards,
Catherine Riva

++++++++++++++++++++

From: gnoc-cochrane (ROYAL UNITED HOSPITALS BATH NHS FOUNDATION TRUST) <ruh-tr.gnoc-cochrane@nhs.net>
To: Catherine Riva <catherine.riva@re-check.ch>
Cc: Serena Tinari <serena.tinari@re-check.ch>; Jean Pierre Spinosa <spinosa@deckpoint.ch>

Subject: RE: PG19 Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors
Sent: 2018-08-09

Dear Catherine,

The Cochrane Library's new platform launched yesterday and we are pleased to inform you that your feedback comments are likely to be published today or tomorrow at the latest.
Best wishes

Cochrane Gynaecological, Neuro--oncology and Orphan Cancers
E ruh--tr.gnoc--cochrane@nhs.net T +44 (0) 1225 826348 **T**witter **@Cochrane_GNOCG**
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From: Cochrane Library Comments <cochrane_feedback@wiley.com>
To: catherine.riva@re-check.ch

Subject: Cochrane Library: Your comment has been published
Sent: 2018-08-09

Dear Catherine Riva,
Your comment on **Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors** has been published.
You can view your comment at https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009069.pub3/detailed-comment/en?messageId=154255807.
Thank you for your contribution. If you have any concerns please contact cochrane_feedback@wiley.com.

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From: Catherine Riva [mailto:catherine.riva@re--check.ch]
To: 'Cochrane Library Comments'
Cc: gnoc--cochrane (ROYAL UNITED HOSPITALS BATH NHS FOUNDATION TRUST);; Serena Tinari;;
Jean Pierre Spinosa

Subject: AW: Cochrane Library: Your comment has been published
Sent: 2018-08-09

Thank you very much.
The text as it is published on your platform presents some format issues (no line breaks and no automatic link to the footnotes, for example). It makes it very difficult to read.
Furthermore, only one author is mentioned.
Please find attached the files we sent originally to GNOC-Cochrane. Could you please publish it with the appendix (Tables)?

Thank you very much in advance.

Best regards,
Catherine Riva

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From: gnoc-cochrane (ROYAL UNITED HOSPITALS BATH NHS FOUNDATION TRUST) <ruh-tr.gnoc-cochrane@nhs.net>
To: Catherine Riva <catherine.riva@re-check.ch>

Subject: RE: Cochrane Library: Your comment has been published
Sent: 2018-08-09

Many thanks Catherine, I have forwarded your comments to the Cochrane platform, where all comments are asked to be directed.
Best wishes
Tracey

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From: Aburrow, Tony <taburrow@wiley.com>
To: gnoc-cochrane (ROYAL UNITED HOSPITALS BATH NHS FOUNDATION TRUST) <ruh-tr.gnoc-cochrane@nhs.net>
Cc: catherine.riva@re-check.ch; Cochrane - JHILTON <jhilton@cochrane.org>

Subject: RE: Cochrane Library: Your comment has been published
Sent: 2018-08-09

Hi Catherine,

I'm afraid we are experiencing a few errors with the rendering of comments on the new Cochrane Library platform. As you noted, line breaks are not showing and neither are the

links in your references. I have raised the issue with our development team to get this fixed.I will keep you posted and will let you know as soon as the comment is published with the correct styling.

Best regards,
Tony

Tony Aburrow
Associate Editor
Cochrane, Evidence Based Health Care
Phone +44 (0)1243 770 664
Skype: taburrowwiley

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From: Catherine Riva [catherine.riva@re-check.ch]
To: dtovey@cochrane.org
Cc: Serena Tinari <serena.tinari@re-check.ch>; Jean Pierre Spinosa spinosa@deckpoint.ch

Subject: HPV vaccine - Cochrane review
Attached: 2018-06-04_RivaC-TinariS-SpinosaJP_Comment-Cochrane-review-HPV-vaccine.pdf / 2018-06-04_RivaC-TinariS-SpinosaJP_Tables- Cochrane-review-HPV-vaccine.pdf
Sent: 2018-08-22

Dear Dr. Tovey,

we submitted on June 4th an analytical comment on the Cochrane HPV Vaccine review (see attachment: 2018-06-04_RivaC-TinariS-SpinosaJP_Comment-Cochrane-review-HPV-vaccine.pdf). As the platform didn't allow us to upload any additional material, we sent the related tables (see attachment: 2018-06-04_RivaC-TinariS-SpinosaJP_Tables-Cochrane-review-HPV-vaccine.pdf) via email to J. Morrison.

As you can see, our analysis points to important methodological flaws in the Cochrane HPV review; the tables contain unpublished information we obtained from FDA with a FOIA request.

In our correspondence, we asked for the authors to react within 60 days and insisted that the tables should be also published, as they entail information that in our view is of relevance to fully understand bias and flaws affecting the HPV vaccine review.

Meanwhile Lars Jørgensen, Peter C Gøtzsche, Tom Jefferson. *The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias* was published, and Cochrane publicly promised to soon address every concern so far raised on methodological flaws, conflicts of interest and bias.

We are wondering why our contribution is still today not available in full to the public, whereas the review authors never replied to our analysis. We believe our remarks are in the public interest and need to be part of this conversation because they are of relevance and totally different from those raised by Jørgensen et al.

We attach here a timeline of the exchanges we had with Cochrane since June 4th.

May we ask you to help us clarify this issue? Can you tell us more about when and how is Cochrane going to address all concerns and if in fact our analysis will be part of it?

Sincerely yours,

Catherine Ria
Serena Tinari
Jean-Pierre Spinosa

Attachment: 2018-06-04_RivaC-TinariS-SpinosaJP_Comment-Cochrane-review-HPV-vaccine.pdf

Cochrane review on HPV vaccines: Concerns over methodological flaws in the assessment of vaccines' efficacy

Catherine Riva (Re-Check)
Serena Tinari (Re-Check)
Jean-Pierre Spinosa, MD (Lecturer at the Faculty of Medicine, Université de Lausanne)

The usefulness of HPV vaccines is controversial.[32,33] In such context, a Cochrane review plays a leading role in assessing the HPV vaccines' risk-benefit ratio. To achieve this goal, it is essential that the review be carried out with all the necessary rigor, circumspection and impartiality, in accordance with the standards of the Cochrane Collaboration.

We therefore welcomed the publication of "Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors (Review)" by Arbyn et al.[34]

However, we regret the choice of title. Shouldn't this Cochrane Review be called "Prophylactic vaccination against human papillomaviruses to prevent cervical cancer's precursors (Review)"? The randomized controlled trials (RCTs) were indeed conducted on the precursors' outcome; no RCTs ever assessed the impact of HPV vaccines on cervical cancer incidence and its associated mortality. Any conclusion on this matter is therefore purely speculative.

Therefore, it is understandable—although very regrettable—that mainstream media from different countries have been misled by the title

[32] Lippman A, Melnychuk R, Shimmin C, Boscoe M. Human papillomavirus, vaccines and women's health: questions and cautions CMAJ. 2007 Aug 28; 177(5): 484–487. doi: 10.1503/cmaj.070944 Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1950169/

[33] Franco EL, de Pokomandy A, Spence AR, Burchell AN, Trottier H, Mayrand MH, Laus S. Vaccination against human papillomavirus. CMAJ. 2007 Dec 4; 177(12): 1524–1525. doi: 10.1503/cmaj.1070120 Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2096514/

[34] Arbyn M, Xu L, Simoens C, Martin-Hirsch PPL. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD009069. DOI: 10.1002/14651858.CD009069.pub3. Available from http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009069.pub3/full

of Arbyn et al.'s publication and have claimed that, according to a Cochrane review, HPV vaccination prevents cervical cancer.[35,36]

It should be noted that Arbyn et al. have evaluated the efficacy of HPV vaccines in the global prevention of CIN2/3+, irrespective of HPV type, thus honoring a suggestion we made in 2014[37]. This outcome is indeed the only relevant one from a public health perspective because it alone can be used to assess the vaccines' efficacy (prophylactic and no therapeutic) in reducing the global incidence of CIN2/3+ and possibly the global incidence of cervical cancer.

In the context of a competition between several virus strains, it cannot be assumed that by preventing the development of cancers due to HPV 16 and 18 (responsible for 70% of cervical cancers), the overall disease incidence will likewise decrease. Indeed, other high-risk strains may replace HPVs held in check by the vaccination.[38,39] The outcome CIN2/3+ irrespective of HPV type allows to avoid the pitfall of viral replacement.

The efficacy of HPV vaccines in preventing high-grade cervical lesions (CIN2 +, CIN3 + and AIS) due to high-risk HPVs has been established 10 years ago in Phases II and III of FUTURE (Gardasil)[40] and PATRICIA (Cervarix)[41] RCTs. The numerous analyses carried out by Arbyn et al. on these outcomes do not bring any new information.

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[35] HPV vaccines prevent cervical cancer, global review confirms. CNN. May 8, 2018. Available from https://edition.cnn.com/2018/05/08/health/hpv-vaccines-cervical-cancer-review/index.html

[36] Le vaccin contre le papillomavirus prévient le cancer du col de l'utérus. Doctissimo. 9 mai 2018. Available from http://www.doctissimo.fr/sante/news/efficacite-vaccin-anti-hpv-contre-cancer-col-de-l-uterus

[37] Riva C, Spinosa JP, Lippman A, Arya N, Biron P, Rail G, Spring L, Taillefer A, Turcotte F. Feedback on Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. 16 December 2014. Available from http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009069.pub2/full#CD009069-sec1-0006

[38] Murall CL, McCann KS, Bauch CT. Revising ecological assumptions about Human papillomavirus interactions and type replacement. J Theor Biol. 2014 Jun 7;350:98-109. doi: 10.1016/j.jtbi.2013.12.028. Available from https://www.ncbi.nlm.nih.gov/pubmed/24412334

[39] Pons-Salort M1, Letort V, Favre M, Heard I, Dervaux B, Opatowski L, Guillemot D. Exploring individual HPV coinfections is essential to predict HPV-vaccination impact on genotype distribution: a model-based approach. Vaccine. 2013 Feb 6;31(8):1238-45. doi: 10.1016/j.vaccine.2012.11.098. Available from https://www.ncbi.nlm.nih.gov/pubmed/23246257

[40] The Future II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 2007; 369: 1861–68. Available from https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(07)60852-6/fulltext

[41] Paavonen J et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women.

For the outcome "CIN2/3+ irrespective of HPV type", the FUTURE and PATRICIA intent-to-treat results were significantly lower than expected, as analyses 3.7, 3.8 and 3.9 provided by Arbyn et al. clearly show (pp. 143-145). As for the per-protocol results (women who are naive to high-risk HPV types at vaccination onset), they were published in medical journals for Cervarix for CIN2 +, but not for CIN3 + (see analyses 2.13 and 2.14). For Gardasil, no publication in medical journals is available to date. In such selective reporting context, the Cochrane review had a highly relevant role to play. We regret that Arbyn et al. did not attempt to fill this knowledge gap by requesting and analyzing these unpublished data, whereas some of them are available,[42,43] which they had been made aware of in August 2014.[44]

The authors chose instead to examine the results of an analysis on a subgroup of women naive to high-risk HPV types. This choice may seem logical from a public health perspective, as girls who have not yet begun their sex life constitute the HPV vaccines' target population.

However, Arbyn et al.'s decision is methodologically problematic. The studies included for analyses 1.7, 1.8 and 1.9 (Lehtinen 2012[45] for Cervarix and Munoz 2010[46] for Gardasil) are indeed post-hoc subgroup analyses and not pre-specified analyses. In the original protocols, such

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Lancet. 2009 Jul 25;374(9686):301-14. doi: 10.1016/S0140-6736(09)61248-4. Epub 2009 Jul 6. Available from https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)61248-4/fulltext

[42] VRBPAC. Background Document, GardasilTM HPV Quadrivalent Vaccine May 18, 2006 VRBPAC Meeting. Table 25. Available from: https://web.archive.org/web/20060815000000*/http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B3.PDF

[43] Spinosa JP, Riva C, Biollaz J. Letter to the editor response to the article of Luisa Lina Villa HPV prophylactic vaccination: the first years and what to expect from now, in press. Cancer Lett. 2011 May 1;304(1):70. doi: 10.1016/j.canlet.2011.01.024. Epub 2011 Feb 19. Available from https://www.cancerletters.info/article/S0304-3835(11)00050-4/fulltext

[44] Riva C, Spinosa JP, Lippman A, Arya N, Biron P, Rail G, Spring L, Taillefer A, Turcotte F. Feedback on Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. 16 December 2014. Available from http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009069.pub2/full#CD009069-sec1-0006

[45] Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland S, Castellsagué X. Overall efficacy of HPV-16/18 ASO4-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncology 2012;13(1):89–99. doi: 10.1016/S1470-2045(11)70286-8. Epub 2011 Nov 8. Erratum in: Lancet Oncol. 2012 Jan;13(1):e1. Available from https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(11)70286-8/fulltext

[46] Munoz N, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. Journal of the National Cancer Institute 2010;102(5):325–39. Available from https://academic.oup.com/jnci/article/102/5/325/889337

analyses were part of neither the FUTURE nor the PATRICIA clinical trials.

While the limitation of this type of analysis is clearly mentioned in Lehtinen's study regarding Cervarix, it is absent in Munoz's study. Most importantly, this limitation does not appear in Arbyn et al.'s review. Mentioning this would have been all the more necessary that Lehtinen and Munoz have not used the tools recommended by good practice to report results of subgroup post-hoc analyses.[47] The latter are strictly exploratory and non-conclusive; they cannot be interpreted as evidence. Basically, the FDA rejects such analysis due to the risk of spurious results. Hindeed, with sufficient covariate measurements, a drug company can always find a subgroup that benefits from a drug.[48]

The above-mentioned publications do not therefore meet the inclusion criteria of this Cochrane review. The results of a subgroup post-hoc analysis cannot be considered equivalent to RCT results. The methodological problem stems from the fact that post-hoc analyses are used to generate a hypothesis and at the same time to verify it. Given this circular situation, they cannot be used as evidence and can only help generating new hypotheses.[49]

The omission of such limitations in Arbyn et al.'s publication is especially problematic considering that Lehtinen and Munoz provide almost 70% of the populations considered by the authors of this Cochrane review for their calculations and their conclusion that "HPV vaccines reduce the risk of any CIN2 + from 287 to 106/10,000 (RR 0.37 (0.25 to 0.55), high certainty)."

Arbyn et al.'s decision to include Munoz in their review is all the more surprising that, as early as August 2014,[50] they had been made aware that this analysis of a subgroup of women naive to 14 HPV types constituted a subgroup post-hoc analysis that was not planned in the initial protocol

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[47] Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in Medicine ─ Reporting of Subgroup Analyses in Clinical Trials.*NEJM*, 2007 https://www.nejm.org/doi/pdf/10.1056/NEJMsr077003

[48] Malani A, Bembom O, van der Laan M. Reforming Subgroup Analysis. April 13, 2008. Available from SSRN https://ssrn.com/abstract=1119970 or http://dx.doi.org/10.2139/ssrn.1119970

[49] Cucherat M., Interprétation des essais cliniques pour la pratique médicale, Faculté de médecine Lyon Laennec. Available from https://www.scribd.com/document/24698055/Lecture-critique-des-essais-cliniques-pour-la-pratique-medicale [only in French]

[50] Riva C, Spinosa JP, Lippman A, Arya N, Biron P, Rail G, Spring L, Taillefer A, Turcotte F. Feedback on Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. 16 December 2014. Available from http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009069.pub2/full#CD009069-sec1-0006

of the FUTURE trials. The tables we put together and we offer in the appendix show that the composition of this subgroup has changed several times between 2005 and 2010, which increases doubt about the validity of Munoz et al.'s analysis.

The Data Analysis Plans (DAP) that we obtained from the FDA through a FOIA request also show that the problem is even more serious in the case of Gardasil. These documents show that the analysis of a "negative to 14 HPV types" population (RMITT-2) was not planned in the first DAP (2003)[51] and that it was added during the trials, with a new DAP (2005)[52] replacing the per-protocol analysis.

This problem of *outcome switching*, a highly controversial practice,[53] shows that Arbyn et al. did not diligently assess the risk of bias in the studies they decided to include. They didn't even mention this issue in their publication.

We are surprised that they have assessed the PATRICIA and FUTURE studies as being at low risk of bias and bias reporting, while problems have been reported on these specific points at least since 2009.[54,55,56,57] Again, they didn't even mention this issue in their publication. We also regret that Arbyn et al. did not pay attention to the quality of the clinical trials' design and to the choice of outcomes, despite the fact that they had been made aware of these issues.[58]

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[51] Statistical Data Analysis Plan (Protocol 015). V501 Reference P015V1. Appendix 3.11. Prepared by Lisa Lupinacci. 2003 July 21. P. 24.
[52] Statistical Data Analysis Plan (Sudies 005, 007, 013, and 015). V501 Data Analysis Plan. Amendement 1. Prepared by Lisa Lupinacci.2005 Aug 04. P. 24.
[53] Altmann DG, Moher D, Schulz KF. Harms of outcome switching in reports of randomised trials: CONSORT perspective, *BMJ* 2017;356:j396. Available from https://www.bmj.com/content/356/bmj.j396
[54] Therapiekritik Neue Daten zu HPV-IMpfstoffen (CERVARIX, GARDASIL). a-t 2009; 40:71-3. Available from https://www.arznei-telegramm.de/html/htmlcontainer.php3?produktid=071_01&artikel=0908071_01k [only in German]
[55] Riva C, Spinosa JP, La piqûre de trop? Ed. Xenia, 2010. [only in French]
[56] Spinosa JP, Riva C, Biollaz J. Letter to the editor response to the article of Luisa Lina Villa HPV prophylactic vaccination: the first years and what to expect from now, in press. Cancer Lett. 2011 May 1;304(1):70. doi: 10.1016/j.canlet.2011.01.024. Epub 2011 Feb 19. Available from https://www.cancerletters.info/article/S0304-3835(11)00050-4/fulltext
[57] Riva C, Spinosa JP. Prescrire en questions: vaccin papillomavirus : quelle efficacité, quel risque ? La Revue Prescrire 2013;33(357):552-556. Available from http://www.prescrire.org/fr/3/31/49012/0/NewsDetails.aspx [only in French]
[58] Riva C, Spinosa JP, Lippman A, Arya N, Biron P, Rail G, Spring L, Taillefer A, Turcotte F. Feedback on Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. 16 December 2014. Available from http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009069.pub2/full#CD009069-sec1-0006

Moreover, we find the imbalance between the number of studies included for Cervarix (n = 18) and the number of studies included for Gardasil (n = 7) highly problematic, notably as the authors attempted to calculate the "global" efficacy of "the" HPV vaccine while dealing with three hardly comparable products with different valences and adjuvants. We also regret that the authors did not mention this imbalance and the resulting limitations. In addition, Arbyn et al. gloss over the significant differences between placebo groups in the FUTURE and PATRICIA trials. In the FUTURE trials' placebo group, there were proportionately many more cases of precancerous lesions than in the PATRICIA trials' placebo group. Interestingly, the recruitment procedures for the two trials do not explain these differences. Finally, it should be noted that in most Western countries, Gardasil dominates the market in an overwhelming way.[59,60] For example, since 2016,[61] Cervarix is no longer marketed in the United States. From the authors of a Cochrane review, we would have expected a mention and a consideration of such issues, which should have been taken into account when analyzing the supposed benefits of these vaccines.

As a result, the analyses and conclusions put forward by Arbyn et al. regarding the alleged benefits of HPV vaccines are based on data whose quality has not been correctly assessed and put into perspective. We are concerned that despite such methodological limitations and problems, the authors stated that there is "high-certainty evidence that HPV vaccines protect against cervical precancer". For the sake of consistency and credibility, it seems to us essential that this Cochrane review be updated in light of the above-mentioned elements.

We encourage Arbyn et al. to review their analyses and conclusions regarding the efficacy of Gardasil® and Cervarix® in protecting from CIN2/3 regardless of the associated HPV type, and to consider all these comments, particularly regarding data quality assessments, and also the clinical trials' design.

Last but not least, we deplore the multiple conflicts of interest plaguing the group of authors of this Cochrane review. We have signaled such

[59] GlobalData. CERVARIX (prophylactic human papillomavirus vaccines) – Forecas and market analysis to 2022. 2014. Available from https://www.marketresearch.com/product/sample-8275218.pdf
[60] GlobalData. GARDASIL (prophylactic human papillomavirus vaccines) – Forecas and market analysis to 2022. 2014. Available from https://www.marketresearch.com/product/sample-8275165.pdf
[61] Mulcahy N. GSK's HPV Vaccine, Cervarix, No Longer Available in US. Medscape May 14, 2018. Available from https://www.medscape.com/viewarticle/870853

conflicts as early as 2012,[62] however, even in the latest panel composition that has signed the review, they do not seem to be resolved.

[62] Riva C, Spinosa JP, Lippman A, Arya N, Biron P, Rail G, Spring L, Taillefer A, Turcotte F. Feedback on Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. 16 December 2014. Available from http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009069.pub2/full#CD009069-sec1-0006

Table II

Evolution of the subgroup RMITT-2 (number of participants, efficacy)

	Gardasil® N	Lesions N	Placebo N	Lesions N	Efficacy %	95% CI
2006 Name of the subgroup: Partially HPV-Naïve population (*) / RMITT-2 (**) Protocols: 007-013-015 Type of lesion: CIN 2/3+ (*) Briefing Document, presented by Merck to VRBPAC on 18-May-2006 (Table 20, p. 59) (**) VRBPAC. Background Document Gardasil™ HPV Quadrivalent Vaccine May 18, 2006. VRBPAC Meeting. Table 13. CBER. Clinical Review of Biologics License Application for Human Papillomavirus 6, 11, 16, 18 L1 Virus Like Particle Vaccine. 2006 June 8. Table 272.	5638	59	5701	96	37.9%	13.2, 55.9%
2007 Name of the subgroup: RMITT-2 (*) Protocols: 013-015 Type of lesion: CIN 2/3+ (*) E. Barr. Updated Efficacy Data – GARDASIL®. 2007 February 2007. [ACIP PPT-presentation] Slide 18. (**) R. Haupt. GARDASIL® Update. Slide 33 (***)R. Haupt. GARDASIL® Update. Slide 31	4658(**) 4616 (***)	52	4732(**) 4675(***)	97	46%	not specified
2008 Name of the subgroup: RMITT-2, close-out, data (*) Protocols: 005-007-013-015 Type of lesion: CIN 2/3+ (*) CBER. Clinical Review of Biologics License Application Supplement for Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant (Gardasil®). 2008 Sept 11. Table 26.	4616	77	4680	136	42.7%	23.7, 57.3%
2010 Name of the subgroup: 14 HPV-neg (*) Protocols: 013-015 Type of lesion: CIN 2/3+ (*) Munoz N, Kjaer SK, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst. 2010 mar 3;102(5):325-339. Table 3.	4616	77	4680	136	42.7%	23.7, 57.3%

Table III

Evolution and changes in the definition of subgroup RMITT-2

	Seroneg. and PCR-neg. HPV 6-11-16-18	PCR-neg. HPV 31-33-35-39-45-51-52-56-58-59	Pap test normal at day 1	Remained free of infection with the relevant vaccine HPV type during the course of vaccination	Any follow up visit 1 month following first injection	Cases counted starting 30 days after Day 1	Endpoint counting after Day 1	Endpoints between Month 1 and Month 7	Subject received < 3 doses	Subject received at least 1 dose	Subject with major protocol violations	Subjects who became infected with a vaccine type during the vaccination period
2006												
Briefing Document, presented by Merck to VRBPAC on 18-May-2006.	x	--	x	x	x	x	--	x	x	not specified	x	x
VRBPAC. Background Document Gardasil™ HPV Quadrivalent Vaccine May 18, 2006. VRBPAC Meeting	x	--	x	not specified	not specified	x	--	not specified	not specified	not specified	not specified	not specified
CBER. Clinical Review of Biologics License Application for Human Papillomavirus 6, 11, 16, 18 L1 Virus Like Particle Vaccine. 2006 June 8.	x	--	x	not specified	not specified	x	--	not specified	not specified	not specified	not specified	not specified
2007												
E. Barr. Updated Efficacy Data – GARDASIL®. 2007 February 2007. [ACIP PPT-presentation] Slide 18.	x	x	x	not specified	not specified	not specified	--	not specified	not specified	not specified	not specified	not specified
2008												
CBER. Clinical Review of Biologics License Application Supplement for Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant (Gardasil®). 2008 Sept 11.	x	x	x	not specified	x	not specified	--	not specified	not specified	x	not specified	not specified

2010 Munoz N, Kjaer SK, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst. 2010 mar 3;102(5):325-339.	x	x	x	not specified	x	--	x	--	not specified	x	x	not specified

From: dtovey@cochrane.org
To: catherine.riva@re-check.ch
Cc: Serena Tinari <serena.tinari@re-check.ch>; Jean Pierre Spinosa spinosa@deckpoint.ch

Subject: HPV vaccine - Cochrane review
Sent: 2018-08-30

Dear Ms Riva

We are planning to respond to the BMJ EBM article soon. I will make enquiries about the response to your comments.

Best wishes

David,

Dr David Tovey FRCGP | Editor in Chief, The Cochrane Library,
Editorial and Methods Department, Cochrane Central Executive

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From: Cochrane Library Comments <cochrane_feedback@wiley.com>
To: catherine.riva@re-check.ch

Subject: Cochrane Library: Your comment has been published
Sent: 2018-10-09

Dear Catherine Riva,

Your comment on **Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors** has been published.

You can view your comment at
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009069.pub3/detailed-comment/en?messageId=154255807.

Thank you for your contribution. If you have any concerns please contact cochrane_feedback@wiley.com.

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From: Catherine Riva <catherine.riva@re-check.ch>
To: 'Cochrane Library Comments' <cochrane_feedback@wiley.com>
Cc: Serena Tinari (serena.tinari@re-check.ch); Jean Pierre Spinosa <spinosa@deckpoint.ch>

Subject: Cochrane Library: Your comment has been published
Sent: 2018-09-12

Dear Cochrane Library,
Thank you for the news.

We realized that our text needs a minor correction.
We stated:
While the limitation of this type of analysis is clearly mentioned in Lehtinen's study regarding Cervarix, it is absent in Munoz's study.

Actually, also Lehtinen's study on Cervarix did NOT mention that the analysis was a post-hoc subgroup analysis and did not mention the limitation of such analysis either.
As such methodological flaws are important and are the core of our comment, we find extremely important to correct the sentence and instead write:
The limitation of this type of analysis is not mentioned in Lehtinen's study regarding Cervarix and in Munoz's study regarding Gardasil.
Could you please make the correction et let us know when it's published?

Last but not least, the form we had to use to submit our comment didn't allow us to be specific in our disclosure of potential conflicts of interest.
Could you please add following disclosures:
Catherine Riva is a freelance investigative journalist. She co-founded Re-Check, an independent agency specialized in investigating and mapping health affairs. She is the co-author of an investigative book on the HPV vaccination ("La piqûre de trop?", Xenia, 2010) and published several articles in Swiss mainstream media on HPV vaccine.
Serena Tinari is a freelance investigative journalist. She co-founded Re-Check, an independent agency specialized in investigating and mapping health affairs. She is the co-chair of investigativ.ch, the Swiss Network of Investigative Journalists, and an advisory board member for www.journalismfund.eu and www.irpi.eu. She authored three investigative TV documentaries on the HPV vaccination (Swiss Public Broadcaster: Falò RSI 2009 ; Falò RSI / Rundschau SRF 2012; Rundschau SRF 2014).
Jean-Pierre Spinosa is a gynecologist and a surgeon. He is a lecturer at the University of Lausanne (Faculty of Medicine). He is the co-author of an investigative book on the HPV vaccination ("La piqûre de trop?", Xenia, 2010).

Thank you very much.

Best regards,
Catherine Riva

From: John Hilton <JHilton@cochrane.org>
To: Catherine Riva <catherine.riva@re-check.ch>
Cc: Serena Tinari <serena.tinari@re-check.ch>; Jean Pierre Spinosa <spinosa@deckpoint.ch>; Wheat, Sophia swheat@wiley.com

Subject: Cochrane Library: Your comment has been published
Sent: 2018-09-13

Dear Catherine Riva,

Thank you for getting in touch requesting this correction. I will look into making this change as soon as possible and confirm, together with a note indicating the correction has been made.

Could you clarify what you mean by the form not allowing you to be specific in your disclosure of potential conflicts of interest? Were you referring to the question asked or the text box provided?

With best wishes,

John Hilton

John Hilton
Editor, Digital Publishing
Editorial & Methods Department
Cochrane Central Executive

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From: Catherine Riva <catherine.riva@re-check.ch>
To: John Hilton <JHilton@cochrane.org>
Cc: 'Serena Tinari' <serena.tinari@re-check.ch>; 'Jean Pierre Spinosa' <spinosa@deckpoint.ch>; 'Wheat, Sophia' <swheat@wiley.com>

Subject: Cochrane Library: Your comment has been published
Sent: 2018-09-13

Dear John Hilton,
When one submits a comment on a Cochrane review, the COI issue is addressed only by this box:

> Do you have any affiliation with or involvement in any organisation with a financial interest in the subject matter of your comment?
>
> ◉ No ○ Yes

So our statements (“No”) was correct, because no one of us is involved in any organization with a financial interest in this subject matter.
But the form automatically translates it in “No conflict of interest declared.”
We think it’s important to provide more information. That’s why we asked you to add what I mentioned in my previous email.
Thank you very much in advance.
Best regards,
Catherine Riva

From: Cochrane Library Comments <cochrane_feedback@wiley.com>
To: Catherine Riva <catherine.riva@re-check.ch>

Subject: Cochrane Library: Your comment has been published
Sent: 2018-09-21

Dear Catherine Riva,

Your comment on **Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors** has been published.

You can view your comment at https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009069.pub3/detailed-comment/en?messageId=154255807.

Thank you for your contribution. If you have any concerns please contact cochrane_feedback@wiley.com.

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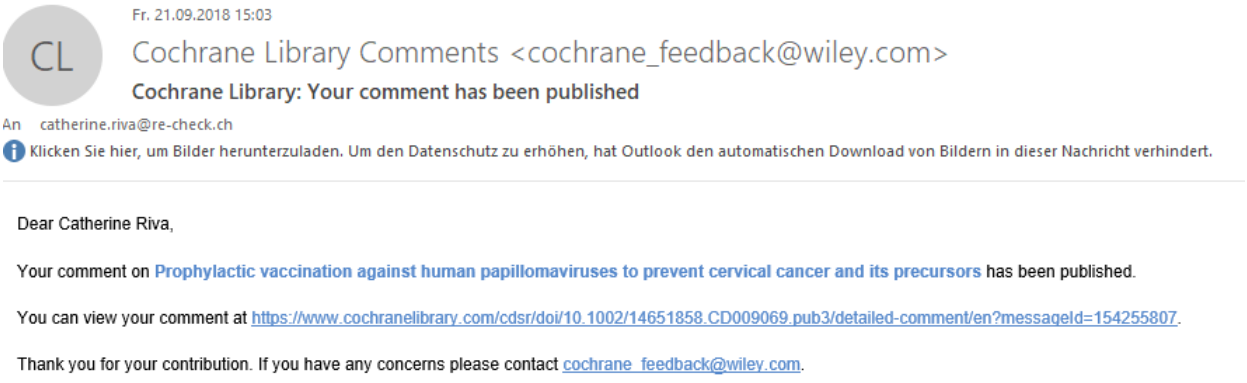
From: Catherine Riva <catherine.riva@re-check.ch>
To: John Hilton <JHilton@cochrane.org>
Cc: 'Serena Tinari' <serena.tinari@re-check.ch>; 'Jean Pierre Spinosa' <spinosa@deckpoint.ch>; 'Wheat, Sophia' <swheat@wiley.com>

Subject: Cochrane Library: Your comment has been published
Sent: 2018-09-21

Dear John Hilton,
I just received the following message:



Fr. 21.09.2018 15:03

CL Cochrane Library Comments <cochrane_feedback@wiley.com>

Cochrane Library: Your comment has been published

An catherine.riva@re-check.ch

Klicken Sie hier, um Bilder herunterzuladen. Um den Datenschutz zu erhöhen, hat Outlook den automatischen Download von Bildern in dieser Nachricht verhindert.

Dear Catherine Riva,

Your comment on **Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors** has been published.

You can view your comment at https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009069.pub3/detailed-comment/en?messageId=154255807.

Thank you for your contribution. If you have any concerns please contact cochrane_feedback@wiley.com.

The requested changes are not done.
And there is still no access to the tables we sent as an appendix.
Could you please make the corrections?
Thank you very much in advance.
Best regards,
Catherine Riva

From: John Hilton <JHilton@cochrane.org>
To: Catherine Riva <catherine.riva@re-check.ch>
Cc: Serena Tinari <serena.tinari@re-check.ch>; Jean Pierre Spinosa <spinosa@deckpoint.ch>; Wheat, Sophia swheat@wiley.com

Subject: Cochrane Library: Your comment has been published
Sent: 2018-09-21

Dear Catherine Riva and colleagues

Apologies for any confusion here. I have now made the changes and published a revised version of the comment, along with a note explaining the change.
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009069.pub3/detailed-comment/en?messageId=154255807

Regards.

John Hilton

John Hilton
Editor, Digital Publishing
Editorial & Methods Department
Cochrane Central Executive

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From: Catherine Riva <catherine.riva@re-check.ch>
To: John Hilton <JHilton@cochrane.org>
Cc: 'Serena Tinari' <serena.tinari@re-check.ch>; 'Jean Pierre Spinosa' <spinosa@deckpoint.ch>; 'Wheat, Sophia' <swheat@wiley.com>

Subject: Cochrane Library: Your comment has been published
Sent: 2018-09-21

Dear John Hilton,
Thank you very much.
Serena Tinari and Jean-Pierre Spinosa are still missing as co-authors. Could you please add their names?
Best regards,
Catherine Riva

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From: John Hilton <JHilton@cochrane.org>
To: Catherine Riva <catherine.riva@re-check.ch>
Cc: Serena Tinari <serena.tinari@re-check.ch>; Jean Pierre Spinosa <spinosa@deckpoint.ch>; Wheat, Sophia swheat@wiley.com

Subject: Cochrane Library: Your comment has been published
Sent: 2018-09-21

Comments on the Cochrane Library can only be submitted by one named person, but the text of the Comment can indicate that there are multiple authors, as you have done
We are unable to include attachments or tables to Comments, but you have sent your materials to the Review Group, which is the best option here.
And thank you for your reply regarding the conflicts of interest statement. We do currently only ask for direct financial conflicts of interest, but we are reviewing a policy for seeking non-financial conflicts.

Best wishes,

John

John Hilton
Editor, Digital Publishing
Editorial & Methods Department
Cochrane Central Executive