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

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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 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.

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

The limitation of this type of analysis is not mentioned in Lehtinen's study regarding Cervarix and in Munoz's study regarding Gardasil. 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 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]

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 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.

Disclosure:

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[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

[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 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

[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

[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
[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
[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