Note:

In July 2014, Catherine Riva received from Prof. Ingrid Mühlhauser (Hamburg University) the detailed protocol of the planned Cochrane HPV vaccines review.

Catherine Riva, Jean-Pierre Spinosa, Abby Lippman, Neil Arya, Pierre Biron, Geneviève Rail, Lyba Spring, Anne Taillefer and Fernand Turcotte did shortly after submit to Cochrane a new comment with detailed suggestions to improve the review protocol.

In this comment, Catherine Riva, Jean-Pierre Spinosa, Abby Lippman, Neil Arya, Pierre Biron, Geneviève Rail, Lyba Spring, Anne Taillefer and Fernand Turcotte made the Cochrane review authors aware about unpublished data Catherine Riva obtained from the FDA through a FOIA request regarding Gardasil® efficacy in preventing all CIN 2+ irrespective of HPV type.

Their comment also pointed to an outcome switching issue in the Gardasil® Phase III studies.

From: Catherine Riva [catherine.riva@bluewin.ch]
To: 'Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS TRUST - RD1)'; 'Jo.Morrison@tst.nhs.uk'; 'chrisjhwilliams@btinternet.com'; 'Marc.Arbyn@wiv-isp.be'
Cc: 'JP Spinosa'; 'Abby Lippman'; 'Genevieve Rail'; 'Anne Taillefer'; 'lybaspring@sympatico.ca'; 'Pierre Biron'; 'Neil Arya'; 'Fernand.Turcotte@fmed.ulaval.ca'; p.foucras@wanadoo.fr; 'jbz@bluewin.ch'; 'a.gunn@uq.edu.au'; 'Serena Tinari'; Peter C. Gøtzsche; 'peter@healthyskepticism.org'; 'President ISDB'; 'redaktion@arznei-telegramm.de'; 'contact@prescrire.org'; 'Serena Tinari'; 'jim.wright@ti.ubc.ca'; 'FGodlee@bmj.com'; 'jefferson.tom@gmail.com'; pharmacritique@voila.fr; 'Ingrid Mühlhauser'; 'masquelier.p@orange.fr'

Subject: Cochrane review - protocol CD009069
Attached: 2014-08-19_Cochrane-reviewCD009069_comments.pdf / CD009069.pdf / 2014-08-19_Lettre-Cochrane.pdf
Sent: 2014-08-19

Dear Mrs Quinn,
Dear Mr Morrison,
Dear Mr Williams,
Dear Mr Arbyn,

We have attached here a letter that provides our detailed comments on the protocol for the Cochrane review “Prophylactic Vaccination Against human papillomaviruses to prevent prevention cervical cancer and Its Precursors”, led by Marc Arbyn, Andrew Bryant, Pierre Martin-Hirsch PL, Lan Xu, Cindy Simoens and Lauri Markowitz. (CD009069 http://summaries.cochrane.org/CD009069/GYNAECA_prophylactic-vaccination-against-human-papillomaviruses-to-prevent-cervical-cancer-and-its-precursors and CD009069.pdf).

If you have any questions or seek further clarification, please do not hesitate to contact us.

Sincerely yours,

Catherine Riva
Dr Jean-Pierre Spinosa
Abby Lippman
Neil Arya
Pierre Biron
Geneviève Rail
Lyba Spring
Anne Taillefer B.SC., M.A.
Fernand Turcotte

Attachment: 2014-08-19_Lettre-Cochrane.pdf

August 19, 2014

Dear Mrs. Quinn,
Dear Mr. Morrison,
Dear Mr Williams,
Dear Mr. Arbyn,

We have read the protocol for the Cochrane review "Prophylactic Vaccination Against human papillomaviruses to prevent prevention cervical cancer and Its Precursors", led by Marc Arbyn, Andrew Bryant, Pierre Martin-Hirsch PL, Lan Xu, Cindy Simoens and Lauri Markowitz. (CD009069 http://summaries.cochrane.org/CD009069/GYNAECA_prophylactic-vaccination-against-human-papillomaviruses-to-prevent-cervical-cancer-and-its-precursors and CD009069.pdf) with great interest.

We are pleased to see that this protocol addresses many important issues related to HPV vaccines. However, we believe that some points of clarification and some changes are necessary. Attached to this e-mail is a document containing our detailed comments.

We thank you in advance for taking our remarks and our suggestions for modifications of the protocol into consideration and hope to see these acted upon.

If you have any questions or seek further clarification, please do not hesitate to contact us.

Sincerely yours,

Catherine Riva
Journaliste indépendante
Rümikerstrasse 112
CH-8409 Wintetrhur

Dr Jean-Pierre Spinosa
Gynécologue-obstétricien
Rue des Terreaux 2
CH – 1003 Lausanne

Abby Lippman
PhD, Professor Emerita
Department of Epidemiology, Biostatistics. and Occupational Health
McGill University
Montréal, Québec

Neil Arya
BASc MD CCFP FCFP D. Litt
Adjunct Professor Environmental Studies University of Waterloo
Assistant Clinical Professor Family Medicine McMaster University

Pierre Biron
Professeur honoraire
Faculté de médecine
Université de Montréal
Canada 3

Geneviève Rail
Ph.D. Concordia University and CIHR recipient of a research grant on HPV vaccination (2012-2015)

Lyba Spring
Sexual Health Education and Consulting Services
414 Rushton Rd.
Toronto, Ontario
M6C 2Y3

Anne Taillefer B.SC., M.A.
Sociologue de la santé
Université du Québec à Montréal

Fernand Turcotte, MD. MPH. FRCPC
Professeur émérite de santé publique,
Université Laval
Québec, Canada

Attachment: 2014-08-19_Cochrane-reviewCD009069_comments.pdf

Cochrane review – Intervention Protocol CD009069

(http://summaries.cochrane.org/CD009069/GYNAECA_prophylactic-vaccination-against-human-papillomaviruses-to-prevent-cervical-cancer-and-its-precursors)

Suggested changes and clarifications

p. 3

> **Why it is important to do this review**
> Several phase II and III studies have been conducted to date and numerous reviews have tried to summarise the results (Arbyn 2007; Ault 2007;Harper 2009; Initiative 2009; Kahn 2009; Kjaer 2009; Koutsky 2006; Medeiros 2009; Rambout 2007; Szarewski 2010). However, none of the reviews combined information on all the available endpoints. This is due to incomplete reporting of data, use of different assays, analyses of different per protocol or intention-to-treat groups, outcome definitions, lumping of different outcomes, and reporting at variable time points in the scientific literature. Previous reports have also not comprehensively evaluated the impact of vaccination by fine categories of age and time since sexual debut, have not systematically evaluated evidence for cross-protection against HPV types phylogenetically related to HPV-16/18, and have not specifically addressed the question of whether vaccination protects against re-infection among younger and older individuals known to be infected at vaccination and who subsequently clear their infections.
> The objective of this reviewis to summarise all available (published and unpublished) evidence by combining outcomes with similar definitions and times of measurement. We will request missing outcomes or outcome data missing at specific time points.

We agree to the points made above.
However, we think the paragraph warrants the following clarifications,

1. This Cochrane review is important in order to examine the validity and trustworthiness of the design of the clinical trials with regard to the choice of outcomes as well as the rigour with which these trials were conducted. Consequently, the reviewers will need to address certain problems and limitations in the design and conduct of the studies:
    - The documents we have obtained from the FDA indicate that there were changes in the protocol during the course of the trials and therefore during the approval process. These changes necessarily had a major impact on the quality of the reporting and redefinition of certain sub-groups in at least three instances[1].
    - The minutes from meetings of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) show that the decision to fast track the research led the American regulatory officials to choose outcomes that would allow them to evaluate **only** the specific effectiveness of the vaccination on lesions associated with HPV 16 and 18 and not its effectiveness on all HPV-associated lesions[2].

[1] Statistical Data Analysis Plan (Protocol 015). V501 Reference P015V1. Appendix 3.11. Prepared by Lisa Lupinacci. 2003 July 21. P. 24.
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
[2] Summary Minutes Vaccine and Related Biological Products Advisory Committee. Meeting #88 November 28-29, 2001.

- The criteria required to satisfy a fast track procedure were not fulfilled[3] but the fast tracking had an impact on the choice of outcomes[4].
- The entries regarding the trials on clinictrials.gov indicate that their primary and secondary outcomes were not registered prospectively[5].

We believe that this Cochrane review should raise these issues with FDA officials[6] and scientific journals which have published results from the Phase III trials[7] because they have broken their own rules of proper scientific conduct.

2. This Cochrane review is important for thoroughly evaluating a potentially increased risk of the subsequent development of precancerous lesions in women who already have HPV infections targeted by the vaccination at the time they are vaccinated. This risk has not been sufficiently examined although existing evidence indicates the need for a thorough and careful examination of the possibility. This evidence includes:
   - Results submitted to VRBPAC in June, 2006[8]
   - The Australian study done by Brotherton et al[9].

   This Cochrane review is important to calculate and report the risk of subsequent development of precancerous lesions in women who already have HPV infections targeted by the vaccination at the time they are vaccinated, and the ways in which it must be communicated to vaccinated women and to vaccinated girls and their legal guardians.

p. 3

OBJECTIVES

To evaluate the immunogenicity, clinical efficacy, and safety of prophylactic HPV vaccines in females. The assessment of clinical efficacy will address protection against HPV infection (for homologous and heterologous HPV types), against re-infection, against cervical cancer and its precursors (high-grade CIN (grade 2 or grade 3), adenocarcinoma in situ) in women previously not exposed to HPV infection (negative at enrolment for both HPV DNA and antibodies against the vaccine HPV types). We will assess clinical effectiveness by evaluating outcomes in all women, irrespective of the HPV DNA or serology status at enrolment. Evaluation by fine age and time since sexual debut categories is also planned.

---

[3] Tomljenovic L, Shaw CA, Too fast or not too fast: the FDA's approval of Merck's HPV vaccine Gardasil. J Law Med Ethics. 2012 Fall;40(3):673-81. doi: 10.1111/j.1748-720X.2012.00698.x.

[4] Vaccine and Related Biological Products Advisory Committee. Open Session (Minutes). 2001 Nov 29, pp 71-72, pp 119-127.

[5] Clincaltrials.gov Archive. History of NCT00365716. [homepage on the Internet]. No date [cited 2012 Feb 22]. Available from: http://clinicaltrials.gov/archive/NCT00365716. Clincaltrials.gov Archive. History of NCT00365378. [homepage on the Internet]. No date [cited 2012 Feb 22]. Available from: http://clinicaltrials.gov/archive/NCT00365378. Clincaltrials.gov Archive. History of NCT00092534. [homepage on the Internet]. No date [cited 2012 Feb 22]. Available from: http://clinicaltrials.gov/archive/NCT00092534. Clincaltrials.gov Archive. History of NCT00092521. [homepage on the Internet]. No date [cited 2012 Feb 22]. Available from: http://clinicaltrials.gov/archive/NCT00092521.

[6] FDA, HHS. 21 CFR § 314.126 Adequate and well-controlled studies**. Available from:** http://www.gpo.gov/fdsys/pkg/CFR-2010-title21-vol5/pdf/CFR-2010-title21-vol5-sec314-126.pdf.

[7] De Angelis C, Drazen JM, et al. Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004; 351:1250-1. Available from: http://www.nejm.org/doi/full/10.1056/NEJMe048225.

[8] VRBPAC. Background Document, Gardasil™ HPV Quadrivalent Vaccine May 18, 2006 VRBPAC Meeting. Table 19, 21, 25. Available from: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B3.PDF

[9] Brotherton JM, Fridman M, May CL, Chappell G, Saville AM, Gertig DM. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet. 2011 Jun 18;377(9783):2085-92.

These objectives seem entirely pertinent.
Nevertheless, it is essential that objectives specify explicitly that the effectiveness of vaccination will be evaluated with regard to all of the high-grade lesions; i.e., CIN2/3+, no matter the HPV types associated with them, and that the focus will be on young girls who were negative only for HPV-types targeted by the vaccines and not for 14 HPV types. This point is essential for methodological reasons, since analyzing the effectiveness of vaccination for young girls who were HPV-negative for 14 HPV types was post hoc and not in the protocols before the trials began. The value of these two analyses is therefore not equal.

p. 3

Types of studies

We will only consider randomised controlled trials (RCTs).

This point strikes us as essential. Moreover, it should be made clear that post hoc analyses of subgroups will be treated, if at all, separately.
Moreover, we believe that the Cochrane reviewers should clearly indicate how they will take into consideration unpublished results that the manufacturer possesses.

p. 3-4

Primary outcomes

1. Histologically confirmed high-grade cervical intraepithelial neoplasia (CIN2, CIN3 and adenocarcinoma in situ (AIS).
2. Invasive cervical cancer.
3. Immunogenicty:
i) percentage of women vaccinated who have seroconverted after the third dose of vaccine;
ii) mean antibody level in International Units (IU) observed after completion of vaccine administration.
4. Safety:
i) immediate and short term adverse events (observed within four weeks after administration):
a) local adverse effects (redness, swelling, pain, itching at the injection place);
b) mild systemic effects;
c) severe systemic effects;
ii) serious adverse events observed after four weeks of administration of the vaccine during the trial;
iii) pregnancy outcomes observed during the trials, in particular occurrence of congenital anomalies.

We believe that primary outcome 1 must state explicitly that histological confirmation will focus specifically on “CIN2, CIN3 and AIS irrespective of HPV type”.

We believe that primary outcome 4 (safety) must include:

- an analysis of the adequacy of the protocol planned for the studies on the safety and innocuousness of the vaccine as well as the effects of the placebo chosen to evaluate these aspects of the research
- a third point (iii) that encompasses an evaluation of the increase in the risk of CIN2/3 for women who were already infected by HPV types targeted by the vaccine

p. 4

> **Secondary outcomes**
> 1. Incident infection with vaccine HPV types (HPV6, HPV11, HPV16 and HPV18, separately and jointly) and with hrHPV types other than HPV16/18.
> 2. Persistent infection with vaccine HPV types and hrHPV types other than HPV16/18.
> 3. Evolution over time of the geometric mean titres of antibodies against the vaccine HPV types.

We believe that the secondary outcomes should include an HPV-specific analysis of the lesions found in the vaccinated population to clarify the possibility of viral replacement. It is essential to know whether during the Phase III trials, the efficacy of the vaccines against high-risk HPV 16 and 18 resulted in an increase in high-grade lesions associated with other high-risk HPV types.

p. 13

> **DECLARATIONS OF INTEREST**
> MA: has received travel grants fromMSD-Sanofi-Pasteur and GSK, (ceased in 2008). AB: no conflict of interest. PM-H: travel grants received fromGSKandMSD-Sanofi-Pasteur. LX: no conflict of interest. CS received travel grant from GSK. LM; no conflict of interest.

All of the research to date has been conducted by authors who have conflicts of interest with the vaccine manufacturer.
In December 2012, we alerted the Cochrane Gynecological and Orphan Cancer Group that the authors originally chosen for this Cochrane review also had conflicts of interest with the manufacturer. Some of these authors were dropped in December 2013. Nevertheless, the question remains, since certain authors did not step aside and state here that they have no conflicts of interest. We believe that the stated conflicts of interest in the protocol are incomplete for Marc Arbyn and Lauri E. Markowitz. As we previously pointed out in December 2012, these two authors have already made favorable pronouncements regarding the vaccine, which constitutes a clear bias.

> Marc Arbyn:
> "HPV vaccination will reduce the burden of cervical precancer and probably also of invasive cervical and other HPV-related disease in women."
> http://www.ncbi.nlm.nih.gov/pubmed/22623137
> Marc Arbyn (with Philippe Beutels):
> "Well-planned introduction of vaccination combined with an organized screening program and active surveillance are crucial for the program to achieve and monitor its desired aims. Such surveillance should include linkage between vaccination, screening and cancer registries." http://www.ncbi.nlm.nih.gov/pubmed/21051840
>
> Lauri E. Markowitz, Team Lead, Centers for Disease Control and Prevention (Atlanta, Georgia): "The CDC has approved these vaccines as safe and effective. Both vaccines were studied in thousands of people around the world, and these studies showed no serious safety concerns. Side effects reported in these studies were mild, including pain where the shot was given, fever, dizziness, and nausea. Vaccine safety continues to be monitored by CDC and the FDA. More than 46 million doses of HPV vaccine have been distributed in the United States as of June 2012." http://www.cdc.gov/std/hpv/stdfact-hpv-vaccine-young-women.htm.
> L. E. Markowitz also transmits his conclusions in the context of events like this (http://www.medscape.org/viewarticle/768633_sidebar2), sponsored by the manufacturer of the quadrivalent vaccine ("supported by an independent educational grant from Merck").

We believe that it is imperative for this information to appear in the declaration of interest for Marc Arbyn and Lauri Markowitz. We also think that this protocol must explicitly state what measures will

be taken in order to limit, as much as possible, the influence of these conflicting ties on the analysis of the results.

From: Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS TRUST - RD1) [gailquinn1@nhs.net]
To: Catherine Riva

Subject: RE:Cochrane review - protocol CD009069
Sent: 2014-09-01

Dear Catherine Riva

Many thanks for your message, the content of which our team will now consider.

Could you please remove Chris Williams from your list of recipients as he has retired from our Group.

Best wishes,

Gail

Gail Quinn | Managing Editor
Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group
Education Centre, Royal United Hospital, Bath, BA1 3NG, UK
Tel: +44 (0) 1225 826349|
Twitter: @Cochrane_GNOCG
gailquinn1@nhs.net | www.cochrane.org

Note:

In December 2014, four months after submission, the comment on Cochrane HPV vaccines review protocol, has still not been published on the Cochrane dedicated website.

Catherine Riva, Jean-Pierre Spinosa, Abby Lippman, Neil Arya, Pierre Biron, Geneviève Rail, Lyba Spring, Anne Taillefer and Fernand Turcotte wrote again to Cochrane to ask why.

From: Catherine Riva [catherine.riva@bluewin.ch]
To: 'Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS TRUST - RD1)'; 'chrisjhwilliams@btinternet.com'; 'Marc.Arbyn@wiv-isp.be'
Cc: abby.lippman@mcgill.ca; 'JP Spinosa'; 'Fernand.Turcotte@fmed.ulaval.ca'; 'lyba spring'; 'Genevieve Rail'; 'Pierre Biron'; 'Anne Taillefer'; 'Neil Arya'; p.foucras@wanadoo.fr; 'masquelier.p@orange.fr'; 'Jérôme Biollaz'; Peter C. Gøtzsche; 'Tom Jefferson'; 'Doshi, Peter'; 'FGodlee@bmj.com'; 'peter@healthyskepticism.org'; 'Andrew Gunn'; 'President ISDB'; 'contact@prescrire.org'; 'redaktion@arznei-telegramm.de'; 'Ingrid Mühlhauser'; 'jim.wright@ti.ubc.ca'; 'Serena Tinari'; 'pharmacritique@voila.fr'

Subject: Cochrane review - protocol CD009069
Sent: 2014-12-08

Dear Mrs Quinn,
Dear Mr Williams,
Dear Mr Arbyn,

On 19 August 2014, we sent you a letter detailing our concerns regarding the Cochrane review "Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors" to be conducted by Marc Arbyn, Andrew Bryant, Pierre Martin-Hirsch PL, Lan Xu, Cindy Simoens and Lauri Markowitz (see CD009069 at http://summaries.cochrane.org/CD009069/GYNAECA_prophylactic-vaccination-against-human-papillomaviruses-to-prevent-cervical-cancer-and-its-precursors).

It is now December, four months later, and we have not yet received a detailed answer from you. Moreover, we are unable to locate our commentary on the website devoted to this review. It is our understanding that all comments regarding Cochrane review protocols either taking place or forthcoming are to be provided in an annex and made freely available.

Furthermore, when we examined this review's "History" rubric ("Publication Status: Edited (no change to conclusions) Published Online: 30 DEC 2013 "), we were surprised to discover that an essential fact was missing. Specifically, there was no mention that the original panel of reviewers was profoundly modified, thanks in large part to our intervention regarding a number of the reviewers' conflicts of interest, an issue which to that point had not been considered by the Cochrane Gynaecological Cancer Group.

The omissions detailed above seem to contradict Cochrane Collaboration's principles of transparency, and we believe that this situation must be corrected.

We are writing now to request answers to our August 2014 letter and to urge you to up-date the HPV vaccination review's web site so as to make available the letters and documents we have sent you since December 2012. If you no longer have these documents, we will be pleased to forward copies to you.

Sincerely yours,

Catherine Riva
Dr Jean-Pierre Spinosa
Abby Lippman
Neil Arya
Pierre Biron
Geneviève Rail

Lyba Spring
Anne Taillefer B.SC., M.A.
Fernand Turcotte

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From: Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS TRUST - RD1) [gailquinn1@nhs.net]
To: Catherine Riva

Subject: Cochrane review - protocol CD009069
Sent: 2014-12-09

Dear Catherine Riva

Many thanks for your message regarding the published Cochrane protocol "Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors".

We are grateful for your constructive comments and we intend to address your concerns as a matter of priority. We will take this opportunity to discuss the next steps with senior colleagues at the office of the Editor in Chief of The Cochrane Library. We expect to be able to collate a formal response to you in the New Year.

Best wishes,

Gail

Gail Quinn | Managing Editor
Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group
Education Centre, Royal United Hospital, Bath, BA1 3NG, UK
Tel: +44 (0) 1225 826349|
Twitter: @Cochrane_GNOCG
gailquinn1@nhs.net | www.cochrane.org

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From: Morrison Jo (TAUNTON AND SOMERSET NHS FOUNDATION TRUST) [jo.morrison1@nhs.net]
To: catherine.riva@bluewin.ch
Cc: Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS FOUNDATION TRUST)

Subject: HPV Cochrane Review Protocol comments
Sent: 2014-12-16

Dear Ms Riva,

Thank you for your email dated 8/12/14, which was passed on to me by Gail Quinn; I have taken over from Dr Williams as co-ordinating editor since this protocol was first published in March 2011. As per our previous correspondence in August, we had passed on your comments to the review authors, for their consideration and so that these could be addressed during writing of the review. I am sorry that we had not appreciated that you would like these to be included as official feedback to the

protocol, since they were not submitted via the formal feedback mechanism, available via the Cochrane Library website.

We would be happy to publish the content of the letter that you sent to us as formal feedback on the published protocol. However, in order for us to incorporate these comments in to the published protocol, we will need you to submit them via the feedback mechanism on the website.

http://onlinelibrary.wiley.com/cdsr/feedback?doi=10.1002/14651858.CD009069.pub2&reviewGroup=GYNAECA&articleTitle=Prophylactic%20vaccination

We will publish the feedback as long as it complies with Cochrane guidance, as described in the feedback tool. We look forward to hearing from you and receiving your formal comments shortly.

Yours sincerely,

Miss Jo Morrison BM BCh MA MRCOG DPhil
Co-ordinating Editor Cochrane Gynae Cancer Group
Consultant Gynaecological Oncologist

Sec: Ann.england@tst.nhs.uk
Tel: 01823 342562
jo.morrison1@nhs.net

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From: Catherine Riva [catherine.riva@bluewin.ch]
To: 'Morrison Jo (TAUNTON AND SOMERSET NHS FOUNDATION TRUST)'
Cc: 'Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS TRUST - RD1)'; 'Jean Pierre Spinosa'; abby.lippman@mcgill.ca; 'Neil Arya'; 'Anne Taillefer'; 'Genevieve Rail'; 'lybaspring'; 'Fernand.Turcotte@fmed.ulaval.ca'; 'Pierre Biron'

Subject: AW: HPV Cochrane Review Protocol comments
Sent: 2014-12-16

Dear Miss Morrison,
Thank you very much for your email. I followed your instructions and sent our letter as formal feedback on the published procotol via the website of the Cochrane Library.
Please let me know if you have received it and tell me when it will be made public.
Best regards,
Catherine Riva

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From: Morrison Jo (TAUNTON AND SOMERSET NHS FOUNDATION TRUST) [jo.morrison1@nhs.net]
To: catherine.riva@bluewin.ch
Cc: Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS FOUNDATION TRUST); Toby Lasserson

Subject: RE: HPV Cochrane Review Protocol comments
Sent: 2014-12-16

Dear Catherine,
Thank you for your reply. It has just been forwarded to me - our emails crossed. We will get back to you once it has been through our review feedback process; this will not be until after the New Year.
Yours sincerely,
Jo Morrison

Miss Jo Morrison BM BCh MA MRCOG DPhil
Co-ordinating Editor Cochrane Gynae Cancer Group
Consultant Gynaecological Oncologist

Sec: Ann.england@tst.nhs.uk
Tel: 01823 342562
jo.morrison1@nhs.net

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From: Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS TRUST - RD1) [gailquinn1@nhs.net]
To: Catherine Riva

Subject: HPV Cochrane Review Protocol comments
Sent: 2015-01-09

Dear Catherine

Could you please confirm that you are the sole signatory on the feedback you have submitted with regard to the published Cochrane protocol *Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors.*

In previous correspondence you have included a number of co-authors and should you wish to include these persons in the formal feedback process we will require individual conflict of interest statements.

Wishing you all the very best for 2015,

Gail

Gail Quinn | Managing Editor
Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group
Education Centre, Royal United Hospital, Bath, BA1 3NG, UK
Tel: +44 (0) 1225 826349|
Twitter: @Cochrane_GNOCG
gailquinn1@nhs.net | www.cochrane.org

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

From: Catherine Riva [catherine.riva@bluewin.ch]
To: Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS TRUST - RD1) [gailquinn1@nhs.net]
Cc: 'Jean Pierre Spinosa'; abby.lippman@mcgill.ca; 'Neil Arya'; 'Anne Taillefer'; 'lybaspring'; 'Genevieve Rail'; 'Fernand.Turcotte@fmed.ulaval.ca'; 'Pierre Biron'

Subject: AW: HPV Cochrane Review Protocol comments
Sent: 2015-01-09

Dear Gail,
We are all signatories of the submitted feedback, i.e. Catherine Riva, Jean-Pierre Spinosa, Abby Lippman, Geneviève Rail, Lyba Spring, Anne Taillefer, Fernand Turcotte, Neil Arya and Pierre Biron.
Where should the other signatories indicate their own conflict of interest statement?
Thank you in advance for your help.
Best wishes,
Catherine Riva

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From: Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS TRUST - RD1) [gailquinn1@nhs.net]
To: Catherine Riva

Subject: HPV Cochrane Review Protocol comments
Sent: 2015-01-12

Dear Catherine

Could you ask your co-signatories to send their full titles, affiliations and any conflicts of interests to me and we will add them to the feedback on their behalf.

I have already heard from Dr Arya.

Many thanks,

Gail

Gail Quinn | Managing Editor
Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group
Education Centre, Royal United Hospital, Bath, BA1 3NG, UK
Tel: +44 (0) 1225 826349|
Twitter: @Cochrane_GNOCG
gailquinn1@nhs.net | www.cochrane.org

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From: Catherine Riva [catherine.riva@bluewin.ch]
To: Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS TRUST - RD1) [gailquinn1@nhs.net]

Subject: AW: HPV Cochrane Review Protocol comments
Sent: 2015-01-12

Dear Gail,
Thank you for your email.
I have informed the other signatories. They will send you all the information your need.
Best regards,
Catherine Riva

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From: Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS TRUST - RD1) [gailquinn1@nhs.net]
To: Catherine Riva

Subject: HPV Cochrane Review Protocol comments
Sent: 2015-02-02

Der Catherine

Just a quick update to let you know that we should be in a position to publish your feedback comments within the next couple of weeks.

Regards,

Gail

Gail Quinn | Managing Editor
Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group
Education Centre, Royal United Hospital, Bath, BA1 3NG, UK
Tel: +44 (0) 1225 826349|
Twitter: @Cochrane_GNOCG
gailquinn1@nhs.net | www.cochrane.org

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

From: Catherine Riva [catherine.riva@bluewin.ch]
To: Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS TRUST - RD1) [gailquinn1@nhs.net]
Cc: 'Abby Lippman'; 'Jean Pierre Spinosa'; 'lybaspring'; 'Genevieve Rail'; 'Anne Taillefer'; 'Pierre Biron'; 'Fernand.Turcotte@fmed.ulaval.ca'; 'Neil Arya'

Subject: AW: HPV Cochrane Review Protocol comments
Sent: 2015-02-02

Dear Gail,
Thank you very much for keeping us informed.
Best regards,
Catherine Riva

From: Catherine Riva [catherine.riva@bluewin.ch]
To: Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS TRUST - RD1) [gailquinn1@nhs.net]

Subject: Cochrane review/protocol CD009069 - disturbing facts and questions
Sent: 2015-02-18

Dear Gail,
I was extremely surprised to learn recently from a colleague that Marc Arbyn, lead author of the Cochrane Review on the HPV vaccine, had publicly presented the intermediate results of that review at a congress.
I was especially shocked, since on 9 December 2014 you had written to me that the review had not even then begun. I quote from your email responding to our concerns about the protocol design:
"We are grateful for your constructive comments and we intend to address your concerns as a matter of priority. We will take this opportunity to discuss the next steps with senior colleagues at the office of the Editor in Chief of The Cochrane Library. We expect to be able to collate a formal response to you in the New Year."
Can you please explain what has happened? Did you know that Marc Arbyn and his group already had results, and that he would be presenting them at a scientific congress?
Moreover, does this mean that the review was actually in progress (or about to be finished) when you wrote to me in December? If so, why did you not say so in your emails?
Finally, and also puzzling and disturbing: what is actually to be done with our comments and suggestions about the protocol?
I hope you will be able to clarify those questions.
Best regards,
Catherine Riva

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

From: Morrison Jo (TAUNTON AND SOMERSET NHS FOUNDATION TRUST) [jo.morrison1@nhs.net]
To: catherine.riva@bluewin.ch
Cc: Quinn Gail (ROYAL UNITED HOSPITAL BATH NHS FOUNDATION TRUST); Toby Lasserson

Subject: HPV vaccine review
Sent: 2015-02-18

Dear Ms Riva, Thank you for your email which was passed on to me by my colleague, Gail Quinn. The email you have quoted dated 9 December 2014 was written in response to the submission of your comments via the formal feedback mechanism on the Cochrane Library website. Your comment and a reply have now been published in the protocol on the Cochrane Library.
The comments you had submitted in August 2014 were passed on to the authors in full and at the time we asked that they incorporate them into the review process. We are now in receipt of the review which is under editorial consideration. This was submitted to us in January of this year. Not only were your comments considered by the authors during the review process as they worked on the review late last year, they will now also be considered by our editors during our own editorial process. It is undergoing the same rigorous editorial assessment as would be applied to all Cochrane reviews.
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.

Yours sincerely,
Dr J Morrison
Co-ordinating Editor
CGNOCG

Note:

The comment on Cochrane HPV vaccines review protocol submitted in August 2014 was finally published on the Cochrane dedicated website in February 2015. At the time, it was available from http://onlinelibrary.wiley.com/enhanced/doi/10.1002/14651858.CD009069.pub2

The Cochrane review' authors replied on the same dedicated website:

> "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."

In March 2015, Catherine Riva, Jean-Pierre Spinosa, Abby Lippman, Neil Arya, Pierre Biron, Geneviève Rail, Lyba Spring, Anne Taillefer and Fernand Turcotte decided to inform some journalists about their concerns regarding the Cochrane HPV vaccines review and on the exchanges they had on the topic with Cochrane since 2012. They provided to these journalists their complete correspondence with Cochrane (letters, comments and e-mails 2012-2015).

For the sake of clarity, they wrote the following exposé where they outlined all concerns. This statement was written in English, in French and in Canadian French.

NB: The 2014 comment on the protocol and the review authors' reply is no more available since Cochrane erased all comments on the protocol after the review was published in May 2018.

2015-03-16_Cochrane_expose_e.pdf

2015-03-16

Is the Cochrane Collaboration Meeting its Own Standards?

The Cochrane Collaboration disseminates systematic reviews which are meant to "represent the highest level of evidence". It enjoys an excellent reputation among physicians and concerned citizens who try to base their medical decisions on the best available data. In the eyes of all who are concerned about the growing influence of the pharmaceutical industry on health policy, it is synonymous with independance and integrity.

Repeatedly, the Cochrane Collaboration has lived up to its reputation of "good science agency", rigorous, reliable and independent. In particular, it demonstrated the lack of efficacy or even harm of some heavily promoted health measures: cancer screening with mammography, vaccination against influenza, Tamiflu®, health checks.

However the history of the soon-to-be published review of the HPV vaccine may raise questions about this entry truly reflecting an independent, transparent review based on the highest quality of evidence without bias from conflicts of interest.

Many questions persist about the approval process of the HPV vaccines: their rapid introduction; the unprecedented marketing of them to the public; the pharmaceutical company funding of medical societies; and the smaller, short term studies with surrogate markers. There was an urgent need for a rigorous and independent assessment.

But from the beginning, the Cochrane review went awry. In December 2012, this review was to be conducted by a panel of fourteen authors, at least two thirds of whom had flagrant conflicts of interest with Merck and GlaxoSmithKline, the makers of HPV vaccines. In fact, two investigators of the Phase III clinical trials funded by Merck were among them. Nevertheless, the Cochrane Gynaecological, Neuro-oncology & Orphan Cancer Group (CGNOCG), senior editor of this review, was about to endorse the review known to have a major risk of bias and influence.

It was then that we wrote a letter explaining these concerns. Following our intervention, Cochrane responded, dismissed the most serious cases of conflict of interest, and the panel was reconstituted in December 2013. However, two authors, including the lead author, Marc Arbyn, whose ties to Merck and GSK resulted in strong public statements in favour of the vaccine even prior to the review, remained on the panel.

The rationale provided by the CGNOCG: "That the authors have an interest and expertise in this area, so have already formed some opinions on the data does not count as conflict of interest (…): equipoise is desirable, but an open mind and ability to systematically, and without bias, review the data is a given. If this were not the case then many Cochrane Reviews would be conducted by people without relevant clinical or topic expertise."

This argument is highly questionable: other Cochrane reviews were conducted by outstanding authors without such conflicts of interest.

A second problem is transparency. While our letter to CGNOCG was submitted as a comment to the review of the website in December 2012, contrary to Cochrane policy it remained unpublished on the website. In August 2014, we reviewed the revised protocol and made suggestions to rectify some flaws in the protocol. The CGNOCG took note of our letter and promised to keep us informed of the results. Having received no news for about 4 months, we wrote again in December 2014 to reiterate our request that our feedback be made public. This was finally done in February 2015, more than two years after our initial correspondence -- but only our suggestions on the protocol from August 2014 were posted.

Our report on massive conflicts of interest of the first panel of authors, from December 2012, still does not appear on the review of the site. And rather than considering it a positive step to remove such authors with clinical ties, the response of CGNOCG and authors to our suggestions concerning the protocol, is instructive: “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.”

Moreover, even before our suggested changes were published on the review's website and while we were waiting to be informed how our feedback might be incorporated in the protocol, we learned that the principal author, Marc Arbyn, was already announcing preliminary results publicly at congresses and that the review was actually finished and under review. The CGNOCG justified this by writing: “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.” Though it was unaware of the presentation, the CGNOCG also found this unremarkable: “this is not something we are in a qui position to stop or approve”. In other words, the Cochrane editorial managers tolerated the lead author of a review that they had not yet adopted, disseminating selective and unconfirmed results. For the public, this is now the Cochrane “approved” HPV vaccination. The damage is done.

To summarize:
We have a Cochrane review conducted by authors who have conflicts of interest with the manufacturers of the products whose efficacy they are supposed to assess. The Cochrane group responsible for the review decides that some of these conflicts of interest are not important enough to ask the authors to withdraw, even if the same authors made numerous public statements in favour of the vaccine and claim that the lack of support of other colleagues with more serious conflicts of interest makes them unable to consider all unpublished data. The Cochrane group manager sees nothing “uncommon” at all with the presentation of preliminary data by the very same leader with conflicts of interest.

Is this the Cochrane Collaboration's way to reflect "highest level of evidence" and provide a "balanced assessment of the available evidence"? Surely this was not Archie Cochrane's original intention.

Catherine Riva
Journaliste indépendante
Rümikerstrasse 112
CH-8409 Wintetrhur

Dr Jean-Pierre Spinosa
Gynécologue-obstétricien
Rue des Terreaux 2
CH – 1003 Lausanne
Abby Lippman
PhD, Professor Emerita
Department of Epidemiology, Biostatistics. and Occupational Health
McGill University
Montréal, Québec

Neil Arya
BASc MD CCFP FCFP D. Litt
Adjunct Professor Environmental Studies University of Waterloo
Assistant Clinical Professor Family Medicine McMaster University

Pierre Biron
Professeur honoraire
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Lyba Spring
Sexual Health Education and Consulting Services
414 Rushton Rd.
Toronto, Ontario M6C 2Y3

Anne Taillefer B.SC., M.A.
Sociologue de la santé
Université du Québec à Montréal

Fernand Turcotte, MD. MPH. FRCPC
Professeur émérite de santé publique,
Université Laval
Québec, Canada

2015-03-16_Cochrane_expose_f.pdf

16.03.2015

La Collaboration Cochrane est-elle à la hauteur de ses propres standards?

La Collaboration Cochrane diffuse des revues systématiques (reviews) qui sont censées représenter «le plus haut niveau de preuve». Elle jouit d'une excellente réputation auprès des médecins et des citoyens soucieux de fonder leurs décisions médicales sur les meilleures données disponibles. Aux yeux de tous ceux qui s'inquiètent de l'influence croissante de l'industrie pharmaceutique sur les politiques de santé, elle est synonyme d'indépendance et d'intégrité.

A maintes reprises, la Collaboration Cochrane a été à la hauteur de sa réputation de passeur de «bonne science», rigoureux, fiable et indépendant. Elle a notamment démontré l'absence d'efficacité, voire la dangerosité de certaines mesures de santé abondamment promues: dépistage du cancer par mammographie, vaccination contre la grippe, Tamiflu®, check ups…

Mais l'histoire du review Cochrane sur la vaccination anti-HPV, qui devrait être prochainement publié, amène à se demander si nous allons véritablement avoir affaire au produit d'un travail indépendant, transparent, basé sur la meilleure évidence, sans biais de conflits d'intérêts.

Bien des faits amènent à s'interroger sur le processus qui a conduit à la mise sur le marché des vaccins anti-HPV : la rapidité de leur introduction, le dispositif marketing sans précédent qui les a portés, le soutien des fabricants aux sociétés de médecine, et des études à court terme menée sur des critères de substitution. La conduite d'une évaluation rigoureuse et indépendante était devenue une nécessité urgente.

Mais dès le début, les choses sont allées de travers. En décembre 2012, ce review était sur le point d'être conduit par un panel de quatorze auteurs, dont deux tiers au moins avaient des conflits d'intérêts flagrants avec Merck et GlaxoSmithKline, les fabricants des vaccins anti-HPV. Deux investigateurs des essais cliniques de phase III financés par Merck figuraient même parmi eux. Manifestement, aucun contrôle n'avait été opéré. Le Cochrane Gynaecological, Neuro-oncology & Orphan Cancer Group (CGNOCG), responsable éditorial de ce review, se préparait à avaliser un travail porteur d'un risque majeur de biais et d'influence.

Nous sommes alors intervenus par le biais d'un courrier où nous avons exprimé la préoccupation que nous inspirait cette situation. La Cochrane a réagi, écarté les cas les plus lourds, et le panel d'auteur a été recomposé en décembre 2013. Néanmoins, deux auteurs, dont l'auteur principal Marc Arbyn, qui avaient des conflits d'intérêts avec Merck et GSK et qui avaient toujours affiché leur sympathie pour la vaccination anti-HPV, ont pu rester.

Motif allégué par le CGNOCG pour justifier leur maintien: «That the authors have an interest and expertise in this area, so have already formed some opinions on the data does not count as conflict of interest (…): equipoise is desirable, but an open mind and ability to systematically, and without bias, review the data is a given. If this were not the case then many Cochrane Reviews would be conducted by people without relevant clinical or topic expertise.»

Cet argument est des plus discutables: d'autres reviews Cochrane ont été conduits par des auteurs extérieurs qui n'avaient pas ce genre de conflits d'intérêts.

Autre problème: la transparence. En décembre 2012, nous avions soumis notre courrier au CGNOCG sous forme de commentaire sur le site Internet du review, afin qu'il soit rendu public. Il n'a jamais été publié, contrairement à ce que prévoit la Cochrane. En août 2014, nous avons révisé le protocole remanié et adressé des suggestions de rectification par rapport à certains défauts. Le CGNOCG en a pris note et promis de nous tenir au courant de la suite. Sans nouvelle de sa part, nous avons réitéré en décembre 2014 notre requête pour que notre feedback soit rendu public, ce qui a été finalement fait en février 2015, soit plus de deux ans après notre première correspondance – mais seules nos suggestions d'août 2014 concernant le protocole ont été publiées.

Nos investigations sur les conflits d'intérêts massifs du premier panel d'auteurs, communiquées en décembre 2012, ne figurent toujours pas sur le site du review. Quant à la réponse du CGNOCG et des auteurs à nos suggestions concernant le protocole, elle est édifiante: «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.»

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Résumons la situation.
Nous avons un review Cochrane mené par des auteurs qui ont des conflits d'intérêts avec les fabricants des produits dont ils sont censés évaluer l'efficacité. Le groupe Cochrane responsable du review estime toutefois que certains de ces conflits d'intérêts ne sont pas assez importants pour demander aux auteurs de se retirer, même si ces auteurs ont affiché à différentes reprises des positions favorables sur la vaccination. Quant aux auteurs, ils affirment qu'ils ne pourront pas examiner toutes les données non publiées parce qu'on les a privés du soutien de collègues, qui avaient des conflits d'intérêts encore plus graves que les leurs. Le groupe Cochrane responsable ne voit rien d'«uncommon» à ce que l'auteur principal, qui a des conflits d'intérêts, présente des

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Dr Jean-Pierre Spinosa
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CH – 1003 Lausanne
Abby Lippman
PhD, Professor Emerita
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Montréal, Québec

Neil Arya
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Abby Lippman
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Department of Epidemiology, Biostatistics. and Occupational Health
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Montréal, Québec

Neil Arya
BASc MD CCFP FCFP D. Litt
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Anne Taillefer B.SC., M.A.
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