Note:

Between February 2015 and April 2017, Catherine Riva, Jean-Pierre Spinosa, Abby Lippman, Neil Arya, Pierre Biron, Geneviève Rail, Lyba Spring, Anne Taillefer and Fernand Turcotte didn't hear from Cochrane.

The Cochrane HPV vaccines review protocol remained unchanged.

Although Marc Arbyn, the first Cochrane HPV vaccines review author had shared some unpublished results at a congress in 2015, the review was still not published.

In April 2017, Catherine Riva, Jean-Pierre Spinosa, Abby Lippman, Neil Arya, Pierre Biron, Geneviève Rail, Lyba Spring, Anne Taillefer and Fernand Turcotte wrote to David Tovey, Cochrane Editor in Chief, asking for information.

From: Catherine Riva [catherine.riva@bluewin.ch]
To: dtovey@cochrane.org
Cc: Jean Pierre Spinosa <spinosa@deckpoint.ch>; abby.lippman@mcgill.ca; Genevieve Rail <Gen.Rail@concordia.ca>; anne taillefer; lyba spring <lybaspring@sympatico.ca>; Fernand Turcotte (Fernand.Turcotte@fmed.ulaval.ca); Neil Arya <narya@sympatico.ca>; Pierre Biron <biron.pierre@videotron.ca>; Tom Jefferson <jefferson.tom@gmail.com>; pcg@cochrane.dk

Subject: concerns about the Cochrane review of HPV vaccination
Attached: 2012-2015_Cochrane.zip / 2017-04-17_Letter-Cochrane-DoveyT.pdf
Sent: 2017-04-17

Dear Dr. Tovey,

We have been raising concerns about the Cochrane review of HPV vaccination ("Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors" by Marc Arbyn, Andrew Bryant, Pierre PL Martin-Hirsch, Lan Xu, Cindy Simoens and Lauri Markowitz (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009069.pub2/full) since December 2012, when we first notified the Cochrane Gynaecological, Neuro-oncology & Orphan Cancer Group (CGNOCG) of various problematic aspects in its report.

In particular, we informed the CGNOCG of the undeclared conflicts of interest of authors, and submitted a number of proposals to clarify the methodology and objectives of the protocol. All our correspondence (emails and letters) can be found in the Annex to this letter.

It is now almost five years since we first raised concerns and the review has still not yet been published. However, we have learned that as long ago as December 2014, the first author of the Cochrane review, Marc Arbyn, had already disseminated intermediate results at conferences, even stating that they were positive and in favor of vaccination.

Would you please let us know why a review of the HPV vaccination has still not yet been published?

Your explanation of this troublesome delay is now quite urgent given the constantly increasing pressure on practitioners and health authorities to generalize this vaccination as well as to alter recommendations for the number and selection of HPV vaccines as well as the populations to reach. A most recent example is the appeal, by a group of specialists, to candidates for the presidency in France (see appendix), where the information put forward as "evidence" comes exclusively from observational studies.

It is clearly important and necessary for the Cochrane Collaboration to make public the latest developments about the review of HPV vaccination. Only when a review on HPV vaccination prepared by individuals with NO conflicts of interest will be made publically available, will it be possible to have an objective and rigorous perspective about issues currently debated on the basis of mere speculations— albeit masked without qualification as "scientific evidence."

We remain ready to respond to any questions you may have and we look forward to news from you about your plans.

Sincerely,

Catherine Riva
Dr. Jean-Pierre Spinosa
Abby Lippman, Ph.D.
Neil Arya, BASc MD CCFP FCFP D. Litt

Dr. Pierre Biron
Geneviève Rail, Ph.D.
Lyba Spring
Anne Taillefer, Ph.D.
Fernand Turcotte, MD. MPH. FRCPC

Attachment: 2017-04-17_Letter-Cochrane-DoveyT.pdf

April 17, 2017

Dear Dr. Tovey,

We have been raising concerns about the Cochrane review of HPV vaccination ("Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors" by Marc Arbyn, Andrew Bryant, Pierre PL Martin-Hirsch, Lan Xu, Cindy Simoens and Lauri Markowitz (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009069.pub2/full) since December 2012, when we first notified the Cochrane Gynaecological, Neuro-oncology & Orphan Cancer Group (CGNOCG) of various problematic aspects in its report.

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It is now almost five years since we first raised concerns and the review has still not yet been published. However, we have learned that as long ago as December 2014, the first author of the Cochrane review, Marc Arbyn, had already disseminated intermediate results at conferences, even stating that they were positive and in favor of vaccination.

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We remain ready to respond to any questions you may have and we look forward to news from you about your plans.

Sincerely,

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Rümikerstrasse 112
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Note:

2012-2015_Cochrane.zip *contained following documents*:

2012-12-10_Letter_Cochrane.pdf
2012-12-10Cochrane_HPV_authorship.pdf
2013-12-08_Letter_Cochrane.pdf
2013-12-22_Letter_Cochrane.pdf
2014-08-19_Cochrane-reviewCD009069_comments.pdf
2014-08-19_Lettre-Cochrane.pdf
2015-03-16_Cochrane_expose_e.pdf
2015-03-16_Cochrane_expose_f.pdf
2015-03-16_Cochrane_expose_f-CAN.pdf

2012_Cochrane-mails.pdf
2013_Cochrane-mails.pdf
2014-2015_Cochrane-mails.pdf

Attachment: 2012-12-10_Letter_Cochrane.pdf

December 10, 2012

Dear Sir or Madam,

We recently learned that a systematic review protocol on HPV vaccine is currently being developed within the framework of the Cochrane Collaboration (http://summaries.cochrane.org/CD009069/prophylactic-vaccination-against-human-papillomaviruses-to-prevent-cervical-cancer-and-its-precursors).

We consider an independent evaluation of this vaccine an important and useful undertaking and will be pleased to see one done. However, we have some concerns about the current plans.

As the Cochrane Collaboration states in its Policy Manual (http://www.cochrane.org/policy-manual/2111-general-principle), "The performance of the review must be free of any real or perceived bias." This principle does not appear to be taken into account for this review: people responsible for the proposed assessment have conflicts of interest that may seriously compromise their work. For example, some have been supported by the pharmaceutical companies that produce HPV vaccines; have already worked as investigators in company-sponsored clinical trials of the vaccines; have already published their conclusions about the effectiveness and safety of vaccines in publications; work for the Authorities that have recommended vaccination, believing that the efficacy and safety of the HPV vaccines are demonstrated and acquired; or have otherwise conveyed support for the vaccines and vaccination programs either through continuing education activities or publications.

Based on these findings, it is clear that the majority of authors responsible for conducting the proposed Cochrane review on the HPV vaccine have serious risks of bias.

More specifically, the panel of reviewers includes two investigators involved in phase III trials on the quadrivalent vaccine (Joakim Dillner and Marc Steben) who have already reported conflicts of interest with manufacturers of vaccines. Another panel member is on the Advisory / Expert Board of GlaxoSmithKline Biologicals and Gen-Probe, and has also reported receiving travel grant honoraria from GlaxoSmithKline Biologicals and Sanofi Pasteur MSD (Andreas Kaufmann).

At least nine of the fourteen potential reviewers (Marc Arby, E. Paraskevaidis, P. Beutels, You-Lin Qiao, Fang-Hui Zhao, Achim Schneider, Andreas Kaufmann, Marc Steben, Joakim Dillner) have signed or co-authored scientific publications concluding that the vaccine was efficacious and safe, or wrote as if these endpoints were established.

Finally, one of the authors works for the CDC (Centers for Disease Control and Prevention), which recommends the HPV vaccine, thereby considering it safe and effective. Moreover, the CDC has used safety arguments to get approval to extend its use (Lauri E. Markowitz).

Attached is a detailed summary of our research on these conflicts of interest.
In other words, there is a high risk of bias, which may influence the selection, analysis and weighting of the data, with much of the data actually coming from the previous work some of the authors have done for the manufacturers and regulatory authorities. Thus, the studies that may be reviewed may already reflect bias in the methodological quality of the design of phase III clinical trials (efficacy and safety), placebos chosen for comparison and their definitions, statistical quality of data provided to

regulators, unpublished data, conclusions drawn by the health authorities and professional medical societies from subgroups analyses and ecological studies, etc..

The Cochrane Collaboration is according to its mission statement independent and free from pharmaceutical interests. The reputation and credibility of the Cochrane Collection is at risk when its basic principles are compromised. We think this is the case here and we urge you to immediately reject these authors and allow others without conflicts of interest to do the rigorous evaluation of the HPV vaccine evaluation we all would welcome.

Please do not hesitate to contact us if you have any questions or seek further information.

Sincerely,

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Université Laval
Québec, Canada

Attachment: 2012-12-10Cochrane_HPV_authorship.pdf

Conflicts of interests:

Marc Steben, quadrivalent vaccine investigator: "Dr. Steben, consulting fees, advisory board fees, and lecture fees from Digene, Merck Frosst, GlaxoSmithKline, and Roche Diagnostics and grant support from Merck Frosst and GlaxoSmithKline." http://www.ncbi.nlm.nih.gov/pubmed/21491420

Joakim Dillner, quadrivalent vaccine investigator: "J. Dillner has received consultancy fees, lecture fees, and research grants from Merck and Co, Inc, and Sanofi Pasteur MSD." http://www.ncbi.nlm.nih.gov/pubmed/20139221

Andreas Kaufmann: "A. M. Kaufmann is a member of the Advisory/Expert Board at GlaxoSmithKline Biologicals and Gen-Probe. He received travel grant honoraria from GlaxoSmithKline Biologicals and Sanofi Pasteur MSD." http://www.hu.ufsc.br/projeto_hpv/HPV%20vaccination%20against%20cervical%20cancer%20in%20women%20above%2025%20years%20of%20age.pdf

Statements:
Marc Steben, quadrivalent vaccine investigator.
Author of an editorial in CMAJ, where he strongly advocates HPV vaccination. Although he admits: "I may be perceived as biased, being an investigator of the quadrivalent vaccine", he speaks of the quadrivalent vaccine as a "super vaccine" and says: "The success rate was 100% against intraepithelial lesions of the cervix, vagina and vulva and condyloma" and "serious adverse events have been reported more rarely than with other vaccines." http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2278298/
On the issue of the higher risk for girls already carriers of HPV 16 or 18, he concluded: "These data suggest HPV vaccination neither reduces nor enhances progression to HPV16/18-related high grade cervical lesions, and cervical cytology screening and corresponding management should continue as per local recommendations." http://www.ncbi.nlm.nih.gov/pubmed/21491420

Joakim Dillner, quadrivalent vaccine investigator.
Co-author of the Munoz N study (2010) on vaccine efficacy in women HPV negative 14 (subgroup analysis): "High-coverage HPV vaccination programs among adolescents and young women may result in a rapid reduction of genital warts, cervical cytological abnormalities, and diagnostic and therapeutic procedures. In the longer term, substantial reductions in the rates of cervical, vulvar, and vaginal cancers may follow." http://www.ncbi.nlm.nih.gov/pubmed/20139221

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 and 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

Evangelos Paraskevaidis: “In this context expanding the indications for HPV vaccination to include women who have been treated for CIN should be considered.” http://www.ncbi.nlm.nih.gov/pubmed/23016771

You-Lin Qia and Fang-Hui Zhao: “Aggressive education is necessary to increase knowledge of HPV and its vaccine. Further proof of vaccine safety and efficacy and government subsidies combined with increased awareness could facilitate development and implementation of HPV vaccination in China.” http://www.ncbi.nlm.nih.gov/pubmed/22901224

Achim Schneider and Andreas Kaufmann: “HPV vaccination is likely to be beneficial to sexually active women due to their continuous risk of acquiring new HPV infections and of developing cervical intraepithelial neoplasia (CIN) and cervical cancer. Clinical trial data show that the HPV-16/18 AS04-adjuvanted vaccine is safe and immunogenic in women up to the age of 55 years, whilst preliminary data with the quadrivalent vaccine demonstrated evidence of safety, immunogenicity and high-level efficacy in women 24 to 45 years of age. HPV vaccination in women over 25 years of age is already approved in several countries, and these women are individually seeking advice on vaccination from healthcare professionals. The predicted reduction in cost benefit of vaccination with increasing age, however, is likely to limit the implementation of routine vaccination beyond the late 20s.” http://www.ncbi.nlm.nih.gov/pubmed/19819540

Member of CDC

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”).

Attachment: 2013-12-23_Letter_Cochrane.pdf

December 23, 2013

Dear Madam Quinn:

Thank you for your response to our letter. We are pleased to learn that the Cochrane Gynaecological and Orphan Cancer Group took action following our inquiry of December 2012.
However, we would still like some further clarification of a few points in your response that remain vague and hope you can provide some details. Specifically.

- What criteria will be used to select authors of future reviews: or have they already been chosen?
- What conflicts of interest criteria/processes has the Cochrane Gynaecological and Orphan Cancer Group established that would exclude an author?
- Does the Cochrane Gynaecological and Orphan Cancer Group itself verify the accuracy of declarations of conflicts of interest of potential or current authors and, if so, how is this done?

We look forward to your responses to these few questions, and thank you in advance for your help.

Sincerely,

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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.

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
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CH-8409 Wintetrhur

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Attachment: 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.

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Attachment: 2015-03-16_Cochrane_expose_f.pdf

16.03.2015

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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.

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16.03.2015

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From: David Tovey [DTovey@cochrane.org]

To: Catherine Riva <catherine.riva@bluewin.ch>
Cc Jean Pierre Spinosa <spinosa@deckpoint.ch>; abby.lippman@mcgill.ca; Genevieve Rail <Gen.Rail@concordia.ca>; anne taillefer <a_taillefer@videotron.ca>; lyba spring <lybaspring@sympatico.ca>; Fernand Turcotte <Fernand.Turcotte@fmed.ulaval.ca>; Neil Arya <narya@sympatico.ca>; Pierre Biron <biron.pierre@videotron.ca>; Tom Jefferson <jefferson.tom@gmail.com>; 'Peter C. Gøtzsche' <pcg@cochrane.dk>

Subject: concerns about the Cochrane review of HPV vaccination
Sent: 2017-04-23

Dear Ms Riva,

Thanks for your email. You are correct that the review is still in the editorial process. From my perspective, the review cannot be published until it meets Cochrane's standards on quality and provides what I believe is the best possible summary of the available evidence. The review also needs to adhere to Cochrane's policies on conflict of interest, which does not specify currently that all members of the author team are free from any commercial or academic conflict, but is more exacting then the requirements of most other scientific journals.

Like you, I am keen to see the review published, but we are not ready to do so yet, and the review remains with the author team pending further detailed editorial assessment.

With best wishes

David

Dr David Tovey FRCGP | Editor in Chief, The Cochrane Library, and Deputy Chief Executive Officer
Cochrane Editorial Unit | Cochrane Central Executive

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