

The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias

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Key findings

- ▶ The Cochrane human papillomavirus (HPV) vaccine review missed nearly half of the eligible trials.
- ▶ The review was influenced by reporting bias and biased trial designs.
- ▶ Authors of Cochrane reviews should make every effort to identify all trials and the trials' limitations.

In May 2018, the Cochrane Collaboration published its review of the human papillomavirus (HPV) vaccines.¹ The review primarily assessed the vaccines' effect on precursors to cervical cancer. Cochrane has high standards for its reviews²; however, there were important limitations in its HPV vaccine review, which we address in this paper.

The Cochrane review missed nearly half of the eligible trials

The Cochrane review conducted trial searches up until June 2017 and included 26 randomised trials with 73 428 women.¹ In January 2018, we published an index of the study programmes of the HPV vaccines that included 206 comparative studies.³ As of June 2017, about one-third of the 206 studies were not published and half of the completed studies listed on ClinicalTrials.gov had no results posted.³ Although we sent our index to the Cochrane group handling the Cochrane review, the review stated that, 'nearly all end-of-study reports have been published in the peer-reviewed literature'. When we applied the Cochrane review's inclusion criteria to the 206 studies, we identified 46 completed and eligible trials. The number of randomised participants could be assessed for 42 of the 46 trials and was 121 704. With nearly half of the trials and half of the participants missing, the Cochrane authors' conclusion, 'that the risk of reporting bias may be small', was inappropriate. Fifteen of the 20 additional trials were listed on ClinicalTrials.gov; the Cochrane authors would therefore have identified more trials if they had searched ClinicalTrials.gov in more depth and searched additional trial registers (we searched 45 trial registers³).

The Cochrane authors stated that they 'did not include the nine-valent vaccine [Gardasil 9] ... since the randomised trials ... did not incorporate an arm with a non-HPV vaccine control'. This is not correct. The only saline placebo trial of approved HPV vaccines is a Gardasil 9 trial (V503-006; NCT01047345) that was published in 2015.⁴ Its participants had previously been

vaccinated with four-valent Gardasil, but according to the Cochrane review protocol,⁵ this was not an exclusion criterion. Since many countries are shifting to Gardasil 9,⁶ it is unfortunate that the Gardasil 9 trial was not included in the Cochrane review.

No included trial in the Cochrane review used a placebo comparator

All 26 trials included in the Cochrane review used active comparators: adjuvants (aluminium hydroxide [Al(OH)₃] or amorphous aluminium hydroxyphosphate sulfate [AAHS]) or hepatitis vaccines.

Adjuvants are not regulated separately from their vaccine antigens. According to the Food and Drug Administration (FDA), adjuvants are unreliable comparators.⁷ One HPV vaccine manufacturer (GlaxoSmithKline that produces Cervarix) states that its aluminium-based comparator induces harms: 'higher incidences of myalgia might namely be attributable to the higher content of aluminium in the HPV vaccine (450 µg Al(OH)₃) than the content of aluminium in the HAV [hepatitis A] vaccine (225 µg Al(OH)₃)'.⁸ The comparator hepatitis vaccines also used the HPV vaccines' aluminium-based adjuvant.

The Cochrane authors mistakenly used the term placebo to describe the active comparators. They acknowledged that 'The comparison of the risks of adverse events was compromised by the use of different products (adjuvants and hepatitis vaccines) administered to participants in the control group'. Nevertheless, this statement can easily be overlooked, as it comes after 7500 words about other issues in the discussion and under the heading 'Potential biases in the review process'. Active comparators was not a bias in the review process but a bias in the design of the HPV vaccine trials.

The use of active comparators probably increased the occurrence of harms in the comparator groups and thereby masked harms caused by the HPV vaccines. It is noteworthy that many women were excluded from the trials if they had received the adjuvants before or had a history of immunological or nervous system disorders; for example, in the PATRICIA trial with 18 644 women⁹ and the FUTURE II trial with 12 167 women.¹⁰ These exclusion criteria lowered the external validity of the trials and suggest that the vaccine manufacturers were worried about harms caused by the adjuvants. The criteria are not listed as warnings on the package inserts of the HPV



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vaccines,^{11–13} which may have led to more vaccine-related harms in clinical practice than in the trials.

The included HPV vaccine trials used composite surrogate outcomes for cervical cancer

In line with World Health Organization (WHO) recommendations,¹⁴ the Cochrane review was based on composite surrogate outcomes: ‘cervical intraepithelial neoplasia grade 2 and above [CIN2⁺], CIN grade 3 and above [CIN3⁺] and adenocarcinoma in situ [AIS]’.¹ The use of such outcomes seemed reasonable for a preliminary assessment of HPV vaccine benefits, but the outcomes can be difficult to interpret. If there were clinically important differences in the severity of the cervical lesions in the two compared groups, they may not have been apparent in the composite outcomes of CIN2⁺ and CIN3⁺. The Cochrane authors did not describe any cervical cancers in the 26 trials, although cancers did occur in the trials; for example, in the ClinicalTrials.gov entry for the VIVIANE trial, one case of ‘Adenocarcinoma of the cervix’ and one case of ‘Cervix cancer metastatic’ are listed in the HPV vaccine group (see ‘Results: Serious Adverse Events’).¹⁵ Furthermore, the relationship between CIN2 and cervical cancer is not clear-cut. Most CIN2 lesions in women below age 30 regress spontaneously; an active surveillance approach has therefore been recommended for this group.¹⁶ The Cochrane review’s 26 trials mainly included women below age 30 and used frequent cervical screening (often every six months) that did not reflect real-life practice (often every three to five years⁶).

The Cochrane review incompletely assessed serious and systemic adverse events

The Cochrane authors reported that they made a ‘Particular effort’ to assess serious adverse events and performed a sensitivity analysis that gave them ‘confidence that published and registry or website-sourced data are similar for the same study’.¹ This seems unlikely. As an example, the PATRICIA trial publication only included two thirds (1400/2028) of the serious adverse events listed on ClinicalTrials.gov. The Cochrane authors included 701 vs 699 serious adverse events (1400) from the PATRICIA trial publication (see the Cochrane reviews’ ‘Figure 10, Analysis 7.6.2’) and 835 vs 829 serious adverse events from its ClinicalTrials.gov entry (see ‘Comparison 7, Analysis 6: 7.6.2’; both analyses were called ‘7.6.2’). We found 1046 vs 982 serious adverse events (2028) when we summarised the data from ClinicalTrials.gov (see ‘Results: Serious Adverse Events’).¹⁷

The Cochrane authors concluded with ‘high certainty’ that the risk of serious adverse events was similar in the HPV vaccine groups and the comparator groups. However, the authors failed to mention that several of the included trials did not report serious adverse events for the whole trial period. For example, FUTURE I,¹⁸ FUTURE II¹⁰ and FUTURE III,¹⁹ which in total included 21 441 women with up to four years follow-up, only reported serious adverse events occurring within 14 days postvaccination. Furthermore, the Cochrane authors did not explain what the serious adverse events consisted of or whether some of them were more common in the HPV vaccine groups.

The Cochrane authors found more deaths in the HPV vaccine groups than in the comparator groups. The death rate was significantly increased in women above age 25 (risk ratio [RR] 2.36, 95% confidence interval [CI] 1.10 to 5.03; no absolute numbers were provided for this subgroup analysis, but the total numbers of deaths were 51 in the HPV vaccine groups and 39 in the comparator groups). The Cochrane authors suggested that this was a

chance occurrence since there was no pattern in the causes of death or in the time between vaccine administration and date of death. However, as the Cochrane review only included randomised trials, the authors cannot rule out that the increase could be caused by the HPV vaccines. A death may be coded in a way that does not raise suspicion that the vaccine caused it; for example, a ‘traumatic head injury’ or ‘drowning’ could have been caused by a ‘syncope’, which is a recognised harm.^{11–13} As of May 2018, WHO’s pharmacovigilance database—VigiBase, managed by the Uppsala Monitoring Centre (UMC)—contained 499 deaths reported as related to HPV vaccination.²⁰

The Cochrane authors concluded that, ‘Systemic events with general mild symptoms were similarly frequent in vaccinated recipients and placebo or control vaccine recipients’. Their Analysis 7.5 showed a non-significant increase in systemic events: RR 1.02 (95% CI 0.98 to 1.07) with a total of 9137 vs 9054 events. The Cochrane authors did not include all of their trials that were eligible for systemic events in Analysis 7.5; for example, the PATRICIA trial was not included. On ClinicalTrials.gov, PATRICIA has 7129 vs 6557 systemic events listed under ‘Results: Other Adverse Events (General disorders)’, which in itself is a significantly increased risk: RR 1.09 (95% CI 1.07 to 1.11).¹⁷

The Cochrane authors ‘planned requesting data from data owners, to fill in gaps with available unpublished data’, but ‘due to constraints in time and other resources’ they were unable to do so.¹ Considering that seven years passed from the publication of the Cochrane protocol in 2011⁵ to the Cochrane review in 2018,¹ lack of time seems a poor excuse for not trying to obtain unpublished trial documents and data. More importantly, harms cannot be assessed reliably in published trial documents—especially in journal publications of industry-funded trials where even serious harms often are missing.²¹ One reason may be the space restrictions that most medical journals have. As an example, the journal publication for the PATRICIA trial is 14 pages long⁹ while its publicly available corresponding clinical study report is over 7000 pages long,²² although it is an interim report that has been shortened. Clinical study reports are usually confidential documents, but they can be requested from the European Medicines Agency (EMA) and ClinicalStudyDataRequest.com (CSDR).

Despite the mentioned examples of reporting bias, the Cochrane authors judged all trials at low risk of reporting bias (see the Cochrane review’s ‘Figure 4: ‘Risk of bias’ summary’).

The Cochrane review did not assess HPV vaccine-related safety signals

The Cochrane authors referred to many observational studies in their discussion that found no safety signals of harms associated with the HPV vaccines.¹ They cited WHO’s Global Advisory Committee on Vaccine Safety (GACVS) that expressed ‘concerns about unjustified claims of harms’. The Cochrane authors did not mention a study from 2017 by the WHO UMC that found serious harms following HPV vaccination overlapping with two syndromes: postural orthostatic tachycardia syndrome (POTS) and complex regional pain syndrome (CRPS).²³ The WHO UMC provided part of the rationale for EMA’s investigation of POTS and CRPS in 2016.²⁴ As of May 2018, the WHO UMC VigiBase contained 526 cases of POTS and 168 cases of CRPS reported related to HPV vaccination.²⁰

The Cochrane authors did not investigate whether the included trial data reported cases of POTS, CRPS or other safety signals. Instead, the authors cited EMA, which concluded that ‘No causal relation could be established’ between POTS or CRPS and the

HPV vaccines.¹ EMA's conclusion was based on the HPV vaccine manufacturers' own unverified assessments²⁴ that only included half of the eligible trials.³ Furthermore, the HPV vaccine manufacturers search strategies for POTS and CRPS were inadequate and led to cases being overlooked.²⁵ As an example, in 2014, the Danish Medicines Agency (DMA) asked the HPV vaccine co-manufacturer Sanofi-Pasteur-MSD to search for specific POTS-related symptoms in its database (including dizziness, palpitations, rapid heart rate, tremor, fatigue and fainting). The manufacturer only searched for 'postural dizziness', 'orthostatic intolerance' and 'palpitations and dizziness'. The Danish Medicines Agency discovered this because only three of 26 Danish reports of POTS showed up in Sanofi's searches.²⁵ As another example, EMA identified six possible cases of POTS and CRPS related to Gardasil 9 that Merck had not identified.²⁶

Industry trial funding and other conflicts of interest

The Cochrane authors assessed the impact of industry funding 'by meta-regression. No significant effects were observed.'¹ They stated that, 'All but one of the trials was funded by the vaccine manufacturers', which is not correct. According to ClinicalTrials.gov, this particular trial ('CVT' or 'Costa Rica trial'¹) was sponsored by GlaxoSmithKline.²⁷ Therefore, all included trials were funded by the HPV vaccine manufacturers and the meta-regression was meaningless.

The Cochrane Collaboration aims to be free from conflicts of interest related to the manufacturers of the reviewed products.²⁸ Most of the 14 Cochrane authors on the first published protocol for the Cochrane review had major conflicts of interest related to the HPV vaccine manufacturers.²⁹ The Cochrane review only has four authors; three of whom had such conflicts of interest a decade ago. The review's first author currently leads EMA's 'post-marketing surveillance of HPV vaccination effects in non-Nordic member states of the European Union', which is funded by Sanofi-Pasteur-MSD that was the co-manufacturer of Gardasil.

Cochrane's public relations of the review were uncritical

The announcement of the Cochrane review on Cochrane.org under 'News' included a 'Science Media Centre roundup of third-party expert reaction to this review'.³⁰ Six experts were cited—all from the UK, although the Cochrane Collaboration is an international organisation. Two of the experts had financial conflicts of interest with the HPV vaccine manufactures. A third expert was responsible for vaccinations in Public Health England (PHE) that promotes the HPV vaccines. The experts highlighted the 'intensive and rigorous Cochrane analysis', 'that the HPV vaccine is the most effective way for young girls to protect themselves against cervical cancer' and that 'the vaccine causes no serious side-effects'. No expert criticised the review. In our view, this is not balanced and people with conflicts of interest in relation to the manufacturers should not be quoted in relation to a Cochrane review. Richard Smith—the former editor of the British Medical Journal (BMJ)—described medical journals as an extension of the marketing arm of the drug industry.³¹ We are concerned that some observers may see Cochrane reviews in the same light when Cochrane publishes such public relation messages.

Conclusion

Part of the Cochrane Collaboration's motto is 'Trusted evidence'. We do not find the Cochrane HPV vaccine review to be 'Trusted evidence', as it was influenced by reporting bias and biased trial

designs. We believe that the Cochrane review does not meet the standards for Cochrane reviews or the needs of the citizens or healthcare providers that consult Cochrane reviews to make 'Informed decisions', which also is part of Cochrane's motto. We recommend that authors of Cochrane reviews make every effort to identify all trials and their limitations and conduct reviews accordingly.

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Contributors LJ: wrote the first draft. LJ, PCG and TJ: contributed to the conception, drafting, critical revision for important intellectual content and the final approval of the article.

Competing interests LJ and PCG have no conflicts of interest to declare. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products. In 2011–2013, TJ acted as an expert witness in a litigation case related to the antiviral oseltamivir, in two litigation cases on potential vaccine related damage and in a labour case on influenza vaccines in healthcare workers in Canada. He has acted as a consultant for Roche (1997–1999), GSK (2001–2002), Sanofi-Synthelabo (2003), and IMS Health (2013) and in 2014 was retained as a scientific adviser to a legal team acting on oseltamivir. TJ was a member of three advisory boards for Boehringer Ingelheim. TJ was holder of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine. Between 1994 and 2013, TJ was the coordinator of the Cochrane Vaccines Field. TJ was a co-signatory of the Nordic Cochrane Centre Complaint to the European Medicines Agency (EMA) over maladministration at the EMA in relation to the investigation of alleged harms of HPV vaccines and consequent complaints to the European Ombudsman. TJ is co-holder of a John and Laura Arnold Foundation grant for development of a RIAT support centre (2017–2020) and Jean Monnet Network Grant, 2017–2020 for The Jean Monnet Health Law and Policy Network. TJ is an unpaid collaborator to the project Beyond Transparency in Pharmaceutical Research and Regulation led by Dalhousie University and funded by the Canadian Institutes of Health Research (2018–2022).

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Cochrane's Editor in Chief responds to a *BMJ Evidence-Based Medicine* article criticizing the Cochrane Review of HPV vaccines

On 27th July 2018, an article was published in the journal *BMJ Evidence-Based Medicine* relating to the recently published Cochrane Review on prophylactic human papillomavirus (HPV) vaccines. The article is based on analyses undertaken at the Nordic Cochrane Centre, and two of the authors are experienced Cochrane researchers: Professors Peter Gøtzsche and Tom Jefferson. It made several criticisms of the Cochrane Review, most notable of which was that the Cochrane Review was incomplete due to missing "nearly half of the eligible trials".

Cochrane takes all criticisms and feedback seriously, seeing this as one mechanism among many to improve the quality of Cochrane Reviews. The organization has 10 long-standing principles that we hold dear, and they include a commitment to quality and the minimization of bias, transparency, and a recognition of the need for our work to be relevant to the needs of evidence users and decision makers. Cochrane aims to create the best current evidence to guide health decisions.

We initiated an investigation in response to the criticisms, working with the review authors and editors and with independent researchers who had not been involved in the original publication. The key findings of our investigation are that:

- The Cochrane Review did not miss "nearly half of the eligible trials". A small number of studies were missed due to the primary focus on peer-reviewed reports in scientific journals, but addition of these data makes little or no difference to the results of the review for the main outcomes;
- The trials comparators were unambiguously, transparently, and accurately described;
- The selection of outcomes for benefits was appropriate and was consistent with World Health Organization guidance;
- The review included published and unpublished data on serious harms, and the findings on mortality were reported transparently and responsibly;
- The review was compliant with Cochrane's current conflict of interest policy;
- Cochrane's media coverage was cautious and balanced, but we recognize that there could be improvements in relation to transparency where external experts are quoted;
- The *BMJ Evidence-Based Medicine* article substantially overstated its criticisms.

David Tovey, Editor in Chief, Cochrane

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Contents

Executive summary	3
Background to the Cochrane Review	4
The Cochrane Review did not miss "nearly half of the eligible trials"	4
The trials comparators were transparently and accurately described	6
The selection of outcomes for benefits was appropriate	6
The review included published and unpublished data on serious harms, and reported the findings on mortality transparently and responsibly	7
The review was compliant with Cochrane's current conflict of interest policy	7
Cochrane's media coverage was cautious and balanced, but we recognize that there could be improvements in relation to transparency where external experts are quoted	8
Conclusion: the <i>BMJ Evidence-Based Medicine</i> article overstated its criticism	9
Acknowledgements	10
References	10
Appendix A: Effect of incorporating data extracted from five missing studies on the findings of the Cochrane Review	12
Appendix B: Characteristics of the additional studies identified in the HPV vaccine study index that met the inclusion criteria of the Cochrane Review	15
Appendix C: Five studies awaiting classification (not recruiting, but no results available) potentially relevant for the current Cochrane Review	24
Appendix D: Eight ongoing studies (actively recruiting, no results available) potentially relevant for the current Cochrane Review	27

Executive summary

On 27th July 2018, an article was published in the journal *BMJ Evidence-Based Medicine* relating to the recently published Cochrane Review on prophylactic human papillomavirus (HPV) vaccines.^{1,2} The article, by Jørgensen et al, is based on analyses undertaken at the Nordic Cochrane Centre, and two of the authors are experienced Cochrane researchers: Professors Peter Gøtzsche and Tom Jefferson. It made several criticisms of the Cochrane Review, most notable of which was that the review was incomplete due to "missing nearly half of the eligible trials".

Cochrane takes all criticisms and feedback seriously, seeing this as one mechanism among many to improve the quality of Cochrane Reviews. The organization has ten long-standing principles that we hold dear, and they include a commitment to quality and the minimization of bias, transparency, and a recognition of the need for our work to be relevant to the needs of evidence users and decision makers. Cochrane aims to create the best current evidence to guide health decisions.

When the Cochrane Review on HPV vaccines was published in May 2018 we were confident that it had been conducted and reported in a manner consistent with the published protocol and with Cochrane's expectations or standards. We believed that the conclusions were an accurate reflection of the results and the analyses. Therefore, we were surprised to see the issues raised by Jørgensen et al, and we initiated an investigation immediately, working with the Cochrane Review authors and editors and with systematic reviewers who had not been involved in the review. Here we present the findings of our investigation, our responses to the most important issues raised by Jørgensen et al, and our plans for the review, including a proposal to incorporate missing data. The *BMJ Evidence-Based Medicine* article reinforces work that forms a key element of Cochrane's Content Strategy in relation to the selection of data sources for reviews.

Following the publication of the criticisms, we contacted two of the authors (Gøtzsche, Jørgensen) requesting details of the list of the 20 "potentially eligible" missing studies they had identified, based on the inclusion criteria of the Cochrane Review. Given the central focus on this issue, we were surprised that this list was not included as an appendix to the article in *BMJ Evidence-Based Medicine*. When we receive this list, we will be able to cross-reference it with the findings of our own investigation.

The key findings of our investigation of the criticisms by Jørgensen and colleagues are that:

- The Cochrane Review did not miss "nearly half of the eligible trials". A small number of studies were missed due to the primary focus on peer-reviewed reports in scientific journals, but addition of these data makes little or no difference to the findings of the review for the main outcomes (see Appendix A);
- The trials comparators were unambiguously, transparently, and accurately described;
- The selection of outcomes for benefits was appropriate and was consistent with World Health Organization guidance;
- The review included published and unpublished data on serious harms, and the findings on mortality were reported transparently and responsibly;
- The review was compliant with Cochrane's current conflict of interest policy;
- Cochrane's media coverage was cautious and balanced, but we recognize that there could be improvements in relation to transparency where external experts are quoted;
- The *BMJ Evidence-Based Medicine* article substantially overstated its criticisms.

We regret that the authors, who are all members and officeholders within Cochrane, did not share their analysis or the conclusions and criticisms contained in the *BMJ Evidence-Based Medicine* article before publication. Having completed our investigation, we conclude that Jørgensen et al made allegations that are not warranted and provided an inaccurate and sensationalized report of their analysis. We believe that there are questions to be asked about the rigour of the peer review and editorial review by *BMJ Evidence-Based Medicine*. We call on BMJ to consider our report and to investigate whether the journal's quality assurance processes were appropriately fulfilled and whether the conclusions of the article are justified and proportionate. This is particularly important given the highly sensitive subject matter and the public health priority of this subject.

Background to the Cochrane Review

Cervical cancer is the fourth most common cancer in women. Half a million women are diagnosed with cervical cancer each year, and half of these women will die from their disease. Eighty-five percent of those with cervical cancer are in low- and middle-income countries, where screening and therapeutic services are most likely to be challenged.³ The large majority of these cancers are causally associated with HPV infection. This is not, therefore, an inconsequential academic debate but a serious global public health issue. Like the authors of the *BMJ Evidence-Based Medicine* article, the authors and editors of the Cochrane Review want to paint as accurate a picture of the effects of the HPV vaccines as possible, to inform individual and community-based decisions.

The Cochrane Review authors and editorial team adhered closely to the methods and guidance described in the [Cochrane Handbook for Systematic Reviews of Interventions](#) and the [Methodological Expectations of Cochrane Intervention Reviews \(MECIR\)](#) standards for conduct and reporting of such reviews. The methods were comprehensively described in the review protocol, which was peer-reviewed and was published in December 2013. The protocol described the 'PICO' (Population, Intervention, Comparison, Outcomes) characteristics for the review and the means of identifying studies and data.

In the published Cochrane Review, the authors relied predominantly on the published and peer-reviewed reports in scientific journals for most outcomes of interest. Given the importance of an assessment of serious adverse events and mortality, the author team accepted the suggestion of Cochrane editors to extend the search for these outcomes to include unpublished data. This post-protocol change is explained in the appropriate section of the review. In these matters, the author team's decisions were consistent with most reviews that were initiated during the period of the review's gestation, and they were consistent with Cochrane's expectations. The screening of unpublished sources for serious adverse events was a collaborative effort between the author team and the Cochrane Editorial and Methods Department.

The Cochrane Review did not miss "nearly half of the eligible trials"

The HPV vaccine study index prepared by Jørgensen and colleagues is complex, and we acknowledge the investment that has gone into its preparation.⁴ The index contained 298 references, 100 of them duplicate records, and reported 137 unique randomized trials (see Figure 1).

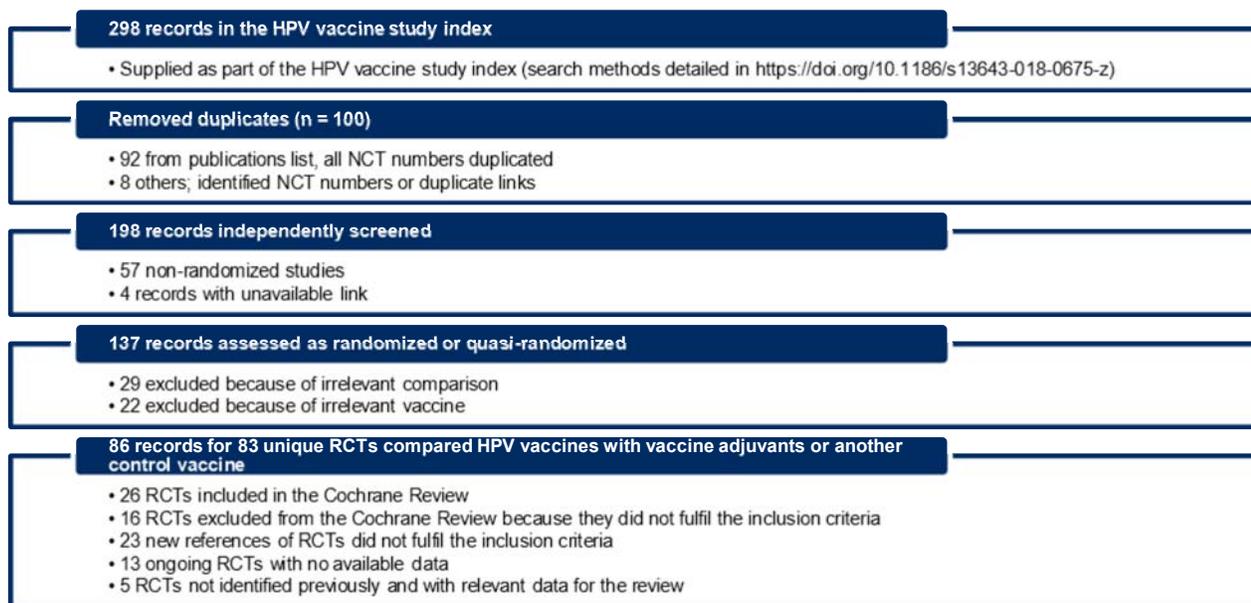


Figure 1: Flowchart investigating the relationship between the HPV vaccine studies⁴ index and the Cochrane Review of HPV vaccines²

As part of our investigation two systematic reviewers independently assessed 137 potentially relevant randomized trials from the index. Of these, 83 trials compared HPV vaccines with vaccine adjuvants or another control vaccine (see Figure 1). The Cochrane Review included 26 trials (73,428 participants) that matched the predetermined study criteria. As a result of our investigations we believe that five eligible completed studies with available data representing 5267 women may have been missed from the Cochrane Review, as a consequence of the search being based on bibliographic databases rather than trials registers. Details of these studies are available in Appendix B. This finding contrasts with the calculation of 20 studies (48,276 women) missed, as suggested by Jørgensen et al in their *BMJ Evidence-Based Medicine* article. Once we have the data from the authors we will seek to understand the difference between these assessments. This might relate to differential understanding of the selection criteria used by the Cochrane authors or to some studies still actively recruiting participants.

The Cochrane Review authors assessed and excluded a phase IV cluster randomized study comparing HPV and hepatitis B vaccines in boys and girls.⁵ We have cross-checked the data in women, now published on the GSK Study Register, which includes data on serious adverse events and pregnancy outcomes. Adding these data to the analyses seems to make little or no difference to the results of the Cochrane Review, but the review update process will enable a more formal appraisal of the evidence using the GRADE process. In addition, 13 studies from the HPV index are ongoing and will be assessed for relevance once the results are available (See Appendices C and D).

We do not underestimate the importance of these missing data, but the figure of missed studies amounts to substantially less than "nearly half the eligible trials", and we submit that in making statements such as this, accuracy matters.

We have now had the opportunity to examine what difference the missing data based on the review inclusion criteria make to future iterations of the Cochrane Review (see Appendix A). For transparency, we also analysed the potential impact of adding data on the 9-valent HPV vaccine.

In summary, adding the studies that were missed by limiting the search to published study reports had no impact on the direction of effect for all outcomes reported. A single study comparing the 9-valent vaccine with placebo (924 participants) showed an increase in local adverse events but no impact on systemic or serious adverse events and deaths (see Appendix A). This trial enrolled only women recruited previously in another trial evaluating the quadrivalent vaccine.

We have made the current version of the review freely available, and we will be updating the review urgently to incorporate all the relevant, publicly available data. This was anticipated by the Cochrane Review authors in the 'Implications for research' section of the Cochrane Review and work has already begun.

The trials comparators were transparently and accurately described

The *BMJ Evidence-Based Medicine* article also raised some concerns about the comparators used in the various trials, which were aluminium based, as described clearly in both the Abstract and Methods sections of the Cochrane Review, and also in the detailed 'Characteristics of included studies' section of the review. For example, under 'Criteria for considering studies for this review' the 'Comparison' is described as: "Administration of placebo containing no active product or only the adjuvant of the HPV vaccine, without L1 VLP, or another non-HPV vaccine".

We recognize that the use of aluminium salts as an adjuvant in vaccines is controversial, and that some groups argue that the controls in the studies should have received water or saline to prevent masking of harms caused by the administration of aluminium salts to both groups in the studies. The Cochrane Review is not an analysis of the possible benefits and harms of aluminium-based adjuvants. Suffice to say that almost all the studies included the use of aluminium salts in the comparator. We consider that this was reported appropriately within the review, but if there are ways of further clarifying this we will be pleased to consider these.

We note that one of the authors of the *BMJ Evidence-Based Medicine* article (Jefferson) published a systematic review in 2004 that found "no evidence" of serious or long-term harms and concluded that further research was not warranted.⁶ Despite this, we note that a new Cochrane Review re-examining the safety of aluminium within all vaccines is underway.⁷

The selection of outcomes for benefits was appropriate

The use of surrogate outcomes in the HPV vaccine trials is, as Jørgensen et al note, "in line with WHO recommendations". This was explained by the authors in the Cochrane Review. Transition from CIN 2 and CIN 3 to cancer is not inevitable if untreated, but it is a clear risk, and for this reason both of these interim states are subject to treatment, which carries its own morbidity. The risk of progression to cancer increases as the lesions progress. Cervical cancer is a malignancy that can be prevented effectively through detection and treatment of the precursor states. Plainly there is no ethical means by which researchers could leave untreated the presence of the precursor states, so that the near complete absence of cervical cancer in any arm of the trials is inevitable. In our judgement it is impossible to see how it could be feasible or ethical to undertake a trial that was large enough and of sufficient duration for cancer outcomes to be reliably demonstrated and where women were denied interventions that are known to prevent cancer.

The review included published and unpublished data on serious harms, and reported the findings on mortality transparently and responsibly

In making their assessment of serious harms, the Cochrane Review authors identified and included unpublished data, and compared these with data from published trial reports. Jørgensen et al claim that the review authors made an error in their reporting of serious adverse events in relation to the PATRICIA study. This is not the case. We have checked the data presented in the Cochrane Review against the reports on ClinicalTrials.gov and the GSK Study Register, and the figures accurately match the number of women experiencing one or more serious adverse events.

In addition, as Jørgensen et al note, the review authors identified and reported the excess of deaths in the older vaccinated women, in both relative and absolute terms, within the Abstract of the review as well as in the main body of the text. We judged it important to present the data transparently, but also to provide further context to ensure responsible reporting. The assessment by World Health Organization experts and the data on the causes of death provide no clear causal mechanism or link with the vaccine. We judged that readers would find this information useful and that its inclusion was appropriate.

Otherwise the reporting of other harms was, as described in the protocol, limited to the published peer-reviewed reports from randomized controlled trials. This is not unusual for systematic reviews from Cochrane or elsewhere.

In relation to harms more generally, we acknowledge that there is a case for including other forms of evidence. The 'Discussion' section of the Cochrane Review and the accompanying Editorial both noted the importance of national surveillance programmes to identify and report harms.^{2,8} This is particularly true when it comes to harms such as autonomic dysfunction syndromes and other syndromes that are not reported (positively or negatively) in most of the journal-published reports, but about which concerns have been raised subsequently from observational reports. This underlines the importance of systematic reviews being used in conjunction with the evidence from national surveillance programmes.

Finally, we believe that this Cochrane Review has raised broader questions for Cochrane in relation to reporting harms. We propose to initiate work aimed at providing updated guidance for author teams on identifying and reporting harms in the current and future data and research environment, as part of our ongoing implementation of Cochrane's content strategy.

The review was compliant with Cochrane's current conflict of interest policy

Cochrane has had rules in place since 2004 aimed at preventing its reviews from either the fact or perception of inappropriate involvement or influence by commercial organizations. The rules were [last updated in 2014](#). A key feature of Cochrane's approach is that declaration of relevant conflicting interests is essential but may not be sufficient. In specific circumstances individuals are barred from involvement as part of an author team, and the lead author and a majority of any

Cochrane Review author team must not have a relevant conflict. The job of overseeing the implementation of the policy falls to an appointed Funding Arbiter (currently a job share), reporting directly to the Governing Board. The Funding Arbiter, working with a panel of experts, some of who are external to the organization, arbitrates in disputed or borderline cases.

In relation to the HPV vaccines review, Cochrane received comments following the publication of the protocol stating that the intended author team was not compliant with Cochrane's financial conflict of interest policy. The first author had invited a team of HPV vaccination trialists, with the purpose of helping to obtain unpublished data. All these experts had declared their conflicts, but their inclusion made the author team non-compliant with Cochrane's policy. We therefore made changes that ensured the work of the review was undertaken by a team whose members were fully compliant and actively involved in the conduct of the review.

Jørgensen et al also stated that the lead author of the review leads the European Medicine Agency's post-marketing surveillance and linked this to funding from a manufacturer. In fact, Professor Arbyn took the initiative to introduce a surveillance study in his country after having been informed that the European Medicine Agency had approved the Gardasil vaccine, remarking that the post-marketing surveillance conducted in Northern Europe was relevant but should include also non-Nordic countries. Professor Arbyn is not funded by the European Medicine Agency nor by any vaccine manufacturer.

In relation to the sponsorship of the studies, Jørgensen et al stated that the Costa Rica trial was not, as stated in the Cochrane Review, publicly funded but was funded by GlaxoSmithKline. This is not the case, as noted in the conflict of interest declaration in the published report of the study in *JAMA*.⁹ This states that the trial was "funded by the NCI (grant N01-CP-11005), with funding support from the National Institutes of Health Office for Research on Women's Health and conducted with support from the Ministry of Health of Costa Rica. Vaccine was provided for our trial by GSK Biologicals, under a Clinical Trials Agreement with the NCI."

Cochrane's media coverage was cautious and balanced, but we recognize that there could be improvements in relation to transparency where external experts are quoted

Cochrane makes strenuous efforts in its media coverage to present conclusions and implications for practice and research from its reviews in a balanced and measured way. The reference to the Science Media Centre round-up of scientific reaction in the *BMJ Evidence-Based Medicine* article reflects simply a response from representatives of public bodies, sought from an independent organization focussed on the benefits of accurate, evidence-based science coverage in the news media. None of the individuals quoted were sought or contacted by Cochrane. Our press and communications teams acknowledge that the source of any future 'scientific reaction' to published reviews or press coverage could be made more explicit on our organizational websites and other communications, essentially noting that these opinions represent personal perspectives from a range of contributors and do not reflect the views or policies of Cochrane.

Conclusion: the *BMJ Evidence-Based Medicine* article overstated its criticism

We take very seriously the implications of Cochrane's strapline: 'Trusted evidence. Informed decisions. Better health.'. Our investigation has sought to explore whether in publishing the review of HPV vaccines we had failed to meet the standard implied in that statement of intent. Our conclusion, based on a thorough investigation, is that the review provides a fair basis for evidence-informed decision making.

Some of the criticisms will inform the next version of this Cochrane Review and the planned review of comparative studies of HPV vaccines.

In our judgement, the criticisms were overstated. For example, the potentially missing studies do not seem to represent anywhere close to "half of the eligible studies". We have analysed the publicly available data from the missing studies, and we believe that including them would make no material difference to the Cochrane Review's results and conclusions (see Appendix A).

We plan to ensure that all relevant studies and associated data are incorporated into an updated version of the review, and we will complete this work urgently. We will also cross-reference the results of our investigation findings against data from the Jørgensen et al to try to understand the discrepancy between the two analyses, and we will seek to identify and report all ongoing studies.

In addition, we believe that the selection of outcomes was appropriate to guide decision making. We recognize public concerns about the aluminium-based adjuvants but judge that this is better addressed by a separate Cochrane Review. We are not aware of compelling evidence of serious harm caused by the adjuvants.

In summary, we believe that the Cochrane Review represents a robust and accurate summary of the evidence.

Scientific debate is to be welcomed, and differences of opinion between different Cochrane 'voices' is not unexpected. However, public confidence may be undermined, unnecessary anxiety caused, and public health put at risk, if that debate is not undertaken in an appropriate way. This is especially true when such debates take place in public. There is already a formidable and growing anti-vaccination lobby. If the result of this controversy is reduced uptake of the vaccine among young women, this has the potential to lead to women suffering and dying unnecessarily from cervical cancer.

The article in *BMJ Evidence-Based Medicine* highlights issues that go beyond the HPV review and which have been the subject of many discussions. In recent years, evidence synthesis researchers in Cochrane and elsewhere have recognized that reliance on the published reports in scientific journals may introduce bias due to incomplete and selective reporting. In addition, the generally poor reporting of harms in reports from randomized controlled trials has led to the reporting of harms in many systematic reviews being sub-optimal. This has led to an increased interest in searching for and identifying studies, reports and data from different and more diverse sources, including clinical study reports and individual participant data from trials, data from trials registries, and non-randomized studies. This has consequences that reach well beyond Cochrane, as shown by a report by Page et al in 2016 comparing the quality of reporting in Cochrane and non-Cochrane systematic reviews.¹⁰ This study found that 62% of Cochrane Reviews searched trials registers, compared with 20% for non-Cochrane reviews. These additional or expanded searches may add value in selected circumstances, but they all also add substantially to the resources needed to

complete the review and are a challenge to Cochrane's traditional model of reliance on unfunded 'volunteer' authors, who have been the engine of the organization for 25 years.

Therefore, it is true to say that both inside and outside Cochrane, the conduct and reporting of systematic reviews is changing. This is fully reflected in Cochrane's recently approved content strategy, which sets targets and objectives around exploring when and how these additional sources of data should be utilized. This work builds on exploratory work funded by Cochrane and is a key part of our strategy for the future Cochrane Review.

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Appendix A: Effect of incorporating data extracted from five missing studies on the findings of the Cochrane Review

RR = risk ratio; CI = confidence interval; RCT = randomized controlled trial

Any HPV vaccine

Main outcome	Current Cochrane Review	New data incorporated
Spontaneous abortion/miscarriage (analysis 8.2)	RR 0.88 (95% CI 0.68 to 1.14) $I^2 = 78\%$	RR 0.89 (95% CI 0.69 to 1.14) $I^2 = 76\%$

Bivalent vaccine

Main outcome	Current Cochrane Review	New data incorporated
Pain at injection site (analysis 7.2.2)	RR 1.49 (95% CI 1.26 to 1.75) $I^2 = 98\%$	RR 1.46 (95% CI 1.26 to 1.68) $I^2 = 98\%$
Redness at injection site (analysis 7.4.2)	RR 1.80 (95% CI 1.53 to 2.11) $I^2 = 76\%$	RR 1.71 (95% CI 1.47 to 2.07) $I^2 = 76\%$
Swelling at injection site (analysis 7.3.1)	RR 1.62 (95% CI 1.15 to 2.29) $I^2 = 81\%$	RR 1.51 (95% CI 1.10 to 2.13) $I^2 = 95\%$
Serious adverse events (analysis 7.6.2)	RR 1.01 (95% CI 0.96 to 1.07) $I^2 = 0\%$	RR 1.01 (95% CI 0.96 to 1.07) $I^2 = 0\%$
Overall local/injection site adverse events (analysis 7.1.1)	RR 1.29 (95% CI 1.26 to 1.33) $I^2 = 98\%$	RR 1.29 (95% CI 1.25 to 1.33) $I^2 = 95\%$
Overall systemic event and general symptoms (analysis 7.5.1)	RR 1.07 (95% CI 0.97 to 1.19) $I^2 = 91\%$	RR 1.06 (95% CI 0.97 to 1.15) $I^2 = 83\%$
Deaths (analysis 7.7.2)	RR 1.21 (95% CI 0.66 to 2.22)	RR 1.21 (95% CI 0.66 to 2.22)

Main outcome	Current Cochrane Review	New data incorporated
	$I^2 = 15\%$	$I^2 = 15\%$

Quadrivalent vaccine

Main outcome	Current Cochrane Review	New data incorporated
Pain at injection site (analysis 7.2.3)	RR 1.13 (95% CI 1.07 to 1.19) $I^2 = 33\%$	RR 1.20 (95% CI 1.10 to 1.32) $I^2 = 74\%$
Redness at injection site (analysis 7.4.1)	RR 1.46 (95% CI 1.32 to 1.63) 1 RCT (659/2673; 450/2672)	RR 1.44 (95% CI 1.31 to 1.59) $I^2 = 0\%$
Swelling at injection site (analysis 7.3.2)	RR 2.79 (95% CI 0.85 to 9.15) $I^2 = 82\%$	RR 2.08 (95% CI 1.54 to 2.83) $I^2 = 64\%$
Serious adverse events (analysis 7.6.3)	RR 0.81 (95% CI 0.65 to 1.02) $I^2 = 10\%$	RR 0.83 (95% CI 0.68 to 1.00) $I^2 = 0\%$
Deaths (analysis 7.7.3)	RR 1.54 (95% CI 0.73 to 3.23) $I^2 = 0\%$	RR 1.65 (95% CI 0.80 to 3.38) $I^2 = 0\%$
CIN2+ associated with HPV 6/11/16/18, at least one dose (analysis 3.2)	RR 0.57 (95% CI 0.38 to 0.86) $I^2 = 54\%$	RR 0.54 (95% CI 0.30 to 0.95) $I^2 = 61\%$
Persistent HPV16/18 infection (12M), at least one dose (analysis 6.4)	RR 0.46 (95% CI 0.40 to 0.54) $I^2 = 42\%$	RR 0.41 (95% CI 0.29 to 0.57) $I^2 = 81\%$
Persistent HPV16/18 infection (6M), at least one dose (analysis 6.2)	RR 0.48 (95% CI 0.41 to 0.57) $I^2 = 69\%$	RR 0.48 (95% CI 0.41 to 0.56) $I^2 = 61\%$
Persistent HPV6/11/16/18 infection (6M), at least one dose (analysis 6.3)	RR 0.52 (95% CI 0.42 to 0.65) 1 RCT (110/1856; 211/1857)	RR 0.40 (95% CI 0.19 to 0.81) $I^2 = 67\%$

Main outcome	Current Cochrane Review	New data incorporated
Overall local/injection site adverse events (analysis 7.1.2)	RR 1.14 (95% CI 1.12 to 1.16) $I^2 = 54\%$	RR 1.14 (95% CI 1.12 to 1.16) $I^2 = 68\%$
Overall systemic event and general symptoms (analysis 7.5.2)	RR 1.01 (95% CI 0.98 to 1.04) $I^2 = 0\%$	RR 1.01 (95% CI 0.98 to 1.04) $I^2 = 0\%$

9-valent vaccine

Main outcome	Current Cochrane Review	New data incorporated
Pain at injection site (analysis 7.2.2)	Not included	RR 2.37 (95% CI 2.05 to 2.75) 1 RCT (549/608; 116/305)
Redness at injection site (analysis 7.4.2)		RR 4.96 (95% CI 3.39 to 7.24) 1 RCT (257/608; 26/305)
Swelling at injection site (analysis 7.3.1)		RR 8.31 (95% CI 5.27 to 13.10) 1 RCT (298/608; 18/305)
Serious adverse events (analysis 7.6.2)		RR 0.50 (95% CI 0.10 to 2.47) 1 RCT (3/608; 3/305)
Deaths (analysis 7.7.2)		Not estimable 1 RCT (0/608; 0/305)
Overall systemic event and general symptoms (analysis 7.5.3)		RR 1.07 (95% CI 0.95 to 1.21) 1 RCT (363/608; 170/305)
Overall local/injection site adverse events (analysis 7.1.3)		RR 2.07 (95% CI 1.82 to 2.36) 1 RCT (554/608; 134/305)

Appendix B: Characteristics of the additional studies identified in the HPV vaccine study index that met the inclusion criteria of the Cochrane Review

NCT01627561

Methods	Phase III, randomized, controlled, single-blind, multicentre study
Participants	<p>Participants: 148 healthy girls (74 in each group) enrolled in 7 study centres from 3 countries (Colombia, Mexico, Panama).</p> <p>Age range: 4 to 6 years.</p> <p>Inclusion criteria: healthy girls who had previously received 4 doses of a DTP (diphtheria, tetanus, poliomyelitis)-containing vaccine (3 doses in 1st year of life and 4th dose in 2nd year of life) and only 1 dose of the measles-mumps-rubella (MMR) vaccine, in their 2nd year of life.</p> <p>Exclusion criteria: previous vaccination against HPV; any other confirmed or suspected immunosuppressive condition; other illness.</p>
Interventions	<p>Vaccine: AS04-HPV-16/18 vaccine - 2-dose schedule at 0 and 6 months.</p> <p>Comparator: 1 dose of MMR (Priorix, GSK) vaccine at 0 months and 1 dose of the diphtheria-tetanus-acellular-pertussis (DTPa; Infanrix, GSK) vaccine at 6 months.</p>
Outcomes	Safety and immunogenicity outcomes
Notes	<p>Main report: Lin 2018</p> <p>Last report average follow-up time: serious adverse events to 6 months after second vaccination. Immunogenicity to 12 months after baseline in last report (follow up at 18, 24, and 36 months planned).</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment allocation at the investigator site was performed using a central randomization system on Internet.

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Treatment allocation at the investigator site was performed using a central randomization system on Internet.
Blinding of participants and personnel (performance bias)	High risk	The study was single-blind up to 6 months after the completion of the vaccination course
Blinding of outcome assessment (detection bias)	Unclear risk	Not described in the paper.
Incomplete outcome data (attrition bias)	Low risk	Outcomes assessed in the total vaccinated cohort. None of the girls in the HPV group were withdrawn up to the M12 visit. Three girls from the control group were withdrawn from the study. Reasons for exclusions were presented.
Selective reporting (reporting bias)	Low risk	All outcomes (safety and immunogenicity) are presented, in line with trial registration and results in registry.

NCT00834106

Methods	Phase III, randomized, placebo-controlled, double-blind study
Participants	<p>Participants: 3006 healthy females (1503 in each group) were enrolled at 6 trial centres in China.</p> <p>Age range: 20 to 45 years.</p> <p>Inclusion criteria: healthy women who have used effective contraception for 2 weeks prior to starting in the study and do not have a temperature within 24 hours before the first injection.</p> <p>Exclusion criteria: prior history of genital warts; more than 4 lifetime sexual partners; have undergone hysterectomy; have active cervical disease or history of cervical disease.</p>
Interventions	<p>Vaccine: quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine at 0, 2, and 6 months.</p> <p>Control: saline injection containing aluminium diluent at 0, 2, and 6 months.</p>

Outcomes	Safety outcomes (adverse events and pregnancy outcomes) and efficacy outcomes (HPV-related persistent infection and vaccine type-specific genital diseases).
Notes	Main report: Merck Sharp & Dohme 2017 confidential report. Last report average follow-up time: 92% of participants were followed to 30 months, 86.6% to 90 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Stated as double-blind, but details not reported.
Blinding of outcome assessment (detection bias)	Unclear risk	Stated as double-blind, but details not reported.
Incomplete outcome data (attrition bias)	Low risk	Low attrition: 92% of participants were followed to 30 months, 86.6% to 90 months.
Selective reporting (reporting bias)	Low risk	All outcomes (safety and efficacy) are reported, in line with trial registration.

NCT00411749

Methods	Phase II randomized, double-blind, controlled trial
Participants	Participants: 107 pre-adolescent females (82 in the vaccine arm and 25 in the placebo arm) enrolled in 8 sites in Japan. Age range: 9 to 17 years. Inclusion criteria: virginal female subject aged 9 to 17 years. Exclusion criteria: male subject.
Interventions	Vaccine: HPV6/11/16/18 vaccine (Gardasil) recombinant vaccine (V501), 0.5 mL injection in 3-dose regimen (at day 1, month 2, and month 6). Placebo: unspecified placebo vaccination 0.5 mL injection in 3-dose regimen (at day 1, month 2, and month 6).

Outcomes	Immunogenicity, safety, and tolerability outcomes.
Notes	<p>Immunogenicity evaluated at month 7 (1 month after last dose) and month 30 (24 months after last dose). Adverse event data were collected from the entire period of the study (to month 7). Other non-serious adverse events data were collected from day 1 to day 15 following vaccination.</p> <p>There is a plan to share individual participant data:</p> <p>http://www.merck.com/clinical-trials/pdf/Merck%20Procedure%20on%20Clinical%20Trial%20Data%20Access%20Final_Updated%20July_9_2014.pdf</p> <p>http://engagezone.msd.com/ds_documentation.php</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in the NCT record.
Allocation concealment (selection bias)	Unclear risk	Not described in the NCT record.
Blinding of participants and personnel (performance bias)	Low risk	The participants and investigator were blinded to the allocated trial arm.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described in the NCT record
Incomplete outcome data (attrition bias)	Low risk	<p>The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at day 1 for the relevant HPV type, and a month 7 serum sample collected within an acceptable time range.</p> <p>Vaccine: completed at 24 months after vaccination series (month 30). Subjects were followed until month 30.</p> <p>Placebo: Completed at 1 month after vaccination series (month 7). Subjects were followed until month 7.</p>
Selective reporting (reporting bias)	Low risk	All outcomes (immunogenicity, safety and tolerability) were presented.

NCT01489527

Methods	Phase II randomized, double-blind, controlled trial
Participants	<p>Participants: 406 females (205 in the vaccine arm and 201 in the placebo arm) enrolled in the Western Cape, South Africa.</p> <p>Age range: 16 to 24 years.</p> <p>Inclusion criteria: HIV-negative women aged 16 to 24 years of age who reported: having vaginal intercourse; had never had Pap testing or had only normal results; had no autoimmune disease requiring steroid use; never had a splenectomy; not currently enrolled in an HIV prevention trial; no IV drug or crystal methamphetamine use in the past 6 months.</p> <p>Exclusion criteria: women who have a history of severe allergic reaction, have a known allergy to any vaccine component (e.g., aluminium, yeast, or benzonase), are currently immuno-compromised, have received a marketed HPV vaccine, or are pregnant and lactating.</p>
Interventions	<p>Vaccine: HPV6/11/16/18 vaccine (Gardasil) in 3 dosing regimen (at day 1, month 2, and month 6)</p> <p>Placebo: saline placebo vaccination in 3 dosing regimen (at day 1, month 2, and month 6)</p>
Outcomes	Efficacy (prevention of HIV infection and prevalence of sexually transmitted infections, including HPV genotypes), compliance (through the 3-dose vaccination series), and safety outcomes.
Notes	<p>Four of the 406 participants randomized had a false HIV-negative test result, reducing the participants to 202 in the Gardasil arm and 200 in the placebo arm.</p> <p>Main reports: Giuliano 2015 and Sudenga 2017.</p> <p>Findings may not be generalizable to all South African women.</p> <p>The EVRI trial had a short duration with limited follow-up time (up to 7 months), so clinical efficacy in reducing HIV acquisition cannot be assessed.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in the papers.

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not described in the papers.
Blinding of participants and personnel (performance bias)	Low risk	The participants, care providers, and investigator were blinded to the allocated trial arm.
Blinding of outcome assessment (detection bias)	Low risk	All staff and study investigators were blinded to participants' vaccine status except the pharmacist dispensing the vaccine.
Incomplete outcome data (attrition bias)	Low risk	Among randomized participants, 91% completed the 3-dose vaccination series, with pregnancy being the predominant reason for trial discontinuation.
Selective reporting (reporting bias)	Low risk	All outcomes (efficacy, compliance and safety) were presented.

NCT01356823

Methods	Phase II randomized, double-blind, controlled trial
Participants	<p>Participants: 1600 females (400 in the 30 µg vaccine arm, 400 in the 60 µg vaccine arm, 400 in the 90 µg vaccine arm, and 400 in the control arm) enrolled in Dongtai County, Jiangsu Province, China.</p> <p>Age range: 18 to 25 years.</p> <p>Inclusion criteria: Healthy female 18 to 25 years of age, not pregnant and having no plan for pregnancy.</p> <p>Exclusion criteria: Pregnant or breastfeeding or having plan for pregnancy during the whole study (months 0 to 7); previous vaccination against HPV; severe allergic history or other immunodeficiency; using chemotherapy or other immunosuppressive agents.</p>
Interventions	<p>Vaccine: 30 µg of HPV16/18 bivalent vaccine at 0, 1, 6 months for 3 doses.</p> <p>Vaccine: 60 µg of HPV16/18 bivalent vaccine at 0, 1, 6 months for 3 doses.</p> <p>Vaccine: 90 µg of HPV16/18 bivalent vaccine at 0, 1, 6 months for 3 doses.</p>

	Control: 10 µg of hepatitis B vaccine at 0, 1, 6 months for 3 doses.
Outcomes	Immunogenicity and safety outcomes.
Notes	Main report: Wu 2015. Last report average follow-up time: 7 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization schedule was computer generated.
Allocation concealment (selection bias)	Low risk	The individuals involved in the randomization and masking did not participate in any other part of the trial.
Blinding of participants and personnel (performance bias)	Low risk	All the participants and investigators were masked to the treatment allocation.
Blinding of outcome assessment (detection bias)	Low risk	All the participants and investigators were masked to the treatment allocation.
Incomplete outcome data (attrition bias)	Low risk	91.4% of the enrolled participants received all the 3 doses per protocol; the rates of drop-out were similar among the 4 groups. None of the recorded reasons for drop-out was associated with adverse events.
Selective reporting (reporting bias)	Low risk	All outcomes (safety and immunogenicity) are presented, in line with trial registry.

Additional 9-valent study

NCT01047345

Methods	Phase III randomized, double-blind, controlled trial
Participants	Participants: 924 women (618 in the vaccine arm and 306 in the placebo arm) enrolled in 32 study sites in 8 countries. Age range: 12 to 26 years.

	<p>Inclusion criteria: women who had previously received a 3-dose regimen of the quadrivalent vaccine; generally healthy.</p> <p>Exclusion criteria: history of abnormal Pap test results; pregnancy; known allergy to any vaccine component; thrombocytopenia; immunosuppression/previous immunosuppressive therapy.</p>
Interventions	<p>Vaccine: 9-valent vaccine at 0, 2, and 6 months</p> <p>Placebo: saline placebo</p>
Outcomes	Safety and immunogenicity outcomes
Notes	<p>Main reports: Garland 2015</p> <p>Last report average follow-up time: 7 months (1 month after third dose)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not clearly stated how the sequence was generated, however, an Interactive Voice Response System was used to allocate participants and assign clinical material, therefore we have assumed that an adequate method of sequence generation was used.
Allocation concealment (selection bias)	Low risk	"An Interactive Voice Response System was used to allocate study subjects."
Blinding of participants and personnel (performance bias)	Low risk	The vaccine and saline placebo were visually distinguishable, therefore they were "prepared and administered by designated unblinded study personnel not otherwise involved in the care and management of the study participants". Otherwise, investigators, study site personnel, and laboratory personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	"clinical, statistical, and data management teams were blinded to vaccination group"
Incomplete outcome data (attrition bias)	Low risk	Safety data were reported on the total vaccinated cohort; immunogenicity data on the PP cohort. Reasons for exclusion were noted and balanced

Bias	Authors' judgement	Support for judgement
		between the vaccine arm and the control arm.
Selective reporting (reporting bias)	Low risk	All outcomes (safety and immunogenicity) were presented.

Appendix C: Five studies awaiting classification (not recruiting, but no results available) potentially relevant for the current Cochrane Review

ISRCTN32729817

Methods	Randomized, partially blind, 2 x 2 factorial trial
Participants	1000 male and female participants with first or repeat episode of clinically diagnosed anogenital warts
Interventions	Intervention: imiquimod cream plus quadrivalent HPV vaccine Intervention: podophyllotoxin cream plus quadrivalent HPV vaccine Control: imiquimod cream plus saline placebo injection Control: podophyllotoxin cream plus saline placebo injection
Outcomes	Clinical (genital warts), safety
Notes	Trial end date: 31 March 2017

NCT02199691

Methods	Phase II, randomized trial
Participants	1715 participants aged 10 to 17 years
Interventions	Intervention: MenACYW conjugate vaccine, Tdap vaccine (Adacel), and HPV vaccine (Gardasil) Intervention: Tdap vaccine (Adacel) and HPV vaccine (Gardasil) Control: MenACYW conjugate vaccine Control: Menveo vaccine
Outcomes	Immunogenicity and safety
Notes	Recruitment completed: 9 February 2018

NCT02564237

Methods	Phase I, randomized, observer-blind, comparator-controlled trial
Participants	39 male and female participants aged 18 to 50 years

Interventions	<p>Intervention: Three 0.5 mL doses of comparator (Hepatitis B vaccine, Hepatitis A vaccine, or HPV vaccine) will be administered on days 0, 30, and 180. Participants will indicate which vaccine they wish to receive.</p> <p>Control: Three 0.6 mL doses (600 µg protein) of group A streptococcal vaccine (StreptAnova) will be administered on days 0, 30, and 180.</p>
Outcomes	Immunogenicity and safety
Notes	<p>Recruitment completed: 19 January 2017</p> <p>Estimated completion date: December 2017.</p>

NCT02740790

Methods	Phase II, randomized, blinded, placebo-controlled trial
Participants	1200 females aged between 9 and 45 years
Interventions	<p>Intervention: 300 women 9 to 17 years of age receiving HPV bivalent (types 16 and 18) vaccine (yeast); 3 doses at 0, 2, and 6 months.</p> <p>Control: 300 women 9 to 17 years of age receiving placebo control; 3 doses at 0, 2, and 6 months.</p> <p>Intervention: 120 women 18 to 26 years of age receiving HPV bivalent (types 16 and 18) vaccine (yeast); 3 doses at 0, 2, and 6 months</p> <p>Control: 120 women 18 to 26 years of age receiving placebo control; 3 doses at 0, 2, and 6 months</p> <p>Intervention: 180 women 27 to 45 years of age receiving HPV bivalent (type 16 and 18) vaccine (yeast); 3 doses at 0, 2, and 6 months</p> <p>Control: 180 women 27 to 45 years of age receiving placebo control; 3 doses at 0, 2, and 6 months</p>
Outcomes	Immunogenicity and safety
Notes	<p>Recruitment completed: 8 March 2017</p> <p>Estimated study completion date: December 2017</p>

NCT03085381

Methods	Phase I, randomized, double-blind, placebo-controlled trial
Participants	90 female participants aged 9 to 45 years
Interventions	<p>Intervention: quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine (<i>Hansenula polymorpha</i>); 3 doses at 0, 2, and 6 months</p> <p>Control: placebo; 3 doses at 0, 2, and 6 months</p>

Outcomes	Safety
Notes	Recruitment completed: 21 March 2017 Estimated study completion date: December 2017

Appendix D: Eight ongoing studies (actively recruiting, no results available) potentially relevant for the current Cochrane Review

EudraCT 2007-006651-39

Study name	A phase IV, randomized, open-label, controlled, post-licensure study to evaluate the safety of GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine (Cervarix®) when administered intramuscularly according to a 0, 1, 6-month schedule in females aged 18-25 years.
Methods	Phase IV, randomized, open-label, controlled trial
Participants	100,000 female participants aged 18 to 25 years
Interventions	Intervention: Cervarix Control: hepatitis A vaccine (Havrix)
Outcomes	Safety
Starting date	20 January 2009 (date entered into EudraCT database)
Contact information	Sponsor: GlaxoSmithKline Biologicals
Notes	Trial status is ongoing; no further details

NCT01735006

Study name	Efficacy and Immunogenicity Study of Recombinant Human Papillomavirus Bivalent (Type 16/18) Vaccine
Methods	Phase III, multicentre, randomized, double-blind trial
Participants	7372 female participants aged 18 to 45 years
Interventions	Intervention: novel recombinant HPV16/18 bivalent vaccine manufactured by Xiamen Inovax Biotech; 3 doses at months 0, 1, and 6. Control: hepatitis E vaccine (Hecolin); 3 doses at months 0, 1, and 6
Outcomes	Safety, immunogenicity and efficacy (persistent HPV16/18 infection and histological lesions of CIN 1+, 2+ and 3+, VIN1+ and 2+, VaIN1+ and 2+)
Starting date	22 November 2012
Contact information	Jun Zhang, Xiamen University
Notes	As of 19 July 2018: recruitment status is active, not recruiting

NCT01824537

Study name	Transmission Reduction and Prevention With HPV Vaccination Study (TRAP-HPV)
Methods	Phase IV, randomized, double-blind, placebo-controlled trial
Participants	1000 participants (500 couples), aged 18 to 45 years
Interventions	Intervention: 9-valent HPV vaccine (Gardasil9, Merck); 3 doses at months 0, 2, and 6. Control: Hepatitis A vaccine (Havrix); 2 doses at months 0 and 6, and 1 dose of saline placebo at month 2.
Outcomes	Immunogenicity (HPV DNA positivity)
Starting date	September 2013
Contact information	Allita Rodrigues (allita.rodrigues@mcgill.ca)
Notes	Recruitment status (as of 4 May 2018): recruiting

NCT02405520

Study name	Safety and Immunogenicity Study of the Recombinant Human Papillomavirus Virus Type 6/11 Bivalent Vaccine
Methods	Phase I, randomized, double-blind, placebo-controlled trial
Participants	144 female participants aged between 18 and 55 years
Interventions	Intervention: low dosage of HPV6/11 bivalent vaccine at 0, 1, 6 months for 3 doses. Intervention: medium dosage of HPV6/11 bivalent vaccine at 0, 1, 6 months for 3 doses. Intervention: high dosage of HPV6/11 bivalent vaccine at 0, 1, 6 months for 3 doses. Control: aluminium adjuvant at 0, 1, 6 months for 3 doses.
Outcomes	Immunogenicity and safety
Starting date	March 2015
Contact information	Jun Zhang, Xiamen University
Notes	As of August 6, 2018: recruitment status is active, not recruiting

NCT02710851

Study name	Immunogenicity Study of the Recombinant Human Papillomavirus Virus Type 6/11 Bivalent Vaccine
Methods	Phase II, randomized, double-blind, placebo-controlled trial
Participants	640 male and female participants aged 18-55 years
Interventions	Intervention: low dosage HPV bivalent vaccine with virus-like particles type 6 and 11 at 1:1 ratio; 3 doses at 0, 1, 6 months. Intervention: low dosage HPV bivalent vaccine with virus-like particles type 6 and 11 at 1:2 ratio; 3 doses at 0, 1, 6 months. Intervention: high dosage HPV bivalent vaccine with virus-like particles type 6 and 11 at 1:1 ratio; 3 doses at 0, 1, 6 months. Control: hepatitis E vaccine (Hecolin) for 3 doses at 0, 1, 6 months.
Outcomes	Immunogenicity and safety
Starting date	March 2016
Contact information	Jun Zhang, Xiamen University
Notes	As of 6 August 2018: recruitment status is active, not recruiting

NCT02733068

Study name	A Phase III Study of Human Papillomavirus (HPV)-16/18 Vaccine
Methods	Phase III, randomized, double-blind, placebo-controlled trial
Participants	12000 female participants aged 18 to 30 years
Interventions	Intervention: HPV16/18 vaccine; 3-dose schedule (0, 2, 6 months) Control: HPV16/18 placebo; 3-dose schedule (0, 2, 6 months)
Outcomes	Cervical intraepithelial neoplasia grade 2 or more (CIN 2+); persistent infection of HPV type 16 and/or 18; safety
Starting date	November 2014
Contact information	Zhaojun Mo, Guangxi Center for Disease Prevention and Control, China
Notes	As of 11 April 2016: recruitment status is active, not recruiting.

NCT02750202

Study name	Effectiveness Study of Human Papilloma Virus (HPV) Vaccines to Prevent Recurrence of Genital Warts (TheraVACCS)
Methods	Phase III, randomized, single-blind, placebo-controlled trial
Participants	75 female participants aged >16 years
Interventions	Intervention: quadrivalent HPV vaccine (Gardasil, Merck); 3 doses at month 0, 2, 6 Control: hepatitis B vaccine; 3 doses at month 0, 2, 6
Outcomes	Clinical (genital warts, surgical treatment of warts or other cervical disease), immunogenicity
Starting date	July 2016
Contact information	Greta G Dreyer (Greta.Dreyer@up.ac.za)
Notes	As of 26 April 2016, recruitment status is not yet recruiting

NCT03296397

Study name	Efficacy of Quadrivalent HPV Vaccine to Prevent Relapses of Genital Warts After Initial Therapeutic Response (CONDYVAC)
Methods	Phase III, randomized, double-blind, placebo-controlled trial
Participants	300 male and female participants completely cured from external genital warts
Interventions	Intervention: quadrivalent HPV vaccine (Gardasil); 3 doses at 0, 2, 6 months Control: placebo; 3 doses at 0, 2, 6 months
Outcomes	Clinical (relapse free survival), safety
Starting date	15 November 2017
Contact information	Sebastien Fouere, Assistance Publique - Hôpitaux de Paris
Notes	Recruitment status (as of 27 February 2018): recruiting

Dear Mark and David, I am writing to formally complain about the content and the tone of the editorial (1) following the publication of the Arbyn et al (2) review of HPV vaccines. The editorial is signed by Jo Morrison and Toby Lasserson.

The editorial is factually wrong. The editorial states that “*This Cochrane Review answers some important questions with high certainty of evidence*”. No such certainty exists for the main questions of the review. There are numerous reasons for this. Perhaps the most important is the omission of many eligible trials. The Arbyn et al review (2) conducted trial searches up until June 2017 and included 26 randomised trials with 73,428 females. In January 2018, we published an index of the study programmes of the HPV vaccines that included 206 comparative studies (3). As of June 2017, about one third of the 206 studies were not published and half of the completed studies listed on ClinicalTrials.gov had no results posted (3). Although we sent our index to the Cochrane group handling the Cochrane review, the review stated that, “nearly all end-of-study reports have been published in the peer-reviewed literature.” When we applied the Cochrane review’s inclusion criteria to the 206 studies, we identified 46 completed and eligible trials. We could calculate the number of randomised participants for 42 of the 46 trials: 121,704 people. With nearly half of the trials and half of the participants missing, the Cochrane authors’ conclusion, “that the risk of reporting bias may be small,” is unwarranted and potentially misleading. It is clearly and unequivocally counter to the evidence available at the time of its publication.

You should note that our index was sent on 19 January to Tracey Harrison (for onward transmission to the authors) to David Tovey, Toby Lasserson and to the Scientific Committee - on 14 March. An informal preliminary warning was sent by me to CEU in early November 2016. At that time we were aware of 113 HPV studies.

There are other major biases and mistakes in the review which we have described elsewhere (4) and have addressed in other submitted publications, but for the purpose of this complaint it is sufficient for you to note that the presence of a sizeable number of trials that the authors did not include was flagged up many months prior to publication and ignored by authors, review group and Editorial Unit.

The editorial may breach the spokesperson policy. The editorial states “*We hope that this review [Arbyn] will be used to support policy or personal decision-making about HPV vaccination that is informed by the best current evidence, balancing facts rather than opinions*” Ever since I have been involved in Cochrane we specifically avoid making any statements on policy. That is not our job. Here we have statements on both personal and general policies. Given the visibility and the role of the authors this seems to infringe the spokesperson policy statement “we can protect against this by clarifying when we are speaking on Cochrane’s behalf or in a personal capacity”. The policy suggests two ways of doing this. By saying (or writing) “in my opinion...” or adding a statement such as “The views expressed are my opinions and not the expressed views of any organization to which I am affiliated.” No such disclaimers or qualifiers were visible in the editorial, leaving readers to assume the statements represented the views of Cochrane.

The editorial states that “all but very rare harms would be captured during large randomized controlled trials.” This is misleading, as not a single trial included in the Arbyn review had a control group where participants were treated with a placebo. They all received a hepatitis vaccine or the adjuvant, and if these cause similar harms as the HPV vaccines, such harms would be overlooked in the trials.

It is unclear to me on what basis editorials are commissioned, by whom, whether they are peer reviewed or not and what is the criterion for preferring an editorial to a humble blog and how the degree of press releasing is decided.

Finally it would be good to know how the six “experts” interviewed in the press release were selected (5). Their gushing statements and the content of the Arbyn et al review are not based on any serious effort to assess the evidence. Collectively, the Review, Editorial, and the press release create the impression that there was an overarching strategy behind their publication to send a political message. This would be counter to the fundamental purposes of the Cochrane Collaboration.

I look forward to hearing from you and would be grateful for an acknowledgment of this letter.



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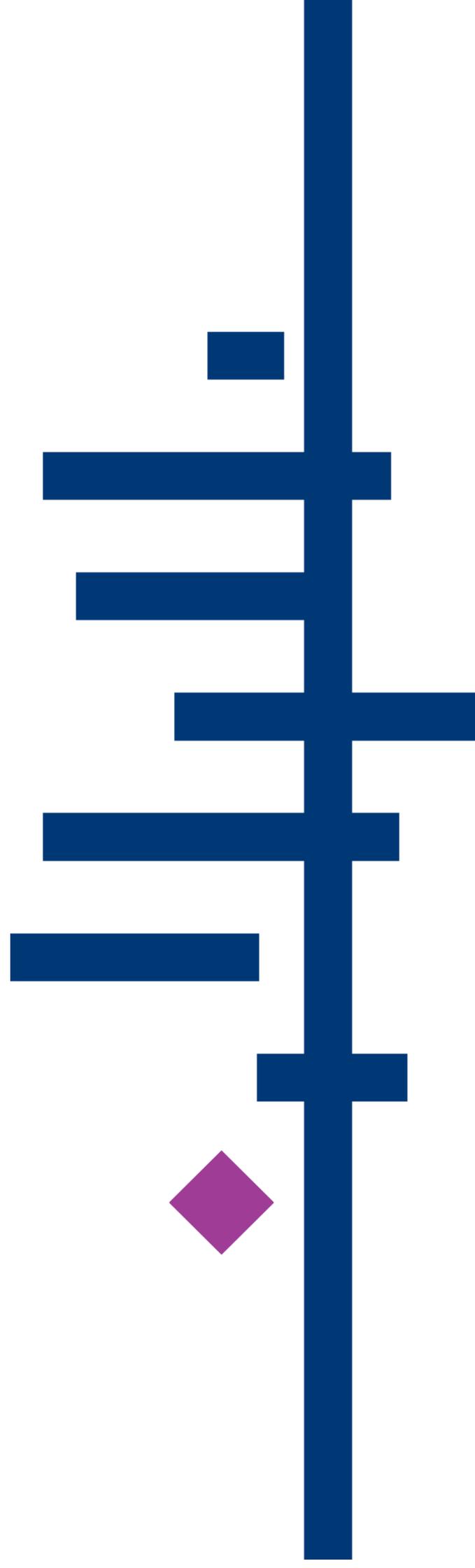
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4. Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. *BMJ Evidence-Based Medicine* Epub ahead of print: 27 July 2018. doi:10.1136/bmjebm-2018-111012
5. Scientific expert reaction to new Cochrane Review on HPV vaccine for cervical cancer prevention in girls and women. Available from <https://www.cochrane.org/news/scientific-expert-reaction-new-cochrane-review-hpv-vaccine-cervical-cancer-prevention-girls-and>

Response to formal complaint by Tom Jefferson

David Tovey
& Mark Wilson

3 September 2018



Dear Tom,

We are in receipt of your formal complaint of 4th August 2018 about the content and tone of the editorial written by Jo Morrison and Toby Lasserson. This is our formal response to the main complaints and allegations you made in that complaint:

‘The editorial is factually wrong’

The Editorial is entirely consistent with the Cochrane Review, which found high certainty evidence for several of the main outcomes.^{1,2} We have investigated the allegations made in the article that you co-authored in the BMJ EBM Journal,³ and have reported separately on this [here](#). The report concludes that although a small number of studies were missed they do not represent anything close to ‘half of the eligible studies’ as reported in the BMJ *Evidence-Based Medicine* Journal, and the inclusion of their available data would make little or no difference to the results – which supports the designation of ‘high certainty’ using the GRADE methodology.

David is in receipt of your email of the 14th March, and also received the index of studies in January 2018. The EMD team sent these to the author team.

In both the Editorial and the Cochrane Review, we were particularly careful to ensure that we adhered to best practice in terms of our reporting: by ensuring that we provided both relative and absolute effect sizes, and that this included the data on mortality. We also did not use the term ‘safe’ and we were careful to recognise that ongoing surveillance played an important part in the monitoring for harms.

‘The editorial may breach the spokesperson policy’

The editorial does not breach the spokesperson policy. The purpose of Editorials is explained in the appropriate section of the Cochrane Library website:

**

1.1.1.1 Editorials

***Editorials** aim to stimulate discussion and ideas around the development of evidence synthesis to promote good decision-making in clinical care and health policy. The Editor in Chief may commission editorials linked to Cochrane Reviews of interest or on topics likely to be of interest to a broad readership. Proposals for editorials are welcome and should be **submitted to the Editor in Chief** for consideration.*

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**

The Editorials represent the views of the authors. They are selected by the Editor in Chief, to whom Cochrane grants editorial independence.³ They do not represent Cochrane’s official policy unless that this is explicit in the text. We acknowledge that this could be made clearer to readers of the Library with an explanatory note alongside each Editorial or on the Editorial homepage. We will discuss with colleagues how such clarification can best be made and implement our conclusions.

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Whether submissions are accepted or not is at the Editor in Chief's discretion. In some cases, peer review is undertaken, and this is made explicit in the accompanying text. On the new Cochrane Library you are also now free to submit comments electronically for publication, if approved by the moderator.

Press release

You ask 'how the six "experts" interviewed in the press release were selected' but this refers to a misunderstanding on your part. The 'expert' reaction collated by the Science Media Centre came 1-5 days after release and dissemination of the press release. It was posted on Cochrane.org, our organizational, external-facing website here: <https://www.cochrane.org/news/scientific-expert-reaction-new-cochrane-review-hpv-vaccine-cervical-cancer-prevention-girls-and>. It is clear from the above that these responses were collected by the SMC. These responses were never at any point part of the Cochrane press release and were never disseminated as such. The press release is available here: <https://www.cochrane.org/news/does-hpv-vaccination-prevent-development-cervical-cancer-are-there-harms-associated-being>

In addition, for clarity, at the bottom of the SMC coverage reaction, we were transparent with DOIs: <https://www.cochrane.org/news/scientific-expert-reaction-new-cochrane-review-hpv-vaccine-cervical-cancer-prevention-girls-and>

'There was an overarching strategy behind (the publication of the review and Editorial) to send a political message'

You are correct that it would be contrary to Cochrane's fundamental purpose, and indeed its charity status 'to send a political message'. You have no evidence on which to base this allegation for the simple reason that there is not a shred of truth in it. The review represents a genuine effort by everyone involved to present the evidence in an appropriate manner. This is why we ensured that unpublished data on Serious Adverse Events and mortality were included in the review and that findings such as the apparent increase in mortality were presented in relative and absolute terms in prominent and well-read parts of the review, such as the Abstract. The Editorial continues with this approach, and explicitly makes the point, also made in the review, that ongoing surveillance data is an essential part of the monitoring of the HPV for potential harms.

We understand that we may not agree on any or all of these issues, but this represents our full and final response to your complaint and we consider that the matter is now closed. However, you may appeal our handling of your complaint with the Governing Board, in which case please contact Co-Chairs Martin Burton (Martin.Burton@cochrane.nhs.uk) and Marguerite Koster (marguerite.a.koster@kp.org).

Yours sincerely,



David Tovey
Editor in Chief



Mark Wilson
CEO

Trusted evidence.
Informed decisions.
Better health.

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3. Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. *BMJ Evidence-Based Medicine* 2018 July 27. <https://doi.org/10.1136/bmjebm-2018-111012>
4. <https://www.cochranelibrary.com/about/about-cochrane-library>

12th August 2018

Professor Cindy Farquhar and Professor Martin Burton
Co-Chairs Cochrane Governing Board

Dear Professor Martin Burton and Professor Cindy Farquhar,

Re: Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. BMJ Evidence-Based Medicine. Published Online First: 27 July 2018. doi: 10.1136/bmjebm-2018-111012

I am writing to formally complain about the conduct of Cochrane colleagues in response to criticism regarding the Cochrane review on prophylactic HPV vaccination, published in BMJ Evidence Based-Medicine (Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. BMJ Evidence-Based Medicine. Published Online First: 27 July 2018. doi: 10.1136/bmjebm-2018-111012).

I am hugely disappointed and somewhat surprised that the authors chose to do this through channels outside of the existing feedback mechanism of the Cochrane Collaboration. That this was done without prior warning to the review authors, the Editor in Chief or myself, as the co-ordinating editor for the Gynaecological, Neuro-oncology and Orphan Cancer (GNOC) Review Group, is unprofessional and undermining in the extreme, calling the reputation of Cochrane into question, with scant regard for the damage this will do long term to women's health world-wide.

I realise that Cochrane welcomes debate and openness and we in the GNOC review group work hard to provide the best level of evidence we can to inform decision-makers, be they the general public, health-care professionals or healthcare systems. We welcome valid and appropriate feedback, as a way to improve our reviews and provide the best evidence available. Indeed, the protocol of this review was changed, and the author team amended, in response to feedback several years after the protocol was first published.

We had realised that a review of vaccination for what is essentially a sexually transmitted disease, given to young women, would be a target for anti-vaccine groups and generate a considerable degree of controversy. This was one reason why we had involved Tom Jefferson, and several other leaders in Cochrane (including a current Governing Board co-chair), at the peer review stage. Their extensive comments were welcomed and addressed, explaining in part why this review has taken so long to come to fruition. The GNOC editorial group and the CEU screening team, with full CEU support, have trodden a difficult path between the review authors, peer reviewers and sustained comments from a number of anti-vaccine groups over this time.

It is therefore with great surprise that Tom Jefferson, in particular should have been involved with this criticism, as one of the original peer reviewers for this review. His concerns at peer

review were taken on board and addressed ([PG19 T Jefferson feedback comments.doc](#)). Furthermore, at that stage he specifically acknowledged that ‘The authors do not have resources to undertake a review of regulatory data but it exists and is accessible. In view of this fact conclusions and general tone of the review need to be toned down’. Much of the GNOC CRG and CEU work was with the specific aim of ensuring that the review claimed only what could be demonstrated from the included studies and to ensure inclusion registry data on harms, outside of those provided in the published studies.

This was an internationally important review, prioritised by the GNOC CRG, working with a volunteer author group. My work as co-editor for this review has been done alongside my fulltime job as surgeon, caring for of women with gynaecological cancer and pre-cancer, much delivered on a voluntary basis. The HPV vaccination review has been particularly challenging and has taken up many hours of CRG time over a number of years. The GNOC CRG have worked hand-in-hand with the Central Editorial Unit and the Screening team over this time to ensure that the review was the best we could make it. The GNOC CRG is not funded by NIHR to the level where it has the resources to repeat every step of the review process and re-do the sift and data extraction, as a double-check on authors.

Earlier in the year Peter Gøtzsche and his team submitted a list of studies which they felt should be included. These were passed onto the author team, who appraised the list and, at that stage, assured us that there were no further papers that met their review inclusion criteria, as per the published protocol. We worked with CEU to ensure that the review represented the data presented from included studies and that the conclusions were founded on this evidence and not over-stated (as per T. Jefferson peer review comments). This included the screening team extracting data from trial registries on harms data, to improve the balance of the review.

I note that Peter Gøtzsche and the Nordic Cochrane Centre have previously complained to the European Medical Agency regarding HPV vaccination and [that complaint was not upheld \(EMA response to PG complaint\)](#). The author team on the BMJ EBM paper therefore have history of criticism of HPV vaccination. This suggests a lack equipoise in this area. Indeed, there may be an argument for a conflict of interest, since ‘heat’ generated around criticism of HPV vaccination increases impact factors, valuable to academic careers; there is more to conflict of interest than just pharmaceutical company involvement.

I am particularly surprised by one of the main criticisms from Jørgensen and co-authors, concerning the use of alternate vaccines or aluminium adjuvants in the control groups, rather than an inert saline ‘placebo’. [This approach was supported by regulatory committees](#) worldwide. Were studies to have 3 arms (saline, aluminium adjuvant and HPV vaccine) this would have significantly changed the size and cost of the studies, delaying or preventing appropriate quality research due to exorbitant costs. This is especially surprising criticism, since Tom Jefferson was a lead author on a systematic review of saline versus aluminium adjuvants published in 2004, which concludes that there was no evidence of an increased risk from aluminium adjuvants and that further trials comparing adjuvants with saline were not indicated ([aluminium adjuvants SR](#)). It is therefore difficult to see how they can now justify this criticism of the aluminium adjuvant controls in the review. Indeed, had the authors only included studies with a saline placebo, it would have been a very sparse and uninformative systematic review.

Alongside CEU involvement in making sure the review was as robust as reasonably possible, we worked with the Cochrane Knowledge Transfer Team to deliver the results of the review, without over-statement, by careful consideration of press-releases and key messages and involvement of the Science Media Centre. The Cochrane Editorial team (myself included) were extremely careful to avoid saying that the vaccine was 'safe' nor to present anything other than the facts of the review, despite vigorous 'encouragement' by the press. As a surgeon, I spend many hours explaining risk and choices to patients and have *never* said that any treatment is 'safe'. Try as we might, we cannot control the press reporting, merely try to carefully and appropriately inform, and are not therefore responsible for media over-interpretation of our very measured choice of words surrounding harms. Specific criticism of this by Jørgensen and co-authors is therefore unfounded.

As a clinician, dealing with women with cervical and vulval cancer and pre-cancer (CIN and VIN) on a daily basis my *only* concern is to reduce the harm caused by high risk HPV infection. I have no other vested interest; indeed lowering the rates of these diseases will reduce my income by reducing the number of clinical sessions I will need to deliver in the future. This is not some intellectual 'game' of one-upmanship and self-promotion, this is literally deadly serious.

In the UK we are privileged to have a world-leading cervical screening programme. However, despite 4.45 million women in the UK having a smear each year, which in itself causes pain and distress to a great many, over 3,000 women are diagnosed with cervical cancer and nearly 1,000 women died from their disease. It is estimated that regular cervical screening prevents less than 76% of cervical cancers in the 25-39 year old age group. The peak age of incidence of cervical cancer is now aged 25-29 years. Many of these women are yet to start a family or have young children. Fewer than 2/3 women in this age group have regular cervical smears, so reducing further the effectiveness of cervical screening.

Cervical cancer is a relatively rare problem in high income countries, due to access to cervical screening programmes. However, world-wide it is the 4th most common cancer in women; half a million women are diagnosed with cervical cancer per year and half of these women will die from their disease. 85% of those with cervical cancer are in low and middle income countries, where cervical screening is poorly delivered and access to effective surgery, radiotherapy and palliative care is even worse.

Death from cervical cancer is painful, slow and undignified, causing urinary and faecal incontinence and offensive vaginal discharge due to invasion of bladder and rectum, which kills slowly in otherwise young and healthy women. This can lead to women being ostracised by their communities and dying a lingering death in pain and alone. Even in the UK, I have seen women die, and despite excellent palliative care services, this has been traumatic for all involved; the memory of many of these women will live with me forever. Even those women treated successfully for cervical cancer have high rates of morbidity with lower limb lymphoedema, bladder denervation and long-term effects of pelvic radiation. Commonly, these cause distressing and life-long symptoms. Treatments for these complications are limited and, as these women are often very young at diagnosis, can severely affect quality of life in cancer survivors for many decades. This is a disease that is well-worth preventing.

Cervical cancer is only the tip of the iceberg in terms of harms caused by HPV. Although Jørgensen and co-authors criticise the use of rates of high grade cervical intra-epithelial neoplasia (CIN) as ‘surrogate outcomes’ forty thousand women per year have treatment for high grade CIN in the UK. This can be distressing for many women and leads to a doubling in the risk of premature delivery and increasing the risk of late miscarriage, as demonstrated by another Cochrane review by Marc Arbyn and co-authors (Kyrgiou M, et al. Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD012847). In addition, treatment of CIN has been shown to lead to psychological distress in many women, which in some cases can be profound. This I see on a daily basis, even in women who have relatively mild cytological abnormalities who attend for colposcopy. As 5% of the 4.45 million smears in the UK are abnormal each year and lead to referral for colposcopy, this is a huge level of morbidity, which, according to the results of the Cochrane HPV vaccination review and overwhelming epidemiological evidence, will be significantly reduced.

HPV also causes vulval cancer and VIN in women and well as head and neck cancers, penile and anal cancer; for these there are no effective methods of screening. Treatment of VIN and vulval cancer is painful and disfiguring, be that with significantly mutilating surgery or radical radiotherapy to the pelvis and perineum. The rates of these cancers are rocketing: vulval cancer has doubled in Germany in the past two decades and increased in Australia by 80% since the 1980s.

There is over-whelming evidence that CIN leads to cervical cancer. In the 1950s and 60s a doctor from New Zealand adopted a ‘watch-and-wait’ approach to women with CIN 3 in an ‘experiment’ as he did not believe that high grade CIN caused cervical cancer. One in 3 women in this ‘experiment’ went on to develop cervical cancer and many died as a result. The WHO and other regulatory bodies therefore determined that reducing CIN was an appropriate surrogate outcome for HPV vaccine studies for the prevention of cervical cancer and that to wait for reduction in cervical cancer rates would be unethical, since these would take another 5-15 years for these outcomes to be available.

The results from the Cochrane review are likely to *under-estimate* the beneficial effects of HPV vaccination due to the relatively short length of follow up of the studies (6 months to 8 years) compared to the natural history of high grade CIN, cervical cancer and other HPV-related cancers (many years to decades). There is now overwhelming population-based epidemiological evidence from several countries that HPV vaccination, already given to millions of girls and women, dramatically reduces the rate of CIN. Obviously, these data cannot be included in the Cochrane review, as most are not from phase 2 and 3 randomised studies and, as do phase 4 studies, lie outside of the strict protocol inclusion criteria. However, population-based registry data support vaccine efficacy and inform us that serious harms due to vaccination are rare and are difficult to link causally to vaccination. In Australia, where they have been vaccinating on a population basis since 2007, the high risk HPV infection rate among women aged 18 to 24 has dropped from 22.7% to 1.1% between 2005 and 2015. There has also been an almost 50% reduction in the incidence of high-grade CIN in girls under 18 years of age over this time period. To suggest that HPV vaccination will not work is disingenuous at best.

Unfounded criticism risks the lives of millions of women world-wide by affecting vaccine uptake rates. The measles scandal demonstrated how dangerous a few anti-vaccine voices in the sea of evidence to the contrary can have profound and serious effects on vaccine uptake and subsequent public health. Similar unfounded campaigns overstating rare harms due to

HPV vaccination have already had a significant effect on vaccine uptake in several countries including Ireland and Japan (<https://www.vox.com/science-and-health/2017/12/1/16723912/japan-hpv-vaccine>; <https://www.theguardian.com/society/2017/dec/03/hpv-vaccine-fears-women-health-take-up-falls>), despite papers claiming harms being withdrawn or refuted.

In summary, I am disappointed by Jørgensen and co-authors and dispute criticisms levelled at my group and the Cochrane CEU team. I find the manner in which this has been conducted to be undermining and damaging to the reputation of the author team, Cochrane in general and myself in particular. It may be that the author group has failed to identify a small number of studies from the trials registry that lie outside of the peer-reviewed literature. However, we are seeking to address this, with the CEU and author team, with extreme urgency. Preliminary data analysis suggests that this is unlikely to significantly alter the conclusions of the review, which we intend to update and re-publish as soon as possible. However, in choosing to criticise the review in such public way, without due warning and outside of normal Cochrane feedback channels, Jørgensen and co-authors risk significant damage to Cochrane with seemingly scant regard for the very real harm that this will cause women in particular for years to come. Please consider this a formal complaint and request appropriate redress on behalf of the review authors, GNOC and the CEU team.

Yours sincerely

Dr Jo Morrison

Consultant Gynaecological Oncologist and Co-ordinating Editor Cochrane Gynaecological, Neuro-oncology and Orphan Cancer review Group

21 August 2018

Gøtzsche's reply to letter from Jo Morrison from 12 August

Dear Martin,

On 15 August, you wrote to Lars Jørgensen, Tom Jefferson and me:

“the attached was sent to us as Co-Chairs. The covering e-mail makes it clear that the writer sends it as a letter of complaint to the Cochrane Governing Board. We therefore intend to share the letter with the Governing Board prior to the next Board Meeting (13th to 15th September 2018). Please will you provide a written response, by not later than 31st August 2018. If you do so, we will then include that response with the original letter, when we circulate it to the Board.”

Please note that we are not all back from holidays before September so we cannot provide a joint reply before your deadline. But perhaps my preliminary reply will suffice.

You say that the complaint – submitted by co-ordinating editor Jo Morrison - was sent to you as co-chairs of the Governing Board and that you therefore intend to share the letter with the Governing Board prior to the next Board Meeting.

I believe this is not the correct procedure. Anyone can send a complaint to the Governing Board. This does not automatically mean that it is then also the Governing Board that should deal with it. The Governing Board deals with strategic matters, not with day-to-day matters, which this is an example of.

According to the Cochrane Governance Structure Flowchart, Morrison should have submitted the complaint to Editor-in-Chief, David Tovey. I therefore copy this email to David who is the person that should deal with the complaint.

I feel, however, that Morrison has no good reason to complain about us and should have engaged in a in a scientific debate instead because this is what the issue is about. At the heart of science is independent replication and criticism, which are what we provided in our paper about the Cochrane HPV vaccine review. These are essential factors for the advancement of science, which we treasure, also in Cochrane.

The Spokesperson Policy says about this: “Many Cochrane contributors are experts in their field and have every right to discuss their work and express their personal views – this may include expressing opinions on Cochrane policies and Cochrane Reviews. This policy is not intended to infringe Cochrane’s long-standing tradition of rigorous academic and scientific debate.”

Thus, it is actually being loyal – and not disloyal - to the principles of Cochrane to highlight publicly when a Cochrane review is problematic, which we found the Cochrane HPV review to be.

In 2003, the Nordic Cochrane Centre upset another co-ordinating editor, Paul Garner, from the Cochrane Infectious Diseases group) because we were working on a systematic review of immunoglobulins for sepsis, which we planned to publish. Garner's group had already published a Cochrane review on this subject.

The then UK Cochrane Centre Director, Mike Clarke, phoned me and reported back to Garner (and Jim Neilson, co-chair of the Steering Group):

"I spoke with Peter Gotzsche about this review on the telephone on 14 April 2003 ... The systematic review by Julie and Peter is part of Julie's PhD (Peter is her supervisor). As such, it is more accurate to think of it as a paper by Julie - a postgraduate student - than by Peter - a Cochrane Centre Director. The reason for not making the manuscript available to the Cochrane reviewers is to protect Julie's chances of getting it published as a new piece of work. If the work she has put into it was to appear first in the Cochrane review this would make separate publication in her name much more difficult (if not impossible)."

The situation with our HPV paper is similar. The first author, Lars Jørgensen, is my PhD student, and it is therefore important for him to have published this paper, which can be included in his PhD.

Specific points related to Morrison's complaint

It is not correct, as Morrison asserts, that our complaint over EMA was not upheld by the EU Ombudsman. The EU Ombudsman refused to go into a scientific discussion of whether or not EMA was guilty of maladministration when it assessed the harms of the HPV vaccines. Apart from this, Morrison's comment is irrelevant for a scientific debate while our criticism of EMA is not, see our assessment of the Ombudsman's decision:

https://nordic.cochrane.org/sites/nordic.cochrane.org/files/public/uploads/nordic_cochrane_views_on_the_ombudsmans_decision_2_nov_2017.pdf.

Immediately after the irrelevant comment about EMA, Morrison writes: "The author team on the BMJ EBM paper therefore have history of criticism of HPV vaccination. This suggests a lack equipoise in this area. Indeed, there may be an argument for a conflict of interest, since 'heat' generated around criticism of HPV vaccination increases impact factors, valuable to academic careers; there is more to conflict of interest than just pharmaceutical company involvement."

This is a non-sequitur. We have provided valid criticism of EMA, which has nothing to do with a "history of criticism of HPV vaccination." Morrison tries to say that we should somehow be against HPV vaccination. This is nonsense and a strawman argument. We always try our best to get as close to the truth as possible, which all Cochrane researchers should do.

Whether or not "regulatory committees" have supported the use of hepatitis vaccines or vaccine adjuvant in the control groups, is also irrelevant for the science. It is a fact that if these active substances cause similar harms as the HPV vaccines, it would be close to impossible to detect these harms in the randomised trials, which is what we criticise. Even EMA has cited research – in a secret report – that shows that this is a real concern, which we highlighted in our complaint to the Ombudsman.

I cannot comment on Jefferson's systematic review of saline versus aluminium adjuvants published in 2004; he should do that himself, if he so wishes, but I do not think his review is not relevant for our current criticism.

Morrison writes: "To suggest that HPV vaccination will not work is disingenuous at best. Unfounded criticism risks the lives of millions of women world-wide by affecting vaccine uptake rates. The measles scandal demonstrated how dangerous a few anti-vaccine voices in the sea of evidence to the contrary can have profound and serious effects on vaccine uptake and subsequent public health."

This is another strawman argument. We have not written that HPV vaccination does not work. We are loyal to our science and do our best to describe what we find, and our criticism is certainly not unfounded. To say that we might be responsible for millions of deaths because we raise valid, scientific criticism has nothing to do with science and being loyal to science. I am first author on the Cochrane review of mammography screening, which questions whether screening does more good than harm, and I have also in that case been accused of having caused huge numbers of deaths, even though mammography screening has never been shown to decrease the total number of deaths; not even the total number of cancer deaths.

We fully share Morrison's view of the measles scandal but this has nothing to do with our valid, scientific criticism.

Morrison's letter ends thus:

"In summary, I am disappointed by Jørgensen and co-authors and dispute criticisms levelled at my group and the Cochrane CEU team. I find the manner in which this has been conducted to be undermining and damaging to the reputation of the author team, Cochrane in general and myself in particular. It may be that the author group has failed to identify a small number of studies from the trials registry that lie outside of the peer-reviewed literature. However, we are seeking to address this, with the CEU and author team, with extreme urgency. Preliminary data analysis suggests that this is unlikely to significantly alter the conclusions of the review, which we intend to update and re-publish as soon as possible. However, in choosing to criticise the review in such public way, without due warning and outside of normal Cochrane feedback channels, Jørgensen and co-authors risk significant damage to Cochrane with seemingly scant regard for the very real harm that this will cause women in particular for years to come. Please consider this a formal complaint and request appropriate redress on behalf of the review authors, GNOC and the CEU team."

This paragraph concerns me greatly. I see a tendency to censorship in it, and to request "appropriate redress" does not have anything to do with an open, scientific debate, which we encourage people to participate in, also Morrison.

There are certainly other views than Morrison's. Some people feel that the Cochrane HPV vaccine review has damaged the reputation of Cochrane because they see it as substandard.

I have already explained why I could not warn about our upcoming paper. On 30 July, I wrote to the first author of the Cochrane review, Marc Arbyn, and copied David Tovey and the review group's managing editor, Gail Quinn:

“It is my first day at work after holidays. It seems that a criticism of your Cochrane review we (three researchers from the Nordic Cochrane Centre) have written has just been published as a prepublication over the weekend, so I wish to inform you immediately and attach our paper. We will submit a formal critique via Cochrane's feedback system in due course when we are all back from holidays. I copy the managing editor and Cochrane's editor-in-chief.”

On 1 August, I wrote to the same people:

“PS. Our paper was prepublished on 27 July. I did not even know it had been accepted. The journal only wrote to the first author and asked him to look at the proofs. He did not copy me, as he knew I was on holiday. I would have wished to inform you earlier but that turned out not to be possible. The first author is a PhD student with me. I will, from now on, ensure that I am always the corresponding author on all papers, which I publish with junior researchers so that I will always know what goes on.”

Regarding the use of normal Cochrane feedback channels, I have these comments:

Our criticism was so substantial that it needed its own article. Furthermore, I – and many other contributors to Cochrane - have experienced on many occasions that the feedback system in Cochrane does not function well. Sometimes the co-ordinating or managing editor has refused to upload our criticism till the authors of the review had responded, and sometimes the authors refused to respond, which meant that it took many months (I think even a good deal more than a year in one case) before our criticism became part of the Cochrane review, after our repeated requests to have it published. Finally, readers are not likely to find criticisms of Cochrane reviews within the reviews themselves, at least not until the new version of the Cochrane Library came out a couple of weeks ago. Readers would not expect to find anything of interest under a heading called “Feedback” with text that comes very late in the review, after the appendices, if I remember correctly. This feedback system in Cochrane has been intensely criticised over many years.

I hope we can close this case with my letter. Morrison should debate with us in the scientific literature, rather than complain about us.

If Lars or Tom have additional views, or disagree with some of what I have written, they will say so when they are back from holidays.

Best wishes



Peter C Gøtzsche
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**To Professor Martin Burton, UKCC
copy Dr David Tovey CEU, Professor Gøtzche, Dr Jørgensen NCC**

Dear Martin, thank you for the opportunity to respond to the complaint letter by Dr Morrison, the Co-ordinating Editor of the Cochrane Gynaecological Neuro-oncology and Orphan Cancer review Group in relation to our Analysis in BMJ EBM (1).

Professor Gøtzche's remarks indicate that the recipient should be Dr David Tovey, so I have copied him this letter. Personally I am surprised that a scientific discussion should be in the arena of the Management Board, unless of course your aim is to impose some kind of censorship.

Dr Morrison's letter raises several issues but as I am repeatedly singled out for criticism in the text I am responding personally, although I may join my co-authors in a further collective response. I deliberately left the issues relating to the statement that preventing CIN is in itself an extremely worthy endpoint, not a surrogate and that the efficacy shown again pre-cancers in short trials suggests the real efficacy is even greater out of my response as they can be addressed collectively.

I shall first stick to what I think are the points directed at me. Dr Morrison's criticism of my actions is based on four points.

One - I had been a referee of the review and knew what was going on and had acknowledged the difficulty of including regulatory data.

Two - I should have followed "normal Cochrane channels" to make my comments and not published them in a journal. My actions may result in damage to women's health long term around the world because of wide publicity of our criticisms.

Three - I was (am) not neutral as I had previously "complained to EMA regarding HPV vaccination."

Four - my remarks concerning the use of "aluminium adjuvants" are difficult to understand as I was "lead author on a systematic review of saline versus aluminium adjuvants published in 2004, which concludes that there was no evidence of an increased risk from aluminium adjuvants and that further trials comparing adjuvants with saline were not indicated"

I disagree with all contentions because of the following.

One - My last involvement with the Arbyn et al review ended in January 2016, two and half years before its publication, when I provided feedback. No further communication was exchanged and I repeatedly asked CEU for updates on the status of the review stressing its potential importance. I had no visibility of the finished product. Had I seen the finished review I would have done my utmost to prevent its publication in its current guise. During the period November 2016 – March 2018 I issued repeated warnings of the substantial reporting bias and spin surrounding the evidence development programmes of Gardasil, Gardasil 9 and Cervarix. My co-authors and I also provided an index of prospective comparative studies for all three vaccines (2), sent to Tracey Bishop on the 19 January 2018. This is incorrectly mentioned in the letter as "a list of studies which they felt should be included". I am not in the habit of telling reviewers what they should or should not include, the decision (as well as the responsibility) is theirs.

At the time I added the following explanatory covering note: "This is the first phase of our systematic review of HPV vaccines based on regulatory data. It is a near-complete index of all prospective comparative studies testing the vaccines. It was constructed developing methods used in our Cochrane neuraminidase review. The construction is a six-step process involving cross referencing from a variety of sources. The results are an index of 206 clinical studies: 145 industry and 61 non-industry funded studies. The index is more complete than either registers or electronic searches and should address some forms of reporting bias. Some of the CSRs are in the public domain. Our sources are described in the article."

The index shows the degree of reporting bias present in the publication and the accessibility of the data set. We will soon be publishing further details of these aspects (see below).

I can see no trace of any of these inputs in the review. Editor-in-Chief, Review Group (to whom the Index was sent on 19 January 2018) and Cochrane Scientific Committee (15 March) provided no feed-back and seemingly took no action.

Arbyn and colleagues could at least have acknowledged the possibility of reporting bias on the basis of the Index and toned down their conclusions. This would have been quite a simple exercise based on a substantial evidence base which they had not collected and would have entailed no extra effort on their part.

Two - I am not aware of the requirement for exclusivity of comments via the Cochrane feedback procedure. I am however aware of the considerable length of time comments are published and responded to in CDSR and of the potential “damage this will do long term to women’s health world-wide”. But this is not for the reasons given by Dr Morrison. The issue for me is science. A biased review is far more dangerous to all of us than the sentiment expressed by Dr Morrison, which carries a strong whiff of censorship.

As you already know, Professor Gøtzche has indicated that we were given no warning that the Analysis had been published online. Our Analysis was not press released by us or the journal and no one has any control over social or other media. Professor Gøtzche separately provided Dr Arbyn with a copy of our paper and has indicated that we will also respond through Cochrane channels in due course. I am not interested in eliciting favour but try sticking to science. I can also reassure Dr Morrison that I have never been interested in impact factors (a much misused measure) to further my career and I do not hold any social media accounts.

Anything on HPV vaccines in the public domain takes on its own life in the social media-verse. If Cochrane feedback channels worked as quickly as they should, it’s hard to see how things would be much different. I cannot think what “due warning” would have done in this case. Arbyn et al. had many days to review everything before publication of the Nigel Hawkes / BMJ News piece (which is the only formal article based on our Analysis that I am aware of).

Three – Dr Morrison misrepresents our complaint to EMA (and subsequently the Ombudsman). The complaint concerned the way that the EMA Pharmacovigilance Risk Assessment Committee (PRAC) had reviewed the evidence of possible serious harms from the HPV vaccines. The complaint had nothing to do with the assessment of vaccines’ performance. I would ask Dr Morrison to read the regulatory evidence which we have made available in its entirety (3) and our in depth criticisms before drawing reassuring conclusions from the actions of regulators. In essence the PRAC asked the manufacturers whether they thought their vaccines caused serious neurological harms. They got “NO” as an answer and adopted the conclusions without checking the underlying partial and selected raw data.

I fully appreciate that reading all the documents hyperlinked in Table 1 of reference 3 may seem a tall order, but examination of the content will allow Dr Morrison to make up her own mind as to where the bias lies and perhaps be more cautious in apportioning blame. Had anyone in the Review Group read the PRAC documents?

Four – The answer to this point requires a longer explanation which I have broken into subparas for ease of reading

Background

We are about to publish the narrative of our partially successful efforts to assemble complete clinical study reports for the 206 prospective comparative studies of all three vaccines. The process started in 2014 and was stopped in 2017 because of funding timelines.

Indexing and trying to reconstruct the evidence base using clinical study reports is a very complicated and error-prone business made even more difficult by lack of meaningful responses from one of the manufacturers and the stop-start nature of EMA releases, as we will document.

As with influenza antivirals, by mid 2016 it became clear that there was sizeable but variable reporting bias in most publications of the three vaccines. Evidence of potential serious neurological harms presented to regulators had subsequently disappeared from any further documentation. This in turn led us to expand our field of enquiry looking at the genesis, development timeline and regulatory pathway of the vaccines and their constituents.

Adjuvants

For example, Merck’s proprietary adjuvant Amorphous Aluminium Hydroxyphosphate (or AAHS) has no known formula, no stoichiometry, no known molecular weight, no known concentrations and variable properties from batch to batch and even within batch, according to its manufacturer. What is even more disturbing is that none of the adjuvants has been tested against an inert comparator in human trials. Their

clinical properties are largely unknown because they are not regulated on their own, as regulators regard them as “inert substances” (see below).

As a consequence, supine acceptance of AAHS as a “placebo” by regulators, editors and reviewers is a superficial interpretation leading to high likelihood of bias.

AAHS is a very powerful stimulator of immunity, capable of providing high and sustained antibody response in recipients and carries within its mesh fragments of nucleic acid, probably from the recombinant antigenic Virus-Like Proteins (VLP) production process. The VLPs direct the anti-HPV response stimulated by the adjuvant. A high and sustained antibody response was what the FDA regulators required to register the cervical cancer indication in 2006 for Merck’s Gardasil.

The core trials were designed with administration of the vaccines in the active arm and their adjuvants in the “placebo” arm. *Ergo* the differences tested were not the effects of the vaccines, but the effects of VLPs (in the best case scenario), the presence or absence of VLPs being the only difference between arms. The presence of AAHS or AS04 (the GSK adjuvant) in both arms of many trials made a fair assessment of possible harms due to powerful immune stimulation difficult, if not impossible. The trials tested the antigens, not the vaccines. In those trials with a vaccine comparator, the same adjuvant (AAHS or AS04) was the control or several schedules of the control vaccines were used, further impeding assessment. As far as we know these control vaccines had never been tested against placebo making them unstable comparators of dubious public health significance.

One reason given by manufacturers for use of adjuvants in the control arms is the need to retain blinding, as aluminium containing vaccines are characteristically cloudy. This objection can easily be overcome as addition of one drop of castor oil provides cloudiness after shaking and blinding is not essential when you are assessing cancer.

Dr Ian Hudson of MHRA (and ex GSK) has recently provided an additional explanation: “The EMA considered that use of aluminium adjuvant as a control was an acceptable way to maintain blinding of the pivotal studies (e.g. saline injection would induce little local reactogenicity and allow identification of what had been administered, thereby compromising the study)”.

If adjuvants are inert substances, how can they induce reactogenicity?

Dr Morrison should take care to distinguish between Al(OH)₃ added to DTP vaccines in the 70s and 80s (4) from novel adjuvants such as AAHS, AS01, AS03, AS04 and MF59 which are known as adjuvant systems, or complex adjuvants. These are very different powerful stimulants which remain untested in large clinical trials. Adjuvants, of course, are not inert substances as they are added to biologics to stimulate the immune system. I would also ask Dr Morrison to read our 2004 review (4). The review did not compare “saline versus aluminium adjuvants”. It compared the effects of exposure to D, T, P antigens alone or in any combination with or without Al(OH)₃ and/or with saline. The indirect comparison that Dr Morrison refers to would have been unstable as no one regulates either saline or adjuvants. The same point we made about the Arbyn et al review.

This brief aside should be enough to explain why I was concerned when I read the Arbyn et al review. This story should also show why reliance on published trial articles of major interventions is no longer acceptable, especially not without warnings as to their shortcomings (5). There is little sign at present that Cochrane reviewers are tackling the issue (6).

I sympathise with Dr Morrison’s comments on groups ideologically opposed to vaccines as I am targeted almost daily by such extreme people.

Please note that **nowhere** have I suggested that HPV vaccines trials should have been designed with three arms, as the use of any active unstable comparator is misleading. A simple HPV vaccines vs placebo or vs screening design would have answered the questions.

Finally Dr Morrison thinks that including the “missed trials” would have made no difference to the conclusions of the review. What evidence does she base this statement on?

In summary I disagree with Dr Morrison’s points and am quite happy to discuss matters face to face in Edinburgh, if schedules allow.

With best wishes,



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Rome, 27 August 2018

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Subject: Conduct of Board Member

Date: Sunday, 2 September 2018 at 08:46:42 British Summer Time

From: Jonathan Craig

To: Marguerite.A.Koster@kp.org, Cindy Farquhar, Burton Martin - UKCC (RTH) OUH

Dear Cindy, Martin and Marguerite

It is with considerable sadness that I write to you as current (and incoming) Chairs of the Governing Board of Cochrane.

It concerns the conduct of the Director of the Nordic Cochrane Centre, most recently in relation to the article he coauthored on the HPV vaccine.

Cochrane has a proud and rich tradition of almost ruthless internal criticism, which although challenging at times, is legitimate for a scientific organization that has a reputation based upon quality and transparency. However, the rules of the game are different as Governing Board member, very different. My concerns are two-fold

1. Reputational damage. There are two elements to this. The first concerns governance. How can a Governing Board member justify fundamental criticisms on the very nature of Cochrane? His actions erode the reputation of Cochrane which he has an obligation to enhance. He accrues a reputation from his public utterances and this he clearly values more than his role as a Board member. The second concerns his judgement, and ironically one of bias. The notion that HPV is not effective is frankly laughable. The impact on invasive cervical cancer is already apparent and profound. The regulatory and scientific community rightly regards his views as ideologically and not empirically based. This speaks to fundamental concerns regarding his judgement.
2. Procedural fairness and transparency. The details and timelines of his publication are not known to me but, if he were acting in the best interests of the organization, one would expect that he would have shared his work with the authors and Cochrane more generally. If he was fulfilling his responsibilities as a Board member, he would have shared his opinions with the Editor of the Cochrane Library, so that any legitimate concerns could have been addressed prior to publication. If this did not occur when one could only conclude that he was promoting his reputation over that of the organization.

I am aware this does not represent an isolated event. Difficult though it is, it is up to the Board to decide whether his conduct is consistent with being a Board member, and if not then whether being removed from the Board needs to occur to ensure that code of conduct is maintained, and Cochrane strengthened.

Thanks for considering

Regards

Jonathan Craig

7 September 2018

Gøtzsche's response to letter to Governing Board co-chairs from 2 September from Jonathan Craig

Craig complains about “the conduct of the Director of the Nordic Cochrane Centre, most recently in relation to the article he coauthored on the HPV vaccine.”¹

Craig implies that there are ‘separate rules’ for Board members who also happen to be scientists that publish in the medical literature. I am not aware of any such rules.

Craig implies there has been some reputational damage but does not provide any evidence for this allegation. For two years, my research group has worked with clinical study reports from the HPV vaccine trials, which we obtained from the European Medicines Agency. Therefore, we have a unique knowledge in this area. As scientists, we are free to constructively criticise science in medical journals – this is what we treasure and call academic freedom, also in Cochrane. In fact so much that we have an annual prize for it: “Cochrane values constructive criticism of its work and publicly recognises this through the Bill Silverman Prize ... with a view to helping to improve its work, and thus achieve its aim of helping people make well-informed decisions about health care.”

In accordance with this, the Spokesperson Policy, introduced in 2015, states: “Many Cochrane contributors are experts in their field and have every right to discuss their work and express their personal views – this may include expressing opinions on Cochrane policies and Cochrane Reviews. This policy is not intended to infringe Cochrane’s long-standing tradition of rigorous academic and scientific debate.”

Thus, we are adhering to the principles of Cochrane by highlighting publicly when a Cochrane review is problematic.

We have criticised Cochrane reviews before and the last time we provided extensive criticism, the review was retracted. Also on that occasion, like our criticism of the HPV vaccine review, we published our criticism in BMJ Evidence-Based Medicine (then called Evidence-Based Medicine).²

Furthermore, my job description includes an obligation to participate in the public debate and I believe the general public and the patients have a right to know when there are scientific uncertainties.

¹ Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. *BMJ Evidence-Based Medicine* 2018; 27 July. <http://dx.doi.org/10.1136/bmjebm-2018-111012>.

² Boesen K, Saiz LC, Erviti J, Storebø OJ, Gluud C, Gøtzsche PC, Jørgensen KJ. The Cochrane Collaboration withdraws a review on methylphenidate for adults with attention deficit hyperactivity disorder. *Evid Based Med* 2017; 10.1136/ebmed-2017-110716.

Craig asks: “How can a Governing Board member justify fundamental criticisms on the very nature of Cochrane? His actions erode the reputation of Cochrane which he has an obligation to enhance.”

The inference drawn from Craig’s comment is that we should censor our criticisms and refrain from having a transparent debate. And yet, transparency is a fundamental tenet of Cochrane. It would be wrong not to publish “fundamental criticisms” of a Cochrane review. Criticism of each others’ work is absolutely essential for the advancement of science and has nothing to do with criticising “the very nature of Cochrane.” Quite the contrary.

Craig writes: “He accrues a reputation from his public utterances and this he clearly values more than his role as a Board member.”

This comment is not only disparaging, but it mischaracterises my motivation to disseminate science to the public. A true scientist’s interest is to get as close to the truth as possible. This is what we attempt to do, and have done, regarding the HPV vaccines.

Craig questions my judgment by saying: “The notion that HPV is not effective is frankly laughable.”

Presumably, the word “vaccine” was missing from this sentence, which is problematic on two fronts. First, Craig’s comment is disrespectful. Second, Craig persists with a strawman argument. At no time did we ever say or write that the HPV vaccines have no effect. We acknowledge that the randomised trials have clearly shown that the vaccines reduce precursors to cervical cancer. Our critique was centred around the harms of the vaccine.

Craig’s arguments are similar to those put forward by Jo Morrison, co-ordinating editor for the Cochrane group that published the Cochrane HPV vaccine review. In a letter to the co-chairs in mid-August, she likewise wrote: “To suggest that HPV vaccination will not work is disingenuous at best.” Neither Craig, nor Morrison has provided any documentation to support this allegation.

In his one-page letter, Craig continues to disparage my scientific expertise by making spurious assumptions about the views of certain “communities”: “The regulatory and scientific community rightly regards his views as ideologically and not empirically based. This speaks to fundamental concerns regarding his judgement.”

It is another strawman argument and highly defamatory to talk about “fundamental concerns regarding his judgement.” And exactly what is “The regulatory and scientific community”? What are the conflicts of interest? And where is the evidence that my views are driven by ideology? My views are firmly evidence-based and published in peer-reviewed journals. In accordance with the tradition of Cochrane, I always thoroughly study the science or do the science myself before I draw conclusions.

Craig asserts, evidently without having any knowledge of what actually happened, that: “if he were acting in the best interests of the organization, one would expect that he would have shared his work with the authors and Cochrane more generally.”

This we did, as Tom Jefferson has already explained in his response to the complaint by Jo Morrison. Jefferson communicated with the relevant researchers, several times since November 2016.

My intention was to inform Cochrane's editor in chief, the first author of the Cochrane review, and the Managing Editor of the review group that published the review, well in advance of the publication of our paper. However, as I have explained, there were circumstances beyond my control.

I wrote to these people on 30 July: "Dear Marc Arbyn. It is my first day at work after holidays. It seems that a criticism of your Cochrane review we (three researchers from the Nordic Cochrane Centre) have written has just been published as a prepublication over the weekend, so I wish to inform you immediately and attach our paper. We will submit a formal critique via Cochrane's feedback system in due course when we are all back from holidays. I copy the managing editor and Cochrane's editor-in-chief."

Two days later, I wrote again: "Our paper was prepublished on 27 July. I did not even know it had been accepted. The journal only wrote to the first author and asked him to look at the proofs. He did not copy me, as he knew I was on holiday. I would have wished to inform you earlier but that turned out not to be possible. The first author is a PhD student with me. I will, from now on, ensure that I am always the corresponding author on all papers, which I publish with junior researchers so that I will always know what goes on."

Craig continues to make erroneous assumptions about me: "If he was fulfilling his responsibilities as a Board member, he would have shared his opinions with the Editor of the Cochrane Library, so that any legitimate concerns could have been addressed prior to publication. If this did not occur when [sic] one could only conclude that he was promoting his reputation over that of the organization."

This conclusion is a non-sequitur and the dichotomy is false. I cannot further the reputation of an organisation, which is what I have done during my 25 years with Cochrane, without inadvertently furthering my own. Furthermore, I have a duty to my PhD students. The first author, Lars Jørgensen, is my PhD student, and it is therefore important for him to have published this paper, which can be included in his PhD.

Craig ends his letter thus: "I am aware this does not represent an isolated event. Difficult though it is, it is up to the Board to decide whether his conduct is consistent with being a Board member, and if not then whether being removed from the Board needs to occur to ensure that code of conduct is maintained, and Cochrane strengthened."

This is deeply worrying. When leading people in an organisation call for the removal of members who have done nothing wrong, and persecute scientists for publishing their scientific observations, it is a sign that something is badly wrong, particularly considering that the Cochrane Collaboration is a scientific organisation. All these letters to the Governing Board appear to be an orchestrated effort to discredit me, among other things, because they are remarkably similar in content. This is also deeply worrying, considering the principles we should abide by in the Collaboration.

Where is Cochrane's appeal to my supporters who will attest to my integrity and my right to independently scrutinise the scientific literature? It seems as if my critics have been given a platform to disparage me and my supporters are being ignored.

Censoring science is embarking on a dangerous downhill course from which it might not be possible to come back.

We ended our paper about the Cochrane HPV vaccine review thus:

“Part of the Cochrane Collaboration’s motto is ‘Trusted evidence’. We do not find the Cochrane HPV vaccine review to be ‘Trusted evidence’, as it was influenced by reporting bias and biased trial designs. We believe that the Cochrane review does not meet the standards for Cochrane reviews or the needs of the citizens or healthcare providers that consult Cochrane reviews to make ‘Informed decisions’, which also is part of Cochrane’s motto. We recommend that authors of Cochrane reviews make every effort to identify all trials and their limitations and conduct reviews accordingly.”

By writing this, we acknowledged that Cochrane reviews are trusted evidence but that Cochrane’s high standards were not met in this particular case.

A handwritten signature in blue ink, appearing to read 'P. Gøtzsche'.

Peter C Gøtzsche
Professor, Director, MD, DrMedSci, MSc
Nordic Cochrane Centre
Rigshospitalet, Dept 7811

Subject: Breach of Trustees Code of Conduct
Date: Tuesday, 4 September 2018 at 10:34:03 British Summer Time
From: Geraldine Macdonald
To: Burton Martin - UKCC (RTH) OUH, marguerite.a.koster@kp.org
CC: David Tovey

Dear Co-Chairs

I write with regard to the matter recently investigated by Dr. David Tovey and his team, namely the publication in the journal *BMJ Evidence-Based Medicine* of a critique of the Cochrane Review on prophylactic human papillomavirus (HPV) vaccines.

As a Coordinating Editor I am dismayed to learn that – yet again – Professor Peter Gøtzsche has acted in a manner that has jeopardised our reputation, which is so important for our standing, and our continued funding. It was bad enough that he did so in the past – seemingly without sanction - whilst holding a senior position at Cochrane Nordic; to do so whilst holding the position of Trustee on the Governing Body is entirely unacceptable, and surely breaches the Board's Code of Conduct?

Certainly, if one has concerns about the accuracy or quality of any Cochrane product, it is perfectly appropriate – indeed essential – that these should be surfaced, but surely one should first do so via our well-established internal avenues and processes? In my view, only when these are exhausted is it appropriate even to consider raising it externally, and - if one is a Board Member – surely then *only* after one has exhausted this forum **and resigned** from the Board?

As a Coordinating Editor I am always anxious that one of my group's reviews might be the subject of this kind of criticism, but I recognise that this comes with the job, and we rely on rigorous internal and external scrutiny to minimise the likelihood of such a thing occurring. We all make mistakes, but I do not expect someone in a leadership position within Cochrane (or any position, come to that), to act in such a high-handed and irresponsibility manner, and I strongly object to someone holding the position of Trustee acting in this way. What makes it worse, is that in this case – as others – the criticisms were entirely, or largely, unfounded.

Personally, I think it is grounds for his removal, hence this email. If he is not removed, I would like the reassurance of the Board that nothing of this kind will be repeated – by any board member – and that if Professor Gøtzsche acts in this way again, that he should not be permitted formally to associate himself with Cochrane. I appreciate the potential backlash of such actions, but it seems to me that our attempts to avoid these by accommodating him have been singularly unsuccessful.

Yours sincerely,

Geraldine

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Geraldine Macdonald
Professor of Social Work
School for Policy Studies
University of Bristol

Tel: +44(0)1179 546729

Coordinating Editor, Cochrane Psychosocial, Developmental and Learning Problems

7 September 2018

Gøtzsche's response to letter to Governing Board co-chairs and Cochrane's editor in chief from 4 September from Geraldine Macdonald

Macdonald is co-ordinating editor in a Cochrane review group. She is “dismayed to learn that – yet again – Professor Peter Gøtzsche has acted in a manner that has jeopardised our reputation, which is so important for our standing, and our continued funding ... whilst holding a senior position at Cochrane Nordic; to do so whilst holding the position of Trustee on the Governing Body is entirely unacceptable, and surely breaches the Board's Code of Conduct?”

Macdonald refers to our paper where we criticise the Cochrane review on the HPV vaccines.¹ She implies that there are ‘separate rules’ for Board members and Cochrane Centre Directors who also happen to be scientists that publish in the medical literature. I am not aware of any such rules.

Macdonald's letter is remarkably similar to the letter by Jonathan Craig to the co-chairs from 2 September. Macdonald alleges reputational damage without providing any evidence. For two years, my research group has worked with clinical study reports from the HPV vaccine trials, which we obtained from the European Medicines Agency. Therefore, we have a unique knowledge in this area. As scientists, we are free to constructively criticise science in medical journals, something we believe is a valued tenet of Cochrane. In fact, so much so, that Cochrane awards an annual prize for it: “Cochrane values constructive criticism of its work and publicly recognises this through the Bill Silverman Prize ... with a view to helping to improve its work, and thus achieve its aim of helping people make well-informed decisions about health care.”

In accordance with this, the Spokesperson Policy, introduced in 2015, states: “Many Cochrane contributors are experts in their field and have every right to discuss their work and express their personal views – this may include expressing opinions on Cochrane policies and Cochrane Reviews. This policy is not intended to infringe Cochrane's long-standing tradition of rigorous academic and scientific debate.”

Thus, we are adhering to the principles of Cochrane by highlighting publicly when a Cochrane review is problematic.

We have criticised Cochrane reviews before and the last time we provided extensive criticism, the review was retracted. Also on that occasion, like our criticism of the HPV vaccine review, we published our criticism in BMJ Evidence-Based Medicine (then called Evidence-Based Medicine).²

¹ Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. *BMJ Evidence-Based Medicine* 2018; 27 July. <http://dx.doi.org/10.1136/bmjebm-2018-111012>.

Macdonald writes: “Certainly, if one has concerns about the accuracy or quality of any Cochrane product, it is perfectly appropriate – indeed essential – that these should be surfaced, but surely one should first do so via our well-established internal avenues and processes? In my view, only when these are exhausted is it appropriate even to consider raising it externally, and - if one is a Board Member – surely then *only* after one has exhausted this forum **and resigned** from the Board?”

I am not aware of any rules that oblige us to first discuss our criticism internally, behind closed doors, and it is not a rule I would favour. We have recently experienced a 19-months delay before our criticism of a Cochrane review was published within the review, and we have also experienced, and people have complained to us, that relevant criticism was never published. It is therefore essential for the timely advancement of science that we also sometimes publish our criticism in medical journals. Furthermore, I have a duty to my PhD students. The first author, Lars Jørgensen, is my PhD student, and it is therefore important for him to have published this paper, which can be included in his PhD.

Macdonald recognises that criticism comes with her job as editor, “but I do not expect someone in a leadership position within Cochrane (or any position, come to that), to act in such a high-handed and irresponsibility [sic] manner, and I strongly object to someone holding the position of Trustee acting in this way. What makes it worse, is that in this case – as others – the criticisms were entirely, or largely, unfounded.”

These are empty allegations. Macdonald does not provide any evidence for them but instead chooses to use emotive language. Our criticism of the Cochrane HPV review is based on the scientific evidence we describe in our paper and we shall publish more on this shortly.

Macdonald ends her complaint thus: “Personally, I think it is grounds for his removal, hence this email. If he is not removed, I would like the reassurance of the Board that nothing of this kind will be repeated – by any board member – and that if Professor Gøtzsche acts in this way again, that he should not be permitted formally to associate himself with Cochrane. I appreciate the potential backlash of such actions, but it seems to me that our attempts to avoid these by accommodating him have been singularly unsuccessful.”

Again, Macdonald’s inferences and appeal to have me removed are remarkably similar to the ending of the letter by Craig.

Therefore, my comments regarding Craig’s letter also apply to Macdonald’s letter. When leading people in an organisation call for the removal of members who have done nothing wrong, and persecute scientists for publishing their scientific observations, it is a sign that something is badly wrong. Particularly considering that the Cochrane Collaboration is a scientific organisation.

All these letters to the Governing Board appear to be an orchestrated effort to discredit me, among other things, because they are remarkably similar in content. This is also deeply worrying, considering the principles we should abide by in the Collaboration.

² Boesen K, Saiz LC, Erviti J, Storebø OJ, Gluud C, Gøtzsche PC, Jørgensen KJ. The Cochrane Collaboration withdraws a review on methylphenidate for adults with attention deficit hyperactivity disorder. *Evid Based Med* 2017; 10.1136/ebmed-2017-110716.

Where is Cochrane's appeal to my supporters who will attest to my integrity and my right to independently scrutinise the scientific literature? It seems as if my critics have been given a platform to disparage me and my supporters are being ignored.

Censoring science is embarking on a dangerous downhill course from which it might not be possible to come back.

A handwritten signature in blue ink, appearing to read 'P. Gøtzsche', with a stylized, cursive script.

Peter C Gøtzsche
Professor, Director, MD, DrMedSci, MSc
Nordic Cochrane Centre
Rigshospitalet, Dept 7811

3rd September 2018

Martin Burton and Marguerite Koster
Co-Chairs
Cochrane Governing Board

Dear Co-Chairs

Re: Breach of the Code of Conduct of the Governing Board

I write to you as a member of Cochrane with regard to a breach of the Code of Conduct of the Governing Board by Professor Gotzsche.

Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. *BMJ Evidence-Based Medicine* 2018.
doi:10.1136/bmjebm-2018-111012

I consider the publication in the BMJ-Evidence Based Medicine journal by Professor Gotzsche breaches several different sections of the Code of Conduct. Whilst I respect the right of individuals to have academic disagreements this article went much further than that and in doing so has caused damage to the reputation of Cochrane and the Cochrane Library. In particular, I draw attention to the following words of the closing paragraph.

“Part of the Cochrane Collaboration’s motto is ‘Trusted evidence’. We do not find the Cochrane HPV vaccine review to be ‘Trusted evidence’, as it was influenced by reporting bias and biased trial designs. We believe that the Cochrane review does not meet the standards for Cochrane reviews or the needs of the citizens or healthcare providers that consult Cochrane reviews to make ‘Informed decisions’, which also is part of Cochrane’s motto.”

These sentences are a direct threat to the reputation of Cochrane. The response to this article written by the Editor in Chief and others has reported so many inaccuracies in the article that one can only conclude that it was not the Cochrane review that was wrong but this article with its many misleading statements.

<https://www.cochrane.org/news/cochranes-editor-chief-responds-bmj-ebm-article-criticizing-hpv-review>

The Code of Conduct of the Governing Board has the following statements:

3.1 Selflessness

Trustees have a general duty to act with probity and prudence in the best interest of the charity as a whole.

3.2 Integrity

The charity's Trustees should conduct themselves in a manner which does not damage of undermine the reputation of the organization or its staff.

3.4 Accountability

The Trustees:

- *Have a duty to comply with constitutional and legal requirements and to adhere to official organisational policies and best practice in such a way as to preserve confidence in the charity;*

3.7 Leadership

When speaking privately (that is, when speaking not as a Board member) adhere to the Spokesperson Policy and make great efforts to uphold the reputation of the charity and those who work in it.

5.0 Trustees Declaration

I will make known any interest in any matter under discussion which creates either a real danger of bias (that is, the interest affects me, or a member of my family, or friends, or organisation, more than the generality affected by the decision); or which might reasonably cause others to think it could influence the decision, and withdraw from the room and not participate in discussion or decision making, unless the remaining Trustees agree otherwise.

- *I will abide by the Code of Conduct for Trustees of the charity.*
- *In the event of my breaching this Code I am prepared to accept sanction as determined by the Board.*

I ask the Governing Board to consider this breach and if in agreement with my view, then act accordingly by removing Professor Gotzsche from the Governing Board.

Cindy Farquhar

Coordinating Editor of the Gynaecology and Fertility Group

7 September 2018

Gøtzsche's response to letter to Governing Board co-chairs from 3 September from Cindy Farquhar

Cindy Farquhar, who was a Board co-chair till August 2018, complains about the paper we published on 27 July where we criticise a Cochrane review of the HPV vaccines.¹

Farquhar claims that our paper has caused damage to the reputation of Cochrane and the Cochrane Library but provides no evidence. Farquhar points to the last paragraph of our paper: "Part of the Cochrane Collaboration's motto is 'Trusted evidence'. We do not find the Cochrane HPV vaccine review to be 'Trusted evidence', as it was influenced by reporting bias and biased trial designs. We believe that the Cochrane review does not meet the standards for Cochrane reviews or the needs of the citizens or healthcare providers that consult Cochrane reviews to make 'Informed decisions', which also is part of Cochrane's motto."

Farquhar omitted the last sentence in our last paragraph: "We recommend that authors of Cochrane reviews make every effort to identify all trials and their limitations and conduct reviews accordingly."

We simply acknowledged that Cochrane reviews are considered 'trusted evidence' and that the high standards of Cochrane should be upheld. For the reasons outlined in our BMJ Evidence-Based Medicine paper, we do not believe the Cochrane HPV vaccine review met those standards.

Furthermore, Farquhar writes that our "sentences are a direct threat to the reputation of Cochrane."

I am alarmed by Farquhar's statement. The implication is that any independent, scientific criticism of Cochrane reviews is somehow undermining the organisation. We would argue that our critique does the opposite. Its purpose was to add to a robust debate about important research, especially regarding the potential harms of HPV vaccines.

Farquhar quotes what the Cochrane's Editor in Chief and Deputy uploaded on Cochrane's website on 3 September,² the same day Farquhar wrote to the co-chairs, to reinforce her own beliefs. Farquhar rushed to judgement without awaiting our reply to the editors. Furthermore, she considered the editors' views the final word and "truth" in an ongoing scientific debate.

¹ Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. *BMJ Evidence-Based Medicine* 2018; 27 July. <http://dx.doi.org/10.1136/bmjebm-2018-111012>.

² Tovey D, Soares-Weiser K. Cochrane's Editor in Chief responds to BMJ EBM article criticizing HPV review. 2018; 3 Sept. <https://www.cochrane.org/news/cochranes-editor-chief-responds-bmj-ebm-article-criticizing-hpv-review>.

We are working on a response to the article written by the Cochrane editors, which we found contained several misleading statements and avoided responding to our most serious criticisms. We shall publish our response in BMJ Evidence-Based Medicine.

Cochrane is about evidence-based medicine, but Farquhar takes on an authority she doesn't have in a scientific matter when she declares that, "The response to this article written by the Editor in Chief and others has reported so many inaccuracies in the article that one can only conclude that it was not the Cochrane review that was wrong but this article with its many misleading statements."

This is eminence-based medicine and it is exactly the way the pharmaceutical industry argues when its wrong-doing has been unequivocally documented and it has no counter arguments. This is when we see emotive statements without any substance or documentation. Our criticism of the Cochrane HPV review is highly justified and based on evidence we have studied very carefully. My research group has worked with clinical study reports obtained from the European Medicines Agency (EMA) about the HPV vaccine trials for two years, and we therefore have a unique knowledge about this.

Furthermore, Farquhar's evidence-free criticism of our paper does not reflect what the Cochrane editors wrote about it. Their report is helpful for advancing our common understanding of the science, and they acknowledge that our paper "reinforces work that forms a key element of Cochrane's Content Strategy in relation to the selection of data sources for reviews." One of our main criticisms of the Cochrane review was that the authors missed many trials and data, particularly on potential serious harms, that could have been included in the review. This will become even clearer when we publish our own systematic review of the HPV vaccine trials, which is based entirely on clinical study reports from EMA. These reports are far more reliable than the reports the drug companies have published and which formed the bulk of the data in the Cochrane review.

The Editor in Chief and his Deputy end their criticism of our criticism thus: "Having completed our investigation, we conclude that Jørgensen et al made allegations that are not warranted and provided an inaccurate and sensationalized report of their analysis." This we consider unfortunate. We wonder why Cochrane's Editor in Chief and Deputy do not limit themselves to a scientific debate but use strongly emotive language in their attempt at discrediting our scientific work. This has nothing to do with the science.

Farquhar ends her letter by citing bits from the Code of Conduct of the Governing Board:

3.1 Selflessness

Trustees have a general duty to act with probity and prudence in the best interest of the charity as a whole.

3.2 Integrity

The charity's Trustees should conduct themselves in a manner which does not damage or undermine the reputation of the organization or its staff.

3.4 Accountability

The Trustees:

- Have a duty to comply with constitutional and legal requirements and to adhere to official organisational policies and best practice in such a way as to preserve confidence in the charity;

3.7 Leadership

When speaking privately (that is, when speaking not as a Board member) adhere to the Spokesperson Policy and make great efforts to uphold the reputation of the charity and those who work in it.

5.0 Trustees Declaration

I will make known any interest in any matter under discussion which creates either a real danger of bias (that is, the interest affects me, or a member of my family, or friends, or organisation, more than the generality affected by the decision); or which might reasonably cause others to think it could influence the decision, and withdraw from the room and not participate in discussion or decision making, unless the remaining Trustees agree otherwise.

- I will abide by the Code of Conduct for Trustees of the charity.
- In the event of my breaching this Code I am prepared to accept sanction as determined by the Board.”

Farquhar writes: “I ask the Governing Board to consider this breach and if in agreement with my view, then act accordingly by removing Professor Gotzsche from the Governing Board.”

I have acted in the best interests of the charity. We are a scientific organisation and if we start censoring ourselves or others, we will lose our integrity and reputation very fast, and it may be impossible to regain it. An open scientific debate advances science and benefits our stakeholders - the general public, the patients, the healthcare providers and the politicians - who have decided to fund all the various Cochrane entities across the world, including my own centre, the Nordic Cochrane Centre, which is on government finances, like the three Cochrane review groups based in Denmark. We have a good dialogue with the Danish Minister of Health who congratulated us one month ago on our efforts to challenge medical dogma.

In science, our loyalty must always be with the science. This will benefit the Cochrane Collaboration in the long run. In 2004, we published a paper in the BMJ, “Quality of Cochrane reviews: assessment of sample from 1998,” which was an analysis of 53 new Cochrane reviews by 11 Cochrane methodologists. We informed our Cochrane colleagues well ahead of publication, which proved to be to our own disadvantage, as it resulted in the Steering Group (now called the Governing Board) putting pressure on us not to publish the results. I was summoned to a Steering Group meeting to explain why we wanted to publish. I said that since we belonged to an organisation that constantly assesses and critiques others’ research and points out when inconvenient results are being suppressed. It would therefore clearly be wrong to suppress our own results, which would also be an act of censorship.

I also said that it would demonstrate Cochrane’s strength that we were willing to criticise ourselves. Furthermore, I explained that it was important for patients, doctors and others to know that conclusions of Cochrane reviews should be viewed with caution, which means that they needed to read more than just the conclusion. As it turned out, nothing untoward happened. People were happy that we published our observations and this did not harm the reputation of Cochrane. In fact, our paper benefited Cochrane. It led to several other quality improvement initiatives being undertaken the following years. Further, BMJ’s editor gave the two co-chairs the opportunity to

publish an editorial in the BMJ alongside our review where they outlined what was currently ongoing in Cochrane, which also benefited Cochrane.

Farquhar says: “The charity’s Trustees should conduct themselves in a manner which does not damage or undermine the reputation of the organization or its staff.”

I reject the allegation that I have damaged or undermined the reputation of the organisation. Cochrane invites open scientific debate, which includes constructive criticism of each other’s research. We even have an annual prize for it: “Cochrane values constructive criticism of its work and publicly recognises this through the Bill Silverman Prize ... with a view to helping to improve its work, and thus achieve its aim of helping people make well-informed decisions about health care.”

In accordance with this, the Spokesperson Policy, introduced in 2015, states: “Many Cochrane contributors are experts in their field and have every right to discuss their work and express their personal views – this may include expressing opinions on Cochrane policies and Cochrane Reviews. This policy is not intended to infringe Cochrane’s long-standing tradition of rigorous academic and scientific debate.”

Farquhar loses the perspective of why we have a Cochrane Collaboration when she focuses entirely on organisational matters. It is actually being loyal – and not disloyal - to the principles of Cochrane to highlight publicly when a Cochrane review is problematic. It is also essential for our stakeholders who need to know when there are important uncertainties about the science.

We have criticised Cochrane reviews before and the last time we provided extensive criticism, the review was retracted. Also on that occasion, like our criticism of the HPV vaccine review, we published our criticism in BMJ Evidence-Based Medicine (then called Evidence-Based Medicine).³

It is curious that, in Farquhar’s letter to the Board, she mentions items 3.4 and 3.7 without addressing how they relate to our paper. To reiterate, I believe I have lived up to these obligations as a trustee. The trustees “Have a duty to comply with constitutional and legal requirements and to adhere to official organisational policies and best practice in such a way as to preserve confidence in the charity;” and “When speaking privately (that is, when speaking not as a Board member) adhere to the Spokesperson Policy and make great efforts to uphold the reputation of the charity and those who work in it.”

As I have not breached any code, it is highly inappropriate that Farquhar now calls for my removal from the Governing Board.

Farquhar has just stepped down as a trustee, in her role as co-chair of the Board, and it is worth noting that she has been involved with tampering with minutes from the Board meeting in Genève in 2017 related to an important item about procedural fairness I brought up. This is clear if one reads the official minutes from the meeting. I protested against this at the time, which is also clear from the minutes. Manipulating with the minutes of a Governing Board meeting for a charity is a serious offence. It is akin to perjury in legal cases and could be considered a criminal act according to the UK

³ Boesen K, Saiz LC, Erviti J, Storebø OJ, Gluud C, Gøtzsche PC, Jørgensen KJ. The Cochrane Collaboration withdraws a review on methylphenidate for adults with attention deficit hyperactivity disorder. Evid Based Med 2017; 10.1136/ebmed-2017-110716.

Forgery and Counterfeiting Act 1981. It would likely also be considered mismanagement by the Charity Commission.

I therefore believe Farquhar has a conflict of interest when asking for my removal from the Governing Board. It is interesting that Farquhar cites "5.0 Trustees Declaration. I will make known any interest in any matter under discussion which creates either a real danger of bias." She did not specify why she mentioned this, but she might have violated this herself since it could be argued that she has a conflict of interest in relation to the events in 2017.

In summary, I find Farquhar's letter deeply worrying. When leading people in an organisation start talking about removing members who have done nothing wrong but have just published their scientific observations, it is a sign that something is badly wrong. Particularly considering that the Cochrane Collaboration is a scientific organisation. These letters to the Governing Board look remarkably similar in content and appear more like an orchestrated effort to discredit me than an attempt to critically assess my scientific work. This is also very worrying, considering the principles we work by in the Collaboration. Censoring science is embarking on a dangerous downhill course from which it might not be possible to come back.

The three most recent letters were sent to the Board on 3 and 5 September. It could be investigated if this was related to the fact that I sent my report to Cochrane's law firm on 30 August where I document serious mismanagement at the top of the Cochrane Collaboration.



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<https://ebm.bmj.com/content/early/2018/07/27/bmjebm-2018-111012.responses#the-cochrane-hpv-vaccine-review-was-incomplete-and-ignored-important-evidence-of-bias-response-to-the-cochrane-editors>

- [The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias: Response to the Cochrane editors](#)

Lars J Jørgensen, Peter C. Gøtzsche and Tom Jefferson

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The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias:
Response to the Cochrane editors

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- Other Contributors:
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The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias:
Response to the Cochrane editors

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Summary

In a report uploaded on the Cochrane.org website on 3 September 2018 (1), Cochrane's Editor in Chief and Deputy Editor in Chief responded to our analysis published in BMJ Evidence-Based Medicine on 27 July 2018 (2) of the Cochrane review of the HPV vaccines published on 9 May 2018 (3).

The Cochrane editors acknowledge (1) that our analysis (2) addresses the importance of the selection of data sources for reviews, and we hope that Cochrane will take the threat posed by reporting bias (4) more seriously by using clinical study reports, rather than journal publications.

The Cochrane editors claimed that we had “substantially overstated” our criticisms and they concluded that “Jørgensen et al made allegations that are not warranted and provided an inaccurate and sensationalized report of their analysis” (1).

Here we address the Cochrane editors' findings and present our further assessment and additional findings.

In summary, we found that our analysis (2) was appropriate and that the Cochrane editors substantially ignored several of our criticisms (1):

- 1) The Cochrane editors' cross referencing (1) with our HPV vaccine study index (5) showed that the Cochrane HPV review was incomplete and resulted in 8% additional eligible female participants (6,191/73,428). Due to the discrepancy with our analysis (2), we assessed our index again and found that the Cochrane HPV review should have included at least 35% (25,550/73,428) additional eligible females in its meta-analyses;
- 2) The Cochrane editors' considerations on harms ignored several of our criticisms including the incomplete reporting of serious adverse events in several of the Cochrane HPV review's included studies;
- 3) The Cochrane editors' considerations of the trials' adjuvant and vaccine comparators was ambiguous, opaque, inaccurate and ignored the fact that the studies only tested the vaccine antigens—not the vaccines;
- 4) The Cochrane editors' response on the Cochrane HPV review's included composite surrogate outcomes was superficial and did not consider the substantial bias and confounding that these outcomes involve;
- 5) The Cochrane editors' assessment of the Cochrane HPV review authors' conflicts of interest was incomplete and ignored several additional important conflicts of interest;
- 6) The Cochrane editors' considerations on the media coverage did not recognize that it should be balanced and free from financial conflicts of interest;
- 7) The Cochrane editors' response appeared to advocate scientific censorship, which we do not approve of;
- 8) In conclusion, our analysis (2) was appropriate, the Cochrane editors substantially ignored several of our criticisms (1) and the Cochrane review is still incomplete and ignores important evidence of bias.

- 1) The Cochrane editors' cross referencing with our HPV vaccine study index

We used our index (5) to identify additional eligible studies for the Cochrane HPV vaccine review that included 73,428 women from 26 studies (3).

From our index (5), the Cochrane editors (1) identified:

1. "five [i.e., 5/26 = 19%] eligible completed studies with available data representing 5267 women [i.e., 5,267/73,428 = 7%, that] may have been missed from the Cochrane Review, as a consequence of the search being based on bibliographic databases rather than trials registers."
2. One "Additional 9-valent [Gardasil 9] study NCT01047345," adding 924 women to the numerator: 6,191/73,428 = 8% additional women.
3. "Five studies awaiting classification (not recruiting, but no results available) potentially relevant for the current Cochrane Review" that included 4,044 participants.
4. "Eight ongoing studies (actively recruiting, no results available) potentially relevant for the current Cochrane Review" that included 121,531 participants.

The Cochrane editors' analysis (1) shows that the Cochrane HPV review was incomplete. In their "Appendix A", the Cochrane editors updated 20 of the Cochrane HPV review's meta-analyses (20/66, 30%) with the additional data and added seven meta-analyses of the HPV vaccine Gardasil 9 (1), but as of September 14 2018 they have not updated the Cochrane review itself with the additional data (3).

It is not clear why the Cochrane editors thought that our study index (5) "did not appear to identify any important eligible studies" (6). Our index was sent to the editors on 19 January 2018. The

Cochrane review was published 110 days later on 9 May 2018 (3), but it seemingly took the editors only 25 days from launching their “investigation” on 9 August 2018 (6) to updating their Cochrane review on 3 September 2018 (7) with the missing studies.

Our initial assessment of the Cochrane HPV review’s included studies:

Initially, we had cross-referenced the study IDs from our index with the 26 included study IDs in the Cochrane HPV review’s “Appendix 6.1.1. Published reports included in the Cochrane review,” and found 20 studies not included in the review. For example, we did not find any of the 20 studies included in the Cochrane HPV review’s two serious adverse events analyses: “Figure 10” of journal publication data and “Analysis 7.6” of data that the Cochrane authors “considered to represent the most complete follow-up” (3). This led us to believe that the studies were not included in the Cochrane review. When we checked again, we found some of the studies in the review’s reference list (3). The Cochrane HPV reviewers chose to use idiosyncratic referencing with study IDs such as “Phase 2 trial (ph2,2v)”, “Immunobridging (ph3,2v)” and “CVT (ph3,2v), which made the study assessment complicated. For numbers of participants, we did not subtract the male participants that were included in three of the studies, as we should have done.

As stated in our index paper (5), our detective work involved a degree of uncertainty, as we did not want to dismiss any possibly eligible studies. Therefore, the index included a “possibly exist” category for studies for which we only had one verification source. Four studies in our analysis (2) had no numbers for randomised participants; these were “probably exist” studies. We have obtained additional information for three of these studies, but we are still not sure that the fourth study exists in clinical study report form, as the manufacturer (Merck) did not answer our request for this information (2,5).

In Table 1, we list the 20 studies (plus the additional one that the Cochrane editors identified: NCT01489527) that we identified as eligible but not included in the Cochrane HPV review.

Table 1: Our reassessment of the studies we had identified as additionally eligible for the Cochrane HPV vaccine review [*Key: RCT = randomised clinical trial]

See: <https://blogs.bmj.com/bmjebmspotlight/files/2018/09/Cochrane-HPV-vaccine...>

Our analysis reinforces the view that Cochrane HPV review is incomplete. We found an additional 25,550 females (and possibly up to 30,195 for the Cochrane HPV review’s serious adverse events meta-analyses) that are eligible for the Cochrane HPV review’s meta-analyses. Furthermore, we found freely available clinical study reports for 6 of the 21 studies on GlaxoSmithKline’s trial register, which the Cochrane authors used data from. Clinical study reports are far more reliable than published reports (4), in particular in relation to possible serious harms. It is therefore not merely the studies the authors of the Cochrane HPV review missed; they also missed benefits and harms data from the studies they included. In addition, the criteria that the Cochrane authors used for inclusion of data in their primary serious adverse events analysis (Analysis 7.6) are not clear: “The primary analysis for these outcomes included data that we considered to represent the most complete follow-up” (3).

2) The Cochrane editors’ considerations on harms

The Cochrane HPV review’s harms analyses (“Comparison 7”) include seven meta-analyses (four of which report injection site harms) where the three most clinically important ones—deaths

(Analysis 7.7), serious adverse events (Analysis 7.6) and systemic adverse events (Analysis 7.5)—contain errors or are incomplete.

Deaths

The Cochrane HPV review's authors found 5% (90 vs. 86) more deaths in "Analysis 7.7" (journal publication and registry data) vs. "Figure 11 (only journal publication data). We found that this discrepancy reflects the difference between the study FUTURE III's (V501-019) journal publication and registry entry (8 vs. 12 deaths). We also found that the Cochrane HPV review gave an incorrect number of deaths for the VIVIANE study (HPV-015): 13 deaths in the HPV vaccine group and 5 deaths in the AIOH3 group; according to VIVIANE's journal publication (8), there were 14 deaths in the HPV vaccine group and 3 deaths in the Al(OH)₃ group.

The Cochrane authors state that "The deaths reported in the trials had an identified cause, and none were assessed to be due to vaccination" (3), but such judgements are biased, particularly in industry sponsored trials, and the analysis of deaths should be based on all events (4).

Serious adverse events

There are 11% (4,758/4,291) more serious adverse events in "Analysis 7.6" (journal publication and register data) compared to "Figure 10" (only journal publication data). Since there were more serious adverse events and more deaths in the register entry data, we wonder why the Cochrane authors did not include register entry data for all their outcomes.

We also wonder why three (possibly four) studies were not included in the Cochrane HPV review's serious adverse events meta-analyses (see Table 1). The Cochrane editors write that we "claim that the [Cochrane] review authors made an error in their reporting of serious adverse events in relation to the PATRICIA [HPV-008] study. This is not the case" (1). We stated that "the Cochrane authors did not explain what the serious adverse events consisted of or whether some of them were more common in the HPV vaccine groups," (2) and gave the example that "the PATRICIA trial publication only included two thirds (1400/2028) of the serious adverse events listed on ClinicalTrials.Gov" (2). The 2,028 individual serious adverse events listed in ClinicalTrials.Gov are listed with the total denominators of randomised women for PATRICIA, for example, "Headache: participants affected/at risk: 5/9319 [in the HPV vaccine group] (0.05%) vs. 1/9325 [in the hepatitis a vaccine group] (0.01%)" (9), suggesting that the numbers represent participants with serious adverse events.

The Cochrane editors did not consider our highly relevant observations about the incomplete reporting of serious harms (1). For example, we wrote that "FUTURE I, FUTURE II and FUTURE III, which in total included 21 441 women with up to 4 years follow-up, only reported serious adverse events occurring within 14 days post-vaccination" (2). The editors did not comment on how such reporting of serious adverse events for only about 3% of the trial periods (FUTURE I, II and III: [(14 days*3 vaccinations)/(365 days*4 years)]) resulted in the Cochrane authors' judgements of "low risk of bias" for reporting bias (1).

Both the 1st Cochrane HPV review protocol from 2011 (10) and the 2nd protocol from 2013 (11) list the primary outcome of "serious adverse events observed after four weeks of administration of the vaccine during the trial" (emphasis added), i.e., an incomplete reporting of serious adverse events was already a criterion at protocol stage.

Systemic adverse events

The Cochrane editors (1) did not comment on our criticism of the lack of studies (2)—including PATRICIA (HPV-008)—from the Cochrane HPV reviews’ “Analysis 7.5: systemic adverse events” (3). Analysis 7.5 is incomplete—in particular, for Cervarix studies where the Cochrane review only included numbers for “solicited general adverse events” for two studies (3): HPV-009 and HPV-015, although data for such events are eligible from several additional studies, for example, HPV-001, HPV-008, HPV-013, HPV-029, HPV-030, HPV-033, HPV-035, HPV-038 and HPV-058. The inclusion of these studies could change the Cochrane review’s conclusion that “Systemic events with general mild symptoms were similarly frequent in vaccinated recipients and placebo or control vaccine recipients” (3). As we wrote, “On ClinicalTrials.gov, PATRICIA has 7129 vs 6557 systemic events listed under ‘Results: Other Adverse Events (General disorders)’, which in itself is a significantly increased risk: RR 1.09 (95% CI 1.07 to 1.11)” (2).

Furthermore, the Cochrane authors did not address that “solicited general adverse events [Cervarix]” only were reported 7-days post-vaccination and “systemic adverse events [Gardasil]” only 14-days post-vaccination (3).

Assessment of safety signals

The Cochrane editors did not comment on our safety signal section (1). Some potential HPV vaccine-related harms to the nervous system—or “autonomic dysfunction syndromes,” as the Cochrane editors described them (1)—have been reported (2). The Cochrane authors should have used trial register data to investigate such safety signals; for example, if they had summarised the nervous system disorders from PATRICIA’s (HPV-008) ClinicalTrials.gov list of serious adverse events (9), they would have found more serious nervous system disorders in the HPV vaccine arm: 39/9,319 vs. 25/9,325 in the hepatitis A vaccine arm, risk ratio 1.56 (95% CI 0.95 to 2.58). The Cochrane authors write that “All estimates of adverse effects in our review were restricted to those reported from randomised trials and therefore could not detect rare events, for which post-marketing surveillance, pharmacovigilance activities and linkage studies, joining vaccine and morbidity registries, are needed” (3), but the review’s results might have been different had the authors included serious adverse events on both an individual and organ system level.

Additional points on the Cochrane editors’ harms assessment

The Cochrane HPV review (3) did not include the following harms categories that were reported in the eligible studies’ clinical study reports and in some journal publications: “unsolicited adverse events” (Cervarix), “medically significant conditions” (Cervarix), “new onset chronic/auto-immune disease” (Cervarix) and “new medical history” (Gardasil), even though the Cochrane authors mention the two first categories (reported in “Angelo 2014”) (3).

3) The editors’ considerations of the trials’ adjuvant and vaccine comparators

The Cochrane editors stated that “The trials comparators [sic] were unambiguously, transparently, and accurately described” (1), but in the Cochrane HPV review’s “Plain language summary” intended for lay readers, the review authors state that “The risk of serious adverse events is similar in HPV and control vaccines (placebo or vaccine against another infection than HPV)” (emphasis added) (3), and the word “placebo” is repeated throughout the review and all its meta-analyses, which make the review ambiguous, opaque and inaccurate, as no included trial in the review used a placebo comparator.

The WHO states that using adjuvant or another vaccine as comparators instead of placebo makes it difficult to assess the harms of a vaccine (12). The HPV vaccine trials' adjuvant comparators—Merck's amorphous aluminium hydroxyphosphate sulphate (AAHS) and GlaxoSmithKline's aluminium hydroxide (Al(OH)₃)—have not been tested against an inert comparator in human trials. The adjuvants' clinical properties are largely unknown; they are not regulated on their own, as regulators do not regard them as “active ingredients” (13). For example, Merck's AAHS has a confidential formula and its properties are variable from batch to batch and even within batches (14). Because the HPV vaccines and their adjuvants had similar harms profiles, the manufacturers and the regulators concluded that the HPV vaccines are safe. However, this is like saying that cigarettes and cigars must be safe because they have similar harms profiles.

In addition, in those trials with a non-HPV vaccine comparator, the HPV vaccine aluminium adjuvant was used in nearly all the non-HPV comparator vaccines; for example, PATRICIA's hepatitis A (Havrix) comparator contains Al(OH)₃ (only the studies HPV-032 and HPV-063 used a non-aluminium containing comparator: the hepatitis a vaccine Aimmugen). Thus, the presence of AAHS or Al(OH)₃ in nearly all arms of the studies thwarted the harms assessment. The studies tested the vaccine antigens—not the vaccines.

The exclusion criteria of the Cochrane HPV review's included trials

The Cochrane editors (1) did not consider our point that many of the Cochrane HPV review's included studies had excluded female participants “if they had received the [aluminium] adjuvants before or had a history of immunological or nervous system disorders; for example, in the PATRICIA trial with 18 644 women and the FUTURE II trial with 12 167 women” (2). These exclusion criteria lower the external validity of the studies and suggest that there were concerns about harms caused in such participants by the adjuvants.

4) The Cochrane editors' response on the Cochrane HPV review's included outcomes

The Cochrane editors state that “The selection of outcomes for benefits was appropriate and was consistent with World Health Organization [WHO] guidance” (1).

In 2004, the WHO recommended the use of cervical intraepithelial neoplasia or worse: CIN2+, as the primary outcome (15). CIN2+ is a composite surrogate outcome for cervical cancer and includes CIN2, CIN3, AIS and cervical cancer. In 2014, the WHO recommended persistent HPV infection instead of CIN2+ (16). The WHO's CIN2+ and persistent HPV infection recommendations were approved to “accelerate vaccine development and evaluation” (16). Since 2014, HPV vaccines have only been required to show benefits against persistent HPV infection for getting regulatory approval as a vaccine against HPV related cancer (16).

According to the 2004 WHO recommendations, “Representatives of industry did NOT participate in the drafting of recommendations” of the use of CIN2+ (15), but researchers with conflicts of interest did participate in the recommendations, for example, Ian Frazer—the co-inventor of the HPV vaccine who “receives royalties from sales of HPV prophylactic vaccines, and is a consultant for Merck, [and] GlaxoSmithKline” (17). In 2014, all 17 members of the WHO group that recommended persistent HPV infection instead of CIN2+ as the primary outcome had financial ties with the HPV vaccine manufacturers. For example, the group included two patent-holders of the

HPV vaccines antigens (or “virus-like particles”), who are entitled “to a limited share of royalties [that] the NIH [National Institutes of Health] receives for these technologies” (16).

Outcomes such as CIN2+ can be difficult to interpret, and significant clinical differences can be hidden in the Cochrane HPV review’s meta-analyses (3). For example, as an extreme example, if there were 5 participants with CIN2+ in the HPV vaccine group and 10 in the comparator group, the 5 participants in the HPV vaccine group could theoretically all have cervical cancer while the 10 in the comparator group could have CIN2 lesions that often regress (18,19).

The Cochrane editors (1) did not address our point that the VIVIANE study (HPV-015) included in its register entry “one case of ‘Adenocarcinoma of the cervix’ and one case of ‘Cervix cancer metastatic’ ... in the HPV vaccine group” (2), and that the Cochrane HPV review includes a death caused by “Cervix cancer metastatic” in the HPV vaccine group, which was not mentioned in the main text (3). The Cochrane editors (1) did not address our point that the “Cochrane review’s 26 trials mainly included women below age 30 and used frequent cervical screening (often every 6 months) that did not reflect real-life practice (often every 3–5 years),” which also lower the external validity of the studies (2).

The Cochrane HPV review’s primary analysis—Analysis 1.1 that includes four trials (CVT, FUTURE I, II and PATRICIA)—was of “High-grade cervical lesions in hr[high risk]HPV DNA negative women at baseline: CIN2+ associated with HPV 16/18 [HPV types 16 and 18 are targeted by the HPV vaccines]”. Analysis 1.1 is affected by selection bias. Up to 15% of cervical cancers may not contain HPV (20), and many cervical cancers are infected with more than one HPV type. For example, in the clinical study report that we received for PATRICIA (HPV-008), 63 of the 102 of CIN2+ cases were co-infected with two or more HPV types. In PATRICIA, if an HPV vaccine and a comparator participant were both diagnosed with CIN2+ and positive for HPV types 31 and 33, and HPV 16/18, 31 and 33, respectively, the HPV vaccine CIN2+ case would be assigned as caused by non-vaccine types (31 and 33) and excluded from the analyses (such as Analysis 1.1), while the comparator case would be caused by HPV 16/18 (HPV vaccine types) and included in the analyses; even though HPV types 31 and 33 could have caused the CIN2+ lesions in both participants. The Cochrane HPV review’s analyses of HPV infection (“Comparison 4, 5 and 6”) include 21 meta-analyses that all analyse infection of HPV vaccine types (i.e., HPV types 6, 11, 16 and 18)—not infection of any HPV type, which would decrease confounding by HPV co-infection.

Another issue with Analysis 1.1 (3) is the large proportion of excluded females: 23,676 participants were included, but the included four studies (CVT, FUTURE I, II and PATRICIA) randomised 43,732 participants, so 46% females were excluded. The Cochrane authors did not mention that FUTURE I, II and PATRICIA—that contained 49% (36,266/73,428) of the Cochrane review’s sample (3)—were stopped early when HPV 16/18-related CIN2+ was significantly reduced for the HPV vaccine populations. Trials stopped early for benefits are known to exaggerate the effects by 29% on average compared to completed trials of the same intervention (21).

The majority (24 of 31) of the Cochrane HPV review’s meta-analyses of histological outcomes (“Comparison 1, 2 and 3”) consider cervical lesions associated with HPV vaccine types (3). A less biased meta-analysis of cervical lesions is “Analysis 3.7: High-grade cervical lesions in women regardless of baseline HPV DNA status: Any CIN2+ irrespective of HPV types, at least 1 dose.” The Cochrane HPV review’s primary analysis—Analysis 1.1—is much more statistically significant than Analysis 3.7 (3): risk ratio 0.01 (95% CI 0.01 to 0.05) vs. 0.79 (95% CI 0.65 to

0.97), i.e., a ratio of relative risks of 0.01 (95% CI 0.006 to 0.03), which may reflect the selection bias in Analysis 1.1.

Both the 1st Cochrane HPV review protocol from 2011 (10) and the 2nd protocol from 2013 (11) list "Invasive cervical cancer" as a primary outcome. The protocols state that the Cochrane authors "will contact study authors or data owners to request data on the outcomes that were not reported" (11), which they did not do for invasive cervical cancer. Also, "If data are reported for grouped end points, we will contact trial authors or data owners to request data on the separated outcomes" (11), which the authors did not do for CIN2+ and CIN3+. But the Cochrane authors could have looked in the journal publications; for example, CIN3 irrespective of HPV type in intention-to-treat populations was reported in FUTURE I (22) ("79/2723 [in the HPV vaccine group] vs. 72/2732 [in the AAHS group]") and FUTURE II (23) ("127/6087 [in the HPV vaccine group] vs. 161/6080 [in the AAHS group]": in total 206/8,810 vs. 233/8,812; risk ratio 0.91 [95% CI 0.66 to 1.27]).

Furthermore, the Cochrane authors write that "No results were found for the outcomes any [sic] CIN3+ or AIS+ irrespective of HPV type" (3). If the Cochrane authors had looked in the freely available clinical study reports on GlaxoSmithKline's trial register that the authors assessed, they would have found the outcomes CIN3+ irrespective of HPV type for PATRICIA (86/9,319 vs. 158/9,325) and HPV-032/063 combined (9/464 vs. 14/463).

5) The Cochrane editors' assessment of the Cochrane authors' conflicts of interest

The Cochrane editors state that "The review was compliant with Cochrane's current conflict of interest policy" (1). If that is the case, we believe Cochrane should reconsider its policy.

The Cochrane HPV vaccines are expensive blockbuster vaccines generating billions of dollars of revenue (24), and the Cochrane review ought, therefore, to have been independent of any financial conflicts of interests.

The Cochrane editors are confident that the Cochrane authors have no relevant conflicts of interest (2). We do not agree. For example, the Cochrane HPV review's first author, Professor Marc Arbyn—who, according to the Cochrane review (3), only "received travel grants from MSD-Sanofi-Pasteur and GSK, (ceased in 2008)"—was until 2008 on GlaxoSmithKline's advisory board: "Marc Arbyn (GSK advisory Board (interrupted in 2008))" (25); in 2011, "EUROGIN covered his [Marc Arbyn's] travel and lodging expenses ... EUROGIN conferences are financially supported by a range of pharmaceutical companies with an interest in cervical cancer" (26); in 2014, "Marc Arbyn's research unit at The Scientific Institute of Public Health received research support not exceeding 48,000 Euros from MSD-Sanofi Pasteur [co-manufacturer of Gardasil] for a surveillance study of the effects of HPV vaccination in Belgium (SEHIB study) ... His [Marc Arbyn's] unit has also received research support from BD, Bio-Greiner, Abbot, and Cepheid for validation studies of HPV genotyping tests (through the VALGENT studies, valued at 21,000, 21,000 & 38,000€ respectively)" (27); and in 2018, Marc Arbyn is on the EUROGIN programme committee where Merck is a platinum sponsor (28). The Cochrane review's last author, Dr. Markowitz is sponsored by Merck via Medscape ("sponsored by the manufacturer of the quadrivalent vaccine ("supported by an independent educational grant from Merck") (29).

The Cochrane editors (1) do not think that the Costa Rica trial ("CVT", aka HPV-009) was industry funded, and they refer to its publication in JAMA that states that the trial was "funded by the NCI

(grant N01-CP-11005).” The editors write, with reference to JAMA, that “Vaccine was provided for our trial by GSK [GlaxoSmithKline] Biologicals, under a Clinical Trials Agreement with the NCI” (1). GlaxoSmithKline also provided support for aspects of the trial associated with regulatory submissions under “FDA BB-IND 7920” (30). We consider this industry funding.

6) The Cochrane editors’ assessment of the media coverage

The Cochrane editors (1) did not comment on our note that “Two of the experts had financial conflicts of interest with the HPV vaccine manufactures ... [and that] No expert criticised the review” (2).

The editors (1) write that “press coverage could be made more explicit on our organizational websites and other communications, essentially noting that these opinions represent personal perspectives from a range of contributors and do not reflect the views or policies of Cochrane” (1). We agree, but stress that Cochrane’s press officer ought to only include researchers with no financial conflicts of interest.

7) The Cochrane editors appear to advocate scientific censorship

The Cochrane editors wrote that “Scientific debate is to be welcomed, and differences of opinion between different Cochrane 'voices' is not unexpected. However, public confidence may be undermined, unnecessary anxiety caused, and public health put at risk if that debate is not undertaken in an appropriate way. This is especially true when such debates take place in public. There is already a formidable and growing anti-vaccination lobby. If the result of this controversy is reduced uptake of the vaccine among young women, this has the potential to lead to women suffering and dying unnecessarily from cervical cancer.” We believe that our criticism of the Cochrane HPV review is appropriate and has general interest. We believe that providing an assessment of all the evidence reduces uncertainty and allows the public to make informed decisions based on the benefits and the harms of HPV vaccines. Debates over sources of evidence must take place in public, especially when public health interventions are at stake.

8) Conclusion

We did not “substantially overstate” (1) our criticisms of the Cochrane HPV vaccine review (2). The Cochrane editors substantially ignored several of our criticisms. The Cochrane HPV review is still incomplete and ignores important evidence of bias.

The Cochrane editors stated that “Some of the criticisms will inform the next version of this Cochrane Review and the planned review of comparative studies of HPV vaccines,” and that the editors “recognize public concerns about the aluminium-based adjuvants” (1).

The editors also stated that “reliance on the published reports in scientific journals may introduce bias due to incomplete and selective reporting” (1). We agree and remind the Cochrane editors that the Cochrane review on neuraminidase inhibitors substantially changed its conclusions after it got updated and became based on clinical study reports instead of journal publications (31).

With our analysis (2), we have contributed to a scientific debate in an area that is complex and biased. The Cochrane authors stated that they will make a “Request for non-published available

data” such as clinical study reports that “will be integrated in future updates of the review” (3). We can offer them these data, which we have used for our own systematic review that we have submitted for publication.

Article info

Conflicts of interest: LJ and PCG have no conflicts of interest to declare. TJ was a recipient of a UK National Institute for Health Research grant for a Cochrane review of neuraminidase inhibitors for influenza. In addition, TJ receives royalties from his books published by Il Pensiero Scientifico Editore, Rome and Blackwells. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products. In 2011-13, TJ acted as an expert witness in litigation related to the antiviral oseltamivir, in two litigation cases on potential vaccine-related damage and in a labour case on influenza vaccines in healthcare workers in Canada. He has acted as a consultant for Roche (1997-99), GSK (2001-2), Sanofi-Synthelabo (2003), and IMS Health (2013). In 2014 he was retained as a scientific adviser to a legal team acting on oseltamivir. TJ has a potential financial conflict of interest in the drug oseltamivir. In 2014-16, TJ was a member of three advisory boards for Boehringer Ingelheim. TJ was holder of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine. Between 1994 and 2013, TJ was the coordinator of the Cochrane Vaccines Field. TJ was a co-signatory of the Nordic Cochrane Centre Complaint to the European Medicines Agency (EMA) over maladministration at the EMA in relation to the investigation of alleged harms of HPV vaccines and consequent complaints to the European Ombudsman. TJ is co-holder of a John and Laura Arnold Foundation grant for development of a RIAT support centre (2017-2020) and Jean Monnet Network Grant, 2017-2020 for The Jean Monnet Health Law and Policy Network. TJ is an unpaid collaborator to the project Beyond Transparency in Pharmaceutical Research and Regulation led by Dalhousie University and funded by the Canadian Institutes of Health Research (2018-2022).

Authors' experience: PCG has co-authored 17 Cochrane reviews, including several reviews based on clinical study reports. TJ has co-authored 17 Cochrane reviews including the first Cochrane review that used clinical study reports. LJ has co-authored several articles on the HPV vaccines.

Authors' contributions: LJ wrote the first draft. LJ, PCG and TJ contributed to the conception, drafting, critical revision for important intellectual content and the final approval of the article.

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The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias: Response to the Cochrane editors

Table 1: Our reassessment of the studies we had identified as additionally eligible for the Cochrane HPV vaccine review

[* Key: RCT = randomised clinical trial]

N	Assessment	Funder	Study ID	NCTID	Type of study	Clinical study report available on trial register	Number of females	Note
1	Eligible for inclusion in the Cochrane review	GSK	HPV-003	Not identified	RCT*	Yes: https://www.gsk-clinicalstudyregister.com/study/580299/003?search=study&#csr	61	HPV-003 is listed in the Cochrane review as "not published"; however, HPV-003's clinical study report can be freely downloaded from GlaxoSmithKline's trial register. The Cochrane review include data from GlaxoSmithKline's trial register, so it could also include HPV-003.
2	Eligible for inclusion in the Cochrane review	GSK	HPV-040	NCT00534638	RCT	Yes: https://www.gsk-clinicalstudyregister.com/files/2/gsk-106636-clinical-study-report-redact.pdf	20,515	HPV-040 was excluded from the Cochrane review, as it was considered a "phase IV" study (the Cochrane review only included phase II and III studies). We included HPV-040 in our list, as it is described as a "phase III/IV" study in the freely available clinical study report from GlaxoSmithKline's trial register. HPV-040 includes the bulk of the additional eligible participants: 32,176 of which 20,515 were females.
3	Eligible for inclusion in the Cochrane review	GSK	HPV-073	NCT01627561	RCT	No	148	HPV-073 was identified and added to the Cochrane review in the Cochrane editors' reassessment (1).
4	Eligible for inclusion in the Cochrane review	Merck	V501-018	NCT00092547	RCT	No	939	V501-018 had been excluded from the Cochrane review, as gender-specific data could not be obtained. However, the gender-specific data are available and can be obtained from EMA. It is unfortunate that these data were not obtained, as V501-018 is the only Gardasil study with a non-aluminium-containing comparator: "carrier solution" (yeast protein, sodium chloride, L-histidine, polysorbate 80 and sodium borate).
5	Eligible for inclusion in the Cochrane review	Merck	V501-028	NCT00411749	RCT	No	107	V501-028 was identified and added to the Cochrane review in the Cochrane editors' reassessment (1).
6	Eligible for inclusion in the Cochrane review	Merck	V501-030	NCT00496626	RCT	No	400	V501-030 had been excluded from the Cochrane review, as gender-specific data could not be obtained. However, the gender-specific data are available and can be obtained from EMA.
7	Eligible for inclusion in the Cochrane review	Merck	V501-046	NCT01245764	RCT	No	250	V501-046 was identified and added to the Cochrane review in the Cochrane editors' reassessment (1).
8	Eligible for inclusion in the Cochrane review	Merck	V503-006	NCT01047345	RCT	No	924	V503-006 was identified and added to the Cochrane review in the Cochrane editors' reassessment (1). The Cochrane review stated that it "did not include the nine-valent vaccine [Gardasil 9] ... since the randomised trials ... did not incorporate an arm with a non-HPV vaccine control" (3), but as we wrote "The only saline

								placebo trial of approved HPV vaccines is a Gardasil 9 trial (V503-006; NCT01047345) that was published in 2015" (2).
9	Eligible for inclusion in the Cochrane review	Merck	Not identified	NCT01489527	RCT	No	406	We had initially not identified this study as eligible.
10	Eligible for inclusion in the Cochrane review	Xiamen	HPV-PRO-002	NCT01356823	RCT	No	1,600	HPV-PRO-002 was identified and added to the Cochrane review in the Cochrane editors' reassessment (1).
11	Eligible for inclusion in the Cochrane review	None	2010-1090/ GaReCo	NCT20101090	RCT	No	200	2010-1090/ GaReCo is not included in Cochrane review, but data for safety outcomes are eligible for inclusion: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2012-004007-13-DE
Total							25,550	
12	Possibly eligible for inclusion in the Cochrane review	GSK	MENACQWY-TT-054	NCT01755689	RCT	No	1,300	MENACQWY-TT-054 is not included in the Cochrane review. MENACQWY-TT-054 is a five-arm trial in which, during a one-month window, exposure to Cervarix was directly compared to another vaccine (Nimenrix), but at study completion all arms may have received Cervarix.
13	Possibly eligible for inclusion in the Cochrane review	Merck	V501-002	Not identified	RCT	No	Numbers not obtained	In our index, V501-002 is a "probably exist" phase 2 trial for which numbers of female participants could not be obtained. We obtained information for V501-002 from an FDA document (http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222S-2_files/frame.htm) and obtained additional verification for V501-002 from V501-005's unpublished clinical study report: "...subjects who received HPV 16 L1 VLP vaccine (Protocol 002 [i.e., V501-002]) represented the active vaccination group."
14	Possibly eligible for inclusion in the Cochrane review	Merck	V501-004	Not identified	RCT	No	Numbers not obtained	In our index, V501-004 is a "probably exist" study for which numbers of female participants could not be obtained. We obtained information for V501-004 from an FDA document (http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222S-2_files/frame.htm) and obtained additional verification for V501-004 from V501-005's unpublished clinical study report: "Protocol 004 [i.e., V501-004] was a Phase IIa study designed to determine the tolerability and immunogenicity of a range of doses of pilot manufacturing material HPV 16 L1 VLP vaccine (made from the bulk HPV 16 vaccine material used in Protocol 005)."
15	Possibly eligible for inclusion in the Cochrane review	Merck	V503-018	Not identified	RCT	No	615	In our index, V503-018 is a "probably exist" study for which we after our reassessment have obtained numbers of female participants; 615 (http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM190977.pdf). V503-018 may be a study that compares females with males that all were vaccinated with Gardasil. Therefore, V503-018 is "possibly eligible."
16	Possibly eligible for inclusion in the Cochrane review	Merck	V503-019	Not identified	RCT	No	Numbers not obtained	In our index, V503-019 is a "probably exist" study for which we have not obtained numbers of female participants (http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM190977.pdf).
17	Possibly eligible for inclusion in the Cochrane review	Merck	V505-001	NCT00520598	RCT	No	511	In our initial assessment, we had noted that one of V505-001's five (or six) arms got "unspecified placebo," as stated in V505-001's Study Description: https://clinicaltrials.gov/ct2/show/NCT00520598 . On http://indinicaltrials.com/cervical-cancer/NCT00520598/details/ , V505-001 appears to have six arms where one arm receives "placebo." However, it is possible that all non-Gardasil-arms got at least one dose of the V505-formulation, which is a "Multivalent Human Papilloma Virus [HPV] L1 Virus Like Particle [VLP] Vaccine."
Total							27,976	

