2015-03-16

Is the Cochrane Collaboration Meeting its Own Standards?

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

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

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

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

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

It was then that we wrote a letter explaining these concerns. Following our intervention, Cochrane responded, dismissed the most serious cases of conflict of interest, and the panel was reconstituted in December 2013. However, two authors, including the lead author, Marc Arbyn,

whose ties to Merck and GSK resulted in strong public statements in favour of the vaccine even prior to the review, remained on the panel.

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

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

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

Our report on massive conflicts of interest of the first panel of authors, from December 2012, still does not appear on the review of the site. And rather than considering it a positive step to remove such authors with clinical ties, the response of CGNOCG and authors to our suggestions concerning the protocol, is instructive: "We thank Catherine Riva and colleagues for their helpful suggestions and comments, many of which we plan to address in the full review, since they have commented on the protocol only. In response to their earlier set of comments and on the advice of the Cochrane Funding Arbiter review authors with ties to clinical trials in this area were removed. Although this has reduced our ability to consider extensive unpublished data we have been able to contact investigators of included studies for additional information, where necessary, in accordance with Cochrane guidance. This is not an individual patient data review and to undertake one would be beyond the scope of the original review question and represent an investment of time and resources that we are not in a position to make."

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

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

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

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