



HPV vaccine safety: Cochrane launches urgent investigation into review after criticisms

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A Cochrane review that gave the all-clear to vaccines designed to prevent cervical cancer did not include all the relevant trials and ignored possible sources of bias, a new analysis has found.¹ The review was published in May 2017 and based its conclusions on 26 studies involving 73 428 women.² But it could have included as many as 46 trials involving more than 120 000 women, say researchers Lars Jørgensen and Peter Gøtzsche from the Nordic Cochrane Centre in Copenhagen, and Tom Jefferson of the Centre for Evidence Based Medicine in Oxford. Cochrane reviews are meant to be the last word in evidence based medicine, winnowing out the most authoritative trials to reach conclusions on the efficacy and safety of treatments. This one provided reassuring conclusions about vaccines against human papillomavirus (HPV), the cause of cervical cancer. It concluded that the vaccines are effective against pre-cancerous changes that lead to cervical cancer and that the risk of side effects is no greater in the vaccinated than in the control groups. Mark Arbyn, from the Belgian Cancer Centre, who led the review said at the time that claims of harm from the vaccine were unjustified and could damage public confidence. The three critics, writing in *BMJ Evidence Based Medicine*, say that the HPV vaccine review fell short of Cochrane standards because it was influenced by reporting bias and biased trial designs, and therefore that it failed to meet the needs of citizens or healthcare providers who rely on Cochrane reviews. Furthermore, the review's authors cannot claim ignorance of the trials they excluded because they had been provided with an index of studies on the vaccines, written by the critics.³ This found 206 studies, but many were unpublished or incomplete. Excluding those, 46 trials appeared eligible for the review. Jørgensen and colleagues say that all the 26 trials considered by the Cochrane group compared the HPV vaccine with active comparators, such as adjuvants or hepatitis vaccines. These are not placebos, as Cochrane calls them, because they can themselves cause harms, possibly masking any harms caused by the HPV vaccine. The review acknowledges this, saying: "Therefore, the pooled risks of adverse effects associated with HPV vaccines and the assumed risks for control groups must be interpreted cautiously."

The Cochrane review did find there were more deaths among women over 25 given the vaccine than in the comparator group, with a risk ratio of 2.36 (95% CI 1.10 to 5.03). It dismissed this as a chance finding, since many of the deaths occurred years later, from causes not obviously related to vaccine administration.

Critics argue the case differently, saying that a death may be coded in a way that does not raise suspicions. Syncope (fainting) is a recognised harm and could lead to deaths through traumatic head injury or drowning, they suggest.

David Tovey, editor-in-chief of the Cochrane Library, said: "We fully understand the severity and importance of the criticisms made, whose implications go well beyond this review in terms of systematic review methodology. For this reason, we have had a team of editors working with the author team to investigate the claims as a matter of urgency."

The Cochrane team had received a copy of the index, he said, but late in the review process. "In their judgement at the time it did not appear to identify any important eligible studies. Our current investigations appear to show that there may be a handful of missed but potentially eligible studies, but that this falls substantially below 'nearly half of the eligible trials'."

He promised a fuller response later. "To date, we also have no reason to believe that the main conclusions of the review relating to benefit and serious adverse effects are unsafe. However, we intend to initiate an urgent update of the review that will incorporate information provided in the *BMJ EBM* study.

"In addition, there is work ongoing on a second review that will tackle matters of comparative benefit and harms from the different forms of HPV vaccine."

- 1 Jørgensen L, Gøtzsche P, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. *BMJ Evid Based Med*. 2018 Jul 27.
- 2 Arbyn M, Xu L, Simoons C, Martin-Hirsch PP. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. *Cochrane Database Syst Rev* 2018;5:CD009069.29740819
- 3 Jørgensen L, Gøtzsche PC, Jefferson T. Index of the human papillomavirus (HPV) vaccine industry clinical study programmes and non-industry funded studies: a necessary basis to address reporting bias in a systematic review. *Syst Rev* 2018;7:8. 10.1186/s13643-018-0675-z 29347995

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