Response to Peter C Gøtzsche

HPV vaccines are safe to use

In 2015, the European Medicines Agency (EMA) conducted a detailed review of all the available scientific evidence and concluded that it does not support a causal link between the HPV vaccines and the development of two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). One year on and following a public exchange of letters with the Nordic Cochrane Centre, EMA stands by its scientific assessment and conclusion.

Cervical cancer kills 20,000 people in Europe each year and human papillomavirus (HPV) vaccines are expected to prevent many of these deaths as well as various other cancers and conditions caused by HPV. The evidence that HPV vaccines are safe and effective is overwhelming. Recent research looked at 58 studies in nine countries from 2007 to February 2016 and showed a nearly 90 % decrease in HPV infection, anogenital warts and cervical lesions in countries with the highest vaccination rates (1). Yet we also see that young girls and boys, their parents, and healthcare professionals choose to reject a potentially life-saving vaccination and that in some European countries, vaccination rates are dropping.

European Medicines Agency is a scientific body that works to protect public health in the best interest of patients in Europe. As a public body, we are open and welcome scientific debate. We recognise that independent analyses may sometimes challenge our scientific positions. This is the nature of science and we are not afraid of this; in fact, we welcome a debate on the basis of sound scientific research in order to jointly solve issues affecting the safe and effective use of medicines. Our decisions are taken based on the best available evidence at the time of the decision. As for any other medicine in Europe, we continue to carefully monitor the safety of these vaccines, and if any future new evidence of possible side effects becomes available we will revise our position as appropriate. We are, however, increasingly concerned by unjustified attempts and personal attacks aiming at discrediting the integrity of our institution or the people who represent it, that replace scientific discourse. These attacks are not guided by science.

During the review of the evidence surrounding reports of complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) in young women given HPV vaccines, the Agency looked at published research, data from clinical trials and reports of suspected side effects from patients and healthcare professionals, as well as data submitted by Member States. It consulted leading neurologists, cardiologists and other experts in the field and also heard detailed information received from a number of patient groups that highlighted the impact these syndromes can have on patients and families. As mentioned in our letters to the Nordic Cochrane Centre (2), all the evidence was assessed in a factual, scientific and objective way. The evidence provided by experts was given equal consideration and this included the publications of Dr Louise Brinth and colleagues, the Danish Health and Medicines Agency and the Uppsala Monitoring Centre. In particular, the publications by Brinth and colleagues present case series – that is a study that reports on data from a subject group without a comparison population. The lack of a comparator group is a key limitation of such studies. While case series can generate ideas for further studies they cannot be relied upon to draw conclusions regarding a causal relationship between intervention and outcome.

One of the sources for the review were completed and controlled trials that supported the marketing authorisations for HPV vaccines. This particular analysis allowed a comparison of the incidence rate between subjects vaccinated with HPV and subjects vaccinated with a control/comparator vaccine(s). In most of the studies, the placebo consisted of an aluminium-containing solution or another vaccine. This is in line with EU scientific guidelines (3) to establish the safety profile of the vaccines for approval, and supported by decades-long epidemiological evidence on the safety of aluminium in vaccines. On the basis of the scientific assessments performed over the years by EMA (4) and other experts such as from Food and Drug Administration (FDA) (5) and WHO (6), the scientific evidence available to date continue to support the safe and effective use of aluminium adjuvants in vaccines.

The outcome of the Agency's evaluation, which is detailed in its published assessment report (7–8), is clear: the overall occurrence of these syndromes in vaccinated girls did not differ from the expected occurrence in these age groups. This applied even when we assumed that most cases of the syndrome would not be reported in a post-authorisation setting.

European Medicines Agency's scientific reviews are multifaceted and bring together scientific experts from across Europe to ensure a comprehensive, transparent and independent assessment of the available evidence. Their outcome is the result of a collective approach designed to minimise the risk of bias. In the review of the HPV vaccines, the Agency's scientific committees reached their conclusions by consensus. There is a need for confidentiality during the scientific process to ensure experts are not under any pressure from companies, their competitors, from opinion groups or media; however, once the decision-making process is over, the duty of confidentiality stops if information has been made public and to the extent that has been released in the public domain.

The Agency takes the issue of competing interests very seriously. Since its initial establishment, the Agency has continuously made the relevant policies more robust and efficient. For the *European Medicines Agency*, transparency is key and the declarations of interests and curriculum vitae of all experts are published on the Agency's website (9). *European Medicines Agency* reiterates that it has applied its policy fully and correctly to all experts involved in the assessment of the HPV vaccines. We would like to refute very strongly all allegations made against the Agency's staff and experts, including its Executive Director. These are unsubstantiated and false. In fact, the Nordic Cochrane Centre has already acknowledged that it has made mistakes in this regard and has apologised publicly for these (10).

European Medicines Agency applied the highest scientific and regulatory standards in its review of the safety of HPV vaccines and stands by its scientific assessment. We are accountable to the European citizens and are ready to discuss this review with the EU Ombudsman, who is looking into whether the Agencty has procedures in place that ensure that all the relevant evidence is available to its scientific committees and whether the Agency has been sufficiently transparent about how its committees reach their scientific conclusions. The

Ombudsman's press office announced mid-December that their staff had not identified any deficiencies to date. In the meantime, we remain focused on our goal to safeguard public health.

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The author has completed the ICMJE form and reports no conflicts of interest.

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