What do we know about the safety of the HPV vaccines?

The HPV vaccine protects against the most common types of cancer-causing HPV. Vaccination of all Norwegian girls has been offered free of charge from 1 November 2016. However, there are several unresolved issues related to potentially serious harms of the vaccine. In its handling of this issue, the European Medicines Agency has not lived up to its role.

Some girls have been severely harmed after receiving an HPV vaccination, and there are good reasons to suspect that many of these harms are caused by an autoimmune reaction (1). It is therefore important to conduct research to determine whether the harms are caused by the HPV vaccine, a virus, or something else.

In July 2015, the Danish Health and Medicines Authority asked the European Medicines Agency (EMA) to assess the research that had raised the possibility that the HPV vaccines in rare cases might cause serious neurological harms (2). The symptoms are similar to those seen in so-called functional disorders such as chronic fatigue syndrome (CFS) and they include postural orthostatic tachycardia syndrome (POTS) and chronic regional pain syndrome (CRPS) (3). These syndromes are difficult to diagnose; their causes are poorly understood; and they are likely to be substantially underreported. This complicates studies of a causal link.

The submission to the EMA included hypothesis-generating scientific articles published by PhD and physician Louise Brinth from the Danish Syncope Unit at Frederiksberg Hospital in Copenhagen (4–6) and a review of the global data on side effects conducted by the Uppsala Monitoring Centre (UMC, a WHO collaborating centre) (2).

On 26 November 2015, the EMA released a 40-page report that gives the impression of a unanimous rejection of the suspected harms (3). However, only seven months earlier, the EMA had concluded that a causal relationship between Gardasil (one of the vaccines) and CFS or POTS can neither be confirmed nor denied (7). Moreover, there is an internal EMA report of 256 pages, which tells a very different story about considerable disagreements among the agency's experts (8). This report, which provided the draft for the EMA's official report, is confidential but has been leaked to us.

As we believed the EMA's handling of the case constituted maladministration, we submitted a complaint to the agency about this on 26 May 2016 (9). In several cases, the EMA's replies to us were either wrong or seriously misleading, or irrelevant to the criticism we had raised (10). We therefore complained to the European ombudsman about the EMA on 10 October 2016 (10). On 8 November, the ombudsman replied that she would look at our complaint, and I shall provide a short summary of our most important criticisms below.

Poor craftsmanship

The European Medicines Agency has not lived up to the scientific standards that must be expected of such an agency. There is so much spin in its official report (3) that it could have been written by a PR agency, and some of the text is nearly identical to the assessments of the vaccines carried out by the drug companies. One of the key arguments, which appeared ten times in the official report (3), was that there was no difference between what was observed and the expected background incidence of serious neurological harms. However, as the EMA admitted that this comparison cannot confirm a causal relationship due to the inherent limitations in such research, then the EMA cannot conclude the opposite, which is that the HPV vaccines are not harmful.

> «The European Medicines Agency has not lived up to the scientific standards that must be expected of such an agency.»

The scientific approach to finding possible harms of the HPV vaccines was very insufficient. The drug companies' searches in their own databases were grossly inadequate, and the agency allowed the companies to exclude a large number of cases diagnosed by a skilled clinician without inspecting the underlying data (10). Furthermore, the EMA allowed one-fourth of the vaccine trials to be omitted from the manufacturers' analyses, and the search strategies for the companies' and the EMA's searches in the published literature were not described (10).

In all the vaccine trials apart from a very small one, the so-called placebo was not a placebo as it contained aluminium adjuvant, which is neurotoxic in high doses (11), or it was another vaccine, for example against hepatitis, which could potentially also be neurotoxic. This makes it difficult to find a difference between harms of the vaccine and the «placebo,» but the EMA failed to address this fundamental problem in its official report (3) and allowed the manufacturers to lump all the «placebo» data together. This is contrary to good scientific practice to such a degree that we consider it outright scientific misconduct.

Contrary to the EMA's statements, the evidence was not assessed in an objective and scientifically acceptable way (8–10). The evidence provided by the vaccine manufacturers was generally accepted at face value, unlike the more reliable and independent publications provided for the case. The EMA's comments about Brinth's research were unprofessional, pejorative and misleading and came close to an accusation of scientific misconduct, and the EMA also misrepresented the facts when it stated that its scientific assessors (co-rapporteurs) did not agree with Brinth about her concerns. The EMA's handling of the observations and concerns the Danish Health and Medicines Authority and the WHO Uppsala Monitoring Centre had raised was not acceptable either, and this was criticised by the Danish authorities in the internal report (8,10).

The EMA's interpretations of the numerous treaties, regulations and rules the agency refers to are inconsistent and illegitimate, and not in the public interest. For example, the EMA redacted a number of important details in the documents it supplied to citizens in accordance with the right to freedom of information, which it was neither necessary nor legitimate to remove. Furthermore, the extreme secrecy, with a requirement of lifelong confidentiality, which the Agency imposed on its experts, is not legitimate and not in the public interest.

Mixed motives

Contrary to the EMA's statements, the EMA's policy regarding conflicts of interest was not correctly applied. It is not correct that none of its experts had financial or other interests that could affect their impartiality, and some of the agency's experts

had failed to declare their conflicts of interest. The EMA's executive director, Guido Rasi, had not declared that he is the inventor of several patents. We believe that, even if the inventor is not the owner of such patents, they should be declared.

We ended our complaint to the ombudsman by quoting Silvio Garattini, a former Italian representative at the EMA, who published a paper in the BMJ in 2016 with the title: «The European Medicines Agency is still too close to industry: Two decades after its inception, the agency still fails to put patients» interests first' (12).

The views we have expressed in our complaints to the agency and to the European ombudsman and our conclusions are our own and are based on the facts we have presented.

I thank Margrete Auken, Tom Jefferson, Karsten Juhl Jørgensen and Louise Brinth who were co-authors on the complaints to the agency and the ombudsman.

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

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