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Our comment on the decision by the European Ombudsman about our complaint over maladministration at the European Medicines Agency related to safety of the HPV vaccines

The Ombudsman made a decision in our case on 16 October 2017. We provide here a comment on this decision in the same order as in the Ombudsman's letter to us. We started the case on the 26th May 2016 by submitting a complaint to the European Medicines Agency (EMA) over the EMA. The documents in the case are available at nordic.cochrane.org/news.

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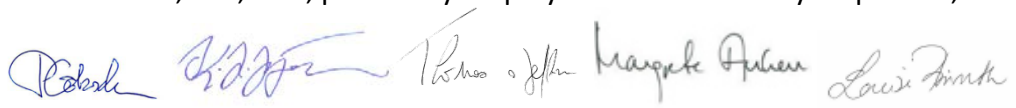

Summary

The Ombudsman concludes that there was no maladministration by the EMA in the handling of the referral procedure on HPV vaccines. We disagree. We found many examples of scientific maladministration. As long as the Ombudsman is not willing to comment on scientific maladministration, even when it is apparent for people without a scientific background, there is, in reality, no public safeguard against poor conduct by EMA. As far as we know, there is no disciplinary committee in the European Union that can take appropriate action against EMA. We find this deeply concerning.

The Ombudsman considers that EMA has abided by the rules about transparency and conflicts of interest in its handling of its investigation into possible serious neurological harms from the HPV vaccines. We believe that if the rules are so flexible, they need to be changed, as they do not allow the public to assess the basis for EMA's conclusions.

We question EMA's independence from industry because chairs of important committees are allowed to have conflicts of interest in relation to the companies whose products are being evaluated.

We acknowledge and welcome the Ombudsman’s recommendation of greater openness and more user-friendliness for researchers and others who wish to get access to EMA’s documents.

The Ombudsman recommends that experts who participate in EMA's assessments should be allowed to participate freely in the public debate. We hope that these recommendations will be the rule and not just friendly calls to EMA.

The main part of our complaint is about the substandard way that EMA evaluates science. This has huge consequences for public health. We acknowledge that it is not the Ombudsman's task to take a view on the science. However, we note that the Ombudsman on many occasions has chosen to trust EMA’s scientific assessments, which are based on the data the drug companies gave them, even though EMA knew that the companies could not be trusted.

The Ombudsman does not challenge that the assessment of a possible relation between a drug or a vaccine and serious harms is provided by the marketing authorisation holders without independent re-analysis of the underlying raw data and scrutiny of the methods used to reach the conclusions. The evidence is, however, that drug companies often underreport even lethal harms for the authorities, and it has been documented, both to EMA and to the Ombudsman, that Sanofi Pasteur MSD, one of the HPV vaccine manufacturers, on two occasions, both in Sweden and Denmark, had seriously underreported neurological harms associated with its HPV vaccine to the authorities.

The Ombudsman does not believe that pooling heterogenous active substances (misreported as "placebos") is scientific misconduct. It also appears to be acceptable to dismiss the results of independent researchers and the Uppsala WHO Monitoring Centre, which found signals that suggested neurological harms. Furthermore, the EMA has not been reprimanded for the excruciating slowness with which it releases clinical study reports of the HPV vaccines, and with its unnecessary redactions that make any independent re-analysis very difficult.

We believe it is important for the public to know about the many problems there are with EMA’s substandard approach to science. We have demonstrated a large number of factual errors and inconsistencies in EMA’s work and arguments, some of which are pretty serious. This is why we repeat in this document some of the issues we have written about earlier, so that newcomers do not need to read the previous documents in the case.

Contents

Confidentiality issues

We had complained that the confidentiality that EMA requires from its scientific experts is too restrictive because EMA imposes a life-long duty of confidentiality. EMA argued that it was required to do so by law: Experts "shall be required, even after their duties have ceased, not to disclose information of the kind covered by the obligation of professional secrecy." "This includes, for example, the fact that there is a meeting, that you have been nominated to participate, the agenda of the meeting, the product or company concerned, the participants, any part of the discussions and outcome." (EMA's internal report, page 2).

After we had complained to EMA about this, EMA reversed its stance and now stated that "the experts who disagreed with a collegial decision may discuss their disagreement in public, provided that they make clear that the views expressed are their own and not the view of the committee and that they do not disclose commercially confidential information."

We had argued that EMA's standard confidentiality clause does not seem to support such freedom of speech. The Ombudsman acknowledged our argument and suggested to EMA that it considers adapting its standard confidentiality clause for experts (the "Confidentiality Undertaking template") so that it reflects better EMA's position expressed post hoc in its reply to us. EMA agreed to review the confidentiality requirements on experts so that they may discuss in public details of the scientific debate once that debate has been completed. The Ombudsman concluded that EMA is in the process of addressing this point and asked EMA to inform her of the outcome of this process.

Scientific disagreements in EMA's committees

We had complained that scientific disagreements were not made public. The Ombudsman suggested that EMA continues to explore ways to explain to the public in more detail how its scientific committees arrive at scientific conclusions, and how differences in views that arise during the assessment are addressed. This could be done, for example, by publishing more information online.

Lack of transparency about documents in EMA's possession

We had argued that if EMA genuinely wanted to be open and transparent, it would have provided a list of all available documents, alongside its official 40-page report on its website. The Ombudsman suggested that EMA considers making publicly available lists of all relevant documents in its possession related to a specific referral procedure, or that EMA considers other ways of helping citizens to identify the documents they wish to obtain. Thereby, both the requester and EMA would need to spend less time on unnecessarily broad requests. Alternatively, EMA might consider other ways of assisting citizens in identifying such documents. This would enable citizens to make specific requests for public access should they wish to obtain a document. The Ombudsman also suggested that EMA could state clearly that citizens requiring more information before submitting a request for public access to documents can obtain such information by first making a request for information that will be handled promptly.

The Ombudsman concluded that, "Unfortunately, EMA did not address this suggestion in its reply to the Ombudsman." The Ombudsman, therefore, repeated her suggestion in her decision closing her inquiry.

Conflicts of interest for Guido Rasi, EMA's executive director

The Ombudsman concluded that there were no conflicts of interest that should have been declared for Guido Rasi, EMA's executive director (called "a senior EMA staff member" in the Ombudsman's report). We are surprised by this conclusion. This ruling is in conflict with international guidelines for declaring conflicts of interest and we, therefore, repeat what we wrote to the Ombudsman on 13 July 2017.

Rasi had not declared - and as of 25 October 2017 has still not declared[1] - that he is the inventor of several patents, which we believe he should declare, both according to EMA's own rules and according to international guidelines for declaring conflicts of interest in healthcare. EMA has changed its form for declaring conflicts of interest since we complained to EMA. In 2016, Rasi replied "none" to all four questions on the form, also to question 4, which was: "Other interests or facts whether or not related to the pharmaceutical industry which you consider should be made known to the Agency and the public, including matter relating to members of your household." Question 4 is now gone.

[1] EMA Public Declaration of Interests. Guido Rasi, dated 20 July 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123382.pdf.

As Rasi's patents go back less than five years,[2] we believe he should have declared them, also according to EMA's regulations concerning the handling of declared interests of its employees.[3]

We did not at any point in time hear from Rasi himself, only from his deputy and his law firm. We were told that although Rasi was the inventor of several patents, he was not the owner of them. We replied that, "We were not aware of the legal subtleties and assumed that an inventor of a patented technology is also an owner of that patent, as it is highly unusual that inventors give away their patents to drug companies without benefiting from them and without having any working relationship with that particular company."

We included our lengthy correspondence with Rasi's law firm in our complaint from 10 October 2016 to the Ombudsman[4] because we believe this correspondence has considerable public interest.

Rasi's lawyers asked us to give a public apology and repeatedly requested from us as part of such an apology that we should accept statements as facts, although we had had no possibility of checking the veracity of these statements. We find this remarkable and replied that lawyers know very well that, in court cases, one cannot force people to accept and declare what others tell them is the truth. We refused to accept the lawyers' suggested amendments, which included this sentence: "On the basis of these assurances we accept that Professor Rasi has never had, and does not have, any economic rights or financial interest or benefit (whether actual or potential) in, or arising from, any of the patents to which the Publication refers." We cannot know whether this is true.

We had never before heard of any case where inventors give away their patents to a drug company without benefiting from them in one way or another and without having any working relationship with that particular company before we were told that this was the case for Rasi. If this is correct, we wonder why Rasi did not simply send us the agreement(s) he made with the company. That would have been much easier, credible and quicker than engaging us in a protracted negotiation with a law firm that advertises itself in this way: "One of the UK's best-known law firms, Carter-Ruck has a longstanding reputation for its expertise in the field of litigation and dispute resolution."[5]

It would have made sense for Rasi to declare his patent inventions, as this has to do with the legitimacy of EMA in the public eye. The general public has so little confidence in the drug industry that it is similar to the confidence they have in tobacco companies and automobile repair shops.[6] Furthermore, the general public has been informed in newspaper articles and TV documentaries that corruption at the upper levels of drug agencies occurs. This corruption is widespread at the US Food and Drug Administration and has included several of its commissioners (see footnote 6).

We find EMA's various arguments in relation to Rasi's declaration of interests untenable. Whatever the rules are, a top executive in an EU institution should ensure that not the slightest suspicion can be raised that he failed to declare his conflicts of interest. A rule of thumb is that if a normal person

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[2] Guido Rasi's patents. http://patents.justia.com/search?q=guido+rasi (downloaded 7 May 2016).
[3] Decision on rules relating to Articles 11a and 13 of the Staff Regulations concerning the handling of declared interests of employees of the European Medicines Agency. 1 February 2012. EMA/MB/500408/2011.
[4] http://nordic.cochrane.org/news/complaint-filed-european-medicines-agency-over-maladministration-related-safety-hpv-vaccines.
[5] http://www.carter-ruck.com/.
[6] Gøtzsche PC. Deadly medicines and organised crime: How big pharma has corrupted healthcare. London: Radcliffe Publishing; 2013.

would be embarrassed if it was revealed that a conflict of interest had not been declared, then it was wrong not to declare it. Rasi has failed this simple and sensible test.

We had hoped and also suggested that the Ombudsman would require of Rasi that he declares his conflicts of interest and that the Ombudsman would launch an investigation to find out if it is true that Rasi does not benefit from his patents. Unfortunately, this will not happen.

Conflicts of interest for Andrew Pollard, chair of SAG (Scientific Advisory Group)

As for the scientific experts involved with the HPV vaccine case, the Ombudsman considered that EMA's conflict of interest policy was fully complied with and that there were no identified conflicts of interest. We disagree. We documented in our complaint to the Ombudsman not only that some of the experts had conflicts of interest but also that EMA was inconsistent when applying its policy, as it excluded some experts who were less conflicted than the chair of SAG who was not excluded.

The Ombudsman notes that EMA's policy on the handling of competing interests of scientific committees' members and experts has since been updated. We, therefore, retrieved the new policy, which is from 6 October 2017 and signed by Guido Rasi.[7] It starts out by saying that EU legislation clearly states that the members of the scientific committees and experts shall not have financial or other interests in the pharmaceutical industry that could affect their impartiality. In addition, all indirect interests which could relate to the pharmaceutical industry shall be entered in a register held by the EMA, which is accessible to the public, on request, at the Agency's offices. Indirect interests are, for example: Principal investigator with the responsibility for the coordination of investigators at different centres participating in a multicentre pharmaceutical industry instigated/sponsored trial; and grant or other funding from a pharmaceutical company to an organisation/institution to which the expert belongs, or for which he/she performs any kind of activity, and which is used to support any activity of the expert whether or not it is related to research work.

We believe it is a set-back that such conflicts of interest shall now no longer be declared on the publicly accessible forms at EMA's website. And we repeat that some of EMA's experts *did* have "financial or other interests in the pharmaceutical industry that could affect their impartiality."

The Ombudsman notes that the chair of SAG (Andrew Pollard) had declared that he had previously carried out, for some of the MAHs (Marketing Authorisation Holders) of HPV vaccines, research work on vaccines other than HPV vaccines, and that he did not declare any relevant current interests, neither financial nor otherwise. The Ombudsman notes that EMA's conflict of interest policy allows for such an expert to participate fully in a meeting and that there is no evidence that the expert's previous research work established any form of dependence on the producers of HPV vaccines. The Ombudsman claims that there is also no evidence that the research done for those companies had any link to the subject under discussion, the safety of the HPV vaccines.

We believe the Ombudsman's interpretation of what constitute conflicts of interest is inappropriate and out of line with how this is generally viewed in healthcare research and specified in guidelines. We are also concerned that the Ombudsman did not take our observations into account and therefore repeat them here.

[7] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/11/WC500216190.pdf

We noted in our letter to the Ombudsman from 13 July 2017 that, when publishing papers in medical journals, authors are required to list all the conflicts of interest they have in relation to drug and device companies, also those that are not about the drugs being described in the paper. This is because research has shown that people become influenced by conflicts of interest, also when they are related to other drugs or other companies than the ones directly involved.[8] The International Committee of Medical Journal Editors writes: "Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so."[9]

It is irrelevant whether or not there is "evidence that this research work established any form of dependence in relation to the producers of HPV vaccines," and it would also - in a legal sense - be close to impossible to prove that such dependence exists in a concrete case. The Ombudsman's inquiry team furthermore makes pure speculations. The team cannot know whether statements offered by experts "simply reflect the fact that the experts work in the relevant area of science and have developed scientific views on that area of science," or whether such statements are influenced by conflicts of interest. We also find it inappropriate for a chair of an EMA committee to communicate publicly the conclusions of the investigation two months before they become publicly known. We cannot see that this is in accordance with EMA's lifelong confidentiality clause either.

Contrary to EMA's statement in its letter to us, "We would like to assure you that the policy was correctly applied to the participants of the SAG meeting on HPV vaccines which took place on 21 October 2015," EMA's policy about restricting members of its SAG meeting to participate fully in the meeting was not correctly applied. There were no restrictions for the chair of the meeting, Andrew Pollard, although he had declared several conflicts of interest in relation to the HPV vaccine manufacturers, GlaxoSmithKline and Sanofi Pasteur MSD, until 2014 and 2013, respectively. In contrast, two of the four people who were not allowed to take part in the final conclusions of the meeting had no such direct conflicts of interest in relation to drug companies selling HPV vaccines: Martin Ballegaard was investigator on a study by Novartis in infants with type 1 spinal muscular atrophy while Rolf Karlsten had multiple conflicts of interest in relation to other drug companies and owned shares in a company.

We asked EMA to inform us of its justification for offering Andrew Pollard, privileges that were denied others with conflicts of interest. EMA did not respond to this but provided a nonsense reply: "Finally, with regard to your claim of a potential conflict of interest of the SAG's chair, please note that the European Medicines Agency takes due care to ensure that its scientific committee members and experts, including SAG members and experts, do not have any financial or other interests that could affect their impartiality." As explained above, it is not correct that none of EMA's scientific committee members and experts had any financial or other interests that could affect their impartiality. EMA used experts with financial ties to the HPV vaccine manufacturers although it is always possible to find experts without such conflicts. Furthermore, a conflict of interest is a conflict of interest; it cannot be a "potential" conflict of interest. It exists or it does not exist.

[8] Gøtzsche PC. Deadly medicines and organised crime: How big pharma has corrupted healthcare. London: Radcliffe Publishing; 2013.
[9] http://www.icmje.org/conflicts-of-interest/

It is pointless to exclude a person from parts of the meeting who is investigator on a study by Novartis in infants with type 1 spinal muscular atrophy, which has nothing to do with the HPV vaccines, while allowing the chair of the meeting to attend the whole meeting although he had recent conflicts of interest in relation to HPV vaccine manufacturers, and who in the press had praised the vaccines one month before the crucial SAG meeting. Pollard spoke about the many lives they saved and said there was no evidence of safety problems. The statement about the lack of harms was inappropriate to make for a chairman of an EMA committee in the middle of an ongoing process to assess whether or not there is a safety signal. Furthermore, we found out that Enrica Alteri from EMA, who had no restrictions on her participation, nonetheless had conflicts of interest declared on EMA's website. She was employed by Merck-Serono till June 2012 and her husband had a consulting contract with Merck-Serono for 2016.

We had hoped that the Ombudsman would ask EMA to respect the rules in future and also ensure that neither chairmen nor other members of EMA committees have current or recent conflicts of interest. If advice from such people is needed, it can be obtained in writing; there is no need to include them in meetings. The Ombudsman ignored our advice.

The science: basic issues

The Ombudsman explicitly noted that she does not take a view on the merits of scientific evaluations carried out by specialised scientific agencies, such as EMA's assessment of the safety of a medicine. The Ombudsman may, however, seek to assess whether scientific bodies such as EMA have the necessary procedural safeguards in place to ensure that the examination of scientific evidence is complete and independent, and whether these safeguards have been properly applied in any given procedure. The Ombudsman found that the examination of the scientific evidence was complete and that it was independent.

We have several problems with these statements. Despite her reassurance of not taking a view on the merits of scientific evaluations, the Ombudsman uses scientific arguments in her report to us. She mentions, for example: "Several countries that have introduced HPV vaccines have reported a 50% decrease in the rate of uterine cervix precancerous lesions among younger women. In contrast, the mortality rate from cervical cancer in other countries, where HPV vaccination is not proactively recommended, increased." The Ombudsman quotes a WHO report from June 2017.[10] Scientifically, this is a misleading comment. It is much too early to expect to see an effect of vaccination on mortality from cervical cancer and no such effect has been reported for any country. Therefore, it is misleading to state that "In contrast, the mortality rate from cervical cancer in other countries, where HPV vaccination is not proactively recommended, increased." There is no such contrast.

The Ombudsman noted that the members of PRAC (Pharmacovigilance Risk Assessment Committee) took their decision on the basis of extensive data, which were provided by "the companies that market HPV vaccines but also from other sources, including EMA's own database on adverse reactions, Member States, and from submissions by patient groups."

We note that the Ombudsman does not address our concerns that the data provided by the companies were grossly incomplete. The Ombudsman only discussed procedures, not whether what

[10] http://www.who.int/vaccine_safety/committee/topics/hpv/June_2017/en/

was processed was reliable. This is worrying. If we leave the testing to the companies themselves, and do not check what they did, we don't really care about public health.

The Ombudsman notes that every member of PRAC stated that the vaccines do not cause the two syndromes under investigation, CRPS (complex regional pain syndrome) and POTS (postural orthostatic tachycardia syndrome). We wish to emphasize that in science, it is not possible to prove that something *does not* exist. One can only say that it is not likely. We, therefore, doubt that every member of PRAC stated that the vaccines do not cause CRPS and POTS.

The Ombudsman acknowledges that our complaint mainly disputes PRAC's scientific work: "They disagree with the scientific findings that PRAC made, which were based on the available data. They also question the scientific appropriateness of the methodology applied to identify that data. As already explained, the Ombudsman is not in a position to take a view on questions of science."

The Ombudsman notes that the statements referred to by us were "comments made by a Member State PRAC member and not comments by the co-rapporteur. The complainants appear to mistake these statements as (allegedly discarded) criticisms made by the co-rapporteur." We explained to the Ombudsman on 13 July 2017: "It is correct that the most critical statements were made by a member state (very likely Denmark) but this distinction is not important. A criticism should be judged by its merits, not by who made it. As EMA explained to us, the document was written by the Belgian co-rapporteur and this rapporteur agreed with some of the member state's criticisms."

This critical and relevant comment was likely made by Denmark: "In the search for cases coded as POTS in the database the MAH (Marketing Authorisation Holder) make a further selection by case definition criteria that appears too limiting ... 83 reports are identified as medically confirmed but out of these almost half (40 cases) are then dismissed for not meeting the case definition for POTS. It appears that they have been dismissed mainly due to lack of information in the reports. This does not appear to be in accordance with good practice, since spontaneous reports cannot be expected to describe all details for a diagnosis given to a patient."

EMA told us that it was only the Belgian co-rapporteur who was critical, but this is not correct. Both the Belgian and the Swedish co-rapporteurs were critical of the observed versus expected analyses (see below, in the subsection: Observed versus expected analyses). It is important that both co-rapporteurs were critical of the observed versus expected analyses because they were the two most important people who participated in EMA's processes. According to EMA's letter to us from 1 July 2016, they are those "who take the lead in the scientific assessment and who have the task of thoroughly assessing the data and draft their recommendations." However, although the co-rapporteurs were supposed to thoroughly assess the data, and therefore also the MAHs' searches, they didn't do this. They accepted most of what they got from the drug companies at face value.

The Ombudsman notes that she has seen no evidence of any pressure being exerted on any member of the SAG and that, similar to the PRAC, the members of SAG are not required to reach a consensus. Therefore, the Ombudsman concludes that if any members of SAG were minded to give a view which differed from the views of his or her colleagues, they were free to do so.

We wrote to the Ombudsman on 13 July 2017: "According to information available to us, those who expressed concerns about vaccine safety at the Scientific Advisory Group (SAG) meeting on 21

October 2015 were pressurised by the leaders to agree to the so-called consensus. The inquiry team states that we have not put forward any evidence to suggest that participants were somehow pressured into adopting a certain point of view. We could not put forward the evidence we have because SAG members were obliged by EMA to life-long confidentiality: 'As an EMA expert you are bound to life-long duty of confidentiality. The duty of confidentiality applies to all information of the kind covered by the obligation of professional secrecy. This includes, for example, the fact that there is a meeting, that you have been nominated to participate, the agenda of the meeting, the product or company concerned, the participants, any part of the discussions and outcome' (EMA's internal report, page 2). According to information we have, the members of EMA's SAG committee clearly felt that this amounted to a life-long prohibition to speak in public about disagreements. We have also been told that a person who posed critical questions was reminded of the life-long confidentiality. We, therefore, cannot say who it was in this document but are willing to convey the names confidentially to the Ombudsman."

We had complained that the information provided by the producers of the vaccines (the MAHs) was not scrutinised and independently assessed by PRAC, but that PRAC simply accepted the data received from the MAHs at face value. The Ombudsman asked EMA whether the raw data, analyses and explanations on the methodology applied, including those originating from the MAHs, were made available to all members of PRAC. EMA explained that the MAHs were legally obliged to provide, to the regulatory authorities, all available data they had in their possession and that there were mechanisms in place to ensure that this was abided by. EMA also confirmed that, in line with standard practice, all documentation submitted in the context of the referral procedure, including from MAHs, was made available to all PRAC members. The Ombudsman notes that the preliminary assessment reports of the rapporteur and co-rapporteurs do in fact contain a detailed assessment of the information provided by the MAHs. Among other things, the (co-)rapporteurs assessed the methodology applied by the MAHs when they collected information. The rapporteur also reviewed the co-rapporteurs' assessments. The Ombudsman states that it is thus not correct that the data provided by the MAHs was accepted "at face value"; rather, it was rigorously examined.

As we explained in our letter to the Ombudsman from 13 July 2017, PRAC did not see the raw data, only a summary of some few cases the MAHs sent to PRAC. There is no doubt that there were many more cases, which PRAC never heard about. We also noted that the work of EMA's various assigned experts was not to verify what the companies had done, but merely to summarise and discuss it. Nowhere in the report is there any information suggesting that the data and analyses delivered by the drug companies had been "thoroughly and critically reviewed," as EMA claimed. EMA uncritically reproduced the incidence rates of CRPS and POTS constructed by the manufacturers. Furthermore, nowhere in the report is there any mentioning that any expert asked the companies for clarification of vitally important issues. We find the lack of independent verification of the aggregate data provided by the two MAHs unacceptable.

As we noted on 13 July, Rasi affirmed that the MAHs provided <u>all</u> individual post marketing safety reports to PRAC. However, that seems not to be the case, as the MAHs preselected what they sent to PRAC: "all individual case safety reports (ICSRs) of cases identified using common search criteria, as defined and assessed in the assessment report, were requested. By exercising this level of due diligence, all ICSRs reporting the events, in addition to the ICSR reports not only containing the two Preferred Terms ("PTs") but also containing PTs as part of the wider search strategy were included in the submission made by the MAHs to the PRAC".

This “wider search strategy” was grossly inadequate and must have missed many cases, see below.

EMA allowed 12% of the study participants in the vaccine trials to be omitted from the manufacturers’ review for unclear reasons and did not review data from some of the trials in their holdings. Rasi’s statement that PRAC “performed a sound and comprehensive assessment of all the available scientific evidence in the context of the referral of the HPV vaccines” is not correct.

The Ombudsman states that PRAC did not rely solely on information provided by the MAHs. During the assessment, the (co-)rapporteurs also took into account the input of the SAG experts, comments provided by Member States, the results of literature searches conducted by EMA, data extracted by EMA from its EudraVigilance database on adverse reactions, additional scientific studies and submissions by doctors and patient groups. In particular, PRAC assessed at length a report submitted by Denmark, the Member State that asked the Commission to trigger the referral procedure. The Ombudsman thus considers that PRAC took due account of all available information.

We are concerned about this explanation. The Ombudsman’s inquiry team noted previously that striving for consensus in PRAC is expressly provided for by law. The inference that there were no remaining disagreements cannot be made when the participants felt obliged to reach consensus.

The Ombudsman states: “In as much the complainants disagree with the scientific conclusions based on the data obtained, or the scientific appropriateness of the methodology applied to identify relevant data, the Ombudsman notes that is not for the Ombudsman to take a position on issues of science.”

The Ombudsman notes that the submission to PRAC by the MAH in question included summary analyses of every identified case, that is, also of those cases that the MAH considered did not meet the criteria for POTS. We find that this comment misses the point because the searches the MAHs did in their databases for possible harms of the vaccines were grossly insufficient (see just below).

The Ombudsman notes that the approach to cases considered not to meet the criteria was discussed among the PRAC members following comments by a Member State. Ultimately, PRAC concluded in its final assessment report concerning this MAH: “It is noted that the MAH did not include a conservative analysis to include all cases of POTS, including those that do not meet the diagnostic criteria, however, it is considered that this approach would not add value and would simply have included cases that are unlikely to be POTS. Furthermore, the number of expected cases would not have been as relevant in such analyses.”

Guesswork is not an adequate scientific approach, especially when the MAH fails to do what is requested.

Search strategies for undiagnosed adverse events

This issue is extremely important. We had complained that the search strategies used by the MAHs to identify cases of undiagnosed CRPS and POTS in their databases were grossly inadequate.

The Ombudsman argues that the search strategies (called algorithms) were reviewed in the preliminary assessment reports of the rapporteur and the co-rapporteurs and shared with all PRAC members and that no objections were raised. While the Ombudsman does not take a view on whether the search terms used by the MAHs are scientifically appropriate, she notes that no PRAC member expressed any view that the search terms were inappropriate.

We believe the Ombudsman should have addressed this crucial issue and in our letter to the Ombudsman from 13 July 2017, we provided several arguments, which we repeat here, as they are so important. It requires no scientific expertise to see that the searches undertaken by the drug companies in their own databases were grossly inadequate and were bound to miss many cases of undiagnosed CRPS and POTS, or that it is unacceptable that EMA did not ask the companies to do better searches and did not check the companies' work for accuracy. EMA surely knows that there are countless examples of drug companies hiding serious - even lethal - harms from the authorities.[11] [12] We believe this is a serious case of maladministration at EMA. As explained in the following, EMA's confidence in the work of the MAHs is totally misguided.

We find that since the search strategies were so clearly inappropriate and must have overlooked many cases, it is unsatisfactory for public health that the Ombudsman refuses to take any scientific view on this. As long as the Ombudsman is not willing to comment on scientific maladministration, even when it apparent for people without a scientific background, there is in reality no public safeguard against poor conduct by EMA. As far as we know, there is no disciplinary committee in the European Union that can take appropriate action against EMA. We find this deeply concerning.

The Uppsala WHO Monitoring Centre had reported that for the largest clusters they identified in the WHO VigiBase(R), the most commonly reported adverse events terms were headache and dizziness and fatigue or syncope.[13] They found that the combination of headache and dizziness with either fatigue or syncope was more common in HPV vaccine reports than in non-HPV vaccine reports for females aged 9--25 years. This disproportionality remained when those countries reporting the signals of CRPS (Japan) and POTS (Denmark) and when recent years - where media attention might have increased reporting - were excluded.

However, the MAHs did not search for headache in their databases and they did not combine the terms in the way the Uppsala centre did. "Dizziness" needed to occur together with either "orthostatic intolerance" or "orthostatic heart rate response increased" in order to count, and there were other restrictions that must have led to many cases being overlooked. When searching for CRPS, "The keywords for the search included 'complex regional pain syndrome' or 'pain syndrome' and 'quadrivalent HPV vaccine' or 'Gardasil'" (EMA's internal report, page 58) and when searching for POTS, "Keywords included 'POTS' or 'tachycardia' or 'postural orthostatic' and quadrivalent and 9-valent Human Papillomavirus vaccine (qHPV and 9vHPV)" (page 69).

[11] Gøtzsche PC. Deadly medicines and organised crime: How big pharma has corrupted healthcare. London: Radcliffe Publishing; 2013.
[12] Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press; 2015.
[13] Chandler RE, Juhlin K, Fransson J, Caster O, Edwards R, Noren GN. Current safety concems with human papillomavirus vaccine: a cluster analysis of reports in Vigibase (R). Drug Saf 2016 Sept 16.

EMA nonetheless uncritically reproduced the incidence rates of CRPS and POTS constructed by the manufacturers.[14]

A colleague provided us with a copy of a report from November 2014 in which a rapporteur and a co-rapporteur had assessed Gardasil 9 from Sanofi Pasteur MSD on behalf of EMA.[15] The rapporteurs were concerned that Sanofi had avoided identifying possible cases of serious harms of the vaccine and their concerns were supported by the GCP [Good Clinical Practice] Inspection report (pages 79 and 101 in their report):

"The reporting procedure for AEs [adverse events] in this trial was complicated by the fact that as per protocol there was only specific, short, AE reporting periods in connection to each vaccination. In between, any new symptoms were only to be reported as 'new medical events' … The information available about new medical events was however limited, as only symptoms were collected and no further medical assessments were made and no outcome was recorded. The reporting of SAEs [serious adverse events] was also not required during the full course of the trial ... in the inspectors' opinion it is not an optimal method of collecting safety data, especially not systemic side effects that could appear long after the vaccinations were given ... A potential concern is that there are 3 subjects in the clinical safety database who have been diagnosed with POTS, an on-going safety concern for the quadrivalent Gardasil, after receipt of Gardasil 9 and that in none of the 3 cases was the event of POTS reported as an AE ... Furthermore, for case AN29076, the Applicant should describe the rationale for inclusion of POTS as 'new medical history' instead of an AE given the report that it occurred 24 days post dose 1. For case AN71508, the Applicant should explain why the hospitalisation for severe dizziness which occurred prior to the end of study visit was not reported as an SAE ... The Applicant should discuss, in the specific terms of case 37083, why the term 'dysautonomia' was not included on the line listing."

The next example also involves Sanofi Pasteur MSD. When the Danish drug agency in 2014 asked Sanofi to review its database for potential side effects of its HPV vaccine, the company searched for POTS in a way that was totally inappropriate. This was discovered by the Danish National Board of Health, partly because, according to a Danish newspaper,[16] only 3 of 26 Danish reports of POTS showed up in the company's searches. Sanofi had been asked to search on specific symptoms including dizziness, palpitations, rapid heart rate, tremor, fatigue and fainting, but the company ignored these clear instructions and instead searched on three symptoms: "postural dizziness", "orthostatic intolerance" and "palpitations and dizziness." As terms used in reports of harms are the ones used by the doctors reporting them, such search terms will yield few results.

In our letter to the Ombudsman from 2 February 2017, we drew attention to this again because we had acquired important additional information. In the document we attached, there was an exchange of emails from the summer of 2014 between the Danish drug regulator and representatives of Sanofi Pasteur MSD. The regulator requests an explanation why the MAH concluded that none of the reports of the possible cases of POTS provided to the MAH by the Danish regulator fitted the diagnostic criteria for POTS. In effect, the regulator is asking for details of the

[14] Jefferson T, Jørgensen L. Human papillomavirus vaccines, complex regional pain syndrome, postural orthostatic tachycardia syndrome, and autonomic dysfunction – a review of the regulatory evidence from the European Medicines Agency. Indian J Med Ethics 2017;2:30-7.
[15] Dunder K, Mueller-Berghaus J. Rapporteurs' Day 150 Joint Response Assessment Report. Gardasil 9. 2014 Nov 23.
[16] Weber C, Andersen S. Firma bag HPV-vaccinen underdrev omfanget af alvorlige bivirkninger [The company behind the HPV vaccine underestimated the prevalence of serious side effects]. Berlingske 2015; 26 Oct.

methods used by the MAH and is openly critical of the MAH's conclusions and dismissal of the work of the Danish Syncope Centre. In addition, the regulator states that the search terms used by the MAH to identify possible cases of POTS in their pharmacovigilance database were too restrictive and failed to identify the cases notified by the same regulator. At the end of the letter dated 24 July 2014, the regulator states: "Please note that the PRAC rapporteur has received a copy of this letter" (which listed the regulator's concerns).

We can find no mention of the Danish regulator's concerns in the PRAC papers, nor any critical assessment of the searches carried out by both MAHs in coordination with each other. We deduce from this that the Danish regulator's concerns were not taken seriously by PRAC, also because we could find no discussion of this issue in relation to the searches performed by the MAHs in their databases, neither in the long internal 256-page report, nor anywhere else. We believe the emails show that the advice received by EMA from PRAC was uncritical and did not take into account the concerns clearly expressed by the referring Danish regulator.

In relation to this, the Ombudsman's inquiry team asked EMA: "The dismissal of this considerable number of safety reports appears to have been criticised by one Member State both during and before the referral procedure. The complainants have recently submitted to the Ombudsman additional supporting material which is annexed to this letter, and which discloses this criticism lodged by the Member State's authorities. Does EMA draw any conclusions from the observed disparity between the positions of the two MAHs in question, both in respect of the referral procedure and of the future handling of such reports?"

Rasi's explanations in relation to this question are nonsensical and seriously misleading: "EMA considers that this would not appear to raise, *prima facie*, any additional safety concern. Indeed, EMA holds the view that a comparative analysis between rates of cases meeting the diagnostic criteria and between the concerned medicinal products is not scientifically sound for spontaneous reports."

The fact that *none* of the reports of POTS (which the Danish regulator had accepted were reports of POTS) were identified by Sanofi Pasteur MSD when the company searched in their database in a way that would almost certainly guarantee that they would come up empty-handed, has nothing to do with what Rasi writes about the reliability of spontaneous reports.

Assessment of raw data not done and hardly possible by independent researchers

The full individual data set (raw data) was never accessed by PRAC. This is of vital importance because the neurological conditions are syndromes, i.e. a conglomerate of signs (e.g. syncope) and symptoms (e.g. headache) which can only be recognised as an aggregate. The MAHs provided PRAC with data in tables produced by them and coded accordingly, with relevant narratives. A credible independent review would have entailed a complete reanalysis.

We have obtained a number of the clinical study reports for the HPV vaccines from EMA, but it is very difficult to do a review of the possible serious harms because we do not have access to all the relevant data and because EMA has redacted patient identifiers in the study reports they have released to us.

One of us (Tom Jefferson) requested the clinical study reports on the HPV vaccines on 29 May 2014. EMA declined the request with the argument that it was commercially confidential information. Jefferson appealed. During the next three years, he was sent batches of study report files (300-400 pages at a time) making it very difficult to keep track of what was going on and needing software to reconstruct single study reports from multiple batches of files.

As of 27 October 2017, Jefferson has still not received all the study reports. On 27 October 2016, he complained to the Ombudsman,[17] pointing out that the excessive unnecessary anonymization and failure to assign fake IDs to line listings and redaction of batch numbers made it difficult or impossible to follow an individual with a serious adverse event through the study report narrative. Jefferson noted that GlaxoSmithKline appeared to have used progressively more redactions, as when GSK released 30 complete study reports directly in 2013, only the participant IDs had been redacted.

EMA explained that the access to documents regulation does not permit it to modify the content of documents released in response to requests for access to documents. Article 10(3) of this Regulation clearly states that "Documents shall be supplied in an existing version and format". Therefore, EMA is not permitted to modify an existing document but only to apply redactions to it in order to protect information covered by the exceptions set out in Article 4 of the ATD Regulation. In accordance with Article 4(1)(b) of the ATD Regulation and the European Union legislation regarding the protection of personal data read in conjunction with Regulation (EC) No 45/2001, EMA has to redact all protected personal data in order to avoid that the disclosure of the document would undermine the privacy and integrity of any individual.

The position of the Agency is that the unique number that is allocated to the research subject allows for the linking of this number to an individual patient. The patient ID numbers are typically made up of a sequence of numbers and letters that are associated with three elements, the study, the study site and the patient.

EMA also noted that when handling requests for access to Periodic Safety Update Reports (PSURs), "the minimum personal data to be deleted to ensure anonymisation of the information would require the deletion of information on 1) Date of birth; 2) (Reporting) country; 3) Patient identification code" and that "it should never be possible to identify a natural person from the information disclosed."

The position adopted by EMA takes into account the advice of the European Data Protection Supervisor (EDPS) regarding the extent to which information received for the purpose of pharmacovigilance, including adverse reactions should be considered personal data in accordance with Article 2(a) of Regulation (EC) 45/2001.

Jefferson pointed out to the Ombudsman that redactions of this type make the release of data a cosmetic exercise and that the situation gets worse when EMA redacts batch numbers from vials of biologics such as vaccines making it impossible to assess whether a suspected adverse event is due to a specific batch of that vaccine.

The Ombudsman has not yet responded to Jefferson's complaint over EMA.

[17] Jefferson T. Complaint to the Ombudsman. 27 October 2016. Available at http://nordic.cochrane.org/news.

Observed versus expected analyses

We had criticised EMA's heavy reliance on the observed versus expected analysis, where the number of reported cases is compared with the number that would be expected to have occurred naturally in the target population. We explained why such a comparison is meaningless, namely because the underlying research was of very poor quality. For some of the analyses, the observed incidence of chronic fatigue syndrome was used to estimate the expected incidence of POTS. Furthermore, EMA writes in its public report that for POTS with the Gardasil/Silgard vaccine, the observed number of cases was generally *lower* than expected under almost all assumptions for all regions and countries except for Denmark. This observation should have alerted EMA to the fact that analyses based on expected incidence are grossly unreliable and that what was reported in the randomised trials was not reliable but an underestimate of the true occurrence of POTS since what is found in the background population is already a serious underestimate, as POTS is often overlooked or not reported, also in clinical practice.

Both the Belgian and the Swedish co-rapporteurs were critical of the observed versus expected analyses: "For both CRPS and POTS, the Co-Rapporteur considers that Observed vs expected methodology used in this CRPS analysis is based on many assumptions, which cannot be verified"[18] and "a wide range of assumptions were used in these calculations ... The recalculation is therefore not considered helpful to reach the overall conclusion. The proposed recalculation of observed versus expected ratios is therefore not endorsed by CoRapp SE" (PRAC co-rapporteur's referral updated assessment report, page 9). Even the rapporteur was critical of these analyses: "Evidence from OE analyses cannot confirm a causal association due to the inherent limitations in spontaneous data" (see footnote 18).

However, EMA's official report does not reflect this substantial doubt about the trustworthiness of observed versus expected analyses. Quite the contrary. In no less than ten places in the 40-page public report are these analyses used to convince the readers that they should not worry about possible serious harms of the HPV vaccines.

The inquiry team (and therefore also the Ombudsman) says that it "takes no view on the scientific aspects of this question. However, it notes that the explanations provided are logical and appear reasonable. Importantly, the inquiry team also notes that it appears that all parties involved in the assessment were fully aware of the technical limitations of the available data. Thus, there is no suggestion that this data was misrepresented."

The Ombudsman notes that PRAC "concluded that in the O/E analysis, the rates of CRPS/POTS in vaccinated girls **were consistent with expected rates in these age groups**, even taking into account a wide range of scenarios regarding underreporting."

We find that the Ombudsman cannot accept EMA's scientific explanations and at the same time say that she takes no view on the scientific aspects of this question. The Ombudsman should not have accepted that EMA emphasizes totally unreliable research in its public report at the same time as EMA dismisses the independent research from Denmark and the Uppsala WHO Monitoring Centre.

[18] Briefing note to experts. EMA/666938/2015. 13 October 2015.

The Ombudsman writes in her report to us: “The Ombudsman takes no view on the scientific aspects of this question, but notes that PRAC was fully aware and open about the limitations of the O/E analysis and explained the measures taken to address these limitations. Ultimately, all experts agreed on the conclusions drawn from the available data.”

We wish to note that the fact that “all experts agreed” on something that is grossly unreliable does not make it reliable, and we note again that, according to the Ombudsman’s inquiry team, striving for consensus in PRAC is expressly provided for by law.

Pooling of placebos that were not placebos

The Ombudsman refers to EMA, which explained that the pooling of the placebo groups in the trials was considered appropriate, despite the different placebos, as the data was used only to gather information on the overall number of cases of POTS and CRPS for the purpose of detecting the potential existence of a safety signal linked to HPV vaccines.

We find that this is not true. It is a post hoc “explanation.” EMA did not report on the overall number of cases of POTS and CRPS in both the HPV vaccine groups and the so-called placebo groups taken together but reported on cases in the two groups separately (see next paragraph and the final assessment report).

The Ombudsman argues that the number of suspected cases of CRPS/POTS amongst the clinical trial data was so low that the pooling of placebo groups was not relevant for the scientific assessment. For one of the vaccines, no cases of CRPS or POTS were identified at all, and for the other group of vaccines, only three reports were suggestive of CRPS (two in the HPV vaccine group and one in the placebo group) and two cases were suggestive of POTS (both in the HPV vaccine group). The reference to these statements is to the final assessment report. However, we note that in this report (page 15), it is stated that “the placebo case does not seem to fulfill the criteria for CRPS.” It is also stated that one of the cases of POTS in the HPV vaccine group “did not fulfill the criteria for POTS.”

The diagnosis of some of these cases were made after a long time but this does not mean that the symptoms were not apparent long before the diagnosis was made. The diagnosis date, which is what the companies often refer to in their reports, can, therefore, be seriously misleading. Furthermore, autoimmune reactions can occur long after the vaccination. It has been firmly established that the influenza vaccine Pandemrix can cause narcolepsy, a very serious condition, several years after vaccination of children and adolescents,[19] and that this disease is immune-mediated. The possible serious neurological harms seen after HPV vaccination are also suspected to be caused by an autoimmune reaction.

It appears to us that, despite the grossly inadequate searches in the MAHs’ databases, what was found was three versus zero cases of CRPS or POTS. We have no idea about what would have been found if the searches had been adequate.

The Ombudsman writes that “Overall, PRAC noted that the incidence of both syndromes was very low, both in the vaccinated group as well as in the placebo groups.” In our view, this should have raised a suspicion of inadequate science, particularly since EMA writes in its final report that for

[19] Institutet för Hälsa och Välfärd. Förhöjd narkolepsirisk i två år efter Pandemrix-vaccinationen. 2014; June.

POTS with the Gardasil/Silgard vaccine, the observed number of cases was generally *lower* than expected under almost all assumptions for all regions and countries except for Denmark.

The Ombudsman claims that contrary to what we argued, PRAC did not compare the number of possible cases of CRPS and POTS among the group that received HPV vaccines with the group that received placebos. We have shown just above that PRAC did this (see also just below). Furthermore, the Ombudsman asked EMA to explain why PRAC and EMA considered it appropriate for the MAHs to pool the safety data of different clinical studies that used different types of "placebos."

Rasi's explanations to the Ombudsman in his letter from 15 May 2017 are remarkable. We, therefore, repeat what we wrote to the Ombudsman on 13 July and add some new relevant information.

Rasi says that "the pooling was considered appropriate despite the different placebos used in order to gather the overall number of cases of postural orthostatic tachycardia syndrome ("POTS") and complex regional pain syndrome ("CRPS") for the purpose of detecting the potential existence of a safety signal. Irrespective of the comparator used, the incidence of POTS and CRPS was very low in the vaccinated group as well as in the placebo groups, in line with the estimated incidence of POTS and CRPS in the general unvaccinated population" (page 3). So here again, EMA looks at the two groups separately, which contradicts EMA's explanation above.

Rasi's explanation is nonsensical. One does not use an active comparator if one is interested in detecting a safety signal (see also below). The assembled data in the trials are NOT valid for an evaluation of the possible harms of the vaccine.

Rasi also explains that, "all studies submitted for the marketing authorisation application for Gardasil were placebo controlled." This is not true, and Rasi mentions himself that in most studies, for both Gardasil and Cervarix, an aluminium adjuvant or a hepatitis vaccine was used as placebo.

Rasi claims that "there are ethical reasons why the placebo cannot always be an inactive control (e.g. saline solution), especially in trials that involve children, i.e. even those subjects enrolled in the placebo group have to gain some benefit from the participation into a study."

This is not true. Firstly, numerous trials are carried out in children where the control group receives a genuine placebo. Secondly, all those children who received an aluminium adjuvant did NOT gain any benefit from this; as Rasi explains (see just below), they are actually harmed through local reactions. Thirdly, they might have been seriously harmed systemically, as the adjuvant is strongly immunogenic.[20] This may create a risk that the children develop an autoimmune disease if they acquire a virus infection around the time they receive the adjuvant (which EMA itself acknowledged could be the case in the report it withheld from its SAG members, see below under "EMA's literature searches").

Rasi notes that, "For both vaccines development, the use of $Al(OH)_3$ (500µg) rather than a true placebo (inactive control) was considered to be acceptable by the Committee for Medicinal Products for Human Use ("CHMP") for the purpose of maintaining the double blinding of the studies and

[20] Beppu H, Minaguchi M, Uchide K, Kumamoto K, Sekiguchi M, Yaju Y. Lessons learnt in Japan from adverse reactions to the HPV vaccine: a medical ethics perspective. Indian J Med Ethics 2017;2:82-8.

consequently the validity of data. Indeed an inactive placebo would have induced little local reactogenicity and may have allowed the subjects and/or study site personnel to identify which vaccine had been administered. As the control product contained the same amount of $Al(OH)_3$ as the study vaccine, it induced some level of local reactions that would have not allowed subjects or study personnel to readily distinguish whether a HPV vaccine or control was administered. In the context of the assessment of the marketing authorisation applications, the approach taken for both vaccines was found by the CHMP to be a reliable way for establishing the safety profile of the vaccines."

There are two competing scientific rationales here. If we want to study whether the specific vaccine component produces an effect above that produced by the vaccine adjuvant, it makes sense to use adjuvant in the control group. If we want to study the harms of the vaccine, it makes sense to use normal saline in the placebo group, as this is a totally inactive and therefore a genuine placebo. However, it is also important to apply an ethical perspective.

Rasi's argument, that aluminium adjuvants should be used as a "placebo" in order to maintain "the double blinding of the studies and consequently the validity of data" is not tenable. Since aluminium adjuvants are so reactogenic that a genuine, inert placebo would cause far fewer reactions (local and systemic), we find it problematic in an ethical sense to use such adjuvants as "placebo." Furthermore, the outcome of primary interest in the trials is cervical cell changes. The assessment of these changes in routine practice is highly unlikely to be influenced by lack of blinding many years earlier when the children were vaccinated. Rasi's defence of the MAHs' priority to maintain blinding, which undermines the possibility to investigate harms of the vaccines, raises serious concerns about the scientific standard at EMA.

Rasi states that, "In addition, it is important to note that the use of aluminium as adjuvant in vaccines and in other products for specific immunotherapy has been established for several decades. Moreover, the substances are defined in the European Pharmacopoeia." Rasi also discusses "the known safety profile of the adjuvants and of the active control" and states that, "The scientific evidence available to date and the assessment of this evidence has been performed over many years not only by EMA (10), but also by other international and EU scientific public health authorities, such as EFSA (11), FDA (12) and WHO (13,14). These authorities continue to support the safe and effective use of aluminium adjuvants in vaccines."

In contrast to Rasi's assertions about the European Pharmacopoeia, the properties of the aluminium adjuvant are not well defined. Rasi also gives the impression that "aluminium adjuvants" used in the HPV vaccines are of the same type as those used since the 1930s. However, the Gardasil adjuvant is amorphous aluminium hydroxyphosphate sulfate, $AlHO_9PS^{-3}$,[21] or AAHS, which is likely to have very different properties from aluminium hydroxide, which is the substance Rasi mentions. According to EMA, it is "used to enhance the immunogenicity of the HPV VLP vaccine."[22]

We have investigated whether the safety of AAHS has ever been tested in comparison with an inert substance in humans. We have been unable to find any evidence that this is the case. We, therefore, checked the five references Rasi gave in support of the claimed safety of the adjuvant (10-15). *We found nothing to support Rasi's claim*:

[21] https://pubchem.ncbi.nlm.nih.gov/compound/86278271#section=Related-Records.
[22] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003852/WC500189113.pdf.

10. http://www.ema.europa.eu/docs/en GB/document library/Scientific guideline/2011/07/WC500108657.pdf. "The electronic version of this document is currently unavailable."

11. http://www.efsa.europa.eu/en/efsajournal/pub/754.htm. "Safety of aluminium from dietary intake[1] - Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC)". This has nothing to do with aluminium adjuvants in vaccines.

12. https://www.fda.gov/BiologicsBioodVaccines/ScienceResearch/ucm284520.htm. "Page Not Found."

13. http://www.who.int/vaccine safety/topics/aluminium/statement 112002/en/index.html. "This page cannot be found."

14. http://www.who.int/vaccine_safety/committee/reports/Jun_2012/en/index.html. In this report, a Global Advisory Committee on Vaccine Safety wrote 280 words about aluminium adjuvants. GACVS reviewed two published papers alleging that aluminium in vaccines is associated with autism spectrum disorders and considered that these two studies are seriously flawed. GACVS also reviewed the evidence generated from quantitative risk assessment by a US FDA pharmacokinetic model of aluminium-containing vaccines and the US FDA risk assessment model of aluminium in vaccines. The FDA analysis indicated that the body burden of aluminium following injections of aluminium-containing vaccines never exceeds safe US regulatory thresholds based on orally ingested aluminium.

Thus, Rasi's claim that aluminium adjuvants in vaccines are safe seems to be groundless. The only two of his five references we could access provided no support for his claim. His quote of the WHO GACVS report is misleading as it confuses orally ingested aluminium with the effect of parenteral aluminium in an adjuvant. Furthermore, clinical effects are unlikely to be linked to the dose of the metal, aluminium, but must be linked to immunogenicity, the reason to administer the adjuvant.[23] This raises further concerns about the scientific standard at EMA.

The MAHs simply lumped the results from trials that had a potentially toxic "placebo", which EMA confirmed in its reply to us: "For both Cervarix and Gardasil, all studies submitted for the marketing authorisation application were placebo controlled. Placebo consisted in most studies of aluminium-containing solution or of a hepatitis B vaccine (Recombivax HB, used in Gardasil development) or a Hepatitis A vaccine (Havrix, used in Cervarix development)."

EMA refers to an immunogenic adjuvant and another vaccine as placebo. Merck's own definition of a placebo is "an inactive pill, liquid, or powder that has no treatment value."[24] There is nothing "inactive" about adjuvants, which were included in the vaccines to stimulate high and prolonged antibody response. The active "placebos" could have similar adverse effects as the HPV vaccines (see also the section about EMA's own literature searches below), which would make it difficult to use the trials to find out if the HPV vaccines cause the suspected rare neurological harms.

[23] Beppu H, Minaguchi M, Uchide K, Kumamoto K, Sekiguchi M, Yaju Y. Lessons learnt in Japan from adverse reactions to the HPV vaccine: a medical ethics perspective. Indian J Med Ethics 2017;2:82-8.
[24] http://www.merck.com/clinical-trials/frequently-asked-questions.html.

None of the vaccine trials was truly placebo controlled. In one trial (Gardasil trial V501-018, NCT00092547), the published abstract said that a saline placebo was used,[25] but this is not true. The 597 children who were supposed to receive a saline placebo did not receive a saline placebo but "identical components to those in the vaccine, with the exception of HPV L1 VLPs and aluminum adjuvant." On page 63 in the clinical study report we have received from EMA, "placebo" is described as being the carrier solution, and according to the FDA, this carrier solution contains L-histidine, polysorbate 80, sodium borate and yeast protein. In another trial (Gardasil 9 trial V503-006, NCT01047345), 306 participants received a saline placebo but all of them had previously been vaccinated with quadrivalent Gardasil before entering the study, so those who did not tolerate the vaccine were likely not randomised. This is therefore not a true placebo controlled study either.

We believe it constitutes scientific misconduct to lump "placebo" groups that are not placebo groups and then claim without caveats that there is no safety signal. EMA accepted this logic and continues to defend it.

The inquiry team claimed it took no view on the scientific aspects of this question but noted that the explanations provided are logical and appear reasonable. We believe the inquiry team cannot have it both ways. It cannot state that it takes no view on the scientific aspects and then conclude that EMA's scientific explanations are logical and reasonable. EMA's explanations are neither, which we had already explained at length in our complaint to the Ombudsman.

EMA's literature searches

This is a crucial issue and the various explanations we have received from EMA are incompatible.

We criticised the fact that EMA's search strategies were not included in the 256-page "Briefing note to the experts" (i.e. to the SAG experts) from 13 October 2016. Two members of SAG have confirmed to us that they never saw EMA's literature searches. This fact was not disputed by the Ombudsman and EMA confirmed that SAG did not see EMA's literature searches.

This raises several serious questions about EMA's approach to science and to truth ascertainment.

1. In a letter to the Ombudsman from 15 May 2017, Rasi explained that, "In processing a request for access to the preliminary reports under Regulation (EC) No 1049/2001, said icon was inadvertently deleted further to a clerical error." The Ombudsman repeats EMA's claim that EMA's literature searches on CRPS and POTS had been inadvertently deleted. *We note, however, that EMA did not make the results of its literature searches available to its SAG experts* (see below).

In her letter to us from 26 June, the Ombudsman encouraged us to obtain the literature searches from EMA. In this, we succeeded. When we scrutinised the 256-page "Briefing note to the experts" again, we found the following on page 167 in the pdf, or page 55/67 of the document:

[25] Reisinger KS, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J 2007;26:201-9.

European Medicines Agency

- **HPV referral – literature search POTS**

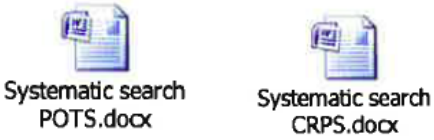
  The EMA has performed a systematic bibliographic search regarding Postural Orthostatic Tachycardia Syndrome:

  [Confidential information was removed]

If "Confidential information was removed," it was not a clerical error that EMA did not share the results of its own literature searches with SAG members.

2. On 10 July, we received a letter from Noel Wathion, Deputy Executive Director of EMA. There were two attachments that contained the search strategies for POTS ("Postural Orthostatic Tachycardia Syndrome" was combined with either HPV or vaccine; 10 publications in total) and CRPS ("Complex regional pain syndrome" was combined with either HPV or vaccine; 15 publications). The search strategies in the EudraVigilance database were "Postural Orthostatic Tachycardia Syndrome" and "Complex regional pain syndrome."

Although we had asked for an explanation, Wathion did not explain how the icons for the search strategies could have been deleted due to a clerical error. The icons are these:



The search strategies appeared in Word documents of 6 and 8 pages, respectively. The documents also contained information about other EMA literature searches and discussions of the findings in the articles EMA identified. These discussions are very relevant to the question whether HPV vaccines or other vaccines may cause POTS or CRPS. What follows are excerpts of EMA's text in the Word documents:

"POTS is more frequent in women, most cases occur between ages 15-25 years, and frequently start after viral illness (Benarroch 2012)."[26]

This is what we had assumed all along could happen and a major reason why we find it unacceptable that the "placebo" was not a placebo but an adjuvant or another vaccine. The changes in the immune system elicited by the very immunogenic vaccines and adjuvants could render the vaccinated young women more susceptible to the development of POTS or CRPS after a subsequent viral illness.

"**Background incidence and prevalence of POTS.** No data is available regarding the prevalence of POTS in both the general population, as well as among female adolescents." EMA does not explain why in such a situation its observed versus expected analyses are meaningless. There are no data in

[26] Bennaroch EE. Postural tachycardia syndrome: A heterogeneous and multifactorial disorder. Maya Clinic Proceedings 2012;87(12):1214-1225.

the literature on the background incidence of POTS; this was also the finding of a 2017 literature review.[27]

EMA discusses studies of patients with POTS compared with healthy controls and observes considerable overlap between patients and controls with respect to the increase in heart rate that is seen in the tilt test, and that some of the controls developed signs of presyncope.[28] [29]

EMA also states: "It is important to note that CFS [chronic fatigue syndrome] has been linked in the literature to other vaccines and vaccine adjuvants, as a search for CFS combined with the word 'vaccine' results in 57 publications, many of which are recent" ... "These studies provide some evidence that a subset of POTS patients might have small-fibre neuropathy, but the majority of POTS patients in these three studies were found to have no small-fibre neuropathy as confirmed by skin biopsy."

In the Word document on CRPS, EMA states:

"five papers concerned case reports of CRPS after other vaccines (tetanus, influenza, rubella, hepatitis B)" ... "Some data has been reported on autoantibodies suggesting autoimmunity, but these data are poorly controlled and have not been independently recapitulated. However, an autoimmune model for CRPS has been developed (Goebel and Blaes 2013). Scanning the published literature after publication of the Borchers and Gershwin (2014) review[30] revealed a recent Dutch study that tested for presence of autoantibodies in 82 CRPS-I patients and 90 healthy controls (Dirckx et al 2015). They found the presence of autoantibodies in 33% of CRPS patients and in 4% of controls."

There was no reference to Goebel and Blaes 2013 in EMA's reference list, but we believe we have identified it.[31] Additional work was also required to find the correct reference to Dirckx 2015 because the first name was wrongly spelled and the page number was also wrong in EMA's reference list.[32]

We believe that these two Word documents are very important. We fail to understand why what we have cited was not mentioned in EMA's confidential 256-page internal document prepared for SAG and why SAG members did not receive these documents.

[27] Butts BN, Fischer PR, Mack KJ. Human Papillomavirus Vaccine and Postural Orthostatic Tachycardia Syndrome: A Review of Current Literature. J Child Neurol. 2017 Jan 1:883073817718731. doi: 10.1177/0883073817718731. [Epub ahead of print].
[28] Singer W, Sletten DM, Opfer-Gehrking TL, Brands CK, Fischer PR, Low PA. Postural tachycardia in children: what is normal? Journal of Pediatrics 2012;160:222-226.
[29] Zhao J, Han Z, Zhang X, Du S, Lui AD, Holmberg L, Li X, Lin J, Xiong Z, Gai Y, Yang J, Lui P, Tang C, Du J, Jin H. A cross-sectional study an upright hear rate and BP changing characteristics: basic data for establishing diagnosis of postural orthostatic tachycardia syndrome and orthostatic hypertension. BMJ Open 2015;5:e007356.
[30] Borehers AT, Gershwin ME. Complex regional pain syndrome: a comprehensive and critical review. Autoimmunity Reviews 2014;13:242-265.
[31] Goebel A, Blaes F. Complex regional pain syndrome, prototype of a novel kind of autoimmune disease. Autoimmun Rev 2013 Apr;12(6):682-6.
[32] Dirckx M, Schreurs MW, de Mos M, Stronks DL, Huygen FJ.The prevalence of autoantibodies in complex regional pain syndrome type I. Mediators Inflamm 2015;2015:718201. doi: 10.1155/2015/718201. Epub 2015 Feb 8.

We note that overlap in the occurrence of autoantibodies between POTS patients and controls have been described by other researchers. For example, autoantibodies directed towards the autonomic nervous system have been described in patients with POTS and other autonomic dysfunctions. One such study showed that patients with POTS had higher levels of such antibodies than patients with vasovagal syncope or healthy controls, and that pharmacological blockade reduced the clinical impact of these antibodies in patients with POTS but not in controls.[33] Another study showed that, after vaccination, agonistic antibodies against β2-adrenoceptors were identified in most girls with POTS combined with other symptoms of dysautonomia but only in a minority of those vaccinated girls who were healthy (Brinth L, personal communication).

The information mentioned just above suggests that HPV vaccines, other vaccines and perhaps also the adjuvant (in combination with an otherwise harmless virus infection) may cause POTS or CRPS in some people. Whether linked or not, the relationship between exposure to HPV vaccines and rare harms needs to be taken seriously to retain confidence in public health.

We believe our observations about the issues outlined above are very important for our complaint over maladministration at EMA. We, therefore, wrote to the Ombudsman on 13 July that we hoped she would ask EMA why it removed its literature searches and also its discussion of the assessed, highly relevant literature from the 256-page "Briefing note to the experts" it sent to its experts in SAG.

The Ombudsman replied to us that she had been able to verify that the literature searches were provided to all PRAC members, as they can be found in the unredacted version of the preliminary assessment report made available to her. She also wrote:

57. The literature searches were not included in the preliminary assessment report provided to the SAG-V experts. The Ombudsman notes, however, that essentially all publications identified by EMA following its literature search were included in the list of **references** provided in the co-rapporteur's preliminary assessment report and were thus available to the SAG-V experts. Furthermore, the co-rapporteur provided a summary of the results of the literature search in the preliminary report that was made available to the SAG-V.

58. EMA has also confirmed to the Ombudsman that the SAG-V experts could have asked for the literature searches if they considered that they had a need for them and would have been provided with the literature searches had they requested them. EMA stated that the briefing material provided to the experts **expressly stated** that any supplementary information, such as the literature searches, was available to the experts upon request. However, no SAG-V expert requested to be provided with the searches.

This information is misleading. Nowhere in the 256-page "Briefing note to the experts" is a "summary of the results of the literature search" reporting what we have outlined above.

It is noted that, "A link between POTS and chronic fatigue syndrome (CFS) has been suggested by different authors (Benarroch 2012, van Cauwenbergh et al 2014), as well a link with small-fibre neuropathy (Martinez-Lavin 2015, Haensch et al. 2014, Gibbons et al 2013)." The text about CRPS is off the point: "The EMA report discusses the possible causes suggested for CRPS (i.e. psychological factors, immobilisation, sympathetic nervous system, neurogenic inflammation and vasomotor

[33] Fedorowski A, Li H, Yu X, Koelsch KA, Harris VM, Liles C, et al. Antiadrenergic autoimmunity in postural tachycardia syndrome. Europace 2016 Oct 4. doi:10.1093/europace/euw154.

disturbances, neuropeptides and pain, cytokines, deep-tissue microvascular pathology hypothesis, small-fibre neuropathy hypothesis, cortical reorganisation, central changes in pain processing, genetic predisposition, and autoimmunity) (Borchers & Gerschwin 2014, Dirckx et al. 2015, Ostergaard et al. 2014, Richards et al. 2012) ."

We searched for any mention of the four most important references in EMA's literature searches, which are in footnotes 26 to 29 above. We found only this:

Bennaroch is one of the references in a list of 43 references. The name does not appear anywhere in the text.

Butts is not mentioned in the 256-page report at all.

Singer is cited in the reference list and appears twice in text, but not in a way that has anything to do with the possibility that a viral infection plus the vaccine or vaccine adjuvant could cause POTS or CRPS: "Two studies have suggested that having a positive tilt-test in an adolescent patient - regardless of symptoms - would not be that uncommon (Singer et al. 2012, Zhao et al. 2015)" and "The diagnostic criteria for POTS have been discussed (i.e. a rise in heart rate of 230 bpm, or a heart rate of >120 bmp, within 10 minutes of head-up tilt or standing but without orthostatic hypotension; and for adolescents an increase in heart rate of at least 40 bpm for [sic]) (Mathias et al. 2012; Singer et al. 2012)."

Zhao is included in the reference list and is mentioned once in the text (see above under Singer).

As just noted, EMA confirmed to the Ombudsman that the SAG experts could have asked for the literature searches if they considered that they had a need for them and would have been provided with the literature searches had they requested them. However, no SAG expert requested the searches.

This is probably because SAG members had been provided with the 256-page report to read and would have no idea that important information had not been included by EMA. Regulators should be impartial and EMA's behaviour would not seem to follow this principle.

EMA did not release the search strategies, or its findings and summaries, although these would have been highly relevant to SAG members.

The Ombudsman notes that the SAG experts were asked by PRAC to provide input on a number of clearly defined questions, and given that the SAG experts did not ask for any additional information, the Ombudsman understands that they were provided with all the information necessary to deal with these specific questions.

We believe that this conclusion is unwarranted. When the SAG experts are totally unaware that EMA did not release important information for them, how would they then know that they should ask for "any additional information"?

PRAC's comments on the research and data from a researcher and the Uppsala WHO Monitoring Centre

We criticised that PRAC's final assessment report contained inappropriate comments about the research conducted by Louise Brinth at the Danish Syncope Centre. PRAC concluded that overall, the case series reported by Brinth "is considered to represent a highly selected sample of patients, apparently chosen to fit a pre-specified hypothesis of vaccine-induced injury." We noted that Brinth had included all consecutively referred patients, with the exception of those that met the exclusion criteria, which is not "a highly selected sample of patients," and that we found that EMA's allegations constitute guesswork ("apparently"), are pejorative and come close to an accusation of scientific misconduct.

We also criticised how PRAC presented and analysed the work of Brinth and the Uppsala WHO Monitoring Centre and we argued that PRAC's approach was unscientific and involved cherry-picking. When comparing the internal 256-page EMA report with the 40-page published report, it becomes clear that relevant criticisms and disagreements have been concealed from the public and that, rather than praising Danish diligence, EMA cast doubts on whether the Danish peer reviewed research and the Uppsala WHO Monitoring Centre should be believed.

Referring to EMA's argument that nothing in PRAC's position was intended to be construed as pejorative or an accusation of misconduct, the Ombudsman concludes that, "Overall, there is nothing to suggest that PRAC's comment was anything more than part of its scientific point of view on the research." The Ombudsman excuses herself with the argument that she is not in a position to evaluate the science behind the views of PRAC on the research and data from Brinth and the Uppsala WHO Monitoring Centre and argues that "PRAC must be able to take a view, on an issue of science, even if that involves disagreeing with hypotheses put forward by other scientists."

We are surprised by the Ombudsman's way of arguing. This is not an issue about evaluating the science. It is about defamatory remarks that are highly misleading and totally inappropriate for a drug regulator to make about the work of an independent scientist who only did her duty as a doctor, raising a hypothesis about serious neurological harms based on the observations she made.

As we wrote in our letter from 13 July, the Ombudsman should have considered what the consequences will be in future if the Ombudsman fails to tell EMA that such behaviour is unacceptable. Bullying that includes inappropriate and unfounded criticism of whistleblowers from those at the top of overseeing agencies might scare health professionals off from raising important concerns about any kind of medical intervention, which could create far greater problems than declining coverage rates in HPV vaccination programmes. It would also be a complete negation of one of the cornerstones of pharmacovigilance. Brinth has reported that she has been contacted by quite a few doctors and researchers from various countries who share her concerns and had seen the same pattern, but that most of them are afraid to speak up.

Access to documents

In our 13 July letter, we wrote about unnecessary redactions and the extremely slow access to documents. We repeat it here because the Ombudsman did not address these important concerns.

Some of the redactions EMA imposed on the documents it delivered to the citizens according to Freedom of Information requests were not needed; were not legitimate according to a 2010 ruling by the Ombudsman;[34] and are not in the public interest. The illegitimate redactions included case numbers of patients for which harms were reported, country names for individual cases, numbers of reported harms for individual countries, names of countries where there is an excess incidence of reported harms, and number of doses of the vaccine used in individual countries.

EMA also redacted the case numbers in the clinical study reports of the HPV vaccines EMA delivered to us from 2014 onwards. Three years later, we have still only acquired a minor part of the documents. This means that EMA's policy 0043 about access to documents is de facto defunct for the purposes of research, and considering also the excessive redactions, EMA has made it very difficult for independent researchers to study the possible serious harms of the HPV vaccines in regulatory material.

EMA provided a very long explanation when it disagreed with our view that it is not possible to identify individual people from a case number, referring to a number of regulations and rules. All such documents are open to interpretation and EMA seems to interpret them in the most restrictive way possible, and inconsistently. The minute risk of identifying a real person needs to be weighed against the risk that many patients are being harmed and die because vitally important research about drug harms is being withheld by EMA by all its unnecessary redactions.

We proposed a simple solution to the Ombudsman: Researchers could sign a confidentiality agreement under punishment by law about not revealing patient identity to anyone. The Ombudsman did not comment on our proposal.

EMA does not disclose the identity of the EU Member State which made the comment, as the agency considers that such disclosure would undermine the collegial and confidential nature of the discussion and would deter the EU Member States from having open and comprehensive discussion in future procedures. We find this argument bizarre. If accepted, one could postulate that members of the European Parliament should all be wearing a disguise and be anonymous when they debate in Parliament in order not to deter them "from having open and comprehensive discussion." In a democracy, people are responsible for their actions and opinions and should be held accountable for them. If people or public institutions have something to hide, it does not foster public confidence in the procedures or give them legitimacy, and it may open the door to corruption.

In our letter from 13 July 2017, we suggested that the Ombudsman examines closely whether EMA's reasons for redactions, with references to numerous regulations and rules, are legitimate and in the public interest. In 2011, the Nordic Cochrane Centre requested clinical study reports on antidepressant drugs from EMA, and some of these contained patient narratives (brief summaries of deaths, serious adverse events, or other events of clinical importance) or listings of adverse events in individual patients with details including the patient identifier. The fact that *nothing* was redacted in the reports we received from EMA meant that it was possible to compare information in the text of the reports with that in tables and narratives.

This led to several important findings. We found that four deaths were misreported by the company within the reports, in all cases favouring the active drug, and we also showed, for the first time, that

[34] Gøtzsche PC, Jørgensen AW. Opening up data at the European Medicines Agency. BMJ 2011;342:d2686.

antidepressants double the incidence of aggression compared to placebo in children and adolescents,[35] which can help explain why antidepressants may drive healthy people into committing suicide or homicide. Thirdly, we demonstrated that the risk of suicide and violence were 4-5 times more common with the antidepressant duloxetine than with placebo in trials in middle-aged women with stress urinary incontinence.[36] We used data from four clinical study reports (totalling 6870 pages and including individual patient data) in order to show this. It would have been quite impossible to demonstrate how dangerous duloxetine and other antidepressants are, if we had only had access to published research.

Rasi's statement to the Ombudsman on 15 May that EMA has a "firm commitment to ensure the maximum level of transparency and public access to documents for every assessment or decision concerning the authorisation and supervision of medicinal products" is contradicted by the de facto end of policy 0043, which we have documented above.

We are concerned that the Ombudsman has not declared that she will investigate whether EMA's reasons for redactions, with references to numerous regulations and rules, are legitimate and in the public interest.

Maladministration

The Ombudsman concludes that there was no maladministration by the EMA in the handling of the referral procedure on HPV vaccines. We disagree. We understand that the Ombudsman cannot go into scientific disputes but we found many examples of scientific maladministration. EMA has not fulfilled its mandate to carry out impartial scientific assessments with an acceptable scientific standard.

There also seems to be double standards. In his letter to the Ombudsman, Rasi talks about science all the time and yet states that the Ombudsman should not take a view on the science.

As long as the Ombudsman is not willing to comment on scientific maladministration, there is no public safeguard against poor conduct by EMA. As far as we know, there is no disciplinary committee in the European Union that can take appropriate action against EMA. We find this deeply concerning.

Can we trust EMA?

In their letter to us from 1 July 2016, EMA noted: "Any evidence is assessed in a factual, scientific and objective way. These high standards were adhered to in the EMA handling [sic] of the safety of HPV vaccines." However, we showed that the evidence provided by the vaccine manufacturers was generally accepted at face value, unlike the more reliable and independent publications by the Danish researcher and her colleagues, the Danish Health and Medicines Agency and the Uppsala WHO Monitoring Centre.

[35] Sharma T, Guski LS, Freund N, Gøtzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. BMJ 2016;352:i65.
[36] Maund E, Guski LS, Gøtzsche PC. Considering benefits and harms of duloxetine for treatment of stress urinary incontinence: a meta-analysis of clinical study reports. CMAJ 2017;189:E194-203.

EMA got it wrong on several crucial points when it investigated the suspected serious neurological harms of the HPV vaccines. EMA did not get it right either when the agency responded to the Ombudsman's questions. And in July 2017, we found out that EMA had left out important information from EMA's literature searches in EMA's confidential 256-page report it delivered to SAG members.

We find it problematic for the trustworthiness of EMA that the agency does not admit its errors, even when they are pointed out to them. Every time EMA has responded in our case, new baseless or misleading statements have been introduced, most recently in relation to EMA's own literature searches.

Another example is that EMA asserted in its final report that the chronic fatigue syndrome has "been reported relatively constantly since 2009." This is not correct. Chronic fatigue syndrome has been increasing since 2012 with a marked increase between 2012 and 2013. In its reply, EMA stated that it may have been misunderstood and that the phrase meant that the event has been continuously recorded over a period of time and does not contain a judgement on the intensity of the reporting. However, EMA clearly misrepresented its own published report: "Fibromyalgia, CFS and ME/PVFS have been reported relatively constantly since 2009 (with a slight decrease in 2011/12), but reports of POTS and CRPS had notably increased since 2013." A text that says that something has increased, and then decreased, and that something else has been reported relatively constantly, cannot be misunderstood.

EMA also seriously misrepresented the facts in relation to the Nordic Cochrane Centre's previous complaint to the Ombudsman in 2007.[37] EMA declared that it would undermine the protection of commercial interests to allow us access to clinical study reports and their corresponding protocols, because the documents represented the full details of the clinical development programme. There are no such details in these documents.

EMA claimed that the redaction of (unspecified) "personal data" would cause EMA a disproportionate effort that would divert attention from its core business, as it would mean redacting 300,000-400,000 pages. It is impossible that the study reports and its protocols could take up to 300,000-400,000 pages. When we ultimately received the reports we had requested (for one of the two drugs we were interested in; the other was withdrawn from the market during our complaint proceedings with the Ombudsman), the total amount of documentation was only 8,716 pages.[38]

EMA also argued back then that, "as a result of the redaction exercise, the documents will be deprived of all the relevant information and the remaining parts of them will be worthless for the interest of the complainant." This was not true either. The Ombudsman noted that the requested documents do not identify patients by name but by their identification and test centre numbers, and he concluded that the only personal data are those identifying the study authors and principal investigators and to redact this information would be quick and easy.

[37] Gøtzsche PC, Jørgensen AW. Opening up data at the European Medicines Agency. BMJ 2011;342:d2686.
[38] Schroll JB, Penninga EI, Gøtzsche PC. Assessment of Adverse Events in Protocols, Clinical Study Reports, and Published Papers of Trials of Orlistat: A Document Analysis. PLoS Med 2016;13:e1002101.

It was only after the Ombudsman had accused EMA of maladministration in a press release on 7 June 2010, three years after our request, that EMA reversed its stance. EMA now gave the impression that it had favoured disclosure all the time.[39] This was also untrue.

We believe that EMA is more concerned with protecting the vaccines and the drug companies than with protecting patients. EMA wrote to us on 1 July 2016 that "The MAHs are the owners of data from clinical trials and data in their safety databases." They are not. Data generated by patients belong to the patients and indeed to all of us, not to drug companies that often misrepresent or misreport the data they collect in their sponsored trials. This is the main reason why our prescription drugs are the third leading cause of death, after heart disease and cancer.[40] [41]

The lack of impartiality of the whole referral procedure is obvious when comparing EMA's initial referral announcement letter from 13 July 2015 stating that EMA would "not address the question of whether the benefits of HPV vaccines outweigh their risks"[42] with its official report stating that the "benefits of HPV vaccines continue to outweigh their risks." EMA's decision to answer this question anyway suggests it was a foregone conclusion. Proper scientific process does not include changing the questions posed after having seen the results.

We also find it concerning that EMA's conclusions are not based on analyses performed by the agency but on inadequate analyses performed by the Marketing Authorisation Holders, which must have missed a lot of cases of POTS and CRPS. EMA did not make this clear in its official report.

Concluding remarks

EMA wrote to us on 1 July 2016 that EMA ensures "maximum transparency, so that the European public can see how decisions were made." This is not correct. It is clear from our complaint to the Ombudsman that it is hard detective work to find out what went on in the HPV case and why, and we have spent many months working on this.

We take issue with several of Rasi's other remarks in his letter to the Ombudsman from 15 May 2017 than those already noted, e.g. "EMA would like to express its concerns on recent media reports around the safety of vaccines in many Member States of the EU that have given rise to undue suspicion and distrust towards scientists' learned societies and healthcare professionals."

This sentiment is reminiscent of sponsors and their Key opinion leaders' reactions when their products come under scrutiny. Regulators should not use such rhetoric as they are supposed to be impartial. Rasi's statement is evidence of a double standard considering the treatment meted out to the Danish whistleblower scientist, and ignoring the critical comments made by the Danish drug agency about EMA's assessments and conclusions.

[39] Gøtzsche PC, Jørgensen AW. Opening up data at the European Medicines Agency. BMJ 2011;342:d2686.
[40] Gøtzsche PC. Deadly medicines and organised crime: How big pharma has corrupted healthcare. London: Radcliffe Publishing; 2013.
[41] Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press; 2015.
[42] http://ijme.in/pdf/b-wc500189476-referral-announcement.pdf.

Rasi writes that "EMA's concerns are echoed by members of the scientific community, who have already expressed their strong criticism to the way the complainants have framed their concerns.[43] This is a misleading statement. We are the complainants, but there is no "strong criticism," which can easily be seen by comparing these authors' one-page commentary with our complaint to the Ombudsman. The authors of the commentary complain that we used the Nordic Cochrane Centre's letterhead and thereby give the readers the impression that our views are representative of the Cochrane Collaboration, and that this impression is promoted by what they call online antivaccine communities.

Firstly, we find it natural to use our letterhead when we write letters. This is what most people do, including Rasi.

Secondly, on the first page in our complaint to the Ombudsman we make it clear that the complaint represents our own views: "It is possible that many of the serious harms that occur after vaccination are autoimmune diseases. However, as we do not know whether these diseases are caused by the HPV vaccines, it must be a research priority to find out. The views we express here and our conclusions are based on the facts we present; they are ours and not those of any organisation."

Thirdly, we are not responsible for how others use or misuse our complaint, which is evidence-based, in the best tradition of the Cochrane Collaboration.

Fourthly, the two references the authors of the commentary give for their claim that those ideologically opposed to vaccination have misinterpreted our complaint as originating from the Cochrane Collaboration do not support their claim. The authors of these two references clearly note that the complaints come from the Nordic Cochrane Centre.

Rasi notes that PRAC performed "a sound and comprehensive assessment of all the available scientific evidence in the context of the referral of the HPV vaccines." This is not true. PRAC only looked at the aggregate material that the MAHs had preselected for PRAC to look at. This is not acceptable science.

We reiterate that our complaint is not about whether the HPV vaccines do more good than harm; it is about EMA's conduct, which we find is an instance of maladministration. It is of paramount importance for public health that concerns about possible serious harms of healthcare interventions can be discussed openly and that the science related to such concerns is carried out in a transparent and unbiased manner. This has not happened.

In his letter, Rasi mentions the need for consensus and for avoiding confusion, and he is concerned about recent media reports around the safety of vaccines in many member states of the EU, as if these concerns were caused by our complaint. The public debate was not generated by us but predated our complaint, and it was and still is fuelled by the culture of secrecy surrounding regulatory decisions and the dismissal of signals of harms, which were ignored. We acknowledge the concerns that groups ideologically opposed to vaccination may exploit scientific uncertainties or propagate fraudulent research, e.g. Andrew Wakefield and co-workers' unfounded claim that the

[43] Head MG, Wind-Mozley M, Flegg PJ. Inadvisable anti-vaccination sentiment: Human Papilloma Virus immunisation falsely under the microscope. npj Vaccines 2017;2:6. Available at: https://www.nature.com/articles/s41541-017-0004-x.

measles, mumps and rubella (MMR) vaccine can cause autism.[44] [45] However, this does not mean that we should not openly discuss and investigate possible harms of vaccines in a misguided attempt to protect their reputation.

The handling of the HPV controversy - pretending that we have sufficient knowledge when we have - has caused many people to lose confidence in the authorities. In one region in Denmark, the uptake of the vaccine decreased from 74% to 31% in just one year,[46] and in Japan, where an unusually high rate of harms has been reported, the vaccination rate has decreased from 80% to less than 1%.[47] The decline took place long before we wrote to EMA.

EMA has not respected the citizens' rights to know about the scientific uncertainties related to the possible harms of the HPV vaccines, as envisaged in Article 6 of the EU Treaty and the Charter of Fundamental Rights of the European Union.[48] Furthermore, EMA has not lived up to the scientific standards that must be expected of the agency. Finally, EMA withheld important information from its expert committee, namely the results of EMA's own literature searches and EMA's interpretation of what it found.

EMA's procedures for evaluating the harms of medical interventions - where the companies are by and large their own judges - need to be fundamentally reworked. And all procedures, information, scientific uncertainties and internal disagreements should be made available to the public. The citizens should decide for themselves whether they think any particular vaccine, drug or other intervention is a good idea. This is not a decision an authority can make for them.

[44] Deer B. How the case against the MMR vaccine was fixed. BMJ 2011;342:c5347.
[45] Godlee F, Smith J, Marcovitch H. Wakefield's article linking MMR vaccine and autism was fraudulent. BMJ 2011;342:c7452.
[46] Flere vælger HPV-vaccine fra - flere vil dø af livmoderkræft. BT 2016; May 6.
[47] Beppu H, Minaguchi M, Uchide K, Kumamoto K, Sekiguchi M, Yaju Y. Lessons learnt in Japan from adverse reactions to the HPV vaccine: a medical ethics perspective. Indian J Med Ethics 2017;2:82-8.
[48] Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents. Official Journal of the European Communities 2001;L145:43-8. www.europarl.europa.eu/RegData/PDF/r1049_en.pdf.