
13 July 2017

To: European Ombudsman, Emily O'Reilly

Complaint 1475/2016/JAS concerning the European Medicines Agency's (EMA) handling of the referral procedure regarding a pharmaceutical product, Human papillomavirus (HPV) vaccines

From:

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This is our reply to the Ombudsman's letter to us from 26 June. Please note that the views we express here and our conclusions are based on the facts we present; they are ours and not those of any organisation apart from the Nordic Cochrane Centre, which two of us represent. Our complaint is not about whether the vaccines do more good than harm, or whether they cause the alleged serious neurological harms, but about EMA's conduct.

For ease of reference, if not otherwise specified, "Rasi" means the letter sent by Guido Rasi, Executive Director of EMA, to the Ombudsman on 15 May 2017, and "EMA" means the letter sent by EMA to us one year ago, on 1 July 2016.

In the interest of transparency, we will upload on the Nordic Cochrane Centre's website¹ this letter to the Ombudsman, the Ombudsman's letter to Rasi from 16 February 2017, and other relevant correspondence.

The scientific aspects of our complaint

The Ombudsman notes that the Ombudsman's Office is not a scientific body and that it is not within the Ombudsman's mandate to examine the merits of scientific evaluations carried out by specialised scientific services. We fully understand that the Ombudsman cannot go into scientific disputes. However, if there is no doubt that an EU institution like the European Medicines Agency (EMA), whose job it is to do scientific assessments, has not lived up to its mandate, we feel it is an issue for the Ombudsman to protect public health by pointing this out to the EMA.

¹ <http://nordic.cochrane.org/news/complaint-filed-european-medicines-agency-over-maladministration-related-safety-hpv-vaccines>.

In case of maladministration at EMA, which we conclude is the case here, the only other option seems to be to launch a case at the European Court, which few people can afford and which funders are not likely to allow researchers to spend their research grants on. Thus, there would in reality be no public safeguard if the Ombudsman is not willing to comment on scientific maladministration, even when it is so apparent that people without any scientific education would be able to see it. We therefore appreciate your comment that, “In my role as Ombudsman, I may seek to assess whether EMA has procedural safeguards in place to ensure that the scientific advice it receives is as complete as possible and independent.” As we shall explain, EMA does not have such safeguards.

The Ombudsman also needs to take a view on the fact that Rasi tries to make EMA immune against criticism from the Ombudsman about maladministration. 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.

It is not a due process if only one of the sides were allowed to discuss the science, and it seems to us that Rasi is afraid of challenges of EMA’s authority. He writes on page 1: “EMA, together with other international, EU and national public authorities, is particularly concerned about the harmful effects of public campaigns aimed at discrediting the scientific validity and soundness of the assessments carried out by public health authorities on the safety of vaccines. EMA, therefore, would like to respectfully ask that any future public communication continues to emphasise, in express and unambiguous terms, that the scope of the current inquiry does not cover the scientific assessment of the EMA Scientific Committees in the context of the referral procedure on HPV vaccines. In the alternative, this inquiry would potentially be misperceived as a *de facto* challenge of the scientific conclusions on the safety of HPV vaccines. Such misperception would expose the health of EU citizens to significant and unnecessary risks.”

The available evidence supports the opposite view of Rasi’s. Challenges of the drug agencies’ scientific conclusions, which are usually based almost exclusively on what the drug companies have told the agencies, like in the HPV vaccine case, have saved hundreds of thousands of lives.²

Rasi ends his letter on the same note (page 15): “We hope that the explanations and information submitted address your questions and that you will be able to close this inquiry soon. We trust that the European Ombudsman may confirm that there has been no instance of maladministration in the conduct of the EMA referral procedure concerning HPV vaccines. Your confirmation would be particularly relevant in this case in order to protect public health and avoid unjustified alarms in the public opinion.”

As we explain in the following, there are many good reasons for concluding that EMA’s handling of the suspected serious neurological harms of the HPV vaccines is an instance of maladministration. Furthermore, Rasi is not protecting public health by calling the alarms unjustified. We consider these alarms justified and we furthermore find that the necessary research that can confirm or refute the suspicion that the vaccines cause serious neurological harms has not yet been carried out. The suspected harms are, in particular: postural orthostatic tachycardia syndrome (POTS) and complex regional pain syndrome (CRPS).

In the following, we use the same headings as in the Ombudsman’s letter to us from 26 June 2017.

² Gøtzsche PC. Deadly medicines and organised crime: How big pharma has corrupted health care. London: Radcliffe Publishing; 2013.

a. The safety referral procedure

The internal preliminary report

We wish to emphasize that when there are scientific uncertainties and disagreements, these should be openly communicated to the public. When scientific advisory boards at the US Food and Drug Administration (FDA) vote about whether or not a drug should be on the market, these votes are made public. This has made it possible to document that doctors with conflicts of interest in relation to the drug industry are less concerned about serious drug harms than other doctors.³ In contrast, at EMA, there is pressure on members of the Pharmacovigilance Risk Assessment Committee (PRAC) to reach consensus even when some of its members do not agree. This creates a false sense of security.

EMA stated to us that the co-rapporteurs are crucial for the validity of the whole scientific process as 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.” It is therefore concerning that they were consistently overruled by the rapporteur when she had another opinion, which invariably favoured the view that the suspected harms were not related to the vaccines.

Science is the antithesis of “consensus.” It is concerning that EMA stated to us that the consensus “recommendation was presented in the final PRAC assessment report which summarised all the data assessed by the committee in support of the PRAC conclusions.” This looks like cherry-picking. What about all the data and evidence-based criticism that did NOT support the PRAC conclusions? When comparing the internal 256-page EMA report with the 40-page published report, it becomes obvious that relevant criticisms and disagreements have been concealed for the public.

The Ombudsman’s inquiry team concludes that, “even if certain members expressed divergent opinions during the course of the procedure, they obviously considered these opinions to be properly addressed by the end of the procedure” since all members, including the co-rapporteurs, voted for the final recommendation adopted by PRAC. We disagree. The inquiry team notes that striving for consensus in PRAC is expressly provided for by law and it cannot be inferred that there were no remaining disagreements when the participants felt obliged to reach consensus.

Publication of the internal preliminary report

The Ombudsman asked EMA to consider making available more information on its assessments, including on any initial concerns expressed and on how these concerns are dealt with during the process.

Rasi replied (page 11) that differences in opinion are made publicly available in the final report if those differences persist until the adoption of the final report, and that if such preliminary views are not maintained at the end of the procedure, “the publication of such information ... would give rise to confusion as to the final conclusions reached.”

The inquiry team considers, nevertheless, that “the Ombudsman might consider suggesting to EMA that it should, in the future, explain **more clearly** to interested parties how differences in views are dealt with during the assessment of its scientific committees.”

³ Gøtzsche PC. *Deadly medicines and organised crime: How big pharma has corrupted health care*. London: Radcliffe Publishing; 2013.

We agree with the inquiry team. Healthcare is often confusing, with no clear answers, and the public has a right to know what we know, what we think we know, and what we don't know. It is wrong to create a false sense of security by concealing uncertainties and disagreements and this may increase the confusion rather than decrease it. Unfortunately, drug regulators routinely do this, which is unduly paternalistic and can be very harmful. Drug regulators have all too often been wrong when they assured the public that there was nothing to worry about. Drug agencies are far too permissive and far too slow to react to signals of serious harm, which is a main reason why several independent studies have found so many drug deaths that they make our prescription drugs the third leading cause of death after heart disease and cancer in the United States and Europe.⁴

The “updated assessment report”

The inquiry team notes that the critical statements were made by Member State representatives on the PRAC and that we mistake these statements as criticisms made by the co-rapporteur.

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 document⁵ was written by the Belgian co-rapporteur and this rapporteur agreed with some of the member state's criticisms.

This highly 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. As also pointed out in the rapporteurs AR [assessment report] p.22, we agree that when a diagnosis is reported and verified by a HCP [health care practitioner], this description should be accepted and used.”

An assessment provided by a clinical expert who sees the patient is likely to be far more reliable than that performed by a company employee with a conflict of interest looking at paperwork where important details about the case are missing. However, in its reply to us, EMA calls it a “very conservative approach” to let the drug companies exclude a large amount of cases diagnosed by a skilled clinician without verifying by inspecting the underlying raw data that this is legitimate. This is absurd, particularly since the internal EMA report reveals that the POTS cases were dismissed without having access to the full medical records. Furthermore, as we have explained earlier, Dr Brinth from the Danish Syncope Unit used the exact same criteria (those by Sheldon et al.) that the EMA repeatedly recommended in both the internal and official report, but many of her cases were nonetheless dismissed by the drug companies and subsequently by the EMA.

Another, equally strong and important criticism, also very likely from Denmark, is this one: “... the review highlights the necessity to evaluate combinations of symptoms rather than only performing

⁴ Götzsche PC. Deadly medicines and organised crime: How big pharma has corrupted health care. London: Radcliffe Publishing; 2013.

⁵ PRAC co-rapporteur's referral updated assessment report. Updated report circulated 28 October 2015.

separate evaluations of individual diagnoses. It shows that although the number of POTS cases is very high in Denmark, compared to the rest of the world, the symptom pattern seen in the Danish dataset is similar to reports submitted from other countries ... This consideration is important for the discussion of consistency regarding the POTS signal, where it is stated that the finding of the majority of POTS cases in Denmark does not support a causal relationship. We do not agree with this conclusion based on the data.”

EMA told us that it was only the Belgian co-rapporteur that was critical, but this is not correct. Both the Belgian and the Swedish co-rapporteurs were highly 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”⁶ and “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” (page 9 in PRAC co-rapporteur’s referral updated assessment report; SE means Swedish co-rapporteur). 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” (page 215 in the pdf, or 36/77 in the subdocument in EMA’s internal report).

It is important that both co-rapporteurs were highly critical of the observed versus expected analyses because they were the two most important of all the people who participated in EMA’s processes. According to EMA’s letter to us from 1 July 2016 (page 4), 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.

Consensus-based decision-making

The inquiry team notes that striving for consensus in PRAC is expressly provided for by law. When this is the case, people are not likely to express disagreement with the majority, particularly not as they would then be exposed publicly. The inquiry team concludes that the fact that no PRAC member recorded any divergent views in the final report was because any questions that PRAC members may have had at the beginning of the deliberations were adequately addressed during the deliberations.

As already noted, we believe that such a conclusion cannot be justified. Psychologically, it is much easier to swallow what comes on the table, even if you disagree with it, when consensus is expected by law. This is the opposite of science. What came out of the PRAC meeting is a cosmetic consensus.

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

⁶ Briefing note to experts. EMA/666938/2015. 13 October 2015 (page 210 or 31/77).

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.

The public’s confidence in EMA and its public report about the HPV vaccines would likely have been greater if EMA had honestly announced that there are uncertainties and disagreements related to the safety of the HPV vaccines.

EMA wrote to us that the members of its committees had the opportunity to ask questions to the pharmaceutical companies but we have found no data suggesting that any important questions were asked at the SAG meeting, which is surprising given the serious criticisms of the companies that were raised in EMA’s internal report.

Information provided by the Marketing Authorisation Holders (MAHs)

The Ombudsman asked EMA: “Are the raw data, analyses and explanations on the methodology applied, including those originating from the Marketing Authorisation Holders (MAHs), made available to all members of EMA’s Pharmacovigilance Risk Assessment Committee (PRAC)?”

Rasi replied “Yes” to this question (page 2) and furthermore explained that “all submitted data were made available to all PRAC members” and “With regard to raw data concerning adverse reactions, EMA manages and therefore has direct access to the EudraVigilance database that records all individual cases reported for medicines authorised in the EU, regardless of the source (clinical trial and post-marketing events). In the concerned referral, both MAHs have included the summary analyses in the information provided to EMA. In addition, the MAH for Gardasil has included the narratives of all reported cases identified in the relevant documentation. The MAH for Cervarix has included a summary of each case with the respective identification number in order to enable linkage to the EudraVigilance cases.”

The inquiry team noted that the explanations provided appear reasonable. We firmly disagree. As we explain below, 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 noted in our complaint to EMA that it is clear from its confidential 254-page report that EMA relied heavily on the companies to come up with honest answers to highly complicated questions, and 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.

This procedure provides poor protection of public health, particularly considering that there are so many egregious examples that companies have cheated by omitting major harms - including deaths - in their reports to the authorities.^{7 8}

We find it unacceptable that EMA believed what the companies told them and did not check the veracity of the MAHs' work. The police don't believe what suspects tell them; they check it. It is noteworthy that the contributions of two doctors external to EMA's committees are the only ones in EMA's 254-page internal report that alert people to the well-documented fact that drug companies cannot be trusted and should not be asked to audit their own work (pages 171-4 in the pdf, or 59-62/67 in the subdocument). EMA trusted almost blindly the drug companies, which is not a legitimate approach.

Furthermore, as we pointed out in our complaint to the Ombudsman (page 29), several trials were not included in the MAHs' analyses, which is unacceptable from a scientific as well as from an ethical perspective. 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.⁹

It is therefore not correct when Rasi writes to the Ombudsman that PRAC "performed a sound and comprehensive assessment of all the available scientific evidence in the context of the referral of the HPV vaccines" (page 2).

MAHs' analyses of adverse events

The Ombudsman asked EMA a number of questions on the difference between the two MAHs involved concerning the number of post marketing safety reports not meeting the criteria for the syndromes under investigation. EMA provided possible explanations for the observed differences. In particular, EMA explained that all individual post marketing safety reports were provided to PRAC and reviewed by the co-rapporteurs. Regarding the concerns expressed by one member state during the procedure, EMA stated that the member state's PRAC member ultimately agreed with the final assessment report after deliberating in PRAC.

We find Rasi's explanations difficult to understand and contradictory (page 7). He affirms that the MAHs provided all individual post marketing safety reports to PRAC but 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".

⁷ Gøtzsche PC. Deadly medicines and organised crime: How big pharma has corrupted health care. London: Radcliffe Publishing, 2013.

⁸ Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press; 2015.

⁹ 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.

This “wider search strategy” was grossly inappropriate and must have missed many cases, see next section.

The inquiry team notes that the explanations provided appear reasonable. We do not agree. Rasi furthermore notes that the “inherent limitations of spontaneous reporting constitute the reason why the analysis was an observed versus expected analysis and not a cross-product comparison” (page 5). Clearly, when the data are so unreliable that they do not allow a comparison of the reports from the two companies, they do not allow a comparison either of observed versus expected incidence of neurological harms. The next section, “Search strategies for undiagnosed adverse events,” shows that Rasi’s explanations are totally unreasonable.

Search strategies for undiagnosed adverse events

The inquiry team notes that the Ombudsman’s Office is not a scientific body and that the inquiry team therefore takes no view on the question of whether the search terms used by the MAHs are scientifically appropriate.

We believe the Ombudsman can and should address this crucial issue. 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 knows perfectly well that there are countless examples of drug companies hiding serious - even lethal - harms from the authorities.^{10 11} We believe this is a serious case of maladministration at the EMA. As explained in the following, it is clear that EMA’s confidence in the work of the MAHs is totally misguided.

The Uppsala 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.¹² 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).

¹⁰ Gøtzsche PC. Deadly medicines and organised crime: How big pharma has corrupted health care. London: Radcliffe Publishing; 2013.

¹¹ Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People’s Press; 2015.

¹² Chandler RE, Juhlin K, Fransson J, Caster O, Edwards R, Noren GN. Current safety concerns 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.¹³

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.¹⁴ 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,¹⁵ 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 affair 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

¹³ 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.

¹⁴ Dunder K, Mueller-Berghaus J. Rapporteurs’ Day 150 Joint Response Assessment Report. Gardasil 9. 2014 Nov 23.

¹⁵ 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.

regulator fitted the diagnostic criteria for POTS. In effect the regulator is asking for details of the methods used by the MAH and is openly critical of the MAH's conclusions and dismissal of the work of the Danish Syncope Centre at Frederiksberg Hospital. 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 the 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 the PRAC was uncritical and did not take into account the concerns clearly expressed by the referring Danish regulator.

Rasi's explanations in relation to the question from the inquiry team are nonsensical and seriously misleading (page 8). About the material we submitted on 2 February, he asserts: "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."

Prima facie means based on the first impression; a curious term to use about something that so clearly should have raised all alarm bells at EMA. 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 absolutely nothing to do with what Rasi writes about the reliability of spontaneous reports.

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 aggregate data in tables produced by them and coded accordingly, with relevant narratives. A credible independent review would have entailed a complete reanalysis, which we are unable to do because we do not have access to the data and because EMA has redacted patient identifiers in the study reports we have obtained.

Pooling of placebos

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 explains 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).

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 on page 4 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 statement is not correct. 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 certainly NOT gain any benefit from this; as Rasi explains (see next paragraph just below), they are actually harmed through local reactions. Thirdly, they might have been seriously harmed, systemically, as the adjuvant is strongly immunogenic.¹⁶ 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.

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 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.”

Since the rationale for using aluminium adjuvants as “placebo” is that they are so reactogenic that a genuine, inert placebo would cause far fewer reactions (systemic or local), it is unethical to use an adjuvant as “placebo.” Further, the outcome of primary interest in the trials is cervical cell changes, the assessment of which 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 while losing the possibility to investigate harms of the vaccines raises serious concerns about EMA procedures.

Rasi notes 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.” He also speaks about “the

¹⁶ 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.

known safety profile of the adjuvants and of the active control” and mentions 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. It is also misleading when Rasi refers to aluminium hydroxide, $Al(OH)_3$, because the adjuvant is not aluminium hydroxide. The Gardasil adjuvant, for example, is amorphous aluminium hydroxyphosphate sulfate, $AlHO_9PS^{-3}$,¹⁷ which has very different properties than aluminium hydroxide. According to EMA, it is “used to enhance the immunogenicity of the HPV VLP vaccine.”¹⁸

We have investigated ourselves whether the safety of aluminium adjuvants 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 absolutely nothing in support of Rasi’s claim:

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/BiologicsBloodVaccines/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 2 published papers alleging that aluminium in vaccines is associated with autism spectrum disorders and considered that these 2 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. And it is misleading to quote the WHO GACVS report because it confuses orally ingested aluminium with the effect of

¹⁷ <https://pubchem.ncbi.nlm.nih.gov/compound/86278271#section=Related-Records>.

¹⁸ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003852/WC500189113.pdf.

aluminium adjuvant, which is not about what dose of the metal aluminium that is toxic but about the adjuvant being strongly immunogenic.¹⁹

It is clear that the MAHs simply lumped the results from trials with a genuine placebo with those 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).”

It is wrong when EMA calls an immunogenic adjuvant and another vaccine for placebo. Merck’s own definition of a placebo is (our emphasis) “A placebo is an inactive pill, liquid, or powder that has no treatment value.”²⁰ 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 “EMA’s literature searches” below), which would make it difficult or impossible to use the trials to find out if the HPV vaccines cause the suspected rare harms.

None of the vaccine trials was truly placebo controlled. In one trial, 597 children received a so-called placebo (Gardasil trial V501-018, NCT00092547) that - apart from aluminium - included all the adjuvants, some of which are highly immunogenic. 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.

The two doctors external to EMA’s committees explained in EMA’s 254-page internal report how absurd all this is (page 173 in the pdf, or 61/67 in the subdocument):

“Initially, the vaccine was compared with a placebo group being vaccinated with physiological serum, whereby the number of adverse reactions was much higher and much more serious than in the control group. After comparing 320 patients in the saline placebo group a quick move was made to an aluminium-containing placebo, in order to be able to only evaluate the effects of the active substance. However, this distorted the comparison ... the difference between the vaccine and the saline placebo is concealed in all publications, as the table below clearly shows. For serious adverse reactions one suddenly takes the saline and aluminium group together, perhaps to cover up the major differences between these two groups.”

We believe it constitutes scientific misconduct to lump “placebo” groups that are not placebo groups and then claim that there is no safety signal. EMA not only accepted this but also defended it, without reservations.

The inquiry team 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 say that it takes no view on the scientific aspects and then conclude that EMA’s

¹⁹ 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.

²⁰ <http://www.merck.com/clinical-trials/frequently-asked-questions.html>.

scientific explanations are logical and reasonable. EMA's explanations are neither of this, which we had already explained at length in our complaint to the Ombudsman. And it does not require any scientific expertise to conclude that the conduct in this matter by EMA is totally unacceptable. We therefore believe the Ombudsman will need to point this out to EMA.

“Observed vs expected analysis”

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 was 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.

Both the Belgian and the Swedish co-rapporteurs were highly 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” (EMA's internal report, page 210 or 31/77) 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” (EMA's internal report, page 215 or 36/77).

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 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 inquiry team 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 inquiry team cannot accept EMA's scientific explanations and at the same time say that it takes no view on the scientific aspects of this question. We feel the Ombudsman is in a position where she can criticise EMA for emphasizing totally unreliable research in its public report

at the same time as it dismisses the independent research from Denmark and the Uppsala WHO Monitoring Centre.

EMA's literature searches

The Ombudsman asked EMA to explain why its literature search strategies are removed from the preliminary reports. EMA explained that when it processed a request for access to the preliminary reports concerning the present procedure, the search strategies had been inadvertently deleted. The inquiry team suggested that if we remained interested in EMA's literature search strategies, we might make a request for public access.

Accordingly, on 28 June 2017, we asked EMA to provide us with the search strategies and to explain how the search icons could have been "inadvertently deleted further to a clerical error" (Rasi, page 10), as we could not imagine that this could have happened due to a simple error. In fact, the search icons seemed to have been deliberately overwritten (redacted):²¹

p62

- **HPV referral – literature search POTS**

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



p63

- **HPV referral – literature search CRPS**

The EMA has performed a systematic bibliographic search regarding Complex Regional Pain Syndrome:



p64

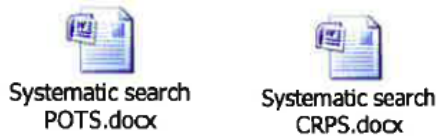
- **EVDAS search**

The EMA has performed a search in the EudraVigilance data base for cases of CRPS and POTS following vaccination with Cervarix. The obtained results are summarised below.

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."

²¹ PRAC (co)-rapporteur's referral 2nd updated preliminary assessment report. Updated report circulated 28 October 2015.

Wathion did not explain how the icons for the search strategies could have been deleted due to a clerical error. The icons are these:



Wathion correctly acknowledged that the redactions we referred to had occurred in "PRAC (co)-rapporteur's referral 2nd updated preliminary assessment report. Updated report circulated 28 October 2015." However, Wathion also wrote: "As EMA has confirmed to the EO [European Ombudsman], the visual icons representing the different documents "embedded" in the draft AR [Assessment Report] are separate attachments (Word document) of the draft AR. The icons had been redacted (blackened) from the copy of the documents you have in your possession due only to a clerical error. In any case, as you state in your complaint, you seem to be already in possession of an unredacted copy of the AR¹, you may already be aware that the only information redacted in that page is the visual representation of embedded documents."

Wathion's comment is extremely misleading. We did not state in our complaint that we were in possession of an unredacted copy of the AR and we have never seen an unredacted copy of the AR. If we had, we would not have asked EMA for it. Furthermore, Wathion, in his footnote 1, does not refer to the updated preliminary assessment report (AR), but to "EMA's confidential 256-page internal document," which is something else. It is true that in the version we have, there are no redactions, but the search strategies have nonetheless been deliberately removed (i.e. no "clerical error" is possible this time) from the internal report (see, for example, page 167, or 55/67):

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]

So, "Confidential information was removed." We wonder why EMA removed its search strategies in a report that was confidential and which was the basis for the discussions in SAG, the expert committee. This makes no sense to us unless there is something EMA wants to hide, even for the members of its committee who EMA had obliged to life-long confidentiality. EMA seems to have deliberately hidden these two documents from SAG members. We have contacted two SAG members and they confirm that they have never received the two documents. We cannot say who it was in this document but are willing to convey the two names confidentially to the Ombudsman.

The search strategies appeared in Word documents of 6 and 8 pages, respectively, which also had information about other EMA literature searches and discussions of the findings in the articles EMA identified. These discussions are highly interesting and relevant for the whole issue about whether HPV vaccines or other vaccines may cause POTS or CRPS and we shall therefore mention some of the issues described 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).”²² This is what we had assumed all along could happen and a major reason why we find it unacceptable that the “placebo” was not placebo but an adjuvant or another vaccine, which might cause POTS or CRPS.

“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 admits here that its observed vs expected analyses are totally worthless. There are no data in the literature that can say anything about the background incidence of POTS; this was also found in a 2017 literature review.²³

EMA discusses studies of patients with POTS compared with healthy controls and says that there is 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.^{24 25}

EMA furthermore 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-fiber neuropathy, but the majority of POTS patients in these three studies were found to have no small-fiber neuropathy as confirmed by skin biopsy.”

In the Word document on CRPS, EMA mentions:

“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) review²⁶ 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.”

²² Benarroch EE. Postural tachycardia syndrome: A heterogeneous and multifactorial disorder. *Maya Clinic Proceedings* 2012;87(12):1214-1225.

²³ 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].

²⁴ 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.

²⁵ 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 on upright heart rate and BP changing characteristics: basic data for establishing diagnosis of postural orthostatic tachycardia syndrome and orthostatic hypertension. *BMJ Open* 2015;5:e007356.

²⁶ Borchers AT, Gershwin ME. Complex regional pain syndrome: a comprehensive and critical review. *Autoimmunity Reviews* 2014;13:242-265.

There was no reference to Goebel and Blaes 2013 in EMA's reference list, but we think we found it.²⁷ It also required some work 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.²⁸

We believe that these two Word documents are highly important and fail to understand why what we have cited just above was not mentioned at all in EMA's confidential 256-page internal document prepared for SAG and why SAG members did not receive these documents. We suspect it is because it detracts substantially from EMA's view that there is nothing to worry about in terms of serious neurological harms of the HPV vaccines.

Overlap 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.²⁹ Another study showed that, after vaccination, agonistic antibodies against β 2-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).

These observations and the information mentioned just above suggest 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.

We believe our observations about this are very important for our complaint over maladministration at EMA. We hope the Ombudsman will ask EMA why it deliberately removed its literature searches and also its discussion of the assessed, highly relevant literature from the 256-page Briefing note document it sent to its experts in the SAG committee.

Drafting of the final report

The Ombudsman asked EMA to explain who drafts PRAC's final assessment reports. Rasi explained that in this case, in line with standard procedure, the rapporteur with the assistance of the EMA Secretariat prepared the draft of the final PRAC assessment report which was subsequently commented upon and adopted by all members of PRAC. The inquiry team notes that the explanations provided appear reasonable.

The reason we asked this question was that there are no authors on EMA's official report, and that the amount of spin generated by EMA on the findings of the MAHs makes the report look like something that could have been written by a PR agency working for a drug company.

²⁷ Goebel A, Blaes F. Complex regional pain syndrome, prototype of a novel kind of autoimmune disease. *Autoimmun Rev* 2013 Apr;12(6):682-6.

²⁸ 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.

²⁹ 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.

PRAC's comments on the research/data from Dr B. and the Uppsala WHO Monitoring Centre

We had noted in our letter to the Ombudsman that EMA asserted in its published report that: "Overall, the case series reported by Brinth and colleagues (2015) is considered to represent a highly selected sample of patients, apparently chosen to fit a pre-specified hypothesis of vaccine-induced injury." We also noted that Brinth stated in her report³⁰ that she and her co-workers included all consecutively referred patients, with the exception of those that met the exclusion criteria. This is not "a highly selected sample of patients." We found that EMA's allegations constitute guesswork ("apparently"), are pejorative and come close to an accusation of scientific misconduct. EMA argued that nothing in PRAC's position was intended to be construed as pejorative or an accusation of misconduct. We had also argued that PRAC's approach was unscientific and involved "cherry-picking".

We found additional evidence that EMA was biased in favour of the vaccines and the drug companies. In a report prepared for the Danish drug agency for its submission to EMA,³¹ the Uppsala WHO Monitoring Centre had highlighted key features when HPV reports from Denmark were compared to HPV reports from the rest of the world, which were: a significantly greater proportion of the reports were considered "good reports" (determined by the amount of clinically relevant information), were classified as "serious", and were received from either a physician, consumer or a lawyer. EMA failed to mention any of this but chose to mention in its official report that "the terms POTS, orthostatic intolerance and autonomic nervous system imbalance are reported disproportionately more in HPV reports from Denmark vs HPV reports in other countries." Thus, rather than praising the Danish diligence, EMA cast doubts on whether the Danish peer reviewed research and the Uppsala WHO Monitoring Centre should be believed.

In its letter to us, 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. All the evidence provided by experts, which constituted a significant element of all data assessed, was given equal consideration and this included the publications of Dr Louise Brinth and colleagues, the Danish Health and Medicines Agency and the Uppsala Monitoring Centre."

Contrary to EMA's statements, the evidence was not assessed in an objective and scientifically acceptable way and the evidence provided by experts was not given equal consideration. We have explained this at length, both in our complaint to the Ombudsman and here. 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 WHO Uppsala Monitoring Centre.

EMA replied to us: "One element that emerged clearly from this assessment is that individual cases did not show a consistent pattern regarding time-to-onset following vaccination or clinical characteristics."

This information is misleading. Symptoms often started appearing shortly after vaccination, but since they were so diffuse, it could take a long time before the girls were seen by a specialist and a

³⁰ Brinth L. Responsum to Assessment Report on HPV-vaccines released by EMA November 26th 2015. 17 December 2015. <http://www.ft.dk/samling/20151/almdel/suu/bilag/109/1581470.pdf>.

³¹ Information from Uppsala Monitoring Centre regarding cases in VigiBase@.

diagnosis of POTS 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 now been firmly established that the influenza vaccine Pandemrix can cause narcolepsy, a very serious condition, several years after vaccination of children and adolescents,³² 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.

The inquiry team notes that the comments in PRAC's final assessment report are points of view on the scientific value of the assessments by Dr Brinth and the Uppsala WHO Monitoring Centre and that PRAC must be able to take a view on an issue of science even if that involves calling into question hypotheses put forward by scientists. The inquiry team also notes that the Ombudsman's Office is not in a position to evaluate the science behind the views of PRAC.

However, this is not an issue about evaluating the science. It is about defamatory remarks that are not only highly misleading but also totally inappropriate for a drug regulator to make about the work of an independent scientist who only did her duty as a doctor, to raise a hypothesis about serious neurological harms based on the observations she made. The same day EMA's report came out, a major Danish newspaper brought the headline: "Danish researchers demolished: no relation between the HPV vaccine and serious symptoms," and the article even insinuated that Brinth and her group had committed scientific misconduct.³³

The Ombudsman should consider what the consequences will be in future if the Ombudsman does not 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 problems orders of magnitude greater than declining participation rates in HPV vaccination programmes. It would also be a complete negation of one of the cornerstones of pharmacovigilance. Brinth reported in her "responsum" that she had been contacted by quite a few doctors and researchers from various countries who shared her concerns and had seen the same pattern, but that most of them were afraid to speak up.

Need for more research

The Ombudsman asked EMA to confirm that it will continuously evaluate any new evidence and will continuously examine if more specific research needs to be requested in the future. In response, EMA provided explanations on its efforts to monitor and analyse pharmacovigilance data. It also described the obligations imposed on the MAHs, as well as the recommendations made by PRAC following the referral procedure. The inquiry team notes that the explanations provided appear reasonable.

We do not agree. As discussed above, there is an urgent need for research that compares people with POTS or CRPS after HPV vaccination with vaccinated people who did not develop these syndromes and also with healthy controls.

³² Institutet för Hälsa och Välfärd. Förhöjd narkolepsirisk i två år efter Pandemrix-vaccinationen. 2014; June.

³³ Trojaborg K. Danske forskere sables ned: Ingen sammenhæng mellem HPV vaccine og alvorlige symptomer. Politiken 2015 Nov 26.

b. Transparency and openness

Confidentiality clause

The Ombudsman suggested to EMA that it consider adapting its standard confidentiality clause for experts so that it reflects EMA's position that "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."

Rasi stated that EMA had initiated a review process of the template to that end, which was currently ongoing. The inquiry team considered that EMA should be asked to inform the Ombudsman's Office of the outcome of this process. We agree. The confidentiality clause must be changed.

Access to documents

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 virtually impossible 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 also, as we explained in our complaint to the Ombudsman, highly 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 propose a very simple solution to the Ombudsman: Researchers could sign a confidentiality agreement under punishment of the law about not revealing patient identity to anyone.

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 (page 13). We find this argument bizarre. If accepted, one could postulate that members of the European Parliament should all be wearing disguise and be anonymous when they debate in Parliament in order not to deter them "from having open and comprehensive discussion."

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

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 doesn't foster public confidence in the procedures or give them legitimacy, and it may open the door to corruption.

The Ombudsman suggested that EMA could consider making publicly available lists of all relevant documents in its possession related to a specific referral procedure. This would enable citizens to make specific requests for public access, should they wish to obtain a document. Thereby, both the requester and EMA would need to spend less time on unnecessarily broad requests.

EMA did not address this suggestion in its reply. The inquiry team considered that this suggestion should again be put to EMA, either during the inquiry or when closing the inquiry.

We agree and furthermore suggest 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 *absolutely 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 revelations. 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 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.

With all the recently introduced obstacles to access to documents, it is not correct when Rasi writes to the Ombudsman 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" (page 2).

Requested meeting minutes

We had complained that parts of the minutes of the SAG had been redacted by EMA. The inquiry team noted that the redacted information concerns the names of EMA support staff only, which it found reasonable.

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.

c. Alleged conflicts of interest

Availability of declarations of interest on EMA website

We had complained that the declarations of interests of two SAG members were missing from EMA's online expert database. On the Ombudsman's request, EMA has now provided the two documents. The two SAG members did not have conflicts of interest.

EMA's analysis of alleged conflicts of interest

SAG chair Andrew Pollard

The inquiry team considers that EMA's explanations on this point are reasonable and does not agree with us that the chair of the SAG, Andrew Pollard, has a conflict of interest. The inquiry team argues that although Pollard previously carried out "research on vaccines for the MAHs **other than the HPV vaccine**," there is no evidence that this research work established any form of dependence in relation to the producers of HPV vaccines. The team furthermore argues that there is no evidence that the research on other vaccines had any link to the subject under discussion, the safety of the HPV vaccine; that it is not unusual for an expert involved in a scientific assessment to express opinions publicly on the scientific subject under discussion; and that the statements simply reflect the fact that the experts work in the relevant area of science and have developed scientific views on that area of science.

We take issue with all of the arguments offered by the inquiry team in support of EMA.

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 that are 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 companies than the ones directly involved.³⁷ 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."³⁸

It is totally 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 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 believe that it is inappropriate for a chair of an EMA committee to communicate publicly what the conclusions of the investigation are two months before they become publicly known, and we cannot see that this is in accordance with EMA's lifelong confidentiality clause either.

³⁷ Götzsche PC. Deadly medicines and organised crime: How big pharma has corrupted health care. London: Radcliffe Publishing; 2013.

³⁸ <http://www.icmje.org/conflicts-of-interest/>

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 conflicts: 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 drug companies and owned shares in a company.

We asked EMA to inform us of its justification for offering the chair of SAG, 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." 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 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.

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 highly the vaccines one month before the crucial SAG meeting. Pollard spoke about the many lives it saved and said there was no evidence of safety problems. The statement about the lack of harms was clearly 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 has a consulting contract with Merck-Serono for 2016.

We hope the ombudsman will 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 such people in meetings.

EMA's executive director Guido Rasi

We are surprised that the inquiry team has not mentioned with one word the undeclared conflicts of interest for EMA's executive director Guido Rasi.

Rasi had not declared - and as of 4 July 2017 has still not declared³⁹ - that he is the inventor of several patents, which we believe he should, even if he is not the owner of the patents, both according to EMA's own rules and according to international guidelines for declaring conflicts of interest in healthcare. Rasi has replied "none" to all four questions on the form "EMA Public Declaration of Interests," also to question 4, which is: "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."

As Rasi's patents go back less than five years,⁴⁰ we believe he should have declared them, according to EMA's regulations concerning the handling of declared interests of its employees.⁴¹

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 Ombudsman⁴² 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 to our proposed apology, 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 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 and quicker and also more trustworthy 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."⁴³

³⁹ 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.

⁴⁰ Guido Rasi's patents. <http://patents.justia.com/search?q=guido+rasi> (downloaded 7 May 2016).

⁴¹ 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.

⁴² <http://nordic.cochrane.org/news/complaint-filed-european-medicines-agency-over-maladministration-related-safety-hpv-vaccines>.

⁴³ <http://www.carter-ruck.com/>.

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.⁴⁴ 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 36).

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 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 failed this simple and sensible test.

We hope the Ombudsman will require of Rasi that he declares his conflicts of interest and that the Ombudsman will launch an investigation to find out if it is true that Rasi does not benefit from his patents.

Can we trust EMA?

We demonstrated in our complaint to the Ombudsman that EMA got it wrong on several crucial points when it investigated the suspected serious neurological harms of the HPV vaccines. We have shown here that EMA did not get it right either when the agency responded to the Ombudsman's questions. And on 10 July 2017, we found out that important information from EMA's literature searches had apparently been left out in EMA confidential 256-page report it delivered to SAG.

We find it problematic that EMA seems to have a problem with admitting when they are wrong. Here is another example that EMA does not admit its errors, which we mentioned in our complaint. EMA asserted in its published report that the chronic fatigue syndrome has "been reported relatively constantly since 2009." This is not correct. It 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 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 2007.⁴⁵ 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

⁴⁴ Gøtzsche PC. *Deadly medicines and organised crime: How big pharma has corrupted health care*. London: Radcliffe Publishing; 2013.

⁴⁵ Gøtzsche PC, Jørgensen AW. Opening up data at the European Medicines Agency. *BMJ* 2011;342:d2686.

core business, as it would mean redacting 300,000-400,000 pages. It was totally impossible that the study reports and its protocols could take up 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.⁴⁶

EMA also argued 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.

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.⁴⁷ This was also untrue.

We believe that EMA is more concerned with protecting the drug companies than with protecting the 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 all of us.

The lack of impartiality of the whole referral procedure is obvious when comparing EMA’s initial referral announcement letter from 13 July 2015 that stated that EMA would “not address the question of whether the benefits of HPV vaccines outweigh their risks”⁴⁸ with its official report that stated that the “benefits of HPV vaccines continue to outweigh their risks.” That EMA decided to answer this question anyway suggests it was a foregone conclusion. It is not a proper scientific process to change 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 drug companies, and that EMA did not make this clear in its official report.

Concluding remarks

It is not correct that EMA ensures “maximum transparency, so that the European public can see how decisions were made.” 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 on this.

We take issue with several of Rasi’s remarks in his introduction in the letter to you, 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 is exactly how drug companies argue when their drugs

⁴⁶ 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.

⁴⁷ Gøtzsche PC, Jørgensen AW. Opening up data at the European Medicines Agency. BMJ 2011;342:d2686.

⁴⁸ <http://ijme.in/pdf/b-wc500189476-referral-announcement.pdf>.

come under attack. Drug agencies should not use such rhetoric. Furthermore, Rasi's remark is hypocritical considering how EMA treated the Danish whistleblower scientist and ignored the highly critical comments made by the Danish drug agency about EMA's assessments and conclusions.

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."⁴⁹ This is a misleading statement. 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 antivaccine communities.

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

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 don't 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 cannot be held responsible for how others use or misuse our complaint, which is thoroughly evidence-based, in the best tradition of the Cochrane Collaboration.

Fourthly, the two references the authors of the commentary give for their claim that antivaccine communities have misinterpreted our complaint as if it had come from the Cochrane Collaboration do not support their claim. The authors of these two references clearly note that the complaints came 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 simply not true, as we have explained above. PRAC only looked at the material that the MAHs had preselected for PRAC to look at.

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 believe 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, but this hasn't happened.

Rasi mentions the need for consensus and for avoiding confusion (page 11), 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 we have demonstrated the drug companies deliberately ignored. There are well founded concerns that antivaccine groups may

⁴⁹ 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>.

exploit scientific uncertainties or propagate fraudulent research, e.g. Andrew Wakefield and co-workers' unfounded claim that the measles, mumps and rubella (MMR) vaccine can cause autism.⁵⁰
⁵¹ 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 haven't - 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,⁵² and in Japan, where an unusually high rate of harms has been reported, the vaccination rate has decreased from 80% to less than 1%.⁵³

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.⁵⁴ Furthermore, EMA has not lived up to the scientific standards that must be expected of the agency. Finally, EMA deliberately concealed important information from its expert committee, namely the results of EMA's own literature searches.

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 vaccination is a good idea. This is not a decision an authority can make for them.

⁵⁰ Deer B. How the case against the MMR vaccine was fixed. *BMJ* 2011;342:c5347.

⁵¹ Godlee F, Smith J, Marcovitch H. Wakefield's article linking MMR vaccine and autism was fraudulent. *BMJ* 2011;342:c7452.

⁵² Flere vælger HPV-vaccine fra - flere vil dø af livmoderkræft. *BT* 2016; May 6.

⁵³ Beppu H, Minaguchi M, Uchida 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.

⁵⁴ 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.