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26 May 2016

### **Complaint to the European Medicines Agency (EMA) over maladministration at the EMA**

According to Article 6 of the EU Treaty and the Charter of Fundamental Rights of the European Union (1), “Openness enables citizens to participate more closely in the decision-making process and guarantees that the administration enjoys greater legitimacy and is more effective and more accountable to the citizen in a democratic system. Openness contributes to strengthening the principles of democracy and respect for fundamental rights.”

On 26 November 2015, the European Medicines Agency (EMA) released a 40-page Assessment Report dated 11 November (2) on the safety of vaccines against human papilloma virus (HPV), which is supposed to decrease deaths from cervical cancer.

We are concerned about the EMA’s handling of this issue as reflected in its official report (2) and ask the EMA to assess:

1. Whether the EMA has been open and accountable to the citizens and has respected their rights to know about the uncertainties related to the safety of the HPV vaccines.
2. Whether the EMA has lived up to the professional and scientific standards that must be expected of the agency to guarantee that the administration enjoys legitimacy when evaluating the science and the data related to the safety of the HPV vaccines.
3. Whether the EMA has treated fairly - in a manner that guarantees that the administration enjoys legitimacy - a Danish whistleblower, PhD Louise Brinth, when she raised concerns about possible serious harms of the HPV vaccines.
4. Whether the EMA has treated fairly - in a manner that guarantees that the administration enjoys legitimacy - the observations and concerns the Danish Health and Medicines Authorities and the Uppsala Monitoring Centre had raised about possible serious harms of the HPV vaccines.
5. Whether the EMA’s procedures for evaluating the safety of medical interventions guarantee that the administration enjoys legitimacy. The EMA asked the manufacturers of the vaccines to assess potential harms of their own products in which they have huge financial interests.
6. Whether the extreme secrecy, with life-long confidentiality agreements, which the EMA imposed on its working group members and scientific experts, is needed; is legitimate; is in the public interest; and guarantees that the administration enjoys legitimacy.

7. Whether the redactions the EMA imposed on documents it delivered to the citizens according to Freedom of Information requests were needed; were legitimate; are in the public interest; and guarantees that the administration enjoys legitimacy.
8. Whether the EMA has behaved in a manner that guarantees that the administration enjoys legitimacy in relation to declaring conflicts of interest. We noticed a Guido Rasi's name associated with patents for inventions and wonder whether this is the same person who is the EMA's director. If so, we believe Rasi has failed to declare his conflicts of interest. We also believe that the rapporteur for the EMA's report, Julie Williams (2), has failed to declare her conflicts of interest.
9. Whether the EMA behaves in a manner that guarantees that the administration enjoys legitimacy when the agency use experts with financial ties to the manufacturers, in particular considering that it is always possible to find experts without such conflicts.
10. In the interest of transparency, we urge the EMA to ensure that the names of all the experts consulted are disclosed together with their conflict of interest declarations. We also urge the EMA to ensure that the conflicts of interest statements from the rapporteur, the co-rapporteurs (Jean-Michel Dogne (BE) and Qun-Ying Vue (SE)), their contact persons at the EMA and everyone else who has given statements to the EMA are brought out in the open. Finally, we urge the EMA to ensure that Declarations of Interests for officials at the EMA are honest.

#### Outline of the case

After Denmark had contacted the European Commission, and the Commission requested the EMA to give its opinion, the Danish Health and Medicines Authorities (DHMA) asked the EMA in July 2015 to assess the research linking HPV vaccines to serious harms, which included peer reviewed articles published by PhD and physician Louise Brinth from the Danish Syncope Unit at Frederiksberg Hospital in Copenhagen describing possible serious neurological harms of the vaccine. In its submission to the EMA, the DHMA included a review of the global data made by the Uppsala Monitoring Centre (UMC, a WHO collaborating centre).

The prominent symptoms, which are suspected of being caused by the vaccine, are similar to those seen in so-called functional disorders such as chronic fatigue syndrome (CFS) and include postural orthostatic tachycardia syndrome (POTS) and chronic regional pain syndrome (CRPS). The hypothetical mechanism is an autoimmune reaction triggered by either the active component of the vaccine or the adjuvant in the vaccine. These syndromes are difficult to diagnose; their causes are poorly understood; and they are likely to be underreported. This complicates studies of a causal link.

The EMA's official report (2) gives the impression of a unanimous rejection of the suspected harms. However, only seven months earlier, the EMA had resolved that "A causal relationship between the dizziness and fatigue syndrome, Postural Orthostatic Tachycardia Syndrome (POTS) and Gardasil [one of the HPV vaccines] can neither be confirmed nor denied" (3). Moreover, the EMA's internal report of 256 pages (4), which provided the draft for its 40-page official report, tells a very different story. The internal report is confidential but has been leaked.

There are many problems with the EMA's official report, and Louise Brinth has drawn attention to them in a 63-page document from 17 December 2015 (5). Brinth did not have access to the confidential internal report (4) when she wrote the document, only to the official one (2).

#### Brinth's observations

1. The EMA asserts 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" (2, p24).

Brinth states in her report that she and her co-workers included all consecutively referred patients, with the exception of the ones excluded because they met the exclusion criteria (5, p17).

We find that the EMA's allegations constitute guesswork ("apparently"), are pejorative and come close to an accusation of scientific misconduct. The EMA's comments are totally inappropriate for an EU authority to make on honest researchers and the criticism is furthermore totally unfounded.

2. EMA: "many of these symptoms would require some sort of objective clinical evaluation, yet there is no information on how this was done or what other clinical assessment may have been undertaken to exclude other causes of the symptoms" (2, p23).

Brinth: Nausea, headache, abdominal pain, fatigue etc. are in essence subjective symptoms and as such they escape "objective clinical evaluation". Orthostatic intolerance was quantified through tilt-testing, which constitutes more than "some sort of objective clinical evaluation" ... "altogether I find the criticism put forth with regard to my work and my scientific approach unjust. I find that the evaluation of my work presented by EMA is based on many assumptions. Most of these assumptions are to my best knowledge wrong. I find this approach strange and unscientific ... In the EMA report, it is concerning that the complete data set was not included. Only specific parts of the report have been reproduced, and it is not defined how these parts were chosen. As a result, there are a number of examples of inconsistency between the representation of UMC data in the original DHMA report and the EMA report" (5, p25-26). Brinth furthermore writes that her observations and hypotheses were supported by the independent review of the global data made by the Uppsala Monitoring Centre (5, p26).

We find that the EMA's comments are unprofessional, misleading, inappropriate and pejorative, and that the EMA's approach involves cherry-picking, which is unscientific. Furthermore, the Uppsala centre compared reports of potential harms from the HPV vaccines with reports of similar harms from all other vaccines offered to women and found that POTS was reported 82 times for HPV vaccines versus once; CRPS 69 times versus 16; autonomic nervous system imbalance 77 times versus 16; and fibromyalgia 62 times versus 39. Several other comparisons were made but did not show differences. In the EMA's opinion, this does not allow any conclusions to be made (4, p230 in the pdf, or 51/77 in the subdocument). The rapporteur noted that the analyses were not corrected for multiple comparisons (although that would not have made a ratio of 82 to 1 disappear) and that the higher frequency of harms could be due to media attention (no evidence for this was presented). The finding by the Uppsala centre that a substantially higher proportion of case reports were serious for the HPV vaccines compared to other vaccines was mentioned but not paid attention to in either of the EMA reports (2, 4).

3. EMA: Chronic fatigue syndrome has “been reported relatively constantly since 2009” (2, p27).

Brinth: According to the UMC report, chronic fatigue syndrome has “been increasing since 2012 with a marked increase between 2012 and 2013” (5, p27).

We believe that the EMA misrepresents the UMC report with regard to possible serious harms of the vaccine (see more examples below).

4. The EMA failed to mention that the Danish reports were more often classified as “serious” and had more often included a large amount of clinical relevant information. Instead, the EMA mentioned 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” (2, p27).

Brinth: The UMC noted that “a significantly greater proportion of the reports from Denmark were considered “good reports”; were classified as “serious”; and were received from either a physician, consumer or a lawyer (5, p28). There were a number of potential side effects, which were statistically significantly over-reported with the HPV vaccine, but which the EMA failed to mention: disturbances in consciousness, muscular weakness, disability issues, and neurological signs and symptoms (5, p29).

We find that the EMA, rather than praising the Danish diligence, casts doubts on whether the Danish peer reviewed research should be believed. This is an inappropriate attitude to safety for a drug agency. We agree with Brinth that the EMA misrepresented the UMC review in its own report, thereby creating the impression that Brinth should have published substandard research. It seems to us that it is the EMA that uses and accepts substandard methods, not Brinth (see more examples below). The EMA omitted some of the important suspected harms of the vaccine, which is another example of cherry-picking.

5. Brinth: “As far as I can see, the minutes of the [EMA] meetings are not released. What data did they get to review? Did they write a report for the PRAC [Pharmacovigilance Risk Assessment Committee] to use? And if they did where is the report – can we see it? To my best knowledge the conclusion of the meetings and the report put forth by EMA is presented as if it is the result of an unanimous discussion and opinion of the SAG [Scientific Advisory Group] and these experts. This makes us unable to judge if all the experts agreed on the conclusion of the final report. I find this a very strange, unscientific and undemocratic approach. In a matter as complex as this I believe that not two single scientists will share exactly the same viewpoints ... Creating a sort of false consensus based on the participants being bound to secrecy will inevitably lead to the impression that “all these many experts agreed on the conclusion set forth by EMA”” (5, p33).

We agree with Brinth. The EMA’s official 40-page report (2) is misleading, as it gives the citizens the impression that there is nothing to worry about in relation to vaccine safety and that the experts consulted by the EMA agreed on this. However, the EMA’s confidential, internal report (4) reveals that several experts had the opinion that the vaccine might not be safe and called for further research, but there was nothing about this in the official report. We find that the extreme level of secrecy imposed by the EMA on its working group members and other experts is inappropriate and

goes against the public interest in openness and transparency about possible serious harms of the vaccine. In the EMA's internal report (4), there is a "**Confidentiality Reminder**" on page 2:

"As an EMA expert you are bound to life-long duty of confidentiality. The duty of confidentiality applies to all information of the kind covered by the obligation of professional secrecy. This includes, for example, the fact that there is a meeting, that you have been nominated to participate, the agenda of the meeting, the product or company concerned, the participants, any part of the discussions and outcome. All documentation (correspondence, reports, minutes, etc.) must be kept as confidential and stored in a secure place or destroyed. The duty of confidentiality stops only if information has been made public and only to the extent that has been released into the public domain."

6. Brinth: "Reading EMA's report it seems to me that the review of the safety data which includes available data from the clinical trials and post-marketing surveillance and the literature review was all collected by the marketing authorization holders (MAHs) [GlaxoSmithKline Biologicals, Merck Sharp & Dohme Limited, and Sanofi Pasteur MSD]? This must have been in the form of a report written by the MAHs to the EMA?. Is this report freely available?" (5, p34).

We find it unacceptable that the EMA in its official report (2) did not make it clear that it allowed the drug companies to be their own judges (4) when evaluating whether the vaccine is safe, particularly since there is a huge amount of money at stake: The global expenditure so far on HPV vaccines can be roughly estimated at €25 billion. The EMA asked the companies to search for side effects of the vaccine in their own databases and did not check the companies' work for accuracy. This is not an acceptable procedure. There are countless examples of drug companies hiding serious - even lethal - harms from the authorities (6) (see also under "8. Brinth" below).

7. Brinth: "Were there any opportunities for PRAC-members, SAG-members or other assessors to ask additional questions or for clarifications? I find it highly problematic that we as readers of the EMA reports – and I as medical professional having diagnosed and evaluated a substantial part of the Danish Cases – my diagnoses and work altogether downed and overruled by MAH/ EMA – have not access to their case detection methods ... I know that a substantial proportion of the POTS-cases reported as suspected side effects from Denmark have been done by me. I therefore find it troubling and strange to see that POTS-cases have been overruled and judged as not meeting or only partially meeting the diagnostic criteria in 50 out of 83 cases given the diagnosis POTS in the AER [Adverse Events Reports] ... I interpreted the report as if it is the MAH who has evaluated the AER – and have found that most of the POTS cases do not meet the proper diagnostic criteria? The EMA report mentions the diagnostic criteria put forth by Raj and Sheldon ... We use the exact same criteria and have experience in diagnosing and treating POTS – and are to some extent quite restrictive in our diagnostic practice. It can be discussed - as we do in our papers – whether POTS is a relevant diagnosis or not. However, that is a whole other issue. Therefore, we need to know: Has the MAH based their evaluation on the AER alone – or have they been through the whole medical record of these patients? It is well known that an AER will not include all the details of the clinical history and therefore it is rare that any spontaneous report will meet diagnostic criteria. Evaluating the diagnosis given in AER will be very difficult bordering on impossible if based only on the AER. But – if they did obtain full medical record – then the discrepancy between the diagnoses given by the clinicians seeing the patient and filing the report and the MAH is a more relevant discussion. But then this discussion should be out in the open. We need to close the gap between the reality as it looks like

from the clinicians (and the patients) point of view and the MAH and EMA. Either I have misunderstood the whole diagnostic approach to POTS – and then I need to know. Or – the reports have been judged on a too lose background. Both scenarios represent - as I see it - a quite serious problem. We have a common interest in reaching consensus on how to use this POTS- diagnosis as it is now very much on the agenda ... Our thoroughness underlined by the fact that WHO has stated that the Danish AER did not in the essense [sic] differ from reports from the rest of world – but were of a higher quality” (5, p34-35).

We find it totally unacceptable that no one - not even the person whose research is so strongly and unfairly criticised in the EMA’s official report (2) - can judge on what grounds and by whom 50 out of 83 cases of POTS were dismissed by the EMA. Furthermore, the secret internal EMA report (4) reveals that the POTS cases were dismissed *without* having access to the full medical records. Clearly, the “research” carried out by the companies did not live up to the accepted standards for such research and the EMA did not ensure that it did. This is very serious, as the EMA used the companies’ assessments to overrule the research done by Brinth, which is of a much higher standard. The Danish Health and Medicines Authorities (DHMA) also criticised pretty strongly the EMA’s approach (7, p9-10):

“The main conclusion in the Danish report is not, as described in the assessment, to change focus to CFS. Rather the review highlights the necessity to evaluate combinations of symptoms rather than only performing 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. Even though it cannot be shown for certain at this point, it is likely based on these data, that patients with the same symptomatology would receive different diagnoses in different member states e.g. POTS in DK and CFS/ME in others. 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.”

Immediately after this, the DHMA states:

**Risk Management Plan/ Post-authorisation Safety Studies/ Conditions**

Need for further studies regarding the signal for POTS:

We agree with the conclusion from the rapporteurs and also state in the Danish report [this shows that these comments come from the DHMA], that the data from spontaneous reports cannot be used to provide evidence for a causal relationship between symptoms and vaccination.

However in view of the methodological limitations of the data available and the fact that the observed cases did exceed the expected cases, especially in Japan and Denmark, the conclusions should be cautious and the signal cannot be dismissed either based on the current evidence.

We recommend that the vaccine SAG and expert meeting include a discussion of the need and possibilities to design appropriate PASS studies to explore POTS further. Similar question as Q3 regarding CRPS.”

8. Brinth writes that the EMA’s official report notes on page 12 that PRAC requested the MAHs to search not only “for reports specifically containing the terms POTS and CRPS” but also to use

“common search strategies” “to identify possible cases of undiagnosed CRPS and POTS.” Brinth says it would have been relevant to have these search strategies clearly defined and given because, to the best of her knowledge, there are no common search strategies which have been previously defined for either POTS or CRPS (5, p35-36).

We agree with Brinth. It is notoriously difficult to identify the harms in question and it is unacceptably poor standards for such research not to define precisely what the search strategies were. It is a fundamental requirement for systematic searches that the combination of search terms is clearly described (8), but not even in the internal 256-page report are these search strategies defined (4). This is extraordinary, as the companies have a huge vested interest in not finding these possible harms in their databases. When the DHMA in 2014 asked Sanofi Pasteur MSD to review its database for potential side effects of its HPV vaccine, the company searched for POTS in a way that made the number of cases retrieved very low (9). This was discovered by the Danish National Board of Health, partly because only 3 of 26 Danish reports of POTS showed up in the company’s searches. Sanofi Pasteur MSD had been asked to search on a number of specific symptoms including dizziness, palpitations, rapid heart rate, tremor, fatigue and fainting, but the company ignored the orders. Instead, the company 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, unusual search terms will yield few results.

9. Brinth: The EMA’s question 2 to the companies “does not make any sense to me: If both the “vaccine group” and the “control group” received aluminium adjuvanted “placebo” or another aluminium adjuvanted vaccine as “placebo” – how does it make sense to ask the company to only discuss potential explanations including risk factors for the development if a **difference** is observed? By asking this question – I find that EMA actually states and take for granted that we know with a very high degree of certainty that we will not see side effects due to the adjuvant?” (2, p37).

We agree with Brinth. In all the vaccine trials apart from a small one, the “placebo” contained aluminium adjuvant, which is suspected of being neurotoxic. It is therefore difficult to find a difference between harms of the vaccine and the “placebo,” but the EMA failed to address this fundamental problem in its official report (2). It is clear from the EMA’s internal report (4) that the MAHs simply lumped the results from trials with a genuine placebo with those that had a potentially neurotoxic “placebo”: **Clinical safety data.** For the purpose of the referral, the MAH was requested to provide an in depth review of the CRPS and POTS cases observed within all clinical studies. To respond to this request, the MAH has pooled the safety data from 18 completed and unblinded studies designed with an active comparator group (either placebo or another vaccine other than an HPV vaccine, i.e. Hepatitis B, Hepatitis A) which includes a total of 42,047 vaccinees (21,268 in HPV group and 20,779 in comparator groups) (4, p119 in the pdf, or 7/67 in the subdocument). We believe this constitutes scientific misconduct, but the EMA accepted it nonetheless, without reservations: “Strength of the potential association. The few cases reported from RCTs [randomised clinical trials] are evenly distributed between the qHPV and placebo groups which does not suggest an association” (4, p20 in the pdf, or p11 in the subdocument).

10. Brinth: The EMA asked the MAHs to provide an analysis of the observed number of post-marketing cases of CRPS and POTS in association with their HPV vaccine in comparison to those expected in the target population. The analysis should discuss the assumptions made with respect to the background incidence in the target population and also the influence of potential under-

reporting of cases in association with HPV vaccines. “I think the whole assumption underlying this question – that it is even possible to establish a reasonable estimate of the background incidence in the target population is a key issue. It is not possible for the time being to give a reasonable estimate of the incidence of these very underrecognized, underdiagnosed and poorly understood disease entities with very different diagnostic practices applied depending on nationality, medical specialty etc” (5, p39).

We agree with Brinth. One of the key arguments in the EMA’s report (2) was that there was no difference between what was observed and the expected background incidence. However, the underlying research is of very poor quality, which renders this observation meaningless. For example, for some of the analyses, the observed incidence of chronic fatigue syndrome was used to estimate the expected incidence of POTS (4, p96, or 87 in subdocument). Furthermore, the EMA writes in its 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 (2, p17). This observation should have alerted the EMA to the fact that analyses based on expected incidence are grossly unreliable. We find it curious and scientifically unacceptable that the official EMA report (2) puts more weight on the “observed versus expected” analyses produced by the companies than the much more reliable Uppsala data.

11. Brinth: The EMA asked the MAHs to provide a critical appraisal of the strength of evidence for a causal association between the HPV vaccine and CRPS and POTS considering the published literature (including epidemiological studies) and the possible causes and pathophysiology of CRPS and POTS, and to discuss whether there is a biological basis for a possible causal association. “I think it would be relevant to know if it was performed by the MAH only or supplemented by the EMA? I think it would be highly relevant to gain insight into the search strategies applied in the literature research. I have an interest in POTS, and have had for many years. I know that POTS is probably associated to autoimmunity, because this is the current perception in the scientific field of POTS. Publications are starting to emerge describing the findings of autoantibodies in patients diagnosed with POTS. The same autoantibodies are also found in CRPS and ME/CFS [myalgic encephalomyelitis/chronic fatigue syndrome]. I know that these studies are small studies, – but I think that they represent some very important information and a hypothesis generating body of evidence” (5, p39).

We find it totally unacceptable to perform a literature review without giving the readers details of its methods, in particular the search strategies used. This is clear from all manuals about systematic literature reviews, e.g. the Cochrane Handbook (8). We also find that the EMA has ridiculed and dismissed the research performed at the Danish Syncope Unit in a way that is unfair, misleading, partly erroneous and pejorative. If drug agencies behave like this when doctors report their observations about possible serious harms of approved products, doctors will be unlikely to alert the public to their observations in future. This would be a tragedy for public health.

#### Many redactions by the EMA in its documents are not legitimate

Various people have obtained redacted documents from the EMA through Freedom of Information requests. As we have access to the unredacted version of the EMA’s confidential 256-page internal document (4), we can see which bits the EMA has redacted. We give some examples of redactions that we find unreasonable (our comments are in brackets):

- 1) Names of contact people at the EMA for the rapporteur and co-rapporteurs. (This does not make sense, particularly since the names for the rapporteur and co-rapporteurs were not redacted).
- 2) Case numbers of patients for which harms were reported. (This is not necessary, as it is not possible to identify individual people from a case number, but it can make it difficult to assess a scientific report when such numbers are missing).
- 3) Country names for individual cases. (This does not make sense unless the idea is to obscure for outsiders whether or not the EMA's assessments are trustworthy, particularly since the EMA considers the Danish cases to be dubious).
- 4) 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. (This is even more difficult to understand unless the idea is to obscure for outsiders whether or not the EMA's report is trustworthy and whether or not the EMA's criticism of the Danish Syncope Centre is warranted).
- 5) While it is indicated that some harms reports come from the Danish Syncope Centre, it is redacted that the centre is located at Frederiksberg Hospital. (This does not make any sense, particularly not when the name of the hospital was not redacted elsewhere).
- 6) The publication identifier for an article in press. (This is pretty meaningless unless the idea is to keep readers of the report in the dark. Scientists routinely refer to papers in press and it should not be hidden where such papers will appear).

Here is an example of an absurd redaction (7). It is clear to anyone familiar with this area that the word left out must be "Denmark." The example also illustrates that there were far more uncertainty and disagreement than the EMA's official report reveals. The co-rapporteur is obviously not happy with the approach taken.

***Assessor's comment:***

Given the substantial uncertainties in the observed versus expected analysis caused by the poor understanding of pathophysiology and unreliable definitions of these conditions and the consequent uncertainty regarding baseline incidence, a wide range of assumptions were used in these calculations. As noted, under some of these assumptions the observed already exceeds the expected in [REDACTED]. The suggested recalculation might actually increase uncertainty around the estimate. A wide definition of observed cases should be accompanied by a similarly wide definition in the estimation of expected cases in order to be correct. 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.

Uncertainties in the science that did not make it to the official report

There was much genuine uncertainty about what the science tells us and whether further research is needed, and there was also a lot of disagreement in the EMA's working group that is not apparent in the official report. Here are some examples from the PRAC co-rapporteurs' referral updated

assessment report from 28 October 2015 (7) (the official title says “co-rapporteur’s”, which is likely an error, as there were two co-rapporteurs, not one).

1. “We agree with the limitations in the current data, but we do find it important not to dismiss the issue at this point but to consider studies or other activities to gain additional information in the future. Also we find that active communication and involvement of all relevant stakeholders is key to address current and future public concerns and ensure the public confidence in the national vaccination programs” (7, p9).

This didn’t happen. The EMA left no doubt in its official report that the vaccine is safe (2).

2. “In the search for cases coded as POTS in the database the MAH make a further selection by case definition criteria that appears too limiting. Only cases that are medically confirmed have been included, which is reasonable for a diagnosis such as POTS that cannot be expected to be verified by a consumer. 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 p.22, we agree that when a diagnosis is reported and verified by a HCP, this description should be accepted and used in the further work e.g. observed versus expected ratios” (7, p9).

The co-rapporteurs are highly critical of the approach of the MAHs and find that “when a diagnosis is reported and verified by a HCP [we assume this means health care practitioner], this description should be accepted and used in the further work e.g. observed versus expected ratios.” It is noteworthy that the co-rapporteurs agree with Brinth (see “7. Brinth” above) and that this support for her arguments did not make it to the EMA’s official report (2). We believe that 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.

3. “The main conclusion in the Danish report is not, as described in the assessment, to change focus to CFS. Rather the review highlights the necessity to evaluate combinations of symptoms rather than only performing 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. Even though it cannot be shown for certain at this point, it is likely based on these data, that patients with the same symptomatology would receive different diagnoses in different member states e.g. POTS in DK and CFS/ME in others. 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” (7, p9).

The co-rapporteurs are highly critical of the EMA’s draft report and yet again, they agree with Brinth, but this strong support for her arguments did not make it to the EMA’s official report (2).

4. “However, as the potential involvement of Cervarix in the occurrence of CRPS cannot be completely ruled out at this stage, the co-rapporteur recommends that this risk should continue to be investigated” (7, p7).

"We agree with the conclusion from the rapporteurs and also state in the Danish report, that the data from spontaneous reports cannot be used to provide evidence for a causal relationship between symptoms and vaccination. However in view of the methodological limitations of the data available and the fact that the observed cases did exceed the expected cases, especially in Japan and Denmark, the conclusions should be cautious and the signal cannot be dismissed either based on the current evidence. We recommend that the vaccine SAG and expert meeting include a discussion of the need and possibilities to design appropriate PASS studies to explore POTS further. Similar question as Q3 regarding CRPS" (7, p10).

The co-rapporteurs agree with Brinth that more research is needed, but this support for her arguments did not make it to the EMA's official report (2). In the EMA's confidential, internal report, the rapporteur dismissed the proposals by the co-rapporteurs:

"The Rapporteur agrees with most conclusions of the Co-Rapporteur (BE) for Cervarix, with the exception of the recommendations in relation to further evaluation of CRPS and POTS" (4, p5).

5. "We support DHMA comment that due to differential clinical practice across countries, similar suspected ADRs [adverse drug reactions] to HPV vaccine are receiving different diagnoses (or indeed no clear diagnosis), which in turn may be potentially 'diluting' a safety signal" (7, p11).

The co-rapporteurs' support to the concerns of the DHMA, which asked the EMA in July 2015 to assess possible serious harms of the vaccine, did not make it to the EMA's official report (2).

There are additional examples in the EMA's confidential, internal report (4) of highly important disagreements and observations that are not revealed in the official report (2). In several of these cases, the rapporteur disagrees with the two co-rapporteurs, but it is only the rapporteur's opinion that is presented in the official report.

6. "**Rapporteur's comments on the Brinth et al case series:** ... In summary, the case series reported by Brinth et al represents a highly selected sample of patients, apparently chosen to fit a pre-specified hypothesis of vaccine-induced injury" (4, p225-6 in pdf, or 46-47/77 in the subdocument).

We note that this defamatory remark about Brinth's research is exactly the same as in the EMA's official report: "apparently chosen to fit a pre-specified hypothesis of vaccine-induced injury" (2, p24).

7. Dr Luc Kiebooms and Dr Andre Devos motivated in their statements why a PRAC study was needed (it is not clear who these people are but they seem to be external experts) (4, p171-4 in the pdf, or 59-62/67 in the subdocument):

"The Vioxx scandal<sup>2</sup> and Diane-35-problems have shown how weak reporting is. In both cases there has been reporting for years, but this was done with the same methodology as suggested here. So the insight into the actual extent and severity of the phenomenon was slowed down tremendously. In both cases afterwards it turned out, that the makers of the medicine knew of the adverse reactions, before the medication was brought into circulation. For HPV now, the same seems to occur. We are at the stage of a reporting of a particularly large number of cases for a

vaccination, for which a zero tolerance regarding the side effects should prevail<sup>3</sup>. Until now all the literature is exclusively under the direct supervision of the industry, probably even all information comes from the industry. There are no independent studies, despite the fact that these were raised on several levels.”

“In this Dutch population at the most around 4% of the female population might have benefitted from vaccination! As for the Danish situation: should we vaccinate 500 000 women to prevent a possible infection in 20 000 unscreened women, knowing that promiscuous behaviour and sex at a young age increase the risk and that this STI [sexually transmitted disease] for a greater part can be avoided<sup>8</sup>? In these unscreened women at most a few hundred will develop cervix cancer, what could be avoided through a cheaper screening. In addition, in any case this screening remains needed for the 30% not covered dangerous HPV infections. Therefore in the Netherlands was advised not to take up the vaccine in the vaccination program<sup>9</sup>” ... “In 2009 Cervarix was added to the Dutch national immunization program in the context of prevention of cervical cancer.”

### **“Are the vaccines safe?**

According to the firms they are safe. 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, because no one voluntarily wants to be vaccinated with toxic aluminium, as this is not really necessary, when inoculation with a harmless saline solution can be done. The differences between Gardasil and the saline placebo group were, however, already noticeable<sup>15</sup>. Here we can refer to the Vioxx scandal, where the adverse reactions in fact were known, but concealed by the firm. Here also 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.”

These two experts question seriously the prevailing assumption, apparently also at the EMA, that the vaccine is so important for public health that it is justified not to communicate to the public 1) that there are uncertainties related to vaccine safety, 2) that drug companies cannot be trusted; and 3) that it is wrong to lump together results obtained with a genuine placebo with those obtained with a potentially neurotoxic placebo. We agree with the two experts when they suggest that this lumping may represent a cover up and we also find that the EMA should have informed the public about this unacceptable lumping of a true placebo with an active placebo instead of keeping it secret. This is totally unacceptable and contrary to good scientific practice to such a degree that we consider it outright scientific misconduct committed by the EMA.

### Conflicts of interest

According to laws of public administration in several European countries, people should never be in a position where they are being asked to evaluate themselves. For example, Danish law states (our translation):

“Anyone who works in the public administration is disqualified in relation to a particular case if he or she has a special personal or financial interest in the outcome ... The person who is disqualified in

relation to a case does not make decisions, participate in decision making or otherwise assist in the consideration of the case.”

1. The EMA asked the MAHs to provide “a cumulative review of available data from clinical trials, post-marketing and literature in order to evaluate the cases of CRPS and POTS with their product” ... an analysis of the observed number of post-marketing cases of CRPS and POTS in association with their HPV vaccine in comparison to those expected in the target population, stratified by region, if available ... a critical appraisal of the strength of evidence for a causal association with HPV vaccine for CRPS and POTS” (4, p5).

“The responses submitted by the different companies were assessed by the PRAC's Rapporteur (attachment 1) and Co-Rapporteurs (attachments 2 and 3) for this procedure. Before adopting a recommendation, the PRAC decided to convene the Scientific advisory group (SAG) on Vaccines and additional experts on vaccine safety, neurology and cardiology to provide an independent advice and responses to the questions below” (4, p5).

It is clear from its confidential document that the EMA relied heavily on the companies to come up with honest answers to highly complicated questions, and that the work of the EMA’s various assigned experts was not to control what the companies had done, but merely to discuss it (4). We find that 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 (6, 10). We find it unacceptable that the EMA did not check the veracity of the MAHs’ work.

2. At a hearing about HPV vaccine safety in the Danish Parliament on 17 December 2015, which was video recorded (11), Enerica Alteri from the EMA told the audience that the EMA’s Scientific Advisory Group consisted of members who were independent. However, she also said that they had declared their conflicts of interest (her remarks on this point were not translated by the simultaneous translation). As stated above, we know from the confidential internal EMA report (4) that the members of the Scientific Advisory Group (SAG) are bound by a life-long secrecy clause that prevents them from discussing their disagreements in public. The EMA keeps it secret who they are and what conflicts of interest they have. We have been informed, however, by one of the persons who participated in meetings at the EMA, that some of the SAG members have financial conflicts of interest in relation to companies that sell an HPV vaccine, which means that they are not independent. Enerica Alteri told the audience that the HPV vaccine can prevent most, if not all, deaths from cervical cancer. She walked out immediately after her presentation with no excuse and did not take questions or participate in the panel discussion. This was perceived by some as being blatantly arrogant and counterproductive in terms of building trust in the vaccine and in the EMA.

We find it totally unprofessional and misleading to the extreme to suggest that the HPV vaccine can prevent all deaths from cervical cancer. Such a claim would not have been tolerated by the EMA if it had come from one of the manufacturers. The different vaccines don’t protect against infection from all HPV strains, only from 70%, 80% and 90% of the strains, respectively, and the vaccines are not 100% effective against the targeted strains (2).

We also find it inappropriate to use experts with financial ties to the manufacturers, as it is always possible to find experts without such conflicts.

3. The rapporteur was Julie Williams (4) who is Professor of Neuropsychological Genetics at Cardiff University and the Chief Scientific Adviser for Wales since 2013. According to Wikipedia, she is one of the world's leading contributors to Alzheimer's research. Since Williams' views seemed to have had a pivotal and overruling role for the EMA's official report, we tried to find out what her conflicts of interests are.

On September 16, 2014, Williams co-authored a paper with 16 others where the authors declared (12): “**Competing interests:** The authors have declared that no competing interests exist.”

However, the funding declaration in the same paper showed that there were numerous financial conflicts of interest in relation to drug companies (we have underlined some of them):

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Dementia Brain Bank acknowledges support from Bristol Research into Alzheimer's and Care of the Elderly. The Charles Wolfson Charitable Trust supported the OPTIMA group. Washington University was funded by NIH grants, Barnes Jewish Foundation, and the Charles and Joanne Knight Alzheimer's Research Initiative. Patient recruitment for the MRC Prion Unit/UCL Department of Neurodegenerative Disease collection was supported by the UCLH/UCL Biomedical Centre. LASER-AD was funded by Lundbeck SA. The Bonn group was supported by the German Federal Ministry of Education and Research (BMBF), Competence Network Dementia and Competence Network Degenerative Dementia, and by the Alfried Krupp von Bohlen und Halbach-Stiftung. The GERAD1 Consortium also used samples ascertained by the NIMH AD Genetics Initiative. The AddNeuroMed study was supported by funds from the National Institutes for Health Research Biomedical Research Centre for Mental Health at the South London and Maudsley National Health Service Foundation Trust and Institute of Psychiatry, King's College London. AddNeuroMed is funded through the EU FP6 program as part of InnoMed. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript."

The UK Alzheimer's Society is funded by Eli Lilly, one of the big pharmaceutical companies committed to the field (10).

With the involvement of all these drug companies in the research, we believe, according to internationally accepted guidelines for declaring conflicts of interest, that the EMA's rapporteur Julie Williams has conflicts of interest. However, in Williams' "Public declaration of interests" on the EMA's homepage from 21 November 2015 (13), no conflicts of interest are declared.

4. We are aware that some of the top officials at the EMA have failed to declare their conflicts of interest in relation to the work they do at the EMA, although they have a legal obligation to do so. For example, the EMA's director, Guido Rasi, declared on 20 July 2015 that he had no conflicts of interest (14). On a form called "EMA Public Declaration of Interests," he replied "none" to all four questions, also to question 4, which is: "Other interests or facts whether or not related to the pharmaceutical industry<sup>4</sup> which you consider should be made known to the Agency and the public, including matter relating to members of your household<sup>5</sup>."

However a Guido Rasi, which we assume is the same person, holds a number of patents, some of which were filed or approved in 2012 or 2013, and where the applicant was a drug company (Applicant: SciClone Pharmaceuticals, Inc.; Inventors: Guido Rasi, Enrico Garaci, Francesco Bistoni, Luigina Romani, Paolo Di Francesco) (15). As they go back less than five years, we believe he should have declared them, according to the EMA's regulations concerning the handling of declared interests of its employees (16).

#### Final remarks

We find that the EMA's requirement of life-long confidentiality is absurd. All available material about suspected harms of a public health intervention directed towards healthy children should be accessible to anyone. The EMA's internal report (4) and all other documents related to this case should therefore be made publicly available, without redactions. We did not find any commercially confidential information anywhere in the documents we reviewed.

The American College of Physicians found that 89 cases of premature ovarian failure reported for HPV vaccines (86 for Gardasil and 3 for Cervarix) versus no reports for other vaccines were sufficiently alarming to motivate an alert in January 2016 making physicians and the public aware of a possible link (17). The confidential EMA report mentions in one sentence that the vaccine is under increased surveillance for this possible harm, but the reason is not given: "Adverse events related to potential immune-mediated disease (piMD) following vaccination with Cervarix, as well as primary ovarian failure are currently under close safety surveillance and in depth discussed in PBRER" (4, p175, or 63/77 in the subdocument). In response to an "Expert Submission to EMA relating to absence of ovarian safety research 17-10-2015" (7, p.110), the "Assessor's comment" is: "This document contains an argumentation that the "ovary safety research" undertaken with the HPV vaccines is insufficient. Ovarian safety is beyond the scope of this referral, and will therefore not be commented in detail. Nevertheless, in October 2013, the PRAC finalised a review of Premature ovarian failure for Gardasii/Silgard. The PRAC concluded that the available evidence did not support a causal association." There is nothing about this important potential harm in the EMA's official report (2) although it is widely suspected that the possible severe toxicity of the vaccine is autoimmune-mediated.

The EMA might also have considered that when doctors first alerted the scientific community to the possibility that Pandemrix, one of the pandemic influenza vaccines used in 2009-2010, could be related to the occurrence of narcolepsy in people with a specific tissue type, the reaction was to ridicule these doctors. It has now been firmly established that Pandemrix can cause narcolepsy, a very serious condition, up to several years after vaccination of children and adolescents, and that this disease is immune-mediated. However, there was nothing about this, neither in the EMA's official report (2), nor in the confidential report (4).

The bottom line for the EMA seems to have been that the vaccine should be protected from criticism at all costs because it is believed to save lives by protecting against development of cervical cancer. One sign of this is that the text in the official report is nearly identical to the assessments of the rapporteur and the companies. However, this paternalistic attitude comes at a great cost. The EMA accepted uncritically substandard research performed by the MAHs and produced a superficial, substandard official report (2) that was clearly flawed and unrepresentative, considering the serious concerns raised in internal discussions, which were sealed by life-long confidentiality agreements. Unprofessional and defamatory criticism, such as the one the EMA raised against the Danish researchers, is not unknown to scientists but it is a serious threat to scientific progress and public health. Those who raise concerns should be complemented for their courage, even if their suspicions are later shown to be wrong. Indeed, it is a requirement by DMHA that Danish doctors raise concerns they might have. Unfounded criticism of whistleblowers from those at the top of the power pyramid are potentially highly damaging as it may prevent important concerns from being raised. Unfounded dismissal of signals from ADR reports as reported by the UMC also seriously undermines this central mechanism to monitor adverse drug reactions. These serious failures on behalf of the EMA could create a problem orders of magnitude greater than declining participation rates in HPV screening programmes. Should the concerns over possible harms of the HPV vaccine be confirmed, the trust in the EMA and in vaccines in general may be damaged beyond repair. In fact, we know that the EMA's handling of the HPV controversy - pretending that we have sufficient knowledge when we haven't - has already become a PR disaster. In Funen, the uptake of the vaccine decreased from 74% to 31% in just one year (18).

The EMA's procedures for evaluating the safety of medical interventions - where the companies are by and large their own judges - need to be fundamentally reworked and all procedures and information should be made transparent to the public. Our societies should no longer accept that assessments of drug safety are left to companies with huge financial interests and to a drug agency that receives 80% of its funding from the drug industry.

The secrecy imposed by the EMA is not in the public interest. Drug regulators tend to have a narrow vision, either because of their remit or because they have become too close to the drug industry by their daily work, which often involves contacts with the industry, and by employment of people with long careers in the industry. As an example, the EMA's director, Guido Rasi, has brought in a number of people from the drug company Sigma Tau that include Stefano Marino, his head of legal affairs. Rasi has worked with this company for many years and apparently owns several patents together with the company (15).

Public health is about the promotion of health and prevention of disease and disability through the organised efforts of society. This entails protection from harms and involves progression of knowledge in open collaboration. As far as we can see, the actions of the EMA in this case indicates that the agency is more concerned about protecting its own previous decisions and the vaccine than about protecting the citizens and giving them the option of choosing for themselves whether or not they would like to get vaccinated against HPV. Some people will prefer to avoid the vaccine, even if the risk of serious harm is very small, and some will prefer screening instead. It is not within the powers of regulatory authorities to deny citizens' right to make informed choices about their own health by withholding important information. The citizens need honest information about the vaccine and the uncertainties related to it; not a paternalistic statement that all is fine based on a flawed EMA report (2).

Sincerely,



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