Responsum to Assessment Report on HPV-vaccines released by EMA November 26th 2015

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Assessment report

Review under Article 20 of Regulation (EC) No 726/2004

Human papillomavirus (HPV) vaccines

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1: Preface

Over the past few years a growing concern has emerged in Denmark - as well as in other countries around the world - with regard to the safety of the HPV-vaccines

The debate was boosted in Denmark as a consequence of the TV2-Denmark documentary “De vaccinerede piger” (The Vaccinated Girls) released March 26th 2015. The Danish Health and Medicines Authorities (DHMA) therefore asked the European Commission to initiate an in depth review. The European Commission requested the European Medicines Agency (EMA) to give its opinion on whether there is a causal association between HPV-vaccines and the two syndromes: Chronic Regional Pain Syndrome (CRPS) and/or Postural Orthostatic Tachycardia Syndrome (POTS). November 27th the assessment report was released.[1] The aim of this assessment was to use the available data to draw a conclusion on causality between HPV vaccine and POTS/CRPS.

In the assessment report written and published by EMA, three of my publications regarding my clinical experience with patients with suspected side effects to the quadrivalent HPV vaccine are directly criticised. Furthermore, my clinical expertise and judgment are indirectly criticised as a substantial part of our adverse event reports (AER) are overruled.

I want to defend my work but most of all I want to join in and encoruage to an open and honest debate. In the following I will primarily adress the critique directed against my work and only touch briefly on a few other aspects of the EMA report that I find is closely related to my own work or the conclusion of my work. I can and will not comment on the report as a whole.

My agenda is not to miscredit the vaccine, rather it is to maintain public confidence in the vaccine itself and the entire childhood vaccine program. To reach this goal, I believe that it is imperative to appreciate that vaccines can have side effects and it is the responsbility of the health care community to monitor and investigate serious problems which are suspected to be related to the vaccines. I will not go into the science behind the benefits. I know that we have strong evidence that both HPV-vaccines prevent development of precursor stades to cervical cancer if the vaccine is given before HPV-infection.

This is a very long responsum. It is even longer than the EMA report that it relates to. You may find that strange – maybe even ridiculous. But – I have been deeply involved in this matter – suspected side effects to the HPV-vaccines – for years now. And I am so frustrated by the trouble and grief I believe that we create for ourselves and each other by not allowing room for the nuances, doubts and uncertainties in this very complex – and highly important matter.

This is a scientific response addressing the critique of the EMA which has been echoed by a number of stakeholders, including the DHMA who surprisingly seem to have partially abandoned their conclusions from July 2015. But – it is also a personal responsum. I have been in this highly explosive field in four years now. I want to voice my ever increasing feeling of our considerable inabillity to be nuanced and balanced when discussing vaccines – both their efficacy and side effects. We are in desperate need of a shift in paradigm, a groundbreaking one, or the future of public confidence in vaccines will be lost.

2: Introduction

My Chief of research at the Syncope Unit at Bispebjerg and Frederiksberg Hospital, Jesper Mehlsen and I have had a constructive and fruitful collaboration with the DHMA. As from October 8th 2015, the former DHMA has been split into three new agencies, The Danish Health Authority, The Danish Medicines Agency and The Danish Patient Safety Authority. In order to avoid confusion I will use the abbreviation DHMA in this responsum as our collaboration with the authorites has primarily taken place while they still existed as DHMA.

We may not always have agreed on the degree of transparency in the process – but I have felt that the DHMA has reacted when we have voiced our concern. They have been willing to discuss and evaluate our concerns, have themselves initiated looking into both the Danish cases, and requested the Uppsala Monitoring Centre (UMC) to participate in the process with an evaluation of adverse event reports in an international context. We have informed them continuously of our findings, our thoughts, our approach, our methods and our publications. I think that both we – at the Syncope Unit – and the DHMA has dared to disagree and dared to admit to ourselves and each other that we had a problem that urgently needed our attention. A question that we needed to answer in collaboration

In July 2015 the “Report from the Danish Health and Medicines Authority for consideration by EMA and rapporteurs in relation to the assessment of the safety profile of HPV-vaccines” was sent to EMA .[2]

I found that this report was the honest and sound consequence and conclusion of our collaborative work trying to get to the bottom of this signal.

2.1: Vaccines

Vaccines are, within medical science, considered a global and groundbreaking health success. Through vaccination programs coordinated and implemented throughout the globe, diseases such as smallpox have been eradicated. Moreover, other infectious diseases have been reduced significantly with impressive impact on both mortality and morbidity worldwide. I can and will not contradict from the obvious revolutionary significance of the vaccination programs. But a considerable and increasing uneasiness surrounding the vaccines and their suspected side effects demonstrates an urgent need for us to discuss the way we handle vaccine safety issues. This includes how we investigate, acknowledge and cope with the possible side effects and the consequences for the individual.

Vaccinomics is the emerging scientific field that: “encompasses the fields of immunogenetics and immunogenomics as applied to understanding the mechanisms of heterogeneity in immune responses to vaccines.”[3] Adversomics is the closely related study of genetically determined vaccine-associated adverse events.[3]

There have been two recent publications within these fields in which a genetic predisposition to adverse events from a vaccine has been demonstrated. Pandemrix, one of the pandemic influenza vaccines used in 2009-2010, has been associated with the occurrence of narcolepsy in subjects of a specific HLA subtype. [4]Also, common variants of certain genes have been found to be associated with an increased risk of febrile seizures after measles mumps rubella vaccination. [5]

Both these relatively new “omics” are mirroring our emerging understanding of the need for an individualized vaccines technology - and our leaving a “one size fits all” approach towards vaccines.

Why do I introduce these two “omics”?. I do so, because I believe that both “omics” and the science and knowledge they represent point the way forward towards “personalized vaccines” based on an emerging understanding of the importance of immune response phenotype regarding both effects and side effects of vaccines. However – this approach focusing on the individual may clash with the whole mindset behind our childhood

vaccination programs and the “one-size-fits-all” approach that lies inherent in these programs and our wish to obtain herd immunity.

So where does that leave us when science is beginning to contradict our “old ways”? I have no answer to this question except that denial is unlikely to be the right way forward.

2.2: HPV-vaccines and their suspected side effects

Infection with HPV has been identified as a carcinogen in an array of cancer types. Nearly 5% of cancers worldwide are thought to be associated with HPV-infection[6] and almost 100% of cervical cancers are associated to HPV infection.[7] The ability to counter that threat by a vaccine is obviously extremely important.

The HPV vaccines in current use have been licensed on surrogate markers, immunological and histological, and therefore have not been shown to have yet prevented a single case of cervical cancer death - which is to be expected as the latency from the time of infection with the cancerogenic HPV-subtypes that the HPV vaccine is directed against to fully developed cervical cancer is very long. It is understandable, that we can not wait for evidence of that robustness before we implement the vaccine. We have evidence demonstrating that the vaccine prevents precursor states and that is as good an indication as it gets. I believe that the HPV-vaccines have the potential to counter both mortality and morbidity – both death and suffering – in the long run. However, we are dealing with a preventive measure and this calls for a very high focus on safety.

The quadrivalent recombinant vaccine, protecting against human papilloma virus types 6, 11, 16, and 18 (qHPV vaccine, Gardasil®), was included in the Danish childhood vaccination program in 2009. Both the clinical studies and post licensure register studies have demonstrated a beneficial safety profile for both the bivalent, the quadrivalent and the new nonavalent HPV-vaccines [8-13]. However, post licensure monitoring may be superior in detecting rare adverse events compared to pre licensure reviews and during the past years, case stories describing patients with suspected severe side effects to the HPV-vaccines are emerging from several countries.[14] [15-20] [21-23]

All medicines have the potential of eliciting side effects, vaccines being no exception. It is well accepted that highly immunogenic vaccines are often associated with both local and systemic reactions. Furthermore, vaccines may carry an inherent risk of provoking autoimmune phenomena in susceptible individuals [24]. We have evaluated more than 300 patients with suspected side effects to the Q-HPV-vaccine in the last four years. We have found consistency in the reported symptoms as well as between our findings and those described by others. A case definition of the patients we have seen would be longlasting

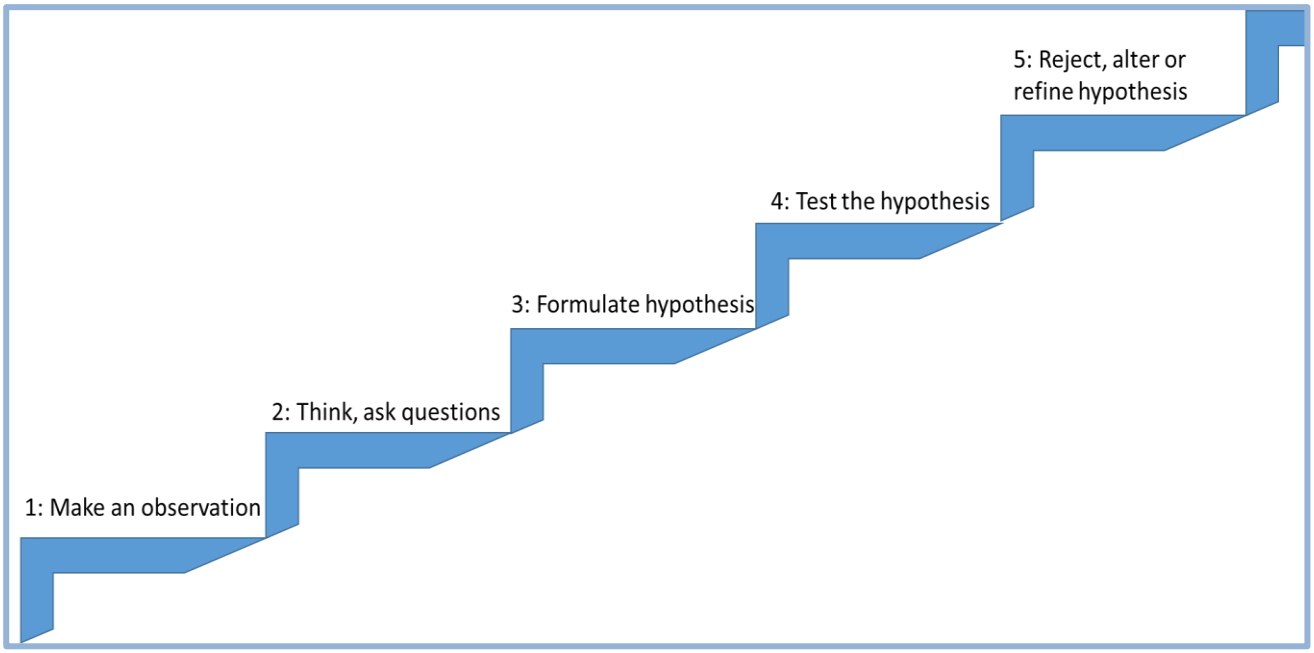
excessive fatigue and pronounced autonomic dysfunction coupled with severe non-migraine-like headache, cognitive dysfunction, gastrointestinal discomfort, and widespread pain of a neuropathic character.[15, 16, 25] The patients described may have been labelled with different diagnoses – and many have not been diagnosed at all. But – the symptoms described are apparently quite similar.

2.3: A scientific approach

We all use the words “scientific”, “evidence”, “hypothesis” and “proof”. The core of all science is and has been for centuries based on hypothesis testing which in turn is based on questions arising from observations. Scientific method is defined by “The Oxford English Dictionary” as:

"a method or procedure that has characterized natural science since the 17th century, consisting in systematic observation, measurement, and experiment, and the formulation, testing, and modification of hypotheses."[26]

So, basically the knowledge and ideas that we base our medical professionalism on are obtained though the following steps on the scientific ladder:



This is very important to keep in mind when we evaluate and discuss the evidence already available to us – and when we plan and discuss how to obtain more and better evidence. This is the scientific toolbox. All the steps are equally important. They all depend on each other. The way we obtain knowledge, the way we get to “know” things are through a never ending ascending through these steps with all new findings leading to new questions, new hypotheses that need testing…..

I have made very clear in my communication with colleagues, authorities and patients that my work is a description of an observation and a formulation of a question – I am working

on the lowest steps of the ladder. Therefore my findings should not be seen as proof of anything. However, they should remind us that we need to initiate research that can test the hypothesis that these patients may be suffering from side effects to the qHPV-vaccine.

3: The work at the Syncope Unit

3.1: Why have we seen these patients at the Syncope Unit – and what patients have we seen?

I am a medical doctor working at a Syncope Unit specializing in orthostatic intolerance and autonomic dysfunction. At the Syncope Unit at Bispebjerg and Frederiksberg Hospital in Copenhagen, we have interest and expertise in and a diagnostic toolbox at hand directed at the evaluation of function and dysfunction of the autonomic nervous system. I have seen more than 200 patients with suspected side effects to the HPV-vaccines through the last four years.

The autonomic nervous system consists of two subsystems: the parasympathetic and the sympathetic nervous systems which in many cases have "opposite" actions: one activates a physiological response - the other inhibits it. For example sympathetic stimulation will increase heart rate, parasympathetic stimulation will decrease heart rate. These two subsystems exert their influence on most of the cells, tissues and organs of the body in an antagonistic but coordinated interplay. The coordination between the two subsystems takes place both centrally in the central autonomic network and in the periphery. The autonomic nervous system senses and responds to both intra and extra somatic stimuli thereby maintaining bodily homeostasis and enabling a shift towards fight and flight mode if so needed. Most of the actions of the autonomic nervous system run in reflexes with sensory input through the afferents, central processing – and an output through the efferents. The autonomic nervous system is intimately connected with the way we interact with the world – both physically and emotionally.

Walking upright on two legs is a challenge and a trait that defines the human race. Rowell writes in his book “Human Cardiovascular Control” that:

“*The circulatory adjustments to upright posture demand the full capabilities of the reflexes that govern cardiovascular function.”[27]*

These important reflexes controlling cardiovascular function is primarily taken care of by the autonomic nervous system and the interaction between the autonomic nervous system and the cardiovascular system.

Therefore, any disease, condition or drug that effects the function of the autonomic nervous system will as one of the first manifestations very often have orthostatic intolerance. Orthostatic intolerance is symptoms related to the upright posture – with symptom relief in recumbence.

Orthostatic intolerance comes in the acute form – syncope, as well as more chronic forms with symptoms related to upright posture seen at a daily basis.

At the Syncope Unit we evaluate both syncopal patients but also specialize in evaluation and treatment of chronic orthostatic intolerance. In our elderly patients referred with chronic orthostatic intolerance the most common finding is orthostatic hypotension which can be understood as an age related inability to maintain a sufficient blood pressure in the upright position. In our younger patients the most common finding is chronic orthostatic intolerance related to tachycardia in the upright position and marked symptoms compatible with autonomic dysfunction and cerebral hypoperfusion and patients often fulfilling the diagnostic criteria for postural orthostatic tachycardia syndrome - POTS.

POTS is a heterogeneous condition of dysautonomia and suspected autoimmunity characterized by abnormal increments in heart rate upon assumption of the upright posture accompanied by orthostatic intolerance and symptoms of cerebral hypoperfusion and sympathoexcitation. An increase in heart rate equal to or greater than 30 min-1 or to levels higher than 120 min-1 during a head-up tilt test is the main diagnostic criterion. POTS can be diagnosed with a standing test or tilt table test, although tilt tests are not always available. A routine physical examination will not diagnose POTS, nor, in most instances, will orthostatic vital sign testing that lasts less than 1-2 minutes. Before diagnosing a patient with POTS other medical conditions causing tachycardia should be ruled out. POTS is more common in women with a 5:1 female-to-male ratio. The overall prevalence is not known but it is estimated that POTS is found in 500.000 patients in the USA which would translate to 10.000 in Denmark . The orthostatic symptoms consist of lightheadedness, visual blurring or tunnel vision, palpitations, tremulousness, and weakness (especially of the legs). Other symptoms include fatigue, exercise intolerance, hyperventilation, nausea, concentration difficulties, and headaches. [28-31]

In 2011 we had the first patient referred to our Syncope Unit for evaluation of orthostatic intolerance as suspected side effect to a qHPV-vaccine. She suffered from both syncopal attacks and chronic orthostatic intolerance – as well as an array of other symptoms – including muscular twitching and weakness, cognitive dysfunction, sleeping disorder, nausea and extreme fatigue. The patient reported symptom onset in the first month after a qHPV-vaccination.

During the next two years a few more patients were referred who described a somewhat similar symptom complex and suspected a causal link to the HPV-vaccine due to a temporal association between the vaccine and symptom onset. In 2013, after having evaluated 6-7 patients who all described that they suspected that it was the qHPV-vaccine which had made them ill – we started to compare the symptoms described and the objective findings we had seen in these patients. We felt that we could not dismiss the possibility that we actually saw a pattern of symptoms in these patients suspecting to suffer from a post-qHPV-vaccine symptom complex. We therefore contacted the DHMA, telling them about our suspicion, asking them how they wanted us to proceed and initiating a collaboration.

Denmark is a small country. Many patients who suspect that they suffer from side effects to a vaccine tell us that they have felt that their suspicion has been ridiculed or dismissed when presented to medical professionals. We have not reported all the patients who suspected to suffer from side effects as AER. However, if we had a suspicion that their symptoms could be related to the vaccine – and we could not dismiss this suspicion by finding other explanations for their symptoms etc – we reported it. We are obliged to do this by Danish law.

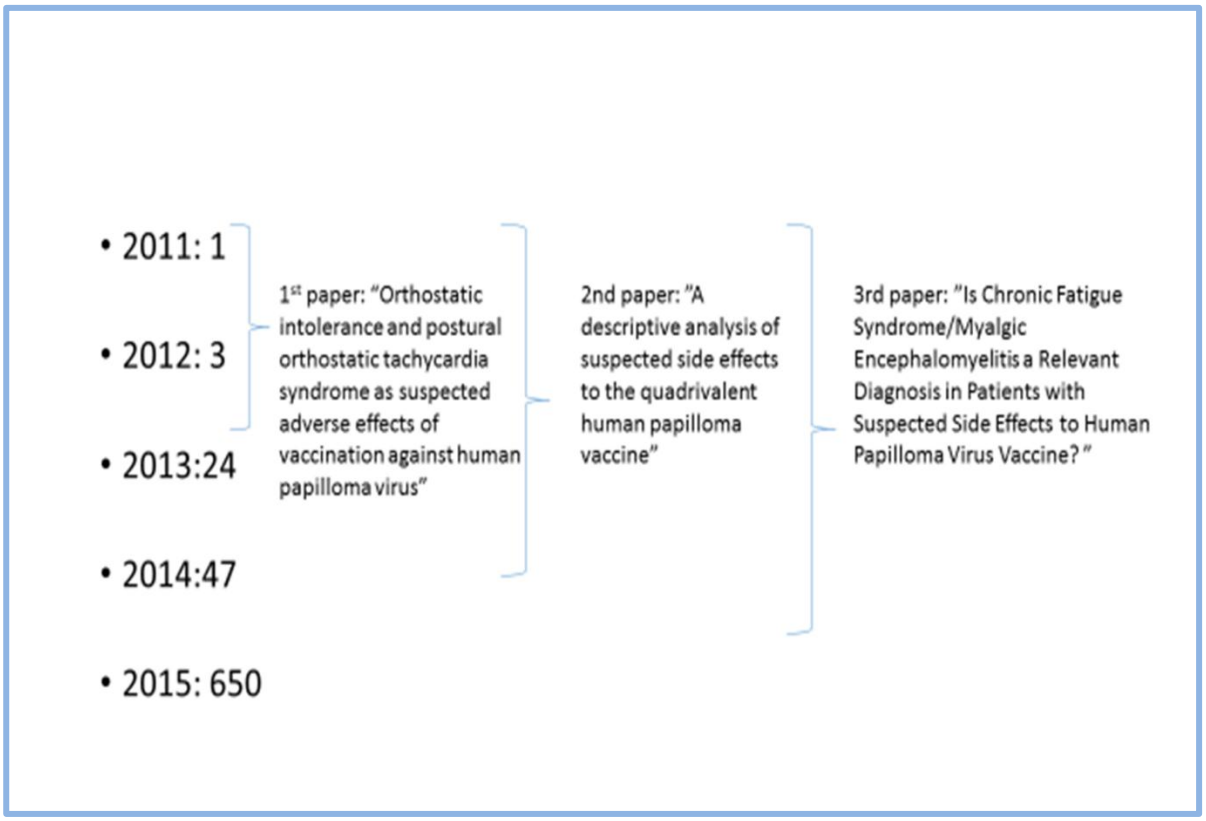
At the Syncope Unit we do tilt table testing. We are good at treating orthostatic intolerance. We were able to give some of these patients a diagnosis. We tell all our patients who receive the POTS-diagnosis that POTS should probably be looked upon more as a symptom than a disease entity.

People became aware that we did not dismiss the idea of the HPV-vaccine being capable of producing side effects in a few susceptible individuals and had some treatment options for the symptoms experienced by the patients – primarily directed against the orthostatic

intolerance. Due to these circumstances, during 2013, 2014 and 2015 we had an ever increasing number of patients referred from all parts of Denmark with suspected side effects to the qHPV-vaccine.

It is important to keep in mind that until June 1st 2015 we were a “normal” Syncope Unit. Danish Regions decided spring 2015 that as of June 1st each of the five Regions of Denmark should offer what was called “One Entrance” for patients with suspected side effects to the HPV-vaccine – who had serious symptoms and were not better helped in another department. We were appointed “One Entrance” in The Capitol Region of Denmark.

In the figure below are given the approximate numbers of patients referred through the last years who themselves or the referring physician suspected that the symptoms they experienced were caused by the qHPV-vaccine. Our three publications on the subject are also given with indications on the period in which the patients presented in the papers were evaluated at our clinic. All three papers were based on data from all patients referred at the time of data analysis. However, with some exclusion criteria used in the two last papers but these exclusion criteria are clearly stated and explained in the papers. All patients described in the papers were evaluated before the big rush of patients seen in 2015 following the TV-documentary in late March 2015 and prior to the massive number of patients referred to us after the start of “One Entrance” in June 2015.


• 2011: 1
• 2012: 3
• 2013:24
• 2014:47
• 2015: 650
1st paper: "Orthostatic intolerance and postural orthostatic tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus"
2nd paper: "A descriptive analysis of suspected side effects to the quadrivalent human papilloma vaccine"
3rd paper: "Is Chronic Fatigue Syndrome/Myalgic Encephalomyelitis a Relevant Diagnosis in Patients with Suspected Side Effects to Human Papilloma Virus Vaccine?"

3.2: The three papers we have published describing our clinical experience with patients suffering from suspected side effects to the HPV-vaccine and a response to the criticism set forth by EMA

EMA writes:

"*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."(Page 24)*

This is the most serious allegation I have ever been presented with. I can only understand this statement and their use of the word "apparently" as if they actually reveal that they just made an assumption. They made a guess. Contrary to this assumption made by the EMA, we did not select patients to fit a pre-specified hypothesis of vaccine-induced injury. We did not select patients based on symptoms in order to make sure that they would fit into a preexisting hypothesis. EMA suggests that we did. **We did not**. We did not ask all patients that we had referred with orthostatic intolerance whether they suspected that their symptoms were causally linked to the qHPV-vaccine. Only when the patients themselves mentioned that they had the suspicion we took it into consideration and discussed with the patient whether other possible eliciting factors could be recognized and whether it was relevant to report their symptoms as possible side effects to the qHPV-vaccine.

I do not mean to be patronizing but we urgently need to create common ground here. Therefore let us start out by clarifying that what I have described in my three papers are case series, that can be defined as:

A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment.[32]

We published case series, which by nature do not do hypothesis-testing – and are prone to selection-bias. To minimize selection bias, we included all consecutively referred patients – with exception of the ones excluded due to exclusion criterias.

EMA writes:

"*The consistency in symptom profile across the case series is highlighted in the papers. However, it is unclear whether or not the absence or presence of specific symptoms was solicited by the interviewer, although the presentation of results suggests this was the case. If so, then it is perhaps not surprising that such a selected case series interviewed retrospectively in this way would yield these symptom characteristics. Furthermore, 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."(Page 23)*

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 in our book constitutes more than "some sort of objective clinical evaluation". The diagnosis of POTS rests upon this – only if combined with severe orthostatic intolerance as defined in the international consensus reports. Assessment of symptoms is fundamental in the dialog between medical doctors and their patients. If the statement put forward by EMA: "the absence or presence of specific symptoms was solicited by the interviewer" was correct, then we would be guilty of malpractice, which is definitely not the case.

I think we did a good job with these case series. But in recognition of the many limitations inherent in case series – and the extremely urgent need for clear answers – we stated very clearly that we were not able to dismiss or confirm a causal link between the symptoms experience in the patients and the HPV-vaccine – but further research was urgently needed.

Through autumn 2013 we had a continuous and constructive dialogue with the DHMA. In December 2013 I was asked by the DHMA to describe our clinical experience and findings in a report with regard to the suspected side effects to the HPV-vaccine in a report. This report was written in the beginning of 2014 and was based on all of the first 35 patients **consecutively** referred to our syncope unit for head-up tilt test under the diagnosis of orthostatic intolerance as a suspected adverse event following vaccination with the qHPV-vaccine and was finalized and submitted to the DHMA March 2014. In other words – the report described the characteristics of the first 35 patients who had told us – spontaneously - that they suspected their symptoms were side effects to the qHPV-vaccine. We did not apply any exclusion criteria in this report. This was not asked for by

the DHMA – and it would not have made sense to us. This was just a “clear” description of the first 35 patients referred to us with suspected side effects to the qHPV-vaccine.

Our paper: “Orthostatic intolerance and postural orthostatic tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus” [16] published in the journal “Vaccine “is based on this report – as agreed upon by the DHMA. It took some time to get it published – that is the reality of publishing scientific papers. All scientists will know this. The report as well as the paper was finished March 2014 and included all the patients that we had evaluated so far with suspected side effects. As the cohort described included ALL patients with suspected side effects consecutively referred at this time we did not write in the methods section in which period we had had the patients referred.I realize it would have been easier for the reader to understand how the cohort described had been “selected”. But – I believe that the report I handed over to the DHMA March 2014 was forwarded immediately to EMA – so it should be very clear from the data available to EMA that it is the same 35 patients described in our paper and in the report.

I believe that communication is the cornerstone of pharmacovigilance and we are obliged to communicate our findings and suspicions. We gave the diagnosis POTS to the patients fulfilling the diagnostic criteria. And we had patients referred from all over Denmark. The POTS-diagnosis received a lot of attention. We repeatedly stated at meetings and in correspondence with health authorities, physicians and all interested that we found it very important not to focus blindly on the POTS-diagnosis – but rather look at the symptoms described by the patients. However – we felt that the focus was still too heavily on POTS. We therefore sat out to demonstrate from the patients that we had seen so far (December 2014), suspecting side effects to the qHPV-vaccine – that they actually presented with the same symptoms independent of the diagnosis given. We therefore wrote the paper: ”A descriptive analysis of suspected side effects to the quadrivalent human papilloma vaccine” that was published in Danish Medical Journal.[15]

EMA writes (and they call this our first paper – but as mentioned above, this was actually our second paper):

“It is clear from the first paper that patients were excluded if they do not meet a pre-defined hypothesis of vaccine-induced illness (symptoms prior to vaccination, onset greater than 2 months after vaccination, unknown onset time or if other causes could be found).”(EMA report page 23)

This was a retrospective analysis based on 75 patients consecutively referred to our Syncope Unit between May 2011 and December 2014 for head-up tilt test on the grounds of orthostatic intolerance and symptoms compatible with autonomic dysfunction as suspected side effect following vaccination with the Q-HPV-vaccine. We included ALL patients referred until December 2014 with symptoms that the patients themselves or the physicians referring them suspected were causally linked to the HPV-vaccine. We did not select the patients – beside from the exclusion criteria given in the methods section:

"We have chosen to include only those patients with onset of symptom within the first two post-vaccination months excluding 11 patients. Patients with known chronic diseases pre-vaccination as well as patients in whom other possible eliciting factors could be recognised (7 patients) were excluded as well as patients who were unable to account for the temporal association between vaccination and symptom onset (4 patients) leaving 53 patient for further analysis."

I find it very strange that EMA apparently criticizes that we excluded patients with pre-existing illnesses etc. We made an observation. We wanted to describe only those patients in whom we thought it plausible to suspect a causal link between symptoms described and the HPV-vaccine. We therefore excluded patients with pre-existing illnesses. If we had not – we would have had a hard time determining and describing which of the symptoms experienced by the patients could be ascribed to a pre-existing medical condition.

We found it important and relevant to write this paper as it clearly showed that the POTS-diagnosis would NOT be a relevant diagnosis or at least not the sole diagnosis relevant when evaluating possible side effects to the qHPV-vaccine. We stated in the discussion section that:

"We may have diagnosed more than half of these patients with POTS – but POTS should probably be looked upon as a symptom secondary to another yet unidentified condition rather than as a disease entity of its own. This is underscored by the fact that patients ex-peri-enced the same degree and pattern of symptoms regardless of the POTS diagnosis."

We found it troubling that often when discussing our clinical experience with colleagues and authorities we were told that this "POTS-thing" was a Danish phenomenon – which is true to that extent that we included that diagnosis POTS in the AER that we filed as we found it relevant information. But still – we kept on stating that this was not "just about POTS".

Therefore, we wanted to establish whether another diagnosis would encompass more of the symptoms described by the patients – and a greater proportion of the patients. We therefore developed a questionnaire asking questions relevant for the diagnosis myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and wrote the paper ”Is Chronic Fatigue Syndrome/Myalgic Encephalomyelitis a Relevant Diagnosis in Patients with Suspected Side Effects to Human Papilloma Virus Vaccine? ”published in International Journal of Vaccines and Vaccination. [25]

This was done as a retrospective analysis based on 90 patients referred to the Syncope Unit from May 2011 to April 2015 for clinical evaluation due to suspected side effect following vaccination with the qHPV vaccine. The questionnaire was sent out to all 90 patients. Only those patients who had returned the relevant questionnaires (see below) (39 patients) where included in the analysis.

We demonstrated that most of the patients (87%) of the patients seemed to fulfill the diagnostic criteria for M/CFSE and that this diagnosis encompassed a greater share of the patients than the POTS diagnosis. Further, it gave a better reflection of their symptom burden related to autonomic dysfunction.

Our study was not designed to establish whether or not a diagnosis of ME/CFS would lead to a correct classification of patients with suspected side effects. However, we suspected from our clinical experience that the ME/CFS diagnosis would encompass most of the symptoms seen and this was confirmed by the analysis. It is important to get an appropriate diagnosis and reach an agreement on this subject in order to provide a more firm basis for pharmacovigilance and thus in the evaluation of the probability and prevalence of suspected side effects to the qHPV vaccine.

We did of course recognize several limitations to our approach and transparently stated those in the paper:

1: The results may be regarded as a mere confirmation by circular reasoning as our clinical impression was tested systematically in the same group of patients.

2. The ME/CFS diagnosis should be used only when possible somatic and psychiatric differential diagnosis have been thoroughly evaluated, which was not done on a systematic basis in our study.

3: Our suggestion of using the ME/CFS diagnosis for the possible side effect should be considered a first methodical approach to reach consensus as to how these patients are classified. I believe that reading the EMA report underscores how impaired our possibilities for creating evidence for the existence or non-existence of a post-HPV-vaccine-syndrome is due to our lack of this diagnostic consensus in patients with complex symptoms – such as the patients at hand.

Regarding the time span between symptom onset and vaccination:

EMA writes:

"As the initial symptoms of POTS and autonomic dysfunction most likely have an insidious onset, objective recall of exact symptom onset (as well as the date/trigger for the symptoms) will be difficult to achieve. This is particularly so given that the mean time between onset of symptoms and examination was stated as 1.9 years (range: 0–5). The reliability and objectivity of such recall is questionable, and inherent recall bias in the methods is likely"(EMA-report page 23)

I agree with EMA that it would have been optimal if this time span between vaccination and symptom onset and evaluation at our clinic had been much shorter bordering on non-existent. But again: This is not a clinical study. Our experience with the patients were not based on a protocol. It was not designed. We report an observation we have done in our clinical work. This was how it was. This is what our patients told us. I do not have the imaginative abilities or academic skills to figure out how we could have done this differently.

I have performed the descriptive case series and put forth a question – a hypothesis. I have added my observations to the growing medical literature reporting observations reported as adverse events after HPV vaccination. This is my role, contribution and obligation as a medical doctor seeing patients. This is my place and role in the whole pharmacovigilance chain. Then it is up to others to do the epidemiological studies. And as we have some serious and fundamental problems with regard to applying the epidemiological approach to this issue – primarily due to the lack of unambiguous

diagnostic practice – we may need to collaborate. I believe that this is what we have been doing on our dialogue and collaboration with the DHMA. We have contributed from each our viewpoint in shared recognition of the need to bridge the gap between the clinical experience with the patients and the epidemiological approach.

EMA criticize that I do not do observed versus expected analysis – and that I do not include a control group. I am a clinician telling you what I have seen. I am not an epidemiologist. These are case series – and one of the main conclusions of my three papers is that we have a huge problems with regard to diagnostic practice in these patients which I believe hampers meaningful O/E observations.

I believe that I address this problem in the discussion of my last paper. We suspected from our clinical experience that the CFS/ME diagnosis would encompass most of the symptoms seen, and this was confirmed by the systematic analysis. It is important to get an appropriate diagnosis and reach an agreement on this subject in order to provide a more firm basis for pharmacovigilance and thus in the evaluation of the probability and prevalence of suspected side effects to the qHPV vaccine. We need to discuss how we approach the pharmacovigilance process when dealing with patients with unclear and diffuse symptoms as suspected side effects. How do we handle a situation where we may suspect that patients with the same complex of symptoms get different - or no - diagnoses dependent on country and/or medical specialty? We suggest that future research should aim at elucidating which diagnosis we should be looking for when assessing the suspected side effects to the qHPV-vaccine on a global scale

It is also important to agree on the diagnostic criteria if a systematic approach to the study of these patients should be attained. We need futures studies aimed at elucidating the disease processes disabling these patients and hopefully thereby enable better and targeted treatment options.

Although we recognize that our studies do not establish whether or not the qHPV vaccine is a cause of the symptoms seen in our patients we are also aware that vaccines have the potential of eliciting side effects and that the rare side effects are only seen when the vaccines are used in a much larger cohort than that used in the registration studies. Genetic susceptibility perhaps coupled with environmental triggers could likely cause new

onset symptoms or a flare in a pre existing condition. Because of the concerns expressed worldwide with regard to the HPV-vaccines, we find that there is an urgent need for a systematic approach to the patients and for solid, scientific studies of the possible relations between the vaccine and their symptoms.

As I understand it, the observed versus expected analyses is a measure of the "observed" rate of the event versus the "expected" background rate. I believe that the "observed" rate is calculated with both an uncertain numerator and an uncertain denominator: the numerator being the total number of AER (which we believe may be a very large underestimation?) and the denominator is the total number of doses of the vaccine sold or distributed (which we know is a very large overestimation – I believe that health clinics buy in bulk and leave on the shelf and use until the expiration date comes). Therefore, of course, if you underestimate the numerator and you overestimate the denominator, you get a smaller-than-true "observed" rate. As I read it, the "expected" rate is taken primarily from literature sources? Given the overwhelming problem with the use of different diagnostic terms – or no diagnosis at all in this group of patients – how does this make any sense?

Back to the way EMA overrules the reported cases of POTS and CRPS as suspected side effects: I can only have an opinion on the POTS-cases. But as I read it, EMA reduce the observed even further (in the Gardasil-analysis by including only those cases that met either the full or partially the case definition. On page 16 in the EMA report it is shown that there were 83 cases where the term POTS was reported and 30 additional cases with suspected POTS. But after evaluation the cases, only 46 of these 113 cases were included in the observed versus expected analysis. I will get back to this later – but I believe that it was the MAH doing this assessment as to what degree the reported cases met the diagnostic criteria? And I cannot read anywhere if they based their evaluation on the text written in the AER only – or gained access to medical records.

The EMA acknowledge the many known weaknesses and limitations of spontaneous reporting systems and that the sensitivity for some types of pain remains uncertain. Despite this statement they make support calculations on observed versus expected. I would suspect that such calculations are premature at this stage due to the limitations just

mentioned by EMA themselves – and the whole issue of the “diagnostic mess” surrounding these patients.

So – 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. I find it very worrying that EMA apparently base their judgement of my work – and thereby indirectly also part of their judgement of the safety of the HPV-vaccines - on guesses. This is too important for guess-work. We need to know and we need to reach consensus on what we know, what we need to know and what should be done.I do not think EMA’s methods, approach and rhetoric encourages this.

4: The assessment of the Uppsala Monitoring Center (UMC) report

Our observations and hypotheses were supported by an independent review of global data made by the Uppsala Monitoring Center (UMC) which was included in a report sent from the Danish Health and Medicines Authorities to EMA July 2015

Overall, the UMC report was written on the request of the Danish Health and Medicines Agency in an attempt to describe the adverse event profile for HPV vaccine using data from VigiBase®, the WHO international database for suspected adverse drug reactions, specifically as it related to the safety concern of postural orthostatic tachycardia syndrome (POTS) and related symptomatology which have been reported from the unexpectedly high proportion of serious adverse event reports from Denmark.

As I understand it, the analysis of the data was intended to be exploratory and hypothesis-generating, as it was based entirely upon spontaneously reported individual case safety reports (ICSRs) which have two very important limitations:

1. The reports are passively collected, meaning that they are received from health care providers and patients who make an individual decision to report a suspicion of causal relationship between an adverse event and a drug. Studies have estimated that spontaneous reporting represents only a small fraction of the true number of adverse events.[33]The reports are limited in the information that they provide; in order words, they are limited to the amount of information that the reporter decides to provide when writing the AER. Reports display a variety of levels of completeness, sometimes limited only to reporter, patient, drug and event, other times with very complete information including exact dates of administration of drug, case narratives, and laboratory and imaging data.

As a result of these limitations, it is not possible to draw firm conclusions upon the data. However, as written in the conclusion of the UMC report, the review of the worldwide data suggested a number of potential findings: that there is an increasing trend in the number of HPV reports of containing the “Preferred terms” (PTs) of POTS and related syndromes; that reports from Denmark were similar to other reports from other parts of the world in the reporting of symptoms but were distinguished by increased amounts of information and certain, specific diagnostic terms; and that a similar constellation of symptoms may have been labelled with different diagnostic labels depending on the country of origin. Finally, it

was hypothesized that the constellation of symptomatology may be consistent with a chronic fatigue – like syndrome which appeared specific to HPV vaccines upon comparison to other vaccines used in this population. These suggestions were put forward as hypotheses, intended to further investigation, prior to either their acceptance or rejection.

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.

Provided below are texts taken from the EMA report and the corresponding paragraphs from the original UMC report which was contained within the "Report from the Danish Health and Medicines Authority for consideration by EMA and rapporteurs in relation to the assessment of the safety profile of HPV-vaccines". [2]

Example 1.

EMA report page 27

"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."

UMC report (page 22, DHMA Report)

"As can been seen, the total number of reports of POTS, CRPS, CFS and fibromyalgia have been increasing since 2012 with a marked increase between 2012 and 2013."

In other words, I believe that the EMA report misinterprets the data, as the total number of reports of CFS (chronic fatigue syndrome) have increased as well (i.e. not "have been reported relatively constantly"). This is clearly seen on the bar graph included on page 22 in the DHMA report.

Example 2.

EMA report page 27:

"The first analysis compared 549 HPV vaccine reports from Denmark vs 45,327 worldwide HPV vaccine reports received for females between the age of 9 to 25 years. This analysis appears to have included all events, rather than only serious events. However, given that Denmark had received 1,228 reports (322 serious) up to Q1 2015, it is unclear how the 549 reports were selected.

This analysis showed 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. Eczema, sensory disturbance, disturbance in attention, memory impairment, palpitations, cognitive disorder, fatigue, infection, visual impairment, influenza-like illness, muscle spasms, and arthralgia also show disproportionality."

UMC report (page 27, DHMA report):

"This analysis has compared 549 reports for HPV vaccine from Denmark with 45,327 HPV reports (all other HPV reports from the rest of the world) which were received from females between the ages of 9-25 years of age.

Key features which were highlighted when HPV reports from Denmark were compared to HPV reports from the rest of the world were: a significantly greater proportion of the reports were considered "good reports" (determined the amount of clinically relevant information in an ICSR of the report 2), were classified as "serious", and were received from either a physician, consumer or a lawyer. The SOC over –represented in Danish reports were "Skin and subcutaneous disorders" and "Cardiac disorders". PTs significantly reported more commonly in Danish reports were the following: autonomic nervous system imbalance, orthostatic intolerance, eczema, sensory disturbance, disturbance in attention, POTS, memory impairment, palpitations, cognitive disorder, fatigue, infection, visual impairment, influenza-like illness, muscle spasms, and arthralgia.

…The PTs significantly reported more commonly in HPV reports from the rest of the world were exposure during pregnancy, vaccination site pain, and injection site pain.

Clinically relevant PTs for which there was no significant difference between Danish reports and reports from the rest of the world were: headache, malaise, myalgia, asthenia, dizziness, dizziness postural, orthostatic hypotension, presyncope, syncope, hyperhidrosis, heart rate increased, tachycardia, muscular weakness, abdominal pain, tremor, hypersomnia, quality of life decreased and activities of daily living impaired. Nor was there a significant difference between Danish reports and reports from the rest of the world for the following diagnosis PTs: chronic fatigue syndrome, post viral fatigue syndrome, fibromyalgia, or CRPS."

Here, the EMA has failed to mention that the Danish reports were more often classified as "serious" and were more often to include a large amount of clinical relevant information. Perhaps more importantly, the EMA has failed to mention all those clinically relevant terms for which there was NO difference between the Danish and "rest of world reports". There were a greater number of such terms for which there was NO observed difference

between Danish and “rest of world reports” – I think that this indicates that we are not dealing with a Danish phenomenon – and it is therefore important information-

Example 3.

EMA report page 28:

“CFS and PVFS/ME showed no statistically significant disproportionate reporting for HPV vaccine, nor did it show a very wide range of more relevant and more specific higher level terms that may potentially include symptoms of undiagnosed CFS (as well as POTS, CRPS, PVFS and fibromyalgia). This includes, autonomic nervous system disorders, asthenic conditions, GI motility disorders, tachyarrhythmia, cognitive disorders, postural dizziness, muscular weakness, mobility decreased, exercise tolerance decreased, various pain terms, and skin discolouration. Although the numbers are small for the non HPV vaccine group, this comparison argues against such reporting patterns pointing to a specific undiagnosed ‘syndrome’ reported with HPV vaccine.”

UMC report (DHMA report, page 31):

“The MedDRA High Level Terms (HLT) most over-represented in HPV reports were imaging procedures, vaccination site reactions and exposures associated with pregnancy, delivery and lactation. The HLT most under-represented in HPV reports were application and instillation site reactions, infections NEC, and allergic conditions NEC.

There were a number of HLT over-represented in the HPV reports into which many of symptoms of interest are located, suggesting that these symptoms are potentially specific for HPV vaccines. Additionally, there are a number of HLT describing diagnostic procedures which implies serious events without a clear diagnosis of clinical grounds. These HLT of interest are bolded in the table below.”

In the table that was provided after this text (page 32 in the DHMA report), one could see that there were a number of HLT which were statistically significantly over-reported with HPV vaccine which were not mentioned in the EMA report: disturbances in consciousness, muscular weakness, disability issues, and neurological signs and symptoms.

Furthermore, the EMA fails to mention at all the large number of HLT describing diagnostic testing which are over-represented in the HPV reports: imaging procedures, neurologic diagnostic procedures, central nervous system imaging procedures, ECG investigations,

autoimmune analyses, gastrointestinal and abdominal imaging procedures, and vascular tests.

I find this highly important – and very problematic that this information as far as I can see was left out in the EMA assessment report. As the symptoms that we describe in Denmark as well as in the rest of the world very clearly make us suspect that we could be dealing with a condition involving the nervous system both the symptoms and the procedures that was over-represented in the HPV-reports seems a highly relevant finding.

Example 4

EMA report page 28:

"Of these more relevant and specific higher level terms, only asthenic conditions shows any apparent disproportionality and this only occurred when the decision was taken to lower the 'signal threshold', but this was only marginal (12.3% of HPV vaccine reports vs 9.3% of other vaccine reports)."

UMC report (DHMA report page 34):

"Given the above results, a decision was taken to explore the impact of lowering the threshold of statistical significance to log OR 005 > 0.25. When this adjustment is made, a number of additional, and more specific, HLT become highlighted as key features; many of these highlighted features contain PTs describing symptoms which are of clinical interest. These HLT of interest are bolded in the table below"

In the table provided below this text (DHMA report page 34, it was displayed that there were many other relevant HLTs which were significantly more reported (it was not just asthenic conditions): Gastrointestinal and abdominal pains (excl oral and throat), Migraine headaches, Gait disturbances, Visual disorders, Muscle related signs and symptoms, Sensory abnormalities, memory loss, musculoskeletal and connective tissue pain and discomfort, mental impairment and musculoskeletal and connective tissue signs and symptoms

These are among the symptoms that we describe in our papers. These are the symptoms that our patients describe. I find it frustrating that the UMC found the same symptoms when looking through their data – but this finding is not communicated in the EMA report.

In spite of the numerous examples of what I find is problematic representation of the data, there are a number of statements of the EMA within the assessment report that can be agreed, or at least partially agreed, such as the following:

1. *"The Uppsala Monitoring Centre report suggests that the same clinical 'syndrome' may be occurring following HPV vaccination but is being diagnosed/coded differently across countries. Whilst it cannot be excluded that this is the case, many factors influence the levels of reporting… and the nature of reports submitted. Overall, the observations included the Uppsala Monitoring Centre report does not allow any conclusions to be made on clinical or diagnostic practice between countries."(EMA report page 28)*

I agree that the data presented in the UMC report do not allow firm conclusions on clinical on diagnostic practice. However, the hypothesis which was generated by the UMC based upon this data "that the same clinical syndrome may be occurring following HPV vaccination but is being diagnosed/coded differently across countries" appears to have been acknowledged by the EMA "…it cannot be excluded that this is the case". I find it strange that the EMA is not interested in further investigating this possibility given the gravity of the situation at hand.

2. *"The PRAC noted that although the analysis appears to incorporate statistical adjustment, this sort of multiple analysis and data-mining of suspected ADR data (at MedDRA SOC, high level and preferred terms level) will inevitably yield some results of disproportionality for HPV vaccines reports as well as non-HPV reports, as shown in the Uppsala Monitoring Centre report. However, the approach taken to selection of SOCs, high level and preferred terms, amendment of a pre-specified 'signal threshold' and selective discussion of disproportionate reporting for HPV vaccines does raise questions about the conclusions."(EMA report page 29)*

It is agreed that multiple analyses of large databases will, by chance, yield some results of disproportionality. This would be the greatest argument against drawing firm conclusions from the review. It has been clearly acknowledged in the UMC report that there is only the suggestion of a pattern in the results; a hypothesis has been generated which should be subject to further study prior to either accepting or discarding the results.

3. *"Overall, it is considered that the Uppsala monitoring centre report serves to highlight what is already known, i.e. that some countries are observing an increasing number of reports of different types of adverse events associated with HPV vaccine and that such reporting has increased over time."(EMA report page 29)*

It is agreed that this is perhaps the most firm conclusion that can be drawn from the data provided. However, the exploration of spontaneous data that was provided here was intended to be hypothesis generating. The assessment by the UMC suggests that more extensive analyses of spontaneous reports (such as the use of vigiPoint) may be able to better inform decisions in pharmacovigilance. Shouldn't we do this?

5: The EMA process

The EMA states in their report that

The PRAC consulted the Scientific advisory group (SAG) on vaccines on 21 October 2015 which provided advice on a number of issues. The expertise of the SAG was enriched by experts on the syndromes, on neurology, cardiology and pharmacoepidemiology. (EMA report page 32)

It should be noted, that we are not told the names, numbers, affiliations etc of these experts. As I understand it, all participants at the SAG meeting held October 21st are bound to secrecy with regard to the details of the meeting. As far as I can see, the minutes of the meetings are not released. What data did they get to review? Did they write a report for the PRAC 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 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. There are so many facets and nuances and so many unknowns and uncertainties – so we will all disagree to some extent, 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". This makes it difficult for solitary scientists and medical professionals as myself to disagree. Who am I to disagree with all these many experts who voice this conclusion unanimously? I am not questioning whether the people selected for the SAG-meeting were qualified. I am not saying that they did not do a good job. But I find it hard to believe that they all agreed on all aspects of this highly complicated and controversial matter. I believe that all the different viewpoints presented at a meeting like this would enable us to grasp a little more of the nuances of this issue.

I can understand why EMA feel the need to come out strong with a simple and strong conclusion. But – what if data does not support a simple and strong conclusion?

The questions that EMA asked the companies as part of this process are freely available[34] – which is good as it enables us to gain some insight into the process:

The questions were the following and they were also quoted in the EMA report:

Question 1

The MAHs should provide a cumulative review of available data from clinical trials, post-marketing surveillance, and literature in order to evaluate the cases of CRPS and POTS with their product.

Review and case detection methods should be clearly described and MAHs were asked to provide in depths reviews of all identified reports, and discuss whether they fulfil published or recognized diagnostic criteria.(EMA page 12)

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)? This must have been in the form of a report written by the MAHs to the EMA?. Is this report freely available?

1: Data from clinical trials

I will comment on that under "Question 2".

2: Data from post-marketing surveillance:

I cannot figure out whether the safety data reviewed came from the MAHs only or if safety data was also drawn from the EudraVigilance – I believe this is where we in Europe gather safety data – and therefore this will be the "safety data of EMA?" Did EMA go looking in the EudraVigilance safety data or did they rely on the data presented by the MAH from the MAHs database and reviewed data from the MAH only? 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.

Regarding the evaluation of the AERs: 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. As I read the EMA assessment I think that 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 [30, 31]. I have the highest regard for these two authors and regard them as some of the worlds leading experts on tilt table testing and POTS. Thus, I agree on the reference to their work with regard to the diagnostic criteria applied. 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.

We have been as thorough as possible when assessing the relevance of reporting and doing the AE reports - given our time schedule and clinical setting. Our thoroughness underlined by the fact that WHO has stated that the Danish AER did not in the essense differ from reports from the rest of world – but were of a higher quality. [2] We have heard

from DHMA through our collaboration and many meetings and close dialogue through the last 3 years that they have appreciated the high quality of our reports.

In the assessment report it is noted on page 12 that the MAH searched their own database for reports including the terms of POTS and CRPS. They explain that PRAC requested that they searched for undiagnosed cases using “"common search strategies". I think it would have been relevant for us to have these search strategies clearly defined and given. To my best knowledge there are no common search strategies which have been previously defined for either POTS or CRPS. In contrast, I believe there are for some common events such as myocardial infarction, anaphylaxis, etc.

3: Litterature review

I will comment on that under “Question 4”

Question 2

Please provide an in depth review of cases of CRPS and POTS observed within all clinical studies; with comparison of HPV vaccine groups and control groups. If differences are observed, please discuss potential explanations including risk factors for the development of CRPS and POTS.

Both CRPS and POTS are difficult syndrome diagnosis with huge overlap to other syndrome diagnosis. For both diagnoses goes that they often will only be diagnosed at specialized clinics. They are applied very differently by different countries. It is difficult to count things that may not necessarily have a label or a labeled differently around the world.

To my best knowledge, in the clinical trials of the HPV-vaccines in currently use, potentially harmful adjuvants or adjuvanted products were used as the control: alum adjuvant for Gardasil and alum adjuvanted hepatitis-A vaccine for Cervarix?. Therefore, even if there was no clear difference in serious adverse events between vaccine groups and controls – it may be too early to conclude that the vaccine is safe?

If data is available evaluating suspected side effects in a vaccine group compared to a "pure" placebo group given pure saline with nothing in it – except saline – then I hope the MAH or EMA will share this very important and relevant knowledge with us. A lot of the mistrust in the vaccines are arising from people failing to understand how this can be a good way to estimate the safety profile of a vaccine - including the adjuvant in both "vaccine" and "placebo". If there is a good explanation – or data to look at – I hope we can see it.

Actually –"Question 2" 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? Have we scientific evidence available that convincingly demonstrates that aluminium adjuvant are not able to elicit serious side effects in few but susceptible individuals? It may be present this evidence – but then we urgently need to communicate this knowledge to the many worried people being afraid that it is the aluminium that causes the suspected serious side effects.

As I understand it, clinical trials have two primary goals:

1: First of all – we need to determine if the drug we are testing actually works. We need to establish "efficacy". How does it work and how well does it work?

2: Secondly – we need to determine if the drug we are testing is safe to use. Does it have side effects? Does it cause cancer? Does it affect our ability to reproduce or the health of the offspring to the recipients?

Clinical trials may not "catch" rare side effects as most of these events are too rare to be observed in the clinical trials. This is OK. That is why we do post licensure safety evaluation. Determining safety from the clinical trials is simple math. We count the cases participating in the clinical trials. Total number of people in the trial who got the vaccine is the denominator. Subjects who reported a specific symptom as suspected side effects are the numerator. Am I right?

In the EMA report it is stated that:

"*No cases suggestive of POTS were identified in clinical trials with Gardasil/Silgard, and two cases suggestive of POTS were identified with Gardasil 9. One Gardasil 9 case did not fulfil the criteria for POTS, and for the second case it is unclear how long had passed between vaccination and onset of symptoms (diagnosis was made 1389 days after administration of dose 3).*

Overall, the incidences of CRPS and POTS observed in clinical studies were less than 1 case per 10,000 person-years in each of the Gardasil 9, Gardasil/Silgard and placebo cohorts.").(EMA report page 15)

However – in order to make the conclusion that we want to make from this – that POTS is not seen post-HPV-vaccines – we need to know how the scientific question was asked: So I would have liked to know: The one case in the Gardasil-9-study that did not fulfill the criteria – who decided this on what evidence? Was it EMA or the MAH? Were the experts in the SAG-group involved in these assessments? And – with regard to the second case – the diagnosis was made 1389 days after the administration - but did the EMA and/or the MAH not have any information with regard to the time span between vaccination and symptom onset? The question we want to answer is: "Do people fall ill from the HPV-vaccines?" – not "when do people that believe they fall ill from the HPV-vaccine get a proper diagnosis?" I think it would be very valuable if EMA would provide us with details on the process.

In the clinical trial data for Gardasil 9 which can be accesses at EMAs homepage [35]it is stated that:

"Within the clinical safety database for 9vHPV, there are 3 cases of POTS (Postural Tachycardia Syndrome) and 1 case of CRPS (Complex Regional Pain Syndrome), which are both on-going signals identified in the post-marketing period for quadrivalent Gardasil. Both signals have been the subject of extensive assessment in the most recent and previous PSURs for quadrivalent Gardasil. It has been concluded in the recent PSUR procedure (EMEA/H/C/000703/PSUV/0052) that there is currently insufficient evidence to support a possible a possible causal association between qHPV vaccine and CRPS and POTS. In light of this and given the uncertainty surrounding the background incidence of these syndromes, especially for POTS, these conditions were not included into the RMP. It is instead suggested that these safety concerns are closely monitored within PSURs during the post-marketing period.."(page 113-114)

I would like to know in detail how these three cases were evaluated. And I would like to understand how three cases in the clinical trial data transforms to two in the EMA report.

Question 3

The MAHs should 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, stratified by region, if available. 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.

Question 4

The MAHs should provide a critical appraisal of the strength of evidence for a causal association with HPV vaccine for CRPS and POTS. This should consider the available published literature, including epidemiological studies, and also the possible causes and pathophysiology of CRPS and POTS and discuss whether there is biological basis for a possible causal association.

In my point of view **if** we are dealing with a causal link between the vaccines and the symptoms described as suspected side effects we could be dealing with pathophysiological changes in the nervous system with an (auto)immune genesis in (genetically) susceptible individuals.

The literature review that lies behind the EMA assessment report – 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. 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. I will get back to this and include references to this in section 6 (“Is myalgic encephalomyelitis/chronic fatigue syndrome a relevant diagnosis?”).

Again – back to the scientific ladder – we now very little about what is going on. At this stage I believe that we have to include all available data in our analysis – and then we have to design case control studies, epidemiological studies etc in order to test the hypothesis generated based on the available literature.

I am not stating that EMA would have reached another conclusion if they had included this specific knowledge in their assessment; however, I find it problematic that we cannot determine from the report if they are aware of these pathophysiological similarities between the diseases that we discuss as possible side effects. Pathophysiological changes that seems relevant in this context as they have previously been described to be seen as side effects to vaccinations.

The study by Klein et al. was sponsored (entirely?) by MERCK, looked only at events with diagnosis codes, did only look at the first 60 days after vaccination, emergency room visits and hospitalizations only. They did not include other relevant medical care visits such as outpatient visits. They state that this is "not a long-term safety study".[36]

The study by Donegan et al. was a one-country study and the vaccine investigated was Cervarix only. This is problematic since the most used vaccine in many countries, including Denmark is Gardasil, which contains another adjuvant. On this basis, the study cannot be used as scientific evidence underlying possible side-effects of Gardasil. Another relevant comment is that limited information about the control group is present in the study. The control group is estimated; however, in the study they specifically pointed that the control group may be biased, since vaccination took place in schools and other institutions with inadequate registration. Further, in the study they It looked at data from the first 2 years of the vaccination campaign and looked specifically at diagnoses related to fatigue, where some of the diagnoses included decreases during the previous 15 years. Those

diagnoses are included in the statistical analyses, which may have confounded the results. [37]

EMA states on their homepage:

"The review noted that some symptoms of CRPS and POTS may overlap with chronic fatigue syndrome (CFS, also known as myalgic encephalomyelitis or ME). Many of the reports considered in the review have features of CFS and some patients had diagnoses of both POTS and CFS. Results of a large published study that showed no link between HPV vaccine and CFS were therefore particularly relevant."[38]

If EMA thinks that the Donegan study is this important, my advice would be that we should be looking at fatigue-related conditions as core issues in this matter. If EMA partially base their conclusion of the report on the Donegan study is it then a way of shifting focus from CRPS/POTS to ME/CFS? I on one hand totally agree with this notion – that we should forget about POTS and CRPS and merely look at them as diagnostic markers for another underlying disease. I find it difficult to understand that EMA have not yet looked into the fatigue-related conditions – or asked the MAH to do it. Why have a new process not been initiated focusing on a case-definition with long-lasting fatigue as core symptom?

I know very well how difficult it will be to use registers for this evaluation – due to all the caveats mentioned. However, being difficult does not mean that it should be ignored or is out of importance.

I believe that I read somewhere but I have not been able to locate it – that LAREB from the Netherlands signaled chronic fatigue as suspected side effect to the HPV-vaccine already in 2013? I am sure that if this is so EMA has access to the underlying data. If there was already a signal raised in 2013 on chronic fatigue I find this highly relevant for the evaluation at hand? And please correct me if I am wrong. This is a question – not an assumption.

<u>Question 5</u>

The MAHs should discuss the need for possible risk minimisation tools and provide proposals as appropriate.

No comments

6: Is myalgic encephalomyelitis/chronic fatigue syndrome a relevant diagnosis?

An array of diagnostic entities that have been described as suspected side effects to the HPV-vaccines share many characteristics – both with regard to symptoms and clinical findings : ME/CFS, POTS, CRPS, Fibromyalgia, Macrophagic myofasciitis and others.

The term "ASIA-Autoimmune/inflammatory Syndrome Induced by Adjuvants" (ASIA-syndrome) encompasses an array of clinical conditions and has many similarities to the above mentioned conditions – and has been reported as suspected side effect to the HPV-vaccine[39]

Furthermore, Nishioka et al. presented in 2014 an abstract as well as a paper (in Japanese) introducing: “Clinical features and preliminary diagnostic criteria of human Papillomavirus vaccination associated with neuroimmunopathic syndrome (HANS)”. They propose a new disease entity – a new HPV-vaccine associated syndrome with widespread pain, memory loss as well as general fatigue as the key symptoms. [20]

Most of the above mentioned conditions have been linked more or less convincingly to autoimmunity.[40-45] Recent publications have demonstrated the findings of autoantibodies directed against and in many instances activating receptors of the autonomic nervous system.[43, 44, 46] This is interesting as many of the symptoms described in these conditions can be explained by autonomic disorder. These are in most cases preliminary studies in small groups of patients – but they are very interesting and should be tested in larger cohorts with well-selected and characterized patients and compared to well-matched subjects.

EMA writes:

“POTS pathophysiology is still poorly understood, and the lack of strict application of diagnostic criteria hampers study of the syndrome. Researchers are currently investigating autonomic dysfunction, autoimmunity and genetic predisposition to POTS, but there is no clear evidence regarding the underlying cause.”(EMA report page 33)

I agree that we do not have clear evidence. But – doing a literature review should demonstrate very clearly that even the evidence is scarce when looked at from each of the

mentioned disease entities – the emerging evidence is strikingly similar in the different conditions – involving autoimmunity, autoinflammation and autonomic dysfunction. I think it would have strengthened the EMA report if this was taken into consideration and if this had been included in the literature review and discussed in the report.

The EMA report refers to a publication by Sheldon et al.:

In this paper the proposed pathophysiological mechanisms behind POTS are mentioned – including peripheral autonomic denervation:

" Reports from tertiary care centers have indicated that up to 50% of patients with POTS have a restricted autonomic neuropathy of small and distal postganglionic sudomotor fibers, predominantly of the feet and toes. It is believed that impaired sympathetic tone (as measured by norepinephrine spillover) reduces venoconstriction, leading to venous pooling in the lower limbs and splanchnic beds. This neuropathic manifestation of POTS requires a high cardiac output to compensate for reduced splanchnic and peripheral resistance and venous pooling. ……The autonomic denervation might be due to an autoimmune disease in some patients.[30]"

I will not go further into the shared patophysiological findings in the mentioned diagnostic entities - I find it will be too comprehensive and out of scope to elaborate on that in this responsum. I will only mention small fiber neuropathy the importance of which is explained in a recent paper by Manuel Martínez-Lavín.[19] Both CRPS and POTS have been associated with small fiber neuropathy [49-51]

I think it is a shame that these new insights were apparently not included in the literature review.

We have in our three papers tried to narrow down a case definition describing patients with suspected side effects to the Q-HPV-vaccine. We have a suspicion that we see a complex of symptoms with long-lasting fatigue and pronounced autonomic dysfunction coupled with severe non-migraine-like headache, excessive fatigue, cognitive dysfunction, gastrointestinal discomfort, and widespread pain of a neuropathic character. We therefore ask the question: do we see this symptom complex more often in vaccinated girls than unvaccinated girls? Further studies are warranted. We find that no existing diagnostic entity fits perfectly well, but suggests that the diagnosis G 93.3 ME/CFS could be worth considering.

This conclusion is in accordance with the UMC, the DHMA and the Lareb (Netherland). We know nothing with certainty, but we need to find out. If we do end up finding a significant association between HPV-vaccine-status and an ME/CFS like syndrome – this will not tell us how the vaccine and symptoms are causally linked. Most of the vaccinated tolerate the vaccine very well. So if we have an association – we are probably looking at individuals with a genotypic and phenotypic susceptibility and maybe an existing sensitivity that renders them susceptible for vaccine-triggered disease.

The "Lareb" of Netherland which as I understand it is the Dutch pharmacovigilance center that work together with but are separate from their medicines board states in their report " Long-lasting adverse events following immunization with Cervarix® " published December 2015:

"A causal relation between Cervarix® vaccination and long-lasting symptoms can not be concluded nor excluded based on the analysis of these reports. In order to study whether long-lasting fatigue occurs more often in vaccinated girls than in unvaccinated girls, epidemiological research is recommended. The National Institute for Public Health and the Environment (RIVM) already started a study."[52]

The DHMA writes [2]:

- In the section discussing the evaluation of reported serious ADR cases for HPV-vaccination in Denmark:

"Approximately one third of those individuals described in the serious ADR reports, exhibit a symptom complex characterized by a combination of severe fatigue, neurological and circulatory symptoms, pain and headache and often accompanied by malaise, abdominal discomfort, thermal dysregulation and possibly proneness to infection. Seventeen percent of the patients reported to be socially handicapped by their condition.

Most of the cases do not have a diagnosis. Based on the review it appears that the symptoms could fit into a number of different diagnoses."(DHMA-report page 7)

……. …."Based on the review we recommend not only to focus any review of reported adverse reactions for HPV-vaccines on diagnoses individually, but to also consider whether a pattern is observed based on symptoms and/or whether different diagnoses reported could represent the same underlying symptom pattern." (DHMA-report page 8)

- In the section describing information obtained through dialogue with the Japanese Ministry of Health, Labour and Welfare:

"The Japanese authorities are currently conducting a large investigation of all adverse event reports received in their pharmacovigilance database. Although the initial concerns have focused on pain and the diagnose CRPS, the adverse event reports in the Japanese database were characterized by a wider variation of symptoms, often difficult to standardize. Often reported symptoms were pain, movement disorders, orthostatic intolerance, dizziness, menstrual abnormalities and fatigue. Symptoms were reported to fluctuate and in some patients lasting for a long time. This pattern reflects much of the same symptoms as are also reported in the Danish cases."(DHMA-report page 10)

Reading the EMA-report and available literature, I find that the only possible conclusion at this stage is that we do not have convincing or enough evidence that support an association between the HPV-vaccines and the two syndromes POTS and CRPS – if we regard these syndromes as well-defined and separate disease-entities.

However, I believe that evidence – or at least observations – are piling up suggesting a signal which warrants further investigation, the question being:

"Is there an association between the HPV-vaccines and a ME/CFS-like syndrome?"

In Denmark – and I guess the same problem will apply to other countries – if you are sick – it is easier to get help if you have a diagnosis. Just "being sick" is not enough. We use diagnoses as a language. When we can match a certain patient with a certain diagnosis - we have a sense of how sick is this patient, what treatment is relevant, is it contagious, can she drive a car etc. Around the world, Denmark is known as one of the leading countries regarding register-based research, because we during decades have developed hospital registers of high validity. However, the vaccinated girls suffering from possible side-effects will not be listed in the registers, if they are not given a diagnosis.

As medical professionals, diagnoses help us to prorate patients. We know which medical specialty we should refer the patient to, and the patients know where to turn for help. We have a shared reality, a common language between patients, medical professionals and health care system.

Patients with more or less unexplained and multiple symptoms may not always have this luxury of a shared reality and a common language. They may not get a diagnosis. Or they

get many different diagnoses. Some of them will have a diagnosis that belongs to a language that people may all understand – but they understand it very differently depending on who you talk to. If a patient is diagnosed with G93.3 Myalgic Encephalomyelitis, some medical professional will understand this as a functional disorder. They may recognize the patient as actually misdiagnosed as the diagnosis is a neurological code (all the diagnosis beginning with a “G”), but they may find that this patient is actually suffering from a disorder in the psychiatric spectrum. Other physicians will look at ME as an immune disorder associated with autoimmunity and disrupted function of the white blood cells. Other physicians again will recognize these patients with the G93.3 diagnosis as suffering from a cellular depletion syndrome – a mitochondrial dysfunction – and so on.

All these physicians may tell you that they can evaluate these patients and that the findings in the actual patient confirm their notion. But the problem arises when we are to treat these patients – to help and support them. What treatment should we give them? And what do we do if the treatment that makes sense in one of the explanatory models may seem harmful when you look at the patient though other glasses? The patient and different medical professionals do not live in a shared reality when it comes to these patients. It is my experience from working with this kind of patients that many of them end up having no trust in the established health care system and simply stay away – receiving no diagnosis, no medical evaluation and no treatment. They are on their own. They are invisible.

Why am I writing all this? Because I want to advocate that these patients – including many of the patients with suspected side effects to the HPV-vaccines – they are impossible to count in register studies. They are difficult to handle and evaluate by an epidemiological approach. They may not pop up having a diagnosis, they may not pop up as visits to the hospital or GP. Many of them almost live in a parallel society seeking help from complementary medicine, or just trying to get on on their own.

This leaves us with many problems as society. We cannot count them when doing the register studies that we are so good at in the Scandinavian countries. Secondly, not belonging self-evidently to one medical specialty will contribute to their being invisible.

It is like the story of the six blind men who all touched different parts of the elephant and began to argue about the true nature of the elephant. Every one of them insisted that he was right. They kept on arguing until a wise man passed by and calmed them and explained to them that they were all right. The reason for their understanding the elephant so differently was because each of them touched different parts of the elephant. The elephant had all the features they saw and described. There was some truth to what everybody said. I think that most of you may agree – that we are acting like these blind men when we discuss a condition like ME – or the patients with suspected side effects to the HPV-vaccines. And rather than fighting and arguing like the blind men – we should value each others view points and get together and appreciate and use our disagreement. Listen to each others description of the corner of the condition that we believe that we understand – in order to get the bigger picture…… I think that one of the core reasons for this debate surrounding the suspected side effects to the HPV-vaccines are the heated debate that has been going on in decades concerning these complex conditions….

Am I saying that all these conditions are one and the same? No, I am not – but I think that some of them to a variable extent share some features – and we understand all of them very poorly. They may to some extent represent different phenotypic representations of similar underlying pathophysiological changes.

I find that all physicians, researchers, patients that I meet who has really invested some time and effort in the deeper understanding of these issues recognizes the shortcomings and drawbacks of our existing diagnostic system with regard to these patients. I believe that the failure to recognize this underlying challenge when evaluating the possibility and the extent of possible side effects to the HPV-vaccines is one of the main reasons that the whole debate is off track.

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As I see it – the "truth" concerning each and every one of the patients suspecting to suffer from side effects to the HPV-vaccines will lie somewhere along this continuum .

At one end of the continuum is the possibility that there is no direct biological causal link between the vaccine administered and the symptoms experienced. But the patient blame the vaccine – attribute the suffering to the vaccine. It is very human and common - the craving for an explanation – a cause for our suffering. Via social media, media attention etc this attribution, this notion that the HPV-vaccines have the potential for eliciting serious side effects spread and is therefore "contagious" – we are dealing with an outbreak of mass psychogenic illness.

At the other end of the continuum we have the possibility that there is a direct biological causal link between the vaccine and the symptoms experienced. We are dealing with actual side effects. The biology of the vaccine and the interaction between the vaccine and the (genetic and otherwise vulnerable and susceptible) individual elicits a biological process in the body of the vaccinee that directly leads to the symptoms experienced.

I think that it is impossible to say with certainty – both with regard to every single patient and with regard to the patients seen as a group – where along this continuum the "truth" lies. We may be able to make more or less qualified guesses – but we all share and face the same frustrating reality: We do not know with 100% certainty. This uncertainty is a huge problem. We want to be certain. But our need for being certain does not automatically equal that we have evidence to qualify a certain quess. We want the vaccine to be safe – but just because it would be so much easier and better for all of us if we knew with 100% certainty that the vaccine is safe – this does not make the vaccine more or less safe.

7: What to do?

This is so very complicated in so very many ways. I strongly advocate that we stop accelerating the aggression and confusion and instead seek common ground. Seek consensus – create the shared reality that I keep talking about.

The more we argue and the more unscientific and heated the debate gets – the further we get away from the fact central in this – we need to optimize health and minimize suffering.

Why don't we try to establish this shared reality – because reality is based on facts. It should be doable to look at facts together. What if we listened to each other – and to data - and then tried to answer the following questions together:

Efficacy of the HPV-vaccines

What do we now about efficacy?

What do we believe we have strong indications for with regard to efficacy?

What do we need to find out about efficacy?

How do we get wiser?

Safety of the HPV-vaccines

What do we now about side effect?:

What do we believe we have strong indications for with regard to safety?

What do we need to find out with regard to safety?

How do we get wiser?

I believe that we can all agree on one thing: The mistrust in the HPV-vaccine is a World wide problem. It is not a Danish problem and it is not a European problem. From many

wide spread countries around the world we hear case stories of young women who have fallen seriously ill as a suspected side effect to the HPV-vaccines. At the same time women die from cervical cancer each day and many suffers from sequela to treatment directed against cervical cancer

I believe that none of us know with certainty to what degree a smaller or bigger proportion of these patients suffer from a condition that is causally linked to the vaccine. We can guess, we can discuss, we can argue. But – as long as we do not know for sure we have to endure not knowing – and at the same time acknowledge the importance of getting answers – fast. Issues are not being clarified or solved just because we find uncertainty unpleasant and inconvenient. A vaccine is not safe just because we want it to be.

I have felt the need to write this responsum in order to oppose the criticism directed very openly and harshly at my person and my publications and scientific method directed against me from EMA and mirrored by the DHMA and other stakeholders in Denmark. But – most important of all – I have written this responsum hoping that it can be of some use in the task I believe we have at hand: We need to recognize that patients, politicians, health authorities, patient organization, parents of patients, health professional….all these stakeholders wants to optimize health, prevent disease and suffering – at a cost that we can afford as society. We want the same.

We want to safeguard our vaccination program. We want to obtain herd immunity. We cannot avoid side effects. However, by doing whatever possible to recognize and understand the mechanisms behind suspected side effects and thereby qualifying and strengthening both prevention and treatment of suspected side effects – we can truly say that we do all in our power to keep the benefit/risk ratio as beneficial as possible. It is not good enough just to keep repeating that “the benefits outweigh the risks” – if we by daring to recognize an eventual problem with side effects and having an honest, impartial and scientific look at it can minimize the suffering suspected to be caused by the vaccines – thereby optimizing the trust in the vaccines – and thereby eventually increase vaccination rates again.

I am afraid that we do not take this seriously enough. No matter to what degree we are dealing with side effects or not I think we need to act much more progressive than we do

now. If the symptoms experienced in these many girls and women around the world are NOT related to the HPV-vaccines we owe it to all of us to find good evidence for this – and then we need to elucidate what else could be the trigger – the common denominator in these patients. We need to know what is going on.

And if the symptoms in these patients are at all related to the HPV-vaccines – I do not think that we are acting proactively and innovative enough in order to establish what actions could be taken to prevent more vaccinees from getting side effects – and how we should treat the patients already afflicted.

There are so many new vaccines in the pipeline. I believe that we will see new vaccines that we will want to include in our childhood vaccination program. We need to be ready for the next challenge. When we next time have a signal – a suspicion regarding vaccine safety – we need to be able to look back at this HPV-vaccine-issue and say – we handled that one right – we know how to handle suspicions with regard to vaccine safety. We need to grow a new kind of responsibility that leaves room for a much more nuanced and targeted approach to vaccines. We owe that to the vaccines – and ourselves.

I really hope that EMA will reconsider their report and their conclusion. I hope that my local health authorities will reconsider their harsh critique of me as well as their conclusion. I will remind EMA, our local health authorities and all of us that a Dutch study demonstrated that the number one reason for people to decline HPV-vaccines were mistrust in the health authorities. [53]

I have been contacted by quite a few fellow- doctors, researchers from Denmark as well as from other countries. Many of them tell me that they have the same suspicion, they see the same pattern – but most of them tell me that they are afraid to speak up. I find that we have established a culture where it is not acceptable to have a critical approach towards vaccines. We may all state that ”of course all medicine, vaccines included, have the potential of eliciting side effects….” But when it gets tangible and concrete – when an actual doctor suspects that an actual patient has contracted an actual disease as a side effect to an actual vaccine – then many of us find it difficult to handle. We want him or her to shut up. We want the suspicion to go away. We want vaccines to be 100% safe. There are many good and also many terrible reasons for this. But we need to discuss how we

handle suspected side effects most reasonably. I think we should learn from the two emerging “omics” that I presented in the beginning of this responsum – vaccinomics and adversomics. They tell us that we have to accept and embrace that the way a vaccine interacts with each and one of us is very variable – both when it comes to efficacy and safety. This may be laboriously – but that is how it is. And this knowledge – that vaccines are complex to a degree that makes me dizzy – it won’t go away. So – we might as well take the discussion about vaccines into a version 2.0.

Back to basics: The aim of the EMA report was to use the available data to draw a conclusion on causality between HPV vaccine and POTS/CRPS. I find it hard to understand how the type of data that is reviewed in the EMA report – and the way the data is reviewed – is enough on which to draw a firm conclusion on causality. Secondly – the review are primarily limited to CRPS and POTS. That is as it should be as that was what was asked of them – but I believe that the question asked was too narrow – which I guess is the conclusion also reached by the EMA report. But they do not conclude that the question should be rephrased – or another report made focusing on conditions with excessive and long-lasting fatigue. I think that we are left with an answer that is not very usable – actually I find it counterproductive for the whole process of getting to the bottom of this.

I have been in a hurry writing this in the weeks before Christmas – after working hours between Christmas preparations. I just wanted to get it out. Therefore I hope that you will acknowledge this as a statement in progress. I will correct it and expand it. I hope that some of you will enter a dialog with this responsum and me. Write me. Also the EMA and the MAH. Tell me where and why I am wrong. Let us all contribute to an open, translucent, democratic and constructive dialog. It may not seem the easiest way out – but I think it is the only way out

Write me: Louise.schouborg.brinth@regionh.dk

8: Concluding remarks

I think that the only possible conclusion at this stage is that we do not have convincing or enough evidence to support an association between the HPV-vaccines and the two syndromes POTS and CRPS – if these syndromes are looked upon as well-defined and separate disease-entities.

However, I believe that evidence – or at least observations – are piling up suggesting a signal which warrants further investigation, the question being:

“Is there an association between the HPV-vaccines and an ME/CFS-like syndrome?”

And – we would do ourselves a favor if we made sure to create consensus on how to “ask” this question using the epidemiological toolbox. I have chosen the diagnostic term ME/CFS – but the important thing is for us to create a “case definition” of the symptoms.. In that way we have the best starting point for estimating whether we see these symptoms involved in the case definition more often in HPV-vaccinated versus non-vaccinated. And we need to gather expertise from all relevant fields of medicine in order to determine if and how it is possible to create a case definition and to formulate that case definition.

If we can agree on a case definition before we do the register studies – then we will end up with a conclusion that will be “our” conclusion. A conclusion that as many as possible will consider trustworthy and useful.

And one last word about elephants and a shared reality: I think much of the aggressive rhetoric, disagreement, mistrust, worry and confusion that we all face in this matter would dissolve instantly if we would do ourselves and each other the favor of having the underlying and fundamental discussion about “functional disorders”, ME/CFS etc. And if we would admit that this whole group of very complex disorders – as well as the whole matter of efficacy and safety of vaccines raises many simple, central and important questions – but mostly we only have inconclusive answers.

But – this is what we are facing together. This is our shared reality. If we actually help each other – and aim at establishing the bigger picture – establishing the nature of the whole elephant by creating a milieu where it is allowed to doubt and allowed to disagree. And

where we encourage humble and qualified scientific curiosity – then I think we would have all the best possible opportunities to solve this issue.

Let us all collaborate to make the best possible estimate of the efficacy of the HPV-vaccines

Let us all collaborate to make the best possible estimate of the safety of the HPV-vaccines

Then we can ask our health authorities to do what is their job and expertise: Evaluate and decide to what degree the benefits of the vaccine outweigh the risks.

Then we can as vaccinees and parents be confident that we have sufficient information available to us in order to give an informed consent when offered the HPV-vaccine.

9: English Summary

During the past years a growing concern with regard to the safety of the human papilloma virus (HPV) vaccines has emerged in Denmark – as well as in other countries around the world.

Denmark therefore asked the European Commission to initiate an in depth review. The European Commission requested the European Medicines Agency (EMA) to use the available data to draw a conclusion on causality between HPV-vaccines and the two syndromes: Chronic Regional Pain Syndrome (CRPS) and/or Postural Orthostatic Tachycardia Syndrome (POTS).

In the assessment report written and published by EMA, three of my publications regarding my clinical experience with patients with suspected side effects to the HPV vaccine are directly criticised. Furthermore, my clinical expertise and judgment are indirectly criticised as a substantial part of our adverse effect reports (AER) are overruled. I want to defend my work but most of all I want to join in and encourage to an open and honest debate.

My agenda is not to miscredit the vaccine, rather it is to maintain public confidence in the vaccine itself and the entire childhood vaccine program. To reach this goal, I believe that it is imperative to appreciate that vaccines can have side effects and it is the responsibility of the health care community to monitor and investigate serious problems which are suspected to be related to the vaccines.

We are in desperate need of a shift in paradigm, a groundbreaking one, or the future of public confidence in vaccines could be lost.

Regarding the critique directed against me I find that EMA suggesting that we selected patients based on symptoms in order to make sure that they would fit into a preexisting hypothesis is one of the most serious allegations I have ever been presented with. We did not. I address this in the responsum.

I think that the only possible conclusion at this stage is that we do not have convincing or enough evidence to support an association between the HPV-vaccines and the two syndromes POTS and CRPS – if these syndromes are looked upon as well-defined and

separate disease-entities. However, I believe that evidence – or at least observations – are piling up suggesting a signal which warrants further investigation, the question being:

“Is there an association between the HPV-vaccines and an ME/CFS-like syndrome?

I think much of the aggressive rhetoric, disagreement, mistrust, worry and confusion that we all face in this matter would dissolve instantly if we would do ourselves and each other the favour of having the underlying and fundamental discussion about “functional disorders”, ME/CFS etc. And if we would admit that this whole group of very complex disorders – as well as the whole matter of efficacy and safety of vaccines raises many simple, central and important questions – but mostly we only have inconclusive answers.

Let us all collaborate to create common ground – a shared reality with regard to these complex disorders – so that we can offer these patients the best possible evaluation and treatment. This will not happen before we have reached consensus at another level than we have for the time being. The Danish Health and Medicines Authority has just initiated this work by establishing a task force on the subject. Let us support and follow this initiative – and let us all join in the discussion and contribute. And let us use are disagreements to create a multifaceted but still targeted approach to these patients. – Both medical professionals, patients, patient organisations.

Let os all collaborate to make the best possible estimate of the efficacy of the HPV-vaccines

Let us all collaborate to make the best possible estimate of the safety of the HPV-vaccines

Then we can ask our health authorities to do what is their job and expertise: Evaluate and decide to what degree the benefits of the vaccine outweigh the risks.

Then we can as vaccinees and parents be confident that we have sufficient information available to us in order to give an informed consent when offered the HPV-vaccines

10: Danish Summary

I de senere år har der i Danmark og andre lande rundt om i verden været en stigende bekymring for sikkerheden ved vacciner mod human papillomavirus (HPV).

Danmark bad på den baggrund Europakommissionen om at sætte en dybdegående undersøgelse i gang. Europakommissionen bad derfor det europæiske medicinagentur (EMA) anvende tilgængelige data til at konkludere på kausaliteten mellem HPV-vaccinerne og de to syndromer: chronic regional pain syndrome (CRPS) og/eller postural ortostatisk takykardisyndrom (POTS).

I rapporten skrevet og udgivet af EMA bliver tre af mine publikationer om mine kliniske erfaringer med patienter med mistænkte bivirkninger til HPV-vaccinen kritiseret direkte. Derudover bliver min kliniske ekspertise og dømmekraft indirekte kritiseret, idet en substantiel del af mine bivirkningsindberetninger bliver underkendt. Med dette responsum ønsker jeg at forsvare mit arbejde, men mest af alt ønsker jeg at deltage i og tilskynde til en åben og ærlig debat.

Det er ikke min dagsorden at miskreditere vaccinen. Tværtimod er det mit primære anliggende overordnet set at bevare tilliden til HPV-vaccinen og til hele børnevaccinationsprogrammet. For at opnå dette mener jeg, at det er afgørende at anerkende, at vacciner, herunder også HPV-vaccinen, kan have bivirkninger, og at det er sundhedsvæsenets og syndhedsmyndighedernes ansvar at overvåge og undersøge de alvorlige problemer, som er mistænkt at hænge sammen med vaccinen.

Der er et akut behov for et helt grundlæggende paradigmeskifte – ellers risikerer vi at den fremtidige tiltro til vacciner går tabt.

EMA kritiserer mig direkte for, at vi i vores artikler skulle have udvalgt patienter efter symptomer – for at være sikre på, at de ville passe ind i en på forhånd eksisterende hypotese. Det er en af de alvorligste anklager, jeg nogensinde er blevet præsenteret for. Det har vi ikke. Jeg adresserer dette i mit responsum.

Jeg mener, at den eneste mulige konklusion på nuværende tidspunkt er, at vi ikke har overbevisende eller nok evidens til at konkludere at der er en sammenhæng mellem HPV-vaccinerne og de to syndromer POTS og CRPS – hvis man ser på disse syndromer som veldefinerede og isolerede sygdoms-enheder. Til gengæld mener jeg, at der hober sig evidens – eller i det mindste observationer – op, der kalder på yderligere undersøgelser, hvor spørgsmålet er:

- Er der en sammenhæng mellem HPV-vaccinerne og et ME/CFS-lignende syndrom?

Jeg mener, at meget af den aggressive retorik, uenighed, mistillid, bekymring og forvirring, som vi alle er vidne til i denne sag, ville forsvinde, hvis vi gjorde os selv og hinanden den tjeneste at tage den underliggende og fundamentale diskussion om "funktionelle lidelser", ME/CFS osv. Og hvis vi ville indrømme, at hele denne gruppe af komplekse og mangelfuldt forståede tilstande - og hele spørgsmålet om vacciners effekt og bivirkninger – rejser mange enkle, men centrale spørgsmål, som vi indtil videre i de fleste tilfælde kun har utilstrækkelige svar på.

Lad os alle samarbejde for at skabe fælles grund – en fælles og delt virkelighed, hvad angår disse komplekse tilstande - så vi kan tilbyde patienterne den bedst mulige evaluering og behandling. Dette vil ikke ske, før vi har nået konsensus på et andet niveau, end vi har nu. Sundhedsstyrelsen har netop sat sådan et arbejde i gang ved at etablere en arbejdsgruppe om emnet. Lad os støtte og følge dette initiativ, og lad os alle bidrage og være med i diskussionen – både læger, patienter og patientorganisationer. Og lad os bruge alle de uenigheder, der måtte være, til at skabe en multifacetteret, men stadig målrettet tilgang til disse patienter.

Og sidst men ikke mindst:

Lad os alle samarbejde om at lave den bedst mulige vurdering af HPV-vaccinernes effekt.

Lad os alle samarbejde om at lave den bedst mulige vurdering af HPV-vaccinernes sikkerhed.

Så kan vi bede vores sundhedsmyndigheder om at gøre, hvad der er deres job og ekspertise: evaluere og beslutte, i hvilken grad HPV-vaccinernes fordele opvejer deres ulemper.

Så kan vi både som dem, der skal vaccineres og som deres forældre være sikre på at vi har tilstrækkelig med information til at afgive et informeret samtykke når vi tilbydes en HPV-vaccine.

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