# 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

## Background

Vaccination against human papillomavirus (HPV) has been included in the Danish childhood vaccination program since 2009. The inclusion was based on a thorough national health technology assessment (HTA)[1]. The quadrivalent HPV-vaccine, Gardasil®, is the vaccine used in the Danish program.

Free vaccination is offered to girls aged 12 years through general practitioners. In addition to this, a temporary catch-up program has been established offering free vaccination to adolescent and young women up to 27 years. The catch-up program offer will run until end of 2015.

Around 0.5 million subjects have been vaccinated in Denmark (which is around 20 % of the entire female population). The vaccine coverage in the target population has been 90 % but has decreased during the past year to 80 %, with a trend towards further decline.

During the first years after introduction of the HPV vaccine the outcome of the routine safety surveillance was in accordance with the expected, as post-marketing experience overall was similar to experiences gained in clinical trials. However, from 2013 an onwards, the Danish Health and Medicines Authority has received a number of reports regarding suspected serious adverse reactions after vaccination with Gardasil®. Some of the cases first received (7 cases up to 10th of September 2013) had been diagnosed with postural orthostatic tachycardia syndrome (POTS), and a number of additional serious cases (24 from 1st of January to 9th of September 2013) was without diagnoses but included symptoms with resemblance of cases of POTS such as long-lasting dizziness, headache, syncope and fatigue.

POTS is characterised by an abnormally large increase in heart rate when changing from a lying down to a standing up position, without any orthostatic hypotension. In POTS, this excessive heart rate increase may be accompanied by a range of symptoms which may include lightheadedness, visual blurring, palpitations, weakness (especially of the legs), as well as fatigue, shortness of breath, chest pain, concentration difficulties, and headaches. Before diagnosing POTS other differential diagnoses such as conditions that cause tachycardia should be excluded[2]. The prevalence especially in children and teens is not known. Also there is no consensus on the diagnostic criteria for pediatric POTS, but it has been suggested that there should be evidence of chronic orthostatic intolerance for > 3 months, excessive postural tachycardia, absence of significant orthostatic hypotension, and absence of a reversible cause[3]. By mid 2013 only a single case report was published on POTS associated with HPV-vaccination[4].

Denmark raised the signal to the EMA Pharmacovigilance Risk Assessment Committee (PRAC) in September 2013, and based on the data and number of cases at that point in time the PRAC concluded that the issue should be evaluated in the yearly periodic safety update reports (PSURs) for Gardasil®.

During the same period a signal regarding complex regional pain syndrome (CRPS) was also raised. For CRPS most common symptoms are severe pain, swelling and changes in the skin temperature and colour of the arms or legs, but may also include amongst other symptoms headache, general fatigue, coldness of the legs, limb pain and weakness. The cases of CRPS were mostly reported for Cervarix® and most case reports originated from Japan. Following a review of all available data on CRPS PRAC concluded in 2014, that the available evidence did not support a causal association and that the issue should be reviewed through the PSURs.

In the latest PSUR assessment for December 2014 it was concluded that for both POTS and CRPS a causal relationship could not be ruled out at the present time.

The majority of the Danish POTS cases is reported from a Copenhagen-based hospital with a center specialized in examining and diagnosing conditions with orthostatic intolerance, often with manifest syncope. The specialized center in Copenhagen has published several case series with detailed data on their patients evaluated for POTS in relation to HPV-vaccination[5,6,7]. In a case-series including 53 patients, they describe a common pattern of symptoms in the patients with headache, orthostatic intolerance and fatigue as the most common combination of symptoms. The average age of the patients is 23 years and they note that a high percentage of the patients has a high or moderate activity level (e.g. physical, social) prior to vaccination[5]. The authors hypothesize that POTS and orthostatic intolerance is only part of the clinical manifestations, and report that within a group of patients referred to their clinic for suspected side effects to HPV vaccination 51% fulfilled the criteria for POTS whereas almost 90% of patients fulfilled criteria for chronic fatigue syndrome[7]. They suggest that a common underlying mechanism could be dysautonomia caused by an autoimmune reaction to vaccination[6].

A case-series of 6 patients presenting with new-onset POTS after HPV-vaccination has also been published from the US recently[8].

Other syndromes than POTS in particular with focus on pain-symptoms have been reported in publications from 2014. Two cases of fibromyalgia-like illness was described in a publication[9], a larger case-series of 45 young women presenting with widespread pain[10] and a series of 44 girls presenting with headache, fatigue and limb pain, in some cases fulfilling criteria for POTS or CRPS, related to HPV-vaccination[11]. A signal from the WHO database was presented in April 2015 regarding gastrointestinal motility disorders in 21 patients after HPV-vaccination. In the signal evaluation from WHO, a common link to POTS and CRPS is proposed[12]. A recent paper from 2015[13] has emphasized that the various syndromes described in cases after HPV-vaccination are difficult to diagnose, and that they have overlapping clinical features.

The various publications in recent years are raising potential signals of concern regarding reactions after HPV-vaccination. Based on the signals of POTS and CRPS as well as the description of case reports of other syndromes like fibromyalgia and chronic fatigue it is found that very similar patterns of symptoms after HPV-vaccination are described despite the differences in diagnoses. It is plausible, that similar types of cases would receive different diagnoses depending on the national clinical setting, and that a safety signal could be present but would potentially be diluted due to different diagnoses in different countries.

Several publications suggest that dysautonomia is the common underlying mechanism for the symptoms presented[e.g. 6,10,12], and some recent publications suggest that dysautonomia caused by small fiber neuropathy is the mechanism behind the various presented clinical symptoms[8,13].The mechanism by which HPV-vaccination should lead to small fiber neuropathy is not clear, but some link between the aluminum adjuvant damage to dorsal root ganglion combined with individual susceptibility is hypothesized[13].

The design of the studies such as theoretical reviews or case series without non-vaccinated control groups only allows for generation of hypotheses of possible mechanisms but provides no firm knowledge of the causal association between vaccination and reported reactions. Since many of the symptoms are seen in the background target population it is a significant challenge to distinguish causal from temporal association.

Studies designed to elucidate whether excess risk of various diseases is seen in the vaccinated population have also been published recently. Studies using US health insurance databases have not found any safety signals for autoimmune disorders[14] or for excess adverse event in the period after vaccination[15]. A French based case-control study found no evidence of an overall increase in autoimmune disorders in young

females in the period after vaccination[16]. A large Scandinavian cohort study was published in 2013. The study included almost 1 million girls and assessed 53 different outcomes for autoimmune, neurological and venous thromboembolic events during a 180 days period after vaccination. The study found no evidence supporting an association between exposure to quadrivalent HPV-vaccine and any of the outcomes[17]. Another Scandinavian study from 2014 has focused specifically on multiple sclerosis and other demyelinating diseases. This study included almost 4 million females from 10-44 years and did not find evidence of association between HPV-vaccination and any of the diseases[18]. The risk of chronic fatigue syndromes in relation to the bivalent HPV vaccine was investigated using database records and reported adverse events in the UK. The study found no increased risk of chronic fatigue after vaccination compared to expected background incidences[19]. The data from these safety studies including a large number of women and with no evidence of increased risk of diseases are reassuring. However, a limitation in the studies is that the use of registers to identify outcome measures is highly dependent on diagnoses. The syndromes suspected as reactions to HPV-vaccination are often difficult to diagnose and has overlap in symptoms between diagnoses. Also many cases reports symptoms without a diagnose. Such cases would not be identified in the currently published register studies.

Since 2013 the number of reported cases of POTS and other symptoms seen after HPV-vaccination has increased dramatically in Denmark. The media attention has been intense since 2013 and the issue has raised considerable public concern, which is also reflected in the decrease in vaccination coverage.

Based on the evolving uncertainty and public concern, and based on the number and severity of reported cases as well as the increasing amount of published scientific literature in the area, the Danish Health and Medicines Authority has initiated a further review of the ADR reports received in Denmark to take stock of the safety of HPV vaccines.

In the present report an overview of the serious adverse drug reaction reports for HPV-vaccination accumulated in the Danish Pharmacovigilance database is provided, together with the outcome of a comparative analysis between Danish and worldwide data performed by the WHO. Furthermore, a short summary of the Japanese experiences is included.

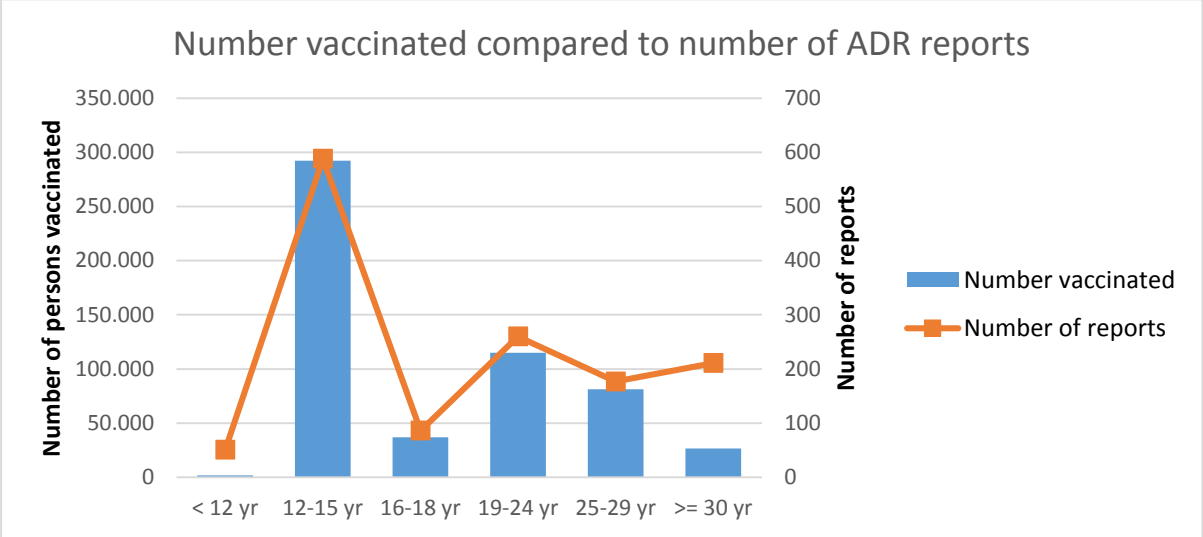
## Overview of ADR reports received in Denmark

Overview of all reports received by the Danish Health and Medicines Authority shows that the number of reports have increased over the past years but also correlated to the number of doses distributed for the vaccine.

| HPV vaccine | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | Q1 2015 | Total |
|---|---|---|---|---|---|---|---|---|
| **Number of reports** | 288 | 66 | 43 | 96 | 511 | 224 | 77* | 1305 |
| **– of which serious** | 25 | 5 | 6 | 18 | 177 | 91 | 41 | 363 |
| **Number of doses sold** | 347,690 | 151,476 | 163,374 | 349,730 | 488,224 | 114,457 | 20,817 | 1,635,768 |

*The number of reports received in 2015 including both Q1-Q2 is 385

Overview of all reports also showed that the age groups for which ADR reports have been received is well correlated with the number of persons vaccinated in various age groups.




Detailed review of the reports categorized as serious revealed a number of characteristics.

The overall data corresponds to what would be expected.

## Evaluation of reported serious ADR cases for HPV-vaccination in Denmark (DLP 19-03-2015)

### Methods

The case review included all spontaneous adverse reaction (ADR) reports received by the Danish Health and Medicines Authority up to March 19, 2015 that were classified as serious according to internationally agreed criteria.

The dataset consisted of 363 serious ADR reports received in the period. An experienced clinician reviewed the information including narratives and reported preferred terms (PTs) in all individual cases.

The information in each case was described as symptoms rather than only individual PTs, since different PTs in some cases could be different descriptions of the same symptom (e.g. burning sensation, hyperesthesia and sensory disturbance all named as the symptom paresthesia). The PTs included in each symptom are provided in appendix 1.

Based on a pilot review of the most recently received reports 5 main symptom categories were identified based on the reviewers impression of the symptoms relatedness within each category, as well as frequency and severity of occurrence. Eight additional categories were added, that included PTs frequently reported, in order not to miss registration of symptoms that might prove relevant, when the whole material was analyzed.

The 5 main categories were: severe fatigue, neurologic symptoms, circulatory symptoms, pain and headache and the 8 additional categories: autonomic imbalance, abdominal discomfort, urinary tract

symptoms, allergy, infections, menstrual disorder, thermal dysregulation and malaise. Details of definition of the categories and symptoms is provided in appendix 1.

No attempt was made to evaluate any causal or time wise relation between the symptoms reported and the HPV vaccination, as information of time of symptom onset and duration was too often missing or not very accurate.

## Results

Most frequently reported symptoms in the serious reports were (ranked order of symptoms occurring in more than 100 cases) were: Headache, Pain, Dizziness, Malaise, Fatigue, Paresthesia and Cognitive disorder.

The review identified 40 verified diagnoses of POTS.

Around 45% of the serious reports were received from non-health care professionals (consumers or lawyers) and among the serious consumer reports about half of them have been medically confirmed.

The table below shows the results of the categorization. In the table 5/5 refers to cases with a minimum of 1 symptom in each of the 5 main categories, 4/5 to patients with a minimum of 1 symptom in 4 of the 5 main categories etc. Many cases have more than one symptom in each main category.

| Category | 5/5 | 4/5 | 3/5 | 2/5 | 1/5 | 0/5 | Specific diagnosis | Total |
|---|---|---|---|---|---|---|---|---|
| Number | 74 | 51 | 45 | 32 | 60 | 24 | 77 | 363 |
| Percent of total | 20.4 | 14.0 | 12.3 | 8.8 | 16.5 | 6.6 | 21.2 | 99.8 |
| Percent of reports without a specific diagnosis (286) | 25.9 | 17.8 | 15.7 | 11.2 | 21.0 | 8.4 | - | 100.0 |

77 out of 363 serious cases reported a specific diagnosis such as MS, ITP, transverse myelitis, Schoenlein-Henoch etc. The remaining reports have been grouped based on how many categories they present symptoms in.

As deducted from the table **125 cases or 34.4 % of the 363** reported, have symptoms in 4 or 5 of the 5 main categories. If those 77 cases with a well-defined, specific diagnosis are excluded **125 cases of 286 or 43.7 %** have symptoms in 4 or 5 of the 5 main categories. In 62 of 117 cases reporting fatigue 53 % of those was associated with a social handicap, i.e. reduced ability to attend school or work or carry out daily activities**. For 17 % of all patients considerable impact on daily life is described.**

The most frequently occurring of the 8 additional categories were malaise, abdominal discomfort, autonomic imbalance, infections and thermal dysregulation in that order. The table below lists how many cases with symptoms in 4 or 5 of the 5 main categories, that also had malaise, abdominal discomfort and thermal dysregulation. Autonomic imbalance and infections are not given, as they are less well defined and of many different kinds, respectively.

| Category | Malaise | | Abdominal discomfort | | Thermal dysregulation. | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| 5/5 | 55 | 74 | 48 | 65 | 41 | 55 |
| 4/5 | 26 | 51 | 17 | 33 | 6 | 12 |
| 4/5+5/5 | 81 | 65 | 65 | 52 | 47 | 38 |

## Discussion

This review reveals a significant increase in Denmark in post-marketing reporting of suspected serious ADRs to the HPV vaccine Gardasil® from 2013 an onwards, following a 4 year period (2009-2012) without remarkable findings and no particular reason for concern. The significant increase in reporting coincides with intensive media and public attention and is likely to be at least partly stimulated reporting.

The overall age distribution of reports in general corresponds to the age groups vaccinated. The age is in many cases higher than the general target population for vaccination (12 years), but corresponds to the large group of young women also vaccinated in Denmark though the national catch-up program.

A high percentage of the case reports were submitted by non-HCPs, but many of these lay reports were medically confirmed afterwards. Many of the case reports were very detailed and of good quality, whereas others lacked important information, e.g. information on time to onset. Based on the reports it is not possible to document a causal relation between the reported ADRs and HPV vaccination.

Review of the 363 serious adverse reaction reports received by the Danish Health and Medicines Authority shows that a considerable number of the cases report a combination of symptoms. Most of the symptoms was observed individually in clinical trials and are listed according to the product information, however the combination, the seriousness and duration seen in the cases is not at all in accordance with the listed safety profile for Gardasil®.

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.

The complex of symptoms observed does have similarity to the condition described in the literature as Chronic Fatigue Syndrome (CFS), Myalgic Encephalomyelitis (ME) and Systemic Exercise Intolerance Disease (SEID). For simplicity, the term CFS is used below.

The clinical description of CFS vary. Different agencies and scientific bodies have produced different guidelines to define the condition although with overlap of symptoms between descriptions. The most widely used criteria for CFS are probably the US Center for Disease Control (CDC) criteria published in 1994.

The CDC criteria specify, that the following criteria must be met:

Clinically evaluated, unexplained, persistent or relapsing chronic fatigue, that has not been lifelong, but has been present for at least 6 months, is not the result of ongoing exertion and is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, social or personal activities.

In addition 4 or more of the following symptoms: self reported impairment in short term memory or concentration severe enough to cause reduction in previous levels of activity, muscle pain, multi-joint pain, headaches of a new type, pattern or severity, unrefreshing sleep, post-exertional malaise for more than 24 hours, sore throat, tender cervical or axillary lymph nodes.

The Canadian criteria from 2003 require two or more neurological/cognitive manifestations and one or more symptoms from at least two of the categories autonomic, neuroendocrine and immune manifestations, in addition to fatigue and post exertional malaise or fatigue, chronic pain and sleep dysfunction. The duration must be a minimum of 6 months.

The 2007 criteria from National Institute for Health and Clinical Excellence (NICE) in England require fatigue, that is new, persistent or recurrent, not explained by other conditions and has resulted in substantial reduction in activity level characterized by post exertional malaise and/or fatigue. In addition one or more of the following symptoms: difficulty with sleeping, muscle and joint pain at multiple sites, headaches, painful not enlarged lymph nodes, sore throat, cognitive dysfunction, worsening of symptoms by physical or mental exertion, general malaise, dizziness or nausea and palpitations without identifiable heart problems. These criteria require symptoms to have been present for only 3 months in children and 4 months in adults.

The Institute of Medicine-IOM-in 2015 proposes the term SEID with 5 main symptoms, characterizing CFS: reduction or impairment to carry out normal daily acitivites accompanied by profound fatigue, post exertional malaise (after physical, cognitive or emotional efforts), unrefreshing sleep, cognitive impairment and orthostatic intolerance. Pain and abnormal immune function may also be present.

The varying quality and completeness of the reports as well as the differences regarding the diagnostic criteria and nomenclature for this condition does not however allow for identifying the syndrome observed as CFS/EM/SEID with certainty. There are also cases in the material that rather resemble Fibromyalgia or Regional Pain Syndrome. For the time being one might consider using the expression Chronic Fatigue Syndrome Like Illness or Chronic Fatigue Like Syndrome.

The occurrence of symptoms, and their worsening in relation to physical, mental and emotional exercise is described in some cases, but not in others and in many not commented on.

A subjective observation from reviewing the reports is that in some cases the succession of events is quite suggestive of a CFS like syndrome with relation to the vaccination, whereas there are others where it appears extremely unlikely. One might speculate that the syndrome observed could be caused by a number of different events like infections, physical and emotional trauma and possibly vaccinations.

A final clarification of whether this symptom complex is related to HPV vaccine will require further scientific research.

## Recommendations for assessments

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.

## Information from Uppsala Monitoring Centre regarding cases in Vigibase

The Danish Health and Medicines Agency (DHMA) requested a consultation with the WHO Collaborating Centre for International Drug Monitoring – Uppsala Monitoring Centre (UMC) for scientific advice regarding a signal for Postural Orthostatic Tachycardia Syndrome (POTS) and HPV vaccine which was identified in Denmark in 2013.

The UMC has provided a review with the aim to describe the adverse event profile for HPV vaccine using worldwide VigiBase data, specifically related to the safety concern of POTS and related symptomology, which have been reported with unexpectedly high proportion of serious adverse event reports from Denmark.

The description of the reports of POTS and the related syndromes of CRPS, CFS, PVFS, fibromyalgia reveal a large overlap between the different syndromes observed in the comparison of the top co-reported PTs (in other words, symptomatology): fatigue is reported in greater than 50% of subjects who co-report POTS (65 %), CFS (51 %), PVFS (63 %), and fibromyalgia (52 %). Headache is also reported in greater than 50 % of subjects who co-report POTS (71 %), CFS (50 %), and PVFS (52 %). Dizziness is also consistently highly reported amongst cases of POTS (61 %), CFS (36 %), and PVFS (44 %). While it is acknowledged that these symptoms can be non-specific and are commonly occuring events, it is noted that the reports of POTS, CFS and PVFS from which these events arose have been largely classified as serious reports (POTS 80 %, CFS 78 %, PVFS 89 %) implying the need for hospitalisation and/or resulting in disability or interruption of normal function.

Geographic differences, specifically within Europe, are noted in the reporting of POTS and other syndromes. A fairly consistent finding is that the majority of reports of POTS and other syndromes arise from the US (POTS 52 %, CFS 51 %, ME/PVFS 40 %). In contrast, DK represents 38 % of reports of POTS and the UK represents only 4.8 %; however, the UK represents 26 % of the reports of CFS and DK represents only 6.4 %. Furthermore, the UK represents 39 % of reports of PVFS and DK represents only 4.8 %. Such differences could be speculated to represent coding variation between Denmark and other European countries (for example, UK): the same constellation of symptoms have been coded to different diagnositic PTs.

The total number of reports of POTS, CRPS, CFS and fibromyalgia have been increasing since 2012 with a marked increase between 2012 and 2013.

Comparison of the most commonly reported PTs and HLTs between the WHO database and the DK database show a consistency in the top reported adverse events. A comparison of HPV vaccines to all other vaccines in females, at both the PT and HLT term levels, showed a consistency between HPV reports in the different age groups and a difference to all other vaccines.

VigiPoint analysis has provided a comparison of HPV reports from Denmark to all other HPV reports and showed that Danish HPV reports more commonly are classified as serious than all other HPV reports; however, it is also noted that they are of a higher quality with more complete information. There were a number of PTs which appear more commonly in Danish reports; however, many of these were of a diagnostic nature (such as POTS, autonomic nervous system imbalance, orthostatic intolerance). There was no difference in the reports from Denmark and those from the rest of the world in those PT which describe symptomatology (such as headache, dizziness, activities of daily living impaired).

VigiPoint analysis also compared the characteristics of HPV reports to all other vaccine reports included in Vigibase which have been reported for the subset of females ages 9-25 years of age. The results show that a greater proportion of HPV reports are serious and describe events which are consistent with symptomatology included in the clinical case working definition for myalgic encephalitis / chronic fatigue syndrome (ME/CFS) as described by the Canadian ME/CFS guidelines in the Journal of Chronic Fatigue Syndrome in 2003. This finding is potentially significant because, although ME/CFS is more common in the adolescent female population, it is being reported more commonly with HPV vaccine in comparison to other vaccines in this same population.

In summary, the UMC review of VigiBase data suggests that there is an increasing trend in the number of HPV reports containing the PTs of POTS and related syndromes. Furthermore, there is the suggestion that a similar constellation of symptoms may have been labelled with different diagnostic labels depending on the country of origin. Also, the HPV case reports from Denmark are distinguished from those from other countries primarily by the fact that there is an increased amount of clinical information provided in the reports and that certain, specific diagnostic PTs are more commonly used; however, there is no difference between Danish HPV reports and all other HPV reports in the reporting of clinical relevant PTs describing symptomatology experienced by young women after HPV vaccination.

Finally, the data suggest that there is an over-representation of serious case reports which describe a constellation of symptomatology and subsequent medical evaluation potentially consistent with a chronic fatigue – like syndrome which may be specific to HPV vaccines.

The full report from UMC can be found in Appendix 2.

## Information from Japanese Ministry of Health, Labour and Welfare

Much of the initial concerns regarding HPV-vaccination came from CRPS cases as well as publications originating in Japan. The Japanese authorities suspended the active recommendation for HPV-vaccination in the public immunization program in 2013.

The Danish Health and Medicines Authority met with the Japanese Ministry of Health, Labour and Welfare in May 2015 in order to gain further knowledge of the current situation in Japan.

The bivalent as well as the quadrivalent HPV-vaccine are approved and have been used in Japan. The bivalent vaccine Cervarix® is the most used and the number of adverse reactions reported for the vaccines are proportional to the usage.

Since the suspension of the vaccine recommendation, the vaccine coverage has fallen dramatically to below 5% although the vaccines are still available and reimbursed.

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.

As in Denmark no firm conclusions could be drawn regarding the association between vaccination and symptoms based on the Japanese experiences, and further knowledge and conduction of studies in the area were considered a key way forward by the Japanese authorities.

## Further information to be obtained from registries in Denmark

Information in ADR reports is based on the data submitted actively by the reporting physician or consumer. In order to obtain more detailed information on the individual ADR cases, work is currently ongoing to collect information from the Danish registries for hospital admissions, diagnoses and GP visits.

Data from the registries can potentially reveal additional information regarding diagnoses, risk factors for reactions or alternative explanations for the symptoms described in the ADR reports.

## Summary and conclusions.

This report provides an overview of post-marketing safety experiences with the HPV vaccines, in terms of a description of data retrieved form the Danish, the Japanese and the WHO databases. Furthermore the most recent literature publications are quoted.

The main observations and interpretations are the following:

The introduction of the HPV vaccines in the publicly funded vaccination program did not give rise to safety concerns during the first 4 years.

From 2013 and onwards an increase in ADR reports have been noted in Denmark (exclusively in relation to use of Gardasil®, the most prominent feature being POTS) and Japan (primarily in relation to use of Cervarix®, the most prominent feature being CRPS).

The evolving safety concern has had impact on the vaccination coverage, which is declining.

Review of the 363 serious reports submitted to the Danish Pharmacovigilance Database for HPV-vaccines shows that a large proportion of the reports (34-43%) describe a symptom complex of headache, pain, fatigue, circulatory symptoms and neurological symptoms. In most cases the patients are left undiagnosed. In some cases the patients fulfill criteria for POTS. Several patients are severely physically and socially incapacitated for months / years.

The disease diagnose encompassing most of the symptoms could be a CFS-like condition. Classification is hampered though by lack of international consensus with regard to diagnostic criteria for CFS (and other syndromes).

The review highlights the necessity to evaluate (combinations of) symptoms rather than only performing separate evaluation of individual diagnoses.

Controlled trials or post-marketing epidemiology studies have not found evidence of any new or unexpected safety issues for the HPV-vaccines. However, the duration of proactive safety follow-up in the clinical trials might not have been adequate to detect the onset of symptoms. It should also be noted that post-marketing studies often rely on disease registries, and that many patients are left undiagnosed, and therefore will not appear in the registries.

Evaluation of data from WHO shows that although the number of cases for POTS is very high in Denmark, compared to the rest of the world, the symptom patterns seen in the Danish dataset is similar to reports submitted from many other countries.

A potential explanation for the huge geographic variation in the observed reporting pattern could be that similar combinations of symptoms could lead to different diagnoses depending on the country, culture or clinical setting.

Several case series have been published in recent years, and various hypotheses have been presented to explain the underlying pathophysiological mechanism, e.g. that symptoms are compatible with autonomic dysfunction, associated with vaccination due to provoked autoimmune phenomena. It is hypothesized that the dysautonomia is caused by small fiber neuropathy, but the mechanism is not clear.

The data provided in spontaneous reports cannot be used to provide evidence for causal relationship between symptoms and vaccination. It is therefore highly important to consider the possibilities for further studies to evaluate any causal relationship with the vaccination.

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## Appendix 1: Legend to forms of symptoms registered

PTs leading to registration are that of the main heading and those others listed below under the heading. All PTs reported more than 10 times for the period covered are included as well as some others considered important.

### Symptoms and PTs included in the 5 main categories:

1. **Severe fatigue**

Fatigue: asthenia, fatigue extreme, fatigue (when described as severe in narrative), lethargy

Muscular weakness: muscle fatigue, physical disability, wheelchair user

Considerable impact on daily life: School or work attendance <30% for min. 3 months, activity of daily living impaired, disability

2. **Neurological symptoms**

Paraestesia: sensory disturbance, hypoaestesia, hyperaestesia, burning sensation, dysaestesia, sensory loss, hypersensitivity, neurological disorder

Paralysis: paresis, hemiplegia, hemiparesis, facial nerve palsy

Convulsions: epilepsy, grand mal epilepsy, petit mal epilepsy, seizure, convulsion, febrile convulsion, cataplexia (when not combined with narcolepsy)

Involuntary movements: muscle spasms, muscle stiffness, muscle twitching, tremor, myoclonia, involuntary muscle contraction, tremor, tics, dyskinesia, clumsiness, gait disturbance, balance disorder, movement disorder, speech disorder, dyslalia, aphasia, eylid twitching, ataxia, dystonia, dystasia , coordination abnormal , eye movement disorder, joint lock

Visual impairment: vision blurred, visual acuity reduced, diplopia, visual field defect, photophobia, visual field defect, eye pain, ocular discomfort, papillary oedema, transient blindness, sudden blindness, eyelid oedema, eye inflammation. (eylid oedema and eye inflammation are included under visual impairment as they in the reports are often accompanied by complaints of difficult vision, which could be an independent symptom or secondary to the oedema/inflammation. No case, however, has been categorized as having neurologic symptoms on the bases of these symptoms alone).

Hearing impaired: hyperacusis, hypacusis, tinnitus,ear pain, ear discomfort, deafness

Cognitive disorder: disturbance in attention, memory impairment, confusional state, amnesia

Mood changes: anxiety, mood swings, depression, depressed mood, feels abnormal, restlessness, stress. (Mood changes have been characterized as neurologic symptoms as they in the narratives are often describes as “unexplained” without relation to other symptoms, but of course they could also be secondary in character. No case, however, has been classified as having neurologic symptoms on the basis of mood changes alone).

Sleep disorder: insomnia, hypersomnia, somnolence, poor quality sleep

3. **Circulatory symptoms**

Palpitations

Dyspnoea: difficulty breathing, fast breathing

Presyncope: orthostatic hypotension, hypotension, blood pressure decreased

Tacycardia: increased heart rate

Dizziness: vertigo

Syncope: loss of consciousness, fall

POTS: registered when fulfilling official, published POTs criteria

Orthostatic intolerance: registered when symptoms occur in upright position and are relieved when lying down

4. **Pain**

Pain: myalgia, arthralgia, pain in extremity, musculosceletal pain, back pain, neck pain, pain in jaw, allodynia, neuralgia, chest pain, chest discomfort, bone pain, orpharyngeal pain.

(does not include hedache, migraine, arthritis, pain at injection site, abdominal pain, bladder pain, dysuria).

5. **Headache**

Headache: head discomfort

Migraine: migraine with aura

### Symptoms and PTs included in the 8 additional categories:

1. **Autonomic imbalance**: registered when Compass-51 is judged positive
2. **Abdominal discomfort**: abdominal pain (upper, lower), abdominal distension, constipation, diarrhoea, change of bowel habits, gasto-intestinal irritation, gasto- intestinal migraine
3. **Urinary tract symptoms:** dysuria, pollakisuria, urinary incontinence, urinary retention, bladder disorder, bladder pain, blood in urine present. (excluded cystitis)
4. **Allergy**

**Allergy after vaccination:** new or worsened symptoms after vaccination of: asthma, urticaria, eczema, allergic rhinitis, rash, erythema, pruritus, erythema nodosum**,** angio-oedema

**Anaphylaxis:** anaphylactic shock

5. **Infections**

**Infection**: cough, pneumonia, lymphadenopathy, cystitis, sinusitis, oral mucosa blisters, otitis, influenza like illness

**Recurrent infection**

**Fever:** pyrexia

6. **Menstrual disorder**: dysmenorrhea, metrorhagia, menorrhagia, menstruation irregular
7. **Thermal dysregulation;** feeling cold, cold sweat, peripheral coldness, body temperature decreased, body temperature fluctuation,, sweating
8. **Malaise**: nausea, vomiting

**Specific diagnosis**: when a specific diagnosis is listed (f.x. MS) the various symptoms already explained by the specific diagnosis have not been listed.

**Others***:* here are other concomitant diagnoses listed, that do not explain the symptoms observed and listed

**Explanation for categories:**

no/5 indicates the number of categories with at least one symptom reported within the category, for the 5 categories: severe fatigue, neurologic symptoms, circulatory symptoms, pain and headache.

no/8 indicates the number of categories with at least one symptom reported within the category for the remaining 8 categories: autonomic dysbalance, abdominal discomfort, urinary tract symptoms, allergy, infections, menstrual disorder, thermal dysregulation and malaise.

## Appendix 2: Information from Uppsala Monitoring Centre regarding cases in VigiBase®

The Danish Health and Medicines Agency (DHMA) requested a consultation with the WHO Collaborating Centre for International Drug Monitoring – Uppsala Monitoring Centre (UMC) for scientific advice regarding a signal for Postural Orthostatic Tachycardia Syndrome (POTS) and HPV vaccine which was identified in Denmark in 2013.

According to the invitation letter,

"Since POTS is a rare and difficult diagnosis to give, we are particularly interested in identification of cases in the WHO database that could be related to the same type of reactions as seen in the POTS cases based on symptoms of autonomic dysfunction rather than only on a specific diagnosis. We will be grateful to have the expert advice and collaboration of WHO on this issue."

The aim of this review therefore was to describe the adverse event profile for HPV vaccine using worldwide VigiBase data, specifically as it relates to the safety concern of POTS and related symptomalogy which have been reported from the unexpectedly high proportion of serious adverse event reports from Denmark.

The data included in Vigibase has been presented in a number of ways in this report: 1) a description of the total number of reports of POTS and related clinical syndromes which have been received into the database, 2) a presentation of the most commonly reported PTs and HLTs from HPV reports classified as serious reports from both the VigiBase and the Danish database, and 3) comparative analyses of Danish HPV reports to all other HPV reports and of all HPV reports to all other vaccine reports and using vigiPoint methodology.

Please note that VigiBase can contain duplicate reports. It should be noted also that VigiBase includes both serious and nonserious reports. Also please note that not all reports come in to UMC/WHO VigiBase with a seriousness designation, and therefore, the analysis in part 2 (focus on serious reports) will have excluded some potential serious cases. Australia is the country of most importance, as they routinely use HPV vaccine in the vaccination program, but their reports do not include seriousness. Finally, it is noted that MedDRA coding terminology has been used throughout this document.

### 1. Description of all (serious, nonserious, seriousness not reported) HPV case reports included in VigiBase which include the MedDRA reported Preferred Terms (PT) of postural orthostatic tachycardia syndrome (POTS) and other similar syndromes

**POTS**

On a data retrieval performed on 03 August 2015, VigiBase included a total of 147 reports for POTS and HPV vaccines contained in VigiBase. For comparison, there were a total of 257 reports for POTS for all drugs. In other words, 57% of all reports of POTS have been reported with HPV vaccine.

One-hundred seventeen (80%) of the reports were considered serious.

The following table displays the top co-reported PTs in all POTS reports received for HPV vaccines.

Table 1. Top 10 co-reported PTs in POTS reports received for HPV vaccines.

| MedDRA PT / PT group | Number of reports |
|---|---|

| | |
|---|---|
| Headache | 104 (71%) |
| Fatigue | 95 (65%) |
| Syncope | 92 (63%) |
| Dizziness | 89 (61%) |
| Pain | 70 (48%) |
| Nausea | 62 (42%) |
| Palpitations | 52 (35%) |
| Abdominal pain | 51 (35%) |
| Autonomic nervous system imbalance | 45 (31%) |
| Orthostatic intolerance | 41 (28%) |

Please note: The following applies to the above table and all other similar tables in this report.

The headache PT group includes the all PTs including the terms headache and migraine.

The dizziness PT group includes the PTs of dizziness and dizziness postural.

The abdominal pain PT group includes the PTs of abdominal pain, abdominal pain upper and abdominal pain lower.

The syncope PT group includes the PTs of syncope and presyncope.

There is a concern that the constellation of symptoms observed in subjects with POTS has been potentially coded to different "diagnosis-type" PTs given the relative unfamiliarity of the diagnosis of POTS outside of the cardiology/neurology practice, the presence of other syndromes with similar and overlapping symptoms, and also potential geographical coding differences. Therefore, a number of other PTs were reviewed in VigiBase: complex regional pain syndrome (CRPS), chronic fatigue syndrome (CFS), myalgic encephalomyelitis (ME/PVFS), and fibromyalgia (FM).

**Complex Regional Pain Syndrome**

On a data retrieval performed on 03 August 2015, VigiBase included a total of 94 reports for CRPS and HPV vaccines contained in Vigibase. For comparison, there are a total of 677 reports for CRPS for all drugs. In other words, 14% of all reports of CRPS have been reported with HPV vaccine.

Sixty-five (69%) of the reports were considered serious. Twenty-six of the reports were considered non-serious. Three reports had no seriousness reported.

The following table displays the top co-reported PTs in all CRPS reports received for HPV vaccines.

Table 2. Top 10 co-reported PTs in CRPS reports received for HPV vaccines.

| **MedDRA PT / PT group** | **Number of reports** |
|---|---|
| Pain | 41 (44%) |
| Pain in extremity | 41 (44%) |
| Headache | 32 (34%) |
| Arthralgia | 28 (30%) |
| Gait disturbance | 26 (28%) |
| Hypoaesthesia | 25 (27%) |
| Muscular weakness | 22 (23%) |
| Nausea | 16 (17%) |
| Abdominal pain | 15 (16%) |

| | |
|---|---|
| Dizziness | 15 (16%) |

**Chronic fatigue syndrome**

On a data retrieval performed on 03 August 2015, VigiBase included a total of 94 reports for chronic fatigue syndrome (CFS) and HPV vaccines contained in VigiBase. For comparison, there were a total of 809 reports for CFS for all drugs. In other words, 12% of all reports of CFS have been reported with HPV vaccine.

Six (6.4%) of these reports also reported the PT of POTS; 3 of these reports were from the USA and 3 were from the UK.

Seventy-three (78%) of the reports were considered serious. Sixteen of the reports were considered non-serious. Five reports had no seriousness reported.

The following table displays the top co-reported PTs in all CFS reports received for HPV vaccines.

Table 3. Top 10 co-reported PTs in CFS reports received for HPV vaccines.

| MedDRA PT / PT group | Number of reports |
|---|---|
| Fatigue | 48 (51%) |
| Headache | 47 (50%) |
| Dizziness | 34 (36%) |
| Arthralgia | 33 (35%) |
| Nausea | 30 (32%) |
| Activities of daily living impaired | 27 (29%) |
| Post-viral fatigue syndrome | 25 (27%) |
| Malaise | 25 (27%) |
| Pain | 24 (26%) |
| Abdominal pain | 23 (24%) |

**Myalgic encephalomyelitis (MedDRA PT = post viral fatigue syndrome)**

On a data retrieval performed on 03 August 2015, VigiBase included a total of 62 reports for myalgic encephalitis / post viral fatigue syndrome (ME/PVFS) and HPV vaccines contained in VigiBase. For comparison, there are a total of 396 reports for ME/PVFS for all drugs. In other words, 16% of all reports of ME/PVFS have been reported with HPV vaccine.

Five (8.0%) of these reports also reported the PT of POTS; 3 of these reports were from the UK, 1 from Denmark and 1 from the UK.

Fifty-five (89%) of the reports were considered serious. Five of the reports were considered non-serious. Two reports had no seriousness reported.

The following table displays the top co-reported PTs in all ME/PVFS reports received for HPV vaccines.

Table 4. Top 10 co-reported PTs in ME/PVFS reports received for HPV vaccines.

| MedDRA PT / PT group | Number of reports |
|---|---|

| | |
|---|---|
| Fatigue | 39 (63%) |
| Headache | 32 (52%) |
| Dizziness | 27 (44%) |
| Chronic fatigue syndrome | 25 (40%) |
| Malaise | 21 (34%) |
| Nausea | 20 (32%) |
| Asthenia | 19 (31%) |
| Arthralgia | 17 (27%) |
| Abdominal pain | 16 (26%) |
| Syncope | 15 (24%) |

**Fibromyalgia**

On a data retrieval on performed 03 August 2015, VigiBase included a total of 87 reports for fibromyalgia (FM) and HPV vaccines contained in VigiBase. For comparison, there are a total of 6297 reports for FM for all drugs. In other words, 1.4% of all reports of FM have been reported with HPV vaccine.

Three (3.4%) of these reports also reported the PT of POTS; all three of these reports came from Denmark.

Sixty-four (74%) of the reports were considered serious. Twenty-two of the reports were considered non-serious. One report had no seriousness reported.

The following table displays the top co-reported PTs in all FM reports received for HPV vaccines.

Table 6. Top 10 co-reported PTs in FM reports received for HPV vaccines.

| MedDRA PT / PT group | Number of reports |
|---|---|
| Pain | 51 (59%) |
| Fatigue | 45 (52%) |
| Arthralgia | 36 (41%) |
| Headache | 34 (39%) |
| Dizziness | 25 (29%) |
| Abdominal pain | 25 (29%) |
| Insomnia | 24 (29%) |
| Activities of daily living impaired | 22 (25%) |
| Nausea | 21 (24%) |
| Myalgia | 20 (23%) |

**Geographic distribution of reports of POTS and related syndromes**

The following table displays the countries from which all reports of POTS and each of the related syndromes have originated. The data reveal that the largest proportion of reports for all of the syndromes come from the US. However, the second largest proportion of reports for each syndrome varies between several different countries: 38% of POTS reports come from Denmark, 26% of CRPS reports come from Japan, 26% of CFS reports and 39% of ME/PVFS come from UK . These data suggest that different diagnostic labels could be being used in different countries to describe a similar constellation of symptoms.

Table 6. Geographic distribution of reports of POTS and related syndromes

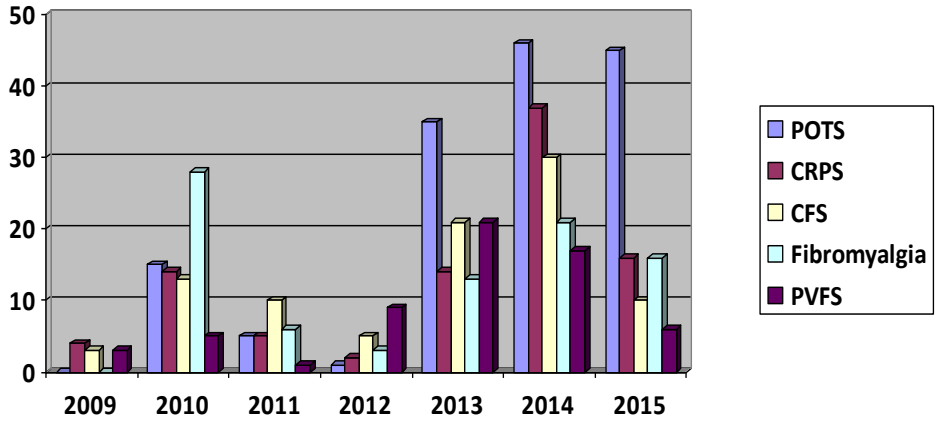
| Country | POTS | CRPS | CFS | ME/PVFS | FM |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| United States | 76 (52%) | 50 (53%) | 48 (51%) | 25 (40%) | 61 (70%) |
| | | | | | |
| Denmark | 56 (38%) | 2 (2.1%) | 6 (6.4%) | 3 (4.8%) | 11 (12.6%) |
| United Kingdom | 7 (4.8%) | 7 (7.4%) | 25 (26%) | 24 (39%) | 1 (1.1%) |
| Ireland | | 1 (1.1%) | 3 (3.2%) | 3 (4.8%) | 1 (1.1%) |
| Norway | | | 1 (1.1%) | 4 (6.4%) | |
| Sweden | 1 (0.7%) | | | 1 (1.6%) | |
| Germany | 3 (2.0%) | 3 (3.2%) | 2 (2.1%) | | |
| France | | 1 (1.1%) | 1 (1.1%) | | 1 (1.1%) |
| Italy | | | | | 1 (1.1%) |
| Spain | | 2 (2.1%) | | | |
| Slovenia | | | | | 1 (1.1%) |
| Malta | | | | | 2 (2.3%) |
| | | | | | |
| Japan | 4 (2.7%) | 25 (26.6%) | 3 (3.2%) | | 7 (8.0%) |
| | | | | | |
| Australia | | 3 (3.2%) | 5 (5.3%) | 2 (3.2%) | 1 (1.1%) |
| | | | | | |
| **Total reports** | **147** | **94** | **94** | **62** | **87** |

**Temporal distribution of reports**

The following figure displays of the total number of reports in VigiBase (x-axis) for each of the clinical syndromes plotted over time (y-axis). 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. Furthermore, the number of POTS cases as of August 2015 are nearly equivalent to the total number of cases reported in the whole of 2014. 2010 stands out in the data with an increased number of cases compared to both 2009 and 2011; the reason for this is likely due to the receipt by the UMC of a large backlog of cases from the US FDA. This pattern is observed for all vaccines included in the database.

Figure 1. Temporal distribution of total number of reports of POTS and related syndromes (x- axis) over time, represented by year (y-axis)



## 2. Presentation of the most commonly reported PTs and HLTs from HPV reports from serious reports from both the Vigibase and the Danish database

The tables below are the product of a search request of the UMC by the Danish Health and Medicines Agency.

**Top 20 events (PT) from serious reports on HPV vaccines in WHO VigiBase (as of 02.06.2015) versus the Danish database of adverse reactions (as of 27.05.2015):**

| HPV vaccines | | | |
|---|---|---|---|
| VigiBase | | DK | |
| **Number of reports** | **MedDRA PT** | **MedDRA PT** | **Number of reports** |
| 2308 | Headache | HEADACHE | 229 |
| 1582 | Dizziness | FATIGUE | 217 |
| 1365 | Nausea | DIZZINESS | 212 |
| 1348 | Syncope | NAUSEA | 149 |
| 1247 | Pyrexia | ARTHRALGIA | 127 |
| 1201 | Fatigue | DISTURBANCE IN ATTENTION | 109 |
| 851 | Vomiting | SYNCOPE | 107 |
| 824 | Arthralgia | ABDOMINAL PAIN | 90 |
| 820 | Malaise | MYALGIA | 87 |
| 780 | Asthenia | PALPITATIONS | 87 |
| 762 | Pain | SENSORY DISTURBANCE | 87 |
| 758 | Pain in extremity | MUSCULAR WEAKNESS | 86 |
| 756 | Seizure | DYSPNOEA | 78 |
| 732 | Hypoaesthesia | PARAESTHESIA | 78 |
| 730 | Paraesthesia | MEMORY IMPAIRMENT | 75 |
| 706 | Dyspnoea | AUTONOMIC NERVOUS SYSTEM IMBALANCE | 67 |
| 687 | Loss of consciousness | VISUAL IMPAIRMENT | 67 |
| 671 | Abdominal pain | MUSCLE SPASMS | 65 |
| 644 | Muscular weakness | PAIN IN EXTREMITY | 62 |
| 584 | Myalgia | HYPOAESTHESIA | 61 |

**Top 20 events (PT) from serious reports on females age 12-17 years in VigiBase for HPV vaccines versus other vaccines (as of 09.06.2015):**

| HPV Vaccines, WHO, Females 12-17 years | | | All other vaccines, WHO, Females 12-17 years | |
|---|---|---|---|---|
| **Number of reports** | **MedDRA PT** | | **Number of reports** | **MedDRA PT** |
| 1540 | Headache | | 269 | Headache |
| 1066 | Dizziness | | 219 | Pyrexia |
| 998 | Syncope | | 143 | Nausea |
| 894 | Nausea | | 139 | Dizziness |
| 831 | Pyrexia | | 125 | Vomiting |
| 780 | Fatigue | | 120 | Syncope |
| 559 | Malaise | | 104 | Asthenia |
| 551 | Vomiting | | 104 | Paraesthesia |
| 531 | Arthralgia | | 88 | Dyspnoea |
| 526 | Asthenia | | 83 | Fatigue |
| 504 | Loss of consciousness | | 77 | Pain |
| 503 | Seizure | | 77 | Seizure |
| 460 | Pain in extremity | | 71 | Muscular weakness |
| 449 | Abdominal pain | | 68 | Pain in extremity |
| 438 | Hypoaesthesia | | 68 | Loss of consciousness |
| 433 | Pain | | 63 | Hypoaesthesia |
| 429 | Dyspnoea | | 62 | Arthralgia |
| 411 | Paraesthesia | | 62 | Myalgia |
| 409 | Muscular weakness | | 62 | Guillain-Barre syndrome |
| 336 | Myalgia | | 59 | Malaise |

**Top 20 events (PT) from serious reports on females age 18-44 years in WHO VigiBase for HPV vaccines versus other vaccines (as of 09.06.2015):**

| HPV Vaccines, WHO, Females 18-44 years | | | All other vaccines, WHO, Females 18-44 years | |
|---|---|---|---|---|
| **Number of reports** | **MedDRA PT** | | **Number of reports** | **MedDRA PT** |
| 459 | Headache | | 743 | Pyrexia |
| 355 | Dizziness | | 460 | Headache |
| 309 | Nausea | | 350 | Pain |
| 289 | Fatigue | | 317 | Injection site pain |
| 259 | Pyrexia | | 303 | Nausea |
| 246 | Paraesthesia | | 272 | Injection site erythema |
| 214 | Arthralgia | | 265 | Myalgia |
| 212 | Hypoaesthesia | | 242 | Arthralgia |
| 211 | Syncope | | 231 | Paraesthesia |
| 202 | Pain | | 229 | Dizziness |
| 196 | Pain in extremity | | 226 | Vomiting |
| 191 | Dyspnoea | | 223 | Dyspnoea |

| | | | | |
|---|---|---|---|---|
| 188 | Vomiting | | 220 | Chills |
| 178 | Myalgia | | 217 | Pain in extremity |
| 177 | Malaise | | 215 | Asthenia |
| 161 | Muscular weakness | | 213 | Cellulitis |
| 158 | Asthenia | | 208 | Malaise |
| 142 | Seizure | | 202 | Fatigue |
| 138 | Abdominal pain | | 187 | Injection site swelling |
| 112 | Exposure during pregnancy | | 179 | Erythema |

**Top 20 events (HLT) from serious reports on females age 9-18 years in the Danish database of adverse reactions for HPV vaccines versus other vaccines (as of 02.07.2015):**

| HPV vaccines, DK, Females 9-18 years | | All other vaccines, DK, Females 9-18 years | |
|---|---|---|---|
| **Number of reports** | **MedDRA HLT** | **Number of reports** | **MedDRA HLT** |
| 148 | Asthenic conditions | 9 | Febrile disorders |
| 141 | Headaches NEC | 8 | Nausea and vomiting symptoms |
| 121 | Neurological signs and symptoms NEC | 8 | Headaches NEC |
| 91 | Nausea and vomiting symptoms | 7 | Asthenic conditions |
| 90 | Disturbances in consciousness NEC | 5 | Neurological signs and symptoms NEC |
| 84 | Mental impairment (excl dementia and memory loss) | 5 | Visual disorders NEC |
| 83 | Gastrointestinal and abdominal pains (excl oral and throat) | 5 | Sensory abnormalities NEC |
| 74 | Joint related signs and symptoms | 4 | General signs and symptoms NEC |
| 66 | Pain and discomfort NEC | 4 | Disturbances in consciousness NEC |
| 52 | Cardiac signs and symptoms NEC | 4 | Lymphatic system disorders NEC |
| 52 | Paraesthesias and dysaesthesias | 4 | Mental impairment (excl dementia and memory loss) |
| 51 | Visual disorders NEC | 3 | Purpura and related conditions |
| 50 | Musculoskeletal and connective tissue pain and discomfort | 3 | Pain and discomfort NEC |
| 49 | Breathing abnormalities | 3 | Muscle weakness conditions |
| 47 | Muscle related signs and symptoms NEC | 3 | Gastrointestinal and abdominal pains (excl oral and throat) |
| 47 | Muscle weakness conditions | 3 | Autonomic nervous system disorders |
| 45 | Muscle pains | 3 | Feelings and sensations NEC |
| 43 | Sensory abnormalities NEC | 3 | Musculoskeletal and connective tissue pain and discomfort |
| 43 | Memory loss (excl dementia) | 3 | Paraesthesias and dysaesthesias |
| 38 | Rate and rhythm disorders NEC | 2 | Seizures and seizure disorders NEC |

**Top 20 events (HLT) from serious reports on females age 19-41 years in the Danish database of adverse reactions for HPV vaccines versus other vaccines (as of 02.07.2015):**

| HPV vaccines, DK, Females 19-41 years | All other vaccines, DK, Females 19-41 years |
|---|---|

| Number of reports | MedDRA HLT | Number of reports | MedDRA HLT |
|---|---|---|---|
| 116 | Neurological signs and symptoms NEC | 12 | Febrile disorders |
| 109 | Asthenic conditions | 11 | General signs and symptoms NEC |
| 108 | Headaches NEC | 11 | Asthenic conditions |
| 81 | Nausea and vomiting symptoms | 10 | Injection site reactions |
| 77 | Paraesthesias and dysaesthesias | 9 | Headaches NEC |
| 65 | Musculoskeletal and connective tissue pain and discomfort | 8 | Musculoskeletal and connective tissue pain and discomfort |
| 61 | Sensory abnormalities NEC | 8 | Paraesthesias and dysaesthesias |
| 59 | Joint related signs and symptoms | 7 | Neurological signs and symptoms NEC |
| 59 | Mental impairment (excl dementia and memory loss) | 7 | Urticarias |
| 57 | Visual disorders NEC | 7 | Gastrointestinal and abdominal pains (excl oral and throat) |
| 54 | Muscle weakness conditions | 7 | Exposures associated with pregnancy, delivery and lactation |
| 53 | Muscle pains | 6 | Anaphylactic responses |
| 53 | Memory loss (excl dementia) | 6 | Sensory abnormalities NEC |
| 48 | Muscle related signs and symptoms NEC | 5 | Disturbances in consciousness NEC |
| 47 | Gastrointestinal and abdominal pains (excl oral and throat) | 5 | Muscle weakness conditions |
| 45 | Cardiac signs and symptoms NEC | 5 | Mental impairment (excl dementia and memory loss) |
| 43 | Disturbances in consciousness NEC | 4 | Nausea and vomiting symptoms |
| 41 | Breathing abnormalities | 4 | Allergic conditions NEC |
| 41 | Pain and discomfort NEC | 4 | Coordination and balance disturbances |
| 34 | Apocrine and eccrine gland disorders | 4 | Joint related signs and symptoms |

## 3. Comparative analyses of HPV reports to all other vaccine reports and of Danish HPV reports to all other HPV reports using vigiPoint methodology

vigiPoint is a methodology by which two subsets (or more) of case reports from VigiBase can be compared on case report characteristics. vigiPoint has here been used to compare of the characteristics for case safety reports describing adverse events with HPV vaccines in females aged 9-25 years. The first comparison was made between the subset of Danish HPV reports to all other HPV reports (worldwide) to investigate if there are differences in the case report characteristics which could explain the Danish ”signal”. The second comparison was made between all HPV reports and all other vaccine reports in females aged 9-25 to investigate if this constellation of symptomatology is specific for HPV vaccines and thus may not be simply explained by the background incidence of this diagnosis in the adolescent, female population.

The analytical framework is called vigiPoint is an analytical framework which relies on the logarithm of shrunk OE ratios to highlight and rank characteristic reporting patterns [1]. It should be noted that the data used in this investigation includes data received into VigiBase up until 1st of January 2015. This data lock point is different from the VigiBase review of POTS and related PTs as provided earlier in this report. Furthermore, the date precedes the media attention generated by the announcement of the Referral

procedure by the EMA in mid July 2015. The entire data set has not been reproduced in this report; only those results with statistical significance are reported. There is mention of clinically relevant results which did not reach the statistical significance threshold (log OR 005 > 0.50) which was determined outside of this current clinical question.

Please observe that this data is as of yet unpublished. It has been accepted as a poster presentation at the annual meeting of the International Society of Pharmacovigilance in Prague, Czech Republic in October of 2015.

**Comparison of all HPV reports from Denmark to all other HPV vaccine reports in females, aged 9-25**

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.

A significantly greater proportion of HPV reports from the rest of the world included terms from the SOCs of General disorders and administration site conditions; Injury, poisoning and procedural complications, and Investigations. 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.

| **Report characteristic** | Number of HPV Reports | Number of other vaccine reports | Log OR | Log OR 005 | Log OR 095 | % of total HPV reports | % of total other vaccine reports |
|---|---|---|---|---|---|---|---|
| Good Report | 495 | 9642 | 4.67 | 4.50 | 4.84 | 90% | 21% |
| Dermatitis atopic | 49 | 12 | 3.40 | 2.85 | 3.87 | 9% | 0% |
| Lawyer | 42 | 12 | 3.15 | 2.56 | 3.65 | 8% | 0% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Autonomic nervous system imbalance | 35 | 41 | 2.87 | 2.23 | 3.41 | 6% | 0% |
| Orthostatic intolerance | 34 | 42 | 2.83 | 2.18 | 3.38 | 6% | 0% |
| Eczema | 34 | 78 | 2.73 | 2.07 | 3.27 | 6% | 0% |
| Sensory disturbance | 35 | 136 | 2.61 | 1.97 | 3.15 | 6% | 0% |
| Disturbance in attention | 37 | 211 | 2.51 | 1.88 | 3.03 | 7% | 0% |
| Postural orthostatic tachycardia syndrome | 24 | 58 | 2.35 | 1.58 | 2.98 | 4% | 0% |
| Memory impairment | 28 | 140 | 2.32 | 1.60 | 2.91 | 5% | 0% |
| Palpitations | 28 | 229 | 2.11 | 1.39 | 2.70 | 5% | 1% |
| Consumer/Non Health Professional | 100 | 1086 | 1.87 | 1.48 | 2.21 | 18% | 5% |
| Skin and subcutaneous tissue disorders | 244 | 8045 | 1.81 | 1.57 | 2.04 | 44% | 18% |
| Cognitive disorder | 14 | 40 | 1.80 | 0.82 | 2.55 | 3% | 0% |
| Physician | 438 | 11759 | 1.70 | 1.52 | 1.87 | 80% | 55% |
| Fatigue | 89 | 2271 | 1.68 | 1.28 | 2.05 | 16% | 5% |
| Infection | 13 | 72 | 1.62 | 0.61 | 2.40 | 2% | 0% |
| Visual impairment | 25 | 410 | 1.62 | 0.86 | 2.23 | 5% | 1% |
| Cardiac disorders | 44 | 982 | 1.60 | 1.02 | 2.09 | 8% | 2% |
| Influenza like illness | 21 | 352 | 1.51 | 0.69 | 2.17 | 4% | 1% |
| Muscle spasms | 22 | 403 | 1.47 | 0.67 | 2.12 | 4% | 1% |
| Arthralgia | 47 | 1543 | 1.20 | 0.64 | 1.67 | 9% | 3% |
| SeriousOrFatal | 199 | 8777 | 1.20 | 0.93 | 1.45 | 36% | 19% |
| | | | | | | | |
| General disorders and administration site conditions | 220 | 24717 | -0.83 | -1.09 | -0.59 | 40% | 55% |
| NonSerious | 350 | 36550 | -1.23 | -1.43 | -1.04 | 64% | 81% |
| Injury, poisoning and procedural complications | 21 | 4438 | -1.26 | -2.08 | -0.60 | 4% | 10% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Investigations | 37 | 8108 | -1.47 | -2.10 | -0.94 | 7% | 18% |
| Exposure during pregnancy | 2 | 1502 | -1.76 | -3.54 | -0.60 | 0% | 3% |
| Vaccination site pain | 0 | 1354 | -2.13 | -4.34 | -0.80 | 0% | 3% |
| Injection site pain | 13 | 6163 | -2.31 | -3.32 | -1.54 | 2% | 14% |
| Pharmacist | 0 | 1038 | -2.71 | -4.92 | -1.38 | 0% | 5% |
| Other Health Professional | 14 | 6129 | -3.52 | -4.49 | -2.76 | 3% | 29% |
| Other | 0 | 2207 | -3.76 | -5.97 | -2.42 | 0% | 10% |
| Bad Report | 54 | 35685 | -4.96 | -5.48 | -4.51 | 10% | 79% |
| Not Conv/Unspecified | 2 | 23825 | -6.45 | -8.23 | -5.29 | 0% | 53% |

**Comparison of all HPV reports to all other vaccine reports in females, aged 9-25**

This analysis has compared 45,876 reports for HPV vaccine with 79,678 reports for all other vaccines which were received from females between the ages of 9-25 years of age. The most frequent vaccines contained in the reports for "other vaccines" were hepatitis B vaccines (12,662 reports), meningococcal vaccines (11,587 reports), influenza vaccines (6,941 reports), varicella zoster vaccines (5690 reports), and MMR vaccines (5,465 reports).

A significantly increased proportion of HPV reports were classified as ***serious*** compared to other vaccine reports.

| **Seriousness** | Number of HPV Reports | Number of other vaccine reports | Log OR | Log OR 005 | Log OR 095 | % of total HPV reports | % of total other vaccine reports |
|---|---|---|---|---|---|---|---|
| SeriousOrFatal | 8976 | 7410 | 0.90 | 0.86 | 0.93 | 19.6% | 11.1% |
| | | | | | | | |
| NonSerious | 36900 | 59316 | -0.95 | -0.97 | -0.93 | 80.4% | 88.9% |

The ***countries*** reporting a significantly increased proportion of HPV reports compared to other vaccine reports were Malaysia, Italy, Japan, Denmark, and Australia. The countries reporting a significantly decreased proportion of HPV reports were Canada, the UK, Sweden, and France.

| **Country** | Number of HPV Reports | Number of other vaccine reports | Log OR | Log OR 005 | Log OR 095 | % of total HPV reports | % of total other vaccine reports |
|---|---|---|---|---|---|---|---|
| Malaysia | 5927 | 135 | 3.56 | 3.52 | 3.61 | 12.9% | 0.2% |
| Italy | 4622 | 1229 | 2.04 | 1.99 | 2.09 | 10.1% | 1.8% |
| Japan | 918 | 141 | 1.31 | 1.21 | 1.41 | 2.0% | 0.2% |
| Denmark | 549 | 210 | 0.74 | 0.62 | 0.86 | 1.2% | 0.3% |
| Australia | 2420 | 1930 | 0.72 | 0.65 | 0.78 | 5.3% | 2.9% |
| | | | | | | | |
| New Zealand | 449 | 1660 | -0.83 | -0.96 | -0.71 | 1.0% | 2.5% |
| France | 620 | 2792 | -1.17 | -1.29 | -1.06 | 1.4% | 4.2% |
| Sweden | 585 | 3236 | -1.41 | -1.52 | -1.29 | 1.3% | 4.8% |
| United Kingdom | 1048 | 8096 | -2.14 | -2.24 | -2.05 | 2.3% | 12.1% |
| Canada | 43 | 6034 | -3.32 | -3.49 | -3.16 | 0.1% | 9.0% |

We are currently investigating the explanation for the geographical differences. It is noted that Japan and Denmark, those countries reporting a high incidence of serious adverse events, are over-represented in the HPV reports. However, there are number of countries which have incorporated HPV into their national vaccination programmes which are under-represented in the HPV reports (the UK, Canada, and Sweden). The differences may be related to the status of the HPV vaccine in the routine childhood vaccination programs, the vaccination coverage or vaccine uptake, and/or potentially administrative issues (for example, there can be a delay in the transfer of adverse event reports from national reporting centers to UMC, and these delays may vary by country ).

The ***MedDRA System Organ Classes (SOC)*** most over-represented in HPV reports were the Reproductive system and breast disorders SOC, the Investigations SOC, and Surgical and medical procedures. The SOC most under-represented in the HPV reports were Immune system disorders, Infections and infestations,

and Skin and subcutaneous disorders. Both the Nervous system disorders and Psychiatric disorders SOC were also over-represented in the HPV reports.

| **MedDRA SOC** | Number of HPV Reports | Number of other vaccine reports | Log OR | Log OR 005 | Log OR 095 | % of total HPV reports | % of total other vaccine reports |
|---|---|---|---|---|---|---|---|
| Reproductive system and breast disorders | 1433 | 291 | 1.53 | 1.45 | 1.62 | 3.1% | 0.4% |
| Investigations | 8145 | 5025 | 1.28 | 1.24 | 1.32 | 17.8% | 7.5% |
| Surgical and medical procedures | 1164 | 396 | 1.16 | 1.07 | 1.25 | 2.5% | 0.6% |
| Social circumstances | 795 | 312 | 0.90 | 0.80 | 1.01 | 1.7% | 0.5% |
| Injury, poisoning and procedural complications | 4459 | 3484 | 0.84 | 0.79 | 0.90 | 9.7% | 5.2% |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 440 | 73 | 0.82 | 0.69 | 0.94 | 1.0% | 0.1% |
| Nervous system disorders | 20963 | 22921 | 0.67 | 0.64 | 0.69 | 45.7% | 34.4% |
| Psychiatric disorders | 2382 | 2151 | 0.57 | 0.50 | 0.64 | 5.2% | 3.2% |
| | | | | | | | |
| Skin and subcutaneous tissue disorders | 8289 | 18476 | -0.76 | -0.80 | -0.72 | 18.1% | 27.7% |
| Infections and infestations | 2434 | 6252 | -0.77 | -0.84 | -0.71 | 5.3% | 9.4% |
| Immune system disorders | 898 | 3032 | -0.94 | -1.04 | -0.84 | 2.0% | 4.5% |

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.

| **MedDRA HLT** | Number of HPV Reports | Number of other vaccine reports | Log OR | Log OR 005 | Log OR 095 | % of total HPV reports | % of total other vaccine reports |
|---|---|---|---|---|---|---|---|
| Imaging procedures NEC | 2277 | 552 | 1.73 | 1.66 | 1.80 | 5.0% | 0.8% |
| Vaccination site reactions | 2237 | 564 | 1.70 | 1.63 | 1.77 | 4.9% | 0.8% |
| Exposures associated with pregnancy, delivery and lactation | 1612 | 655 | 1.21 | 1.12 | 1.29 | 3.5% | 1.0% |
| **Neurologic diagnostic procedures** | 1116 | 354 | **1.17** | 1.08 | 1.27 | 2.4% | 0.5% |
| **Disturbances in consciousness NEC** | 7268 | 4936 | **1.12** | 1.08 | 1.17 | 15.8% | 7.4% |
| Reproductive hormone analyses | 830 | 206 | 1.11 | 1.00 | 1.21 | 1.8% | 0.3% |
| **Muscle weakness conditions** | 1260 | 525 | **1.08** | 0.99 | 1.17 | 2.7% | 0.8% |
| Investigations NEC | 1810 | 1068 | 0.95 | 0.87 | 1.03 | 3.9% | 1.6% |
| **Disability issues** | 709 | 233 | **0.92** | 0.81 | 1.03 | 1.5% | 0.3% |
| Seizures and seizure disorders NEC | 2086 | 1327 | 0.92 | 0.84 | 0.99 | 4.5% | 2.0% |
| Menstruation and uterine bleeding NEC | 494 | 71 | 0.91 | 0.79 | 1.03 | 1.1% | 0.1% |
| Non-site specific injuries NEC | 1120 | 574 | 0.90 | 0.80 | 0.99 | 2.4% | 0.9% |
| **Central nervous system imaging procedures** | 640 | 222 | **0.85** | 0.74 | 0.96 | 1.4% | 0.3% |
| Reproductive organ and breast histopathology procedures | 376 | 7 | 0.85 | 0.72 | 0.97 | 0.8% | 0.0% |
| Blood counts NEC | 774 | 351 | 0.82 | 0.71 | 0.93 | 1.7% | 0.5% |
| Site specific injuries NEC | 524 | 150 | 0.81 | 0.69 | 0.93 | 1.1% | 0.2% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **ECG investigations** | 578 | 201 | **0.80** | 0.68 | 0.91 | 1.3% | 0.3% |
| Protein analyses NEC | 575 | 204 | 0.79 | 0.67 | 0.90 | 1.3% | 0.3% |
| Autoimmunity analyses | 523 | 184 | 0.75 | 0.63 | 0.87 | 1.1% | 0.3% |
| Bacteria identification and serology (excl mycobacteria) | 615 | 302 | 0.69 | 0.58 | 0.80 | 1.3% | 0.5% |
| **Neurological signs and symptoms NEC** | 7315 | 6769 | **0.69** | 0.65 | 0.73 | 15.9% | 10.1% |
| Physical examination procedures and organ system status | 1430 | 1051 | 0.69 | 0.60 | 0.78 | 3.1% | 1.6% |
| Virus identification and serology | 765 | 446 | 0.68 | 0.57 | 0.79 | 1.7% | 0.7% |
| **Gastrointestinal and abdominal imaging procedures** | 332 | 52 | **0.68** | 0.54 | 0.81 | 0.7% | 0.1% |
| **Vascular tests NEC (incl blood pressure)** | 603 | 305 | 0.67 | 0.56 | 0.78 | 1.3% | 0.5% |
| Therapeutic and nontherapeutic responses | 1834 | 1468 | 0.66 | 0.58 | 0.74 | 4.0% | 2.2% |
| | | | | | | | |
| Erythemas | 1493 | 3590 | -0.61 | -0.70 | -0.53 | 3.3% | 5.4% |
| Pruritus NEC | 1856 | 4438 | -0.64 | -0.71 | -0.56 | 4.0% | 6.7% |
| Dermal and epidermal conditions NEC | 763 | 2065 | -0.64 | -0.74 | -0.53 | 1.7% | 3.1% |
| Febrile disorders | 4388 | 9904 | -0.67 | -0.72 | -0.61 | 9.6% | 14.8% |
| Bacterial infections NEC | 214 | 884 | -0.67 | -0.82 | -0.53 | 0.5% | 1.3% |
| Rashes, eruptions and exanthems NEC | 2413 | 6370 | -0.81 | -0.88 | -0.74 | 5.3% | 9.5% |
| Oedema NEC | 917 | 3029 | -0.92 | -1.02 | -0.82 | 2.0% | 4.5% |
| Non-site specific vascular disorders NEC | 32 | 826 | -1.07 | -1.25 | -0.91 | 0.1% | 1.2% |
| Allergic conditions NEC | 389 | 2241 | -1.27 | -1.40 | -1.14 | 0.8% | 3.4% |
| Infections NEC | 208 | 1842 | -1.40 | -1.54 | -1.26 | 0.5% | 2.8% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Application and instillation site reactions | 123 | 1930 | -1.65 | -1.80 | -1.50 | 0.3% | 2.9% |

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.

| **MedDRA HLT** | Number of HPV Reports | Number of other vaccine reports | Log OR | Log OR 005 | Log OR 095 | % of total HPV reports | % of total other vaccine reports |
|---|---|---|---|---|---|---|---|
| Haematological analyses NEC | 458 | 221 | 0.59 | 0.46 | 0.71 | 1.0% | 0.3% |
| White blood cell analyses | 613 | 383 | 0.57 | 0.46 | 0.69 | 1.3% | 0.6% |
| Urinalysis NEC | 490 | 262 | 0.57 | 0.45 | 0.69 | 1.1% | 0.4% |
| **Gastrointestinal and abdominal pains (excl oral and throat)** | 2139 | 1995 | **0.52** | 0.45 | 0.60 | 4.7% | 3.0% |
| **Migraine headaches** | 486 | 261 | **0.57** | 0.45 | 0.69 | 1.1% | 0.4% |
| Cardiac function diagnostic procedures | 282 | 57 | 0.57 | 0.43 | 0.71 | 0.6% | 0.1% |
| Menstruation with decreased bleeding | 250 | 27 | 0.57 | 0.43 | 0.71 | 0.5% | 0.0% |
| Red blood cell analyses | 347 | 133 | 0.55 | 0.42 | 0.68 | 0.8% | 0.2% |
| **Gait disturbances** | 698 | 506 | **0.52** | 0.41 | 0.63 | 1.5% | 0.8% |
| **Visual disorders NEC** | 1067 | 904 | 0**.51** | 0.41 | 0.60 | 2.3% | 1.4% |
| Skin neoplasms benign | 218 | 12 | 0.54 | 0.39 | 0.67 | 0.5% | 0.0% |
| Alopecias | 347 | 153 | 0.52 | 0.38 | 0.64 | 0.8% | 0.2% |
| **Muscle related signs and symptoms NEC** | 760 | 610 | **0.48** | 0.37 | 0.58 | 1.7% | 0.9% |
| Therapeutic procedures NEC | 363 | 180 | 0.50 | 0.37 | 0.63 | 0.8% | 0.3% |
| **Asthenic conditions** | 5626 | 6197 | **0.41** | 0.36 | 0.46 | 12.3% | 9.3% |
| Microbiology and serology tests NEC | 389 | 214 | 0.49 | 0.36 | 0.61 | 0.8% | 0.3% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Sensory abnormalities NEC** | 485 | 324 | **0.47** | 0.35 | 0.59 | 1.1% | 0.5% |
| Carbohydrate tolerance analyses (incl diabetes) | 354 | 180 | 0.48 | 0.35 | 0.61 | 0.8% | 0.3% |
| Skin injuries NEC | 369 | 199 | 0.48 | 0.34 | 0.60 | 0.8% | 0.3% |
| Ocular nerve and muscle disorders | 474 | 318 | 0.46 | 0.34 | 0.58 | 1.0% | 0.5% |
| **Memory loss (excl dementia)** | 336 | 168 | **0.47** | 0.34 | 0.60 | 0.7% | 0.3% |
| **Musculoskeletal and connective tissue pain and discomfort** | 2871 | 3058 | **0.40** | 0.33 | 0.46 | 6.3% | 4.6% |
| Inflammations | 319 | 151 | 0.47 | 0.33 | 0.60 | 0.7% | 0.2% |
| Metabolism tests NEC | 292 | 129 | 0.46 | 0.32 | 0.59 | 0.6% | 0.2% |
| Thyroid analyses | 214 | 44 | 0.46 | 0.31 | 0.60 | 0.5% | 0.1% |
| Cervix disorders NEC | 179 | 7 | 0.46 | 0.31 | 0.60 | 0.4% | 0.0% |
| Respiratory tract and thoracic imaging procedures | 302 | 159 | 0.42 | 0.28 | 0.55 | 0.7% | 0.2% |
| Platelet analyses | 258 | 109 | 0.43 | 0.28 | 0.56 | 0.6% | 0.2% |
| **Mental impairment (excl dementia and memory loss)** | 318 | 179 | **0.42** | 0.28 | 0.55 | 0.7% | 0.3% |
| **Musculoskeletal and connective tissue signs and symptoms NEC** | 749 | 681 | **0.39** | 0.28 | 0.49 | 1.6% | 1.0% |
| Tremor (excl congenital) | 944 | 911 | 0.38 | 0.28 | 0.47 | 2.1% | 1.4% |
| Site specific vascular disorders NEC | 1773 | 1899 | 0.35 | 0.27 | 0.43 | 3.9% | 2.8% |
| Mineral and electrolyte analyses | 241 | 103 | 0.40 | 0.26 | 0.54 | 0.5% | 0.2% |
| Pituitary analyses anterior | 200 | 56 | 0.41 | 0.26 | 0.55 | 0.4% | 0.1% |
| Papilloma viral infections | 153 | 3 | 0.41 | 0.25 | 0.56 | 0.3% | 0.0% |
| Induced abortions | 164 | 20 | 0.40 | 0.25 | 0.54 | 0.4% | 0.0% |

The ***MedDRA preferred terms (PT)*** most over-represented in HPV reports were vaccination site pain, loss of consciousness, exposure during pregnancy, presyncope, syncope, and muscular weakness. Also

significantly over-represented in the HPV reports were the PTs of activities of daily living impaired, computerised tomography normal, and magnetic resonance imaging normal.

The PTs most under-represented in HPV reports were application site reaction, injection site reaction, injection site inflammation, injection site hypersensitivity, and injection site oedema. Also significantly under-represented were maculopapular rash, rash and face oedema.

| **MedDRA PT** | Number of HPV Reports | Number of other vaccine reports | Log OR | Log OR 005 | Log OR 095 | % of total HPV reports | % of total other vaccine reports |
|---|---|---|---|---|---|---|---|
| Vaccination site pain | 1354 | 266 | 1.51 | 1.42 | 1.59 | 3.0% | 0.4% |
| Loss of consciousness | 2146 | 879 | 1.32 | 1.25 | 1.39 | 4.7% | 1.3% |
| Exposure during pregnancy | 1504 | 580 | 1.21 | 1.13 | 1.29 | 3.3% | 0.9% |
| Presyncope | 974 | 310 | 1.10 | 1.00 | 1.20 | 2.1% | 0.5% |
| Syncope | 4673 | 3003 | 1.10 | 1.04 | 1.15 | 10.2% | 4.5% |
| Muscular weakness | 1260 | 525 | 1.08 | 0.99 | 1.17 | 2.7% | 0.8% |
| Fall | 1039 | 386 | 1.06 | 0.96 | 1.15 | 2.3% | 0.6% |
| Injection site pain | 6176 | 4457 | 1.01 | 0.96 | 1.05 | 13.5% | 6.7% |
| Immediate post-injection reaction | 911 | 343 | 0.99 | 0.88 | 1.09 | 2.0% | 0.5% |
| Vaccine positive rechallenge | 502 | 67 | 0.93 | 0.81 | 1.05 | 1.1% | 0.1% |
| Vaccination site reaction | 470 | 79 | 0.86 | 0.73 | 0.98 | 1.0% | 0.1% |
| Computerised tomogram normal | 514 | 127 | 0.83 | 0.71 | 0.95 | 1.1% | 0.2% |
| Laboratory test normal | 501 | 137 | 0.80 | 0.68 | 0.92 | 1.1% | 0.2% |
| Activities of daily living impaired | 531 | 165 | 0.79 | 0.67 | 0.91 | 1.2% | 0.2% |
| Nuclear magnetic resonance imaging normal | 438 | 91 | 0.78 | 0.66 | 0.91 | 1.0% | 0.1% |
| Convulsion | 1645 | 1148 | 0.77 | 0.69 | 0.85 | 3.6% | 1.7% |
| Lethargy | 652 | 324 | 0.71 | 0.60 | 0.82 | 1.4% | 0.5% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Head injury | 435 | 130 | 0.71 | 0.58 | 0.83 | 0.9% | 0.2% |
| Blood test | 431 | 130 | 0.70 | 0.57 | 0.82 | 0.9% | 0.2% |
| Smear cervix abnormal | 277 | 1 | 0.68 | 0.54 | 0.81 | 0.6% | 0.0% |
| Vaccination site swelling | 389 | 106 | 0.67 | 0.54 | 0.80 | 0.8% | 0.2% |
| Laboratory test | 415 | 131 | 0.67 | 0.54 | 0.80 | 0.9% | 0.2% |
| Full blood count normal | 449 | 167 | 0.66 | 0.54 | 0.79 | 1.0% | 0.3% |
| Electroencephalogram normal | 309 | 41 | 0.66 | 0.52 | 0.79 | 0.7% | 0.1% |
| No reaction on previous exposure to drug | 321 | 57 | 0.65 | 0.51 | 0.78 | 0.7% | 0.1% |
| Injection site swelling | 2719 | 2413 | 0.61 | 0.55 | 0.68 | 5.9% | 3.6% |
| | | | | | | | |
| Chills | 626 | 1745 | -0.63 | -0.74 | -0.51 | 1.4% | 2.6% |
| Pyrexia | 4242 | 9794 | -0.70 | -0.75 | -0.64 | 9.2% | 14.7% |
| Cellulitis | 99 | 661 | -0.72 | -0.88 | -0.56 | 0.2% | 1.0% |
| Infection | 85 | 635 | -0.72 | -0.89 | -0.57 | 0.2% | 1.0% |
| Oedema | 130 | 766 | -0.75 | -0.91 | -0.60 | 0.3% | 1.1% |
| Face oedema | 87 | 702 | -0.79 | -0.96 | -0.64 | 0.2% | 1.1% |
| Injection site warmth | 344 | 1363 | -0.81 | -0.94 | -0.68 | 0.7% | 2.0% |
| Rash | 1788 | 4892 | -0.81 | -0.89 | -0.74 | 3.9% | 7.3% |
| Rash maculo-papular | 110 | 787 | -0.82 | -0.98 | -0.67 | 0.2% | 1.2% |
| Pruritus | 1333 | 3906 | -0.85 | -0.94 | -0.76 | 2.9% | 5.9% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Drug ineffective | 14 | 679 | -0.98 | -1.15 | -0.81 | 0.0% | 1.0% |
| Skin reaction | 48 | 789 | -0.99 | -1.16 | -0.83 | 0.1% | 1.2% |
| Vasodilatation | 9 | 793 | -1.11 | -1.29 | -0.94 | 0.0% | 1.2% |
| Injection site abscess | 12 | 935 | -1.24 | -1.41 | -1.07 | 0.0% | 1.4% |
| Hypersensitivity | 339 | 2127 | -1.30 | -1.43 | -1.17 | 0.7% | 3.2% |
| Injection site oedema | 81 | 1325 | -1.36 | -1.52 | -1.20 | 0.2% | 2.0% |
| Injection site hypersensitivity | 4 | 1196 | -1.49 | -1.66 | -1.32 | 0.0% | 1.8% |
| Injection site inflammation | 106 | 1607 | -1.49 | -1.65 | -1.34 | 0.2% | 2.4% |
| Injection site reaction | 400 | 3221 | -1.69 | -1.82 | -1.56 | 0.9% | 4.8% |
| Application site reaction | 33 | 1733 | -1.77 | -1.94 | -1.61 | 0.1% | 2.6% |

There were no statistically significant differences noted between the groups of reports for any specific diagnoses. Postural orthostatic tachycardia syndrome had been reported 82 times for HPV vaccine and 1 time for other vaccines (0.2% vs 0.0%), complex regional pain syndrome: 69 times for HPV vaccine and 16 times for other vaccines (0.2% vs 0.0%). autonomic nervous system imbalance: 76 times for HPV vaccine and 16 times for other vaccines (0.2% vs 0.0%), chronic fatigue syndrome: 65 for HPV vaccine and 30 times for other vaccines (0.1% vs 0.0%), fibromyalgia: 62 times for HPV vaccine and 39 times for other vaccines (0.1% vs 0.1%), post viral fatigue syndrome: 47 times and 53 times for other vaccines (0.1% and 0.1%) and finally autonomic nervous system imbalance: 76 times for HPV vaccine and 16 times for other vaccines (0.2% vs 0.0%).

## 4. Conclusions

This report has been prepared to describe the adverse event profile for HPV vaccine using worldwide VigiBase data, specifically as it relates to the safety concern of POTS and related symptomalogy which have been reported from the unexpectedly high proportion of serious adverse event reports from Denmark.

The description of the reports of POTS and the related syndromes of CRPS, CFS, PVFS, fibromyalgia reveal a number of potentially important findings. First, there is a large overlap between the different syndromes observed in the comparison of the top co-reported PTs (in other words, symptomatology): fatigue is

reported in greater than 50% of subjects who co-report POTS (65%), CFS (51%), PVFS (63%), and fibromyalgia (52%). Headache is also reported in greater than 50% of subjects who co-report POTS (71%), CFS (50%), and PVFS (52%). Dizziness is an important PT which is also consistently highly reported amongst cases of POTS (61%), CFS (36%), and PVFS (44%). While it is acknowledged that these symptoms can be non-specific and are commonly occuring events, it is noted that the reports of POTS, CFS and PVFS from which these events arose have been largely classified as serious reports (POTS 80%, CFS 78%, PVFS 89%) implying the need for hospitalisation and/or resulting in disability or interruption of normal function. Second, there are geographic differences, specifically within Europe, noted in the reporting of POTS and other syndromes. A fairly consistent finding is that the majority of reports of POTS and other syndromes arise from the US (POTS 52%, CFS 51%, ME/PVFS 40%). In contrast, DK represents 38% of reports of POTS and the UK represents only 4.8%; however, the UK represents 26% of the reports of CFS and DK represents only 6.4%. Furthermore, the UK represents 39% of reports of PVFS and DK represents only 4.8%. Such differences could be speculated to represent coding variation between Denmark and other European countries (for example, UK): the same constellation of symptoms have been coded to different diagnositic PTs. Finally, the graphical display of reports over time demonstrate that the total number of reports of POTS, CRPS, CFS and fibromyalgia have been increasing since 2012 with a marked increase between 2012 and 2013. A review of the introduction of HPV into the routine vaccination programmes throughout the world, specifically in Europe, would be of interest to explore this finding further. Furthermore, the total number of POTS cases for half of the year of 2015 is equivalent to the total number of cases for the whole of 2014.

The presentation of the most commonly reported PTs and HLTs has also allowed a number of observations. First, the comparison between the WHO database and the DK database show a consistency in the top reported adverse events: for example, headache and dizziness are both within the top 3 reported terms and there is a 60% similarity in the listing of the top 10 events between the databases. A comparison of HPV vaccines to all other vaccines in females, at both the PT and HLT term levels, showed a consistency between HPV reports in the different age groups (neurological and asthenia symptoms: headache, dizziness, syncope) and a difference to all other vaccines (febrile and general signs and symptoms: fever, nausea, headache).

The first vigiPoint analysis has provided a comparison of HPV reports from Denmark to all other HPV reports included in VigiBase. Danish HPV reports more commonly are classified as serious than all other HPV reports; however, it is also noted that they are of a higher quality with more complete information. There were a number of PTs which appear more commonly in Danish reports; however, many of these were of a diagnostic nature (such as POTS, autonomic nervous system imbalance, orthostatic intolerance). There was no difference in the reports from Denmark and those from the rest of the world in those PT which describe symptomatology (such as headache, dizziness, activities of daily living impaired).

The second vigiPoint analysis have allowed for a comparison of the characteristics of HPV reports to all other vaccine reports included in Vigibase which have been reported for the subset of females ages 9-25 years of age. The results show that a greater proportion of HPV reports are serious and describe events which are consistent with symptomatology included in the clinical case working definition for myalgic encephalitis / chronic fatigue syndrome (ME/CFS) as described by the Canadian ME/CFS guidelines in the Journal of Chronic Fatigue Syndrome in 2003. This finding is potentially significant because, although ME/CFS is more common the adolescent female population, it is being reported more commonly with HPV vaccine in comparison to other vaccines in this same population.

According to the diagnostic protocol for ME/CFS, a patient will meet the criteria for fatigue, post-exertional malaise, sleep dysfunction, and pain. Furthermore, the patient will have two or more neurological / cognitive manifestations and one or more symptoms from two of the categories of autonomic, neuroendocrine and immune manifestations. Finally, the illness should have a distinct onset and have persisted for at least 3 months in a pediatric subject.

The corresponding highlighted HLT when HPV reports were compared with all other vaccine reports in females 9-25 years of age were:

Fatigue: Asthenia conditions (12.3% in HPV reports compared to 9.3% in all other vaccine reports)

Post-exertional malaise: Disability issues (1.5% compared to 0.3%), Muscle weakness conditions (2.7% compared to 0.8%) and Gait disturbances (1.5% compared to 0.8%)

Pain: Gastrointestinal and abdominal pains (4.7% compared to 3.0%), Migraine headaches (1.1% compared to 0.4%), and Musculoskeletal and connective tissue pain and discomfort (6.3% compared to 4.6%).

Neurological / Cognitive manifestations: Neurological signs and symptoms NEC (15.9% compared to 10.1%), Visual disorders NEC (2.3% compared to 1.4%), Sensory abnormalities NEC (1.1% compared to 0.5%); Mental impairment (excluding dementia and memory loss) (0.7% compared to 0.3%), and Tremor (excluding congenital) (2.1% compared to 1.4%).

Furthermore, there is evidence from the reports that the HPV patients reporting these symptoms have undergone extensive medical evaluation, as there are a number of relevant HLT which suggest abnormality of cardiac, nervous system dysfunction; all of which were significantly over-represented in the HPV reports compared to all other vaccine reports in the same age group: Neurological diagnostic procedures (2.4% compared to 0.5%), Central nervous system imaging procedures (1.4% compared to 0.3%), ECG investigations (1.3% compared to 0.3%), Gastrointestinal and abdominal imaging procedures (0.7% compared to 0.1%), Vascular tests (1.3% compared to 0.5%).

In summary, this review of VigiBase data suggests that there is an increasing trend in the number of HPV reports of containing the PTs of POTS and related syndromes. Furthermore, there is the suggestion that a similar constellation of symptoms may have been labelled with different diagnostic labels depending on the country of origin. Also, the HPV case reports from Denmark are distinguished from those from other countries primarily by the fact that there is an increased amount of clinical information provided in the reports and that certain, specific diagnostic PTs are more commonly used; however, there is no difference between Danish HPV reports and all other HPV reports in the reporting of clinical relevant PTs describing symptomatology experienced by young women after HPV vaccination.

Finally, the data suggest that there is an over-representation of serious case reports which describe a constellation of symptomatology and subsequent medical evaluation potentially consistent with a chronic fatigue – like syndrome which may be specific to HPV vaccines.

References

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