

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

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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 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 excluded². 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 cause³. By mid 2013 only a single case report was published on POTS associated with HPV-vaccination⁴.

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.

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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 vaccination⁵. 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 syndrome⁷. They suggest that a common underlying mechanism could be dysautonomia caused by an autoimmune reaction to vaccination⁶.

A case-series of 6 patients presenting with new-onset POTS after HPV-vaccination has also been published from the US recently⁸.

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 publication⁹, a larger case-series of 45 young women presenting with widespread pain¹⁰ 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-vaccination¹¹. 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 proposed¹². A recent paper from 2015¹³ 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 hypothesized¹³.

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 disorders¹⁴ or for excess adverse event in the period after vaccination¹⁵. A French based case-control study found no evidence of an overall increase in autoimmune disorders in young

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females in the period after vaccination¹⁶. 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 outcomes¹⁷. 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 diseases¹⁸. 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 incidences¹⁹. 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

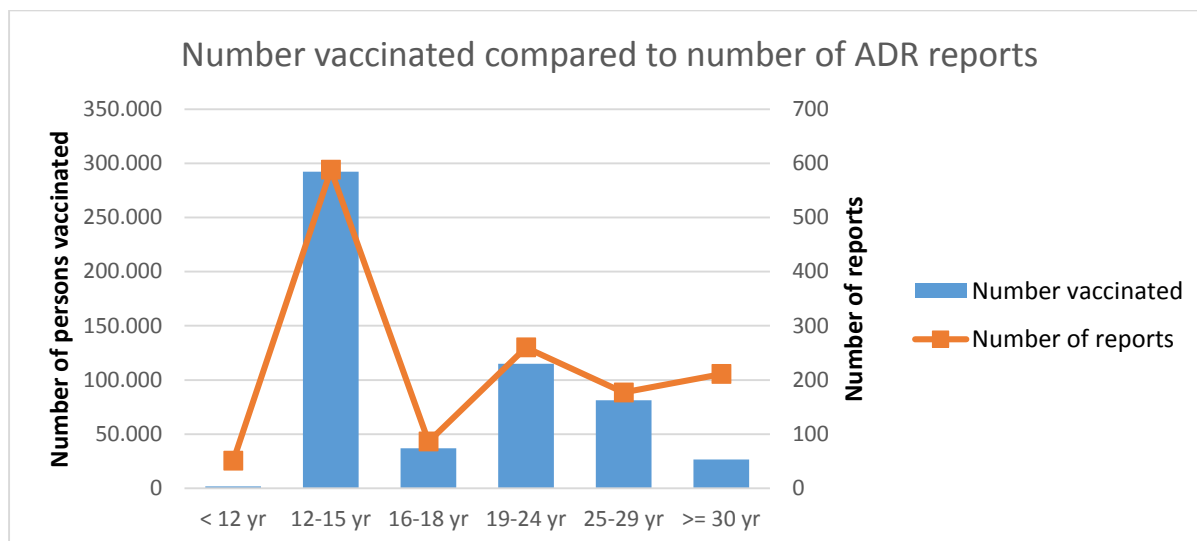
Overview of all reports received by the Danish Health and Medicines Authority shows that the number of reports have increased over the past years but also correlated to the number of doses distributed for the vaccine.

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

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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

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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 deduced 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.

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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 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 through 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:

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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 activities 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.

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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 symptomatology, 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 occurring 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 diagnostic 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).

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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.

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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 from 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.

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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

Paraesthesia: sensory disturbance, hypoaesthesia, hyperaesthesia, burning sensation, dysaesthesia, 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, eyelid 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

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Dyspnoea: difficulty breathing, fast breathing

Presyncope: orthostatic hypotension, hypotension, blood pressure decreased

Tachycardia: 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, musculoskeletal pain, back pain, neck pain, pain in jaw, allodynia, neuralgia, chest pain, chest discomfort, bone pain, oropharyngeal pain.

(does not include headache, 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, gastro-intestinal irritation, gastro-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, metrorrhagia, menorrhagia, menstruation irregular
7. **Thermal dysregulation;** feeling cold, cold sweat, peripheral coldness, body temperature decreased, body temperature fluctuation,, sweating
8. **Malaise:** nausea, vomiting

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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.

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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 symptomatology 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
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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%)

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Dizziness	15 (16%)
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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
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04/09/2015

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
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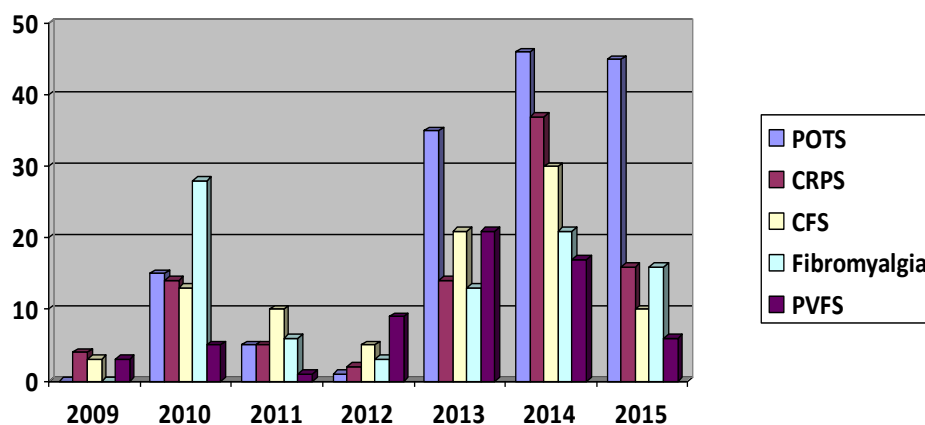
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United States	76 (52%)	50 (53%)	48 (51%)	25 (40%)	61 (70%)
Denmark	56 (38%)	2 (2.1%)	6 (6.4%)	3 (4.8%)	11 (12.6%)
United Kingdom	7 (4.8%)	7 (7.4%)	25 (26%)	24 (39%)	1 (1.1%)
Ireland		1 (1.1%)	3 (3.2%)	3 (4.8%)	1 (1.1%)
Norway			1 (1.1%)	4 (6.4%)	
Sweden	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 be 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)



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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):

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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

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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
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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 patterns¹. 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

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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%

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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%

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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%

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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,

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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.

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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%

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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%

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

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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

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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%

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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%

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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 symptomatology 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

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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 occurring 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 diagnostic 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.

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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.

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