# 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.

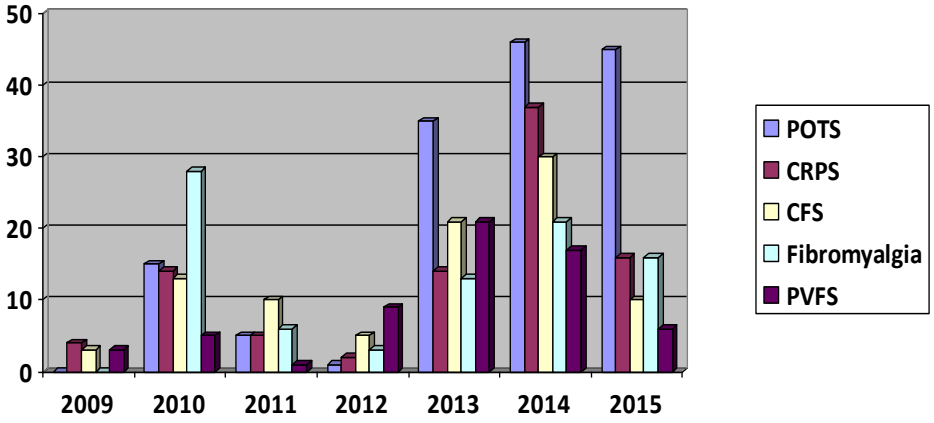
Table 6. Geographic distribution of reports of POTS and related syndromes

| **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 | 24 | 58 | 2.35 | 1.58 | 2.98 | 4% | 0% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| syndrome | | | | | | | |
| 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 | - | - | - | 0% | 5% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | 2.71 | 4.92 | 1.38 | | |
| 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 | Number | Log | Log | Log | % of total | % of |
|---|---|---|---|---|---|---|---|

| | of HPV Reports | of other vaccine reports | OR | OR 005 | OR 095 | HPV reports | 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 | - | -1.43 | -1.17 | 0.7% | 3.2% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1.30 | | | | |
| 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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