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LIST OF APPENDIX

A SAFETY REFERRAL PROCEDURE UNDER ARTICLE 20 OF REGULATION (EC) NO 726/2004 WAS INITIATED ON THE 9TH OF JULY 2015 BY THE EUROPEAN COMMISSION. THE OFFICIAL LIST OF QUESTIONS REGARDING COMPLEX REGIONAL PAIN SYNDROME (CRPS) AND POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS) WAS PUBLISHED ON THE EMA WEBSITE ON THE 13TH OF JULY 2015. A CLARIFICATION TELECONFERENCE WAS HELD WITH THE EMA AND PRAC (CO-) RAPPORTEURS ON THE 17TH OF JULY 2015.

BACKGROUND

Human papillomavirus (HPV) vaccines have been authorised in Europe for prevention of cervical and various other cancers caused by HPV infection since 2006. Routine surveillance of suspected serious adverse drug reaction reports of the HPV vaccines have raised questions on the potential association between the use of the vaccines and in particular two syndromes, known as Complex Regional Pain Syndrome (CRPS) and Postural Orthostatic Tachycardia Syndrome (POTS). Occurrence of these syndromes following HPV vaccination has been reviewed several times by the Pharmacovigilance Risk Assessment Committee (PRAC) within routine safety follow-up procedures. A relationship with HPV vaccination has not been established in these previous procedures.

More recently, the Danish Health and Medicines Authority (DHMA) drew the attention of the EMA and the PRAC. The DHMA considers that in view of the seriousness and increasing number of reports and publications raising concern in EU member States, this safety issue should be evaluated.

The vast majority of the reported cases do not have a well-defined diagnosis. The need was identified that overall scientific evidence of a potential association between HPV vaccination and the two syndromes should be reviewed and methodologies to further investigate the concerns should be defined, if appropriate. In addition, discussion is needed on whether there is evidence of a causal association between HPV vaccination and CRPS and/or POTS, if research efforts should be strengthened, and if available information may require updates to the advice to healthcare professionals and patients, including changes to product information or other regulatory measures.

In that respect the marketing authorisation holders (MAHs) are requested to respond to the questions outlined below.

For Merck Sharp & Dohme (MSD) and Sanofi Pasteur MSD , this request concerns:

- quadrivalent HPV vaccines (qHPV vaccine = V501): Gardasil (Sanofi Pasteur MSD is the MAH) and the duplicate license Silgard (MSD is the MAH)
- 9-valent HPV vaccine (9vHPV vaccine = V503): Gardasil 9 (Sanofi Pasteur MSD is the MAH)

The questions to be addressed by the MAH are listed below and are followed by the question response document.

Question 1

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

Review and case detection methods should be clearly described and the evaluation should discuss whether the reported cases fulfil published or recognised diagnostic criteria.

Question 2

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

Question 3

The MAHs should provide an analysis of the observed number of post-marketing cases of CRPS and POTS in association with their HPV vaccine in comparison to those expected in the target population, stratified by region, if available. The analysis should discuss the assumptions made with respect to the background incidence in the target population and also the influence of potential under-reporting of cases in association with HPV vaccines.

Question 4

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

Question 5

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

1 RESPONSE DOCUMENT

1.1 PRAC Question 1

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

Review and case detection methods should be clearly described and the evaluation should discuss whether the reported cases fulfil published or recognized diagnostic criteria.

MAH RESPONSE

1.1.1 Clinical Trial Data

The safety database from clinical studies of the quadrivalent HPV (types 6, 11, 16, 18) vaccine (qHPV vaccine) and the 9-valent HPV (types 6, 11, 16, 18, 31, 33, 45, 52, 58) vaccine (9vHPV vaccine) was searched for cases suggestive of CRPS and POTS. Queries were conducted for the preferred term CRPS, combination of symptoms suggestive of CRPS, preferred term POTS, and combination of symptoms suggestive of POTS. From a database of 60,594 subjects with 197,983 person-years follow-up, three cases suggestive of CRPS (1 in each of 9vHPV vaccine, qHPV vaccine, and placebo groups) and 2 cases suggestive of POTS (both in the 9vHPV vaccine group) were identified. The incidence of the cases suggestive of CRPS or POTS was found to be extremely low, and similar between the 9vHPV vaccine, qHPV vaccine, and placebo groups. A medical review of the cases (using diagnosis criteria based on the published literature) indicated insufficient evidence to meet the diagnosis criteria for the 3 cases of CRPS and for 1 case of POTS. One case of POTS appeared to meet the diagnosis criteria for POTS. Overall, this assessment does not suggest an association between HPV vaccination and CRPS or POTS.

1.1.1.1 Clinical Studies Included in the Review

The MAH has reviewed data from all clinical studies of the qHPV vaccine (V501 clinical program) and 9vHPV vaccine (V503 clinical program) which supported global filings where subjects received the qHPV vaccine, or 9vHPV vaccine, or placebo. Additionally, the qHPV vaccine arm of Phase II studies conducted to assess other second generation HPV vaccine candidates (Protocols V502-001, V502-002, V504-001, V505-001) are also included (data from the investigational arm for these non-licensed investigational HPV vaccines were not included). Table 1 provides the person-years of follow-up accumulated in each of the clinical studies reviewed.

Per study protocol, safety information was collected for the entire duration of all of these studies. Safety surveillance was supported by a vaccination report card (VRC) for adverse events occurring days 1 to 15 following any vaccination. Outside of the days 1 to 15 post-vaccination periods, serious and non-serious events were collected at every scheduled study visit (in the study protocols, non-serious events occurring outside of the days 1 to 15 post-

vaccination periods are termed 'new medical history'). All safety information was entered in the clinical database. All of the events reported are included in this review.

It should be noted that the following cohorts of subjects were **not** included in the review:

- Subjects who received non-licensed investigational HPV vaccines in Phase II studies, such as various dose formulations of a 8-valent HPV vaccine (Protocol V502-001), various dose formulations of a 8-valent HPV vaccine formulated with a proprietary adjuvant (Protocol V502-002), the low-dose and high-dose formulations of 9-valent HPV vaccine (Phase II portion of Protocol V503-001), a 5-valent HPV vaccine given concomitantly with qHPV vaccine (Protocol V504-001), or various dose formulations of a 9-valent HPV vaccine formulated with a proprietary adjuvant (Protocol V505-001), since these investigational HPV vaccines differ from the qHPV vaccine and 9vHPV vaccine.
- Subjects in Protocol V503-006 who received placebo during the study since they had received marketed qHPV vaccine prior to enrolling in the V503-006 study.
- Subjects in local registration studies of qHPV vaccine.

Table 1

Person-Years of Follow-up Across Studies Contributing to the Summary of CRPS and POTS Incidence Rates V501[†], V502[‡], V503[§], V504[‖], and V505[‖] Programs

	9vHPV		qHPV		Placebo		All Subjects	
	N	Total Person-Years	n	Total Person-Years	N	Total Person-Years	n	Total Person-Years
All Studies	15,801	39,995	31,206	111,230	13,587	46,758	60,594	197,983
V501-007	0	0	405	1,108	292	1,068	697	2,176
V501-011	0	0	934	3,350	935	3,361	1,869	6,712
V501-012	0	0	1,779	6,293	1,786	6,286	3,565	12,579
V501-015	0	0	8,116	36,490	6,075	22,003	14,191	58,493
V501-016	0	0	3,043	2,164	0	0	3,043	2,164
V501-018	0	0	1,655	8,766	592	1,402	2,247	10,168
V501-019	0	0	2,555	12,115	1,900	7,244	4,455	19,360
V501-020	0	0	2,861	10,568	2,007	5,394	4,868	15,961
V501-024	0	0	843	475	0	0	843	475
V501-025	0	0	1,018	584	0	0	1,018	584
V502-001	0	0	168	104	0	0	168	104
V502-002	0	0	30	58	0	0	30	58
V503-001	7,082	28,488	7,090	28,533	0	0	14,172	57,022
V503-002	3,060	7,358	0	0	0	0	3,060	7,358
V503-003	2,462	2,351	0	0	0	0	2,462	2,351
V503-005	1,233	693	0	0	0	0	1,233	693
V503-006	612	350	0	0	0	0	612	350
V503-007	1,052	583	0	0	0	0	1,052	583
V503-009	300	171	298	171	0	0	598	342
V504-001	0	0	312	171	0	0	312	171
V505-001	0	0	99	279	0	0	99	279

[†] Includes data from the base study protocols 007, 011, 012, 015, 016, 018, 019, 020, 024, and 025 as well as data from the extension/long-term follow-up study of protocols 007, 015, 018, 019, and 020.
[‡] Includes data from protocols 001 and 002.
[§] Includes data from protocols 001, 002, 003, 005, 006, 007, and 009.
[‖] Includes data from protocol 001.
n = Number of subjects vaccinated with the indicated vaccine or placebo who had follow-up post dose 1.
9vHPV = Human Papillomavirus 9-valent Vaccine, Recombinant.
qHPV = Human Papillomavirus Quadrivalent (Types 6, 11, 16 ,18) Vaccine, Recombinant.
CRPS = Complex regional pain syndrome; POTS = Postural orthostatic tachychardia syndrome.

1.1.1.2 Methodology

Search for Cases in the Clinical Study Database Which Could be Suggestive of CRPS

The MAH has performed queries of the integrated clinical safety database to identify any potential cases of CRPS among subjects who received the 9vHPV vaccine, or qHPV vaccine or placebo, including

- one query to research in the clinical database the preferred term '*complex regional pain syndrome*' and
- several queries to research combinations of specific signs/symptoms of CRPS as shown below. The queries to research combinations of specific symptoms were the same as those used to search the MAH post-marketing database for qHPV and 9HPV vaccines; see below for additional details.

The following queries were run on the integrated safety data set of subjects who received the 9vHPV vaccine, qHPV vaccine, or placebo to identify cases which could be suggestive of CRPS:

Group	Preferred Term
Group A	'back pain' OR 'flank pain' OR 'musculoskeletal pain' OR 'neck pain' OR 'pain in extremity' OR ' pain'
Group B	'hyperaesthesia' OR 'allodynia' OR 'hypoaesthesia'
Group C	'feeling hot' OR 'skin discoloration' OR 'skin hyperpigmentation' OR 'skin hypopigmentation' OR 'skin warm' OR 'feeling cold' OR 'cold sweat' OR 'onychoclasis' OR 'hair growth abnormal' OR peripheral coldness OR 'skin atrophy'
Group D	'oedema' OR 'hyperhidrosis' OR 'cold sweat'
Group E	'muscular weakness' OR 'tremor' OR 'dystonia' OR 'motor dysfunction' OR 'orthostatic tremor' OR 'mobility decreased' OR 'abasia' OR paresis
Group F	'complex regional pain syndrome'

The following six queries were run using the logic displayed below:

Query	Query Logic
Query 1	Group A AND Group B AND Group C AND Group D
Query 2	Group A AND Group B AND Group D AND Group E
Query 3	Group A AND Group B AND Group C AND Group E
Query 4	Group A AND Group C AND Group D AND Group E
Query 5	Group A AND Group B AND Group C AND Group D AND Group E
Query 6	Group F

The following assessment was then conducted:

- The incidence rate of the cases suggestive of CRPS was determined in subjects who received 9vHPV vaccine, qHPV vaccine, or placebo.
- Each identified case suggestive of CRPS was summarized as a narrative based on the information available in the clinical database.

Each case was reviewed individually using the clinical diagnostic criteria for CRPS type 1 discussed by Harden *et al* in a 2007 publication of Pain Medicine. This paper summarizes the latest international consensus group's action in Budapest, Hungary, to approve and codify empirically validated, statistically derived revisions of the International Association for the Study of Pain [IASP]) criteria for CRPS (the Budapest Criteria) [Ref. 5.4: 03TWYK]. This case definition was the subject of a more recent paper in 2010 which further validated its use [Ref. 5.4: 046WN3]. This approach is consistent with the advice from the PRAC (Co-) Rapporteurs (*PRAC post-meeting note: "On the case definition the Harden et al., 2010 publication may need to be taken as basis for CRPS."*) and is the same as that used to assess potential cases in the post-marketing database below. Throughout this document, the terms CRPS and CRPS type 1 are used interchangeably. CRPS type 1 excludes cases which are caused by a direct injury to a nerve (CRPS type 2). In general the large majority of cases defined as CRPS are CRPS type 1. Therefore where CRPS is not specified in a case report as being of a particular type and there is no indication that the cause was a nerve injury, it is assumed to be relevant to discussion of CRPS type 1.

The diagnosis criteria for CRPS are as follows:

1. Continuing pain which is disproportionate to any inciting event.

2. Must report at least one symptom in 3 of the 4 following categories:

CATEGORY	Symptoms
Sensory:	Reports of hyperaesthesia and/or allodynia
Vasomotor:	Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
Sudomotor/ edema:	Reports of edema and/or sweating changes and/or sweating asymmetry
Motor/trophic:	Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and /or trophic changes (hair, nail, skin)

3. Must display at least one sign at time of evaluation in 2 or more of the following categories:

CATEGORY	Signs
Sensory:	Evidence of hyperalgesia and/or allodynia
Vasomotor:	Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
Sudomotor/ edema:	Evidence of edema and/or sweating changes and/or sweating asymmetry
Motor/trophic:	Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and /or trophic changes (hair, nail, skin)

4. There is no other diagnosis that better explains the signs and symptoms.

Search for Cases in the Clinical Study Database Which Could be Suggestive of POTS

The MAH has performed queries of the integrated clinical safety database to identify any potential cases of POTS among subjects who received the 9vHPV vaccine, qHPV vaccine or placebo, including

- one query to research in the clinical database the preferred term '*postural orthostatic tachycardia syndrome*' and
- several queries to research combinations of specific signs/symptoms of POTS as shown below. The queries to research combinations of specific symptoms were the same as those used to search the MAH post-marketing database for qHPV and 9HPV vaccines; see below for additional details.

The approach used for the queries to research combinations of signs/symptoms is based on recent feedback from the PRAC in March, 2014 and from the DHMA regarding identification of possible POTS cases in the qHPV vaccine post-marketing database. The MAH used the proposed DHMA's list of signs/symptoms of POTS to identify 8 groups of preferred terms that represent signs/symptoms and their associated synonyms of POTS. However, since these symptoms (and associated synonyms) alone would not be specific in identifying potential POTS cases, database queries were conducted in such a way that combinations of symptoms would need to appear in the clinical database. Utilizing the 8 groups of preferred terms, 6 queries were run utilizing various combinations of the signs/symptoms starting with query #1 which included all 8 groups of signs/ symptoms. The queries were devised to account for various combinations of cardiac, dysautonomia, and sensory symptoms without being overly exclusive (i.e., as more symptom groups are added to the query logic, the return of case reports diminishes). This search strategy (shown below) is the same as that used to search the MAH post-marketing database for qHPV and 9HPV vaccines (see below for additional details). The following groups of preferred terms were specified to be used in the queries:

Group	Preferred Term
Group A	'palpitations' OR 'tremor' OR 'heart rate increased' OR 'tachycardia' OR 'tachyarrhythmia'
Group B	'dizziness' OR 'dizziness exertional' OR 'dizziness postural' OR 'exercise tolerance decreased' **OR** 'muscular weakness' **OR** 'fatigue'
Group C	'syncope' OR 'presyncope' OR 'loss of consciousness'
Group D	'orthostatic intolerance' OR 'orthostatic heart rate response increased'
Group E	'paraesthesia' OR 'sensory disturbance' OR 'blurred vision'
Group F	'hyperhidrosis'
Group G	'memory impairment' OR 'disturbance in attention' OR 'confusional state' OR 'cognitive disorder'
Group H	'autonomic nervous system imbalance' OR 'urinary retention' OR 'constipation' OR 'diarrhoea'
Group I	'postural orthostatic tachycardia syndrome'

The following six queries were run using the logic displayed below:

Query	Query Logic
Query 1	Group A AND Group B AND Group C AND Group D AND Group E AND Group F AND Group G AND Group H
Query 2	Group A AND Group B AND Group D AND Group F
Query 3	Group A AND Group B AND Group D AND Group E
Query 4	Group C AND Group E AND Group F
Query 5	Group C AND Group D AND Group E AND Group F
Query 6	Group C AND Group D AND Group E AND Group H
Query 7	Group 1

The following assessment was then conducted:

- The incidence rate of the cases suggestive of POTS was determined in subjects who received 9vHPV vaccine, qHPV vaccine, or placebo.
- Each identified case suggestive of POTS was summarized as a narrative based on the information available in the clinical database.

The identified cases suggestive of POTS were reviewed individually using the clinical diagnostic criteria for POTS discussed by SR Raj in a 2013 publication of Circulation [Ref. 5.4: 03SW00] and Sheldon 2015 [Ref. 5.4: 046WN6] as well Jarjour 2015 [Ref. 5.4: 03SWR7] and Freeman [Ref. 5.4: 03SWQZ] (in line with the PRAC Rapporteur's expectations raised during the Teleconference of 17 July 2015). The case definition used for POTS is as follows:

Case definition based on **Raj 2013** and **Sheldon 2015** Publications
Postural tachycardia syndrome (POTS) is defined as a clinical syndrome that is usually characterized by (1) frequent symptoms that occur with standing such as light headedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue which improve with recumbence (2) an increase in heart rate of ≥30 bpm when moving from a recumbent to a standing position held for more than 30 seconds (or ≥40 bpm in individuals 12 to19 years of age) in the absence of orthostatic hypotension (>20 mmHg drop in systolic blood pressure) (3) Symptoms last > 6 months (4) Absence of other overt cause of orthostatic symptoms or tachycardia (e.g., active bleeding, acute dehydration, medications)

1.1.1.3 Results

Incidence of Cases Suggestive of CRPS or POTS in the Clinical Database

Table 2 provides the total count and incidence per 10,000 person-years of cases of CRPS and POTS observed in the clinical studies reviewed, based on criteria summarized below.

A high-level summary of the review of data from the clinical studies are as follows:

- The incidences of CRPS and POTS observed in clinical studies were extremely low; less than 1 case per 10,000 person-years in each of 9vHPV vaccine, qHPV vaccine, and placebo cohorts.
- There was no pattern evident in the time to onset for the few cases of CRPS and POTS that were observed.
- The incidences of CRPS and POTS in the 9vHPV vaccine and qHPV vaccine cohorts were comparable to the incidence observed in the placebo cohort.
- The incidences of CRPS and POTS in the 9vHPV vaccine and qHPV vaccine cohorts are not different in Europe compared to the rest of the world.

Table 2

Incidence of CRPS and POTS per 10,000 Person-Years of Follow-up
V501[†], V502[‡], V503[§], V504[‖], and V505[‖] Programs

	9vHPV			qHPV			Placebo		
Endpoint	Cases/n	Person-Years of Follow-up	Rate (95% CI)	Cases/n	Person-Years of Follow-up	Rate (95% CI)	Cases/n	Person-Years of Follow-up	Rate (95% CI)
CRPS	1/15,801	39,995	0.3 (0.0, 1.4)	1/31,206	111,230	0.1 (0.0, 0.5)	1/13,587	46,758	0.2 (0.0, 1.2)
Europe	0/5,648	13,321	0.0 (0.0, 2.8)	1/12,024	46,495	0.2 (0.0, 1.2)	0/5,198	18,646	0.0 (0.0, 2.0)
Rest of the world	1/10,153	26,673	0.4 (0.0, 2.1)	0/19,182	64,734	0.0 (0.0, 0.6)	1/8,389	28,112	0.4 (0.0, 2.0)
POTS	2/15,801	39,995	0.5 (0.1, 1.8)	0/31,206	111,230	0.0 (0.0, 0.3)	0/13,587	46,758	0.0 (0.0, 0.8)
Europe	1/5,648	13,321	0.8 (0.0, 4.2)	0/12,024	46,495	0.0 (0.0, 0.8)	0/5,198	18,646	0.0 (0.0, 2.0)
Rest of the world	1/10,153	26,673	0.4 (0.0, 2.1)	0/19,182	64,734	0.0 (0.0, 0.6)	0/8,389	28,112	0.0 (0.0, 1.3)

[†] Includes data from the base study protocols 007, 011, 012, 015, 016, 018, 019, 020, 024, and 025 as well as data from the extension/long-term follow-up study of protocols 007, 015, 018, 019, and 020.

[‡] Includes data from protocols 001 and 002.

[§] Includes data from protocols 001, 002, 003, 005, 006, 007, and 009.

[‖] Includes data from protocol 001.

Rate is the estimated number of cases per 10,000 person-years of follow-up.

n = Number of subjects vaccinated with the indicated vaccine or placebo who had follow-up post dose 1.

9vHPV = Human Papillomavirus 9-valent Vaccine, Recombinant.

qHPV = Human Papillomavirus Quadrivalent (Types 6, 11, 16 ,18) Vaccine, Recombinant.

CI = Confidence interval; CRPS = Complex regional pain syndrome; POTS = Postural orthostatic tachycardia syndrome.

Narratives of Cases Suggestive of CRPS

As seen in Table 2, 3 cases suggestive of CRPS were identified in the clinical database, including 1 case in the 9vHPV vaccine group, 1 case in the qHPV vaccine group, and 1 case in the placebo group. There was no pattern in the date of onset of the CRPS cases. Narratives summarizing all the relevant information available for these 3 cases are provided below. No additional queries on these cases are outstanding.

Results for 9vHPV vaccine

One case suggestive of CRPS was identified based on the preferred term CRPS. A diagnosis of CRPS was reported by the investigator at the Month 3 visit. The investigator indicated that the CRPS was consecutive to an injury during physical activity that occurred prior to vaccination 1, and that CRPS was not related to vaccination. The diagnosis of CRPS was based on persistence following the injury; however, none of the diagnostic criteria outlined above (sensory, vasomotor, sudomotor/edema, motor/trophic) were reported. The condition of CRPS was reported only at one study visit. No other symptom or new medical condition was reported at subsequent study visits during approximately 4 years of follow-up.

[redacted], a 24 year old female enrolled in Protocol V503-001 on 26-May-2009 in [redacted] with no reported medical history at Day 1. This subject received her first dose of 9vHPV vaccine on 26-May-2009, second dose of 9vHPV vaccine 30-Jul-2009, and third dose of 9vHPV vaccine 19-Nov-2009. The subject reported adverse events of rhinorrhea, headache, oropharyngeal pain, and nasal obstruction following the first vaccination (all of mild intensity, lasting a few hours to ~20 days for the rhinorrhea). The subject reported adverse events of headache, neck pain, and injection-site pain following the second vaccination (all of mild intensity, lasting a few hours to 1 day) and reported neck pain and injection site pain following the third vaccination (of moderate intensity, lasting 12 hours to 1 day). In addition, the subject reported new medical history at the vaccination 2 visit (Month 2) of influenza, **complex regional pain syndrome** (CRPS) at Month 3, and upper respiratory tract infection at Month 6. The following additional information was provided by the investigator regarding CRPS: the subject had an onset of pain in the 4th and 5th fingers of her right hand following physical activity in April 2009 (before receiving the first vaccine dose). The pain persisted for several months with no injury ever being diagnosed; it was therefore attributed to CRPS. The subject was seen by an orthopedic surgeon in February 2010 who advised no intervention and thought that the symptoms were likely to settle. The investigator indicated that no further information is available and that this event is clearly unrelated to vaccination. The subject continued in the study and reported no additional new medical history or adverse events until she completed the study. The subject completed the Month 48 visit and subsequently completed the study on 15-Oct-2013.

Results for qHPV vaccine

One case suggestive of CRPS was identified based on the preferred term CRPS. A diagnosis of CRPS was reported by the investigator with an onset at day 736 post-vaccination 3. However, the basis for this diagnosis was not reported, and none of the diagnostic criteria outlined above (sensory, vasomotor, sudomotor/edema) were reported. The condition of CRPS was reported only at one study visit. No other symptom or new medical condition was reported at subsequent study visits during an additional year of follow-up.

[redacted]a 21 year old female enrolled in Protocol V503-001 on 29-Jul-2009 in [redacted] with a medical history at Day 1 of injury (unspecified) and migraine. This subject received first dose of qHPV vaccine 29-Jul-2009, second dose of qHPV vaccine on 23-Sep-2009, and third dose of qHPV vaccine on 27-Jan-2010. This subject reported the following adverse events form day 1 to 15 following vaccination visits: after vaccination 1- injection-site erythema, injection-site swelling, injection-site pain, injection-site paresthesia, and headache; after vaccination 2 - injection-site swelling, injection-site erythema, and injection-site pain; after vaccination 3 - injection-site swelling, injection-site pain, injection-site erythema, migraine, hyperhidrosis, muscle rigidity, dizziness, nausea. Post-day 1, the subjects medical history includes gastrointestinal infection (start 2010), metrorrhagia ("due to Belara"; 2010), adverse drug reaction ("adverse reaction of Belara" 2010), otitis media (2010), tinnitus (2010), epilepsy (2011), and cerebral cyst (2011). At a visit on the 736th day after the last vaccination with qHPV vaccine the subject reported new medical history of **complex regional pain syndrome** (2012). The subject was not administered any medications or therapies for the complex regional pain syndrome. Concomitant medications at this visit included: flunarizine hydrochloride (for epilepsy) and chlormadinone acetate/ethinyl estradiol (contraceptive). After that study visit, this subject reported gastroenteritis at a subsequent visit; the subject did not report any other new medical condition until she completed the study. The subject completed the study on 7-Aug-2013. No additional information regarding the CRPS is available.

Results for placebo

One case suggestive of CRPS was identified based on the queries for a combination of symptoms. A diagnosis of CRPS was not reported by the investigator. The narrative suggests that several of the diagnostic criteria outlined above (vasomotor, sudomotor/edema, motor/trophic) occurred on two occasions (on 22-Mar-2005 and 18-Aug-2005). However, the prompt recovery (after 1 day and after 4 days, respectively), and the concurrent report of nasopharyngitis and chills suggest two occurrences of acute infection rather than CRPS.

[redacted]was a 37 year old Hispanic woman who enrolled in Protocol V501-019 in [redacted] on 15-Mar-2005 with prior medical history of haemorrhoids, overweight and gastritis. Concomitant medication included ethinyl estradiol + levonorgestrel and ranitidine. The subject received her first dose of placebo on 15-Mar-2005. That same

day the subject experienced injection site pain. On 19-Mar-2005 the subject experienced back pain and nasopharyngitis. On 22-Mar-2005 the subject experienced pallor, tremor and hyperhidrosis. That same day the subject recovered from pallor, tremor, hyperhidrosis and nasopharyngitis. On 28-Mar-2005 the back pain resolved. The investigator considered injection site reaction, back pain, and nasopharyngitis as related to study vaccination and considered pallor, tremor, and hyperhidrosis as not related to study vaccination. On 25-Apr-2005 the subject received her second dose of placebo. On 18-Aug-2005 the subject received her third dose of placebo. That same day the subject experienced chills, feeling cold and hypothermia. The subject recovered from the chills and hypothermia on 22-Apr-2005 and from the feeling cold on 26-Apr-2005. The investigator considered chills, feeling cold and hypothermia related to study vaccination. The subject continued in the study with visits approximately every 6 months between 18-Aug-2005 and 20-Feb-2009. No additional new adverse events were reported. No conditions related to CRPS were reported at new medical history. The subject completed the study at the scheduled Month 48 visit on 20-Feb-2009.

Narratives of Cases Suggestive of POTS

As seen in Table 2, 2 cases suggestive of POTS were identified in the clinical database, both in the 9vHPV vaccine group. There was no pattern in the date of onset of the POTS cases. Narratives summarizing all the relevant information available for these 2 cases are provided below. No additional queries on these cases are outstanding._A narrative for a third case which was reported directly to the SPONSOR by the Danish Health Authority is also provided. The case occurred after the end of the clinical trial, and no allocation number was reported.

Results for 9vHPV vaccine

Case #1 – One case of POTS was identified in a 12 year old female subject ([redacted]) in Protocol V503-002 approximately 24 days post-dose 1. The basis of the diagnosis has not been reported. The subject received all 3 doses of 9vHPV vaccine and completed the base study at Month 12. Follow-up during the study included collection of new medical conditions at each study visit. The diagnosis criteria indicate that symptoms should be frequent and last > 6 months. However, there were no additional symptoms reported in the study database that suggested that this condition was recurrent or chronic. The absence of recurrent episodes is not suggestive of POTS. A narrative is provided below.

[redacted] a 12 year old White female from [redacted] with no prior medical history received her first dose of 9vHPV vaccine on 12-Mar-2010. The subject reported no adverse events within 15 days following the first dose of vaccine. At the next visit (11-Jun-2010), the subject reported new medical conditions of syncope and **postural orthostatic tachycardia syndrome** (POTS); both with onset dates of 05-Apr-2010. The subject went on to receive her second and third dose of 9vHPV vaccine on 11-Jun-2010 and 08-Oct-2010, respectively. No new medical conditions and no symptoms related to POTS

were reported as adverse events following the second and third vaccinations. The subject completed the study at Month 12.

Case #2 – One case of POTS was identified in a 24 year old female subject ([redacted]) randomized to 9vHPV vaccine in Protocol V503-001 approximately 1389 days post-dose 3. The diagnosis appears based on a rigorous evaluation.

The Patient Compensation Association assessed that anxiety attacks with dizziness and nausea as sequel were not due to vaccination with 9vHPV vaccine but rather other conditions in this subject's life. It indicated that the cause could be emotional stress, which has been described in the patient's hospital records or the patient's migraine. The patient's discomforts in the form of POTS and migraine and the sequel of this were not assessed as a cause of the vaccination with 9vHPV vaccine. The Patient Compensation Association also emphasized that this subject's hospital records describe that she had migraine since she were 16 years old, which was before the vaccination, and that there was no timely relationship between the vaccinations and the migraine.

Detailed information about this case as available in the clinical database is shown below.

[redacted] a 19 year-old White female from [redacted] (site [redacted]) with a medical history of migraines at Day 1 (since the age of 16 years) received her first, second and third dose of 9vHPV vaccine on 06-Jul-2009, 02-Sep-2009 and 12-Jan-2010, respectively, in the V503-001 study. The subject had her last study visit on 10-Oct-2013. On 01-Nov-2013 (1389 days post-dose 3), the subject was diagnosed with **postural orthostatic tachycardia syndrome** (POTS). On 04-Oct-2013, the general practitioner referred the subject to the syncope unit of the [redacted] Hospital for symptoms of syncope, dizziness, nausea, headache, tired, low muscle strength and low sensitivity in left side arm and leg (based on physical examination by a hospital physician). The investigator noted in the report that this referral took place after a media campaign about possible side effects of HPV vaccination. On 01-Nov-2013, a head-up tilt test was performed as part of the diagnostic work-up for autonomic dysfunction. The subject was diagnosed with non-progressive POTS disease on the basis of her clinical symptoms, an abnormal tilt test (heart rate increased from 52/min to 83/min despite treatment with 60 mg propranolol b.i.d), normal heart rate variability (showing normal function of the parasympathetic nervous system), and a positive COMPASS-31 score (standardized questionnaire on autonomic dysfunction developed by the Mayo Clinic). Having already completed the study, the subject did not report this adverse event to the investigator at this time. The syncope unit of the [redacted] Hospital reported this condition to the [redacted] Health Authority in November 2013. The Danish Health Authority subsequently reported this event to site. The site reported the event of POTS in the V503-001 clinical database in November, 2013. The onset date of the POTS was reported as 01-Nov-2013. Upon further follow-up, it was learned that the subject had a history of severe dizziness and was hospitalized for investigation from 13 to 16-Aug-2013. The patient was recommended to

take 2-3L of water daily and ibuprofen as needed. On 09-Dec-2013, the subject reported rotatory dizziness, near fainting attacks, and migraines, and the subject was taking propranolol hydrochloride and rizatriptan benzoate for migraines. The general practitioner was contacted by the sub-investigator on 20-Feb-2014. At that time, there was no new additional information. The subject cancelled her visit with her family doctor that was scheduled for 9-May-2014. No additional information is expected. The study investigator felt that the event of POTS was related to study therapy. The rationale for assigning a possible relation between vaccination and POTS included that a possible relation between HPV vaccination and POTS has been mentioned in scientific publications. The investigator specifically cited the following two publications: Blitshteyn S. *Eur J Neurol* 21:135-9, 2014; Wang XL *Proteomics Clin Appl* 6:615-25, 2012.

Results that could not be not attributed to a specific cohort

The Danish Health Authority reported directly to the SPONSOR a case of POTS in a subject in the V503-006 study. The reporting occurred after the end of the V503-006 study, and no allocation number was reported. This case is not reported in Table 2 as it was not captured in the clinical database because it was reported outside of the context of the V503-006 study. There is no study extension for this study in Denmark. The MAH was not able to gather additional information. The information provided in the report is not sufficient to assess whether the diagnosis criteria are met. All participants in the V503-006 study were prior recipients of qHPV vaccine (i.e., they completed a 3-dose series of commercial qHPV vaccine at least 12 months before entering in the study). In the V503-006 study, subjects were randomized to 9vHPV vaccine or saline placebo. Information about this case is provided here for completeness.

On 21-Oct-2013, the Sponsor received a report from the Danish Health and Medicines Authority indicating a female with a history of syncope who participated in the V503-006 study had experienced **postural orthostatic tachycardia syndrome**. According to the report, the female received the 9vHPV vaccine on 01-Aug-2010 and 10-Oct-2010. Following the second vaccination, the patient experienced POTS, exhaustion, and syncope vasovagal and had to give up her studies and leisure activities. She was hospitalized on an unknown date with severe muscle cramps. According to the report, the patient presented fluctuating symptoms in subsequent years that never completely disappeared and was treated with increased intake of potassium and water, fludocortisonacetate, and ivabradine. The reporting health professional (not a study investigator) saw the subject for a tilt test in 2012 and diagnosed POTS. Per the report, the adverse events improved (no timing provided) and the subject is recovering from POTS after medical treatment and rehabilitation. According to the report, the reporting health professional considered the events were related to the 9vHPV vaccine. The base study is completed (and no study extension in Denmark). The MAH has not been able to gather additional information nor confirm the allocation number of this subject.

1.1.2 Post marketing data

1.1.2.1 Complex Regional Pain Syndrome (CRPS)

Methods

Identifying Case Reports
The Company aggregate analytical tool, METEOR, was utilized to identify medically confirmed reports that include the Preferred Term (PT) of '*Complex Regional Pain Syndrome'* (CRPS) reported as temporally associated with the administration of qHPV vaccine or 9vHPV vaccine received worldwide from the marketed environment cumulative to 15-Jun-2015. Note that Reflex Sympathetic Dystrophy (RSD) also codes to the Preferred Term of CRPS in the Medical Dictionary for Regulatory Activities (MedDRA).

Additionally, the Company safety data base was queried for case reports that include various combinations of symptoms of CRPS in an effort to identify cases where a clinical course suggests possible CRPS which may not yet be identified or diagnosed. This approach is consistent with the advice from the PRAC (Co-) Rapporteurs (*PRAC* post-meeting note to the teleconference of 17 July*: "On the case definition the Harden et al., 2010 publication may need to be taken as basis for CRPS."*) and is the same as that used to assess potential cases in the clinical database below. This querying was done as described below.

Step 1: The PTs representing symptoms of CRPS to be used in the queries were grouped as follows:
Group A: 'back pain' OR 'flank pain' OR 'musculoskeletal pain' OR 'neck pain' OR 'pain in extremity' OR 'pain'
Group B: 'hyperaesthesia' OR 'allodynia'
Group C: 'feeling hot' OR 'skin discoloration' OR 'skin hyperpigmentation' OR 'skin hypopigmentation' OR 'skin warm' OR 'feeling cold' OR 'cold sweat' OR 'onychoclasis' OR 'hair growth abnormal' OR peripheral coldness
Group D: 'oedema' OR 'hyperhidrosis' OR 'cold sweat' OR 'skin atrophy'
Group E: 'muscular weakness' OR 'tremor' OR 'dystonia' OR 'motor dysfunction' OR 'orthostatic tremor' OR 'mobility decreased' OR 'abasia' OR paresis

Step 2: Five queries were run using the logic displayed below:
Query #1: Group A AND Group B AND Group C AND Group D
Query #2: Group A AND Group B AND Group D AND Group E
Query #3: Group A AND Group B AND Group C AND Group E
Query #4: Group A AND Group C AND Group D AND Group E
Query #5: Group A AND Group B AND Group C AND Group D AND Group E

Evaluating Case Reports

The identified reports of CRPS were reviewed individually using the clinical diagnostic criteria for CRPS type 1 discussed by Harden *et al* in a 2007 publication of Pain Medicine. This paper summarizes the latest international consensus group's action in Budapest, Hungary to approve and codify empirically validated, statistically derived revisions of the International Association for the Study of Pain [IASP]) criteria for CRPS (the Budapest Criteria)[Ref. 5.4: 03TWYK]. This case definition was the subject of a more recent paper in 2010 which further validated its use [Ref. 5.4: 046WN3]. This approach is consistent with the advice from the PRAC (Co-) Rapporteurs (*PRAC post-meeting note: "On the case definition the Harden et al., 2010 publication may need to be taken as basis for CRPS."*).

The 4 criteria are as follows:

1. Continuing pain which is disproportionate to any inciting event.

2. Must report at least one symptom in 3 of the 4 following categories:

CATEGORY	Symptoms
Sensory:	Reports of hyperaesthesia and/or allodynia
Vasomotor:	Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
Sudomotor/ edema:	Reports of edema and/or sweating changes and/or sweating asymmetry
Motor/trophic:	Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and /or trophic changes (hair, nail, skin)

3. Must display at least one sign at time of evaluation in 2 or more of the following categories:

CATEGORY	Signs
Sensory:	Evidence of hyperalgesia and/or allodynia
Vasomotor:	Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
Sudomotor/ edema:	Evidence of edema and/or sweating changes and/or sweating asymmetry
Motor/trophic:	Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and /or trophic changes (hair, nail, skin)

4. There is no other diagnosis that better explains the signs and symptoms.

<u>Applying the criteria to Spontaneous Reports</u>

It is important to note that due to the nature of spontaneous reporting, it is sometimes difficult to determine whether an event included in a case report is subjectively reported (i.e. meets the definition of criteria #2), or is objectively reported by the HCP (i.e. meets the definition of criteria #3). Generally speaking, for the purposes of this analysis, if the report included evidence of symptoms in 3 or more of the 4 categories in criterion #2, then it was considered that criteria #2 AND #3 were met.

Additionally, it is difficult to determine the thoroughness of the medical work-ups conducted to rule out other diagnoses. Generally speaking, for the purposes of this analysis, if the report mentioned that numerous tests such as MRI, EMG, x-ray etc. were conducted and included normal results, then it was considered that criterion #4 was met.

In summary, assessment of the case reports relied heavily on medical judgment in assessing the wording used in a report, the presentation of the data, and possible inferences made by reporters. For this reason and in order to be transparent, cases were reviewed and are presented as those that met the diagnostic criteria, those that only partially met the diagnostic criteria and those that did not meet diagnostic criteria.
The Worldwide Financial Reporting System was queried to determine the number of doses distributed cumulative to 31-May-2015 worldwide (WW), in EU only, in US, Denmark, UK, Germany, and Japan.

The number of doses distributed for each region (WW, US, EU, Denmark, and Japan) will be divided by 3 for an estimated number of patients vaccinated as per the PRAC recommendation (this provides a "conservative" estimate of number of people exposed to the vaccine). This estimated number of patients vaccinated will be used in the calculations of reporting rates by region as follows:
reports of CRPS/ number of patients vaccinated X 1 million.

Results

The query of the Company safety data base that includes the Preferred Term (PT) of 'Complex Regional Pain Syndrome' (CRPS) yielded 54 medically confirmed reports (see attached line listing) reported as temporally associated with the administration of qHPV vaccine received worldwide from the marketed environment cumulative to 15-Jun-2015. Upon review, it was determined that there were 2 case reports, MARRS [redacted] and [redacted], which referred to the same patient experience of CRPS following 2 separate doses, i.e. duplicate reports. Therefore, there are actually 53 cases to be analyzed. The CIOMS forms are appended to this response document [Ref. 5.3.6: 046WDL].

There were no post marketing reports of CRPS identified as temporally associated with the administration of 9vHPV vaccine.

30 of the 53 cases were reported as serious at the event level for the event of CRPS; the remaining 23 cases were reported as serious due to an adverse event other than CRPS. Geographically, 11 reports were received from the US, 13 from the EU (3 France; 4 Germany; 2 Spain, 2 Denmark, 1 each from Ireland and the UK), 7 from Australia, and 18 from Japan and the remaining 4 from Brazil, Mexico and United Arab Emirates.

Age was reported in 48 reports as follows: 4 were between 9 and 11 years of age; 11 were age 12; 30 were older than 12 and up to 17 years of age; 2 were between 18 and 20; and 1 was 46 years of age. Gender was reported in 49 cases as involving 48 females and 1 male.

Review of the reports reveals that 7 cases appear to meet the clinical diagnostic criteria for CRPS type 1 described above in the Methods section. Sixteen additional cases only partially meet the clinical diagnostic criteria for CRPS type 1. A case was considered to partially meet criteria, when clinical data was available to meet several of the criteria but the information was incomplete and therefore, lacking in meeting all criteria required. Oftentimes, it was failure to meet criterion #4, in that it was not clear from the report that a medical workup was conducted to rule out other potential diagnoses or the results were not provided. These 16 cases immediately follow the 7 cases that met the diagnostic criteria as displayed in Table 3 below.

The remaining 30 cases did not meet the clinical diagnostic criteria for CRPS-type 1. The majority of the 30 cases did not include any of the signs or symptoms of the disorder. In some cases, the symptoms were included but there was no reference to diagnostics, workups etc. used to rule out other possible diagnoses. In a few cases, diagnostics or concurrent medical conditions ultimately supported diagnoses other than CRPS. These 30 cases also appear in Table 3; they follow the first 7 and 16 cases discussed above which met or partially met the diagnostic criteria.

Table 3 displays the details of the 53 cases returned by querying the database for the Preferred Term (PT) of 'Complex Regional Pain Syndrome' (CRPS) against Harden *et al* diagnostic criteria for CRPS type 1 as well as time to onset of the CRPS relative to the prior proximal dose of vaccine.

Table 3
Post-marketing case reports with PT of Complex Regional Pain Syndrome: Application of the 4 diagnostic criteria for CRPS type 1

Meets case definition *Y= yes; P= partially meets; N= no				**Criterion 1**	**Criteria 2 and 3**				**Criterion 4**			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
Y	[redacted]		17, F	Chest pain	Y 'pins and needles" in LUE then LLE; paraesthesia	Y temp and color asymmetry of left hand	No	Y decreased strength left UE and limp on left side	Y Essential tremor(C) Anxiety(C) Depression(C) Insomnia(C) Upper respiratory infection (C) 9 days post vaccination but 7 days prior to onset of symptoms. Vocal cord disorder(P) Knee	Y Normal MRI of brain and cervical spine; no left brachial plexus EKG and CT normal per mother; Chest x-ray and EMG normal;	ethinyl estradiol (+) etonogestrel	Day 15 (1) which was also Day 7 post onset of URI symptoms.

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
									operation(P) Knee deformity(P)			
Y	[redacted]		14, F	Y "sudden pain in extremities"	Y hypoesthesia upper arms and legs	Y temp in shoulder area	No	Y gait disturbance- unable to move legs properly	Stress headaches; Unspecified condition post mastoiditis as child; FMH: neurodermatitis (sister),lactose intolerance (mother) polyarthritis (grandfather)	Y MRI, CSF, EEG, Infect disease testing all negative ENG, EMG, SEP, and NLG results show no pertinent findings.	No concomitant therapies	5 months (2) Not recovered at 6 months.
Y	[redacted]		17, F	Y "discomfort", "pain off and on", left hand forearm pain and tenderness	Y numbness reported	Y cool feet	Y swelling of hand/ feet	Y difficulty walking/	"Asthma(C) Food allergy(C) Fatigue(P) Abdominal pain upper(P) Chronic sinusitis(C) Croup	Y Many studies to R/O other diagnoses	Depo-Provera Meningoccal vaccine	~Day 50 (2) Outcome not reported

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	Case #	Country	Age (yr) Sex (M,F)	Continuing pain disproportionate to the stimulus	Sensory disturbances	Vaso motor symptoms	Sudo motor symptoms	Motor symptoms	Co-morbidity	Investigations / Rule out other potential causes of pain	Concomitant therapies	TTO from preceding dose (dose #)
									infectious(P) Dysmenorrhoea(P) Ear pain(P) Endometriosis(P) Headache(P) Ingrowing nail(P) Laryngitis(P) Limb injury(P) Localised infection(P) Localised infection(P) Melanocytic naevus(P) Ovarian cyst(C) Apicectomy(P) Cyst removal(P) Chronic pigmented purpura(P) Skin			

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	Case #	Country	Age (yr) Sex (M,F)	Continuing pain disproportionate to the stimulus	Sensory disturbances	Vaso motor symptoms	Sudo motor symptoms	Motor symptoms	Co-morbidity	Investigations / Rule out other potential causes of pain	Concomitant therapies	TTO from preceding dose (dose #)
									papilloma(P) Upper respiratory tract infection(P) Vulvovaginitis (P) Learning disability(C) Abscess(P) Eustachian tube dysfunction(P) Hair follicle tumour benign(P) Head injury(P) Impetigo(P) Loss of consciousness(P) Rash pustular(P) Sinus tachycardia(P) Staphylococcal			

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
									infection(P) Viral infection(P) Visual impairment(P) Bronchial hyperreactivity (C) Drug hypersensitivity(C) Paronychia(P) Appendicectomy(P)"			
Y	[redacted]	[redacted]	14,F	Y wrist, hand, fingers and forearm of injected limb extremely painful; shooting pains	Y loss of sensation in right forearm	Y cyanosis and pain of right upper limb	Y edema of right upper limb	Y weakness of rt arm	Y None reported	Y Full work up ruled out other potential diagnoses	None reported	Onset of wrist pain 12 days post dose 1; Diagnosed with CRPS Day 137 post dose 2.
Y	[redacted]	[redacted]	14, F	Y Severe pain	Y Numbnes	Y Coldness	Y Swelling	Y Lack of	Y None reported	Y US, Sensory	None reported	24 hours (1)

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
	Literature			of rt arm and hand	s of right arm/ hand	of right hand	of right arm/ hand	function (of arm)	FMH: MS in patient's mother diagnosed 2 years prior	evoked potentials, nerve conduction results WNL. MRI of rt arm and brachial plexus: normal.		Condition improving.
Y	[redacted]		13/ F	Y Rt. thigh to knee pain	Y Sensitivity of rt. Foot	Y Pain sensitive to cold	Y Rt. thigh swelling	No	Atopic dermatitis (MH) Pollinosis (MH) Asthma (FMH)	Some studies included in report: Labs and x-ray normal; MRI normal	None	Day 38 (dose 2)
Y	[redacted]		11, F	Y Severe pain at injection and hand then to other arm and to whole body	Y Severe paraesthesia; generalized allodynia	Y Hot hand	Y Swollen hand	Y Loss of muscle strength	None reported	Y Full work up ruled out other potential diagnoses.	None reported	Day 5 (dose 3). **Follow up did not reveal any new clinical data.**
P	[redacted] Literature	[redacted]	15, F	Y pain in entire left arm	Y numbness paraesthe	Y skin temp decreased	No	Y pain with movement	No	No MRI brain normal	Not reported	within hours post vaccination

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
					sia, light touch sensation decreased			; weakness left arm	Asthma(C) Chronic fatigue syndrome(C) Food allergy(C)			(3) Treated with analgesics, physiotherapy, hydrotherapy and psychological therapy. Recovered
P	[redacted]	[redacted]	15, F	Y "pains in base of rt thumb, then rt arm and forearm"	Y hyperesthesia poorly systematized	Y temp and color of hands	No	No	No previous medical history	Y EMG, cervical cerebral MRIs, neck doppler arterial vessels and rt axillary US negative	Not reported	1- 2 weeks (2) Treated with analgesics/ corticosteroids; Partial recovery; rt thumb still affected.
P	[redacted]		NR,	Y	Y	Y	Y	No	Not reported	No	Not	Immediate

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
		TRA LIA	NR	"lt arm pain" "exquisitely sensitive to touch"	Numbness and allodynia	purplish hand	Swollen hand				reported	(2) Recovered in 5 days
P	[redacted]		15, F	Y "painful joints UE and LE	No	Y legs turned blue	Y swelling ankles, then hands, feet, and legs,	No	Goitre(C) Hypothyroidism(P) Depression(P) Drug hypersensitivity(C)	Y Negative workup for Lyme, ANA, Cancer, lupus; Probable Dx: Reflex neurovascular dystrophy	meningoccal vax and hep A vax in opposite arm from qHPV dose 1; events occurred after dose 2 of qHPV.	Not reported (2)
P	[redacted]		12, F	Y Right hand; exquisite pain in rt fingertips/ palm	Y tingling	Y redness of fingertips	Y swelling of Rt fingertips, palm, wrist, arm	No	None	No Sed. Rate normal; MRI and x-ray performed but results not reported- no details other than RSD	DPT same arm same date as qHPV vaccine; Meningoccal vaccine lt arm same	Day 2 (1) Outcome unknown

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
										diagnosed by orthopedic MD	date as qHPV vaccine	
P	[redacted]		17, F	Y Leg pain; bilateral LE pain	No	No	Y Tests revealed fluid on hip	Y bilateral leg pain/ weakness; requires walker	No Had concurrent strept illness and received penicillin (PCN) shot (site not specified) prior to start of LE pain. Which confounds analysis of the case	MRI, CT, bone scan revealed fluid on hip Dx; CRPS	Oral BCP and Penicillin as treatment med	Within 24 hours (1) which was also ~ 12 hours post penicillin IM for strept infection; Outcome = recovering
P	[redacted]		17, F	Y "pain in sole and back of foot"	No	Y blue color and cold temp of foot	Y edema seen on MRI	No	Not reported	No Scintigraphy showed algodystrophy. MRI detected an oedema; onset while	Not reported	Day 15 (2)

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
										"practicing forced walking in the snow" which confounds the assessment of the case.		
P	[redacted] Literature	[redacted]	13, F	Y Lt upper and forearm pain	Y numbness and allodynia 'extremely sensitive to touch'	Y purple discoloring of hand	Y swollen fingers	No	Not reported	N Not described in literature article	Not reported	immediately (2) Treatment: exercises. Recovered in 5 days
P	[redacted]	[redacted]	12, F	Y Pain at fingertips of Lt hand	Y subjective paraesthesia	Y hyperhidrosis	No	Y grip strength Lt hand decreased; tremor	Not reported	No Not discussed; nerve conduction velocity normal	Not reported	2-3 minutes (1) Recovered; Negative rechallenge post dose 2 was reported.
P	[redacted]	[redacted]	12,F	Y pain is in	Y Foot	Y skin color	Y excess	Y involuntar	No Asthma (HC),	No Blood tests	Not reported	Day 8 (1)

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
				arm; other in hands, thighs, upper arm, forearm, foot/ fingers	numbness	change hands	sweating both hands	y twitching of an arm and a foot	Pain (HC), Viral hepatitis carrier (CC)	normal;tendon reflex norml;EEG, EMG, EKG, bone marrow exam NOT PERFORMED		
P	[redacted] Literature POTS also coded	[redacted]	11, F	Y Severe limb pain; hands and feet "uncomfortable pain in legs"	No	Y Toe cold	Y Gait disturbance	No Restricted shoulders/ thigh movement; weakness rt. side of body; limb paresis were reported; however, manual muscle tests and	MH: lt. ovarian CA and oorphectomy CC: None	No EEG; MRI head/ spine/ neck/ CT and PETnormal; Manual muscle tests, objective sensory exams and deep tendon reflexes all normal.	None reported	7 months (dose 1) The patient recovered from all events.

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
								deep tendon reflexes were normal				
P	[redacted]	[redacted]	9/ F	Y Severe pain in lt foot	Y Allodynia lt foot	No	No	Muscular dystrophy of the LLL.	Not reported	Not reported	Not reported	2 months (3) Treated with opioids, immobilization of foot; spinal electrical stimulus implant
P	[redacted] Literature	[redacted]	15, F	Y "Limb pain"	Y Hyperpathy	Y Decreased skin temperature	Not reported	Y Gait disturbance and limb paresis	Not reported	Not reported; Case report states "CRPS was consistent with criteria of IASP".	Not reported	Not reported; Outcome is unknown after several attempts to obtain follow-up.

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
P	[redacted] Literature	[redacted]	18, F	Y Pain in extremity	Y Hyperpathy	Y Excess sweating	Not reported	Y Limb tremor	Not reported	Not reported	Not reported	Not reported.
P	[redacted]	[redacted]	13, F	Y Upper limb and vertebral algia; knee and hip pain	Y Myofascial systemic pain syndrome; foot numbness	Y Body temperature drop	Y Severe edema, rt hand, arm and shoulder	Y Muscular dystrophy	No Dx: Pseudo cerebral tumor; Muscular dystrophy; Cerebral thrombosis	No	Not reported	Day 4 post dose 1; Patient recovered from CRPS and pseudo cerebri tumor.
P	[redacted]	[redacted]	12, F	Y Intense pain in left wrist then spread to shoulder	Y Intolerant to rubbing or movement of affected areas	Y Asymmetric temperature in both extremities	Y Intermittent color changes of short duration	Not specifically addressed	No None reported	No Not reported	Not reported	Day 4 (dose number not reported). At the time of the report, the patient was recovering.
N	[redacted] literature	[redacted]	16, F	Y shooting pain down lt arm then LLE	Y Numbness, paraesthesia	Y skin temp of forearm	No	Y L arm and leg parlaysis; absent	No Spinal laminectomy(C) Polycystic	No as results of MRI reveal other potential causative	"ethinyl estradiol (+) levonorgestrel	Day 6 (1)

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
								reflexes left arm; limited ROM	ovaries(P) Drug hypersensitivity(C) Intervertebral disc protrusion(P) Sciatica(C)	factors. MRI showed neuritis at C5,6,and 7 nerve roots	ranitidine "	
N	[redacted]	[redacted]	14, F	Not reported	No	No	Y Periph circ d/o?/ sweating	No	"Immunisation (P) Arthropathy(P) Pre-existing left knee disorder	Serology MRI EKG Neurological exam No results	Not reported	Day 44 (2)
N	[redacted]	[redacted]	14, F	Y Rt sided temporal pain with Bells palsy Neck pain	No	No	No	No	Facial weakness Irregular menses	No MRI: T2 abnormalities at Lt lateral ventricle; "could represent gliosis and antiphospholipid"	Progesterone	Day 2 (1)
N	[redacted]	[redacted]	NR, NR	Y neck and arm	No	Y hand cold	No	No	Not reported	Ist MRI showed	Not reported	1 hour (1)

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
										inflammation of brachial plexus; MRI brachial plexus, spinal cord and brain normal; nerve conduction studies normal		
N	[redacted]	[redacted]	NR, NR	N "pain", not otherwise specified	Y presented with numbness and pins and needles in arm	Y arm cool on exam	No	Y c/o Lt arm weakness	Not reported	No MRI brain normal; neuro exam conducted (no report)	Not reported	Not reported (3)
N	[redacted]	[redacted]	NR, NR	Y rt arm felt very painful	No	No	No	Y Right arm weakness	Not reported	No No details	Not reported	Within minutes (2) Recovered in 10 days
N	[redacted]	[redacted]	16, F	Y LLE pain	No	No	No	Y LLE weakness reported by mother	None	No	Meningoccal vaccine	Day 53 (NR) 'Recovered 90%'

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
N	[redacted]	[redacted]	13, F	Y Arm pain distal to injection site	No	Y purplish hand; colder temp of hand	Y swelling of injected arm distal to inj site	No	None reported	No details of workup;	None	Day 2 (2) Recovered
N	[redacted]	[redacted]	12, F	Intermittent burning pain in both legs	No	No	No	No	None	No Tests were scheduled; No details of workup; consumer reported but received as FOIA	Not reported	Day 2 (2) Outcome unknown
N	[redacted]	[redacted]	14, F	Y Right wrist and knee moderate pain	No	No	No	No	None	Ortho, rheumatol consults were unremarkable; MRI, xray, single photon emission computed tomography	Not reported	Not reported (3) Outcome not reported; Case reported as non-

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
										(SCPECT) all negative		serious
N	[redacted]	[redacted]	19,F	Y Shin pain, bone pain	No	No	swollen knees	difficulty walking/ muscle weakness; signs of tremor/ clonus	None Family MH: Autoimmune ulcerative colitis	No Multiple MRIs (brain, spinal cord, extremities), EMGs and bone scans initially reported as negative. In follow up mentionned MRI and other unspecified tests Dx: Upper motor neuron disease with demyelination of motor neurons (not further specified)	None	~ 1 month (2)
N	[redacted]	[redacted]	12, F	Y	Y	Y	Y	Y	"Immunisation	No	Not	Day 8 (1)

Meets case definition *Y= yes; P= partially meets; N= no				**Criterion 1**	**Criteria 2 and 3**				**Criterion 4**			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
	[redacted]			shooting pain down left arm	numbness in fingers and arm	Cold, clammy arm	swelling in Lt arm	weakness in Lt arm	(C) Horse riding accident 2-3 weeks prior to dose 2 of vaccine	Many tests done and ruled out other etiologies; however, case is confounded by horseback riding accident which preceded the medically confirmed events and trips to ERs etc. Follow up received with Final Dx: somatization disorder, therefore, does not meet criteria #4	reported except for treatment meds	
N	[redacted]		16,M	Y Arm pain	Y numbness	No	No	Y slightly	Familial risk factor(CC)	No Dx was	None	Day 7 (1)

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
				only when grabbing something	tingling forearm to fingertips			weakened grip	Appeared to have an old bruise; no other significant personal history	Moderate chronic lower trunk (Lt) brachial plexopathy supported by EMG		
N	[redacted]		12, F	Y Legs and low back pain	No	No	No	Y mobility decreased	Not reported	No No details	Not reported	Day 2 (2); Recovered
N			13, F	No Not reported	No	No	No	No	Not reported	No details	None	Not reported
N			NR, F	Y Arm (not further specified)	No	No	No	Y pain and decreased mobility of arm	Not reported	No details	Not reported	Not reported
N			13, F	Y Low back pain, trunk/ flank and lower extremity pain;	Y Numbness in hand; low back numbness	No Not reported	No Not reported	No Not reported	No Bacterial infection was diagnosed and treated with IV antibiotics. CRPS was	No Increased WBC and CRP.	Not reproted	Day 2 post dose 3. Though pain was reported as mild, the patient was

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
				abdominal pain; eye pain. Pain severity reported as mild.					diagnosed.			hospitalized. Pain of trunk, lower extremities and abdominal pain were not recovered at the time of the report.
N	[redacted]		12, F	No Not reported	Y numbness of fingers	No	No	Y "sensorimotor disorder"	Not reported	No details	Not reported	Day 1 (NR)
N	[redacted]		15, F	Y Left hand pain and pain in feet, generalized joint pain reported	Y Numbness in right fingertips and visual field disturbance	No Not reported	Y Swelling of knee	Y Weakness in right hand and left upper limb reported; and LE	Convulsion (HC) Abnormal left visual field prior to vaccination (HC)	No MRI of head "mildly abnormal", Nerve conduction studies, blood tests, x-rays	None reported	Unclear when reported symptoms of CRPS started. Despite multiple

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
								gait disturbance		all with normal results; EEG abnormal but epilepsy ruled out; single photon emission computed tomography (SPECT) revealed decreased blood flow in the left temporal lobe and the basal ganglia; Suspected Encephalitis		attempts to get follow-up, outcome of events is unknown. Note that physician's objective exam does not support patient's subjective report of symptoms.
N	[redacted]		13, F	No pain is not mentioned	Y numbness of hands	No	No	Y shaking of hands	Asthma (HC), Pneumonia (HC), Poisoning (HC) Cold symptoms (CC)	No unclear; "no abnormal blood tests, autoimmune disorders or brain waves were found"	Not reported	Day 1 (NR)

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
N	[redacted]		17, F	Pain in ankles wrist, and other joints.	Not reported	Not reported	Not reported	Reported as "bedridden" without details.	Autoimmune urticaria in 2008 (not further specified). Dx: Autoimmune hypothyroiditis Hyperprolactinemia	Unspecified tests, scans, blood tests reported; near normal tilt table test; celiac and lactose intolerance tests normal. Negative tilt test for POTS but orthostatic intolerance and autonomic dysfunction diagnosed. MRI cerebrum shows small 8 mm corpus pineale cyst.		3 months post dose 3. No details of CRPS symptoms were included in the report but the patient was reportedly diagnosed at the national hospital pain center. This case was retrospectively reported 4 years post onset and follow up received in 5th year included CRPS.
N	[redacted]		12/ F	No No details	No No details	No No details	No No	No No details	No No details	No No details	Not reported	Not reported

Meets case definition *Y= yes; P= partially meets; N= no				**Criterion 1**	**Criteria 2 and 3**				**Criterion 4**			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
				reported	reported	reported	details reported	reported	reported	reported		
N	[redacted]		10/ F	Y Injection site pain/ rt arm pain	Y paresthesia	Y Red spots on all 4 limbs; Coldness of skin; cyanosis of extremities	No	Y Paresis	No Patient experienced a hypersensitivity reaction.	No Immediate Hypersensitivity reaction	Yellow fever virus vaccine	20 minutes (dose number not reported) Recovered; treatment and duration not reported.
N	[redacted] Literature	[redacted]	13, F	Pain in extremity	No Not reported	No Not reported	No Not reported	Y Limb paresis and gait disturbance	Not reported	Not reported	None reported	Not reported; Outcome unknown despite attempts to obtain follow-up.
N	[redacted] Literature	[redacted]	12, F	No Not detailed in the report	No Not detailed in the report	No Not detailed in the report	No Not detailed in the report	No Not detailed in the report	No Not detailed in the report	No Not detailed in the report	Prior vaccinations with DPT vaccine	Day 3 (dose 1) Recovered (date not reported)

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
											and Japanese encephalitis vaccine 3 months prior to onset of events; and Measles/ rubella vaccine 2 months prior to onset of events.	
N	[redacted]		13, F	No Not detailed in the report	No Not detailed in the report	No Not detailed in the report	No Not detailed in the report	No Not detailed in the report	No Not detailed in the report	No Not detailed in the report	Not reported	Not reported; Outcome unknown
N	[redacted]		14, F	Y Irradiating pain from left deltoid	Y Numbness of left upper arm	No Not reported	No Not reported	Y Muscular weakness of left	No Not reported	No Not reported	No Not reported	Day 1 (dose2) Symptoms improved

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
				injection site to left side of neck	(diagnosed with paresis of left axillary nerve)			upper arm				several weeks later; totally recovered from CRPS and left axillary nerve paresis within 2 months.
N	[redacted] Literature	[redacted]	12,F	No Pain reported at injection site and to Middle left forearm to fingers of injected arm	No Numbness of forearm to fingers	No Hyperhidrosis was mentioned but not clear if it was temporally related to vaccination or venipunct	No Not reported	Y "Weakness" not further specified	Confounded by venipuncture with similar clinical course; Patient reported to be emotionally unstable with hysterical predisposition. Prior episode of local	No Not reported	None reported	5 to 10 minutes (dose 1) "suspected CRPS" but reporter noted that pain did not meet criteria. Recovered within 1 day;

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
						ure events.			swelling post influenza vaccine.			Experienced a similar episode in other arm after venipuncture at school; also recovered completely.
N	[redacted]	[redacted]	14, F	Y Severe pain reported at injection site only; Myalgia	No	No Not reported.	Y Joint swelling	Y Gait disturbance; muscular weakness	No Encephalitis reported as a intercurrent condition. Surgical history of tympanoplasty and resection of cholesteatoma.	No MRI and blood tests results were within normal limits. Peripheral circulatory disorder was diagnosed. Atrophy and decreased blood perfusion	None reported	1 month (dose 2); some symptoms resolving but overall condition still not recovered.

Meets case definition *Y= yes; P= partially meets; N= no				Criterion 1	Criteria 2 and 3				Criterion 4			
Meets case definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M,F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations / Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
										noted in left hippocampus (Feb 2014); CSF analysis revealed glutamate receptor antibody.		
N	[redacted]		46	Unspecified pain reported	No	Not reported.	Not reported.	Not reported.	Not reported.	Numerous blood counts; results within normal limits except increased leukocytes	None reported	2.5 years (dose not reported); not recovered.
Y= yes; P= partially meets; N= No: NR = Not reported; TTO= time to onset from proximate preceding dose												

CRPS Symptom Queries

The query of the company safety data base for case reports that include various combinations of symptoms of CRPS referred to as the "CRPS Symptom Queries" yielded 37 additional distinct case reports; the query excluded case reports if the PT of CRPS was also coded since these cases were already presented in Table 3. The CIOMS forms are appended to this response document [Ref. 5.3.6: 0476JD].

The CRPS symptom queries did not identify any post marketing reports temporally associated with the administration of 9vHPV vaccine.

All 37 cases were reported as serious. Geographically, 24 reports were from Europe with 19 from Denmark, 2 from Sweden, and 1 each from France, Germany, and Spain. Eleven (11) reports were received from the US, and 1 each from Japan, and Israel.

Age was reported in 37 reports as follows: 3 were age 12; 16 were older than 12 and up to 17 years of age; 5 were between 18 and 20; and 12 were older than 20 years of age. Gender was reported in all 37 cases as involving 36 females and 1 male.

Review of the reports reveals that no cases appear to meet all of the clinical diagnostic criteria for CRPS type 1 described above in the Methods section. Six cases partially meet the clinical diagnostic criteria for CRPS type 1. A case was considered to partially meet criteria, when clinical data was available to meet several of the criteria but the information was incomplete and therefore, lacking in meeting all criteria required. Oftentimes, it was failure to meet criterion #4, in that it was not clear from the report that a medical workup was conducted to rule out other potential diagnoses or the results were not provided. These 6 cases are the initial 6 cases displayed in Table 4 below.

The remaining 31 cases did not meet the clinical diagnostic criteria for CRPS-type 1. The majority of the cases made no reference to diagnostics, workups etc. used to rule out other possible diagnoses or did not include enough of the signs or symptoms of the disorder. In some cases, the symptoms were included but the focus of the report was not on the issue of pain but rather, pain was mentioned and the focus was on some other event such as a syncopal episode. In a few cases, diagnostics or concurrent medical conditions ultimately supported diagnoses other than CRPS. These 31 cases appear in Table 4; they follow the first 6 cases, discussed above, which partially met the diagnostic criteria.

Table 4 presents the details of the 37 case reports returned by querying the database for symptoms of CRPS against the Harden case criteria as well as the time to onset of the symptoms of CRPS relative to the prior proximal dose of vaccine.

Table 4
37 Post-marketing case reports identified by "Symptom queries for CRPS": Application of the 4 diagnostic criteria for CRPS type 1

Meets Case Definition *Y= yes; P= partially meets; N= no				**Criteria 1**	**Criteria 2 and 3**				**Criteria 4**			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
P	[redacted]		27/ F	Y Abdominal pain, muscle and joint pain; neck and upper back pain	Y Sensory disturbance	Y But reported in conjunction with fever.	No	Y Decreased mobility / paralysis of the right leg for short periods/ loss of strength and control of legs	N Asthma (CC) which emerged along with flu-like symptoms (cold sweat and fever) post dose 1 of qHPV vaccine MH includes: Borderline personality D/O; whiplash injury; Depression Herniated disc	Y Investigated for vitamin deficiency, sclerosis, brain tumors, neurological disorders; results not provided. MR cerebrum and LP results were normal. Neuro exam did not reveal a diagnosis.	Not reported	Day 4 (2)

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
									Respiratory tract infection			
P	[redacted]		13/ F	Yes Back pain; pain in neck and shoulders; pain in knees;	Y Sensory disturbance on right side of face and right hand.	No	Y Swollen knee	Y Reduced strength in right arm.	No Severe case of flu post vaccination and prior to onset of POTS. Onset of back pain was 1 month following intense flu episode which confounds assessment.	No LP reveals high spinal fluid pressure; POTS diagnosed by tilt table test. No other investigtions detailed in the report.	Not reported	3 months (3)
P	[redacted]		22/ F	Y Pain in body/ limbs	Y “Pain by touch of skin”	Y Increased sweating and chills	No	Y Reduced strength	No Ovarian cyst (CC) Influenza	No	Not reported	Day 1 (NR)

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
								in body and limbs;	like symptoms with blood in urine, stool and vomitus; Throat infection			
P	[redacted]		13/ F	Y Neck pain	Y Numbness in Rt UE and legs;	Y Peripheral coldness	No	Y Weakness of LUE and LEs; unable to walk due to pain;	No During hospitalization, signs of criteria 1, 2 and 3 were not seen	Y General lab tests normal; Abdominal CT normal; knee and hand x-ray was normal;	None	Day 33 (3) Recovered
P	[redacted]		12/ F	Y Leg/ muscle pain and burning of soles of feet and palms of	Y Tingling/ numbness soles of feet and palms of	Y Sweats Cold forehead	No	Y Leg muscle weakness; reduced	No MH includes Vitamin D deficiency	No Dx: Fibromyalgia Acquired mitochondriopathy	Not reported	9 months (2) Recovering from muscle pain

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
				hands	hands Allodynia			walking function and unsteady gait		POTS		
P	[redacted]		14, F	Severe joint pain with burning sensation	Y Allodynia Tingling	Y Hot flushes and cold sweats	Y Intermittent swelling of hands	Muscle weakness; walking difficulty	No Vitamin B12 deficiency Vitamin D deficiency	No Bloodwork revealed the vitamin deficiencies No other investigations were reported.	Not reported	Not reported (3) Recovered
N	[redacted]		18/ F	No	Y Numb left arm and 3 fingers	Y sweating attacks; cold left arm and 3 fingers	No	No	No Convulsive syncopal episode	No	Not reported	Immediate (2)
N	[redacted]		16/ F	No	Y Arm numb and heavy	Y Cold sweat/ hypoaesthesia	No	No	No Syncopal episode	No	None	Immediate (2)

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
N	[redacted]		14/ F	Y Spine burning	Y Head felt numb	No	No	No	No Conversion d/o	No Migraine diagnosed	Meningoccocal vaccine	Day 7 (3)
N	[redacted]		14/ F	Y Diffuse joint pain	No	Y White cold hands; blue hands; and sweating	No	No	No Syncopal episode	No ID workup was negative; Lyme negative; Full physical, labs and diagnostic tests WNL.	Dydrogesterone	One month (3)
N	[redacted]		23/ F	Y Back pain, neck pain	Y Leg numbness	Y Cold sweat	No	Y Muscle weakness all over body	No Small disc herniaion at L4-5	No MRI cerebrum/ spine normal; spinal fluid normal; VEP and SSEP normal; labs performed but no results	Not reported	Day 15 (1)

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
N	[redacted]		23/ F	Y Back, chest, and neck pain which may have preceded vaccination	Y Numbness arm and leg (preceding vaccination)	Y Cold sweat	No	No	No Pre-existing bicycle trauma with severe concussion and hypersensitivity to sensory input; PTSD Influenza like symptoms	No Pre-existing symptoms confound analysis of this case	Not reported	TTO and dose # not reported due to conflicting data
N	[redacted]		13/ F	Y Shoulder pain; back and pelvic pain	Y Tingling hands and feet	Y Cold sweat and hot flush	No	Y Muscular weakness; required wheelchair	No Pre-existing pelvic and groin pain; Vertebral prolapse; bulimia and anorexia. Developed	No MRI 2 disc prolapses Not medically confirmed	Not reported	2 months(2)

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
									Fibromyalgia			
N	[redacted]		12/ F	Y Pain in entire body especially lungs, legs, and arms	Y Hyperaesthesia in legs and rt arm	Y Hyperhidrosis	No	Y Weakness	No POTS diagnosed;	No Not medically confirmed	Not reported	Not reported (dose 2)
N	[redacted]		14/ F	Y Abdominal pain; neck and back pain	No	Y Hyperhidrosis	No	Y Muscular weakness	No	No POTS negative; other test results not reported	Not reported	Day 1 (3)
N	[redacted]		13/ F	Y Left leg pain Back pain	Y Numbness legs	Y Hyperhidrosis	No	Y Weak/ heavy legs/ myalgia and muscle cramps	No Mild disc degenerative T11-12 and L4-5; Toe fracture and secondary injury of a hematoma	Yes EMG/ NCS normal	Not reported	Day 63 (3)

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
									under a nail confounds assessment of the case; Dizziness is secondary to a ball injury			
N	[redacted]		19/ F	Y Head, back, neck and chest pain	Y Tingling and numbness	No	Y Sweats and chills	No	CC includes: Nasopharyngitis Hoarseness of voice MH includes: ETOH user Hypoglycemia, pharyngitis, peritonsillar abscess and recurrent throat infection,	Y Rheumatology, MRI, CT, LP with no definitive diagnosis	Ethinyl estradiol + norethindrone	Day 38 (2) Outcome NR

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
									hearing loss, anemia, amoxicillin allergy, mood disorder and dizziness			
N	[redacted]		20/ F	No Back pain mentioned briefly but not focus of case report Seizure vs syncope is the focus of case report	Y Paresthesia	Y Sweating	No	No Loss of motor skills during syncopal episode	No MH includes concussion in high school and head injury as a child Marijuana use the night of the event (CC)	No MRI + for demyelination Workup conducted for MS Dx: Vasovagal syncope, dehydration and anemia	None reported	Not reported (2)
N	[redacted]		18/ F	Y Pain arms and legs Abdominal colic pain	Y Paraesthesia	Y Sweats	No	Y Weak legs Unsteady gait	No GBS	No US negative Increased WBC Dx: GBS	Not reported	Day 40 (2) Recovered

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
N	[redacted]		13/ F	No Low back and neck pain mentioned but not the focus Fatigue is the focus	No	Y Nail changes Hot/ cold	Y Edema	Y Weakness	No Chronic fatigue	No Labs: chronic fatigue with joint pain	Not reported	Day 46 (1)
N	[redacted]		16/ F	Y Back pain Thigh pain	Y Numbness	Y Cold feet	No	Y Weakness Difficulty walking	No GBS	No EMG CSF Dx: mild GBS	Varicella vaccine Menactra vaccine Hepatitis A vaccine	Day 11 (1) Outcome recovering
N	[redacted]		12/ F	No	Y Numbness left leg	No	No	No	No Immediate allergic reaction with urticaria and again on Day 3 and Day 7 Asthma	No MRI fluid in sinuses Crystals inner ear LP normal MRI brain/ spine normal	Not reported	Day 15 (1) Not recovered

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
									(CC)			
N	[redacted]		26/ F	Y Hand/ feet/ back and joint pain	Y Arm tingling	No	No Swollen finger joints arthritis	Yes Weakness can't lift heavy items	No Psoriatic arthritis (CC) Polycystic ovarian syndrome	No Us shows arthritic changes Lumbar MRI and Cerebrum MRI normal	Not reported	Day 3 (1)
N	[redacted]		24/ F	Y Pain in neck and shoulders	No	No	No	No	No MH cervical spine flattening HCP does not confirm evaluations	No	Not reported	Not reported (NR) Outcome not reported
N	[redacted]		32/ F	Y Burning pain in arms and legs	Y Hypoaeshtesia arms and legs	No	No	Y Decreased strength arms and legs	MH includes Epilepsy Palpitations	No Dx; pernicious anemia	Not reported	Not reported (2)
N	[redacted]		22/ F	No Focus of the	No	No	No	No	No Syncope	No Exams and labs	Not reported	Immediate and again

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
	literature			report was syncopal episodes in patient with history of syncope related to needle procedures.					(MH) Lyme's disease (MH)	(CBC, Lyme titer, CK etc) were normal		at Day 6 (1) Outcome not reported
N	[redacted]		35/ F	Y Diffuse abdominal pain Syncopal episodes were the focus of the report	No	Y cold	No	No	No CIN 3 (MH and CC)	No Full clinical workup done- all results were normal High noradrenaline levels were noted CIN 3		Not reported (NR) Outcome not reported
N	[redacted]		14, F	Y Consumer reports pain, chest pain not	Y Consumer reports pins and needles	No	No	Y Consumer reports	No Allergies (mold, cockroach,	No Consults with neurology, pulmonology,	lnfluenza vaccine; ethinyl estradiol/n	Within 30 days (1)

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
				further described	in extremities			muscle weakness associated with fainting	smoke, dust, dust mite, trees, grass and perfume) Polycystic ovarian syndrome Hypoglycemia Depression On date of vaccination developed flu-like symptoms which lasted 2 weeks	podiatry, endocrinology Labwork done Some AEs are confounded by pre-existing conditions and concomitant flu vaccine.	orgestrel; vitamins; Metanx, metformin HCl, fluoxetine HCL; trazodone HCl; spironolactone	
N	[redacted]		20/ M	No "aching' reported by patient	No	No "sweating episodes reported in	No	Yes Loss of hand strength	No Intercurrent flu-like symptoms	No None were conducted	None reported	Not reported (3) Recovered

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
						conjunction with fever and flu-like symptoms			with palpable lymph nodes, aching, and fever occurred 2 days post vaccination			
N	[redacted]		23/ F	No Muscle pain reported by patient	No	No	Yes Increased sweating reported	Y Muscle weakness not otherwise described reported by patient	No Mononucleosis infection (Summer 2014) Patient states that symptoms worsened following mono infection.	No No investigations were conducted.	None reported	Not reported relative to CRPS symptoms (NR)
N	[redacted]		30/ F	Y Burning sensation in	Y Tingling feeling left	Y Sweating increased/	No	Y Left arm	No Autoimmune hepatitis	No Dx:Autoimmune hepatitis	None reported	Day 5 (3) Outcome not

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
				neck, spine, left shoulder, lower back	arm/ leg	"skin coloring yellow spots"		paralysis followed by muscle spasms	confounds the clinical picture	Labs showed elevated liver function studies Mammogram + for swollen lymph gland		recovered; Events reported as non-serious
N	[redacted]		28/ F	Y Pain in chest, shoulders, arms and legs	No	Y Severe night sweats	No	No "possible muscle weakness" not confirmed	No POTS was diagnosed with tilt table test	No Lab tests including metabolic and infectious disease panel, kidney and liver function and CBC conducted; results not reported.	Not reported	Day 2 (1)
N	[redacted]		14/ F	Y Body pain; bones especially feet legs, lower back, neck	No	Y Cold feet Hot flashes/ sweats	No	No	No Dx: Chronic recurrent multifocal osteomyelitis; Sinusitis	Full neurological work-up; all results normal. MRI revealed sinusitis in the right frontal sinus and		4 months (3)

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
				shoulder, sternum, and jaw.						maxillary sinus. CSF pressure measurement normal. Laboratory reveals normal blood counts, liver and kidney function tests.		
N	[redacted]		NR/ F	No	No	No	No	No	Not reported; case report refers to aggregate data and not an individual patient.	Not reported	Not reported	Not reported

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
N	[redacted] Literature		14/ F	Y Severe pain in right leg	Y Sensory disturbance not specified	Y	No	Y Muscular weakness	No Recurrent infections (CC) Congenital neurological malfunction (MH)	No POTS diagnosed MRI shows Chiari malformation MRI changes reported that could account for symptoms	Not reported	Day 8 (1)
N	[redacted]		16/ F	No Stomack pain and chest pain not further described	No	Y Cold sweat reported	No	No	Knee clicking (MH)	No Not reported	Not reported	Not reported (2)
N	[redacted]		15/ F	Y Muscle pain and chest pain	Y Numb feet	Y Cold extremities	No	No	No ADHD, Anorexia, Binge eater Sleep walker	No Rheumatology consult Dx autoimmune disorder MRI revealed shin splints (patient is a	Methylphenidate HCl	Not reported (2)

Meets Case Definition *Y= yes; P= partially meets; N= no				Criteria 1	Criteria 2 and 3				Criteria 4			
Meets case Definition (Y, P, N)*	**Case #**	**Country**	**Age (yr) Sex (M, F)**	**Continuing pain disproportionate to the stimulus**	**Sensory disturbances**	**Vaso motor symptoms**	**Sudo motor symptoms**	**Motor symptoms**	**Co-morbidity**	**Investigations/ Rule out other potential causes of pain**	**Concomitant therapies**	**TTO from preceding dose (dose #)**
										cross country runner) Possible dx: chronic exertional compartment syndrome		

Y= yes; P= partially meets; N= No: NR = Not reported; TTO= time to onset from proximate preceding dose

Reporting Rates for cases reported with the PT of CRPS and for cases reported with combinations of symptoms of CRPS associated with qHPV vaccine are presented in Table 5. Reporting rates are presented per million people vaccinated. These calculations were not done for 9vHPV vaccine since there were no case reports, involving 9vHPV vaccine, received.

Table 5
CRPS Reporting Rates per Million Vaccinees

Quadrivalent HPV Vaccine Cumulative to 31-May-2015 for Doses Distributed and to 15-Jun-2015 for Cases Reported				
Gardasil (V501) Estimated Number of Marketed qHPV Vaccine Doses Distributed			Reporting rate for Cases with the PT of CRPS per Million Vaccinees by Region or Country (# Reports/ # People vaccinated x 1 million)	Reporting rate for Cases Reported with Combinations of Symptoms of CRPS per Million Vaccinees by Region or Country (# Reports/ # People vaccinated x 1 million)
	Cumulative to 31-May-2015	Number of persons vaccinated (assuming 3 doses administered per person)		
Worldwide	190,897,611	63,632,537	<1 case (53/ 63,632,537)	<1 case (37/ 63,632,537)
EU	35,907,186	11,969,062	1 case (13/ 11,969,062)	2 cases (24/ 11,969,062)
US	[redacted]		<1 case (11/[redacted])	<1 case (11/[redacted])
Denmark			~4 cases (2/[redacted])	42 cases (19/[redacted])
Japan			29 cases (18/[redacted])	~2 cases (1/[redacted])

Discussion and Conclusion

This analysis involved 53 case reports with the PT of CRPS reported and 37 case reports generated using symptom queries. Of the combined 90 case reports that were reviewed against the Harden criteria for CRPS, 7 cases were assessed to have met the criteria completely and 22 cases were assessed to have partially met the criteria; that is, several criteria including symptoms were reported but information was incomplete. In some reports, analysis of the case was confounded by other factors that could have potentially contributed to the development of pain in the patient's clinical course. The data base search strategy of querying on the signs/ symptoms, did not seem to be very specific in identifying true cases of CRPS as it did not yield any additional case reports with the clinical detail required to medically assess for CRPS.

A conservative estimate of the number of people exposed to the vaccine was used to calculate reporting rates and yet overall the reporting rates worldwide are not remarkable. It

is recognized that there are regional differences, notably Japan for reports of CRPS, and Denmark for reports of symptoms of CRPS.

The case reports reviewed did not raise a safety concern for reports of CRPS beyond what may be considered the background rate (please see response to Question 3). There are clearly some regional differences in reporting, some of which may be due to stimulated reporting due to media attention. Although review of post marketing cases cannot conclusively rule it out, no causal relationship to qHPV vaccine has been established. The MAH will continue to monitor reports of CPRS in patients receiving qHPV and 9vHPV vaccines.

1.1.2.2 Postural Orthostatic Tachycardia Syndrome (POTS)

Methods

Identifying Case Reports
The Company aggregate analytical tool, METEOR, was utilized to identify medically confirmed cases that contained the MedDRA preferred term (PT) of 'Postural Orthostatic Tachycardia Syndrome' (POTS) reported as temporally associated with the administration of qHPV and 9vHPV vaccines received worldwide from the marketed environment cumulative to 15-JUN-2015.

In addition to the PT of POTS, the Company safety database was queried to find medically confirmed cases of POTS-like reports. The POTS-like reports included relevant symptoms and synonyms as described in Step 1 below reported as temporally associated with the administration of qHPV and 9vHPV vaccines received for the period 1-JUN-2006 to 15-JUN-2015.

The MAH used the proposed Danish Health Authority's list of signs/symptoms of POTS to identify 8 groups of PTs that represent signs/symptoms and their associated synonyms of POTS. However, since these symptoms (and associated synonyms) alone would not be specific in identifying potential POTS cases, data base queries were conducted in such a way that combinations of symptoms would need to appear in a report. Utilizing the 8 groups of PTs, 6 queries were run utilizing various combinations of the signs/symptoms starting with query #1 which included all 8 groups of signs/ symptoms. The queries were devised to account for various combinations of cardiac, dysautonomia, and sensory symptoms without being overly exclusive (i.e. as more symptom groups are added to the query logic, the return of case reports diminishes).

Step 1: The PTs representing symptoms of POTS to be used in the queries were grouped as follows:
Group A: 'palpitations' **OR** 'tremor' **OR** 'heart rate increased' **OR** 'tachycardia' **OR** 'tachyarrhythmia'

Group B: 'dizziness' **OR** 'dizziness exertional' **OR** 'dizziness postural' **OR** 'exercise tolerance decreased' **OR** 'muscular weakness' **OR** 'fatigue'
Group C: 'syncope' **OR** 'presyncope' **OR** 'loss of consciousness'
Group D: 'orthostatic intolerance' **OR** 'orthostatic heart rate response increased'
Group E: 'paraesthesia' **OR** 'sensory disturbance' **OR** 'blurred vision'
Group F: 'hyperhidrosis'
Group G: 'memory impairment' **OR** 'disturbance in attention' **OR** 'confusional state' **OR** 'cognitive disorder'
Group H: 'autonomic nervous system imbalance' **OR** 'urinary retention' **OR** 'constipation' **OR** 'diarrhoea'

Step 2: Six queries were run using the logic displayed above:
Query #1: Group A AND Group B AND Group C AND Group D AND Group E AND Group F AND Group G AND Group H.
Query #2: Group A AND Group B AND Group D AND Group F
Query #3: Group A AND Group B AND Group D AND Group E
Query #4: Group C AND Group E AND Group F
Query #5: Group C AND Group D AND Group E AND Group F
Query #6: Group C AND Group D AND Group E AND Group H

Evaluating Case Reports
The identified reports from both the POTS and POTS-Like Symptom queries were reviewed individually using the clinical diagnostic criteria for POTS discussed by SR Raj in a 2013 publication of Circulation [Ref. 5.4: 03SW00] and Sheldon 2015 [Ref. 5.4: 046WN6]as well Jarjour 2015 [Ref. 5.4: 03SWR7] and Freeman [Ref. 5.4: 03SWQZ]. In line with PRAC expectations raised during the Teleconference of 17 July, Table 6 lists the case definition used for POTS.

Table 6
Case definition based on Raj 2013 and Sheldon 2015 Publications [Ref. 5.4: 03SW00], [Ref. 5.4: 046WN6]

Postural tachycardia syndrome (POTS) is defined as a clinical syndrome that is usually characterized by (1) frequent symptoms that occur with standing such as light headedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue which improve with recumbence (2) an increase in heart rate of ≥30 bpm when moving from a recumbent to a standing position held for more than 30 seconds (or ≥40 bpm in individuals 12 to19 years of age) in the absence of orthostatic hypotension (>20 mmHg drop in systolic blood pressure) (3) Symptoms last > 6 months (4) Absence of other overt cause of orthostatic symptoms or tachycardia (e.g., active bleeding, acute dehydration, medications)

Applying the criteria to Spontaneous Reports
It is important to note that due to the nature of spontaneous reporting, it is sometimes difficult to determine whether an event included in a case report is objectively or subjectively reported. Generally speaking, for the purposes of this analysis, the report needs to include evidence in all of the 4 categories above.

Additionally, it is difficult to determine the thoroughness of the medical work-ups conducted to rule out other diagnoses. Generally speaking, for the purposes of this analysis, if the report mentioned that numerous tests such as ECG, x-ray, laboratory tests, MRI etc. were conducted and included normal results, then it was considered that criterion #4 was met.

In summary, assessment of the case reports relied heavily on medical judgment in assessing the wording used in a report, the presentation of the data, and possible inferences made by reporters. For this reason and in order to be transparent, cases were reviewed and are presented as those that met the diagnostic criteria, those that only partially met the diagnostic criteria and those that did not meet diagnostic criteria.

The Worldwide Financial Reporting System was queried to determine the number of doses distributed cumulative to 31-May-2015 worldwide (WW), in US, Denmark and in Japan. The number of doses distributed for each region (WW, US, Denmark and Japan) will be divided by 3 for an estimated number of patients vaccinated. This is in line with the PRAC recommendation and provides a "conservative" estimate of number of people exposed to the vaccine.

This estimated number of patients vaccinated will be used in the calculations of reporting rates by region as follows:
reports of CRPS/ number of patients vaccinated X 1 million.

Results

The query of the Company safety data base for cases that include the Preferred Term (PT) of 'Postural Orthostatic Tachycardia Syndrome' (POTS) yielded 83 medically confirmed reports of POTS reported as temporally associated with the administration of qHPV vaccine received worldwide from the marketed environment cumulative to 15-Jun-2015. The qHPV vaccine cases were reviewed using the above case definition and are described in Table 7. The CIOMS forms for those cases are attached [Ref. 5.3.6: 046SV8].

The 9vHPV query did not reveal any cases containing the PT of POTS.

Of the total of 83 qHPV POTS cases identified, 72 were serious and 11 were non-serious. Seventy-nine (79) cases were females, 2 were males and 2 were unknown gender.

Geographically, there 48 cases from the EU, 28 from the Unites States, and 7 were from the Rest of World. By country, 41 cases were received from Denmark, 28 from United States, 4 from Japan, 2 each from Germany, Ireland and United Kingdom, 1 each from Australia, France, Israel and South Africa. By age, 41 cases were below 17 years, 35 cases were between 17-46 years, and 7 cases did not have age reported. The average age was 19 years old. Outcome was reported as not recovered in 50 cases, 15 cases were recovered/recovering, and 18 cases had unknown outcome. The average Time to Onset (TTO) reported from the proximal preceding dose is 142 days. The average TTO after dose 1 is 259 days, after dose 2 is 319 days, and after dose 3 is 263 days.

Thirty-three (33) of the 83 cases fully met the case definition for POTS as outlined above. Thirty (30) of those 33 cases were received from Denmark, with 27 (90%) originating from the Syncope Centre at Frederiksberg Hospital, and 28 reported within the last 2 years. The 3 remaining case reports were from the United States. Despite meeting the case definition, 18 of the 33 cases were noted to have confounding concurrent conditions or medical histories (i.e. episodes of syncope prior to vaccination, pre-syncope and syncope, POTS, headaches, cerebral vasculitis, stress, severe concussion after assault with resulting dizziness and PTSD-like condition, pregnancy, diarrhea, bloody stools, severe influenza, neurological abnormalities, Epstein-Barr, epilepsy, bleeding disorders, anemia, asthma, severe mononucleosis, dizziness, Arnold-Chiari malformation, and a "congenital neurological disorder") that could provide alternative explanations for the symptoms displayed in the case reports. Many cases did not provide any clinical or laboratory evidence to support meeting the case definition.

Ten (10) of the 83 cases partially met the case definition for POTS. Of those 10 cases, half also had confounding conditions (i.e. suspected pernicious anemia, anxiety disorder, neuroses, stress, irritable bowel syndrome, alcohol use, and vomiting) that could also provide alternative explanations.

The remaining 40 of the 83 cases did not meet the case definition for POTS.

Table 7
Cases with PT of POTS

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
Y	[redacted]	[redacted]	21 Years Female	Y	Y	Y	Y	Symptoms did not improve with recumbence	28 days after D1
Y	[redacted]	[redacted]	18 Years Female	Y	Y	Y	Y	CC: "Head turns to the left", Arm twitching and numbness, headaches, radiculopathy	Same day after D1
Y	[redacted] Literature	[redacted]	20 Years Female	NR	Y	Y	Y	Eating Disorder ruled out	2 weeks after D1
Y	[redacted]	[redacted]	23 Years Female	Y	Y	Y	Y	Information mostly about pain. Diagnosed with vasculitis. POTS not mentioned until seen in Frederiksberg Hospital	7 months after D2
Y	[redacted]	[redacted]	24 Years Female	Y	Y	Y	Y	CC: Stress	Same day after D2

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
Y	[redacted]	[redacted]	12 Years Female	Y	Y	Y	Y	No MH or CC provided	14 days after D3
Y			28 Years Female	Y	Y	Y	Y	No MH or CC provided	TTO=NR after D2
Y			31 Years Female	Y	Y	Y	Y	No MH or CC provided	1 day after D2
Y			23 Years Female	Y	Y	Y	Y	MH: severe concussion after assault with resulting CC of dizziness and tiredness. Evaluated for PTSD-like condition with results not reported	TTO=NR after D2
Y			23 Years Female	Y	Y	Y	Y	Patient was 4 months pregnant at time of tilt test	TTO=NR after D1
Y	Literature		15 Years Female	Y	Y	Y	Y	No MH or CC reported	1 month after D1
Y	[redacted]		22 Years Female	Y	Y	Y	Y	Diarrhea, bloody stools	TTO=same day Dose=NR
Y			13 Years Female	Y	Y	Y	Y	Concomitant amitriptyline. Tilt test positive,	Approximately 12 months after D3

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
								severe influenza episode after dose 3, but prior to symptoms of POTS.	
Y			27 Years Female	Y	Y	Y	Y	After trip abroad, (date not reported), experienced alternating temperature with diarrhea and neurological abnormalities	30 days after D1
Y			12 Years Female	Y	Y	Y	Y	No MH or CC reported	2 days after dose=NR
Y			27 Years Female	Y	Y	Y	Y	No MH or CC reported. Diagnosed with fibromyalgia	2 days after D3
Y			13 Years Female	Y	Y	Y	Y	CC: ltchy Rash, eczema, Cat allergies. Seen by psychiatrist,	107 days after D3

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
								results not reported	
Y			13 Years Female	Y	Y	Y	Y	MH: Epstein-Barr and Herpes virus 6 positive, CC: Celiac disease	2 days after dose=NR
Y			32 Years Female	Y	Y	Y	Y	CC: Epilepsy on concomitant topiramate. MH: malaise, bleeding disorders, anemia.	Approximately 4 months after D2
Y			14 Years Female	Y	Y	Y	Y	CC:Asthma	6 month after D3
Y			29 Years Female	Y	Y	Y	Y	No MH or CC provided	2 days after D2
Y			12 Years Female	Y	Y	Y	Y	No MH or CC provided	TTO=NR after D1
Y			14 Years Female	Y	Y	Y	Y	Autonomic nervous system imbalance also coded.	Approximately 7 months after D3
Y			14 Years Female	Y	Y	Y	Y	Symptoms appeared after	Low BP and palpitations started 14 months after D3

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
								course of severe mononucleosis .	
Y	[redacted]		12 Years Female	Y	Y	Y	Y	MH: Asthma	4 days after D3
Y			12 Years female	Y	Y	Y	Y	MH:NR	Approx. 1 month after D2

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
Y	[redacted]	[redacted]	17 Years Female	Y	Y	Y	Y	MH: non-celiac gluten sensitivity and asthma	Same day as D1
Y	[redacted]	[redacted]	26 Years Female	Y	Y	Y	Y	MH: dizziness, POTS, pre-syncope and syncope. Conditions worsened after vaccination	Approx. 1 month after D2
Y	[redacted]	[redacted]	12 Years Female	Y	Y	Y	Y	MH:NR	TTO=NR D2
Y	[redacted]	[redacted]	12 Years Female	Y	Y	Y	Y	MH:MR	TTO=NR after D3
Y	[redacted]	[redacted]	24 Years Female	Y	Y	Y	Y	MH: Allergies	37 Days after D3
Y	[redacted]	[redacted]	14 Years Female	Y	Y	Y	Y	MH: Arnold-Chiari malformation, polycystic ovaries, retroverted uterus, congenital neurological disorder not described	1 week after D1
Y	Literature [redacted]	[redacted]	Not	Y	Y	Y	Y	MH: one	3 months after D3

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
			provided - Female					episode syncope prior to vaccination	
P	[redacted]		15 Years Female	Y	Y	NR	N	Tested for Pernicious Anemia – results not reported	Approx. 3 months after D2
P			16 Years Female	NR	Y	Y	NR	First dose given prior to market inception of Gardasil	20 Days after D1
P			22 Years Female	Y	Y	Y	N	CC: Anxiety disorder, neurotic, SLE	TTO=NR after D2
P	Literature		11 Years Female	NR	Y	Y	Y	MH: Left ovarian teratoma. CRPS noted. No AE after D2. Patient symptoms improved after D3.	TTO=NR after D1
P	[redacted] Literature		18 Years Female	NR	Y	Y	Y	Tilt test not done	TTO=NR after D2
P	[redacted] Literature		22 Years Female	NR	Y	Y	NR	Diagnosed with Irritable Bowel	TTO=NR after D3

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
								Syndrome, positive tilt test	
P	[redacted] Literature	[redacted]	12 Years Female	NR	Y	Y	Y	Tilt test not performed	6 days after D2
P	[redacted] Literature		14 Years Female	NR	Y	Y	NR	No MH or CC reported	2 weeks after D1
P	[redacted]		39 Years	NR	Y	Y	N	Concentration and memory issues related to stress and depression	5 months after D1
P	[redacted]		21 Years Female	Y	Y	Y	NR	MH: Gluten intolerance, itching with rash, cat allergies, smoker, alcohol use, depression, gastroscopy for vomiting, deformed shoulder with locked muscles	TTO and dose=NR
N	[redacted] Literature	[redacted]	15 Years Female	NR	N	Y	N	Also diagnosed with cerebral vasculitis, seizure activity	TTO and Dose=NR

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
N	[redacted]	[redacted]	15 Years Female	NR	Y	NR	NR	'Functional vomiting diagnosed'	TTO and Dose =NR
N			16 Years Female	NR	NR	NR	NR	MH: febrile convulsions	4 weeks after D1
N			16 Years Female	NR	NR	Y	NR	CC: Infectious mononucleosis , Borrelia positive,	6 days after D1
N			18 Years Female	NR	Y	Y	N	MH: Celiac Disease. EEG with irregular brain pattern. Dose 2 administered 2 weeks after flu-like respiratory illness. Diagnosed with panic/anxiety attacks.	15 minutes after D2
N			15 Years Female	NR	NR	Y	N	Diagnosed with Epilepsy with complex focal seizures	2 weeks, Dose =NR
N			18 Years Female	NR	NR	Y	N	CC: Headache, hyperlipidemia , deletion of	28 days after D1

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
								SHOX gene	
N	[redacted]		14 Years Female	NR	Y	NR	Y	CC: Undergoing psychological therapy,	50 days after D3
N			13 Years Female	NR	NR	NR	NR	Limited information	4 months after D3
N			16 Years Female	NR	NR	NR	NR	Limited information, Vaccine administration dates discrepant	23 months after D3
N			15 Years Female	NR	NR	NR	NR	Limited information	NR after D1
N			15 Years Female	NR	NR	NR	NR	Limited information about POTS	TTO and Dose=NR
N			18 Years Female	NR	NR	Y	N	CC: Orthostatic hypotension, asthma, GERD, severe acute respiratory syndrome	Recurrent symptoms Approx. 30-58 days After D3
N			18 Years Male	NR	NR	NR	NR	Limited information , dates discrepant	TTO=NR D2

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
N	[redacted]	[redacted]	NR	NR	NR	NR	NR	No information provided	TTO and Dose=NR
N	[redacted]	[redacted]	15 Years Female	Y	NR	Y	N	CC: Colitis, anxiety. Diagnosed with volume depletion, minimal information related to POTS	Approx. 1 month after D3
N	[redacted]	[redacted]	18 Years Female	NR	NR	NR	NR	Limited information	39 days after D1
N	[redacted]	[redacted]	24 Years Female	N	N	N	N	CC: Acute stress disorder, anxiety attacks, back pain. Pt was pregnant during + tilt test limiting results. Did not fulfill criteria for POTS per reporter	27 days after D3
N	[redacted]	[redacted]	21 Years Female	NR	NR	NR	NR	CC: junctional tachycardia with MH of	TTO= NR Dose =NR

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
								pathway ablation	
N	[redacted]		13 Years Female	NR	NR	NR	NR	MH: Frequent viral infections. Tilt test with not enough findings for diagnosis of POTS per reporter	21 days after D1
N	[redacted]		13 Years Female	NR	NR	NR	NR	Concomitant atorvastatin and anti-asthmatics, CC: asthma	Fainting within same month after D2
N	Literature [redacted]		15 Years Female	NR	N	NR	NR	CRPS also coded	TTO=NR Dose=NR
N	[redacted]		18 Years Female	NR	NR	NR	NR	Minimal information	TTO and dose=NR
N	[redacted]		14 Years Female	NR	NR	NR	NR	Food allergies noted	TTO=NR after D3
N	Literature [redacted]		14 Years Female	Y	NR	Y	NR	Chronic Fatigue also noted. MH: headache, dizziness, photophobia & phonophobia	2 months after D2

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
N	[redacted]		13 Years Female	NR	NR	NR	NR	MH:NR	3 months after D2
N			14 Years female	NR	NR	NR	NR	MH: Back pain after fall	19 days after D1
N			12 Years Female	Y	Y	Y	N	Diagnosed with Ehlers Danlos Syndrome	TTO and dose=NR
N			Not provided - Female	NR	NR	NR	NR	MH:NR	TTO and dose=NR
N			30 Years Female	NR	NR	NR	NR	MH:NR	Within same month after D1
N			12 Years Female	NR	NR	NR	NR	MH: Depression. Developed prolonged mononucleosis after dose 2.	TTO=NR after D2
N			Not provided - Female	NR	NR	NR	NR	MH:NR	TTO and dose=NR
N			24 Years Female	NR	NR	NR	NR	MH:NR	Approx. 2 months after D2
N			Not provided -Male	NR	NR	NR	NR	MH:NR	TTO and dose=NR

Met Criteria	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
N	[redacted]	[redacted]	15 Years Female	NR	NR	NR	NR	MH:NR	14 days after D1
N			Not provided - Female	NR	NR	NR	NR	Physician confirms "fainting episodes in 2006 prior to vaccination"	TTO and dose=NR
N			46 Years Female	NR	NR	NR	NR	MH:NR. Also diagnosed with CRPS	2 years & 5 months after D3
N			34 Years Female	NR	NR	NR	NR	MH:NR. Taking unspecified concomitant medication	TTO=NR after D2
N			12 Years Female	NR	NR	NR	NR	No MH or CC provided	14 months after D3
N	Literature		21 Years Female	NR	NR	NR	NR	No MH or CC provided	9 days after vaccination, dose=NR

Results of POTS Symptom Queries

The query of the Company safety data base for case reports that include various combinations of symptoms of POTS referred to as the "POTS Symptom Queries" yielded 90 case reports (Table 8) reported as temporally associated with the administration of qHPV vaccine received worldwide from the marketed environment cumulative to 15-Jun-2015. qHPV queries #1 and #5 only returned cases that included the preferred term of POTS. Those cases were previously reviewed in Table 7 and will not be again discussed. qHPV queries #2, #3, #4 and #6 retrieved some cases with POTS coded, in addition to other cases with only symptoms coded. The vast majority of cases identified in these POTS symptom queries were either cases of syncope occurring immediately post vaccination with a very short duration or cases that already had POTS coded in the reports. Six cases have orthostatic intolerance coded. The CIOMS forms for those cases are attached [Ref. 5.3.6: 0476J3].

Thirty (30) distinct cases, that did not contain the PT of POTS but contained only symptoms, were reviewed using the Raj and Sheldon case definition, and all are summarized in Table 9.

Fifteen (15) cases were serious and 15 were non-serious. Twenty-eight (28) cases were females and 2 were males. Geographically, there were 15 cases from the EU, 13 from the United States, and 2 were from the Rest of World. By country, 13 cases were from the United States; 6 cases were received from Denmark; 5 from Spain; 2 from Japan; 1 each from Germany, Ireland, France and Norway. By age, 15 cases were below 17 years, 15 cases were between 17-46 years. The average age was 19 years old. The average Time to Onset (TTO) reported from the proximal preceding dose is 25 days.

None of the cases retrieved in the qHPV POTS symptom queries fully met the case definition for POTS. Three cases (3) partially met the case definition. In 2 of the 3 cases that partially met the case definition, the patients were diagnosed with alternative conditions (i.e. CRPS, narcolepsy) that could explain the symptoms.

The 9vHPV synonym queries did not yield any cases for review.

Table 8
qHPV POTS Symptom Queries

Gardasil/Silgard Query #	# of case reports identified by the Gardasil/Silgard query	Review of Gardasil/Silgard cases
1	7	All cases have POTS coded
2	9	7 cases have POTS coded, 1 case has syncope and orthostatic intolerance coded ([redacted]), and 1 case has orthostatic intolerance coded ([redacted])
3	20	15 cases have POTS coded, 5 cases have orthostatic intolerance coded ([redacted], [redacted], [redacted], [redacted], and [redacted])
4	32	8 cases have POTS coded, and 24 cases have syncope/pre-syncope coded ([redacted])
5	7	All cases have POTS coded
6	15	13 cases have POTS coded, and 2 cases have syncope coded ([redacted], and [redacted])

Table 9
Cases Retrieved from qHPV POTS Symptom Queries

Met Criteria P= partially met N= no	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
P	[redacted]	[redacted]	14 Years Female	NR	NR	Y	Y	MH: Scoliosis, Congenital hip dislocation. Dx with Narcolepsy with cataplexy	Same day after D1
P			13 Years Female	Y	N	Y	NR	No MH or CC provided.	200 days after D3
P			14 Years Female	Y	NR	Y	NR	Diagnosed with CRPS	TTO=NR after D1
N			24 Years Female	NR	NR	N	NR	Minimal information	Same day after D1
N			15 Years Female	NR	NR	N	NR	Minimal information	Same day, Dose = NR
N			23 Years Female	NR	NR	NR	NR	Minimal information	Same day after D 2
N			12 Years Female	NR	NR	NR	NR	Minimal information	Same day, Dose = NR
N			23 Years Female	NR	NR	NR	NR	Hx of asthma and drug hypersensitivity	4 weeks after D 1
N			16 Years Female	NR	NR	N	NR	Limited information	10 minutes after D1
N			17 Years Female	NR	NR	N	NR	Dx with "heart problems" after D1	14 weeks after D1; approximately 3 months after D2

Met Criteria P= partially met N= no	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
N	[redacted]	[redacted]	13 Years Female	NR	NR	N	NR	Vaccinated with varicella virus vaccine, meningococcal vaccine and TDAP 12 days prior to Gardasil.	Minutes after D1
N			24 Years Female	NR	NR	NR	NR	Limited information	Same day after D1
N			18 Years Female	NR	NR	N	NR	No adverse events w/prior doses	Same day after D3
N			24 years Female	NR	NR	N	NR	Limited information	Same day after D2
N			35 Years Female	NR	NR	Y	NR	Lab tests revealed high levels of noradrenaline Abnormal Pap-CIN 1ll; No confirmed diagnosis	After D1, 2 & 3 TTO: NR
N			13 Years Female	NR	NR	Y	NR	MH: NR	After D2 TTO: NR
N			23 Years Female	NR	NR	NR	N	Diagnosed with fibromyalgia and Raynaud's disease	One month prior and after D3 TTO:NR
N			20 Years Female	NR	NR	N	NR	Limited information	24 hours after D2
N			13 Years Male	NR	NR	NR	NR	Limited information Vaccinated with DPT and Flu vaccines same day.	Immediately after D1

Met Criteria P= partially met N= no	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
N	[redacted]	[redacted]	14 Years Male	NR	NR	NR	NR	Limited information Vaccinated with hepatitis A vaccine same day	Same day after D3
N	[redacted]	[redacted]	19 Years Female	NR	NR	NR	N	MH: ETOH user, hypoglycemia, pharyngitis, peritonsillar abscess, hearing loss, anemia, mood disorder, allergy to amoxicillin, dizziness. Dx: Migraine	14 weeks after D1
N	[redacted]	[redacted]	14 Years Female	NR	NR	Y	NR	Syncope occurred while doing rehab for shoulder	NR
N	[redacted]	[redacted]	23 Years Female	Y	Y	Y	Y	Tilt test did not fulfill criteria for POTS per Frederiksberg physician	Same day as D1
N	[redacted]	[redacted]	20 Years Female	NR	NR	Y	Y	MH: Head injury	12 weeks after D2

Met Criteria P= partially met N= no	Case number	Country of incidence	Age/ Gender	Criteria #1 Met- Symptoms improve with recumbence	Criteria #2 Met- HR>30-40 BPM	Criteria #3 Met- Duration ≥6 month	Criteria #4 Met- Absence of other Overt Causes	Comment	TTO of POTS symptoms relative to vaccination
N	[redacted]	[redacted]	36 Years Female	Y	Y	Y	N	Tilt test performed, patient not diagnosed with POTS per Frederiksberg physician. Patient was diagnosed with Myalgic Encephalomyelitis or Post-viral fatigue syndrome	35 days after D1
N			12 Years Female	Y	NR	NR	N	POTS investigation was negative. "Events of psychosomatic nature"	80 days after D2
N			20 Years Female	Y	NR	Y	N	Chronic headache and epilepsy since age 14 (2006). Seizure activity noted to be at least twice per week.	14 days after D1
N			14 Years Female	NR	NR	NR	NR	Con Med: Amitriptyline; technetium Tc	Same day after D3
N			21 Years Female	NR	NR	NR	NR	MH: Drug hypersensitivity, Fruit allergy. Syncope Depression	Same day Dose: NR
N			14 Years Female	NR	NR	NR	NR	Limited information	Same day after D3

Reporting Rates for cases reported with the PT of POTS and for cases reported with various combinations of symptoms of POTS associated with qHPV vaccine are presented in Table 10. Reporting rates are presented per million people vaccinated. These calculations were not done for 9vHPV vaccine since there were no case reports, involving POTS and 9vHPV vaccine, received.

Table 10
POTS Reporting Rates per Million Vaccinees

Quadrivalent HPV Vaccine Cumulative to 31-May-2015 for Doses Distributed and to 15-Jun-2015 for Cases Reported				
Gardasil (V501) Estimated Number of Marketed qHPV Vaccine Doses Distributed			Reporting rate for Cases with the PT of POTS per Million Vaccinees by Region or Country (# Reports/ # People vaccinated x 1million)	Reporting rate for Cases Reported with Combinations of Symptoms of POTS per Million Vaccinees by Region or Country (# Reports/ # People vaccinated x 1 million)
	Cumulative to 31-May-2015	Number of persons vaccinated (assuming 3 doses per person)		
Worldwide	190,897,611	63,632,537	1 (83/ 63,632,537)	<1 (30/ 63,632,537)
EU	35,907,186	11,969,062	4 (48/ 11,969,062)	1 (15/ 11,969,062)
US	[redacted]		1 (28/ [redacted])	<1 (13/ [redacted]
Denmark			91 (41/ [redacted])	13 (6/ [redacted])
Japan			~7 (4/ [redacted]	3 (2/ [redacted]

Discussion and Conclusion

POTS is a syndrome involving orthostatic intolerance, with manifestations in different systems, that is not well understood. The manifestations could in fact, represent other medical conditions that have been misdiagnosed or misinterpreted. It is generally accepted that there are subtypes of POTS, further complicating diagnosis and treatment of the individual patient. With research advances and growing physician education, the number of people found to have POTS symptoms is steadily rising. The overwhelming majority of patients with POTS are women (80% to 85%) and most cases occur between the ages of 15 and 25 years[Ref. 5.4: 03SW00], which is the very population indicated to receive qHPV and 9vHPV vaccines. The HPV vaccines (qHPV, 9vHPV) have been widely studied not only by the vaccine manufacturer but also by US federal agencies (e.g. FDA, CDC) and national European research institutes through independent post licensure vaccine safety and monitoring activities [Ref. 5.4: 04752V].

It is important to recognize that data collected through post-marketing surveillance to Merck has limitations; it is a passive, spontaneous, voluntary, and incomplete reporting system. The association between the adverse events and vaccination is temporal. Post-marketing surveillance data does not prove causality. The clinical assessment of these events depends of the information available in the reports at a certain point of time. Analyses of the reports do not indicate any causal association with the vaccine instead they appear compatible with background cases. The reporting rate for these events is very low given the number of doses distributed in the marketplace worldwide.

Review of the post-marketing data for POTS and POTS-like cases does not reveal a trend of reports, and the analysis of cases did not identify any pattern of symptoms or presentation that suggest a causal relationship to the vaccine. There are clearly some regional differences in reporting, some of which may be due to stimulated reporting due to recent media attention.

These conclusions are based on the fact that some reports contain insufficient information to assess; some reports are confounded by medical history, concurrent conditions, or concomitant medications; and that there is a lack of consistent patterns in specific diagnoses, time-to-onset, or dose relationship. No new safety issue has been identified with respect to this condition. The MAH will continue to monitor reports of POTS in patients receiving qHPV and 9vHPV vaccines though routine Pharmacovigilance activities.

1.1.3 Literature Review

Complex Regional Pain Syndrome (CRPS) in the literature in association with receipt of Gardasil

Methods

The MAH carried out a literature review using the Merck Clinical Literature Information Center (CLIC) to identify all Complex Regional Pain Syndrome (CRSP) cases associated with quadrivalent Human Papillomavirus vaccine (qHPV) from 01-Jan-2006 through 15-Jun-2015. CLIC database is the Sponsor database of published clinical literature from Medline (PubMed) and Embase, with additional input from other sources such as local journals. For scientific articles published in non-English language but with English versions, the English version was reviewed and the reference of the non-English article was added.
The keywords for the search included 'complex regional pain syndrome' or 'pain syndrome' and 'quadrivalent HPV vaccine' or 'Gardasil'. In addition, the Merck Adverse Reporting and Review System (MARRS) database was queried for all literature reported cases which include the Preferred Term (PT) of CRPS temporally associated with the administration of qHPV vaccine.

The information is presented below and includes a description of each case, the Sponsor's case number, additional information obtained by the Sponsor where applicable, and the Sponsor's comment. These case reports are also included in the post-marketing tables above. All corresponding CIOMS reports are attached [Ref. 5.3.6: 046WDL].

Results

Richards et al. (2012) [Ref. 5.4: 03RTWM] point out that the pathogenesis of the Complex Regional Pain Syndrome type 1 (CRPS-1) is poorly understood, and that its onset is often precipitated by a physical injury such as minor trauma, fracture, infection or a surgical procedure. CRPS-1 affects one or more extremities and is characterized by persistent pain disproportionate to any inciting event, and at least one sign of autonomic dysfunction in the affected limb(s).
The authors draw attention to published reports of CRPS-1 following immunization with rubella and hepatitis B vaccines, and present 5 cases of CRPS-1 following immunizations in adolescents, with either diphtheria-tetanus-acellular pertussis (1 case), or human papillomavirus vaccines (4 cases, including 3 cases where qHPV vaccine was given):

In the case of a 16-year-old female (*MARRS* [redacted] who received her first dose of qHPV vaccine in her left deltoid muscle and immediately following immunization, she experienced numbness at the injection site, which resolved over 15–20 min. She was symptom free until day 4 post-immunization when she developed numbness and paresthesia of the left forearm and upper arm. On day 7 post-immunization, she was admitted to hospital following sudden onset of left arm and leg paralysis associated with upper arm and neck pain. She had multiple normal investigations while an inpatient, and was discharged home with physiotherapy and pharmacotherapy management. A follow-up at 2 weeks post-vaccine confirmed resolution of most of her CRPS-1 symptoms except for mild tenderness of the left shoulder and upper arm with a normal neurological examination.

Comment: This female adolescent patient with a history of sciatica, slipped discs in the lumbar area and laminectomy, experienced an injection site reaction in temporal relationship with the qHPV vaccine administration and showed "some neuritis of C5, C6 and C7" in a spinal cord MRI while a brachial plexus nerve conduction study provided normal results. Since this patient complained of continuing pain, hyperesthesia/hypoesthesia and weakness, the patient was diagnosed with CRPS-1. However, CRPS should be an exclusion diagnosis and it is not selective of a specific side of the body. The involvement of upper and lower extremities of the left side would not support an injury post-vaccine intramuscular (IM) administration. The report of hypoesthesia in the left arm, and then hyperalgesia during the physical examination without any specific sensory distribution, and "recurrent" paralysis of the arm, suggests a conversion disorder. In a conversion disorder, the most common motor symptoms include paralysis, gait disturbance, incoordination, tremor, and loss of speech while the sensory manifestations include paresthesia, intractable pain, tunnel vision and blindness. It is unclear whether in this patient with

a family history of spastic paraparesis other causes were excluded. This case is confounded by the patient's medical and family history, limited diagnostic information, lacking psychiatric evaluation and a dubious diagnosis of CRPS-1, all precluding a causality assessment.

In case MARRS [redacted] a 13-year-old girl developed severe left upper and forearm pain, numbness in her left hand, swollen fingers and purplish discoloration of her hand immediately after she received the second dose of qHPV in her left deltoid muscle. The hand was also extremely sensitive to touch. She was reviewed by a pediatrician on the following day and given exercises to actively mobilize her arm. Symptoms resolved within 5 days without any further treatment.

Comment: Although, there is limited information about the pediatrician findings and no information on a neurological assessment with only partially met CRPS definition requirements, the events seem directly related to the IM administration technique. The injection probably occurred in close proximity of the radial nerve and brachial artery. Injection site reactions (ISRs) such as pain, erythema, induration and swelling at the injection site are commonly recognized transient sequelae of IM vaccination but other less frequent complications have been reported such as persistent dysfunction following injection of the subdeltoid/subacromial bursa, anterior branch of the axillary nerve and the radial nerve. The injury of the radial nerve can result in numbness, tingling, burning pain, trouble straightening the arm or moving the writs and fingers, and weakness in a hand grip. Although there is limited information in this case, the lack of adverse events (AE) after the first administration of qHPV and the immediate appearance of events post-vaccine IM administration suggest an alternative explanation.

After receiving the third dose of qHPV in her left deltoid muscle, a 15-year-old girl (*MARRS* [redacted] developed pain in her left upper arm within hours of the immunization, progressing to severe forearm and upper arm pain, numbness and paresthesia over the next 3 days. Five days post-immunization she was admitted for 1 day to maximize CRPS-1 management. Later, she presented with left facial, arm and leg hemiparesis but the signs and symptoms were inconsistent with normal MRI results. Her symptoms persisted over the next 2 months but slowly resolved with simple analgesia, physiotherapy and hydrotherapy.

Comment: Although there is limited information about the clinical findings, psychiatric evaluation and electrophysiological exams, the involvement of upper arm, leg and face with normal MRI results, and the occurrence of events immediately after the qHPV administration suggest an alternative etiology. This case partially met the criteria for the case definition of CRPS as noted in Table 3 of Section 1.1.2.1.

The remaining cases associated with diphtheria-tetanus-acellular pertussis vaccine and the 2-valent human papillomavirus vaccine, appear to represent similar directly IM administration related incidents.

Haug et al. (2013) [Ref. 5.4: 03RTWM]highlight that CRPS was formerly known as Sudeck dystrophie and may develop following limb trauma, lesions of the peripheral or central nervous system or fractures with an incidence ranging in adults from 5.46 to 26.2/100,000/year, while it is less common in the pediatric population. As pathophysiological concepts neuroinflammation,

pathological regulation of the sympathetic nervous system and affection of the central nervous system are discussed. As per the authors, CRPS after vaccination is described after immunization against rubella and hepatitis B, and the first cases published of CRPS-I after immunization with Gardasil suggest a higher risk of developing this complication compared with other vaccines.

One case (*MARRS* [redacted]; [redacted] under qHPV is described: Within 24 hours after a 14-year-old girl received her first dose of qHPV in the right deltoid muscle, she developed severe pain, swelling, numbness, and coldness of the right arm and hand. Diagnostics with ultrasound, nerve conduction, and sensory evoked potentials were normal. An MRI scan of the right arm and brachial plexus showed no nerve injury but revealed a small inflammatory focus in the right deltoids in the course of the Nervus cutaneous brachialis lateralis, and an increase in size of the lymph nodes of the right axilla. Neurological, immunological, and microbiological tests, sonogram, and nerve conduction studies were negative. There were conflicts at school which could have led to secondary disease avoidance behavior with reduced use of the right hand. The patient was diagnosed with somatoform disorder. The symptoms improved under physical and occupational therapy, and after 2 months the skin temperature was normal and swelling was reduced. However, pain and lack of function was ongoing.

Comment: The small inflammatory focus in the right muscle deltoids probably reflects an injection site reaction. Given the negative results of neurological, immunological, and microbiological tests, and nerve conduction studies without signs of CRPS, the patient was diagnosed with somatoform disorder. This case met the criteria for the case definition of CRPS as noted in Table 3 of Section 1.1.2.1.

Kinoshita et al. (2014) [Ref. 5.4: 040HS8] investigated neurological manifestations in girls immunized with HPV vaccine. Out of 44 girls complaining of several symptoms after HPV vaccination 40 subjects were enrolled in their study. The age at initial vaccination ranged from 11 to 17 years, and the average incubation period after the first dose of the vaccine was 5.47±5.00 months. Frequent manifestations included headaches, general fatigue, coldness of the legs, limb pain and weakness. The skin temperature examined in 28 girls with limb symptoms exhibited a slight decrease in the fingers (30.4±2.6°C) and a moderate decrease in the toes (27.1±3.7°C). Digital plethysmograms revealed a reduced height of the waves, especially in the toes. The limb symptoms of 4 girls were compatible with the Japanese clinical diagnostic criteria for complex regional pain syndrome (CRPS), while those in the other 14 girls were consistent with foreign diagnostic criteria for CRPS. The Schellong test identified 8 patients with orthostatic hypotension and 4 patients with postural orthostatic tachycardia syndrome. The girls with orthostatic intolerance and CRPS commonly experienced transient violent tremors and persistent asthenia. Electron-microscopic examinations of the intradermal nerves showed an abnormal pathology in the unmyelinated fibers in 2 of the 3 girls examined. The authors conclude that the symptoms observed in this study can be explained by abnormal peripheral sympathetic responses.

The following 2 case reports describe patients who received qHPV:

In case (*MARRS* [redacted] a 15-year-old [redacted] girl (Case [redacted], serial patient number: [redacted]) felt pain and weakness in the lower limbs, especially in the left leg, leading to difficulty in walking a few days after she received her third dose of qHPV. These symptoms subsided within the following 3 days; however, after one month, she developed numbness and weakness in both hands lasting for 2 days. Transient weakness repeatedly appeared in both the hands and legs, and the patient subsequently experienced orthostatic fainting and abdominal discomfort. After the family moved from [redacted] approximately 1 ½ years after her last dose of qHPV, a medical examination (not specified) revealed no specific findings. In addition to recurrent limb weakness, the patient newly exhibited a decreased ability to learn at school; she was unable to memorize different themes simultaneously and her understanding of textbooks was incomplete. On a physical examination at the author's hospital her general physical findings were normal, although a neurological examination showed slight weakness in both hands and the left leg (grip power: 18 kg in the right hand; 10 kg in the left hand). Her skin temperature was 21.8°C in the right first toe and 31.1°C in the right second finger at a room temperature of 27.0°C, and plethysmograms of both the toes and fingers showed reduced heights of the waves in the toes. The findings of peripheral nerve conduction studies of the left median and tibial nerves were normal. On the Schellong test, the patient's heart rate and BP changed from 70 bpm and 105/62 mmHg to 109 bpm and 102/52 mmHg, respectively, at seven minutes after standing. The WAIS-III disclosed the following scores: FIQ=82, VIQ=88, PIQ=79, VC=92, PO=70, WM=85, AS=105. Furthermore, the patient had remarkable difficulty in quickly understanding long sentences. She was therefore diagnosed with CRPS-I and postural orthostatic tachycardia syndrome (POTS), and her slight cognitive decline was thought to be potentially related to POTS. She was treated with the oral administration of limaprost alfadex at a dose of 5 mg (limaprost alfadex) three times daily, and her limb symptoms disappeared.

Comment: Although this case report offers limited diagnostic information, particularly no reports of immunological tests, electrophysiological tests, or MRI results, the female adolescent received two doses of qHPV without any event suggesting that the described events are unlikely related to the qHPV. Her clinical signs and symptoms were documented first approximately 1 ½ years after the last vaccination. It remains unclear whether her family's move from [redacted] had any psychological and/or social consequences which could have contributed to the events.

Case (*MARRS* [redacted] describes a 13-year-old girl (Case [redacted], serial patient number [redacted]) with a medical history of surgical removal of a left ovarian tumor at 10 years of age. Two weeks after she received her first dose of qHPV the patient began to suffer from a continuous high fever (39.0 - 40.0°C) and headaches. She was evaluated at a local hospital, where no abnormal findings were detected on a routine laboratory examination, endoscopy or CT. Various NSAIDs were prescribed; however, all were ineffective in relieving the patient's symptoms. She was tentatively diagnosed as having a psychosomatic fever and stopped participating in all sport activities on campus. Seven months after she received her first dose of qHPV she received the third dose and her high body temperature and general malaise gradually resolved; however, paroxysmal limb tremors subsequently appeared, especially while lying down, which caused the patient serious anxiety at night, resulting in insomnia. Approximately 5 weeks after her last

vaccination she developed severe limb pain and palpitations; the limb pain restricted her shoulder and thigh movement, sometimes accompanied by temporal paresis of the hands and legs, and the palpitations and chest discomfort were remarkably exacerbated when the patient changed from a sitting to standing position. Both conditions resulted in difficulties in writing and walking. The patient's condition was considered to be due to psychosomatic behavior at the hospital and at school. Four weeks later she stopped going to school. On a physical examination conducted at the author's hospital, the patient was 155 cm tall and weighed 51 kg. Her pulse rate was 98 bpm, with a BP of 112/78 mmHg in the sitting position. Her body temperature was 37.1°C, and her general physical findings were normal. Neurologically, she complained of uncomfortable pain in the legs; however, manual muscle tests, objective sensory examinations and deep tendon reflex studies were all normal. No limb tremors were noted at that time. The patient was able to walk using a handrail for short distances, exhibiting a very unsteady posture that easily led to squatting. The awkward gait appeared to be of hysteric origin. Her skin temperature was 28.8°C in the right first toe and 30.8°C in the right second finger at a room temperature of 23.5°C, and plethysmograms of both the toes and fingers showed reduced heights of the waves in the toes. On the Schellong test, the patient's heart rate and BP changed from 91 bpm and 105/91 mmHg to 126 bpm and 98/59 mmHg, respectively, at nine minutes after standing. A cardiac scintigram obtained using 123I-metaiodobenzylguanidine (MIBG) revealed a reduced uptake of the isotope, indicating the loss of post-ganglionic nerve terminals containing noradrenaline. She was therefore diagnosed as having CRPS-I and POTS and treated with the oral administration of bisoprolol fumarate (bisoprolol fumarate) at a dose of 2.5 mg daily. Four months later, her gait improved, and she was able to walk with the use of stick, although she did not return to her previous school life.

Comment: Two weeks after the female adolescent patient with a history of left ovarian tumor received qHPV, she developed fever and headaches which was tentatively diagnosed as psychosomatic fever after a negative clinical evaluation. She received a second dose of qHPV with no AE reported. After receiving the third dose of qHPV vaccine, the fever and malaise resolved, but then, she experienced limb tremor, limb pain, and palpitations, which did not correspond to normal neurological examination results. After multiple exams and tests, the only positive test was a cardiac scintigram obtained using MIBG revealing a reduced uptake of the isotope. It remains unclear whether any further diagnostic measures were undertaken to exclude Parkinson's disease.

Although there is no information on the type of ovarian tumor of this patient, the improvement of patient's symptoms after the third dose of qHPV, and lack of symptomatology after the second dose suggest an alternative etiology. Depending on the type of ovarian tumor, the fever could be a manifestation of tumor activity or an associated infection.

In a separate presentation, *Kinoshita et al. (2014)* [Ref. 5.4: 046Y94] suggest that the cases described above indicate possible peripheral circulatory failure and sympathicopathy, and anticipate that in many cases the symptoms correspond to the general picture of orthostatic disturbance.

In 48 young female patients aged 13-19 years of age (mean age: 15.6) the authors undertook autonomic nerve function testing, including orthostatic testing which combined measurement of the skin temperature, measurement of digital pulse volume and measurement of norepinephrine levels. In 3 of the patients, skin biopsies were performed on skin taken from the toes where digital pulse volume and skin temperature had been measured, to observe the cutaneous nerves in the tissue using an electron microscope.
A detailed breakdown of adverse events indicated a high incidence of findings suggestive of dysautonomia, including headaches (66%: 29 patients), general malaise (50%: 22 patients), cold sensations in the lower extremities (50%: 22 patients), pains in the limbs (45%: 20 patients) and difficulties with rising in the morning (45%: 20 patients). Skin temperature was measured in 14 of the patients, with a mean temperature of 30.1°C observed for the digitus secundus versus 27.7°C for the hallux, suggesting a tendency for skin temperatures to be particularly low in the lower extremities. Digital pulse volume was measured in 13 patients, with diminished wave height observed in 12 patients. Orthostatic testing and measurement of catecholamine levels were performed in 18 patients. 12 patients fulfilled the diagnostic criteria for orthostatic hypotension (OH), while 4 patients fulfilled the criteria for POTS unaccompanied by hypotension. In healthy individuals, the plasma norepinephrine (NE) level when the individual is in a standing position rises to 60-120% of the resting level. In 9 patients examined in this study, the percentage increase in NE was low, suggesting diminished responsiveness of NE secretion in response to the standing position. The orthostatic testing and catecholamine level measurement produced abnormal findings for 14 of the 18 patients who were tested. The skin biopsies in 2 out of 3 probes indicated degeneration of the non-medullated nerve fibers. Measurement of ganglionic acetylcholine receptor antibodies was undertaken in 14 of the patients, producing negative results for all 14 patients.
The authors consider that one possible explanation for the extremely varied range of symptoms including headaches and general malaise was that these were symptoms of orthostatic disturbance, and suggest peripheral dysautonomia as a cause. Although it cannot be definitively stated that orthostatic disturbance is triggered by vaccination, the incidence of the condition is remarkably high among the cohort of young female patients in this study. However, the possibility that the high incidence is coincidental cannot be ruled out, given that this condition is common among the age group which overlaps the period when this vaccine is administered. A high incidence of intractable pain in the extremities was also observed, with 18 of the young female patients fulfilling the diagnostic criteria for CRPS-I as established by the International Association for the Study of Pain, and with 4 of these patients also fulfilling the Japanese diagnostic criteria.

In an additional presentation *Kinoshita et al (2014)* [Ref. 5.4: 0470R6] focused on the ultramicromorphological findings presented above, where in 2 cases sporadic degeneration of the myelin sheath was observed as well as other findings leading to suspicion of decreased concentration of non-myelinated nerve fibers and growth of collagen fibers in the surrounding

areas. Irregular and electron-dense granular abnormality inside the non-myelinated nerve fibers was found.
Peripheral sympathicopathy was considered to be a cause from the degenerative findings of the intradermal nerves. Although the link to cervical cancer vaccines is unknown, the authors believe that women who visited their hospital for limb pain had peripheral autonomic disorder.
In a HPV vaccines review of AE in 2014, *Rev Prescrire (2015)* [Ref. 5.4: 046WK7] the authors summarize AE associated with qHPV based on pharmacovigilance data extracted from publications and reporting entities worldwide and conclude with regard to CRPS, that this syndrome is poorly understood and appears linked to the vaccination procedure rather than the vaccine itself, as this adverse event has been reported with other vaccines.

Martinez-Lavin (2014) [Ref. 5.4: 046WK3] presents 2 case reports chronic, incapacitating fibromyalgia-like illnesses after receiving qHPV.

The first case (*MARRS* [redacted] describes an 11-yr-old girl who 11 months after receiving a single injection of qHPV started a new 3-dose regimen. The illness in this patient began as CRPS, with severe pain in the injected arm that started right after the second injection and lasted for a week. Four days after the third dose was administered, she again developed severe pain in the injected arm, as well as a swollen red hand. Symptoms spread to the opposite arm two weeks later, and then affected her whole body. In addition to pain, severe paresthesias were also present. The patient developed insomnia and profound fatigue, and became unable to attend school. Before the onset of her chronic illness, there was no history of trauma or psychiatric or family problems. Extensive diagnostic workup was normal. Blood test was negative for infectious, inflammatory, or autoimmune markers. Cerebrospinal fluid analysis, head and neck magnetic resonance imaging, and electromyography were normal. Various symptomatic treatments were tried, including analgesics, steroids, antineuropathic agents, and anti-inflammatory drugs, but these failed to provide any sustained relief. The only abnormal finding on the neurologic exam was severe, generalized allodynia, and the rest of the physical exam was unrevealing. The patient tested positive for all 18 fibromyalgia tender points. Widespread pain and paresthesias persisted seven months after the onset of her illness.
The patient underwent several studies (lumbar puncture, encephalogram, magnetic resonance and electromyography) to discard some illness such as: lupus, autoimmune reactions, arthritis and Guillain–Barre syndrome. All test results were normal. Approximately 8 months after the last dose of qHPV, she was diagnosed with fibromyalgia; however, after further clinical evaluation this diagnosis was discarded as well.

The second case report (*MARRS* [redacted] describes a 14-yr-old girl who developed severe neck pain 4 weeks after her second injection of Gardasil. Over the following weeks, the pain spread to the patient's arms and then to her legs; paresthesias were present in all four limbs. The patient's symptoms interfered with sleep and with school attendance. As in the first case, the only abnormality found in the physical exam was exquisite tenderness affecting all 18 fibromyalgia tender points. The patient had a family history of spondyloarthropathy, but was negative for HLAB27. Symptomatic treatments provided only transient relief. Persistence of

widespread pain and paresthesias persisted at five months after the onset of illness.
As per the authors, both cases fulfill the International Association for the Study of Pain diagnostic criteria for CRPS. Both girls had typical fibromyalgia features, such as insomnia and chronic fatigue. The first patient had an immediate temporal cause-effect relationship, but the pain/vaccination relationship was less clear in the second case, as the illness did not develop until 4 weeks after the second injection. Multiple specialist consultations and diagnostic procedures in both girls were unsuccessful in identifying any other plausible explanation for the severe, persistent fibromyalgia-like illness that developed. The prominence of the paresthesias and allodynia were suggestive of a neuropathic, rather than a myopathic, pain etiology. Both complex regional pain syndrome and fibromyalgia are controversial entities.
The authors propose that fibromyalgia is a generalized complex regional pain syndrome based on the following arguments: In both conditions, there is female predominance, frequent onset after trauma, chronic nonnociceptive pain, paresthesias, sympathetic instability, and allodynia/hyperesthesia. Dorsal root ganglia may play a key role in fibromyalgia pain; trauma or viral infection can induce dorsal root ganglia sympathetic fiber sprouting establishing abnormal sympathetic-nociceptive short circuits. It is tempting to speculate that in genetically susceptible individual an intramuscular-injected vaccine containing noninfectious virus plus the aluminum adjuvant substance could elicit similar changes.

Comment: In the first case the 11-year-old female patient received 2 doses of qHPV without reporting an AE. Right after the third injection (the second of the restarted 3-dose regimen) she complaint about severe pain in the injected arm which lasted for a week. Four days after the third dose was administered, she again developed severe pain in the injected arm, as well as a swollen red hand. Symptoms spread to the opposite arm two weeks later, and then affected her whole body. She developed multiple symptoms including paresthesias, insomnia and profound fatigue. Extensive diagnostic measures did not reveal a cause for these symptoms and a tentative diagnosis of fibromyalgia could not be confirmed. The immediate onset of the pain syndrome after the third dose of qHPV in this case suggests a local injection site reaction which was possibly intensified after the patient received the last dose. Without any diagnostic clarification any assessment of the course of the events remains speculative.
In the second case a 14-yr-old girl developed severe neck pain 4 weeks after her second dose of qHPV. Over the following weeks, the pain spread to the patient's arms and then to her legs; paresthesias were present in all four limbs. As in the first case, the only abnormality found in the physical exam was exquisite tenderness affecting all 18 fibromyalgia tender points without confirmation of this tentative diagnosis. Also in this case assessment of the course of the events without any diagnostic clarification any remains speculative.

Okuyama (2014) [Ref. 5.4: 0474KP] presents a summary of 8 cases of Complex Regional Pain Syndrome (CRPS) due to HPV vaccine (bivalent type in 5 and qHPV in 3) and 2 cases due to trauma. The 8 cases due to HPV vaccine all occurred in adolescent females, with the triggering event being the first injection of vaccine in 3 cases and the second injection in 5 cases. The author describes in detail the clinical course, diagnosis, and treatment in four of the cases

associated with HPV vaccine (bivalent in 3 and qHPV in 1).

The *first of the 3 qHPV-associated cases* was a 12-year-old female (*MARRS* [redacted] who was reportedly emotionally unstable and had hysterical predisposition. She developed hyperpnoea and cried with kicking her mother while the drug injected into the muscle slowly. Soon after vaccination to the left arm, the patient experienced pain and numbness of the middle of the left forearm to the fingers. She was so excited that she kept crying. After 5-10 minutes, she complained that she could not move the left wrist to fingers with numbness. She also had weakness. After another 10-15 minutes, the patient's condition improved and the symptoms of numbness and inability to move with no sensation were noted only in the second to fifth fingers. As per the reporter the patient developed CRPS, hyperpnoea, excitement, peripheral nerve disorder (numbness of the left wrist to fingers), abnormal sensation (unable to move with no sensation) and vasovagal reaction. The next day the numbness disappeared around and she could move. Approximately 2 weeks after the vaccination, while a blood collection was performed at her school for lifestyle-related diseases examinations, when the needle was inserted into the flexor side of the right elbow, she experienced numbness from the periphery of the right forearm. Since the blood could not be collected successfully, the needle had been inserted into the right arm for 3 times, and numbness began to appear after the second attempt. Thereafter, she could not hold chopsticks or write any letters. The patient developed numbness and motor disorder of finger tips of right hand, a painful arm, paralysis and increased perspiration. Within a week all symptoms disappeared. But 1 day later the patient suddenly noticed that she could not move her fingers. Within 2 days her grip strength had recovered and the patient reported that the symptoms including numbness were no longer present.

Comment: In this case the signs and symptoms reported immediately after and even during the vaccination as well as after an attempted blood draw 2 weeks later probably represent a conversion disorder. The events resolved without treatment.

In the *second case* (*MARRS* [redacted] only limited information was provided. A 12-year-old female received qHPV (dose #1) and [redacted]ncephalitis vaccine, and immediately after the vaccination felt pain (not further described). The onset of CRPS symptoms (headache, dizziness, pain in the extremities, and a febrile sensation) occurred 5 weeks later with objective evidence of sensation of heat in the thighs. Without treatment improvement was noted 3 months later.

Comment: In this case the information provided does not allow a causality assessment.

The *third case* report (*MARRS* [redacted]) describes a 15-yr-old girl with a history of somatoform disorder and an episode of weakness at the age of 12, who received 3 doses of qHPV in her left deltoid. One month after the second dose she experienced headaches, difficulty getting up, falling asleep during mealtime, not remembering conversations, and speaking in a monotone voice. She was suspected of having psychiatric issues before she was evaluated by another physician. Three months after the second dose personality changes were observed (self-neglect and being suicidal), but there was some improvement after the girl was sent to live with her grandparents. The day after the third dose of vaccine was administered, the patient developed severe headaches and back pain; at this point, she came to the author's hospital for evaluation.

Initially, it was believed that the patient was suffering from migraines and orthostatic dysfunction. However, within the same month, she was frequently confined to bed with symptoms such as paralysis, memory problems, and lack of strength in both hands. On the basis of news coverage, the patient suspected a connection between her symptoms and the vaccine. When she presented at the author's hospital, she was suffering from severe malaise and irregular sleep patterns, and had lack of strength in both hands, especially the left. There were no abnormalities seen on an MRI of the head and no abnormalities in lab tests. Despite her diminished grip strength, the patient was able to play the piano for long periods of time, so this was recommended as exercise therapy. The suspected diagnoses in this case were orthostatic dysfunction, vaccine-associated chronic fatigue syndrome, chronic pain, and conversion disorder. The patient started treatment with amitriptyline (10 mg before bedtime), but this caused her to have problems waking in the morning, so the drug was stopped. Next, a trial of Lyrica (25 mg) was started at a dosage of 2 tablets/day; this was markedly effective in decreasing the patient's pain. During the course of the events Guillain-Barre syndrome was diagnosed at one point but no information on the diagnostic criteria was provided.
With medication and cognitive behavioral therapy and physiotherapy the patient's condition improved after 10 months, and she resumed her usual activities of daily life.

Comment: In this patient with a history of somatoform disorder and an episode of weakness at the age of 12, experienced pain and fatigue related symptoms 1 month after the second dose of qHPV. Two months later personality changes were observed and 1 day after the third dose of qHPV pain related symptoms developed. The following course of the signs and symptoms with no corresponding diagnostic findings and the successful cognitive behavioral therapy suggest a conversion disorder.

Discussion and Conclusion

In some of the case reports identified from the literature, the CRPS-related events appeared immediately after the qHPV vaccination with a risk window of minutes, which suggests that the events might be related to the IM administration technique. It has been reported that the injection site reactions post-IM administration might trigger the development of CRPS-1, and this is supported by reports of CRPS following other needle-based interventions, including venipuncture and intravenous drug administration [Ref. 5.4: 03RTWM].
CRPS is characterized by autonomic, sensory and motor disturbances, but the lack of more objective diagnostic tools represents a challenge particularly in the establishment of a causal association with vaccines. The pathogenesis of CRPS is poorly understood, but its onset is often precipitated by a physical injury, such as minor trauma, fracture, infection or a surgical procedure.
Some literature reports have insufficient diagnostic information, which limits the ability to completely assess the causal relationship between CRPS and qHPV vaccine. For those literature reports with more information, the clinical picture did not correspond to negative neurological exams and/or imaging results, and the report of symptoms that appeared and disappeared

spontaneously raise the suspicion of the presence of a somatoform disorder. CRPS and somatoform disorders are exclusion diagnosis, which require complete information of each case to disregard other diagnosis.
There were some cases where the events occurred after the administration of dose 3 of qHPV vaccine without any reported adverse event with the previous administration of the vaccine. Although, this is possible, the immunological memory is usually triggered after the first administration of a vaccine. Furthermore, there was a case where the events improved after the administration of dose 3, demonstrating no clear picture or pattern.
CRPS-1 is more frequent in women than men and its highest incidence occurs around puberty, but the reason of this pattern is unknown. In adults, the incidence of CRPS has been reported of 5.46 to 26.2/100,000 person-years with a lower frequency in pediatric population. In females 10-19 years old and 20-29 years old, the incidence rates of CRPS-1 have been reported of 14.9 and 28.0 per 100,000 person-years, respectively. Since market introduction of qHPV to 30-June-2015, more than 190 million doses have been distributed worldwide, and the reported frequency of CRPS from the literature is very low.
In conclusion, based on the published case reports there is no evidence to establish a causal relationship between HPV vaccine and CRPS.

Postural Orthostatic Tachycardia Syndrome (POTS) in the literature in association with receipt of Gardasil

Methods

The Sponsor carried out a literature review using the Clinical Literature Information Center (CLIC) to identify all Postural Orthostatic Tachycardia Syndrome (POTS) cases associated with quadrivalent and 9-valent Human Papillomavirus vaccine (qHPV and 9vHPV) from 01-Jan-2006 through 15-Jun-2015. The CLIC database is the Sponsor database of published clinical literature from Medline (PubMed) and Embase, with additional input from other sources such as local journals published outside of the US.
For the search, the keywords included 'POTS' or 'tachycardia' or 'postural orthostatic' and quadrivalent and 9-valent Human Papillomavirus vaccine (qHPV and 9vHPV). In addition, the Merck Adverse Reporting and Review System (MARRS) database was queried for all literature reported cases which include the Preferred Term (PT) of POTS and qHPV and 9vHPV.
The information is presented below and includes the *reference, author's abstract, author's description of each case in italics*, additional information obtained by the Sponsor, and the Sponsor's comment. These case reports are included in the post-marketing tables above. All corresponding CIOMS reports are appended [Ref. 5.3.6: 046SV8].

Results

Blitshteyn S. (2014) [Ref. 5.4: 03T3DX]describes 6 patients who developed new onset POTS 6 days to 2 months following human papillomavirus vaccination with 3 patients also experiencing neurocardiogenic syncope. Three patients were diagnosed with possible small fiber neuropathy. Symptoms in all patients improved over 3 years with pharmacotherapy and non-pharmacological measures but residual symptoms persisted. Molecular mimicry with formation of cross-reacting autoantibodies to the potential targets of the autonomic ganglia, neurons, cardiac proteins or vascular receptors is considered as a possible pathogenesis of new onset POTS after immunization.

In case MARRS [redacted] a 20-year-old athletic female with no pre-existing medical history developed weight loss, dizziness, fatigue, nausea, tachycardia and exercise intolerance 2 weeks after receiving the first out of the three-series vaccination with qHPV. After thorough diagnostic investigations excluded possible cardiac, endocrine, infectious, Rheumatological and psychiatric causes, a tilt table test was done. The tilt table test demonstrated an increase in heart rate from 72 bpm supine to 140 bpm within 10 min of tilt without any changes in blood pressure, consistent with the diagnostic criteria for POTS. With the use of pharmacotherapy consisting of pyridostigmine for postural tachycardia and orthostatic intolerance and bupropion and modafinil for fatigue and daytime somnolence, as well as non-pharmacological management with increased salt and fluid consumption, the patient's symptoms of orthostatic intolerance and gastrointestinal

disturbance have gradually improved over the course of 15 months. The patient was able to return to school full-time but continued to experience some functional limitations and was unable to resume her previous athletic activities. (This case was also reported as a letter to the editor *(Blitshteyn S. 2010)*.

Comment : Although, this patient was studied to exclude a cardiac, endocrine, infectious, rheumatological and psychiatric etiology, the specific tests and results were no provided. In the description of the case, there was confirmation of POTS through the tilt table test, but the patient tested negative for ganglionic acetylcholine receptor antibody. Other antibodies related to POTS such as antibodies to various cardiac proteins and antibodies to b1/2-adrenergic and M2/3 muscarinic receptors were not reported. This patient showed a good response to administration of salt and fluids, and antianxiety medications, probably secondary to hypovolemia and chronic fatigue, conditions that per se have been associated with POTS. Since POTS can occur with multiple conditions such as autoimmune neuropathies, anxiety, pheochromocytoma, mast cell activation disorders, hypovolemia, cardiac disorders, prolonged bed rest, pain, and chronic fatigue, a complete set of tests are required to exclude other causes. In this patient, there was no information of the cardiac and other evaluations, plasma catecholamines, 24-hour blood pressure and heart rate monitoring, exercise test, cortisol, thyroid hormones, plasma and urinary metanephrines and MRI of the head, which limits the POTS-qHPV vaccine causal assessment.

In case MARRS [redacted] a 22-year-old previously healthy female experienced a sudden onset of diarrhea, nausea and weight loss approximately 2 months after receiving the third dose of qHPV. A thorough gastrointestinal diagnostic workup failed to reveal any underlying etiology, and the patient was diagnosed with irritable bowel syndrome. In addition to persistent gastrointestinal symptoms, the patient also developed lightheadedness, dizziness, pre-syncope and episodic tachycardia. A tilt table test revealed a rise in heart rate from 90 bpm supine to 134 bpm standing, within 1 min of tilt. At the twentieth minute of tilt, the patient experienced a drop in blood pressure to 88/43 accompanied by symptoms of pre-syncope. The tilt table test was consistent with POTS and neurocardiogenic syncope (NCS). Further autonomic testing revealed normal heart rate variability and Valsalva response, and quantitative sudomotor test showed mild reduction in the distal leg suggestive of a small fiber neuropathy. In addition to an increased fluid/salt intake, the patient was treated with midodrine for vasoconstriction and fludrocortisone for volume expansion, and her symptoms have gradually improved over the course of 2 years.

Comment: In this patient, the events of sudden diarrhea, nausea and weight loss occurred two months after receiving the qHPV, which compatible with the diagnosis of irritable bowel syndrome. Irritable Bowel Syndrome is frequently associated with POTS due to the presence of the related autonomic dysfunction, and complications related to IBS such as hypovolemia. Therefore, the events in this patient seem to be more related to her underlying disease than qHPV.

In case MARRS [redacted] a 12-year-old previously healthy female 6 days after receiving the second dose of qHPV, began experiencing episodic loss of consciousness, which after neurological and cardiac evaluation was determined to be secondary to NCS. Holter

monitor demonstrated a heart rate range from 44 bpm to 212 bpm with the patient reporting shortness of breath and palpitations at the time of sinus tachycardia occurring with exertion. Orthostatic blood pressure and heart rate assessment demonstrated a supine heart rate of 65 bpm and a maximum heart rate of 122 bpm without orthostatic hypotension during a 5 min standing test, which was consistent with POTS; a tilt table test was not obtained. The patient's symptoms improved significantly with the use of fludrocortisone and high sodium diet for volume expansion, and she was able to attend school full-time and play sports. Subsequently, she received a third dose of qHPV, and 3 weeks after vaccination her symptoms of dizziness and episodes of loss of consciousness intensified. After a second MRI of the brain and 24-h video EEG at the epilepsy monitoring unit revealed no abnormalities, the etiology of the episodes was determined to be once again secondary to NCS. The course of her symptoms over the following 12 months after the third dose of qHPV appeared to be relapsing and remitting, with several syncope-free months followed by recurrence of syncope. Three years after the onset of syncope, the patient's daily symptoms have mostly resolved, and she experiences syncope only occasionally.

Comment: This young patient has a cardiac abnormality with episodes of bradycardia and tachycardia demonstrated by Holter. However, there were no reports of cardiac MRI, echocardiogram or autonomic function tests (e.g. Valsalva maneuver, cold pressor test and static handgrip), which limits the assessment of cardiac size, mass and blood volume of the patient's heart. The events seem to be of a cardiac origin. If the events would be associated with the qHPV, it would be expected to see the events in a shorter period of time after the 3rd dose administration; but events occurred six days and 3 weeks after the second and third dose of the vaccine, respectively.

In case MARRS [redacted] healthy 15-year-old female developed new onset dizziness and headache 4 weeks after receiving the first injection with qHPV. In the following 2 months she began to experience syncope and presyncope, along with dizziness, shaking, muscle twitching, hyperventilation and generalized weakness. MRI of the brain and magnetic resonance angiography of the head and neck, as well as the EEG, were unremarkable. A tilt table test demonstrated an increase in heart rate from 75 bpm supine to 112 bpm within 1 min of tilt without orthostatic hypotension. After 7 min of tilt, the heart rate decreased to 60 bpm with an unobtainable blood pressure, at which time the patient became unresponsive. She regained consciousness and her vital signs stabilized on assuming a supine position. The tilt table test was consistent with POTS and NCS. With pharmacotherapy consisting of a selective serotonin reuptake inhibitor (sertraline), which can be helpful in patients with POTS and NCS, her symptoms improved but persisted over the following 2 years. She was able to attend school 4 hours per day with pre-syncope occurring between one and four times per month.

Comment: This young female patient developed dizziness, headache and syncope one month after receiving qHPV, and she improved after the administration of a serotonin receptor inhibitor, which is indicated for the treatment of depression and anxiety disorders. Given the limited information on the family and medical history of this patient, neurological and psychiatric evaluations as well the basis for the neurocardiogenic syncope diagnosis, a clinical causality

assessment of POTS is not possible.

In case MARRS [redacted] a previously healthy 14-year-old female experienced numbness and tingling in her toes 5 days after receiving the first injection of qHPV. Over the following 2 weeks, the numbness and tingling increased to involve the lower extremities and pelvis. Other symptoms, such as fatigue, headache, nausea, diarrhea, weight loss and tachycardia, ensued. MRI of the brain and cervical spine were unremarkable, and laboratory testing showed positive antinuclear antibodies (ANA) with titers 1:160 with speckled pattern. Rheumatological evaluation was unrevealing raising a possibility of fibromyalgia. A tilt table test demonstrated a supine heart rate of 72 bpm which increased to a maximum of 123 bpm within 10 min of tilt without evidence of orthostatic hypotension. Heart rate responses to the Valsalva maneuver and deep breathing test were unremarkable, and sweat output in the leg with the quantitative sudomotor test was borderline reduced. The results of the autonomic testing indicated POTS and possible small fiber neuropathy, and the patient was started on metoprolol tartrate to control the tachycardia. Over the following 2 years, her symptoms had improved with the use of metoprolol tartrate for POTS and amitriptyline for headache prophylaxis.

Comment: Although there is limited information on the medical history, family history, other immunological tests, the positive ANA suggests an immune disorder. The determination of subtypes of ANA (e.g. anti-Ro antibodies, anti-La antibodies, anti-Sm antibodies, anti-nRNP antibodies, anti-dsDNA antibodies, anti-histone antibodies, antibodies to nuclear pore complexes, anti-centromere antibodies or anti-sp100 antibodies) could be useful to clarify the specific disorder.

In the last case presented by the authors (*MARRS* [redacted] an 18-year-old healthy female experienced numbness and tingling in the right arm 3 weeks after receiving the first qHPV injection into the right deltoid muscle. Over the following 3 months, she developed lower back pain, neck stiffness and pain in the legs resulting in difficulty sitting in class. Diagnostic tests obtained at that time included an unremarkable MRI of the cervical and lumbar spine and elevated ANA titers of 1:320 with speckled and homogeneous pattern. She received a second dose of qHPV 3 months after the first injection, and experienced a significant exacerbation of previous symptoms. Additional symptoms, such as fatigue, orthostatic intolerance, dizziness, urinary incontinence and blurry vision appeared which in conjunction with pain and numbness resulted in significant functional impairment. The patient became wheelchair-bound at that point and had to take medical leave from college for a full semester. Bedside heart rate assessment revealed a supine heart rate of 88 bpm and a maximum heart rate of 128 bpm within 5 min of standing. Neurological examination demonstrated reduced temperature sensation in the hands and feet without motor weakness. MRI of the brain, cervical, thoracic and lumbar spine, electromyography and cerebrospinal fluid analysis were unrevealing. Serological tests were only remarkable for elevated Antinuclear antibody (ANA) titers of 1:320 with speckled and homogeneous pattern. Based on clinical presentation, the patient was diagnosed with POTS and possible small fiber neuropathy; a tilt table test and further autonomic reflex screen testing were not performed. Over the following 3 years, the patient's symptoms improved significantly with the use of duloxetine and doxepin for neuropathic pain, and she was able to return to college full-

time.

Comment: As with the previous case, this patient experienced pain, numbness and tingling with positive ANA but no additional immunological tests were reported. A differential diagnosis with an immune disorder should be established. Given the limited diagnostic information provided, the causal relationship cannot be assessed.
In general it has to be pointed out that these case reports do not establish a clear pattern on time to onset of the symptoms, the diagnostic findings, or the symptoms themselves.

Kinoshita T et al. (2014) [Ref. 5.4: 040HS8] investigated the causes of neurological manifestations in girls immunized with the human papillomavirus (HPV) vaccine. Within nine months, 44 girls visited the authors' facility complaining of several symptoms after HPV vaccination. Four patients with other proven disorders were excluded, and the remaining 40 subjects were enrolled in this study. The age at initial vaccination ranged from 11 to 17 years, and the average incubation period after the first dose of the vaccine was 5.47±5.00 months. Frequent manifestations included headaches, general fatigue, coldness of the legs, limb pain and weakness. The skin temperature examined in 28 girls with limb symptoms exhibited a slight decrease in the fingers (30.4±2.6°C) and a moderate decrease in the toes (27.1±3.7°C). Digital plethysmograms revealed a reduced height of the waves, especially in the toes. The limb symptoms of four girls were compatible with the Japanese clinical diagnostic criteria for complex regional pain syndrome (CRPS), while those in the other 14 girls were consistent with foreign diagnostic criteria for CRPS. The Schellong test identified eight patients with orthostatic hypotension and four patients with postural orthostatic tachycardia syndrome. The girls with orthostatic intolerance and CRPS commonly experienced transient violent tremors and persistent asthenia. Electron-microscopic examinations of the intradermal nerves showed an abnormal pathology in the unmyelinated fibers in two of the three girls examined.
The authors conclude that the symptoms observed in this study can be explained by abnormal peripheral sympathetic responses. The most common previous diagnosis in the studied girls was psychosomatic disease. The social problems of the study participants remained unresolved in that the severely disabled girls stopped going to school.

In case MARRS [redacted] a 15-year-old [redacted] girl (Case [redacted] serial patient number: [redacted] visited our hospital complaining of transient limb weakness and orthostatic fainting. Four years earlier, she had received her first dose of qHPV in a clinic in the [redacted] since she was living there at the time. After 7 months later, she received the third dose of the vaccine. A few days later, she felt pain and weakness in the lower limbs, especially in the left leg, leading to difficulty in walking. This symptom subsided within the following 3 days; however, after one month, she developed numbness and weakness in both hands that lasted for 2 days. Transient weakness repeatedly appeared in both the hands and legs, and the patient subsequently experienced orthostatic fainting and abdominal discomfort. She returned to Japan in 16 months later and was examined at a local hospital, where no specific findings were noted. In addition to recurrent limb weakness, the patient newly exhibited a decreased ability to learn at school; she was unable to memorize different themes simultaneously and her understanding of textbooks was incomplete,

both of which were noticed by her mother. The patient and her family were seriously worried about her symptoms. On a physical examination conducted at the authors' hospital, the patient was 162 cm tall and weighed 47 kg. Her pulse rate was 74 bpm, with a BP of 94/62 mmHg in the sitting position. Her general physical findings were normal, although a neurological examination showed slight weakness in both hands and the left leg (grip power: 18 kg in the right hand; 10 kg in the left hand). Her skin temperature was 21.8°C in the right first toe and 31.1°C in the right second finger at a room temperature of 27.0°C, and plethysmograms of both the toes and fingers showed reduced heights of the waves in the toes. The findings of peripheral nerve conduction studies of the left median and tibial nerves were normal. On the Schellong test, the patient's heart rate and BP changed from 70 bpm and 105/62 mmHg to 109 bpm and 102/52 mmHg, respectively, at seven minutes after standing. The WAIS-III disclosed the following scores: FIQ=82, VIQ=88, PIQ=79, VC=92, PO=70, WM=85, AS=105. Furthermore, the patient had remarkable difficulty in quickly understanding long sentences. She was therefore diagnosed with CRPS-I and POTS, and her slight cognitive decline was thought to be potentially related to POTS. She was treated with the oral administration of limaprost alfadex at a dose of 5 mg (limaprost alfadex) three times daily, and her limb symptoms disappeared.

Comment: This female adolescent received two doses of qHPV without any event, and a few days after the third dose, she complained of pain in the lower limbs, especially in the left leg, numbness and weakness in both hands; weakness, abdominal discomfort and orthostatic fainting. At the physical examination, she was a thin woman with normal blood pressure but in the lowest normal range, normal plethysmogram and normal peripheral nerve conduction, and she was diagnosed with CRPS and POTS. Although, there is limited diagnostic information particularly no reports of immunological tests, electrophysiological tests, MRI or any other study, the patient received two previous doses of qHPV without any event, which suggests that the current events are unlikely related to the qHPV. Her clinical signs and symptoms were documented first approximately 1 ½ years after the last vaccination. It remains unclear whether her family's move from [redacted] had any psychological and/or social consequences which could have contributed to the events.

In case MARRS [redacted] a 13-year-old girl (Case[redacted], serial patient number[redacted]) was referred to the authors' hospital due to paroxysmal limb pain with headaches and a gait disturbance. She had a history of surgical removal of a left ovarian tumor at 10 years of age. She received her first dose of qHPV 16 months earlier, and two weeks later, began to suffer from a continuous high fever (39.0-40.0°C) and headaches. She was evaluated at a local hospital, where no abnormal findings were detected on a routine laboratory examination, endoscopy or CT. Various NSAIDs were prescribed; however, all were ineffective in relieving the patient's symptoms. She was tentatively diagnosed as having a psychosomatic fever and stopped participating in all sport activities on campus. Six months later, she received the third dose of the vaccine. Her high body temperature and general malaise gradually resolved; however, paroxysmal limb tremors subsequently appeared, especially while lying down, which caused the patient serious anxiety at night, resulting in insomnia. After approximately 4 weeks, she developed severe limb pain and palpitations; the limb pain restricted her shoulder and thigh

movement, sometimes accompanied by temporal paresis of the hands and legs, and the palpitations and chest discomfort were remarkably exacerbated when the patient changed from a sitting to standing position. Both conditions resulted in difficulties in writing and walking. The patient's condition was considered to be due to psychosomatic behavior at the hospital and at school. Therefore, she stopped going to school and had stayed home since late. On a physical examination conducted at the authors' hospital, the patient was 155 cm tall and weighed 51 kg. Her pulse rate was 98 bpm, with a BP of 112/78 mmHg in the sitting position. Her body temperature was 37.1°C, and her general physical findings were normal. Neurologically, she complained of uncomfortable pain in the legs; however, manual muscle tests, objective sensory examinations and deep tendon reflex studies were all normal. No limb tremors were noted at that time. The patient was able to walk using a handrail for short distances, exhibiting a very unsteady posture that easily led to squatting. The awkward gait appeared to us to be of hysteric origin. Her skin temperature was 28.8°C in the right first toe and 30.8°C in the right second finger at a room temperature of 23.5°C, and plethysmograms of both the toes and fingers showed reduced heights of the waves in the toes. On the Schellong test, the patient's heart rate and BP changed from 91 bpm and 105/91 mmHg to 126 bpm and 98/59 mmHg, respectively, at nine minutes after standing. A cardiac scintigram obtained using 123I-metaiodobenzylguanidine (MIBG) revealed a reduced uptake of the isotope, indicating the loss of post-ganglionic nerve terminals containing noradrenaline. She was therefore diagnosed as having CRPS-I and POTS and treated with the oral administration of bisoprolol fumarate (bisoprolol fumarate) at a dose of 2.5 mg daily. Four months later, her gait improved, and she was able to walk with the use of stick, although she did not return to her previous school life.

Comment: This female adolescent with history of left ovarian tumor, received qHPV and developed continuous fever and headaches. She received a second dose with no AEs reported. After receiving the third dose of qHPV, the fever and malaise resolved, but then, she experienced limb tremor, limb pain, and palpitations, which did not correspond to neurological examination. After multiple exams and tests, the only positive test was a cardiac scintigram obtained using MIBG revealing a reduced uptake of the isotope. . It remains unclear whether any further diagnostic measures were undertaken to exclude Parkinson's disease.
Although there is no information provided on the type of ovarian tumor of this patient, the improvement of patient's symptoms after the third dose of qHPV, and lack of symptomatology after the administration of the second dose suggest an alternative etiology. Depending on the type of ovarian tumor, the fever could be a manifestation of tumor activity or an associated infection. Both case reports are also reflected in the CRPS literature review.

Tomljenovic L et al. 2012 [Ref. 5.4: 040NH7]tried to determine whether or not some serious autoimmune and neurological ADRs following HPV vaccination are causal or merely coincidental and to validate a biomarker-based immunohistochemical (IHC) protocol for assessing causality in case of vaccination-suspected serious adverse neurological outcomes. Methods: Post-mortem brain tissue specimens from two young women who suffered from cerebral vasculitis type symptoms following vaccination with qHPV were analysed by IHC for

various immunoinflammatory markers. Brain sections were also stained for antibodies recognizing HPV-16L1 and HPV-18L1 antigen which are present in qHPV.
Results: In both cases, the autopsy revealed no anatomical, microbiological nor toxicological findings that might have explained the death of the individuals. In contrast, our IHC analysis showed evidence of an autoimmune vasculitis potentially triggered by the cross-reactive HPV-16L1 antibodies binding to the wall of cerebral blood vessels in all examined brain samples. We also detected the presence of HPV-16L1 particles within the cerebral vasculature with some HPV-16L1 particles adhering to the blood vessel walls. HPV-18L1 antibodies did not bind to cerebral blood vessels nor any other neural tissues. IHC also showed increased T-cell signaling and marked activation of the classical antibody-dependent complement pathway in cerebral vascular tissues from both cases. This pattern of complement activation in the absence of an active brain infection indicates an abnormal triggering of the immune response in which the immune attack is directed towards self-tissue.
Conclusions: Our study suggests that HPV vaccines containing HPV-16L1 antigens pose an inherent risk for triggering potentially fatal autoimmune vasculopathies.
Practice implications: Cerebral vasculitis is a serious disease which typically results in fatal outcomes when undiagnosed and left untreated. The fact that many of the symptoms reported to vaccine safety surveillance databases following HPV vaccination are indicative of cerebral vasculitis, but are unrecognized as such (i.e., intense persistent migraines, syncope, seizures, tremors and tingling, myalgia, locomotor abnormalities, psychotic symptoms and cognitive deficits), is a serious concern in light of the present findings. It thus appears that in some cases vaccination may be the triggering factor of fatal autoimmune/neurological events. Physicians should be aware of this association.

The authors report *in case MARRS* [redacted] a14-year-old female with a previous history of migraines and oral contraceptive use developed more severe migraines, speech problems, dizziness, weakness, inability to walk, depressed consciousness, confusion, amnesia and vomiting 14 days after receiving her first qHPV injection. These symptoms gradually resolved. However, 15 days after her second qHPV booster she was found unconscious in her bathtub by her mother 30 minutes after she had entered the bathroom to have a shower. Emergency help was summoned and arrived quickly. Resuscitation efforts were attempted. The paramedic noted that the patient was found without a pulse. Upon arrival at the hospital and approximately 30 minutes later, the patient suffered cardiac arrest. Resuscitation was terminated approximately 40 minutes later and the patient was pronounced dead. The autopsy failed to identify a precise cause of death. In particular, there were no anatomical, microbiological nor toxicological findings that could explain this case of death which was classified as "sudden and unexpected death". Nonetheless, autopsy revealed cerebral edema and cerebellar herniation indicative of a focally disrupted blood-brain barrier. Although no specific antibodies to inflammatory markers were used in IHC analysis of brain sections, the autopsy reported that there was no evidence of inflammatory processes or microglial reactions in the patient's brain. There were however acidophilic changes of the Purkinje cells in the cerebellum with vacuolation of the overlying molecular layer. According to the coroner, these changes were consistent with

terminal ischemic-hypoxic encephalopathy. Neuropathological examination did not demonstrate an underlying structural brain disorder. In addition, the coroner's report commented that the ischemic-hypoxic encephalopathy was terminal as was the cerebral edema and that either one could have been caused by the other. Based on the autopsy findings, the coroner was unable to establish a precise sequence of events and the specific etiology remained undetermined. Follow-up information stated that the patient had developed lupus.

Comment: This young female patient developed a severe generalized vasculitis with multiple complications including tonic-clonic generalized seizures, persistent migraines, syncope, and tremors and tingling, with a suspicion of a probable SLE. She also had renal lithiasis, POTS and her vasculitis progressed to death. The patient has a history of chronic migraine before the administration of qHPV, which might have been related to a preexisting cerebral vasculitis. The cause of death and autopsy showed cerebral vasculitis. The presence of POTS is likely related to vasculitis.

Tomljenovic L et al. (2014) [Ref. 5.4: 040ML9], report the case of a 14-year-old girl who developed POTS with chronic fatigue 2 months following qHPV vaccination. The patient suffered from persistent headaches, dizziness, recurrent syncope, poor motor coordination, weakness, fatigue, myalgias, numbness, tachycardia, dyspnea, visual disturbances, phonophobia, cognitive impairment, insomnia, gastrointestinal disturbances, and a weight loss of 20 pounds. The psychiatric evaluation ruled out the possibility that her symptoms were psychogenic or related to anxiety disorders. Furthermore, the patient tested positive for ANA (1:1280), lupus anticoagulant, and antiphospholipid. On clinical examination she presented livedo reticularis and was diagnosed with Raynaud's syndrome.
This case fulfills the criteria for the autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA). Because human papillomavirus vaccination is universally recommended to teenagers and because POTS frequently results in long-term disabilities (as was the case in this patient), a thorough follow-up of patients who present with relevant complaints after vaccination is strongly recommended.

In case (*MARRS* [redacted] a 14-year-old previously healthy girl presented with flu-like symptoms, sore throat, low-grade fever, fatigue, swollen glands, and intense headaches in February 2009, approximately 2 months after her second qHPV injection. Over the course of 1 week, the headache intensified and the patient further presented with photophobia, phonophobia, altered sense of taste, diminished appetite, gait disturbances, leg weakness, and inability to walk without assistance. By March 2009, her condition worsened and she quit regular school attendance due to progressively disabling symptoms. At that time she developed syncope and incapacitating chronic fatigue. Although the patient subsequently resumed attending school (by the end of 2009), her attendance was limited to 2 hours per day due to fatigue, diminished ability to focus, weakness, and severely impaired balance and coordination. She attended school in a wheel-chair and was exhausted after the 2-hour period. Her illness continue to progress, and by the end of 2010, she had the following symptoms: persistent incapacitating headaches, dizziness, recurrent syncope, lower extremity weakness, poor motor coordination, fatigue, neck pain, joint

pains, numbness in the legs, blurred vision, photophobia, phonophobia, cognitive impairment, insomnia, tachycardia, dyspnea, impaired thermoregulation, cold extremities, blush discoloration of toes, excessive hair loss, gastrointestinal (GI) disturbances, altered sense of taste, diminished appetite, and weight loss (20 pounds within 3 months of symptoms onset). The psychiatric evaluation in September 2009 ruled out the possibility that the patient's symptom were of psychosomatic origin, and the subsequent evaluation in 2010 found no evident signs of panic and anxiety disorders. Serological evaluations revealed a number of abnormalities, including an elevated ANA at 1:1280, a positive lupus anticoagulant, and a weakly positive antiphospholipid of 7.3 in October 2009. On clinical examination, the patient presented livedo reticularis. She was then diagnosed with an undifferentiated connective tissue disease and Raynaud's syndrome. Serology results for Epstein–Barr virus, Lyme, Babesia, and Ehrlichia were negative. Titers to Streptococcus pneumoniae indicated previous exposure but were however within a normal range, thus ruling out recent exposure. Over the course of her illness, the patient experienced a complete loss of consciousness with syncope approximately 12 times. These problems were never present prior to the onset of the illness in February 2009. On further testing, the patient was diagnosed with orthostatic intolerance. In particular, on the standing test the patient's lowest heart rate supine was 47 bpm with a blood pressure 103/56 mm Hg. On standing, the patient's heart rate increased immediately to 82 bpm and continued to increase to a maximum of 98 bpm after 9 minutes. According to the electrophysiologist, the patient's recurrent syncope was thus consistent with neurally mediated hypotension, and in December 2009, she was finally diagnosed with vasovagal syncope and associated POTS. In addition, her illness met the criteria for CSF given her persisting fatigue of over 6 months, new-onset disabling headaches, postexertional worsening of the fatigue, myalgias, cognitive dysfunction, and unrefreshing sleep. The patient's relevant medical history includes a family history of Raynaud's (patient's mother) and a personal history of headaches, dizziness, photophobia, and phonophobia in 2007, all of which however resolved completely in the same year.

Comment: This young female patient has a family history of Raynaud syndrome and developed a connective tissue disease. Connective tissue diseases are associated with vasculitis, and POTS is probably secondary to vasculitis. POTS can occur in association with multiple sclerosis, Sjorgen's syndrome, lupus, and Raynaud' Syndrome. Before the qHPV administration the patient had photophobia, headache and chronic fatigue, which often occur before the diagnosis of a connective tissue disease, suggesting that the current events are likely related to her underlying disease.

Brinth et al (2015) [Ref. 5.4: 046X0L]conducted a retrospective analysis of patients referred to their Syncope Unit at Frederiksberg Hospital in Denmark from May 2011 to December 2014 for a head-up tilt test to evaluate orthostatic intolerance and other symptoms compatible with autonomic dysfunction in patients with suspected side effects to qHPV. A total of 75 patients were evaluated; results are presented for 53 girls and women (age, 12-39 years; mean age at symptom onset, 21.0 years) who had onset of autonomic dysfunction-like symptoms within the first two months following vaccination. The mean time between vaccination and the onset of

symptoms was 11.1 days (range, 0-58 days). Symptoms occurred following dose 1 in 21 patients (40%), dose 2 in 19 patients (36%), and dose 3 in 13 patients (25%). All patients had symptoms consistent with pronounced autonomic dysfunction, including orthostatic intolerance in 51 (96%). In all, 24 (45%) suffered from recurrent syncopal attacks, and 38 (53%) were diagnosed with POTS. Other symptoms suspected as side effects of the quadrivalent HPV vaccine that occurred in >25% of patients were as follows: headache, fatigue, nausea, cognitive dysfunction, disordered sleep, blurred vision, feeling bloated, abdominal pain, light sensitivity, involuntary muscle activity (tremor, myoclonic twitches), neuropathic pain, dyspnea, skin problems (relapse of aggravation of acne), voiding dysfunction (including new-onset incontinence in one), limb weakness, constipation, diarrhea, vascular abnormalities (changes in skin color, sometimes with limb swelling), dry mouth, hyperventilation, irregular periods, and dry eyes. A comparison of patients with and without the POTS diagnosis showed that the two groups did not differ in patterns or severities of the above-listed symptoms, regardless of POTS diagnosis. Prior to symptom onset, 67% of individuals had a high level of activity in their daily lives and 33% had a moderate level of activity; five of the patients had been competing in sports at a national or international level. Fifty-two (98%) patients reported that their activities of daily living were seriously affected and 40 (75%) had to quit school or work for longer than 2 mo because of symptoms. The main finding of this analysis was consistency in symptoms experienced by patients. In analyzing their data, the authors considered the possibility of the phenomenon known as mass psychogenic illness, which has been defined as the collective occurrence of a constellation of symptoms suggestive of organic illness, but without an identified cause in a group of people with shared beliefs about the cause of the symptoms [11]. However, we do not find it likely that such a reaction constitutes the background for symptoms and signs found in our patients given their pre-vaccination history, the chronicity of their symptoms and the temporal and geographical dispersion.

Some of the patients have been suspected of suffering from a functional disorder. However, as the autonomic nervous system innervates monitors and controls most of the tissues and organs in the body – autonomic dysfunction often presents with a very diffuse and widespread pattern of symptoms [12]. The differential diagnostic procedure – especially with emphasis on the differentiation between functional disorder and autonomic dysfunction – is highly important in this group of patients and may require a faceted approach with involvement of expertise from different medical specialties.

The underlying etiology behind POTS is still somewhat elusive and the prevalence of POTS is most common in the same subset of the population that are receiving the HPV vaccine (young women) [13], which complicates the etiological discussion. We found a close chronologic association to the vaccination, but are well aware that this does not necessarily imply a causal relationship. Given the symptomatology, we suggest that the pathogenic alteration is located in the autonomic nervous system.

A causal link to the HPV vaccine cannot be confirmed or dismissed on the basis of the above findings, but the findings do suggest the need for further research regarding the link to the vaccine, the pathophysiology of the symptoms, and targeted treatment options for affected

patients.

Comment: Please see comment on the *Brinth et al. (2015)* publication below.

In another publication *Brinth et al. (2015)* [Ref. 5.4: 046WRP]describe their retrospective case review of the characteristics of 35 women (age 13-39 years; mean age, 23.3 years) who were referred to their clinic for orthostatic intolerance and autonomic dysfunction-like symptoms that began in close relation to vaccination with quadrivalent vaccine; one case report is presented in detail. The patients were referred consecutively to the syncope unit at the authors' institution in Frederiksberg, Denmark for a head-up tilt test to evaluate orthostatic intolerance as a suspected adverse event following vaccination with qHPV. The patients were interviewed with a special focus on symptoms that included the central and peripheral nervous system, exercise habits, and menstrual cycle. The narrative report was supplemented by two questionnaires, i.e., COMPASS-31 and the International Physical Activity Questionnaire-Short Form (IPAQ-SF). Symptoms developed after the first vaccination in 24%, after the second in 51%, and after the third in 25%. Symptoms in addition to orthostatic intolerance that were reported in more than half of the women were nausea (94%), chronic headache (82%), fatigue (82%), palpitations (77%), reduced cognitive dysfunction (77%), skin changes (76%), intermittent tremor/myoclonic twitches (72%), neuropathic pain (68%), sleep disturbances (61%), and muscular weakness (61%). The headache symptoms occurred daily and were described as severe, chronic, and bilateral. Cognitive dysfunction was described as mental fatigability, difficulty concentrating, memory impairment, shortened attention span, and verbal dyspraxia. Skin disorders consisted primarily of relapse of acne. The intensity of motor symptoms led to a dependency on a wheelchair in five cases. Segmental dystonia appeared in the form of intermittent tremor and myoclonic twitches. Descriptions of sensory symptoms included burning, deep stabbing, and jolts of electricity; most patients also described dysesthesia/allodynia. Disturbances in sleeping pattern were described as new-onset insomnia and nocturia. The heart rate in the resting supine position was a mean of 81 beats/ min, with a mean systolic/diastolic pressure of 123/82 mmHg. Three patients had sinus tachycardia in supine rest, three had elevated systolic pressure, and five had elevated diastolic pressure. Criteria for a diagnosis of POTS were met by 21 patients (60%). During the tilt test, the heart rate increased from 75 to 109 bpm in patients with POTS and from 73 to 94 bpm in patients without POTS ($p<0.001$). The mean time between the onset of symptoms and the examination was 1.9 yr (range, 0-5 yr); if there had been a shorter delay between onset of symptoms and testing, the authors feel that the incidence of POTS may have been higher. The total weighted COMPASS-31 scores did not differ significantly between those with POTS and those without POTS. On the basis of the IPAQ-SF questionnaire, 71% of patients had a high level of activity and 29% had a moderate level of activity prior to symptom onset. Half of the women with a high activity level were competing in their sport at a national or international level. Oral contraceptives were used by 24 of 35 patients; the remaining 11 patients all reported having irregular periods. Activities of daily living were reported as being seriously affected in 34 of 35 patients, and 21 had quit school or work because of the symptoms. Bilirubin levels in study patients were low (median, <5 mcmol/L; range, undetectable to 13 mcmol/L). A high level of

physical activity before symptom onset, a high incidence of irregular menstruation, and low levels of bilirubin may all have affected their immune response to vaccination. Exercise may increase both pro- and anti-inflammatory cytokines as well as leukocyte subsets and exercise has been found to enhance the response to vaccination.
The development of symptoms is illustrated by the following case: A 12-year-old girl (MARRS [redacted] who was healthy and physically active developed general malaise, sore throat, and fever and a slight fever a few days after dose #1 of her HPV vaccine series. Two days after her second dose of HPV, she fainted; in the days following this episode, she developed orthostatic intolerance with dizziness, palpitations, and frequent near-syncope, deep limb pain, exercise intolerance, and fatigue. Over a period of months, other symptoms appeared, including chronic severe headache and cognitive dysfunction with impaired memory, difficulty concentrating, and verbal dyspraxia. Lab tests were normal except for a low vitamin D level. Currently, the girl is limited in her daily activities, and she is socially isolated and cannot attend school. The tilt test in this child was associated with marked orthostatic discomfort.
The authors state that in this retrospective review, the high physical activity levels, high incidence of irregular menstruation, and low bilirubin levels may have all affected the patients' immune response. And they speculate that, because bilirubin acts as an inhibitor of the complement cascade, the low bilirubin levels may have enhanced the immune and inflammatory response to antigens. However, it is unknown if the patients had low levels of bilirubin before the vaccination.
The authors are aware of several study limitations. The first being the lack of a control group and the possibility of reduced representativeness of their cases compared to the underlying population – as patients are not referred to their unit because of suspected side effects –but because of orthostatic intolerance. The second major limitation is the long and variable delay between the onset of symptoms and orthostatic testing. It is perceivable that the incidence of POTS would be higher if the orthostatic test was conducted after a shorter delay between onset of symptoms and testing as the 40% who did not receive a POTS diagnosis also reported symptoms of orthostatic intolerance. On the other hand, the incidence could have been lower if performed in closer proximity to symptom onset as patients may become deconditioned in the interval between symptom onset and testing. A third limitation is the frequent use of 10-minute tilt table test as this study would miss other forms of chronic orthostatic intolerance such as delayed orthostatic hypotension or neurally mediated hypotension (also known as vasovagal hypotension). These generally require orthostatic stress duration of more than 10 minutes. POTS has been suggested to have an immune-mediated pathogenesis and may be related to other autoimmune conditions such as multiple sclerosis and antiphospholipid syndrome.
Findings from this study neither rule out nor confirm a causal link between symptoms and the HPV vaccine, but do suggest that further research is urgently warranted.

Comment: This respective case review reveals several common aspects in the patients described: with a mean age of 23.3 years they were generally older than the target population for HPV vaccination programs, 71% appeared to have a high level of physical activity prior to vaccination (with half of them even competing in their sport at a national or international level),

a high incidence of irregular menstruation, and low Bilirubin levels (median, <5 mcmol/L; range, undetectable to 13 mcmol/L). The authors discuss that all these conditions may have an effect on the immune system, and that exercise may increase both pro- and anti-inflammatory cytokines as well as leukocyte subsets and may have enhanced the response to vaccination. Indeed, bilirubin is under discussion of being a powerful immunomodulatory agent, as it could be shown that treatment with bilirubin effectively suppressed experimental autoimmune encephalomyelitis in mice, while depletion of endogenous bilirubin dramatically exacerbated this disease. These results raised the hypothesis that bilirubin as an immunomodulator may protect mammals against autoimmune diseases [Ref. 5.4: 0476K4]. Regarding the case description provided in this publication, it should be noted that in a similar way vitamin D seems to have a contributory role in the pathophysiology of autoimmune diseases. This is supported by various experimental findings showing vitamin D's capability to regulate chemokine production, counteracting autoimmune inflammation and to induce differentiation of immune cells in a way that promotes self-tolerance [Ref. 5.4: 0476KB]. Since vitamin D is actively used in many metabolic pathways, it is possible that a high level of physical activity may require an increased intake of vitamin D to assure adequate availability [Ref. 5.4: 0476KL]). This could be specifically of importance in areas with less sunlight and/or for physical activities mainly performed indoors.
As the authors point out, POTS has been suggested to have an immune-mediated pathogenesis; it appears possible in this case that individual predisposition and an altered immunomodulation may have caused the described signs and symptoms with or without the accused vaccination. This emphasizes a major limitation of the presented case review is the lack of a control group. In addition, with a symptom onset distribution of 24% after the first vaccination, 51% after the second and 25 % after the third vaccination no clear pattern could be demonstrated.

Ikeda (2014) [Ref. 5.4: 046Z4F] states his point of view on side-effects and autonomic nerve disorders of cervical cancer vaccines including POTS: Accompanying the revision of the Japanese Preventive Vaccinations Act in April 2013, free regular inoculations with cervical cancer vaccines were started for students from primary school Year 6 to high school Year 1. Around that time, the media started reporting situations in which girls who underwent the present vaccination suffered from strange symptoms, and the images of girls at junior high school and high school crying particularly due to episodic extreme pain in the extremities with trembling limbs made a strong impact on the nation. The incidence rate of side-effects at present, as of June 2013, is 0.01%; however, the media reports inflamed the situation, which has never been experienced before, and these cervical cancer vaccine side-effects have become a societal issue. The Ministry of Health, Labor, and Welfare rapidly established an investigation group from amongst experts, and investigated cases submitted to the Ministry. The results of this investigation found that this cannot be ignored. Therefore, in June 2013, the Ministry stopped encouraging cervical cancer vaccine inoculation. At the same time, the Ministry set up a study group in order to investigate the situation of chronic pain in the limbs following cervical cancer vaccine inoculation and to clarify the causes of it. The author stated being involved in the present issue as the senior manager of one of the research groups.

Results of the investigation into the situation as of the end of January 2014: A request to the National Cervical Cancer Vaccine Communication Group was made on 38 patients who voluntarily attended consultations. Ages were between 12 and 19 years (mean 15.8 +/- 1.9 years), and the mean age at initial inoculation was 13.9 +/- 1.6 years. The average period from the initial inoculation until the occurrence of symptoms was 5.47 +/- 5.00 months, and the average time from the final inoculation until the occurrence of symptoms was 1.94 +/- 3.06 months. Main symptoms were headache in 24 cases (71%), systemic malaise 1 in 9 cases (56%), lower limb cold sensation in 18 cases (53%), pain in the extremities in 17 cases (50%), difficulty in waking up in 17 cases (50%), trembling in the extremities in 15 cases 15 (44%), and walking difficulties in 14 cases (41%). The author got the impression that the extremities of those who complained of pain in the limbs were very cold and performed finger and toe plethysmograms and measured skin temperature, and found abnormalities in the former in 53% and in the latter in 58% of cases. Therefore, he performed a skin biopsy in two of the cases at sites where the finger plethysmogram was performed, and observed the tissue under an electron microscope. He observed a decrease in unmyelinated nerve fiber and an image of remaining unmyelinated nerve deforming within intradermal nerves.
Mechanism and cause of onset: The author believes that the main cause of headache, systemic malaise, and chronic pain in the extremities, which are symptoms similar to orthostatic intolerance, is advanced peripheral sympathetic nerve disorder. Meanwhile, the specialist group of the Ministry of Health, Labor, and Welfare, provided the opinion that no organic lesions have been observed in patients with serious side-effects following cervical cancer vaccine inoculation, and all the symptoms are functional abnormalities. Moreover, their pathology is physical symptoms affected by psychological and social factors. The author strongly opposes this opinion. Psychological reactions do not lead to declines in skin temperature in the limbs, nor do they cause significant declines in plasma noradrenaline concentrations. It is true that these can deteriorate due to symptoms because of certain organic lesions (e.g. pain due to autonomic nerve disorder), and that psychological and social factors have certain impacts in the process of developing other symptoms. He will continue the present research, with the aim of clarifying the cause and establishing an efficacious treatment.

Comment: It is noteworthy that all publications in the sponsor's literature review originating from Japan, including the 2 following publications, are from the same site, the Neurology Department and Rheumatology and Connective Tissue Disease Department of the Shinshu University, Nagano. Probably all 3 publications include at least in part the same patient reports and evaluations. The author provides the average period from the initial inoculation until the occurrence of symptoms as 5.47 +/- 5.00 months, and the average time from the final inoculation until the occurrence of symptoms as 1.94 +/- 3.06 months. Both periods do not establish a clear time pattern to onset of any symptoms. With headache being the most common symptom (71%) experienced by his patients, a very common symptom in this age group in general is highlighted. Walking difficulties and trembling (in 41 – 50% of the cases) appear to be the most disabling symptoms but only a unspecific pathomechanism (advanced peripheral sympathetic nerve

disorder) is proposed, and it remains unclear why the author so passionately excludes a possible conversion disorder in these cases.

Kinoshita et al. (abstract #2-B-2, 2014) [Ref. 5.4: 046Y94], discuss dysautonomia in young female patients following the administration of HPV vaccine for the prevention of cervical cancer.
Objective: In Japan, a large number of cases have been reported in which symptoms such as pains in the extremities and headaches have developed with some severity in young female patients following the administration of HPV vaccine for the prevention of cervical cancer, impeding their everyday lives and school careers. These cases have come to be considered a social problem. When such patients have undergone examination, cold sensations in the limbs and diminished wave height of the digital pulse volume have been observed. The authors suggested that these findings indicated possible peripheral circulatory failure and sympathicopathy, and anticipated that in many cases they would correspond to the general picture of orthostatic disturbance. Having performed autonomic nerve testing in the patients including measurement of the skin temperature, measurement of the digital pulse volume and orthostatic testing, they inferred that the appearance of these symptoms in these young female patients could be connected with the presence of dysautonomia, and conducted a review into this possibility.
Subjects and methods: The subjects comprised 48 young female patients aged 13-19 years of age (mean age: 15.6 +/- 1.8 years), from among 53 such patients who were examined at our hospital after presenting with various symptoms following administration of the HPV vaccine between June 2013 and July 2014. We excluded 5 patients who were judged to be obviously suffering from other complaints. We performed autonomic nerve function testing, including orthostatic testing which combined measurement of the skin temperature, measurement of digital pulse volume and measurement of norepinephrine levels. In 3 of the patients, we also performed skin biopsies on skin taken from the toes where digital pulse volume and skin temperature had been measured, and observed the cutaneous nerves in the tissue using an electron microscope.
Results: A detailed breakdown of adverse events indicated a high incidence of findings suggestive of dysautonomia, including headaches (66%: 29 patients), general malaise (50%: 22 patients), cold sensations in the lower extremities (50%: 22 patients), pains in the limbs (45%: 20 patients) and difficulties with rising in the morning (45%: 20 patients). Skin temperature was measured in 14 of the patients, with a mean temperature of 30.1 +/- 2.3 C observed for the digitus secundus versus 27.7 +/- 3.2 C for the hallux, suggesting a tendency for skin temperatures to be particularly low in the lower extremities. Digital pulse volume was measured in 13 patients, with diminished wave height observed in 12 patients. Orthostatic testing and measurement of catecholamine levels were performed in 18 patients. 12 patients fulfilled the diagnostic criteria for orthostatic hypotension (OH), while 4 patients fulfilled the criteria for POTS unaccompanied by hypotension. In healthy individuals, the plasma norepinephrine (NE) level when the individual is in a standing position rises to 60-120% of the resting level. In 9 patients examined in this study, the percentage increase in NE was low, suggesting diminished

responsiveness of NE secretion in response to the standing position. The orthostatic testing and catecholamine level measurement produced abnormal findings for 14 of the 18 patients who were tested. Skin biopsies of tissue taken from the digitus secundus and hallux were performed for 3 patients; when the cutaneous nerves were observed using an electron microscope, the findings in 2 of the patients indicated degeneration of the non-medullated nerve fibers. Measurement of ganglionic acetylcholine receptor antibodies was undertaken in 14 of the patients, producing negative results for all 14 patients.
Discussion: The authors consider that of the symptoms which had appeared among the young female patients who were examined at their hospital following administration of the HPV vaccine, one possible explanation of the headaches and general malaise was that these were symptoms of orthostatic disturbance. They suggest peripheral dysautonomia as a cause, based on the diminished pulse wave height, diminished skin temperature, the results of the orthostatic testing and the findings suggesting degeneration of the cutaneous nerves. Although it cannot be definitively stated that orthostatic disturbance is triggered by vaccination, the incidence of the condition is remarkably high among the cohort of young female patients in this study. However, the possibility that the high incidence is coincidental also cannot be ruled out, given that this condition is common among the age group which overlaps the period when this vaccine is administered. A high incidence of intractable pain in the extremities was also observed, with 18 of the young female patients fulfilling the diagnostic criteria for complex regional pain syndrome Type I (CRPS-I) as established by the International Association for the Study of Pain, and with 4 of these patients also fulfilling the Japanese diagnostic criteria.
Conclusion: The authors consider that the extremely varied range of symptoms with which the young female patients presented suggests the underlying presence of dysautonomia, although any connection with the HPV vaccine is unclear. Possible presence of peripheral dysautonomia was inferred from the results of autonomic nerve testing including orthostatic testing and from the abnormal findings for the cutaneous nerves.

Comment: The authors provide no information on the number of doses of HPV vaccine received, time to onset of first signs and symptoms, concurrent or preexisting conditions or possible other causes for the investigated symptoms, and present a vague theory as a cause for these events. It has to pointed out that no clear pattern of signs and symptoms including microscopic findings was observed, and the authors themselves emphasize that the possibility for a high incidence of these symptoms observed in their review is coincidental also cannot be ruled out, given that this condition is common among the age group which overlaps the period when this vaccine is administered.

Kinoshita et al. (2014) [Ref. 5.4: 047650] state that there have been reports on females with difficulties in everyday life and school life due to certain symptoms following cervical cancer-preventive human papilloma virus (HPV) vaccine inoculation. These females have made many complaints, such as of headache, systemic malaise, and difficulty waking up in the morning; and coldness of the limbs is observed at consultation. Based on this, the authors assumed that autonomic neuropathy is related to the cause of such symptoms, and conducted an investigation.

Method: Subjects were 17 females aged 12-17. Standing-up tests were performed in which skin temperature was measured, plethysmograms were performed, and catecholamines were measured; and also MIBG-I[123] (meta-iodobenzylguanidine) myocardial perfusion scintigraphy was performed. Results: Skin temperature was measured in 14 patients. The average index temperature was 30.1 +/- 2.3 C, and that of the great toe was 27.7 +/- 3.2 C, with a particular tendency for decreases in the lower limbs. Plethysmograms were performed in 13 patients, and decreased wave heights were observed in 12 cases. Stand-up tests were performed and catecholamines were measured in 14 patients, of which three met the diagnosis criteria for orthostatic hypotension, and three satisfied the criteria for postural tachycardia syndrome not accompanied by blood pressure reductions. In healthy people, plasma norepinephrine (NE) increases by 60-120% upon standing up compared to at rest. In the present study, we considered that nine patients had a small rate of increase in NE, and decreased responsiveness to NE secretion upon standing up. From amongst 14 patients, 12 were found to have abnormalities based on the results of catecholamine measurement and stand-up tests. MIBG-I[123] was performed in four patients, and one was found to have a progressed washout rate. Conclusion: While a relationship between HPV vaccines and peripheral symptomatic neuropathy is unknown, the authors consider that the background to symptoms which cause decreases in ADL involves peripheral symptomatic neuropathy.

Comment: Also this publication presents no information on the number of doses of HPV vaccine received, time to onset of first signs and symptoms, concurrent or preexisting conditions or possible other causes for the investigated symptoms.

The pharmacovigilance update of listings and concerns regarding suspected adverse drug reactions (ADRs) for HPV vaccine published by the *Danish Health and Medicines Authority (DHMA) in 2014* [Ref. 5.4: 046Z40] covers the period from 10 September to 30 November 2013. All but two of the reports received of suspected serious ADRs received during the specified period concerned qHPV, which accounts for the majority of HPV vaccines administered in Denmark. The listings show that the DHMA received more ADRs associated with HPV vaccine in 2013 than it did in previous years; that the most frequently reported serious ADRs consisted of severe and long-term cases of fainting/dizziness, headache, and general malaise; and that there have been four additional reports of a diagnosis of POTS since the last listing. To date, the DHMA has received 16 Danish reports with a diagnosis of POTS and 2 cases with a suspected diagnosis of POTS that have been referred for further investigation. Based on the ADR reports concerning the diagnosis of POTS and the symptoms coinciding with this diagnosis, the DHMA has requested that the European Medicines Agency, EMA, investigates POTS as a new potential ADR from the HPV vaccine. Since 2009, there have been a total of 1,488,509 doses of HPV sold, 970 reports of ADRs, and 221 reports of serious ADRs. The DHMA assessments of the correlation between the HPV vaccine and a suspected ADR were in the following 4 categories: possible, less likely, and not possible to assess based on available information. ADRs classified as "possible" and whether each specified ADR is listed in the Summary of Product Characteristics (SPC) included POTS "possible" in 3 of 4 cases with long-term symptoms (ADR

not in SPC).
POTS is a relatively new diagnosis, and the causal mechanisms of the development of POTS remain unclear. For example, the condition has been described following rapid growth in teenagers, infectious diseases and severe traumas. It is known that the condition may emerge following, e.g., a virus infection. POTS is characterized by a dramatic increase in the heart rate following a change from the supine to the upright position and a labile blood pressure in the upright position. The typical symptoms are dizziness, marked fatigue and fainting. Not all sufferers experience fainting. POTS may be diagnosed with a tilt table test. POTS occurs in both genders, but most frequently in girls/women aged 15-50 years. The exact prevalence is not known. Figures from the Danish National Patient Registry shows that 96 patients diagnosed with POTS were hospitalized during the period 2006-2012. POTS also occurs in non-vaccinees in the same age group. Since the exact incidence and prevalence of the disease POTS are not known, it is difficult to determine whether the numbers are increased in HPV vaccinees. However, in many of the women/girls, the symptoms started shortly after the vaccination. Once the results of the European Medicines Agency's investigation of a possible correlation between the HPV vaccine and POTS are available, the DHMA will report on them.
Although the vaccine may cause serious ADRs, the Danish Health and Medicines Authority and the authorities in the rest of Europe consider the benefits of HPV vaccine to outweigh the potential risks.

Comment: This report does not provide case information and is included here for completeness.

Tomljenovic et al. (2014) [Ref. 5.4: 040ML9]report the case of a 14-yr-old girl (*MARRS* [redacted] with a history of headaches, dizziness, photophobia, and phonophobia 2 years prior to qHPV vaccination and a family history of Raynaud's syndrome, who experienced POTS and chronic fatigue syndrome (CFS) of autoimmune origin approximately 2 months after she received her second dose of qHPV, presenting with flu-like symptoms, sore throat, low-grade fever, fatigue, swollen glands, and intense headaches. Over the course of a week, her headache intensified, and she reported additional symptoms of photophobia, phonophobia, altered sense of taste, and diminished appetite. The patient also had gait disturbances and leg weakness, and was unable to walk without assistance. One month later deterioration in her condition interfered with school attendance because of progressively disabling symptoms. Syncope and incapacitating chronic fatigue were also noted at this time. Approximately 10 months after receiving the second dose of qHPV, the patient resumed attending school, but she was in a wheelchair and her attendance was limited to 2 hours per day because of fatigue, diminished ability to focus, and severe impairment of balance and coordination. A psychiatric evaluation ruled out a psychosomatic etiology; a further examination in the following year ruled out panic and anxiety disorders. Eight months after receiving the second dose, a number of abnormalities were detected in the serological evaluations, including an elevated ANA (1:1280), a positive lupus anticoagulant, and a weakly positive antiphospholipid level. Clinical examination revealed livedo reticularis, and a diagnosis of undifferentiated connective tissue disease and Raynaud's syndrome

was made. There was further progression in the patient's illness and, by the end of the following year, her symptoms also included a weight loss of 20 lbs. within 3 months of onset; tachycardia; dizziness; neck and joint pains; cognitive impairment; blurred vision; cold extremities, with bluish discoloration of toes; impaired regulation of body temperature; GI disturbances; dyspnea; insomnia; and excessive hair loss. At this time, headaches were persistent and incapacitating, and syncope was recurrent; over the course of the illness, the patient had complete loss of consciousness with syncope about 12 times. Further testing resulted in a diagnosis of orthostatic intolerance. According to the electrophysiologist, the recurrent syncope was consistent with neurally mediated hypotension. The authors felt that this case clearly fulfills the criteria for POTS/CFS. In addition, the patient fulfilled the first 2 major criteria and 3 minor criteria for Autoimmune/autoinflammatory Syndrome Induced by Adjuvant (ASIA). The authors assume that the unusual frequency of adverse reactions following HPV vaccination cannot solely attributed to the aluminum adjuvant, as many other vaccines also contain aluminum (i.e. tetanus, diphtheria, etc.) but are not associated with as many adverse reactions. However, it is the aluminum that evokes the enhanced immune reaction necessary for inducing the production of the elevated titers of antibodies. The antigen on its own is not capable of evoking this strong immune response. Because of this, any adverse effect arising from the antigen (or other constituents in the vaccine) is ultimately linked to the action of the adjuvant.

Comment: Based on this case the authors speculate that as a general mechanism the vaccines adjuvant in combination with the specific HPV antigen may lead to a strong immune response which is linked to the development of the patient's symptoms. In this case though the patient's medical history of headaches, dizziness, photophobia, and phonophobia and her family history (mother) of Raynaud's syndrome need to be taken into account. It appears that the patient was predisposed to develop the described signs and symptoms due to an underlying connective tissue disease. The development of the first symptoms 2 months after the second vaccination was probably coincidental.

Discussion and Conclusion

POTS is characterized by a defined increase in the heart rate following a change from the supine to the upright position and a labile blood pressure in the upright position. The typical symptoms are dizziness, marked fatigue and fainting. POTS may be diagnosed with a tilt table test. POTS occurs in both genders, but most frequently in females aged 15-50 years. The exact prevalence is not known.

The published case reports of POTS or Chronic Orthostatic Intolerance described in the scientific articles listed above, provide in most cases incomplete clinical information to establish a differential diagnosis, including results of tests or immunological determinations. In some cases, the patients had clinical manifestations (e.g. migraine, chronic fatigue) before the administration of the qHPV. In a number of cases other potential triggers of POTS such as exhaustive physical activity that produces loss of electrolytes and fluids, particularly in a young athletic population,

were reported. In some patients, a predisposition to develop connective tissue disease cannot be excluded. All cases were women, and sex difference (5:1 female-male ratio) is well known for POTS. This is an important factor to consider because the target population (young women) is the same for POTS and for recipients of qHPV, as well as for some autoimmune disorders such as SLE.

As a syndrome, POTS can be the result of various diseases such as pheochromocytoma, mast cell activation disorders, autoimmune neuropathies, and autoimmune diseases, conditions associated with hypovolemia, prolonged bed rest, pain or chronic fatigue. The role of vaccines and vasculitis continues to be investigated, and the publications include cases of POTS secondary to vasculitis, one of them being a fatal case in a young patient with generalized and severe vasculitis. In some of the reported cases, the cause of POTS was probably related to underlying diseases, such as irritable bowel syndrome and cardiac disorder.

It is noteworthy that all publications in the sponsor's literature review are from the same site, the Neurology Department and Rheumatology and Connective Tissue Disease Department of the Shinshu University, Nagano, Japan. It appears that all publications include, at least in part, the same patient reports and evaluations. And 30 of the 33 cases that fully met the case definition for POTS were received from Denmark, with 27 (90%) originating from the Syncope Centre at Frederiksberg Hospital. Also, it appears that the same patient cases are discussed repeatedly in successive publications. In their retrospective case review, the Danish authors point out several common aspects in their patients: with a mean age of 23.3 years, they were generally older than the target population for HPV vaccination programs, 71% appeared to have a high level of physical activity prior to vaccination (with half of them even competing in their sport at a national or international level), a high incidence of irregular menstruation, and low bilirubin levels (median, <5 mcmol/L; range, undetectable to 13 mcmol/L). The authors discuss that all these conditions may have an effect on the immune system, and that exercise may increase both pro- and anti-inflammatory cytokines as well as leukocyte subsets and may have enhanced the response to vaccination. Bilirubin is indeed under discussion of being a powerful immunomodulatory agent, and may protect mammals against autoimmune diseases. Also vitamin D seems to have a contributory role in the pathophysiology of autoimmune diseases, and may counteract autoimmune inflammation. Since vitamin D is actively used in many metabolic pathways, it is possible that a high level of physical activity as described in most of the Danish patients may require an increased intake of vitamin D to assure adequate availability. This could be specifically of importance in areas with less sunlight and/or for physical activities mainly performed indoors. POTS has been suggested to have an immune-mediated pathogenesis, hence it is possible that individual predisposition and an altered immunomodulation may have caused the described signs and symptoms with or without the preceding vaccination. In addition, taken the publications together, no clear pattern of time to onset and doses received could be demonstrated. Overall, no causal relationship can be established.

1.2 PRAC Question 2

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

MAH RESPONSE

1.2.1 Complex Regional Pain Syndrome

Three cases suggestive of CRPS (1 in each of 9vHPV vaccine, qHPV vaccine, and placebo groups) were identified. Quantitative analysis of incidence rates in the clinical database showed that the incidence rates were similar with largely overlapping 95% confidence intervals indicating no statistical difference between the HPV vaccine groups and placebo group. As summarized below, medical review of the cases indicated that in two cases the diagnosis criteria of CRPS were not reported which makes it difficult to verify the diagnosis. Moreover, these two subjects had prior injury which could have caused the CRPS. For the third case, some of diagnosis criteria of CRPS were reported; however, the symptoms were more likely explained by an infection.

- A diagnosis of CRPS was reported for [redacted], a subject who received 9vHPV vaccine, at the Month 3 study visit; at that time, the subject had received 2 doses of 9vHPV vaccine (at the Day 1 and Month 2 study visits). The investigator indicated that the CRPS was consecutive to an injury during physical activity that occurred prior to vaccination 1, and that CRPS was not related to vaccination The diagnosis of CRPS was based on persistence of pain following the injury; however, none of the diagnostic criteria used to support a diagnosis of CRPS (sensory, vasomotor, sudomotor/edema, motor/trophic symptoms) were reported for this subject. The subject received a third dose of 9vHPV vaccine approximately 4 months later; no adverse events or new medical conditions were reported following the third dose of 9vHPV vaccine. Also, no further symptoms or new medical conditions were reported at any subsequent study visit over more than 4 years of follow-up in the study does not seem consistent with a diagnosis of CRPS.

- A diagnosis of CRPS was reported for [redacted], a subject who received qHPV vaccine, at Day 736 post-vaccination 3. The subject had received 3 doses of qHPV vaccine (at the Day 1, Month 2, and Month 6 study visits). None of the diagnosis criteria of CRPS (sensory, vasomotor, sudomotor/edema, motor/trophic symptoms) were reported. A prior medical history (pre-vaccination) of injury (unspecified) was noted, which may be a contributing factor to CRPS. New medical conditions of epilepsy and cerebral cyst were reported in 2011; these neurological conditions may conceivably contribute to a pain syndrome. No further symptoms or new medical conditions (aside from gastroenteritis) were reported at any subsequent study visit (over more than one year).

- A combination of symptoms suggestive of a CRPS case was reported for [redacted], a subject who received placebo. Even though several of the diagnostic criteria outlined above (vasomotor, sudomotor/edema, motor/trophic symptoms) occurred on two occasions, the prompt recovery (within 1 day and 4 days, respectively), and the concurrent report of nasopharyngitis and chills, respectively, suggest two occurrences of acute infection rather than CRPS. Moroever, no further symptoms or new medical conditions were reported at any subsequent study visit over nearly 4 years of follow-up in the study.

1.2.2 Postural Orthostatic Tachycardia Syndrome

Two cases suggestive of POTS (both in the 9vHPV vaccine group) were identified. Quantitative analysis of incidence rates in the clinical database showed that the incidence rates were similar with largely overlapping 95% confidence intervals indicating no statistical difference between the 9vHPV vaccine group and placebo group. As summarized below, medical review of the cases suggested that only one of the two cases met the diagnosis criteria of POTS.

- A diagnosis of POTS was reported for [redacted], a subject who received 9vHPV vaccine, at the Month 3 study visit; at that time, the subject had received 1 doses of 9vHPV vaccine (at the Day 1 study visit). The subject received a second and a third dose of 9vHPV vaccine approximately 3 and 7 months later, respectively; no adverse events or new medical conditions were reported following the second and third doses of 9vHPV vaccine. Also, no further symptoms or new medical conditions were reported at any subsequent study visit over 1 year of follow-up in the study. No additional symptoms reported in the study database that suggested that this condition was recurrent or chronic. The absence of recurrent episodes is not suggestive of POTS.

- A diagnosis of POTS was reported for [redacted], a subject who received 3 doses of 9vHPV vaccine (at the Day 1, Month 2, and Month 6 study visits). This subject was diagnosed with POTS at Day 1389 post-dose 3, after the subject completed her last study visit. No symptoms suggestive of POTS were reported by this subject during the study, over more than 4 years of follow-up. The diagnosis of POTS appears based on a rigorous evaluation, including a positive Tilt table test and the use of a questionnaire designed for diagnosis of POTS. However, the investigator indicated that this event was reported by the subject following a local media campaign on potential adverse effects of HPV vaccination which may complicate the assessment of this case. As noted, the local Patient Compensation Association assessed this case as not related to the 9vHPV vaccine.

A third report of diagnosis of POTS was reported to have occurred in a subject who participated in Protocol V503-006. This event occurred after the end of the study. Only limited information is available. All subjects in Protocol V503-006 were prior qHPV vaccine recipients. Thus, this case may be considered as a post-marketing case in a prior qHPV vaccine recipient. In Protocol

V503-006, subjects received 9vHPV vaccine or placebo. If the subject was randomized to 9vHPV vaccine, it could also be considered as a case occurring in a clinical study in a subject who received 9vHPV vaccine. The information provided in the report is not sufficient to decide whether or not this subject met the diagnostic criteria of P

1.3 PRAC Question 3

The MAHs should provide an analysis of the observed number of post-marketing cases of CRPS and POTS in association with their HPV vaccine in comparison to those expected in the target population, stratified by region, if available. The analysis should discuss the assumptions made with respect to the background incidence in the target population and also the influence of potential under-reporting of cases in association with HPV vaccines.

MAH RESPONSE

Summary: An analysis of observed versus expected counts was undertaken for CRPS and POTS. As described below and well-known about this type of approach, this analysis should be interpreted with caution, given the paucity of incidence data in the literature, the different methods used to ascertain cases in epidemiological studies and in spontaneous reporting, the range of assumptions used, and the small sample sizes involved. Notwithstanding, the results of this analysis do not support an association between qHPV vaccination and CRPS or POTS.

1.3.1 Observed vs Expected Analysis: General Methods Considerations

Expected Number of Cases:

Standard methods were used to calculate a range of expected numbers of cases, consistent with the EMA guideline on Good Pharmacovigilance Practices, and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

The expected number of cases within specific periods of time in the absence of qHPV vaccination (i.e., the "background" number of cases) was calculated for the following regions/countries: Worldwide, European Union (EU), Denmark, Germany, United Kingdom (UK), United States (US), and Japan.

Expected cases were estimated for vaccinated females. Potential expected cases in vaccinated males were not added because the incidence of CRPS and POTS is much lower in males and dose use in males is still low (estimated to be ~10% of worldwide use since 2006). As a result, the expected numbers provided in this response, based only on vaccinated females, are slightly

conservative (that is, if males were included in this analysis, the expected number of cases would be slightly higher).

To calculate expected numbers, assumptions were estimated for the following parameters: incidence rate of the condition, number of doses administered to females, and rates of reporting cases to postmarketing surveillance systems. Details on how these assumptions were derived are provided below.

Incidence rate of CRPS and POTS: A literature review was conducted to identify background incidence rates and prevalence of CRPS and POTS in females in the age range of approximately 9-26 years. For CRPS, incidence rates were different in 10-19 and 20-29 year olds and the age distribution of females who received qHPV vaccine was used to calculate a weighted average incidence rate. The age distribution of females who receive Gardasil is generally about 90% in the 10-19 year old age range and 10% in the 20-29 year old age range. For Denmark, the age distribution used was 75% in 10-19 year olds and 25% in 20-29 year olds, as reported by Blomberg [Ref. 5.4: 04736R]. For the UK where the national program targets 12-13 year old girls, the age distribution used was 95% in 10-19 year olds and 5% in 20-29 year olds. In Japan where the government funded Gardasil vaccination for females 12 through 16 years of age, it was assumed that 100% of females vaccinated were in the 10-19 year old age cohort. Please refer to **Appendix A** for further details on incidence rate assumptions for CRPS and POTS.

Number of Doses Administered: The number of doses administered to females was based on the number of doses distributed, after accounting for a proportion of doses distributed that may not have been used for females (e.g., due to vaccine loss, damage, ongoing storage, use in males, etc.). Please refer to **Appendix B** for further details of number of doses administered assumptions.

Reporting rate: The spontaneous reporting rate of cases of CRPS and POTS to pharmacovigilance systems is not known and likely to vary by country; therefore, the largest span of rates possible was used, ranging from 1% to 100%: 1%, 10%, 20%, 50%, 75% and 100%. Most likely assumptions for each country/region are discussed in the results section.

Risk period: Calculation of expected numbers was performed for several risk periods following the administration of a vaccine dose: 1 week, 1 month, 2 months, 6 months, 1 year and 2 years (to include observed cases reported beyond 1 year of vaccination). Based on the recommended vaccine schedule of Gardasil and an assumption of 3 doses per person, these risk periods would correspond to a total risk period per person of 3 weeks, 3 months, 6 months, ~1 to 1.5 years, ~1.5 to 3 years, and ~2 to 6 years, respectively.

Observed Number of Cases:

The observed numbers of spontaneously reported CRPS and POTS cases for in each geographic region/country and each risk period (similar to the risk periods above) following a dose of qHPV vaccine were derived from the listing of individual case reports provided in response to Question 1 above.

For both CRPS and POTS, all spontaneously reported cases, whether from the specific Preferred Term (CRPS or POTS) query or from the symptom query described in Section 1.1.2.1 and 1.1.2.2, were combined. As reported in Section 1.1.2.1 and 1.1.2.2, a specific case definition was used to identify cases that met all criteria (C) and cases that partially met the criteria (P). This corresponds to 'Y" and "P" cases in the tables of post marketing cases in Question 1. A case was considered to partially meet criteria when clinical data were available to meet several of the criteria, but the information was incomplete, and therefore lacking in meeting all criteria required. For each risk period, the observed numbers of spontaneously reported cases were summarized in the following 2 ways: 1) all cases that met all criteria (C); and 2) the sum of all cases that met all criteria (C) and all cases that partially met the criteria (P), i.e., (C+P).

Time to onset (TTO) was used to determine the risk period following a dose of qHPV vaccine. For cases without a reported TTO, TTO was assigned based on the distribution of the known TTO in the country/region, assigning first missing TTO for the cases that meet all case definition criteria (based on the distribution of known TTO for C cases) and then missing TTO for the cases that partially meet criteria (based on the distribution of known TTO for P and for C+P cases). If no country/region-specific data were available (e.g., POTs cases in Japan), the worldwide TTO distribution was used for assigning TTO.

The counts of observed CRPS cases used in this analysis are summarized in Table 11 according to region/country, type of case (meet all criteria (C) and/or partially meet criteria (C+P)) and risk period (TTO).

Table 11
Summary counts of observed CRPS and POTS cases used in this analysis, by region, type of case, and time to onset

Country or Region	Case Type*	Time to Onset after qHPV Vaccination					
		1 wk	1 mon	2 mon	6 mon	1 yr	2 yr
CRPS							
Worldwide	C	2	3	5	7	7	7
	P+C	14	19	23	27	29	29
US	C	0	1	2	2	2	2
	P+C	3	5	6	6	6	6
EU	C	1	1	1	3	3	3
	P+C	5	7	7	10	11	11
Germany	C	1	1	1	2	2	2
	P+C	1	1	1	2	2	2
UK	C	0	0	0	0	0	0
	P+C	0	0	0	0	0	0
Denmark	C	0	0	0	0	0	0
	P+C	3	3	3	4	5	5
Japan	C	0	0	1	1	1	1
	P+C	1	2	4	5	6	6
POTS							
Worldwide	C	14	21	23	28	32	33
	P+C	17	29	31	40	45	46
US	C	0	3	3	3	3	3
	P+C	2	9	9	10	10	10
EU	C	14	18	20	25	29	30
	P+C	15	19	21	28	33	34
Germany	C	0	0	0	0	0	0
	P+C	0	0	0	0	0	0
UK	C	0	0	0	0	0	0
	P+C	0	0	0	0	0	0
Denmark	C	14	18	20	25	29	30
	P+C	14	18	20	27	32	33
Japan	C	0	0	0	0	0	0
	P+C	0	1	1	2	2	2

*C= Meet case criteria; P+C= Meet case criteria + partially meet case criteria; including those cases in which time to onset was not reported

1.3.2 CRPS Observed vs Expected Analysis

The assumptions used for the calculation of expected counts of CRPS in this analysis are summarized in Table 12.

Table 12
Assumptions for the calculations of expected counts of CRPS*

	WW	US	EU	Denmark	Germany	UK	Japan
Doses Distributed as of 31-May-2015	191,472,401	82,805,539	35,907,186	1,351,593	6,873,327	4,807,238	1,850,998
% Doses Administered							
high end	80%	75%	90%	95%	90%	95%	95%
low end	65%	60%	75%	80%	75%	80%	80%
Dose distribution by age							
10-19 yo	90%	90%	90%	75%	90%	95%	100%
20-29yo	10%	10%	10%	25%	10%	5%	
CRPS incidence by age (per 100,000 PY)							
10-19 yo	14.9	14.9	14.9	14.9	14.9	14.9	14.9
20-29 yo	28.0	28.0	28.0	28.0	28.0	28.0	28.0
10-29 yo (weighted by dose dist)	16.2	16.2	16.2	18.2	16.2	15.6	14.9

* Further description of these assumptions are provided in Section 1.3.1, **Appendix A** (incidence rates) and Appendix B (proportion of doses distributed that were administered).

Results for CRPS: The calculated range of expected counts of CRPS cases, in comparison to reported counts, is shown in Table 13 (Worldwide, US, EU, Germany, UK, displaying reporting rates up to 20%) and Table 14 (Denmark, Japan, displaying reporting rates up to 100%). In Table 13, the range of reporting rates was truncated at 20% because displaying additional reporting rates seems unnecessary for meaningful interpretation of the data at this time. However, this is not intended to imply that a 20% reporting rate is the maximum likely rate in these regions/countries. The findings are also graphically displayed in Figure 1 (Worldwide), Figure 2 (US), Figure 3 (EU), Figure 4 (Denmark), and Figure 5 (Japan).

The analysis of cases that meet all case definition criteria (C) was based on 7 worldwide reported cases, including 3 from the EU (2 from Germany), 2 from the US, and 1 from Japan. The observed numbers of cases that meet the case definition were less than the expected for all

assumptions (Table 13 and Table 14; Figure 1 to Figure 5), with only 2 minor exceptions: Germany for the 1 week risk period and Japan for the 2 month risk period, both at the 1% reporting rate assumption. In both instances, the observed number of cases was only 1 when the expected number was 0.

When considering cases that meet or partially meet the case definition criteria (C+P), the numbers of observed cases were also within the range of expected for virtually all reporting rates and risk periods, with a few exceptions, almost all at the 1% reporting rate assumption (Table 13 and Table 14). In the US, observed numbers of cases were lower than expected for all assumptions, except at the 1% reporting rate for the 1 week risk period, based on 3 cases that partially meet criteria (expected=2). For Japan (Table 14, Figure 5), there was an observed number greater than expected for the 1 week risk window at a reporting rate up to 10%, which was based on 1 reported case that partially meet criteria (expected=0). For Denmark (Table 14, Figure 4), there were several instances in which the observed cases that meet or partially meet the case definition were greater than the expected at the 10%, 20%, and 50% reporting rates for several risk periods, mainly driven by 3 cases that partially meet criteria reported within 1 week of vaccine dose (there were no cases that meet the case definition criteria in Denmark). In the EU, observed numbers of cases were lower than expected for all assumptions, except at the 1% reporting rate for the 1 week and 1 month risk periods, based on 5 and 7 cases respectively, including 1 that meet the case definition (from Germany).

Conclusions for CRPS: The overall findings of this analysis do not support an association between qHPV vaccination and CRPS. This conclusion is supported by the following observations:

- The counts of observed cases that meet the case definition criteria were less than expected counts in almost all instances.
- In the instances in which the observed number of cases that meet or partially meet the case definition criteria was greater than the expected, it was usually assumed that only 1% of cases were reported. While presented for completeness, the estimates of expected cases based the assumption that 1% of cases are reported is likely to be unrealistically low, especially in the context of stimulated reporting, as may have occurred, particularly in Denmark and Japan.
- The instances in which observed counts of cases that meet or partially meet the case definition criteria exceeded expected counts at reporting rates greater than 1% were all from Japan and Denmark. The observed counts never exceeded the expected counts for an assumption of more than 50% of cases reported within a 1 week risk period for Denmark, or more than 10% of cases reported within 1 week risk period for Japan (Table 14, Figures 4 and 5). This is unlikely to represent a causative effect of qHPV vaccination for the following reasons:
    - In instances in which the observed cases were greater than expected, the

exceedance was minimal and both the observed and expected were based on small numbers; these exceedances are consistent with chance findings due to small numbers.

- Given the media attention on this topic in these 2 countries, reporting rates of 10%-50% are within range of what might be expected and in fact, may be underestimates of the actual reporting rates. It is likely that there has been enhanced case reporting in Denmark and Japan.
- The observed counts are greater than the expected counts only when reported cases that only partially meet the case definition criteria are included.
- It is not known if cases that partially meet the case definition criteria are actually CRPS.
- It is possible that some reported cases may have been already prevalent at the time of vaccination (i.e., were not new onset after vaccination, as assumed in this analysis using CRPS incidence rates).
- The findings for Denmark and Japan are not replicated in analyses for the EU, Germany, UK, US, or Worldwide. If a biological association with vaccination existed, this finding would likely be found in other countries or regions, in addition to Denmark and Japan.

Table 13
Observed and expected cases of CRPS- Worldwide, US, EU, UK, and Germany, by risk period, reporting rate, and proportion of doses administered

(For expected numbers: dark shading indicates O<E for cases that meet/partially meet definition; light shading indicates O<E for cases that meet definition; no shading indicates O>E)

A. Worldwide

Risk Period Per Dose (*)	Observed		Expected Number of Cases					
	C	C+P	1% Reporting rate		10% Reporting rate		20% Reporting rate	
			% Dose Administered					
			65%	80%	65%	80%	65%	80%
1wk (3wk)	2	14	4	5	39	48	77	95
1mon (3mon)	3	19	17	21	168	207	336	414
2mon (6mon)	5	23	34	41	336	414	672	828
6mon (~1-1.5yr)	7	27	101	124	1,009	1,242	2,017	2,483
1yr (~1.5-3yr)	7	29	202	248	2,017	2,483	4,035	4,966
2yr (~2-6yr)	7	29	403	497	4,035	4,966	8,070	9,932

*Risk period per person assuming 3 doses per person shown in parentheses.

B. US

Risk Period Per Dose (*)	Observed		Expected Number of Cases					
	C	C+P	1% Reporting rate		10% Reporting rate		20% Reporting rate	
			% Dose Administered					
			60%	75%	60%	75%	60%	75%
1wk (3wk)	0	3	2	2	15	19	31	39
1mon (3mon)	1	5	7	8	67	84	134	168
2mon (6mon)	2	6	13	17	134	168	268	336
6mon (~1-1.5yr)	2	6	40	50	403	503	805	1,007
1yr (~1.5-3yr)	2	6	81	101	805	1,007	1,611	2,013
2yr (~2-6yr)	2	6	161	201	1,611	2,013	3,221	4,027

*Risk period per person assuming 3 doses per person shown in parentheses.

C. EU

Risk Period Per Dose (*)	Observed		Expected Number of Cases					
	C	C+P	1% Reporting rate		10% Reporting rate		20% Reporting rate	
			% Dose Administered					
			75%	90%	75%	90%	75%	90%
1wk (3wk)	1	5	1	1	8	10	17	20
1mon (3mon)	1	7	4	4	36	44	73	87
2mon (6mon)	1	7	7	9	73	87	146	175
6mon (~1-1.5yr)	3	10	22	26	218	262	437	524
1yr (~1.5-3yr)	3	11	44	52	437	524	873	1,048
2yr (~2-6yr)	3	11	87	105	873	1,048	1,746	2,095

*Risk period per person assuming 3 doses per person shown in parentheses.

D. UK

Risk Period Per Dose (*)	Observed		Expected Number of Cases					
	C	C+P	1% Reporting rate		10% Reporting rate		20% Reporting rate	
			% Dose Administered					
			80%	95%	80%	95%	80%	95%
1wk (3wk)	0	0	0	0	1	1	2	3
1mon (3mon)	0	0	0	1	5	6	10	12
2mon (6mon)	0	0	1	1	10	12	20	24
6mon (~1-1.5yr)	0	0	3	4	30	36	60	71
1yr (~1.5-3yr)	0	0	6	7	60	71	120	142
2yr (~2-6yr)	0	0	12	14	120	142	239	284

*Risk period per person assuming 3 doses per person shown in parentheses.

E. Germany

Risk Period Per Dose (*)	Observed		Expected Number of Cases					
	C	C+P	1% Reporting rate		10% Reporting rate		20% Reporting rate	
			% Dose Administered					
			75%	90%	75%	90%	75%	90%
1wk (3wk)	1	1	0	0	2	2	3	4
1mon (3mon)	1	1	1	1	7	8	14	17
2mon (6mon)	1	1	1	2	14	17	28	33
6mon (~1-1.5yr)	2	2	4	5	42	50	84	100
1yr (~1.5-3yr)	2	2	8	10	84	100	167	201
2yr (~2-6yr)	2	2	17	20	167	201	334	401

*Risk period per person assuming 3 doses per person shown in parentheses.

Table 14

Observed and expected cases of CRPS- Denmark and Japan, by risk period, reporting rate, proportion of doses administered

(For expected numbers: dark shading indicates O<E for cases that meet/partially meet definition; light shading indicates O<E for cases that meet definition; no shading indicates O>E)

A. Denmark

Risk Period Per Dose (*)	Observed		Expected Number of Cases											
	C	C+P	1% Reporting rate		10% Reporting rate		20% Reporting rate		50% Reporting rate		75% Reporting rate		100% Reporting rate	
			% dose administered											
			80%	95%	80%	95%	80%	95%	80%	95%	80%	95%	80%	95%
1wk (3wk)	0	3	0	0	0	0	1	1	2	2	3	3	4	4
1mon (3mon)	0	3	0	0	2	2	3	4	8	10	12	15	16	19
2mon (6mon)	0	3	0	0	3	4	7	8	16	19	25	29	33	39
6mon (~1-1.5yr)	0	4	1	1	10	12	20	23	49	58	74	88	98	117
1yr (~1.5-3yr)	0	5	2	2	20	23	39	47	98	117	147	175	197	233
2yr (~2-6yr)	0	5	4	5	39	47	79	93	197	233	295	350	393	467

*Risk period per person assuming 3 doses per person shown in parentheses.

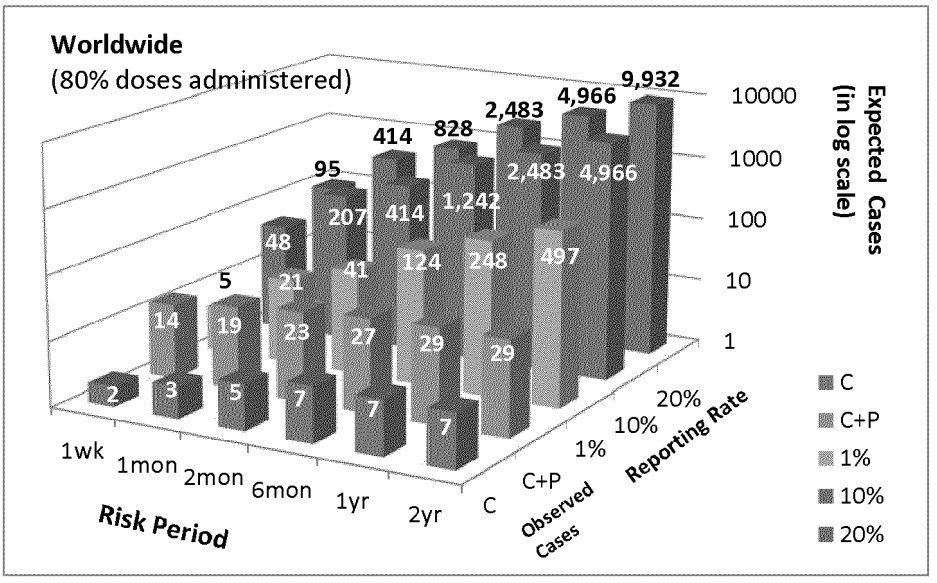
B. Japan

Risk Period Per Dose (*)	Observed		Expected Number of Cases											
	C	C+P	1% Reporting rate		10% Reporting rate		20% Reporting rate		50% Reporting rate		75% Reporting rate		100% Reporting rate	
			% dose administered											
			80%	95%	80%	95%	80%	95%	80%	95%	80%	95%	80%	95%
1wk (3wk)	0	1	0	0	0	1	1	1	2	3	3	4	4	5
1mon (3mon)	0	2	0	0	2	2	4	4	9	11	14	16	18	22
2mon (6mon)	1	4	0	0	4	4	7	9	18	22	28	33	37	44
6mon (~1-1.5yr)	1	5	1	1	11	13	22	26	55	66	83	98	110	131
1yr (~1.5-3yr)	1	6	2	3	22	26	44	52	110	131	165	197	221	262
2yr (~2-6yr)	1	6	4	5	44	52	88	105	221	262	331	393	441	524

*Risk period per person assuming 3 doses per person shown in parentheses.

Figure 1 Observed and expected cases of CRPS - Worldwide
by risk period, reporting rate, proportion of doses administered

(C= cases that meet case criteria; C+P= cases that meet/partially meet criteria)



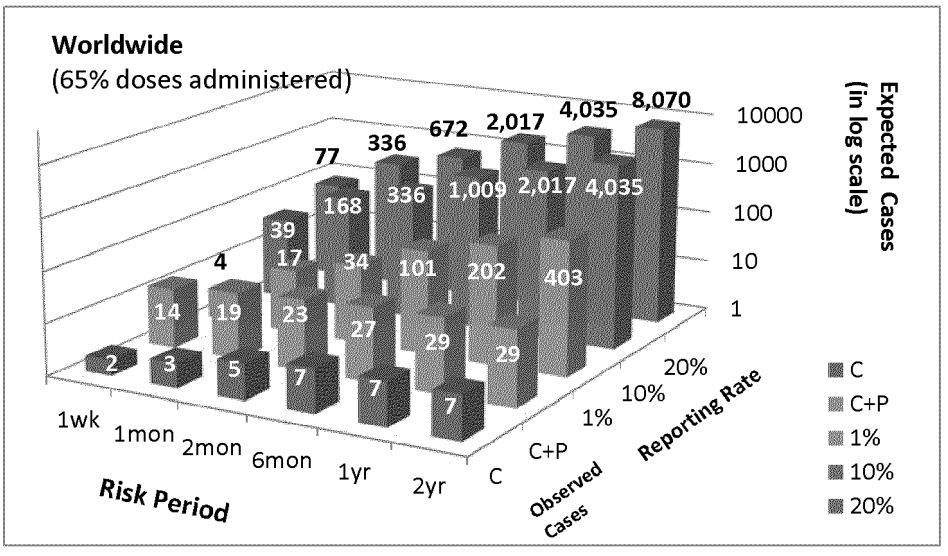
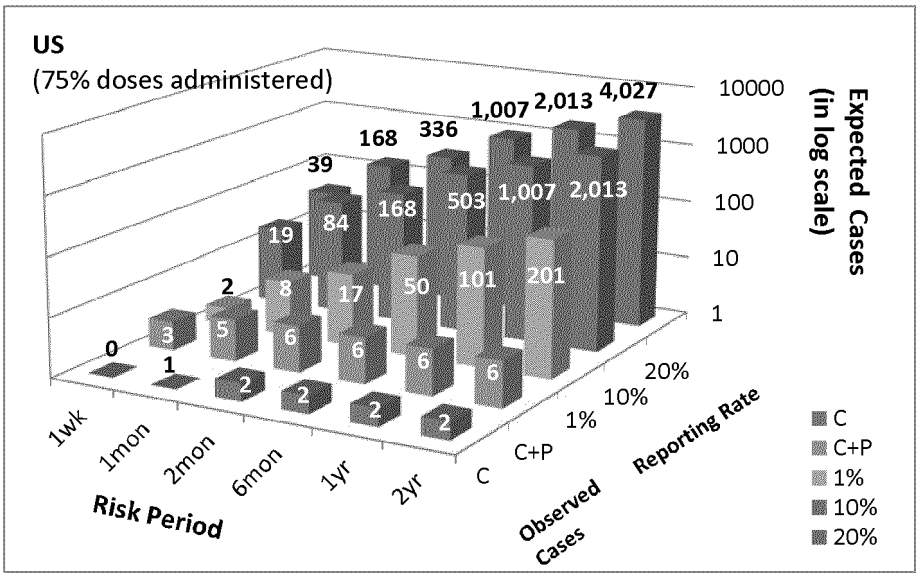


Figure 2 Observed and expected cases of CRPS- United States
by risk period, reporting rate, proportion of doses administered

(C= cases that meet case criteria; C+P= cases that meet/partially meet criteria)



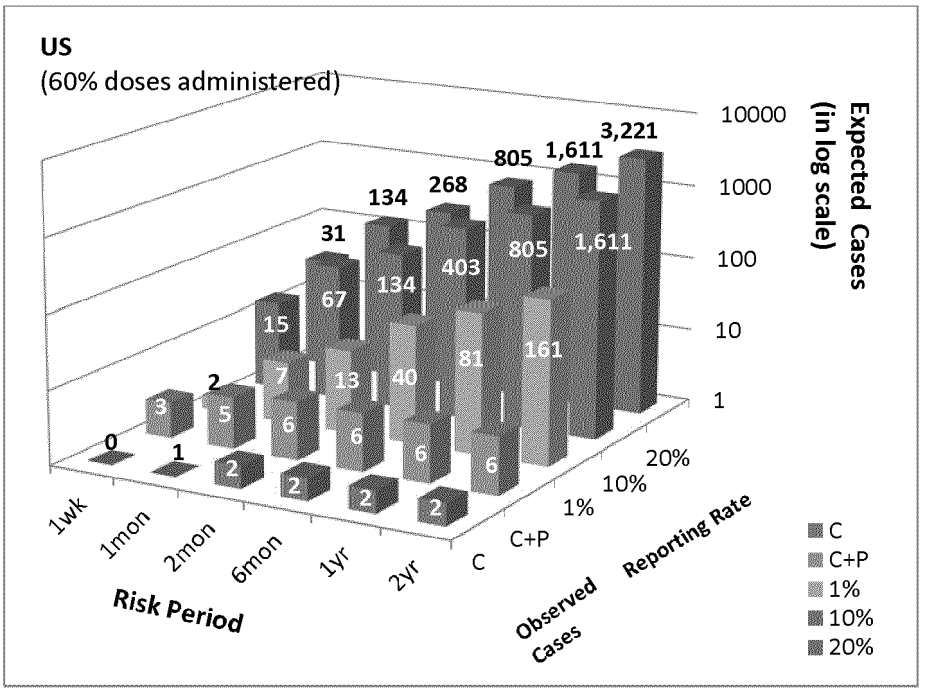
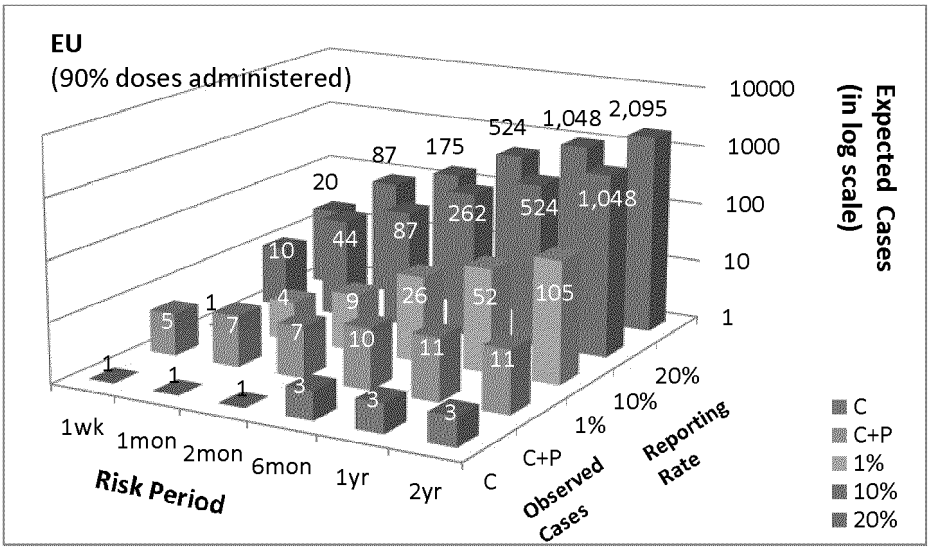


Figure 3. Observed and expected cases of CRPS– European Union by risk period, reporting rate, proportion of doses administered

(C= cases that meet case criteria; C+P= cases that meet/partially meet criteria)



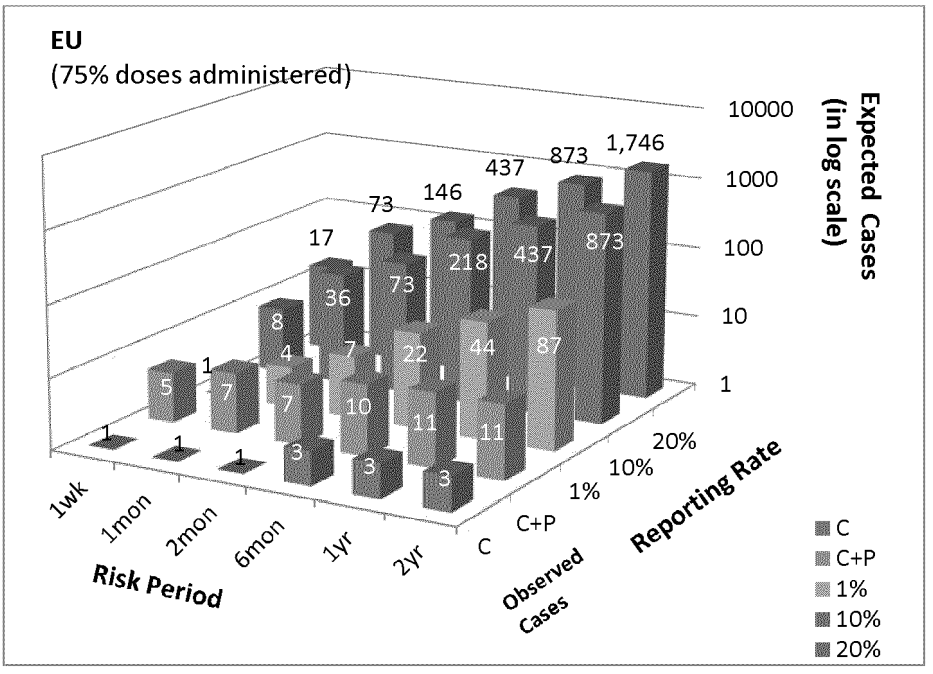
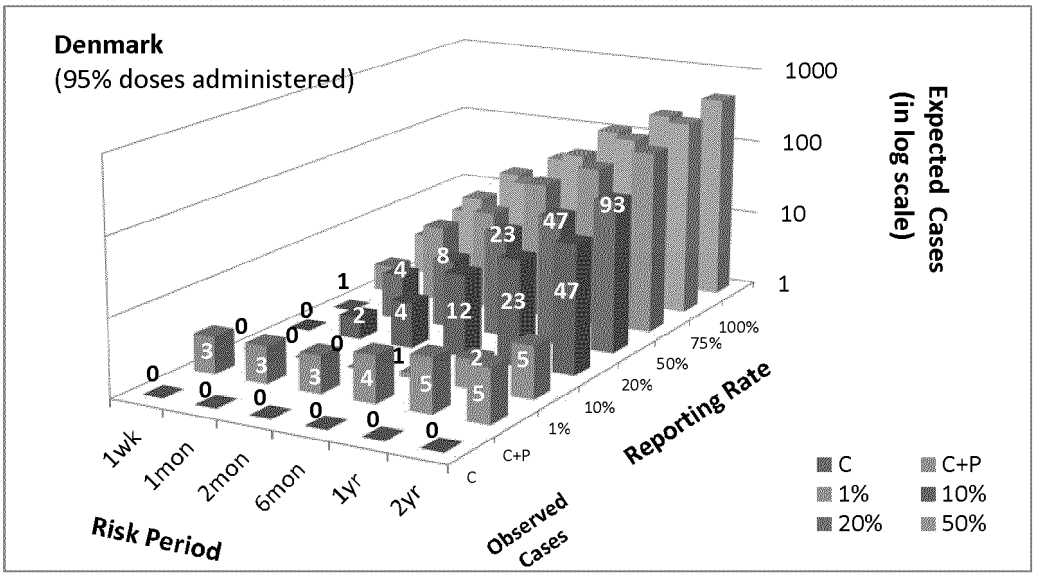


Figure 4 Observed and expected cases of CRPS – Denmark
by risk period, reporting rate, proportion of doses administered

(C= cases that meet case criteria; C+P= cases that meet/partially meet criteria)



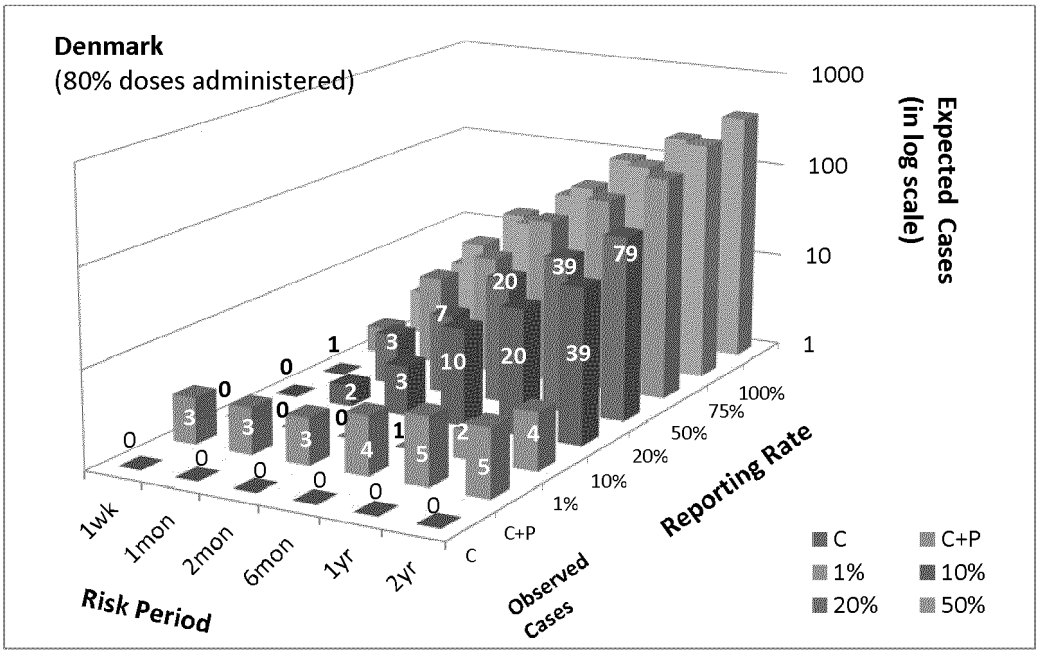
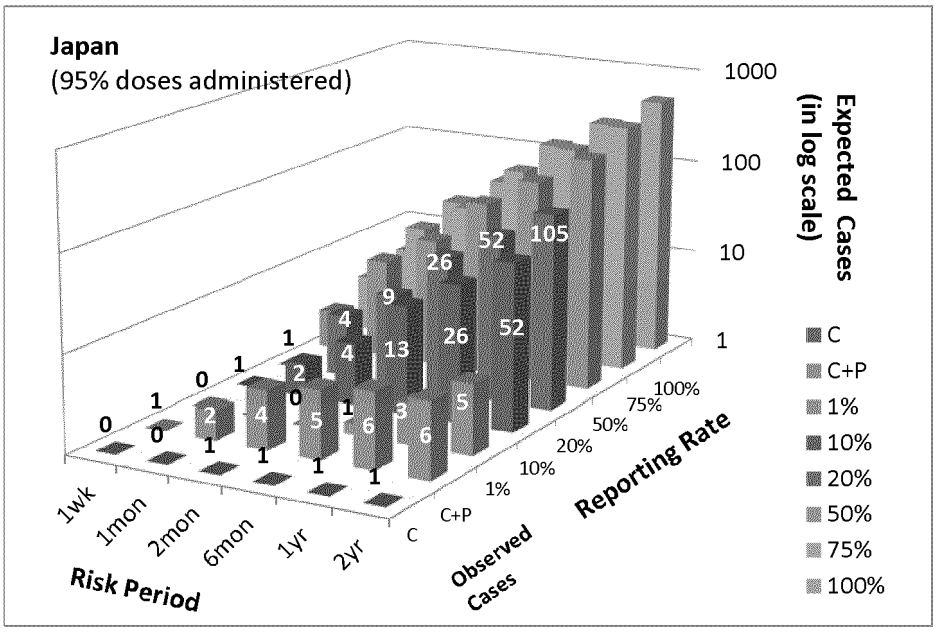
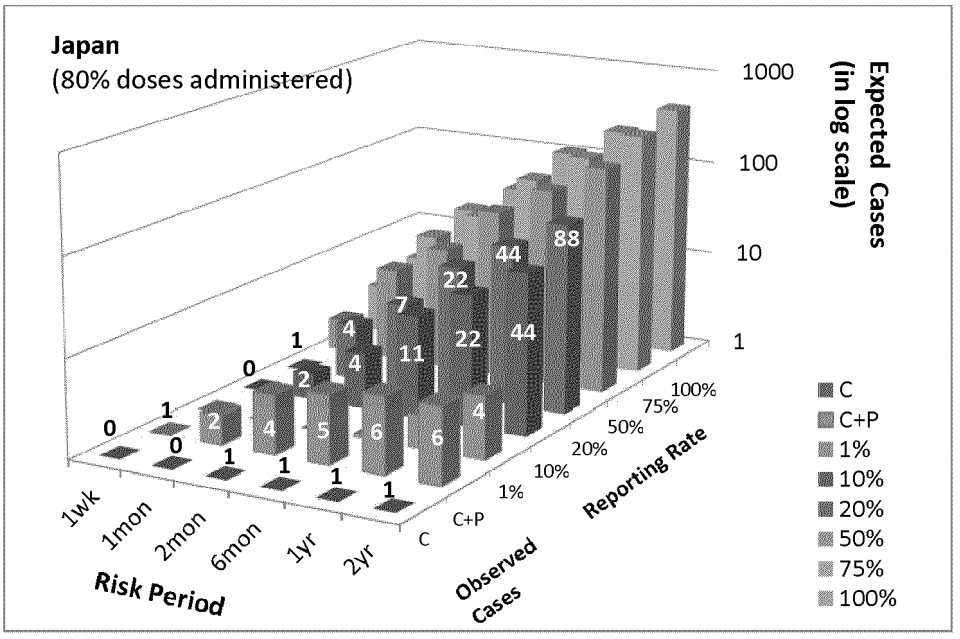


Figure 5 Observed and expected cases of CRPS - Japan,
by country, risk period, reporting rate, proportion of doses administered
(C= cases that meet case definition; C+P= cases that meet/partially meet definition)





1.3.3 POTS Observed vs Expected Analysis

The counts of observed POTS cases used in this analysis are summarized in Table 11 above by region/country, type of case (met all criteria (C) and/or partially meet criteria (P)) and risk period (TTO).

The assumptions used for the calculation of expected counts of POTS in this analysis are summarized as follows:
- Doses administered (same as for CRPS expected counts calculations)
- Background incidence rates of POTS in females 10-39 years of age: 15, 35, 60 and 140 per 100,000 person-years, based on the following (see Appendix A for details):
    - CFS incidence rates of 30 to 70/100,000 person-years in 10-39 year old females
    - Proportion of CFS cases with POTS: 10% to 40%
    - Proportion of POTS cases with CFS: 20%

Further description of these assumptions are provided in Section 1.3.1, **Appendix A** (incidence rates) and **Appendix B** (proportion of doses distributed that were administered).

Results for POTS: The calculated range of expected counts of POTS cases, in comparison to reported counts, is shown in Table 15-Table 21 and graphically displayed in **Figure 3**-Figure 6. For Germany, UK, Japan and the US, the range of reporting rates was truncated at 20% because displaying additional reporting rates seems unnecessary for meaningful interpretation of the data at this time. As show in the tables and figures, the observed number of cases was lower than the expected under almost all assumptions for all regions and countries, with the notable exception of Denmark and of cases reported within 1 week, almost all coming from Denmark.

More specifically, the observed numbers of cases were lower than expected in Japan and the US for all assumptions except when considering cases that only partially meet criteria at the 1% reporting rate assumption for the shorter risk periods following a vaccine dose and the lowest POTS incidence rate assumptions. In the EU, all cases were from Denmark except 1 case with missing TTO that partially meet criteria and was assigned to the 1 week risk period, based on the EU TTO distribution driven by Denmark. There were no cases from the UK or Germany. In the EU, the observed numbers of cases were lower than the expected for all assumptions, except at the 1% reporting rate for risk periods up to 6 months following a vaccine dose, entirely driven by cases from Denmark. Similarly at the Worldwide level, the observed numbers of cases were lower than expected for all assumptions, except at the 1% reporting rate for the 1 week and 1 month risk periods, mostly driven by cases from Denmark.

The number of POTS cases reported from Denmark is the largest contributor to EU and Worldwide cases (70% (33/46) of worldwide cases; 91% (30/33) of worldwide cases that meet all case definition criteria). In Denmark, most cases meet criteria (91% (30/33)) and were reported to have occurred within 1 month after vaccination (18/33), with most of them reported within 1 week (14 cases, including 11 with TTO within 1 week and 3 with missing TTO that

were assigned to a risk period of 1 week, based on the time period distribution of cases in Denmark). In Denmark, observed counts were greater than the expected for several reporting rates and POTS incidence assumptions, in particular for short risk periods of 1 week and 1 month. This was mainly related to observed cases reported to have occurred within 1 week of vaccination for which observed were greater than expected counts, even at the 100% reporting rate assumption for most POTS incidence rate assumptions.

In contrast, the rest of the world contributed only 28% (13/46) of worldwide cases, most coming from the US (10/46) and only partially meeting case definition criteria (only 23% (3/13) meet criteria, all from the US), as expected based on dose distribution and difficulty in meeting the diagnostic criteria. All 14 worldwide cases that meet case definition criteria, reported to have occurred within 1 week, come from Denmark. Overall, Denmark, which contributes less than 1% of the doses of Gardasil used worldwide, appears to be an outlier for POTS in many ways.

Conclusions for POTS: As described above for CRPS, the overall findings of this analysis do not support an association between qHPV vaccination and POTS. Denmark seems to be a notable exception. As mentioned in the postmarketing section, 30 of the 33 cases that meet case definition criteria reported worldwide were received from Denmark, with 27 (90%) originating from one centre, and 28 reported within the last 2 years despite the vaccine program having started in 2007. In Denmark, there may be enhanced reporting due to recent attention from media and elsewhere on this topic. There is no biologic plausibility explaining why observed cases would be greater than expected only in Denmark. Such a strong association between vaccination and POTS would most likely emerge in more places than Denmark, particularly given the more than 190 million doses distributed worldwide. The fact that many Danish cases come from a centre specializing in diagnostic tests for syncope may explain the high proportion of cases meeting case definition criteria. The diagnostic criteria include duration of symptoms > 6 months. In these cases, it is possible that the assessment of symptom onset was done retrospectively and may have been subject to recall bias, especially with respect to the timing of vaccination. It is also possible that some pre-existing cases were included in the counts of observed cases, as suggested by the fact that several cases were reported to have a history of syncope or even POTS before vaccination. Additionally, in scenarios of reporting with high referring rates to specialized diagnostic centres, such as in Denmark, the data used to determine expected case counts (such as background incidence rates in the general population) might not be applicable.

Table 15
Observed and expected cases of POTS- Worldwide
by risk period, reporting rate, and proportion of distributed doses administered *(For expected numbers: dark shading indicates O<E for cases that meet/partially meet definition; light shading indicates O<E for cases that meet definition; no shading indicates O>E)*

Worldwide																	
Risk Period Per Dose (*)	**Observed**		**% Doses Administered**	**Expected Number of Cases**													
				1% Reporting Rate				10% Reporting Rate				20% Reporting Rate				100% Reporting Rate			
				Incidence Rate (per 100,000 py)													
	C	C+P		15	35	60	140	15	35	60	140	15	35	60	140	15	35	60	140
1wk (3wk)	14	17	65%	4	8	14	33	36	84	143	334	72	167	286	668	358	835	1432	3342
			80%	4	10	18	41	44	103	176	411	88	206	353	823	441	1,028	1,763	4,113
1mon (3mon)	21	29	65%	16	36	62	145	156	363	622	1,452	311	726	1,245	2,904	1,556	3,630	6,223	14,520
			80%	19	45	77	179	191	447	766	1,787	383	894	1,532	3,574	1,915	4,468	7,659	17,871
2mon (6mon)	23	31	65%	31	73	124	290	311	726	1,245	2,904	622	1,452	2,489	5,808	3,111	7,260	12,446	29,040
			80%	38	89	153	357	383	894	1,532	3,574	766	1,787	3,064	7,148	3,829	8,935	15,318	35,742
6mon (~1-1.5yr)	28	40	65%	93	218	373	871												
			80%	115	268	460	1,072												
1yr (~1.5-3yr)	32	45	65%	187	436	747	1,742												
			80%	230	536	919	2,144												
2yr (~2-6yr)	33	46	65%	373	871	1,493	3,485												
			80%	460	1,072	1,838	4,289												

*Risk period per person assuming 3 doses per person shown in parentheses.

Table 16
Observed and expected cases of POTS- European Union
by risk period, reporting rate, and proportion of distributed doses administered (continued) *(For expected numbers: dark shading indicates O<E for cases that meet/partially meet definition; light shading indicates O<E for cases that meet definition; no shading indicates O>E)*

EU																	
Risk Period Per Dose (*)	**Observed**		**% Doses Administered**	**Expected Number of Cases**													
				1% Reporting Rate				10% Reporting Rate				20% Reporting Rate				100% Reporting Rate			
				Incidence Rate (per 100,000 py)													
	C	C+P		15	35	60	140	15	35	60	140	15	35	60	140	15	35	60	140
1wk	14	15	75%	1	2	3	7	8	18	31	72	15	36	62	145	77	181	310	723
(3wk)			90%	1	2	4	9	9	22	37	87	19	43	74	174	93	217	372	868
1mon	18	19	75%	3	8	13	31	34	79	135	314	67	157	269	628	337	785	1,347	3,142
(3mon)			90%	4	9	16	38	40	94	162	377	81	189	323	754	404	943	1,616	3,770
2mon	20	21	75%	7	16	27	63	67	157	269	628	135	314	539	1,257	673	1,571	2,693	6,284
(6mon)			90%	8	19	32	75	81	189	323	754	162	377	646	1,508	808	1,885	3,232	7,541
6mon	25	28	75%	20	47	81	189												
(~1-1.5yr)			90%	24	57	97	226												
1yr	29	33	75%	40	94	162	377												
(~1.5-3yr)			90%	48	113	194	452												
2yr	30	34	75%	81	189	323	754												
(~2-6yr)			90%	97	226	388	905												

*Risk period per person assuming 3 doses per person shown in parentheses.

Table 17
Observed and expected cases of POTS- Denmark
by risk period, reporting rate, and proportion of distributed doses administered (continued) *(For expected numbers: dark shading indicates O<E for cases that meet/partially meet definition; light shading indicates O<E for cases that meet definition; no shading indicates O>E)*

DENMARK																	
Risk Period Per Dose (*)	**Observed**		**% Dose Administered**	**Expected Number of Cases**													
				1% Reporting Rate				10% Reporting Rate				20% Reporting Rate				100% Reporting Rate			
				Incidence Rate (per 100,000 py)													
	C	C+P		15	35	60	140	15	35	60	140	15	35	60	140	15	35	60	140
1wk	14	14	80%	0	0	0	0	0	1	1	3	1	1	2	6	3	7	12	29
(3wk)			95%	0	0	0	0	0	1	1	3	1	2	3	7	4	9	15	34
1mon (3mon)	18	18	80%	0	0	1	1	1	3	5	13	3	6	11	25	14	32	54	126
			95%	0	0	1	1	2	4	6	15	3	7	13	30	16	37	64	150
2mon (6mon)	20	20	80%	0	1	1	3	3	6	11	25	5	13	22	50	27	63	108	252
			95%	0	1	1	3	3	7	13	30	6	15	26	60	32	75	128	300
6mon (~1-1.5yr)	25	27	80%	1	2	3	8	8	19	32	76	16	38	65	151	81	189	324	757
			95%	1	2	4	9	10	22	39	90	19	45	77	180	96	225	385	899
1yr (~1.5-3yr)	29	32	80%	2	4	6	15	16	38	65	151	32	76	130	303	162	378	649	1,514
			95%	2	4	8	18	19	45	77	180	39	90	154	360	193	449	770	1,798
2yr (~2-6yr)	30	33	80%	3	8	13	30	32	76	130	303	65	151	260	606	324	757	1,298	3,028
			95%	4	9	15	36	39	90	154	360	77	180	308	719	385	899	1,541	3,595

*Risk period per person assuming 3 doses per person shown in parentheses.

Table 18
Observed and expected cases of POTS- Germany
by risk period, reporting rate, and proportion of distributed doses administered (continued) *(For expected numbers: dark shading indicates O<E for cases that meet/partially meet definition; light shading indicates O<E for cases that meet definition; no shading indicates O>E)*

GERMANY														
Risk Period Per Dose (*)	**Observed**		**% Dose Administered**	**Expected Number of Cases**											
				1% Reporting rate				10% Reporting rate				20% Reporting rate			
	C	C+P		Incidence Rate (per 100,000 py)											
				15	35	60	140	15	35	60	140	15	35	60	140
1wk (3wk)	0	0	75%	0	0	1	1	1	3	6	14	3	7	12	28
			90%	0	0	1	2	2	4	7	17	4	8	14	33
1mon (3mon)	0	0	75%	1	2	3	6	6	15	26	60	13	30	52	120
			90%	1	2	3	7	8	18	31	72	15	36	62	144
2mon (6mon)	0	0	75%	1	3	5	12	13	30	52	120	26	60	103	241
			90%	2	4	6	14	15	36	62	144	31	72	124	289
6mon (~1-1.5yr)	0	0	75%	4	9	15	36	39	90	155	361	77	180	309	722
			90%	5	11	19	43	46	108	186	433	93	217	371	866
1yr (~1.5-3yr)	0	0	75%	8	18	31	72	77	180	309	722	155	361	619	1,443
			90%	9	22	37	87	93	217	371	866	186	433	742	1,732
2yr (~2-6yr)	0	0	75%	15	36	62	144	155	361	619	1,443	309	722	1,237	2,887
			90%	19	43	74	173	186	433	742	1,732	371	866	1,485	3,464

*Risk period per person assuming 3 doses per person shown in parentheses.

Table 19
Observed and expected cases of POTS- United Kingdom
by risk period, reporting rate, and proportion of distributed doses administered (continued) *(For expected numbers: dark shading indicates O<E for cases that meet/partially meet definition; light shading indicates O<E for cases that meet definition; no shading indicates O>E)*

UNITED KINGDOM													
Risk Period Per Dose (*)	**Observed**		**% Dose Administered**	**Expected Number of Cases**											
				1% Reporting rate				10% Reporting rate				20% Reporting rate			
	C	C+P		Incidence Rate (per 100,000 py)											
				15	35	60	140	15	35	60	140	15	35	60	140
1wk (3wk)	0	0	80%	0	0	0	1	1	3	4	10	2	5	9	21
			95%	0	0	1	1	1	3	5	12	3	6	11	25
1mon (3mon)	0	0	80%	0	1	2	4	5	11	19	45	10	22	38	90
			95%	1	1	2	5	6	13	23	53	11	27	46	107
2mon (6mon)	0	0	80%	1	2	4	9	10	22	38	90	19	45	77	179
			95%	1	3	5	11	11	27	46	107	23	53	91	213
6mon (~1-1.5yr)	0	0	80%	3	7	12	27	29	67	115	269	58	135	231	538
			95%	3	8	14	32	34	80	137	320	69	160	274	639
1yr (~1.5-3yr)	0	0	80%	6	13	23	54	58	135	231	538	115	269	461	1,077
			95%	7	16	27	64	69	160	274	639	137	320	548	1,279
2yr (~2-6yr)	0	0	80%	12	27	46	108	115	269	461	1,077	231	538	923	2,154
			95%	14	32	55	128	137	320	548	1,279	274	639	1,096	2,557

*Risk period per person assuming 3 doses per person shown in parentheses.

Table 20
Observed and expected cases of POTS- Japan
by risk period, reporting rate, and proportion of distributed doses administered (continued) *(For expected numbers: dark shading indicates O<E for cases that meet/partially meet definition; light shading indicates O<E for cases that meet definition; no shading indicates O>E)*

JAPAN													
Risk Period Per Dose (*)	**Observed**		**% Dose Administered**	**Expected Number of Cases**											
				1% Reporting rate				10% Reporting rate				20% Reporting rate			
				Incidence Rate (per 100,000 py)											
	C	C+P		15	35	60	140	15	35	60	140	15	35	60	140
1wk (3wk)	0	0	80%	0	0	0	0	0	1	2	4	1	2	3	8
			95%	0	0	0	0	1	1	2	5	1	2	4	9
1mon (3mon)	0	1	80%	0	0	1	2	2	4	7	17	4	9	15	35
			95%	0	1	1	2	2	5	9	21	4	10	18	41
2mon (6mon)	0	1	80%	0	1	1	3	4	9	15	35	7	17	30	69
			95%	0	1	2	4	4	10	18	41	9	21	35	82
6mon (~1-1.5yr)	0	2	80%	1	3	4	10	11	26	44	104	22	52	89	207
			95%	1	3	5	12	13	31	53	123	26	62	106	246
1yr (~1.5-3yr)	0	2	80%	2	5	9	21	22	52	89	207	44	104	178	415
			95%	3	6	11	25	26	62	106	246	53	123	211	492
2yr (~2-6yr)	0	2	80%	4	10	18	41	44	104	178	415	89	207	355	829
			95%	5	12	21	49	53	123	211	492	106	246	422	985

*Risk period per person assuming 3 doses per person shown in parentheses.

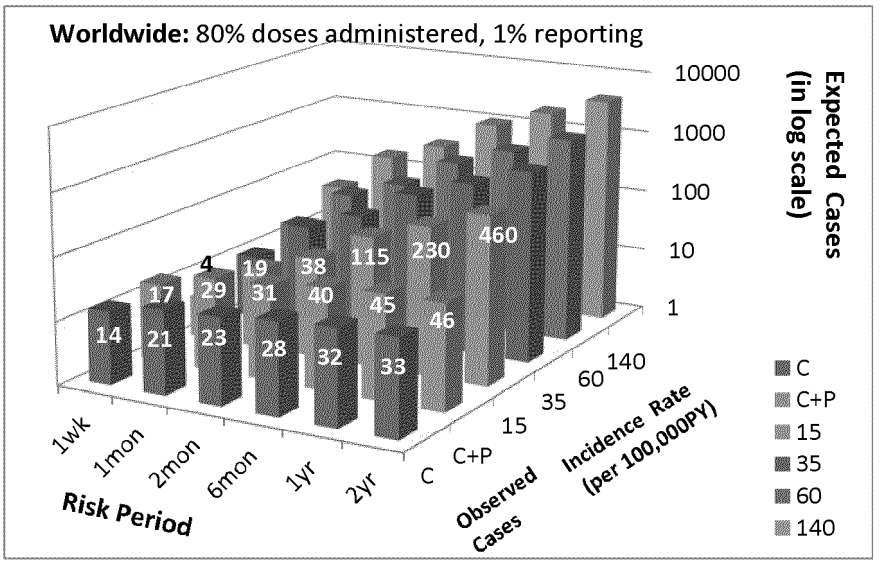
Table 21
Observed and expected cases of POTS- United States
by risk period, reporting rate, and proportion of distributed doses administered (continued) *(For expected numbers: dark shading indicates O<E for cases that meet/partially meet definition; light shading indicates O<E for* cases *that meet definition; no shading indicates O>E)*

UNITED STATES													
Risk Period Per Dose (*)	**Observed**		**% Dose Administered**	**Expected Number of Cases**											
				1% Reporting rate				10% Reporting rate				20% Reporting rate			
	C	C+P		Incidence Rate (per 100,000 py)											
				15	35	60	140	15	35	60	140	15	35	60	140
1wk (3wk)	0	2	60%	1	3	6	13	14	33	57	133	29	67	114	267
			75%	2	4	7	17	18	42	71	167	36	83	143	333
1mon (3mon)	3	9	60%	6	14	25	58	62	145	248	580	124	290	497	1,159
			75%	8	18	31	72	78	181	311	725	155	362	621	1,449
2mon (6mon)	3	9	60%	12	29	50	116	124	290	497	1,159	248	580	994	2,319
			75%	16	36	62	145	155	362	621	1,449	311	725	1,242	2,898
6mon (~1-1.5yr)	3	10	60%	37	87	149	348	373	869	1,490	3,478	745	1,739	2,981	6,956
			75%	47	109	186	435	466	1,087	1,863	4,347	932	2,174	3,726	8,695
1yr (~1.5-3yr)	3	10	60%	75	174	298	696	745	1,739	2,981	6,956	1,490	3,478	5,962	13,911
			75%	93	217	373	869	932	2,174	3,726	8,695	1,863	4,347	7,452	17,389
2yr (~2-6yr)			60%	149	348	596	1391	1,490	3,478	5,962	13,911	2,981	6,956	11,924	27,823
	3	10	75%	186	435	745	1,739	1,863	4,347	7,452	17,389	3,726	8,695	14,905	34,778

*Risk period per person assuming 3 doses per person shown in parentheses.

Figure 6. Observed and expected cases of POTS- Worldwide
by risk period, incidence rate, reporting rate, proportion of doses administered
(C= cases that meet case definition; C+P= cases that meet/partially meet definition)

A. 80% doses administered; 1% and 10% reporting rates



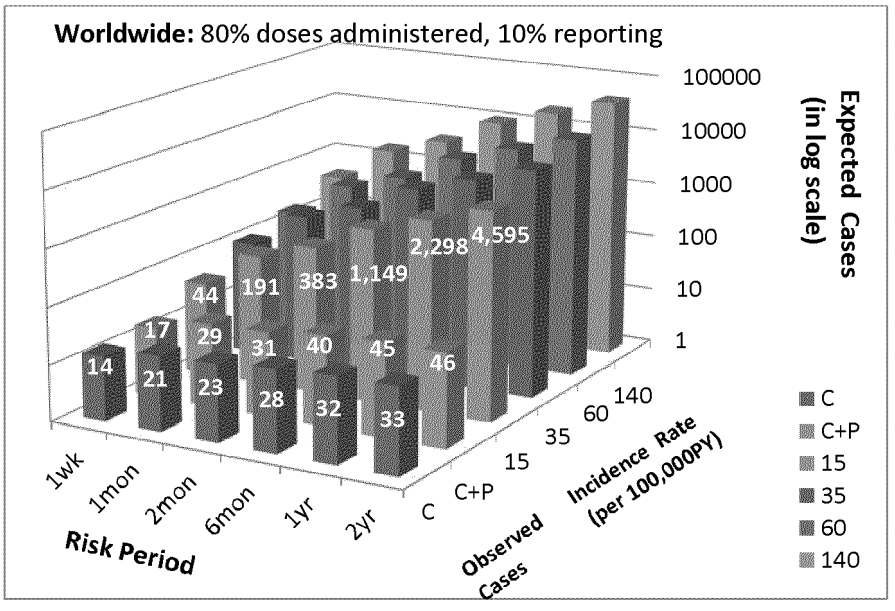
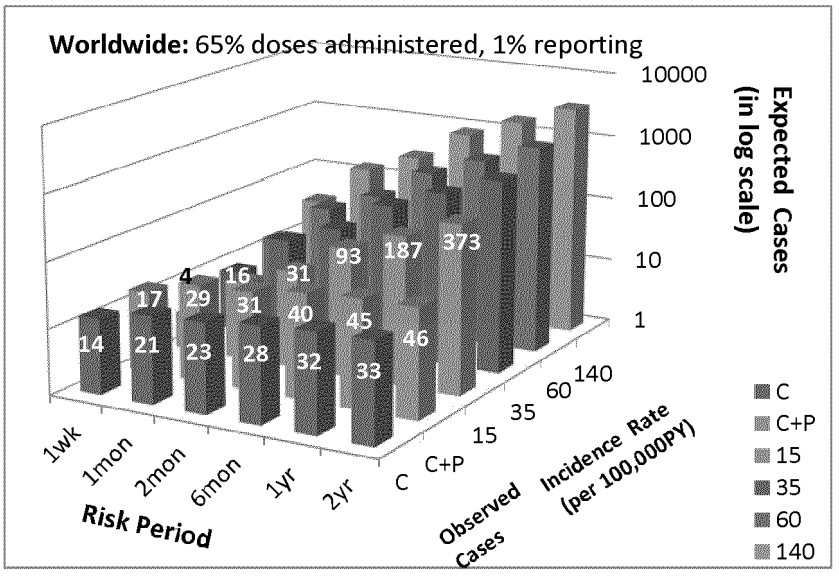


Figure 6. Observed and expected cases of POTS- Worldwide
by risk period, incidence rate, reporting rate, proportion of doses administered (cont.)
(C= cases that meet case definition; C+P= cases that meet/partially meet definition)

B. 65% doses administered; 1% and 10% reporting rates



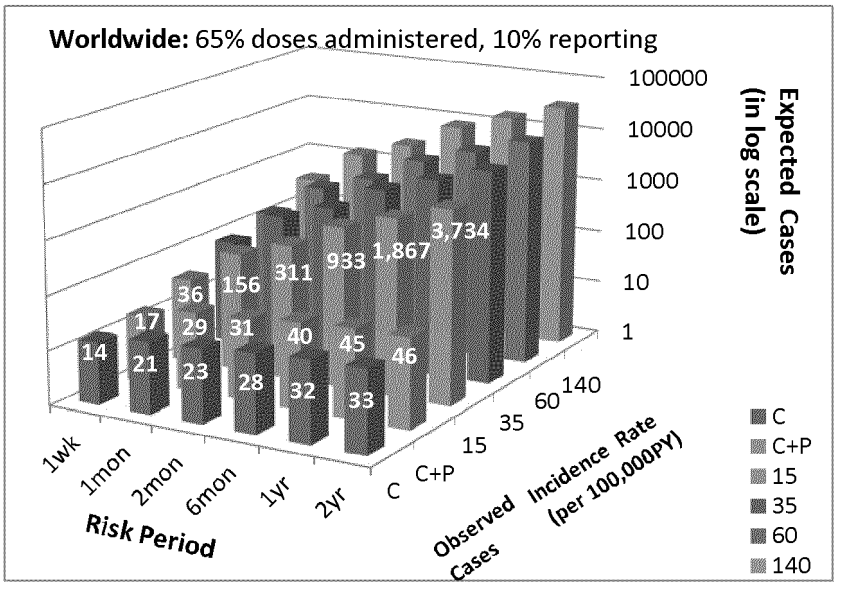
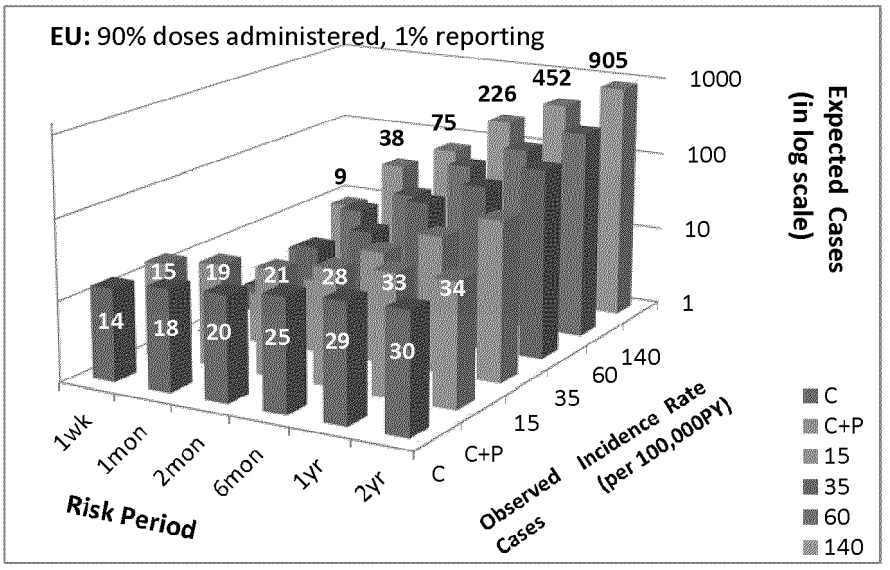


Figure 7. Observed and expected cases of POTS- EU
by risk period, incidence rate, reporting rate, proportion of doses administered
(C= cases that meet case definition; C+P= cases that meet/partially meet definition)

A. 90% doses administered; 1% and 10% reporting rates



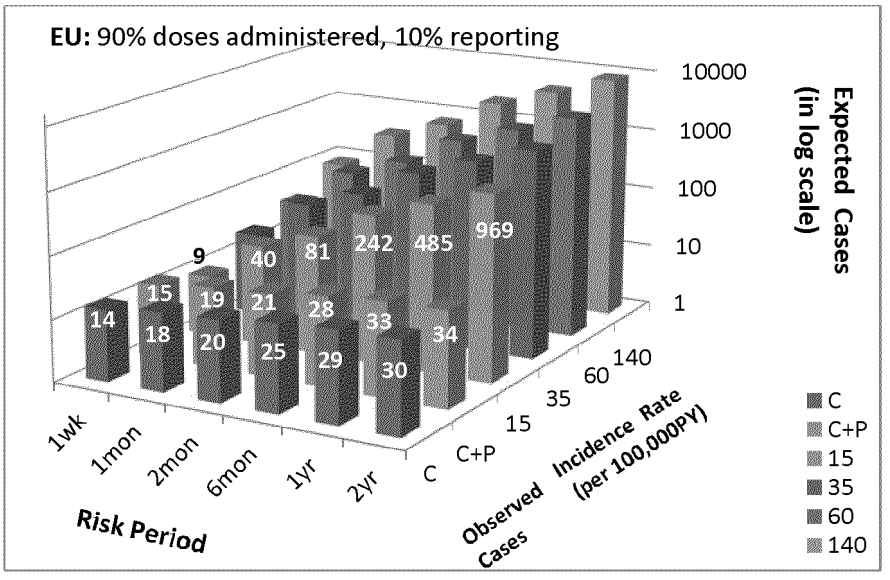
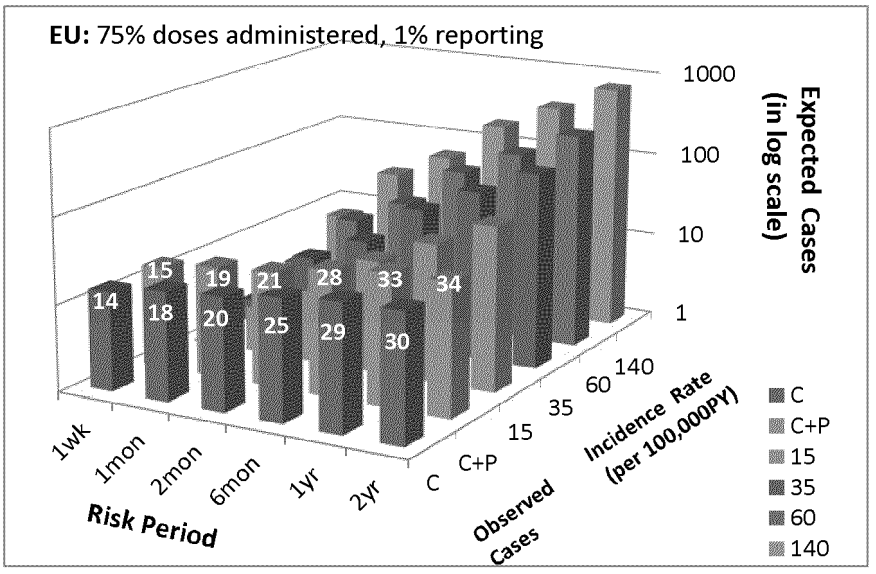


Figure 7. Observed and expected cases of POTS- EU
by risk period, incidence rate, reporting rate, proportion of doses administered (cont.)
(C= cases that meet case definition; C+P= cases that meet/partially meet definition)

B. 75% doses administered; 1% and 10% reporting rates



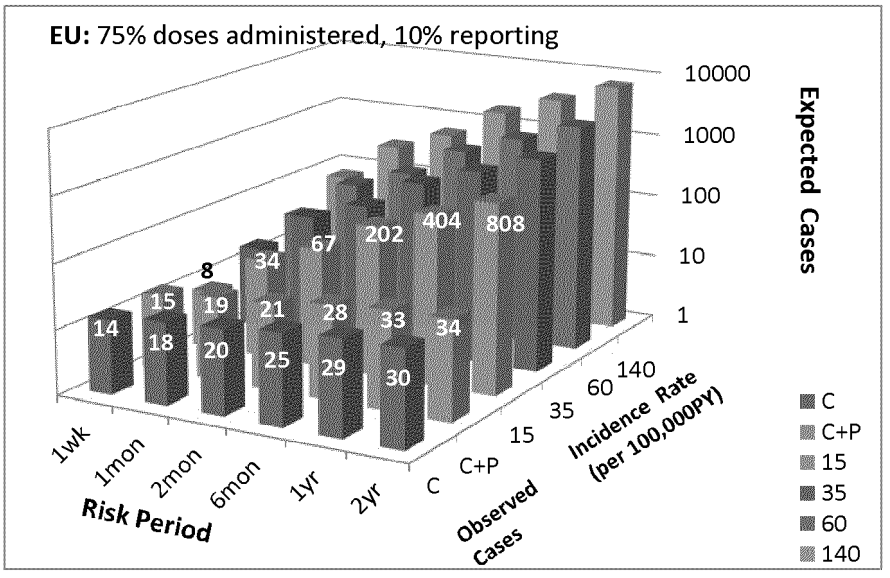
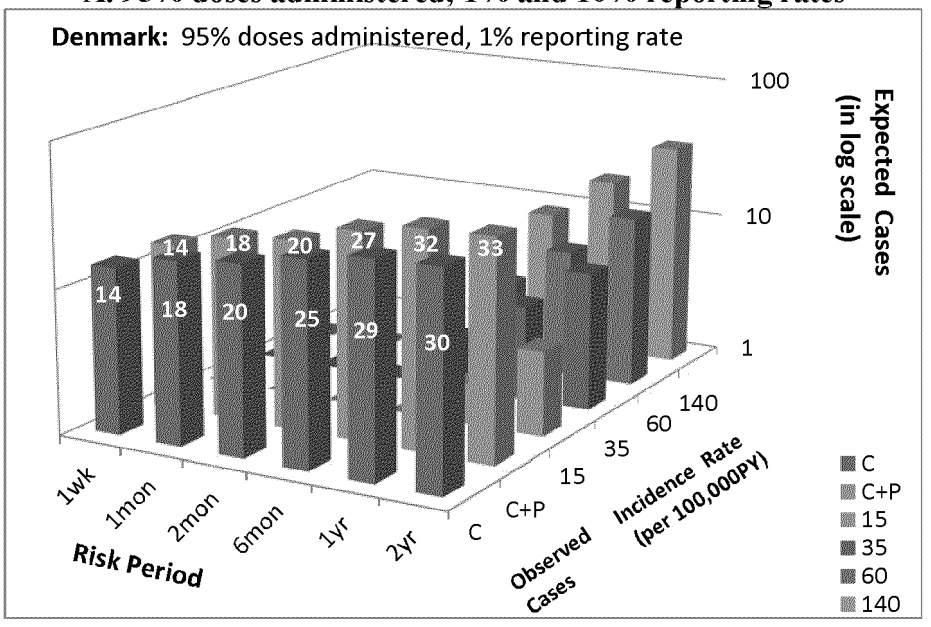


Figure 8. Observed and expected cases of POTS- Denmark
by risk period, incidence rate, reporting rate, proportion of doses administered
(C= cases that meet case definition; C+P= cases that meet/partially meet definition)

A. 95% doses administered; 1% and 10% reporting rates



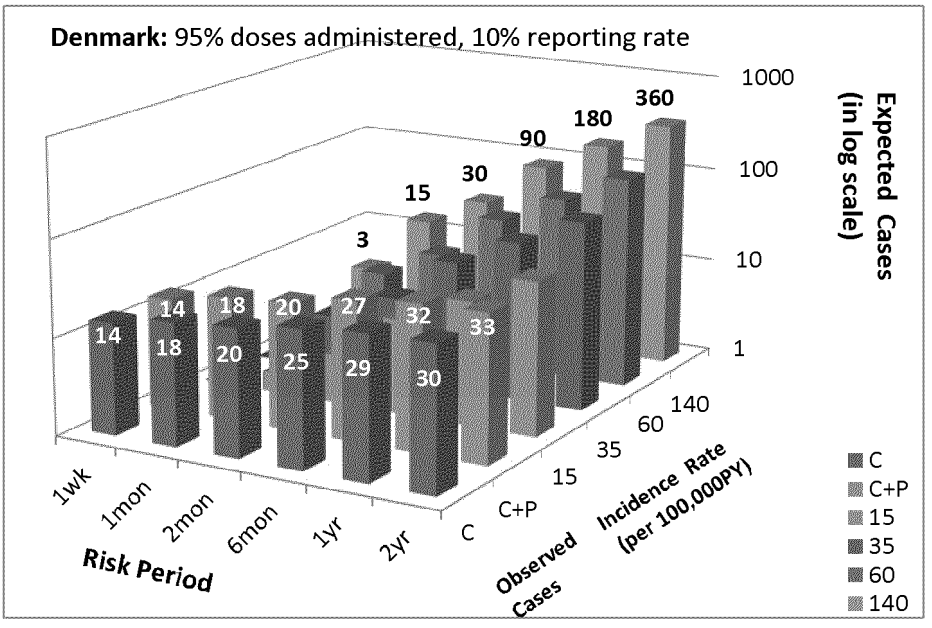
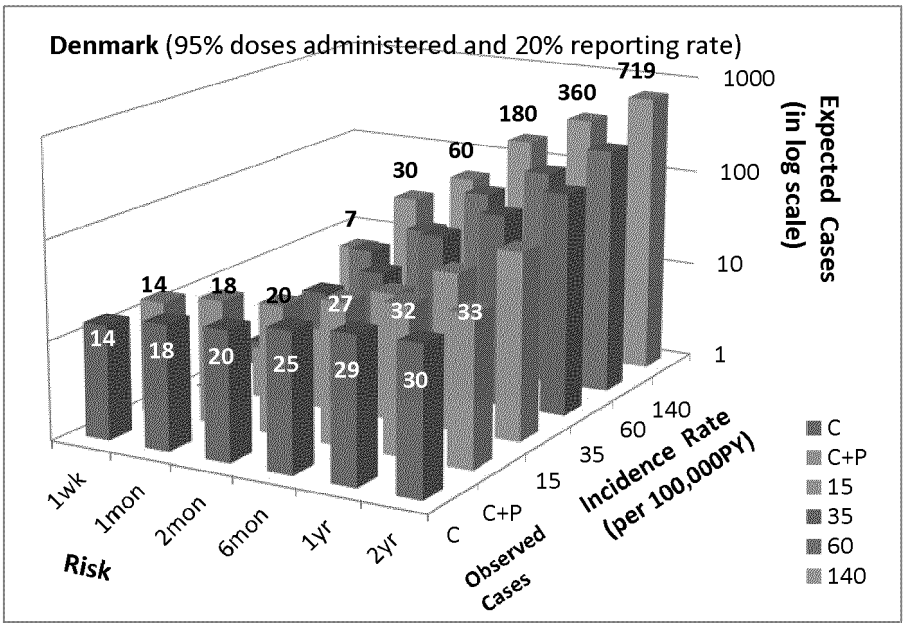


Figure 8. Observed and expected cases of POTS- Denmark
by risk period, incidence rate, reporting rate, proportion of doses administered (cont)
(C= cases that meet case definition; C+P= cases that meet/partially meet definition)

A. 95% doses administered; 20% and 100% reporting rates



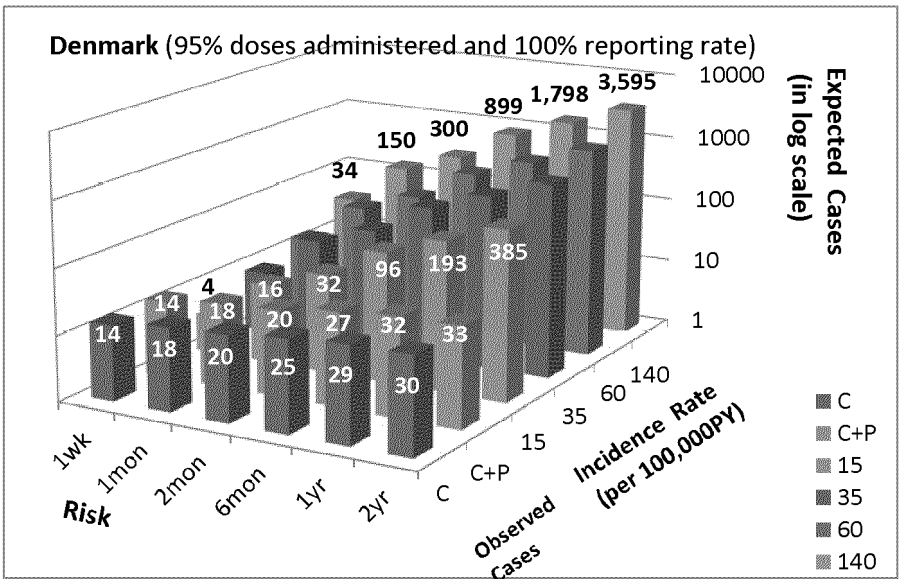
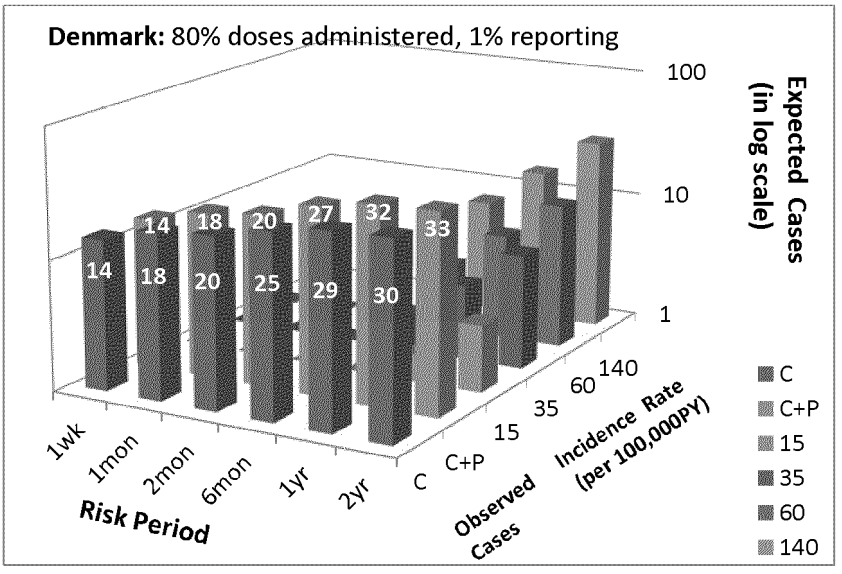


Figure 8. Observed and expected cases of POTS- Denmark
by risk period, incidence rate, reporting rate, proportion of doses administered (cont)
(C= cases that meet case definition; C+P= cases that meet/partially meet definition)

B. 80% doses administered; 1% and 10%reporting rate



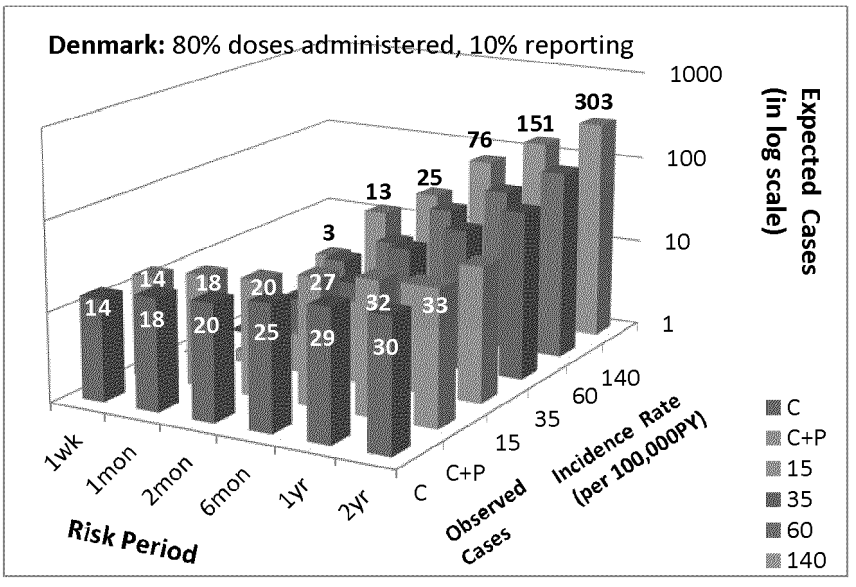
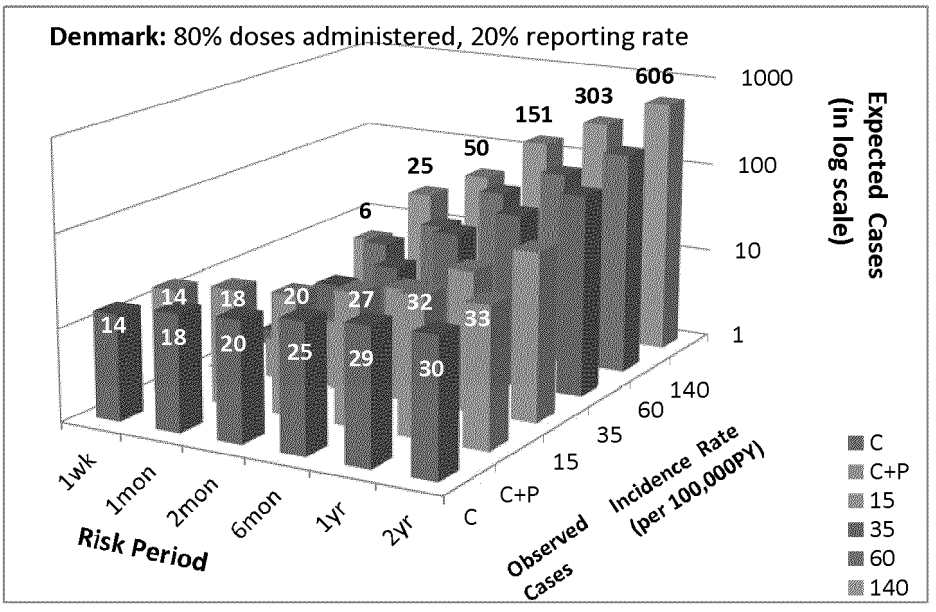


Figure 8. Observed and expected cases of POTS- Denmark
by risk period, incidence rate, reporting rate, proportion of doses administered (cont)
(C= cases that meet case definition; C+P= cases that meet/partially meet definition)

B. 80% doses administered; 20% and 100% reporting rates



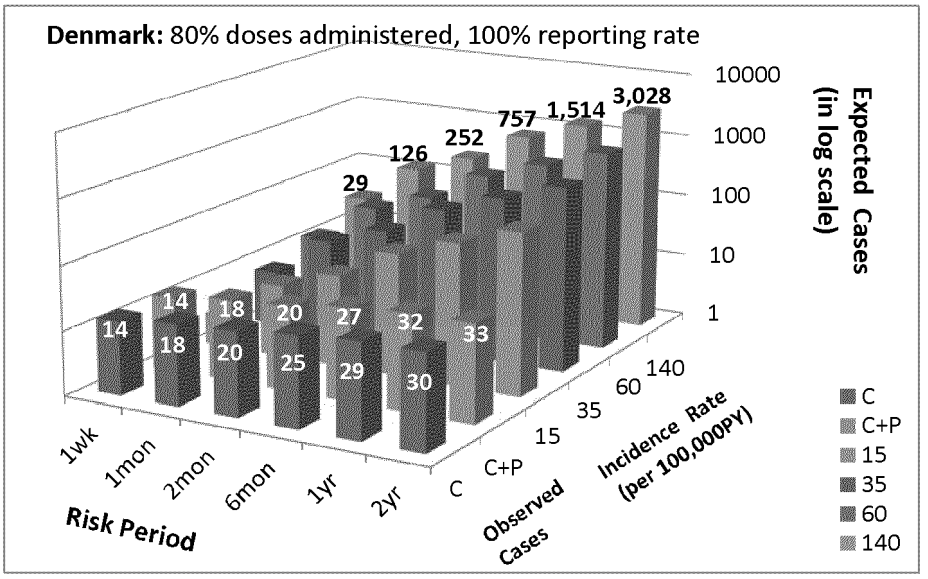
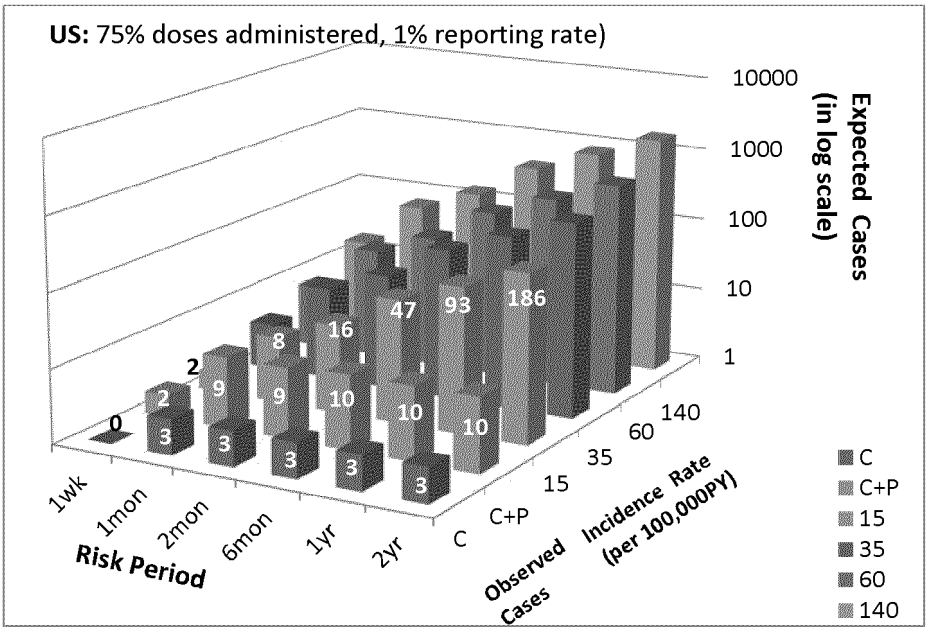


Figure 9. Observed and expected cases of POTS- United States
by risk period, incidence rate, reporting rate, proportion of doses administered
(C= cases that meet case definition; C+P= cases that meet/partially meet definition)

A. 75% doses administered; 1% and 10%reporting rate



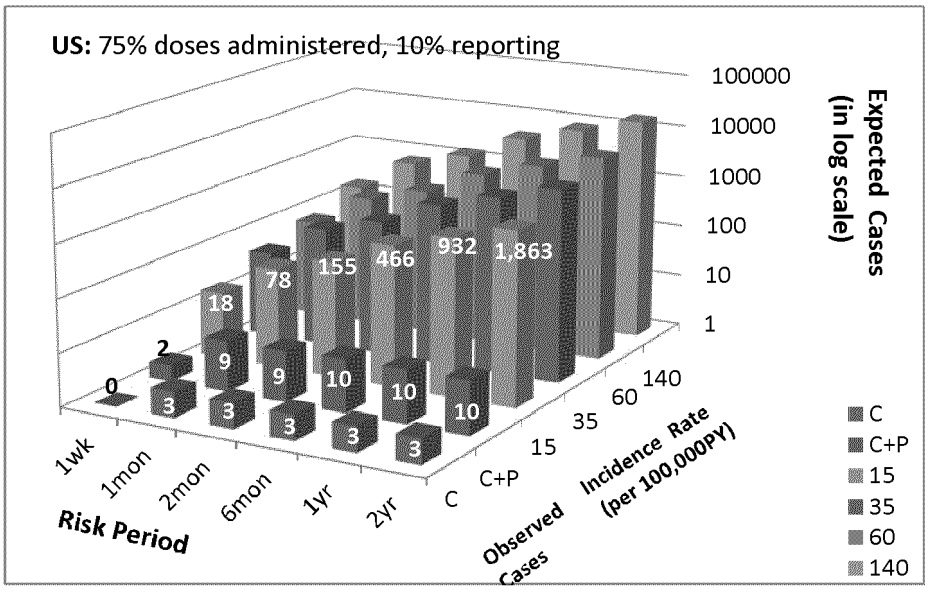
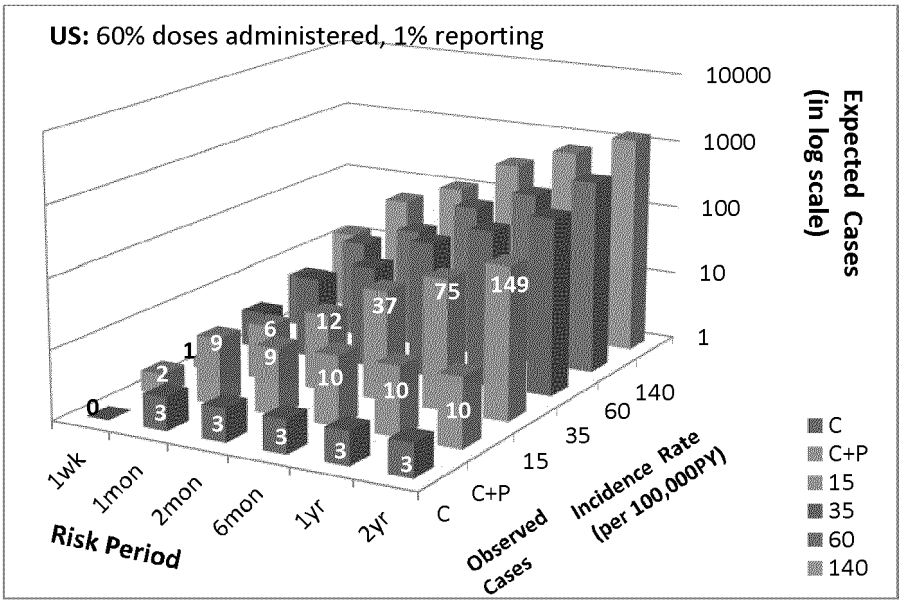
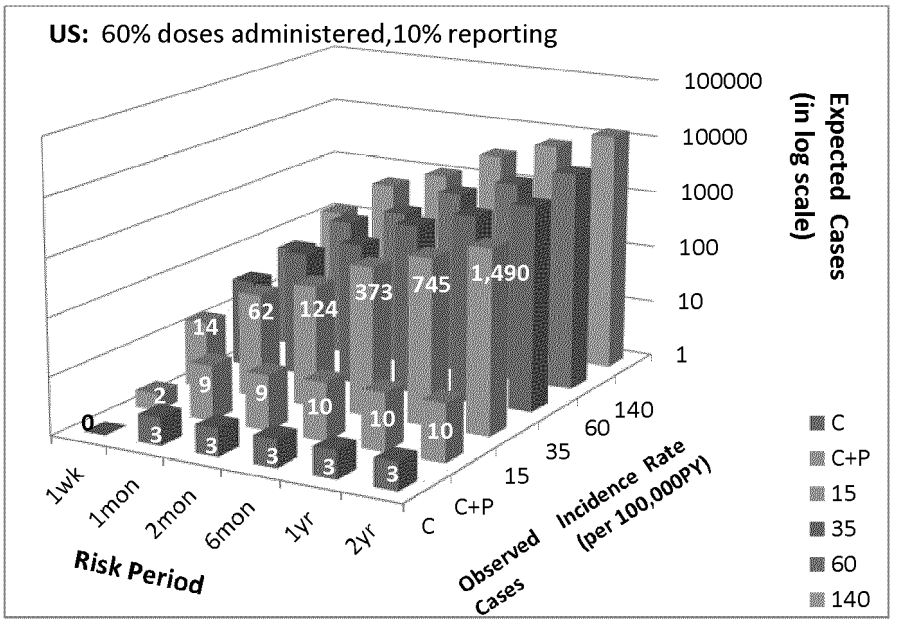


Figure 9. Observed and expected cases of POTS- United States
by risk period, incidence rate, reporting rate, proportion of doses administered (cont.)
(C= cases that meet case definition; C+P= cases that meet/partially meet definition)

B. 60% doses administered; 1% and 10%reporting rate





1.4 PRAC Question 4

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

MAH RESPONSE

Epidemiological studies of association between qHPV and CRPS or POTS

To our knowledge, there are no published studies evaluating the association between HPV vaccines and CRPS or POTS. Some pathophysiology hypotheses have suggested that POTS may have an immune-mediated pathogenesis and that CRPS and POTS may be related. Epidemiological studies of the association between qHPV and autoimmune conditions have shown no evidence of causal association, as summarized below.

<u>No evidence of causal association between qHPV vaccine and autoimmune conditions has been identified in epidemiological studies.</u>

Five large observational studies published to date have reported no association between vaccination with qHPV and autoimmune conditions. The studies included a variety of autoimmune conditions, and they each categorized autoimmune conditions in different ways, as described below. The studies were conducted in health care organizations and academic research institutes in Europe and the United States (US). Three studies were sponsored independently and two were sponsored by the MAH. All safety findings from the MAH-sponsored studies were reviewed and interpreted by independent expert scientific committees, who were external to the research organizations conducting the study and to the MAH. The findings of these five studies regarding autoimmune conditions are described in further detail below.

1. Cohort Study of Girls and Women in the Kaiser Permanente Northern and Southern California Managed Care Organizations (Chao et al., 2011; Klein et al., 2012, Final Study Report- December 2010). A large retrospective cohort study was conducted at Kaiser Permanente Northern and Southern California among approximately 190,000 females enrolled who received qHPV vaccine between August 2006 and March 2008. The study analyzed disorders of the autonomic and central nervous system, including POTS and CPRS. The study also analysed diagnostic codes occurring within the grouping of fatigue/malaise (including asthenia, lethargy, chronic fatigue syndrome, exhaustion, and similar symptoms). No association was found between these conditions and vaccination with qHPV vaccine.

2. Nationwide Cohort Study of Girls Aged 10-17 in Denmark and Sweden (Arnheim-Dahlstrom et al., 2013). No evidence of an increased risk of autoimmune or neurological conditions after

vaccination with Gardasil was found in a nationwide study of girls from Sweden and Denmark. The study included 997,585 girls aged 10-17 with approximately 2.8 million years of follow-up. The girls were identified from national health care registries. Vaccination status was obtained from vaccination/prescription registries, and diagnoses after vaccination were identified from national hospital inpatient and outpatient registries. Among the cohort, 296,826 girls (30%) had been vaccinated with 696,420 doses of Gardasil between October 2006 and December 2010.

3. Case-Control Study of Girls and Women Aged 14-26 Across France (Grimaldi-Bensouda et al., 2013). No evidence of an increased risk of 6 types of autoimmune conditions after vaccination with Gardasil was found in a large matched case-control study conducted among girls and women aged 14-26 residing in France. This case-control study was conducted by LA-SER, a private organization in France, using the Pharmacoepidemiologic General Research eXtension (PGRx) information system. The PGRx system collects cases of diseases and a reference pool of controls (without the diseases), independent of exposure to drugs or vaccines. Between 2007 and 2011, cases of autoimmune disorders were recruited from specialty centers (neurology, internal medicine, endocrinology, rheumatology, pediatrics), and controls were recruited from general practices. Cases of idiopathic thrombocytopenic purpura (ITP), central demyelination/multiple sclerosis (MS), Guillain–Barre syndrome, connective tissue disorders (systemic lupus erythematosus, rheumatoid arthritis/juvenile arthritis), type 1 diabetes mellitus and autoimmune thyroiditis were identified. Medical records were reviewed and patients were interviewed to confirm diagnosis. A total 211 newly diagnosed autoimmune cases and 875 controls were identified; of these, 25 and 192, respectively, had prior vaccination with Gardasil. Duration of follow-up (i.e., the window "at risk" for each autoimmune condition of interest) varied by AI disorder, and ranged from 2 months up to 2 years. No evidence of an increased risk of the studied autoimmune disorders was observed following vaccination. Though sample sizes for the individual disorders were small, limiting power, the study observed no unusual accrual of incident autoimmune conditions in 14-26 year old females between 2007 and 2011, from a large series of centres in France that specialize in autoimmune disorders.

4. Nationwide Cohort and Case Series Study of Girls and Women Aged 10-44 in Sweden and Denmark (Scheller et al., 2015). No evidence of an increased risk of autoimmune conditions (specifically, demyelinating diseases, after vaccination with Gardasil was found in a nationwide study of girls and women in Sweden and Denmark. The study was conducted among 3,983,824 girls and women aged 10-44 between 2006 and 2012 (Sweden) or 2013 (Denmark) and had more than 21 million person-years of follow-up time. Within the study cohort, 789,082 girls and women had been vaccinated with 1,927,581 doses of Gardasil. The study used two different analysis methods (a cohort analysis and a self-controlled case series analysis), and included adjustment for potential confounding factors. Vaccination status was identified from nationwide vaccination/prescription databases and diagnoses were obtained from nationwide hospital inpatient and outpatient registries.

5. Nested Case-Control Study of Girls and Women Aged 9-26 in the Kaiser Permanente Southern California Managed Care Organization (Langer-Gould et al., 2014). A study of females enrolled at Kaiser Permanente Southern California did not find increased risk of MS or other central nervous system demyelinating diseases within 3 years after vaccination with Gardasil. In total, 780 girls and women with newly diagnosed MS, ADEM or clinically isolated syndrome (CIS, including optic neuritis, transverse myelitis, and monofocal or multifocal CIS) were identified and matched to 3885 controls (female Kaiser members without these conditions) between 2008 and 2011. Incident diagnoses were identified from both inpatient and outpatient medical records and confirmed with expert medical record review. No association between vaccination with Gardasil and development of any of these conditions within 3 years afterward was found in this cohort. While the study findings were inconclusive due to small sample sizes (36 vaccinated cases and 175 vaccinated controls within 3 years after vaccination), the investigators also concluded that the findings do not indicate an increased risk of these autoimmune conditions within 3 years after vaccination.

Possible causes and pathophysiology of CRPS

Despite the fact that not all case reports of CRPS fulfill the Budapest clinical diagnostic criteria for CRPS (continuing pain, which is disproportionate to any inciting event; experience of at least one symptom in three of the four following categories: sensory, vasomotor, sudomotor/edema, and/or motor/trophic, and must display at least one sign at time of evaluation in two or more of the former categories, and there is no other diagnosis that better explains the signs and symptoms), it is beyond dispute that the reported signs and symptoms are burdensome for the affected patients. Most of the reports originate in Japan and this is also where the following pathophysiological theories developed.

Kinoshita et al. (2014) [Ref. 5.4: 046Y94] suggest a possible peripheral circulatory failure and sympathicopathy, and anticipate that in many cases the symptoms correspond to the general picture of orthostatic disturbance. Regarding the extremely varied range of symptoms, the authors consider that one possible explanation was that these were all symptoms of orthostatic disturbance, and suggest peripheral dysautonomia as a cause. *Kinoshita et al (2014) [Ref. 5.4: 0470R6]* then focus on ultramicromorphological findings where in single cases sporadic degeneration of the myelin sheath was observed leading to the suspicion of decreased concentration of non-myelinated nerve fibers and growth of collagen fibers in the surrounding areas. They also find irregular and electron-dense granular abnormality inside the non-myelinated nerve fibers. *Okuyama (2014) [Ref. 5.4: 0474KP]* suspects vaccine-associated chronic fatigue syndrome, orthostatic dysfunction, and conversion disorder. All cases present a mixed picture of signs and symptoms and no clear patterns of time to onset and/or relationship to the number of doses given. The authors could not demonstrate a consistent, biologically plausible temporal relationship between vaccination and the disease. In addition, there is no

evidence for the subjective impression of a "high incidence" of neurological symptoms following vaccination.

While *Richards et al. (2012) [Ref. 5.4: 03RTWM]* point out that the onset of the CRPS-1 is often precipitated by a physical injury such as minor trauma, fracture, infection or a surgical procedure, and the cases they describe appear to be related to the local injection itself.
Also *Haug et al. (2013) [Ref. 5.4: 03RTWM]* highlight that CRPS (formerly known as Sudeck dystrophie) may develop following limb trauma, lesions of the peripheral or central nervous system, or fractures. As pathophysiological concepts they discuss neuroinflammation, pathological regulation of the sympathetic nervous system and affection of the central nervous system. These authors think that, although CRPS after vaccination is described after immunization against rubella and hepatitis B, the first published cases CRPS-I after immunization with Gardasil suggest a higher risk of developing this complication. Nevertheless, in the case they describe the small inflammatory focus in the right muscle deltoideus probably reflects an injection site reaction. And given the negative results of neurological, immunological, microbiological tests, and nerve conduction studies, the patient was diagnosed with somatoform disorder.
In a review of HPV vaccines associated adverse events *Rev Prescrire (2015) [Ref. 5.4: 046WK7]*, the authors conclude cases of CRPS appear to be linked to the vaccination procedure rather than the vaccine itself, as this adverse event has been reported with other vaccines.
Martinez-Lavin (2014) [Ref. 5.4: 046WK3] presents 2 case reports of chronic, incapacitating fibromyalgia-like illnesses after receiving qHPV. The author proposes that fibromyalgia is a generalized complex regional pain syndrome based on the following arguments: In both conditions, there is female predominance, frequent onset after trauma, chronic nonnociceptive pain, paresthesias, sympathetic instability, and allodynia/hyperesthesia. Dorsal root ganglia may play a key role in fibromyalgia pain, as trauma or viral infection can induce dorsal root ganglia sympathetic fiber sprouting establishing abnormal sympathetic-nociceptive short circuits, leading him to speculate that in a genetically susceptible individual an intramuscular-injected vaccine containing noninfectious virus plus the aluminum adjuvant substance could elicit similar changes. In one of his patients though the immediate onset of the pain syndrome after the third dose of qHPV suggests a local injection site reaction which was possibly intensified after the patient received the last dose. Without any further diagnostic clarification in both patients any assessment of the course of the events remains speculative.

Conclusion

Overall, there is no epidemiologic evidence or known potential biological mechanism for an association between HPV vaccine and CRPS. All presented hypotheses and speculations may reflect events independent of any vaccination. The safety evaluation of HPV vaccine in animals and humans has not yielded any concerning findings. The only treatment-related effects that

were observed in animals were indicative of the expected effects at the site of vaccine injection and an antigen-specific immune response against the vaccine components. Importantly, there was no evidence of general immune-mediated effects and no findings indicative of effects on the central nervous system.
There is no evidence to establish a causal relationship between HPV vaccine and CRPS; the small number of cases reported despite the large number of doses distributed, which are in line to the expected frequency in non-vaccinated population, suggest an unlikely causal relationship.

Possible causes and pathophysiology of POTS

In the publication in which *Blitshteyn S. (2014) [Ref. 5.4: 03T3DX]* describes 6 patients who developed POTS following human papillomavirus vaccination, she postulates molecular mimicry with a formation of cross-reacting autoantibodies to the potential targets of the autonomic ganglia, neurons, cardiac proteins or vascular receptors as a possible pathogenesis of new onset POTS after immunization. In none of the cases reported this hypothesis could be verified. The signs and symptoms were probably related to an underlying Irritable Bowel Syndrome, or of a cardiac origin, but in most cases a causality assessment based on the information provided is not possible. Also *Kinoshita T et al. (2014) [Ref. 5.4: 040HS8]* try to link adverse experiences following HPV vaccine administration to small fiber neuropathy as an underlying cause for POTS and CRPS. In their report they could not demonstrate a clear pattern of signs and symptoms or proving microscopic findings. Quoting *Hanley S et al. (2015)* [Ref. 5.4: 0477QS] from their response to the Kinoshita T et al. publication [Ref. 5.4: 040HS8], the authors did: "not demonstrate any relationship between vaccination and a wide range of adverse events. As described by the authors, the conditions they report peak in adolescent females and occur without HPV vaccination. To assess whether HPV vaccination is associated with disease development, one needs a robust specific case definition and demonstration of a consistent, biologically plausible temporal relationship between vaccination and the disease. In this paper we see neither. Clearly, we believe and understand that the girls described in this paper are indeed suffering. However, we do not believe that this suffering has been shown to be related to HPV vaccination."

Tomljenovic L et al. 2012 [Ref. 5.4: 040NH7] tried to validate a biomarker-based immunohistochemical (IHC) protocol for assessing causality in case of vaccination-suspected serious adverse neurological outcomes by analyzing post-mortem brain tissue specimens from two young women who suffered from cerebral vasculitis type symptoms following vaccination with qHPV using various immunoinflammatory markers. Brain sections were also stained for antibodies recognizing HPV-16L1 and HPV-18L1 antigen which are present in qHPV. Based on their findings, the authors postulate that HPV vaccines containing HPV-16L1 antigens pose an inherent risk for triggering potentially fatal autoimmune vasculopathies. In the case they describe for qHPV the patient developed a severe generalized vasculitis with multiple complications including tonic-clonic generalized seizures, persistent migraines, syncope, and tremors and

tingling, with a suspicion of a probable SLE. The patient had a history of chronic migraine before the administration of qHPV, which might have been related to a preexisting cerebral vasculitis. The cause of death and autopsy showed cerebral vasculitis. The presence of POTS in this case was likely related to vasculitis.

In a later publication, *Tomljenovic et al. (2014)* [Ref. 5.4: 040ML9] assume that the adverse reactions following HPV vaccination cannot solely attributed to the aluminum adjuvant, as many other vaccines also contain aluminum but are not associated with as many adverse reactions. However, aluminum would evoke the enhanced immune reaction necessary for inducing the production of the elevated titers of antibodies. The antigen on its own is not capable of evoking this strong immune response. Because of this, they hypothesize any adverse effect arising from the antigen (or other constituents in the vaccine) is ultimately linked to the action of the adjuvant, leading to a strong immune response which is linked to the development of the adverse events. In the case the authors describe though, the patient's medical history of headaches, dizziness, photophobia, and phonophobia and her family history (mother) of Raynaud's syndrome indicate a predisposition if not an underlying connective tissue disease independent of any vaccination.

Brinth et al. (2015) [Ref. 5.4: 046X0L] and [Ref. 5.4: 046WRP] present the majority of the reported cases of POTS due to the fact that patients with orthostatic intolerance and other symptoms compatible with autonomic dysfunction are referred to their Syncope Unit at Frederiksberg Hospital, Denmark. The authors note in their patients low levels of bilirubin, a high level of physical activity before symptom onset, and a high incidence of irregular menstruation. They speculate that these conditions may all have affected their immune response to vaccination, in that for example exercise may increase both pro- and anti-inflammatory cytokines as well as leukocyte subsets, and bilirubin could not sufficiently act as an inhibitor of the complement cascade. In at least one case the authors point out the patient's a low vitamin D level.
Bilirubin is under discussion of being a powerful immunomodulatory agent, and may protect mammals against autoimmune diseases (Liu Y 2008 [Ref. 5.4: 0476K4]). Also vitamin D seems to have a contributory role in the pathophysiology of autoimmune diseases. This is supported by various experimental findings showing vitamin D's capability to regulate chemokine production, counteracting autoimmune inflammation and to induce differentiation of immune cells in a way that promotes self-tolerance (Wacker M et al. 2013 [Ref. 5.4: 0476KB]).Since vitamin D is actively used in many metabolic pathways, it is possible that a high level of physical activity may require an increased intake of vitamin D to assure adequate availability (Ogan D et al. 2013 [Ref. 5.4: 0476KL]). This could be specifically of importance in areas with less sunlight and/or for physical activities mainly performed indoors. As *Brinth et al.* emphasize, POTS has been suggested to have an immune-mediated pathogenesis, and therefore it appears possible that individual predisposition and an altered immunomodulation may have caused the described signs and symptoms with or without the preceding vaccination. This underlines a major limitation of the presented case review, the lack of a control group. In addition, with a symptom onset

distribution of 24% after the first vaccination, 51% after the second and 25 % after the third vaccination no clear pattern could be demonstrated.

Conclusion

The pathophysiology of POTS appears to be heterogeneous and manifests as different clinical phenotypes, which are postulated to have differing etiologies, and there is no epidemiologic or other evidence and no known potential biological mechanism for an association between HPV vaccine and POTS.

1.5 PRAC Question 5

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

MAH RESPONSE

1. *MAH consolidated conclusion based on answers to question 1 – 4.*

   Altogether, there is no evidence for a causative relationship or a potential biological mechanism for an association between HPV vaccine and POTS or CRPS. Although a temporal relationship between the vaccination and the onset of the various neurological signs and symptoms has been postulated, no clear pattern for time to onset and/or number of HPV vaccination doses given could be demonstrated. The observed versus expected analysis did not reveal an increased number of spontaneously reported cases as compared to what was expected, based on background rates of these conditions in the general population of that age under a wide range of assumptions. A notable exception was the analysis of POTS in Denmark, the country from which most worldwide cases were reported, including more than 90% of worldwide cases that meet criteria, and 100% of those that meet criteria and reported to have occurred within a week of a vaccine dose. As discussed in response to Question 3, this could be related to the fact that many of these cases come from a center specializing in syncope evaluation and a possible bias in the retrospective assessment of time to onset relative to vaccination. Some authors point out that, if symptoms were psychogenic and not related to a specific vaccine but rather a reaction to the injection procedure itself, one would expect a more even distribution of reports with different vaccines; instead they highlight a disproportional reporting of syncope following HPV compared with other vaccines. These arguments however do not take into account the specific age group receiving HPV vaccines with a higher prevalence of syncope and POTS or CRPS.
   The safety evaluation of HPV vaccine in animals and humans has not yielded any concerning findings. The only treatment-related effects that were observed in animals were indicative of the expected effects at the site of vaccine injection and an antigen-specific immune response against the vaccine components. Importantly, there was no evidence of general immune-mediated effects and no findings indicative of effects on the central nervous system. In the absence of clear biological or epidemiological evidence for a causal association between HPV vaccination and POTS and CRPS, additional risk minimisation measures are not warranted.
   The MAH's ongoing review of the safety profile of the vaccines continues to support its positive Benefit-Risk profile.

2. *Current Measures already in place for POTS*

Gardasil / Silgard	Gardasil 9
• Routine pharmacovigilance (including 6-monthly PSURs for the initial 3 years of marketing authorization followed by annual reports and Quarterly signaling review for a minimum of the initial 5 years of marketing authorization) • A questionnaire for obtaining follow-up on case reports that include POTS or symptoms of POTS has been put into use worldwide.	• Routine pharmacovigilance (including 6-monthly PSURs for the initial 3 years of marketing authorization followed by annual reports and Quarterly signaling review for a minimum of the initial 5 years of marketing authorization) • A questionnaire for obtaining follow-up on case reports that include POTS or symptoms of POTS has been put into use worldwide.

3. *Current Measures already in place for CRPS*

Gardasil / Silgard	Gardasil 9
• Routine pharmacovigilance (including 6-monthly PSURs for the initial 3 years of marketing authorization followed by annual reports and Quarterly signaling review for a minimum of the initial 5 years of marketing authorization) • A questionnaire for obtaining follow-up on case reports that include CRPS or symptoms of CRPS has been put into use worldwide.	• Routine pharmacovigilance (including 6-monthly PSURs for the initial 3 years of marketing authorization followed by annual reports and Quarterly signaling review for a minimum of the initial 5 years of marketing authorization) • A questionnaire for obtaining follow-up on case reports that include CRPS or symptoms of CRPS has been put into use worldwide.

4. MAHs proposals

The MAH's ongoing review of the safety profile of the vaccines continues to support its positive Benefit-Risk profile.

No update is required to the Risk Management Plan or SmPC for both HPV vaccines.

The MAH will continue to monitor reports of POTS and CRPS through routine pharmacovigilance, which is the most appropriate method to examine these rare events.

Appendices

Appendix A

Background incidence rates of CRPS and POTS used for expected calculations in Observed versus Expected comparison (Response to Question 3)

The calculation of expected numbers of events in the vaccinated population requires knowledge of the incidence (occurrence of new cases) of the condition in the target population. Background incidence rates for each of two conditions of interest for this request, Complex Regional Pain Syndrome (CRPS) and Postural Orthostatic Tachycardia Syndrome (POTS) were derived from a detailed review of the published literature.

Background incidence rates for CRPS

A literature review was conducted to identify background incidence rates of CRPS in females in the age range of approximately 9-29 years. Only 2 published studies of incidence rates of CRPS were identified, one from the US, one from the Netherlands. They are summarized in Table A1.

The Sandroni *et al* 2003 US study was a population-based analysis from Olmsted County, Minnesota for the period 1989-1999 [Ref. 5.4: 03RTWP]. It has been subject to criticism, in part due to the retrospective application of CRPS diagnostic criteria to diagnoses based on clinical signs and symptoms before the criteria were published, which is thought to have been overly strict and resulted in possible underestimate of incidence rates. The de Mos *et al* 2007 study from the Netherlands was a population-based analysis of medical records from 600,000 patients throughout the Netherlands during the period 1995-2006 [Ref. 5.4: 040LYZ]. In this study, detection and validation of CRPS cases included a broad detection algorithm in the electronic medical records and diagnosis reconfirmation of potential cases through a supplemental questionnaire sent to the treating physician. In addition, fulfilment of the diagnosis according to CRPS criteria of a subset of specialist-diagnosed cases with detailed letters from specialists was conducted independently by 2 physicians and resulted in high confirmation rate of CRPS diagnosis according to the International Association for the Study of Pain (IASP) criteria. Both studies showed higher incidence rates of CRPS in females than males and an increase in incidence rates with age.

Because the Netherlands study had a superior methodological quality and was conducted more recently, incidence rates from this study were considered more reliable. In this study, the incidence rates of CRPS-1 were 14.9 and 28.0 per 100,000 person-years in females 10-19 years old and 20-29 years old, respectively. Of note, corresponding rates were lower in males,

reported to be 1.8 and 6.2 per 100,000 in males 10-19 years old and 20-29 years old, respectively. These age-specific incidence rates were used as background rates for the calculation of expected numbers of CRPS, using a weighted average incidence based on the respective proportions of 10-19 and 20-29 year-old females in the vaccinated populations of each country/geographic region, as needed. For example, in a country where an estimated 90% of vaccinated females were 10-19 years old and 10% were 20-29 years old, an average background incidence rate of 14.9*90% + 28.0*10%, i.e., 16.21 per 100,000 person-years was used as the background incidence rate of CRPS in that country for the purpose of expected numbers calculation. Most if not all doses were distributed in 10-19 year olds in most countries.

In summary, we used the following assumptions for the background incidence rates of CRPS for the calculation of expected numbers of CRPS:

- **14.9 and 28.0 per 100,000 person-years in females 10-19 and 20-29 years old, respectively**

A single incidence rate assumption was used per country/geographic region, calculated as a weighted average incidence based on the respective proportions of 10-19 and 20-29 year-old females in the vaccinated population of that country/geographic region, as needed.

Background prevalence rates (i.e., frequency of existing cases in the target population) are provided per EMA request, but not used in Observed vs. Expected calculations. For context, Sandroni *et al* reported on the natural history of CRPS in their Olmsted County study [Ref. 5.4: 03RTWP]. Their main findings was that CRPS is a fairly rare condition with a high rate of spontaneous resolution, with many cases being mild and transient, and only a minority becoming chronic and severely disabled. In this study, the prevalence of CRPS was 0 and 36 per 100,000 in 10-19 and 20-29 year-old females [Ref. 5.4: 03RTWP], possibly underestimated due to the limitations mentioned above about the retrospective assessment of CRPS diagnostic criteria.

Background incidence rates for POTS

POTS is a common syndrome [Ref. 5.4: 040MLZ] predominantly impacting females younger than 40 years old [Ref. 5.4: 03SXYT, 040MJB, 03SW8C, 03SXX2, 03SXY8]. Although the existence of POTS was documented decades ago [Ref. 5.4: 040MJB], recognition of POTS in the medical community has increased over the past 20 years, based on work conducted at the Mayo Clinic (Rochester, MN, USA) [Ref. 5.4: 040MJ5]. While POTS is increasingly being recognized by clinicians [Ref. 5.4: 040MB5], it is still an underdiagnosed and underestimated entity [Ref. 5.4: 03SW8C, 03SXX2, 040MJB]. As a result, there are minimal prevalence data for POTS in the literature, and to our knowledge, no incidence rates for POTS have been reported.

It is well established that some patients with chronic fatigue syndrome (CFS) have comorbid POTS [Ref. 5.4: 040MCJ, 040MJ5, 040MB9, 040MBH, 040LZF, 040MBC, 040MC5]. Given the limited data on the burden of POTS and drawing upon the relationship between CFS and POTS, the MAH estimated a range of incidence rates for POTS derived from data on CFS, using the following equation

..... $= \frac{(\qquad) * (\%\qquad h\qquad)}{\%\qquad h}$

Incidence of CFS: Several studies have been published on the incidence of CFS, representing a wide range of incidence rates of CFS summarized in Table A2. Variations were mainly related to differences in diagnosis criteria and different study methods. These studies consistently show higher incidence rates of CFS in females than males. They also suggest that the incidence of CFS is higher in younger age groups. On the lower end, a study from the Netherlands reported an annual rate of 12/100,000 in 10-18 year old females, though the investigators acknowledged the rates were probably underestimated [Ref. 5.4: 040KYK]. A study of 18-70 year old women in Olmsted County, Minnesota, US reported a rate of 21.7 per 100,000 [Ref. 5.4: 040MKG], while 41/100,000 was reported for 18-64 year-old females in England [Ref. 5.4: 040KYH]. At the upper end of the reported annual incidence rates of CFS, in a Kansas (US) study, a rate of 180 per 100,000 18-69 year-old females was reported [Ref. 5.4: 040MCG], a rate of 370 per 100,000 adults was reported in Scotland [Ref. 5.4: 040KYG], and a rate of 950 per 100,000 in 11-12 year-old females was reported from the UK [Ref. 5.4: 040MCR]. A recent population-based registry study by Bakken *et al* 2014 in Norway reported the incidence of CFS between 2008 and 2012 to range from approximately 50 to 65 per 100,000 person-years in 10-39 year-old females, and from 10 to 25 per 100,000 person-years in 10-39 year-old males [Ref. 5.4: 040LJV]. The incidence rates reported from this Norway study are toward the lower end of the literature estimates described above, and used robust methods. Another recent study by Donegan *et al* 2013 in the UK reported similar annual incidence rates ranging from 31 to 70 per 100,000 in 12-20 year old females [Ref. 5.4: 04756V]. Therefore, a range of 30 to 70 per 100,000 person-years in females 10-39 years old was used as background incidence rate of CFS. Of note, for males, based on these publications, an acceptable the range would be 10 to 20 per 100,000 person-years.

Proportion of CFS cases with POTS: The proportion of CFS cases who have POTS has been reported in several studies summarized in Table A3. Some studies have reported proportions of 11% to 13% [Ref. 5.4: 040MJ5, 040MCJ, 040MBH], whereas others have reported higher proportions of 25% to 42% [Ref. 5.4: 04757B, 040LZF, 040MBD, 040MB9]. We used a range of **10% to 40%** as the proportion of CFS cases with POTS for the estimation of POTS incidence and calculation of expected numbers of POTS.

Proportion of POTS cases with CFS: While many POTS cases have fatigue, only a small fraction of POTS cases have a diagnosis of CFS. The only study providing an estimate of the proportion of POTS cases having a diagnosis of CFS was a recent study by McDonald *et al* 2014 [Ref. 5.4: 0475H0] that suggested a proportion of 21% (Table A3). We assumed that a

proportion of **20%** of incident cases of POTS also had CFS for the estimation of POTS incidence and calculation of expected numbers of POTS.

Summary estimates: In summary, we used the following assumptions for the estimation of the background incidence rates of POTS:

- CFS incidence rates of 30 to 70/100,000 person-years in 10-39 year old females
- Proportion of CFS cases with POTS: 10% to 40%
- Proportion of POTS cases with CFS: 20%

Based on the equation shown above for the calculation of POTS incidence, we obtained the following estimates for the incidence of POTS: 15, 35, 60 and 140 per 100,000 person-years in females.

In summary, the following assumptions were used for background incidence rates of POTS for the calculation of expected numbers of POTS:

- **15, 35, 60 and 140 per 100,000 person-years in females 10-39 year old**

Background prevalence rates (i.e., frequency of existing cases in the target population) are provided per EMA request, but not used in Observed vs. Expected calculations. For context, prevalence rates of POTS are unavailable but, using the same approach as for incidence, could be approximated from available prevalence rates of CFS. Prevalence rates of CFS have been reported to range from 0.006% to 3% worldwide [Ref. 5.4: 0476TJ, 0476VJ, 0476TS], mainly depending on the criteria used. A CFS prevalence of 0.2% was reported in England [Ref. 5.4: 040KYH]. Using the same calculation as for POTS incidence based on proportion of CFS cases that have POTS (10% to 40%) and proportion of POTS that have CFS (20%), the prevalence of POTS would range approximately from 0.003% to 6%, corresponding to 3 to 6000 per 100,000.

Table A1. Publications on CRPS incidence rates (IR per 100,000 person-years)

Author, publication year	Disease	Country/Region	Study Design/Setting	Study Period	Age (years)	Females, Incidence Rate (/100,000 py)	Males, Incidence Rate (/100,000 py)
De Mos, 2007	CRPS	The Netherlands	IPCI database	1996-2005	10-19 y	14.9	1.8
					20-29 y	28.0	6.2
					30-39y	27.7	9.0
					40-49y	27.2	15.5
					50-59y	72.1	24.4
					60-69y	121.3	31.4
Sandroni, 2003	CRPS	US, Olmsted County	Mayo Clinics, medical charts review	1989-1999	10-19y	2.15	1.04
					20-29y	6.81	1.05

CRPS: Complex regional pain syndrome

Table A2. Publications on CFS incidence rates (IR per 100,000 person-years)

Author, publication year	Disease	Country/Region	Study Design/Setting	Study Period	Age (years)	Females, Incidence Rate (/100,000 py)	Males, Incidence Rate (/100,000 py)	Both genders, Incidence Rate (/100,000 py)
Gallagher, 2004	CFS/ME	UK	CPRD	1998-2001	All (8-83y)	-	-	50-55
Rimes, 2007	CFS	UK	Questionnaires	-	11-15y	-	-	1000
Nacul, 2011	CFS/ME	UK	General practices	2007-2010	18-64y	13 (6-24)	4 (1-11)	9 (5-15)
Donegan, 2013	Fatigue syndromes	UK	CPRD	2009-2011*	12-20y	40	15	-
					21+y	-	-	55
	CFS			2008-2009	12-13y	31.2	-	-
					17-18y	69.5	-	-
				2009-2010	12-18y	47.4	-	-
				2009-2011	12-20y	32 (incident diagnosis)	-	-
Lawrie, 1997	CFS	Scotland	Clinic, Penicuik Health Center	1991-1992	>18y	-	-	370 (40-1330)
Bakken, 2014	CFS/ME	Norway	Registry data	2008-2012	All	39.4	12.9	-
					10-14y	60*	25*	43.7
					15-19y	65*	18*	43.1
					20-24y	50*	10*	31.9
					25-29y	50*	15*	32.3
Nijhof, 2011	CFS	The Netherlands	General practices	2008-2009	10-18y	-	-	12
Minowa, 1996	CFS	Japan	Clinics	1992	All	0.51 (0.43-0.58)	0.36 (0.30-0.43)	0.46 (0.41-0.51)
Reyes, 1997	CFS	US, 4 cities	Physicians based surveillance	1989-1993	>18y	-	-	<1
Reyes, 2003	CFS	US, Kansas	Clinics	1997-2000	19-69y	-	-	180 (0-466)
Vincent, 2012	CFS	US, Olmsted Co.	Medical charts review	1998-2002	18-70y	21.74	4.39	13.16

CFS/ME: Chronic fatigue syndrome/myalgic encephalomyelitis ; * approximation

Table A3. Publications on proportion of CFS with POTS and proportion of POTS with CFS

Author, publication year	Country/Region	Study Design/Setting	Study Period	Number of subjects	Mean Age (years)	% of CFS cases with POTS	% of POTS cases with CFS
Reynold, 2014	Australia	Hospitals	2009-2012	306	25.33	11%	-
Lewis, 2013	UK	Hospitals	2008-2011	179	40	13%	-
Hoad, 2008	UK	-	-	59	47	27%	-
Galland, 2008	New Zeland	GPs and pediatric Outpatients	-	26	Between 11-19 y	42%	-
Jones, 2005	US	-	-	10	52	30%	-
Freeman, 1997	US	Hospitals	1993-1996	20	38.9	25%	-
Schondorf, 1999	Canada	Hospitals + Specialists	1995-1996	75 (75 with CFS)	39.1	12% (9 cases with POTS)	-
Mc Donald, 2014	UK	Hospitals	2009-2012	136	33	-	21%

CFS: chronic fatigue syndrome ; POTS: Postural orthostatic tachycardia syndrome

Appendix B

Doses administered used for expected calculations in Observed versus Expected comparison (Response to Question 3)

The calculation of expected numbers of events in the vaccinated population requires knowledge of the proportion of doses distributed that have actually been administered. Reasonable assumptions have been derived from a combination of information sources, including Merck Commercial, vaccine coverage, and vaccine policy data available for each country/region.

Region/countries:
Expected numbers were calculated for the following regions/countries: Worldwide, European Union, Denmark, Germany, United Kingdom, United States, and Japan.

Doses distributed:
Doses distributed as of 31-May-2015 are provided below. They included estimated numbers of doses of Gardasil distributed, to which [redacted] doses of Gardasil 9 distributed primarily in the US in 2015 were added.

	Worldwide	US	EU28	Denmark	Germany	UK	Japan
Doses Distributed	191,472,401	[redacted]	35,907,186	[redacted]			

This information was also available by calendar year since first Gardasil approval in 2006.

Estimates of doses administered

Estimates of doses distributed that were administered in females were based on a combination of the following information:

- Dose use ranging from 95%-100% of doses distributed up to 2012 and then use of approximately 80% of doses in 2013, 50% of doses in 2014 and 10% of doses in 2015 resulted in estimates of 85% to 95% of doses distributed used in the various regions/countries

Male use:

- In the US, use in males started more recently (approval in 2011) and has increased sharply in recent years; based on coverage data from CDC and internal estimates, doses used in males may represent approximately 15%-20% of all doses distributed in the US since 2006 and 8% of all doses distributed worldwide since 2006
- Use in males in Europe can be considered negligible overall up to mid-2015; only Austria and Portugal may have non-negligible male uptake, while some male use may have started recently in some regions of Italy, Saxony in Germany, and for MSM in a few additional countries (e.g., Ireland, UK and Greece); male use can be considered negligible for Denmark, UK and Germany
- There is no male use in Japan
- In other parts of the world, there is some male use in a few countries (e.g., Canada and Australia), but it can be considered negligible overall
- Worldwide, doses used in males can be estimated to represent approximately 10% of all doses distributed since 2006, to take into account male use in the US and other countries

Additional considerations:
- In Denmark, UK and Japan due to national programs or specific circumstances, a slightly higher proportion of doses distributed have been used through 2014

Lower bound of the range of estimates:
- For each region/country, the range of doses distributed that were administered will include a conservative estimate that is 10-15% lower than the best estimate for that region/country

As a result, the assumptions of doses distributed that were administered in females were as follows:

	Worldwide	US	EU28	Denmark	Germany	UK	Japan
% Doses Administered	65%-80%	60%-75%	75%-90%	80%-95%	75%-90%	80%-95%	80%-95%

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