PRAC co-rapporteur's referral preliminary assessment report

Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Human papillomavirus (HPV) vaccines

Gardasil: EMEA/H/A20/1421/C/0703/0060

Silgard: EMEA/H/A20/1421/C/0732/0054

PRAC Rapporteur	Julie Williams (UK)
PRAC Co-rapporteurs:	Jean Michel-Dogne (BE) Qun-Ying Yue (SE)
Start of the procedure: Date of circulation of 1st round AR <Date of circulation of 2nd round AR >	9 July 2015 25 September 2015

Timelines for current round of assessment

Date report circulated:	18 September 2015
Deadline for comments:	1 October 2015
<Updated report circulated:>	28 October 2015

Administrative information

INN (or common name) of the active substance(s)	- Gardasil (quadrivalent HPV vaccine (types 6, 11, 16, 18) - Silgard (quadrivalent HPV vaccine (types 6, 11, 16, 18)
Pharmaco-therapeutic group (ATC code)	J07BM01
Pharmaceutical form(s) and strength(s)	All approved: Gardasil Silgard

Co-rapporteur's contact person	[redacted] Tel: [redacted] E-mail: [redacted]
Co-rapporteur's assessors	[redacted] Tel: [redacted] E-mail: [redacted]

Commercially confidential information

Does this AR contain any information which may potentially be considered CCI*? *(e.g. personal data, unpublished studies, info on manufacturing process, other info highlighted as confidential by the MAHs)*	No ☒ Yes ☐ specify type of info and relevant pages:

**Further information on the definition of CCI can be found in EMEA/45422/2006.*

Table of contents

Background information

Human papillomavirus (HPV) vaccines have been authorised in Europe for prevention of cervical and various other cancers caused by HPV infection since 2006. Following approval, these vaccines have been introduced in national immunisation programs worldwide, including in most EU member states.

The efficacy and safety of these medicinal products has been clearly demonstrated and the benefit of these vaccines in protecting against HPV related diseases is well established. Since launch, approximately 55 million subjects are estimated to have been vaccinated with Gardasil worldwide. Cumulative marketing exposure to Cervarix is estimated as being around 17 million subjects worldwide.

Routine surveillance of suspected serious adverse drug reaction reports have raised questions on the potential association between the use of the vaccines and two syndromes in particular, which are known as Complex Regional Pain Syndrome (CRPS) and Postural Orthostatic Tachycardia Syndrome (POTS). The vast majority of the reported cases do not have a well-defined diagnosis. These syndromes have been reviewed repeatedly by the PRAC within routine safety follow up procedures, and a relationship with vaccination has not been established in these previous procedures.

For CRPS most common symptoms are severe pain, swelling and changes in the skin temperature and colour of the arms or legs, but may also include amongst other symptoms headache, general fatigue, coldness of the legs, limb pain and weakness. POTS is characterised by an abnormally large increase in heart rate when changing from a lying down to a standing up position, without any orthostatic hypotension. In POTS, this excessive heart rate increase may be accompanied by a range of symptoms which may include light headedness, visual blurring, palpitations, tremulousness and weakness (especially of the legs), as well as fatigue, shortness of breath, chest pain, concentration difficulties, and headaches.

Individual case reports and case series of CRPS and POTS have been reported in the literature following HPV vaccination from several geographically distinct locations. Literature reports of CRPS come from Australia, Germany and Japan and reports of POTS originate from USA, Japan and Denmark.

There are uncertainties regarding the underlying pathogenesis for CRPS and POTS and an association between HPV vaccination and CRPS or POTS has also not been established. These conditions have been well known for a long time and before the introduction of the HPV vaccines.

It is recognised that these conditions can occur in the general non-vaccinated population and it is considered important to undertake further review to determine whether the number of cases reported with HPV vaccine is greater than would ordinarily be expected.

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.

1. Referral notification

On 9 July 2015 the EC triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and asked the Agency to give its opinion at the latest by 31 July 2016 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.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

2. Assessment

As agreed with the Rapporteur, the following sections are left empty. Assessment of the responses are found in Appendix A.

3. Consultation with expert group

An expert meeting will take place on 21/10/2015(?) to discuss the following issues:

CoRapp SE does not currently have any questions to suggest for the Ad Hoc Expert Meeting. We have not found any scientific issues that remain unclear in the responses from the MAH that would be suitable for consultation.

4. Benefit-risk assessment

The benefit risk of Gardasil has not been suggested to be changed by this referral procedure. For clarity, a benefit risk discussion including the conclusions of this AR is provided below.

Benefits

Beneficial effects

At the time of approval Gardasil was found to be highly efficient in preventing high-grade cervical precancerous lesions (CIN 2/3), and non-invasive cervical cancers (CIN 3/adenocarcinoma in situ (AIS) related to HPV 16 and 18 in a population of women 16-26 years of age. Efficacy has also been demonstrated against persistent HPV 16 and 18 infection. The efficacy has been extrapolated to younger girls based on immune responses. In subsequent studies protection has also been demonstrated against anal premalignant lesions (AIN 2/3), and anal persistent infection in men. Thus, the current indication which reads:

> Gardasil is a vaccine for use from the age of 9 years for the prevention of:
>
> – premalignant genital lesions (cervical, vulvar and vaginal), premalignant anal lesions, cervical cancers and anal cancers causally related to certain oncogenic Human Papillomavirus (HPV) types
>
> – genital warts (condyloma acuminata) causally related to specific HPV types.

is still considered to be supported by clinical study results.

The protective effect has been statistically significant for up to 6 years following vaccination, and immune responses remain on a plateau level for at least 8 years. The exact duration of protection has not yet been determined.

Uncertainties in beneficial effects

The vaccine efficacy against cancers is not possible to determine in clinical studies, as precancerous lesions are screened for, and removed as appropriate. Thus, no cases of cervical or genital cancers are expected in a clinical trial setting. Precancerous lesions related to HPV 16 and 18 are considered a valid surrogate marker for protection against cancer caused by these HPV types. In addition, protection has not been demonstrated in children below 16 years of age, but immunological bridging to this population is considered fully adequate.

Risks

Unfavourable effects

Pyrexia, pain, erythema and swelling at the injection site were the most common local adverse reactions observed in clinical studies, and headach was the most common systemic adverse reaction in clinical studies. The safety profile of Gardasil was considered favourable at the time of approval. For a more detailed description of the safety profile of Gardasil, see section 4.8 of the SPC.

The current referral procedure relates to a safety signal of increased reporting of POTS and CRPS. In conclusion, the available data provides some support for a causal association between injection trauma and CRPS but not for a causal relation between the qHPV vaccine itself and CRPS. It is not considered appropriate with any addition to SmPC regarding a potential risk related to the injection trauma.

Available data does not provide support for a causal relation between the qHPV vaccine and POTS. No changes to the product information or other risk minimisation measures are proposed.

Benefit risk balance

The benefits of Gardasil clearly outweigh the risks. No support for a causal relationship between CRPS and POTS and Gardasil has been found in the safety data from clinical trials, spontaneous reporting and literature searches. There is a possible relationship between the injection trauma and CRPS, but this is not product specific.

5. Recommendations

6. Next steps

7. References

8. Annex 1 Proposed List of Outstanding Issues

Proposed List of Outstanding Issues for adoption by PRAC in October 2015

- **Question 1**

The search for CRPS cases as described by the MAH differs slightly between the clinical study database and the spontaneously reported: I.e. in the clinical study database in group B, hypoaesthesia is also included and in group C skin atrophy is included, while these PTs are not included among the spontaneous reports. The MAH is asked to verify if there was indeed an difference between the search terms, and if so, explain the difference.

- **Question 2**

The search terms for the literature search may be adequate. The MAH should verify that MeSH terms have been used, so that alternative and older terms are also included, such as "Reflex Sympathetic Dystrophy" and "Causalgia" for CRPS and "Orthostatic intolerance" and "Postural Orthostatic Tachycardia Syndrome" for POTS, or that addition of such terms does not add to the references currently identified.

- **Question 3**

The publication Haug et al 2013 is a congress abstract and no subsequent peer-review publication of this case has been identified. The finding on MRI of a small inflammatory focus in direct relation to a nerve in the deltoid muscle is suggestive of direct neural injury from the injection. This report of MRI findings is, however, not present in the literature reference provided (in the reference MRI is reported as normal). The MAH should explain the source of information for these findings.

9. Annex 2 Recommended changes to the product information

10. Annex 3 Proposed Dear Healthcare Professional Communication

Not applicable.

11. Annex 4 Comments received

12. Appendix A Detailed assessment of the MAH's responses

Assessment of the List of Questions adopted by PRAC in July, 2015

The following MAHs submitted responses:

Responses submitted by
Sanofi Pasteur MSD

12.1. CoRapp (SE) EXECUTIVE SUMMARY based on the response concerning the quadrivalent human papillomavirus (qHPV) vaccine (Gardasil®)

The quadrivalent human papillomavirus (qHPV) vaccine has been authorised in Europe for prevention of cervical and various other cancers caused by HPV infection since 2006. These HPV vaccines have been introduced in national immunisation programs worldwide, including most EU member states. Worldwide 190,897,611 doses of qHPV vaccine have been distributed until 31 May 2015, corresponding to more than 63 million individuals exposed (assuming 3 doses per individual).

The focus on the safety evaluation in this referral is on two conditions, the Complex Regional Pain Syndrome (CRPS) and Postural Orthostatic Tachycardia Syndrome (POTS). Both conditions have been assessed in recent PSURs for qHPV but a causal relation has not been inferred based on those evaluations. A critical discussion and summary of the conclusions made based on the MAHs responses to the questions from PRAC in the present referral is provided below for each condition separately. This is followed by a detailed assessment of the MAHs responses to each particular question.

12.1.1. Complex Regional Pain Syndrome (CRPS)

CRPS is a pain syndrome with multifactorial but incompletely characterised pathophysiology involving both central and peripheral mechanisms as well as inflammation and features related to the autonomic nervous system (Bruehl, 2015). CRPS is exclusively diagnosed from clinical signs and symptoms. It is known to be triggered by even low grade trauma, most commonly seen after fractures. CRPS is more common in women. Attempts to estimate incidence in the general population have yielded variable results, likely in part due to differences in diagnostic criteria used. New international consensus criteria from 2012 reduced diagnostic rates with 50%. Paediatric CRPS is overall uncommon, but more common among girls, and similar to the adult population in most cases related to some form of trauma (Walco et al 2010). CRPS has been granted orphan disease status in the EU.

Clinical Trial Data

There were three cases suggestive of CRPS (1 in 9vHPV, 1 in 4vHPV and 1 in placebo) in the clinical trial data base (60,594 subjects with 197,983 person-years follow-up). The case in the 9vHPV vaccine group had a likely onset of symptoms before vaccination. The case in the qHPV group was reported 736 days after vaccination, and the placebo case does not seem to fulfill the criteria for CRPS. Thus, there is no signal of increased risk of CRPS in the clinical trial data base.

Spontaneous reporting

The query of the Company safety data base that includes the Preferred Term (PT) of 'Complex Regional Pain Syndrome' (CRPS) yielded 53 unique medically confirmed reports temporally associated with the administration of qHPV vaccine. A separate query for case reports that include various combinations of symptoms of CRPS ("CRPS Symptom Queries") yielded 37 additional distinct case reports. The case reports are summarized in the table below:

	Based on PT "CRPS"	Based on symptom query
Total	53	37
Serious	30	37
From EU	13	24
From the US	11	11
From Japan	18	1
From Rest of World	11	1
Met case definition criteria	7	0
Partially met criteria	16	6

Literature review

A Japanese article (Kinoshita, Abe et al. 2014) generates the majority of CRPS cases identified in the literature. This article reports cases from one centre but mechanisms for referral/presentation to the centre are not described. Only two of the CRPS cases are described in some detail. Descriptive data relevant specifically for the CRPS cases are limited. The average interval from the first dose of the vaccine to the adverse event was overall in the study population 5.47±5.00 months, i.e. highly variable. It is, however, not clear from the methods description what measure of variability has been used, i.e. if "±5.00" represents the standard deviation, range, or something else. Individual values for time to onset are not presented. This means that it is not possible to compile a description of time to onset from the CRPS cases as presented in the literature.

The literature references describing CRPS in relation to qHPV vaccination are summarized in the table below. As expected, and as described in Richards et al 2012, CRPS may be the consequence of the direct trauma from the intramuscular injection.

Summary table of publications reporting cases of CRPS.

Study type / reference	**Population / setting / exposure**	**Key result / authors conclusion**	**Assessor comment**
Case series (Richards et al. 2012)	5 adolescents from Australia and UK. **4** exposed to HPV vaccine (3 qHPV)	The 4 HPV exposed had TTO of 0, 0, 0, and 4 days, respectively. Symptom resolution was seen within 5, 14, 60, and 201 days, respectively. Intramuscular immunisation is sufficient to trigger the	Harden criteria used. Supported by observations of CRPS following veni-puncture and intravenous drug administration.

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment
		development of CRPS-1, rather than a particular vaccine antigen.	
Case report in congress abstract (Haug et al. 2013)	**1** individual exposed to qHPV	Within 24 hours severe pain, swelling, numbness, and coldness of the right arm and hand. On MRI small inflammatory focus in the right deltoids in the course of the Nervus cutaneous brachialis lateralis.	Suggestive of direct injection trauma as trigger event. Unclear source for information on MRI finding (not in abstract).
Case series (Kinoshita et al. 2014)	15 adolescents from Japan with CRPS. 40 patients in total (**7** exposed to Gardasil, 22 to Cervarix). 3 with CRPS+POTS. 1 with POTS.	15 cases with CRPS. In 2 cases (of 3) morphology results with endoneurial edema and selective degeneration of unmyelinated fibers.	Harden criteria used for CRPS cases. One hospital department, unclear referral /selection mechanism. 5 cases of 40 selected for presentation as "representative". Time to onset not presented for individual cases, only as "5.47±5.00 months", unclear measure of variability.
Abstract *(Kinoshita et al. 2014)*	*48 patients (from same clinic as above and largely overlapping time period). 18 fulfilling the diagnostic criteria for CRPS-I.*	-	*Interpreted as a presentation of cases in the above publication with the addition of a few more cases.*
Abstract *(Kinoshita et al. 2014)*	*17 patients from an unknown time period.*	-	*Interpreted as a subset of cases in the above publication*
Letter to the editor (Martinez-Lavin 2014)	**2** adolescents from Mexico.	Both patients fulfilled the fibromyalgia criteria and were considered fibromyalgia-like illness after HPV immunization.	Unclear if Harden criteria used. Unclear referral /selection mechanism. One of the cases is compatible with CRPS and suggestive of direct trauma by the injection as triggering event. The other case not clearly CRPS.
Paper presented	8 cases from Japan (bivalent type in 5	"Adolescents, especially girls, may experience symptoms that	The cases presented after qHPV exposure are not

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment
at meeting (Okuyama 2014)	and qHPV in **3**)	are pathologically difficult to explain, including pain in the limbs after HPV vaccination. Based on the temporal sequence these are understood to be side effects from the vaccine… rare to satisfy strict diagnostic indices of CRPS"	considered to meet the Harden criteria for CRPS.

12.1.1.1. Discussion on causality - CRPS

The discussion on the potential causal relation has been structured according to Hill's criteria (Rothman, Greenland, Lash 2008). The limitations of such criteria are obvious, but they are used here to provide a framework for presenting the discussion on potential causality.

Strength of the potential association

The few cases reported from RCTs are evenly distributed between the qHPV and placebo groups which does not suggest an association. There are no data from comparative pharmacoepidemiological studies that could provide an estimate of the strength of a potential association between qHPV vaccination and CRPS. CRPS occurs with variable incidence in the general population and while the estimates of background incidence are fraught with uncertainty, the comparison of observed to expected number of spontaneously reported cases does not suggest an increased occurrence of CRPS in relation to vaccination. Also in Japan and Denmark a very low reporting rate (1%) must be assumed in combination with relaxed diagnostic criteria for the observed rate to reach and exceed the expected rate, and even then this is based on very few cases. In summary, currently available data does not indicate a meaningful increase of CRPS incidence in association with qHPV vaccination.

Consistency

Repeated observations in different populations under different circumstances could strengthen the relevance of an observation. In the case of CRPS most of the few cases reported have been from one hospital department in Japan. This is contrasted by the complete lack of reports from most other countries and very few cases from RCTs. This lack of consistency is noted and does not provide support for a causal association.

Specificity

If a cause leads to a single effect or an effect has only one cause, this can be seen as supportive of a causal effect. In the case of CRPS all patients vaccinated with qHPV vaccine are by necessity also simultaneously subjected to the trauma of an intramuscular injection. Development of CRPS has been described following other types of vaccination and veni-puncture from other causes. There are well described cases with pain with paraesthesia immediate after injection, suggestive of injection trauma as a trigger of CRPS.

Temporality (temporal association)

There is no specific pattern among spontaneously reported cases regarding time to onset (TTO) following vaccination. It is often, however, unclear if the TTO refers to time of diagnosis or time of first

symptoms. From the cases presented in the literature the data on TTO is insufficient to allow a detailed analysis, other than that the overall TTO in the key reference (Kinoshita 2014) appears long and variable. Data on temporality does not support a causal relation.

Biological gradient

A dose-response pattern could be supportive for a causal association. For CRPS no specific pattern regarding preferential occurrence after the 1st, 2nd, or 3rd dose can be detected.

Plausibility

Since direct injection trauma is a known potential trigger of CRPS, this is the most obvious mechanistic explanation for a relation between qHPV vaccination and CRPS. There are, however, both preclinical and clinical data suggesting a possible autoimmune mechanism in a subset of CRPS patients (Bruehl, 2015). Pharmacoepidemiological studies trying to identify autoimmune outcomes associated with qHPV vaccination (see summary table below) has until recently been unable to detect any such signal. A recent large French study (unpublished data) was also unable to find an overall association between qHPV and autoimmune conditions with the possible exception of the Guillain-Barré syndrome. There is currently therefore not sufficiently plausible direct or indirect support for a specific autoimmune mechanism.

Summary table (prepared by assessor) of epidemiological studies of qHPV vaccination and autoimmune disease

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment
Cohort Study *(Chao et al 2012)*	Two managed care organizations in California. 189 629 women exposed to qHPV between August 2006 and March 2008.	347 cases sampled for case review. No positive finding except Hashimoto's thyreoiditis (IRR 1.29; 95% CI 1.08-1.56) which was not considered a plausible signal.	Company funded study. Neither CRPS nor POTS (or potentially related symptoms/conditions) were specified outcomes.
Cohort Study *(Arnheim-Dahlström et al 2013)*	Denmark and Sweden. 296 826 women exposed to qHPV October 2006 to December 2010.	Exposure to qHPV significantly associated with Behcet's syndrome, Raynaud's disease, and type 1 diabetes. Each fulfilled only one of three predefined signal strengthening criteria.	Academic study. Authors have received grants from MAHs involved in the referral. Neither CRPS nor POTS were specified outcomes. Outcome "paralysis" studied and lower risk among exposed.
Case–control study *(Grimaldi-Bensouda et al 2014)*	219 specialist centers at hospitals across France, participating in the PGRx programme.	211 definite cases of ADs. Adjusted odds ratio (OR) for any qHPV vaccine use was 0.9 [95% CI 0.5–1.5].	Company funded study. Study size did not allow conclusions on individual ADs. Neither CRPS nor POTS were specified outcomes.

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment
Cohort Study *(Scheller et al 2013)*	Denmark and Sweden (3 983 824 females) 789 082 females aged 10-44 years exposed to qHPV from 2006 to 2013.	Adjusted IRR for MS 0.90 [95%CI 0.70-1.15] and for other demyelinating diseases 1.00 [95%CI 0.80-1.26]	Authors have received grants from MAHs involved in the referral. Neither CRPS nor POTS were specified outcomes.
Nested case–control study *(Langer-Gould et al 2014)*	Kaiser Permanente Southern California (KPSC) members. Exposure to any vaccine (not only HPV)	780 incident cases of multiple sclerosis (MS) or other acquired central nervous system demyelinating syndromes. No association with HPV vaccination (OR 1.05; 95%CI 0.62-1.78). Increased risk of onset within the first 30 days after <u>any</u> vaccination only in younger (<50 years) individuals (OR 2.32; 95%CI 1.18-4.57).	Academic study. Authors have received grants from pharmaceutical companies. Neither CRPS nor POTS were specified outcomes.

Experimental evidence

In the review of clinical trial data a total of 60,594 subjects with 197,983 person-years follow-up were included. The incidence of CRPS was less than 1 case per 10,000 person-years and comparable in the qHPV vaccine and placebo cohorts. The presented cases do not suggest any relationship to vaccination with HPV vaccines. Furthermore, a vaccine exposure cannot generate observations of dechallenge and rechallenge. Experimental evidence is therefore limited and available data does not provide support for a causal association.

Analogy

If data suggest that other similar exposures (in this case vaccines or comparable immune reactions) have been credibly linked to the outcome of interest, this could support a causal association. While some preclinical and clinical data suggest autoimmune mechanisms at least in some cases of CRPS, no such association has been found for any other type of vaccine. For HPV vaccines large pharmacoepidemiological studies have overall been unable to imply association with various autoimmune conditions, with the possible exception for Guillain-Barré syndrome in a recent French study (unpublished data, 2015). For the injection trauma as a potential causal trigger of CRPS there is, however, a reasonably clear association with the development of CRPS. There is consequently support from analogy for an association between injection trauma and CRPS but no substantial support from analogy for a causal link the qHPV vaccine itself and CRPS.

In summary, available data provide some support for a causal association between injection trauma and CRPS but not for a causal relation between the qHPV vaccine itself and CRPS.

Uncertainty about the assessment on risk for CRPS

CRPS is a rare condition, especially in the age group targeted with qHPV vaccination. Our understanding of the pathophysiology of this condition is limited. A particular and unavoidable uncertainty is that injection trauma in itself is a plausible trigger for CRPS, meaning that all cases are confounded by injection trauma in an assessment of any potential direct relation between the qHPV vaccine and CRPS. The data on TTO is also very limited, often being unclear whether it refers to time of diagnosis or time of first symptoms.

The search terms used in the literature search may be adequate. The MAH should, however, verify that MeSH terms have been used, so that alternative and older terms are also included, such as "Reflex Sympathetic Dystrophy" and "Causalgia".

Conclusion CRPS

Available data provides some support for a causal association between injection trauma and CRPS but not for a causal relation between the qHPV vaccine itself and CRPS. It is not considered appropriate with any addition to SmPC regarding a potential risk related to the injection trauma.

12.1.2. Postural Orthostatic Tachycardia Syndrome (POTS)

POTS is a clinical syndrome usually characterised by (Sheldon 2015):

- frequent symptoms that occur with standing, such as light-headedness, palpitations, tremor, generalized weakness, blurred vision, exercise intolerance, and fatigue;
- an increase in heart rate of ≥30 beats per minute (bpm) when moving from a recumbent to a standing position (or ≥40 bpm in individuals 12 to 19 years of age); and
- absence of orthostatic hypotension (>20 mm Hg drop in systolic blood pressure).

The prevalence of POTS is approximately 0.2%, with little variance among published reports. Most patients present with POTS between the ages of 15 and 25 years, and more than 75% are female. The syndrome is not well defined. There is not an obvious correlation between the POTS diagnosis, autonomic function, and symptoms, as noted in prospective studies on healthy individuals (Gibbons et al 2014, Corkal et al 2014, Lin et al 2014). In the study by Lin et al on 600 healthy school children 7-18 years old 6.8% were diagnosed with POTS. Supine HR, daily water intake and sleeping hours to some extent predicted the POTS diagnosis.

The treatment of POTS is difficult; there are no therapies that are uniformly successful, and combinations of approaches are often needed (Sheldon 2015). The perception is that POTS is a chronic condition with no known mortality, and with eventual improvement.

Clinical Trial Data

No cases suggestive of POTS were identified in the clinical trials in the qvHPV or placebo groups. Two cases were reported in the 9vHPV group. However, one case did not fulfill the criteria for POTS, and for the second case it is unclear how long time had passed between vaccination and onset of symptoms, making a causality assessment difficult.

Spontaneous reporting

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 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 30 distinct case reports (excluding those that contained POTS as PT) reported as temporally associated with the administration of qHPV vaccine.

	Based on PT "POTS"	Based on symptom query
Total	83	30
Serious	72	15
From EU	48	15
From the US	28	13
From Japan	4	2
From Rest of World	3	0
Met case definition criteria	33	0
Partially met criteria	10	3

Literature review

Literature references reporting cases of POTS in relation to qHPV vaccination are summarised in the table below. The majority of cases described in the literature review are from one Danish centre. These reports have notable limitations when causality assessment is attempted:

- The overall distribution of TTO and the relation between TTO and clinical presentation is not assessable since patients where TTO is longer than 2 months or uncertain have been excluded from the study.
- A further bias of the distribution of TTO is the fact that patients have been referred with a particular suspicion of association with the qHPV vaccination. This would be expected to cause a selection bias when the TTO distribution is analysed.
- Apart from the tilt-table test there is no reporting of further examination results or investigations that would be expected based on the nature of the symptoms reported by the patients. Clinical description of severe symptoms such as new onset, continuous and debilitating headache, blurred vision, cognitive dysfunction, motor symptoms including limb weakness (in six cases leading to invalidity) are not accompanied by results from thorough clinical neurological, neurophysiological, and neuroradiological examinations. Given the poor understanding of the pathophysiology such results would have been of great interest.

Apart from the Danish reports and a US case series (Blitshteyn 2014), these references provide minimal data to inform a causality assessment.

Summary table (prepared by assessor) of publications reporting cases of POTS.

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment
Case series (Blitshteyn et al. 2014)	**6** patients in the US (qHPV). Unclear referral /selection mechanism.	Symptoms 6 days to 2 months following HPV vaccination. 3 patients also experiencing NCS. 3 patients with small fibre neuropathy.	Brief descriptions but seemingly thoroughly evaluated patients. Very weak evidence for small fibre neuropathy. One patient with fluctuation of symptoms temporally related to repeated exposure.
Case series (Kinoshita et al. 2014)	15 adolescents from Japan with CRPS. 40 patients in total (7 exposed to Gardasil, 22 to Cervarix). **3** with CRPS+POTS. **1** with POTS. One hospital department, unclear referral /selection mechanism.	4 cases of POTS. 2 cases presented in more detail, none of those strictly fulfilling POTS criteria.	Overall in the case series 5 cases of 40 selected for presentation as representative. Time to onset not presented for all individual cases, only as "5.47±5.00 months".
Brief report (unclear context) (Ikeda 2014)	Apparently from the same population described in Kinoshita et al 2014a above	The author strongly opposes the opinion of the specialist group of the Japanese 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.	No new data that can support a causality assessment.
Case series (abstract) (Kinoshita et al. 2014b)	Appears to be mainly the same patients being reported in Kinoshita et al 2014a above.	-	No new data that can support a causality assessment.
Case report (Tomljenovic et al 2012)	2 adolescents in the US (qHPV)	Post-mortem brain tissue specimens from two young women who suffered from cerebral vasculitis type symptoms following vaccination with qHPV.	No direct link to POTS. Cannot support a causality assessment.
Case series (Brinth et al. 2015a)	53 patients in Denmark included (out of 75 referred for suspected side effects to qHPV	A close chronologic association to the vaccination observed. POTS should probably be looked upon as a symptom secondary to another yet unidentified	Temporal association not possible to evaluate since patients with longer TTO were excluded. Symptoms not supported by clinical

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment
	vaccination), **38** diagnosed with POTS.	condition rather than as a disease entity of its own. Patients experienced the same degree and pattern of symptoms regardless of the POTS diagnosis.	examination and objective findings. Long and variable delay between the onset of symptoms and orthostatic testing.
Case series (Brinth et al. 2015b)	**35** women in Denmark (exposed to qHPV).	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.	As above. The case presented confounded.
Case report (Tomljenovic et al 2014)	**1** girl in US (qHPV)	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 case is considered confounded based on the data available. Severe neurological symptoms are reported but not accompanied by relevant examinations.

12.1.2.1. Discussion on causality - POTS

The discussion on the potential causal relation has been structured according to Hill's criteria (Rothman, Greenland, Lash 2008). The limitations of such criteria are obvious, but they are used here to provide a framework for presenting the discussion on potential causality.

Strength of the potential association

The few cases reported from RCTs do not suggest an imbalance between the qHPV and placebo groups and does not suggest an association. There are no data from comparative pharmacoepidemiological studies that could provide an estimate of the strength of a potential association between qHPV vaccination and POTS. POTS has been prevalent in the general population for many decades before start of HPV vaccinations, more common among adolescent and young women. While the estimates of background incidence are fraught with uncertainty, the comparison of observed to expected number of spontaneously reported cases do not suggest an increased occurrence of POTS in relation to vaccination, with the notable exception of Denmark. Danish data suggests an observed rate above what would be expected, but this pattern is not seen in other countries.

Consistency

Repeated observations in different populations under different circumstances could strengthen the relevance of an observation. In the case of POTS most of the cases reported have been from one hospital department in Denmark. This is contrasted by the very few reports from most other countries and very few cases from RCTs. The concentrated reporting within Denmark could at least partly be explained by referral patterns and POTS being a diagnosis where regular health care services have

limited experience. The lack of consistency does not have a clear biological rationale, and does not provide support for a causal association.

Specificity

If a cause leads to a single effect or an effect has only one cause, this can be seen as supportive of a causal effect. POTS presents a particular problem from this perspective, being a poorly defined condition with unclear pathophysiology, and little knowledge available on risk factors. This hampers the causality assessment.

Temporality

As for CRPS, no specific pattern of reported TTO or risk window can be seen. It is often, however, unclear if the TTO refers to time of diagnosis or time of first symptoms. From the cases presented in the literature the data on TTO is biased since most cases have been referred based on a specific suspicion of an adverse effect from qHPV vaccination and exclusion of cases with TTO >2 months. Data on temporality is therefore not reliable and does not support a causal relation.

Biological gradient

A dose-response pattern could be supportive for a causal association. For POTS no specific pattern regarding preferential occurrence after the 1st, 2nd, or 3rd dose can be detected.

Plausibility

The potential mechanistic link between qHPV vaccination and POTS is unknown. The pathophysiology behind POTS is poorly understood. There is some evidence of a potential autoimmune mechanism at least in a small subset of the patients (Thieben 2007). Pharmacoepidemiological studies trying to identify autoimmune outcomes in general associated with qHPV vaccination (see summary table above) have until recently been unable to detect any such signal. A recent large French study (unpublished data) was also unable to find an overall association between qHPV and autoimmune conditions with a possible exception for the Guillain-Barré syndrome. There is currently therefore not sufficiently plausible direct or indirect support for a specific autoimmune mechanism.

Experimental evidence

In the review of clinical trial data a total of 60,594 subjects with 197,983 person-years follow-up were included. The incidence of POTS was less than 1 case per 10,000 person-years and did not suggest an imbalance between the qHPV vaccine and placebo cohorts. The presented cases do not suggest any relationship to vaccination with HPV vaccines. In addition, a vaccine exposure cannot generate observations of dechallenge and rechallenge. Available experimental type of evidence is limited and do not provide support for a causal association.

Analogy

If data suggest that other similar exposures (in this case vaccines or comparable immune reactions) have been credibly linked to the outcome of interest, this could support a causal association. While some data suggests autoimmune mechanisms at least in some cases of POTS, no such association has been found for any other type of vaccine. For HPV vaccines large pharmacoepidemiological studies have overall been unable to imply association with various autoimmune conditions, with the possible exception for Guillain-Barré syndrome in a recent French study (unpublished data, 2015). There is consequently no support from analogy for a causal link the qHPV vaccine itself and POTS.

In summary, available data does not provide support for a causal relation between the qHPV vaccine and POTS.

Uncertainty about the assessment on risk for POTS

There are several factors contributing to uncertainty in the evaluation of a potential causal link between qHPV vaccination and POTS. The syndrome is not well defined which provides an obvious difficulty in the interpretation of case reports but this would also constitute a severe obstacle to attempts to a comparative pharmacoepidemiological study. The apparently poor correlation between symptoms and the current definition is further evidence for that. The fact that reporting is highly concentrated to one country is also difficult to explain from a biological or mechanistic perspective.

Conclusion POTS

Available data do not provide support for a causal relation between the qHPV vaccine and POTS. No changes to the product information or other risk minimisation measures are proposed.

12.2. 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 (summary)

12.2.1. Clinical Trial Data

Clinical Studies Included in the Review

The MAH has reviewed data from all clinical studies of the qHPV vaccine (V501 clinical program, 10 studies) and 9vHPV vaccine (V503 clinical program, 7 studies) 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). A total of 60,594 subjects with 197,983 person-years follow-up were included.

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.

Assessor's comment: The clinical study database is extensive. Although the reasons for excluding the local registration studies with qHPV vaccine are not understood, it seems unlikely that they would provide sufficient data to alter the overall picture considering that they are likely to include limited numbers of subjects.

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). This case definition was the subject of a more recent paper in 2010 which further validated its use. 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.

Assessor's comment: The search criteria used are in agreement with the Budapest criteria as described by Harden et al.

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 I

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 and Sheldon 2015 as well as Jarjour 2015 and Freeman (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)

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 4^{th} and 5^{th} 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.

Assessor's comment: It is agreed that this case most likely had an onset before the first dose of vaccine, and therefore can be considered unrelated to vaccination.

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.

Assessor's comment: The time to onset is almost 2 years after the last dose of qHPV vaccination, which makes it less likely to be caused by the vaccination. Symptoms of CRPS are more likely to appear in closer relation to the vaccination. It is not known whether the adverse reactions immediately following vaccination, especially dose 3, resolved before the onset of symptoms of CRPS.

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.

Assessor's comment: This case does not appear to fulfill the criteria for CRPS based on the above information, considering the rapid recovery of symptoms.

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.

Assessor's comment: It is agreed that this case does not appear to fulfill the criteria for POTS.

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 [redacted] 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.

Assessor's comment: The referral to a specialist unit and diagnosis, occurred a long time after the last vaccine dose, and it is unclear when symptoms first appeared. This makes a causality assessment much more difficult.

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 [redacted] 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.

Assessor's comment: This case cannot be evaluated since it is unclear if it is verified whether the subject was given vaccine or placebo, in the study. It is possible that the case fulfills the criteria for POTS, but sufficient information is not available.

Assessor's overall comment on clinical trial data

There were three cases suggestive of CRPS (1 in 9vHPV, 1 in 4vHPV and 1 in placebo) in the clinical trial data base. The case in the 9vHPV vaccine group had a likely onset of symptoms before vaccination. The case in the qHPV group was reported 736 days after vaccination, and the placebo case does not seem to fulfill the criteria for CRPS. Thus, there is no signal of increased risk of CRPS in the clinical trial data base.

There were two cases of POTS reported in the clinical trials, both in the 9vHPV group. However, one case did not fulfill the criteria for POTS, and for the second case it is unclear how long time had passed between vaccination and onset of symptoms, making a causality assessment difficult.

The available data exclude a large risk of CRPS and POTS based on the available clinical trial data base comprising a total of 60,594 subjects with 197,983 person-years follow-up. However, a smaller risk cannot be excluded based on these data.

12.2.2. Post marketing data

12.2.2.1. 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 above.

Assessor's comment: The search as described by the MAH differs slightly between the clinical study database and the spontaneously reported: I.e. in the clinical study database in group B, hypoaesthesia is also included and in group C skin atrophy is included, while these PTs are not included among the spontaneous reports. The MAH is asked to verify if there was indeed a difference between the search terms, and if so, explain the difference.

The cases were evaluated as the clinical study database cases (see description above).

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 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 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, [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 the response document from the MAH.

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 cases are not included in Table 3.

Table 3. Post-marketing case reports with PT of Complex Regional Pain Syndrome: Application of the 4 diagnostic criteria for CRPS type 1
(Assessor's comment: The table is summarised in this AR, please see MAH response for further details.)

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]	[redacted]	17, F	Chest pain	Y	Y	No	Y	Y	Y	ethinyl estradiol (+) etonogestrel	Day 15 (1) which was also Day 7 post onset of URI symptoms.
Y			14, F	Y	Y	Y	No	Y	Y	Y	No concomitant therapies	5 months (2) Not recovered at 6 months.
Y			17, F	Y	Y	Y	Y	Y	Y	Y	Depo- Provera Meningococcal vaccine	~Day 50 (2) Outcome not reported
Y			14,F	Y	Y	Y	Y	Y	Y None reported	Y	None reported	Onset of wrist pain 12 days post dose 1; Diagnosed with CRPS Day 137 post dose 2.
Y	Literature		14, F	Y	Y	Y	Y	Y	Y None reported	Y	None reported	24 hours (1) Condition improving.
Y	[redacted]		13/ F	Y	Y	Y	Y	No	Y	Y	None	Day 38 (dose 2)
Y			11, F	Y	Y	Y	Y	Y	None reported	Y	None reported	Day 5 (dose 3). Follow up did not reveal any new clinical data.
P	Literature		15, F	Y	Y	Y	No	Y	No	No MRI brain normal	Not reported	within hours post vaccination (3) Treated with analgesics,

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 #)
												physiotherapy, hydrotherapy and psychological therapy. Recovered
P	[redacted]	[redacted]	15, F	Y	Y	Y	No	No	No previous medical history	Y	Not reported	1- 2 weeks (2) Treated with analgesics/ corticosteroids; Partial recovery; rt thumb still affected.
P			NR, NR	Y	Y	Y	Y	No	Not reported	No	Not reported	Immediate (2) Recovered in 5 days
P			15, F	Y	No	Y	Y	No	Goitre(C) Hypothyroidism(P) Depression (P) Drug hypersensitivity(C)	Y	meningococcal vax and hep A vax in opposite arm from qHPV dose 1; events occurred after dose 2 of qHPV.	Not reported (2)
P			12, F	Y	Y	Ys	Y	No	None	No	DPT same arm same date as qHPV vaccine; Meningococcal vaccine lt arm same date as qHPV vaccine	Day 2 (1) Outcome unknown
P			17, F	Y	No	No	Y	Y	No	MRI, CT,	Oral BCP and	Within 24 hours

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 #)
									Had concurrent strept illness and received penicillin shot prior to start of LE pain.	bone scan revealed fluid on hip Dx; CRPS	Penicillin as treatment med	(1) which was also ~ 12 hours post penicillin IM for strept infection; Outcome = recovering
P	[redacted]	[redacted]	17, F	Y	No	Y	Y	No	Not reported	No	Not reported	Day 15 (2)
P	Literature		13, F	Y	Y	Y	Y	No	Not reported	N	Not reported	immediately (2) Treatment: exercises. Recovered in 5 days
P	[redacted]		12, F	Y nd	Y	Y	No	Y	Not reported	No N	Not reported	2-3 minutes (1) Recovered; Negative rechallenge post dose 2 was reported.
P			12,F	Y	Y	Y	Y	Y	No	No	Not reported	Day 8 (1)
P	Literature POTS also coded		11, F	Y	No	Y	Y	No		No	None reported	7 months (dose 1) The patient recovered from all events.
P	[redacted]		9/ F	Y	Y	No	No	.	Not reported	Not reported	Not reported	2 months (3) Treated with opioids, immobilization

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 #)
												of foot; spinal electrical stimulus implant
P	[redacted] Literature	[redacted]	15, F	Y	Y	Y	Not reported	Y	Not reported	Not reported;	Not reported	Not reported; Outcome is unknown after several attempts to obtain follow-up.
P	[redacted] Literature		18, F	Y	Y	Y	Not reported	Y	Not reported	Not reported	Not reported	Not reported.
P	[redacted]		13, F	Y	Y	Y	Y	Y	No	No	Not reported	Day 4 post dose 1; Patient recovered from CRPS and pseudo cerebri tumor.
P	[redacted]		12, F	Y	Y	Y	Y	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.

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 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 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.

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

(Assessor's comment: The table is summarised in this AR, please see MAH response for further details.)

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]	[redacted]	27/ F	Y	Y	Y But reported in conjunction with fever.	No	Y	N	Y	Not reported	Day 4 (2)
P			13/ F	Yes ;	Y	No	Y	Y	No .	No	Not reported	3 months (3)
P			22/ F	Y	Y	Y	No	Y	No	No	Not reported	Day 1 (NR)
P			13/ F	Y	Y	Y	No	Y	No	Y	None	Day 33 (3) Recovered
P			12/ F	Y	Y	Y	No	Y	No	No	Not reported	9 months (2) Recovering from muscle pain
P			14, F	Y	Y	Y	Y	Y	No	No	Not reported	Not reported (3) Recovered

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 [redacted]	<1 case
Denmark			~4 cases [redacted]	42 cases
Japan			29 cases [redacted]	~2 cases

MAH 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.

Assessors' comment: The MAH has made an extensive database search for spontaneously reported cases, and the classification of cases as fulfilling the agreed criteria for CPRS, partially fulfilling them, or not being CPRS is agreed. See responses to remaining PRAC questions for conclusions on observed vs expected analyses, possible mechanism and possible causality.

12.2.2.2. 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). The 8 groups of PTs and the queries run were identical to the one for the clinical study data base search.

The cases were identified as described above for the clinical study database evaluation.

Assessor's comment: The search and evaluation strategy is considered acceptable.

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 to the MAH responses.

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	TTO of POTS symptoms relative to vaccination
Y	[redacted]	[redacted]	21 Years Female	Y	Y	Y	Y	28 days after D1
Y	[redacted]	[redacted]	18 Years Female	Y	Y	Y	Y	Same day after D1
Y	Literature	[redacted]	20 Years Female	NR	Y	Y	Y	2 weeks after D1
Y	[redacted]	[redacted]	23 Years Female	Y	Y	Y	Y	7 months after D2
Y	[redacted]	[redacted]	24 Years Female	Y	Y	Y	Y	Same day after D2
Y	[redacted]	[redacted]	12 Years Female	Y	Y	Y	Y	14 days after D3
Y	[redacted]	[redacted]	28 Years Female	Y	Y	Y	Y	TTO=NR after D2
Y	[redacted]	[redacted]	31 Years Female	Y	Y	Y	Y	1 day after D2
Y	[redacted]	[redacted]	23 Years Female	Y	Y	Y	Y	TTO=NR after D2
Y	[redacted]	[redacted]	23 Years Female	Y	Y	Y	Y	TTO=NR after D1
Y	Literature	[redacted]	15 Years Female	Y	Y	Y	Y	1 month after D1
Y	[redacted]	[redacted]	22 Years Female	Y	Y	Y	Y	TTO=same day Dose=NR
Y	[redacted]	[redacted]	13 Years Female	Y	Y	Y	Y	Approximately 12 months after D3
Y	[redacted]	[redacted]	27 Years Female	Y	Y	Y	Y	30 days after D1
Y	[redacted]	[redacted]	12 Years Female	Y	Y	Y	Y	2 days after dose=NR
Y	[redacted]	[redacted]	27 Years Female	Y	Y	Y	Y	2 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	TTO of POTS symptoms relative to vaccination
Y	[redacted]	[redacted]	13 Years Female	Y	Y	Y	Y	107 days after D3
Y			13 Years Female	Y	Y	Y	Y	2 days after dose=NR
Y			32 Years Female	Y	Y	Y	Y	Approximately 4 months after D2
Y			14 Years Female	Y	Y	Y	Y	6 month after D3
Y			29 Years Female	Y	Y	Y	Y	2 days after D2
Y			12 Years Female	Y	Y	Y	Y	TTO=NR after D1
Y			14 Years Female	Y	Y	Y	Y	Approximately 7 months after D3
Y			14 Years Female	Y	Y	Y	Y	Low BP and palpitations started 14 months after D3
Y			12 Years Female	Y	Y	Y	Y	4 days after D3
Y			12 Years female	Y	Y	Y	Y	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	TTO of POTS symptoms relative to vaccination
Y	[redacted]	[redacted]	17 Years Female	Y	Y	Y	Y	Same day as D1
Y			26 Years Female	Y	Y	Y	Y	Approx. 1 month after D2
Y			12 Years Female	Y	Y	Y	Y	TTO=NR D2
Y			12 Years Female	Y	Y	Y	Y	TTO=NR after D3
Y			24 Years Female	Y	Y	Y	Y	37 Days after D3
Y	Literature		14 Years Female	Y	Y	Y	Y	1 week after D1
Y	[redacted]		Not provided- Female	Y	Y	Y	Y	3 months after D3
P			15 Years Female	Y	Y	NR	N	Approx. 3 months after D2
P			16 Years Female	NR	Y	Y	NR	20 Days after D1
P			22 Years Female	Y	Y	Y	N	TTO=NR after D2
P	Literature		11 Years Female	NR	Y	Y	Y	TTO=NR after D1
P	[redacted] Literature		18 Years Female	NR	Y	Y	Y	TTO=NR after D2
P	[redacted] Literature		22 Years Female	NR	Y	Y	NR	TTO=NR after D3
P	[redacted] Literature		12 Years Female	NR	Y	Y	Y	6 days after D2
P	[redacted] Literature		14 Years Female	NR	Y	Y	NR	2 weeks after D1
P	[redacted]		39 Years	NR	Y	Y	N	5 months after D1
P	[redacted]		21 Years Female	Y	Y	Y	NR	TTO and 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.

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.

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 (Table 9). 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.

Table8. . 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
4	32	8 cases have POTS coded, and 24 cases have syncope/pre-syncope coded
5	7	All cases have POTS coded
6	15	13 cases have POTS coded, and 2 cases have syncope coded

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	TTO of POTS symptoms relative to vaccination
P	[redacted]	[redacted]	14 Years Female	NR	NR	Y	Y	Same day after D1
P	[redacted]	[redacted]	13 Years Female	Y	N	Y	NR	200 days after D3
P	[redacted] Literature	[redacted]	14 Years Female	Y	NR	Y	NR	TTO=NR after D1

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 [redacted]	<1 [redacted]
Denmark			91 [redacted]	13 [redacted]
Japan			~7 [redacted]	3 [redacted]

MAH 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, 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.

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.

Assessors' comment: The MAH has made an extensive database search for spontaneously reported cases, and the classification of cases as fulfilling the agreed criteria for POTS, partially fulfilling them, or not being POTS is agreed. See responses to remaining PRAC questions for conclusions on observed vs expected analyses, possible mechanism and possible causality.

12.2.3. Literature Review

12.2.3.1. Complex Regional Pain Syndrome CRPS in the literature in association with receipt of Gardasil

Methods

The MAH carried out a literature review from 01-Jan-2006 through 15-Jun-2015 using literature from Medline PubMed and Embase with additional input from other sources such as local journals.

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. These case reports are also included in the post marketing tables above.

Assessor's comment:
The time period used for the literature search is relevant for the specific question. The search terms may be adequate. The MAH should verify that MeSH terms have been used, so that alternative and older terms are also included, such as "Reflex Sympathetic Dystrophy" and "Causalgia" or that addition of such terms does not add to the references identified **(RSI)**.

Results

Richards S, Chalkiadis G, Lakshman R, et al. Complex regional pain syndrome following immunisation. Archives of disease in childhood 2012;97(10):913-5.

Assessor's comment:
Table 2 from the original publication is provided below as a summary overview of the 5 cases.

Table 2 Complex regional pain syndrome type 1 post-immunisation: patient characteristics, investigations, treatment and outcome

Case	Age (years)	Sex	Vaccine (dose No.)	Co-morbidity	Affected limb	Pain	Sensory disturbances	Vasomotor symptoms	Sudomotor symptoms	Motor symptoms	Investigations (result)	Therapy	Outcome
#1	16	F	4vHPV* (1)	L4/L5 disc prolapse, polycystic ovarian syndrome (PCOS)	Left arm	Yes	Numbness, paraesthesia	Skin temperature↓	No	Paralysis of left arm and leg, absent reflexes left arm, limited range of movement	MRI brachial plexus, brain and spinal cord —normal Nerve conduction studies—normal	Physiotherapy, mobilisation, carbemazepine, amitryptyline	Resolution of symptoms
#2	13	F	4vHPV (2)	Hashimoto thyroiditis	Left arm	Yes	Allodynia, numbness	Dusky discolouration	Oedema	No	Nil	Physiotherapy	Resolution of symptoms
#3	15	F	4vHPV (3)	Infrequent episodic asthma, chronic fatigue syndrome, food allergies	Left arm	Yes	Numbness, paraesthesia, ↓ light touch sensation	Skin temperature↓	No	Pain on movement, weakness of left arm	MRI brain—normal	Physiotherapy, hydrotherapy, simple analgesia, psychology	Resolution of symptoms
#4	12	F	2vHPV† (3)	Headaches	Left arm	Yes	Paraesthesia	Dusky discolouration, skin temperature ↓	Oedema	Weakness of left arm, limited range of movement	MRI brain—normal	Physiotherapy, analgesia, psychology	Resolution of symptoms
#5	15	M	dTap‡ (booster)	Migraine, enuresis	Left arm, left leg	Yes	No	Dusky discolouration	No	Pain on movement	MRI brain—normal EMG—normal Ultrasound (left arm) —normal Hip plain radiograph —normal	Steroids, antibiotics, amitryptyline, gabapentin, opioids, physiotherapy	Ongoing symptoms

*4vHPV—quadrivalent human papillomavirus vaccine (Gardasil—(CSL/Merck)).
†2vHPV—bivalent human papillomavirus vaccine (Cervarix—(GSK)).
‡dTap—diphtheria, tetanus and acellular pertussis (Boostrix—(GSK)). GSK, GlaxoSmithKline.

In the case of a *16-year-old female (*[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.

MAH 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. 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.

A *13-year-old girl (*[redacted]*)* 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.

MAH 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* ([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.

MAH 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.

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.

Assessor's comment:

Three of the four cases exposed to HPV (3 to 4vHPV and 1 to 2vHPV) had immediate reactions including distal paresthesias in the injection arm, suggesting direct neural injury at the time of injection. The fourth case developed symptoms from day 4 which resolved within 2 weeks. It is acknowledged that this case appears confounded. The cases suggest that the injection trauma may trigger CRPS but a specific causal link to vaccine exposure is not supported. This is in line with the authors' conclusion "that it is the process of a needle penetrating the skin that is the trigger, rather than a particular vaccine antigen or adjuvant being causally related."

Haug V, Hauke K, Hofmann C. Complex regional pain syndrome I following vaccination against human papillomavirus. Neuropediatrics, 2013:PS23_1083.

One case ([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. 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.

MAH 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.

Assessor's comment:
The publication is a congress abstract and no subsequent peer-reviewed publication of this case has been identified. The finding on MRI of a small inflammatory focus in direct relation to a nerve in the deltoid muscle is suggestive of direct neural injury from the injection. This report of MRI findings is, however, not present in the literature reference provided (in the reference MRI is reported as normal). The MAH should explain the source of information for these findings **(RSI)**.

Kinoshita T, Abe RT, Hineno A, et al. Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine. Internal medicine 2014;53(19):2185-200.

40 subjects were enrolled in the 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. 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.

Assessor's comment:
Table 4 from the original publication is provided below as a summary overview of 29/40 patients with sympathetic nerve dysfunction.

Table 4. Summary of Clinical Picture in 29 Girls Showing Obvious Sympathetic Nerve Dysfunction

Patient No.	Age	Type of vaccine	Initial symptom	Headache	Limb pain	Limb paresis	Limb tremors	Gait disturbanc	Decreased skin temperature in toe	Hyperpathy	Over sweating	CRPS (Japan)	CRPS (IASP)	OD	OH	POTS
[redacted]	13	G	Fatigue	+	+	-	-	-	n.e.	-	-	-	-	+	+	-
	13	G	Fever	+	+	+	+	+	-	-	-	-	+	+	-	+
	13	G	Headache	+	+	+	+*	+	-	-	-	-	+	+	+	-
	13	C	Hyperventilation	+	+	+	+*	+	-	+	-	-	+	+	-	-
	14	G	Headache	+	-	-	-	-	+	-	-	-	-	+	-	-
	15	C	Headache	+	-	+	-	+	n.e.	-	-	-	-	+	-	-
	15	G	Headache, nausia, fever	+	+	+	-	+	+	+	-	-	+	+	-	-
	15	C	Pain in eye ball, double vision	+	+	+	+*	+	+	-	-	-	+	+	+	-
	15	C	Fever	-	-	+	+	-	-	-	-	-	+	-	-	-
	15	C	Headache	+	+	-	+	-	+	-	+	+	+	+	+	-
	15	C	Limb pain	-	+	-	+	-	+	-	-	-	+	+	-	+
	15	G	Limb pain and weakness	+	+	+	+	-	+	+	+	+	+	+	-	+
	16	C	Limb pain	-	+	-	-	+	n.e.	-	-	-	+	-	-	-
	16	C	Limb pain	+	+	+	-	+	-	+	-	-	+	-	-	-
	16	C	Fatigue	+	-	+	-	+	-	-	-	-	-	+	-	+
	16	C	Limb weakness	-	+	+	+	+	-	-	-	-	+	-	-	-
	16	C	Arthralgia	-	+	-	+	-	-	+	-	-	+	+	+	-
	16	C	Arthralgia	-	+	+	-	+	-	+	-	-	+	-	-	-
	16	C	Fatigue, difficulty in getting up	-	-	-	-	-	+	-	+	-	-	+	+	-
	17	C	Arthralgia	+	+	-	-	-	-	-	-	-	-	+	-	-
	17	C	Limb pain and weakness, paresthesia	+	+	+	+	-	+	+	-	-	+	+	-	-
	17	C	Nausea	+	-	-	+	-	-	-	+	-	-	+	-	-
	18	G	Fatigue, limb paresthesia	+	-	+	-	+	-	-	-	-	-	+	+	-
	18	C	Headache	+	-	-	-	-	+	-	-	-	-	+	-	-
	18	C	Fever, gait disturbance	+	-	+	-	+	-	+	-	-	+	+	-	-
	18	C	Abdominal pain	+	-	-	-	-	+	-	-	-	-	+	-	-
	18	C	Difficulty in getting up	+	+	-	+	-	n.e.	+	+	+	+	+	+	-
	19	C	Syncope	+	-	+	-	+	n.e.	-	-	-	-	+	-	-
	19	C	Abdominal pain	+	+	+	-	+	+	+	+	+	+	+	-	-
Total number	29			19	17	16	12	14	11	10	6	4	18	24	8	4

G: Gardasil®, C: Cervarix®, CRPS: complex regional pain syndrome, IASP: international association for the study of pain, OD: orthostatic dysregulation, OH: orthostatic hypotension, POTS: postual orthostatic tachycardia, n.e.: not examined, *: limb tremors that could be observed at our examinations. Decreased skin temperature in 1st toe is defined as lower level than examination room temperature kept at 23-25°C.

The following 2 case reports describe patients who received qHPV:

A *15-year-old* [redacted] *girl* ([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 1½ 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° in the right first toe and 31.1° in the right second finger at a room temperature of 27.0°, 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. 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.

MAH 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 1½ 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.

Assessor's comment:
The rationale for the CRPS diagnosis is not entirely clear from the description provided. A rise in heart rate of 39 is not strictly fulfilling the consensus POTS criteria (Sheldon 2015) for this age category. The very transient symptoms immediately following vaccination and the delayed development of symptoms do not support a causal association between vaccination and these late symptoms.

A *13-year-old girl* ([redacted]) (Case 3, serial patient number 2) 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°) 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°, 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. Her skin temperature was 28.8° in the right first toe and 30.8° in the right second finger at a room temperature of 23.5°, 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 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.

MAH 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.

Assessor's comment:

Patient referred to the authors' hospital 9 months following the 3rd dose of Gardasil (and 16 months after the 1st dose). Symptoms developed two weeks following the 1st dose. Symptoms were numerous and variable over time. The rationale for the CRPS diagnosis and the details in the clinical picture in that respects is not entirely clear from the description in the publication. A rise in heart rate of 35 is not strictly fulfilling the consensus POTS criteria (Sheldon 2015) for this age category. The protracted time course and complicated and variable clinical picture does not contribute substantially to a case-based causality assessment.

The publication is from a peer-reviewed journal. Financial support was provided by the Japanese Government. Overall this article reports cases from one centre but it is difficult from the description to understand details regarding mechanisms for referral/presentation to the centre. Only two of the CRPS cases are described. Descriptive data for the cases are limited. The average interval from the first dose of the vaccine to the adverse event was overall 5.47±5.00 months, i.e. highly variable. It is, however, not clear from the methods description what measure of variability has been used, i.e. if "±5.00" represents the standard deviation, range, or something else. Individual values for time to onset are not presented.

The results from pathological examinations are presented for 3 cases, two diagnosed with small fiber neuropathy based on signs of injury to thin, unmyelinated nerve fibers. The methodology appears appropriate and the findings support the CRPS diagnosis in these cases. The findings do not, however, provide any support for a causal relation with the qHPV vaccine.

The MAH also reviews two presentations made by the authors of this publication, both mainly interpreted as referring to the data in the publication. These presentations are further discussed below in relation to POTS.

Martinez-Lavin M. Fibromyalgia-like illness in 2 girls after human papillomavirus vaccination. Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases 2014;20(7):392-3.

The first case ([redacted]) describes an *11-yr-old girl* who 11 months after receiving a single injection of qHPV started a new 3-dose regimen. 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. Severe paresthesias were also present. The patient developed insomnia and profound fatigue, and became unable to attend school. There was no history of trauma or psychiatric or family problems. 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. Widespread pain and paresthesias persisted seven months after the onset of her illness. Lumbar puncture, encephalogram, magnetic resonance and electromyography 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 ([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. 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.

MAH 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.

Assessor's comment:
The publication is a letter to the editor and consequently not a peer-reviewed research report. The 1st case suggests a direct neural injury at the time of injection and the described symptomatology appears compatible with CRPS, with the injection itself is a plausible trigger. The 2nd case describes severe neck pain 4 weeks after vaccination developing into pain and paresthesias in all extremities. This patient has a family history of spondyloarthropathy. A diagnosis of CRPS is not obvious in the second case based on the limited information available. In conclusion, one of the cases is compatible with CRPS and suggestive of direct trauma by the injection as triggering event. Apart from that the publication does not contribute substantially to a causality assessment.

Okuyama N. Complex Regional Pain Syndrome (CRPS) occurring after HPV vaccination. Paper presented at Academic Meeting of the Pediatric Association; 2014 Nov 18; Yamato, JP.

Summary of 8 cases of Complex Regional Pain Syndrome (CRPS) due to HPV vaccine (bivalent type in 5 and qHPV in 3) in adolescent females, with the triggering event being the first injection of vaccine in 3 cases and the second injection in 5 cases. The first of the 3 qHPV-associated cases was a *12-year-old female* [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.

MAH 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.

Assessor's comment:
The case presentation does not provide clear criteria to support a diagnosis of CRPS. It consequently does not add substantial information to support a causal association between HPV vaccination and CRPS.

In the second case ([redacted]) only limited information was provided. A *12- year-old female* received qHPV (dose #1) and [redacted] encephalitis vaccine, and immediately after the vaccination felt pain. 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.

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

Assessor's comment:
The case presentation does not provide clear criteria to support a diagnosis of CRPS. It consequently does not add substantial information to support a causal association between HPV vaccination and CRPS.

The third case report ([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 (selfneglect 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.

MAH 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.

Assessor's comment:
The case presentation does not provide clear criteria to support a diagnosis of CRPS. It consequently does not add substantial information to support a causal association between HPV vaccination and CRPS.

MAH Discussion and Conclusion on the literature cases of CRPS

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.

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.

Assessor's comment:
The MAHs conclusions regarding cases of CRPS identified from the literature are overall endorsed.

The Japanese paper by Kinoshita et al generates the majority of CRPS cases in the literature. This article reports cases from one centre but the mechanisms for referral/presentation to the centre are not sufficiently described. Only two of the CRPS cases are described. Descriptive data relevant for the

CRPS cases are limited. The average interval from the first dose of the vaccine to the adverse event was overall in the study population 5.47±5.00 months, i.e. highly variable. It is, however, not clear from the methods description what measure of variability has been used, i.e. if "±5.00" represents the standard deviation, range, or something else. Individual values for time to onset are not presented. This means that it is not possible to compile a description of time to onset from the CRPS cases in the literature.

Summary table (prepared by assessor) of publications reporting cases of CRPS.

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment
Case series (Richards et al. 2012)	5 adolescents from Australia and UK. **4** exposed to HPV vaccine	The 4 HPV exposed had symptom resolution within 5, 14, 60, and 201 days, respectively. Intramuscular immunisation is sufficient to trigger the development of CRPS-1, rather than a particular vaccine antigen.	Harden criteria used. Supported by observations of CRPS following veni-puncture and intravenous drug administration.
Case report in congress abstract (Haug et al. 2013)	**1** individual exposed to qHPV	Within 24 hours severe pain, swelling, numbness, and coldness of the right arm and hand. On MRI small inflammatory focus in the right deltoids in the course of the Nervus cutaneous brachialis lateralis.	Suggestive of direct injection trauma as trigger event. Unclear source for information on MRI finding (not in abstract).
Case series (Kinoshita et al. 2014)	15 adolescents from Japan with CRPS. 40 patients in total (**7** exposed to Gardasil, 22 to Cervarix). 3 with CRPS+POTS. 1 with POTS.	15 cases with CRPS. In 2 cases (of 3) morphology results with endoneurial edema and selective degeneration of unmyelinated fibers.	Harden criteria used for CRPS cases. One hospital department, unclear referral /selection mechanism. 5 cases of 40 selected for presentation as "representative". Time to onset not presented for individual cases, only as "5.47±5.00 months", unclear measure of variability.
Abstract *(Kinoshita et al. 2014)*	*48 patients (from same clinic as above and largely overlapping time period). 18 fulfilling the diagnostic criteria for CRPS-I.*	-	*Interpreted as a presentation of cases in the above publication with the addition of a few more cases.*
Abstract *(Kinoshita et al. 2014)*	*17 patients from an unknown time period.*	-	*Interpreted as a subset of cases in the above publication*
Letter to the editor (Martinez-Lavin 2014)	**2** adolescents from Mexico.	Both patients fulfilled the fibromyalgia criteria and were considered fibromyalgia-like illness after HPV immunization.	Unclear if Harden criteria used. Unclear referral /selection mechanism. One of the cases is compatible with CRPS and suggestive of direct trauma by the injection as triggering event. The other case not clearly CRPS.
Paper presented at meeting	8 cases from Japan (bivalent type in 5 and qHPV in **3**)	"Adolescents, especially girls, may experience symptoms that are pathologically difficult to explain, including pain in the limbs after HPV	The cases presented after qHPV exposure are not considered to meet the Harden criteria for CRPS.

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment
(Okuyama 2014)		vaccination. Based on the temporal sequence these are understood to be side effects from the vaccine… rare to satisfy strict diagnostic indices of CRPS"	

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

Methods

The Sponsor carried out a literature review to identify all Postural Orthostatic Tachycardia Syndrome (POTS) cases associated with quadrivalent and 9-valent Human Papillomavirus vaccine (qHPV and 9vHPV) from Medline (PubMed) and Embase (and other sources) 01-Jan-2006 through 15-Jun-2015.

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.

Assessor's comment:
The time period used for the literature search is relevant for the specific question. The search terms may be adequate. The MAH should verify that MeSH terms have been used, such as "Orthostatic intolerance" and "Postural Orthostatic Tachycardia Syndrome" or that addition of such terms does not add to the references identified **(RSI)**.

Results

Blitshteyn S. Postural tachycardia syndrome following human papillomavirus vaccination. European journal of neurology : the official journal of the European Federation of Neurological Societies 2014;21(1):135-9.

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.

Assessor's comment:
Table 1 from the original publication is provided below as a summary overview of these cases.

Table 1 POTS after HPV vaccine: patient characteristics, investigations, treatment and outcome

Patient	Age (years)	Onset after HPV vaccine dose	Symptoms	Diagnostic tests	Treatment	Outcome
1	20	2 weeks after 1st dose	Weight loss, dizziness, fatigue, exercise intolerance	TTT: POTS	Bupropion, pyridostigmine, modafinil	Improved over 15 months
2	22	2 months after 3rd dose	Diarrhea, weight loss, fatigue, dizziness, syncope	TTT: POTS, NCS; QSART: possible SFN	Midodrine, fludrocortisone	Improved over 2 years
3	12	5 days after 2nd dose; worsening 3 weeks after 3rd dose	Syncope, pre-syncope, dizziness, SOB	Holter monitor: episodic sinus tachycardia; clinical diagnosis of POTS, NCS	Fludrocortisone	Improved over 3 years
4	15	4 weeks after 1st dose	Dizziness, headache, pre-syncope, syncope	TTT: POTS, NCS	Sertraline	Improved over 2 years
5	14	5 days after 1st dose	Paresthesia, tachycardia, fatigue, headache, diarrhea, weight loss	TTT: POTS, NCS; QSART: possible SFN; ANA 1:160	Metoprolol, amitriptyline	Improved over 2 years
6	18	3 weeks after 1st dose; worsening 3 months after 2nd dose	Paresthesia, leg pain, orthostatic intolerance, fatigue, dizziness	Clinical diagnosis of POTS and possible SFN; ANA 1:320	Duloxetine, doxepin	Improved over 3 years

POTS, postural tachycardia syndrome; HPV, quadrivalent human papillomavirus vaccine – Gardasil (Merck); TTT, tilt table test; NCS, neurocardiogenic syncope; QSART, quantitative sudomotor axon reflex screen; SFN, small fiber neuropathy; SOB, shortness of breath; ANA, antinuclear antibodies.

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.

MAH 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.

Assessor's comment:
Detailed diagnostic investigations are reported as performed but not specified and the actual results are not provided. As an example a detailed analysis of the time course of the reported weight loss would have been informative. A substantial weight loss already 2 weeks after a triggering event may signal an earlier onset of the disease process.

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.

MAH 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.

Assessor's comment:
A quantitative sudomotor test showed mild reduction in the distal leg suggestive of a small fiber neuropathy.

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.

MAH 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.

Assessor's comment:
Symptoms of NCS developed 6 days after the second dose of HPV vaccine. Thorough diagnostic evaluation performed. The heart rate reaction compatible with POTS. Relapsing and remitting symptoms. Intensified symptoms were reported 3 weeks following the third dose of HPV vaccine. Three years after the onset of syncope, the patient's daily symptoms have mostly resolved. This case provides some support for a temporal relation between the symptoms and repeated HPV vaccination. The MAHs comments are not entirely endorsed. Variability in terms of the interval between triggering event and development of symptoms are not entirely unexpected.

A 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.

MAH 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.

Assessor's comment:
The symptoms described have orthostatic components with TTO of 4 weeks. An increase in heart rate of 37 during a tilt-table test is not entirely fulfilling the criteria for POTS (Sheldon 2015).

A previously healthy *14-year-old female* ([redacted]) 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.

MAH 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.

Assessor's comment:
The case description is very brief and the orthostatic component in the symptoms is unclear. The tilt-test is compatible with POTS. The borderline reduction in sweat output in the leg with the quantitative sudomotor test is considered weak evidence of possible small fiber neuropathy. The finding of an ANA titre is unspecific but may in the clinical setting justify a follow-up of the clinical course for potential rheumatological manifestations.

An 18-year-old healthy female ([redacted]) 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.

MAH 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.

Assessor's comment:
It is agreed that the combination of the symptoms described with the (unspecific) ANA titre presents a challenge in terms of differential diagnostic considerations. Standing test was compatible with a POTS diagnosis, but a tilt-test or further autonomic reflex screen testing were not performed. Weak evidence for small fiber neuropathy presented. The finding of an ANA titre is unspecific but may in the clinical setting justify a follow-up of the clinical course for potential rheumatological manifestations.

The article briefly reports six cases and is published in a journal indexed in Medline/PubMed. No financial or other COI stated. The selection/referral mechanisms for identifying these cases are not reported. There are uncertainties regarding diagnoses and uncertain diagnoses of small fibre neuropathy. Some support is provided for a temporal association between the symptoms and HPV vaccination especially from the one case with the response to repeated vaccination described.

Kinoshita T, Abe RT, Hineno A, et al. Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine. Internal medicine 2014;53(19):2185-200.

[See previous general description of the study in relation to CRPS]

A *15-year-old* [redacted] *girl* (Case 5, serial patient number: 19,[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℃ in the right first toe and 31.1℃ in the right second finger at a room temperature of 27.0℃, 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.

MAH 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 [redacted] had any psychological and/or social consequences which could have contributed to the events.

Assessor's comment:
The patient was apparently interviewed and examined at the reporting centre approximately 3½ years after the last exposure to qHPV. The rise in heart rate from 70 to 109 is not strictly fulfilling the definition of POTS (Sheldon 2015).

A *13-year-old girl* (Case [redacted], serial patient number [redacted], [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℃) 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℃, 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℃ in the right first toe and 30.8℃ in the right second finger at a room temperature of 23.5℃, 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.

MAH 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.

Assessor's comment:
Several aspects of the clinical presentation appear uncharacteristic of POTS, i.e. some of the symptoms being more pronounced when lying down and the pattern of pareses described. The rise in heart rate from 91 to 126 is not strictly fulfilling the definition of POTS (Sheldon 2015).The case does not in itself provide sufficient information to infer a causal relation.

Overall comments on the Kinoshita et al 2014 publication:
The publication is from a peer-reviewed journal indexed in Medline/PubMed. Financial support was provided by the Japanese Government.
4 cases with POTS are reported with two descriptions provided as above. The referral /selection mechanism that brings these patients to this particular hospital department is unclear and not described. The selection of the patients described in some detail is stated to be based on them being representative. Descriptive data for the cases are limited.

Tomljenovic L, Shaw CA. Death after Quadrivalent Human Papillomavirus (HPV) Vaccination: Causal or Coincidental? Pharmaceutical Regulatory Affairs: Open Access 2012;S12:001.

Tries 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.

A *14-year-old female* [redacted] 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.

MAH 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.

Assessor's comment:
Case report published in a journal not indexed in Medline/PubMed. One case describes symptoms present before vaccination consistent with the symptom development after vaccination reflecting progression of disease. The cases do not provide information that supports a causal relation with HPV vaccination.

Brinth L, Theibel AC, Pors K, et al. Suspected side effects to the quadrivalent human papilloma vaccine. Danish medical journal 2015;62(4):A5064.

Brinth et al 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.

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

Assessor's comment:

The authors describe 53 patients referred to their Syncope Unit for a tilt table test and evaluation of autonomic nervous system function specifically because side effects to the Q-HPV vaccine were suspected. This selection mechanism for referral of patients to the clinic is a concern when evaluating characteristics of the case series. The distribution of TTO will inevitably be biased and also other consequences of the selection bias are likely.

The patients were referred to the authors' clinic during a 3½ year period from May 2011 to December 2014 but it is unclear during what time period the first symptoms appeared, i.e. the delay between first symptom and evaluation at the clinic.

Patients who reported onset of symptoms consistent with autonomic dysfunction after the first two post-vaccination months (11 patients) were excluded. Also patients with other potentially triggering factors (7) and those unable to report the time interval between vaccination and first symptom (4) were excluded. The distribution of TTO and comparison of the clinical presentation between groups with different TTO is thus not possible. The reported mean time between vaccination and onset of symptoms of 11.1 ± 12.5 days (range: 0-58 days) is therefore biased since patients with a TTO longer than two months were excluded from the calculation. The selective reporting of patients referred because of a suspected adverse effect form HPV vaccine further adds bias to any attempt to draw conclusions from TTO.

The authors' reporting of these patients is important since the majority of the POTS cases reviewed in this referral procedure are from this particular clinic. Based on their large case series they conclude that "POTS should probably be looked upon as a symptom secondary to another yet unidentified condition rather than as a disease entity of its own" and also note that "…patients experienced the same degree and pattern of symptoms regardless of the POTS diagnosis". This observation, that there is poor correlation between the POTS diagnosis and symptoms reported is important. The lack of utility of the strict postural tachycardia limit used for the definition of POTS has been discussed in relation to the prospective study of POTS in a healthy reference population (Corkal and Kimpinski 2014, Gibbons 2014). A postural tachycardia as currently defined may therefore represent normal variation and not necessarily suggest autonomic dysfunction. In a study on 600 healthy Chinese school children 41 (6.8%) were diagnosed with POTS, again bringing the relevance of the diagnostic criteria into question (Lin, Han et al. 2014).

Apart from the tilt-table test there is no reporting of further examination results or investigations that would have been expected based on the nature of the symptoms reported by the patients. The clinical descriptions of severe symptoms such as new onset, continuous and debilitating headache, blurred vision, cognitive dysfunction, motor symptoms including limb weakness (in six cases leading to invalidity) are not accompanied by results from thorough clinical neurological, neurophysiological, and neuroradiological examinations. Given the poor understanding of the pathophysiology of POTS such results would have been of great interest.

The vascular abnormalities described are exclusively based on patients' reports of episodically occurring symptoms, and no clinical observations are presented. It is also a concern that hyperventilation and incomplete bladder emptying are reported as symptoms. Neither can be detected by the patient as such but require clinical measurements to be confirmed. Given the potential severity of conditions potentially underlying takypnea and new onset urinary symptoms careful clinical evaluation would have been expected and the reporting of results from such investigations would have been highly informative.

Brinth LS, Pors K, Theibel AC, et al. Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus. Vaccine 2015;33(22):2602-5.

In another publication Brinth et al. (2015) 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 ([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.

MAH 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.

Assessor's comment:
It is noted by the authors that most patients described a gradual development in both number and severity of symptoms. The TTO was determined by the patients' reports of first symptom. Since the patients are stated to be "consecutively referred to our syncope unit for head-up tilt test under the diagnosis of orthostatic intolerance as a suspected adverse event following vaccination with the quadrivalent HPV vaccine (Gardasil®)" it means that the patients when reporting the time for first symptom did so being well aware that the vaccination was the very reason for their visit at the center. This unfortunately, in combination with the gradual onset of symptoms, makes information bias an

important concern when the TTO is considered as a component of the causality analysis. This problem is also reinforced by the short TTO reported (The mean delay between vaccination and onset of symptoms was 9.3 days (range: 0–30)).

It is not stated what time period these cases where collected from (time for first symptom) or the intervals between vaccination and examination at the centre. It is stated by the authors that there was a long and variable delay between the onset of symptoms and orthostatic testing.

71% of the patients had a high and 29% had a moderate physical activity level before symptom-onset. Half of those with a high activity level were competing at a national or international level in their sport.

The case presented was physically active and developed general malaise, sore throat, and a slight fever a few days after dose #1 of her HPV vaccine series. These symptoms are consistent with an upper respiratory tract viral infection, also suggested as a potential trigger event for POTS (Freeman 2011). The case is consequently considered confounded based on the data available.

Further limitations of the study are that no measurements of cognitive function are presented even though 77% of the patients reported cognitive dysfunction. No measurements of motor function are presented even though 66% reported muscular weakness, some case even to the degree of dependency of a wheelchair. Severe neurological symptoms such as headache and tremor/myoclonic twitches are reported by the majority of patients but no results of neurological or neurophysiological examinations are presented.

Taken together; it is agreed with the authors that this case series does not provide sufficient data to establish a reasonable possibility of a causal relation between the qHPV vaccine and POTS.

Ikeda S. Side-effects and autonomic nerve disorders of cervical cancer vaccines: including POTS: Neurology Department, Rheumatology & Connective Tissue Disease Department, Faculty of Medicine, Shinshu University, 2014.

Ikeda (2014) states his point of view on side-effects and autonomic nerve disorders of cervical cancer vaccines including POTS: /…/ 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.

MAH 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.

Assessor's comment:
The brief report is of unclear background. The data reported appear to some extent to be derived from the same patients reported in Kinoshita el al 2014 "Peripheral Sympathetic Nerve Dysfunction in Adolescent Japanese Girls Following Immunization with the Human Papillomavirus Vaccine". The report does not contribute to the scientific evaluation of a possible causal relation between HPV vaccination and POTS.

Kinoshita T, Ikeda J, Abe R, et al. Discussion of dysautonomia in young female patients following the administration of the human papilloma virus (HPV) vaccine for the prevention of cervical cancer, 2014.

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.

MAH 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.

Assessor's comment:
This abstract reports 48 patients during the period June 2013 and July 2014 while the main authors' in April 2014 submitted the manuscript "Peripheral Sympathetic Nerve Dysfunction in Adolescent Japanese Girls Following Immunization with the Human Papillomavirus Vaccine" which reports 44 girls from the period June 21, 2013 to March 31, 2014 and the same hospital department.
It appears to be mainly the same patients being reported and this abstract is not considered to add substantial data to the evaluation of causality between HPV vaccination and POTS.

Kinoshita T. An investigation into autonomic neuropathy in women following cervical cancer inoculation. 55th annual meeting of the Japanese society of neurology, 2014.

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.

MAH 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.

Assessor's comment:
This abstract reports 17 patients from an unknown time period. The main authors' in April 2014 submitted the manuscript "Peripheral Sympathetic Nerve Dysfunction in Adolescent Japanese Girls Following Immunization with the Human Papillomavirus Vaccine" which reports 44 girls from the period June 21, 2013 to March 31, 2014 and the same hospital department. It is unknown to what extent the patients reported in this abstract are also present in the peer-reviewed article. This abstract is not considered to add substantial data to the evaluation of causality between HPV vaccination and POTS.

Tomljenovic L, Colafrancesco S, Perricone C, et al. Postural Orthostatic Tachycardia With Chronic Fatigue After HPV Vaccination as Part of the "Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants": Case Report and Literature Review. Journal of Investigative Medicine High Impact Case Reports 2014(January-March):1-8.

Report the case of a *14-yr-old girl* ([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.

MAH 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.

Assessor's comment:
This case report is published in a journal not currently indexed in Medline/PubMed. The first author LT reports research funding from the Dwoskin Family Foundation.
The case presents 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 vaccine injection. These symptoms are consistent with an upper respiratory tract viral infection, also suggested as a potential trigger event for POTS (Medow et al 2007). The case is consequently considered confounded based on the data available. The reporting of severe neurological symptoms are not accompanied by results from neurological, neuroradiological, or neurophysiological examinations.
This case is not considered to support causality between HPV vaccination and POTS.

MAH Discussion and Conclusion on literature cases of POTS

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.

Assessor's comment:
The cases described in this literature review are not considered to provide sufficient evidence for a plausible causal relation between qHPV vaccination and POTS. The difficulty of studying such a potential causality is severely hampered by the heterogeneity of POTS, with unspecific and varied symptomatology and poorly understood pathophysiology. It is also pointed out by the authors from the Danish centre reporting the absolute majority of these cases that "…POTS should probably be looked upon as a symptom secondary to another yet unidentified condition rather than as a disease entity of its own. This is underscored by the fact that patients experienced the same degree and pattern of symptoms regardless of the POTS diagnosis." (Brinth et al 2015).

The reports from the Danish centre as presented in the literature have notable limitations when causality assessment is attempted:
- The overall distribution of TTO and the relation between TTO and clinical presentation is not assessable since patients where TTO is longer than 2 months or uncertain have been excluded from the study.
- Apart from the tilt-table test there is no reporting of further examination results or investigations that would be expected based on the nature of the symptoms reported by the patients. The clinical description of severe symptoms such as new onset, continuous and debilitating headache, blurred vision, cognitive dysfunction, motor symptoms including limb weakness (in six cases leading to invalidity) is not accompanied by results from thorough clinical neurological, neurophysiological, and neuroradiological examinations. Given the poor understanding of the pathophysiology such results would have been of great interest.

While overall some of the case reports describe a potential temporal association with vaccination this is not sufficient to support causality. In most instances the referral to the reporting centre is based on a specific suspicion of a causal relation to vaccination, and the period between vaccination and evaluation of POTS is undefined or very long.

The overall conclusion is that the case presentations and case series available in this review do not provide any support for a plausible causal link between qHPV vaccination and POTS.

Summary table (prepared by assessor) of publications reporting cases of POTS.

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment
Case series (Blitshteyn et al. 2014)	**6** patients in the US (qHPV). Unclear referral /selection mechanism.	Symptoms 6 days to 2 months following HPV vaccination. 3 patients also experiencing NC5. 3 patients with small fibre neuropathy.	Brief descriptions but seemingly thoroughly evaluated patients. Very weak evidence for small fibre neuropathy. One patient with fluctuation of symptoms temporally related to repeated exposure.
Case series (Kinoshita et al. 2014)	15 adolescents from Japan with CRPS. 40 patients in total (7 exposed to Gardasil, 22 to Cervarix). **3** with CRPS+POTS. **1** with POTS.	4 cases of POTS. 2 cases presented in more detail, none of those strictly fulfilling POTS criteria.	Overall in the case series 5 cases of 40 selected for presentation as representative. Time to onset not presented for all individual cases, only as "5.47±5.00 months".

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment
	One hospital department, unclear referral /selection mechanism.		
Brief report (unclear context) (Ikeda 2014)	Apparently from the same population described in Kinoshita et al 2014a above	The author strongly opposes the opinion of the specialist group of the Japanese 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.	No new data that can support a causality assessment.
Case series (abstract) (Kinoshita et al. 2014b)	Appears to be mainly the same patients being reported in Kinoshita et al 2014a above.	-	No new data that can support a causality assessment.
Case report (Tomljenovic et al 2012)	2 adolescents in the US (qHPV)	Post-mortem brain tissue specimens from two young women who suffered from cerebral vasculitis type symptoms following vaccination with qHPV.	No direct link to POTS. Cannot support a causality assessment.
Case series (Brinth et al. 2015a)	53 patients in Denmark included (out of 75 referred for suspected side effects to qHPV vaccination), **38** diagnosed with POTS.	A close chronologic association to the vaccination observed. POTS should probably be looked upon as a symptom secondary to another yet unidentified condition rather than as a disease entity of its own. Patients experienced the same degree and pattern of symptoms regardless of the POTS diagnosis.	Temporal association not possible to evaluate since patients with longer TTO were excluded. Symptoms not supported by clinical examination and objective findings. Long and variable delay between the onset of symptoms and orthostatic testing.
Case series (Brinth et al. 2015b)	**35** women in Denmark (exposed to qHPV).	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.	As above. The case presented confounded.
Case report (Tomljenovic et al 2014)	**1** girl in US (qHPV)	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 case is considered confounded based on the data available. Severe neurological symptoms are reported but not accompanied by relevant examinations.

12.3. 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

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.

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 POTS

Assessment: The numbers of cases for each diagnosis are very low. For CRPS three cases were reported (1 each in 9vHPV, qHPV and placebo groups) and there are confounding and uncertainties regarding the diagnosis. The reported cases do not support concern regarding a relationship between CRPS and HPV vaccination.

Likewise, there were only two cases of POTS identified in the clinical study database. One of these cases was unlikely to be a POTS case, and the other had a very long time to onset, which does not support a relationship between POTS and HPV vaccination.

12.4. 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

12.4.1. 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. 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 Afor 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 Bfor 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.

Assessor's comment:
The difficulties with observed/expected calculations are acknowledged and the approach and assumptions made are considered acceptable.

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).

Table11. 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

CRPS Observed vs Expected Analysis

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

Table12. 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	[redacted]	35,907,186	[redacted]			
% 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 is provided in MAH responses.

12.4.2. CRPS observed vs. expected analysis

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 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 (Tables 13 and 14), 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 (Tables 13 and 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,), 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,), 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).

MAH 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). 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.

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.

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.

Assessor's comment:
The methods for calculating observed versus expected counts of CRPS are overall endorsed. The interpretations by the MAH are also acceptable. There are several limitations to these calculations. The fact that many cases come from one single centre in Japan makes the interpretation of the observed count difficult. It is, however, reassuring that a very low reporting rate must be assumed in combination with relaxed diagnostic criteria for the observed rate to reach the expected rate.

As noted elsewhere the overall difficulty to define CRPS as a condition also complicates the estimation of background incidence.

Overall, the results from the observed vs. expected counts are considered reassuring but the methodological limitations must be remembered.

12.4.3. 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, Appenix 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 Tables 15-21. 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.

Assessor's comment:
The methods for calculating observed versus expected counts of POTS are overall endorsed. The interpretations by the MAH are also acceptable. There are several limitations to these calculations. The fact that many cases come from one single centre in Denmark makes the interpretation of the observed count difficult, and the discussion by the MAH is considered relevant. The pattern reported from Denmark is distinctly different from other countries. No plausible biological explanation has been identified to explain this discrepancy and there are notable limitations in the published case series from Denmark.

As noted elsewhere the overall difficulty to define POTS as a condition also complicates the estimation of background incidence.

Overall, the results from the observed vs. expected counts are not considered to support a causal relation between qHPV vaccination and POTS but the methodological limitations must be remembered and the Danish reporting is notable.

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			
	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	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			
				Incidence Rate (per 100,000 py)											
	C	C+P		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.

12.5. 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. No evidence of causal association between qHPV vaccine and autoimmune conditions has been identified in epidemiological studies. 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 LASER, 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.

Assessor's comment

No study specifically addressing the potential association between CRPS or POTS has been identified. The 5 studies referred to by the MAH (summarized in the table below) are focused on the potential relation to autoimmune diseases in general or MS/demyelinating disease. These outcomes are not within the scope of this referral procedure and do not provide any evidence considered to of relevance for a potential association with CRPS or POTS.

Subsequently to the submission of the report by the MAH, it has been announced that a French pharmaco-epidemiological study conducted jointly by the French medicines agency (ANSM) and the French national health insurance fund (CNAMTS) has been completed. The study, which will be evaluated by the EMA, compared the incidence of autoimmune conditions in girls given HPV vaccines with the incidence in girls not given the vaccines. The cohort comprised 2,256,716 girls of whom 842,120 had received at least one dose of anti-HPV vaccine. The study concluded that there was no

increase in the risk of autoimmune conditions among girls given HPV vaccines, with the exception of Guillain-Barré syndrome. The study estimated the potential risk of Guillain-Barré syndrome to be equivalent to 1 to 2 extra cases of Guillain-Barré syndrome per 100,000 girls vaccinated. Neither CRPS nor POTS were specifically investigated in the study.

Summary table (prepared by assessor) of epidemiological studies of qHPV vaccination and autoimmune disease

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment
Cohort Study *(Chao et al 2012)*	Two managed care organizations in California. 189 629 women exposed to qHPV between August 2006 and March 2008.	347 cases sampled for case review. No positive finding except Hashimoto's thyreoiditis (IRR 1.29; 95% CI 1.08-1.56) which was not considered a plausible signal.	Company funded study. Neither CRPS nor POTS (or potentially related symptoms/conditions) were specified outcomes.
Cohort Study *(Arnheim-Dahlström et al 2013)*	Denmark and Sweden. 296 826 women exposed to qHPV October 2006 to December 2010.	Exposure to qHPV significantly associated with Behcet's syndrome, Raynaud's disease, and type 1 diabetes. Each fulfilled only one of three predefined signal strengthening criteria.	Academic study. Authors have received grants from MAHs involved in the referral. Neither CRPS nor POTS were specified outcomes. Outcome "paralysis" studied and lower risk among exposed.
Case–control study *(Grimaldi-Bensouda et al 2014)*	219 specialist centers at hospitals across France, participating in the PGRx programme.	211 definite cases of ADs. Adjusted odds ratio (OR) for any qHPV vaccine use was 0.9 [95% CI 0.5–1.5].	Company funded study. Study size did not allow conclusions on individual ADs. Neither CRPS nor POTS were specified outcomes.
Cohort Study *(Scheller et al 2013)*	Denmark and Sweden (3 983 824 females) 789 082 females aged 10-44 years exposed to qHPV from 2006 to 2013.	Adjusted IRR for MS 0.90 [95%CI 0.70-1.15] and for other demyelinating diseases 1.00 [95%CI 0.80-1.26]	Authors have received grants from MAHs involved in the referral. Neither CRPS nor POTS were specified outcomes.
Nested case–control study *(Langer-Gould et al 2014)*	Kaiser Permanente Southern California (KPSC) members. Exposure to any vaccine (not only HPV)	780 incident cases of multiple sclerosis (MS) or other acquired central nervous system demyelinating syndromes. No association with HPV vaccination (OR 1.05; 95%CI 0.62-1.78). Increased risk of onset within the first 30 days after any vaccination only in younger (<50 years) individuals (OR 2.32; 95%CI 1.18-4.57).	Academic study. Authors have received grants from pharmaceutical companies. Neither CRPS nor POTS were specified outcomes.

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 nonmyelinated 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.

MAH 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.

Assessor's comment

While potential mechanisms have been proposed in the cited articles there are no analytical results which would indicate a common origin of the presented signs and symptoms. Time to onset of symptoms and relationship to administration of the individual doses is heterogeneous with no discernible pattern. The incidence rate is low and comparable to the expected background frequency. The increased reporting rate from a centre in Japan is discussed under 12.3.2. In summary, there are at present no data to suggest a causal relationship between qHPV vaccination and CRPS.

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 vaccination no clear pattern could be demonstrated.

MAH 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.

Assessor's comment:

The reported cases of POTS display a heterogeneous clinical presentation, lack of pattern in terms of time to onset or relation to administration of the individual doses and in the majority of cases lack additional clinical investigative results or pre-vaccination baseline values (see 12.3.3). This precludes the possibility to merge signs and symptoms into meaningful clusters which could provide hypotheses for a common biological mechanism. The incidence rate is low and comparable to the expected

background frequency, with the exception of Denmark (discussed in comments to 12.1.3.2 and 12.3.3). In summary, there are at present no data to suggest a causal relationship between qHPV vaccination and POTS.

Thus, to conclude on the strength of epidemiological data regarding a relationship between CRPS and POTS and qHPV vaccine, the available epidemiological data are not relevant for these syndromes. In addition we currently lack sufficient knowledge about the respective syndrome to suggest a plausible mechanism of action for at potential causal relationship.

12.6. PRAC Question 5

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

MAH RESPONSE

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.

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.

Assessor's comment:

Based on the assessment of the responses above, there is no support for a causal relationship between CRPS and POTS and qHPV vaccination.

The actions proposed by the MAH are endorsed.

12.7. References

Blitshteyn, S. (2014). "Postural tachycardia syndrome following human papillomavirus vaccination." Eur J Neurol 21(1): 135-139.

Brinth, L. (2015). "Suspected side effects to the quadrivalent human papilloma vaccine." Dan Med J 62(4): A5064.

Bruehl, S. (2015). "Complex regional pain syndrome." BMJ 351: h2730.

Corkal, J. C. (2014). "A prospective study of excessive postural heart rate change on head-up tilt." Clin Auton Res 24(6): 253-258.

Freeman, R. (2011). "Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome." Clin Auton Res 21(2): 69-72.

Gibbons, C. (2014). "Postural tachycardia syndrome, the debate continues." Clin Auton Res 24(6): 245-246.

Kinoshita, T. (2014). "Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine." Intern Med 53(19): 2185-2200.

Lin, J. (2014). "Risk factors for postural tachycardia syndrome in children and adolescents." PLoS One 9(12): e113625.

Medow, M. S. (2007). "The postural tachycardia syndrome." Cardiol Rev 15(2): 67-75.

Rothman, K., S. Greenland and T. Lash (2008). Modern Epidemiology. Philadelphia, Lippincott Williams & Wilkins.

Sheldon, R. S. (2015). "2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope." Heart Rhythm 12(6): e41-63.

Thieben, M. J. (2007). "Postural orthostatic tachycardia syndrome: the Mayo clinic experience." Mayo Clin Proc 82(3): 308-313.

Walco, G. A. (2010). "Neuropathic pain in children: Special considerations." Mayo Clin Proc 85(3 Suppl): S33-41.