EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Confidential

Briefing note to the experts

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

Human papillomavirus (HPV) vaccines

Cervarix: EMEA/H/A20/1421/C/0721/0071

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

Gardasil 9: EMEA/H/A20/1421/C/3852/0001

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

Marketing authorisation holders: GlaxoSmithKline Biologicals; Merck Sharp & Dohme Limited; Sanofi Pasteur MSD

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This briefing note is intended for the experts participating in the meeting. This document provides a summary of the previous steps of the assessment and relevant documentation.

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Administrative information

INN (or common name) of the active substance:	Gardasil/Silgard: Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed) Cervarix: Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed) Gardasil 9: Human Papillomavirus 9-valent Vaccine (Recombinant, adsorbed)
Type of procedure:	Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data
Procedure no:	Cervarix: EMEA/H/A20/1421/C/0721/0071 Gardasil: EMEA/H/A20/1421/C/0703/0060 Gardasil 9: EMEA/H/A20/1421/C/3852/0001 Silgard: EMEA/H/A20/1421/C/0732/0054
Rapporteur:	Julie Williams (UK)
Co-Rapporteurs:	Jean-Michel Dogné (BE) Qun-Ying Yue (SE)
EMA Procedure Manager:	Efstratia Vatzaki
EMA Product Lead and SAG Secretariat:	Manuela Mura

1. Background

Human papillomavirus (HPV) vaccines have been authorised in Europe for prevention of cervical and various other diseases caused by HPV infection since 2006. Routine surveillance of suspected serious adverse drug reaction reports of the HPV vaccines has raised questions on the potential association between the use of the vaccines and in particular two syndromes, known as complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). These syndromes have been reviewed repeatedly by the PRAC within routine safety follow up procedures (e.g. PSURs), and a relationship with vaccination has not been established in these previous procedures. Individual case reports and case series of CRPS and POTS have been reported in the literature following HPV vaccination from geographically distinct locations. Literature reports of CRPS come from Australia, Germany and Japan and reports of POTS originate from USA, Japan and Denmark. The vast majority of the reported cases do not have a well-defined diagnosis.

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.

There are many uncertainties regarding the underlying pathogenesis for CRPS and POTS, which is currently poorly understood. These conditions have been prevalent in the general population for decades before the introduction of the HPV vaccines.

Since these conditions can occur in the general non-vaccinated population, it is considered important to determine whether the number of cases reported in association with HPV vaccines is greater than would ordinarily be expected.

When triggering this referral (see below), the EC requested that overall scientific evidence of a potential association between HPV vaccination and the two syndromes should be reviewed and methodologies to further investigate the concerns should be defined, if appropriate. Based on the above, discussion is needed on whether available information may require updates to the advice to healthcare professionals and patients, including changes to product information or other regulatory measures.

2. Procedure

On 9 July 2015 the European Commission triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data and asked the Pharmacovigilance Risk Assessment Committee (PRAC) to assess whether there is evidence of a causal association between HPV vaccination and CRPS and POTS with the HPV vaccines products, if research efforts should be emphasised, and if available information may require updates to the advice to healthcare professionals and patients, including changes to product information or other regulatory measures. The review started at the July 2015 PRAC meeting and all European companies who hold marketing authorisations for HPV vaccines were asked to answer the following questions:

Question 1

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

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

Question 2

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

Question 3

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

Question 4

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

Question 5

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

The responses submitted by the different companies were assessed by the PRAC's Rapporteur (attachment 1) and Co-Rapporteurs (attachments 2 and 3) for this procedure.

Before adopting a recommendation, the PRAC decided to convene the Scientific advisory group (SAG) on Vaccines and additional experts on vaccine safety, neurology and cardiology to provide an independent advice and responses to the questions below.

3. Current conclusions and Recommendations

Overall current conclusions of Rapporteur

The Rapporteur agrees with the overall conclusions of the Co-Rapporteur (SE) for Gardasil.

The Rapporteur agrees with most conclusions of the Co-Rapporteur (BE) for Cervarix, with the exception of the recommendations in relation to further evaluation of CRPS and POTS. This is described further below. On a worldwide basis and in most individual countries, it is reasonable to conclude that the most likely assumptions and scenarios around 'observed vs expected' analyses do not indicate a safety signal. Denmark and Japan clearly have higher reporting rates of certain ADRs than other countries, and the publicity around HPV vaccine safety has not only stimulated higher reporting in those countries, but in other countries subsequent to 2013. Such publicity may stimulate not only

increased reporting, but a bias in reporting towards events that more closely 'fit' vaccine induced illness – from the perspective of the Danish reports, the high proportion of cases from Brinth and colleagues (2015) support this notion.

Aside from the interpretation of the observed versus expected analysis, the cases included displayed no clear clinical pattern or dose relationship. Furthermore, the majority of cases have a relatively short symptom onset after vaccination. Symptom onset within 2 weeks is unlikely to be indicative of an autoimmune process (if an autoimmune basis for these conditions is to be believed).

It could be argued that given the very high vaccine uptake in most countries in which these ADRs are being reported, given that the reported illnesses/symptoms are usually most common in adolescence and much more common in females than males, and given the likelihood of recent stimulated reporting in several countries, then the observed pattern of spontaneous reports is not unexpected.

Therefore, on balance, the view of the Rapporteur is that the available evidence does not indicate a strong safety signal nor does it support a causal association with HPV vaccine.

Given the nature of the Brinth and colleagues (2015) case series and the Uppsala analysis, the Rapporteur also does not agree that overall ADR reporting indicates a syndrome or constellation of symptoms that is specific to HPV vaccine. POTS, chronic fatigue syndrome (CFS), CRPS and fibromyalgia all occur naturally amongst adolescent females and are known to have some symptom overlap. There is no robust basis to suggest that a common pathophysiological pathway exists, nor that this could be autoimmune in origin.

Nonetheless, Brinth and colleagues now suggest that the cases referred to them should be regarded as CFS (including a subset of POTS secondary/concurrent with CFS). The existing findings of Donegan and colleagues (2013) are relevant to this, as well as post-viral fatigue syndrome and fibromyalgia following HPV vaccination. This study further supports the lack of a safety signal and any causal association with HPV vaccine.

In relation to POTS, the Rapporteur does not agree with the proposal to further identify a set of relevant PTs/codes relating to autonomic disorders to monitor in enhanced surveillance of HPV vaccines. This form of analysis has already been undertaken in the current referral via the wider search strategy to identify possible cases not reported with the specific MedDRA PT of POTS and CRPS. The Uppsala analysis has also done this, and has not found any specific signal if all relevant HLTs/PTs are taken into account. Furthermore, the Cervarix Co-Rapporteur's proposal to identify specific markers to eventually permit to classify cases of POTS after HPV vaccine as auto-immune disorders is unclear. Other than the Danish reports, there is a lack of a clear signal in relation to POTS and no clear basis to suggest that POTS has an autoimmune origin.

In relation to CRPS, the Rapporteur does not consider there is a signal for CRPS. Based on data from The Netherlands, the background incidence rate of CRPS is ~15 person-years in females 10-19 years old. Given that many countries have up to 90% HPV vaccine uptake in girls in this age range, the reporting rate remains consistent with chance, and does not indicate a specific risk for HPV vaccine (over and above what any vaccine or needle injection may theoretically trigger). The Rapporteur agrees that a relationship to needle stick injection cannot be ruled out, although this would not be specific to HPV vaccine and is a theoretical risk with any injection procedure and does not require further evaluation or risk minimisation.

Rapporteur's and Co-Rapporteurs' current conclusions and recommendations on individual products

Cervarix

Based on the review of all available data on safety, the co-rapporteur considers that the benefit-risk balance of bivalent HPV vaccine (types 16, 18) remains favourable and therefore recommends the maintenance of the marketing authorisation.

However, as the potential involvement of Cervarix in the occurrence of CRPS cannot be completely ruled out at this stage, the co-rapporteur recommends that this risk should continue to be investigated. This could be accomplished by further monitoring in periodic safety update report (PSUR). However, monitoring is difficult because of the complexity of the disease, the risk of under diagnosis, and the existence of different diagnostic criteria. As suggested by three independent external experts, a post-authorisation safety study (PASS) could be considered to further clarify the potential link between CRPS and Cervarix vaccination. The feasibility of such a study should be thoroughly examined by the scientific advisory group as the majority of CRPS cases normally occur in elderly women and the target population would be adolescents. A clear definition of CRPS cases should be provided before the beginning of the PASS study, as well as the risk period. In order to obtain cases, data from specialised centres could be used. Finally, a PASS could also provide some answers to the growing public attention to the HPV vaccine safety.

Similarly, a potential involvement of Cervarix in the occurrence of POTS cannot be completely ruled out. However, the monitoring of POTS after HPV vaccine is complicated by the difficulty to diagnose the syndrome, the rarity of POTS fully fitting the case definition (when considering all factors of exclusion), and the variety of conditions which could be associated to POTS, some of these being also considered for potential association to HPV vaccine. To make sense, the requirements of future monitoring of POTS after HPV vaccine should be better defined and the co-Rapporteur recommends:

1) to identify PTs/codes which could be associated to autonomic disorders, including POTS (assuming that the POTS PT is not sufficient to identify POTS) and to define a POTS/autonomic disorders search strategy in pharmacovigilance data bases and other data bases;

2) to identify specific markers to eventually permit to classify cases of POTS after HPV vaccine as auto-immune disorders.

Gardasil/Silgard

The benefit risk ratio of Gardasil has not been suggested to be changed by this referral procedure.

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 infections. 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 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.

The vaccine efficacy against cancers is not possible to be determined 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.

Pyrexia, pain, erythema and swelling at the injection site were the most common local adverse reactions observed in clinical studies, and headache was the most common systemic adverse reaction in clinical studies. The safety profile of Gardasil was considered favourable at the time of approval.

The current referral procedure relates to 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 this vaccine itself and CRPS. It is not considered appropriate with any addition to summary of product characteristics (SmPC) regarding a potential risk related to the injection trauma.

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

Overall the conclusion of the Co-Rapporteur is that 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.

Gardasil 9

For Gardasil 9, the one report of CRPS and one of the reports of POTS do not necessarily fulfil the respective diagnostic criteria. The other report had an apparently long onset time from vaccination. As stated by the Co-Rapporteur, the few cases reported from RCTs are evenly distributed between the qHPV/HPV9 and placebo groups which do not suggest an association. The details of these reports in the context of the pooled trial data do not raise any safety concern for Gardasil 9. There are no post-marketing data.

The benefit risk of Gardasil 9 has not been suggested to be changed by this referral procedure.

4. List of questions for the scientific advisory group

The SAG is invited to provide answers to the following questions:

1. What is the current understanding about the pathophysiology of CRPS and POTS?
2. What is the strength of the available information with respect to the cases of CRPS and POTS which have been reported in girls previously exposed to HPV vaccination?
3. a) Based on the available information, are there specific characteristics that should be monitored in post-marketing surveillance?

   b) If yes, then:

   i. What are these characteristics and

   ii. Discuss the feasibility of performing further studies with the potential to provide robust and meaningful results within existing data sources in Europe.

5. Documentation

The participants are provided with:

1. Overall Rapporteur's assessment report (including assessment report of Gardasil 9) dated 25 September 2015
2. Co-Rapporteur assessment report (Gardasil/Silgard) dated 25 September 2015
3. Co-Rapporteur assessment report (Cervarix) dated 25 September 2015

Additional documentation can be found in this EMA link:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Human_papillomavirus_vaccines/human_referral_prac_000053.jsp&mid=WC0b01ac05805c516f&source=homeMedSearch&category=human

Any supplementary information is available upon request.

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	***[Confidential information was removed]***
Co-rapporteur's assessors	***[Confidential information was removed]***

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.*

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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 November 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 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.

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.

AN 68424, a 24 year old female enrolled in Protocol V503-001 on 26-May-2009 in New Zealand with no reported medical history at Day 1. This subject received her first dose of 9vHPV vaccine on 26-May-2009, second dose of 9vHPV vaccine 30-Jul-2009, and third dose of 9vHPV vaccine 19-Nov-2009. The subject reported adverse events of rhinorrhea, headache, oropharyngeal pain, and nasal obstruction following the first vaccination (all of mild intensity, lasting a few hours to ~20 days for the rhinorrhea). The subject reported adverse events of headache, neck pain, and injection-site pain following the second vaccination (all of mild intensity, lasting a few hours to 1 day) and reported neck pain and injection site pain following the third vaccination (of moderate intensity, lasting 12 hours to 1 day). In addition, the subject reported new medical history at the vaccination 2 visit (Month 2) of influenza, **complex regional pain syndrome** (CRPS) at Month 3, and upper respiratory tract infection at Month 6. The following additional information was provided by the investigator regarding CRPS: the subject had an onset of pain in the 4th and 5th fingers of her right hand following physical activity in April 2009 (before receiving the first vaccine dose). The pain persisted for several months with no injury ever being diagnosed; it was therefore attributed to CRPS. The subject was seen by an orthopedic surgeon in February 2010 who advised no intervention and thought that the symptoms were likely to settle. The investigator indicated that no further information is available and that this event is clearly unrelated to vaccination. The subject continued in the study and reported no additional new medical history or adverse events until she completed the study. The subject completed the Month 48 visit and subsequently completed the study on 15-Oct-2013.

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.

AN 72386, a 21 year old female enrolled in Protocol V503-001 on 29-Jul-2009 in Germany 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.

AN 84857 was a 37 year old Hispanic woman who enrolled in Protocol V501-019 in Columbia 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 (AN 29076) 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.

AN 29076, a 12 year old White female from Chile 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 (AN 71508) 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.

AN 71508, a 19 year-old White female from Denmark (site 090) 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 Frederiksberg 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 Frederiksberg Hospital reported this condition to the Danish Health Authority in November 2013. The Danish Health Authority subsequently reported this event to site. The site reported the event of POTS in the V503-001 clinical database in November, 2013. The onset date of the POTS was reported as 01-Nov-2013. Upon further follow-up, it was learned that the subject had a history of severe dizziness and was hospitalized for investigation from 13 to 16-Aug-2013. The patient was recommended to take 2-3L of water daily and ibuprofen as needed. On 09-Dec-2013, the subject reported rotatory dizziness, near fainting attacks, and migraines, and the subject was taking propranolol hydrochloride and rizatriptan benzoate for migraines. The general practitioner was contacted by the sub-investigator on 20-Feb-2014. At that time, there was no new additional information. The subject cancelled her visit with her family doctor that was scheduled for 9-May-2014. No additional information is expected. The study investigator felt that the event of POTS was related to study therapy. The rationale for assigning a possible relation between vaccination and POTS included that a possible relation between HPV vaccination and POTS has been mentioned in scientific publications. The investigator specifically cited the following two publications: Blitshteyn S. *Eur J Neurol* 21:135-9, 2014; Wang XL *Proteomics Clin Appl* 6:615-25, 2012.

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

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, MARRS 0806USA03241 and 0804USA02118, 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	0702USA04736	US	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	0806USA03270	GERMANY	14, F	Y	Y	Y	No	Y	Y	Y	No concomitant therapies	5 months (2) Not recovered at 6 months.
Y	0908USA03159	US	17, F	Y	Y	Y	Y	Y	Y	Y	Depo- Provera Meningococcal vaccine	~Day 50 (2) Outcome not reported
Y	1111USA01829	SPAIN	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	1308DEU013656 Literature	Germany	14, F	Y	Y	Y	Y	Y	Y None reported	Y	None reported	24 hours (1) Condition improving.
Y	1309JPN009987	Japan	13/ F	Y	Y	Y	Y	No	Y	Y	None	Day 38 (dose 2)
Y	1404MEX009272	Mexico	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	0808AUS00032 Literature	AUSTRALIA	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	0809USA04882	FRANCE	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	0906USA03645	AUSTRALIA	NR, NR	Y	Y	Y	Y	No	Not reported	No	Not reported	Immediate (2) Recovered in 5 days
P	1004USA00828	US	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	1008USA00351	US	12, F	Y	Y	Y s	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	1012USA01863	US	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	1108USA02310	FRANCE	17, F	Y	No	Y	Y	No	Not reported	No	Not reported	Day 15 (2)
P	1208AUS002322 Literature	AUSTRALIA	13, F	Y	Y	Y	Y	No	Not reported	N	Not reported	immediately (2) Treatment: exercises. Recovered in 5 days
P	1208JPN008063	JAPAN	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	1306JPN011000	JAPAN	12.F	Y	Y	Y	Y	Y	No	No	Not reported	Day 8 (1)
P	1308JPN014199 Literature POTS also coded	JAPAN	11, F	Y	No	Y	Y	No		No	None reported	7 months (dose 1) The patient recovered from all events.
P	1403BRA005302	UAE/	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	1406JPN009071 Literature	United States	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	1406JPN010622 Literature	JAPAN	18, F	Y	Y	Y	Not reported	Y	Not reported	Not reported	Not reported	Not reported.
P	1407BRA005135	BRAZIL	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	1407ESP012192	SPAIN	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	1310DNK001347	DNK	27/F	Y	Y	Y But reported in conjunction with fever.	No	Y	N	Y	Not reported	Day 4 (2)
P	1311DNK007560	DNK	13/F	Yes;	Y	No	Y	Y	No	No	Not reported	3 months (3)
P	1311DNK007473	DNK	22/F	Y	Y	Y	No	Y	No	No	Not reported	Day 1 (NR)
P	1311JPN003454	JPN	13/F	Y	Y	Y	No	Y	No	Y	None	Day 33 (3) Recovered
P	1312DNK005120	DNK	12/F	Y	Y	Y	No	Y	No	No	Not reported	9 months (2) Recovering from muscle pain
P	1506DNK001547	DNK	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	82,237,971	27,412,657	<1 case (11/ 27, 412,657)	<1 case (11/ 27,412,657)
Denmark	1,351,593	450,531	~4 cases (2/ 450,531)	42 cases (19/ 450,531)
Japan	1,850,998	616,999	29 cases (18/ 616, 999)	~2 cases (1/ 616, 999)

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	0707USA00729	UNITED STATES	21 Years Female	Y	Y	Y	Y	28 days after D1
Y	0911USA01319	DENMARK	18 Years Female	Y	Y	Y	Y	Same day after D1
Y	1007USA02012 Literature	UNITED STATES	20 Years Female	NR	Y	Y	Y	2 weeks after D1
Y	1307DNK010012	DENMARK	23 Years Female	Y	Y	Y	Y	7 months after D2
Y	1308DNK006725	DENMARK	24 Years Female	Y	Y	Y	Y	Same day after D2
Y	1309DNK009116	DENMARK	12 Years Female	Y	Y	Y	Y	14 days after D3
Y	1309DNK010697	DENMARK	28 Years Female	Y	Y	Y	Y	TTO=NR after D2
Y	1309DNK012502	DENMARK	31 Years Female	Y	Y	Y	Y	1 day after D2
Y	1310DNK004981	DENMARK	23 Years Female	Y	Y	Y	Y	TTO=NR after D2
Y	1310DNK009529	DENMARK	23 Years Female	Y	Y	Y	Y	TTO=NR after D1
Y	1310USA003813 Literature	UNITED STATES	15 Years Female	Y	Y	Y	Y	1 month after D1
Y	1311DNK007473	DENMARK	22 Years Female	Y	Y	Y	Y	TTO=same day Dose=NR
Y	1311DNK007560	DENMARK	13 Years Female	Y	Y	Y	Y	Approximately 12 months after D3
Y	1311DNK008839	DENMARK	27 Years Female	Y	Y	Y	Y	30 days after D1
Y	1312DNK005120	DENMARK	12 Years Female	Y	Y	Y	Y	2 days after dose=NR
Y	1401DNK012424	DENMARK	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	1402DNK008557	DENMARK	13 Years Female	Y	Y	Y	Y	107 days after D3
Y	1403DNK007125	DENMARK	13 Years Female	Y	Y	Y	Y	2 days after dose=NR
Y	1403DNK007127	DENMARK	32 Years Female	Y	Y	Y	Y	Approximately 4 months after D2
Y	1404DNK002224	DENMARK	14 Years Female	Y	Y	Y	Y	6 month after D3
Y	1404DNK014832	DENMARK	29 Years Female	Y	Y	Y	Y	2 days after D2
Y	1406DNK001737	DENMARK	12 Years Female	Y	Y	Y	Y	TTO=NR after D1
Y	1409DNK015109	DENMARK	14 Years Female	Y	Y	Y	Y	Approximately 7 months after D3
Y	1410DNK002919	DENMARK	14 Years Female	Y	Y	Y	Y	Low BP and palpitations started 14 months after D3
Y	1410DNK015879	DENMARK	12 Years Female	Y	Y	Y	Y	4 days after D3
Y	1412DNK000912	DENMARK	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	1412DNK004677	DENMARK	17 Years Female	Y	Y	Y	Y	Same day as D1
Y	1412DNK005008	DENMARK	26 Years Female	Y	Y	Y	Y	Approx. 1 month after D2
Y	1501DNK000803	DENMARK	12 Years Female	Y	Y	Y	Y	TTO=NR D2
Y	1501DNK010257	DENMARK	12 Years Female	Y	Y	Y	Y	TTO=NR after D3
Y	1502DNK001010	DENMARK	24 Years Female	Y	Y	Y	Y	37 Days after D3
Y	1503DNK006617 Literature	DENMARK	14 Years Female	Y	Y	Y	Y	1 week after D1
Y	1504DNK018866	DENMARK	Not provided- Female	Y	Y	Y	Y	3 months after D3
P	0808USA01382	UNITED STATES	15 Years Female	Y	Y	NR	N	Approx. 3 months after D2
P	0809USA04359	UNITED STATES	16 Years Female	NR	Y	Y	NR	20 Days after D1
P	1302DNK003426	UNITED STATES	22 Years Female	Y	Y	Y	N	TTO=NR after D2
P	1308JPN014199 Literature	JAPAN	11 Years Female	NR	Y	Y	Y	TTO=NR after D1
P	1310USA000643 Literature	UNITED STATES	18 Years Female	NR	Y	Y	Y	TTO=NR after D2
P	1310USA003785 Literature	UNITED STATES	22 Years Female	NR	Y	Y	NR	TTO=NR after D3
P	1310USA003799 Literature	UNITED STATES	12 Years Female	NR	Y	Y	Y	6 days after D2
P	1310USA003819 Literature	UNITED STATES	14 Years Female	NR	Y	Y	NR	2 weeks after D1
P	1311DNK006376	DENMARK	39 Years	NR	Y	Y	N	5 months after D1
P	1502DNK012109	DENMARK	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 (1407DNK003660), and 1 case has orthostatic intolerance coded (1302DNK003438)
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	1111USA00812	France	14 Years Female	NR	NR	Y	Y	Same day after D1
P	1310DNK014329	DENMARK	13 Years Female	Y	N	Y	NR	200 days after D3
P	1504JPN001108 Literature	JAPAN	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**	**Reporting rate for Cases Reported with Combinations of Symptoms of POTS per Million Vaccinees by Region or Country**
	Cumulative to 31-May-2015	**Number of persons vaccinated (assuming 3 doses per person)**	**(# Reports/ # People vaccinated x 1million)**	**(# Reports/ # People vaccinated x 1 million)**
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	82,237,971	27,412,657	1 (28/ 27,412,657)	<1 (13/ 27,412,657)
Denmark	1,351,593	450,531	91 (41/ 450,531)	13 (6/ 450,531)
Japan	1,850,998	616,999	~7 (4/ 616, 999)	3 (2/ 616, 999)

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, carbamazepine, 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	2vHPVt (2)	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	Nil	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 (MARRS 0705AUS00191)* 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* (*MARRS 1208AUS002322*) 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* (*MARRS 0808AUS00032*) 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 (MARRS 1308DEU013656; E2013-06268, PEI2012055361, E2012-08427) 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 disturbance	Decreased skin temperature in toe	Hyperpathy	Over sweating	CRPS (Japan)	CRPS (IASP)	OD	OH	POTS
1	13	G	Fatigue	+	+	−	−	−	n.e.	−	−	−	−	+	−	−
2	13	G	Fever	+	+	−	+	+	−	−	−	−	+	+	−	−
3	13	G	Headache	+	+	+	+*	+	−	−	−	−	+	+	−	−
5	13	C	Hyperventilation	+	+	−	+*	+	−	−	−	−	−	+	−	−
8	14	G	Headache	+	+	−	−	+	−	−	−	−		+	−	−
12	15	C	Headache	+	−	−	−	+	n.e.	−	−	−	−	+	−	−
13	15	G	Headache, nausea, fever	+	+	+	−	+	+	+	−	−	+	+	+	−
14	15	C	Pain in eye ball, double vision	+	−	−	+*	+	+	−	−	−	+	+	−	−
16	15	C	Fever	+	−	−	+	+	−	+	−	−	−	−	−	−
17	15	C	Headache	+	+	−	+	−	+	−	−	−	+	+	+	−
18	15	C	Limb pain	−	+	−	+	−	+	+	+	−	+	+	−	−
19	15	G	Limb pain and weakness	+	+	−	+	−	+	−	−	−	+	+	−	−
20	16	C	Limb pain	−	+	−	−	+	n.e.	+	−	−	+	−	−	−
21	16	C	Limb pain	+	+	+	−	+	−	+	−	−	+	−	−	−
22	16	C	Fatigue	+	−	+	−	+	−	−	−	−	−	+	−	−
23	16	C	Limb weakness	−	+	+	+	+	−	+	−	−	+	−	−	
24	16	C	Arthralgia	−	+	−	+	−	−	+	+	−	−	+	+	−
25	16	C	Arthralgia	−	+	+	−	+	+	−	−	−	+	+	−	
27	16	C	Fatigue, difficulty in getting up	+	+	−	−	−	+	−	+	−	−	+	+	−
28	17	C	Arthralgia	+	+	−	−	−	−	+	−	−	−	+	−	−
29	17	C	Limb pain and weakness	+	+	+	+	+	+	+	−	−	+	+	−	−
31	17	C	Dysphonia	+	−	−	+	−	+	−	+	−	−	+	+	−
32	18	G	Fatigue, limb paralysis	+	−	−	+	+	−	+	−	−	−	+	+	−
34	18	C	Headache	+	−	−	−	−	+	+	−	−	−	+	−	−
36	18	C	Fever, gait disturbance	+	−	+	−	+	−	+	−	−	+	+	−	−
37	18	C	Abdominal pain	+	+	+	+	+	+	+	−	−	−	+	−	−
38	18	C	Difficulty in getting up	+	+	−	+	+	n.e.	−	+	−	+	+	−	−
39	19	C	Syncope	+	+	+	+	+	n.e.	−	−	−	−	+	−	−
40	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 Japanese girl* (MARRS 1406JPN009071) 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 USA to Japan 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 USA to Japan 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* (MARRS 1308JPN014199) (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 (MARRS 1404MEX009272) 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 (MARRS 1404MEX009808) 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* (MARRS 1412JPN005760) 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 (MARRS 1410JPN011728) only limited information was provided. A *12- year-old female* received qHPV (dose #1) and Japanese 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 (MARRS 1411JPN011609) 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* (*MARRS 1310USA003819*) 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 (*MARRS 1310USA000643*) 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 Japanese girl* (Case 5, serial patient number: 19, ***MARRS 1406JPN009071***) 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 U.S. 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 from USA to Japan 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 3, serial patient number 2, ***MARRS 1409JPN015529***) 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* (*MARRS 0812USA03226*) 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 (MARRS 1503DNK006617) 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* (*MARRS 14111SR001520*) 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 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.	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 **AN68424**, 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 **AN72386**, 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 **AN84857**, 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 **AN29076**, 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 **AN71508**, 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	82,805,539	35,907,186	1,351,593	6,873,327	4,807,238	1,850,998
% Doses Administered							
high end	80%	75%	90%	95%	90%	95%	95%
low end	65%	60%	75%	80%	75%	80%	80%
Dose distribution by age							
10-19 yo	90%	90%	90%	75%	90%	95%	100%
20-29yo	10%	10%	10%	25%	10%	5%	
CRPS incidence by age (per 100,000 PY)							
10-19 yo	14.9	14.9	14.9	14.9	14.9	14.9	14.9
20-29 yo	28.0	28.0	28.0	28.0	28.0	28.0	28.0
10-29 yo (weighted by dose dist)	16.2	16.2	16.2	18.3	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 (3wk)	14	15	75%	1	2	3	7	8	18	31	72	15	36	62	145	77	181	310	723
			90%	1	2	4	9	9	22	37	87	19	43	74	174	93	217	372	868
1mon (3mon)	18	19	75%	3	8	13	31	34	79	135	314	67	157	269	628	337	785	1,347	3,142
			90%	4	9	16	38	40	94	162	377	81	189	323	754	404	943	1,616	3,770
2mon (6mon)	20	21	75%	7	16	27	63	67	157	269	628	135	314	539	1,257	673	1,571	2,693	6,284
			90%	8	19	32	75	81	189	323	754	162	377	646	1,508	808	1,885	3,232	7,541
6mon (~1-1.5yr)	25	28	75%	20	47	81	189												
			90%	24	57	97	226												
1yr (~1.5-3yr)	29	33	75%	40	94	162	377												
			90%	48	113	194	452												
2yr (~2-6yr)	30	34	75%	81	189	323	754												
			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 (3wk)	14	14	80%	0	0	0	0	0	1	1	3	1	1	2	6	3	7	12	29
			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			
				Incidence Rate (per 100,000 py)											
	C	C+P		15	35	60	140	15	35	60	140	15	35	60	140
1wk (3wk)	0	0	80%	0	0	0	1	1	3	4	10	2	5	9	21
			95%	0	0	1	1	1	3	5	12	3	6	11	25
1mon (3mon)	0	0	80%	0	1	2	4	5	11	19	45	10	22	38	90
			95%	1	1	2	5	6	13	23	53	11	27	46	107
2mon (6mon)	0	0	80%	1	2	4	9	10	22	38	90	19	45	77	179
			95%	1	3	5	11	11	27	46	107	23	53	91	213
6mon (~1-1.5yr)	0	0	80%	3	7	12	27	29	67	115	269	58	135	231	538
			95%	3	8	14	32	34	80	137	320	69	160	274	639
1yr (~1.5-3yr)	0	0	80%	6	13	23	54	58	135	231	538	115	269	461	1,077
			95%	7	16	27	64	69	160	274	639	137	320	548	1,279
2yr (~2-6yr)	0	0	80%	12	27	46	108	115	269	461	1,077	231	538	923	2,154
			95%	14	32	55	128	137	320	548	1,279	274	639	1,096	2,557

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

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

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

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

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

UNITED STATES													
Risk Period Per Dose (*)	Observed		% Dose Administered	Expected Number of Cases											
				1% Reporting rate				10% Reporting rate				20% Reporting rate			
				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)	3	10	60%	149	348	596	1391	1,490	3,478	5,962	13,911	2,981	6,956	11,924	27,823
			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

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PRAC (co)-rapporteur's referral preliminary assessment report

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

Human papillomavirus (HPV) vaccines

Cervarix: EMEA/H/A20/1421/C/0721/0071

PRAC Rapporteur	Julie Williams (UK)
PRAC Co-rapporteurs:	Jean Michel-Dogne (BE) Qun-Ying Yue (SE)
EMA referral Procedure Manager:	Efstratia Vatzaki
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:	*<Date>*
Deadline for comments:	1 October 2015
<Updated report circulated:>	28 October 2015

Administrative information

INN (or common name) of the active substance(s)	Cervarix (Bivalent HPV vaccine (types 16, 18))
Pharmaco-therapeutic group (ATC code)	J07BM02
Pharmaceutical form(s) and strength(s)	All approved

Co-rapporteur's contact person	*[Confidential information was removed]*
Co-rapporteur's assessors	***[Confidential information was removed]***

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

List of abbreviations

AE	Adverse event
CRPS	Complex Regional Pain Syndrome
DLP	Data Lock point
EMA	European Medicines Agency
HPV	Human papilloma virus
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MSC	Medically significant condition
O/E	Observerd vs Expected
pIMDs	Potentially immune-mediated diseases
POTS	Postural Orthostatic Tachycardia Syndrome
PT	Preferred term
TVC	Total vaccinated cohort

1. Background information

Human papillomavirus (HPV) vaccines have been authorised in Europe for the prevention of premalignant lesions and 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 19 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) (1 signal raised in 2013 on POTS and 1 signal raised in 2013 on CRPS). 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.

CRPS symptoms are severe chronic pain which is out-of-proportion to what would be expected, allodynia, hyperesthesia, swelling, changes in the skin temperature and colour of the arms or legs, sweating, movement disturbances (tremor, weakness, dystonia) and trophic changes (abnormal hair and nail growth). 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.

2. 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 May 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.

3. Assessment

3.1. Introduction

Cervarix (Bivalent HPV vaccine (types 16, 18)) is a non-infectious recombinant vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of oncogenic HPV types 16 and 18. This vaccine is adjuvanted with AS04 (composed of aluminium hydroxide and 3-O-desacyl-4'-monophosphoryl lipid A (MPL)) which has been shown to induce a high and long lasting immune response in clinical trials.

Up to the data lock point (DLP) of this referral (15 June 2015), *Cervarix* is indicated in females from 9 years of age onwards for the prevention of persistent infection, premalignant genital (cervical, vulvar and vaginal) lesions and cervical, vulvar and vaginal cancers (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic Human Papillomaviruses (HPV). Besides, a type II variation (procedure EMEA/H/C/000721/II/0067) is currently under assessment to extend the indication of the Product Information for Cervarix to the prevention of premalignant anal lesion and anal cancer.

The age at which people receive the vaccine, e.g. in the context of a national vaccination programme, can vary between countries depending on their official recommendations. The vaccination schedule depends on the age of the subject:

- From 9 up to and including 14 years: 2 doses each of 0.5 ml. The second dose given between 5 and 13 months after the first dose*; or 3 doses each of 0.5 ml at 0, 1, 6 months†
- From 15 years and above: 3 doses each of 0.5 ml at 0, 1, 6 months†

Although the necessity for a booster dose has not been established, an anamnestic response has been observed after the administration of a challenge dose.

Cervarix is for intramuscular injection in the deltoid region.

Cervarix was first approved on 18 May 2007 in Australia and is currently approved in 135 countries worldwide.

At the data lock point (15 June 2015) used for this analysis, a total of 57 094 396 doses have been distributed worldwide, and the number of subjects exposed to at least one dose of Cervarix can be estimated to be between 19 031 465 and 57 094 396.

3.2. Quality aspects

N/A

3.3. Non-clinical aspects

N/A

3.4. Clinical aspects

3.4.1. Efficacy

N/A

* If the second vaccine dose is administered before the 5th month after the first dose, a third dose should always be administered
† If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose

3.4.2. Safety

Data on safety

Clinical safety data

For the purpose of the referral, the MAH was requested to provide an in depth review of the CRPS and POTS cases observed within all clinical studies. To respond to this request, the MAH has pooled the safety data from 18 completed and unblinded studies designed with an active comparator group (either placebo or another vaccine other than an HPV vaccine, i.e. Hepatitis B, Hepatitis A) which includes a total of 42,047 vaccinees (21,268 in HPV group and 20,779 in comparator groups) (DLP of 15 June 2015).

The analysis of available data did not identify any serious or non-serious adverse event of CRPS or POTS, regardless of the search strategy method, i.e. when searching for cases which contain the MedDRA PT 'CRPS' or 'POTS', or when searching for any cases that include signs and symptoms of CRPS (as according to *Harden et al. 2010*), or POTS (as according to *Raj 2013 and Sheldon et al. 2015*).

Post marketing safety data

CRPS

The assessment of the post-marketing data provided by the MAH has shown that:

- out of 49 spontaneous reports of CRPS (i.e. PT CRPS), 5 cases have been considered as confirmed CRPS, i.e. with fulfilment of the Budapest clinical diagnostic criteria for CRPS. In 3 of these cases, a causal relationship with Cervarix vaccination cannot be ruled out, including 1 serious case resolved with sequelae. Among the 44 remaining *potential* CRPS cases (i.e. PT CRPS reported but insufficient information or incomplete fulfilment of the diagnostic criteria), only in 8 cases, including 4 serious cases with an unknown outcome in 50% and recovering/resolving in the other half, the involvement of Cervarix cannot be ruled out;

- besides, 10 cases of *potential* CRPS have been identified by applying the search strategy of signs and symptoms of CRPS (cases not reporting PT CRPS). In 2 cases the involvement of Cervarix administration could not be ruled out, one of which was serious and no recovery was observed;

- the number of CRPS cases following administration of Cervarix is considered low compared to 57 million doses of Cervarix distributed globally. However, the low number might be contributed by the problem of underreporting of ADRs in general, and more specific, the difficulty of diagnosing CRPS being a complex syndrome with a variety of signs and symptoms in highly variable combinations with a variable progression over time. Furthermore, there is no golden standard diagnostic test for CRPS available, remaining CRPS as a syndrome of exclusion of other diseases with similar signs and symptoms, and no overall consensus on the clinical diagnostic criteria of CRPS (*Rockett 2014*). However the most widely accepted diagnostic criteria are the Budapest criteria described by *Harden et al. 2010*. All taken together, many patients could be undiagnosed;

- despite the fact that the Observed vs Expected analysis is based on many assumptions, which cannot be verified, this analysis has suggested that the number of observed CRPS cases is low compared to those expected, except in Japan. Based on reported cases in Japan and UK, a reporting rate at 0.31 cases per 100,000 doses (48/15,668,109) can be estimated. When this rate is applied to the number of doses distributed worldwide, 175 cases would have been reported, assuming that the reporting pattern is similar in other countries.

POTS

The assessment of the post-marketing data provided by the MAH has shown that:

- out of the 19 cases identified with POTS PT and 7 cases identified with combinations of proxy PTs, 2 cases could likely be cases of POTS following HPV vaccination, 4 cases are possibly cases of POTS following HPV vaccination, and the other cases are not POTs, or possible POTS not following vaccination, or unclassifiable cases;
- The O/E analysis suggest that the number of observed POTS cases is low compared to those expected, even in Japan. However, as for CRPS, the O/E methodology used in this analysis is also based on many assumptions, which cannot be verified.

Literature

CRPS

Data from the literature do not point out a causal relationship between HPV vaccination and the onset of CRPS. However this cannot be ruled out for the following reasons:

- the disease is probably caused by a multi-factorial process, including inflammatory and immune related factors (*Bruehl 2015*),
- CRPS occurs most commonly in women between 50 and 70 years of age *(Rockett 2014)* and is relatively rare in childhood and adolescence (*Borchers & Gerschwin 2014*) which is the target population of HPV vaccination,
- paediatric CRPS is mostly triggered by minor trauma (*Borucki & Greco 2015*).

POTS

Few cases of POTS following a vaccination with Cervarix were published and those cases were included in the MAH safety data base and discussed here-above (*Kinoshita et al. 2014*).

An expert group published recently a consensus statement on the definition , physiology, diagnosis, and treatment of POTS (*Sheldon et al. 2015*). The physiology of the condition include peripheral autonomic denervation, heperadrenergism, deconditioning, and anxiety. Beside physical examination and personal and family history, the diagnosis of the patient involve cardiologic investigations, biology (including thyroid, norepinephrine), autonomic neuropathies, modifying factors, potential triggers. A full autonomic system review should assess symptoms of autonomic neuropathy. A tilt-table test may be useful

Demonstrated risks

CRPS

Within the data submitted by the MAH, 3 confirmed and 10 potential cases of CRPS for which the involvement of Cervarix cannot be excluded, have been identified. This is based on a strong temporal relationship between the events and administration of the vaccine, the absence or unknown relevant medical history, and the absence of other events which might explain the symptoms.

POTS

In conclusion, very few cases of POTS following HPV vaccination were identified. From data available, all conditions other than vaccination which could potentially be associated to POTS cannot be systematically excluded. However, a potential association between HPV vaccination and POTS cannot be ruled out

Uncertainty about risks

CRPS

A potential involvement of Cervarix in the occurrence of CRPS has not been demonstrated, but cannot be completely excluded at this stage. Whether the development of CRPS post-vaccination could be due to the injection or the vaccine itself cannot be determined as in literature, CRPS was also reported following venipuncture, intravenous drug administration and other vaccinations (*Richards et al. 2012*; *Kwun et al. 2012*; *Genc et al. 2005*; *Jastaniah et al. 2003; Bilic et al. 2013*). However, if the injection itself triggers the event, and given the large number of people that receive injections for various medical reasons, one would expect a much larger number of reports of CRPS triggered by injections.

It appears that CRPS is caused by a multifactorial process involving both peripheral and central mechanisms. Potential mechanisms include nerve injury, ischemic reperfusion injury or oxidative stress, central sensitization, peripheral sensitization, altered sympathetic nervous system function or sympatho-afferent coupling, inflammatory and immune related factors, brain changes, genetic factors, psychological factors and disuse (*Bruehl 2015*). Little is known how these mechanisms might interact. Given the diversity of presentations seen in CRPS, the relative contributions of different mechanisms probably differ across individual patients and even within patients over time (*Bruehl 2015*). The heterogeneity in the constellations of signs and symptoms in individuals and the great variability in the response to specific treatments suggest the existence of distinct subgroups with different underlying pathophysiological mechanisms (*Borchers & Gerschwin 2014*).

CRPS can occur at any age, but is relatively rare in childhood and adolescence, with paediatric patients constituting <10% of CRPS patients seen at tertiary centres. Onset of paediatric CRPS occurs most frequently in early adolescence (peak age of onset is around 12-13 years of age), with the lower end of the range usually being 7 to 9 years (*Borchers & Gerschwin 2014*; *Borucki & Greco 2015*). CRPS is rarely seen in young children before the age of 6 (*Borucki & Greco 2015*).

Whether paediatric CRPS is a subgroup of the same disorder as in adults or a different entity entirely is still being questioned, because of a potential different presentation of signs and symptoms in children/adolescents compared to adults (*Borchers & Gerschwin 2014*).

POTS

As pointed by Raj et al., POTS is a syndrome, not a disease (*Raj 2013*). Although orthostatic tachycardia is the main sign of the condition, the syndrome can be associated (or not) to a variety of conditions.

When considering the possibility of POTS after HPV vaccination, two conditions are of major interest:

1) POTS as an autoimmune condition: the autoimmune theory which is supported by the identification in a significant proportion of the cases of antibodies, the report of viral infections before onset and the presence of autoimmune markers (*Blitshteyn 2015*).

2) POTS as a dysfunction of the autonomic nervous system: in a recent publication, WHO identified in Vigibase 21 cases of gastrointestinal motility disorders after HPV vaccine (*Chandler 2015*), those conditions being suspected to be caused by autonomic neuropathies. Dysfunctions of the autonomic nervous system may present under various forms. The identification of dysautonomic conditions of interest should be discussed for future surveillance.

The background incidence of POTS in the general population in unknown, but based on our external expert's experience should be low.

The diagnostic criteria of POTS are based on the tilt-test or active standing test. Two studies have suggested that having a positive tilt-test in an adolescent patient – regardless of symptoms – would not be that uncommon (*Singer et al. 2012, Zhao et al. 2015*). However, for a definite diagnosis of POTS other symptoms – such as light-headedness, dizziness, or fatigue – need to be present as well. It is not known how commonly these symptoms occur in the adolescent population in combination with a positive tilt-test, which would be required for a definite diagnosis of POTS

4. Consultation with expert group

Not applicable.

5. Benefit-risk assessment

The scope of this referral procedure does not reflect efficacy data. The submitted safety data as well as safety data from the literature do **not** provide **sufficient evidence to alter the benefit risk balance** of Cervarix. However, the link between CRPS or POTS and vaccination with Cervarix needs to be further investigated (cfr section 6 Recommendations and Appendix A – Question 5).

6. Recommendations

Based on the review of all available data on safety, the co-rapporteur considers that the benefit-risk balance of Bivalent HPV vaccine (types 16, 18) **remains favourable** and therefore **recommends the maintenance of the marketing authorisation**.

However, as the potential involvement of Cervarix in the occurrence of CRPS cannot be completely ruled out at this stage, the co-rapporteur recommends that this risk should continue to be investigated. This could be accomplished by further monitoring in PSUR. However, monitoring is difficult because of the complexity of the disease, the risk of underdiagnosis, and the existence of different diagnostic criteria. As suggested by three independent external experts, a PASS study could be considered to further clarify the potential link between CRPS and Cervarix vaccination. The feasibility of such a study should be thoroughly examined by the SAG (see Section 7) as the majority of CRPS cases normally occurs in elderly women and the target population would be adolescents. A clear definition of CRPS cases should be provided before the beginning of the PASS study, as well as the risk period. In order to obtain cases, data from specialised centres could be used. Finally, a PASS could also provide some answers to the growing public attention to the HPV vaccine safety.

Similarly, a potential involvement of Cervarix in the occurrence of POTS cannot be completely ruled out. However, the monitoring of POTS after HPV vaccine is complicated by the difficulty to diagnose the syndrome, the rarity of POTS fully fitting the case definition (when considering all factors of exclusion), and the variety of conditions which could be associated to POTS, some of these being also considered for potential association to HPV vaccine. To make sense, the requirements of a future monitoring of POTS after HPV vaccine should be better defined and the co-rapporteur recommends:

1) to identify PTs/codes which could be associated to autonomic disorders, including POTS (assuming that the POTS PT is not sufficient to identify POTS) and to define a POTS/autonomic disorders search strategy in pharmacovigilance data bases and other data bases;

2) to identify specific markers to eventually permit to classify cases of POTS after HPV vaccine as auto-immune disorders.

In conclusion, deciding upon a PASS study in the light of the current evidence could be premature as the parameters to investigate are still unclear (cfr List of questions to the SAG in section 7).

7. Next steps

The co-rapporteur proposes:

- A SAG/Ad-Hoc expert group meeting to discuss the following issues:
  - Are the Budapest clinical diagnostic criteria for CRPS described by Harden et al. (2010) still up-to-date, as for instance they do not include the possibility that CRPS can spread outside of the originally affected limb?
  - Would a PASS study be useful to provide additional information regarding the potential link between CRPS and vaccination with Cervarix. Which design should be the most appropriate?
  - For the POTS, is it useful to identify a set of relevant autonomic disorders to monitor in enhanced surveillance of HPV vaccines? (referring to gastrointestinal motility disorders identified by *Chandler 2015*).

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Annex 1 Proposed List of Outstanding Issues

Not applicable.

Annex 2 Recommended changes to the product information

Not applicable.

Annex 3 Proposed Dear Healthcare Professional Communication

Not applicable.

Annex 4 Comments received

Not applicable.

Appendix A Detailed assessment of the MAH's responses

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

Introduction

MAH's response

Continuous management of safety signals is an integral part of GSK's Pharmacovigilance system. We take a proactive and holistic approach to signal detection and evaluation. This includes regular review of emerging safety data from clinical studies and regular signal detection for marketed products based on an aggregate review, using disproportionality analysis, of adverse event reports from the GSK global safety database. As signals may also emerge from literature reviews, enquiries from external sources, epidemiological studies, registry data, pre-clinical information (e.g., animal toxicology, pharmacology) and competitor data, these sources are also interrogated, as appropriate, when evaluating signals at GSK. All signals from all sources are prioritised for evaluation and at the same time, signals meeting criteria for expedited reporting are communicated to the regulatory authorities.

Reports of CRPS (Complex Regional Pain Syndrome) and POTS (Postural Orthostatic Tachycardia Syndrome) following vaccination with Cervarix are adverse events (AEs) that have been reviewed in the context of Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) that are shared to regulatory agencies worldwide according to local regulation.

As requested in response to the Article 20 procedure, GSK has conducted a review of all available data from clinical trials, as well as from spontaneous, post-marketing case reports to evaluate the potential risk of CRPS and POTS with Cervarix. Case reports identified in the scientific literature are also entered in the GSK global safety database as a post-marketing case.

Since clinical trials are designed with a control/comparator group, for the purpose of this exercise, analysis of clinical trial safety data is conducted separately to allow a comparison of the reporting rate between subjects vaccinated with HPV and subjects vaccinated with a control/comparator vaccine(s). Hence, analysis of serious and nonserious AEs reported in the clinical programme is presented in the response to Question 2.

Since the first launch of Cervarix (May 2007) up to the data lock point of 15 June 2015, more than 24,000 case reports have been recorded in the GSK global safety database following vaccination with Cervarix in post-marketing setting.

CRPS

MAH's response

CRPS has been described as locally appearing painful conditions following a trauma which chiefly occur distally and exceed in intensity and duration of the expected clinical course of the original trauma. It occurs slightly more often in the upper extremities. Fracture is the most common initial event (43%). Women are affected 3.4 times more often than men with mean age at diagnosis of 52 years (De Mos , 2007). The clinical entity of CRPS remains incompletely understood. CRPS is subdivided into CRPS-I

and CRPS-II, reflecting the absence or presence of documented nerve injury, respectively. Despite this traditional diagnostic distinction, signs and symptoms of the two CRPS subtypes are similar, and there is no evidence that they differ in terms of pathophysiologic mechanisms or treatment responsiveness (Bruehl , 2010; Marinus 2011). The diagnosis is only based on clinical criteria, i.e. presence of pain, as well as sensory, vasomotor, pseudomotor/oedema, trophic, and motor disturbances (Harden et al. 2010), as presented in Table 1.

Table 1: Budapest clinical diagnostic criteria for CRPS

(1) Continuing pain, which is disproportionate to any inciting event

(2) Must report at least one symptom in three of the four following categories:

- Sensory: reports of hyperesthesia and/or allodynia
- Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
- Pseudomotor/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 two or more of the following categories:

- Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
- Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry
- Pseudomotor/oedema: evidence of oedema 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.

The GSK global safety database was searched using the following criteria:

Data lock point(s): 15 June 2015

Report types: All spontaneous and post-marketing case reports

Cervarix was reported as a suspect vaccine.

A stepwise approach in the analysis of cases was performed: (1) analysis of case reports that included the MedDRA Preferred Terms (PTs) of CRPS, and (2) Analysis of case reports that included signs and symptoms of CRPS (suspected cases of CRPS). Outcome of this evaluation is outlined below:

1. Analysis of cases that included the MedDRA Preferred Term (PT) of CRPS

Since launch (17 May 2007) until 15 June 2015, a total of 49 case reports were identified in the GSK global safety database that included the MedDRA PT of CRPS. This corresponds to a reporting rate of 0.086 per 100,000 doses distributed worldwide. All individual cases were reviewed and classified according to the established case definition by Harden et al 2010, as described above.

In summary, five cases, that reported disproportionate continuous pain, allodynia and other signs of autonomic system disturbance in an injected limb, were identified as confirmed cases of CRPS as

presented in Table 2 including the company comments that summarizes the medical assessment of each case.

Thirty-seven (37) cases were classified as unconfirmed cases of CRPS and six as unlikely cases of CRPS according to the established case definition for CRPS. Details of the assessment for these cases are presented in Annex 1.

One case from Japan that was identified in an article contains insufficient information to perform further assessment (e.g. subject's details and adverse events experienced). It was classified as unassessable case and therefore excluded from the assessment.

Table 2: Confirmed cases of CRPS according to the established case definition of CRPS by Harden et al 2010 (n=5)

Argus Case ID	Age / Gender	Country	List of events (MedDRA PTs)	Total number of doses received (dates of vaccination)	Dose numbers administered after onset of pain	Case Outcome	List of Medical Conditions	Company Comments
A201012743	45/F	Japan	Bone atrophy, Periarthritis, Arthritis, Bursitis, Synovitis, Synovectomy, Arthralgia, Injection site pain, Injection site movement impairment, Injected limb mobility decreased, Musculoskeletal pain, Musculoskeletal stiffness, Joint swelling, Polyarthritis, Pain, Incorrect route of drug administration, Complex regional pain syndrome, Injection site erythema, Fluid retention, Myositis, Muscular weakness, Pain in extremity, Injection site swelling, Tenosynitis, Red blood cell sedimentation rate increased, C-reactive protein increased, Rotator cuff syndrome, Synovial disorder, Inflammation, Excessive granulation tissue, Fibrosis, Hypoaesthesia, Temperature regulation disorder, Oedema, Hyperhidrosis, Hypohidrosis, Dystonia, Joint contracture, Soft tissue disorder	3 (06-Apr-10, 13-May-10, 19-Oct-10)	All 3 doses administered, the onset of injected limb mobility decreased was at 196 days after the first dose. Duration of AEs was not reported	Unknown	Current Condition: Allergy to fermented products	*Fulfils diagnostic criteria of CRPS. The subject experience of intense persistent pain, oedema, decreased range of motion of vaccinated limb. However, vaccine was administered at wrong place, close to acromion and the subject was concurrently diagnosed with bursitis and synovitis. The events can be considered related to the method of administration (maladministration). Usual daily activities were affected*
A201114533	12/F	Japan	Oedema peripheral, Pain in extremity, Musculoskeletal pain, Hypoaesthesia, Injected limb mobility decreased, Pyrexia, Skin discolouration, Pain, Injection site irritation, Peripheral coldness, Movement disorder, Back pain, Injection site paraesthesia, Extensive swelling of vaccinated limb, Complex regional pain syndrome, Gait disturbance, Hyperhidrosis, Injection site pain, Injection site swelling, Allodynia, Oedema, Diplopia, Swelling, Dysgeusia, Seizure, Dysculculia, Abnormal behaviour, Screaming, Platelet count decreased, Dissociation, Photophobia, Nausea, Anxiety, Headache, Pruritus, Rash, Dysphagia, Injection site hypoaesthesia, Peripheral swelling, Vomiting, Arthralgia, Myalgia, Memory impairment, Sleep disorder, Fatigue, Feeling abnormal, Amnesia, Moaning, Fall, Neuralgia, Mental impairment, Abnormal sleep-related event, Nervous system disorder, Tremor, Bell's palsy, Asthenia, Depressed level of consciousness, Abnormal dreams, Malaise, Abdominal pain, Loss of consciousness, Dysmenorrhoea, Visual acuity reduced, Dizziness, Judgment impaired, Anaphylactic reaction, Menstruation irregular, Limb reduction	2 (16-Sep-11, 19-Oct-11)	2 doses administered, onset of oedema, oedema peripheral and pain in extremity at 33 days after the first dose, the onset of hypoaesthesia at 34 days after the first dose, duration of AEs were reported to be >1,200 days	Recovering/ Resolving	Historical Conditions: Appendicitis, Intermittent joint syndrome, Enteritis infectious, Appendicectomy	*Fulfils diagnostic criteria of CRPS. Intense pain, allodynia was mentioned, extensive swelling, hyperhidrosis, skin discolouration of vaccinated limb. Usual daily activities were affected. Medical history includes abdominal pain with diagnosis of chronic appendicitis, and occasional abdominal pain after surgery*
A201201723	14/F	Japan	Injection site pain, Injected limb mobility decreased, Myalgia, Loss of consciousness, Shock, Guillain-Barre syndrome, Peripheral swelling, Pallor, Grip strength decreased, Headache, Musculoskeletal pain, Nausea, Asthenia, Syncope, Coordination abnormal, Dizziness, Oedema peripheral, Photopsia, Malaise, Urticaria, Insomnia, Dysgeusia, Hypoaesthesia, Anxiety, Contusion, and	3 (06-Aug-11, 06-Sep-11, 07-Feb-12)	3 doses administered, the onset of injected limb mobility decreased at 29 days after the first dose, the onset of hypoaesthesia, muscular weakness, oedema	Not Recovered/Not Resolved		*Fulfils diagnostic criteria of CRPS. Continuous severe pain was reported in vaccinated arm, weakness, and coldness of upper and lower extremities, lower limb oedema, pain in the chest and leg, dyspnoea, hyperpnoea, slight fever, stomatitis, worsening of painful coarse, and taste disturbance. Initially, no symptoms*

Argus Case ID	Age / Gender	Country	List of events (MedDRA PTs)	Total number of doses received (dates of vaccination)	Dose numbers administered after onset of pain	Case Outcome	List of Medical Conditions	Company Comments
			Depressed mood, Dysgeusia, Decreased appetite, Complex regional pain syndrome, Hyperventilation, Chest pain, Peripheral coldness, Feeling cold, Abdominal pain, Pain, Muscular weakness, Muscle atrophy, Neuralgia, Muscle spasms, Nervous system disorder, Pain in extremity, Pyrexia, Orthostatic intolerance, Menstruation irregular, Memory impairment, Arthralgia, Myalgia		peripheral and pain in extremity was at >555 days after the first dose; complex regional pain syndrome was reported at 605 days after the first dose. Duration of reported AEs was unknown			*related to local presentation of CRPS were reported. Usual daily activities were affected*
B0992284A	14/F	United Kingdom	Complex regional pain syndrome	1 (date not reported)	1 dose administered, the date of vaccination was not reported, the onset of CRPS at 1 day after vaccination with unknown date and duration	Resolved with Sequelae	Historical Condition: Gastritis. No adverse event	*Fulfils diagnostic criteria of CRPS. Intense pain, increasing in severity, swollen (oedema) arm, sweating, with intermittent cold, warm hand, blue discolouration and restricted hand movement of vaccinated limb. Usual daily activities were affected*
B0992657A	12/F	UK	Complex regional pain syndrome, Paraesthesia, Muscular weakness, Pain in extremity, Pallor, Skin discolouration, Body temperature decreased, Oedema, Injected limb mobility decreased	1 (date not reported)	1 dose administered, the date of vaccination and the onset of pain symptoms were not reported, CRPS was reported to have lasted for 210 days	Resolved	Current Condition: Headache	*Fulfils diagnostic criteria for CRPS with symptoms disproportionate to inciting events, as paraesthesia progressing to left arm weakness and pain, skin discolouration, temperature changes, oedema and decreased limb mobility. It was not reported that daily activities were impacted*

2. Analysis of cases that included signs and symptoms of CRPS (suspected cases of CRPS)

For this analysis, a stepwise methodology was followed to evaluate cases reporting signs and symptoms of CRPS to determine potential undiagnosed or unrecognized cases of CRPS in the GSK global safety database for Cervarix.

To retrieve cases for evaluation, symptoms described in the Budapest criteria of CRPS (Harden et al. 2010) were matched to the MedDRA PTs as presented in Table 3.

Table 3: Criteria established by Harden et al 2010 matched to the MedDRA Preferred Terms (PTs)

Symptoms of CRPS, Harden, 2010	MedDRA PTs
Pain: Continuing pain disproportionate to vaccination	Pain; Pain in extremity
Sensory: Allodynia deep pressure pain, Allodynia pain after movement, Allodynia after light touch, Hyperesthesia, Hypoesthesia, Hyperalgesia, Hypoalgesia	Allodynia, Hyperaesthesia, Hypoaesthesia, Sensory disturbance, Skin burning sensation
Vasomotor: Color change/difference, temperature difference	Skin discolouration, Skin hyperpigmentation, Skin hypopigmentation, Skin atrophy, Temperature difference of extremities, Skin warm, Skin depigmentation, Skin dystrophy
Pseudomotor /oedema: Transpiration disturbance, Edema	Oedema, Oedema peripheral, Hyperhidrosis, Hypohydrosis, Cold sweat, Skin oedema
Trophic: Hair growth change, Nail growth change, Trophic skin disturbance	Hair growth abnormal, Nail growth abnormal, Onychoclasis
Motor: limitation of movement, Limitation of strength, Dystonia, Tremor, Bradykinesia	Injection site movement impairment, injected limb mobility decreased, Muscular weakness, Dystonia, Tremor, Bradykinesia, Motor dysfunction

a) The GSK global safety database was queried to identify cases which reported MedDRA PT of "Pain" or "Pain in extremity'. As a result, a total of 2,001 were identified.

b) It is expected that some subjects would report pain or pain in extremity, as a substitute of injection site pain which should resolve within 2 weeks at maximum. Therefore, only cases of pain or pain in extremity with duration of more than two weeks were included for further analysis. This subset of data was classified as 'longterm pain'. Case reports that also included the MedDRA PT of CRPS were excluded in this analysis since these cases had been analyzed separately as described above. As a result, a total of 1,580 cases were included in the further step.

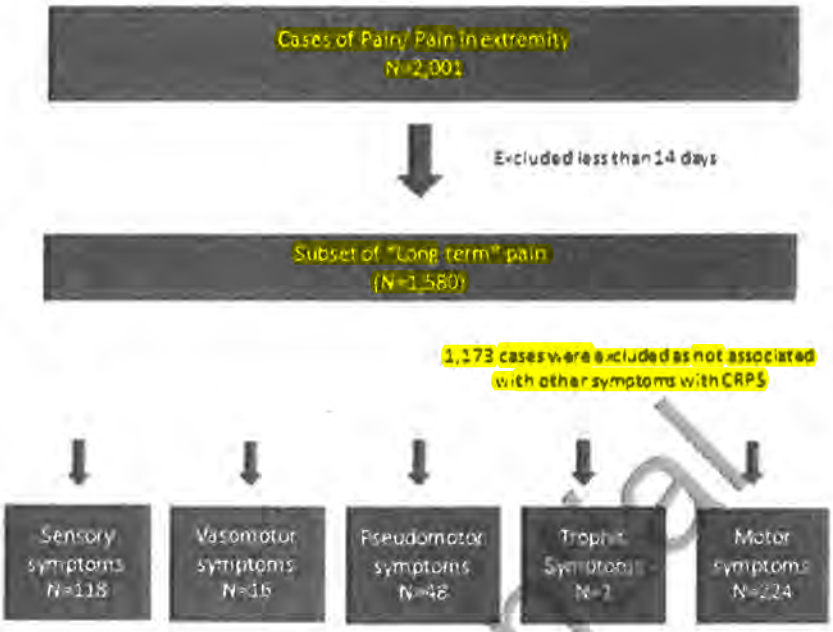
c) The subset of 'long-term pain' cases was used to identify cases with other possible symptoms of CRPS, as below:

- **i.** Subset of 'long-term pain' + sensory symptoms
- **ii.** Subset of 'long-term pain' + vasomotor symptoms
- **iii.** Subset of 'long-term pain' + pseudomotor symptoms
- **iv.** Subset of 'long-term pain' + trophic symptoms
- **v.** Subset of 'long-term pain' + motor symptoms
- **vi.** Subset of 'long-term pain' + all symptoms

d) Cases identified in step c were reviewed and assessed against the established case definition of CRPS by Harden 2010.

e) Results of this search are presented in Figure 1.

Figure 1 CRPS: Search strategy and number of cases identified



In summary, for the cases that reported a combination of pain or pain in extremity:

- 118 cases were associated with sensory symptoms. Of these,
  - 45 cases were reported in the context of concurrent diseases such as neuropathy peripheral, Guillan-Barre syndrome, fibromyalgia, arthritis and other rheumatoid diseases.
  - character of pain and location of pain and sensory symptoms were missing in 68 cases
  - 3 cases were suggestive of injection site reactions that persisted beyond two weeks,
  - diagnosis of CRPS was not confirmed following investigation in 1 case
  - CRPS could not be excluded in 1 case, as severe persistent pain, numbness and burning sensation were all reported in vaccinated limb, the subject was treated with analgesics, it was also reported that pain spread over the body. As only pain in extremity and sensory disturbance were present and therefore a diagnosis of CRPS could not be confirmed.
- 16 cases were associated with vasomotor symptoms. Of these,
  - 1 case was reported in the context of concurrent disease as neuropathy peripheral,
  - 2 cases were suggestive for injection site reaction that persisted beyond two weeks
  - for 12 cases, character of pain and location of pain and vasomotor symptoms were missing or the information provided did not fit with the definition of CRPS,
  - CRPS could not be excluded in 1 case, as pain and skin discoloration of vaccinated limb were reported, the events worsen 1 day after vaccination. No further information has been reported to confirm a CRPS diagnosis.

- 48 cases were associated with pseudomotor symptoms. Of these,
  - 13 cases were reported in the context of concurrent diseases, such as neuropathy peripheral, GBS, juvenile arthritis, paralysis.
  - 25 cases were suggestive of injection site reaction that persisted beyond two weeks
  - for 10 cases, the character of pain and location of pain and pseudomotor symptoms were missing or the information provided did not fit with the definition of CRPS.
- One case was associated with trophic symptoms. This case was reported in the context of a concurrent disease – cutaneous vasculitis.
- 224 cases were associated with motor symptoms. Of these,
  - 54 cases were reported in the context of concurrent disease, such as juvenile arthritis, paralysis, fracture, GBS, herpes zoster, periatritis, phlebitis etc,
  - 136 cases were suggestive of injection site reaction that persisted beyond two weeks,
  - For 33 cases, character of pain and location of pain and motor symptoms were missing or the information which provided did not fit with the definition of CRPS.
  - CRPS could not be excluded in 1 case, as pain and injected limb mobility decreased were reported in vaccinated limb with decreased grip strength. The subject was treated with pregabalin with slight improvement. No further information has been reported to confirm a CRPS diagnosis.

As a result of this review, 3 suspected cases of CRPS were identified that reported a combination of pain or pain in extremity, however the level of information including the absence of other required symptoms of CRPS and objective confirmation of these symptoms do not allow to confirm a diagnosis of CRPS.

In summary, no cases of CRPS were identified as confirmed from this analysis.

3. Additional analysis following the search criteria suggested by Sanofi Pasteur/Merck Sharp and Dohme (SP/MSD).

Although both GSK and SP/MSD agreed to use the same CRPS case definition based on Harden 2010, slight differences remained on CRPS search methodology regarding the list of MedDRA PTs and its combination. GSK decided to keep the search methodology used in previous analyses conducted by the Company, previously communicated to the PRAC and published in the medical literature (Huygen 2015). While it is acknowledged that no significant differences would result in using both search methodologies, an additional analysis was performed based on search methodology by SP/MSD to ensure that all suspected cases of CRPS are retrieved, as outlined below.

Step 1:

Table 4 presents five groups that included a combination of MedDRA PTs representing symptoms of CRPS. These five groups were used in the 5 queries, as described below.

Table 4: SP/MSD criteria: MedDRA PTs representing symptoms of CRPS

Groups	MedDRA PTs
Group A	back pain, flank pain, musculoskeletal pain, neck pain, pain in extremity, pain
Group B	hyperaesthesia, allodynia, hypoaesthesia
Group C	feeling hot, skin discoloration, skin hyperpigmentation, skin hypopigmentation, skin warm, feeling cold, cold sweat, onychoclasis, hair growth abnormal, peripheral coldness, skin atrophy
Group D	oedema, hyperhidrosis, cold sweat
Group E	muscular weakness, tremor, dystonia, motor dysfunction, orthostatic tremor, mobility decreased, abasia , paresis

Step 2:

Five queries were run using the logic displayed below:

Query #1: Group A AND Group B AND Group C AND Group D

Query #2: Group A AND Group B AND Group D AND Group E

Query #3: Group A AND Group B AND Group C AND Group E

Query #4: Group A AND Group C AND Group D AND Group E

Query #5: Group A AND Group B AND Group C AND Group D AND Group E

As a result of these queries, 23 cases were identified in the GSK global safety database.

Of these cases:

- 10 cases contained the MedDRA PT of CRPS (these cases were included in the first analysis provided above),
- For 5 cases, the description and/or location of pain was missing or the information provided was limited and did not fit with the definition of CRPS
- The remaining cases were reported with concurrent diagnosis, such as paralysis, fibromyalgia, epilepsy, nervous system disorder, etc.

No additional cases of suspected CRPS were identified, as a result of this analysis.

Based on the search methodology by SP/MSD, 3 cases were identified that were not included in the GSK analysis. For 2 cases, the symptom of pain or pain in extremity lasted less than 2 weeks and one case reported back pain but the MedDRA PTs of pain or pain in extremity was not reported.

Conclusion

Altogether, using different search methodologies to retrieve all case reports indicative of CRPS in the GSK global safety database for Cervarix (total N = > 24,000 spontaneous and literature reports) and following over 57 million doses of Cervarix distributed globally, five case reports fulfilled the criteria of CRPS according to the established case definition (Harden 2010). A broader search strategy using more sensitive but less specific event terms in order to identify suspected cases of CRPS, including an additional search based on SP/MSD search criteria, did not identify additional cases in these analyses.

Given the heightened public concern regarding the safety of HPV vaccines in Japan, triggered by the case reports of CRPS in Japan in 2013, GSK has since conducted comprehensive analyses with regard to CRPS, including consultation with an independent expert panel for 'pain'. Following similar methodology to that outlined in response to Question 1 and after the preliminary review of the

identified CRPS cases by a GSK safety physician, the two independent external experts were provided with the individual clinical narratives of identified cases for review using the same case definition. The assessment of cases by GSK and the results of the quantitative analyses were only shared with the experts once their own separate assessments of individual cases were completed. Results of this safety evaluation have just been published (Huygen 2015) and are very much in line with the outcome of these investigations.

In conclusion, it is GSK's opinion that the outcome of this analysis is not sufficient to establish a causal association between CRPS and vaccination with Cervarix.

CRPS will remain under safety surveillance, as described in the current Risk Management Plan for Cervarix (version 10.1), the results of ongoing safety evaluation will be discussed in the annual Periodic Safety Update Report cycles.

Assessor's comments

Cases with PT=CRPS

In total, 49 cases with PT CRPS have been retrieved by GSK since the first launch of Cervarix (May 2007) until the DLP of 15 June 2015. Diagnosis of CRPS cases is hampered due to the variety of signs and symptoms in highly variable combinations with a variable progression over time and the absence of a gold standard test to confirm CRPS. The Budapest clinical diagnostic criteria for CRPS of Harden et al. (2010) were applied to assess each case. The Co-Rapporteur categorized the cases according to the following scheme:

PT CRPS	Criteria Harden followed: YES	Criteria Harden followed: NO/UNKNOWN
Diagnosed cases	**2**	**12**
Suspected cases	**0**	**9**
Mentioned cases	**3**	**23**

1/ In 5 out of 49 cases, the diagnostic criteria for CRPS of *Harden et al. (2010)* were met (B0681574A, A201306725, A201409041, B0605284A, B0902657A) and can be considered as CRPS cases. **In 3 of these 5 cases (A201409041, B0605284A, B0902657A), the involvement of Cervarix in the occurrence of CRPS cannot be ruled out due to:**

- a strong temporal relationship between the events and administration of the vaccine (same day to less than 2 weeks),

- the absence or unknown relevant medical history

- the absence of other events which might explain the symptoms.

Details of these 3 CRPS cases:

The age group affected ranged from 12 to 20 years of age, one report originated from Japan, the other two reports from UK. The occurrence of the events varied from being present after first or third dose. Outcome was unknown or positive (resolved or resolved with sequelae) in respectively one and two reports. In one case the events were considered serious due to disability or incapacity. CRPS has been diagnosed in one report, one week after the administration of the first dose of Cervarix.

Two remaining cases describe either events occurring after maladministration of the vaccine (A201012743) or some events occurring within 1 hour after vaccination which would expect to be taken place after a certain delay (i.e. numbness of lower extremities, generalized pain) (A201306725). In these cases, no conclusion can be made.

2/ The remaining 44 cases can be considered as potential CRPS cases, because of insufficient information regarding the diagnostic criteria or incompletely fulfilled diagnostic criteria of Harden et al.

Nevertheless, 12 cases were **still *diagnosed or reported by a physician***. **In 6 out of the 12 *diagnosed* cases (A201211331, A201307874, A201309945, A201310607, A201313129, B0739052A), the involvement of Cervarix in the occurrence of a *potential* CRPS cannot be ruled out due the same reasons mentioned above.**

Details of these 6 potential CRPS cases:

The age group affected ranged from 13 to 16 years of age; in one case age was not specified but ranged between 10-19 years of age. These cases were originated from Japan, except one from UK (B0739052A). The events started within the first month or earlier after administration of the vaccine. Half of the cases presented with a positive outcome (recovering/resolving), the remaining cases presented with an unknown outcome (n=2) or resulted in unresolved events (n=1). In half of the cases the events were considered serious due to hospitalization or disability/incapacity. In half of the cases time of diagnosis was unspecified, in the other half it varied from 1 week to 1 month after vaccination.

For the following cases it is not possible to draw a conclusion:

In one case differential diagnosis of fibromyalgia with somatoform disorder was made. Another case was confounded by other events which might explain the symptoms (Guillain-Barré syndrome). Other cases did not report a strong temporal relationship with the vaccination (2 to 4 months after the second dose, n=2) or did not specify the time to onset of the events (n=1). In 1 case diagnosis was made 1 day after vaccination which is unlikely as CRPS diagnosis is made after exclusion of other diseases and no specific diagnostic test is available.

In 9 out of the 44 cases, CRPS was ***suspected.*** **In only 1 case (A201310042) the involvement of Cervarix in the occurrence of a *potential* CRPS cannot be ruled out due to the same reasons mentioned above. Events occurred in a 14 years old girl starting within 1 month after the first dose. Outcome of the events is unknown, nevertheless the case is considered non-serious.**

In the remaining cases (n=8), other diseases could not be ruled out, such as fibromyalgia (n=2), psychosomatic or psychological disease (n=2), myositis (n=1) and/or temperal relationship was not strong (2 to 6 months after vaccination) (n=2). In two cases further examination was required or planned. For these cases it is not possible to draw a conclusion.

In 23 out of 44 cases, CRPS was ***mentioned.*** **In only 1 case (JP2014JPN000388) the involvement of Cervarix in the occurrence of a *potential* CRPS cannot be ruled out due to the same reasons mentioned above. Events occurred in a 16 years old girl starting 1 month after the third dose. Outcome of the events is unknown, however the case is considered serious due to hospitalization and disability/incapacity.**

In the majority of the remaining cases, temporal relationship was unknown (15 out of 23 cases) or not strong (1 out of 23 cases). Other cases were poorly described (4 cases) or were diagnosed with other diseases which might explain symptoms, such as somatoform disorder (n=1), bruising (n=1) or a normal injection site reaction (n=1). For these cases it is not possible to draw a conclusion.

Cases with PT of the signs and symptoms of CRPS – SP/MSD search

As a result of the query of SP/MSD, 23 cases were identified in the GSK global safety database.

Of these cases, 10 cases contained the MedDRA PT of CRPS (these cases were included in the first analysis provided above).

In 4 cases out of 13, the occurrence of CRPS is unlikely due to temporary pain (less than 2 weeks) or other events which disappeared after 1 day.

In 9 cases out of 13, CRPS-like symptoms are described, therefore considered to be *potential* CRPS cases:

- Eight cases did not completely meet the diagnostic criteria of Harden et al. or contained insufficient information to verify the criteria (i.e. in some cases it was unknown whether pain was continuing or not). **Therefore, these cases do not allow to confirm a diagnosis of CRPS**. In 6 of these 8 cases it is not possible to draw a conclusion because of unknown time-to-onset of the events (n=2) or no strong temporal relationship with Cervarix (n=3) and/or the presence of confounders like other (suspected) diseases (n=4) (i.e. fibromyalgia, psychogenic factors) or tetanus vaccination on an unknown date (n=1). In these cases no conclusion can be made. **In 2 of the 8 cases (A201108547, B0838757A) the involvement of Cervarix in the occurrence of CRPS-like symptoms cannot be excluded due to: temporal association between the events and the administration of the vaccine (events started same day after vaccination), the absence or unknown relevant medical history and the absence of other events which might explain the symptoms. In both cases, the events occurred in adolescents (13 and 16 years of age) in different countries (Japan vs. the Netherlands) with a different outcome and severity (not recovered, serious case vs. recovering, non-serious case).**

- One case fulfills the diagnostic criteria of Harden et al. 2010 but lacks information regarding time-to-onset of the events. In this case, no conclusion can be made.

Cases with PT of the signs and symptoms of CRPS – GSK search

GSK refined their search strategy by retrieving cases with pain with duration of 2 weeks or longer or pain of unspecified duration, both combined with at least one symptom in three of the four following categories: sensory, vasomotor, pseudomotor/edema, motor/trophic, as mentioned in Huygen et al. *(2015)*. As a result of this query of GSK, 5 cases were identified in the GSK global safety database.

Of these cases, 4 cases were identified that were included in the SP/MSD search.

In the remaining case, time-to-onset of CRPS-like symptoms varied from unspecified to late time-to-onset. Furthermore this case was confounded by diagnosis of Guillain-Barré syndrome. Therefore, no conclusion can be made.

Overall conclusion

In 3 CRPS cases and 10 potential CRPS cases, which were retrieved since the first launch of Cervarix (May 2007) until the DLP of 15 June 2015, the causal relationship between the administration of Cervarix and the occurrence of CRPS/potential CRPS cannot be ruled out. Whether this is due to the injection or the vaccine itself cannot be determined as in literature CRPS was also reported following venipuncture, intravenous drug administration and other vaccinations *(Richards et al. 2012; Kwun et al. 2012; Genc et al. 2005; Jastaniah et al. 2003; Bilic et al. 2013)*. However, if the injection itself triggers the event, and given the large number of people that receive injections for various medical reasons, one would expect a much larger number of reports of CRPS triggered by injections.

The number of CRPS cases following administration of Cervarix is considered low compared to 57 million doses of Cervarix distributed globally. The low number might be contributed by the problem of underreporting of ADRs in general, and more specifically, the difficulty of diagnosing CRPS being a complex syndrome with a variety of signs and symptoms in highly variable combinations with a variable progression over time. Furthermore, there is no gold standard diagnostic test for CRPS available, remaining CRPS as a syndrome of exclusion of other diseases with similar signs and symptoms, and no overall consensus on the clinical diagnostic criteria of CRPS *(Rockett 2014)*. However the most widely accepted diagnostic criteria are the Budapest criteria described by *Harden et al. (2010)*. All taken together, many patients could be undiagnosed.

POTS

MAH's response

POTS is a poorly understood cause of orthostatic intolerance resulting from cardiovascular autonomic dysfunction. POTS is distinct from the syndromes of autonomic failure usually associated with orthostatic hypotension, such as pure autonomic failure and multiple system atrophy. Individuals affected by POTS are mainly young (aged between 15 years and 40 years) and predominantly female (Marinus J et al. Clinical features and pathophysiology of complex regional pain syndrome. July 2011. The Lancet Neurology. Volume 10 (7), p637-648. Mathias 2

Case definition

The MAH is proposing to use the case definition for POTS based on the recent publications by Raj 2013 and Sheldon 2015:

Postural orthostatic 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)

Post-marketing data

The MAH's global safety database was searched using the following criteria:

- **Data lock point(s)**: 15 June 2015
- **Report types**: All spontaneous and post-marketing case reports
- **Cervarix** was reported as a suspect vaccine.

A stepwise approach in the analysis of cases was performed: (1) analysis of case reports that included the MedDRA Preferred Terms (PTs) of POTS, and (2) Analysis of case reports that included signs and symptoms of POTS (suspected cases of POTS). Outcome of this evaluation is outlined below:

1. Analysis of case reports that contain the MedDRA PT of POTS

A total of 19 case reports were identified in the MAH's global safety database since launch until 15 June 2015.

- Five cases were identified as confirmed cases of POTS as they contain information about symptoms suggestive of POTS and confirmation of increased pulse following the different tests (mainly Schellong's test). Table 1 provides the detail description of these confirmed cases including company's medical assessment of each case.
- Thirteen cases were classified as unconfirmed cases of POTS, as no information on BP or pulse was provided.
- One case from Japan (identified in an article) that reported both CRPS and POTS is classified as unassessable for the same reason described in the CRPS analysis.

Confirmed Cases of POTS

Table 1: Confirmed cases of POTS according to case definition by Raj et al., 2013 and Sheldon et al, 2015 (n=5)

Case ID	Age/ gender	Country Of Reporter	Events reported (MedDRA Preferred Terms)	Onset of events from first dose	Total number of doses received /Duration of AEs	List of Medical Conditions	Case outcome	Company Comments
A201400155	13/F	Japan	Pain, Pain in extremity, Headache, Arthralgia, Abdominal pain, Myalgia, Back pain, Injection site pain, Hyperhidrosis, Peripheral coldness, Tachycardia, Neuropathy peripheral, Postural orthostatic tachycardia syndrome, Menstrual disorder	0 month after 3rd dose	3 doses administered (16-MAY-2012, 26-Jun-2012, 26-Dec-2012). Duration of reported AEs was not reported	Hemiplegic migr; Amenorrhoea; Historical Conditions: Low birth weight baby	Recovering/ Resolving	*Tachycardia only was reported with positive standing test showing increase of 46 bpm at 10 minute with concurrent increase in BP. Initial BP and pulse were low. One episode of tachycardia was reported. No other reasons that could cause orthostatic hypotension were reported. No Tilt test was reported.*
A201403100	12/F	Japan	Neuropathy peripheral, Illusion, Injection site pain, Dizziness postural, Dizziness, Palpitations, Malaise, Hypoaesthesia, Pain, Asthenia, Chest pain, Headache, Anxiety, Insomnia, Arthralgia, Memory impairment, Depression, Depressive symptom, Mobility decreased, Muscular weakness, Crying, Panic reaction, Dyspnoea, Nausea, Anxiety disorder, Heart rate increased, Postural orthostatic tachycardia syndrome, Orthostatic intolerance, Tremor	3 days after 2nd dose	2 doses received (15-APR-2012, 15-May-2012). Duration of reported AEs was not reported	Intentional self-injury;Current Condition;Stress	Not Recovered/ Not Resolved	*Dizziness, palpitation were reported. No BP or pulse measurements were reported. Blood tests NOS, ECG, head MRI, EchoCG all normal including N thyroid function. Schelong's test reported to show POTS without details. No Tilt test was reported*
B0643830A	21/F	UK	Chronic fatigue syndrome, Encephalitis autoimmune, Dizziness, Status epilepticus, Throat tightness, Fatigue, Visual impairment, Abdominal distension, Decreased appetite, Nausea, Asthenia, Presyncope, Gastrointestinal disorder, Altered visual depth perception, Visual field defect, Malaise, Abdominal pain upper, Autonomic nervous system imbalance, Activities of daily living impaired, Dysstasia, Impaired work ability, Head discomfort, Postural orthostatic tachycardia syndrome, Paraesthesia, Pruritus, Mastocytosis, Tremor, Vertigo, Impaired gastric emptying, Small intestinal bacterial overgrowth, Disorientation, Vomiting	2 days after 1st dose	2 doses received (05-Mar-2009, 20-Apr-2009).	Historical Drug:TOPIRAMATE, PIZOTIFEN, METOCLOPRAMIDE, CYCLIZINE, DOMPERIDONE, MEBEVERINE	Unknown	*Dizziness, visual impairment, presyncope were reported. Increase from 68 to 120 in the morning, low pulse in supine position was observed. BP monitoring confirmed POTS features, test was conducted in the morning. Tilt test reported slight tachycardia. EEG showed sinus tachycardia. Some difference was observed in reporting test results and diagnosis, however as worst case scenario this case is considered as confirmed.*
JP2014JPN009776	15/F	Japan	Complex regional pain syndrome, Orthostatic intolerance, Postural orthostatic tachycardia syndrome, Pain in extremity, Tremor, Peripheral coldness	Unknown	1 dose received (date of vaccination not reported). Duration of AEs not reported.	No information reported.	Unknown	*Orthostatic intolerance was reported. Increase in heart rate of 48 bpm per minute during Schellong test was observed. No Tilt test was reported.*
JP2014JPN009778	16/F	Japan	Orthostatic intolerance, Postural orthostatic tachycardia syndrome, Fatigue, Headache, Monoparesis, Gait disturbance	Unknown	1 dose received (date of vaccination not reported). Duration of AEs not reported.	No information reported.	Unknown	*Orthostatic intolerance, tachycardia were reported. Increase in heart rate of 48 bpm per minute during Schellong test was observed. No Tilt test was reported.*

The individual case details including the medical assessment of each case is provided in Table 2.

Unconfirmed Cases of POTS

The company classified 13 cases as unconfirmed (see annex A of the "Responses to questions"). All cases included the MedDRA PT of POTS but the method used to diagnose the syndrome was not specified and the measure of increase in bpm was not indicated. In some cases, dates of vaccination and dates of onset were unknown. Those cases are discussed the co-Rapporteur comments section.

Table 2: Overview of case reports that included the MedDRA PT of POTS (Worldwide, DLP 15 June 2015, n=19)

Case ID	Age/ gender	Country Of Reporter	Events reported (MedDRA Preferred Terms)	Onset of events from first dose	Total number of doses received /duration of AEs	List of Medical Conditions	Case outcome	Company Comments	Case categories
A201011686	16/F	Japan	Urticaria, Syncope, Seizure, Pruritus, Depressed level of consciousness, Muscle spasms, Pulse absent, Erythema, Rash, Postural orthostatic tachycardia syndrome, Epileptic aura	1 day 2nd dose	2 doses received Duration of AEs was not reported.	Historical Condition: Asthma, Syncope, Confusion	Recovered/ Resolved	*Several episodes of syncope at the same time as subject had urticaria 1 day following vaccination with the 2nd dose. The subject has a medical history of head confusion and syncope. Tilt test performed at the same time was diagnostic for POTS without any details. The subject was treated with corticosteroids and antihistamine. All events seemed to have resolved within 1 week. EEG showed epileptic activities. No work-up for other causes. No details on pulse and BP.*	unconfirmed case
A201315405	13/F	Japan	Orthostatic intolerance, Fatigue, Gait disturbance, Limb discomfort, Orthostatic hypotension, Postural orthostatic tachycardia syndrome, Mental impairment, Muscular weakness, Malaise, Chronic fatigue syndrome, Learning disorder, Feeling abnormal	5 months after 3rd dose	3 doses received (14/10/2010, 11/11/2010, 28/04/2011). Onset of orthostatic intolerance event at around 5 months after the 3rd dose that lasted for 637 days.	No information reported.	Recovering/ Resolving	*Orthostatic intolerance and hypotension were reported. No test confirming the DS, an unspecified orthostatic test was mentioned without any details. PET with normal findings. duration of the events longer than 6 months. No work-up for other causes. No details on pulse and BP. No Tilt test was reported.*	unconfirmed case
B0749951A	13/F	UK	Post viral fatigue syndrome, Malaise, Limb discomfort, Pyrexia, Vomiting, Abdominal pain lower, Myalgia, Fatigue, Headache, Blood iron decreased, Menstruation irregular, Menorrhagia, Allergy to animal, Skin papilloma, Lethargy, Nasopharyngitis, Influenza, Decreased activity, Chills, Oropharyngeal pain, Rash generalised, Arthralgia, Hypoaesthesia, Dyspnoea, Emotional disorder, Mood altered, Dizziness, Menstrual disorder, Paraesthesia, Peripheral coldness, Hyperhidrosis, Alopecia, Food intolerance, Nausea, Dyspepsia, Disturbance in attention, Memory impairment, Insomnia, Increased tendency to bruise, Photophobia, Hypersomnia, Tachycardia, Postural orthostatic tachycardia syndrome, Gastrooesophageal reflux disease, Confusion	0 month after 2nd dose	2 doses received (date of vaccination was not reported); duration of AEs was not reported.	Current Condition: Seasonal allergy; Drug hypersensitivity; Historical Condition: No adverse event	Unresolved	*Decreased activity, tachycardia, dizziness were reported. No BP or pulse or diagnostic tests, including Tilt test were reported. Medical history included low Ferritin in blood test.*	unconfirmed case

Case ID	Age/ gender	Country Of Reporter	Events reported (MedDRA Preferred Terms)	Onset of events from first dose	Total number of doses received /duration of AEs	List of Medical Conditions	Case outcome	Company Comments	Case categories
B0820497A	12/F	UK	Seizure, Seizure like phenomena, Malaise, Pain, Headache, Influenza like illness, Dysstasia, Pain in extremity, Dizziness, Nausea, Viral infection, Nasopharyngitis, Oropharyngeal pain, Fatigue, Post viral fatigue syndrome, Chest pain, Muscle spasms, Hot flush, Nervousness, Asthenia, Chest discomfort, Dyspnoea, Abdominal pain upper, Syncope, Postural orthostatic tachycardia syndrome, Gastrointestinal disorder	1 day after 2 dose	2 doses received (date of vaccination was not reported); onset of Postural orthostatic tachycardia syndrome was reported to be >3 years after vaccination	Historical Condition: Post viral fatigue syndrome	Unknown	*Dizziness, syncope were reported. No BP or pulse or diagnostic tests, including Tilt test were reported.*	unconfirmed case
B0920064A	13/F	UK	Lethargy, Fatigue, Tachycardia, Myalgia, Food intolerance, Memory impairment, Menstrual disorder, Hypoaesthesia, Abdominal pain lower, Oropharyngeal pain, Alopecia, Confusion, Dyspepsia, Allergy to animal, Rash, Influenza like illness, Chest pain, Pyrexia, Increased tendency to bruise, Chronic fatigue syndrome, Photophobia, Postural orthostatic tachycardia syndrome, Headache, Peripheral coldness, Dyspnoea, Hypersomnia, Malaise, Paraesthesia, Post viral fatigue syndrome, Skin papilloma, Nausea, Menorrhagia, Gastrooesophageal reflux disease, Arthralgia, Hyperhidrosis, Disturbance in attention, Insomnia, Dizziness postural	1 week after dose 3	Dates of vaccination were not reported. Duration of AEs was not reported.	Current Condition: Seasonal allergy; Historical Drug: CERVARIX	Unknown	*Consumer case. Tachycardia, fatigue and disturbance in attention were reported. No BP or pulse or diagnostic tests, including Tilt test were reported.*	unconfirmed case
B0926664A	16/F	UK	Loss of consciousness, Unresponsive to stimuli, Headache, Dizziness, Malaise, Chronic fatigue syndrome, Confusional state, Gait disturbance, Arthralgia, Vision blurred, Feeling hot, Musculoskeletal stiffness, Photosensitivity reaction, Hyperhidrosis, Post viral fatigue syndrome, Abdominal pain, Insomnia, Depressed mood, Neck pain, Musculoskeletal pain, Aggression, Agnosia, Seizure, Consciousness fluctuating, Oropharyngeal pain, Gingival pain, Swelling, Tonsillar hypertrophy, Tonsillitis, Infection susceptibility increased, Bedridden, Herpes zoster, Menstrual disorder, Postural orthostatic tachycardia syndrome, Syncope, Dysphagia, Disorganised speech, Hyperacusis	0 days after 3rd dose	Complete dates of vaccination were not reported. Duration of AEs was not reported.	Historical Drug: DTPA VACCINE, CERVARIX	Unknown	*Consumer case. Repetitive episodes of syncope with onset of 0 days after 3rd dose. BP and pulse at several occasions were reported as normal. Tilt test was reported as without abnormal results.*	unconfirmed case

Case ID	Age/ gender	Country Of Reporter	Events reported (MedDRA Preferred Terms)	Onset of events from first dose	Total number of doses received /duration of AEs	List of Medical Conditions	Case outcome	Company Comments	Case categories
B0930106A	12/F	UK	Malaise, Dizziness, Chest discomfort, Influenza like illness, Headache, Syncope, Nasopharyngitis, Oropharyngeal pain, Dysstasia, Fatigue, Pain in extremity, Gastrointestinal disorder, Viral infection, Post viral fatigue syndrome, Abdominal pain upper, Hot flush, Seizure like phenomena, Pain, Chest pain, Chronic fatigue syndrome, Asthenia, Postural orthostatic tachycardia syndrome, Dyspnoea, Nervousness, Muscle spasms, Nausea	0 month after 2nd dose	Complete dates of vaccination were not reported Reported onset of dizziness at 1065 Days after last dose	Historical Condition: Post viral fatigue syndrome	Unknown	Consumer case. Syncope and fatigue were reported. No BP or pulse or diagnostic tests, including Tilt test were reported.	unconfirmed case
B0954483A	13/F	UK	Postural orthostatic tachycardia syndrome, Orthostatic hypotension, Autonomic nervous system imbalance, Fatigue, Malaise, Presyncope	1 month after 2nd dose	Dates of vaccination were not reported. Duration of AEs was not reported.	Historical Drug Generic	Unresolved	Orthostatic hypotension, fatigue and presyncope were reported No BP or pulse or diagnostic tests, including Tilt test were reported.	unconfirmed case
B0992702A		UK	Pain in extremity, Viral infection, Vomiting, Dizziness, Pyrexia, Oropharyngeal pain, Fatigue, Rash, Asthenia, Gait disturbance, Pallor, Nausea, Chronic fatigue syndrome, Postural orthostatic tachycardia syndrome, Scoliosis, Malaise, Autonomic nervous system imbalance, Chest pain, Abdominal pain, Dyspepsia, Movement disorder	2 weeks after 2nd dose	Dates of vaccination were not reported. Duration of AEs was not reported.	No information reported.	Unknown	Dizziness and fatigue were reported. No BP or pulse or diagnostic tests, including Tilt test were reported.	unconfirmed case
GB2015082562	12/F	UK	Dizziness, Syncope, Pyrexia, Chronic fatigue syndrome, Dyspnoea, Postural orthostatic tachycardia syndrome, Chest pain, Fatigue, Hypokinesia, Pain	0 days after unknown dose	Vaccinated on 25-Sept-2012. Duration of AEs was not reported.	No information reported.	Not Recovered/ Not Resolved.	Consumer case. Dizziness, syncope and fatigue were reported. No BP or pulse or diagnostic tests, including Tilt test were reported.	unconfirmed case
GB2015083040	14	UK	Fatigue, Headache, Photophobia, Myalgia, Malaise, Palpitations, Nausea, Dizziness, Feeling abnormal, Chronic fatigue syndrome, Postural orthostatic tachycardia syndrome, Mast cell activation syndrome	11 days after 1st dose	Vaccinated on 14/10/2011. Onset of dizziness around 10 days after vaccination with unknown duration.	Historical Condition: Malaise, Viral infection, Blood iron decreased, Rhinitis	Unknown	Consumer case. Fatigue and dizziness were reported. No BP or pulse or diagnostic tests, including Tilt test were reported.	unconfirmed case

Case ID	Age/ gender	Country Of Reporter	Events reported (MedDRA Preferred Terms)	Onset of events from first dose	Total number of doses received /duration of AEs	List of Medical Conditions	Case outcome	Company Comments	Case categories
JP2015JPN014874	13	Japan	Post vaccination syndrome, Postural orthostatic tachycardia syndrome, Arthritis, Abdominal pain lower, Dizziness, Malaise, Hypersomnia, Dysmenorrhoea, Arthralgia, Pollakiuria, Pruritus, Nail discolouration, Head discomfort, Hearing impaired, Disturbance in attention	11 months after 3rd dose	3 doses received (17/06/2011, 29/09/2011 16/02/2012); Postural orthostatic tachycardia syndrome lasted for 656 days.	No information reported.	Unknown	Dizziness and disturbance in attention were abolished. No BP or pulse or diagnostic tests, including Tilt test were reported.	unconfirmed case
US2014GSK041878	14	US	Urticaria, Syncope, Seizure, Pruritus, Depressed level of consciousness, Muscle spasms, Pulse absent, Erythema, Rash, Postural orthostatic tachycardia syndrome, Epileptic aura	Within 1 week after 3rd dose	Complete dates of vaccinations were not reported Duration of AEs was not reported.	Historical Drug CERVARIX	Not Recovered/ Not Resolved.	Syncope and depressed level of consciousness was reported. No BP or pulse or diagnostic tests, including Tilt test were reported.	unconfirmed case
JP2014JPN009767		Japan	Muscular weakness, Pain in extremity, Monoparesis, Tremor, Gait disturbance, Complex regional pain syndrome	Not reported	Date of vaccination & duration of AEs were not reported.	Not reported	unknown	Case does not fulfil CRPS criteria based on reported events. Literature case. No description of pain was reported. It was reported that symptoms were disabling.	Unconfirmed case
JP2015JPN016251		Japan	Headache, Malaise, Muscular weakness, Somnolence, Dizziness postural, Pain, Learning disorder, Hypersomnia, School refusal, Orthostatic hypotension, Postural orthostatic tachycardia syndrome, Complex regional pain syndrome, Neurofibromatosis, Single photon emission computerised tomogram abnormal, Autonomic neuropathy, Memory impairment	-	-	-	-	Pending for LOC confirmation.	Undassifiable

2. Analysis of cases that included signs and symptoms of POTS (suspected cases of POTS)

The following methodology was conducted to retrieve cases reporting signs and symptoms of POTS to determine potential undiagnosed or unrecognized cases in the GSK global safety database according to the case definition based on Raj 2013, and Sheldon 2015, as described above.

Table 3 presents possible symptoms of POTS matched to the MedDRA PTs grouped into eight.

Table 3: Groups of MedDRA Preferred Terms (PTs) for symptoms of POTS

Groups	**MedDRA PTs**
Group A	Palpitations, tremor, heart rate increased, tachycardia, tachyarrhythmia
Group B	Dizziness, dizziness exertional, dizziness postural, exercise tolerance decreased, muscular weakness, fatigue
Group C	Syncope, presyncope, loss of consciousness
Group D	Orthostatic intolerance, orthostatic heart rate response increased
Group E	Paraesthesia, sensory disturbance, blurred vision
Group F	Hyperhidrosis,
Group G	Memory impairment, disturbance in attention, confusional state, cognitive disorder,
Group H	Autonomic nervous system imbalance, urinary retention, constipation, diarrhea

To identify and determine suspected cases of POTS, 6 queries in the GSK global data base were run using the logic as presented below to explore different combination of the symptoms.

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

As a result of these queries, 7 potential cases were identified and further evaluated. Five cases were reported with other concurrent conditions: epilepsy (2 cases), syncope/vasovagal syncope (2 cases), viral encephalitis (1 case). One consumer case, reported episodes of syncope which started 0 days after 3rd dose with a final diagnosis of early menopause, that resolved meanwhile, did not report data on BP, pulse and Tilt test.

One case, that also contains the MedDRA PT of POTS, was considered as unconfirmed case as Tilt test resulted in no abnormal findings.

No cases of POTS were identified in this analysis.

Altogether, using different search methodologies to retrieve all case reports indicative of POTS in the GSK global safety database for Cervarix (total N = > 24,000 spontaneous and literature reports) and following over 57 million doses of Cervarix distributed globally, five case reports fulfilled the criteria of POTS according to the established case definition (Raj 2013 and Sheldon 2015). A broader search strategy using more sensitive but less specific event terms in order to identify suspected cases of POTS did not identify additional cases in this analysis.

In conclusion, it is GSK's opinion that the outcome of this analysis is not sufficient to establish a causal association between POTS and vaccination with Cervarix. POTS will remain under close safety surveillance through routine pharmacovigilance and will be considered for evaluation as adverse events of interest in each PSUR/PBRER cycle, including development of a targeted follow-up questionnaire.

Assessor's comments

Case definition

The MAH proposed a case definition in line with Raj and Sheldon publications.

The fulfilment of point (4) of the case definition is certainly the most difficult to assess. The list of conditions to exclude should be more extended, including cardiac causes of inappropriate tachycardia, endocrine causes of hyperadrenergism, or other known causes of dysautonomia. Deficit in vitamin B12 may be associated to POTS. A special attention should be paid to the exclusion of infectious triggers other than HPV vaccination such as viral infections. In a review of a series of 152 patients conducted at the Mayo clinic in 1993-2003 (i.e. before HPV vaccination), 90.5% of patients reports suggested an antecedent of viral infection (*Thieben et al. 2007*). In a literature search of PubMed for articles published from 1990 to 2012, Benarroch found that up to 50% of cases have antecedent of viral illness (*Benarroch 2012*).

To note that POTS may also occur during pregnancy or after major surgery (*Raj 2013*).

Review of the 5 cases classified as confirmed by the company

According to the case definition (Table 1), the company selected 5 cases as confirmed POTS. The CIOMs of those 5 cases were reviewed for the fulfilment of the 4 diagnostic criteria (Table 4) and a

short description has been provided below. The assessor classified 2 of the 5 cases as POTS, 1 case as possible POTS, and two cases as unlikely (due to the lack of symptoms). A former viral infection is reported absent in only one case (case 4).

Table 4: Synthetic overview of the fulfilment of diagnosis criteria for 5 cases selected as confirmed.

POTS diagnostic criteria**	**Cases**				
	1	**2**	**3**	**4**	**5**
(1) symptoms	Not	Yes	Yes	Yes	tremor
(2) Orthostatic tachycardia*	Yes	Yes	Yes	Yes	Yes
(3) ≥6 months	Yes	Yes	Yes	unk	unk
(4) other associated disorder	unk	unk	Autonomic disfunction	unk	CRPS I
- viral infection	unk	unk	1st diagnose by GP	Not	unk
- Autoimmune disorder	-	-	Encephalitis Mastocytosis	-	-
Assessor's classification	**Not**	**POTS**	**POTS**	**Possible**	**Not**

* : orthostatic tachycardia demonstrated by tilt table test or Schellong test
** : unk = unknown

Case 1 (CIOMS A201400155): Pain dominates the clinical picture in this report, with paroxysmal pain in the extremity 5 months after the second dose of Cervarix and chronic pain starting one week after the third dose. Typical symptoms of POTS are not described. Finger plethysmogram confirmed peripheral neuropathy.

Case 2 (CIOMS A201403100): The medical history included self-injury, stress and school related anxiety. Stress does not exclude POTS but may favor the development of the syndrome. Peripheral neuropathy is diagnosed with no other indication of diagnostic test.

Case 3 (CIOMS B0843830A): Symptoms started 2 days after the 1st vaccination. There is evidence of re-challenge after the 2nd vaccination. Other diagnosis of interest include: 1) NMDA encephalitis with positive anti-NMDA receptor antibodies (possibly associated with immune-mediated post-vaccination reaction), 2) Mast cell activation (Some patients with POTS have mast cell activation (Raj, 2013)). A viral infection was not excluded and this was the early diagnostic from the general practitioner. Time of vaccination remains unclear.

Case 4 (JP2014JPN009778): This case was reported in the literature. It is a poor documented case: time of vaccination, time of onset, history of treatment, and medical condition were not provided.

Case 5 (JP2014JPN009776): This case was reported in the literature. Time of vaccination, time of onset, history of treatment, and medical condition were not provided.

Review of 13 cases classified as unconfirmed by the company

All cases reports included MedDRA PT of POTS but the diagnostic tests (tilt test table, Schoelong test) were not specified and results were not reported. In consequence, the fulfilment of the case definition cannot be assessed.

Unconfirmed cases were most frequently (8/13) reported by non health professionals. Most cases experienced chronic fatigue syndrome or myalgic encephalopathy (8/13). POTS is often a late diagnosis, sometimes confirmed several year after the beginning of the symptoms, and usually after history of chronic fatigue syndrome. In all cases, the narratives did not permit to assess if other known causes of orthostatic tachycardia were systematically excluded.

The assessor classified 3 of those cases as possible cases of POTS following HPV vaccination. The information provided in 7 cases did not permit to classify the case with a sufficient level of confidence, but POTS following vaccination cannot be ruled out. In three case, the assessor considered that the diagnose of POTS or the association of the syndrome with HPV vaccination was doubtful (Table 4)

Table 5 Summary of unconfirmed cases (based on CIOMS)

Case	POTS post-HPV vaccination	Argument from Summary of the history
6	not	Resolution within 1 week .
7	Possible	Symptoms started 5 months after 3rd dose.
8	not	Alternative diagnoses are reported: flu-like syndrome >1week, post-viral fatigue syndrome, low blood iron.
9	Unclassified	History of post-viral fatigue. Influenza-like illness <2 days (fever unspecified) following 1st dose. Symptoms started 1 days after 2nd dose but a viral episode cannot be ruled out from the narrative.
~~10~~	not	Excluded because this case (CIOMS B0925064A) is probably a duplicate of case 8 (CIOMS B0749391A): same wording of history, same batch number.
11	Unclassified	Onset of symptoms less than one month after 3rd dose. Tilt test is reported to be negative 4 years after 3rd dose.
12	Unclassified	History of post-viral fatigue. Date of vaccination unspecified. Flu-like syndrome (undescribed) 1 day after the first dose of Cervarix. Symptoms started 1 day after 2nd dose.
13	Possible	The subject was diagnosed with POTS, orthostatic hypotension and autonomic dysfunction. The subject experienced increased symptoms after the 3rd dose of Cervarix which was given by mistake. The reporter refers to multiple medical visits (including cardiology, neurology) but no details about the diagnosis of POTs are provided.
14	Unclassified	Occurrence of a one week virus-like illness (fever reported) between 1st and 2nd dose. However, symptoms were reported to increase after 2nd and 3rd dose. Dates of vaccination unknown.
15	Unclassified	Onset immediately after 1st dose. POTS was diagnosed after vaccination but the narrative is incomplete and does not allow more assessment.
16	unclassified	Other diagnoses: decreased blood iron and low grade nasal infection. However, symptoms of chronic fatigue started 11 days after the 1st dose of Cervarix. POTS was diagnosed 11 months after the vaccination, and mast cell activation syndrome was diagnosed 3,5 years after the vaccination.
17	Possible	Symptoms started 7 months after the 3rd dose of Cervarix and POTS was diagnosed (unknown test) at that time.
18	Unclassified	POTS is reported to develop within 1 month after the 3rd dose of Cervarix but the information provided is too incomplete for more assessment.

Review of 7 cases classified as potential by the company

In order to identify potential POTS in cases without MedDRA POTS PT reported, the company used an algorithm which is considered to be more specific and less sensitive. Group F 'Hyperhidrosis' does not fit to the case definition. More sensitive queries including for example "Orthostatic intolerance" AND

"one other symptom/sign" would have been preferred, although the difficulty to interpret results is well-understood.

The company selected 7 cases by using the algorithm. One case (CIOMS B0926664A) actually had POTS listed among PTs and is already listed in Table 4 (case 11). The assessor agrees that the narrative of other cases do not permit to classify those cases with sufficient confidence.

Conclusion

The MAH identified 19 cases with POTS PT and 7 cases with combinations of proxy PTs. Although no level of certainty can be reached from the analysis of CIOMS, the assessor considers that two cases could likely be cases of POTS following HPV vaccination, four cases are possibly cases of POTS following HPV vaccination, and that other cases are not POTs, or possible POTS not following vaccination, or unclassifiable.

In conclusion, very few cases of POTS following HPV vaccination were identified. From data available, all conditions other than vaccination which could potentially be associated with POTS cannot be systematically excluded. However, a potential association between HPV vaccination and POTS cannot be ruled out.

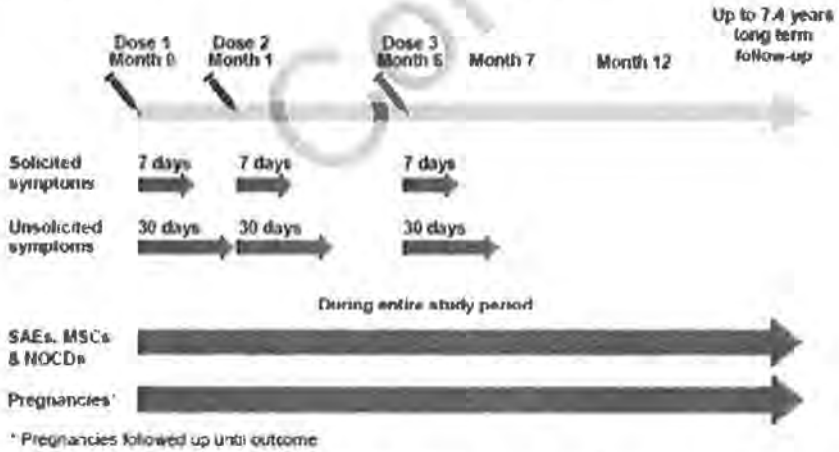
Question 2

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's response

Introduction

The figure below shows an example of the safety follow-up in an HPV vaccine clinical trial.



In order to evaluate reactogenicity, diary cards are provided to record solicited local and general signs and symptoms for 7 days after each vaccination.

All 'unsolicited' symptoms reported within 30 days (day 0–29) after each dose are recorded. In most studies, medically significant conditions (MSCs), serious adverse events (SAEs), potentially immune-mediated diseases (pIMDs) are captured until study completion.

pIMDs are events either reported as such in some studies, or detected in the database by a search of MedDRA PTs related to immune-mediated diseases. A predefined list of pIMDs includes autoimmune diseases and other inflammatory disorders of interest, which may or may not have an autoimmune aetiology, including new onset of pIMD or exacerbations of pre-existing pIMDs. The list of pIMDs is thus broad, potentially including events previously classified as 'new onset of autoimmune disease' in the HPV clinical development programme.

A pooled analysis of safety data from Cervarix clinical trials including 57 580 subjects and 96 704 HPV-16/18-vaccine doses administered was published (Angelo 2014).

For the purpose of the requested analysis on CRPS and POTS, 18 completed and unblinded studies designed with an active comparator group (either placebo or another vaccine other than an HPV vaccine, i.e. Hepatitis B, Hepatitis A) were pooled together.

Three follow - up periods were considered for the analysis: within 30 days after any dose, within 6 months post last vaccination and during the entire study period. All analyses were conducted on the Total Vaccinated Cohort (TVC), which includes all subjects who received at least one dose of study vaccine, and for whom data are available. A total of 42,047 subjects (21,268 in HPV group and 20,779 in comparator groups) were included in the analysis with the Data Lock point (DLP) of 15 June 2015. The study groups were comparable for age distribution including age at the time of first vaccination.

CRPS

As discussed in response to Question 1, the company uses case definition of CRPS proposed by Harden 2010.

1. Analysis of cases that included the MedDRA Preferred Term (PT) of CRPS

No serious or non-serious adverse events that contained the MedDRA PT of CRPS were identified in the clinical trial database in this analysis.

2. Analysis of cases that included signs and symptoms of CRPS (suspected cases of CRPS)

Following the same approach as described in response to Question 1:

- a search of events that contain MedDRA PT 'Pain' or 'Pain in extremity' with duration of longer than 14 days was performed.
- Secondly, combination of events suggestive for CRPS symptoms and 'Pain' or 'Pain in extremity' were searched to determine potential undiagnosed or unrecognized cases of CRPS, refer to the Table 2. For this search it was considered that difference between the onset of Pain or Pain in extremity and onset of any of other possible symptoms of CRPS cannot be more than one month.

Table 2 Criteria established by Harden et al 2010 matched to the MedDRA Preferred Terms (PTs)

Symptoms of CRPS, Harden, 2010	MedDRA PTs
Pain: Continuing pain disproportionate to vaccination	Pain; Pain in extremity
Sensory: Allodynia deep pressure pain, Allodynia pain after movement, Allodynia after light touch, Hyperesthesia, Hypoesthesia, Hyperalgesia, Hypoalgesia	Allodynia, Hyperaesthesia, Hypoaesthesia, Sensory disturbance, Skin burning sensation
Vasomotor: Color change/difference, temperature difference	Skin discolouration, Skin hyperpigmentation, Skin hypopigmentation, Skin atrophy, Temperature difference of extremities, Skin warm, Skin depigmentation, Skin dystrophy
Pseudomotor /oedema: Transpiration disturbance, Edema	Oedema, Oedema peripheral, Hyperhidrosis, Hypohydrosis, Cold sweat, Skin oedema
Trophic: Hair growth change, Nail growth change, Trophic skin disturbance	Hair growth abnormal, Nail growth abnormal, Onychoclasis
Motor: limitation of movement, Limitation of strength, Dystonia, Tremor, Bradykinesia	Injection site movement impairment, injected limb mobility decreased, Muscular weakness, Dystonia, Tremor, Bradykinesia, Motor dysfunction

Results

The reporting frequencies of these events were similar between the groups that received HPV and control/comparator vaccines, resulting in RRs below 1.8 with 95% Confidence intervals including 1 in each of the analyses performed.

As a result of six queries described above, no subjects were reported with a combination of symptoms suggestive of POTS.

Overall, no suspected cases of POTS have been identified in this analysis. There was no evidence for a significant difference between groups for any of the follow-up periods evaluated (30 days after vaccination, 6 months after vaccination or for the entire duration of the study), with relative risks ≤ 1.80 and 95% Confidence intervals including 1 in each of the analyses performed.

In conclusion based on this analysis, there was no evidence of differences between the study groups in the reporting rates for adverse events suggestive of CRPS or POTS.

Assessor's comments

The MAH has pooled the safety data from 18 completed and unblinded studies designed with an active comparator group (either placebo or another vaccine other than an HPV vaccine, i.e. Hepatitis B, Hepatitis A) which includes a total of 42,047 vaccinees (21,268 in HPV group and 20,779 in comparator groups) (DLP of 15 June 2015).

The analysis of available data **did not identify any serious or non-serious adverse event of CRPS**, which contained the MedDRA PT of CRPS or which included signs and symptoms of CRPS, as according to *Harden et al. (2010)*.

POTS

As discussed in response to Question 1, the company uses case definition of POTS based on Raj et al, 2013 and Sheldon et al, 2015.

1. Analysis of cases that included the MedDRA Preferred Term (PT) of POTS

No serious or non-serious events that contained the MedDRA PT of POTS were identified in the clinical trial database in this analysis.

2. Analysis of cases that included signs and symptoms of POTS (suspected cases of POTS)

A search for suspected cases of POTS was performed similarly to what was described in response to Question1.

Possible symptoms of POTS were matched to the MedDRA PTs which were grouped in eight as described in Table 5.

Table 6: Groups of MedDRA Preferred Terms (PTs) for symptoms of POTS.

Groups	**MedDRA PTs**
Group A	Palpitations. tremor. heart rate increased. tachycardia. tachyarrhythmia
Group B	Dizziness. dizziness exertional. dizziness postural. exercise tolerance decreased. muscular weakness. fatigue
Group C	Syncope. presyncope. loss of consciousness
Group D	Orthostatic intolerance. orthostatic heart rate response increased
Group E	Paraesthesia. sensory disturbance. blurred vision
Group F	Hyperhidrosis.
Group G	Memory impairment. disturbance in attention. confusional state. cognitive disorder.
Group H	Autonomic nervous system imbalance. urinary retention. constipation. diarrhea

To identify and determine suspected cases of POTS, 6 queries were run using the logic as presented below to explore different combination of the symptoms.

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

Again, the onset of symptoms should not be more than 1 month as compared to group A for categories 1, 2, 3 and not more than 1 month as compared to group C for categories 4, 5, 6.

Results

The reporting frequencies of these events were similar between the groups that received HPV and control/comparator vaccines in each of the analyses performed within 30 days after vaccination, within 6 months after the vaccination, and during the study period.

As a result of six queries described above, no subjects were reported with a combination of symptoms suggestive of POTS.

Overall, no suspected cases of POTS have been identified in this analysis. There was no evidence for a significant difference between groups for any of the follow-up periods evaluated (30 days after vaccination, 6 months after vaccination or for the entire duration of the study), with relative risks ≤ 1.80 and 95% Confidence intervals including 1 in each of the analyses performed.

In conclusion based on this analysis, there was no evidence of differences between the study groups in the reporting rates for adverse events suggestive of CRPS or POTS.

Assessor's comments

Similarly to CRPS, **no serious nor non-serious cases of POTS** have been identified under the PT POTS, or using diagnostic criteria of POTS (*Raj 2013* and *Sheldon et al. 2015*).

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.

Introduction

The assessor summarized here-after the method used by the MAH to compare the observed and the expected numbers of cases of CRPS and POTS following vaccination with Cervarix (see Annnex 1 of the Responses to Questions). The MAH provided also the comprehensive review of published literature conducted by MAH and SP/MSD to derive the background incidence rates for CRPS and POTS for consideration in observed/expected analyses (see Annex 2 of the *Responses to Questions*).

CRPS

Summary of the MAH's response

- **Methods**

The MAH proposed a model to compare observed and expected number of cases of CRPS following Cervarix vaccination with:

- $Observed\ number = observed\ number\ of\ CRPS\ cases\ within\ the\ risk\ period$
- $$Expected\ number = \frac{age-adjusted\ background\ incidence\ rate}{100{,}000} \times \frac{number\ of\ doses\ sold * 0.75}{3} \times \frac{Time\ at\ risk\ per\ person\ (in\ weeks)}{52} \times reported\ fraction$$

The assumptions were:

- 75% (0.75) of the doses distributed are administered. This proportion was derived from the UK vaccination campaign data by comparing the number of doses distributed with the measured vaccine coverage;
- All beneficiaries received the three (3) doses of the full vaccine schedule.

The "observed" number of CRPS cases was based on the 49 spontaneous case reports from the MAH safety database (see the response to question 1 and Table 5). Five cases were classified as confirmed, 37 cases were classified as unconfirmed, 6 cases were classified as unlikely, and 1 case was considered to be unassessable.

Table 7: Number of cases and number of doses of Cervarix distributed per Region/countries (at the DLP 15 June 2015)

Country	Cervarix doses distributed (nb)	CRPS spontaneous case reports (nb)	CRPS reporting rate (per 100,000 doses)
Japan	6,998,367	40	0.57
UK	8,669,742	8	0.092
R. of Korea	2,278,546	1	0.043
Worldwide	57,094,396	49	0.086

A best-case safety scenario included only confirmed cases of CRPS, a midcase safety scenario included the confirmed and unconfirmed cases of CRPS and the worst-case safety scenario included the confirmed, the unconfirmed and the unlikely cases of CRPS. For the observed-to-expected analysis, only cases occurring in the pre-defined risk periods were considered (risk periods are defined below). In addition, cases with missing Time-To-Onset (TTO) data were added in proportion to those in the time window of interest for the mid-case safety scenario, and all of them for the worst-case safety scenario.

The analysis was performed for worldwide data, for Japan, for the UK and the Republic of Korea. The analysis was not performed for Europe as no cases were reported from other European countries than the UK.

The "expected number of cases was based on estimated background incidence rate from the Netherlands (40.4 per 100,000 person-years for females, de Mos 2007). Each age stratum was provided with an estimated weight based on the age distribution of the population exposed to the vaccine that reported an adverse event. As the actual age distribution of the exposed (vaccinated) population is not available, the age distribution across all worldwide, Japanese, British and Korean spontaneous cases identified in the global safety database for Cervarix was used as a proxy. The age-adjusted background incidence rates corresponding to vaccinated females was estimated by taking the weighted average of the incidence rates within each age stratum.

Different risk periods post exposure to a Cervarix dose were used (ranging from 1 week to 2 years), as well as different percentages of cases actually spontaneously reported among all those that occurred within the risk period (ranging between 1% and 100%).

- **Results**

The results have been summarized by the assessor in the Table below. Exact figures are not provided in the report but are extracted from the figures.

Table: Reporting fraction of CRPS observed cases (O) when O is higher or lower than the expected number of cases (E) according safety scenarios, for a risk period of 1 week.

	Best case	Mid case	Worst case
Worldwide			
O > E	≤2%	≤15%	≤23%
O > E significantly	never	≤~9%	≤~16%
Japan			
O > E	≤12%	≤71%	any
O > E significantly	≤~1%	≤~35%	≤~99%
United Kingdom			
O > E	≤10%	≤36%	≤42%
O > E significantly	≤~1%	≤~14%	≤~18%

For worldwide reported cases, if we consider 1 week as risk period, the number of cases observed is equal or lower than the expected number if at least 2%, 15% and 23% of the cases occurring within 1 week of Cervarix vaccination were reported in the best-, the mid- and the worst-case safety scenario, respectively. For longer risk periods, the reported fraction can be lower and still allow an observed number of cases lower than expected.

For Japan, considering a risk period after each dose of 1 week, the number of CRPS cases observed is equal or lower to the number expected if at least 12% and 71% of the cases occurring within 1 week of Cervarix vaccination were reported in the best- and the mid-case safety scenario, respectively. For longer risk periods, the reported fraction can be lower and still allow an observed number of cases lower than expected. In a worst-case safety scenario, whatever the reported fraction, the observed number of CRPS cases is higher than expected in the risk period of 1 week post Cervarix dose. However, the worst case safety scenario included all confirmed, unconfirmed and unlikely cases of CRPS and considered all cases with unknown time to onset as having occurred within the risk period. The media attention in Japan could have generated the reporting of CRPS cases post Cervarix which would finally have been diagnosed as unconfirmed or unlikely making the worst case scenario sensitive to a media effect. Indeed, increased reporting of suspected CRPS cases in Japan coincided with extensive media coverage of a CRPS case in Japan (Wilson 2014). For longer risk periods, the observed number of cases is lower than expected for some thresholds of reported fraction.

For United Kingdom, considering a 1 week risk period (time at risk per person of 3 weeks), the number of CRPS cases observed is equal or lower than the expected if at least 10%, 36% and 42% of the cases occurring within 1 week of Cervarix vaccination were reported in the best-, the mid- and the worst-case safety scenario, respectively. For longer risk periods, the reported fraction can be lower and still allow an observed number of cases lower than expected.

For the Republic of Korea, there is only one unconfirmed case of CRPS in that country so no best-case or worst-case safety scenario is presented. This observed number of CRPS cases is equal or lower than the expected number if at least 10% of the cases occurring within 1 week of Cervarix vaccination were reported. For longer risk periods, the reported fraction can be lower and still allow an observed number of cases lower than expected.

- **Conclusions**

Considering the specificities of spontaneous reports, the longer the time between vaccination and the onset of event, the less chance it has to be reported. It means that the longer the risk period, the lower the reported fraction is. Taking a risk period of 1 week is consequently probably the most

sensitive scenario for detecting an excess of cases by using spontaneous report data. And even in that situation, for plausible values of reported fraction (10 to 70%), the observed number of cases is lower than the expected number whatever the safety scenario considered for CRPS case confirmation except for Japan in the worst case safety scenario. The media attention in Japan may have generated the reporting of CRPS cases which would finally have been diagnosed as unconfirmed or unlikely, making the worst case scenario sensitive to a media effect. Overall, the observed-to-expected analysis suggested that the observed incidence rate of CRPS following Cervarix vaccination is not significantly higher than the expected rate for a range of plausible combinations of risk periods and reporting fraction.

Assessor's comment

The Observed vs expected methodology used in this CRPS analysis is based on many assumptions, which cannot be verified. However, it is acknowledged that it is probably not possible to conduct better analyses at this stage, given the wide uncertainty around the reporting fraction for observed cases.

It is assumed by the MAH that the reported fraction of CRPS cases should be about 10 to 70%. However, adverse events have been shown to be reported at a much lower rate, i.e. from less than 1% to 10% depending of the authors (*Agarwal et al. 2013*, *Gavaza et al. 2011*, *Mirbaha et al. 2015*). Moreover, because of the difficulty of diagnosing CRPS, many patients could be undiagnosed. Therefore, the reporting rate for CRPS might be much lower than those observed for other adverse events.

The CRPS case reported by Korea relates to a woman aged 60 years and should be considered as an outlier. To note that Korean recommendations target females aged 15-17 years with a catch-up vaccination recommended for females aged 18-26 years (*Kim et al. 2014*). This case should preferably not be considered in this analysis.

The results of the Observed vs Expected analysis suggest that the number of observed CRPS cases is low compared to those expected, except in Japan. The high number of cases observed in Japan is a concern. Even if the media attention may have increased the fraction of reported cases, a reporting fraction of 71% (which is quite high for spontaneous reporting) would imply that more cases are observed than expected in the mid-case scenario – although not with statistical significance. This high number suggests that CRPS should be under further surveillance.

Based on reported cases in Japan and UK, a reporting rate at 0.31 cases per 100,000 doses (48/15,668,109) can be estimated. When this rate is applied to the number of doses distributed worldwide, 175 cases would have been reported, would the "rest of the world" had a similar reporting pattern than those two countries. Would the reporting rate in Japan be chosen, 325 cases would have been reported.

POTS

Summary of the MAH's response

- **Methods**

The GSK global safety database contained 19 spontaneous case reports for Cervarix that included the MedDRA PT of POTS for 57 094 396 doses sold worldwide (reporting rate 0.033 per 100,000 doses distributed). Among these POTS cases, 8 were reported in Japan for 6,998,367 doses distributed (reporting rate 0.11 per 100,000 doses); 10 cases were reported in the United Kingdom for 8,669,742 doses distributed (reporting rate 0.012 per 100,000 doses) and 1 case was reported in the United States for 711,072 doses distributed (reporting rate 0.14 per 100,000 doses).

All cases were reviewed according to the criteria suggested by Sheldon , 2015 and Raj 2013 and defined as confirmed cases of POTS or unconfirmed cases of POTS (due to lack of information). There are no unlikely cases of POTS so no worst-case safety scenario is provided. One case from Japan could not be classified and is excluded from the analysis. A best-case safety scenario for Cervarix vaccine included only confirmed cases of POTS and a mid-case safety scenario included the confirmed and unconfirmed cases of POTS.

For the observed-to-expected analysis, only cases occurring in the pre-defined risk periods were considered. In addition, cases with missing time-to-onset (TTO) data were added in proportion to those in the time window of interest for the mid-case safety scenario.

The analysis was performed for worldwide data, for Japan, for the UK and the US. The analysis was not performed for Europe as no cases were reported from other European countries than the UK.

As for the observed-to-expected analysis for CRPS, we considered that on average 75% of doses distributed/sold are administered. For all countries and region we made the assumption that all vaccinated persons received 3 doses of the vaccine.

In the observed-to-expected analysis for POTS, several risk periods post Cervarix dose were assessed: 1 week, 1 month, 6 months and 1 year (the 1 year includes the longest TTO for POTS cases reported in GSK global safety database).

There are no POTS incidence rates published in the literature so Chronic Fatigue Syndrome (CFS) incidence rates were used to give indirect estimates. Donegan provided an estimated background incidence rate of CFS among adolescent girls of 30 per 100,000 person-years in the UK and Bakken et al. provided an estimate of 70 per 100,000 person-years in Norway. The percentage of CFS cases presenting with POTS was reported by Reynolds et al. as being of 10% and by Galland et al. as being of 40%. The percentage of POTS cases presenting with CFS was reported by McDonald et al. as being of 20%. Based on these values, 4 scenarios were considered for the background incidence rate as stated in the table below.

A similar analysis as for CRPS assumed different magnitudes of reporting fraction.

Table 8 **Different scenarios for the estimation of the POTS background Incidence Rates (IR)**

	Assumption 1	Assumption 2	Assumption 3	Assumption 4
Incidence of CFS (100,000py)	30	70	30	70
%CFS cases with POTS	10	10	40	40
%POTS cases with CFS	20	20	20	20
Incidence of POTS (/100,000py)	**15**	**35**	**60**	**140**

- **Results**

For worldwide analyses, looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS worldwide and a risk period of 1 week, the observed reporting rate is equal or lower than the expected if at least 2% of the POTS cases occurring within 1 week of Cervarix

vaccination were reported for the best-case safety scenario and at least 7% of the POTS cases occurring within 1 week of Cervarix vaccination were reported for the mid-case safety scenario (Table 8). For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected. The results for other risk periods are described in the table below, and the reporting fraction is even lower.

In United Kingdom, there is no case with a TTO longer than 6 months. No confirmed cases have a TTO longer than 1 month and no best case scenario is thus presented (Table 8).

Table 9: **Reporting fraction of POTS observed cases (O) when O is higher than the expected number of cases (E) according safety scenarios, for the worst assumption for background rate and for different risk periods.**

Risk period	Best case	Mid case
Worldwide		
One week	≤2%	≤7%
One month	≤1%	≤3%
6 months	≤1%	<1%
1 year	<0.6%	≤0.6%
Japan		
One week	≤13%	≤20%
One month	≤6%	≤8%
6 months	<2%	≤2%
1 year	<1%	≤1%
United Kingdom		
One week	≤5%	≤27%
One month	No confirmed case	≤11%
6 months	No confirmed case	≤2%
United States		
One week	No confirmed case	≤65%

In the US, there are no confirmed cases, so no best case safety scenario is presented. There are no cases with a TTO beyond 1 week so no figures are presented for the risk periods beyond 1 week.

For the other assumptions, the reported fraction can be lower and still allow an observed number of cases lower than expected.

- **Conclusions**

Looking at the worst assumption (assumption 1) in terms of background incidence rate of POTS and a risk period of 1 week whatever the region or safety scenario for case confirmation, the observed reporting rate of POTS is lower than the expected for plausible ranges of reported fraction (5 to 65%). For other assumptions and risk periods, the reported fraction can be even lower and still allow an observed reporting rate of POTS lower than the expected.

The observed-to-expected analysis suggested that the observed incidence rate of POTS following Cervarix vaccination is not significantly higher than the expected rate for a range of plausible combinations of incidence rates and reporting fraction.

Assessor's comments

The Observed vs Expected methodology used in this analysis is also based on many assumptions, which cannot be verified. However, as for CRPS it is probably impossible to conduct better analyses at

this stage, given the wide uncertainty around the reporting fraction for observed cases and around the background rates. The analyses presented are based on the worst case scenario for background incidence rate.

The results of the Observed vs Expected analysis suggest that the number of observed POTS cases is low compared to those expected, even in Japan.

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 OTS and discuss whether there is biological basis for a possible causal association.

MAH's response

CRPS

Complex regional pain syndrome is a chronic pain disorder that typically develops in anextremity after (minor) tissue trauma (De Mos 2009; Huygen 2015; Harden 2010). Several reports have been published describing cases of CRPS occurring in adolescent girls with symptoms occurring after vaccination with human papilloma virus (HPV) vaccines (Kinoshita 2014; Richards 2012), raising questions on potential causal links that led to temporary suspension of the recommendation for HPV vaccination in Japan.

This potential safety issue was investigated by GSK and the results of an expert consultation were published (Huygen 2015). From this it was concluded that there is, at this time, not enough evidence to suggest that Cervarix causes CRPS.

A deeper analysis of the potential mechanisms behind CRPS, based on extensive literature review, considered several potential explanations that could have an impact on responses to minor trauma (De Mos 2009):

- Autonomic nervous system dysfunction
- Somatic nervous system dysfunction
- Inflammation
- Hypoxia
- Psychological factors

The potential role of inflammation is of most interest when considering any involvement of the immune system in the aetiology of CRPS. The role of inflammation was investigated by analysing artificially induced blisters (De Mos 2009). When comparing blisters from CRPS affected sites with non-affected site, increased levels of the cytokines IL-6 and TNF-α were measured as well as markers for monocyte and macrophage activation. Similarly, changes in levels of proinflammatory cytokines (IL-1β, TNF-α) in cerebrospinal fluid were detected in CRPS patients (De Mos 2009). An additional finding, supporting a role of inflammation, is the detection of enhanced migration of radio-labelled autologous leukocytes towards affected limbs (De Mos 2009). However, several standard inflammation parameters such as serum levels of C-reactive protein and white blood cell counts were normal in CRPS patients (De Mos 2009). A putative role of inflammation is consistent with reports describing successful treatment with immune-modulating agents such as infliximab (monoclonal anti-TNF-α antibody) and thalidomide (unknown mode of action but inhibition of pro-inflammatory cytokines such as IL-6) (De Mos 2009).

Whereas a role for inflammation appears plausible, it is less clear how inflammation leads to symptoms and how inflammation could be triggered. With regards to the first question, there is evidence for

cross-talk between the immune system, e.g. inflammatory responses, and the nervous system. Neurogenic inflammation can be mediated by a number of neuropeptides, such as substance P (SP), calcitonin gene-related protein (CGRP) and neuropeptide Y. Thus, a link between excessive inflammation and some neurogenic response appears possible. The second question, i.e., the trigger of the kind of inflammation that could lead to the cascade of events ultimately resulting in CRPS, is considerably less clear. It is of interest that often some sort of trauma appears to be an initiating event for CRPS. Case studies describe a variety of events as potential initiating trauma, such as wrist fractures, cancer, infections and cardiovascular events (De Mos 2009). Among antecedent infections, a variety of pathogens have been implicated (e.g., Severity of the trauma is not related to risk of CRPS. From this, it was hypothesized that symptoms occur as the result of an exaggerated neuro-inflammatory response to injury (De Mos 2009). If that is the case, then some genetic predisposition seems plausible. Indeed, polymorphisms in the TNF-α promoter, angiotensin converting enzyme and HLA genes have been described as being associated with CRPS (De Mos 2009).

The wide variety of stimuli or triggering events suggests that a single, auto-immune or antigenic mimicry cause is unlikely. Given the wide variety of triggering events, it has in fact been suggested that, in the case of vaccination, the injection event itself in susceptible persons, rather than the specific antigen, could be a triggering event (Huygen 2015). In that setting, it was considered of interest that the subcutaneous route of injection often used for vaccination in Japan could generate innate immune responses in the vicinity of skin nerves.

POTS

Postural orthostatic tachycardia syndrome is a complex disorder that is primarily characterized by an excessive increase in heart rate upon standing up (Freeman 2011). The aetiology of POTS is unknown, although the syndrome appears to be associated with conditions such as recent viral illness, chronic fatigue syndrome and a limited autonomic neuropathy (Freeman 2011). Several recent reports describe onset of POTS symptoms following vaccination with HPV vaccines (Blitshteyn 2014; Brinth 2015). Patients are predominantly female, of childbearing age, and often characterized by high levels of physical activity and irregular menstruation (Blitshteyn 2014). Of note, the number of cases that were described is small (6 and 35, respectively, in the two publications, Blitshteyn 2014; Brinth 2015). Clearly any temporal association with vaccination does not necessarily translate into causality. In fact, another study (Lin 2014) identified daily water intake, supine heart rate and sleeping hours as potential risk factors for POTS.

Mechanistically, and given that the excessive increase in heart rate is the main finding, there has been an interest in studying changes in the α/ß-adrenergic receptor system as well as levels of circulating catecholamines and norepinephrine in patients (Li 2014). This approach, combined with the observation of antecedent viral illness, has led to a hypothesis of potential auto-immune origin of POTS, focussing on detection of auto-antibodies. A single publication reported the presence of auto-antibodies against the α1-adrenergic receptor (α1AR) in patients (Li 2014). These antibodies were functional in different in vitro assays and the functional activity measured in these assays could be blocked by the α1AR antagonist prazosin (Li 2014). The proposed mode of action of such α1AR-targeted antagonistic antibodies is that the change in blood pressure following change in posture is insufficiently compensated by α1AR-mediated vasoconstriction and that this results in an exaggerated sympatho-neural response to low blood pressure (Li 2014). This 'overshoot' response could then lead to tachycardia (Li 2014).

Whereas this hypothesis is of interest and could explain the symptoms, it remains to be confirmed. The presence of anti-cardiac lipid raft proteins (Wang 2013) may provide some support for this hypothesis that auto-antibodies may play a role. Auto-antibodies against a number of proteins, including proteins associated with caveolae structure, adrenergic signalling, calcium signalling, cytostructures, chaperone

and energy metabolism were identified (Wang 2013). Moreover, it has been shown that 14% of patients with POTS had antibodies against the ganglionic acetylcholine receptor (Thieben 2007).

Finally, it has been proposed that anti-phospholipid antibodies could play a role, as described for antiphospholipid (Hughes) syndrome (APS) (Schofield 2014). As the authors of that paper state, a link between POTS and APS has not previously been described, and therefore they performed a clinical evaluation of patients diagnosed with APS and an autonomic disorder, e.g., POTS (Schofield 2014). Although the authors indicate that APS and autonomic disorder symptoms can occur together (Schofield 2014), their report does not shed any new light on the proposed autoimmune aetiology. Similarly, a single study describes occurrence of POTS in multiple sclerosis (MS) patients and reports some differences in, amongst others, norepinephrine levels between POTS patients with concomitant MS or not (Adamec 2013). Whereas the authors conclude from these data that POTS is associated with MS, it must be emphasized that the numbers of patients are small, that there is no evidence for causality and that these observations could represent an epiphenomenon. Thus, it seems premature to consider the data suggesting associations with immune-mediated disorders such as APS and MS (Adamec 2013; Schofield 2014) as evidence or r indication of an auto-immune aetiology of POTS. Nevertheless, a recent analysis of 100 patients diagnosed with POTS (Blitshteyn 2015) focussing on anti-nuclear antibodies, other markers of auto-immunity and co-morbid auto-immune disorders concluded that patients with POTS have a higher prevalence of auto-immune markers and co-morbidities. 25% of patients had anti-nuclear antibodies and 20% had any form of auto-immune co-morbidity (Blitshteyn 2015), leading to a conclusion that there could either be a link between auto-immune disorders and POTS or that POTS itself could be an auto-immune disorder. An acknowledged limitation of the study is the statistical drawback of comparing prevalence of auto-immune disorders and –markers in a predominantly female POTS patient population to the prevalence in the general population (Blitshteyn 2015). The strength of the study is the relatively large cohort that was evaluated.

The complex nature of both CRPS and POTS and the facts that both conditions received attention linked to HPV vaccination and have some common symptoms, has led to a hypothesis that both disorders could be part of a spectrum of small-fibre neuropathy and dysautonomia disorders (Martinez-Lavin 2015). In brief, the author argues that common symptoms can be explained by assuming that post-vaccination immune responses trigger small-fiber neuropathy, defined by its clinical features of painful paraesthesias and autonomic dysfunction (Martinez- Lavin 2015). A criticism of this analysis is that it is solely based on the occurrence of common symptoms and that it does not propose any plausible mechanism that could link such symptoms with HPV vaccination (Martinez-Lavin 2015). The alternative hypothesis is that these are in fact different disorders with different aetiology, that share some of the downstream pathogenic pathways linked to sympathic dysfunction. Nevertheless, what can be concluded based on the available data is that some auto-immune aetiology, characterized by either auto-immune antibodies or co-morbidities cannot be excluded. However, the wide variety of auto-immune antibodies that are identified preclude concluding on any specific single mechanism. This may be consistent with the complexity of the condition itself.

Conclusion

Overall, it is concluded that there is not sufficient evidence to consider CRPS and POTS as two variants of a single spectrum of disorders. In terms of mechanisms, the most convincing explanation for CRPS points towards exaggerated responses to minor trauma whereas for POTS a role of a variety of auto-antibodies cannot be excluded. A link with HPV vaccination is not obvious in either situation given the diversity of symptoms and proposed causative mechanisms.

In the case of CRPS, a role of the method of needle injection itself cannot be excluded.

Assessor's comments

CRPS

It appears that CRPS is caused by a **multifactorial process** involving both peripheral and central mechanisms. Potential mechanisms include nerve injury, ischemic reperfusion injury or oxidative stress, central sensitization, peripheral sensitization, altered sympathetic nervous system function or sympatho-afferent coupling, inflammatory and immune related factors, brain changes, genetic factors, psychological factors and disuse *(Bruehl 2015)*. Little is known how these mechanisms might interact. Given the diversity of presentations seen in CRPS, the relative contributions of different mechanisms probably differ across individual patients and even within patients over time *(Bruehl 2015)*. The heterogeneity in the constellations of signs and symptoms in individuals and the great variability in the response to specific treatments suggest the existence of distinct **subgroups** with different underlying pathophysiological mechanisms *(Borchers & Gerschwin 2014)*.

The **events that precipitate CRPS** most commonly are fractures, sprains, and surgery, but also include injections, local infections, burns, frostbites, even pregnancy, as well as stroke or myocardial infarction *(Borchers & Gerschwin 2014)*. The exact nature and combination of symptoms and their severity are not related to the severity of trauma, and more than 10% of patients may not recall any precipitating event *(Borchers & Gerschwin 2014)*. Although it is often thought that CRPS is of psychogenic nature, there is no convincing evidence to support this hypothesis and different studies have resulted in conflicting outcomes *(Borchers & Gerschwin 2014)*.

Potential risk factors for the onset of CRPS 1 were found to include being **female, particularly postmenopausal female, ankle dislocation or intra-articular fracture, immobilisation, and a report of higher than usual levels of pain in the early phases of trauma.** It is not possible to draw definite conclusions as this evidence is heterogeneous and of mixed quality, relevance, and weighting strength against bias and has not been confirmed across multiple trials or in homogenous studies *(Pons et al. 2015)*. It has been suggested that CRPS is rare in people of non-European ancestry both in adults and children, but actual data on this issue are lacking *(Borchers & Gerschwin 2014)*.

CRPS can occur at any age, but is **relatively rare in childhood and adolescence**, with paediatric patients constituting <10% of CRPS patients seen at tertiary centres. Mean or median age at onset varies from ~37–52 years in population-based and cohort studies. The age group with the highest incidence is even more variable, ranging from the 4th to the 7th decade of life. Familial cases of CRPS I are characterized by a significantly younger age of onset, and this has also been observed for patients with spontaneous onset of CRPS I, i.e. without a known precipitating trauma or tissue injury. Onset of **paediatric CRPS** occurs most frequently in **early adolescence (peak age of onset is around 12-13 years of age)**, with the lower end of the range usually being 7 to 9 years *(Borchers & Gerschwin 2014; Borucki & Greco 2015)*. CRPS is rarely seen in young children before the age of 6 *(Borucki & Greco 2015)*.

Paediatric CRPS is mostly seen in **girls**. Often **minor trauma** is the inciting event such as a minor sprain or twist. Unlike adult patients, **lower extremity** involvement is more common by a ratio of 6:1 in paediatric patients. *(Borucki & Greco 2015)*. The affected lower limb is more often blue and colder than the healthy side and frequently shows hypoperfusion in three-phase bone scintigraphy. While primarily cold CRPS is a poor prognosticator in adults, the majority of pediatric patients achieve improvement or symptom resolution mainly with PT and cognitive–behavioural interventions, even if relapses are common *(Borchers & Gerschwin 2014)*. This is in contrast to a longitudinal study of patients (n=42) diagnosed as having CRPS in childhood found that on follow-up in adulthood an average of 12 years later, 52% still experienced pain, with 36% having documented recurrences of

CRPS.179 This suggests that in many cases of childhood CRPS there may be no sustained recovery *(Bruehl 2015)*.

In contrast, adults more often have involvement of an upper extremity, which initially is red and warmer than the healthy side, and only later may become cold and bluish and which shows hyperperfusion. In addition, RSD/CRPS appears to become chronic and resistant to any therapy more often in adults. **This raises the question of whether paediatric CRPS is a subgroup of the same disorder as in adults or a different entity entirely** *(Borchers & Gerschwin 2014)*. The assumption that CRPS presents differently in children than in adults, has been questioned *(Bruehl 2015)*. Two detailed detailed clinical evaluation studies (n=20; n=42) suggest that the same objective signs are seen in children and adolescents with CRPS as are seen in adults, including allodynia and hyperalgesia, edema, skin color and temperature changes, and motor changes *(Bruehl 2015)*.

Case reports of **CRPS after HPV vaccination** in adolescent girls have been described in literature *(Kinoshita et al. 2014; Richards et al. 2012)*. Richards et al. report one patient who was diagnosed with CRPS after vaccination with a bivalent HPV vaccine, for which the involvement of the HPV vaccine cannot be ruled out, and three patients with a quadrivalent HPV vaccine. Kinoshita et al. report 44 girls that were referred after HPV vaccination (31 received Cervarix, 13 Gardasil). In a number of girls, CRPS was diagnosed. However, the number differ depending on the use of the Japanese diagnostic criteria (4 CRPS cases) or the international diagnostic criteria (the Budapest criteria; 18 cases). It seems that there might be an error in this publication as the authors might have wrongly interpreted the Budapest criteria. It is very unlikely that the Budapest criteria would result in more confirmed diagnoses than the Japanese criteria, as the Budapest criteria are more specific.

It is hypothesized that intramuscular immunization is a sufficient painful stimulus to trigger the development of CRPS-1, and that is the **process of a needle penetrating the skin** that is the trigger, rather than a particular vaccine antigen or adjuvant being causally related *(Richards et al. 2012)*. This is supported by reports of CRPS following other needle-based interventions, including **venipuncture, intravenous drug administration** and **other vaccinations** (influenza, rubella, hepatitis B and diphtheria-tetanus with or without acellular pertussis) *(Richards et al. 2012; Kwun et al. 2012; Genc et al. 2005; Jastaniah et al. 2003; Bilic et al. 2013)*. However, if the injection itself triggers the event, and given the large number of people that receive injections for various medical reasons, one would expect a much larger number of reports of CRPS triggered by injections

Conclusion : At this moment, literature does not point out a causal relationship between HPV vaccination and the onset of CRPS, however this cannot be ruled out for the following reasons:

- the disease is probably caused by a **multifactorial process, including inflammatory and immune related factors**. Evidence of the involvement of inflammatory mechanisms, especially in the acute phase, comes from studies documenting raised concentrations of proinflammatory neuropeptides and mediators (substance P, calcitonin gene related peptide, bradykinin) and cytokines (IL-1β, IL-2, and IL-6, and tumor necrosis factor α (TNF- α) in the systemic circulation, cerebrospinal fluid, and affected limbs of patients with CRPS *(Bruehl 2015)*.

- an autoimmune cause has also been suggested for CRPS in a subset of patients. For example, *Dirckx et al. (2015)* have found the presence of autoantibodies in 33% of CRPS patients and in 4% of controls. Furthermore, motor impairment, a characteristic of CRPS, has been observed in healthy mice when transferring IgG from CRPS patients *Goebel et al. (2011)*.

- CRPS occurs most commonly in women between 50 and 70 years of age *(Rockett 2014)* and is **relatively rare in childhood and adolescence which is the target population of HPV vaccination** *(Borchers & Gerschwin 2014)*.

- Paediatric CRPS is mostly triggered by **minor trauma** *(Borucki & Greco 2015).*

POTS

As Raj pointed, POTS is a syndrome, not a disease (*Raj 2013*). Although orthostatic tachycardia is the main sign of the condition, the syndrome can be associated (or not) to a variety of conditions: in many patients, elevated levels of plasma norepinephrine; in some patients, autonomic neuropathy with preferential denervation of sympathetic nerve; in rare patients, a single point mutation causing a loss of function in the norepinephrine transporter; in some patients, co-existent mast cell activation; finally, in some patients, POTS is caused by plasma volume deficit (*Raj 2013*).

When considering the possibility of POTS after HPV vaccination, two conditions are of major interest.

1) POTS as an autoimmune condition: the MAH discussed the pro- and contra- of the autoimmune theory which is supported by the identification in a significant proportion of the cases of antibodies, the report of viral infections before onset and the presence of autoimmune markers (*Blitshteyn 2015*).

2) POTS as a dysfunction of the autonomic nervous system: In a recent publication, WHO identified in Vigibase 21 cases of gastrointestinal motility disorders after HPV vaccine (*Chandler 2015*), those conditions being suspected to be caused by autonomic neuropathies. Dysfunctions of the autonomic nervous system may present under various forms. The identification of dysautonomic conditions of interest should be discussed for future surveillance.

Is there a link between CRPS and POTS?

Recently it has been hypothesized that **small fiber neuropathy** and dysautonomia could be a common underlying pathogenesis to CRPS and POTS that follow HPV vaccination, **based on clinical manifestations** of small fiber neuropathy (pain and dysautonomia) in CRPS and POTS *(Martinez-Lavin 2015; Chandler 2015).*

Small fiber neuropathy is a disease of the most distal nociceptive and sympathetic fibers. The outstanding clinical features of small fiber neuropathy are pain paresthesias and autonomic dysfunction. Neurological examination is usually normal, as are the electromyography and clinically available nerve conduction studies. The diagnosis of small fiber neuropathy is confirmed by skin biopsy. Corneal confocal microscopy is a new method to assess small nerve fiber pathology. These objective procedures show diminished intraepidermal or corneal small fiber innervations *(Martinez-Lavin 2015).*

Evidence for small-fiber neuropathy has been found in some patients with CRPS, and may be prevalent in paediatric patients with a variety of chronic pain syndromes *(Borucki et al. 2015).* However, data on small-fiber degeneration come either from patients with long-standing disease severe enough to necessitate amputation, or almost exclusively from patients with chronic disease of > 2 years duration. **Therefore, it cannot be determined whether these neuropathological changes are causally involved in the development of CRPS I or arise as a consequence of other disease-associated processes**, such as tissue hypoxia or inflammation (*Borchers & Gerschwin 2014*). Furthermore, evidence supports that small fiber neuropathy **does not constitute a major pathogenetic mechanism** in CRPS I. It appears that warm and cold hypoesthesia is significantly worse in patients with chronic (> 12 months) CRPS compared to those in the more acute stages of the disorder (≤ 12 months). **This suggests that small fiber dysfunction or loss results from, rather than being the cause of, the disease process** *(Borchers & Gerschwin 2014).*

A study of patients aged 6–21 years with a variety of widespread pain syndromes showed that **59% of patients met the diagnostic criteria for small-fiber predominant polyneuropathy** (SFPN),

indicating that this disease process may be prevalent in paediatric patients with a variety of chronic pain syndromes, although additional data are needed *(Borucki & Greco 2015)*.

An altered process of **inactivated HPV virus and aluminum adjuvant** that damage dorsal root ganglia could be suggested as a preliminary pathogenetic speculation for the development of small fiber neuropathy. In animal models, aluminium is able to damage dorsal root ganglia *(Martinez-Lavin 2015)*.

Although pediatric CRPS patients reported multiple systemic autonomic symptoms and regional sensory, motor, and autonomic complaints at presentation, they exhibited relatively milder abnormalities in observable signs by physical examination and tilt table testing. In this respect, they appear different from both patients with POTS and from controls (*Meier et al. 2006*).

Conclusion

The proposed common underlying pathogenesis of CRPS and POTS, i.e. small fiber neuropathy and autonomic dysfunction, cannot be explained in all CRPS cases. Furthermore, more than one mechanism seem to be involved in the pathogenesis of CRPS. There are some doubts whether small fiber neuropathy results from CRPS or causes the disease. On the other hand, there is more evidence which underlies an autoimmune hypothesis for POTS.

The link between POTS and CRPS is largely unknown and it is doubtful that both syndromes should be associated if additional investigations are required. It is preferable to investigate potential associations of HPV vaccination with POTS and HPV vaccination with CRPS separately without extrapolating on hypothetical common causal patterns.

Question 5

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

MAH's response

The MAH has conducted different analysis of all available data on CRPS and POTS that have been reported to the company following vaccination with Cervarix from launch (17 May 2007) up to the data lock point of 15 June 2015, including data sources from:

- spontaneous reports in post-marketing from over 24,000 reports following over 57 million doses distributed globally,
- all serious and non-serious AEs in the overall clinical trial programme; overall N evaluated= 42,047(21,444[HPV]; 20,603 [control/comparator vaccines] and
- case reports identified in the literature

To ensure that all cases of CRPS and POTS were identified, various search methodologies to retrieve case reports from the GSK safety database were used to identify suspected cases. For CRPS, an additional search was also performed based on search criteria used by SPMSD.

In addition to the review of individual case reports according to the established case definition of CRPS and POTS (see responses provided in Question 1 and Question 2), quantitative analyses were also conducted showing observed/expected analyses based on different scenarios (reporting rate, case classification, risk period, countries, underreporting and background rates) (see response provided in Question 3). Importantly, an appraisal of the strength of evidence was also provided to determine any

biological basis for possible causal association of CRPS and POTS with HPV (Cervarix) vaccination (see response provided in Question 4).

Overall, following over 57 million doses of Cervarix distributed worldwide, five case reports fulfil the criteria of CRPS according to the established case definition. No additional confirmed cases of CRPS were identified in the global safety database considering the other broader search criteria for suspected cases. For the three suspected cases of CRPS that reported the combination of pain or pain in extremity which have been identified following the broad search criteria, the information reported for these cases was insufficient to confirm a diagnosis of CRPS. No cases of CRPS were identified in the overall clinical trial program with Cervarix and quantitative analyses did not show any indication of a potential association between Cervarix and CRPS. In terms of mechanism, the most convincing explanation for CRPS points towards exaggerated responses to minor trauma where the role of the method of needle injection itself cannot be excluded.

Given the increased reporting and heightened public concern on the safety of HPV vaccines in Japan, triggered by the case report of CRPS in Japan in 2013, GSK have since conducted comprehensive analyses with regard to CRPS including consultation with an independent expert panel for 'pain'. Following the similar methodology outlined in response to Question 1 and after the preliminary review of the identified CRPS cases by a GSK safety physician, the two independent external experts were provided with the individual clinical narratives of identified cases for review using the same case definition (Harden 2010). The assessment of cases by GSK and the results of the quantitative analyses were only shared with the experts once their own separate assessments of individual cases were completed. Results of this safety evaluation have just been published (Huygen, 2015) and are very much in line with the outcome of these investigations.

Based on current data on POTS as provided in response to Question 1, five case reports fulfilled the criteria according to the established case definition (Raj 2013 and Sheldon 2015). The broader search strategy has not identified any suspected cases of POTS.

In conclusion, the outcomes of the different analyses performed are not sufficient to establish a causal association between CRPS or POTS and vaccination with Cervarix. It is GSK's opinion that the known benefit:risk profile of Cervarix remains unchanged and that no change is warranted to the current Reference Safety Information for Cervarix as an outcome of the assessments made in these investigations.

Given the current scientific evidence available at this time, CRPS and POTS will remain under close safety surveillance through routine pharmacovigilance including the use of targeted follow up questionnaires. The questionnaire has been implemented for CRPS and is currently being used for any case report indicative of CRPS to ensure complete documentation of suspected case which will allow a robust data evaluation/validation.

Similarly as part of routine pharmacovigilance, both CRPS and POTS will be considered for evaluation as adverse events of interest in each PSUR/PBRER cycle to determine the need for additional risk minimisation measures (if any).

Assessor's comments

CRPS

The assessment of the data provided by the MAH and of the literature has shown that:

- out of 49 spontaneous reports of CRPS (i.e. PT CRPS), 5 cases have been considered as confirmed CRPS, i.e. with fulfilment of the Budapest clinical diagnostic criteria for CRPS. In 3 of these cases, a causal relationship with Cervarix vaccination cannot be ruled out, including 1 serious case

resolved with sequelae. Among the 44 remaining *potential* CRPS cases (i.e. PT CRPS reported but insufficient information or incomplete fulfilment of the diagnostic criteria), only in 8 cases, including 4 serious cases, with an unknown outcome in 50%, and recovering/resolving in the other half, the involvement of Cervarix cannot be ruled out;

- besides, 10 cases of *potential* CRPS have been identified by applying the search strategy of signs and symptoms of CRPS (cases not reporting PT CRPS). In 2 cases the involvement of Cervarix administration could not be ruled out, one of which was serious and no recovery was observed;

- no cases of CRPS have been identified during clinical trials with Cervarix;

- the number of CRPS cases following administration of Cervarix is considered low compared to 57 million doses of Cervarix distributed globally. However, the low number might be contributed by the problem of underreporting of ADRs in general, and more specific, the difficulty of diagnosing CRPS being a complex syndrome with a variety of signs and symptoms in highly variable combinations with a variable progression over time. Furthermore, there is no golden standard diagnostic test for CRPS available, remaining CRPS as a syndrome of exclusion of other diseases with similar signs and symptoms, and no overall consensus on the clinical diagnostic criteria of CRPS (*Rockett 2014*). However the most widely accepted diagnostic criteria are the Budapest criteria described by *Harden et al. (2010)*. All taken together, many patients could be undiagnosed;

- the Observed vs expected analysis has suggested that the number of observed CRPS cases is low compared to those expected, except in Japan. Based on reported cases in Japan and UK, a reporting rate at 0.31 cases per 100,000 doses (48/15,668,109) can be estimated. When this rate is applied to the number of doses distributed worldwide, 175 cases would have been reported, assuming that the reporting pattern is similar in other countries;

- data from the literature do not point out a causal relationship between HPV vaccination and the onset of CRPS, however this cannot be ruled out for the following reasons: (i) the disease is probably caused by a multifactorial process, including inflammatory and immune related factors, (ii) CRPS occurs most commonly in women between 50 and 70 years of age *(Rockett 2014)* and is relatively rare in childhood and adolescence which is the target population of HPV vaccination (*Borchers & Gerschwin 2015*), and (iii) paediatric CRPS is mostly triggered by minor trauma.

Taken all these data together, a causal relationship between vaccination with Cervarix and the occurrence of CRPS cannot be excluded at this stage. Therefore, additional data are needed, which could also respond to the growing public attention.

This could be accomplished by further monitoring in PSUR. However, monitoring is difficult because of the complexity of the disease and the risk of underdiagnosis. On the other hand, the high number of cases observed in Japan suggests that CRPS should be under further surveillance. As also suggested by three independent external experts, a PASS study could be useful to obtain further data regarding the potential link between CRPS and Cervarix vaccination. The feasibility of such a study should be thoroughly examined as the majority of CRPS cases normally occurs in elderly women and the target population would be adolescents. A clear definition of CRPS cases should be provided before the beginning of the PASS study, as well as the risk period. In order to obtain cases, data from specialised centres could be used.

POTS

The assessment of the data provided by the MAH and of the literature has shown that:

* Very rare documented cases support the hypothesis that POTS follow a HPV vaccination;

* POTS is most common in female adolescent and female young adults. This range of ages partially overlap the range of ages for HPV vaccination. Yet, the expected occurrence of POTS in this population is unknown and it is currently not possible to demonstrate whether HPV vaccination programmes impacted the incidence of POTS.

* To the current knowledge, there is no evidence that a causal association between HPV vaccine and POTS is biologically supported. However, two hypothesis are of interest: POTS as a autoimmune disorder and POTS as a dysfunction of the autonomic nervous system.

In consequences, the assessment is based on many unknowns. The question is:

Is it useful to identify a set of relevant autonomic disorders to monitor in enhanced surveillance of HPV vaccines? (referring to gastrointestinal motility disorders identified by *Chandler 2015*).

Moreover, the assessor would recommend to:

1) to identify PTs/codes which could be associated to autonomic disorders, including POTS (assuming that the POTS PT is not sufficient to identify POTS) and to define a POTS/autonomic disorders search strategy in pharmacovigilance data bases and other data bases;

2) to identify specific markers to eventually permit to classify cases of POTS after HPV vaccine as auto-immune disorders.

Appendix B Additional data

The following additional submissions were received:

Submission by	Date
EMA	
HPV referral – literature search POTS	21/07/2015
HPV referral – literature search POTS	30/07/2015
EV data on HPV vaccines and CRPS, POTS	12/08/2015
Dr Luc Kiebooms and Dr Andre Devos	
Motivation PRAC study	17/08/2015
Danish Health and Medicines Authority	
Report from the Danish Health and Medicines Authority for consideration by EMA and rapporteurs in relation to the assessment of the safety profile of HPV-vaccines	04/09/2015

European Medicines Agency

- **HPV referral – literature search POTS**

  The EMA has performed a systematic bibliographic search regarding Postural Orthostatic Tachycardia Syndrome:

  [Confidential information was removed]

  Assessor's comments

  The bibliographic references provided by the EMA have been integrated in the assessment of MAH's responses.

  Briefly:

  - Four publications that report POTS in patients who received the HPV vaccine have been identified (*Blitshteyn 2010; Blitshteyn 2014; Brinth et al. 2015; Martinez-Lavin 2015*).

  - The diagnostic criteria for POTS have been discussed (i.e. a rise in heart rate of ≥30 bpm, or a heart rate of >120 bmp, within 10 minutes of head-up tilt or standing, but without orthostatic hypotension; and for adolescents an increase in heart rate of at least 40 bpm for) (*Mathias et al. 2012; Singer et al. 2012*). A description of the most common symptoms of POTS have been provided (i.e. orthostatic intolerance with either syncope or presyncope, fatigue, light-headedness, dizziness, palpitations, visual disturbances, clamminess, nausea, headache, pain (chest or upper abdomen), shortness of breath, and non-specific symptoms such as lethargy, impaired cognitive function, difficulty concentrating (*Mathias et al. 2012*; *Schondorf et al. 1993*; *Deb. et al 2015*)

- The possible causes of POTS have also been reviewed (i.e. neuropathic POTS, hyperadrenergic POTS, volume dysregulation, and physical deconditioning) (*Benarroch 2012; Mathias et al. 2012*)

- A link between POTS and chronic fatigue syndrome (CFS) has been suggested by different authors (*Benarroch 2012, van Cauwenbergh et al 2014*), as well a link with small-fiber neuropathy (*Martinez-Lavin 2015, Haensch et al. 2014, Gibbons et al 2013*).

- Regarding the background incidence of POTS in the general population, no data is available to date. However, it has been suggested that the prevalence of POTS in patients with chronique fatigue syndrome could be estimated to 170 cases per 100,000 persons (*Schondorf et al 1999*).

- Data from a LAREB Report in HPV reports provided in systematic bibliographic search on CRPS have shown that no report with a diagnosis of POTS has been identified at the time of report. Besides, in the reports of side effects with combinations that match the symptoms of POTS - such as dizziness and fainting – there was no clear evidence for POTS. In six reports of fatigue where there was also fainting in combination with dizziness symptoms had not resolved at the time of reporting. Lareb will investigate these reports of prolonged fatigue and reports of (near) fainting combined with dizziness. This will include the progress and current symptoms, whether further medical examination was performed, and whether a diagnosis was made. We will also ask for symptoms that could indicate POTS.

- **HPV referral – literature search CRPS**

The EMA has performed a systematic bibliographic search regarding Complex Regional Pain Syndrome:

[Confidential information was removed]

Assessor's comments

The bibliographic references provided by the EMA have been integrated in the assessment of MAH's responses.

Briefly:

- Two publications that report CRPS in patients who received the HPV vaccine have been identified (*Richards et al. 2012*; Kinoshita et al. 2014).

- A description of the criteria used for the CRPS diagnostic have been provided. A discussion regarding the differences between the mostly used 'Budapest criteria' and the Japanese diagnostic criteria has been provided and pointed out that using the Japanese criteria would diagnose more patients than the Budapest criteria. It has also been outlined that there is no consensus on the diagnosis of CRPS, and that the question whether CRPS is a syndrome in its own right has been raised (*Borchers & Gerschwin 2014, Rockett 2014, Kinoshita et al. 2014*).

- The EMA report discusses the possible causes suggested for CRPS (i.e. psychological factors, immobilisation, sympathetic nervous system, neurogenic inflammation and vasomotor disturbances, neuropeptides and pain, cytokines, deep-tissue microvascular pathology hypothesis, small-fiber neuropathy hypothesis, cortical reorganisation, central changes in pain processing, genetic predisposition, and autoimmunity) (*Borchers & Gerschwin 2014, Dirckx et al. 2015, Ostergaard et al. 2014, Richards et al. 2012*).

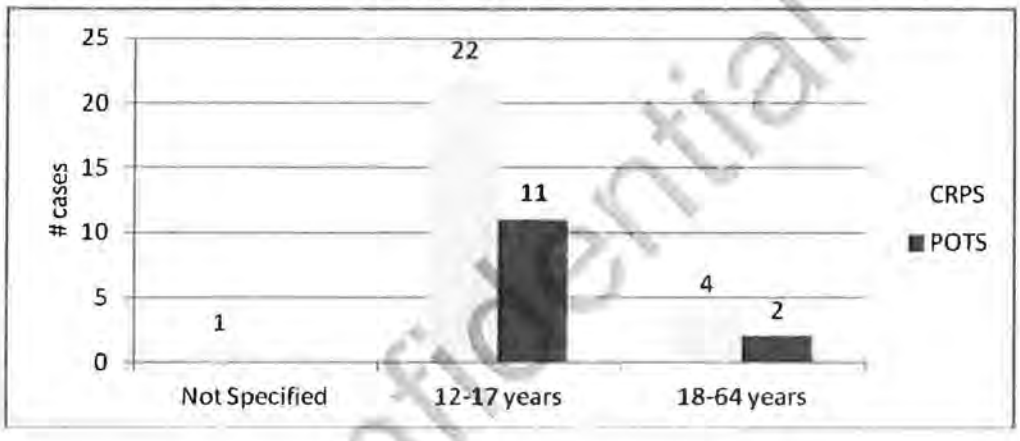
- According to *de Mos et al. 2007* and *Sandroni et al. 2003*, the background incidence rate should vary between 5.46 (US) and 26.2 (NL) per 100,000 person-years. Besides, in the target population, i.e. females 10-19 years, the incidence rate is 2.15 per 100,000 person-years in the US study and 14.9 per 100,000 person-years in the Dutch study.

- Data from a LAREB Report from HPV vaccinated patients have also been provided: Lareb received 1142 reports of suspected adverse reactions following vaccination Cervarix. Most were mild and transient. There were 48 serious reports according to international criteria. There were no reports received with a diagnosis of CRPS or POTS at the time of report. One case reported chronic pain at the injection site.

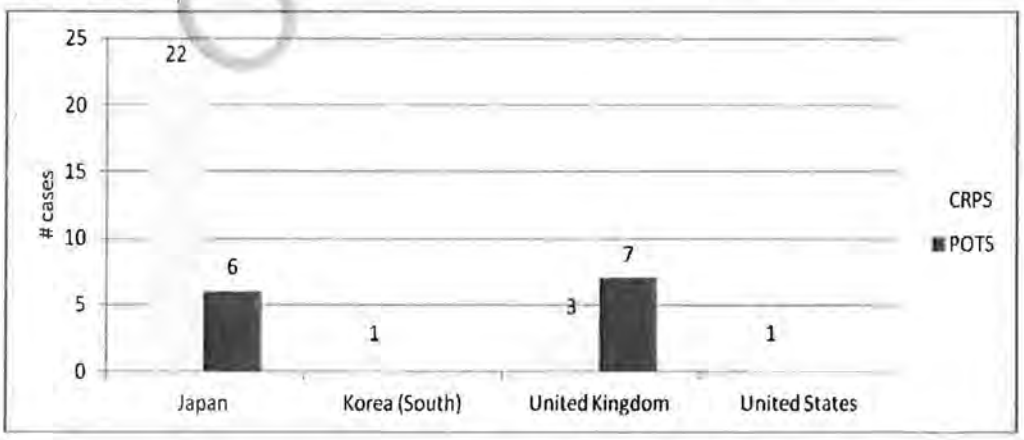
- **EVDAS search**

The EMA has performed a search in the EudraVigilance data base for cases of CRPS and POTS following vaccination with Cervarix. The obtained results are summarised below.

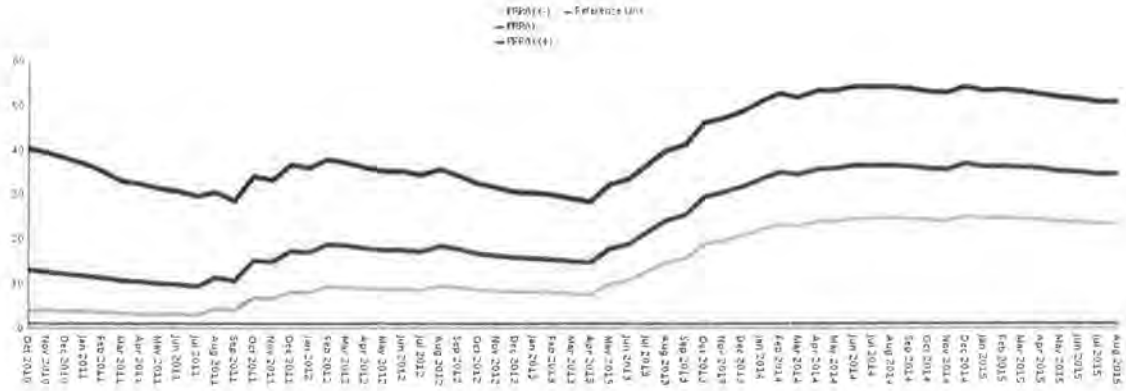
Cervarix – number of cases of CRPS (N=27) and POTS (N=13) per age range



CERVARIX - number of cases of CRPS (N=27) and POTS (N=13) per occurrence country



CERVARIX - Complex Regional Pain Syndrome - dynamic PRR and cases over time



CERVARIX - Postural Orthostatic Tachycardia Syndrome - dynamic PRR and cases over time

Assessor's comments

CRPS

A total of 27 cases of CRPS have been reported in the EudraVigilance database, mainly in girls between 12 and 17 years old (81%), who belong to the target population for HPV vaccination. Most of the cases have occurred in Japan, and an increase in the number of reported cases has been observed in 2013. These two observations may be explained by the initial concerns regarding HPV vaccination and CRPS that originate in Japan and have led the Japanese authorities to suspend their active recommendation for HPV-vaccination.

Of note, according to EVDAS, a case has occur in the US. This case was not included in the cumulative review provided by the MAH. This case relates to a 13-years-old girl who reported several adverse events following vaccination with Cervarix, Menveo, Boostrix, and Varivax (reported PTs for the case are complex regional pain syndrome, fibromyalgia, hypoaesthesia, local swelling, pain, pain in extremity, and tremor). Her medical history included asthma, tonsillectomy, Helicobacter pylori infection, allergic rhinitis and lactose intolerance. As this case was confounded by other vaccines and poorly documented, it was not included in the assessment of CRPS cases (cfr question 1).

POTS

A total of 13 cases of CRPS have been reported in the EudraVigilance database, mainly in girls between 12 and 17 years old (84%). Cases have occurred in Japan and UK. The reporting rate seems quite stable over the time.

Dr Luc Kiebooms and Dr Andre Devos

- **Motivation PRAC study**

Summary

More than 1000 spontaneous reports in Denmark, of which 283 seriously, are the occasion of a review by the PRAC[1]. This concerns a complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). Are the 283/500.000 serious side effects sufficient to put vaccination into question?

The EMA uses exclusively the reporting, which has amounted to a large number of cases. But reporting is a particularly weak method to evaluate the side effects.

The Vioxx scandal[2] and Diane-35-problems have shown how weak reporting is. In both cases there has been reporting for years, but this was done with the same methodology as suggested here. So the insight into the actual extent and severity of the phenomenon was slowed down tremendously. In both cases afterwards it turned out, that the makers of the medicine knew of the adverse reactions, before the medication was brought into circulation.

For HPV now, the same seems to occur. We are at the stage of a reporting of a particularly large number of cases for a vaccination, for which a zero tolerance regarding the side effects should prevail[3]. Until now all the literature is exclusively under the direct supervision of the industry, probably even all information comes from the industry. There are no independent studies, despite the fact that these were raised on several levels (see below).

We ask from now a fully independent monitoring of the medication. Given the widespread underreporting, the current one after all can in no way be a scientific argument.

A number of elements should be taken into consideration. Next, they are referred to in the form of question and answer.

Are the HPV vaccines Gardasil and Cervarix relevant to public health?

Cervical cancer is the second most common cancer in women worldwide, but in Europe this cancer amounts only to 15% of cancers in women (68 000 cases in 1995)[4]. The prognosis of cervical cancer is relatively favourable in terms of life expectancy. In Europe 62% of women with cervical cancer are still alive after 5 years[5]. The mortality is thus about a third of the incidence. In developed countries cervical cancer comes only on the 7e place, much behind breast cancer, colon, stomach and lung cancer, also behind endometrial and ovarian cancer[6].

According to the model-based studies of the firms, in optimal conditions (100% efficacy) these vaccines would prevent 70% of cervical cancers. This is up to now only a hypothesis, no 'evidence based medicine'.

For example, in the Netherlands the reality is completely different.

A cross-sectional study, part of a large prospective epidemiologic study performed among 2065 unscreened women aged 18 to 29 years gave a point prevalence of 19% HPV-types 16 (2.8%) and 18 (1.4%) were found concomitantly in only 3 women (0.1%). There was an increase in HPV prevalence till 22 years. Multivariate analysis showed that number of lifetime sexual

partners was the most powerful predictor of HPV positivity, followed by type of relationship, frequency of sexual contact, age, and number of sexual partners over the past 6 months[7].

In this Dutch population at the most around 4% of the female population might have benefitted from vaccination! As for the Danish situation: should we vaccinate 500 000 women to prevent a possible infection in 20 000 unscreened women, knowing that promiscuous behaviour and sex at a young age increase the risk and that this STI for a greater part can be avoided[8]? In these unscreened women at most a few hundred will develop cervix cancer, what could be by avoided through a cheaper screening.

In addition, in any case this screening remains needed for the 30% not covered dangerous HPV infections. Therefore in the Netherlands was advised not to take up the vaccine in the vaccination program[9].

Assessor's comments

Cervical cancer is a vaccine preventable infectious disease and one of the world's deadliest forms of cancer for women, responsible for more than 270 000 deaths annually, 85% of which occur in developing countries.

The 2013 World Health Assembly identified cervical cancer as among the priority interventions in the action plan for the prevention and control of noncommunicable diseases (NCDs) 2013-2020, which was agreed by Member States, committing them to including cervical cancer and other NCD interventions in national health plans.

The position of the WHO is summarised as follows (Human papillomavirus vaccines: WHO position paper, October 2014):

"WHO recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and reiterates its recommendation that HPV vaccines should be included in national immunization programmes, provided that: prevention of cervical cancer and/or other HPV-related diseases constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost-effectiveness of vaccination strategies in the country or region is considered. Both the quadrivalent and bivalent HPV vaccines have excellent safety and efficacy profiles."

Thus, HPV vaccines are a key element in cancer prevention programmes worldwide.

In 2009 Cervarix was added to the Dutch national immunization program in the context of prevention of cervical cancer. All girls living in The Netherlands receive an invitation for vaccination in the year they turn 13.

Are the HPV vaccines Gardasil and Cervarix efficient?

Also here the pharmaceutical companies give a positive answer in terms of avoiding CIN2/3 within 5 years for the HPV-16 and 18-related, though it is not 100%.

> *By the summer of 2007, there were definitely promising results with regard to the effectiveness of the HPV vaccine in the prevention of precancerous lesions (i.e., CIN 2/3) caused by the HPV-16 and HPV-18 serotypes. However, serious questions regarding the overall effectiveness of the vaccine in the protection against cervical cancer remained to be answered, and more long-term studies were called for before large-scale vaccination programs could be recommended. Unfortunately, no longerterm results from such studies have been published since then[10].*

This statement still applies in 2015. There are no reliable follow-up studies known, independent of the firms which have been able to prove the effectiveness of the vaccine.

In addition, it was not the aim of the vaccine to prevent CIN2/3 lesions, but indeed cervix cancer. We know from the practice that on the one hand CIN2/3 lesions also can clear spontaneously what makes in fact CIN2/3 lesions an almost uncontrollable endpoint. In the long term, new lesions could also occur, eventually caused by viruses not accounted for in the used vaccines, so that they would be allowed to develop to cervical cancer.

On the other hand, in the course of their life 50 to 75 percent of all women are exposed to HPV. The virus is, however, for more than 90% of all women spontaneously cleared by the immune system within two years, and does not present any risk[11,12,13,14].

Assessor's comments

Cervarix is indicated for the prevention of premalignant genital lesions and cervical cancer, causally related to certain oncogenic Human Papillomavirus (HPV) types from the age of 9 years.

The efficacy of Cervarix was assessed in two controlled, double-blind, randomised Phase II and III clinical trials that included a total of 19,778 women aged 15 to 25 years. Endpoints included CIN2+ associated with HPV-16 and/or HPV-18 and 12-month persistent infection.

In the Patricia trial, high efficacy against CIN 3+ was observed in the TVC-naïve cohort, irrespective of HPV type, of 93.2% (95% CI: 78.9-98.7). This cohort is a subset of the TVC that includes women with normal cytology, and who were HPV DNA negative for 14 oncogenic HPV types and seronegative for HPV-16 and HPV-18 at baseline. In the TVC analysis, the efficacy was 45.6% (95% CI: 28.8–58.7) against CIN 3+ irrespective of HPV type. In the Costa Rica trial, efficacy was 89.8% (95% CI: 39.5–99.5) against CIN 2+ associated with HPV-16/18, and 59.9% (95% CI:20.7–80.8) against CIN 2+ associated with non-HPV16/18 oncogenic HPVs.

In two further clinical trials performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose with GMTs at least 2-fold higher as compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 10 to 14 years of age.

Cervarix induces some cross-protection against infection and disease caused by the phylogenetically-related non-vaccine types HPV-31, 33 and 45.

Although the exact duration of protection could not yet be established, high serum antibody titers continue to persist more than 8 years following Cervarix vaccination, with no signs of waning protection to date.

Are the vaccines safe?

According to the firms they are safe. Initially, the vaccine was compared with a placebo group being vaccinated with physiological serum, whereby the number of adverse reactions was much higher and much more serious than in the control group. After comparing 320 patients in the saline placebo group a quick move was made to an aluminium-containing placebo, in order to be able to only evaluate the effects of the active substance. However, this distorted the comparison, because no one voluntarily wants to be vaccinated with toxic aluminium, as this is not really necessary, when inoculation with a harmless saline solution can be done. The differences between Gardasil and the saline placebo group were, however, already

noticeable[15]. Here we can refer to the Vioxx scandal, where the adverse reactions in fact were known, but concealed by the firm. Here also the difference between the vaccine and the saline placebo is concealed in all publications, as the table below clearly shows. For serious adverse reactions one suddenly takes the saline and aluminium group together, perhaps to cover up the major differences between these two groups.

GARDASIL®
[Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine] 968;

Table 6
Vaccine-related Injection-site and Systemic Adverse Experiences*

Adverse Experience (1 to 5 Days Postvaccination)	GARDASIL (N = 5088) %	Aluminum-Containing Placebo (N = 3470) %	Saline Placebo (N = 320) %
Injection Site			
Pain	83.9	75.4	48.6
Swelling	25.4	15.6	7.3
Erythema	24.6	18.4	12.1
Pruritus	3.1	2.8	0.6

Adverse Experience (1 to 15 Days Postvaccination)	GARDASIL (N = 5088) %	Placebo (N = 3790) %
Systemic		
Fever	10.3	8.6
Nausea	4.2	4.1
Dizziness	2.8	2.6

*The vaccine-related adverse experiences that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.

The question about the toxicity should be taken seriously, because of the under reporting. Do doctors not inform objectively about possible side effects, because than a refusal might follow? Thereby it is well known that case reporting means a strong under reporting of reality.

> *The medical profession's ethical duty is to provide a full and accurate explanation of the benefits as well as the risks associated with a particular drug so that a patient is able to make an informed decision regarding a treatment. If a physician fails to do so and/or if financial interests take precedence over public health, breaches of informed consent guidelines may occur. For instance, presenting information in a way which promotes fear of a disease while undervaluing potential vaccine risks is likely to encourage patients to give consent to the treatment, even when the latter has no proven significant health benefit*[16].

It is also amazing that questions about the deadly accidents (India, but also in the original studies and the one's reported by the VAERS) were no longer asked, although these accidents are published. The company says that there is no link with the vaccine and that is adopted without any comment and not followed up. Probably there is no connection with the immune active substance, but this does not rule out the fact that there may be a link with the toxic additive aluminium, especially when this is compared to the administration of a saline solution.

Assessor's comments

HPV vaccines are currently considered as safe, and the WHO Advisory Committee for Vaccine Safety (GACVS) concluded in March 2014, after the review of post-licensure surveillance data from the United States, Australia, Japan and the MAH, that both HPV vaccines continue to have an excellent safety profile (*WHO 2014*).

Regarding the safety of adjuvants, some authors have hypothesised that an ASIA syndrome (autoimmunity/inflammatory syndrome induced by adjuvants) could occur following

vaccination (*Guimarães et al. 2015*). However, this hypothesis is highly controversial, and no epidemiological study has clearly evidenced this syndrome up-to-date.

At the European level, the safety profile of Cervarix is reviewed on a yearly basis via the periodic benefit-risk evaluation report. Adverse events related to potential immune-mediated disease (pIMD) following vaccination with Cervarix, as well as primary ovarian failure are currently under close safety surveillance and in depth discussed in PBRER. Moreover, as a GVP specific requirement for vaccines, vaccination failure, vaccination errors, cases with a fatal outcome, co-administration of vaccines, and vaccination anxiety-related reactions such as syncope will be also monitored. The next PBRER should be submitted by the 26/01/2016 (DLP: 17/11/2015). The safety concerns identified for Cervarix are:

Important Identified Risks	• None
Important Potential Risks	• Theoretical risk of acquiring vaccine-induced autoimmune disease after vaccination
Missing Information	• Use of HPV-16/18 vaccine in HIV-infected women or subjects with known immune deficiencies • Impact of HPV-16/18 vaccine in pregnant women who are inadvertently exposed to the vaccine

Should the approval of the vaccines be reviewed?

> *In matters pertaining to life and death, it is essential to choose the sure thing, and, by definition, dangerous to choose otherwise. With regard to cervical cancer prevention, Papanicolaou cytological screening, done correctly, is a sure thing; HPV vaccination, done correctly, is not. We must not allow our hopes to cloud these observations. Therefore, developing countries should allocate their limited resources to cervical screening, rather than HPV vaccination, until the possibility has been excluded that HPV vaccines may be ineffective for cervical cancer prevention, or until full coverage of target demographic groups by screening services has been achieved, whichever comes first*[17].

According to this, it seems obvious to stop the general promotion of the vaccines and to develop more seriously the follow up studies. Indeed, it concerns a sexually transmitted disease that needs decades to develop and in the meantime, on the understanding that screening is provided, can be treated conveniently. It also still is not proved that one cervix cancer finally was avoided.

Assessor's comments

The scope of this referral procedure does not reflect efficacy data. The submitted safety data as well as safety data from the literature do not provide sufficient evidence to alter the benefit risk balance of Cervarix. However, the link between CRPS or POTS and vaccination with Cervarix needs to be further investigated (cfr section 6 Recommendations and Appendix A – Question 5).

What control should be implemented?

In the past various authorities have insisted upon the necessary control, so that both the efficacy of the vaccines and the adverse reactions could be mapped.

In Belgium, the Belgian Health Council (HGR)[18] has recommended to improve the screening according to the European recommendations and those of the Belgian Health care Knowledge Centre (KCE).

On the basis of a good registration of the results of the cervical screening, linked to the registration of HPV vaccinations and the cancer registration, the actual short-and long-term effects of HPV vaccination could be measured. The HGR recommends that a legal framework allowing the linking of individual HPV vaccination data to the above registers should be created and made legally possible.

A monitoring mechanism after the introduction of vaccination is needed, supported by the above mentioned registers, with attention for the long-term efficiency and adverse reactions on the vaccination, and with monitoring of circulating HPV types in various populations and specimens to detect in time any drift away to other HPV types.

Neither at European, national, nor at the regional level was this realized. This makes it impossible to identify which adverse reactions are listed, nor the effectiveness of the vaccine. After all, we ignore which women may or may not have been vaccinated. We will surely in 10-15 years not know if the fatalities from cancer were vaccinated or not, or if a possible decrease in deaths was due to the vaccine, to a better screening or to other factors such as reducing promiscuity, or a reduced use of hormonal contraception (increasing the risk of cervical cancer significantly).

Assessor's comments

At the European level, the safety profile of Cervarix is reviewed on a yearly basis via the periodic benefit-risk evaluation report. Adverse events related to potential immune-mediated disease (pIMD) following vaccination with Cervarix, as well as primary ovarian failure are currently under close safety surveillance and in depth discussed in PBRER. Moreover, as a GVP specific requirement for vaccines, vaccination failure, vaccination errors, cases with a fatal outcome, co-administration of vaccines, and vaccination anxiety-related reactions such as syncope will be also monitored. The data provided by the MAH are deeply assessed by the authorities.

Conclusion

If despite the above arguments the EMA decides to continue supporting the vaccination, the EMA could propose that the companies provide a budget for an independent control. Such action should be coordinated by the responsible government authorities in full independence from the firms.

The patients should first be objectively informed about the vaccination and the alternatives (monogamous sexual life and regular screening, what still is the general code of conduct for the vast majority of the population). Then they need to be registered in a national database, to which they themselves should be able to have access, to add any adverse reactions in consultation with the doctor. These data must be analysed by scientists who have no connection whatsoever with the pharmaceutical industry.

Assessor's comments

As already stated above, the current available data do not provide sufficient evidence to review the B/R balance of Cervarix.

Besides, it is important to highlight that, even if a PASS is performed by a MAH, the protocol must be reviewed and approved by the authorities before starting the study. Moreover, in contrast to what is published in literature, all the data obtained during the study are provided to the authorities who perform an in-depth assessment.

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18 HGR 8204, May 2nd 2007

Danish Health and Medicines Authority

- **Report from the Danish Health and Medicines Authority for consideration by EMA and rapporteurs in relation to the assessment of the safety profile of HPV-vaccines**

  As part of national obligations the Danish Health and Medicines Authority has prepared and shared a report regarding HPV vaccines and ADRs.

  The 'Summary and conclusions' of the report is provided below.

Summary and conclusions

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

The main observations and interpretations are the following:

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

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

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

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

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

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

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

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

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

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

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

Assessor's comments

As discussed in question 4, it is the assessor's view that, on the basis of the available data, the link between POTS and CRPS is highly hypothetical and requests more investigation to be confirmed.

Besides, as the involvement of Cervarix vaccination and the occurrence of CRPS or POTS cannot be completely ruled out to date, it is agreed, as also suggested by the Danish and Japanese Authorities, that this potential causal relationship should be further investigated. However, it is the assessor's view that it is preferable to investigate potential associations of HPV vaccination with POTS and HPV vaccination with CRPS separately without extrapolating on hypothetical common causal patterns.

PRAC rapporteur's referral preliminary assessment report for Gardasil -9 and Overall PRAC rapporteur's referral preliminary assessment report

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

Human papillomavirus (HPV) vaccines

Cervarix: EMEA/H/A20/1421/C/0721/0071
Gardasil: EMEA/H/A20/1421/C/0703/0060
Gardasil 9: EMEA/H/A20/1421/C/3852/0001
Silgard: EMEA/H/A20/1421/C/0732/0054

PRAC Rapporteur	Julie Williams (UK)
PRAC Co-rapporteurs:	Jean Michel-Dogne (BE) Qun-Ying Yue (SE)
EMA referral Procedure Manager:	Efstratia Vatzaki
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:	<Date>
Deadline for comments:	1 October 2015
<Updated report circulated:>	28 October 2015

Administrative information

INN (or common name) of the active substance(s)	- Cervarix (Bivalent HPV vaccine (types 16, 18) - Gardasil (quadrivalent HPV vaccine (types 6, 11, 16, 18) - Gardasil 9 (9-valent HPV vaccine (types 6, 11, 16, 18, 31, 33, 45, 52 and 58) - Silgard (quadrivalent HPV vaccine (types 6, 11, 16, 18)
Pharmaco-therapeutic group (ATC code)	J07BM01
Pharmaceutical form(s) and strength(s)	All approved Cervarix Gardasil Gardasil-9 Silgard

<Co->rapporteur's contact person	Name(s): Tel: E-mail:
<Co->rapporteur's assessors	Name(s): Tel: E-mail:

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

List of abbreviations

1. 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 19 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.

CRPS symptoms are severe chronic pain which is out-of-proportion to what would be expected, allodynia, hyperesthesia, swelling, changes in the skin temperature and colour of the arms or legs, sweating, movement disturbances (tremor, weakness, dystonia) and trophic changes (abnormal hair and nail growth). . 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.

2. 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 May 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.

3. Assessment

3.1. Introduction

Gardasil 9 is an adjuvanted non-infectious recombinant 9-valent vaccine. It is prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein from the same four HPV types (6, 11, 16, 18) in qHPV vaccine Gardasil or Silgard and from 5 additional HPV types (31, 33, 45, 52, 58). It uses the same amorphous aluminium hydroxyphosphate sulphate adjuvant as qHPV vaccine. The VLPs cannot infect cells, reproduce or cause disease. The efficacy of L1 VLP vaccines is thought to be mediated by the development of a humoral immune response.

Based on epidemiology studies, Gardasil 9 is anticipated to protect against the HPV types that cause approximately: 90% of cervical cancers, more than 95% of adenocarcinoma in situ (AIS), 75-85% of high-grade cervical intraepithelial neoplasia (CIN 2/3), 85-90% of HPV related vulvar cancers, 90-95% of HPV related high-grade vulvar intraepithelial neoplasia (VIN 2/3), 80-85% of HPV related vaginal cancers, 75-85% of HPV related high-grade vaginal intraepithelial neoplasia (VaIN 2/3), 90-95% of HPV related anal cancer, 85-90% of HPV related high-grade anal intraepithelial neoplasia (AIN2/3), and 90% of genital warts.

Gardasil 9 is indicated for active immunisation of individuals from the age of 9 years against the following HPV diseases:

- Premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types
- Genital warts (*Condyloma acuminata*) caused by specific HPV types.

This assessment report focuses on Gardasil 9 and the overall assessment taking account of the Co-Rapporteur's evaluation of the MAH's responses to the list of questions relating to Cervarix and Gardasil. In addition, on 4 September the Danish Health and Medicines Authority (DHMA) submitted a detailed report[1] for consideration by the (Co)-Rapporteurs as part of the ongoing referral, entitled "*Report from the Danish Health and Medicines Authority for consideration by EMA and rapporteurs in relation to the assessment of the safety profile of HPV-vaccines*". The Netherlands also submitted an overview of national data relating to HPV vaccine. These submissions are both evaluated in the Rapporteur's overall assessment below.

3.2. <Quality aspects>

n/a

3.3. <Non-clinical aspects>

n/a

3.4. Clinical aspects

The order in which the information on clinical aspects is presented (efficacy/safety or safety/efficacy) can vary depending on the specific issue under assessment.

3.4.1. <Efficacy>

n/a

[1] http://sundhedsstyrelsen.dk/~/media/0A404AD71555435BB311CD59CB63071A.ashx

3.4.2. Safety

3.4.2.1 Rapporteur's overview of CRPS and POTS

CRPS

Complex regional pain syndrome (CRPS) is a debilitating, painful condition in a limb, associated with sensory, vasomotor, sudomotor, motor and dystrophic changes after injury to that limb. The events that precipitate CRPS most commonly are fractures, sprains, and surgery, but also include injections, local infections, burns, frostbites, even pregnancy, as well as stroke or myocardial infarction. However, the exact nature and combination of symptoms and their severity are not related to the severity of trauma, and more than 10% of patients may not recall any precipitating event. CRPS can be divided into two types based on the absence (type 1, much more common) or presence (type 2) of a lesion to a major nerve.

CRPS usually affects one limb, but in a small proportion of cases may later spread to additional limbs. Pain is typically the leading symptom of CRPS and is often associated with limb dysfunction and psychological distress.

Since the condition is uncommon, and the range of symptoms can mimic a large number of other possible conditions seen by practitioners from various professional backgrounds, patients commonly experience a delay in diagnosis and the start of appropriate therapies.

The diagnosis of CRPS cannot be made on imaging or laboratory tests and may be based on clinical examination and is given when patients meet the 'Budapest' diagnostic criteria described in the responses to question 1 below.

The onset of symptoms for the majority occurs within one month of the trauma or immobilisation of the limb. There is no proven cure for CRPS. Prompt diagnosis and early treatment are considered best practice in order to avoid secondary physical problems associated with disuse of the affected limb and the psychological consequences of living with undiagnosed chronic pain.

There are only two population-based studies of outcome in CRPS. One suggested that 74% of patients experienced disease resolution, with symptoms lasting a median of 7 months. Another suggested that only 30% of CRPS patients considered themselves recovered, 16% still suffered from severe progressive disease, and the remainder was stable an average of 5.8 years after onset.

A definition of recovery from CRPS has not yet been agreed. Limb signs (such as swelling, sweating and colour changes) usually reduce with time, even where pain persists. However, such reduction of limb signs is in itself not 'recovery'. Where pain persists, the condition is best considered to be active. Approximately 15% of sufferers will have unrelenting pain and physical impairment >5 years after CRPS onset, although more patients will have a lesser degree of ongoing pain and dysfunction impacting on their ability to work and function normally. For those in whom pain persists, psychological symptoms (anxiety, depression), and loss of sleep are likely to develop, even if they are not prominent at the outset.

The cause of CRPS is currently unknown, and earlier concepts that the predominant problem is sympathetic dysfunction and that CRPS is associated with a history of pain-preceding psychological problems or with somatisation no longer appear supported.

Based on data from The Netherlands, the incidence rate of CRPS-1 were 14.9 and 28.0 per 100,000 person-years in females 10-19 years old and 20-29 years old, respectively. Corresponding rates were lower in males, reported to be 1.8 and 6.2 per 100,000 in males 10-19 years old and 20-29 years old, respectively.

Overall, given the complexity of the syndrome and likely differential practice in approaches to diagnosis and management across countries, reported background incidence may differ between countries.

POTS

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 is usually accompanied by a range of symptoms of orthostatic intolerance. These symptoms may include palpitations, light headedness, weakness, 'brain-fog', peripheral coldness and purplish skin discolouration and blurred vision. Some sufferers also experience fainting.

Although defined and diagnosed mainly by the tachycardia and orthostatic symptoms, POTS is often associated with a wide range of other symptoms such as migraine-like headaches, chronic aches and pains, gastrointestinal symptoms (nausea, bloating, abdominal pain), sleep disturbance and shortness of breath. In particular, fatigue is a very common feature. However, there is no set pattern of symptoms in POTS sufferers and, aside from the defining symptom of tachycardia, different people will show different symptoms. This wide spectrum of symptoms probably reflects that the fact that the syndrome has several distinct pathophysiological mechanisms.

Sufferers will generally present with gradual and chronic symptoms of orthostatic intolerance and fatigue. Such symptoms can be non-specific and have causes other than POTS, and so a diagnosis of POTS may not be clear cut. Many people diagnosed with POTS are chronically fatigued, have sleep disturbance and are unable to perform daily functions. There is now recognised to be a significant overlap between POTS and Chronic Fatigue Syndrome (CFS).

In many people diagnosed with POTS, the range of symptoms can have a detrimental impact on the overall quality of life. Anxiety, depression, and other psychiatric disorders can also add to the complexity of the syndrome. Patients with POTS are sometimes clinically diagnosed as having anxiety disorders such as panic disorder

If other causes are ruled out, POTS may be diagnosed if these chronic symptoms are also associated with an excessive increase in heart rate when changing from supine to a standing up position. For POTS to be diagnosed, patients need to experience a sustained increase of 30 beats per minute or more within 10 minutes of standing (or with tilt table test), without a fall in blood pressure. For those aged 12–19 years this increase should be least 40 beats/min (Sheldon et al; 2015).

A recent review by Kizilbash et al (2014), from the US Mayo Clinic, summarises what is currently known about POTS in adolescence. Whilst each patient has a unique set of symptoms, it is said that their stories often sound familiar. Parents and adolescent patients with POTS often describe the long and difficult process they experience from the moment they became ill, to decreased school attendance with dropped extracurricular activities and poor academic performance, to visiting a variety of doctors in order to find answers about their child's illness. In this process, they often receive different diagnoses. Acording to Kizilbash et al, there are several typical features retrospectively identified in many adolescent POTS patients at presentation, including symptom onset during early puberty, high achievers in school and athletics, joint hypermobility, and recent illness or injury. Many adolescents with POTS have hyperextensibility, and some are thought to have "benign joint hypermobility syndrome". It is not clear whether the elastic soft tissues actually predispose to the development of POTS or if the lax tissues simply allow further increases in vasodilatation that make it more likely for hyperextensible individuals to report more venous pooling and dizziness when they get POTS.

Overlap with CFS

Many patients diagnosed with CFS also show symptoms of orthostatic intolerance and signs of autonomic dysfunction, and several studies in UK patients have shown that POTS can also be diagnosed in those with CFS, ranging from 13% (Lewis et al 2013) to 27% (Hoad et al). Some studies in the US suggest the proportion of CFS patients with POTS is even higher. The level of overlap will likely depend on the selection criteria within in each study, and it is unclear how generalisable these estimates may be.

It is currently unclear whether POTS is a separate clinical entity distinct from CFS, or whether patients with POTS form a subset of those with CFS with a specific group of particularly marked symptoms (Lewis et al 2013). As chronic fatigue is a common presenting feature in POTS, CFS may often be diagnosed initially (or co-diagnosed) particularly in adolescents.With increasing recognition of POTS in subsets of CFS patients, POTS may be a differential diagnosis in many who are under evaluation for

CFS. According to MacDonald et al (2014), it is becoming increasingly clear that, historically, many patients with POTS were given a diagnosis of CFS.

POTS can affect people of all ages, but the overwhelming majority of patients are women (80% to 85%) of child-bearing age (13–50 years). In adolescence, the majority of affected individuals report symptoms beginning within a year or two of the beginning of puberty, with worsening symptoms until the age of 16. About 80% of female patients report an exacerbation of symptoms around menstruation (Raj; 2013). In 1999, the prevalence in the Unites States was estimated in adults at 170 per 100,000 [Low et al 2009]. Although POTS is thought to be under-diagnosed, there is a gradually increasing awareness of POTS and diagnoses may be increasing.

The causes and pathophysiology process of POTS are not well understood, and there is no single precipitating factor. Although a decrease in return of blood to the heart generally underlies the symptoms of POTS, the causes of this likely involve multiple abnormal physiological processes that differ between sufferers. This is why POTS is classed as a syndrome, rather than a specific disease.

Patients frequently report that their symptoms began after acute stressors such as pregnancy, major surgery, or a presumed viral illness, but in others cases, symptoms develop more insidiously. (Raj; 2013). A large number of patients initially become symptomatic following a significant febrile illness, often mononucleosis or influenza (Kizilbash et al).

The prognosis of POTS depends on the underlying aetiology. Many sufferers experience full recovery over time with or without treatment, but some have persistent symptoms. About 50% of patients with post-viral POTS will have partial or complete recovery within two to five years. Prognosis is generally better in younger people. Ninety per cent of patients will respond to a combination of physical and pharmacotherapy (Grubb et al 2006). Occasionally, some patients experience deterioration in their daily life activity over time to such an extent that they are unable to continue normal employment or educational activities, and many will become depressed.

For the purpose of the referral, the MAH was requested to respond to the following five questions:

3.4.2.2 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 fulfill published or recognized diagnostic criteria.

Note: In identifying and evaluating diagnosis of cases of CRPS and POTS, and as agreed with the (Co)-Rapporteurs, both MAH's have used the same criteria, i.e. the 'Budapest'criteria for CRPS, and the Raj 2013/Sheldon 2015 for POTS:

CRPS

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.

POTS

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)

3.4.2.2.1 Gardasil 9

Gardasil 9 was authorised for use in Europe on 10 June 2015, however, it is not known how many doses have been distributed or administered in Europe to date (if any). According to the MAH ~600,000 doses of Gardasil 9 have been distributed primarily in the US in 2015. Given this limited usage to date, the MAH's safety analysis **has not identified any post-marketing reports in association with Gardasil 9** relevant to the issue.

The only data specific to Gardasil 9 included in the MAH submission were one case suggestive of CRPS, and two reports of POTS, from qHPV (Gardasil)-controlled studies.

CRPS

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.

POTS

Two cases suggestive of POTS were identified in the clinical database, both in the 9vHPV vaccine group.

AN 29076, a 12 year old White female from Chile 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.

AN 71508, a 19 year-old White female from Denmark (site 090) 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 Frederiksberg 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 Frederiksberg Hospital reported this condition to the Danish Health Authority in November 2013. The Danish Health Authority subsequently reported this event to site. The site reported the event of POTS in the V503-001 clinical database in November, 2013. The onset date of the POTS was reported as 01-Nov-2013. Upon further follow-up, it was learned that the subject had a history of severe dizziness and was hospitalized for investigation from 13 to 16-Aug-2013. The patient was recommended to take 2-3L of water daily and ibuprofen as needed. On 09-Dec-2013, the subject reported rotatory dizziness, near fainting attacks, and migraines, and the subject was taking propranolol

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

The incidence of reports from pooled trials data relative to the comparator groups is summarised in the table below:

Table 2

Incidence of CRPS and POTS per 10,000 Person-Years of Follow-up V501[1], V502[2], V503[3], V504[4], and V505[5] 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)

[1] 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.
[2] Includes data from protocols 001 and 002.
[3] Includes data from protocols 001, 002, 003, 005, 006, 007, and 009.
[4] 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.

Rapporteur's comments:

For Gardasil 9, the one report of CRPS and one of the reports of POTS do not necessarily fulfil the respective diagnostic criteria. The other report had an apparently long onset time from vaccination. The details of these reports in the context of the pooled trial data do not raise a safety concern for Gardasil 9.

3.4.2.2.2 Gardasil

The detailed assessment of the MAH's response can be found in pages 19-77 of the Co-Rapporteur's assessment. The key aspects of the MAH's response is summarised belowThe MAH performed queries to identify any cases of the preferred term '*complex regional pain syndrome*' and '*postural orthostatic tachycardia syndrome*', as well as queries of combinations of a range of specific signs/symptoms of CRPS and POTS to identify additional cases that may be suggestive of these syndromes, but not

reported/diagnosed as such. The same search strategy was used to identify relevant clinical trials and post-marketing case reports for qHPV and 9HPV vaccines.

For CRPS, 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 (the Budapest Criteria). For POTS, the MAH used the DHMA's proposed 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. 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.

CRPS

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.

A high-level summary of the review of data from the clinical studies is 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.

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

	Based on PT "CRPS"	Based on symptom query
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

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**	**Reporting rate for Cases Reported with Combinations of Symptoms of CRPS per Million Vaccinees by Region or Country**
	Cumulative to 31-May-2015	**Number of persons vaccinated (assuming 3 doses administered per person)**	**(# Reports/ # People vaccinated x 1 million)**	**(# Reports/ # People vaccinated x 1 million)**
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	82,237,971	27,412,657	<1 case (11/ 27, 412,657)	<1 case (11/ 27,412,657)
Denmark	1,351,593	450,531	~4 cases (2/ 450,531)	42 cases (19/ 450,531)
Japan	1,850,998	616,999	29 cases (18/ 616, 999)	~2 cases (1/ 616, 999)

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 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

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment
			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 (Okuyama 2014)	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 vaccination. Based on the temporal sequence these are understood to be side effects from the vaccine... rare to satisfy strict diagnostic indices of CRPS"	The cases presented after qHPV exposure are not considered to meet the Harden criteria for CRPS.

POTS

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

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**	**Reporting rate for Cases Reported with Combinations of Symptoms of POTS per Million Vaccinees by Region or Country**
	Cumulative to 31-May-2015	**Number of persons vaccinated (assuming 3 doses per person)**	**(# Reports/ # People vaccinated x 1million)**	**(# Reports/ # People vaccinated x 1 million)**
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	82,237,971	27,412,657	1 (28/ 27,412,657)	<1 (13/ 27,412,657)
Denmark	1,351,593	450,531	91 (41/ 450,531)	13 (6/ 450,531)
Japan	1,850,998	616,999	~7 (4/ 616, 999)	3 (2/ 616, 999)

Literature review

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
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	15 adolescents from Japan with CRPS. 40 patients in total (7	4 cases of POTS. 2 cases presented in more detail, none of those strictly fulfilling POTS	Overall in the case series 5 cases of 40 selected for presentation as

Study type / reference	Population / setting / exposure	Key result / authors conclusion	Assessor comment
al. 2014)	exposed to Gardasil, 22 to Cervarix). **3** with CRPS+POTS. **1** with POTS. One hospital department, unclear referral /selection mechanism.	criteria.	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 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	As above. The case presented confounded.

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

Gardasil Co-Rapporteur's conclusions on question 1:

The Co-Rapporteur considers that the MAH's overall case search strategy was appropriate to the question, however, a slight difference in the criteria for identifying clinical trial and post-marketing cases of POTS was noted (hypoaesthesia and skin atrophy not included in the latter). A question to the MAH is raised on this point. A question is also raised to confirm that the relevant older MeSH terms are also included for CRPS, such as "Reflex Sympathetic Dystrophy" and "Causalgia, and terms such as "Orthostatic intolerance" and "Postural Orthostatic Tachycardia Syndrome" for POTS, or to confirm that addition of such terms does not add to the references identified.

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.

The Co-Rapporteur agrees with the MAH's database search for post-marketing reported cases of CRPS and POTS, as well as the MAH's classification of cases as fulfilling the relevant agreed diagnostic criteria for partially fulfilling them, or not being cases.

The Co-Rapporteur also agrees with the MAHs conclusions regarding cases of CRPS identified from the literature. In particular, Kinoshita et al generates the majority of CRPS cases in the literature (and some POTS), but the mechanisms for referral/presentation to the centre are not sufficiently described. Descriptive data relevant for the CRPS cases are limited, and the time to onset highly variable or not well-described. In relation to the case series from Brinth et al, the Co-Rapporteur considers 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 the observed poor correlation between the POTS diagnosis and symptoms reported by Brinth et al, and the lack of utility of the strict postural tachycardia limit used for the definition of POTS (e.g. Corkal and Kimpinski 2014, Gibbons 2014), the

Co-Rapporteur states that a postural tachycardia as currently defined may represent normal variation and not necessarily suggest autonomic dysfunction. A study on 600 healthy Chinese school children 41 (6.8%) were diagnosed with POTS is highlighted, bringing the relevance of the diagnostic criteria into question (Lin, Han et al. 2014). The Co-Rapporteur considers that the Kinoshita et al and the Brinth et al case series do not provide sufficient data to establish a reasonable possibility of a causal relation between the qHPV vaccine and POTS or CRPS.

3.4.2.2.3 Cervarix The detailed assessment of the MAH's response can be found in pages 19-36 of the Co-Rapporteur's assessment. The key aspects of the MAH's response is summarised below:

The MAH for Cervarix adopted a similar search strategy as the MAH for Gardasil to identify the relevant PTs, as well as well as queries of combinations of a range of specific signs/symptoms of CRPS and POTS to identify additional cases that may be suggestive of these syndromes. Both MAHs also evaluated cases against the same diagnostic criteria.

Clinical safety data

The MAH has pooled the safety data from 18 completed and unblinded studies designed with an active comparator group (either placebo or another vaccine other than an HPV vaccine, i.e. Hepatitis B, Hepatitis A) which includes a total of 42,047 vaccinees (21,268 in HPV group and 20,779 in comparator groups) (DLP of 15 June 2015).

The analysis of available data did not identify any serious or non-serious adverse event of CRPS or POTS, regardless of the search strategy method, i.e. when searching for cases which contain the MedDRA PT 'CRPS' or 'POTS', or when searching for any cases that include signs and symptoms of CRPS (as according to *Harden et al. 2010*), or POTS (as according to *Raj 2013 and Sheldon et al. 2015*).

Post marketing safety data

CRPS

A total of 49 case reports were identified that included the MedDRA PT of CRPS. This corresponds to a reporting rate of 0.086 per 100,000 doses distributed worldwide.

In summary, the Co-Rapporteur has identified 5 cases which followed the 'Budapest' diagnostic criteria and were considered as 'confirmed' cases of CRPS. The 44 other cases were considered as 'unconfirmed/potential' cases as CRPS was diagnosed or suspected, but the individual reported events did not fulfill the diagnostic criteria. The Co-Rapporteur considers that in 3 of the 'confirmed' cases, and in 8 of the 'unconfirmed/potential' cases, a causal relationship with Cervarix vaccination cannot be ruled out.

Besides, in 2 additional 'potential' cases of CRPS, which were identified by the wider search strategy, the Co-Rapporteur considers a causal relationship with Cervarix vaccination cannot be ruled out.

The Co-Rapporteur considers that whether this is due to the injection or the vaccine itself cannot be determined as in literature CRPS was also reported following venipuncture, intravenous drug administration and other vaccinations *(Richards et al. 2012; Kwun et al. 2012; Genc et al. 2005; Jastaniah et al. 2003; Bilic et al. 2013).* However, if the injection itself triggers the event, and given the large number of people that receive injections for various medical reasons, one would expect a

much larger number of reports of CRPS triggered by injections. Despite data from the literature do not point out a causal relationship between HPV vaccine and the onset of CRPS, this cannot be ruled out as the disease is probably caused by a multifactorial process, including inflammatory and immune related factors (*Bruehl 2015*).

The Co-Rapporteur considers the number of CRPS cases following administration of Cervarix to be low compared to 57 million doses of Cervarix distributed globally. The low number might be contributed to by the problem of underreporting of ADRs in general, and more specifically, the difficulty of diagnosing CRPS this being a complex syndrome with a variety of signs and symptoms in highly variable combinations with a variable progression over time, and thereby underdiagnosis.

POTS

A total of 19 case reports with the POTS PT were identified in the MAH's global safety database since launch until 15 June 2015. Five cases were identified as confirmed cases of POTS as they contain information about symptoms suggestive of POTS and confirmation of increased pulse following the different tests (mainly Schellong's test). Thirteen cases were classified as unconfirmed cases of POTS, as no information on BP or pulse was provided. One case from Japan (identified in an article) that reported both CRPS and POTS is classified as unassessable.

Seven 'potential' reports were identified with the wider search strategy (i.e. not reported as POTS but with some related symptoms), although none of these were confirmed as POTS based on case review.

Of these 19 and 7 reports, the Co-Rapporteur considers that 2 cases could likely be cases of POTS, 4 cases are possibly cases of POTS, and the other cases are not POTs or unclassifiable cases.

In conclusion, the Co-Rapporteur states that very few cases of POTS following HPV vaccination were identified. From data available, all conditions other than vaccination which could potentially be associated with POTS cannot be systematically excluded. However, a potential association between HPV vaccination and POTS cannot be ruled out.

Overall Rapporteur's conclusions on responses to Question 1

The Rapporteur agrees that both MAHs have adopted an appropriate strategy for identification of possible cases of POTS and CRPS, and agrees with the MAH's evaluation of diagnostic certainty in most cases. However, as many cases reported as POTS or CRPS (i.e. as a PT) are considered to be 'unconfirmed' based mainly on a lack of information, as opposed to good information that is inconsistent with the diagnosis, it is important that these are still considered as 'cases' for the context of the 'observed vs expected' analysis and not dismissed. This is discussed further in relation to question 3 below.

The Rapporteur agrees that available case details in the context of worldwide usage, and available literature, do not suggest a causal association between HPV vaccine and either CRPS or POTS. This is also discussed further below in relation to question 3. The case series published by Brinth *et al* is discussed in further detail below, in the context of the DHMA submission.

In relation to CRPS, the Rapporteur agrees that although a relationship to needlestick injection cannot be ruled, this would not be specific to HPV vaccine and is a theoretical risk with any injection procedure. Any such risk, if real, is likely to be extremely small.

3.4.2.3 ***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.

3.4.2.3.1 Gardasil 9

This is assessed in the context of question 1 above.

3.4.2.3.2 Gardasil

The few cases from clinical trials were considered in the context of the response to question 1. This is therefore not discussed further here.

3.4.2.3.3 Cervarix

No cases were identified from clinical studies.

Overall Rapporteur's conclusions on responses to Question 2
The answer to this question was addressed in the context of the response to question 1

3.4.2.4 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.

Note: Both MAH's have provided a detailed 'observed vs expected' analysis of their spontaneous case reports, which are summarised and discussed in detail in each Co-Rapporteur's assessment report. Therefore, for brevity, this detail is not replicated in the Rapporteur's overall assessment and cross-reference is made to the relevant pages of the Co-Rapporteur's reports. Selected graphs/tables are replicated below for ease of reference.

3.4.2.4.1 Gardasil 9

As no post-marketing reports have been identified, this is not applicable.

3.4.2.4.2 Gardasil

The detailed assessment of the MAH's response can be found in pages 80-95 of the Co-Rapporteur's assessment.

The Co-Rapporteur considers that the MAH's overall approach to the 'observed vs expected' analysis and assumptions are acceptable, but that such analyses have inherent methodological limitations.

For CRPS, the Co-Rapporteur notes the fact that many cases come from one single centre in Japan makes the interpretation of the observed count difficult, but is reassured that a very low reporting rate must be assumed in combination with relaxed diagnostic criteria for the observed rate to reach the expected rate.

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

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

B. US

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

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

C. EU

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

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

D. UK

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

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

E. Germany

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

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

Table 14

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

A. Denmark

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

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

B. Japan

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

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

Similarly for POTS, 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.

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	836	1432	3342
			80%	4	10	18	41	44	103	176	411	88	206	353	823	441	1,029	1,763	4,113
1mon (3mon)	21	29	65%	16	36	62	145	158	363	622	1,452	311	726	1,245	2,904	1,556	3,630	6,223	14,520
			80%	19	45	77	179	181	447	766	1,787	383	894	1,532	3,574	1,915	4,468	7,658	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	15,316	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	1,836	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 (3wk)	14	15	75%	1	2	3	7	8	18	31	72	15	36	62	145	77	181	310	723
			90%	1	2	4	9	9	22	37	87	19	43	74	174	93	217	372	868
1mon (3mon)	18	19	75%	3	8	13	31	34	79	135	314	67	157	269	628	337	785	1,347	3,142
			90%	4	9	16	38	40	94	162	377	81	189	323	754	404	943	1,616	3,770
2mon (6mon)	20	21	75%	7	16	27	63	67	157	269	628	135	314	539	1,257	673	1,571	2,693	6,284
			90%	8	19	32	75	81	189	323	754	162	377	646	1,508	808	1,886	3,232	7,541
6mon (~1-1.5yr)	25	28	75%	20	47	81	189												
			90%	24	57	97	226												
1yr (~1.5-3yr)	29	33	75%	40	94	162	377												
			90%	48	113	194	452												
2yr (~2-6yr)	30	34	75%	81	189	323	754												
			90%	97	226	388	905												

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

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 (3wk)	14	14	80%	0	0	0	0	0	1	1	3	1	1	2	6	3	7	12	29
			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	26	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	226	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	605	324	757	1,298	3,028
			95%	4	9	15	36	39	90	154	360	77	180	308	719	385	899	1,541	3,596

*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						
				Incidence Rate (per 100,000 py)														
	C	C+P		15	35	60	140	15	35	60	140	15	35	60	140			
1wk (3wk)	0	0	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	35	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	185	433	93	217	371	866			
1yr (~1.5-3yr)	0	0	75%	9	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			
				Incidence Rate (per 100,000 py)											
	C	C+P		15	35	60	140	15	35	60	140	15	35	60	140
1wk (3wk)	0	0	80%	0	0	0	1	1	3	4	10	2	5	9	21
			95%	0	0	1	1	1	3	5	12	3	6	11	25
1mon (3mon)	0	0	80%	0	1	2	4	5	11	19	45	10	22	38	90
			95%	1	1	2	5	6	13	23	53	11	27	46	107
2mon (6mon)	0	0	80%	1	2	4	9	10	22	38	90	19	45	77	179
			95%	1	3	5	11	11	27	46	107	23	53	91	213
6mon (~1-1.5yr)	0	0	80%	3	7	12	27	29	67	115	269	58	135	231	538
			95%	3	8	14	32	34	80	137	320	69	160	274	639
1yr (~1.5-3yr)	0	0	80%	6	13	23	54	58	135	231	538	115	269	461	1,077
			95%	7	16	27	64	69	160	274	639	137	320	548	1,279
2yr (~2-6yr)	0	0	80%	12	27	46	108	115	269	461	1,077	231	538	923	2,154
			95%	14	32	55	128	137	320	548	1,279	274	639	1,096	2,557

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

Table 20

Observed and expected cases of POTS- Japan

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

JAPAN														
Risk Period Per Dose (*)	Observed		% Dose Administered	Expected Number of Cases											
				1% Reporting rate				10% Reporting rate				20% Reporting rate			
				Incidence Rate (per 100,000 py)											
	C	C+P		15	35	60	140	15	35	60	140	15	35	60	140
1wk (3wk)	0	0	60%	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	60%	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	60%	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	60%	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	60%	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	60%	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)	3	10	60%	149	348	596	1391	1,490	3,478	5,962	13,911	2,981	6,956	11,924	27,823
			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.

The Co-Rapporteur's conclusion on the POTs is that 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.

3.4.2.4.3 Cervarix

The detailed assessment of the MAH's response can be found in pages 40-46 of the Co-Rapporteur's assessment.

CRPS

Figure 3 Heat map of the worldwide worst-case safety scenario observed-to-expected analysis conclusion in the parameter plane defined by the risk period and the reported fraction (two unknown parameters).

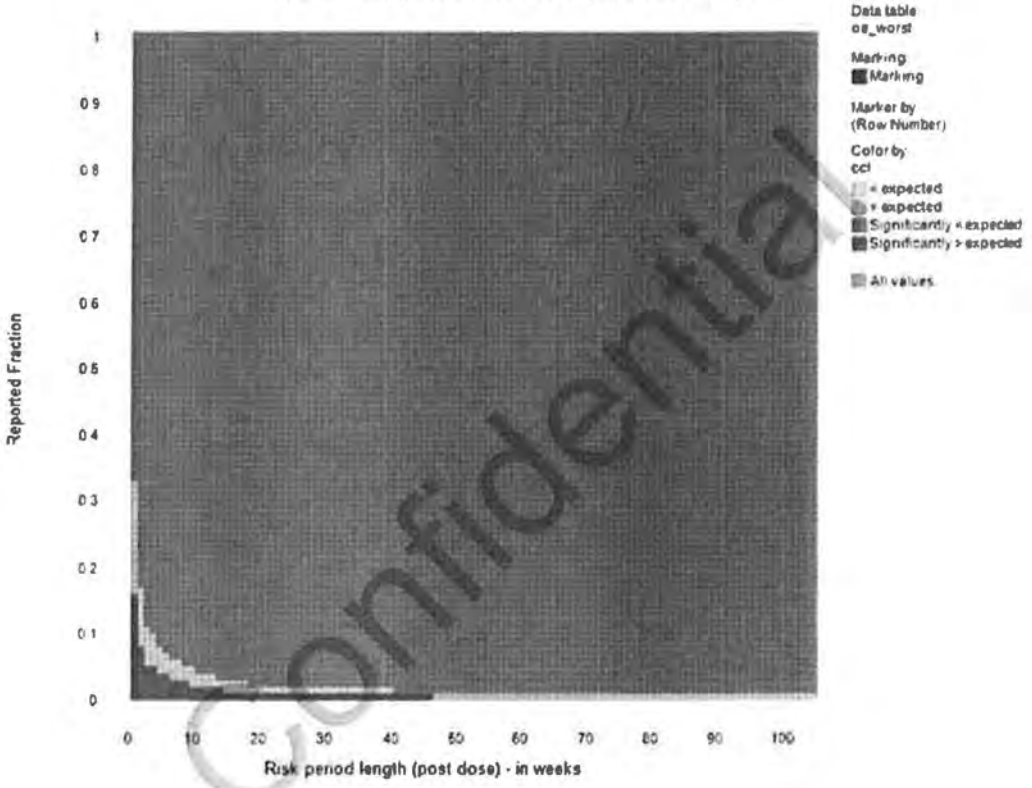


Figure 6 **Heat map of the Japan worst-case safety scenario observed-to-expected analysis conclusion in the parameter plane defined by the risk period and the reported fraction (two unknown parameters).**

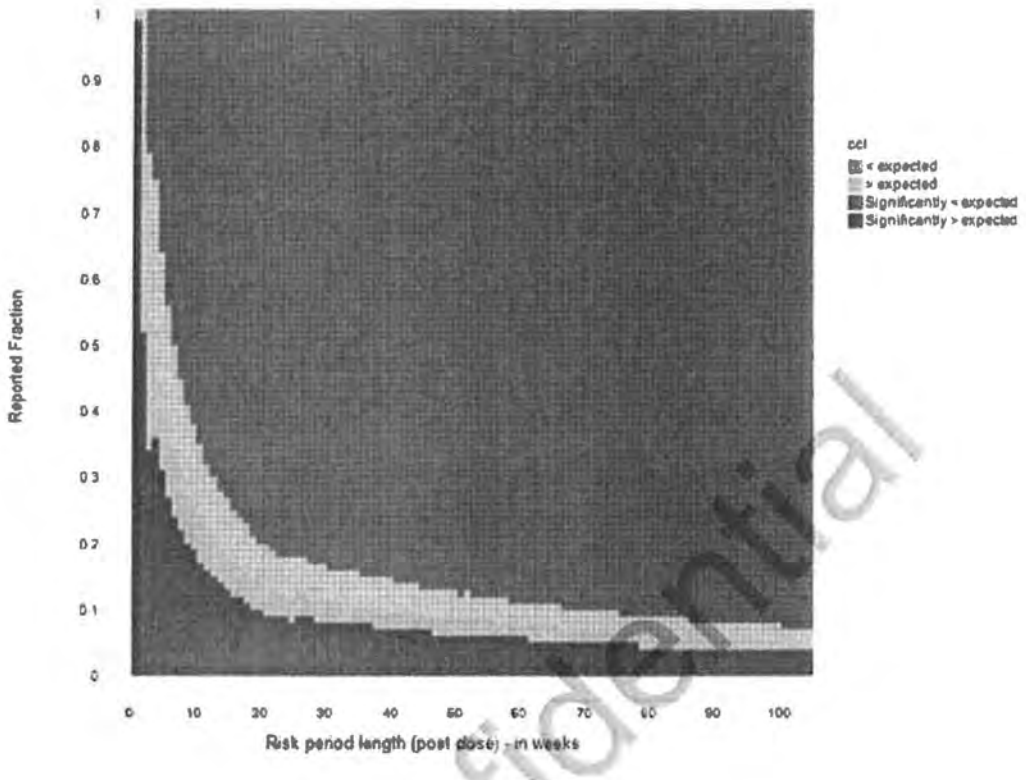
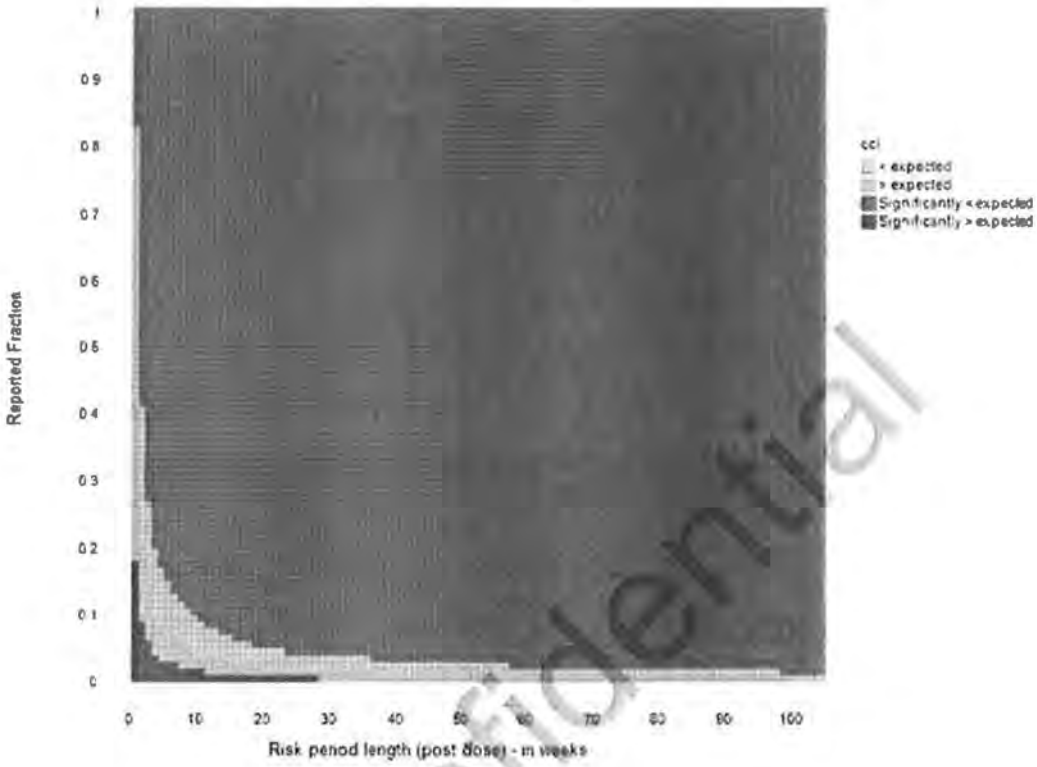


Figure 9 **Heat map of the UK worst-case safety scenario observed-to-expected analysis conclusion in the parameter plane defined by the risk period and the reported fraction (two unknown parameters).**



For both CRPS and POTS, the Co-Rapporteur considers that Observed vs expected methodology used in this CRPS analysis is based on many assumptions, which cannot be verified. However, it is acknowledged that it is probably not possible to conduct better analyses at this stage, given the wide uncertainty around the reporting fraction for observed cases.

It is assumed by the MAH that the reported fraction of CRPS cases should be about 10 to 70%. However, adverse events have been shown to be reported at a much lower rate, i.e. from less than 1% to 10% depending of the authors (*Agarwal et al. 2013*, *Gavaza et al. 2011*, *Mirbaha et al. 2015*). Moreover, because of the difficulty of diagnosing CRPS, many patients could be undiagnosed. Therefore, the reporting rate for CRPS might be much lower than those observed for other adverse events.

The CRPS case reported by Korea relates to a woman aged 60 years and should be considered as an outlier. To note that Korean recommendations target females aged 15-17 years with a catch-up vaccination recommended for females aged 18-26 years (*Kim et al. 2014*). This case should preferably not be considered in this analysis.

The Co-Rapporteur considers that the results of the Observed vs Expected analysis suggest that the number of observed CRPS cases is low compared to those expected, except in Japan. The high number of cases observed in Japan is a concern. Even if the media attention may have increased the fraction of reported cases, a reporting fraction of 71% (which is quite high for spontaneous reporting) would

imply that more cases are observed than expected in the mid-case scenario – although not with statistical significance. This high number suggests that CRPS should be under further surveillance.

POTS

Figure 12 Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=worldwide and risk period=1 month

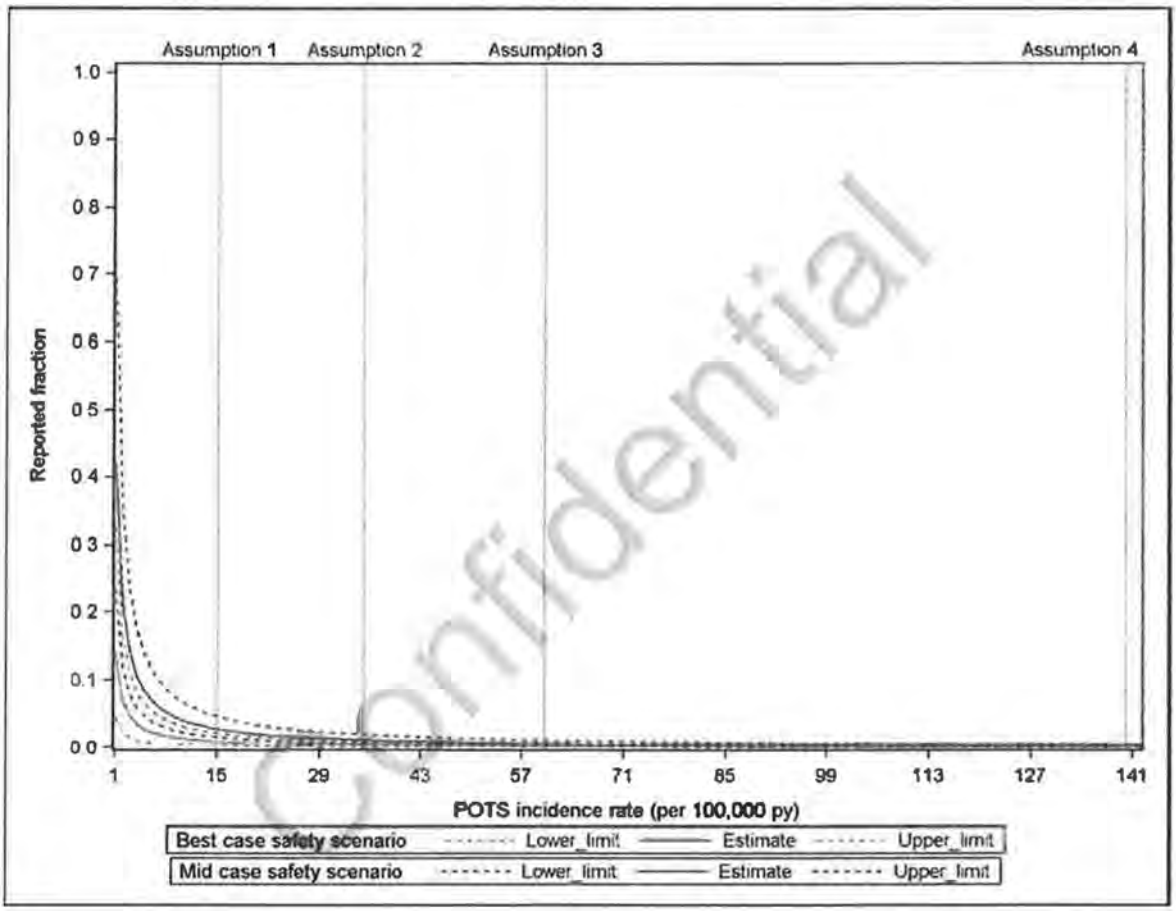


Figure 16 **Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=Japan and risk period=1 month.**

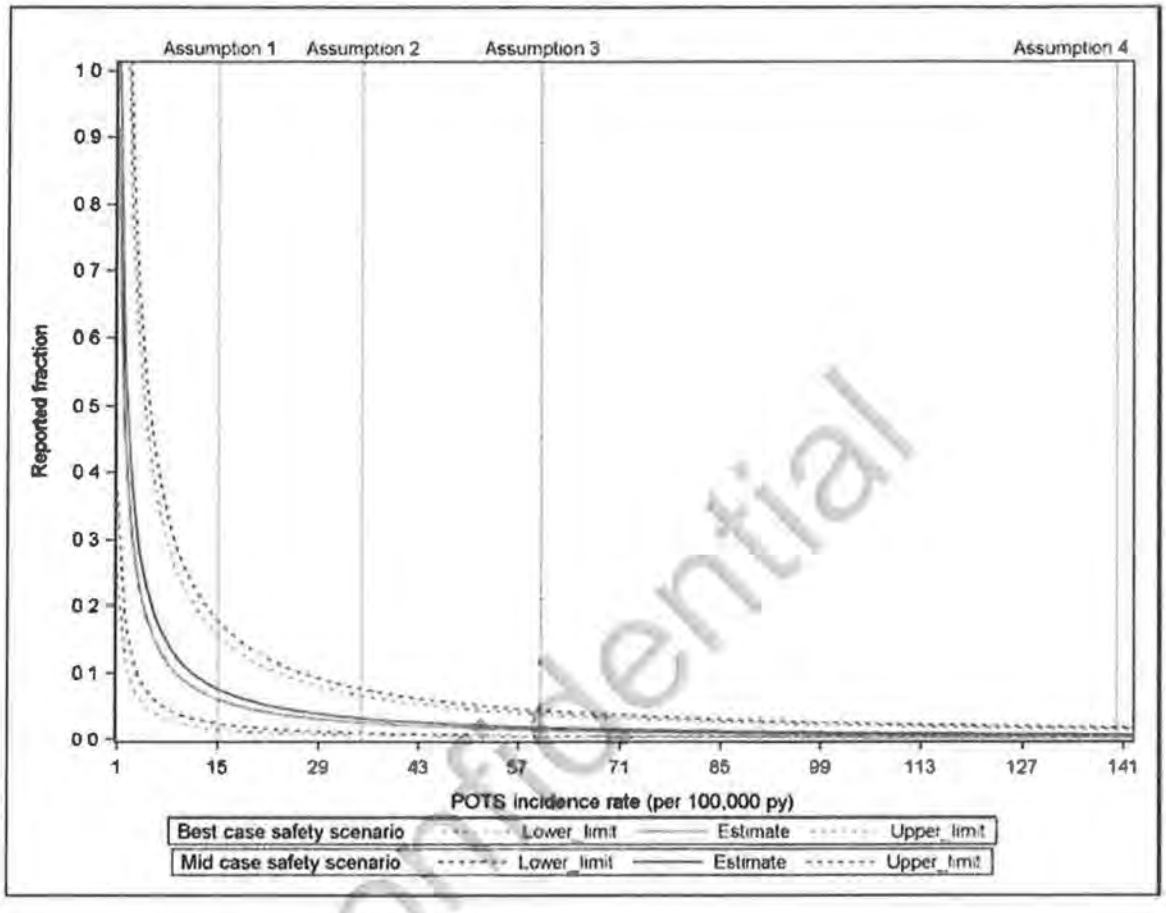
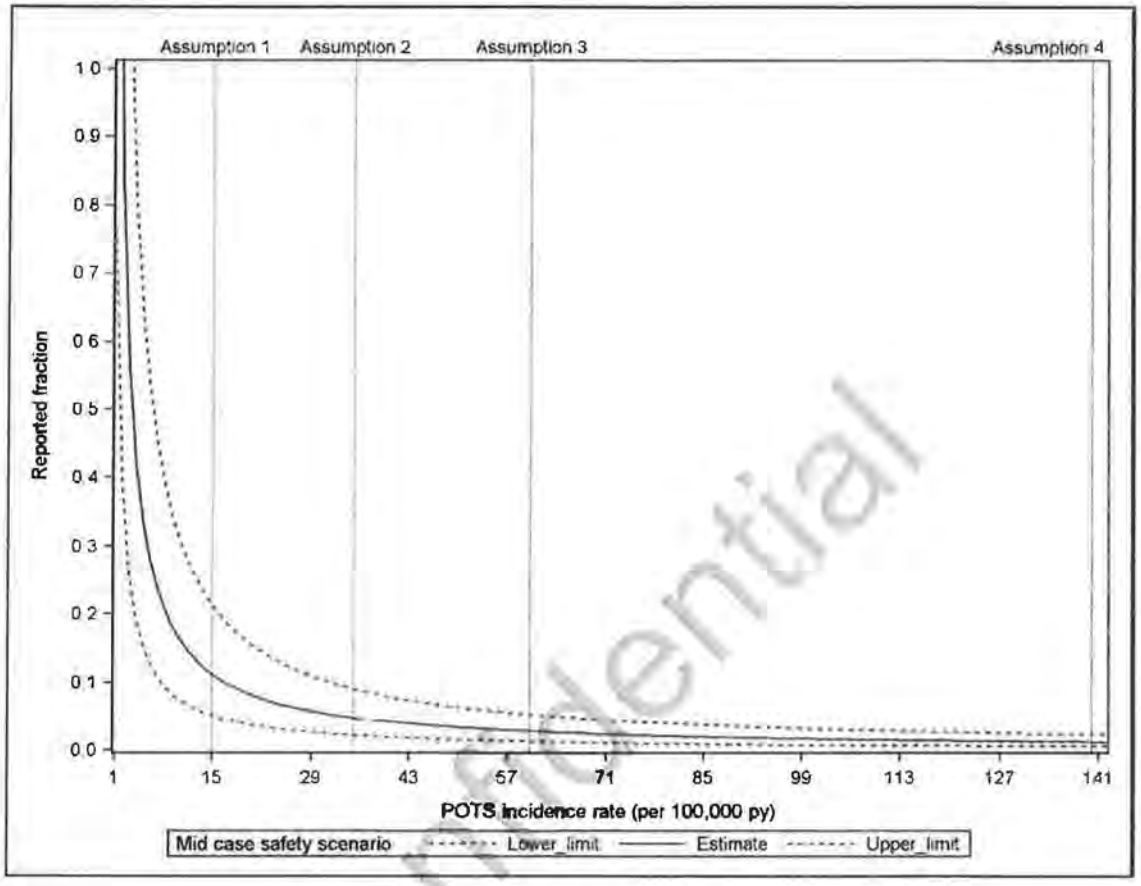


Figure 20 **Observed-to-Expected analysis conclusions for POTS and Cervarix depending on different scenarios for the reported fraction, the POTS background incidence rate and the level of diagnostic certainty. Country=UK and risk period=1 month.**



In relation to POTS, the Co-Rapporteur considers that the analyses presented are based on the worst case scenario for background incidence rate and suggest that the number of observed POTS cases is low compared to those expected, even in Japan.

Overall Rapporteur's conclusions on responses to Question 3:

Observed vs expected analyses compare the number of spontaneously reported cases with an expected number derived from the background incidence rate of the condition of interest and the number of exposed subjects within a particular risk period post vaccination. If information on any of the elements of the analysis are uncertain then the analyses rely on a number of assumptions which can lead to differing results depending on the assumption made.

CRPS

OE Assumptions:

The background incidence rate used for the CRPS analyses by both MAHs was reported by de Mos et al. of 14.9 - 28 per 100,000 person-years for females aged 10-19 and 20-29 years respectively in The

Netherlands. A weighted average incidence rate was calculated to account for the proportion of females vaccinated in each age stratum.

The number of vaccinated subjects was estimated using dose distribution data. The MAH for Cervarix assumed 75% of doses distributed were administered as this is close to an estimated figure obtained when comparing UK coverage data with the number of doses distributed in the same period. The MAH for Gardasil/Silgard estimated between 60-95% of distributed doses were administered based on regional information and accounting for use in males.

The risk period used by both MAHs for the analyses ranged from 1 week to 2 years following each dose of HPV vaccine. The MAH for Cervarix assumed all subjects received 3 doses according to the recommended time schedule and accounted for overlapping risk periods occurring with subsequent doses. The MAH for Gardasil also assumed all subjected received 3 doses according to the recommended schedule and multiplied all risk periods by 3 but with no adjustment for overlapping risk periods.

A range of possible reporting rates was also considered by the analyses ranging from 1-100% for both MAHs.

Observed cases were classified according to the CRPS case definition proposed by Harden et al. for both MAHs. Cervarix cases were classified as confirmed, unconfirmed or unlikely with best, mid and worst-case scenarios including some or all of the cases. Gardasil cases were classified as either having met all criteria or partially met the criteria. For Gardasil only cases that either met all the criteria or partially met the criteria were included in the OE analyses.

Observed cases were included in the OE analyses if the time-to-onset fell within the risk period. For Cervarix cases with missing time-to-onset information, these were included in proportion to those in the time window of interest for mid-case scenario and all in the worst-case scenario. For Gardasil these were included using the distribution of known time-to-onset for each region/country.

Results:

A total of 90 potential cases of CRPS were identified worldwide for Gardasil/Silgard based on the PT for CRPS (n=53) or a combination of symptoms (n=37). Of these 90 cases, 7 were classified as having fully met the CRPS criteria and 22 cases having partially met the criteria. Of those cases with a PT for CRPS, 30/53 cases were considered as not having met the diagnostic criteria. Only the 29 cases that either fully or partially met the criteria were included in the OE analyses.

The results of the OE analysis for Gardasil/Silgard showed that the observed counts were less than expected in most scenarios of under-reporting, case definition and risk period. The observed count exceeded the expected generally in scenarios that included partial criteria cases and at the lowest 1% reporting level. Only in Denmark and Japan did the observed exceed the expected for higher reporting levels. The reporting rate levels required for the observed count to be within the expected were 10-50% for Denmark (depending on risk period) and 10% for Japan. These could arguably be plausible given the high public awareness in those countries. Further details have been summarised in the Co-Rapporteur's report for Gardasil/Silgard.

For Cervarix, a total of 49 potential cases of CRPS were identified worldwide based on the PT for CRPS (n=49). Five cases were classified as confirmed cases of CRPS, 37 cases as unconfirmed and 6 as unlikely and 1 was excluded due to lack of information required to assess the case.

The results of the OE analysis for Cervarix showed that observed cases were equal or lower than expected if 2-23% of cases were reported worldwide (depending on case definition), if 12-71% of

cases were reported in Japan and if 10-42% of cases were reported in the UK. Further details have been summarised in the Co-Rapporteur's report for Cervarix.

Comments:

The Co-Rapporteur for Gardasil/Silgard has accepted the MAH OE approach and interpretation of the results. The main conclusions were that where the observed cases exceeded expected, the excess was minimal and both observed and expected were based on small numbers and therefore consistent with chance. Additionally given the media attention in Japan and Denmark for CRPS, the reporting rates of 10-50% are likely to be within the range expected due to enhanced reporting. The Co-Rapporteur considers the results reassuring but that the methodological limitations of the analysis must be taken into account.

The Co-Rapporteur for Cervarix comments that the OE methodology is based on many assumptions but that it cannot be improved upon at present. The Co-Rapporteur comments that the results of the OE analysis show that the number of observed cases is low compared with expected except in Japan where the high number of cases are a concern and suggests that CRPS should be under further surveillance.

The overall Rapporteur is in agreement with the two Co-Rapporteur's that the OE analyses have many limitations most of which cannot be improved upon further. In relation to the analysis for Gardasil/Silgard it is noted that the MAH did not include a conservative analysis to include all cases of CRPS (to include those that do not meet the diagnostic criteria). Inclusion of these cases would result in a higher reported fraction being required for the observed to be within the expected range. It is questionable however whether this approach would add value and not simply be including cases that are unlikely to be CRPS. It is also noted that the MAH for Gardasil did not account for overlapping risk periods following each dose. With doses scheduled at 0, 2, and 6 months, risk periods of greater than 2 months will overlap and therefore it is not appropriate to simply multiply the risk period by 3. A shorter risk period is more likely for CRPS however and therefore this is not considered to be a concern. The overall Rapporteur is of the opinion that despite the limitations of the OE analyses due to the many assumptions made, further OE analyses would not provide any additional meaningful information at this stage. Evidence from OE analyses cannot confirm a causal association due to the inherent limitations of spontaneous data. .

The overall Rapporteur considers that the OE analyses are generally reassuring with observed counts exceeding the expected only at low reporting rates and in individual countries that have experienced significant media attention that is likely to have increased reporting rates.

POTS

OE Assumptions:

The background incidence rate used for the POTS analyses by both MAHs used assumptions reported by MacDonald et al. that between 10-40% of patients with chronic fatigue syndrome (CFS) also have POTS and that 20% of all POTS cases also have co-existing CFS. The CFS incidence was estimated from the literature as 30-70 per 100,000 person-years in 10-39 year old females giving an overall background incidence rate for POTS of 15, 35, 60 or 140 per 100,000 person-years.

The number of vaccinated subjects was estimated from distribution data as before for the CRPS analysis.

The risk period used by the MAH for Gardasil/Silgard ranged from 1 week to 2 years following each dose of HPV vaccine whilst that used by the MAH for Cervarix ranged from 1 week to 1 year. As before,

the MAH for Cervarix assumed all subjects received 3 doses according to the recommended time schedule and accounted for overlapping risk periods occurring with subsequent doses. The MAH for Gardasil also assumed all subjected received 3 doses according to the recommended schedule and multiplied all risk periods by 3 but with no adjustment for overlapping risk periods.

A range of possible reporting rates was also considered by the analyses ranging from 1-100% for both MAHs.

Observed cases were classified according to the POTS case definition proposed by Raj 2013 and Sheldon 2015 for both MAHs. Cervarix cases were classified as confirmed, unconfirmed or unlikely with best, mid and worst-case scenarios including some or all of the cases. Gardasil cases were classified as either having met all criteria or partially met the criteria. For Gardasil only cases that either met all the criteria or partially met the criteria were included in the OE analyses.

Observed cases were included in the OE analyses if the time-to-onset fell within the risk period. For Cervarix cases with missing time-to-onset information, these were included in proportion to those in the time window of interest for mid-case scenario and all in the worst-case scenario. For Gardasil these were included using the distribution of known time-to-onset for each region/country.

Results:

A total of 83 potential cases of POTS were identified worldwide for Gardasil/Silgard. Of these, 33 fully met the case definition and 10 cases partially met the definition. 30/33 of those fully meeting the case definition were from Denmark. The remaining 40 did not meet the case definition.

The results of the OE showed that the observed number of cases was generally lower than expected under almost all assumptions for all regions and countries except for Denmark. The MAH has suggested that media attention and potential recall bias regarding the timing of vaccination may account for the large number of cases seen. Further details have been summarised in the Co-Rapporteur's report for Gardasil/Silgard.

For Cervarix, a total of 19 potential cases of POTS were identified worldwide. All cases were defined as either confirmed or unconfirmed. No unlikely cases were received.

The results of the OE analysis for Cervarix showed that the observed number of cases worldwide was equal or lower than expected at very low reporting rates of under 10%. For individual countries the reporting fraction was higher at around 20-30% (Japan and the UK) of cases required in order for the observed to equal or be lower than expected and 65% for the US. These higher reporting fractions were considering a risk period of 1 week. Further details have been summarised in the Co-Rapporteur's report for Cervarix.

Comment:

The Co-Rapporteur for Gardasil/Silgard has accepted the MAH OE approach and interpretation of the results. Again the limitations of the OE approach are noted and especially the fact that many cases are from a single centre in Denmark. The opinion of the Co-Rapporteur is that the results of the OE analysis for POTS do not support a causal association with HPV vaccination.

The Co-Rapporteur for Cervarix again comments on the many assumptions that underlie these analyses and that these cannot be improved on at this stage. It is noted that the results of the OE analysis suggests that the number of observed cases is low compared to those expected, even in Japan.

The overall Rapporteur is again in agreement with the two Co-Rapporteurs that the OE analyses have many limitations. As with the CRPS analyses, the MAH for Gardasil/Silgard did not conduct the most conservative analysis to include all cases and has not accounted for overlapping risk periods. As noted above however it is not considered necessary to conduct further OE analyses are these are unlikely to provide any further meaningful information at this stage.

The overall Rapporteur is also in agreement with the two Co-Rapporteurs that the results of the OE analyses do not support a causal association with the vaccine and are generally reassuring. The data show that only in Denmark is the observed number of reports higher than expected for certain reporting scenarios. Considering the recent media attention in Denmark and active identification of cases it seems unlikely that any of the lower reporting rate scenarios are applicable. The OE analysis for the US shows the observed to exceed the expected but the analysis is based on only 1 case and is therefore not interpretable.

3.4.2.5 ***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 OTS and discuss whether there is biological basis for a possible causal association.

3.4.2.5.1 Gardasil 9

A separate reply has not been submitted for Gardasil 9.

3.4.2.5.2 Gardasil

The detailed assessment of the MAH's response can be found in pages 96-101 of the Co-Rapporteur's assessment.

It is noted that no study specifically addressing the potential association between CRPS or POTS has been identified. The 5 studies referred to by the MAH 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 be of relevance for a potential association with CRPS or POTS.

The Co-Rapporteur also notes the findings of a recent study announced by the French medicines agency (ANSM) and the French national health insurance fund (CNAMTS)[2], which 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.

[2] http://ansm.sante.fr/var/ansm_site/storage/original/application/0611bc63c4bdadd763749f13e4126377.pdf

In relation to CRPS, the Co-Rapporteur notes that whilst potential mechanisms have been proposed in the articles provided, 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.

In relation to POTS, the Co-Rapporteur considers that 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. 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.

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 there is currently a lack sufficient knowledge about the respective syndromes to suggest a plausible mechanism of action for a potential causal relationship.

In summary, the Co-Rapporteur considers that at present there are no data to suggest a causal relationship between qHPV vaccination and CRPS or POTS.

3.4.2.5.3 Cervarix

The detailed assessment of the MAH's response can be found in pages 46-52 of the Co-Rapporteur's assessment.

In relation to CRPS, the Co-Rapporteur concludes that, at this moment, the literature does not point out a causal relationship between HPV vaccination and the onset of CRPS, however this cannot be ruled out for the following reasons:

- the disease is probably caused by a multifactorial process, including inflammatory and immune related factors. Evidence of the involvement of inflammatory mechanisms, especially in the acute phase, comes from studies documenting raised concentrations of proinflammatory neuropeptides and mediators (substance P, calcitonin gene related peptide, bradykinin) and cytokines (IL-1β, IL-2, and IL-6, and tumor necrosis factor α (TNF- α) in the systemic circulation, cerebrospinal fluid, and affected limbs of patients with CRPS *(Bruehl 2015)*.

- an autoimmune cause has also been suggested for CRPS in a subset of patients. For example, *Dirckx et al. (2015)* have found the presence of autoantibodies in 33% of CRPS patients and in 4% of controls. Furthermore, motor impairment, a characteristic of CRPS, has been observed in healthy mice when transferring IgG from CRPS patients *Goebel et al. (2011)*.

- CRPS occurs most commonly in women between 50 and 70 years of age *(Rockett 2014)* and is relatively rare in childhood and adolescence which is the target population of HPV vaccination *(Borchers & Gerschwin 2014)*.

- Paediatric CRPS is mostly triggered by minor trauma *(Borucki & Greco 2015)*.

In relation to whether POTS and CRPS may share a common pathophysiology, the Co-Rapporteur concludes that small fiber neuropathy and autonomic dysfunction, cannot be explained in all CRPS cases and more than one mechanism seems to be involved in the pathogenesis of CRPS. There are

some doubts whether small fiber neuropathy results from CRPS or causes the disease. The Co-Rapporteur considers there is more evidence which underlies an autoimmune hypothesis for POTS.

The link between POTS and CRPS is largely unknown and it is doubtful that both syndromes should be associated if additional investigations are required.

The Co-Rapporteur considers that it is preferable to investigate potential associations of HPV vaccination with POTS and CRPS separately without extrapolating on hypothetical common causal patterns.

Overall Rapporteur's conclusions on responses to Question 4:

The Rapporteur agrees fully with the Gardasil Co-Rapporteur's comments as summarised above. The reporting characteristics and rates of POTS and CRPS may be considered consistent with the background incidence amongst populations of females with high uptake, and given the notable high level of public awareness in Denmark and Japan.

The Rapporteur also agrees that there is no obvious biological mechanism underpinning any potential vaccine-induced risk, with only speculative suggestions so far. Similarly, whilst CRPS and POTS do exhibit some overlapping symptoms, there is no clear basis to suggest a common vaccine-induced pathophysiology. It is known that POTS and CRPS, as well as CFS and fibromyalgia, have some overlapping symptoms given that these are syndromes, and not specific defined disease states. This is discussed in further detail below, in the context of available epidemiological data. The Rapporteur agrees that there is no basis to pursue this hypothesis of a common pathway.

The question of whether there is a plausible common biological mechanism underpinning reports of CRPS and POTS following HPV vaccine is discussed further below, in the context of the hypotheses raised in the DHMA report, by the ADR analysis from Uppsala, and from the most recent publication from Brinth *et al* (i.e. that the reports should all be considered as a chronic fatigue-like syndrome)..

In relation to the Cervarix Co-Rapporteur's comments on CRPS, the Rapporteur does not consider this to be a signal for Cervarix. Based on data from The Netherlands, the background incidence rate of CRP were is ~15 person-years in females 10-19 years old. Given that many countries have up to 90% HPV vaccine uptake in girls in this age range, the reporting rate remains consistent with chance, and not indicate a specific risk for HPV vaccine (over and above what any vaccine or needle injection may theoretically trigger).

3.4.2.6 ***Question 5***

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

3.4.2.6.1 Gardasil 9

A separate reply has not been submitted for Gardasil 9.

3.4.2.6.2 Gardasil

The detailed assessment of the MAH's response can be found in pages 96-101 of the Co-Rapporteur's assessment.

The MAH proposes no regulatory action or risk minimisation, on the basis that there is no evidence for a causative relationship or a potential biological mechanism for an association between HPV vaccine and POTS or CRPS. The MAH will continue to monitor reports of POTS and CRPS through routine pharmacovigilance.

The Co-Rapporteur endorses the MAH's proposal. The Co-Rapporteur considers that 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, and therefore does not support any amendment to SmPC regarding a potential risk related to the injection trauma.

3.4.2.6.3 Cervarix

The detailed assessment of the MAH's response can be found in pages 52-55 of the Co-Rapporteur's assessment.

The MAH proposes no regulatory action or risk minimisation, and will continue to monitor reports of POTS and CRPS through routine pharmacovigilance.

The Co-Rapporteur considers that a causal relationship between vaccination with Cervarix and the occurrence of CRPS cannot be excluded at this stage and that additional data are needed, which could also respond to the growing public attention.

The Co-Rapporteur considers that there is no evidence that a causal association between HPV vaccine and POTS is biologically supported. However, it considers two hypothesis are of interest: POTS as a autoimmune disorder and POTS as a dysfunction of the autonomic nervous system, and suggests that it may be useful to identify a set of relevant autonomic disorders to monitor in enhanced surveillance of HPV vaccines (referring to gastrointestinal motility disorders identified by *Chandler 2015*).

The Co-Rapporteur therefore recommends:

1) to identify PTs/codes which could be associated to autonomic disorders, including POTS (assuming that the POTS PT is not sufficient to identify POTS) and to define a POTS/autonomic disorders search strategy in pharmacovigilance data bases and other data bases;

2) to identify specific markers to eventually permit to classify cases of POTS after HPV vaccine as auto-immune disorders.

Overall Rapporteur's conclusions on responses to Question 5:

The Rapporteur agrees with the Gardasil Co-Rapporteur's evaluation of the MAH's response, and that no risk minimisation measures are warranted.

The Rapporteur does not endorse the Cervarix Co-Rapporteur's proposal for additional evaluation of CRPS and POTS. In relation to CRPS, any association with HPV is not likely to be vaccine-specific, but due to needle trauma and further regulatory action would not be warranted on this basis. In relation to POTS, the available evidence does not support a signal for Cervarix and further evaluation of spontaneous data in this way will not allow any conclusions to be drawn.

3.4.2.6 Rapporteur's evaluation of the DHMA submission

The DHMA is attached as an Annex to this report.

On 4 September, DHMA submitted a report for consideration by the (Co)-Rapporteurs as part of the ongoing referral, entitled "*Report from the Danish Health and Medicines Authority for consideration by EMA and rapporteurs in relation to the assessment of the safety profile of HPV-vaccines*".

The report includes a descriptive overview of serious suspected ADR reports following HPV vaccine from Denmark, a summary of available literature, comparative analysis of worldwide data provided to DHMA by the Uppsala Monitoring Centre and a summary of the situation in Japan.

As the reports and public interest in Denmark is influenced heavily by a case series analysis from Brinth *et al* at a syncope centre based in Copenhagen, three publications from these authors referred to in the DHMA report are also considered in detail below.

Overview of Danish ADR data

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

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

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

The report then includes a descriptive overview of serious suspected ADRs (n=363). Based on a pilot review of the most recently received reports, 5 main symptom categories were identified based on the reviewers impression of the symptoms relatedness within each category, as well as frequency and severity of occurrence; severe fatigue, neurologic symptoms, circulatory symptoms, pain and headache. Eight additional categories were added, that included PTs frequently reported; autonomic imbalance, abdominal discomfort, urinary tract symptoms, allergy, infections, menstrual disorder, thermal dysregulation and malaise.

The report did not evaluate any causal or time wise relation between the symptoms reported and the HPV vaccination, as information of time of symptom onset and duration was too often missing or not very accurate.

Most frequently reported symptoms in the serious reports (ranked order of symptoms occurring in more than 100 cases) were: Headache, Pain, Dizziness, Malaise, Fatigue, Paresthesia and Cognitive disorder. The review identified 40 verified diagnoses of POTS.

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

Of the 363 reports, 77 had a well-defined, specific diagnosis. Of the remaining reports, 43.7 % have symptoms in 4 or 5 of the 5 main categories. In 62 of 117 cases reporting fatigue 53 % were reportedly associated with a social handicap, i.e. reduced ability to attend school or work or carry out daily activities. For 17 % of all patients considerable impact on daily life is described. The most frequently occurring of the 8 additional categories were malaise, abdominal discomfort, autonomic imbalance, infections and thermal dysregulation in that order.

Rapporteur's comments on the Danish ADR data:

The overall reporting rate of suspected ADRs in Denmark is ~0.8 per 1,000 doses distributed. Aside from the specific case reports under evaluation in this referral and discussed in detail separately, this overall reporting rate is not dissimilar from the overall ADR reporting in the UK (~ 1 per 1,000 doses administered), or the global ADR reporting rate (~180,000 adverse events per 165 million doses distributed). The reporting rate of serious ADRs is ~0.22/1,000 doses, also similar to that in the UK (~0.24/1,000 doses).

There is a notable increase in serious ADRs in 2013 and, as acknowledged in the report, the characteristics of these reports in Denmark is likely to be influenced by the recent resulting publicity in Denmark, and thereby the Brinth *et al* case series (discussed in detail below). It is noted that half of these have been reported from non-health care professionals (consumers or lawyers), and half of these have not been medically confirmed.

In conclusion, this descriptive analysis is noted, however, it is not sufficient to inform the causality assessment in the context of the ongoing referral.

As most of the reports do not have a specific diagnosis but an overlapping symptom complex, the report states that the reports show similarity to chronic fatigue syndrome (CFS). Based on an analysis of data provided by the Uppsala Monitoring Centre, the report argues that there is an increasing trend in worldwide reports that could fit this category of undiagnosed but similar 'chronic fatigue-like syndrome' which may be specific to HPV vaccine. This notion, and the Uppsala report, is reviewed in detail below.

Case series from Brinth *et al*

The majority of reports of POTS from Denmark have been reported by a Copenhagen-based syncope centre, and are therefore most likely the same case series described by Brinth *et al* in their three publications to date. It is likely that all three publications by Brinth *et al* relate to the same case series of patients, although it is unclear why only a different subset is described in each paper.
As these reports constitute a large proportion of the majority of worldwide reports of POTS and orthostatic intolerance to date, it is important to critically evaluate these three publications.

Dan Med J 2015;62(4)

The first paper (Dan Med J 2015;62(4)) refers to 75 patients referred consecutively to the Frederiksberg Hospital Syncope Unit from May 2011 to December 2014 for a head-up tilt test due to orthostatic intolerance and symptoms compatible with autonomic dysfunction as suspected side effects following vaccination with Gardasil.

The paper states that "*patients were interviewed with a special focus on symptoms and on the temporal association between vaccination and symptom onset*" and that "*The narrative report was supplemented by the short form of the International Physical Activity Questionnaire (IPAQ-SF) quantifying the patient's physical activity at the time of referral and just before vaccinations on a recall basis*". Patients were excluded if they could not account for the temporal association between vaccination and symptom onset, had possible triggering factors other than vaccination or had chronic pre-existing illness.

The authors then include only 53 patients who reported onset of symptoms consistent with autonomic dysfunction within the first two months post-vaccination. The paper goes on to describe the findings of

head-up tilt tests (for POTS diagnosis) as well as the frequency of the most common symptoms in this group of patients.

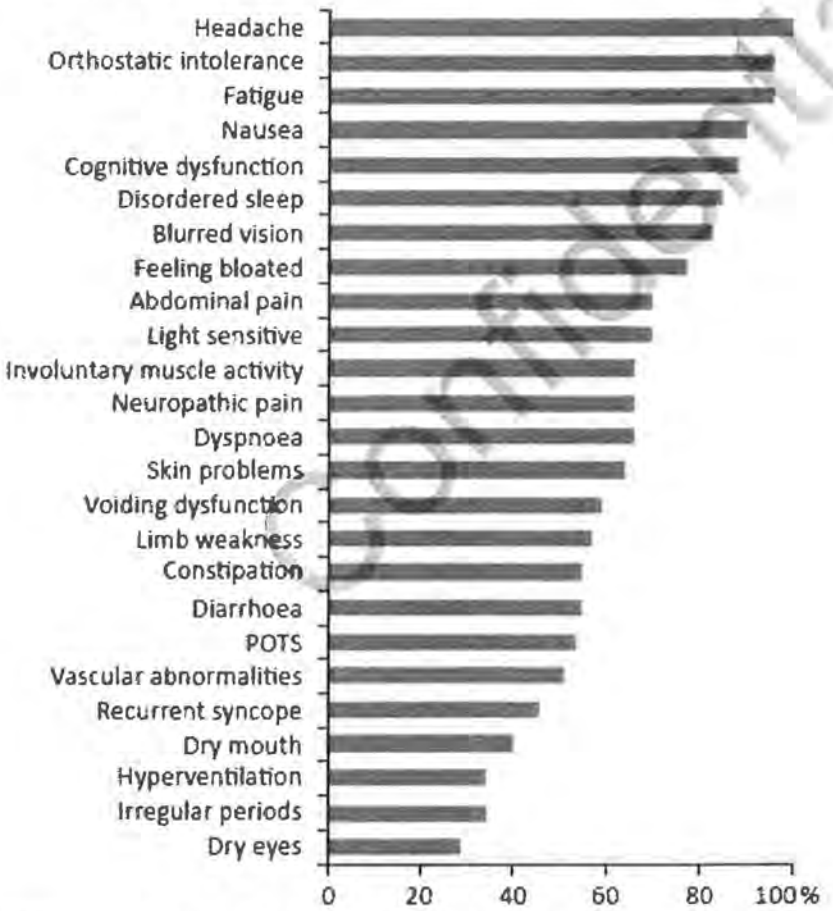
In this paper, the mean age at symptom onset was 21.0 ± 7.4 years (range: 12-39 years). The mean time between vaccination and onset of symptoms was 11.1 ± 12.5 days (range: 0-58 days) and symptoms were reported to appear after the first vaccination in 21 patients (40%), after the second vaccination in 19 patients (36%), and after the third vaccination in 13 patients (25%).

Based on the physical activity questionnaire, 67% had a high and 33% had a moderate activity level before symptom onset. Five patients had a very high activity level and were competing on a national or international level in their sport.

The proportion of patients with each symptom was described as follows:

FIGURE 1

Symptoms suspected to be side effects to vaccination against human papilloma virus. The frequency of the symptoms is given as percentages of patients reporting the given symptom out of all patients included in the descriptive analysis.



POTS = postural orthostatic tachycardia syndrome.

Twenty eight (53%) patients were diagnosed with POTS at tilt table test.

The authors conclude that "*We may have diagnosed more than half of these patients with POTS – but 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*".

Vaccine 2015

The second paper (Vaccine 2015) is very similar to the first, again describing the frequency of symptoms in a group of patients consecutively referred to the same syncope unit for the same reason. This paper describes only 35 patients, with no reference to how this specific subset of cases was selected for inclusion in the analysis.

Unlike the first paper, this paper additionally included an analysis of 'standard' blood tests, as well as use of a specific questionnaire (COMPASS 31) to evaluate the severity of specified symptoms of autonomic dysfunction. The methods state "*as most patients described a gradual development in both number and severity of symptoms we asked them to specify the time passed from vaccination to development of the first symptom suspected to be related to the vaccine*".

This paper states that the mean age at onset of symptoms was 22.0 years (range: 12–39). There was a mean delay between vaccination and onset of symptoms of 9.3 days (range: 0–30), and mean time between onset of symptoms and examination was 1.9 years (range: 0–5). Symptoms were reported to appear after the first vaccination in 24%, after the second vaccination in 51%, and after the third vaccination in 25%. Twenty-one of the referred patients (60%) fulfilled the criteria for a diagnosis of POTS.

Before symptom onset 71% of the patients had a high and 29% had a moderate activity level. As stated in the first paper, half of those with a high activity level were competing at a national or international level in their sport. Twenty-four of the 35 patients used oral contraception. The remaining 11 patients all reported irregular periods. Median serum bilirubin level was 5 (range: below detection **limit to 13 micromol l−1). All other laboratory tests were within normal range.**

The authors comment that the observed low levels of bilirubin may have affected the immune response to vaccination, and that high levels of physical activity may increase both pro- and anti-inflammatory cytokines as well as leukocyte subsets. They also suggest that irregular periods could contribute to development of autoimmune conditions. Coupled with references to a study that suggested exercise may enhance the immune response to vaccination and other data suggesting gender-based differences in immune responses to endurance exercise, the authors speculate that all of these factors could increase the susceptibility to HPV vaccine- induced in this subset of vaccinees.

International Journal of Vaccines and Vaccination; Vol.1 Issue 1 – 2015

The third paper from Brinth *et al* (International Journal of Vaccines and Vaccination; Volume 1 Issue 1 – 2015) apparently reports on the same case series as the previous two. This time, they refer to 90 patients referred to the Syncope Unit from May 2011 to April 2015, presumably reflecting an additional 15 referrals between December 2014 and April 2015. However, in this paper the authors decided to investigate to what extent these patients fulfilled the diagnostic criteria for chronic fatigue syndrome (CFS).

The authors included 39 of the 90 subjects who voluntarily responded to a questionnaire about symptoms and onset following vaccination.

The study included 39 girls/women aged 22.9 ± 7.2years (mean±sd) (range 13-39) at time of examination. Twenty of the patients (51%) fulfilled the criteria for a diagnosis of POTS. Thirty-four (87%) and 35 (90%) of the patients fulfilled the Canadian and IOM criteria for CFS/ME, respectively. POTS were diagnosed in 56% and 55% of patients diagnosed according to the Canadian and the IOM criteria, respectively.

Rapporteur's comments on the Brinth *et al* case series:

In the three papers from Brinth *et al*, all patients appear to have been referred to the same syncope unit for evaluation for an existing suspicion of HPV vaccine-induced illness. This prior suspicion and reason for referral in itself makes the case series unrepresentative of the general population who may present for evaluation and diagnosis of such illnesses.

The methods then used by Brinth *et al* to further evaluate and present this case series for publication are inherently selective and biased. It is clear from the first paper that patients were excluded if they do not meet a pre-defined hypothesis of vaccine-induced illness (symptoms prior to vaccination, onset greater than 2 weeks after vaccination, unknown onset time or if other causes could be found). Patients appear to have been included in the third paper based only on voluntary responses to a questionnaire that was sent out. It is of note that the third publication included an additional 15 referrals from between December 2014 and April 2015 – this coincides with intense media scrutiny in Denmark following a TV2 programme aired on 26 March 2015. This potentially introduces further bias into the selected case series.

Much is made in these three papers of the consistency in symptom profile across the case series. However, what is unclear is whether or not the absence or presence of specific symptoms was solicited by the interviewer, although the presentation of results suggests this was the case. If so, then it is perhaps not surprising that such a selected case series interviewed retrospectively in this way would yield these symptom characteristics. Furthermore, many of these symptoms would require some sort of objective clinical evaluation, yet there is no information on how this was done or what other clinical assessment may have been undertaken to determine other causes of the symptoms.

As the initial symptoms of POTS and autonomic dysfunction most likely have an insidious onset, objective recall of exact symptom onset (as well as the date/trigger for the symptoms) will be difficult to achieve. This is particularly so given that the mean time between onset of symptoms and examination by Brinth *et al* was stated as 1.9 years (range: 0-5). Indeed, the second paper states "*as most patients described a gradual development in both number and severity of symptoms we asked them to specify the time passed from vaccination to development of the first symptom suspected to be related to the vaccine", and* "patients were interviewed "*with a special focus on .... the temporal association between vaccination and symptom onset*". The reliability and objectivity of such recall given the pre-existing suspicion of vaccine-induced illness is highly questionable, and inherent recall bias in their methods cannot be ruled out. Recalling a needle injection, or the occurrence of real but benign/transient adverse effects of vaccination (including a psychogenic fainting episode), as the preceding event when specifically questioned is much easier than recalling a preceding viral infection (or other postulated trigger of POTS or CFS).

Although the case series included only patients with self-reported symptom onset within 2 months of vaccination, it is notable that the mean reported onset time after vaccination was very short at around 9 to 11 days (with day zero included in the range). Brinth *et al* speculate that these symptoms could be caused by an autoimmune response to the vaccine. However, a short onset would not necessarily support this, on the basis that it would take longer than this for the body to mount a specific auto-immune response and then for this to have an obvious clinical consequence. The lack of any consistent relationship with the dose sequence also argues against this case series being suggestive of a specific autoimmune response to the vaccine.

Furthermore, there appears to be no correlation between the likely age-specific exposure to HPV vaccine in the Danish population and the age characteristics of these patients at symptom onset. The mean age of vaccinees in Denmark from May 2011 to April 2015 was most likely closer to 12 years, yet the mean age of the case series was 21 years (17% were aged between 12 and 15 years, 21% between 15 and 19 years, 37% between 19 and 27 years, and 25% were 27 years or older). If HPV vaccine was truly a cause of the reported symptoms, we would expect a lower mean age of symptom onset amongst the case series and a distribution of ages more closely aligned to the likely age-specific vaccine exposure.

Finally, in this case series two thirds of patients had a high level of physical activity (one third had a moderate level) prior to symptom onset, half of whom were competing at a national or international level in their sport. Based on this, Brinth *et al* speculate that exercise may be a risk factor for HPV vaccine-induced illness. However, available medical literature on POTS suggests that high athletic (and academic) achievement is a common pre-existing characteristic of POTS sufferers. The authors'

suggestion that high levels of physical activity in females, whether or not coupled with low bilirubin levels and irregular periods, is a risk factor for vaccine-induced injury is entirely speculative.

Taken together, it is much more likely that the case series reported by Brinth *et al*, although highly selective in nature and without reference to a comparable unvaccinated group of patients (over the time period of the referrals vaccine uptake was 90% in the reported age range), represents the natural background characteristics and epidemiology of POTS (and chronic fatigue-like syndromes) in those eligible for vaccination in Denmark (and other countries).

This likelihood is further supported by Brinth *et al*'s analysis in the third paper. The first two papers report cases diagnosed as POTS, and a subset (almost half) with similar symptoms of autonomic dysfunction which do not meet the POTS criteria. Brinth *et al* first state 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. Indeed, POTS is syndrome and not a specific disease state. However, in the third paper they now speculate that this unidentified condition is likely to be CFS.

There is existing evidence in the medical literature that up to 40% of patients diagnosed with POTS also meet the diagnostic criteria for CFS, with some authors suggesting the overlap could be higher. The finding by Brinth *et al* that just over half of their case series diagnosed with CFS also meet the criteria for POTS is therefore consistent with the background epidemiology of POTS in the absence of HPV vaccination.

In the discussion in the third paper, Brinth *et al* appear to confuse the clinical diagnosis and management of such patients (with presumed vaccine-induced illness) with the process of pharmacovigilance and causality assessment. Nonetheless, what the authors now appear to suggest is that CFS should be considered as a diagnosis in patients who report chronic symptoms of orthostatic intolerance and autonomic dysfunction following HPV vaccine (whether or not they also meet the POTS criteria).

In this paper, the authors briefly acknowledge the published study based on UK data (Donegan et al. 2013) which found no evidence of an increased risk of CFS following bivalent HPV vaccine. They appear to suggest that the UK study was of limited value, based on an assumption that CFS is under-diagnosed in the UK. Although not explicit, Brinth *et al* may be suggesting that vaccinated cases were under-ascertained in this study. Regardless of the validity of their assumption, Brinth *et al* fail to acknowledge that the UK study used the self-controlled case series method, which relies only on inclusion of vaccinated cases. Even if their assumption was true, there is no good reason to suspect that under-diagnosis of CFS would differentially apply to vaccinated and non-vaccinated subjects. Furthermore, they do not acknowledge that the UK study included a sensitivity analysis of cases referred by their GP for symptoms of chronic fatigue, but had not yet received a diagnosis. The study also evaluated cases of fibromyalgia and neurasthenia and found no association between HPV vaccine and any of these conditions.

In fact the existing UK study, although it included data only from the time when bivalent HPV vaccine (Cervarix) was in routine use and did not therefore evaluate Gardasil, was of appropriate design to evaluate the new hypothesis of Brinth *et al*. that POTS may be secondary to CFS.

In summary, the case series reported by Brinth *et al* represents a highly selected sample of patients, apparently chosen to fit a pre-specified hypothesis of vaccine-induced injury. The methods used to ascertain the trigger and time to onset of specified symptoms of autonomic dysfunction may inherently bias patient recall. Whilst Brinth *et al* acknowledge that their cases series cannot prove a causal association with HPV vaccine, they fail to acknowledge or discuss the possibility that their case series simply reflects the expected characteristics and prevalence of POTS and autonomic dysfunction amongst a population cohort with 90% vaccine uptake. The authors speculate that high intensity physical exercise may be a risk factor for development of HPV vaccine-induced illness, but ignore the available medical literature suggesting that this is a commonly-reported characteristic in POTS patients, regardless of putative trigger. Finally, Brinth *et al* now propose that their case series should be considered as having CFS induced by HPV vaccine and that this requires further, robust study, but dismiss an existing UK-based study that has already tested this hypothesis and found no association.

The data provided by Uppsala Monitoring Centre

At the request of DHMA, the Uppsala Monitoring Centre has provided an overview of worldwide suspected ADRs associated with HPV vaccines from Vigibase. This focused on POTS, CRPS, CFS, ME/PVFS, fibromyalgia, and reports without a specific diagnosis but including symptoms that may potentially relate to autonomic dysfunction.

As of 3 August 2015, Vigibase contains 147 reports with the MedDRA POTS associated with HPV vaccines. Vigibase also includes 94 CRPS, 94 CFS, 62 ME/PVFS and 87 fibromyalgia. Most reports for each of these PTs originated in the US. Denmark and Japan reported the second highest number of POTS and CRPS, respectively. The UK reported the second highest number of CFS, ME/PVFS.
For each of the above PTs, a table of co-reported symptoms was also included.
A graph in the report shows that fibromyalgia, CFS and ME/PVFS have been reported relatively constantly since 2009 (with a slight decrease in 2011/12), but reports of POTS and CRPS had notably increased since 2013. It does not state in the report if these dates relate to symptom onset, diagnosis or report receipt date, although the latter is most likely (based on a comment concerning a backlog of US reported submitted in 2010).

The report includes several tables comparing the 'top 20' reported events for HPV vs other vaccines, and for Denmark vs worldwide data. The first table includes the top 20 reported symptoms from serious HPV reports in Vigibase (presumably worldwide), compared to the same from the Danish ADR database. It is not stated if the Vigibase data includes or excludes reports with the above PTs, or if the Vigibase data excludes Danish reports. The 2nd and 3rd tables compare the top 20 reported symptoms worldwide in Vigibase in associated with serious HPV reports to that of all other vaccines in females combined, broken down into two age bands.

The 4th and 5th tables compare the top 20 reported higher level MedDRA terms (HLTs) from serious HPV reports in Denmark against all other vaccines in Denmark, again in two age bands.

The report highlights that there is consistency between the WHO database and the Danish database in the top 20, with 60% similarity in the listing of the top 10 events. It then states that the comparison of HPV vaccines to all other vaccines in females, at both the PT and HLT term levels, showed a difference to all other vaccines (febrile and general signs and symptoms: fever, nausea, headache).

The report then applies its 'VigiPoint' methodology to a comparison of worldwide HPV events against all Danish HPV events, and worldwide HPV events against worldwide events for other vaccines, in females aged 9-25 years. It states that 'VigiPoint' is an "analytical framework which relies on the logarithm of shrunk OE ratios to highlight and rank characteristic reporting patterns", and that the methodology 'compares case characteristics'. It is unclear precisely what this analysis involves, but based on the information provided, it appears to be a form of disproportionality analysis that compares subsets of reports grouped according to a case characteristic of interest. A log odds ratio (OR) 005 greater than 0.5 is considered to show a statistically significant disproportionality of the characteristic of interest (such as reported PT/HLT/SOC, but also reporter source, country of origin, report quality, country of origin and seriousness).

The first analysis compared 549 HPV reports from Denmark vs 45,327 worldwide HPV reports. This analysis appears to have included all events, rather than only serious events. However, given that Denmark had received 1,228 reports (322 serious) up to Q1 2015 [the same datalock as the 'VigiPoint' analysis], it is unclear how the 549 reports were selected.

This analysis showed the PTs POTS, orthostatic intolerance and autonomic nervous system imbalance are reported disproportionately more in HPV reports from Denmark vs HPV reports in other countries. Eczema, sensory disturbance, disturbance in attention, memory impairment, palpitations, cognitive disorder, fatigue, infection, visual impairment, influenza-like illness, muscle spasms, and arthralgia also show disproportionality.

The second analysis compared 45,876 worldwide HPV reports against 79,678 worldwide reports for all other vaccines combined.

This found that disproportionately more HPV reports were coded as serious compared to other vaccine reports. It found that Malaysia, Italy, Japan, Denmark, and Australia report disproportionately more

HPV reports compared to other vaccines, but that Canada, the UK, Sweden, and France report disproportionately fewer HPV reports compared to other vaccines.

In terms of reporting within MedDRA SOCs, disproportionately more HPV reports related to Reproductive system, the Investigations SOC, Surgical and medical procedures, Nervous system disorders and Psychiatric disorders SOC, Social circumstances, Neoplasms and Injury and poisoning are received.

In terms of MedDRA HLTs, the report selects the following HLTs as showing disproportionality; Neurologic diagnostic procedures, Disturbances in consciousness NEC, Muscle weakness conditions, Disability issues, Central nervous system imaging procedures, ECG investigations, Neurological signs and symptoms NEC, Gastrointestinal and abdominal imaging procedures, Vascular tests NEC (incl blood pressure).

On the basis of the above selected HLTs, a decision was taken to lower the threshold of statistical significance to log OR 005 > 0.25. When this adjustment is made, a number of additional, HLTs are highlighted. These included Gastrointestinal and abdominal pains (excl oral and throat), Migraine headaches, Gait disturbances, Muscle related signs and symptoms NEC, Asthenic conditions, Memory loss (excl dementia), Musculoskeletal and connective tissue pain and discomfort , Mental impairment (excl dementia and memory loss), Musculoskeletal and connective tissue signs and symptoms NEC.

In terms of PTs, possibly the most relevant ones that showed some disproportionality were syncope, presyncope, muscular weakness and activities of daily living impaired. There were no statistically significant differences noted between the groups of reports for any specific diagnoses. Postural orthostatic tachycardia syndrome had been reported 82 times for HPV vaccine and 1 time for other vaccines (0.2% vs 0.0%), complex regional pain syndrome: 69 times for HPV vaccine and 16 times for other vaccines (0.2% vs 0.0%), autonomic nervous system imbalance: 76 times for HPV vaccine and 16 times for other vaccines (0.2% vs 0.0%), chronic fatigue syndrome: 65 for HPV vaccine and 30 times for other vaccines (0.1% vs 0.0%), fibromyalgia: 62 times for HPV vaccine and 39 times for other vaccines (0.1% vs 0.1%) and post viral fatigue syndrome: 47 times and 53 times for other vaccines (0.1% and 0.1%).

In its conclusions, the Uppsala report highlights an overlap in symptoms in reported cases of POTS, CRPS, CFS, PVFS and fibromyalgia, notably fatigue, headache and dizziness. Whilst it acknowledges that these symptoms can be non-specific and are commonly occurring events, it notes that the reports of POTS, CFS and PVFS from which these events arose have been largely classified as serious reports (POTS 80%, CFS 78%, PVFS 89%) stating that this "[implies] the need for hospitalisation and/or resulting in disability or interruption of normal function".

The report then speculates that the different levels of reporting of the different syndromes across countries could be explained by the same syndrome being diagnosed/coded different depending on different national practices.

Rapporteur's conclusions on the Uppsala report:
In relation to the summary of symptoms (such as fatigue, dizziness, headache) between cases co-reported with cases of POTS, CRPS, CFS, PVFS/ME, fibromyalgia, this observation is not unexpected given the known characteristics of these syndromes in the general population. This observed symptom overlap in suspected ADR reports therefore does not strengthen the 'signal' or inform causality assessment. However, based on these observations, alongside the differential reporting patterns of POTS, CRPS, CFS, PVFS/ME, fibromyalgia between countries, the Uppsala report speculates that the same clinical 'syndrome' may be occurring following HPV vaccination but is being diagnosed/coded differently across countries. Whilst it can't be excluded that this is the case, many factors can influence the levels of reporting (e.g. the US accounts for about half of the worldwide use of Gardasil, which is a likely reason most reports of each syndrome originate in the US) and the nature of reports submitted (e.g. public awareness of a specific event such as POTS and CRPS will influence this).

The report notes that the HPV case reports from Denmark are distinguished from those from other countries by the fact that they contain an increased amount of clinical information and that certain, specific diagnostic PTs are more commonly used. Given that the case series from Brinth *et al* contribute many cases to the Danish data, this is perhaps unsurprising. We already know that a high proportion of HPV reports from Denmark relate to POTS and that Denmark has higher overall reporting rates for events coded as serious for HPV.

It is likely that the apparent increase in reports since 2013 across countries has been stimulated by the concerns in Japan and Denmark. This overall trend in reporting over time is therefore not unexpected given the known influences on spontaneous reporting. However, as the report includes no information on the number of doses of vaccine used over this time period, conclusions cannot be drawn on this. It is stated that the datalock for the analysis precedes the media attention generated by the announcement of the current referral. Whether this reduces any bias of stimulated reporting in the analysis is debatable, given that most of the public awareness and concern preceded 2015.

The 'top 20' comparisons of events and the 'VigiPoint' analyses appear to have been undertaken in order to detect any apparent signals of disproportionate symptom constellations that may not necessarily have been reported (or diagnosed) specifically as POTS, CRPS, CFS, ME/PVFS, fibromyalgia. As cases that included these specific PTs also include a high proportion of the relevant related symptoms, such cases should have been excluded from these separate analyses. However, this does not appear to have been done.

Overall, the observations included this report allow no conclusions to be made on clinical or diagnostic practice between countries. The report concludes that the worldwide spontaneous data indicate a pattern of reporting consistent with a HPV vaccine-specific 'syndrome'. However, the interpretation of the data is selective and, for the reasons further discussed below, this conclusion is not supported by the data.

'Top 20' comparisons

In relation to the comparison of the top 20 reported symptoms worldwide from serious reports for HPV vaccines against all other vaccines, the report concludes that this showed a difference between and HPV and all other vaccines. However, the comparison actually shows very few differences and a lot of consistency, in terms of the type of event reported at the various age bands.

This consistency is perhaps not surprising given that the majority of these top 20 serious events include the signs and symptoms (or related PTs) of the most common, expected events of most vaccines given to adults and adolescents, which are usually transient. Many of these top 20 reports may also include the signs and symptoms of immediate faints following vaccination (e.g. it is common for the likes of tonic-clonic limb movements to be reported as seizures in this context, as well as loss of consciousness and paraesthesia to be co-reported with this).

Although such 'expected' reports would not always be expected to be clinically serious, the designation of serious in Vigibase does not necessarily mean that such events are always clinically serious. The Uppsala report states that the serious coding implies "*the need for hospitalisation and/or resulting in disability or interruption of normal function*". However, a report may be coded as serious for many reasons, and this statement is a generalisation. For example, of the 2,652 Yellow Card reports for HPV vaccines coded as serious in the UK, only 23% included one or more of the specific 'CIOMS' criteria, a further 37% were judged as serious by the reporter for individual reasons other than these five criteria (however this reason is not specified) and a further 40% were considered non-serious by the reporter but automatically coded as serious by the MHRA database.

Although there are some differences between HPV and all other vaccines when focusing only the top 20 Danish reports (HLTs), the numbers are surprisingly small for other vaccines (ranging from only 2 to 9 events per HLT). Given that we know POTS contributes largely to the symptoms in the Danish reports, this comparison probably shows what we expect to see. Nonetheless, even this comparison still shows a high level of consistency between HPV and other vaccines. For instance, HLTs highlighted as relevant to a 'syndrome' elsewhere in report (i.e. HLTs such as asthenic conditions, neurological signs and symptoms, mental impairment, pain and discomfort, muscle pain, muscle weakness, GI and abdominal pains), appear in the top 20 of both the HPV and non-HPV groups but are largely ignored in the conclusions. Although the numbers are small for the non-HPV group, this comparison argues against such reporting patterns pointing to a specific undiagnosed 'syndrome' reported with HPV, despite the conclusions suggesting otherwise. An alternative conclusion could be that these comparisons reflect events that we may expect to see in adolescent females after vaccination.

Without any reference to relative denominators and without a detailed analysis of individual reports (for instance to evaluate symptom severity, onset time, longevity etc), these high level comparisons of

absolute event numbers and most frequent symptoms reported for different vaccines add little value to the current causality assessment.

'VigiPoint' analyses

In relation to the 'VigiPoint' analysis, the report states that this was done to "*investigate if this constellation of symptomatology is specific for HPV vaccines and thus may not be simply explained by the background incidence of this diagnosis in the adolescent, female population*". This seems to imply that the analysis can differentiate between events that are coincidental or causally-associated. The nature of spontaneous data and this sort of disproportionality analysis would not allow any such conclusion, and can only highlight differential reporting trends between vaccines/regions, to inform signal generation. Any observed reporting trends can be explained/influenced by many factors other than causal associations.

The VigiPoint analysis of total numbers of reports for HPV vs other vaccines across different countries is not informative to the issue. As acknowledged in the report, many factors will influence the absolute number of ADR reports received, not least the denominator (the number of doses and types of vaccine given to those aged 9-25 yrs will differ across countries across the data extraction period), which is lacking in this analysis.

The VigiPoint analysis of Danish HPV events vs worldwide HPV events not surprisingly showed that the PTs POTS, orthostatic intolerance and autonomic nervous system imbalance are reported disproportionately more vs HPV reports in other countries. However, the report states that other PTs that are also clinically-relevant [to undiagnosed POTS and related syndromes] did not show disproportionality (specifically, headache, malaise, myalgia, asthenia, dizziness, dizziness postural, orthostatic hypotension, presyncope, syncope, hyperhidrosis, heart rate increased, tachycardia, muscular weakness, abdominal pain, tremor, hypersomnia, quality of life decreased and activities of daily living impaired).

In the VigiPoint analysis of worldwide HPV events vs worldwide events for all other vaccines given to 9-25 yr old females, aside from Nervous system disorders, arguably the most relevant MedDRA SOCs to consider in order to detect any relevant symptom clusters would be General disorders, Gastrointestinal disorders, Musculoskeletal disorders and Cardiac disorders. Yet these SOCs did not show any apparent disproportionality in reporting for HPV vaccines, although this is not acknowledged in the report. The report then selectively highlights some potentially relevant HLTs as showing some disproportionate reporting, stating that "*that these symptoms are potentially specific for HPV vaccines*". The report further states "*there are a number of HLT describing diagnostic procedures which implies serious events without a clear diagnosis of clinical grounds*". However, without reviewing individual case details to determine whether or not a diagnosis was made, this remains an assumption. Based on this VigiPoint analysis, the report then concludes that "*a greater proportion of HPV reports are serious and describe events which are consistent with symptomatology included in the clinical case working definition for myalgic encephalitis / chronic fatigue syndrome (ME/CFS)....*", and that "*..this finding is potentially significant because, although ME/CFS is more common the adolescent female population, it is being reported more commonly with HPV vaccine in comparison to other vaccines in this same population*".

Aside from the fact that CFS and PVFS/ME showed no statistically significant disproportionate reporting for HPV vaccine, the report does not acknowledge that there is a very wide range of more relevant and more specific HLTs that may potentially include symptoms of undiagnosed CFS (as well as POTS, CRPS, PVFS and fibromyalgia) that, presumably, did not show any disproportionality. This includes, to name but a few, autonomic nervous system disorders, asthenic conditions, GI motility disorders, tachyarrhythmia, cognitive disorders, postural dizziness, muscular weakness, mobility decreased, exercise tolerance decreased, various pain HLTs, skin discolouration.

Of these more relevant and specific HLTs, only asthenic conditions shows any apparent disproportionality when the decision was taken to lower the 'signal threshold', but this was only marginal (12.3% of HPV reports vs 9.3% of other vaccine reports). However, it should be noted that this HLT includes fatigue (as a PT), which is one of the most common yet benign adverse effects of any adult or adolescent vaccine. In terms of PTs, possibly the most relevant ones that showed some disproportionality were syncope, presyncope, muscular weakness and activities of daily living impaired. However, this is a very small number of PTs, and there are many more relevant and more specific PTs that did not show any disproportionality for HPV vaccines.

Although the VigiPoint analysis appears to incorporate statistical adjustment, this sort of multiple analysis and data-mining of every MedDRA SOC, HLT and PT will inevitably yield some 'signals' of disproportionality for HPV as well as non-HPV reports, as shown in the report. However, the approach taken to selection of SOCs, HLTs and PTs, amendment of a pre-specified 'signal threshold' and selective discussion of disproportionate reporting for HPV does raise concerns about whether the conclusions reached are evidence based.

If the apparent lack of disproportionate reporting for most relevant events is acknowledged and taken into account, then the data, overall, would actually show no specific reporting profile for HPV vaccine compared to other vaccines that may indicate a particular undiagnosed syndrome.

Conclusion

The Uppsala report serves to highlight what is already known, i.e. that some countries are observing an increasing number of reports of different types of adverse events associated with HPV vaccine and that such reporting has increased over time.
The final conclusion of the report is that "*the data suggest that there is an over-representation of serious case reports which describe a constellation of symptomatology and subsequent medical evaluation potentially consistent with a chronic fatigue – like syndrome which may be specific to HPV vaccines*". For the reasons highlighted above, this specificity to HPV is not supported by the data presented.

Many relevant events that presumably did not show disproportionality, and therefore would not support this hypothesis, are not acknowledged. Furthermore, the non-HPV vaccine group also included many relevant symptoms that, arguably, could fit these symptom profiles. Without detailed case review, and because most of these reported symptoms can also relate to known, transient adverse effects of any vaccination, the conclusions in the report do not appear to be supported.

Data-mining of spontaneous ADR data cannot further inform causality assessment. Analysis of spontaneous data, including the 'observed vs expected' conducted by the MAHs and MSs, has already served its purpose in exploring whether or not there is a 'signal' for further evaluation. The view of the Rapporteur is that the data do not support a signal for POTS or CRPS.

It is known that there is some overlap between POTS and CFS, and there is some symptom overlap between these syndromes and CRPS and fibromyalgia. But accepting 'chronic fatigue–like syndrome' as a new hypothesis to pursue is debatable. As described above and below, Donegan *et al* have already partly evaluated this.

Overview of Japan data

The DHMA report includes a brief description of the situation in Japan. It states that although the initial concerns in Japan focused on pain and the diagnosis of CRPS, the adverse event reports in the Japanese database have been characterized by a wider variation of symptoms, often difficult to standardise. It states that often reported symptoms were pain, movement disorders, orthostatic intolerance, dizziness, menstrual abnormalities and fatigue. Symptoms were reported to fluctuate and in some patients lasting for a long time. The DHMA report states that the pattern reflects much of the same symptoms as are also reported in the Danish cases.

Rapporteur's overall conclusions on the DHMA report

The DHMA report speculates that due to differential clinical practice across countries, similar suspected ADRs to HPV vaccine are receiving different diagnoses (or indeed no clear diagnosis), which in turn is potentially 'diluting' a safety signal. This theory appears to have prompted the comparative overview of all serious ADRs, including the worldwide data obtained from Uppsala, in order to identify any potential 'non-specific' safety signals.

As many of the serious suspected ADRs reported following HPV vaccine have no confirmed diagnosis but a wide range of overlapping symptoms, and based on recent literature articles speculating that POTS, CRPS, fibromyalgia and CFS may have a common pathophysiology (i.e. autonomic dysfunction, possibly due to small fibre neuropathy), the DHMA report proposes that the constellation of symptoms

and reports should be considered as 'chronic fatigue-like' illness, which accords with the current opinion of Brinth *et al* – see above.

Several of the existing safety studies referred to in the DHMA report relevant to POTS and CRPS are evaluated separately in the referral in the context of the MAH's replies. However, the report also refers to studies looking at a range of autoimmune disorders, other serious events and chronic fatigue syndrome (CFS).

These were generally large studies that used electronic health record data and used a variety of study designs, from cohort, case control and risk interval or self-controlled case series analysis. None of the studies found conclusive evidence of increased risks for the included outcomes. Some were funded by the MAHs.

The DHMA report then states that these studies have a limitation in that the use of 'registers' (which presumably means electronic health record data) is highly dependent on diagnosis. The report argues that because the adverse events being reported following HPV vaccine are difficult to diagnose and have overlapping symptoms, the currently-available studies could not identify cases relevant to the current issue.

Of course, any such observational study will have limitations, as well as strengths. It is important that, when relevant to the objectives, observational studies are based on medically-diagnosed illness using valid case definitions, and the study should minimise information bias (such as differential diagnostic likelihood/practice between the groups under comparison). It is acknowledged that not all of these studies included outcomes that are directly relevant to the current review.

However, the DHMA report under-estimates the value of two of these studies to the current issue, i.e. Klein et al, and Donegan et al, and the statement that cases relevant to the current issue would not have been identified in these studies is not fully supported.

Klein et al (2012)

The study by Klein *et al* (2012) was not reliant on diagnosed illness and evaluated hospital visits amongst 189 629 females aged 9 to 26 years, for a very wide variety of clinical reasons (256 ICD categories were included, based on discharge coding) within 14 and 60 days of vaccination (the study used risk interval analysis). An increased risk for syncope was identified only on the day of vaccination. Other categories included that could be relevant to the current issue where "Hereditary and degenerative nervous system conditions" (which included the subcategory of autonomic nervous system disorders), ear disorders (which included the subcategory of dizziness), "ill-defined conditions and factors influencing health status, which also included the subcategory of malaise and fatigue. There were very few cases in the category that would have included a discharge summary for autonomic nervous system disorders, and discharges for malaise and fatigue were not significantly raised in the post vaccine risk period following adjustment for multiple analyses. Ear conditions showed a slightly elevated risk, but individual case review revealed most events were either present before vaccination, were opportunistic evaluation/coding at the vaccine visit, or had obvious aetiologies not associated with vaccination (it is not stated if or how many cases of dizziness contributed to this category).

Although this study was not of direct relevance to the current issue and was largely a data-mining exercise, it does give some insight into the general healthcare seeking behaviour in a large cohort following vaccination for a wide variety of clinical reasons, and revealed no obvious clusters of concern.

Donegan et al (2013)

The study by Donegan *et al* (2013), as well as using the self-controlled case series design (and therefore avoiding the issue of differential diagnostic practice in vaccinated and unvaccinated), evaluated not only diagnosed CFS, but also referrals from General Practice for as yet undiagnosed symptoms of chronic fatigue and exhaustion, as well as diagnoses for fibromyalgia, post viral syndrome and neurasthenia. The study found no association between HPV vaccine and any of the conditions studied.

The study by Donegan *et al* does not address all of the current issues. The study period only allowed Cervarix-exposed subjects to be included as at that time the UK routinely used Cervarix. Although the

study included conditions related to CFS such as fibromyalgia, CRPS and POTS were not specifically studied. The study was however well powered to detect a relative risk of 3 or more

However, given the current suggestion in the DHMA report is that the constellation of undiagnosed symptoms should be considered a chronic fatigue-like syndrome, as CFS and POTS are known to have a high level of overlap, and as Brinth *et al* now consider that CFS may be a more relevant diagnosis in the Danish cases (see critique of Brinth *et al* above), the study by Donegan *et al* is arguably the most relevant epidemiological study to the current issue to date.

3.4.2.7 Rapporteur's evaluation of the submission from The Netherlands

On 16 October, The Netherlands submitted a document entitled "Long-lasting and unexplained symptoms following vaccination with Cervarix®: overview of reports received after media attention". This was an overview of spontaneous ADR data from the Dutch Pharmacovigilance Database Lareb. The details of the report are replicated below, so this is not included as an annex.

It states that in 2009, Cervarix was added to the Dutch national immunization program, offered to all girls in the year they turn 13. Prior to 2014, the schedule was three doses, but has been two doses since then. Vaccination coverage has ranged from 52-59%.

In response to the annoucement of the current referral, Lareb made available to the public (in Dutch) an overview of all ADRs reported in relation to Cervarix. This overview concluded that most of the ADRs reported after Cervarix were relatively mild and of short duration. There were no reports where the diagnosis CRPS and POTS were explicitly mentioned at the time of reporting. There was one report of chronic pain on the injection site. In the reports where combinations of events were reported which might be indicative for POTS, such as syncope and dizziness, there was no clear information available which could label these cases as POTS. In a few cases of fatigue, in combination with syncope and dizziness, it was reported that the events were still ongoing at the time of reporting.

Since publication of the abovementioned overview, the information was picked up by national media. In the following month, Lareb received more than one hundred reports on Cervarix. Given the discussions regarding an association between HPV vaccines and POTS and CRPS, active follow up (by phone or e-mail) was initiated on all reports in order to have sufficient information for the assessment of the report.

This new report therefore summarises 106 reports received by Lareb between 12 July 2015 and 25 August 2015, focusing on long-lasting (duration ≥ 2 months), medically unexplained events received in this period.

Reporting pattern 2009 - 2015

Although this overview focusses on the reports received in July and August 2015, to give an impression of the reporting pattern, number and type of reports received on Cervarix®, a few figures are presented in which all reports on Cervarix® are included.

From the moment the HPV-vaccine Cervarix® was introduced to the Dutch national immunization program 1-1-2009 until 25 August 2015, in total 1239 spontaneous reports were received concerning adverse events following immunization (AEFI's). Figure 1 shows the reporting pattern throughout the years. Peak A, C and D are preceded by media attention for the HPV-vaccine. Peak-B is due to a transition of responsibility for the collection of spontaneous reports of vaccines from the national institute of public health and the environment (RIVM) to the Netherlands Pharmacovigilance Center Lareb.

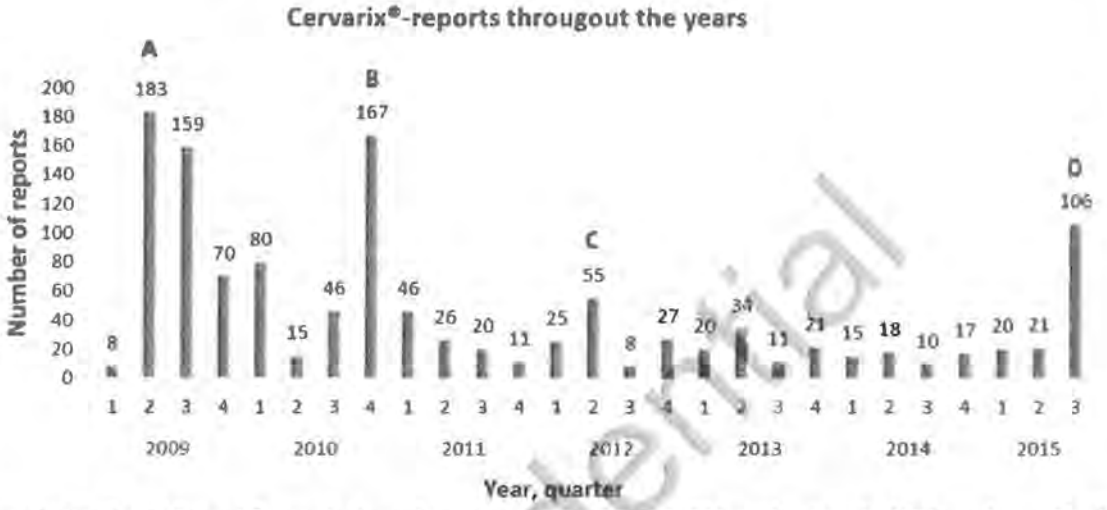


Figure 1. Number of Cervarix®-reports throughout the years. A: 09-03-2009 broadcast on the HPV-vaccine on Dutch television (Radar) [8]. B: Transition of Cervarix®-reports from the RIVM to Lareb. C: 20-03-2012 Article on AEFI's following HPV-vaccination in a Dutch newspaper "De Telegraaf" [9]. D: 29-07-2015 Lareb announces further investigation on possible AEFI's in relation to Cervarix® on Dutch radio and TV [10, 11].

Frequently reported AEFI's 2009 – 2015

To get a general idea of the spectrum of AEFIs reported, an overview is given of the most frequently reported AEFIs.

AEFI's	Times reported
Headache	464
Pain	409
Pyrexia	367
Nausea	290
Dizziness	283
Fatigue	257
Inflammation	164
Myalgia	147
Malaise	122
Abdominal pain	119

Table 1. Top 10 reported AEFIs in association with Cervarix® 01-01-2009 to 25-08-2015

Reported Adverse Events Following Immunization (AEFI's) since the last overview

As seen in figure 1, attention for this possible association on national radio and TV lead to an increase in reporting. In total 106 HPV-reports were received between 12-07-2015 and 25-08-2015. Only reports concerning girls who received Cervarix® in the context of the Dutch national immunization program were included for analysis. This criterion led to the inclusion of 104 Cervarix®-reports in total which will be described further below.

Year of vaccination

The figure below shows that most reports concern patients who were vaccinated in 2009. In this year the birth cohorts of 1993-1996 were vaccinated.

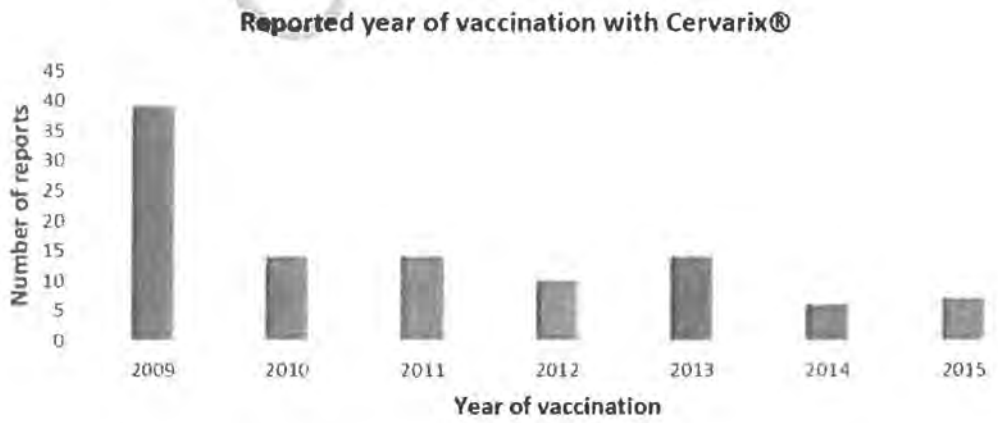


Figure 2. Reported year of vaccination in reports received in the period 12-07-2015 to 25-08-2015.

Frequently reported AEFI's
A top 10 of all reported AEFI's are listed in table 2.

AEFI's	Times reported
Fatigue	90
Headache	57
Dizziness	46
Myalgia	24
Syncope	17
Presyncope	13
Nausea	10
Disturbance in attention	6
Palpitations	5
Feeling cold	4

Table 2. Top 10 reported AEFI's in the period 12-07-2015 till 25-08-2015

Frequently reported combinations of AEFI's
In the majority of the received reports, there was more than one reported adverse event. In total 378 AEFI's were reporting, giving an average of 3.6 AEFI's per report. These 378 AEFI's were coded as 84 distinct MEdDRA Preferred Terms. To get an idea of what kind of which combinations of symptoms the individual patients experienced, an analysis of the most frequently reported combinations of symptoms were made, see table 3.

Combinations of reported AEFI's	Times reported
Fatigue + headache + dizziness + syncope	9
Fatigue + headache + dizziness	9
Fatigue + headache	8
Fatigue + headache + dizziness + myalgia	5
Fatigue + dizziness	5
Fatigue + myalgia	5

Table 3. Six most reported combinations of AEFIs in the period 12-07-2015 to 25-08-2015.

Complex Regional Pain Syndrome (CRPS)

CRPS was not reported as an AEFI. As CRPS often affects one of the limbs (arms, legs, hands or feet) [13], all reports of AEFIs involving limbs were reviewed. In two reports the AEFI involved one of the limbs: a case of bursitis in an arm and a case of muscle weakness in a leg. In ten other reports the AEFI involved more than one limb: pain, myalgia or muscle weakness in both arms, hands and/or legs were reported.

Postural Orthostatic Tachycardia Syndrome (POTS)

POTS was not explicitly reported as an AEFI. As POTS consists of a heart rate increment during orthostatic challenge [14], all reports of AEFIs involving tachycardia or palpitations were reviewed. In all four reports of tachycardia or increased heart rate, the symptoms were provoked or aggravated by standing up or mild exertion. This was not reported in the five cases of palpitations. Symptoms that can accompany POTS, such as fatigue, dizziness, (pre)syncope and headache were reported frequently, as shown in table 2 and 3.

Health care consultation

Of the 104 recently received cases, 97 patients reported to have consulted a medicine practitioner due to the AEFI. In 66 of these cases, the patient was referred to a medical specialist. In 15 cases, the patients were reported to have consulted a complementary practitioner as well as a medicine practitioner.

In 83 cases, the patients were reported to have undergone one or more medical tests. Blood tests were performed most frequently, followed by specialized tests and medical imaging. Common blood tests included Epstein-Barr virus serology, Borrelia Burgdorferi serology, liver function, thyroid function, complete blood count, vitamin D status and vitamin B12 status. The specialized tests included electrocardiography, exercise tests, vestibular function and a tilt table test. The medical imaging included echocardiography and MRI or CT scans of the brain. In 20 of the 104 cases it was not known whether medical tests were performed. In only one case it was specifically mentioned that no medical tests were performed.

Latency to onset of long-lasting AEFI's

The majority of reports concern several long-lasting AEFIs, often with a different time to onset for each event. For the current overview, latency was therefore defined as the time between the suspect injection moment and the onset of the (first) long-lasting AEFI. The suspect injection moment was defined as the most recent injection prior

to the onset of the (first) long-lasting AEFI, unless the reporter indicated otherwise. Figure 3 gives a list of reporte latencies and the frequency with which these latencies have been reported.

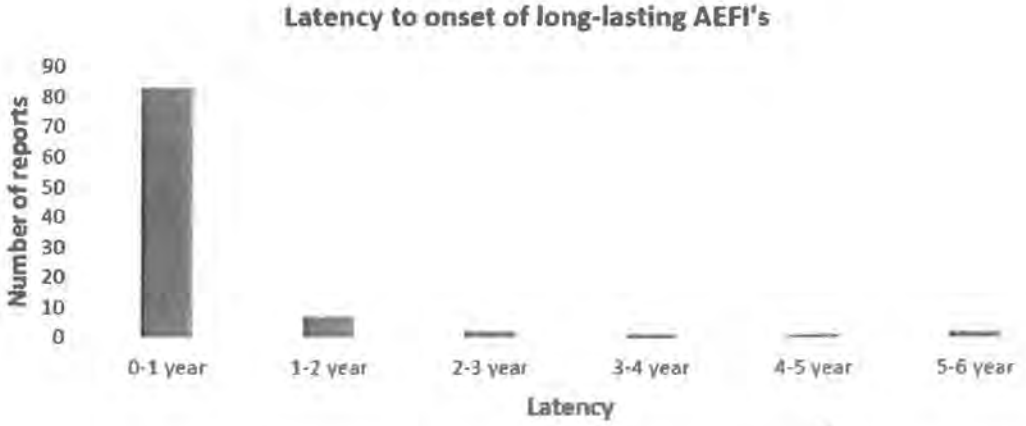


Figure 3. Latency to onset of long-lasting AEFI's reported in association with Cervarix® 12-07-2015 to 25-08-2015.

Latency: 0-1 year	Number of reports
Not further specified	26
0-7 days	8
1-4 weeks	21
1-4 months	22
4-8 months	3
8-12 months	3

Table 4. Latency to onset of long-lasting AEFI's – first year after vaccination

Figure 3 shows that the majority of the reported long-lasting AEFI's started in the first year after vaccination. It should be noted that in these reports recall bias forms a confounding factor for the determination of an accurate latency to onset.

Duration

Duration was defined as the time between the onset of the (first) long-lasting AEFI and either the recovery of the patient or, if the patient did not fully recover, the receive date of the report. Of the 104 reports that were received between 12-07 to 25-08, 103 reports concerned AEFIs which lasted 2 months or more at the time of reporting. As shown in figure 4, most AEFIs were already existent for several years before the reporting was done.

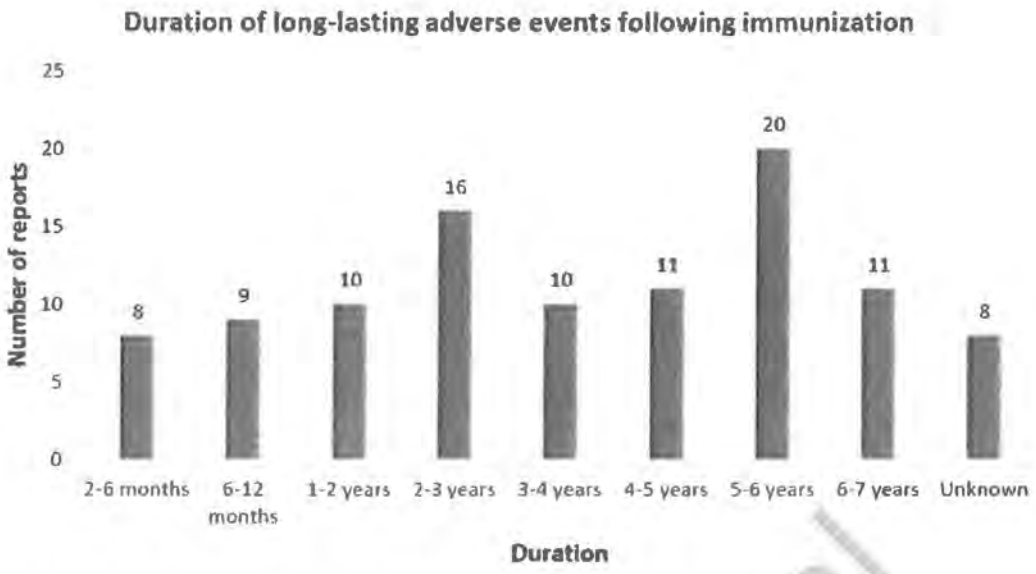


Figure 4. Duration of reported long-lasting AEFI's 12-07-2015 to 25-08-2015

Outcome

Figure 5. Outcome at time of reporting. Receive date: 12-07-2015 to 25-08-2015.

As shown in Figure 5, the majority of the reports received between 12-07-2015 and 25-08-2015 concerned patients who were not fully recovered at the time of reporting. This is a difference compared to the reports received prior to 12-07-2015, which is shown in Figure 6.

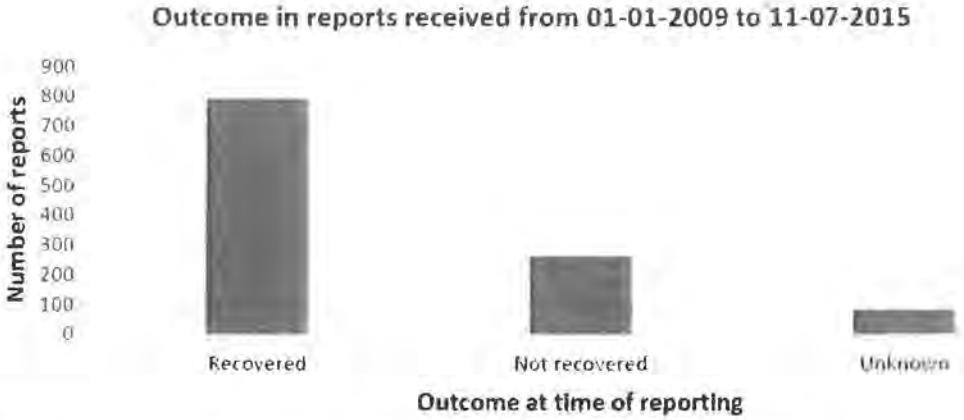


Figure 6. Outcome at time of reporting. Receive date: 01-01-2009 to 11-07-2015

Considerations

In the summer of 2015 there was media attention in the Netherlands concerning AEFIs, after attention for POTS and CRPS in some other countries in relation to Cervarix®. Between 12-07-2015 and 25-08-2015 the Netherlands Pharmacovigilance Centre Lareb received 104 reports on Cervarix® given in the context of the Dutch national immunization program. The received reports were all clinical reviewed with an open mind in order to identify possible patterns in the reported AEFI's and active follow up was acquired for all reports. The most reported combinations of AEFIs were the combination of fatigue, headache, dizziness and syncope and the combination of fatigue, headache and dizziness. All 104 reports, aside from one, concerned long-lasting symptoms for which the majority of girls underwent further diagnostic tests. In most cases no cause for the symptoms was found.

The syndromes POTS and CRPS were not reported as such, but symptoms which are indicative of POTS have been reported. POTS require dedicated diagnostic tests. No or limited information was available whether or not these diagnostic procedures were carried out and what their outcome was. It is questionable if the treating physicians of the girls involved, actually did take the aforementioned diagnoses into account, given the fact that the characteristics of the events were published only recently in specialized journals. Although the existence of POTS could not be established in these reports, some reports contain symptoms which could be indicative of POTS and therefore the existence thereof cannot be ruled out.

This report was prepared in order to share the data from the Netherlands Pharmacovigilance Centre Lareb with the PRAC. At the moment Lareb is also trying to obtain more information from the cases described in the overview which was made in July [7] and in the near feature we will provide an updated overview of all cases of long-lasting unexplained symptoms after Cervarix® vaccination.

The results presented above are based on spontaneous reporting. Spontaneous reporting is a signal generated methodology which is sensitive to media attention. It should be noted that results originating from this type of data cannot be used to determine if there is a causal relation between the suspect vaccine and the reported AEFI's. In order to confirm or reject a causal relationship of long-lasting complaints following immunization with Cervarix®, additional epidemiological research is needed.

Rapporteur's comments:

The update from the Lareb database is noted. As acknowledged in the report, media interest has stimulated retrospective reporting of suspected ADRs and these data cannot inform causality. The suggestion that under-diagnosis of POTS may be in factor in these reports is noted, and is addressed elsewhere in the broader assessment of the (Co)-Rapporteur's. It should also be acknowledged that

any underdiagnosis of POTS would apply equally to unvaccinated cohorts as well as in the time period before HPV was introduced. Therefore, a pertinent question is whether the background incidence of POTS in the adolescent female population is higher than currently estimated, and whether the reporting rate following vaccination is any greater than on would expect in the absence of vaccination. Spontaneous data cannot answer this question, although the broader 'observed vs expected' analysis discussed separately in this assessment report would suggest reporting rates following HPV vaccine are consistent with chance.

4. Consultation with expert group

5. Benefit-risk assessment

5.1 Cervarix Co-Rapporteur's conclusions

Based on the review of all available data on safety, the Co-rapporteur considers that the benefit-risk balance of Bivalent HPV vaccine (types 16, 18) **remains favourable** and therefore **recommends the maintenance of the marketing authorisation**.

However, as the potential involvement of Cervarix in the occurrence of CRPS cannot be completely ruled out at this stage, the co-rapporteur recommends that this risk should continue to be investigated. This could be accomplished by further monitoring in PSUR. However, monitoring is difficult because of the complexity of the disease, the risk of underdiagnosis, and the existence of different diagnostic criteria. As suggested by three independent external experts, a PASS study could be considered to further clarify the potential link between CRPS and Cervarix vaccination. The feasibility of such a study should be thoroughly examined by the SAG (see Section 7) as the majority of CRPS cases normally occurs in elderly women and the target population would be adolescents. A clear definition of CRPS cases should be provided before the beginning of the PASS study, as well as the risk period. In order to obtain cases, data from specialised centres could be used. Finally, a PASS could also provide some answers to the growing public attention to the HPV vaccine safety.

Similarly, a potential involvement of Cervarix in the occurrence of POTS cannot be completely ruled out. However, the monitoring of POTS after HPV vaccine is complicated by the difficulty to diagnose the syndrome, the rarity of POTS fully fitting the case definition (when considering all factors of exclusion), and the variety of conditions which could be associated to POTS, some of these being also considered for potential association to HPV vaccine. To make sense, the requirements of a future monitoring of POTS after HPV vaccine should be better defined and the co-rapporteur recommends:

1) to identify PTs/codes which could be associated to autonomic disorders, including POTS (assuming that the POTS PT is not sufficient to identify POTS) and to define a POTS/autonomic disorders search strategy in pharmacovigilance data bases and other data bases;

2) to identify specific markers to eventually permit to classify cases of POTS after HPV vaccine as auto-immune disorders.

In conclusion, deciding upon a PASS study in the light of the current evidence could be premature as the parameters to investigate are still unclear.

5.2 Gardasil Co-Rapporteur's conclusions

Page 8-19 of the Co-Rapporteur's assessment report includes an executive summary of their assessment, including a causality assessment in the context of Hill's criteria (Rothman, Greenland, Lash 2008).

5.2.1 Discussion on causality - CRPS

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.

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.

5.2.2 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.

5.2.3 Benefits

The benefit risk of Gardasil has not been suggested to be changed by this referral procedure. For clarity, the Co-Rapporteur has provided a benefit risk discussion.

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.

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 headache 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.

5.3 Rapporteur's conclusions on Gardasil 9, and the overall assessment

Gardasil 9

For Gardasil 9, the one report of CRPS and one of the reports of POTS do not necessarily fulfil the respective diagnostic criteria. The other report had an apparently long onset time from vaccination. As stated by the Co-Rapporteur, the few cases reported from RCTs are evenly distributed between the qHPV/HPV9 and placebo groups which does not suggest an association. The details of these reports in the context of the pooled trial data do not raise any safety concern for Gardasil 9. There are no post-marketing data.

The benefit risk of Gardasil 9 has not been suggested to be changed by this referral procedure.

Overall conclusions

The Rapporteur agrees with the overall conclusions of the Gardasil Co-Rapporteur.

The Rapporteur agrees with most conclusions of the Cervarix Co-Rapporteur, with the exception of the recommendations in relation to further evaluation of CRPS and POTS. This is described further below. On a worldwide basis and in most individual countries, it is reasonable to conclude that the most likely assumptions and scenarios around 'observed vs expected' analyses do not indicate a safety signal. Denmark and Japan clearly have higher reporting rates of certain ADRs than other countries, and the publicity around HPV vaccine safety has not only stimulated higher reporting in those countries, but in other countries subsequent to 2013. Such publicity may stimulate not only increased reporting, but a bias in reporting towards events that more closely 'fit' vaccine induced illness – from the perspective of the Danish reports, the high proportion of cases from Brinth *et al* support this notion.

Aside from the interpretation of the O/E analysis, the cases included displayed no clear clinical pattern or dose relationship. Furthermore, the majority of cases have a relatively short symptom onset after vaccination (even when not accounting for the selection of such cases by Brinth *et al*). Symptom onset within 2 weeks is unlikely to be indicative of an autoimmune process (if an autoimmune basis for these conditions is to be believed).

It could be argued that given the very high vaccine uptake in most countries in which these ADRs are being reported, given that the reported illnesses/symptoms are usually most common in adolescence and much more common in females than males, and given the likelihood of recent stimulated reporting in several countries, then the observed pattern of spontaneous reports is not unexpected.

Therefore, on balance, the view of the Rapporteur is that the available evidence does not indicate a strong safety signal nor does it support a causal association with HPV vaccine.

Given the nature of the Brinth *et al* case series and the Uppsala analysis, the Rapporteur also does not agree that overall ADR reporting indicates a syndrome or constellation of symptoms that is specific to HPV vaccine. POTS, CFS, CRPS and fibromyalgia all occur naturally amongst adolescent females and are known to have some symptom overlap. There is no robust basis to suggest that a common pathophysiological pathway exists, nor that this could be autoimmune in origin.

Nonetheless, Brinth *et al* now suggest that the cases referred to them should be regarded as CFS (including a subset of POTS secondary/concurrent with CFS). The existing findings of Donegan *et al* (2013) are relevant to this, as well as post-viral fatigue syndrome and fibromyalgia following HPV vaccination. This study further supports the lack of a safety signal and any causal association with HPV vaccine.

In relation to POTS, the Rapporteur does not agree with the proposal to further identify a set of relevant PTs/codes relating to autonomic disorders to monitor in enhanced surveillance of HPV vaccines. This form of analysis has already been undertaken in the current referral via the wider search strategy to identify possible cases not reported with the specific MedDRA PT of POTS and CRPS. The Uppsala analysis has also done this, and not found any specific signal if all relevant HLTs/PTs are taken into account. Furthermore, the Cervarix Co-Rapporteur's proposal to identify specific markers to eventually permit to classify cases of POTS after HPV vaccine as auto-immune disorders is unclear. Other than the Danish reports, there is a lack of a clear signal in relation to POTS and no clear basis to suggest that POTS has an autoimmune origin.

In relation to CRPS, Rapporteur does not consider there is a signal for CRPS. Based on data from The Netherlands, the background incidence rate of CRPS is ~15 person-years in females 10-19 years old. Given that many countries have up to 90% HPV vaccine uptake in girls in this age range, the reporting rate remains consistent with chance, and does not indicate a specific risk for HPV vaccine (over and

above what any vaccine or needle injection may theoretically trigger). The Rapporteur agrees that a relationship to needlestick injection cannot be ruled out, although this would not be specific to HPV vaccine and is a theoretical risk with any injection procedure and does not require further evaluation or risk minimisation.

6. <Recommendations>

7. Next steps

A meeting of the Vaccine SAG is planned for the 21st October, which will be supplemented with experts in CRPS and POTS

The following are possible areas for further discussions within this SAG subject to agreement by PRAC.

- Q1. What is the current understanding about the pathophysiology and diagnosis of CRPS and POTS?
- Q2. Based on the response to question 1, please discuss any consequences for the interpretation of the clinical presentation of the cases described in this referral.
- Q3. Given the available data, is there a need for a PASS study to explore the potential link between CRPS and vaccination with HPV vaccine. If yes, which design should be the most appropriate?
- Q4. Based on the responses to questions 1 and 2, please discuss if there are any specific characteristics or outcomes that would be justified and meaningful for additional surveillance of HPV vaccines. If so, please discuss feasibility and design of such activities.

8. References

Annex 1 Proposed List of Outstanding Issues

The Overall Rapporteur and Cervarix Co-Rapporteur (BE) propose no additional questions to the MAHs.

The Gardasil Co-Rapporteur proposes the following List of Outstanding Issues

- **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.

Annex 2 Recommended changes to the product information

It is recognised that it is not always possible to identify clear and precise changes to the PI in the early stages of the procedure, nevertheless, the need for PI amendments and the actual wording of the amendments should be considered as early as possible in the procedure. This is particularly important in the case of procedures under Article 107i as the timetable only allows for one round of assessment. It is also possible to request the MAH(s) to propose and provide revised PI texts.

In case no changes are recommended to the PI:

Not applicable.

In case changes are recommended to the PI:

The changes proposed are based on the latest assessment by the <co->rapporteur. This proposal may be updated following further assessment and/or Committee discussion.

<The wording should be added or replaced as appropriate. If the current <SmPC> <or> <package leaflet> includes corresponding information in any other sections, it should be deleted in order to avoid repeated information.>

The following changes to the product information of medicinal products containing <name of active substance> are recommended:

It is critical to ensure that this annex is updated after each round of assessment and after relevant comments are received from Member States, so that the PI proposal is always kept up to date.

<Summary of product characteristics>

[Further sections may be added/deleted as necessary]

- Section 4.1 Therapeutic indications
- Section 4.2 Posology and method of administration
- Section 4.3 Contraindications
- Section 4.4 Special warnings and precautions for use
- Section 4.5 Interaction with other medicinal products and other forms of interaction
- Section 4.6 Fertility, pregnancy and lactation
- Section 4.7 Effects on ability to drive and use machines
- Section 4.8 Undesirable effects
- Section 4.9 Overdose
- Section 5.1 Pharmacodynamic properties

- Section 5.2 Pharmacokinetic properties
- Section 5.3 Preclinical safety data

<Conditions to the marketing authorisation>

For centralised products, conditions will be included in annex II.

<Package leaflet>

Add sections as relevant (see below), ensuring that the above proposed changes to the SmPC are adequately reflected in lay terms in the package leaflet, in accordance with the QRD template.

- Section 1: What X is and what it is used for
- Section 2: What you need to know before you <take> <use> X
  - <Do not <take> <use> X<:>>
  - <Warnings and precautions>
  - <Children <and adolescents>
  - <Other medicines and X>
  - <X with <food> <and> <,> <drink> <and> <alcohol>
  - <Pregnancy <and> <,> breast-feeding <and fertility>
  - <Driving and using machines>
- Section 3: How to <take> <use> X
  - <Use in children <and adolescents>>
  - <If you <take> <use> more X than you should>
  - <If you forget to <take> <use> X>
  - <If you stop <taking> <using> X>
- Section 4: Possible side effects

Links to:

- *General guidance on how to prepare a SmPC, including training materials on the content of specific sections.*
- *Product Information templates.*

Annex 3 Proposed Dear Healthcare Professional Communication

The need for a DHPC is usually only clearly identified at later stages of the procedure and a proposal may therefore not be needed in the early rounds of assessment.

Note that in accordance with the Guideline on good pharmacovigilance practices (GVP) module XV, a DHPC should be disseminated in the following situations when there is a need to take immediate action or change current practice in relation to a medicinal product:

- *Suspension, withdrawal or revocation of a marketing authorisation for safety reasons;*
- *Important change to the use of a medicine due to the restriction of an indication, a new contraindication, or a change in the recommended dose due to safety reasons;*
- *Restriction in availability or discontinuation of a medicine with potential detrimental effects on patient care.*

There are other situations where dissemination of a DHPC should be considered. For additional guidance please consult module XV of the GVP.

Where relevant, the MAH(s) should be requested to provide a draft DHPC proposal for review by the Rapporteurs. When multiple MAHs are involved, consider providing key messages at an early stage to streamline further assessment.

In case no DHPC is proposed:

Not applicable.

In case circulation of a DHPC is proposed:

The DHPC below is proposed to be circulated to the following target group within the deadlines specified:

- [Describe here the proposed target group (e.g. GPs, paediatricians, cardiologists, pharmacists, etc)]
- [Timelines for submission of translations to NCAs, agreement on translations with NCAs and dissemination of the DHPC]

(This information will be used by the EMA PM to draft the communication plan).

Dear Healthcare Professional Communication

Please follow the template as described in annex II of the GVP.

If appropriate, the proposed DHPC should be updated following receipt of comments from Member States).

Annex 4 Comments received

List of <Questions><Outstanding Issues> adopted by <PRAC><CHMP> in <month, year>

<No comments were received.>

or

<The following comments were received:>

[Commenting party 1]

- **Comment**

  [...]

- **<co->rapporteur's comment**

  [...]

[Commenting party 2]

- **Comment**

  [...]

- **<co->rapporteur's comment**

  [...]

After reflecting each round of comments, ensure that whenever appropriate, the relevant sections of the overall summary of assessment, proposed list of outstanding issues and/or PI are updated accordingly.

Comments received during previous rounds should be deleted from the document to avoid confusion.

Appendix A Detailed assessment of the MAH's responses

In case this is not the first round of assessment, include the following sentence:

See <co->rapporteur Assessment Report dated <> for the assessment of the responses to the <LoQ><LoOI> adopted by <PRAC><CHMP> in <month, year>.

Assessment of the List of <Questions><Outstanding Issues> adopted by <PRAC><CHMP> in <month, year>

If there is more than 1 MAH in the procedure:

The following MAHs submitted responses:

Responses submitted by
<Name of MAH 1>
<Name of MAH 2>
<...>

The optimal format for the assessment of the data should be considered on a case-by-case basis by the assessment teams, based on the number and nature of the questions and the number of MAHs involved. Consideration should also be given to the relevance of presenting the data by indication, patient population and/or safety concerns to be discussed, as well as the presentation of the supporting data.

Repetitions and multiple presentations of the same data should be avoided, if possible.

After each round of assessment ensure that whenever appropriate, the relevant sections of the overall summary of assessment, proposed list of outstanding issues and/or PI are updated.

The detailed assessment of previous rounds should be deleted from the document to avoid confusion.

Appendix B Additional data

Any additional information submitted by other parties (e.g. third party interventions by a member of the public, Eudravigilance analysis/study) should be listed here. Repeat this structure for every additional submission received. The extent of the <co->Rapporteur's comments on each of these submissions is expected to depend on the content and the relevance of such submission.

Ensure that whenever appropriate, the relevant sections of the overall summary of assessment and/or other relevant documents are updated following the receipt of information from the above mentioned parties.

In case no additional submissions were received:

Not applicable.

In case additional submissions were received:

The following additional submissions were received:

Submission by	Date
<Name of party 1>	
<Name of party 2>	
<...>	

[Name of party 1]

- **Summary of submission**

  [...]
- **Rapporteur's comment**

  [...]

[Name of party 2]

- **Summary of submission**

  [...]
- **Rapporteur's comment**

  [...]

Additional submissions received during previous rounds should be deleted from the document to avoid confusion.